Navigating Clinical Trials

A Guide for Parkinson's Patients and Families

"Cures aren't going to fall from the sky. We have to climb up and get them."

–Michael J. Fox

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A Letter from The Michael J. Fox Foundation Patient Council

A Parkinson's diagnosis affects everyone differently. For some, the news may inspire a desire to take action, though it's often hard to know where to go or what to do.

For others, diagnosis may bring uncertainty, fear or denial. There is no wrong response to such a life-changing event—only your response. As active members of the Parkinson's community, and colleagues on The Michael J. Fox Foundation's Patient Council, we have found common ground in our belief that clinical research participation is a critical part of our experiences. It motivates us, inspires us, empowers us and gives us purpose as we navigate daily life with the disease.

We each took a different path to volunteering. While a few of us were champing at the bit from literally the day of diagnosis, most took some time to get here. (That's natural, though we also want you to know that some of the most important studies are open only to those in the very earliest stages of disease.) Many factors, such as age at diagnosis, geographic location, access to care and knowledge of research opportunities, influenced our decisions along the way. Trials, in turn, need us—as well as people who don't have Parkinson's—at different times and for different reasons. While some trials need people who are new to Parkinson's, others need those who have lived with the disease for years. Sometimes people are excluded by their genetic status or having had deep brain stimulation surgery; other times, those are exactly what the study requires.

We hope our experiences help you find your own path with Parkinson's, and, more importantly, remind you that you are not alone in the journey.

Seeing the right doctor matters

It took me several months to come to terms with what my diagnosis meant for my future. Even then, I wasn't quite sure what was in store for me. I realised I had to do what I could to help myself, and ultimately help others, while I was able. But I didn't know where to begin. My local neurologist recommended a movement disorder specialist—a neurologist with specialised training in Parkinson's. Movement disorder specialists bridge the gap between research and patient care, so they are uniquely positioned to suggest ongoing trials that may be well suited to specific individuals. I registered for my first study shortly after my doctor recommended it. The experience has given me confidence, hope and motivation. Now I use social media to encourage other people with Parkinson's to connect with movement disorder specialists and ask about trials. Simply put, there is nothing more empowering than being part of research towards a cure.

Israel Robledo, Texas, US

Research comes in many forms

As a family doctor, I knew the importance of research to advance disease understanding and therapeutic breakthroughs. I often encouraged my patients to join clinical trials, but I never participated myself. I was convinced I was too busy and rested on that excuse for years. Slowly,

The Michael J. Fox Foundation Patient Council advises the Foundation on programmatic strategies to best convey patient priorities to the research community and its funders, content and emphasis for patient education and outreach relevant to our mission to find a cure, patient roles in developing novel ways to conduct research and mechanisms for impact assessment.

though, I allowed myself to see what I already knew to be true: meaningful contribution does not necessarily require demanding, time-consuming trials. There are many types of studies, some more compatible than others with my time constraints. As I explored my options, I realised my level of involvement could change over time to suit my evolving lifestyle and commitments. Since then, I've done online studies, trials that require just a single visit to a clinic and some long-term research. One of the most important things patients can do now is contribute to genetic research, which may, in some studies, simply involve sending in a sample of saliva. In whatever way life allows, participation in clinical studies is vital. Research is only possible with volunteers. In this way, we play a critical role in changing our own lives.

Dr Soania Mathur Ontario, Canada

Fighting back through research

My first reaction to my Parkinson's diagnosis was to fight back. I agreed to participate in a clinical study the very day I was diagnosed. I knew the best way to fight the disease was to advance treatments that could slow or stop it from progressing. I continue to enrol in as many studies as possible, and have no plans to stop. It excites me to work directly with researchers on the front lines of science that could lead to a cure. That interaction is what gives me energy. It makes me optimistic to see progress and know that I'm actively taking part in it. I can feel the enormity and the power of being involved in something so important for myself and for everyone who lives with Parkinson's.

Lynn Hagerbrant, Connecticut, US

Changing personal perspectives

One of my biggest struggles with the disease was knowing that Parkinson's gets progressively worse over time. I worried about my future, my sense of identity and the potential loss of my independence. As a researcher myself (albeit not in the life sciences), I understood the importance of clinical trials to advance disease understanding and treatments, but I wasn't sure I wanted to be on this side of them. But I decided to get off the bench, and the interactions that I had with the scientists themselves quickly affirmed that decision. Many trial investigators I met had personal reasons for being in the field. These connections drive them to spend hours in the labs or caring for patients. This notion continues to fuel my passion for research participation today. Fighting Parkinson's can feel like such a solitary battle, but research unites us. The connection to the broader Parkinson's community has changed the lens through which I view my own disease.

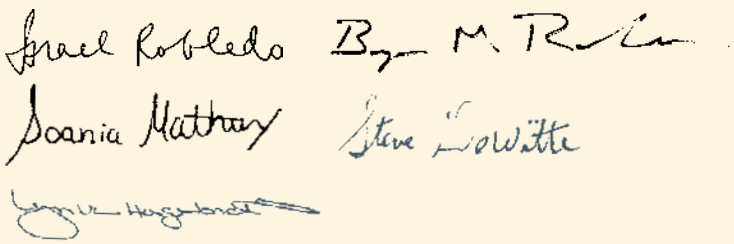
Bryan Roberts, New York, US

Addressing logistical challenges

When my doctor told me that my increasing twitching and tremors were caused by Parkinson's disease, I said "Okay. So, what does that mean?" I scoured Google and discovered professional websites with a wealth of information. But my searches also uncovered chat rooms, websites, workshops, conferences and support groups. I ventured out into the community and met many people with Parkinson's at different stages of their disease. With them, I shared a desire to make a difference and discovered the critical need for research participants. When we learned a dismal stat — less than one patient is recruited per clinical site per month — we created the Clinical Trial Transportation Program to help organise travel to different clinical trials in the region. By channelling our motivation to help willing participants overcome transportation or access concerns, we hope more trials can be conducted more efficiently, leading to more Parkinson's treatments.

Steve DeWitte, Connecticut, US

The passion we feel about being part of advancing the Parkinson's cure binds us, and the realisation that we are in this together empowers us. How each of us came to research participation was as individual as our experiences with the disease itself, but the uniting thread was our desire to change the course of Parkinson's and change lives—including our own. You, too, are an important part of this community. You, too, hold the power to directly impact your future and the future of millions living with Parkinson's disease. You, too, can experience the tremendous power of research participation.



Six Facts about Clinical Research Participation

No. 1

Patients Are Key Research Partners

You are the expert on Parkinson's disease (PD). Scientists need your partnership in research trials and studies to understand, measure, predict, prevent, slow and stop this disease. Every treatment that exists today is the direct result of individuals raising their hands to volunteer for research.

No. 2

There Is a Study (or Several) for You

Whether you were just diagnosed or have been living with Parkinson's for decades, have had deep brain stimulation, or live hours from a clinical site, you can contribute to our understanding of Parkinson's and the development of new treatments. Even if you don't have Parkinson's, you can participate in PD research.

No. 3

Not Every Study Tests a Drug

Many studies collect data and samples to better understand the biology of Parkinson's. Some trials and studies test exercise, physical therapy or other non-invasive treatments rather than medication.

No. 4

Participation Brings Risks and Benefits

While some risks, such as potential side effects of a new drug, are inherent in research, participation also may bring benefits. Some people say they gain a sense of control over their disease. Research could also offer more time with Parkinson's experts and early access to emerging treatments.

No. 5

Your Safety Is Top Priority

Safeguards are in place to minimise risk in research trials and studies. Researchers must have all study plans and materials approved by an outside committee of experts, and must monitor for and report any undesirable changes in a person's health—whether a result of the study or something else—throughout the course of the research.

No. 6

There Are Many Ways to Find Trials and Studies

Start by asking your doctor about opportunities for research participation, but also look to your support group or your PD community for referrals. Some health care centres and patient organisations hold in-person research events, and there are opportunities to learn about trials on the internet too. You can register online with the Foundation's Fox Trial Finder (foxtrialfinder.org) to be matched with recruiting trials that need volunteers as well.

"When the cure for Parkinson's is found—and it will be—it will be because of all of us."

Michael J. Fox

Chapter 1

Clinical Research Basics

To get just one new drug from the initial "Aha!" moment in the laboratory into the hands of people with Parkinson's can take several decades, billions of dollars and thousands of volunteers, researchers and doctors. Even before a therapy can be tested in people, years of basic and pre-clinical research must prove that it has the potential to work and is safe. And the odds are stacked against therapies making it through this thorough vetting.

So, when drugs do "graduate" to being tested in people, it's reason for cautious celebration. Clinical trials and studies are a final and crucial step on the path to developing better treatments for Parkinson's. They also are an opportunity for volunteers to step forward. New therapies can move towards approved use only with the participation of people with Parkinson's.

The Michael J. Fox Foundation supports early-stage testing of new therapies and addresses systemic challenges in the drug approval process so that more Parkinson's drugs can cross the finish line faster. But while financial investment is important to accelerate research, it's research volunteers who give us the best chances of understanding this disease and finding a cure. In the 200 years since Parkinson's disease (PD) was initially described, researchers have made significant gains in knowledge of Parkinson's—recognising the non-motor symptoms, such as mood and memory problems, that can accompany PD and realising Parkinson's genetic connections, for example. These understandings have shifted care and research, and none of this progress would have been possible without clinical trials and volunteers.

By participating in clinical research, you give something money can't buy. Funding and other resources can't make up for a lack of volunteers—an issue many clinical studies grapple with. Across all research, 85 per cent of trials face delays, and 30 per cent never even get off the ground. This dramatically slows research progress.

You can be an agent of change by taking a more active role in your own health care and contributing to Parkinson's research. You have the power to propel clinical research towards breakthroughs that help people with Parkinson's in their everyday lives. You could be the key that unlocks a cure.

In this chapter, you'll learn the basics of clinical trials and studies: how researchers conduct them, who can volunteer and what their potential risks and benefits are. You'll also find information on how to connect with trials and studies and talk to your doctor about research, as well as what to consider when deciding if and how to participate.

Types of Clinical Trials

The many different types of clinical trials can be broadly divided into two main categories:

+ **Observational studies** do not test drugs or treatments. Instead, researchers examine participants' health and may monitor volunteers over a certain period. With observational studies, researchers collect data to advance their understanding of how to track and treat Parkinson's, and how the disease naturally changes with time. Participating in some observational studies could include visiting a clinic for examinations, having blood drawn or undergoing brain scans. Other studies, such as The Michael J. Fox Foundation's Fox Insight (foxinsight.org), only require that you log on to your computer or smartphone to complete a questionnaire every few months. (See: "A Technological Revolution in Research," pg. 13.)
+ **Interventional trials** test whether a drug or other type of therapy works and is safe. Experimental therapies could include not only medications, but also exercise, surgical procedures, vitamins, supplements and even complementary therapies such as acupuncture or meditation. Each trial has a different objective and a unique plan called a protocol, so the level of volunteer commitment for each varies.

Phases of Interventional Clinical Trials

Clinical trial testing of a new therapy follows a sequence of phases. Each phase answers different questions and requires a thoughtfully designed trial and new group of willing volunteers:

+ **Phase I trials** test a potential therapy, procedure or drug for the first time in a small number of people (usually about 10 to 100). Often these are "control," volunteers—people without Parkinson's. These trials typically evaluate the safety of a new therapy. They also often yield information on side effects, effectiveness of delivery method (e.g., by mouth, injection etc.) and appropriate dosage levels. For most interventions, they last several months on average, but they may be much longer for certain surgical therapies.
+ **Phase II trials** more comprehensively assess a treatment's safety, and determine preliminary efficacy and side effects in a larger group of people (usually a few hundred) with Parkinson's. They can last from months to a few years.

  Typically, these trials are randomised, controlled studies. This means that one group of participants receives the experimental treatment, while the other (a "control" group) receives either the standard of care or a placebo (an inactive substance that looks exactly like the treatment). The standard of care is one that medical experts accept as the proper one and widely use. When this doesn't exist, researchers use a placebo. For example, we don't currently have Parkinson's disease-modifying therapies (medications that slow or stop disease progression). So, in trials testing new potential disease-modifying therapies, researchers use placebos for comparison to evaluate the therapy's effects.

  Participants are assigned to groups by a strategy that mimics chance, or the flip of a coin. Often these studies are "double-blind" as well, meaning that neither patients nor the research team know who is getting the experimental treatment.
+ **Phase III trials** confirm or disprove a therapy's efficacy, safety and side effects in an even larger group of people with Parkinson's (anywhere from 200 to 2,000, although trials testing surgical therapies may be smaller). Phase III trials, which also are randomised and controlled, last several years. Rather than being carried out at one location, Phase III are often multicentre trials, meaning they combine the results from volunteers who participate at many different medical centres.

In order for a therapy to move forward through Phase I and II, it must meet safety and efficacy standards. When Phase III studies confirm these results, a drug maker can submit a new drug application to the US Food and Drug Administration or an equivalent application to the European Medicines Agency or another governmental body. From there, the review process can take six to 12 or more months, depending on the agency's protocol. If approved, a drug then can be manufactured and sent to pharmacy shelves.

Once therapies reach the market and doctors and patients are using them in the "real world", companies conduct Phase IV clinical trials. These studies primarily evaluate long-term side effects in people known to be taking the drug, but they also could uncover potential new uses for the therapy to treat other conditions.

**Underlined words indicate a commonly used term. Find the definitions in the glossary, starting on page 46.*

The Clinical Trial Process

+ **Strict protocols direct each study.** Each trial follows an extensive and carefully monitored protocol, which is a plan that spells out the entire study process. This details how many volunteers are needed, who is eligible, what tests will be used to evaluate participants' health at the beginning and throughout the study, how long the study will last, what information will be recorded and other considerations. Similar to how a team delivers your medical care, a staff of doctors, researchers, nurses and study coordinators carry out clinical trials. The principal investigator, typically a doctor, leads the entire team and trial.
+ **Informed consent is obtained before you enrol.** Before you join a study, you'll meet with the trial team so that they can discuss relevant aspects of the protocol, answer your questions and go over a consent form. This document, referred to as informed consent, lists your rights as a volunteer, the potential risks of participation and what you can expect during the study. Once you understand what the trial entails and you feel comfortable and want to enrol, you sign the informed consent. This isn't a binding contract; you can still withdraw at any time for any reason. (You also can refuse study tests or treatments, but doing so may exclude you from continuing in the trial.)
+ **Independent committees review and approve studies.** An Institutional Review Board (IRB)—an independent group of doctors, researchers and others (usually at least one "non-scientific" person who represents the patient voice)—evaluates and approves each study's protocol and informed consent document. This committee also monitors ongoing study activities. The IRB is in place to protect the rights and welfare of people participating in a study.

What Happens When the Study Ends

Once a clinical trial is over, the trial team analyses the data, distils key findings and publishes the results or presents them to other researchers at a conference. (You can inquire with your trial team and search online for the published results.) At trial conclusion, teams also determine next steps for the therapy. They may recommend evaluation in the next phase of clinical trial testing, or, equally as important, they may suggest no further study because safety and efficacy data are not compelling.

People who have enrolled in a placebo-controlled trial often wonder whether they received placebo or the study drug. If the protocol allows, this information is made available when all participants have completed the trial. Some participants also want to know if they can continue to get a study drug once a trial ends. Often this is not possible, but the trial protocol and informed consent documents spell out in advance what will happen should this question come up. And if the therapy continues to the next phase of clinical testing, people who have participated in the earlier research may be given the option to continue with it. Because of many factors, though, enrolling in the next study phase may not guarantee that a person will continue the study drug. (A new study may require re-randomisation, for example.)

Public Policy Matters in Clinical Research

The work of drug development is more than clinical trials and volunteers. It's important to stay informed about public policy—government laws and regulations—because it can directly affect how treatments move from lab bench to pharmacy shelves, and how they are evaluated and approved.

Upholding Rigorous Approval Standards

Clinical trials test potential therapies for two important factors: Are they safe for patients to use and do they actually work? Researchers spend significant amounts of time and money investigating these questions. At the end of the clinical trial process, the US Food and Drug Administration, the European Medicines Agency and other governmental organisations review medications to ensure that they meet strict safety and efficacy standards. While these regulatory agencies make the final approval decision, public policy can influence their evaluation criteria.

Encouraging Drug Developers to Meet Patients' Needs

People living with Parkinson's disease (PD) are well aware of the gap in treatment options for many symptoms, such as cognitive impairment, balance problems and constipation. In the United States, policymakers created pathways to get crucial drugs to market quickly while maintaining strong FDA safety and efficacy measures.

The "breakthrough therapy" designation, for example, allows the FDA to expedite the development and review of a therapy that may offer substantial improvement over existing treatments. Nuplazid (pimavanserin), the first drug approved to treat hallucinations and delusions associated with PD, got to market faster through this program. Up to 50 per cent of people with PD can experience these symptoms at some point (they're more common in those with longer duration of disease, dementia or older age), and no approved treatments were previously available. Based on preliminary evidence, the FDA shortened Nuplazid's clinical trial development and review timeline while still preserving strict safety and efficacy guidelines.

Recognising Changing Research Trends and Tools

The Parkinson's drug development pipeline encompasses a broad array of experimental therapies, including motor and non-motor symptomatic options and varied disease-modifying therapies (ones that could slow or stop PD progression). Therapies in testing include everything from antibody infusions that clear out alpha-synuclein (the sticky protein that clumps in the brains of people with PD) to surgical procedures to drugs for people with specific genetic mutations. Research is evolving to address patient priorities and incorporate new devices and technologies. Regulators must be in tune with patients' needs and the latest ways to meet them, including unique trial designs and the right measurements to determine if they are successful.

When it comes to priorities, treatments to lessen or prevent dyskinesia (involuntary movements that can occur as a complication of long-term PD drug use) are towards the top of the list. But to make sure that these therapies work, we need a way to measure their impact in trials. When a standardised approach to rate dyskinesia did not exist, The Michael J. Fox Foundation funded the development and validation of the Unified Dyskinesia Rating Scale. This tool is now widely accepted by clinicians, researchers and regulators as a method for evaluating the potential benefit of new dyskinesia therapies.

Genetic research is another area where we're all working together. Parkinson's genetic clinical trials are just beginning, and they're an avenue towards precision medicine. As this research progresses, governmental organisations and researchers have to determine the right numbers and types of participants (with and without genetic mutations) to include in which trials so they can gather the best data.

Policy and research also intersect with technology. Data collected through online studies and smartphones can help scientists form a more complete picture of what life is like with Parkinson's. Wearable devices can capture how movement changes in real time when medication is taken. Governmental organisations must determine how trials can use new and existing technologies and what types of data they can gather to achieve the most robust results.

Who Can Participate in Clinical Trials?

Because clinical trials vary, many different types of volunteers are needed. One thing that stays the same, though, is the consistent need for participants both with and without Parkinson's disease (PD). Some people are surprised to discover that family members of people with PD, as well as people who have no connection to the disease, are as important as patients in moving research forward.

People Who Have Parkinson's

There is no one type of Parkinson's. Each person experiences his or her own version of the disease. That's why clinical trials need people across the spectrum of PD, with varied motor and non-motor symptoms. Every single person aids researchers' efforts to capture a fuller picture of disease and to develop targeted treatments.

Remember fact 1: Patients Are Key Research Partners.

In interventional trials, researchers seek volunteers representative of the people who will ultimately use the therapy outside of trials: women and men of varied ages, races and ethnicities. Clinical studies require a wide range of participants because—aside from the uniqueness of Parkinson's—we're all individuals who may have different responses to therapies. When investigators include diverse populations, they can be sure their intervention will be safe and effective in a broad group of people with PD.

In some cases, researchers may seek out specific subsets of people with PD. For example, some genetic mutations associated with Parkinson's are more common in people of certain backgrounds, such as those of Ashkenazi Jewish descent and North African Berbers. When studying these mutations and therapies, it makes sense to start by looking at people from these populations and their families.

People Who Do Not Have Parkinson's

Study participants who do not have PD provide essential information in clinical research. Often referred to as "control" volunteers, these individuals can contribute to both interventional and observational trials. In Phase I trials, they test new therapies for safety. In observational studies, they can help researchers define "non-Parkinson's disease" measurements and be a bar against which natural changes in Parkinson's are compared. When researchers match control and patient volunteers on age, gender and other characteristics, they can evaluate whether differences on surveys or exams (e.g., blood tests, brain scans or memory scales) are due to Parkinson's.

Another area control volunteers, especially those who have a family member with PD, can contribute is through genetic research. Studies might compare genes of family members with and without PD to identify which may be associated with the disease. Or, they may look to first-degree relatives who carry PD-associated genetic mutations for insights on disease causes, risk factors and potential protective factors. (See "Chapter 3: Genetics and Parkinson's Research," pg. 29.)

Different Trials Need Different Volunteers

Because trials look at different aspects of Parkinson's, each needs specific types of volunteer. At the outset, researchers establish guidelines—known as inclusion and exclusion criteria—for who can and can't participate. Qualified volunteers must (or must not) possess the outlined characteristics, which can include age, gender, symptoms, disease stage, medication, other medical conditions or genetic factors. This checklist isn't meant to keep people out of trials, but rather to get the right people into the right trials and keep researchers on track towards the answers they need. It's also intended to minimise risks. People taking medications that could interact with the study medication, for example, often are excluded.

Supporting Loved Ones through Research

When Karen Jaffe was diagnosed with Parkinson's disease (PD), her husband, Marc, looked for ways to help. He learned studies need control volunteers, and was eager to participate. "I wanted to provide more than emotional support to Karen, and this was a tangible way to do that," says Marc.

Still, he didn't jump immediately at the chance. He admits he had hesitancies about certain study procedures, and worried that testing might uncover an abnormality in his otherwise good health.

But six months later, Marc gave Karen an unexpected gift—his enrolment papers for MJFF's Parkinson's Progression Markers Initiative (PPMI).

Marc jokes that he joined PPMI, an observational study looking for PD biomarkers (objective measures to diagnose and track disease), because he didn't have an anniversary present. On a serious note, he adds, "When I learned how critical biomarker research is, it made it easier to set aside any concerns I had."

As part of PPMI, Marc now undergoes annual testing. He's had pictures of his brain taken, and given blood and spinal fluid. He's also filled out questionnaires about his sleep and had his memory tested. In the years since he joined, Marc hasn't missed an appointment. He has had procedures done at different centres with different doctors, and says each makes the experience as comfortable as possible.

Marc participates in other trials, too. When he and Karen are both eligible for a study, they use the opportunity to drive research together. "We see so much progress," Marc shares. "When you're in research, you feel things moving, and you see the finish line in the distance. It's great to be part of the process pushing us closer."

Watch more of Karen and Marc's story at michaeljfox.org/ParticipantPack.

A Technological Revolution in Research

In the 21st century, innovations in technology are accelerating the pace of Parkinson's research. People with Parkinson's disease (PD) and researchers alike benefit from these new tools. For people with PD, it is now easier to find and participate in clinical trials, and to track their experiences with the disease. And with new means of analysing data, researchers are working to create a more complete picture of PD than was possible in the past.

Clinical Studies Go Online

Widespread use of the internet has opened new ways for people with Parkinson's to participate in clinical research. Some studies are now carried out mainly or entirely online. That makes participation easier for many people who might not otherwise: those who live far from academic medical centres where much research takes place, who have difficulty traveling, who have not shared their PD diagnosis with others, or who simply don't have much spare time.

For example, MJFF's online study, Fox Insight (foxinsight.org) gathers data directly from people with PD about their experience living with the disease. Every 90 days, participants log on from wherever is convenient to tell researchers about their symptoms, medications and other aspects of life with PD. When analysed as a collective dataset, this information can give scientists insights that could lead to better understandings of disease and new treatments.

In addition to widening the scope and diversity of people who can get involved, computer access has made it simpler to get started. Resources such as MJFF's Fox Trial Finder (foxtrialfinder.org), an online clinical trial matching tool, make it easier for volunteers to connect with the studies that need them, including those they can do from home. Facebook and other social media platforms have also become a source of information on clinical trials.

Mobile Technology Puts Research in Patients' Hands

During a typical office visit, a doctor spends five to 10 minutes examining a patient with Parkinson's. It's essential to PD care but, given the variability of symptoms an individual may experience day to day and even throughout the same day, it's only a snapshot of a person's PD.

With smartphones, apps and wearable devices, such as fitness monitors, people with PD now can record how they live with the disease 24/7—their symptoms, medication effects and activity levels. Researchers are using this technology in stand-alone trials and within traditional clinical trials to supplement their understanding of potential interventions, and to find better ways to adjust medications and monitor disease progression. Technology is also bringing researchers to patients. Telemedicine—electronic methods of real-time interactive communication, such as two-way video—enables investigators to talk to and evaluate participants in their own homes.

Data Drives Discovery

Online studies and wearable devices have enabled the collection of large amounts of data from thousands of people, both with and without PD, over long periods. These substantial datasets can demonstrate patterns to uncover Parkinson's-specific insights—information that was never previously available to researchers. This holds enormous promise in the pursuit of a cure.

Learn more about MJFF's online trial resources in the Appendix, pg. 42.

Collaborating across the Globe to Speed Trials

I'd been bulletproof healthy all my life. So, when I was 44 and Parkinson's came up, it seemed completely out of the blue. Once I accepted my diagnosis—I think acceptance is a big part of being happy moving forward—it was all about what I was going to do about it. I said, "Do I want to be Clyde that has Parkinson's or Clyde that does something about having Parkinson's?" I decided I wanted to help myself, my family and the tens of thousands of other Australians living with Parkinson's disease (PD). I knew the best way to accomplish this was through research, but I didn't have the tools I needed to get involved.

I quickly transitioned from a newly diagnosed patient to a research funder, establishing an organisation called Shake It Up Australia Foundation. With no medical background, I was on a steep learning curve to understand how research is conducted and funded. In Australia, I found good researchers but inadequate funding, so I partnered with The Michael J. Fox Foundation to bring their strategic direction and patient-focused funding model here. Since Shake It Up Australia Foundation's 2011 launch, we've co-funded over US$6 million in Parkinson's research, making us the largest non-government supporter in the country.

We realised funding wasn't enough, though, and we needed to connect volunteers with the trials that needed them. Again, we worked with MJFF to make their online clinical trial matching tool, Fox Trial Finder, available in Australia. Since 2013, more than 2,000 Australians have used this resource to find recruiting clinical trials.

We're making progress in our quest to find ways and means to slow, modify and cure PD. I'm planning for a better tomorrow, even though with PD some of my tomorrows will be different than my todays. I passionately believe there is a way for everyone to make a difference and that the combined result of our contributions will ultimately lead to a cure.

Clyde Campbell is the founder of Shake It Up Australia Foundation. He lives with his wife and three children in Sydney, Australia.

How Do You Get Involved in Parkinson's Research?

Thinking about volunteering for a clinical study means weighing the potential benefits and risks, just as you would when starting a new medication or considering a surgical procedure to manage your Parkinson's symptoms. With every decision you make in life, you want to make sure that the pros outnumber the cons.

Taking part in research can be empowering and provide access to Parkinson's experts and the latest treatments. But it also can expose you to risk, side effects or discomfort. Discuss your thoughts on research with your family and care partner, and talk to the trial team about the requirements for a specific study. Your doctor can help you decide which research is right for your individual situation.

Weigh Potential Benefits and Risks

You may find it helpful to write out general pros and cons as well as those specific to the study. People with Parkinson's often say that the pros of research participation include:

+ playing an active role in your care;
+ advancing science for yourself, others in the Parkinson's community and future generations;
+ accessing promising new treatments that aren't available outside of clinical research;
+ partnering with Parkinson's experts, often at leading health care facilities; and
+ being at the forefront of the latest treatments and research.

In general, research risks typically involve potential side effects or adverse events related to trials that test new therapies. During the informed consent process, you will learn about specific risks of particular trials. Safeguards are in place to minimise serious side effects, but these may be a possibility in some studies. Other potential cons of research participation may include:

+ lack of benefit from an investigational treatment;
+ not getting to choose the group (treatment or placebo) you're assigned to in a randomised study;
+ costs that are not covered by your insurance company; or
+ increased visits to a clinic or hospital.

If the time and effort associated with certain trials is a deterrent, remember that there are many trials requiring varying levels of commitment. An online trial or one that requires just a single in-person visit may be a better fit.

Learn about Parkinson's Trials

As you consider your involvement, look into the trials that need volunteers. There's a lot you can do to educate yourself about available trials:

Remember fact 6: There Are Many Ways to Find Trials and Studies.

+ Talk to your doctor about clinical research they or their colleagues may be leading.
+ Ask others in the Parkinson's community who have participated in trials about their experiences.
+ Sign up for Fox Trial Finder (foxtrialfinder.org), MJFF's online tool that matches eligible volunteers to recruiting clinical trials.
+ Visit a local clinical trial fair, where you can learn more about different types of trials in your area.
+ Search www.clinicaltrials.gov, a site maintained by the National Institutes of Health that holds information on clinical trials and studies in all 50 states and more than 200 countries.
+ Check out MJFF's and other Parkinson's organisations' websites and resources.

Talking to Your Doctor

Your doctor knows your medical situation best, so it's important to get his or her take on research and how you can volunteer. Some questions you may want to discuss with your doctor, in addition to the trial team:

+ **Can I keep my own health care provider?**
  The short answer is: yes. Although you will have appointments with the clinical research team in the context of the trial, this is not the same as your usual medical care. The Parkinson's doctors you may see as part of a clinical trial will not make treatment decisions about your ongoing medical and

Parkinson's care. You can and should continue seeing your regular health care providers and, if possible, they should coordinate with the trial team so that they are kept up to date on your involvement. It's especially important for your Parkinson's doctor to know if and how your PD medications will be adjusted while you are in the trial. And if you undergo tests and receive the results, your regular doctors may want to see them as well.

+ **What about medications I take or other conditions I live with?**
Trial protocols and inclusion and exclusion criteria take medications and medical conditions into account so that the right people are selected for the right trials. A certain medical condition, such as memory loss, could make you ineligible for one trial but make you the exact type of participant needed in another. Researchers carefully consider all medical conditions, such as high blood pressure or heart disease, and medications taken for them. They will exclude you from participating in a trial if doing so would create too great of a risk for you. Trial teams also won't adjust non-Parkinson's medications during a study. However, your PD drugs might need to be changed as part of a trial. It's worth discussing this ahead of time with your Parkinson's doctor.

+ **What about insurance coverage and costs?**
There are two types of costs associated with a clinical trial: standard patient care and research. Standard patient care costs are those related to treating your Parkinson's, whether you are in a trial or not. These include doctor visits, medication, and lab and imaging tests. Health insurance providers often cover these, but you may want to check with your insurer to determine the extent of your coverage. Research costs—the study drug and labs and imaging or other tests performed solely for the trial—typically are not covered by insurance but are covered by the study funder. Costs related to problems that might develop during a research study are handled differently from study to study. Coverage and cost are good topics to go over in depth with your insurance provider and trial team.

+ **What if I get a placebo?**
Some people volunteer for clinical trials in hopes of receiving a new drug. Unfortunately, you don't get to choose the group you are randomised in. (Assigning participants through randomisation ensures that the treatment and placebo groups are similar, which means the science and maths behind the study are stronger.) The potential benefits and risks of new therapies need to be measured against the benefits and risks of not getting them (i.e., getting a placebo). The people who take placebo in trials serve an extremely important role. They help researchers ensure that any effects—good or bad—are from the treatment and not another factor. Placebo-controlled trials give the highest level of scientific evidence for (or against) therapies in clinical research. Ask what the chances are of getting placebo. In many trials, it's not 50:50, and more people may get the investigational treatment than the placebo.

+ **What if I want to quit?**
You're a volunteer, which means that, although ideally you remain enrolled until the study's completion, you can leave at any time. Life circumstances, changes in health or other factors may contribute to a participant's decision to leave a trial. This is permissible at any time. To officially withdraw from a study, you would inform the trial team and follow a specific protocol. Sometimes it is still possible to continue in a study even if you stop the study drug, which helps researchers continue to collect valuable data.

+ **How should I decide whether to volunteer?**
Ultimately, the choice to get involved in research is yours. But it's not one that should be made in isolation. Get perspectives from those you trust, including your care partner, family members and doctor. Make sure that the trial team answers all your questions, so that you can make an informed decision. Consider these questions for specific trials:

+ What is the goal of this study?
+ What is the exact intervention? For example, if it's a medication, how many times per day will I need to take pills?
+ What are the potential benefits and risks? How do these compare to the treatment I am currently taking?
+ In an interventional trial, what are the chances I will be assigned to the placebo group?
+ What types of side effects might I experience?
+ How could the study affect my daily life? How often will I need to meet the study team and how long will the visits last?
+ Where and when will testing occur?
+ What type of information will be collected?
+ Will a care partner or other person need to accompany me to on-site visits?
+ Will I have to stay in the hospital?
+ Will my expenses be covered?
+ How long will the study last?
+ Will I need to stop taking my Parkinson's medication or change my dosage?
+ If the treatment works for me, can I continue it after the trial?
+ What happens if I no longer wish to participate?

You will most likely think of many more questions that are unique to your situation or trial. Take the time to get the information you need so that you feel secure with your decision to take part in Parkinson's research.

Cures Won't Happen Without Research

I could not practise medicine without doing research. I see people who have had Parkinson's disease for 20 or 30 years as they deal with the limitations and complications of current therapies. I want to be part of the process of making it better for patients in the future, and march forward to a place where people don't ever have to have Parkinson's.

That's what people with Parkinson's want: a cure. And we are getting there—I am so optimistic—but it's not going to happen without research and volunteers.

I tell people, there's a comfort level for everybody—an observational study or an intervention trial, however you're comfortable. Do you want to be part of a Phase II trial with a lumbar puncture? Maybe yes; maybe no. Do you want to fill out a form so we can look at some environmental interactions? Why not? There's a comfort level, for everyone.

And every level of participation is informative. The clinical trials of new therapies are obviously important, but clinical observations can be critical. The little stuff matters, too.

People have different motivations for enrolling in research. I go back and forth with one of my patients: Is research participation altruistic or selfish? It can be self-serving, but you're also helping everybody. It is one of the few times in life when you can be selfish and altruistic at the same time. How often can you say that?

Dr Susan Bressman is the Mirken Chair and professor of neurology at Icahn School of Medicine at Mount Sinai in New York City.

Watch more of Susan's story at michaeljfox.org/ParticipantPack.

"We only can't if we don't."

Michael J. Fox

Chapter 2

Research Participation throughout Your Parkinson's Journey

As life with Parkinson's unfolds, options for research participation evolve with it. Wherever you are with Parkinson's, you can contribute. If you're newly diagnosed and haven't yet started medication, you may be eligible to participate in trials testing therapies to slow disease progression. Or, if you've tried a number of Parkinson's disease (PD) drugs over the years, investigators may be seeking people like you to study how to improve upon existing therapies. If you have dyskinesia, imbalance or memory problems, you may be able to advance new treatments for these symptoms.

Hundreds of Parkinson's studies are under way right now and all of them need volunteers with PD. Some focus on ways to diagnose PD, others on treatments for unmet needs—difficulties, such as falls and dementia, for which there are few approved medical strategies. Still, others test novel drugs with the potential to modify the course of disease. In-person and online studies offer people with wide-ranging symptoms and medication regimens the chance to become more engaged in their own care and with the Parkinson's community.

You can join at any time. Some people connect with a variety of studies throughout the course of their PD. No matter when you volunteer, or why, research participation is a way to actively pursue answers. Most people find it to be part of an empowering and rewarding experience.

Research on every step of PD is meaningful. This chapter describes what types of clinical trials and studies are available at different points in your Parkinson's and why each is critical.

Research Participation in the Early Years with Parkinson's

The first few months and years following a Parkinson's diagnosis can be overwhelming. While processing emotions, wondering where Parkinson's disease (PD) may take you and considering treatment options, you (like many others) may choose to keep Parkinson's a secret. It's no surprise then that few people think about participating in clinical trials during this time. With so much to cope with, volunteering for research may seem like a low priority.

But people within the first few years of their PD diagnosis are in a unique position to contribute to research. Moreover, clinical studies may offer access to an emerging new treatment, exposure to top Parkinson's specialists and an opportunity to take control of your health. Early in Parkinson's, it may feel as though life has been turned upside down. Research participation may act as a compass, helping provide direction.

Stopping Parkinson's Progression

A disease-modifying therapy—one that would slow, stop or even reverse PD progression—would be a great discovery for people with Parkinson's. Several therapies with this potential are in or close to clinical trials. These medications have shown in laboratory and population studies that they may slow progression or lower Parkinson's

risk, and now scientists are testing their safety and efficacy.

Many trials require participants who have been recently diagnosed and often not yet treated with PD medications. (Researchers refer to this as de novo Parkinson's.) Some studies do allow people who are taking certain PD drugs, and each trial sets specific criteria. However, with many in the early years of PD keeping a low profile or unaware of studies that need volunteers, these trials often struggle to enrol enough participants.

Even so, trials of disease-modifying therapies aren't right for everyone. Because of the nature or severity of symptoms, some people need to start medication right away. Others don't like the idea of possibly receiving a placebo. (Many trials are placebo-controlled, meaning one group of participants takes placebo for comparison to the group on the investigational therapy.) Either way, newly diagnosed people can still make many valuable contributions to PD research.

Treating Early Symptoms

People are diagnosed with Parkinson's based on the cardinal motor symptoms: tremor, rigidity and slowness of movement. Other non-motor symptoms, such as depression and constipation, can arise even before these movement changes. There are many clinical studies testing therapies for these symptoms—both motor and non-motor. Some clinical trials do not test new drugs.

Remember fact 2:
There Is a Study (or Several) for You.

For example, you could take part in an exercise trial for fatigue or a study of cognitive behavioural therapy for mood changes. And not all trials in early Parkinson's require people who have not yet started medication. A non-motor symptom study, for example, may not ask participants to change their motor symptom medications.

Learning about Disease Onset and Progression

People early in their Parkinson's also can teach scientists a lot about the disease. We have much to learn about why and how Parkinson's starts, and recently diagnosed volunteers can help. Participating in a study over time also allows researchers to study how Parkinson's progresses. This information can help us learn how to predict an individual's disease course and develop and test new treatments to stop its progression.

Studies that help us learn about disease onset and progression—and do not test a new treatment—are called observational studies, and they come in many shapes and sizes. As part of an observational study, you might undergo a brain imaging scan to look for changes that could diagnose and track disease progression (i.e. biomarkers), complete online questionnaires about your symptoms to see how your disease changes over time or fill out one-time surveys to see if you've been exposed to certain risk factors. Or, you may give skin cells that scientists turn into dopamine cells to study Parkinson's "in a dish"—another way to look at what goes wrong in PD (and identify potential drug targets).

Some observational studies need brain tissue to help researchers understand the hows and whys of PD. While something like brain donation may not cross your mind until later in life or well into your journey with Parkinson's, people both with and without PD can consider this at any time. When brain tissue is coupled with information on your symptoms and disease experience, it is often even more beneficial to researchers, so thinking about this earlier rather than later is important. (See "Donating Brain Tissue to Research," pg. 24.)

Knowing Your Options Early On

If you've recently been diagnosed with PD, you may want to think about the benefits and risks of research participation and find out what studies are available to you before you start medication, particularly if your symptoms are mild. You can then have an informed, thoughtful discussion with your doctor to help decide what's best for you.

Remember fact 1:
Patients Are Key Research Partners.

Many doctors, especially if their practice is geographically remote from clinical trials, may not bring up research participation. In a 2014 Harris Poll conducted on behalf of MJFF and pharmaceutical company AbbVie, only one in 10 doctors said they talked about research frequently with their patients. Time constraints may prevent these conversations, especially when providers focus primarily on care as opposed to research. Yet people with Parkinson's say they look to their doctors for information on research and opportunities to participate. See "Chapter 1: Clinical Research Basics", pg. 7, for tips on talking to your doctor and learning about available trials.

The key is knowing your options early on so that you can make an informed decision. Early in the disease course—a time that can be overwhelming—research participation is a way many find they are able to gain the upper hand on their disease and make a difference.

Making Sense of a Parkinson's Diagnosis

Dan Kinel began participating in research just three months after learning he had Parkinson's disease (PD). It was an unanticipated decision.

Research was the last thing on his mind. Like many who are newly diagnosed, Dan struggled to understand and accept the potential implications of PD on his lifestyle. He was a partner in a law firm, and had a young family and a busy social life. "I went from feeling completely healthy to having Parkinson's disease. It sent me into a deep depression."

When two of his friends took Dan on a weekend getaway to New York City to lift his spirits, he found himself, coincidentally, at the Foundation's inaugural clinical trials fair. At this expo, which connects people with PD to recruiting trials, he learned of the critical need for volunteers—particularly those who are recently diagnosed and not yet taking medication. That information gave Dan the sense of purpose he'd been seeking since the day of his diagnosis. He signed up for two trials before leaving the event.

Since then, Dan hasn't stopped. Over the past four years, he's participated in more than a dozen observational and interventional studies, both in-person and online. "I get a different perspective from each trial I do," he explains. "I use each as an opportunity to ask questions, learn from researchers and do something meaningful to help myself and others with PD."

He also has become an ambassador for research, spreading the word in his community about the importance of participating in clinical trials, the need for volunteers and ways to get involved. Dan says being on the front lines of research towards a cure energises and empowers him. "Participating in research changes the way you view your diagnosis, the people who provide care and the world around you. It makes you feel like you are playing an important role in solving a problem that affects millions of people."

Watch more of Dan's story at michaeljfox.org/ParticipantPack.

Research Participation Later in Your Parkinson's Course

While some clinical trials and studies need people early in their disease course, many need people who were diagnosed with Parkinson's some time ago. Individuals with moderate or advancing Parkinson's—including those who have had surgical procedures to treat the disease—may be eligible for a variety of interventional and observational trials.

Remember fact 2:
There Is a Study (or Several) for You.

However, participation at a later stage of disease may require more assistance from loved ones and care partners. Speak to your doctor and support network about which studies may be right and appropriate for you.

Studying Later-Stage Symptoms

Many aspects of Parkinson's disease (PD) cannot be studied until later in the disease course. Certain symptoms—dementia, gait and balance issues and dyskinesia (uncontrolled movements), for example—mainly appear in people with moderate or advancing Parkinson's disease. Studies to better understand these features of PD and test treatments to ease their impact (e.g. drugs, exercise, physical therapy) need volunteers who experience them.

Observational studies, too, may call for people with long-established disease. Fox Insight, MJFF's online study, is capturing data on the lived experience of Parkinson's at every stage. Sharing with researchers what life is like with advancing PD can help allocate resources, design studies and advocate for new treatments.

Certain trials evaluating disease-modifying therapies are also open to people who have had Parkinson's for several years and are taking PD medications.

Participation after DBS and Other Surgical Procedures

A commonly asked question is, "Can I still participate in research if I've had deep brain stimulation (DBS)?" The short answer is yes—there is a study for everyone. However, some trials may not include people who have had DBS or other surgical procedures on the brain, or who take certain medications. Many, though, welcome people who have undergone or are using a number of treatments. Review the inclusion and exclusion criteria of a study to see if you may be eligible, and speak with your doctor about the effects of research participation on your care regimen.

Calling on Your Loved Ones

With later-stage Parkinson's may come limitations and a greater need for support and assistance from others. Volunteering for clinical research may not be a priority. Care partners also may not be aware of the range of opportunities for participating. In a 2014 Harris Poll survey, only 41 per cent of those caring for someone with advancing PD said they would be likely to encourage the patient to participate in research.

It can take time and effort for a care partner to help their loved one volunteer. Consider, though, that studies come with varied levels of commitment and helpful resources. Care partners could help complete an online survey. And some study sites are piloting the use of rideshare services, such as Lyft, to transport volunteers to site visits.

When deciding to participate in a trial or study, your care partner can help evaluate the costs and benefits. It may take time and energy to volunteer for a trial, but that study could help test a new treatment and offer more face time with Parkinson's experts. Bear in mind that some research focuses on care partners' needs too, so research participation can extend beyond treating PD per se.

Remember fact 5:
Your Safety Is Top Priority.

Donating Brain Tissue to Research

Researchers can learn much by studying the brains of people who have lived with Parkinson's disease. For example, they analyse brain tissue to understand the effects of Parkinson's and where to target treatments. There are a number of brain donation programs around the country. Some require advance consent and visits to a study site for periodic assessments.

You should discuss this decision with your loved ones, and ensure that they know your intentions. Expressing your wishes to your family now can help them plan for and coordinate your donation. Your doctor also can help answer questions and connect you with a donation program.

Dancing for Science

A decade has passed since Manny Torrijos discovered he has Parkinson's, and he's been contributing to research ever since. Over the years, he's done a variety of trials—everything from filling out online surveys about his non-motor symptoms to testing a therapy to ease motor symptoms. Knowing that every case of Parkinson's is unique, Manny experiments to find opportunities that work for him.

"Awareness of my changing body helps me develop my own strategy for continued research participation," Manny explains. As his Parkinson's evolves, he's noticed increasing imbalance, stooped posture and rigidity. Balance and posture problems are hard to correct with the currently available medications but even so, Manny's medications may not be working as well as they used to. The benefit they provide can be irregular or short-lived.

Manny sees his situation as a way to push forward research towards new and better therapies. When he found a dance study targeting many of his symptoms, he quickly enrolled. Because he enjoys dance and feels it "lets him move in ways his body is able", this is his preferred type of research. He's participated in several studies of different forms of dance for both motor and non-motor symptoms.

It is a little harder for him to get around these days, but that doesn't stop Manny from keeping weekly research commitments. He simply makes adjustments such as adding extra travel time. For him, the extra effort is worth the positive feelings he has when interacting with other patients and researchers.

Manny's take on research: "If we all focus on what matters to us rather than what is the matter with us, we will find that we can all be part of the cure. There are research opportunities we all can do to enrich our lives." People with Parkinson's may experience changes in movement, emotion and memory. Dance helps Manny manage these changes, and for him, he says "it's the next best thing to a cure."

Watch more of Manny's story at michaeljfox.org/ParticipantPack.

Partners in Research

When Steven Spencer received his Parkinson's diagnosis 13 years ago, he didn't hesitate to sign up as a clinical trial participant. And neither did his wife, Kae, who joined him as a control volunteer. The couple, who've been married for more than 40 years, are used to doing things together—studying for college exams, working as speech pathologists and raising their children. When Parkinson's disease (PD) entered their lives, it was natural to partner in research.

Steven and Kae have participated in several studies—some together, some independently. For instance, they can take part in Fox Insight, MJFF's online study, at the same time from their living room. Steven completes quarterly questionnaires to tell researchers about life with PD; Kae fills out the same surveys as a control volunteer. Other trials require Kae's assistance so that just Steven can participate—she drives him to appointments and helps him navigate the medical centre, for example. Kae sees this as her contribution, too: "We're a team," she states matter-of-factly. "We're in it together."

Steven's deep brain stimulation (DBS) surgery three years ago hasn't stopped the pair either. In fact, it may have given Steven more energy to pursue the studies that need him—the procedure lessened his fatigue and eased his motor symptoms. But as with all medical conditions or medications, DBS makes him eligible for some studies and excludes him from others.

Steven and Kae's involvement in research goes beyond clinical trials. In February 2017, they attended MJFF's Public Policy Forum in Washington, D.C. There, they joined 200 other care partners and people with Parkinson's to advocate for Parkinson's research, drug development and health care.

Of their experiences in Parkinson's research, Kae observes, "There are thousands working on a cure, and they're chasing down thousands of pathways." She goes on, "It's humbling to see so many at work, and it's empowering to know we are part of that."

Watch more of Kae and Steven's story at michaeljfox.org/ParticipantPack.

Key Takeaways

Research Participation throughout Your Parkinson's Journey

Science needs a broad range of research participants—not only women and men of diverse races and ethnicities, but also people at every stage of Parkinson's. No matter your personal experience with Parkinson's, there is a way to contribute to greater understanding and improved treatment of this disease.

+ **There are hundreds of studies addressing the many aspects of Parkinson's disease.** No matter what your situation or level of comfort with research, there is likely a trial or study for you. You can take part in interventional trials or observational studies, volunteer in person or online, contribute one time or over many years.
+ **Different kinds of trials or studies may be right for you at different times in your Parkinson's journey.** Some types of studies may be more relevant or easier at different points in disease: disease modifying in early-stage Parkinson's, symptomatic later in disease course or online studies if travel is difficult.
+ **Consider your care partner's contribution.** Talk it over before joining a trial or study. Volunteering for research can take time and effort from loved ones, and they may need to be involved in some studies. This is especially true if Parkinson's moves into moderate and advancing phases.

"The answer is in all of us."

Michael J. Fox

Chapter 3

Genetics and Parkinson's Research

Some of the greatest strides in understanding Parkinson's disease (PD) and developing new therapies have come from advances in genetics made possible by people who volunteered for clinical studies.

Just 20 years ago, most scientists believed that unknown environmental factors were completely responsible for Parkinson's disease. Then researchers collected and analysed DNA samples from a large family, in which many members over several generations developed Parkinson's. In these samples, scientists found the first gene (*SNCA*) linked to PD.

It was a game-changing discovery that established a genetic connection to Parkinson's and led to a new understanding: The clumps found in the brain cells of all people with PD (called Lewy bodies) are made mostly of the protein alpha-synuclein, which is made by the *SNCA* gene. Today, alpha-synuclein is a leading suspect in Parkinson's disease. Many studies are looking to measure this protein as a way to diagnose and track Parkinson's and to develop therapies to slow or stop its progression.

This detective work is why genetic research is one of the best routes to overcoming knowledge gaps in PD. It's pushing PD research forward in ways that promise to change medicine. It's helping unlock causes, and guiding the development of therapies targeted towards an individual's genetic make-up as well as disease-modifying drugs that could benefit everyone with PD.

Today, dozens of genetic mutations have been associated with an increased risk of Parkinson's and scientists are tracking the ways they influence disease. We know, though, there is still much to learn.

We can't get there without a wide range of volunteers—people with PD, their family members and people without PD. Compared to other clinical research, genetic studies may bring some additional issues to consider before participating. You may have questions about the privacy of your genetic information or how to make sense of your genetic testing results. This chapter will help you understand what participating in genetics research could mean for you.

Parkinson's Genetics 101

Genes are the material of heredity, passed down through the generations from parents to children. These inherited bits of DNA make us who we are—visible features such as eye colour, as well as ones that can't be seen, including an individual's risk of disease. While we all have the same types of genes, some people have a change in gene sequence; these are called genetic mutations.

Everyone gets two copies of each gene, one from each parent. In some cases, a mutation in just one of those copies is enough to raise the risk of Parkinson's disease (PD). These are called "dominant" mutations. In other cases, PD only develops if both copies are affected—these are called "recessive" mutations. Some mutations cause PD in younger patients, but others lead to PD at the typical age. And some mutations may affect how a person's PD progresses or how symptoms respond to medications. The science is complicated, but your doctor and a genetic counsellor (See "What is a Genetic Counsellor?" pg. 37) can help break it down for you.

Scientists long thought Parkinson's had no genetic connection. Most people with PD do not have a family history of the disease. But in the past two decades, researchers have identified a number of genetic mutations that play a role in Parkinson's. These discoveries are important because they give us a starting point from which to study disease biology and to design treatments to prevent or stop progression.

While we still have much to learn about Parkinson's genetics, there are some things to know now.

Parkinson's Disease is Not Inevitable

Most genetic mutations associated with Parkinson's disease raise one's risk a small amount. Even people with higher-risk mutations will not definitely get PD. In other words, no known mutation carries a 100 per cent chance of causing Parkinson's. Researchers are studying people with mutations linked to PD but who do not exhibit symptoms to uncover protective factors (genetic or otherwise), which could lead to treatments to prevent Parkinson's.

Certain PD Mutations Are More Common in Some Groups

Some genetic mutations are more common in certain familial and ethnic groups. For example, these three mutations are of great research interest:

+ *SNCA*: very rare mutation found in families with many PD diagnoses
+ *LRRK2*: more common in people of Ashkenazi Jewish, Basque or North African Berber descent
+ *GBA*: fairly common in people of Ashkenazi Jewish descent

While people of other descents can carry these mutations, researchers often recruit for genetic studies from these populations because there is a greater likelihood of finding mutation carriers.

Mutations May Impact One's Type of Disease

No one with Parkinson's has the same disease experience. Even people with the same genetic mutation experience PD differently—such as being diagnosed at different ages. There are some trends, though. People with a rare type of *GBA* mutation, for example, are more likely to develop cognitive impairment. Scientists are studying these known genetic connections and looking for other genes or biological or lifestyle factors that may influence when and how people get Parkinson's disease.

Genetics and Environment Can Interact to Cause Parkinson's

While some cases of PD may be attributed more heavily to genetic mutations (*SNCA*, for example), for many, an environmental factor (or combination of factors) tips the scale. An old saying is that "genetics loads the gun and environment pulls the trigger." For example, pesticide exposure can contribute to the risk of developing PD. Some studies have found those who do develop PD after contact with pesticides have genetic mutations that affect the way the body metabolises these toxins. It's that combination of genetic susceptibility and environmental exposure that influences disease risk. It is possible, too, that environmental factors, such as eating a healthy diet, could play a protective role.

Genetic Mutations Teach Us about Disease

Within the body's cells, the role of genes is to direct the production of proteins—worker molecules that are responsible for many aspects of life, including what we look like and how our bodies function. Genetic mutations can change how much protein is made or how proteins work. This can ultimately lead to disease, such as Parkinson's. Studying how changes in genes and proteins lead to disease allows researchers to get a better understanding of how PD develops and how we can hopefully stop it from progressing or even beginning in the first place. For example, mutations in a gene called *LRRK2* are believed to increase activity of the LRRK2 protein, which is not good for our brain or other cells, and can result in PD. Scientists are developing medications, called LRRK2 inhibitors, to block these LRRK2 proteins and keep cells healthy.

Genetics Could One Day Dictate Your Treatment

Science is moving away from a "one-size-fits-all" treatment approach for disease. Your genetics may soon tell doctors what therapy is best for you. Clinical trials are already under way to assess whether new therapies may benefit people with genetic mutations linked to PD. Ultimately, tailoring a treatment regimen to one's individual biology—precision medicine—brings greater likelihood of success.

Bringing therapies from the laboratory to the pharmacy requires the participation of thousands of volunteers in clinical trials. Look at how far we've come in Parkinson's genetics research in a short time, and imagine where we'll be in another 20 years with your help.

An Investment in Research

When Ofer Nemirovsky was diagnosed with Parkinson's disease (PD), he already knew that he carried a genetic mutation. What he didn't know was that the mutation could explain his PD.

Ofer had genetic testing at the time he and his wife were starting a family. (Some genetic mutations are more common in certain ethnic groups, and many people undergo prenatal testing to find out if their children could inherit a genetic disease.) It was then Ofer discovered that he carried a mutation in the *GBA* gene.

Twenty years later, Ofer noticed a change in the way he walked—his first symptom of Parkinson's. By then, researchers had learned that some genetic mutations, such as *GBA*, increase a person's risk of PD.

After his PD diagnosis, Ofer drew on three decades of professional investment experience to invest in learning about PD and research. "I developed a new frame of mind," he says. "I decided to immerse myself in the subject."

He also looked for opportunities to participate in clinical research, beginning with studies that required donating blood and skin cells. That led him to participate in the first clinical trial testing a Parkinson's drug that targets *GBA* mutations. "Being on the front lines of research helps calm my worries about my future with Parkinson's and gives me a lot of hope," he says.

"When you're living with a genetic mutation and a disease, you think a lot about your kids," says Ofer. "Ours range in age from 17 to 20. Maybe I'm being naïve, but I'd like to think that by the time they get tested for *GBA* mutations, if the results are positive, it won't be as big a deal—in some small part because of my decision to take part in research today."

Watch more of Ofer's story at michaeljfox.org/ParticipantPack.

Participating in Genetic Research

What to Expect

Both people with Parkinson's disease (PD) and their loved ones can play a critical role in the pursuit of a PD cure by participating in genetic research. And everyone with PD, not only those with a genetic mutation, can benefit from the insights of genetic research. So, it's important to understand what genetic research entails, if and how it involves genetic testing and what the benefits and risks are.

Everyone Can Advance Genetic Research

No matter whether you have Parkinson's, a family member with PD or a Parkinson's-associated genetic mutation—you can help push breakthroughs forward. By studying the genes of people with PD, their relatives and control volunteers, researchers learn about the genes linked to Parkinson's, how they interact with other genes and environmental factors to cause (or protect against) disease, how they correlate with specific PD symptoms and progression and how they could be modified or targeted to treat disease. By studying broad populations of people both with and without PD, researchers also can find as-yet undiscovered mutations associated with Parkinson's.

Genetic Research Versus Genetic Testing

Participating in genetic research is different than simply getting genetic testing. In research, DNA samples from study participants are collected and analysed to help answer a scientific question. Genetic testing carried out as part of a research study is not necessarily intended to provide you with personal medical information and, in some studies, you may not even learn your results.

Each study has a protocol that specifies whether, and how, participants will learn the results of their genetic testing. The reasons why trials don't share individuals' data vary, but often it's because this information does not directly impact medical care or other decision making.

Mutations May Impact One's Type of Disease

No one with Parkinson's has the same disease experience. Even people with the same genetic mutation experience Parkinson's differently, such as showing different symptoms. There are some trends, though. A mutation in the *PRKN* gene, for example, is associated with young-onset Parkinson's (before age 50). Scientists are studying these known genetic connections and looking for other genes or biological or lifestyle factors that may influence when and how people get Parkinson's disease.

Genetic Testing is Primarily for Research, Not Care

As of this writing, genetic testing for Parkinson's disease (PD) is most commonly performed in the context of a research study because results don't alter your personal medical care. If you have PD, finding out you have a mutation will not necessarily tell you about your future symptoms or disease course, nor will it impact which Parkinson's treatments you take. This may change as therapies targeting specific PD mutations move through the pipeline of clinical trials. And knowing your status can get you connected with genetic trials in the first place.

For those who don't have Parkinson's, interpreting genetic testing can be a bit tricky. Testing positive for a genetic mutation doesn't guarantee that you will develop PD, and different mutations raise risk to different degrees. On the other hand, a negative test does not mean you won't get Parkinson's. It's likely that many mutations linked to PD have not yet been discovered. And we have much to learn about how environmental factors interact with genetics to raise or lower the risk of PD. (See "Parkinson's Genetics 101," pg. 30.) Without a cure for PD or a way to prevent it, some people would rather not know their genetic information. Others, both with and without Parkinson's, have used this data to inform healthy lifestyles and participate in certain clinical trials.

Individuals pursue genetic testing outside of research—through their doctor or through an online service—for various reasons. People with PD might want to understand the likelihood of passing on a mutation to their children and those with an affected family member may be concerned about their own risk of Parkinson's. Sometimes people have no connection to Parkinson's and are simply curious about what information their genes hold.

Genetic Research Has Benefits and Risks

Some genetic studies look at one particular gene; others sequence all of your genes (i.e., your genome). Participating may involve little more than giving blood or providing a saliva sample, which sometimes can be done from your own home. If researchers need additional information to go along with genetic data, they may interview you over the phone, examine you in person or conduct other laboratory or imaging tests. During the informed consent process of these studies, all procedures, including how your genetic data will be collected and stored and if your samples of genetic information may be used for future research, will be discussed. You'll also go over potential risks and benefits of participation, as well as whether you'll have access to your genetic results and a genetic counsellor who can talk to you about the risks and benefits of genetic testing and research participation. (See "What is a Genetic Counsellor?" pg. 37.)

Potential risks may centre primarily on your genetic information. Test results, particularly if unexpected, may cause stress or anxiety. And although confidentiality and security are maintained to the highest levels, accidental data sharing may be a concern. Talk to your personal health care provider about how your genetic information is protected.

The decision to participate in any research is a personal one, but genetic research may bring additional considerations for you and your loved ones. A discussion with your doctor or genetic counsellor can help address concerns you might have before deciding to participate in genetic testing or research.

Remember fact 4: Research Participation Brings Risks and Benefits.

A Family Rallies to Support Genetic Research

In 2008, Patti Meese was having fun, enjoying her family and loving life. She had a successful career and lots of friends. "When Parkinson's hit, I spiralled into a deep depression," she says. "I stopped talking to my friends, going out and exercising. I started shuffling and walking with a cane for balance, and my left leg was dragging."

Things turned around for Patti after she began physical therapy. As she gained strength and stamina, she decided to educate herself about Parkinson's disease (PD) and the latest research. "I wanted to help myself feel better and move better," she says.

While participating in a study, Patti got surprising news: she carries a mutation in the *LRRK2* gene, which is linked to PD.

Although no other members of her family have shown signs of PD, Patti wondered if any of them also carried a mutation. "I gathered everyone together at a family barbecue," she recalls, "and asked if they would help move Parkinson's research forward by getting tested for this mutation."

Patti explained that a genetic counsellor would guide them through the process, answer questions and help them understand the results. Her daughter and four sisters volunteered right away. Ultimately, her daughter and one sister found that they carry *LRRK2* mutations. Neither has PD, but both are now enrolled in Parkinson's studies.

Participating in research has made Patti feel more confident in her life with PD, and being a research advocate gives her a sense of purpose. Over time, she has come to see her PD journey as an opportunity or even a gift calling her to action to help others with this disease. She says, "I hope to help people live a better life and move research forward—maybe even help pave the way for finding a cure."

Watch more of Patti's story at michaeljfox.org/ParticipantPack.

What to Consider before Genetic Testing

The results of genetic testing can affect different aspects of your and your family's life. So the decision to seek genetic testing on your own or to participate in research that includes genetic testing deserves extra attention. Remember that not all research studies disclose your results, and in some cases you can choose not to learn your results. Your doctor and, if available in your area, a genetic counsellor, can talk you through what it means to participate in genetic testing and specific considerations surrounding employment, insurance, family and cost.

What is a Genetic Counsellor?

Genetic counsellors are professionals with expertise in both medical genetics and counselling. They can provide education and emotional support to people who are considering or have undergone genetic testing for any reason: people who have Parkinson's disease (PD) or are at risk for the disease (because of a genetic mutation or family history of PD), or individuals who are just curious about their genetics.

Jennifer Verbrugge, MS, CGC, LGC, a certified genetic counsellor at Indiana University who works with participants in MJFF's Parkinson's Progression Markers Initiative biomarker study, says, "The term 'counselling' can have negative connotations, but genetic counselling is primarily a discussion about inherited aspects of disease and a place for you to ask questions before and after genetic testing is performed."

She adds, "Anyone who's considering genetic testing—whether it's solely for their own knowledge or to participate in a genetic research study—could benefit from sitting down with a genetic counsellor."

Genetic counsellors can help you explore the pros and cons of genetic testing, and what genetic testing can and can't tell you and your loved ones. They can offer practical advice and assistance, such as on how to talk with your loved ones about Parkinson's. (See "What to Consider before Genetic Testing," on opposite page.)

When meeting with a genetic counsellor, you can expect to go over much more than your genetic test results and their potential implications for you and your family. You'll also review:

+ basic information on Parkinson's;
+ details on Parkinson's genetics, including what is and isn't currently known, and how different mutations are inherited;
+ your family's history of Parkinson's, whether anyone has had genetic testing and which, if any, mutations they carry; and
+ specific questions you have. Common concerns often centre on an individual's and family members' exact PD risk and what can be done to mitigate this. Research in this area is active, but doctors don't yet have definitive answers.

You can prepare for your visit by gathering any genetic information from your family that you may have. Genetic counsellors are primarily interested in older relatives (e.g. grandparents, parents, aunts, uncles and older siblings) but information about younger siblings and children can be important too. You should also write down the main concerns you'd like to address.

If genetic counsellors are available in your area, your doctor can refer you or you may be able to find one near you by searching online. Be sure to look for counsellors who specialise in adult genetics or neurogenetics. Or, if you've gotten testing on your own, through an online service, for example, you may want a counsellor with expertise in "at-home" or "direct-to-consumer" testing.

Watch more of Jennifer's story at michaeljfox.org/ParticipantPack.

Employment

Questions may arise about how genetic test results could affect your job, and whether current or prospective employers can or should know this information. You likely won't have to disclose your (or your family members') genetic status, and laws may make it illegal for an employer to use your genetic data to make work-related decisions (e.g. hiring, promotion or termination). Your doctor or a genetic counsellor can help familiarise you with the laws in your area and how they apply to your situation.

Insurance

Before testing, consider how results could affect your health care and other types of insurance. Health care insurers may not be able to raise premiums or deny coverage based on your or your family members' genetic status. But protections might not extend to long-term care, life or disability insurances. Your doctor or a genetic counsellor can talk through these considerations with you before genetic testing.

Family

Getting genetic testing may mean learning more, not only about yourself, but also about your family. If you find out you have a genetic mutation that increases PD risk, for example, you may wonder about your children's or siblings' risk as well. A genetic counsellor can discuss these scenarios and help you create a plan to communicate results to your family, if you decide you want to do so.

Cost

The cost of genetic testing can vary depending on how it is performed, how detailed it is and what type of insurance coverage you have.

Genetic testing can be done through research studies, online services or your doctor's office. When testing is a part of research, there is usually no cost to you.

For online services offering basic testing, you will likely pay out of your own pocket. If recommended by your doctor, at least part of the cost may fall to you, so you'll want to check with your insurance company ahead of time. Health insurance may cover associated genetic counselling, but you could be responsible for a portion of those costs as well.

Key Takeaways

Genetics and Parkinson's Clinical Research

Genetic research is immensely important to our pursuit of a Parkinson's cure. Studies need people with and without Parkinson's genetic mutations to help us learn what may cause this disease and how we may stop it. Before participating in genetic research, though, thoroughly think through the benefits and risks, and talk to a genetic counsellor (if available) and study team to get answers to all of your questions.

+ **Genetic research volunteers can help us uncover the many unknowns about Parkinson's.** Much of our core knowledge about the underlying biology of Parkinson's disease (PD) comes from studying genetics. Participating in genetic research can help scientists illuminate more about disease causes and develop treatments to slow or stop it. There are opportunities for all type of volunteers—people both with and without PD, as well as those with and without PD-linked genetic mutations.
+ **The future of Parkinson's treatment may be precision medicine—led by genetics.** In the future, doctors may prescribe treatments based on one's genetics rather than one's symptoms (as they do now for people with certain cancers). Drug makers are currently testing therapies that may slow PD progression in people with genetic types of PD.
+ **Learning your genetic status is a personal decision; genetic counsellors can help you navigate this choice.** Some people may not want to learn their Parkinson's genetic status because we don't yet have therapies to slow or stop disease progression and this knowledge does not impact PD care. Others may want to know so they can participate in specific research studies. Before undergoing genetic testing, talk to your family and perhaps also a genetic counsellor. Counsellors can help you weigh the pros and cons and give practical advice and assistance.

Afterword: Where Do We Go from Here?

Reflections from a Repeat Research Volunteer

By Gary Rafaloff

I was diagnosed with Parkinson's disease (PD) in 2012. Like most people, I was left reeling with uncertainty and confusion. Probably a little different from most people, my wife and I signed up for our first clinical trial that same day. (Granted, I have a professional background in research and statistics, so I may have been more comfortable than most with the ins and outs of joining a study.)

But as it turns out, that first trial was just the beginning of a new role in my life: repeat research volunteer. I've participated in more than 20 scientific projects so far. I've worn a smartwatch to monitor my movements, undergone genetic testing, even received infusions of a potentially neuroprotective therapy three times a week (I later learned I had been in the placebo group).

You'd think a relentless volunteer like me would know everything there is to know about taking part in research. Still, the guide you're holding was so informative that I have wanted to read it more than once. Each time I pick it up, I find myself focusing on different aspects and experiencing new emotions. I'm energised by the hundreds of research trials taking place today. (Believe me, this is a significant increase even from just five years ago in Parkinson's research.) I'm intrigued by the scientific advances in understanding the causes of the disease and its relationship to genetic and cellular pathways. And the stories of the Foundation's Patient Council and vocal research advocates motivate me and keep me wanting to do more, as much as I can, for as long as I can.

I will never stop feeling astounded at the sheer length of time it takes—literally decades—for researchers and regulators to discover, test and approve new treatments for brain diseases. Science has always been a long march, but it's not lost on me, or on any of the patients I've met, that trials simply need more people with Parkinson's to participate. (It's hard to wrap my mind around the fact that 85 per cent of clinical trials are delayed or never even get off the ground, simply because nobody shows up to take part.)

But strangely enough, this also makes me feel hopeful. After all, you and I are living through a moment of immense opportunity. Parkinson's disease is a diagnosis you wouldn't wish on anyone. But if I have to have it, I'm grateful it's at a time when I can play a personal role in bringing ground-breaking new treatments to market.

Today, there are interventional trials testing therapies to ease some of the most troublesome PD symptoms, and therapies to slow or stop the progression of disease, which no current treatment can yet do. There are observational

> *"Never doubt that everyday people like you and me are the most important part of the complex and expensive drug development process."*

studies gathering new knowledge about the causes of disease, how it changes over time and how it's linked to genetics. And there are studies that need loved ones of patients and even people with no familial link to PD. Every one of these represents a different way to get involved.

Never doubt that everyday people like you and me are the most important part of the complex and expensive drug development process. Don't believe me? Ask a scientist. They'll tell you: All the research funding in the world doesn't matter without the only people who can answer the question of whether the science is helping anyone—those living with the disease.

So where do we go from here? After reading this book, you and I both have a lot of options. We've gained a better understanding of how clinical trials work. We've been reminded of the importance of research. And our consciousness has been raised to the critical need for more participants. So, let's put that information into action. Start with small steps: Talk to your doctor about clinical studies in your area, ask people you know with PD what's caught their attention and register for Fox Trial Finder (foxtrialfinder.org). You'll be participating in a trial before you know it.

People volunteer for research for different reasons: to take control, get early access to new medications or be seen by doctors at top research centres. But when all is said and done, the why of it doesn't matter as much as that more of us simply do it.

I started out with one objective—to get into a trial for a new drug that may slow progression. Over time, I continued for more altruistic reasons—I don't want my children and grandchildren to have to deal with Parkinson's.

As it turns out, even if I think I'm doing this for other people, with every study I benefit too. I learn something new about the disease, myself, or both. And I come away from every appointment feeling a renewed sense of my own power to change the course of Parkinson's disease history.

There are still too many questions about Parkinson's. But as Michael J. Fox has said, we can be part of the answer. In fact, we're the only ones who can. Join me.

Gary Rafaloff

Gary Rafaloff, 65, was diagnosed with Parkinson's at age 60. He lives in Marlboro, New Jersey, with his wife, Bobbi. When he's not "shaking up the community" to advance Parkinson's research, Gary can be found spending time with his three children and two grandchildren, practicing tai chi and adding a second scoop to his nightly dish of Rocky Road ice cream.

Appendix

Additional Resources for Clinical Trial Participation

FOX TRIAL FINDER
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Fox Trial Finder

Fox Trial Finder is a clinical research matching tool developed by The Michael J. Fox Foundation to help increase the flow of willing participants—both people with Parkinson's disease (PD) and control participants who do not have PD—into the clinical trials and studies that need them. Fox Trial Finder lists clinical trials and studies on PD and atypical parkinsonism in the United States and other countries. Volunteers who sign up for Fox Trial Finder receive a list of recruiting trials and studies for which they are eligible. Using the site's secure and anonymous messaging system, they can then act on suitable opportunities as they wish.

By helping patients and their loved ones connect with Parkinson's trials and studies, Fox Trial Finder speeds progress towards therapeutic breakthroughs, bringing better treatments to patients faster.

Find out more about Fox Trial Finder by visiting foxtrialfinder.org.

Fox Insight

Fox Insight is an online clinical study that collects day-to-day information about the lived experience of Parkinson's directly from patients. People with and without the disease can contribute to Fox Insight by providing real-world information on symptoms, medication and other factors in quarterly online questionnaires. This information could increase understanding of Parkinson's, influence research and inform drug development.

Fox Insight also offers opportunities to contribute additional data via supplemental surveys and sub-studies, such as the Fox Insight Genetic Sub-study. This collaboration between The Michael J. Fox Foundation and personal genetics company 23andMe allows people with Parkinson's to expand the value of information they contribute by pairing their Fox Insight data with their genetic profile. Participants are eligible for genetic counselling on Parkinson's risk genes at no cost. The combined dataset can provide scientists a more holistic view of Parkinson's to speed better treatments and a cure.

All data contributed through Fox Insight and its sub-studies are de-identified and made available to qualified researchers to advance understandings of Parkinson's disease.

Register for Fox Insight at foxinsight.org.

The Parkinson's Progression Markers Initiative

The Parkinson's Progression Markers Initiative (PPMI) is The Michael J. Fox Foundation's landmark observational clinical study that launched in 2010 to find Parkinson's biomarkers—disease indicators that are critical missing links in the search for better Parkinson's disease (PD) treatments. At PPMI's 33 clinical sites in 11 countries, more than 1,500 participants—people with and without PD, at risk for PD or with genetic connections to PD—contribute invaluable data and biosamples (e.g. blood, spinal fluid) into the most robust Parkinson's database and specimen bank ever created.

As an observational study, PPMI does not test an intervention, such as a drug or treatment. Instead, PPMI follows participants for at least five years to better understand biologic changes that occur over time. This helps researchers understand the progression of Parkinson's and potentially identify one or more biomarkers of PD. PPMI is sponsored by MJFF and funded in partnership with 21 biotech and pharmaceutical companies.

Find out more about PPMI at michaeljfox.org/ppmi.

Additional Resources for Genetic Counselling and Brain Donation Programs

Australia

Australasian Society of Genetic Counsellors
Directory of genetic counsellors in Australia and New Zealand
www.hgsa.org.au/asgc

Australian Brain Bank Network
Network of brain donation programs across Australia
www.austbrainbank.org.au

Canada

Canadian Association of Genetic Counsellors
Directory of genetics clinics in Canada
www.cagc-accg.ca

Brain Donation Programs
There are local brain donation centres throughout Canada. Speak to your doctor for information about centres near you.

France

Neuro-CEB
Brain donation program for research on neurodegenerative diseases
www.neuroceb.org

Association Françaises des Conseillers en Génétique
Directory of genetic counsellors in France
www.af-cg.fr/cg-par-region-2

Germany

NeuroBiobank München
Brain donation program for research on neurological and/or psychiatric diseases
www.neuropathologie.med.uni-muenchen.de

Deutsche Gesellschaft für Neurogenetik
Directory of leading researchers in Parkinson's genetics
www.dgng.de

Deutsche Gesellschaft für Humangenetik e.V.
Directory of genetic counsellors in Germany
www.gfhev.de

Italy

Il Nodo Nazionale della Infrastruttura di Ricerca Europea delle Biobanche e delle Risorse BioMolecolari

Network of brain donation programs for research in Italy

www.bbmri.it

Genetic Counselling

Speak to your doctor for information on local resources related to genetic testing and counselling.

Spain

Red Nacional de Biobancos

Cooperative network of repositories that accept donations of biological samples for research

www.redbiobancos.es

La Sociedad Española de Asesoramiento Genetico

National network of genetic counsellors

www.seagen.org

United Kingdom

Parkinson's UK Brain Bank

Brain donation program dedicated to Parkinson's research

www.parkinsons.org.uk/brainbank

Association for Clinical Genomic Science

Regional genetics centres in the United Kingdom and Ireland

www.acgs.uk.com/geneticscentres

Glossary

Adverse event

An unfavourable change in health that can occur during a clinical trial or study or within a certain time period after. These can range from mild (e.g. nausea) to serious or life-threatening (e.g. stroke). This change may or may not be related to the intervention being studied.

See also: intervention

Alpha-synuclein

A protein normally found in brain cells and the main component of clumps, called Lewy bodies, in the brains of people with Parkinson's. Researchers believe that the alpha-synuclein in Lewy bodies is associated with death or damage to brain cells. A mutation in the gene *SNCA* that directs the production of the alpha-synuclein protein is the basis for a rare, inherited form of Parkinson's disease.

See also: *SNCA*

Arm

A specific group of study participants within a clinical trial. For example, in an interventional trial, one "arm" may receive the investigational treatment and another "arm" receives placebo.

See also: interventional trial

Baseline data

Demographic information (e.g. age and gender) and other information such as symptoms, medications or measurements on specific tests that is collected from participants at the beginning of a clinical trial or study.

Biomarker

A measurable, biological characteristic that can be used to determine the risk, presence or progression of a disease. For example, high blood pressure is a biomarker of potential heart disease. No biomarker of Parkinson's has yet been validated, but researchers are working towards such a measure.

Blinding

A clinical trial strategy where the researchers and participants do not know which participants are taking placebo (inactive substance) and which are receiving the intervention. In single blinding, only one group (either researchers or participants) knows which participants are taking placebo or intervention. In double blinding, neither group knows.

See also: intervention; placebo

Breakthrough therapy designation

A US FDA process that speeds the development and review of new therapies that may treat a serious condition if early clinical trial data indicate that the drug may be more efficacious than available therapies.

See also: efficacy; US Food and Drug Administration

Clinical studies

Research studies conducted in human volunteers to better understand the nature of a disease or to evaluate the effect of an intervention (e.g. medication, surgical procedure, exercise) on that disease. There are two main types of clinical studies: clinical trials and observational studies.

Clinical trials

Research studies conducted in human volunteers that evaluate the effect of an intervention (e.g. medication, surgical procedure, exercise) on symptoms or other features of a disease.

See also: interventional trial

Cohort

A group of individuals participating in clinical research. Cohort studies may follow a large group of people over time, for example, to see who does and doesn't develop Parkinson's and learn about potential causes and risk factors.

Comorbidity

Two or more diseases, such as anxiety and Parkinson's disease, that occur in the same person at the same time.

Computed Tomography (CT) scan

A Computed Tomography (CT) scan, sometimes called CAT scan (for Computed Axial Tomography), uses x-rays to create two-dimensional images of different regions of the body.

Control volunteer

A person with no known significant health problems who participates in research to test a drug, device or other intervention. These individuals can also contribute to observational studies. Control volunteers serve as comparisons for patient groups when they are matched on certain characteristics, such as age and gender. In Parkinson's research, they can test new therapies for safety, help researchers define "non-Parkinson's disease" measurements or be a bar against which natural changes in Parkinson's are compared.

Controlled trial

A type of study in which a new medication or procedure is compared to a standard, called the control. The control may be a placebo (inactive substance) or the standard of care, which is what medical experts widely use and accept as the proper one.

See also: placebo-controlled

DaTscan™

DaTscan is a specialised imaging technique that uses small amounts of a radioactive drug to evaluate the dopamine-producing cells in the brain. By itself, it can't diagnose Parkinson's, but it can help confirm a doctor's diagnosis. DaTscan is being studied as a possible biomarker of Parkinson's.

See also: biomarker

De novo Parkinson's

This describes Parkinson's that was recently diagnosed and often is not yet treated with medication. (Some studies do allow participants who are on certain Parkinson's medications, and each study sets specific criteria.)

Digital health

A broad scope of health initiatives that include mobile health (devices to track measures such as physical activity), health information technology, wearables (body sensors to measure movement, sleep etc.), telemedicine and online studies.

See also: telemedicine; virtual study; wearable

Disease-modifying therapies

Treatments that can prevent, slow, stop or reverse disease progression. No therapy has yet been proven to modify the course of Parkinson's, but several drugs with this potential are in various stages of clinical testing.

Efficacy

A measure of a drug's ability to treat a certain condition; efficacy does not reflect tolerability or ease of use. A drug may be very efficacious but be so unpleasant to take that its actual use is very limited. Efficacy (as well as tolerability and safety) is determined in clinical trials.

See also: tolerability

Eligibility criteria

Guidelines for who can and cannot participate in a specific clinical trial. Criteria are comprised of certain characteristics, such as age, gender, time since diagnosis, stage of Parkinson's disease and other medical conditions. Eligibility criteria include both inclusion and exclusion criteria.

See also: exclusion criteria; inclusion criteria

European Medicines Agency (EMA)

A decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision, safety and monitoring of medicines in the EU.

Exclusion criteria

Factors that prevent a person from participating in a specific clinical trial or study.

Familial Parkinson's disease

A type of Parkinson's that runs in families and is thought to have a primarily genetic cause. Familial Parkinson's disease accounts for less than 10 per cent of PD cases worldwide.

See also: idiopathic Parkinson's disease

Gaucher disease
A rare condition that causes fatty substances to build up and organs to swell. This disease develops in people who carry two copies of the mutated *GBA* gene. People with this mutation do not produce enough glucocerebrosidase, an enzyme that breaks down a fatty chemical called glucocerebroside.

See also: *GBA*

GBA
The *GBA* gene directs the production of the glucocerebrosidase protein, which breaks down substances called glycolipids. Mutations in the *GBA* gene are the most common genetic risk factor associated with Parkinson's, and *GBA* mutations may lead to build-up of alpha-synuclein protein clumps.

See also: alpha-synuclein

Gene
The material of heredity, passed down through the generations from parents to children. These inherited bits of DNA determine many of the body's traits—visible features such as eye colour, as well as ones that can't be seen, including an individual's risk of a particular disease.

Genetic mutation
A permanent change in the sequence of a gene that can affect health or risk of disease.

Genetic counsellor
A health professional with expertise in medical genetics and counselling who provides education and emotional support to people considering or undergoing genetic testing.

Genetic testing
A type of medical test that identifies changes in genetic material. Genetic tests can evaluate a suspected genetic condition to help determine a person's chance of developing or passing on a genetic disorder.

Hoehn and Yahr (H&Y) scale
The Hoehn and Yahr (H&Y) scale divides Parkinson's into stages based on the severity of motor symptoms. Clinical trials often include H&Y stages as part of their eligibility criteria so that they can ensure that the intervention evaluated will include people with the right symptoms.

Idiopathic Parkinson's disease
The most common form of Parkinson's, accounting for upwards of 90 per cent of cases. Idiopathic, or sporadic, Parkinson's typically does not run in families and is likely caused by a combination of genetic and environmental factors.

See also: familial Parkinson's disease

Inclusion criteria
Factors that need to be met to qualify a person to participate in a clinical trial or study.

Informed consent
A process used to educate potential participants about the possible benefits and risks of a specific clinical trial or study. Prior to enrolling, all study participants must sign an informed consent document that explains the details of the trial or study and the rights and responsibilities of the participant.

Institutional Review Board (IRB)
An independent committee of scientists, doctors and others (usually at least one "non-scientific" person who represents the patient voice) that evaluates and approves each study's protocol and informed consent document, and monitors ongoing study activities. The Institutional Review Board (IRB) is in place to protect the rights and welfare of people participating in a study.

Intervention
A potential therapy or treatment that is tested in clinical trials. These may include drugs, medical devices or procedures, and they may be investigational products or therapies that are already available. (See: repurposing.) Interventions can also include non-invasive approaches, such as exercise or physical therapy.

Interventional trial
A type of trial in which participants receive an intervention (e.g. drug or surgical procedure) so that researchers can evaluate the effects of the intervention on certain symptoms or other features associated with a disease.

See also: intervention

Longitudinal study
A study that follows participants over an extended period of time, often years or decades, and is generally observational in nature. This type of study is particularly useful for evaluating risk factors or progression of a disease.

See also: observational study

LRRK2

The *LRRK2* gene directs the production of the LRRK2 protein kinase, an enzyme that modifies the function of other proteins. The *LRRK2* gene is implicated in one to two per cent of all Parkinson's disease cases.

Lumbar puncture (LP)

A lumbar puncture (LP), or spinal tap, is a procedure where a small needle is inserted below the spinal cord between the bones of the lower back to obtain a small amount of spinal fluid for analysis.

Magnetic Resonance Imaging (MRI) scan

A Magnetic Resonance Imaging (MRI) scan uses magnetic waves to create detailed pictures of areas inside the body. MRIs are especially useful for imaging the brain, and give clues about structure but not function. Some forms of MRI are being looked at as possible biomarkers.

See also: biomarker

Multicentre trial

A clinical trial performed at more than one medical or research institution.

Neuroprotective treatment

A therapy that guards against death or damage of the dopamine cells in the brain that are at risk of being lost in Parkinson's disease (PD). There is currently no approved neuroprotective therapy for Parkinson's, but research in this area is ongoing. These types of therapies could theoretically be used in people with early signs of PD or even those who are at risk.

Neuroregenerative treatment

A therapy that stimulates regrowth of dopamine-producing cells in the brain. There is currently no approved neuroregenerative therapy for Parkinson's, but research in this area is ongoing.

New Drug Application (NDA)

A new drug application (NDA) is a formal request from a drug sponsor to the US FDA to ask for approval of a new drug. Data from pre-clinical research and all phases of human clinical trials are submitted as part of the NDA.

See also: US Food and Drug Administration

Observational studies

A clinical study in which participants' health and other data is measured, but volunteers do not receive an intervention or drug.

See also: intervention

Open label

Clinical trials in which both investigators and participants know which participants have been assigned the intervention or placebo.

See also: blinding

Outcome measure

A test or examination used to measure the effects of an intervention on certain symptoms or other features associated with a disease. Investigators decide on the measures that they are interested in evaluating before the trial or study begins. Every interventional study has a primary outcome measure, which is most important for evaluating the effect of the intervention. Studies may also include secondary outcome measures, which are not as important but are still of interest in evaluating the effect.

Patient-reported outcomes (PROs)

Data that is provided directly by participants. Patient-reported outcomes (PROs) complement traditional measures used during in-person clinical trial and study visits to give researchers a more complete picture of disease.

Placebo

A substance or device that does not contain active ingredients but is made to look, feel and taste just like the actual drug or therapy being studied so that all participants have a similar research experience.

See also: placebo-controlled

Placebo-controlled

A type of clinical trial in which a group of participants is randomly assigned to receive a placebo (inactive substance) for comparison to the standard of care (control) or intervention.

See also: placebo

Placebo effect

A beneficial physical or emotional change that occurs after taking a placebo (inactive substance). This phenomenon is thought to result, at least in part, from expectations of benefit. (In other words, the more a person believes that they will benefit, the more likely it is that they will experience benefit.) To separate out this effect from a drug or therapy's true benefits, clinical trials typically use placebo-controlled designs.

See also: placebo; placebo-controlled

Positron Emission Tomography (PET) scan

A Positron Emission Tomography (PET) scan is a specialised imaging test that uses a small amount of radioactive medication to study the function of the brain. For example, researchers are looking to visualise alpha-synuclein protein in the brain with PET scans; this could serve as a biomarker and way to measure the impact of drugs in trials.

See also: alpha-synuclein, biomarker

Pre-clinical

Research that is not conducted on humans. Before a drug can enter clinical trials, pre-clinical models must first evaluate its feasibility and safety.

Principal investigator

The researcher, often a doctor, who oversees and leads an entire clinical trial or study.

Protocol

The written description of a clinical trial or study that describes its objectives, design and methods, as well as inclusion and exclusion criteria.

See also: exclusion criteria; inclusion criteria

Randomised

A strategy in which participants are assigned to one group in a clinical trial or study by a methodological process that mimics chance. In placebo-controlled interventional trials, one group of participants is randomised to an intervention and another is assigned to placebo.

See also: placebo

Recruiting

A term used to indicate that a study is open for enrolment and needs participants.

Repurposing

Taking an existing drug that has been developed (and typically FDA-approved) for one condition and using it to treat another. Clinical trials are necessary to repurpose, or reposition, a therapy to ensure that it is safe and efficacious in those with Parkinson's.

SNCA

A gene that directs the production of the alpha-synuclein protein. A mutation in the *SNCA* gene is the basis for a rare, inherited form of Parkinson's.

See also: alpha-synuclein

Statistical significance

A number that refers to whether the study's results are highly likely to be true or could have occurred purely by chance. Note that statistically significant does not necessarily mean highly important.

Study funder

The study funder provides financial support for research. Funding can come from a variety of individuals or organisations, including foundations, pharmaceutical companies and federal agencies, such as the National Institutes of Health.

Study sponsor

The study sponsor is the individual or organisation who oversees the study. The sponsor initiates, conducts and is responsible for the research.

Symptomatic therapy

A treatment that eases the symptoms of a disease but does not address the underlying disease process. All currently available Parkinson's therapies are symptomatic; they do not slow disease progression.

Telemedicine

A field of medicine that delivers health care through electronic, two-way, real-time interactive communication between individuals and their doctors or other providers.

Tolerability

The degree to which effects of a drug or therapy can be tolerated by a patient, or how much these effects impact a person's lifestyle or day-to-day activities.

Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS) is a rating scale that includes clinical examinations of motor symptoms, as well as questionnaires about daily activities, non-motor symptoms and medication complications. Parts of or the entire scale are often used to evaluate response to interventions in Parkinson's clinical trials.

US Food and Drug Administration (FDA)

An agency within the US Department of Health and Human Services, the FDA ensures that human drugs, biological products, medical devices, the food supply, cosmetics and other products are safe and efficacious for consumers.

Virtual study

Studies conducted online or through other digital modalities (e.g. smartphone, telephone etc.). Virtual studies complement traditional research by allowing participants who might otherwise not be able to participate in traditional clinical trials (e.g. those with transportation or mobility issues) the opportunity to engage in research. These studies also are valuable in providing data outside of the "snapshot" of a face-to-face study visit.

Wearable

A device that can be worn (e.g. watch, fitness tracker) to capture health-related information, such as movement, sleep or heart rate. Wearable data complements traditional research by providing an objective, continuous window into the daily experience of Parkinson's.

See also: digital health

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michaeljfox.org
+1 800 708 7644

michaeljfoxfoundation
@michaeljfoxorg
@michaeljfoxorg
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