Introduction to Session 1: Bringing emerging science to people with Parkinson's disease through clinical research
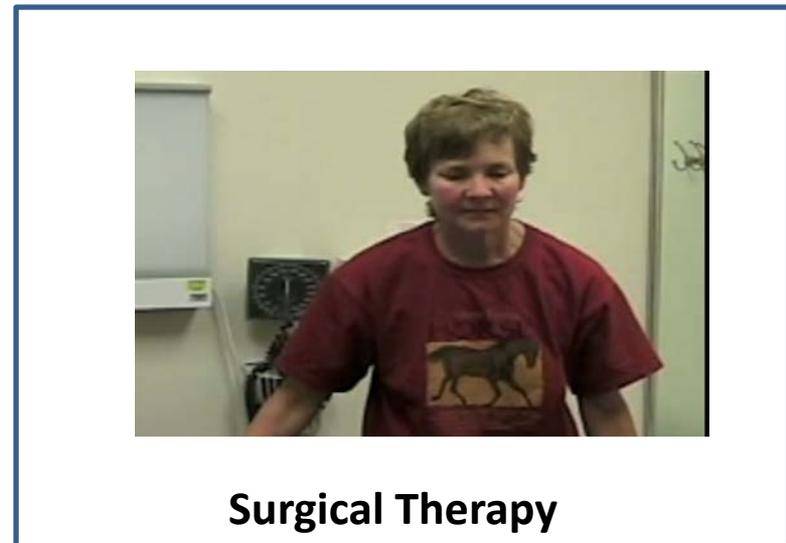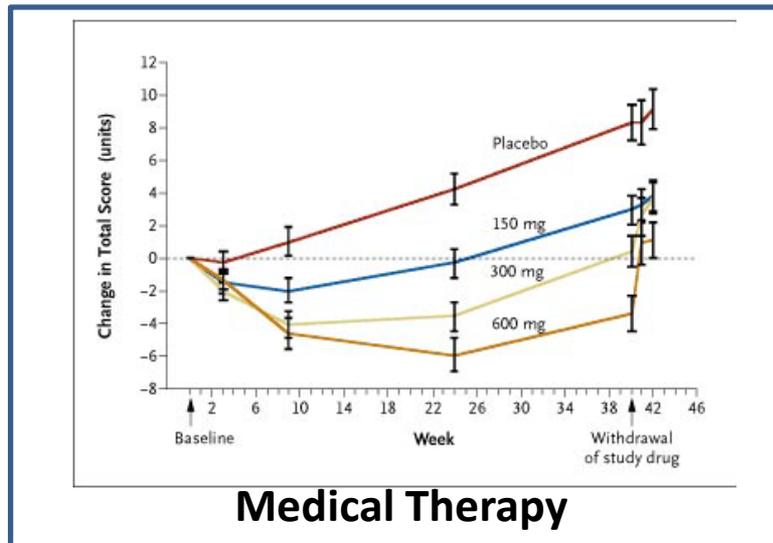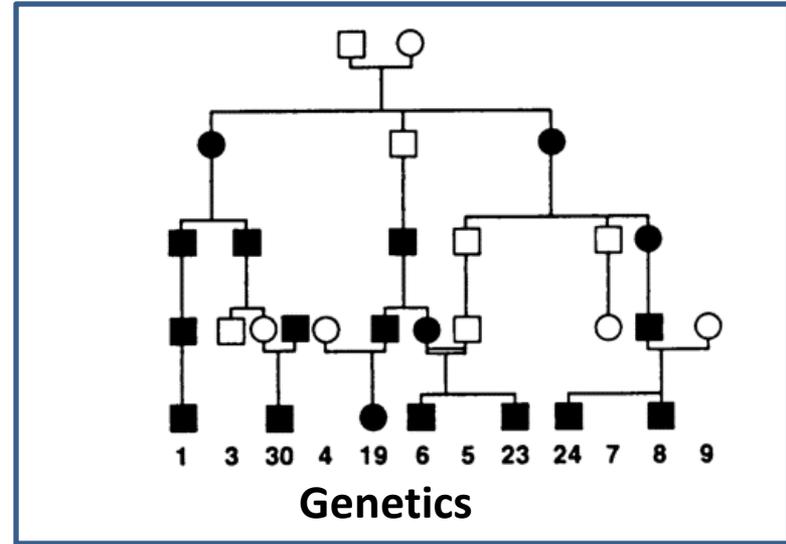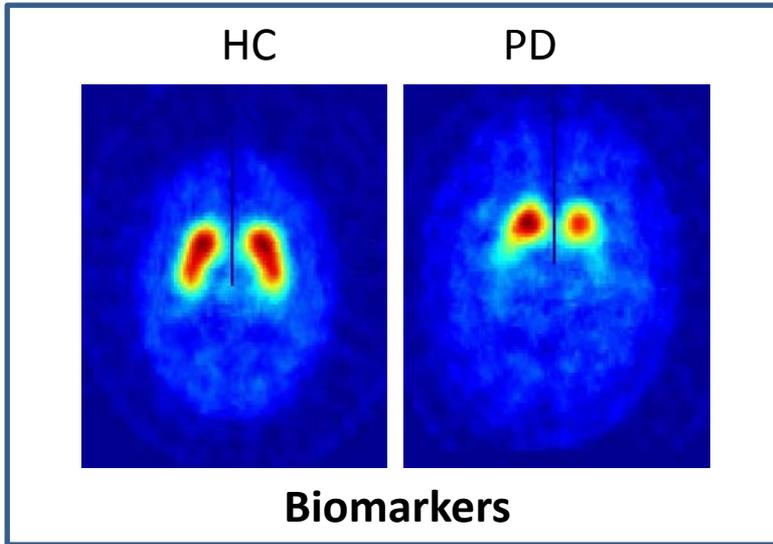
Co-Chairs: Randall Bateman, MD and Andrew Siderowf, MD

NIH Liaisons: Wendy Galpern, MD, PhD and Walter Koroshetz, MD

Contributions from clinical research

Biomarkers

HC   PD

Genetics

Medical Therapy

Surgical Therapy

Recommendations: People and Process

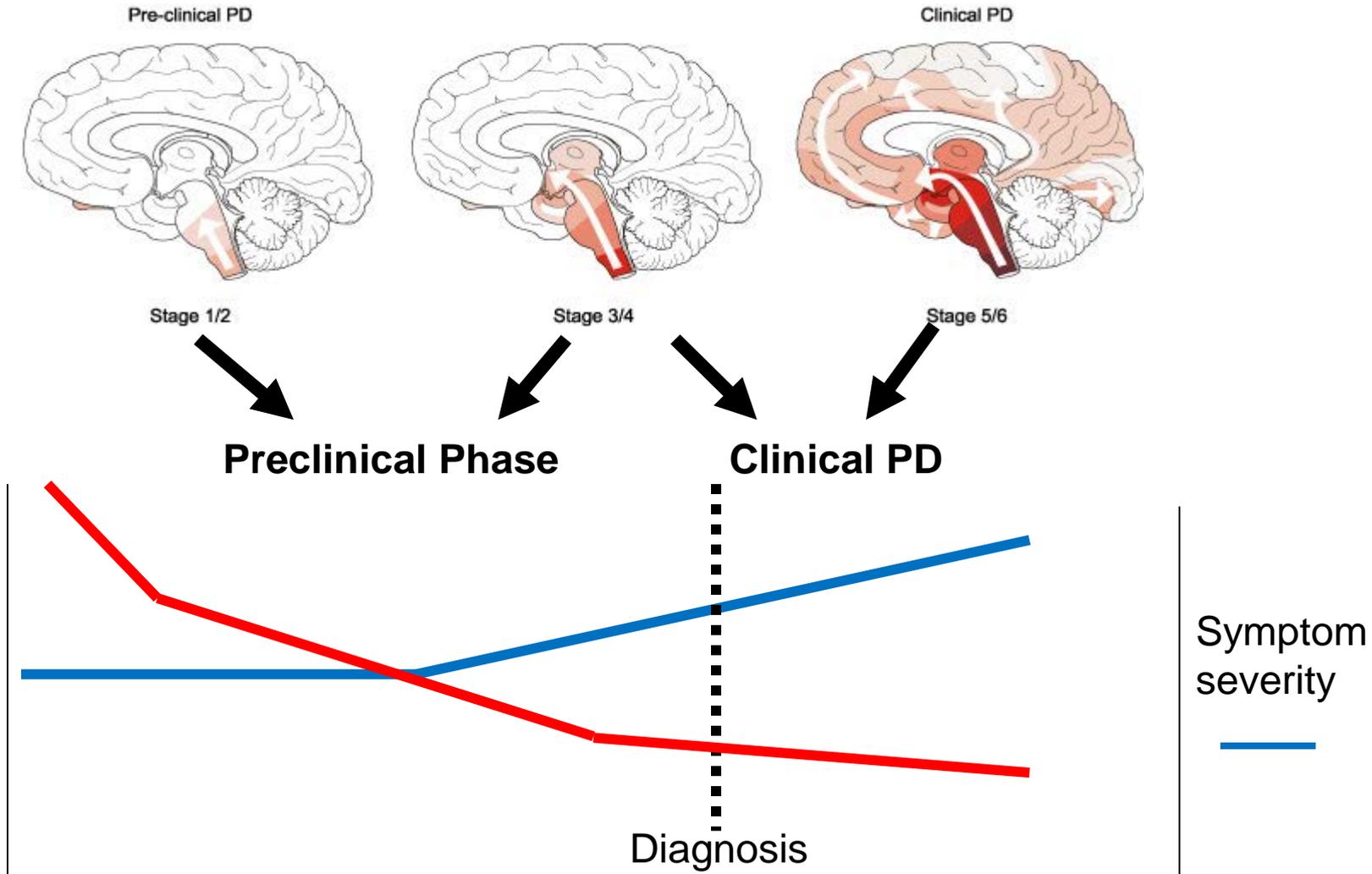**People**

- Christopher Coffey
- Jordan Elm*
- Nicholas Kozauer*
- Karen Marder
- Werner Poewe
- Bernard Ravina
- Ira Shoulson*
- Lisa Shulman
- Philip Starr
- Matthew Stern*
- Caroline Tanner

Process

- Sub-groups created >20 recommendations
- Entire group ranked recommendations
- Top 12 selected
- Group discussion
- Re-ranking of recommendations into final order

Natural History of PD

Pre-clinical PD

Clinical PD

Stage 1/2

Stage 3/4

Stage 5/6

Preclinical Phase

Clinical PD

Dopamine neurons

Symptom severity

Diagnosis

Braak H, *et al. Neurobiol Aging*, 2003;24:197-211.

Symptomatic treatment

- Conduct studies to improve understanding and treatment of:
  - non-motor features (4)
  - levodopa-resistant motor symptoms (6)
  - motor fluctuations and dyskinesias (12)

Outcome Measures

- Apply cutting edge approaches to outcomes assessment in clinical trials (9)
- Increase participation of underserved groups in PD research (11)

Trial Design

- Develop biomarkers for early-stage clinical trials (5)
- Improve methods for identifying long-term efficacy in clinical trials (7)
- Use informatics to improve understanding of PD biology and improve trials (10)

Disease Progression

- Conduct proof-of-concept prevention trials (1)
- Understand features and biology of prodromal PD (2)
- Study strategies to prevent long-term disability in established disease (3)
- Understand risk factors for PD (8)
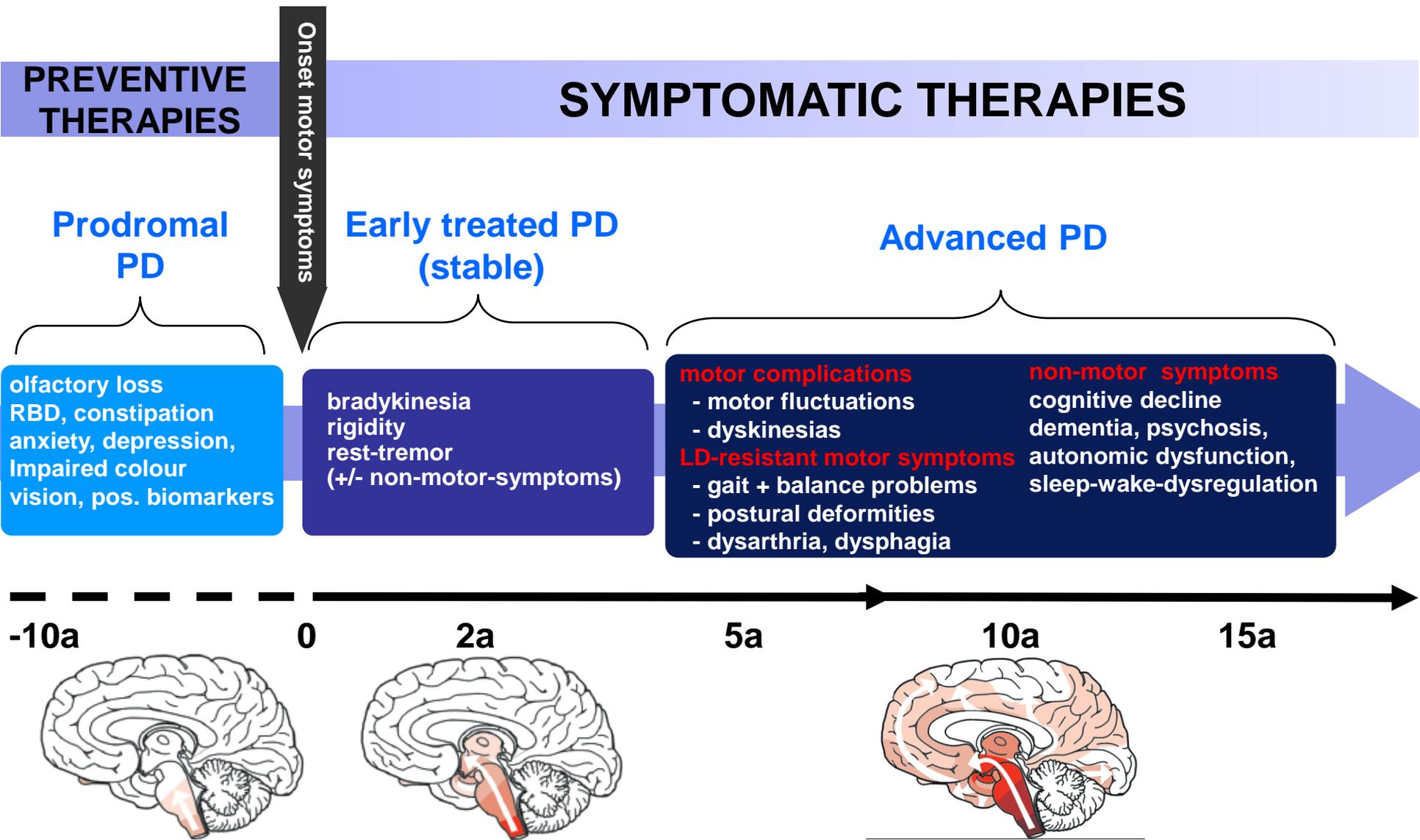
Opportunities to advance symptomatic treatment of motor and non-motor features

Werner Poewe, MD

Innsbruck Medical University

On Behalf of:

Karen Marder, Bernard Ravina, Lisa Shulman, Andrew Siderowf, Philip Starr, Matthew Stern

The Evolution of PD

PREVENTIVE THERAPIES

Onset motor symptoms

SYMPTOMATIC THERAPIES

Prodromal PD

Early treated PD (stable)

Advanced PD

olfactory loss
RBD, constipation
anxiety, depression,
Impaired colour
vision, pos. biomarkers

bradykinesia
rigidity
rest-tremor
(+/- non-motor-symptoms)

motor complications
 - motor fluctuations
 - dyskinesias
LD-resistant motor symptoms
 - gait + balance problems
 - postural deformities
 - dysarthria, dysphagia

non-motor symptoms
cognitive decline
dementia, psychosis,
autonomic dysfunction,
sleep-wake-dysregulation

-10a   0   2a   5a   10a   15a

Motor complication rates* with initial levodopa therapy

Retrospective uncontrolled studies (Poewe et al., 1986)	50–80% after 5–6 years
Community-based studies (Schrag et al., 2000)	30–40% after 5 years
Young-onset PD (Quinn et al., 1987; Schrag et al., 1998)	90% after 5 years
Randomised controlled trials (RCTs) (PSG 2000; Whone et al., 2003; ELLDOPA)	16% after 9 months 30–40% after 2 years

Currently established risk factors: age, LD-dose, treatment duration

*Refers to motor fluctuations and dyskinesias
– most of the studies listed assessed both;
young-onset PD refers to dyskinesias only

Poewe et al. Neurology 1986; 36 (11): 1528;
Schrag et al. Brain 2000; 123 (Pt 11): 2297;
Quinn et al. Mov Disord 1987; 2 (2): 73;
Schrag et al. Mov Disord 1998; 13 (6): 885;
PSG. JAMA 2000; 284: 1931; Whone et al. Ann Neurol
2003; 54 (1): 93; Fahn et al. N Engl J Med 2004; 351 (24): 2498

Treatments for levodopa-related motor complications in PD

- Motor fluctuations
  - DA-agonists (pramipexole, ropinirole, rotigotine, apomorphine, pergolide)
  - L-dopa (enteral infusions, rapid onset formulations)
  - COMT inhibitors (entacapone, tolcapone)
  - MAO-B inhibitors (rasagiline)
  - DBS surgery (STN, GPi)
  - Unilateral pallidotomy

- Dyskinesias
  - Amantadine
  - DBS surgery (STN, GPi)
  - Unilateral pallidotomy

DBS=deep brain stimulation; STN=subthalamic nucleus;
GPi=Globus Pallidus pars interna

Fox et al, MDS Task Force 2011

Treatment and Prevention of Motor Complications - What do we need to know ? -

- Genetic and other biomarkers to identify at-risk subjects

- Role of maldaptive plasticity in the development of motor complications and neuronal systems involved

- Role of age and gender in maladaptive brain plasticity

- Role of non-dopaminergic mechanisms

- Role of continuous drug delivery in preventing motor complications

Treatment and Prevention of Motor Complications - Future Research Approaches -

- Identification of genetic and other risk markers

- Neurophysiological and imaging approaches to study neural networks involved in dyskinesias

- Studies of age and gender effects on neural network plasticity

- Studies of continuous drug delivery to prevent motor complications

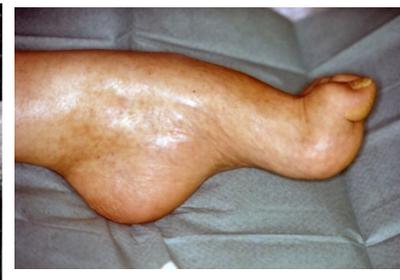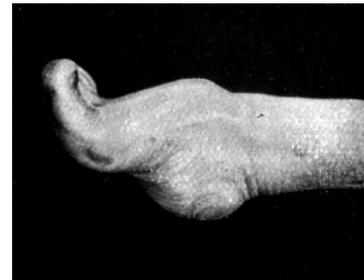- Identification of novel targets and development of novel therapies to treat motor complications
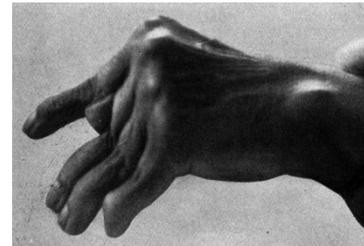
L-dopa resistant motor symptoms in PD

- **Axial and limb deformities**
  - camptocormia
  - antecollis
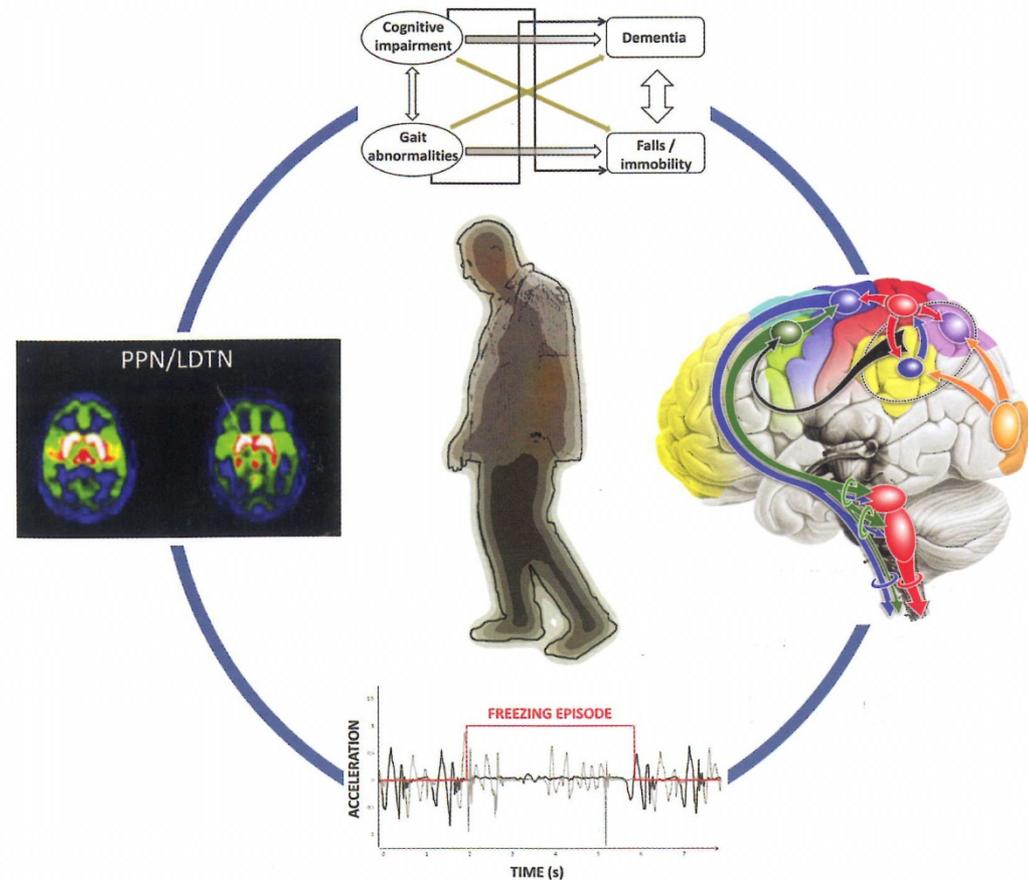 - lateral trunk flexion
  - „striatal" limb deformities

- **Postural instability**

- **Falls**

- **Freezing of gait**

- **Dysarthria**

- **Dysphagia**

Freezing of gait and falls in advanced PD

- **70–80% report regular falling** [1,2]

- **20% have fractures related to falls** [3]

- **Gait disordered falling common reason for institutionalisation** [4]

- **Associated with increased mortality** [4]

1. Hely et al. Mov Disord 2008; 23: 837; 2. Williams et al. J Neurol Neurosurg Psychiatry 2006; 77: 468;
3. Coelho et al. J Neurol 2010; 257: 1524; 4. Williams et al. 2010
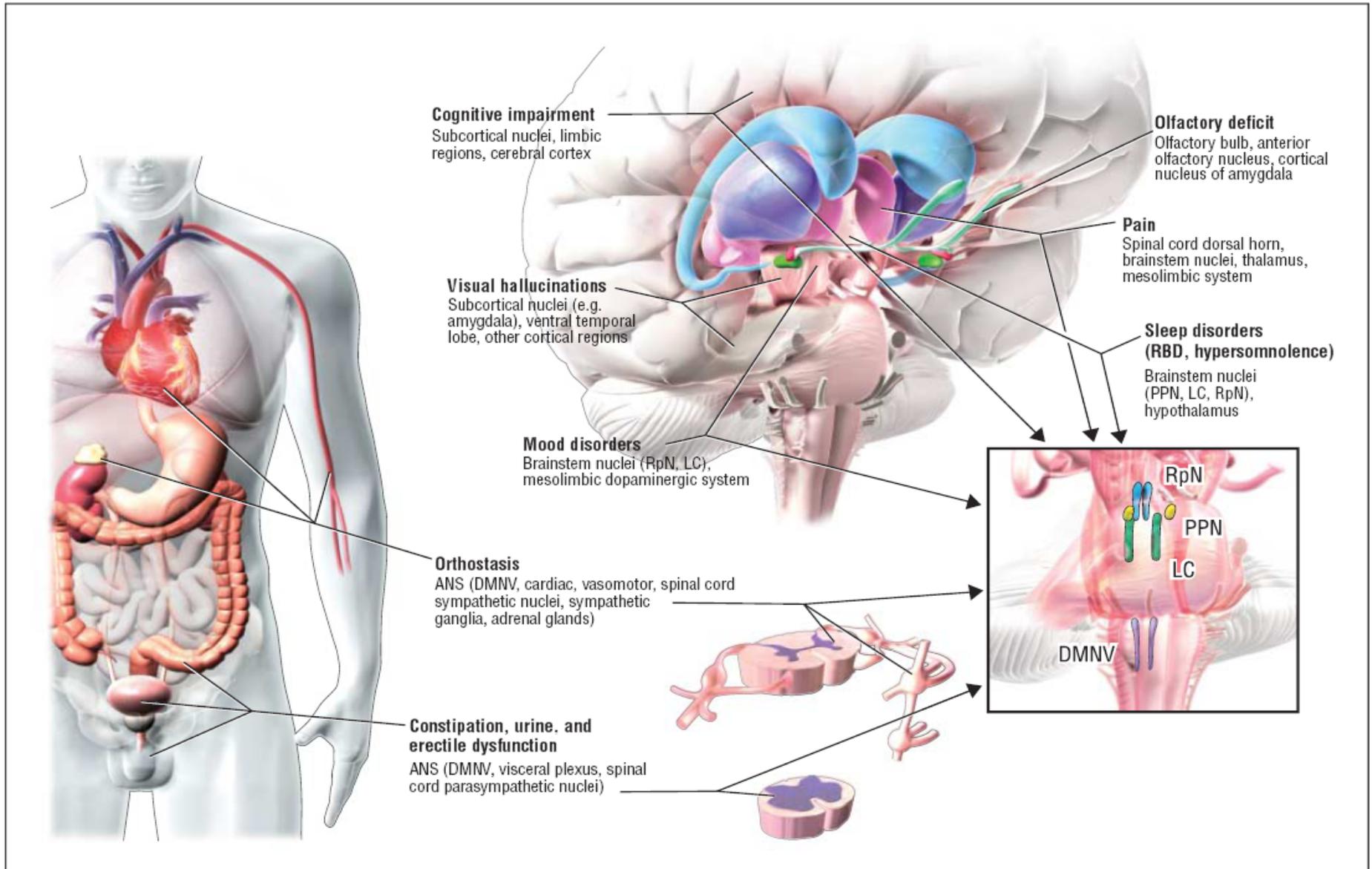
Treatment of LD-resistant Symptoms in PD - What do we need to know ? -

- Clinico-pathological correlations and neuronal mechanisms underlying LD-resistant ‚axial' symptoms

- Risk factors for the development of posture, gait and balance problems

- Neural systems and motor control mechanisms to be targeted by therapeutic interventions

Treatment of LD-resistant Symptoms
- Future Research Approaches -

- Biomarkers studies for the development of axial symptoms in PD

- Define dysfunctional motor patterns in patients with gait and balance problems using BFS and other novel computational technology

- Studies into the association of LD-resistant motor symptoms and cognitive and autonimic dysfunction

- Identify novel targets for pharmacological and DBS therapy

- Clinical trials of behavioural and exercise-based therapies

Non-motor features of PD

Cognitive impairment
Subcortical nuclei, limbic regions, cerebral cortex

Olfactory deficit
Olfactory bulb, anterior olfactory nucleus, cortical nucleus of amygdala

Pain
Spinal cord dorsal horn, brainstem nuclei, thalamus, mesolimbic system

Visual hallucinations
Subcortical nuclei (e.g. amygdala), ventral temporal lobe, other cortical regions

Sleep disorders (RBD, hypersomnolence)
Brainstem nuclei (PPN, LC, RpN), hypothalamus

Mood disorders
Brainstem nuclei (RpN, LC), mesolimbic dopaminergic system

Orthostasis
ANS (DMNV, cardiac, vasomotor, spinal cord sympathetic nuclei, sympathetic ganglia, adrenal glands)

Constipation, urine, and erectile dysfunction
ANS (DMNV, visceral plexus, spinal cord parasympathetic nuclei)

RpN

PPN

LC

DMNV

Lim et al Arch Neurology 2009

Impact of NMS of PD

- **Tighter correlation with QoL than motor symptoms [1]**

- **Key driver of disability in advanced PD [2,3]**

- **Cognitive dysfunction major risk factor for nursing home placement and mortality [3,4]**

- **Lack of evidence from clinical trials to support treatment decisions [5]**

1 Martinez-Martin&al, Mov Disord 2011; 2 Hely&al, Mov Disord 2008;

3 Goetz&Stebbins, Neurology 1993; 4 Kempster&al, Brain 2007; 5 Seppi&al, Mov Disord 2011

Symptomatic therapy of NMS
- What do we need to know ? -

- Clinico-pathological correlations and pathophysiological mechanism underlying NMS

- Genetic and other risk factors for specific NMS

- Prognostic value of different clusters of NMS on PD natural history

- Role of NMS for PD subtyping

- Mechanisms driving NMS progression

- Targets for the drug treatment and prevention of NMS, including role of non-pharmacological therapies (DBS)

- Evidence for therapeutic efficacy and safety from RCT's

Symptomatic Therapy of NMS
- Future Research Approaches -

- Prospective studies to define the evolution of NMS in early PD and PD subgroups by NMS profiles

- Neuroimaging, neurophysiological and other biomarker studies to define NMS mechanisms, risk factors and novel treatment targets

- Use patient and caregiver information to prioritize NMS studies

- Define sensitivities and specificities of validated NMS instruments for individual NMS domains

- Clinical trials of pharmacological and non-pharmacological interventions to reduce NMS burden and prevent NMS progression
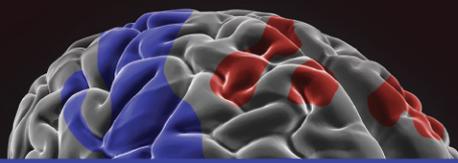
4. Initiate prospective studies to define the evolution of non-motor symptoms (NMS, e.g., dementia; psychosis; dysautonomia) and define patient subgroups based on clinical NMS profiles with the goal of developing strategies for treatment and prevention of NMS.

6. Identify mechanisms responsible for the development of levodopa-resistant motor symptoms (gait and balance problems including gait freezing) and develop novel therapeutic approaches to these problems.

12. Identify risk factors and pathogenic mechanisms of motor fluctuations and dyskinesias to identify novel targets for prevention and symptomatic therapy for these problems.

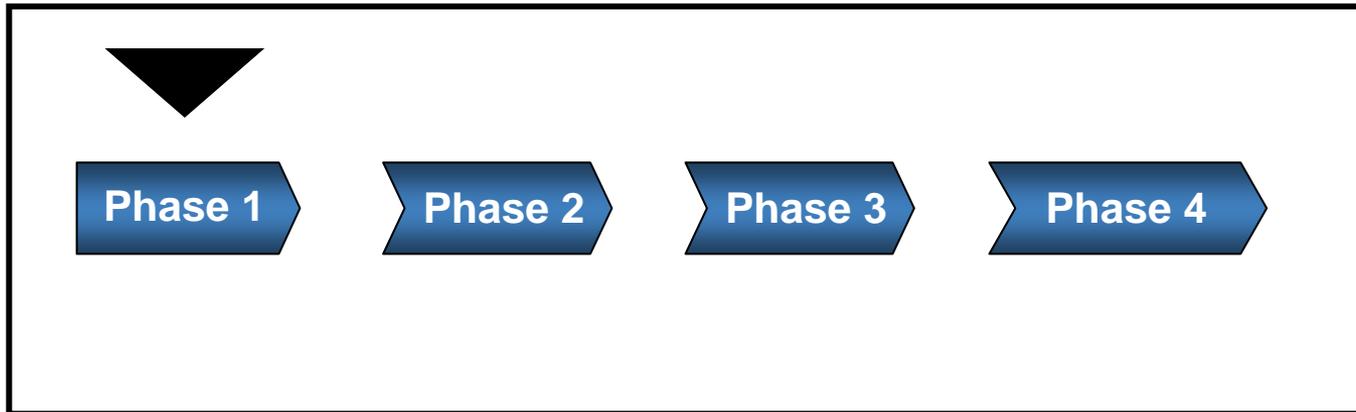# Opportunities for innovation in trial design

Christopher S. Coffey, PhD

University of Iowa

On Behalf of:

Randall Bateman, Jordan Elm,

Nicholas Kozauer, Bernard Ravina,

Ira Shoulson, Philip Starr

Clinical Trial Methods:
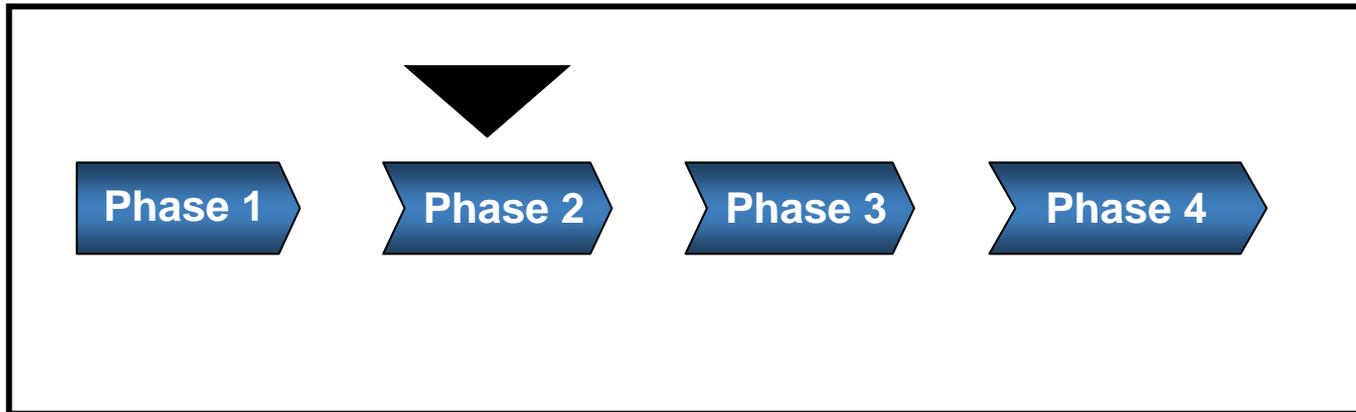# What We Know

Summary of Drug Development Process:

Phase I:

- Focus on safety/toxicity profile
  - First in humans
- Dose-Escalation protocols – Maximum tolerated dose

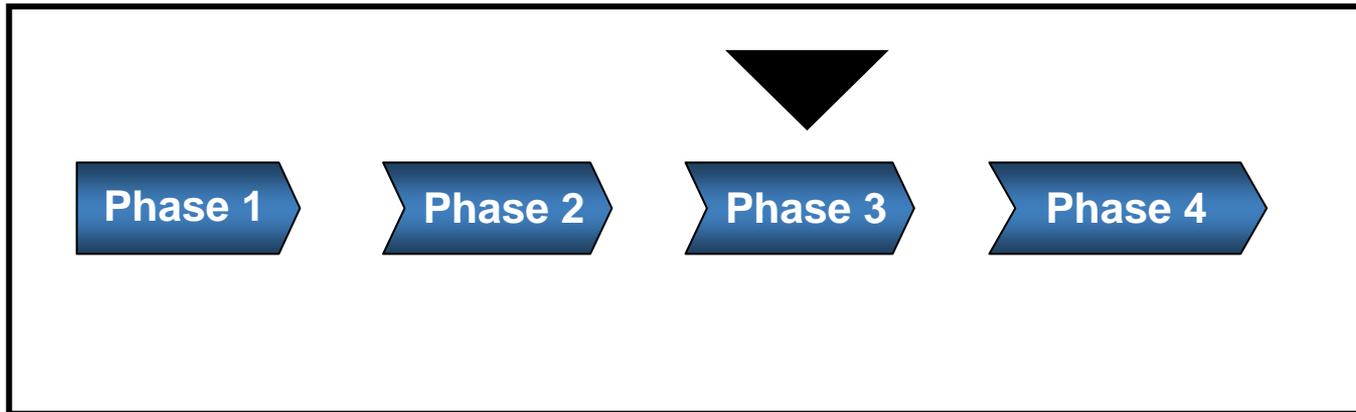# Clinical Trial Methods: What We Know

Summary of Drug Development Process:

Phase II:

- "Proof of Concept" – Examine whether treatment has sufficient biologic activity/effect

Clinical Trial Methods: What We Know

Summary of Drug Development Process:

Phase 1	Phase 2	Phase 3	Phase 4

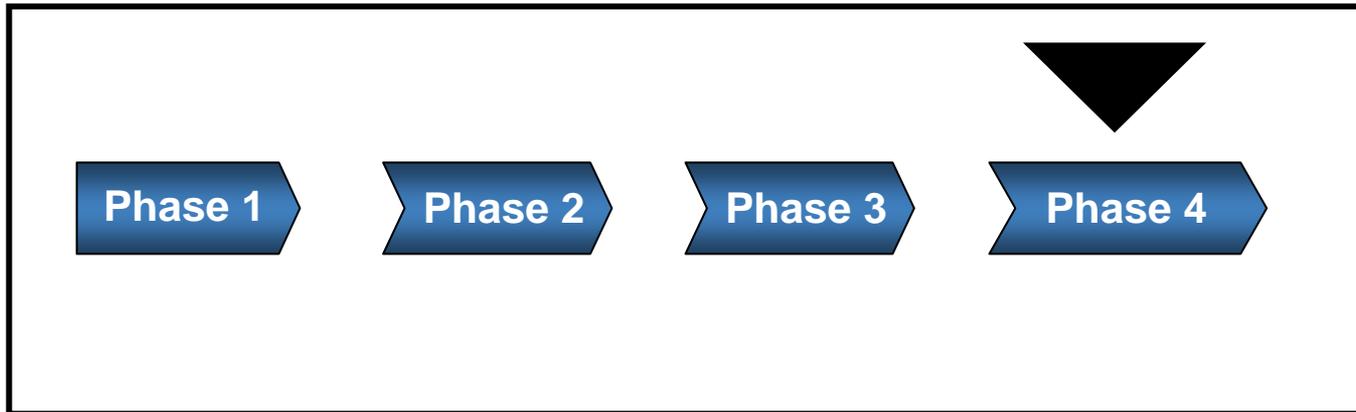**Phase III:**

- Confirmative evaluation of effectiveness
  - Overall benefit to risk assessment
  - Generally multi-site w/ large sample size

Clinical Trial Methods:
What We Know

Summary of Drug Development Process:

Phase IV:

- Long term surveillance studies ("post marketing") for safety
  - Look for rare side effects & interactions with other treatments
  - Can lead to new warning labels or withdrawal of drug from market

Clinical Trial Methods: What We Know

Early Stage Designs for Disease Modification:

- Selection Design (ALS, HD)
  - Used to select treatment with best response out of k potential treatments
  - Helpful to address 'pipeline' problem
- Multi-Dose Parallel Arm – Linear Trend of Dose (QE2)
  - Limitations due to small sample size
- Futility/Non-Superiority Designs (NET-PD)
  - Identify treatments that should not be candidates for phase III, while minimizing costs/sample size
  - Avoids running underpowered efficacy trials in phase II or conducting phase III trials as first rigorous test of efficacy for a new treatment

Clinical Trial Methods: What We Know

Confirmatory Designs for Disease Modification:

- 2 x 2 Factorial Design (DATATOP)
  - De novo, 1-2 year, Time to dopaminergic therapy
- Randomized, Placebo-Controlled Parallel Design (CoQ10)
  - De novo patients, 1-2 year change in UPDRS
- Delayed Start Design (ADAGIO)
- "Large/Simple" Design in Patients Receiving Optimal PD Care (LS-1)
  - 5 year change in multiple disease domains (GST)
- Pragmatic Trials (PD-MED, PD-SURG)
  - No placebo, comparative effectiveness, PDQ-39

Clinical Trial Methods: What We Know

Futility Design:

- To use a futility design, a researcher must define what would be considered "futile"
  - For example, suppose a 10 point increase in outcome is clinically meaningful
  - A futility design would be set up to determine if one can rule out that the new treatment is at least 10% better than the standard treatment (or placebo)

	Null (H_0)	Alt (H_A)	Implication of Rejecting H_0
Usual Design	$\mu_T = \mu_P$	$\mu_T \neq \mu_P$	New Treatment is Effective (Harmful)
Futility Design	$\mu_T - \mu_P \geq 10$	$\mu_T - \mu_P < 10$	New Treatment is Futile

Clinical Trial Methods:
What We Know

Futility Design:

- Negative predictive values are high
  Pr(Not Effective | Futile)

- Positive predictive values are not so high
  Pr(Effective | Not Futile)

- Thus, futility designs are good at identifying ineffective agents, but not good at identifying effective agents

Clinical Trial Methods: What We Don't Know

Biomarkers / Screening of Potential Treatments

- Need better biomarkers to determine if experimental agent engages intended biological target, and to ensure subjects express biological target at sufficient levels (e.g., amyloid imaging)
  - Critical information for determining dose/regimen
  - In absence of these markers, not possible to know if biological hypothesis was truly tested
  - Possible markers: alpha-synuclein, GBA, LRRK2, Parkin, abeta, tau
- Efficient designs to screen potential agents needed for PD
  - Assess more than one treatment
  - Assess multiple doses of same treatment

Clinical Trial Methods:
What We Don't Know

Assessment of Study Designs

- If a treatment fails to show efficacy in a clinical trial, is it the treatment or the design that is failing?
  - One cannot blame design for failure if treatment does not work
  - But, without knowing that design "works" one cannot rule out issues with design
    - Important to examine performance of designs in situations where "truth" is known (e.g., short-term vs. long-term treatment effects) – taking into account disease modeling process over time, and assumed treatment effect for an effective intervention.
    - Few mechanisms exist to support time & effort needed to develop and validate these simulation studies
    - Not efficient to do this during implementation of actual trial – may needlessly delay recruitment of subjects
    - Will require collaborations between clinicians & statisticians – independent of any specific trial

Clinical Trial Methods: What We Don't Know

Access to Existing PD Data

- Natural history of PD (before and after diagnosis) and characterization of PD subtypes needs to be better understood

- When designing trials, investigators need access to existing longitudinal data to model design operating characteristics

- PD trials, and well designed cohort studies are a resource that needs to be preserved

  - Recommended common data elements and requirements for sharing data

  - However, technical aspects of combining data sets across multiple sources is a considerable investment of time and expertise

  - Administrative data sources (e.g., electronic medical records) are another growing resource – and requires planning to utilize

Clinical Trial Methods: How Will We Find Out

Develop biomarkers

- Need focused efforts to develop imaging (e.g., alpha synuclein imaging agent) or other assays for limited set of genetically defined targets likely to be key targets for disease modification
  - Different from progression markers; Need not have longitudinal follow-up
  - Variety of in vitro and in vivo approaches may be used
- Need focused efforts to study evolving biomarkers from AD and related neurodegenerative disorders (e.g., beta amyloid & tau imaging ligands) to determine association with features of PD (such as cognitive impairment)

# Clinical Trial Methods: How Will We Find Out

Develop designs/methodology

- Development of improved designs for detecting interventions with disease modifying effects could be accomplished by devoting resources to groups with appropriate expertise in the area

- Assessment of novel designs could be accomplished through simulation studies by these same groups of individuals

  - Would also require input from clinical experts to determine potential scenarios where an "effective" treatment might be shown to work

  - Inclusion of both groups of individuals would allow assessment of design properties as a function of real-world expectations, rather than theoretical assumptions

Clinical Trial Methods: How Will We Find Out

Develop Improved Informatics Capability

- Develop central repository to standardize & uniformly archive existing and future trial data

- Develop central body to manage standardization of data sets and provide a user-friendly end product to ensure existing trial data may be used to appropriately answer questions beyond original intent for which they were collected

  - Central body should involve ongoing team of data managers, programmers, & statisticians with appropriate expertise

- Support development of informatics to archive administrative data sources and explore ways to overcome barriers (access, ethical challenges, de-identification of data, common data items)
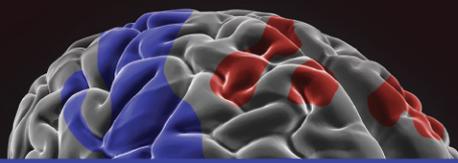
5. Develop biomarkers of target engagement and proximal pharmacodynamic effects for use in early stage clinical trials.

7. Develop improved methods to assess long-term efficacy and potential for disease modification in clinical trials, including: 1) more efficient (better & faster) strategies for screening potential agents; and 2) trial design simulations to assess the performance of trial designs for predicting long-term benefits.

10. Develop improved informatics capability that could include: 1) exploration of ways in which "big data" may contribute to learning in the PD space; 2) further develop and promote access to a central data repository for PD trial data; 3) a resource for trial design simulations to inform decisions about efficient trial design for a given intervention.

Opportunities to improve outcome measures in PD

Lisa M. Shulman, MD

University of Maryland

On Behalf of:

Jordan Elm, Nicholas Kozauer,

Andrew Siderowf, Caroline Tanner

Outcomes Measurement
A Cornerstone of Clinical Research

- Outcome measures: a "common denominator" resulting in limitations across clinical research
- Research quality capped by the quality of outcome measures
- Measures have not kept pace with expanded understanding of PD's diverse manifestations
- Modern measurement principles and IT provide new opportunities
  - Improved sensitivity, precision and practicality

Beyond the UPDRS…
Identifying Optimum Outcome Measures in PD

- Patient-reported outcome measures (PROs)
  - The cornerstone of patient-centered research
- Clinician-reported outcome measures (CROs)
- Physical & Cognitive Performance Measures
  - e.g. timed gait speed, cognitive domains, dual-tasking, ADL performance
- Symptom cluster measures
  - Motor & Non-motor
  - Focus: cognitive, psychiatric, autonomic, fatigue/sleep
- Composite outcomes

Applying advances in measurement science to PD

- NIH Initiatives
  - Patient Reported Outcomes Measurement Information System (PROMIS®)
  - Neuro-QoL
  - NIH Toolbox
  - NIH Common Data Elements
- Advances in Technology
  - EMR and Remote Assessment
 - Computerized Adaptive Testing

- **NIH PROMIS-NeuroQoL-Toolbox** use <u>measurement science</u> to create state-of-the-art assessment systems

  - **Precise, efficient, responsive**
  - **Item response theory**
  - **Standard Metric: T Score**
    - **(Mean=50, SD=10, US Pop Ref)**
  - **Nearly 40,000 people tested**
  - **Diverse domains and formats**
    - **Computerized Adaptive Testing**
    - **Short forms- ~ 8-10 items**
    - **Health Profiles (-29, -43, -57 items)**

PROMIS Domain Framework
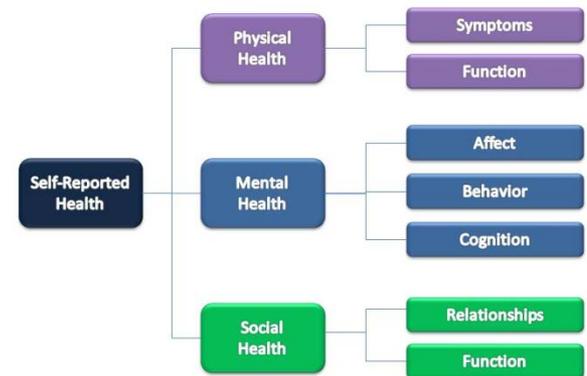
Physical Functioning Item Bank

Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 | Item n
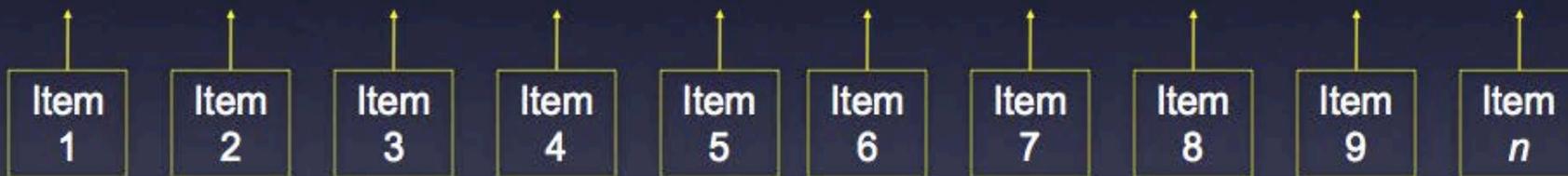
Are you able to get in and out of bed?
Are you able to stand without losing your balance for 1 minute?
Are you able to walk from one room to another?
Are you able to walk a block on flat ground?
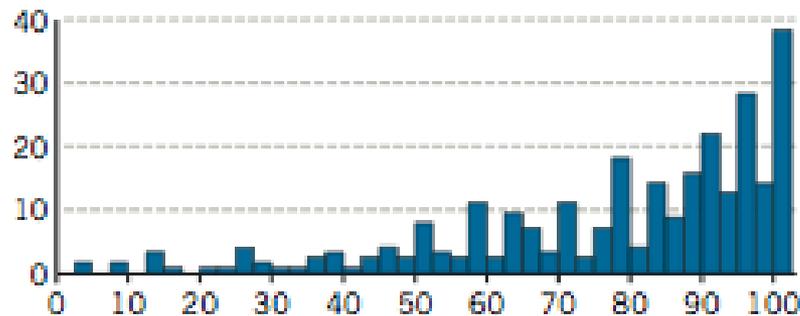Are you able to run or jog for two miles?
Are you able to run five miles?

Improved Measurement Science Reduced Floor and Ceiling Effects

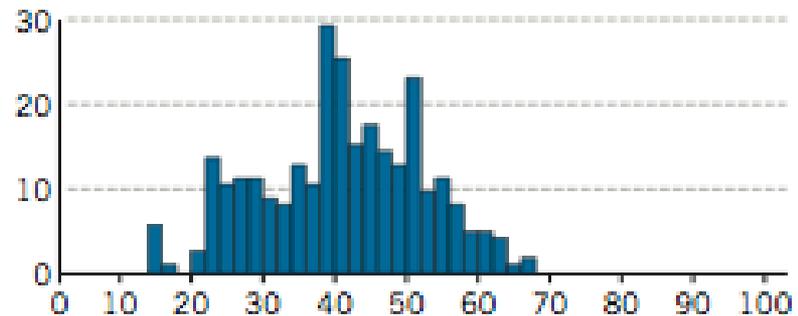Comparison of PROMIS Physical Function Scale With Stroke Impact Scale-16 (N = 348)

2012

The Stroke Impact Scale-16 (SIS-16) is a 16-item scale designed specifically to measure a broad range of poststroke physical limitations. Score range is 0 to 100, with 100 indicating no limitations. In this comparison between the SIS-16 and the PROMIS Physical Function scale, the SIS-16 demonstrated a ceiling effect, with approximately 20% of patients scoring the maximum of 100. In contrast, there was a normal distribution of PROMIS scores with little indication of a ceiling effect, allowing an improved ability to discriminate between milder degrees of physical limitations. In addition, the PROMIS Physical Function scale, which utilizes computer adaptive testing, was associated with lower patient burden. All patients answered all 16 questions in the SIS-16, whereas 75% completed the PROMIS scale by answering only four questions. The SIS-16 mean score was 78.33 (SD = 22.28); the PROMIS mean score was 41.01 (SD = 11.20). N = consecutive patients seen in the Cerebrovascular Center who completed both the SIS-16 and PROMIS Physical Function scale.

Computerized Adaptive Testing (CAT)

CAT successively selects questions to maximize precision based on what is known about the examinee from previous questions

Computerized Adaptive Tests
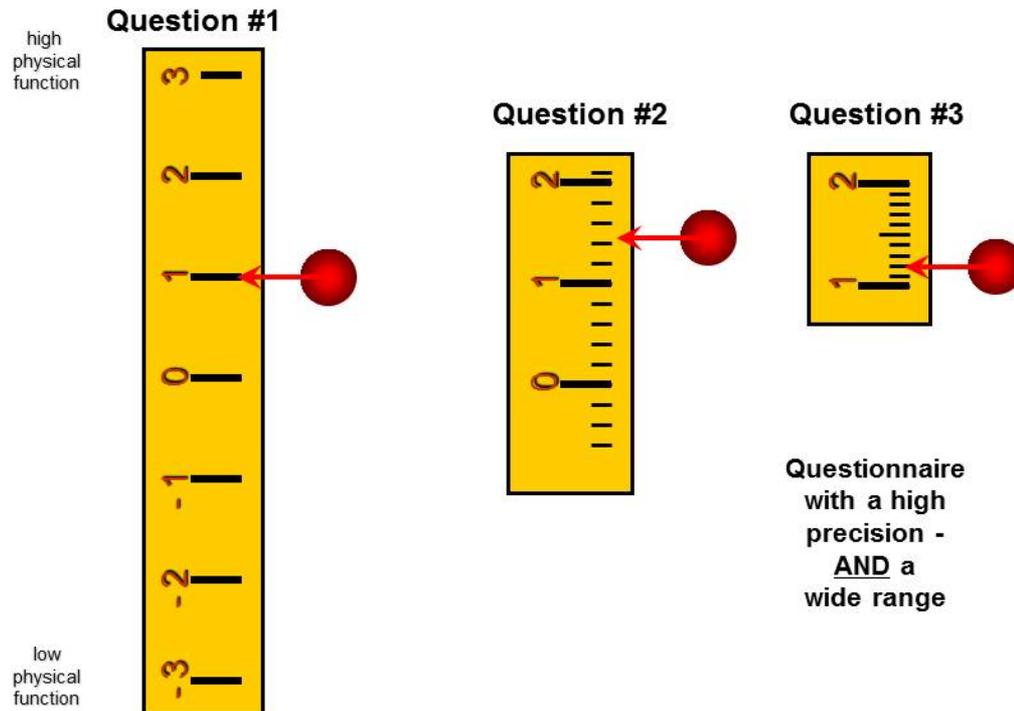
CAT Graph

Your scores for the CATs you completed are shown below.

The diamond ♦ is placed where we think your score lies. This diamond is placed on your T-Score, which is a standardized score that is based on an average score of 50, based on responses to the same questions in the United States general population. The T-score also has a standard deviation of 10 points, so a score of 40 or 60 represents a score that is one standard deviation away from the average score of the general US population.
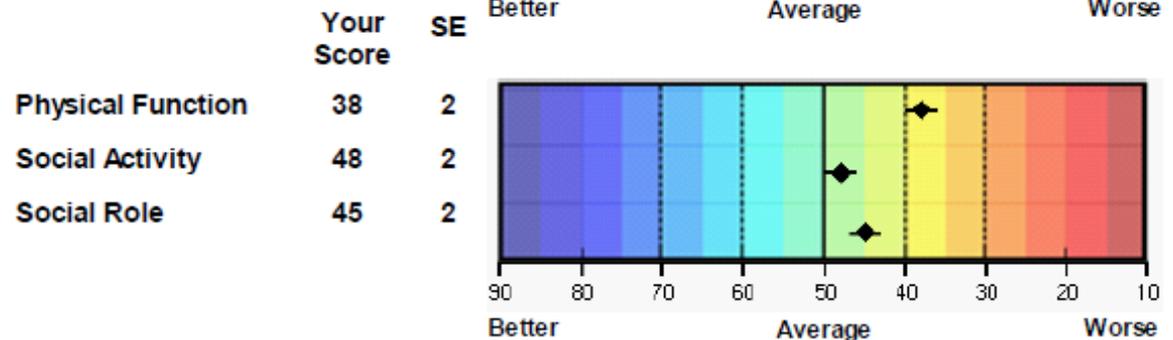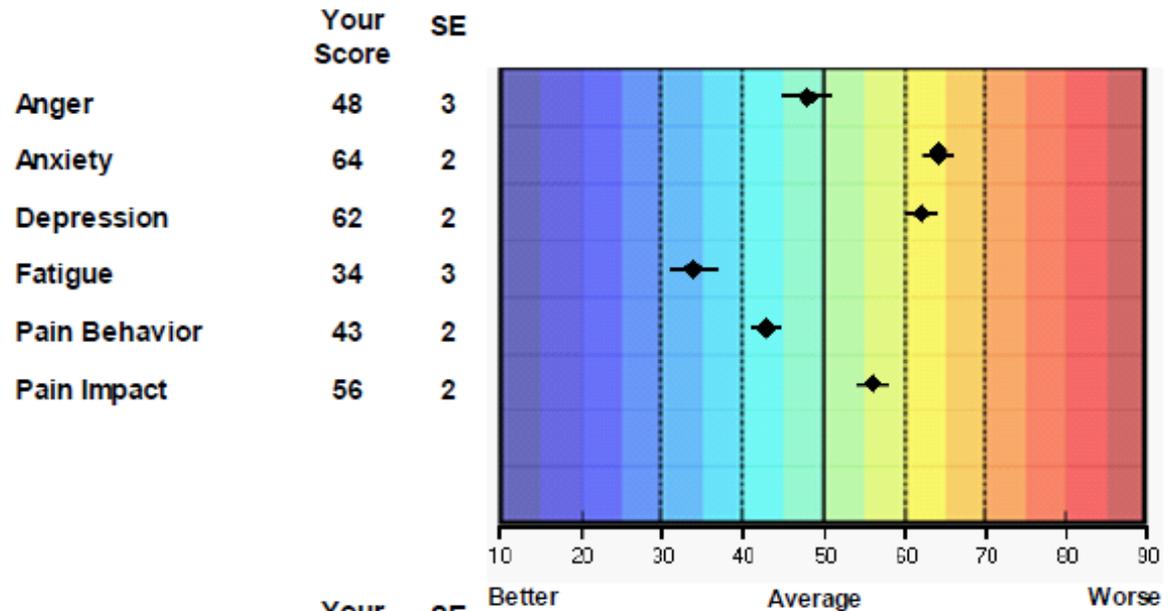
The Standard Error (SE) is a statistical measure of variance and represents the possible range of your score. The lines on either side of the diamond in your profile report show the possible range of your actual score around this estimated score. It is very likely that your score is in the range of these lines.
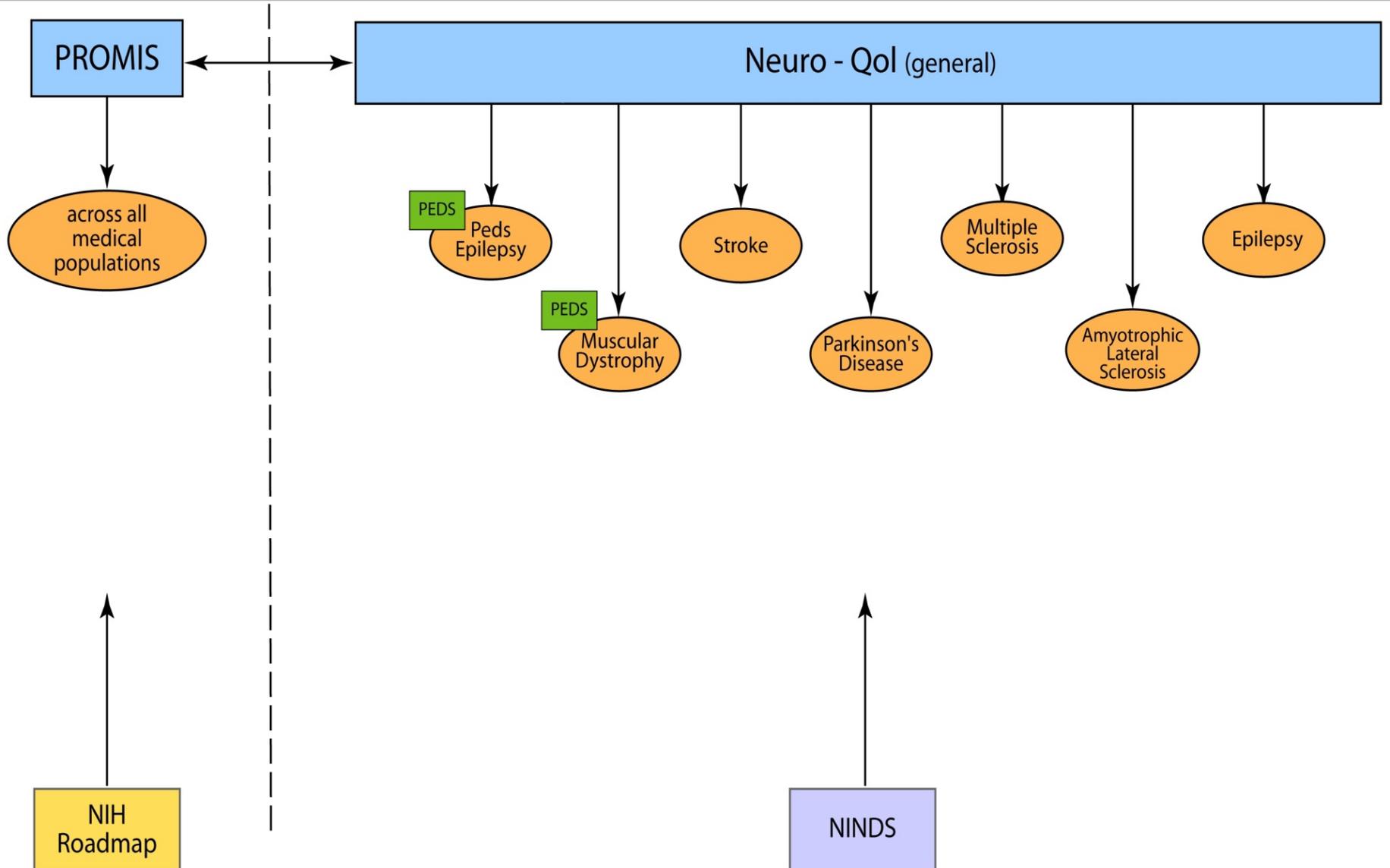
Comparability

> Comparing *different domains* in a *single condition*

> Comparing a *single domain* in *multiple Conditions*

       - Fatigue in PD vs. COPD

	Your Score	SE
Anger	48	3
Anxiety	64	2
Depression	62	2
Fatigue	34	3
Pain Behavior	43	2
Pain Impact	56	2

	Your Score	SE
Physical Function	38	2
Social Activity	48	2
Social Role	45	2

Neuro•QOL Quality of Life in Neurological Disorders

PROMIS ←→ **Neuro - Qol** (general)

across all medical populations

PEDS — Peds Epilepsy

PEDS — Muscular Dystrophy

Stroke

Parkinson's Disease

Multiple Sclerosis

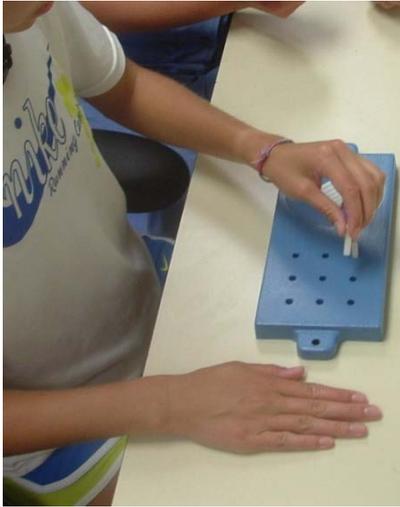Amyotrophic Lateral Sclerosis

Epilepsy

NIH Roadmap

NINDS

NIH Toolbox
to Assess Healthy Ageing

- Brief, comprehensive assessments
- Accessible data on performance across diverse demographic groups
- Motor, Cognition, Emotion, Sensation
- Example: Motor Domain Framework
  - Dexterity
  - Strength
  - Balance
  - Locomotion
  - Endurance

Dexterity

Locomotion

Balance
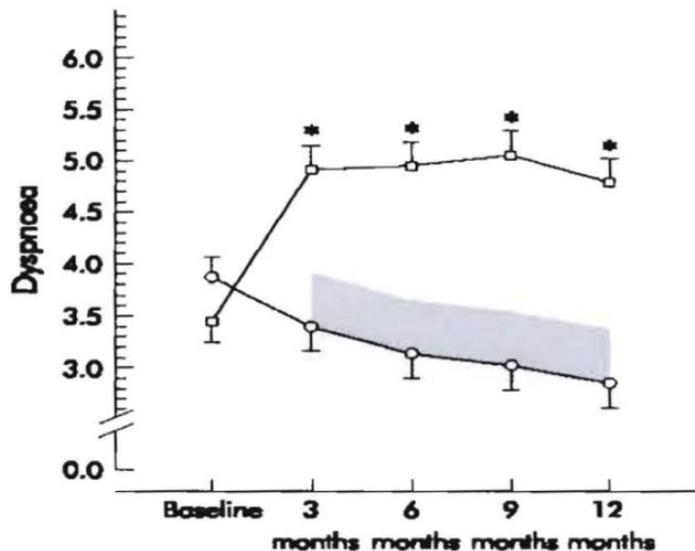

Endurance

NIH
TOOLBOX

Motor
Emotion
Sensation
Cognition

Clinically Important Differences

- *Is an intervention successful when…*
  - *Outcomes reveal statistical differences that are not clinically important?*

- **Linking efficacy outcomes to <u>meaningful change</u>**

Fig. 1 Dyspnea scores in emphysema patients receiving or not receiving lung volume reduction surgery, means and standard errors. Possible range of scores from 1 to 7, with higher numbers representing less dyspnea in daily life. The MID, represented by the shaded bar, is .5. The points showing higher values after baseline are those of surgical group; the difference between treatment and control is appreciably greater than the MID throughout the follow-up period. The * symbols represent p-values less than .05

*Needed –
Analysis of CIDs
for Diverse Outcome
Measures in PD*

Guyatt, Qual Lif Res. 2007

Do different modes of administration result in differences in response?
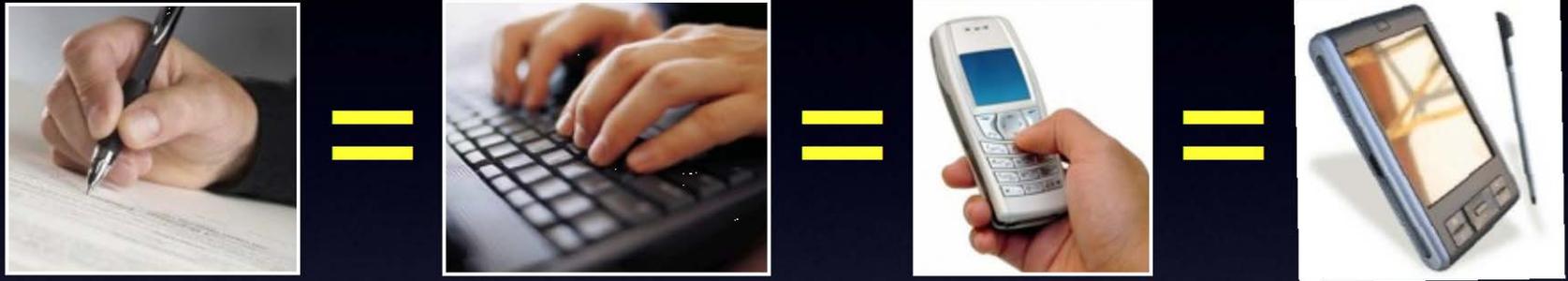
No meaningful differences found between modes of administration
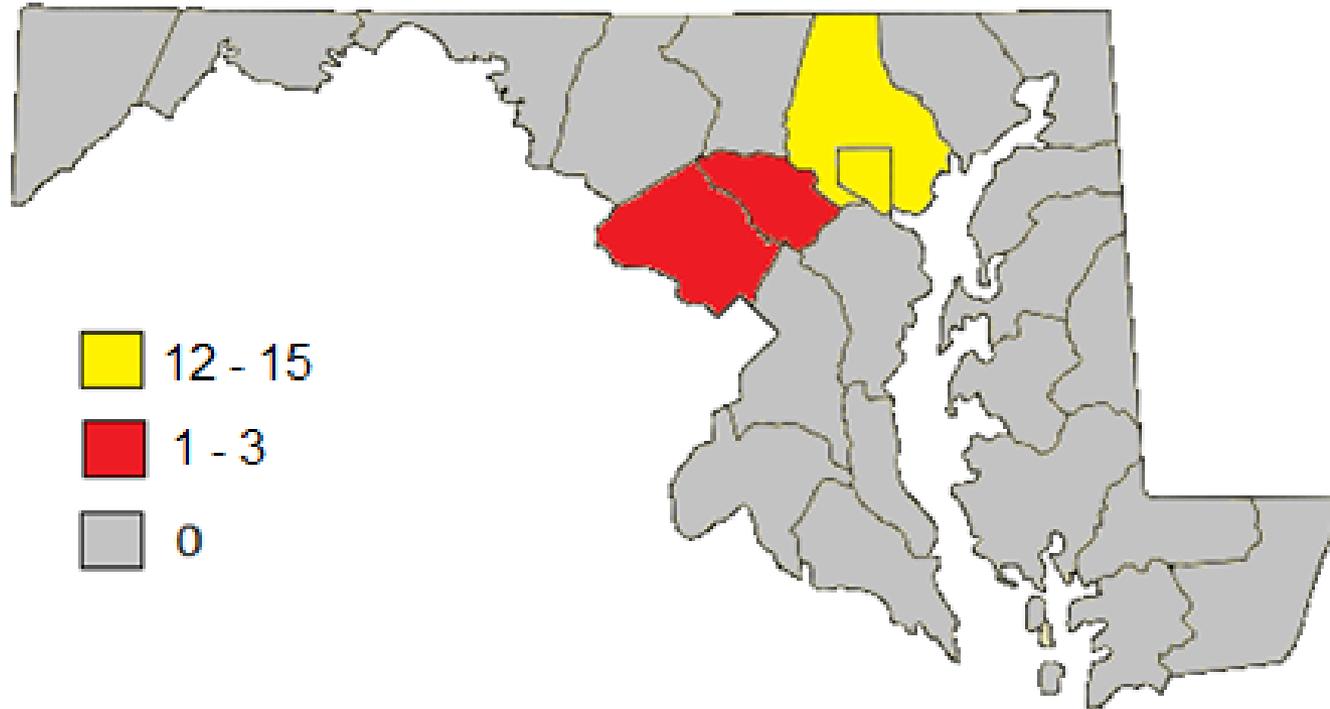
< 1.5 points on 100-point scale

EMRs & Outcome Measures

- **Integrating outcome measures into EMRs**

- **To promote-**
  - **Research**
  - **Quality of care**
  - **Regulatory mandates**

Access to specialty care and clinical trials is geographically restricted in the US

Distribution of Parkinson disease specialists in Maryland*

12 - 15
1 - 3
0

In Maryland, 20 of 23 counties do not have access to a Parkinson disease specialist

*excludes NIH/NINDS, FDA, neurosurgery, and the Washington D.C. area

Sources: Movement Disorders Society directory; wemove.org

Courtesy of E. Ray Dorsey, MD MBA

Potential benefits of remote assessments in clinical trials

|	
Reduce costs	• Decrease number of in-person visits • Save time on recruitment • Utilize centralized rater to reduce variability and therefore, sample size
Facilitate recruitment	• Reduce travel burden on participants and caregivers to encourage participation and retention • Increase geographic scope for recruitment • Expand participant pool additional populations (e.g., mobile populations, nursing homes)
Improve data collection	• Collect data and monitor safety in real-time • Decrease need for subjective diaries • Capture data directly into electronic databases

Courtesy of E. Ray Dorsey, MD MBA

Source: Neurology 2008;71:1883-8

Minority participation in clinical research has not lived up to expectations

- Diverse subjects are needed in trials to collect data with broad application
  - Evidence suggests disparities in prevalence and natural history of PD

- Minorities account for *one-third* of the American population, but **less than *one-tenth* of U.S. clinical trial participants**

- Pub Med search: 17% of PD trials over the past 20 yrs reported racial/ethnic participation
  - Only 8% of subjects were non-white

Schneider MG et al. Parkinsonism & Rel Disord 2009; NIMHD 2012.

Minority recruitment: Lessons and opportunities

- Initiatives to increase PD participant diversity-unsuccessful
  - NINDS LS-1: Ancillary trial to increase diversity stopped early for lack of efficacy
    - Hi enrollers of diverse subjects reported greater efforts to overcome barriers & community outreach
    - Low enrollers placed greater responsibility for low enrollment on prospective participants

- New approaches are needed
  - Better understanding of barriers to minority participation
  - Collaborations with NIH and NIMHD funded resources (e.g. Minority Involvement in Neurological Clinical Trials (NIMICT) Program
  - Novel approaches (e.g. community-based participatory research initiatives)

Tilley BC et al., Clinical Trials, 2012
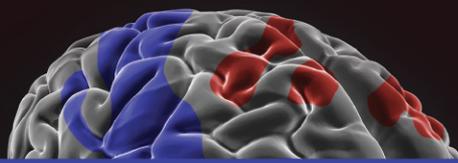
9. Investigate the use of innovative outcome measures to evaluate motor and non-motor features, including patient- and clinician-reported outcomes that leverage emerging IT opportunities, enhance sensitivity and specificity of measurement, and facilitate long-term follow-up of well-characterized cohorts.

11. Develop strategies to increase minority participation in research. These initiatives should include mechanisms to assess the effectiveness of these programs and could lead to the establishment of shared resources to facilitate minority recruitment in PD clinical trials.

Opportunities for understanding and addressing disease progression

Caroline M. Tanner, MD, PhD
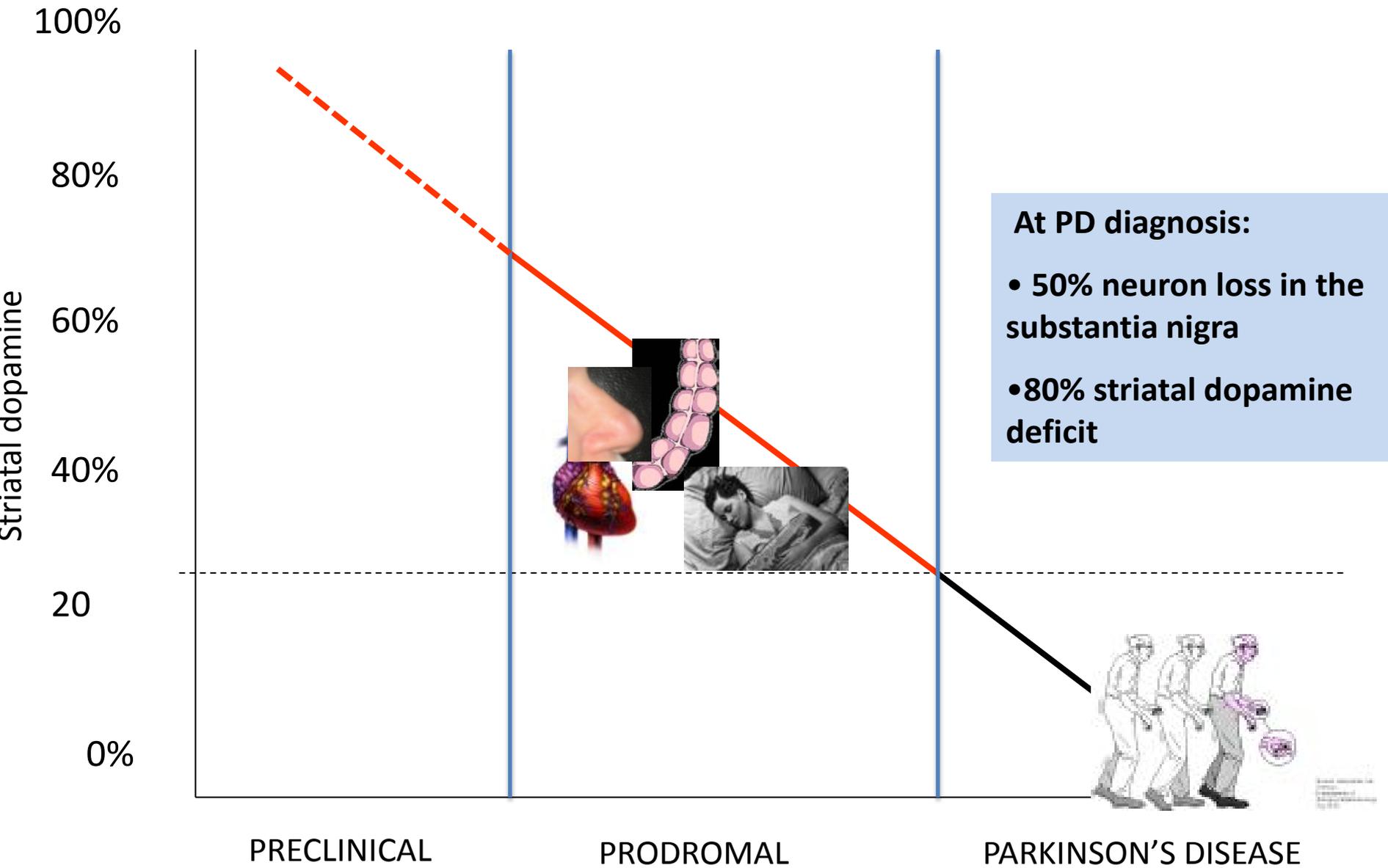
Parkinson's Institute & SFVAMC/UCSF

On Behalf of:

Randall Bateman, Christopher Coffey,

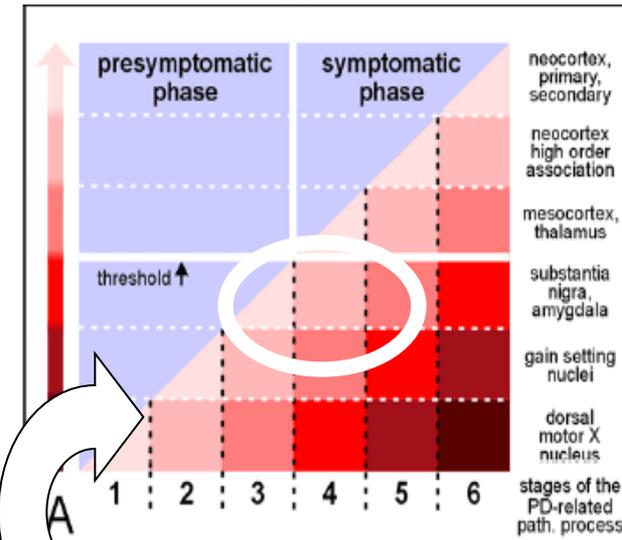Karen Marder, Werner Poewe,

Ira Shoulson, Matthew Stern

What do we know about disease progression and how to address it?

Background

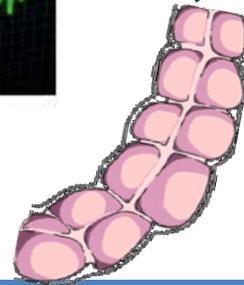# Neurodegeneration Begins Before Onset of Motor Signs

Hyposmia

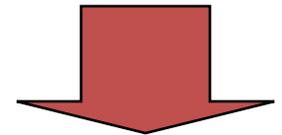**REM Sleep BD**

↓Heart Rate Variability

Constipation

Substantia nigra not first site of injury in PD

Lewy neurites found in olfactory bulb & autonomic nervous system

Prodromal features may identify an "at risk" population

A number of populations "At Risk" for PD have been proposed

- Persons with clinical features highly predictive of the onset of PD in the future: "prodromal" PD: e.g., RBD, hyposmia

- Persons with genetic susceptibility: primary & "risk" genotypes

- Persons exposed to certain toxicants, traumatic brain injury, other exposures

A number of populations "At Risk" for PD have been proposed

THE DILEMMA:

Predictive value very low for most "at risk" features

What is the ideal approach for preventing Parkinson's disease?

→ Identify persons "at risk" for PD *before motor symptoms manifest*: an efficient screening process is critical

→Intervene to prevent the development of motor features of PD: a safe treatment critical

Why Have Trials of Disease Modifying Therapies Been Inconclusive?

Was the intervention ineffective?
Was the intervention too late?

KEY QUESTIONS:
Can progression of PD be slowed or stopped?
Can the clinical features of PD be prevented?
Can prodromal PD be prevented?

What Do We Need to Know:
Critical Gaps in Understanding & Addressing Disease Progression

CLINICAL COURSE:

➢ **No diagnostic test**

➢ **No predictor of risk (for most)**

➢ **No reliable marker of progression**

➢ **No reliable predictor of prognosis**

TREATMENT:

➢ **No way to prevent disease**

➢ **No way to slow disease progression**

Needed: Biomarkers of Parkinson's Disease

Healthy people ⟶ Disease ⟶ Disease outcomes

Markers of risk

- Genes
- CSF
- Other Tissues?
- Imaging?
- Exposure group?

Prodromal

- Olfaction
- ANS
- RBD
- Imaging?
- CSF?
- Other Tissues?

Diagnosis

- Clinical
- Post-mortem
- Imaging (adjunct)
- CSF?
- Other Tissues?

Progression

- Clinical exam
- CSF ?
- Other Tissues?
- Imaging?

How will we find out?

Study existing populations & resources - examples

Prospective Cohorts w/ Clinical & Biological Data:

Honolulu Asia Aging Study *(+ autopsy, risk factors)*

Arizona PD Consortium *(+ autopsy)*

Parkinson's At Risk Study (PARS)

Parkinson's Progressive Markers Initiative (PPMI)

NINDS PD Biomarkers Program (PDBP)

Genetic Cohorts

Prospective Clinical Trials Populations w/ Clinical & Biological Data: DATATOP, LABS-PD

Health Care System Utilization-Derived Cohorts:

Kaiser Permanente, VAMC, (theoretically: CMS)

Biospecimen Repository: NINDS Repository – NINDS PDBP and MJFF BioFind

Initiate New Studies

- – Establish data and tissue repositories
- – Determine risk and prognostic markers (clinical and biological)
- – Develop efficient screening for at risk populations
- – Proof of concept prevention trials in high risk populations
- – Collaboration with basic scientists critical for discovery & validation of biomarkers, identification of disease mechanisms & therapeutic targets
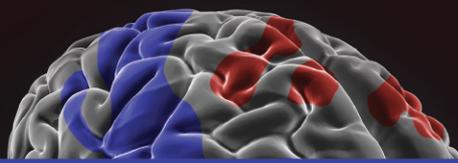
1. Conduct proof-of-concept prevention trials, initially targeting high risk and/or prodromal populations, including biomarker assessment. Observations will be available as a data and tissue resource for future clinical and laboratory investigations.

2. Conduct studies to define the natural history of prodromal PD (clinical, imaging, biomarkers, pathology including post-mortem), to characterize progression and phenoconversion, to identify the determinants of clinical subtypes, to establish a data and tissue resource for future clinical and laboratory investigation, and develop cost-effective methods for health screening to identify persons with prodromal PD.

3. Devise and implement longitudinal observational studies, biomarker investigations, randomized clinical trials, and data and bio-specimen sharing resources aimed at characterizing the progressive course of clinically manifest illness, establishing markers of disease, and identifying safe and effective treatments that postpone or ameliorate the intractable disabilities of PD.

8. Determine factors that could facilitate public health interventions, including risk factor reduction and health services interventions (population-wide and/or individual).

Symptomatic treatment

- Conduct studies to improve understanding and treatment of:
  - non-motor features (4)
  - levodopa-resistant motor symptoms (6)
  - motor fluctuations and dyskinesias (12)

Outcome Measures

- Apply cutting edge approaches to outcomes assessment in clinical trials (9)
- Increase participation of underserved groups in PD research (11)

Trial Design

- Develop biomarkers for early-stage clinical trials (5)
- Improve methods for identifying long-term efficacy in clinical trials (7)
- Use informatics to improve understanding of PD biology and improve trials (10)

Disease Progression

- Conduct proof-of-concept prevention trials (1)
- Understand features and biology of prodromal PD (2)
- Study strategies to prevent long-term disability in established disease (3)
- Understand risk factors for PD (8)

1. Conduct proof-of-concept prevention trials
2. Understand features and biology of prodromal PD
3. Study strategies to prevent long-term disability in established disease
4. Conduct studies to improve understanding and treatment of non-motor features
5. Develop biomarkers for early-stage clinical trials
6. Conduct studies to improve understanding and treatment of levodopa-resistant motor symptoms
7. Improve methods for identifying long-term efficacy in clinical trials
8. Understand risk factors for PD
9. Apply cutting edge approaches to outcomes assessment in clinical trials
10. Use informatics to improve understanding of PD biology and improve trials
11. Increase participation of underserved groups in PD research
12. Conduct studies to improve understanding and treatment of motor fluctuations and dyskinesias