National Institute of Neurological Disorders and Stroke

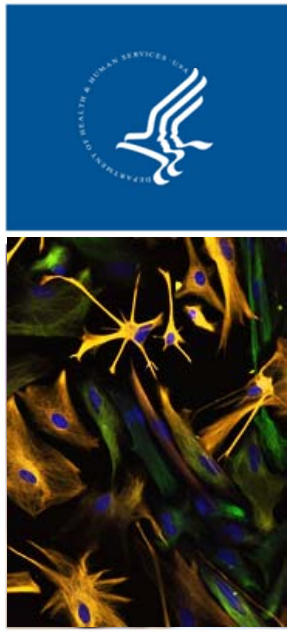
NINDS Parkinson's Disease Recommendations

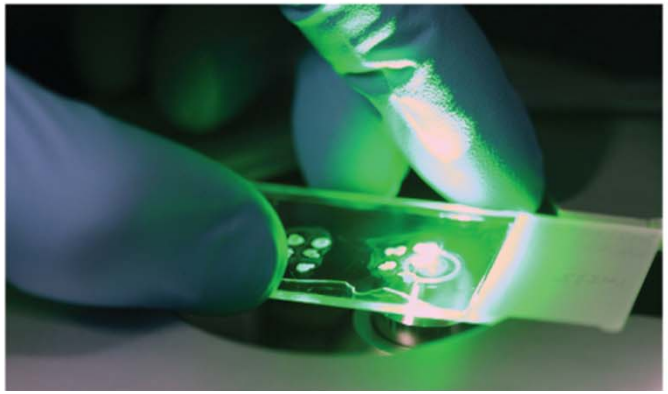
Filling gaps for PD drug development

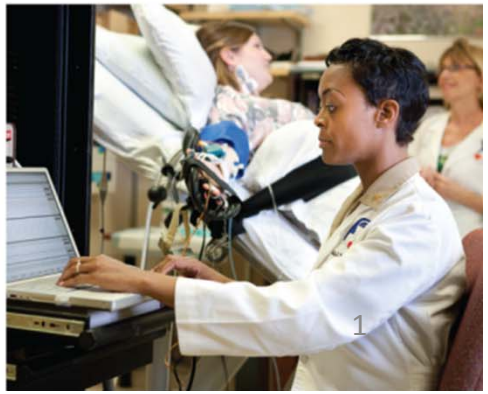
Walter Koroshetz, M.D.

Acting Director, National Institute of Neurological Disorders and Stroke, NIH

20 October 2014







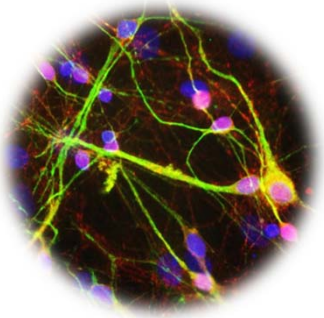
NIH/NINDS Investment in Parkinson's Disease (PD)

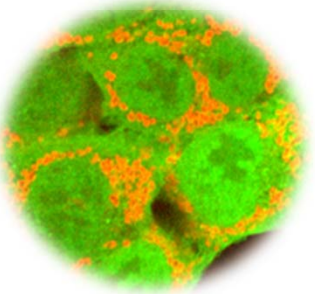
Estimates of Funding from Research, Condition, and Disease Categories (RCDC)					
(Dollars in millions and rounded)	FY 2010	FY 2011	FY 2012	FY2013	FY2014 (estimated)
NIH	$154 (+$18 ARRA)	$151	$154	$135	$139
NINDS	$111 (+$7 ARRA)	$96	$98	$90	$92

- NIH/NINDS is the leading funder of neuroscience research, including research on Parkinson's Disease
- NINDS is committed to:
  - Building a strong foundation of research discovery
  - Rapidly translating basic research findings into clinical practice
  - Decreasing the burden of neurological disease

NINDS Supports PD Research Across the Spectrum

- Mechanisms of disease
  - Role of α-synuclein in cytotoxicity and spreading of PD
- Genetic and environmental risk factors
- Biomarkers
  - PD Biomarkers Program (PDBP)
  - BioFIND
- Clinical research
  - Clinical trials identify successful (DBS, Tai Chi) and unsuccessful (CoQ10, creatine) therapies
  - Trials of GDNF, pioglitazone and exercise underway
- Training next generation of researchers and clinicians
- Workshops
- Resources





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NIH Supported Medical Advances:
2014 Lasker-DeBakey Research Award

Subthalamic Nucleus (STN) Deep Brain Stimulation (DBS)

Mahlon R. DeLong

Since 1974 DeLong has received > $25M from NIH + Intramural support

1960s – DeLong fellow at **NIH IRP**

1970s – DeLong models basal ganglia movement circuits, (**NIH IRP and extramural support**)

1980s – **NIH IRP** develops MPTP primate model

– Benabid demonstrates DBS of thalamus reduces tremors in human patients

1990s – DeLong targets STN to improve akinesia, rigidity, tremor in MPTP primate (**NINDS**, others)

– As a result of DeLong's paper, Benabid switches to DBS of STN with similar, dramatic results

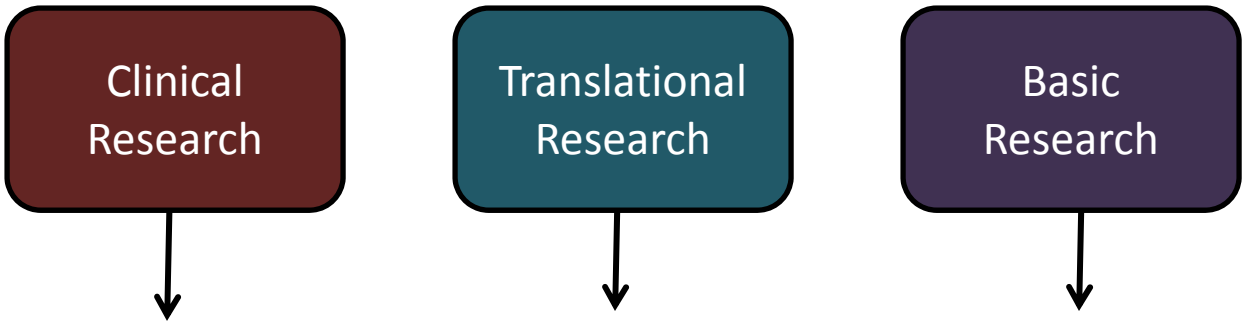
2000s – FDA approves DBS for PD (**Neuroprosthesis Program data contributes**)

NINDS/VA trial shows DBS superior to best medical therapy

Alim Louis Benabid

Parkinson's Disease 2014:
Development of Recommendations

VERTICAL



Pre-Conference

- **Process**: three panels of international experts from academia, industry, and government were convened to formulate highest priorities for advancing PD research
- **Charge**: develop up to 12 independent prioritized research recommendations
  - Many more proposed than made the final recommendations
  - Each panel reached consensus on content and priority
  - Drafts posted and distributed prior to conference

Summer 2013
Planning and RFI

Sept 2013
Steering Committee
3 Panels, 3 Topic Areas

Dec 2013
Draft posted on website

Jan 2014
- Conference
- Feedback and input, including from people with PD, care partners, and their advocates
- Revision
- **Council Report**

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Parkinson's Disease 2014: *Vision*

Data sharing is key to prosecuting the vision.

- **Develop precision medicine for the molecular and clinical heterogeneity of PD**
  - Right person, right treatment, at the right time
  - Requires longitudinal data from thousands of individuals
- **Support key infrastructure for data sharing**
  - Coordinated repositories,
  - CDE's, data sharing requires common language.

Parkinson's Disease 2014: *Strategy*

Big DATA

- **Genetic risk architecture** for PD motor, NMS, and progression
- Bridging from molecular clues to **mechanisms** both molecular and pathogenic
  - Systems biology: Central role for α-synuclein but also its interaction with products of other risk genes, biological processes.
- Developing **technologies to measure PD** processes
  - Biomarkers and neuroimaging, peripheral biopsy
  - Body-worn continuous sensors, intraoperative monitoring
  - Patient reported outcomes
- **Prevent, slow, or stop PD**
  - Focus on "learning" trials: Phases 1 and 2
  - Continuous access to patients and their families for trials
  - Incorporate clinical trials into clinical care
    - Larger numbers, less expensive, more generalizable results.

Parkinson's Disease 2014:
Highest Priority Clinical Recommendations

1	Define prodromal PD and determinants of subtypes to initiate proof-of-concept prevention trials. • *Will require screening of large numbers of individuals to identify high risk cohorts.*
2	Develop effective treatments and companion biomarkers for dopa-resistant features of PD- Motor and Non Motor • *Will require new means of identifying impactful clinical outcomes, such as patient reported outcomes, continuous sensors of balance, gait, and cognitive activities.*
3	Characterize the long-term progression of PD and determine mechanisms that underlie the heterogeneity in clinical presentation and rates of progression. • *Will require economical means of collecting data over the entire course of the illness in large numbers of patients.*

Parkinson's Disease 2014:
Additional Priority Clinical Recommendations

4	Biomarkers of target engagement and proximal pharmacodynamic effect
5	Methods to assess long-term efficacy and disease modification in clinical trials • *Will require economical solutions to collecting data over long time periods.*
6	Determine factors that facilitate public health interventions
7	Innovative outcome measures to evaluate motor and non-motor features • *Might include continuous sensors of motor and non motor activity.*
8	Improved informatics to include investigation of "big data" to improve trial design
9	Strategies to increase minority participation in PD research • *Will require outreach to care systems rich in minority populations.*
10	Risk factors and pathogenic mechanisms of motor fluctuations and dyskinesias for prevention and symptomatic therapy • *Getting at risk factors will require collection of deep level data on large number sof patients*

Parkinson's Disease 2014:
Highest Priority Translational Recommendations

1	Develop patient stratification tools with emphasis on slow- vs. fast-progressing PD, prodromal PD, and NMS
2	Develop PET imaging agents and assays to measure α-synuclein burden
3	Develop resources with greater power to predict outcomes in clinical trials, especially, iPS cell lines from sporadic, dominant, and recessive PD

Parkinson's Disease 2014:
Additional Priority Translational Recommendations

4	Integrated PD knowledge base that includes data from genetic, biomarker, clinical research, and clinical trials
5	Consensus guidelines for preclinical therapeutic studies targeting α-synuclein
6	Intermediate markers of drug efficacy to support more efficient proof-of-concept studies
7	Required attributes of targets emerging from basic science efforts that justify advancement into translation
8	Thorough understanding of targets, pathways, and pathophysiologic mechanisms with emphasis on those validated by human genetics and biology.
9	Converging pathways in PD, for example α-synuclein misfolding and mitochondrial function.
10	Pathway architecture and flux in PD and integrate into a systems-level understanding of pathogenesis

Parkinson's Disease 2014:
Highest Priority Basic Recommendations

1	Develop transmission models of pathologic α-synuclein and tau, and determine the mechanisms of propagation, release, and uptake including the role of "strains."
2	Elucidate the normal and abnormal function of α-synuclein and its relationship to other PD genes (*e.g.*, *ATP13A2, GBA, LRRK2, PINK1*, and *PARK2*).
3	Deeper understand of neural circuit dynamics, how these relate to behavior and motor control, and impact of therapeutic interventions

Parkinson's Disease 2014:
Additional Priority Basic Recommendations

4	PD-specific iPS cells
5	Integrate large datasets and perform functional and genetic analyses
6	Approaches for direct access to the human brain in individuals with PD during neurosurgical procedures
7	Genetic basis of PD
8	Molecular determinants and mechanisms of α-synuclein and tau aggregation, disaggregation and clearance
9	Sensor technologies and imaging for neural circuit dynamics in PD
10	Role of catabolic pathways in PD, including ubiquitin-proteasome and autophagy-lysosomal systems
11	Circuit analysis techniques, PD animal models, and optogenetics and related imaging technologies

What is the CDE Project?

- Identification of **common definitions** and the **standardization** of case report forms and other instruments
- Clinical trials and research studies with CDEs
  - *Systematically collect, analyze, share data*
  - *Decrease study start-up time and cost*
  - *Facilitate data sharing and comparisons across studies*
- **NINDS goals:**
  - Future NINDS-funded trials will use CDEs or be CDE-compatible
  - All types of clinical research can use part of the CDEs
    - Observational clinical studies can be linked to trial datasets
  - Clinical research progress will be accelerated
    - New investigators can build on consensus data elements
    - Start-up of multi-center and international clinical research efforts will be facilitated

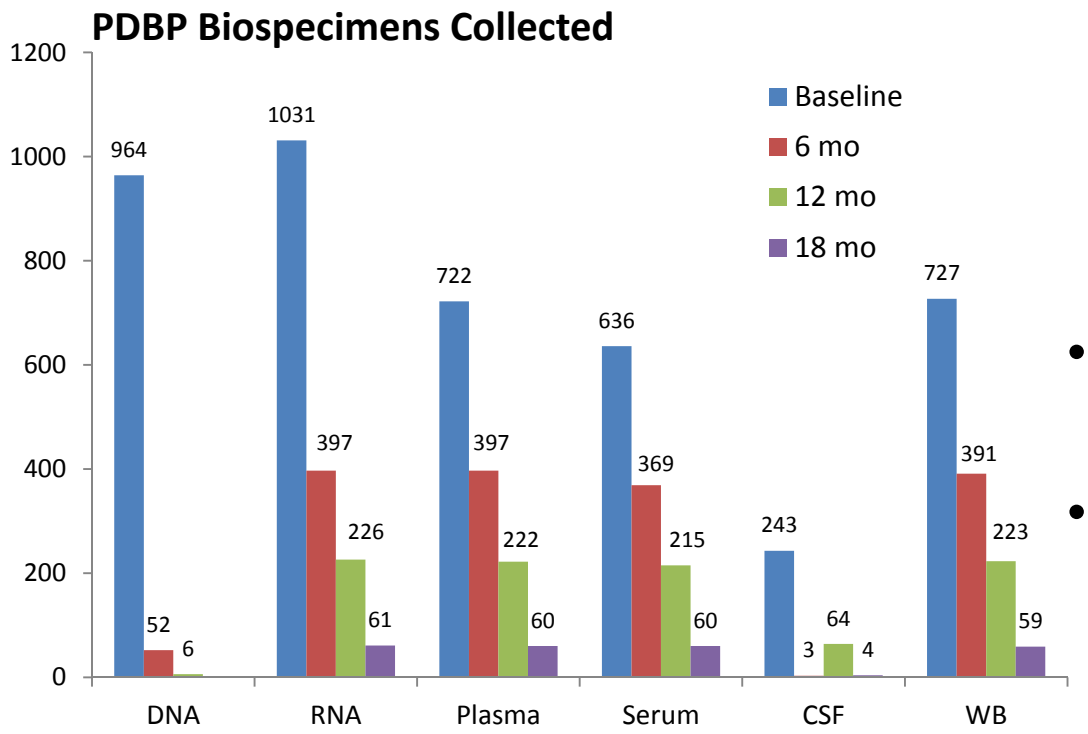
Developing New Recommendations for Clinical Research CDEs

- **Working Groups with support from NINDS CDE team to develop disease specific research CDEs/CRFs:**
  - Collect and review data report forms from PD-specific and other outcomes databases, identify appropriate outcome measures.
  - Test drive the CDE's in clinical research
  - Search for appropriate data repository and curate and annotate data coming in from investigators
  - Translate CDE's to CDISC for general use in the field
- **PD Working Groups:**
  - General and Motor
  - Imaging
  - Neuropathology
  - Genetics
  - Epidemiology/Environment
  - Psychiatry
  - Functional Neurosurgery
  - Other Non-Motor
  - Quality of Life
  - Operations
  - Cognitive
  - Scale Metrics and Statistics

Parkinson's Disease Biomarker's Program (PDBP)

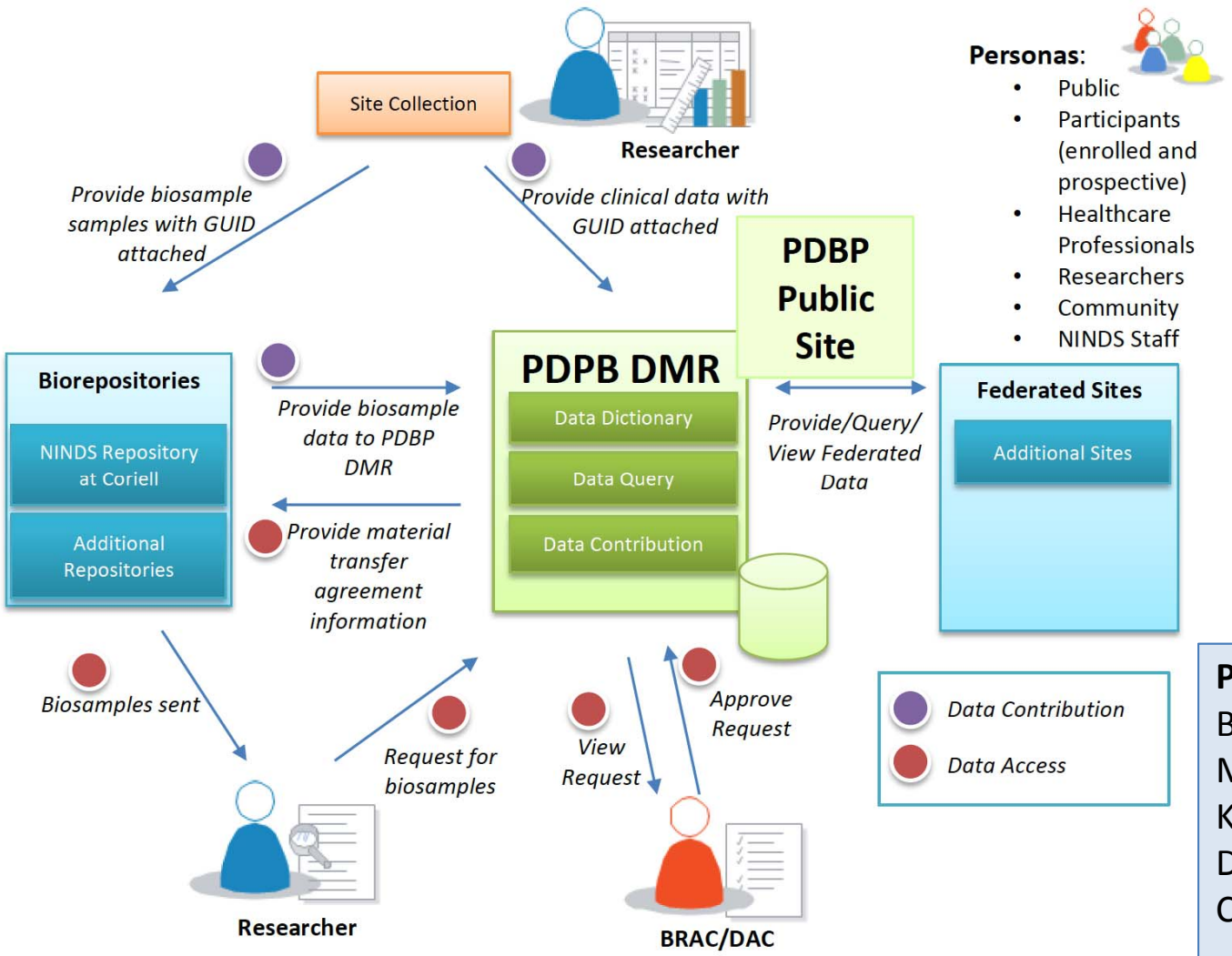
- PDBP promotes discovery of biomarker candidates for early detection and measurement of disease progression.
- PDBP coordinates the efforts of multiple stakeholders through a common Data Management Resource and web portal.
- PDBP will serve as a multi-faceted platform for:
  - Integrating existing biomarker efforts
  - Standardizing data collection and management across these efforts
  - Accelerating the discovery of new biomarkers
  - Fostering and expanding collaborative opportunities for all stakeholders

PDBP Data Management Resource (DMR)



- DMR is a web-based data management system that provides tools to PDBP supported projects for both the standardization of collection of clinical data
- 21,233 data forms entered in the PDBP DMR (9/11/14)
- The "Query" data informatics program within the PDBP DMR searches PDBP datasets and other NINDS-funded PD clinical studies
- The Query tool is based on NINDS PD common data elements and unique PDBP DMR elements

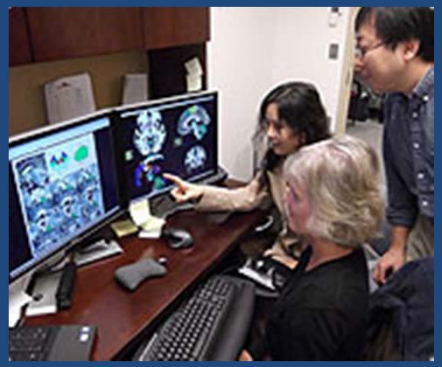
How the PDBP DMR Works



National Institute of Neurological Disorders and Stroke

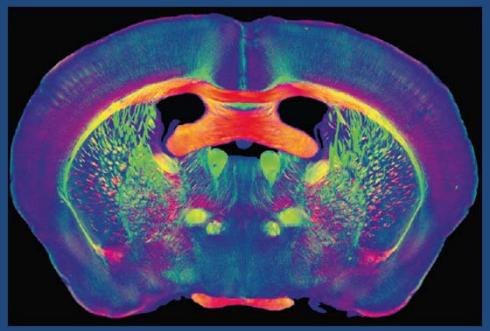
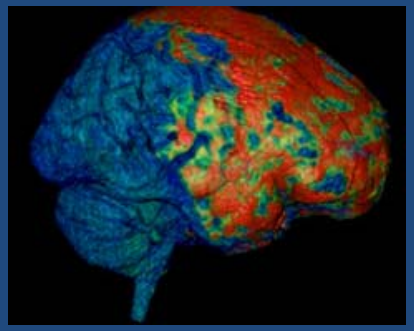
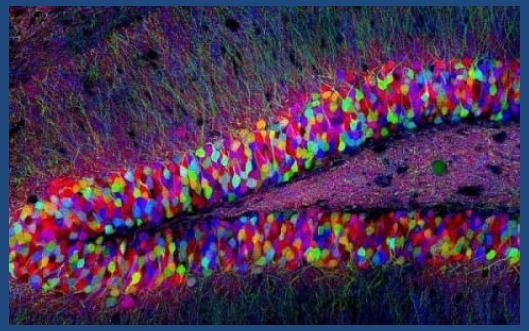
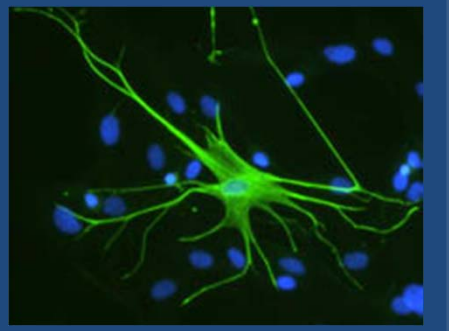
PDBP Leaders:
Beth-Anne Sieber, Ph.D.
Margaret Sutherland, Ph.D.
Katrina Gwinn, M.D.
Debra Babcock, M.D., Ph.D.
Coryse St. Hillaire-Clarke, Ph.D.

DMR:
Matthew McAuliffe, Ph.D.

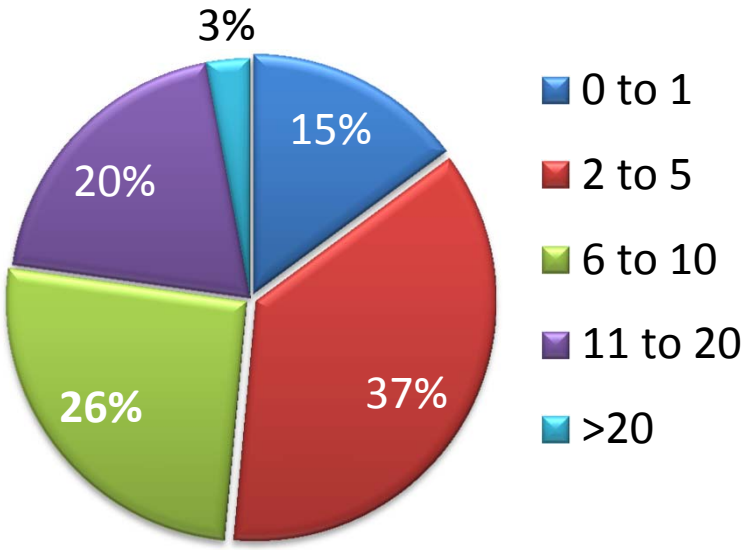
NINDS

Seeking Knowledge about the Brain . . .
Reducing the Burden of Disease

PDBP Participants

PDBP Participants: Years since PD Diagnosis



Number of PDBP participants based on diagnosis