

# 2018 in Review: *Research Progress*

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THE MICHAEL J. FOX FOUNDATION  
FOR PARKINSON'S RESEARCH

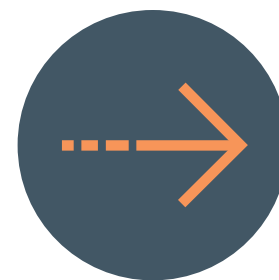




Discoveries are crystallizing at a rapid pace through the most robust Parkinson's disease (PD) drug development pipeline in the history of the disease. And, Parkinson's patients and volunteers are rallying worldwide to shape the future of PD research through clinical trial participation, advocacy and grassroots community engagement. At The Michael J. Fox Foundation for Parkinson's Research (MJFF), we continue building on current research momentum to further speed disease knowledge so we can usher in a future without Parkinson's disease.

Visit [\*\*michaeljfox.org/2018inreview\*\*](https://michaeljfox.org/2018inreview) for in-depth reporting on the projects described throughout.

# Therapeutics on the Fast Track



## To Pharmacy Shelves and Patient Hands

MJFF's philosophy is to do whatever it takes to get to an “aha” moment — so more drugs are market-bound and into the hands of waiting patients. Our world-class research program is focused on promoting promising ideas to the next step and, ultimately, attracting investors who can get them to patients. As such, we take no IP position on the research we fund, evaluating return on investments based on the opportunity to transform patients' lives.

As this publication went to print, the U.S. Food and Drug Administration (FDA) is reviewing two experimental drugs to treat “off” times in Parkinson's. If approved, they will be the first treatments directly funded by the Foundation to come to market.

Foundation grants of \$1.3 million and \$1.5 million (respectively) funded early clinical trials of the inhaled levodopa and dissolvable apomorphine, and helped drug makers secure hundreds of millions of dollars in additional investment to push the therapies through Phase II and Phase III clinical trials. Both are “rescue therapies,” designed to rapidly alleviate movement symptoms including tremor, stiffness and slowness during “off” times.

The inhaled levodopa, to be marketed as “Inbrija,” was developed by biotech Civitas Therapeutics, which received MJFF grants in 2011 and 2013. After promising early results helped the company raise three rounds of capital totaling \$121 million, Civitas was acquired by biopharmaceutical company Acorda for \$525 million in 2014.

*“We only can't if we don't.”*

—Michael J. Fox





In a similar chain of events, Fox-funded biotech Cynapsus Therapeutics received MJFF grants for early trials of its apomorphine strip in 2012 and 2014. It went on to raise \$99 million in follow-on funding (including its 2015 IPO) and was acquired by pharmaceutical company Sunovion for \$624 million in 2016.

These aren't the only two companies funded by MJFF to sign big deals to advance promising therapies. In 2018, Lundbeck bought biotech Prexton Therapeutics, which MJFF funded in 2014 to test treatments for dyskinesia (i.e., involuntary movements linked to long-term levodopa use and advancing disease). A Phase II trial of its drug foliglurax is underway. Also in 2018, Vanderbilt University signed a deal with Appello Pharmaceuticals to further develop its

drugs for movement symptoms. MJFF funded this program with a series of grants from 2007 through 2014.

While patients need new options to ease tremor and slowness, many non-movement issues remain difficult to treat. MJFF is supporting trials of therapies against anxiety, constipation and swallowing problems. In 2018, we also started funding a project in the Netherlands testing in-home therapy with video conferencing and a smartphone app to improve speech.

## Toward a Cure

Of course, patients' greatest unmet need is a cure. The largest percentage of Foundation funds and resources goes to programs that push us closer to slowing or stopping Parkinson's progression.



One way scientists begin developing new therapies is to look at genetic changes associated with disease. Finding mutations in the SNCA, LRRK2 and GBA genes has led to understanding of what goes wrong in Parkinson's and strategies to fix it.

Identifying changes in the SNCA gene showed scientists that nearly all Parkinson's patients have clumps of the protein alpha-synuclein in their cells. Seven therapies against those aggregates are now in human testing. MJFF directly funded three of these programs, and our tools and resources are helping them all advance.

LRRK2 findings also may lead to a widespread treatment. An MJFF-funded study found patients even without the LRRK2 mutation showed higher levels of the protein's activity. In 2018, Denali Therapeutics announced positive results from early trials of its drug against too

much LRRK2 activity. Now the drug will move to testing in patients with and without a LRRK2 mutation.

There's also momentum around therapies targeting dysfunction associated with GBA gene mutations. Sanofi Genzyme began a Phase II trial of its drug against the GBA pathway in 2018. MJFF-grantee Lysosomal Therapeutics and its development partner Allergan (another "de-risking" success) are awaiting results from its GBA trial. And a group in Canada is testing ambroxol, a drug already approved for respiratory diseases, for its effects on GBA after a small study showed it was safe and hit its target.

## From Existing Drugs to New Treatments

Like in the ambroxol studies, researchers are pulling from across the medicine cabinet and "repurposing" treatments

approved for other conditions that show promise in treating Parkinson's.

A Phase III trial of isradipine, a high blood pressure drug, is underway. MJFF funded the successful Phase II trial of this treatment. Our Foundation also is funding a trial of nilotinib, a leukemia drug that may also benefit people with brain diseases.

MJFF-supported scientists at Michigan State University are studying an asthma drug's application in Parkinson's, and Mount Sinai researchers in New York are exploring if medications for inflammatory bowel disease lower Parkinson's risk.

## Following Multiple Tracks

Researchers working urgently to develop improved treatments must address the concern that even the most promising

candidate drug is at risk of failing in clinical trials if introduced too late in the disease process.

The litany of unsuccessful Alzheimer's trials is a sobering reminder of the rationale and persistent need to treat brain diseases earlier, ideally in the window prior to clinical diagnosis and onset of symptoms.

At MJFF, we've taken their lead by pursuing treatments against multiple targets and pathways, rather than placing all our bets on one therapeutic approach.

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# Quest for an Objective Test

## Disease Measures Speed Drug Development

This is a critical time for biomarker research in Parkinson's. As more potential therapies move into clinical trials, researchers need tests to understand how those therapies are working and which patients might benefit most from them.

Biomarkers are ways to measure biological processes in our bodies, like blood pressure or heart rate. They can be used to diagnose a disease, monitor its progression and assess how a treatment is working. Of the very few available biomarkers in Parkinson's, none have been approved by the FDA.



*“AMP PD would not have been possible without previous investment in [PPMI] and the contributions of thousands of research volunteers.”*

—Walter Koroshetz, MD

*Director, National Institute of Neurological Disorders and Stroke*

Because biomarkers are essential for drug development, MJFF is devoting significant resources to identifying them. Our ambitious Parkinson’s Progression Markers Initiative (PPMI) began eight years ago, and it continues to drive progress. This year, we announced that we are joining with the National Institutes of Health (NIH) and five life sciences companies in the \$24 million Accelerating Medicines Partnership: Parkinson’s Disease (AMP PD). PPMI is a cornerstone of AMP PD, which will use its samples along with those from other studies to deepen our understanding of the biology of Parkinson’s and develop biomarker tests for the disease.

AMP PD was one of several partnerships we launched in 2018 to advance new ways to measure the disease. Verily Life Sciences LLC, an Alphabet company, brought its Verily Study Watch to PPMI to collect data

on everyday movement and physiologic and environmental measures of select participants. Wearable technologies have the potential to provide a wealth of information about the daily experience of patients, and MJFF is proud to incorporate them in our study and make the anonymous data available to researchers. We also partnered with Roche this year to deploy its digital tool to PPMI volunteers in Europe. The Roche smartphone app monitors patients’ symptoms in a noninvasive way to advance biomarker discovery.

These digital devices aren’t the only noninvasive biomarkers we are exploring. In 2018, The Michael J. Fox Foundation awarded a grant to San Diego-based biotechnology company Amydis Inc. to develop a tool to detect alpha-synuclein in the eye. This protein can become toxic and form clumps in both the brains and retinas of people with



Parkinson's. We are also funding the FACE-PD study by the Italian National Research Council. The project aims to measure facial expressivity, which can be a sign of early motor dysfunction in Parkinson's. If successful, the FACE-PD program could become an early detection tool.

Traditional biomarker testing methods have also made great strides this year thanks to MJFF. In July, the European Medicines Agency (EMA) endorsed the first imaging

scan for use in clinical trials of therapies for Parkinson's disease. Data from PPMI helped prove the value of the test, called a DAT scan, and was used in the EMA's decision. And a team of researchers are analyzing changes in alpha-synuclein levels in blood, spinal fluid and tissue that correlate to Parkinson's progression in the MJFF-sponsored Systemic Synuclein Sampling Study (S4).



MJFF-funded researchers help identify the underlying biological mechanisms that lead to Parkinson's and could be targeted by new drugs.

# Convergence toward Research and Care



## Mapping the Causes of Parkinson's

This year, MJFF launched a two-year, \$6 million dollar project to examine the factors that lead to Parkinson's onset and progression. Existing research points to three areas — environmental exposures, genetics and aging biology — as the main contributors to Parkinson's. The goal is to develop a holistic understanding of how these factors intersect and how they vary across different groups of patients.

Three research teams have each received \$2 million to spearhead a key area. J. Timothy Greenamyre, MD, PhD, of the University of Pittsburgh is directing the investigation of links between environmental and genetic triggers. This year, Dr. Greenamyre discovered that activity of the *LRRK2* protein is increased even in Parkinson's patients without a *LRRK2* mutation. Drugs in development for people with a *LRRK2* mutation could potentially benefit a broader population.

Andrew Singleton, PhD, of the National Institute on Aging, is leading exploration into how genetic changes lead to cellular and molecular changes associated with Parkinson's. Dr. Singleton published two papers this year identifying dozens of new

genetic loci in Parkinson's, the first piece of the puzzle. Now, researchers must find out what these PD-associated genes actually do in the body.

The final team, led by D. James Surmeier, PhD, of Northwestern University, is working to understand how the biology of aging contributes to Parkinson's. Dr. Surmeier's research into the biological causes of Parkinson's has already led to a Phase III clinical trial of a drug to protect brain cells from damage. Earlier this year, Dr. Surmeier explained that this collaborative effort is so important because it could lead to the "identification of the shortest possible path to a real strategy for stopping Parkinson's disease."

## Improving Care Today for Better Tomorrows

One of the tenets to living well with Parkinson's is building the right care team, which includes a movement disorder specialist, a neurologist with additional training in treating Parkinson's. But not enough people with Parkinson's see this type of physician, partly because there aren't enough of them. The MJFF solution: train more movement disorder specialists.

Every year, The Edmond J. Safra Fellowship in Movement Disorders — a partnership between





MJFF and the Edmond J. Safra Foundation — awards five academic centers funding to train one new movement disorder clinician-researcher over a two-year period.

This summer, the first class of The Edmond J. Safra Fellowship in Movement Disorders graduated. After completing intensive clinical and research training at top-tier international institutions, these five physicians have now moved on to careers that combine caring for people with Parkinson's and leading research toward better disease understanding and treatments. At the same time, MJFF also announced the five centers — three in the United States, one in the Netherlands and one in Germany — selected to train the fourth class of The Edmond J. Safra Fellowship in Movement Disorders which will begin in 2019.

To ensure sustained interest and enthusiasm for these movement disorder fellowships, the MDS-PAS Movement Disorders School

for Neurology Residents offers physicians-in-training education on Parkinson's and other movement disorders during a time when they are choosing future careers. The 2018 two-day immersion program in Dallas, Texas attracted 90 participants from all levels of neurology training at centers across the United States and Canada. Since 2016, nearly 250 neurology residents have attended the annual program. The course helps inform physicians' career decision-making to increase the number who select movement disorder fellowships.

These initiatives are growing the global base of talented, dedicated and passionate professionals who can optimize care and advance research — improving patients' lives today and shaping a better tomorrow.

# Gaining Strength in Numbers



## More Clinical Trials, More Volunteers Needed

Clinical trials are the vital last step in moving new Parkinson's therapies from the lab into the hands of people with Parkinson's. Yet, the chronic shortage of volunteers for these trials is one of the biggest roadblocks to new treatments and cures.

With more potential treatments moving toward pharmacy shelves than ever before, there are many opportunities for people with Parkinson's and their loved ones to help carry new therapies over the finish line. People with PD often experience benefits with research participation, taking an active role in their care and partnering with experts in the field. Still, most patients and families aren't aware of these opportunities, and research teams struggle with lack of participation.

In 2018, MJFF continued to engage and motivate patients, families and researchers to increase the flow of participants into clinical trials that need them. We developed the Parkinson's Clinical Trial Companion, a comprehensive multimedia suite that tackles the issue from two sides: educating potential study participants and supporting trial teams' recruitment efforts. Released in April, the Parkinson's Clinical Trial Companion features a downloadable book and video

testimonials from patients, care partners, a clinician-researcher and a genetic counselor.

For people with PD and their loved ones interested in volunteering, the resource illuminates and demystifies multiple aspects of clinical research including participation at every stage of disease, genetic testing, technology-enabled research opportunities and more. On the other side of the coin, the resource serves the scientific teams conducting the clinical trials, equipping them with high quality tools to recruit and retain study participants ([michaeljfox.org/pdcompanion](http://michaeljfox.org/pdcompanion)).

The Parkinson's Clinical Trial Companion was sponsored by the 2017 Parkinson's Disease Education Consortium, an alliance of industry partners that covers the costs associated with patient education so that the Foundation can put donor dollars toward high-impact research.

## Speeding Research from Home

In 2017, MJFF launched Fox Insight ([foxinsight.org](http://foxinsight.org)), an online clinical study that individuals can take part in from their own home. Through quarterly questionnaires, Fox Insight collects self-reported data on symptoms, daily activities

*“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.”*

—Gary Rafaloff

*Parkinson’s patient and research volunteer*

and other health factors from people with and without Parkinson’s to learn more about life with the disease and accelerate research breakthroughs. In the last year, Fox Insight enrollment has more than quadrupled to over 27,000 participants — and that’s just the beginning. The study aims to recruit hundreds of thousands of people to contribute data in order to help find better treatments.

Through the Foundation’s collaboration with consumer genetics company 23andMe, Fox Insight participants with Parkinson’s can receive access to the 23andMe Health + Ancestry Service at no cost and add their genetic information to the study. This can help researchers create a more holistic understanding of the disease. Already, over 4,600 people have added their genetic data to Fox Insight. All data gathered through the

study is de-identified and made available to qualified Parkinson’s scientists worldwide.

Fox Insight participants can expand their contributions to science by completing one-time surveys and sub-studies through the platform. In 2018, Fox Insight enrollees had the chance to take part in supplementary research focused on “off” time, the financial costs associated with Parkinson’s and other topics.

## Community Rooted in Funding a Cure

Team Fox members wear many hats. They are fundraisers and donors, event hosts and guests, participants and volunteers, competitors and cheerleaders. Some members are living with PD, some are inspired by a loved one with PD, and some

are simply motivated by MJFF's mission. In 2018, the Team Fox community has engaged with more than 33,000 individuals who were brand new to MJFF.

Competition in the Team Fox community exists for one reason: to raise as much money as possible for Parkinson's disease research. Team Fox members support other members, sharing words of encouragement online or from the sidelines, and buying a ticket or captaining a team for multiple events.

MJFF's Fox Trot 5K Run/Walk Series began as a way to meet new members of the Parkinson's community in different cities across the country. Thanks to overwhelming response from local Team Fox communities on the ground, the Fox Trot Series expanded in 2018. This year, we hosted events in Los Angeles, Orlando, New York City, the Bay Area and Boston, attracting over 2,500 runners, walkers and supporters — more than 140 of which have Parkinson's disease.

Just as innovation drives momentum in Parkinson's research, it defines the continued success of the Team Fox community. Each year introduces creative fundraisers — the first-ever Parkour 4 Parkinson's event in Los Angeles, for example — and returns established events that have existed for a decade (or more!). Team Fox Delaware, for example, has raised \$800,000 since 2008 at their annual pancake breakfast. If there's one thing we know about what Team Fox will deliver in 2019, it's that new members and 10-year veterans alike will show up to support the community and the pursuit of a cure.

## Amplifying the Patient Voice in Policy

Because the federal government is the largest public funder of Parkinson's research, public policy is key to ensuring scientific breakthroughs continue to move forward. That's why, in our third year of policy and advocacy work, the Foundation focused heavily on increasing federal investments in Parkinson's research.

At the Foundation's annual Parkinson's Policy Forum, co-hosted this year by the Parkinson's Foundation, nearly 300 patient and care partner advocates convened in our nation's capital for three days of advocacy training and action. The goal of the event: urge Congress to fund and implement the National Neurological Conditions Surveillance System, a database to collect patient demographic information that will help researchers target and refine their work. On the final day of the event, attendees joined with advocates across the country to send Congress 14,000 emails asking for the necessary funds. In late September, lawmakers provided the money to make this database a reality.

Throughout 2018, the Foundation addressed other policy issues relevant to our community, including those that increase comprehensive access to health care. We successfully advocated for the repeal of the Medicare Therapy Cap, which limited how much physical, occupational and speech therapy a patient could receive. And, we urged the Environmental Protection Agency to reject a proposed rule that would negatively impact how the agency regulates chemicals linked to increased

# Finding a Clinical Trial with MJFF's Smart-Match Tool

Fox Trial Finder, MJFF's online clinical research matching tool connects willing participants — with and without Parkinson's — to the trials that need them. With over 81,000 registrants (and counting), Fox Trial Finder ([foxtrialfinder.org](https://foxtrialfinder.org)) is continuing to help studies recruit volunteers faster in order to accelerate research progress.

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The Parkinson's community lent its crucial voice to these policy efforts. Between January and October, more than 18,000 advocates contacted their policymakers more than 52,000 times on various issues important to patients and families. Speaking up together helped lawmakers understand how their votes can support our community and brought us closer to reaching our policy goals.



# MJFF by the Numbers

*As of October 15, 2018*

Every number tells a story. At **The Michael J. Fox Foundation**, we have **one audacious goal: curing Parkinson's disease**. And we count on many factors to get there. From research investments and community engagement to dedicated staff, researchers and donors. Combined together, the impact is greater than the sum of its parts.

Research programs  
funded since inception

**\$800M+**

Number of research grants  
funded this year

**300+**

Volunteers registered on  
FoxTrialFinder.org, MJFF's  
clinical trial matching tool

**81,000+**

Participants sharing their lived  
experience of Parkinson's disease  
through Fox Insight

**27,000+**

Researchers convened by MJFF  
for workshops, summits and  
assessments this year

**400+**

Fellows currently training in  
The Edmond J. Safra Fellowship  
in Movement Disorders

**15**

Number of data downloads from our Parkinson's Progression Markers  
Initiative by researchers across the globe for independent study

**2.4M**



Since inception, the amount of every dollar spent that has gone straight to research programs to speed a cure

88¢

Donors supporting our mission to speed a cure in 2018

82,000+

Number of times advocates contacted their lawmakers this year

52,000+

Team Fox members on the frontline of community fundraising efforts including participants joining our signature Fox Trot and Tour de Fox events

7,000+

Total individuals following, sharing, commenting and engaging on MJFF social channels

1M+

Number of visits to MJFF's blog featuring the latest research, community and Foundation news

1.4M+

Number of dollars we hold in an endowment

\$0

We act with efficiency and urgency to deploy funds raised as quickly as possible for immediate impact.



THE MICHAEL J. FOX FOUNDATION  
FOR PARKINSON'S RESEARCH



2019 in  
Focus:  
*Research  
Plans*





As we look ahead to 2019, much work remains that requires a dedicated supply of human and financial capital — more volunteers participating in clinical trials, more advocates talking to their policymakers and more resources to support the high-priority Parkinson’s research we have identified. We are determined to let no worthy idea go unpursued for lack of funding. The ambition of The Michael J. Fox Foundation can be met only if we are all working together toward a common goal: a cure.

Visit **[michaeljfox.org/2019infocus](https://michaeljfox.org/2019infocus)** for more details on the projects described throughout.

# Enabling Therapeutic Progress



## Evolving with the Field: 'De-risking' 2.0

Since its inception, The Michael J. Fox Foundation (MJFF) has provided early investment — as well as scientific guidance and non-financial resources — to promising studies that may otherwise never get off the ground. As Parkinson's research gains momentum and more industry investment, MJFF's research strategy is evolving. The year ahead focuses on providing more of the resources required to get innovative therapies across the finish line and into patients' hands.

## Tools

Scientists require many specialized tools — such as assays, antibodies and viral vectors — to conduct research and develop new drugs.

In Parkinson's, many of these don't exist. We want researchers to be spending their time advancing new treatments, not making their own tools. And we want to ensure that tools maintain high standards and are easily obtained and affordable. MJFF has made more than 100 such tools available for researchers, and we are working with academic labs and contract research organizations to bring many more to the field in 2019.

## Cohorts

In simplest terms, cohorts are groups of people who share a certain characteristic. In Parkinson's research, cohorts are important for developing biomarkers and new drugs, and for recruiting the right people into clinical trials. Through several initiatives, we are identifying the characteristics that define these groups and making their anonymous data available to researchers. The MJFF-led Parkinson's Progression Markers Initiative (PPMI) now includes more than 1,500 people, who contributed comprehensive biological and clinical data over many years. They have not only helped paint a picture of how Parkinson's develops, but also they have helped us identify Parkinson's cohorts, including those at increased risk, different genetic carriers, and both fast and slow progressors. Data from these cohorts is driving the development of tests to identify other people with these characteristics. And it is providing drug developers with a better understanding of the patients most likely to benefit from their therapies.

Fox Insight, our online clinical study, is also creating cohorts (see 2018 in Review, page 13).



*“MJFF has launched and sustained myriad breakthrough initiatives that have radically changed the face of Parkinson’s disease research.”*

—Variety, August 8, 2018



## Recruitment and Trial Support

After years of development, drugs that demonstrate safety and efficacy are tested in people. These trials face many hurdles including finding the right people to test the therapy and ensuring the trial design will measure its impact clearly. MJFF has a team of professionals dedicated to the success of Parkinson’s clinical trials. As previously

mentioned, we are identifying cohorts to include in drug trials and funding the development of biomarkers for them. For example, if you’re testing a LRRK2 inhibitor therapy, you’d want to recruit people with a LRRK2 mutation and, potentially, people who have abnormal levels of LRRK2 activity in their brains.



Biosamples collected through the Parkinson's Progression Markers Initiative are freely available to researchers worldwide.

# Progress toward Prevention



## A One-Size-Does-Not-Fit-All Approach

Since the National Institutes of Health (NIH) charted the course for the Precision Medicine Initiative in 2015, more attention and funding has been devoted to this important area of research. NIH Director Francis Collins, MD, PhD, explained it as “prevention and treatment strategies that take individual variability into account.”

Individual variability is particularly common in Parkinson’s disease (PD). Patients experience a unique range of disease causes, symptoms and rates of progression. Treating each patient effectively will require tailored approaches. And The Michael J. Fox Foundation is committed to making that possible.

As MJFF CEO Todd Sherer, PhD, explained in 2018 during the Precision Medicine Leaders Summit, our objectives are to better understand the causes of Parkinson’s and “convert that understanding into smarter therapies.” Several large MJFF-led studies, including the Parkinson’s Progression Markers Initiative and Fox Insight, are mapping the different causes of Parkinson’s to help identify cohorts with similar characteristics, such as genetic mutations or environmental exposure. The next step is to develop diagnostic tools called biomarkers

that can reliably distinguish these patients. MJFF-supported biomarkers are advancing rapidly (see 2019 in Focus, page 13).

All of this work increases our ability to develop precision medicine. In diseases that already have precision medicine approaches, such as cancer, researchers began by developing drugs that helped one group of patients with a single disease cause, then built on those successes to help more and more still.

We expect a similar trajectory in Parkinson’s. Tests exist for people with a LRRK2 gene mutation and therapies targeting LRRK2 are already being tested in human trials (see 2018 in Review, page 4). These trials will provide valuable information about PD that will help us develop other drugs.

## Laying Critical Groundwork for Prevention Studies

Disease prevention is the Holy Grail of all therapeutic development. In Parkinson’s, achieving this goal requires in-depth understanding of the disease and a rational strategy to predict it. Since day one, our Foundation has never stopped working toward this objective.

Parkinson’s research today stands on the cusp of answering persistent questions



*“This promising genetic hint [LRRK2] to a Parkinson’s treatment looked as if it would never be investigated. Then the Fox Foundation stepped in...”*

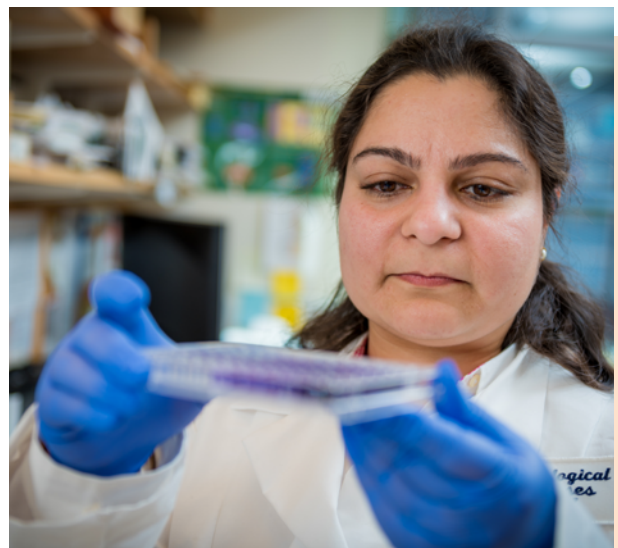
—Forbes, October 25, 2018

that have been roadblocks to realizing this vision. Recent data emerging from investigations spearheaded by The Michael J. Fox Foundation have deepened our understanding of the disease process, including the complex biological events occurring in the years just prior to diagnosis. For the first time ever, through both objective molecular data and outward clinical symptomology, we can reliably identify pools of individuals at risk for developing PD.

Today, the vast majority of academic and industry stakeholders believe that in the next five to 10 years, we can use this methodology to validate frameworks for future drug trials. The field is united in the belief that this is the most critical next step in Parkinson’s research.

The Parkinson’s Progression Markers Initiative’s robust logistical and intellectual platform already exists to enable immediate

action. The Michael J. Fox Foundation is prepared to lead the charge toward prevention through the development of a scientifically rigorous, large-scale trial in 2019. Prevention would mean that no one at risk, or in the earliest stages of the disease process, would ever advance to full-scale PD again.



# Opening a New Dialogue on Dementia



## Multimedia Resources Coming Soon

We often don't talk about certain topics — they may be uncomfortable to bring up or we might not know where to start. Some topics, such as dementia, are confusing and scary. But not talking about dementia can lead to more misunderstanding and fear. With the help of Parkinson's patients, care partners and clinicians, MJFF is building resources to open discussion, connect to research, and clarify patient and family experiences around dementia. Given that Parkinson's research holds promise for people living with dementia, now is an opportune time for this dialogue.

Dementia — memory or thinking changes (such as difficulty paying attention or multitasking) that interfere with daily activities — can be a symptom of Parkinson's in later stages of disease. Dementia occurs in other diseases, too. The most common is Alzheimer's disease. Some people experience dementia with Lewy bodies — a condition that shares the movement symptoms of Parkinson's, but shows dementia in the early years with disease.

Parkinson's (with or without dementia), Alzheimer's disease and dementia with Lewy bodies are separate diseases, but they have a lot in common. They share many symptoms as well as similar genetic risk factors and brain changes. This means that research

*“When we live in silence, we perpetuate a stigma that doesn't belong.”*

—Bret Parker  
MJFF Patient Council Co-Chair

focused in one condition can provide insights and potential benefits in another. And studying commonalities can lead to understanding of what causes disease, diagnostic tests, and treatments to slow or stop symptom progression. For example, alpha-synuclein — the protein that clumps in the brains of everyone with Parkinson’s — plays a central role in Parkinson’s dementia and dementia with Lewy bodies. Work to

understand and target alpha-synuclein (an MJFF priority) therefore has potential applicability not only in PD, but also for those living with dementia.

As the Michael J. Fox Foundation continues to fund work in Parkinson’s as well as dementia, we will develop multimedia resources in 2019 to explain and link to the latest research, and help patients and families navigate symptoms.



“All-Star Team” approaches build in multiple viewpoints to speed results and shorten the timeline from discovery to validation.



# Putting the Puzzle Together



## The Genetics Revolution Marches Forward

For many years, scientists believed that Parkinson's disease had no genetic basis. We now know that is not true. Determined researchers uncovered mutations in the *SNCA*, *PRKN*, *PINK1*, *LRRK2*, *GBA* and other genes that are responsible for approximately 10 percent of Parkinson's cases. And we are learning more every day.

In 2018, researchers from the MJFF-funded Parkinson's Disease Genetics Sequencing Consortium found dozens of new genetic loci associated with Parkinson's risk. Essentially, they located the area in DNA containing risk genes. The task ahead is to pinpoint the exact genes responsible and learn how they increase Parkinson's risk. The consortium's analysis contained comprehensive biological and clinical data from PPMI participants, including genetic mutation carriers. Now, we are supporting geneticists and data scientists at the National Institute on Aging and Weill Cornell Medicine to perform sophisticated analyses of PPMI data. We expect more results over the next year.

Research is also advancing with the genes we have already identified. Genes give directions to make proteins. When you identify a genetic mutation or risk factor, you then need to understand how that

change influences the protein and its role in the body, as well as how to safely develop therapies to fix it. The MJFF-led LRRK2 Safety Initiative (LSI), which published its findings in 2018, exemplifies the importance of this research. As companies began developing drugs to lower activity of the LRRK2 protein in the brain, they found that these therapies affected other areas of the body where LRRK2 was active, including the lungs. The LSI study determined that the inhibitors did not pose a serious risk, and drug development continues.

In 2019, MJFF-supported research will provide even more insights into genetic factors in Parkinson's. Through our LRRK2 Biology Consortium, we are funding a dozen projects delving into the mechanisms of LRRK2, including the link between Parkinson's and gastrointestinal disorders. We are also supporting research into *PINK1* and *PRKN*, including a team at Mayo Clinic examining changes in cells with and without these genetic mutations, and another at the University of Nebraska studying how the proteins coded by these genes damage brain cells in the region associated with Parkinson's.

# Building on Our Momentum in Biomarkers



## Tests for Parkinson's Are within Reach

In 2019, we will continue to prioritize the development of objective measurement tools (i.e., biomarkers) for Parkinson's disease. These efforts are at the heart of many of our largest initiatives.

In 2011, we established the Alpha-Synuclein Imaging Consortium to catalyze the development of PET tracers for alpha-synuclein. In 2016, we went even further, announcing a \$2 million prize for the first team to create one and make it broadly

available. In 2019, we may reach that goal. Researchers are closing in on a viable alpha-synuclein PET tracer, which would be a game changer. In Parkinson's and some other brain diseases, alpha-synuclein proteins become toxic and can clump into Lewy bodies. A viable PET tracer would bind to these toxic proteins (and nothing else), allowing doctors to see them on a PET scan. Such a test could detect Parkinson's, possibly even years before symptoms appear. It could also be used in clinical trials to choose patients and monitor their response to treatments. As drugs targeting alpha-synuclein enter





clinical trials, a PET tracer will be invaluable for determining their effectiveness.

Early diagnosis is also a priority in the year ahead for the Parkinson's Progression Markers Initiative (PPMI). Researchers have already begun using PPMI data to identify people at risk for Parkinson's and those who may be developing it but not yet exhibiting symptoms (i.e., prodromal). They are poised to make great strides in 2019 toward trials of therapies and lifestyle interventions to prevent Parkinson's.

PPMI data was also used in the European Medicines Agency's endorsement of DAT scan for use in clinical trials of therapies for Parkinson's disease. The task ahead is to advocate for the same endorsement from the U.S. Food and Drug Administration (FDA), which would allow the use of the DAT scan in identifying patients likely to show benefit in certain clinical trials, ultimately improving their likelihood of success.

We also expect to see progress from several other biomarker initiatives over the coming year. In 2018, we awarded grants to eight research teams through our Mitochondrial Biomarkers Program. Early results from these innovative projects will give us a roadmap for future investments. Mitochondria are the energy powerhouses of our cells, and mitochondrial dysfunction can contribute to Parkinson's and other brain diseases. Biomarkers would help us identify people with mitochondrial dysfunction and, potentially, understand what is causing it (e.g., genetic factors). MJFF's Systemic Synuclein Sampling Study (S4) — launched in 2016 to identify which fluids or tissues show levels of alpha-synuclein as a Parkinson's biomarker — has concluded. Now, scientists are sharing their findings with the research community in order to advance the development of tools to measure alpha-synuclein.

# The Evolving Role of Technology



## Bridging Knowledge Gaps with Digital Health Technology

Digital health tools are poised to make a major impact in how we monitor diseases and how we develop drugs to treat them. MJFF believes in the promise of these tools, which can provide a critical window into how individual patients experience Parkinson's disease.

Digital health tools are not new — lots of people track their steps or train for races using them — but their value in disease research is still emerging. MJFF was an early adopter through our partnership with Intel, which launched in 2014. Our focus was on how digital technology and big data approaches could accelerate Parkinson's drug research. Together, we developed a wearable device and smartphone app used in a Phase III clinical trial of thin-film apomorphine, now under FDA review with a decision expected early next year (see 2018 in Review, page 2). The device and app provided insights into the disease and potential patient reactions to the therapy.

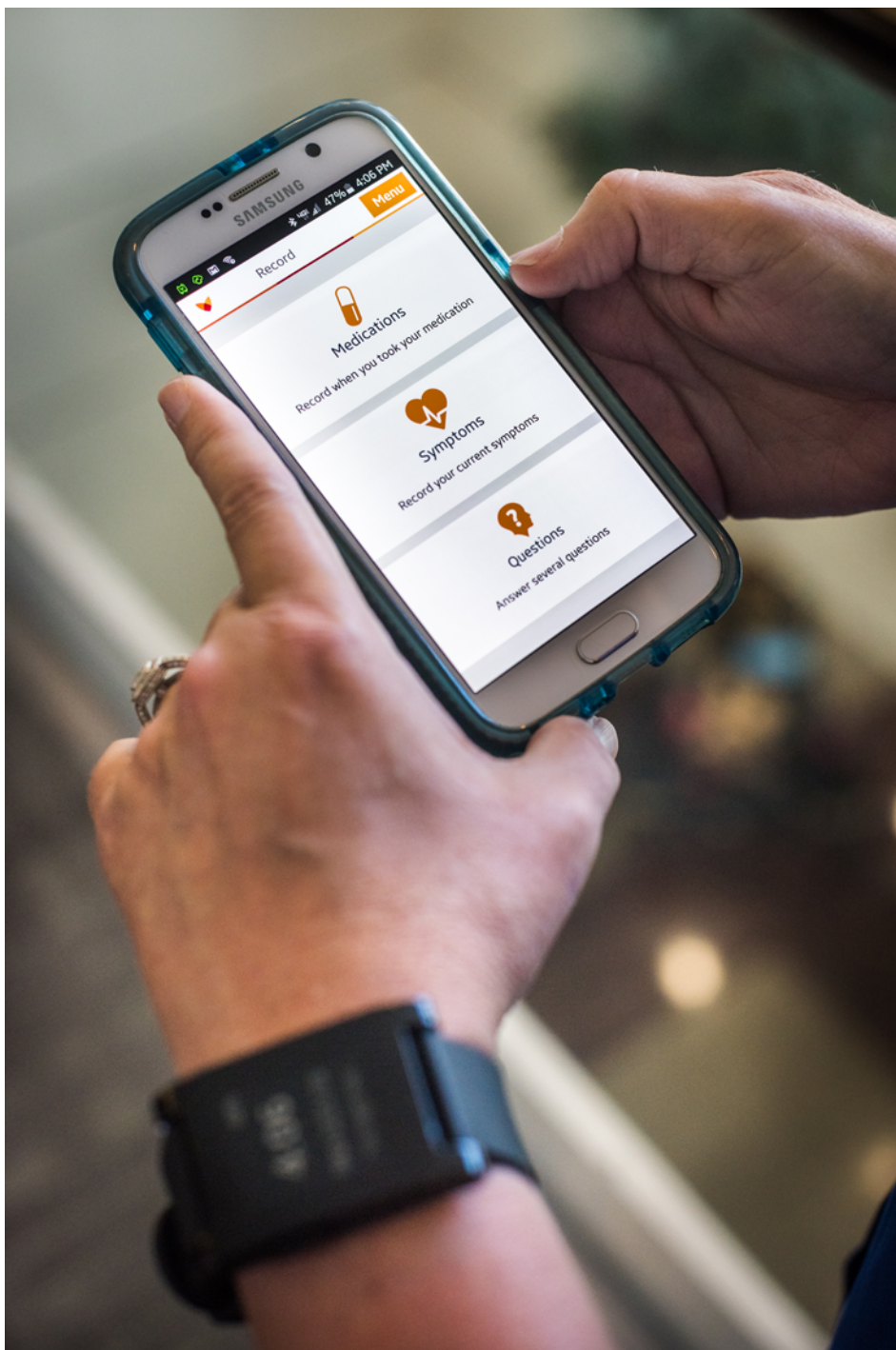
In 2018, we launched another digital health collaboration with Verily Life Sciences LLC, an Alphabet company. Hundreds of volunteers in the Foundation-led PPMI

study received a Verily Study Watch. The watch collects data on movement as well as measuring physiologic and environmental conditions throughout the day. This de-identified data will be combined with clinical assessments and biosamples collected from participant, to create a rich trove of information for researchers.

And Roche's smartphone app, deployed to PPMI participants in Europe in late 2018, passively collects movement information and includes daily assessment tests. In 2019, we will launch additional wearable devices in MJFF-led studies.

Parkinson's disease is a good model to assess the value of digital health tools because patient experience varies. Patients might have motor symptoms such as tremors, slowness or stiffness as well as dyskinesia, dystonia and "off" periods. These symptoms can change over time and even day by day. Wearables such as smartwatches and sensors along with mobile phone apps collect information about such symptoms in real time, alleviating the need for patients to remember and write down what happened. We look forward to seeing the data provided by these tools in the coming year and using it to better understand patient experience, prioritize areas for drug development and improve clinical trials.





Several years ago, our CEO Todd Sherer, PhD, said he was “optimistic about the potential of this technology to help speed breakthroughs that patients need.” With the pending FDA approval of thin-film

apomorphine and the data we are making available from wearable devices in PPMI, that potential is being realized.



# New Ways to Participate and Engage



## Budding Community Event Program

In 2019, MJFF will bring education directly to the community through a series of on-the-ground events focused on optimizing care, living well with Parkinson's and clinical research participation. These free events will be hosted in cities across the country with funding from our Parkinson's Disease Education Consortium, an alliance of biotechnology and pharmaceutical firms committed to increasing knowledge among patients, families and care partners. The events will feature interactive panels and breakout sessions on life with Parkinson's; help patients maximize time with a Parkinson's specialist or their own physician; and offer the latest updates on research, including opportunities to take part in ongoing trials. And, an expo of local Parkinson's organizations will allow attendees to learn about resources and activities in their community.

## A Voice in Every Congressional District

Public policy initiatives succeed when an actively engaged community advocates for the cause. MJFF is working to enhance its network of grassroots advocates by establishing Fox 435. This program will seek to identify and train at least one community advocacy leader in each of the 435 congressional districts across the United States. These individuals will build relationships with their U.S. senators and representatives in order to educate them on Parkinson's policy priorities. These leaders will serve as a key resource for other patients and supporters looking to get involved in this work, helping to expand the number of passionate advocates throughout the country speaking out for policy change.