

How Do We Get to a Cure for Parkinson's Disease and How Do We Get There Faster?

Todd Sherer, PhD

Vice President of Research Programs

The Michael J. Fox Foundation for Parkinson's Research

MJFF was founded with clear objectives

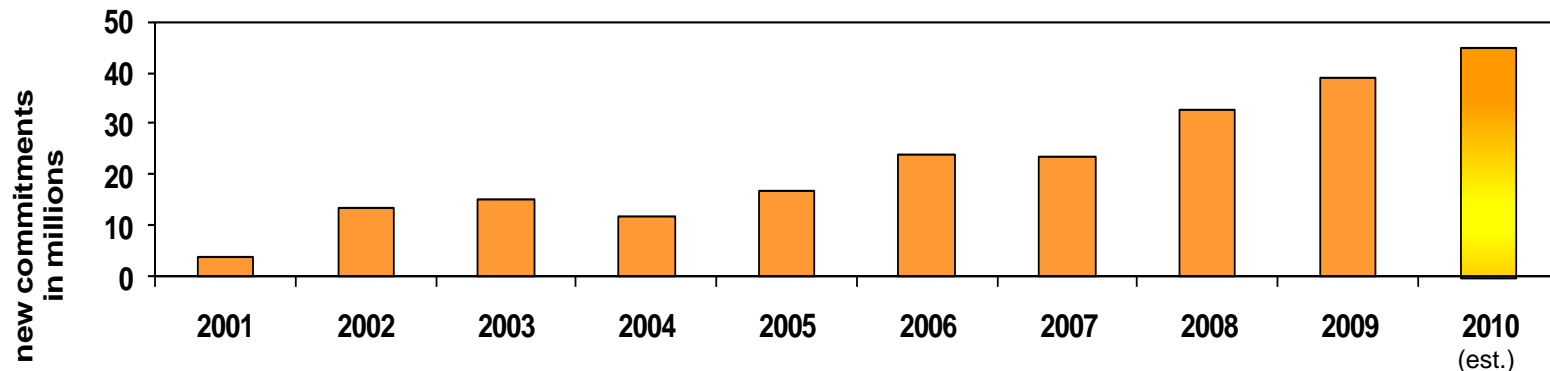
Drive the Best Parkinson's Research



Deliver Improved Therapies and a Cure

MJFF has funded nearly \$196 million in research since inception

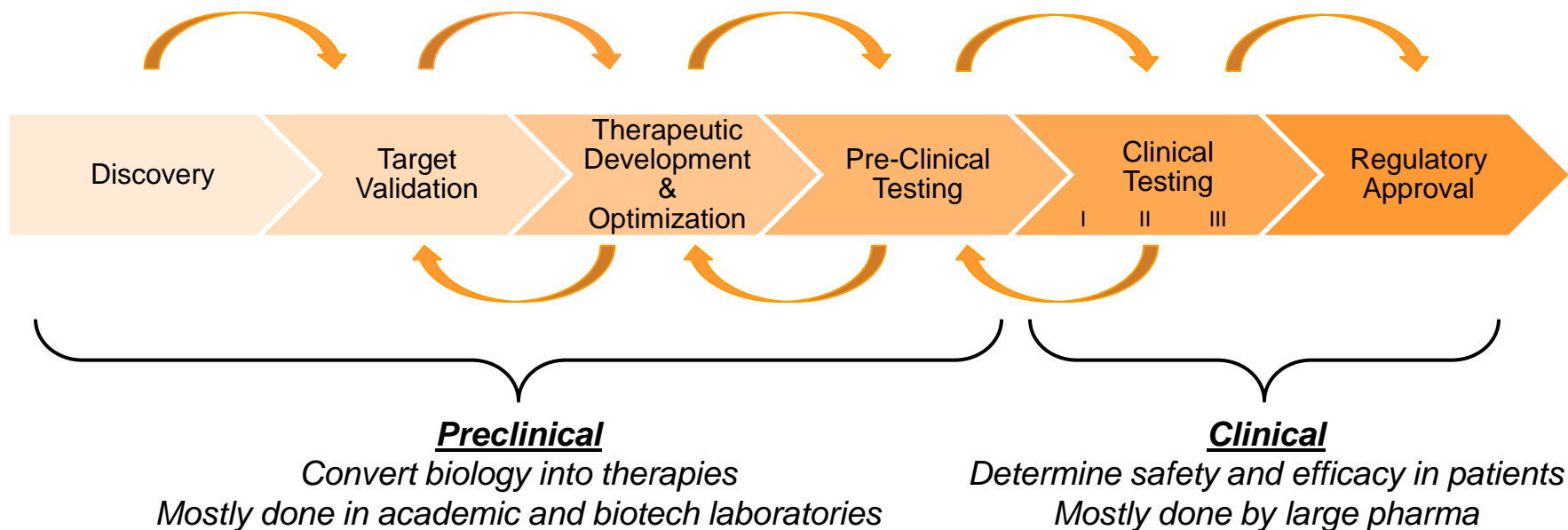
- In 2009, we received over 56,000 contributions. We work to redeploy all donations quickly. We have no endowment or excess reserves.
- Core MJFF values are efficiency and accountability: 86 cents of every \$1 spent goes straight to research program efforts



- Strategic funding led by in-house staff of 7 PhD's and 4 business strategists who work directly with over 500 researchers and clinicians from academia and industry.
- In 2009 MJFF reviewed over 700 PD-specific grants and currently has nearly 250 active grants

How do we get to cures?

Progress requires the methodological translation of new discoveries through the therapeutic development pipeline to clinical reality

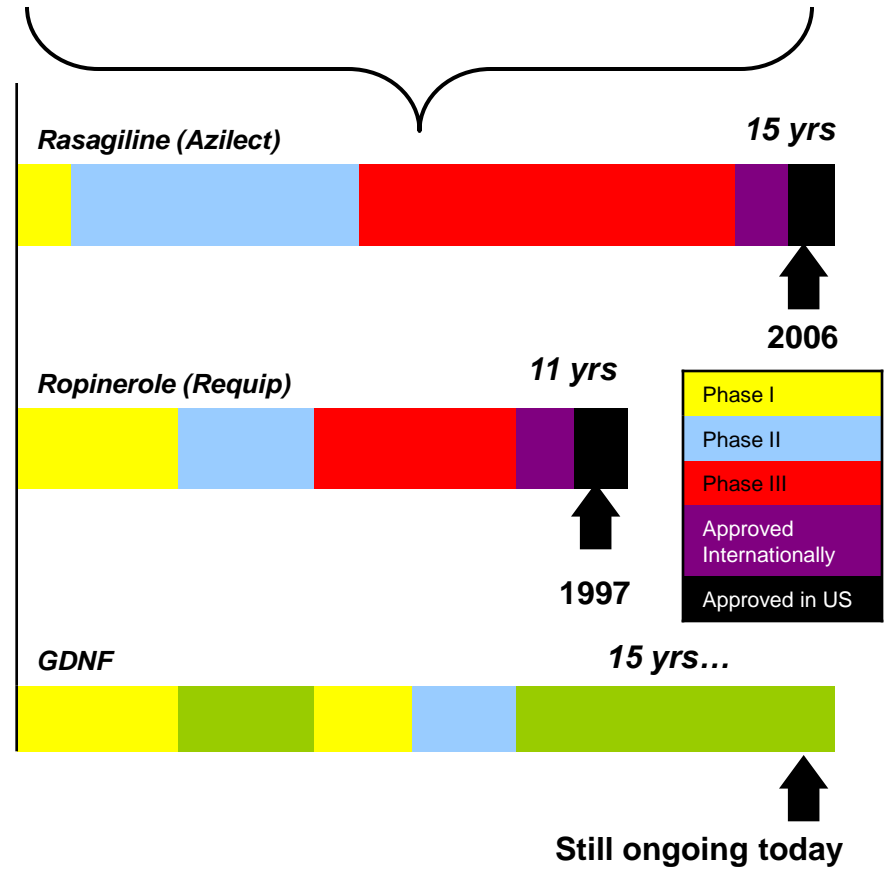


It typically takes over \$1 billion and decades to develop a new drug/treatment!

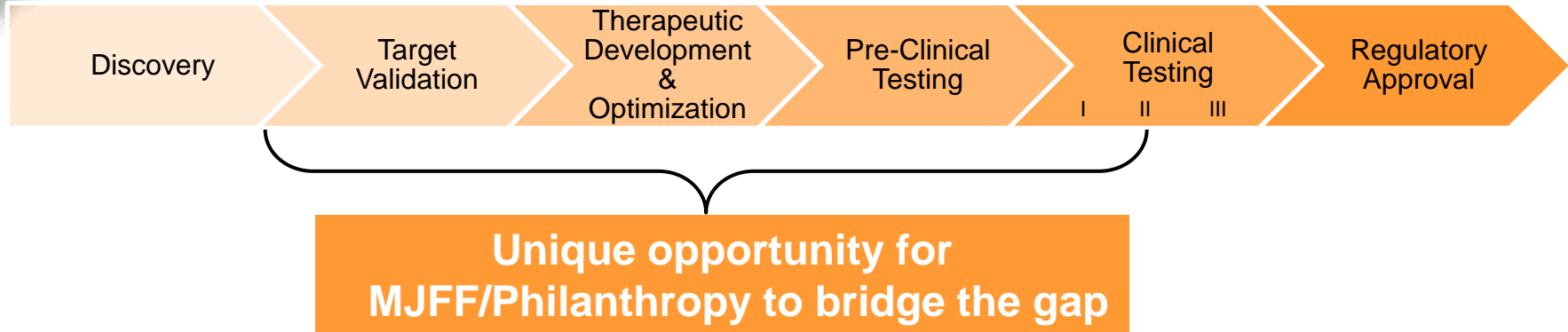
Despite translation “success”, a long road awaits...



Even after leaving the lab, a new therapy still has as many as 15 years of additional development before reaching patients



Why does drug development take so long?



Realities

- Biology is hard
- Inadequate focus on linking discoveries to improvements in patients' health
- No one is "in charge of" charting a course for PD
- Industry averse to risk

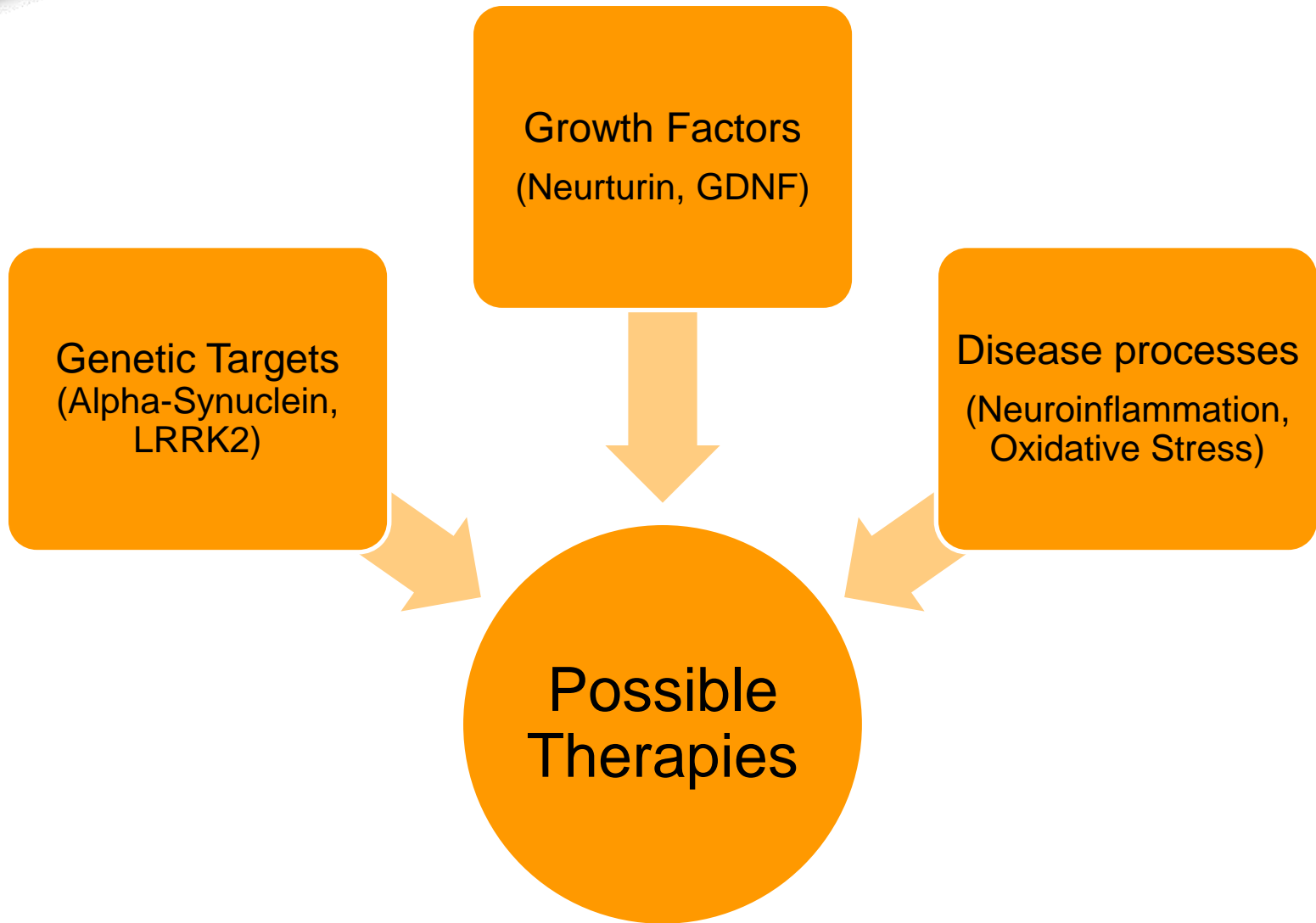
How does MJFF create impact?

- Convene around intractable problems
- Focus funding on patient relevant outcomes
- Provide strategic vision and prioritization
- Facilitate 'de-risking' of ideas

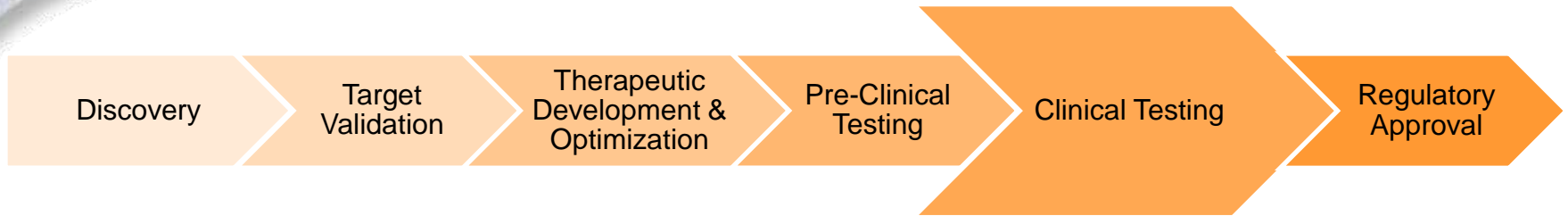
Two major needs for improved Parkinson's disease treatments

- 1. Improved Symptomatic treatment:** Current treatments only address a subset of symptoms, lose effectiveness over time, and are marked by significant side effects
 - Need improved motor treatments without side effects such as dyskinesia
 - Need treatments for untreated motor symptoms such as posture and gait disorders
 - Need treatments for non-motor symptoms (mood, cognitive, sleep, etc)
- 2. Disease modifying approaches:** No current treatments significantly alter the progression of PD or address the underlying disease process
 - A disease-modifying treatment could delay, stop, or even reverse the disease progression

The preclinical pipeline is filled with disease-modifying possibilities



The time is now to address a critical failpoint in the pipeline



- There are no biological indications of disease-modifying effect that complement clinical changes
- Reliance on clinical measures alone confounds trial interpretation
- Lack of clear endpoint measures requires large number of subjects to be followed over long periods of time
- Recruiting difficulties mean most trials are delayed and some never even get off the ground

The long process of efficacy testing not only keeps patients waiting but ultimately discourages investment by drug makers

Why are biomarkers so important for clinical testing?

Biomarkers

Diagnostic Markers

- Identify PD patients and, perhaps, even determine who is at risk for developing PD
- Assist with patient selection for clinical studies...Are we studying the right population of people?

Progression Markers

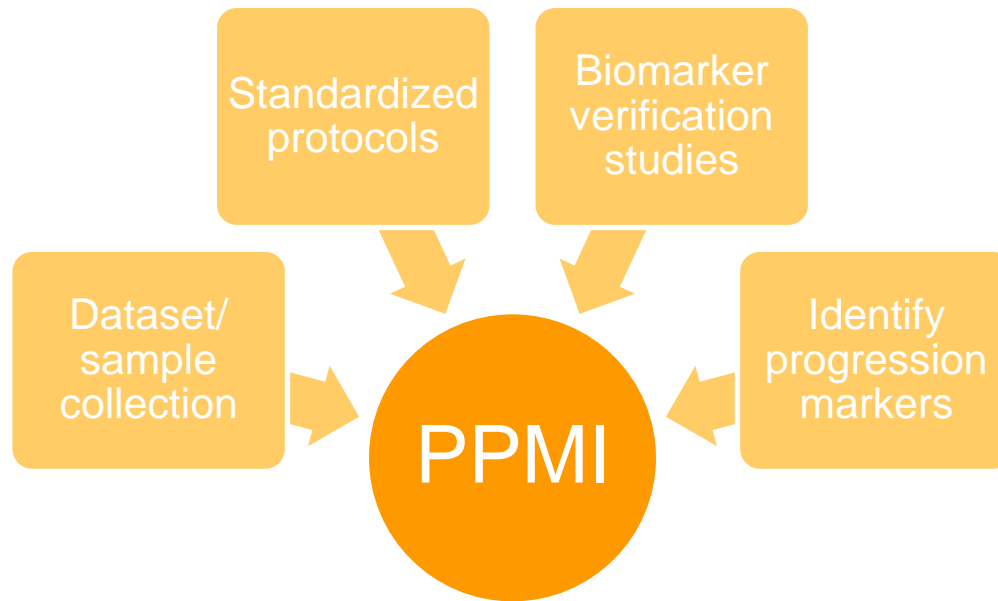
- Facilitate measurement of modifications in the disease – biological effects and changes-- could provide valid clinical trial endpoints
- Help guide clinical trial design parameters like patient numbers, stratification, duration of treatment

Therapeutic Markers

- Is the therapeutic reaching its target?
- Is the therapeutic having its desired effect?

Without markers of progression, clinical trials to test new therapies in patients are at risk of yielding inconclusive results

The Parkinson's Progression Markers Initiative (PPMI)



PPMI, led by Principal Investigator, Ken Marek, MD, has four core objectives:

1. Develop/collect comprehensive clinical/imaging dataset and biological samples from large group of *de novo* patients and controls
2. Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biologic data
3. Conduct preliminary verification and validation studies on imaging and biologic markers
4. Identify and correlate clinical, imaging and biologic markers for use in future trials

PPMI Study Details: Synopsis

Study population	<ul style="list-style-type: none">400 <i>de novo</i> PD subjects (“possible PD” with positive DaT and unmedicated)200 age- and gender-matched healthy controlsSubjects will be followed for a minimum of 3 years and a maximum of 5 years
Assessments/ Clinical data collection	<ul style="list-style-type: none">Motor assessmentsNeuropsychiatric/cognitive testingOlfactionDaTSCAN imaging, MRI
Biologic collection/	<ul style="list-style-type: none">DNA collected at screeningSerum and plasma collected at each visit; urine collected annuallyCSF collected at baseline, 6mo and then annuallySamples aliquoted and stored in central biorepository
Initial Verification studies	<ul style="list-style-type: none">Lead biologic candidates to be tested:<ul style="list-style-type: none">Alpha-synuclein (CSF)DJ-1 (CSF and blood)Urate (blood)Abeta 1-42 (CSF)Total tau, Phospho-tau (p-181) (CSF)
PD treatment	<ul style="list-style-type: none"><i>De novo</i> for ~6 monthsCan participate in other clinical trials (including interventional trials) after 12 months
Status	<ul style="list-style-type: none">6 study subjects enrolled as of September 7th

PPMI study infrastructure is in place

Cores

Clinical Coordination	<ul style="list-style-type: none"> University of Rochester's Clinical Trials Coordination Center <ul style="list-style-type: none"> PI: Bernard Ravina
Statistics	<ul style="list-style-type: none"> University of Iowa <ul style="list-style-type: none"> PI: Christopher Coffey
Imaging	<ul style="list-style-type: none"> Institute for Neurodegenerative Disorders <ul style="list-style-type: none"> PI: John Seibyl
Genetics	<ul style="list-style-type: none"> National Institute on Aging/NIH <ul style="list-style-type: none"> PI: Andy Singleton
Bioinformatics	<ul style="list-style-type: none"> Laboratory of Neuroimaging (LONI) at UCLA <ul style="list-style-type: none"> PI: Arthur Toga
BioRepository	<ul style="list-style-type: none"> Coriell <ul style="list-style-type: none"> PI: Alison Ansbach
Bioanalytics	<ul style="list-style-type: none"> University of Pennsylvania <ul style="list-style-type: none"> PI: John Trojanowski and Les Shaw

Study Sites

US sites	<ul style="list-style-type: none"> Arizona PD Consortium (Sun City, AZ) Baylor College of Medicine (Houston, TX) Boston University (Boston, MA) Emory University (Atlanta, GA) Institute of Neurodegenerative Disorders (New Haven, CT) Johns Hopkins University (Baltimore, MD) Northwestern University (Chicago, IL) Oregon Health and Science University (Portland, OR) The Parkinson's Institute (Sunnyvale, CA) University of Alabama at Birmingham (Birmingham, AL) University of Pennsylvania (Philadelphia, PA) University of Rochester (Rochester, NY) University of South Florida (Tampa, FL) University of Washington (Seattle, WA)
	<ul style="list-style-type: none"> Innsbruck University (Innsbruck, Austria) Paracelsus-Elena Clinic Kassel/University of Marburg (Kassel and Marburg, Germany) University of Napoli (Naples, Italy) University of Tübingen (Tübingen, Germany)

Rates of clinical trial recruitment delay progress

30%

The percentage of clinical trials that fail to enroll a single subject

85%

The percentage of clinical trials that finish late because of enrollment troubles

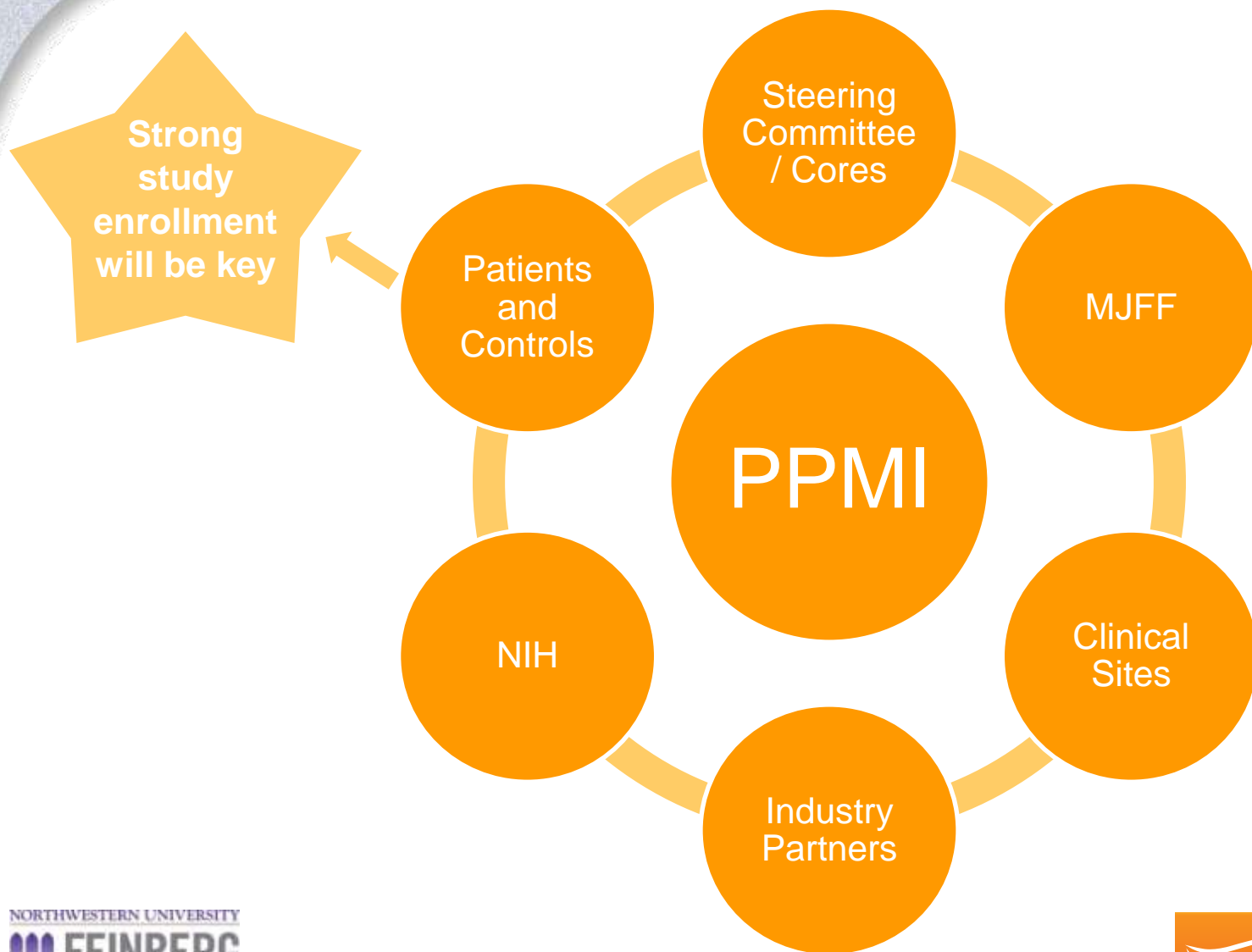
23,403

The number of PD patients currently called for on clinicaltrials.gov

Estimates hold that fewer than 1 in 10 people with Parkinson's participate in clinical trials... even a small improvement in this number will mean dramatic acceleration in filling this need.

PPMI is a \$40 million, 5-year collaborative effort

Success requires teamwork, creativity, and perseverance



How can we accelerate impact on patients' lives

✓ Verified markers of progression



- By validating existing candidates:
 - More efficient clinical trials: fewer participants needed
 - Accurate, conclusive clinical trial results: clinical endpoints can be identified
- By establishing a lingering data set:
 - Faster studies in the future

✓ Increased clinical trial participation



- Trial needs can be filled more efficiently if willing volunteers are proactively matched
- The faster we recruit, the faster we get information:
 - Doubling participation rate halves the time spent on recruiting