PPMI Recruitment and Retention Update

Genetic Kick-off Meeting

September 17 , 2013

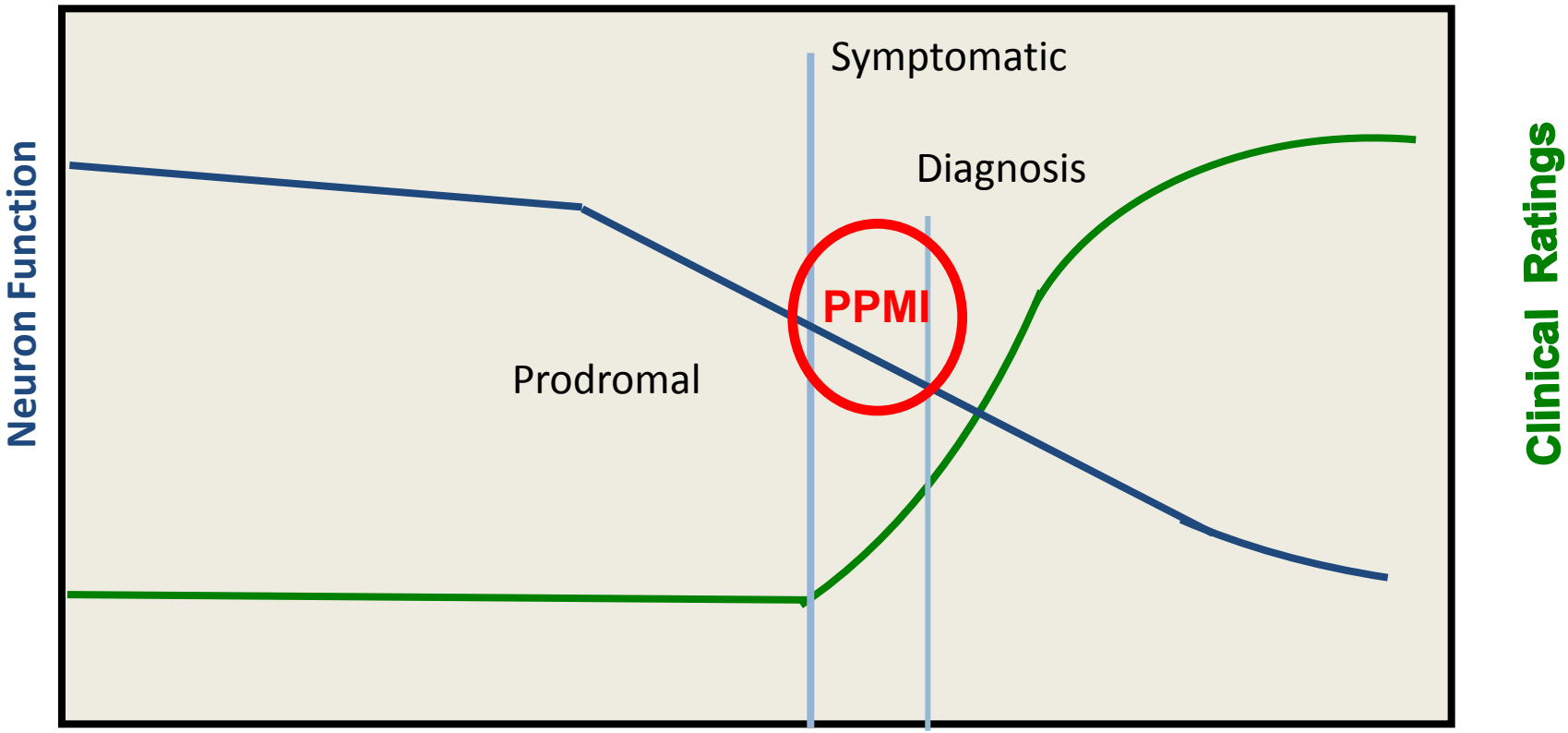
PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

PPMI: Original Cohort

- Enrollment July 2010 - June 2013:
  683 subjects (423 PD; 196 HC; 64 SW)
- Retention - 20 subjects withdrew (10 PD; 8 HC; SW 2)
- Incorporation of Prodromal PD cohort began Jan 2013 and is ongoing

Natural History of Parkinson disease



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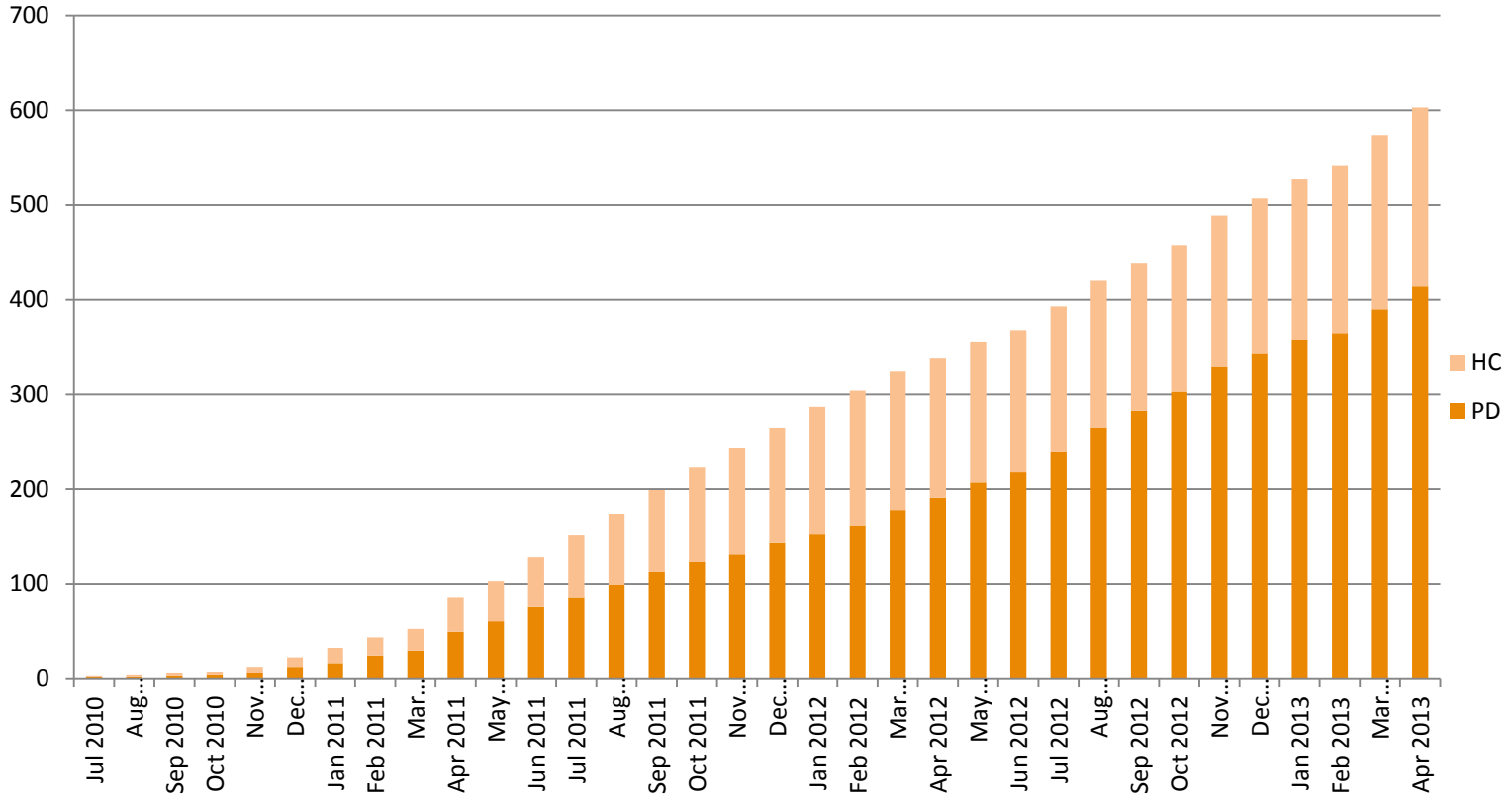
Play a Part in Parkinson's Research

Recruitment completed June 2013



- 423 PD
- 196 Controls
- 64 SWEDDs

PARKINSON'S PROGRESSION MARKERS INITIATIVE

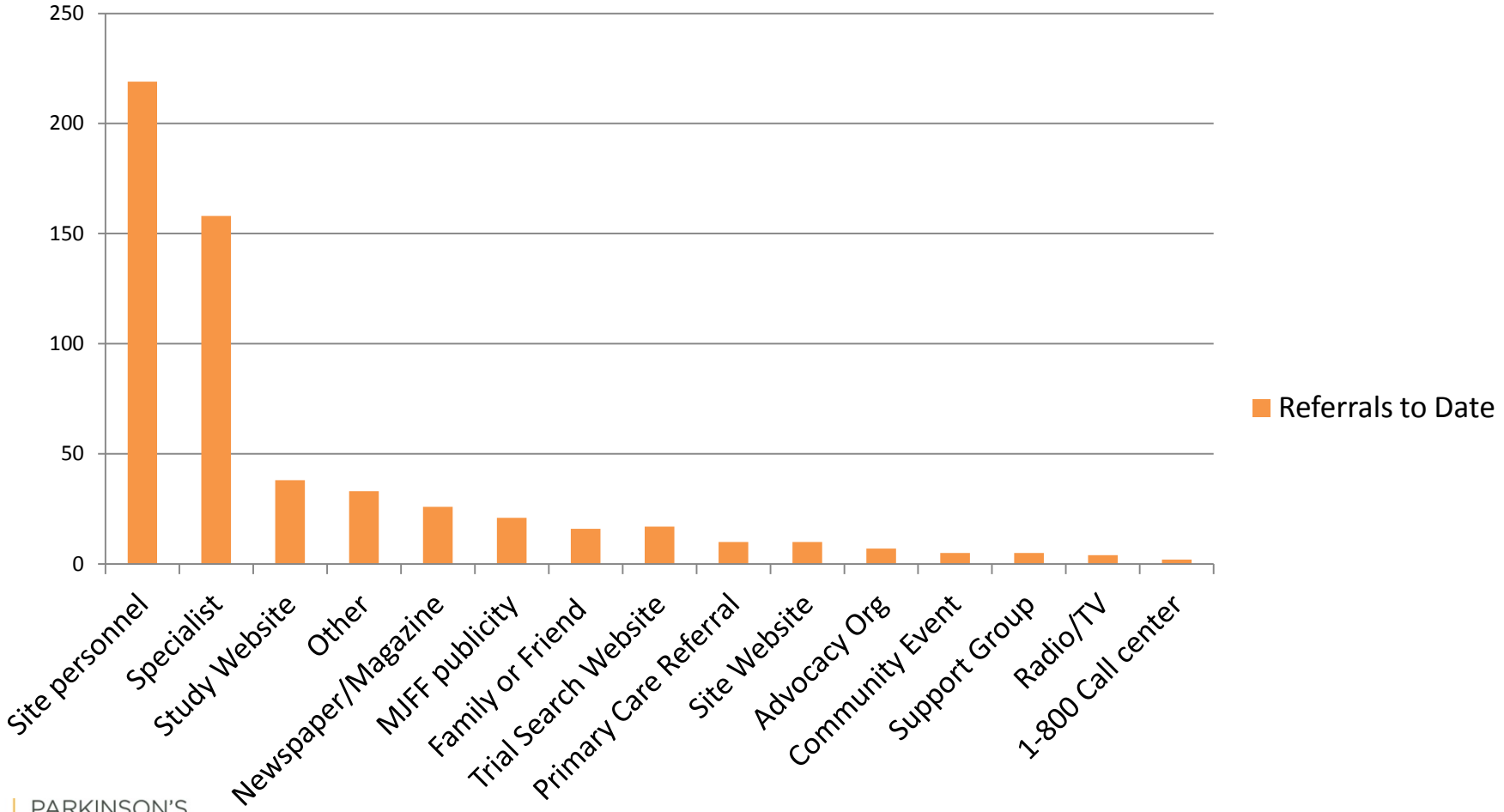
Play a Part in Parkinson's Research

Recruitment Strategies and Activities

- Site Efforts
  - Recruitment from clinic practices; consistent outreach and reminders to clinical colleagues and physicians who are affiliated with site, as well as cultivation of colleagues in the community who refer
  - Community outreach (support groups, symposia, physician networks, etc)
  - Partnerships with imaging centers to recruit non-site-referred DaT patients

- MJFF strategies
  - Study launch events to introduce study to community and seek controls
  - Physician salons to cultivate MD relationships (Sites are primary drivers of continuing to foster these relationships)
  - Outreach through MJFF communications– newsletters, social media, events, etc.
  - Many media stories on the study in local markets and nationally
  - Veterans mailing to get male controls over 55 resulted in additional HC enrollments

Recruitment Sources for Consented PD and SWEDD Participants



PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Retention Activities

- Annual retention events at 21 sites over the last three years
- Subject newsletter twice a year with study updates
- Retention call series reviewing a key topic or a new PPMI publication (first call next week!)
- Site relationship with subjects and accommodating needs of subjects

Retention/Visit Compliance

	Baseline 0 months Expected (% seen)	Visit 2 6 months Expected (% seen)	Visit 4 12 months Expected (% seen)	Visit 6 24 months Expected (% seen)
GROUPS:				
PD Subjects	423 (100%)	357 (91%)	256 (87%)	89 (87%)
Healthy Controls	196 (100%)	166 (95%)	149 (97%)	70 (83%)
SWEDD Subjects	64 (100%)	55 (80%)	38 (95%)	7 (57%)

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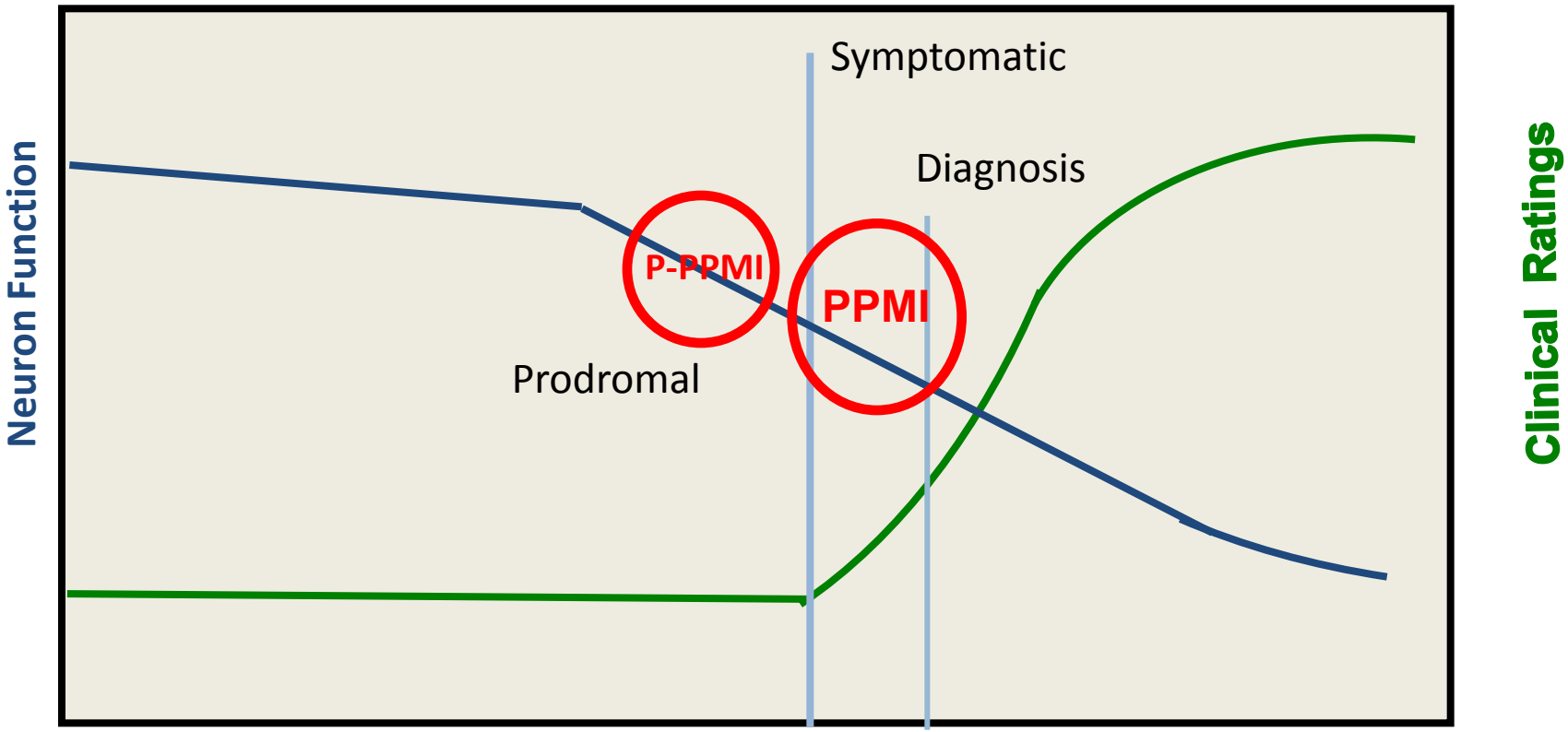
CSF Acquisition and Retention

Group	Baseline	Month 6	Month 12	Month 24
PD Subjects	423 (98%)	357 (82%)	256 (78%)	89 (74%)
Healthy Controls	196 (97%)	166 (82%)	149 (81%)	70 (67%)
SWEDD Subjects	64 (92%)	55 (67%)	38 (79%)	7 (57%)

- LP well tolerated – HA – 4-7%
- CSF Volume collected 15.25 (mean)
- Sprotte needle used in 82%
- Syringe suction 63%
- Sitting position in 63%
- Flouroscopy in 5%

Natural History of Parkinson disease



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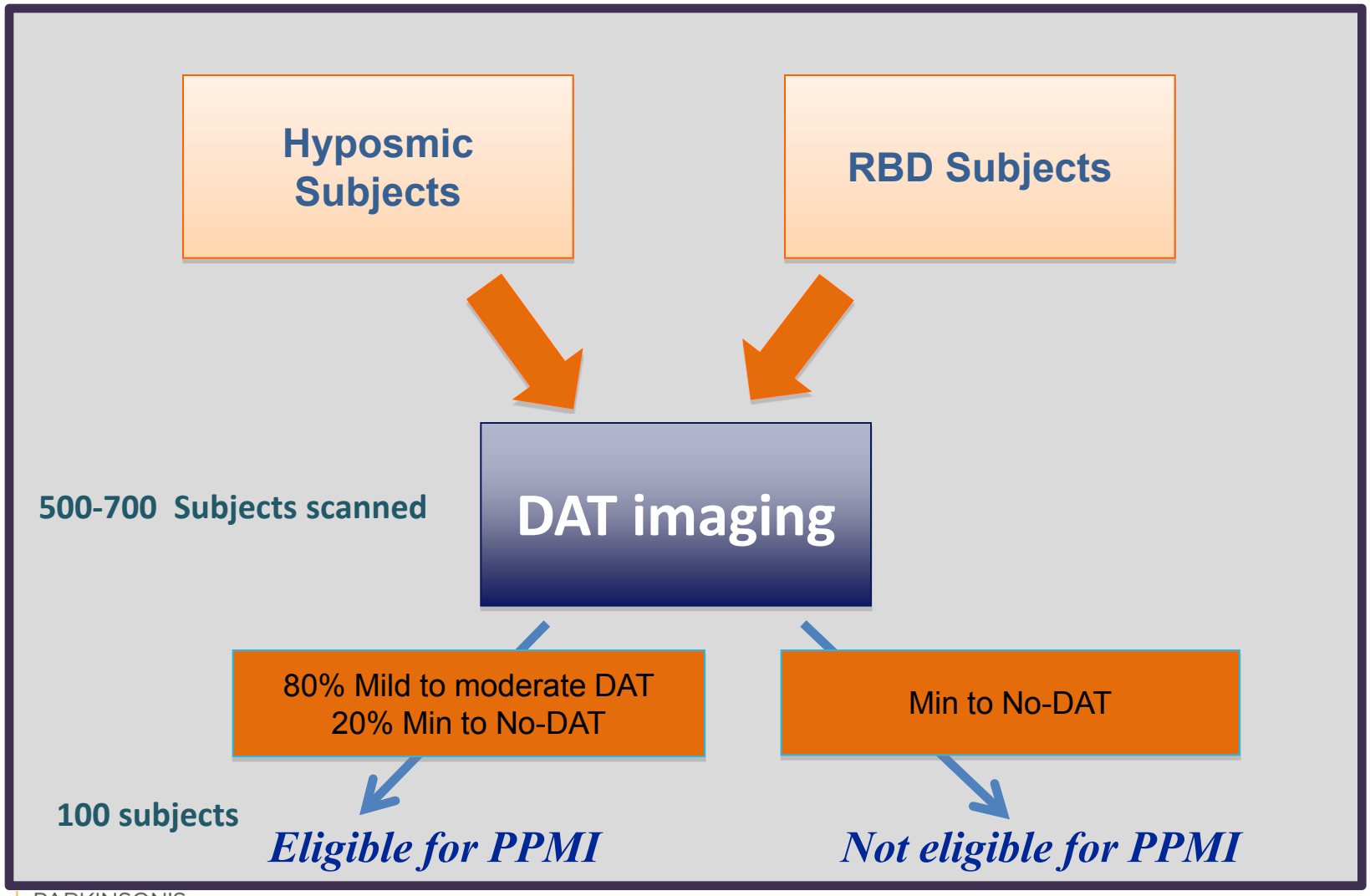
Prodromal Cohort for PPMI



Prodromal Recruitment Sources: Hyposmia

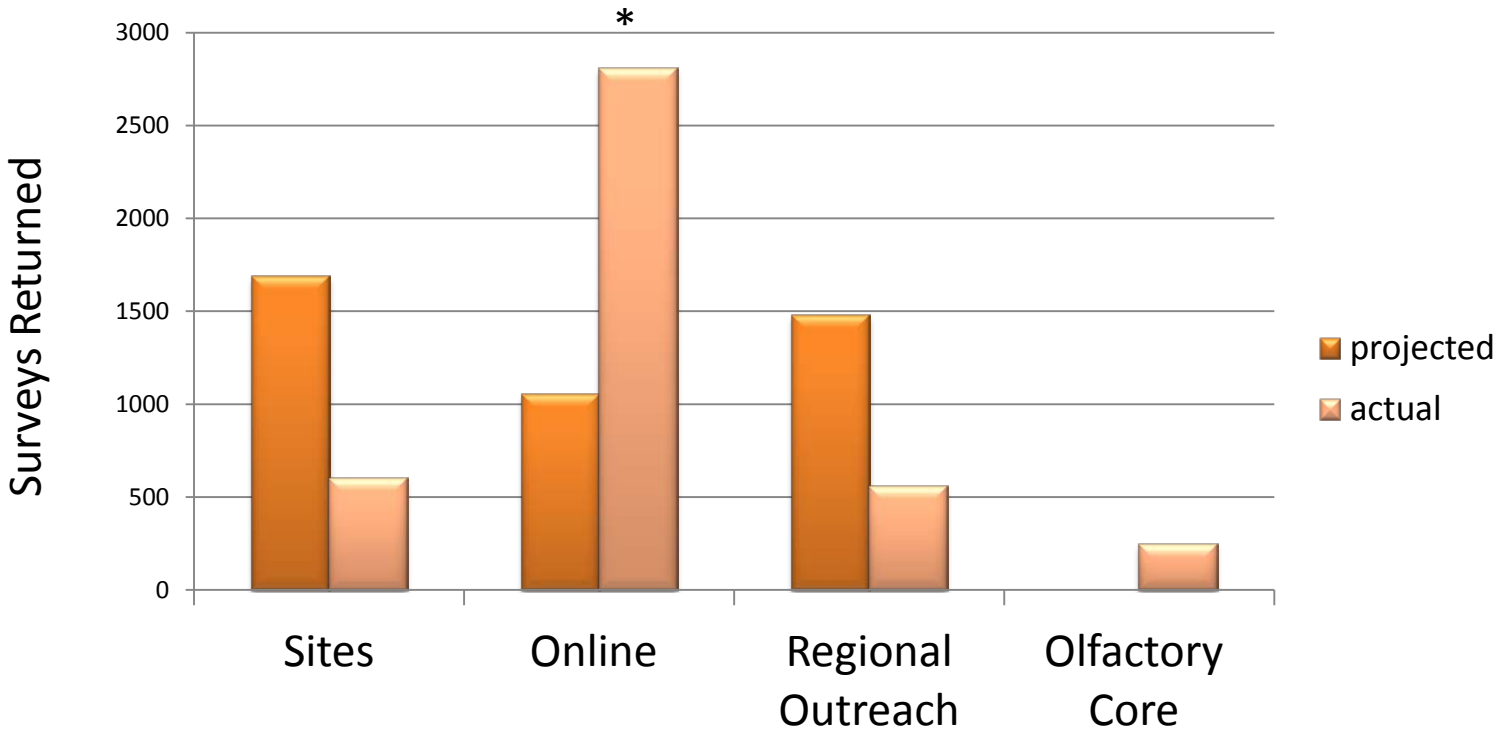
- Centralized outreach:
  - FTF contacts
  - mailings (veteran's, homeowners?)
  - email blasts
  - web ads
  - registry mailings
- Local outreach
  - Clinic providing surveys directly to PD and family members
  - Local media opportunities arranged by MJFF
- Olfactory infographic recently developed
  - wide local and centralized underway

Smell & Your Brain Infographic

Outreach approaches:

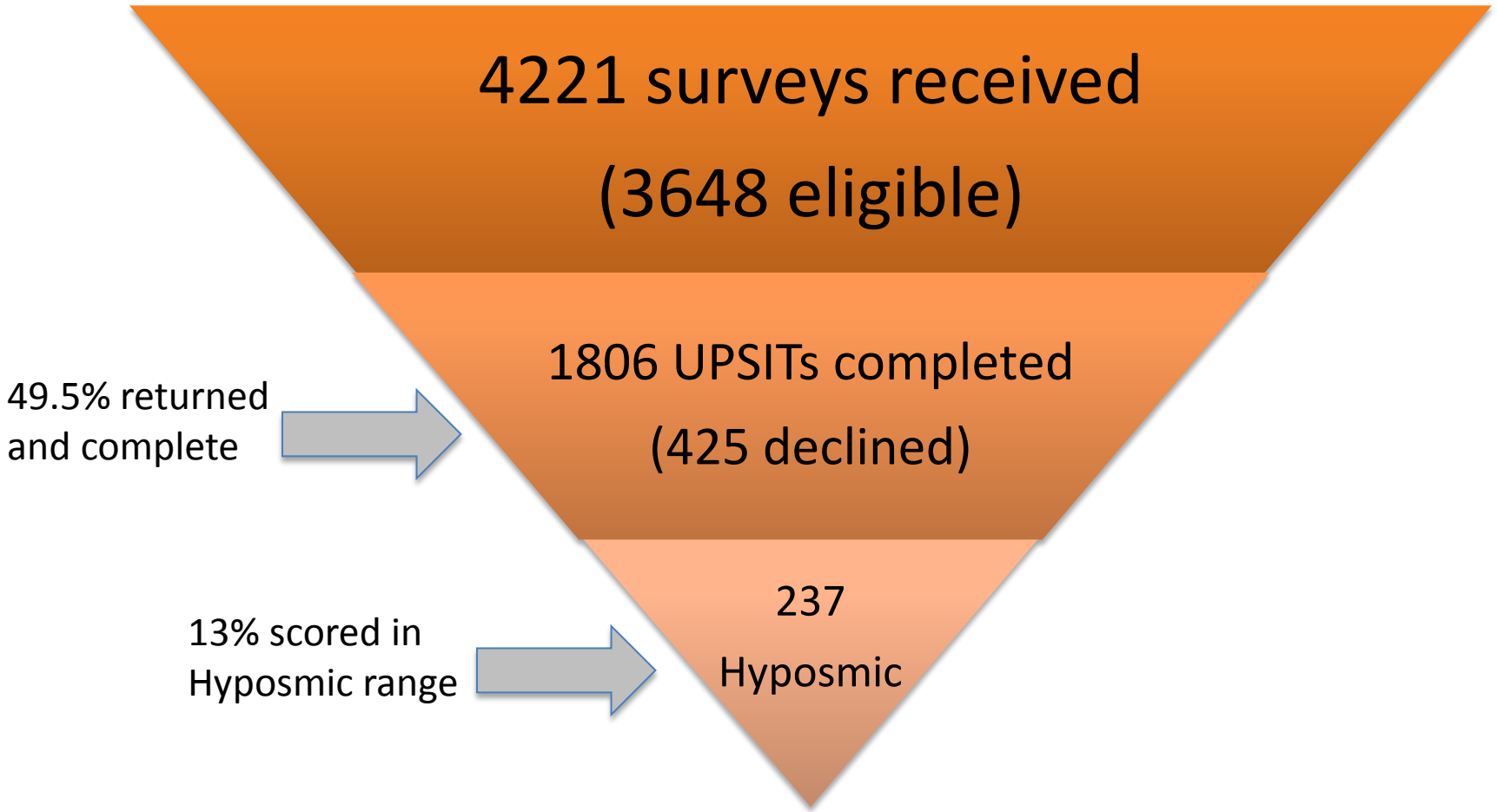
- Currently pitching *WebMD* first exclusive use of infographic
- Infographic distribution service will disseminate to local and national news outlets nationwide
- Use in national and local media pitching (ongoing coordinated efforts at active PPMI prodromal sites)

Prodromal Recruitment Sources: Hyposmia



***Approximately 140 listed a specific site as their primary source for learning about the study**

Prodromal Recruitment: Identifying Hyposmics



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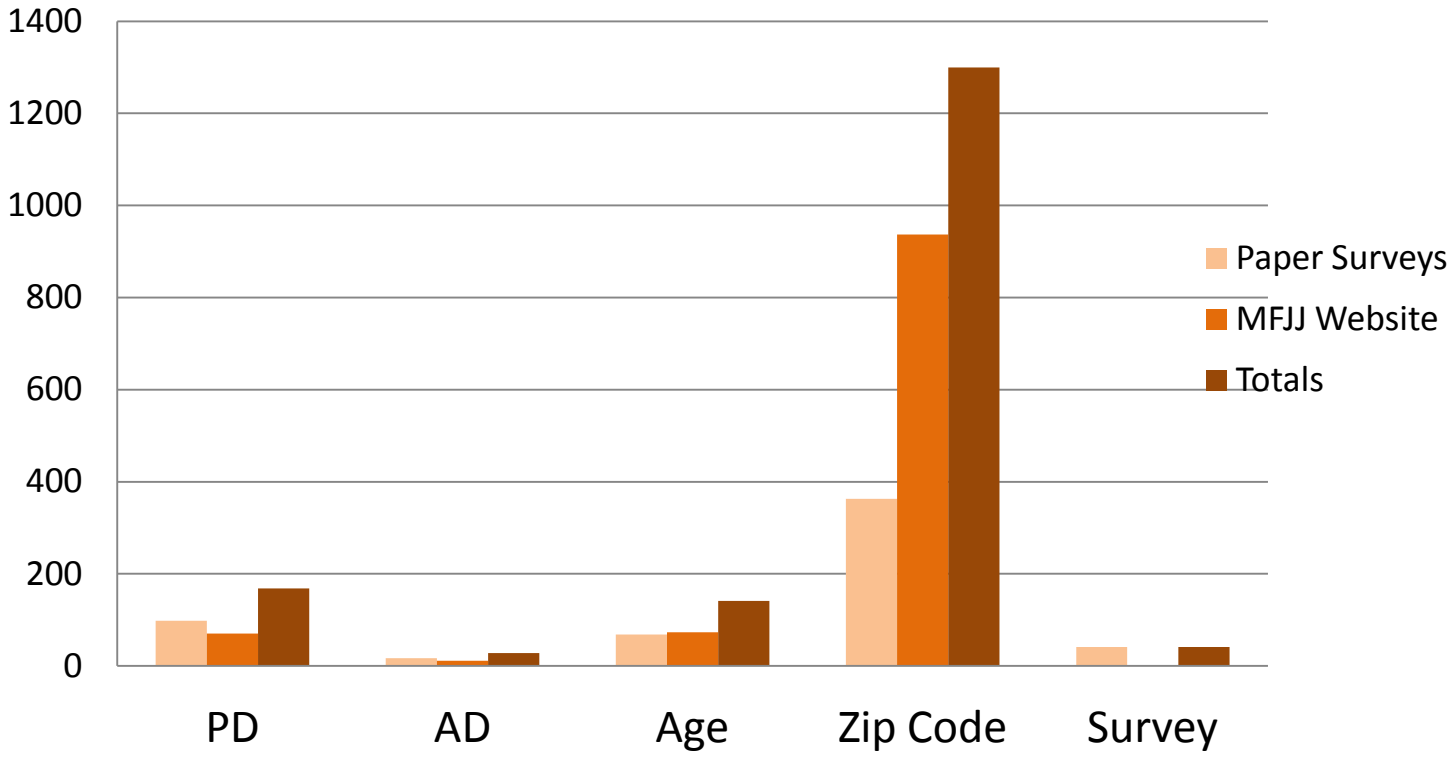
Hyposmic Recruitment: Ineligible Surveys



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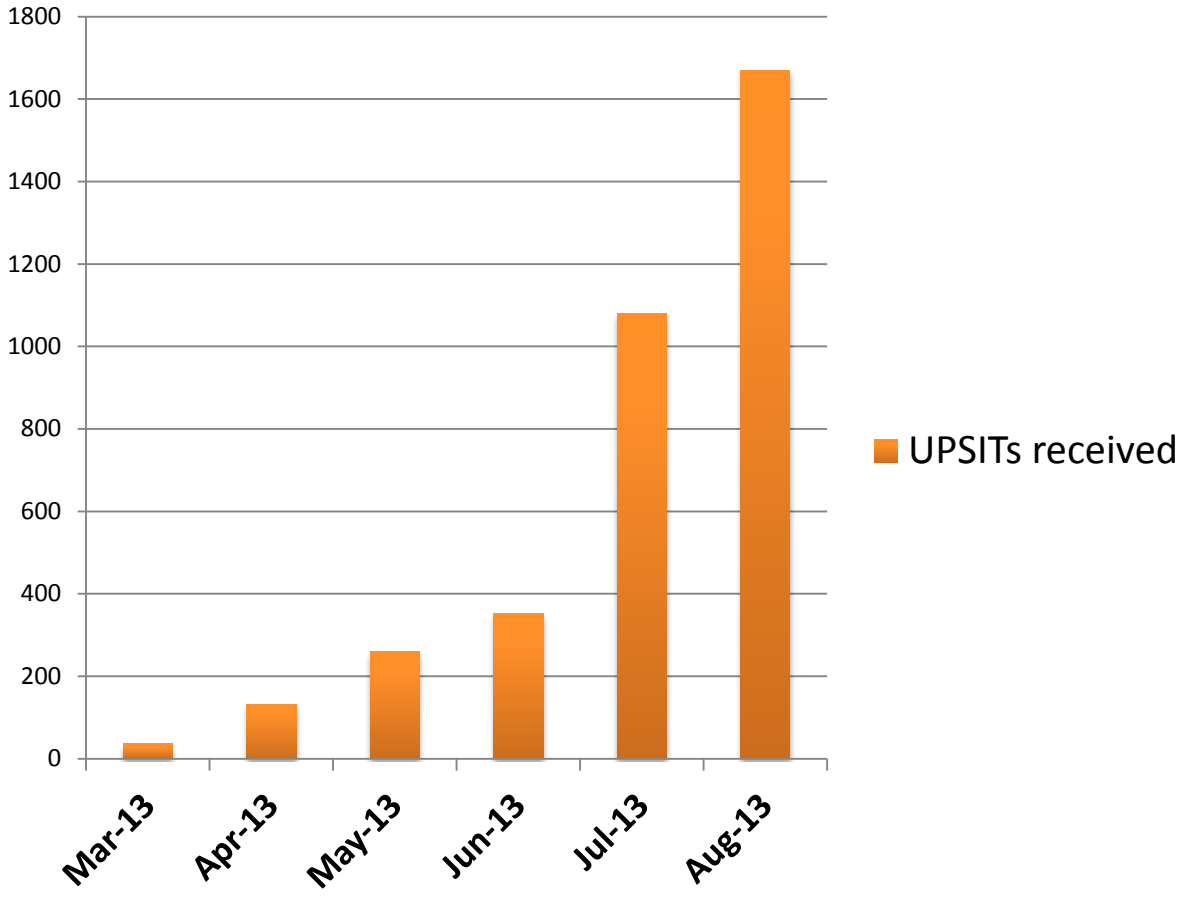
Hyposmic Recruitment: UPSITs Returned



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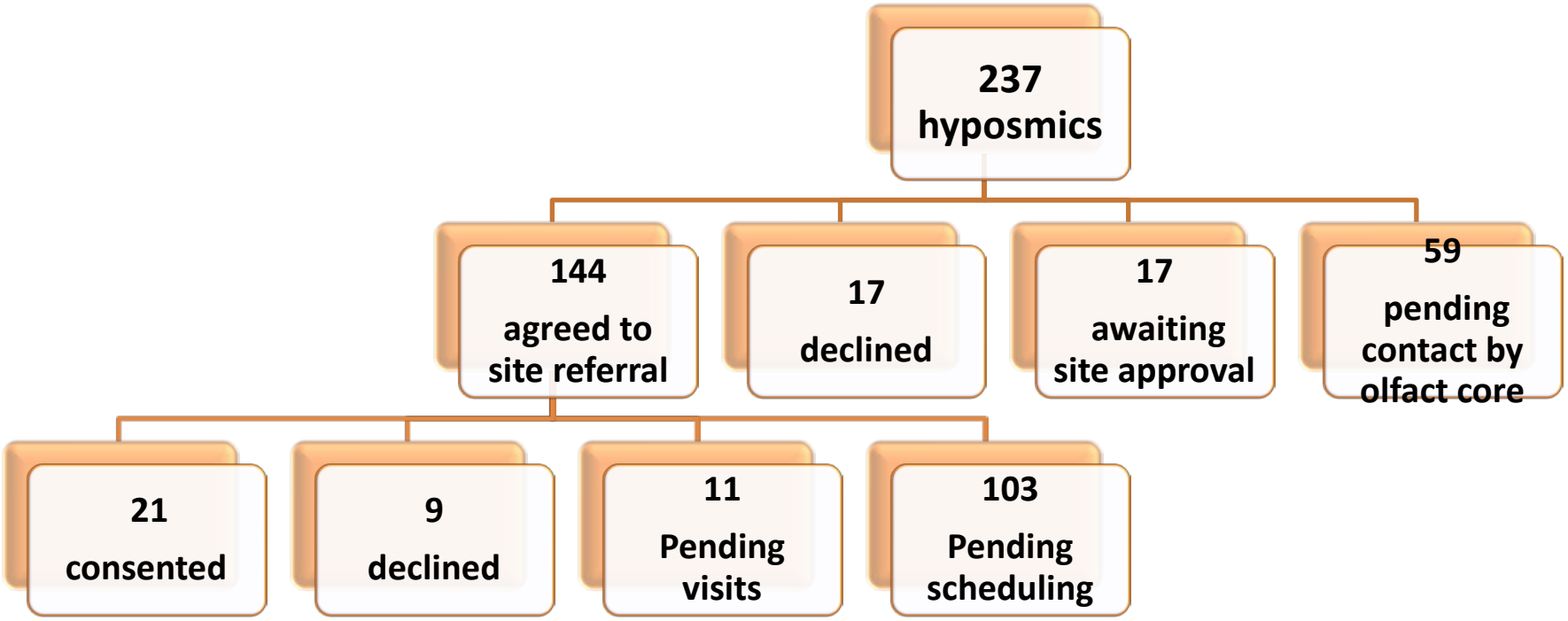
Prodromal Recruitment: Hyposmia



15 completed DAT imaging = 2 eligible

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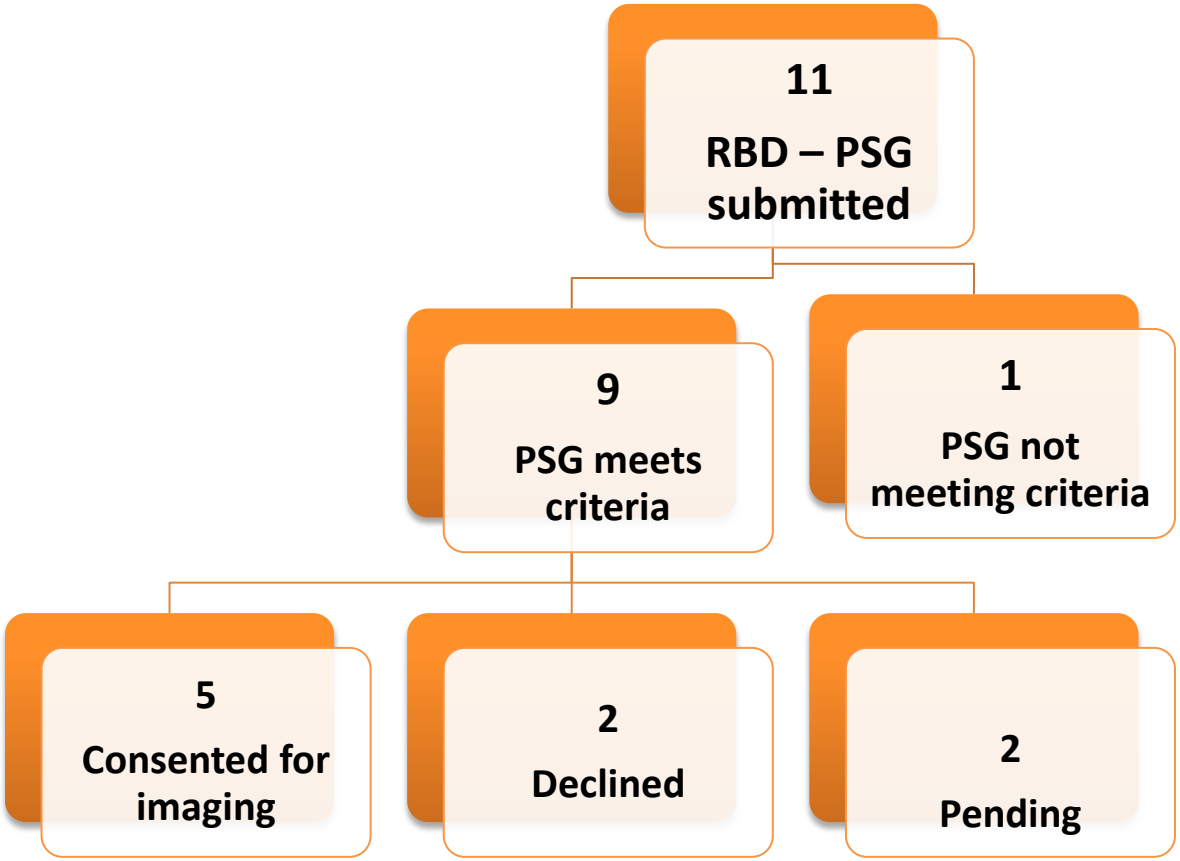
Prodromal Recruitment: RBD



4 completed DAT imaging = 2 eligible

Prodromal Recruitment Adding Genetic Sites

- For newly added Genetic sites:
  - See me and/or Shirley Lasch if you are interested in being involved in olfactory recruitment

PPMI Recruitment Strategies: Genetic Cohort & Registry

Genetic Kick-off Meeting

September 17 , 2013

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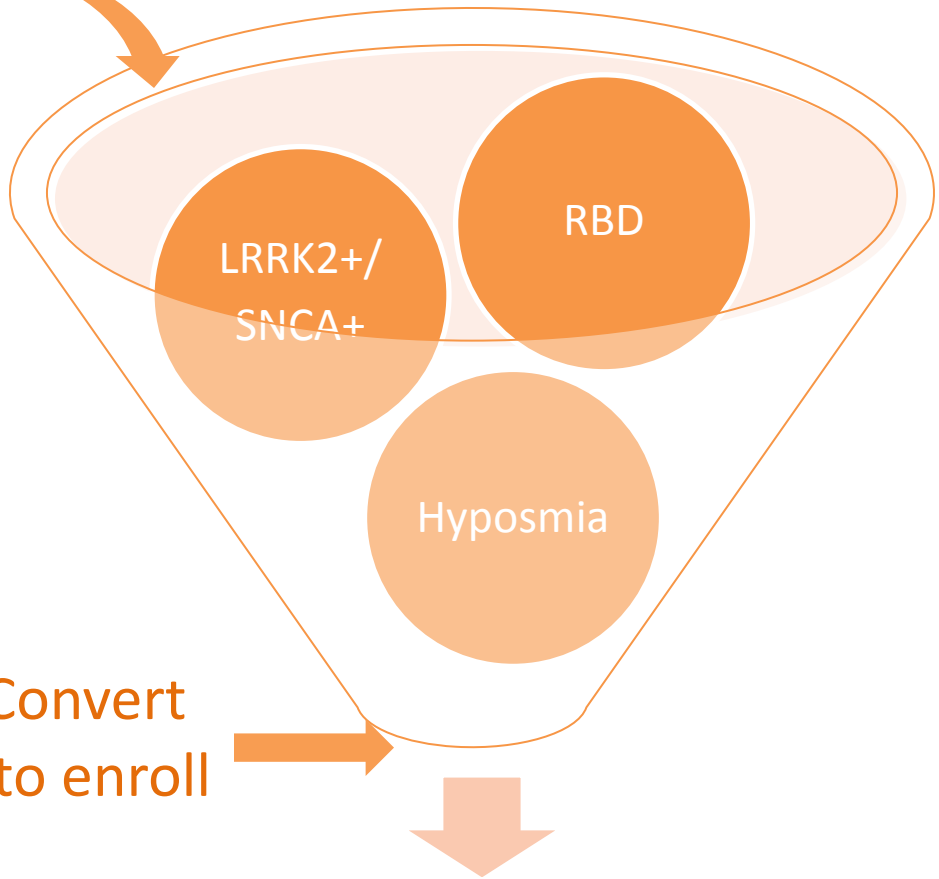
Play a Part in Parkinson's Research

Prodromal PPMI: Genetic At-risk Cohort

- Ultimate goal of PPMI is to follow individuals who are unaffected but will develop PD

Prodromal Cohort: Hyposmia and RBD
Genetic Cohort: LRRK2+/SNCA+

Objective #1: Fill the funnel



Objective #2: Convert qualified leads to enroll

Goal: Enroll subjects with potential to phenoconvert to PD

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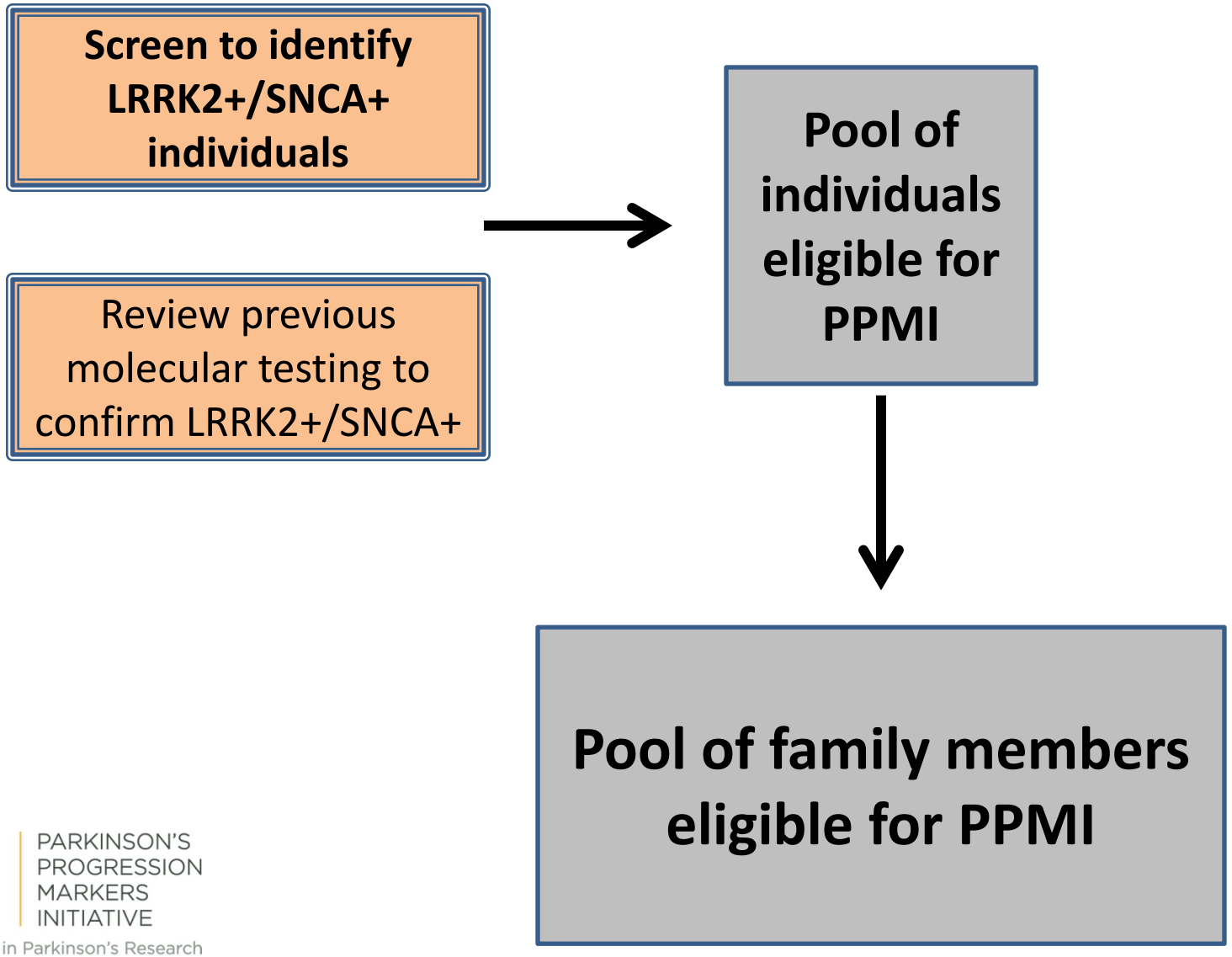
Recruitment and the GCC



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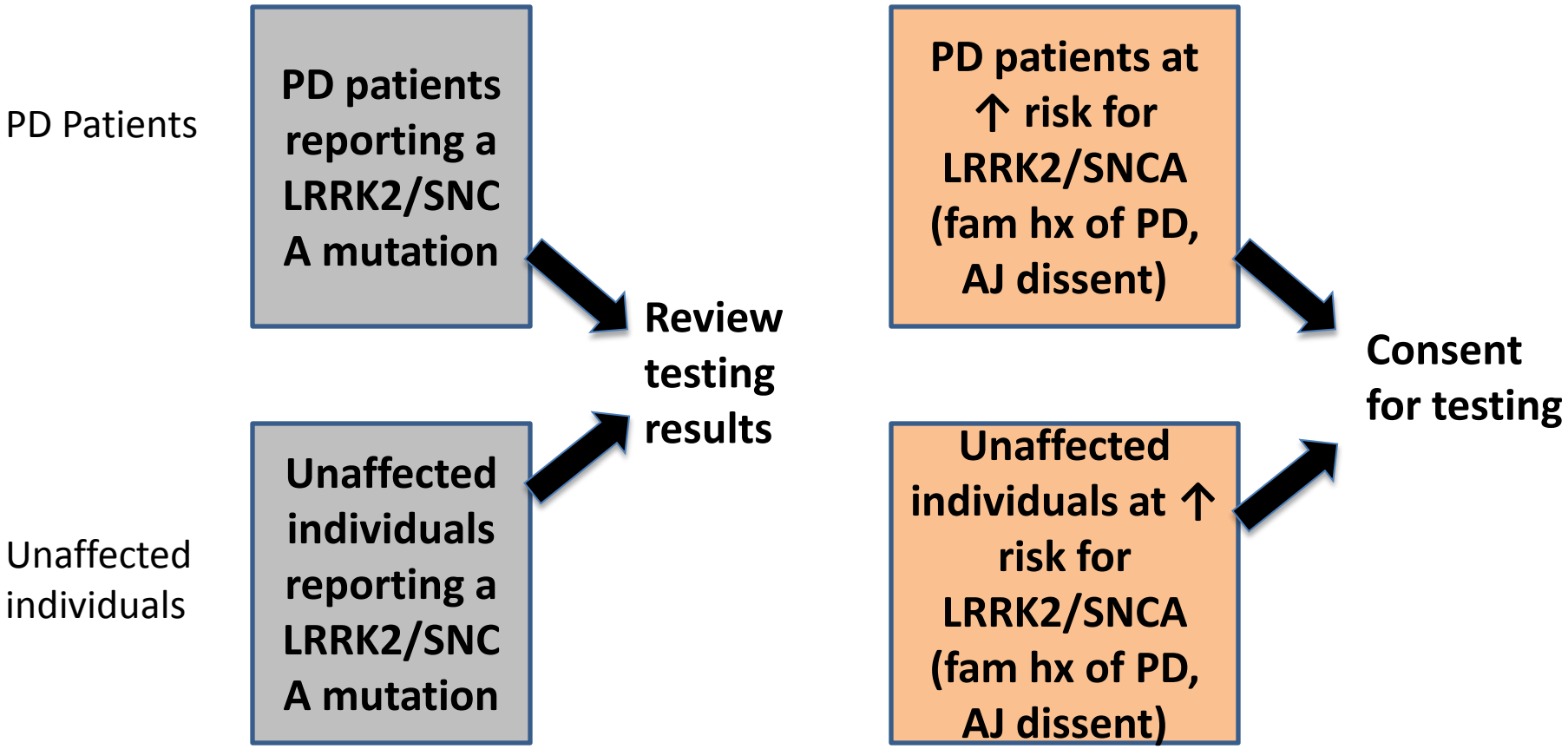
Identifying individuals for the genetic cohort



Local site outreach to LRRK2+/SNCA+ individuals

Clinical Sites

- Identify LRRK2+ and SNCA+ PD and unaffected individuals within clinic population
- Hold a seminar to discuss and invite LRRK2+/SNCA+ individuals and their family members to participate in the study
- Set an appointment with LRRK2+/SNCA+ individuals to review family history in detail
- Provide brochures for LRRK2+/SNCA+ to provide to family members

Key site activity

Medical Community Outreach

- In regions in which testing occurs broadly among physicians (eg France), host a meeting with local MDs to discuss the study and encourage referral
- For individuals that have provided samples, but do not know their gene status, offer them the opportunity to learn their status through participation in this study
  - Provide feedback to referring MDs regarding ultimate enrollment of their patient and status in the study

Review genetic testing results and provide to Genetics core for approval

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Local site outreach to genetic at-risk populations

Local Community Outreach

- Connect with key individuals in Jewish communities to:
  - Arrange for local seminar/educational sessions re LRRK2+
  - Place study flyers/brochures in synagogues and Jewish community centers
  - Newsletter stories/information about LRRK2+/SNCA+ PD connection and study participation

Key site activity

Clinic Outreach

- Reach out to other neurologists and movement disorder specialists in your area to engage them in identifying individuals in their practice at risk based on family hx of PD and family background
- Provide info about PD genetic risk factors and study in institution newsletter/websites

Complete genetic testing and counseling for those willing

Centralized Outreach via MJFF and FTF to Individuals with Genetic Risk

MJFF Outreach and Communications

- Key talking point in all constituents presentations and events
- Newsletter (e-newsletter and paper)
- Social Media
- Online Ads
- MJFF Website
- National and local media

Fox Trial Finder

- Messages to individuals with LRRK2+/SNCA+ individuals to share trial opportunity with family members

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Genetic Cohort Recruitment Materials

- Brochure for PD/At-risk LRRK2+ individuals to distribute to family members
- Brochure to provide to individuals of Ashkenazi Jewish dissent with PD relative regarding LRRK2 screening
- MD pocket cards to distribute to community physicians as a reminder regarding the study and basic criteria

- Language for newsletter articles/blurbs to be provided to
  - local synagogues and Jewish Community Centers
  - local center/institutional newsletters

- PPMI Study Update Newsletter Articles
  - Short and long newsletter stories that can be shared with local PD groups and included in your own center publications about the progress of the study

Genetic At-risk Recruitment Additional Key Points

- Think broadly regarding screening procedures – this will likely be site specific
- Engage individuals in at-risk populations to serve as ambassadors
- There will be additional funding available for travel for LRRK2+ and SNCA+ subjects – if travel is the issue, please ask
  - Subjects in PPMI have been willing to travel longer distances to participate than we projected
- Once a LRRK2+/SNCA+ individual is identified, be diligent about getting detailed family history…even if they do not ultimately participate, other family members may

Breaking Apart the Process

Identifying Related Individuals

Recruiting Across the Age and Disease Spectrum

- PD patients at any stage of disease to identify those with a LRRK2/SNCA mutation
  - Some can complete a more extensive protocol (Genetic Cohort)
  - Some cannot due to disease progression (Genetic Registry)
- Recruit family members of the LRRK2+/SNCA+ proband
  - Some family members may carry the mutation
  - Some family members will not carry the mutation
- Mutation carrier
  - Some too young to be expected to develop disease soon
  - Some at a critical age and more extensive protocol desired

PPMI – Amendment 6 enrolls across the spectrum

Identifying Related Individuals in PPMI

- We want family members to participate in PPMI
  - Need a way to identify people as being from the same family
  - Family members may go to different sites
  - Family members may not mention that they have another family member in the study

Importance of Relatedness

- Many kinds of analyses will be performed using data from PPMI
  - Some analyses require (assume) subjects are independent (unrelated)
  - GCC can provide information to indicate how PPMI subjects are related
  - DNA studies later will confirm the reported relationships (and identify more)

Family History

- IU will have IRB approval to obtain family history information (with names) from study subjects
  - Subjects will be given a family history packet at their first PPMI study visit
  - Each packet is labeled with a packet ID
  - Subjects will complete the questionnaire and return all documents, including IU IC, directly to GCC

Family History Packet

Site gives subject Family History Packet

Site completes Family History Packet Distribution Fax and faxes to GCC

Subject takes home:

- **IU Family History Substudy IC**
- **IU Family History Substudy HIPAA**
- **IU Family History Questionnaire**

Family History Packet

Subject takes home and completes, Mails to GCC

Contact ID # ☐☐☐☐ Site # ☐☐☐ Family # ☐☐☐☐☐

PPMI Family History Substudy
FAMILY HISTORY QUESTIONNAIRE (FHQ)

IRB #

Indiana University Informed Consent Statement for Parkinson's Progression Marker Initiative (PPMI) – Family History Substudy

INTRODUCTION

You are being asked to participate in the Family History substudy of the "Parkinson's Progression Markers Initiative" (PPMI). Please read this form carefully. Ask the person presenting this form any questions that you have before making a decision about whether or not you will participate.

Site completes and faxes to GCC

PPMI Family History Packet Distribution Fax

This form is used to track this packet and to help link family members together.

Please record below the **PPMI Subject ID, Sex and Year of Birth**.
Record the date the packet was given to the subject.
Fax the completed form to: **Fax#: 1-317-274-5734**

To:
Cheryl A. Halter, MS, CCRC
Indiana University
Hereditary Genomics
Phone: 1-317-274-5734
FAX: 1-317-278-4507
E-mail: chalter@iu.edu

From: Site#: ☐☐☐
Contact Name: _____
Contact Phone: _____
Contact Fax: _____
Contact Email: _____

Date Packet Given to Subject: ___/___/___ (Month / Day / Year)

PPMI Subject ID: ☐☐☐☐ PPMI Packet ID: **Pre-assigned**

Male ☐ Female ☐ Year of Birth: ☐☐☐☐

Comments:

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Linking Subject to Packet

- Site records on the Family Packet Distribution fax the PPMI Subject ID of the subject receiving this packet
- Site faxes the Family Packet Distribution fax to GCC
- **Now, PPMI Subject ID is linked to the Family History Packet ID**

Linking Family Members

- Subject sends the completed Family History Questionnaire, IU IC and HIPAA directly to GCC
- GCC will recognize related individuals through common family members
- All related individuals will receive the same family number, providing a link between them

Relatives in PPMI

PPMI2

1	5	4

GENETIC MUTATION TESTING FORM

0	1

SUBJECT ID | | | | | |

VISIT NO | G | M | U |

INITIALS | | | | SITE NO | | | | VISIT DATE | | | (MM) | | (DD) | | | | | (YYYY)

5. Does the subject have a first degree relative (father, mother, sibling, child) who is also participating in the study? (0 = No, 1 = Yes) 5. | |

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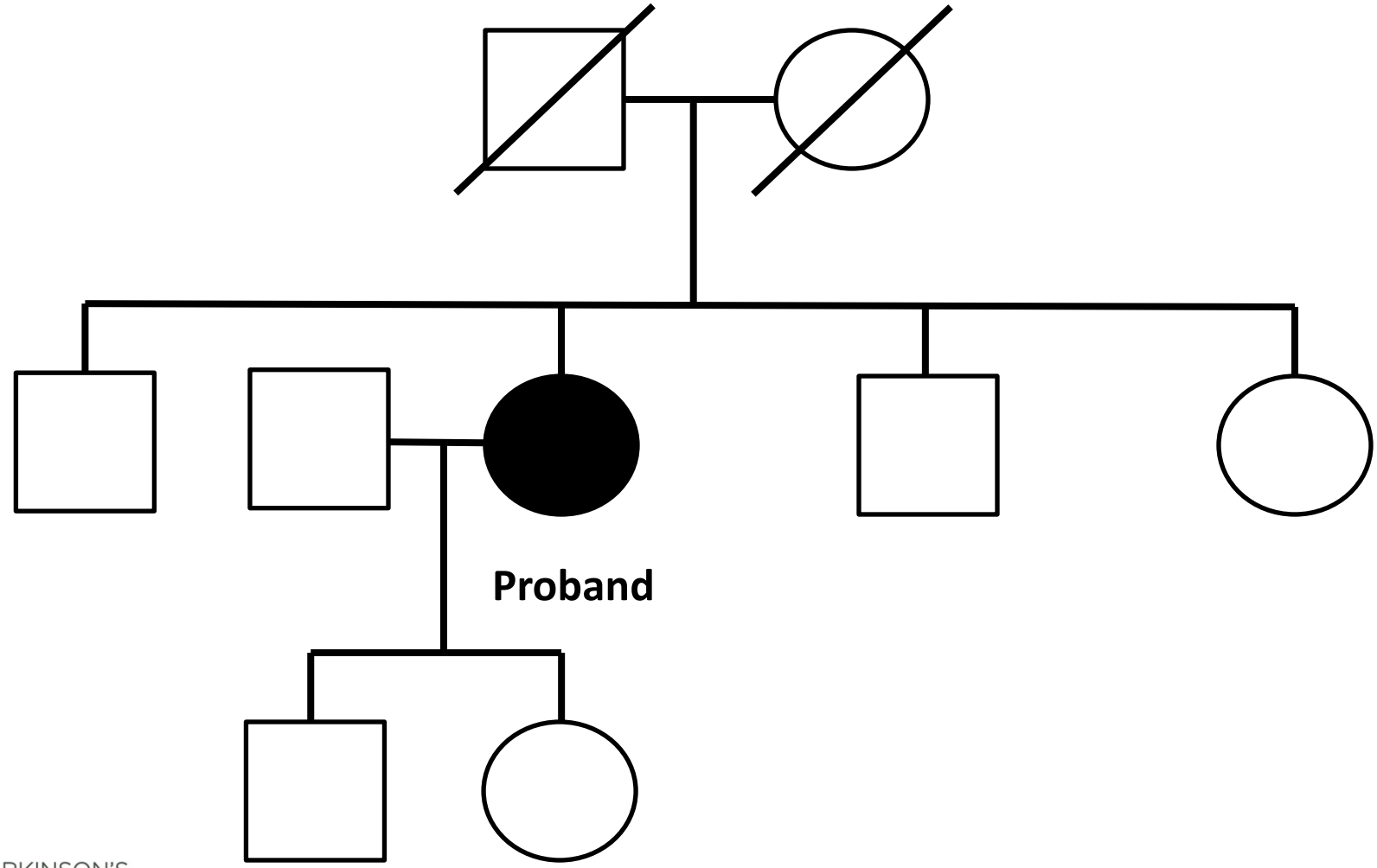
Family Recruitment



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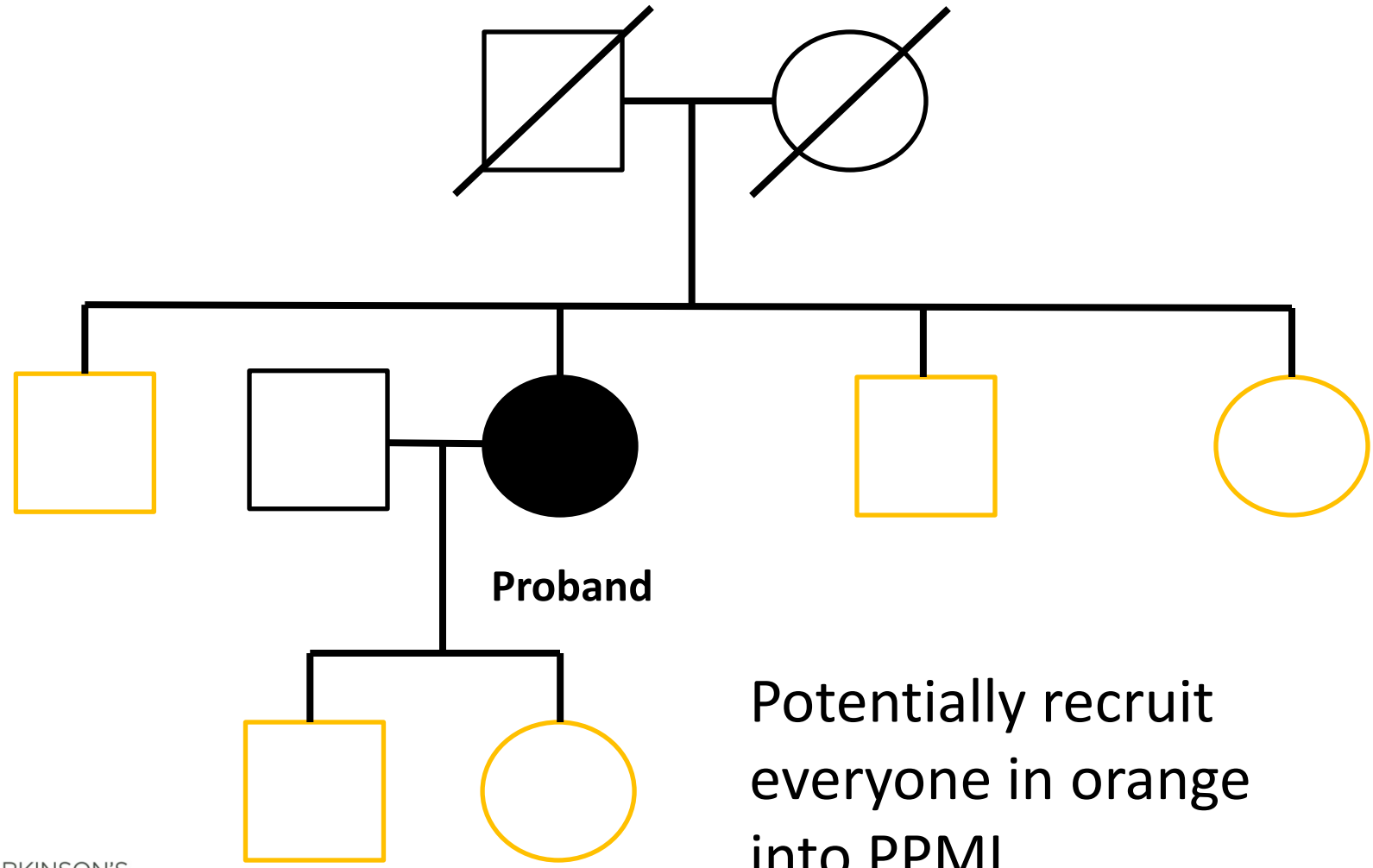
Family Recruitment



Potentially recruit everyone in orange into PPMI

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Play a Part in Parkinson's Research

How to Discuss Testing Results with Family members

- MJFF has led the development of a new brochure
- Given to a PPMI subject with a genetic mutation (LRRK2 or SNCA)
- They can use this brochure as a way to discuss PPMI and their test results with other family members

Brochure

Dear Friend,

In the years since my diagnosis, the love and support of my family have been vital to living well with Parkinson's disease. Today, the role of all families supporting Parkinson's research is more crucial than ever.

Studying the genetics of Parkinson's disease could revolutionize the development of new treatments for patients worldwide. Families connected to people who carry genetic mutations of Parkinson's play a unique role in the pursuit of a cure.

A decision to get genetic testing in PPMI is an opportunity to join forces with thousands of families worldwide committed to speeding scientific progress toward cures for diseases that touch countless lives.

We're all in this together. I hope you'll consider joining our movement.

All my best,

Michael J. Fox

Who is Eligible to Participate in PPMI?

Parents, children, brothers or sisters of an individual who carry a LRRK2 mutation are invited to receive genetic testing free of charge through the PPMI study. PPMI seeks volunteers both with and without Parkinson's disease. People who do not have Parkinson's disease must be 50 years or older to participate.

PPMI Sites Worldwide

Clinical sites in the following locations offer genetic counseling and testing for the LRRK2 gene free of charge.

United States	International
Atlanta, GA	Athens, Greece
Baltimore, MD	Barcelona, Spain
Birmingham, AL	Innsbrück, Austria
Boca Raton, FL	Kassel, Germany
Boston, MA	London, United Kingdom
Chicago, IL	Paris, France
Cincinnati, OH	San Sebastian, Spain
Cleveland, OH	Sydney, Australia
Houston, TX	Tel Aviv, Israel
New Haven, CT	Trondheim, Norway
New York, NY	Tübingen, Germany
Philadelphia, PA	
Portland, OR	
Rochester, NY	
San Diego, CA	
Seattle, WA	
Sun City, AZ	
Sunnyvale, CA	
Tampa, FL	

Play a Part in Parkinson's Research. Participate in PPMI.
888.525.PPMI *or* **www.michaeljfox.org/PPMI/genetics.**

BE PART OF THE GENETICS REVOLUTION:
THE ROLE OF FAMILIES IN PARKINSON'S DISEASE RESEARCH

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part In Biomarker Research

PARKINSON'S PROGRESSION MARKERS INITIATIVE
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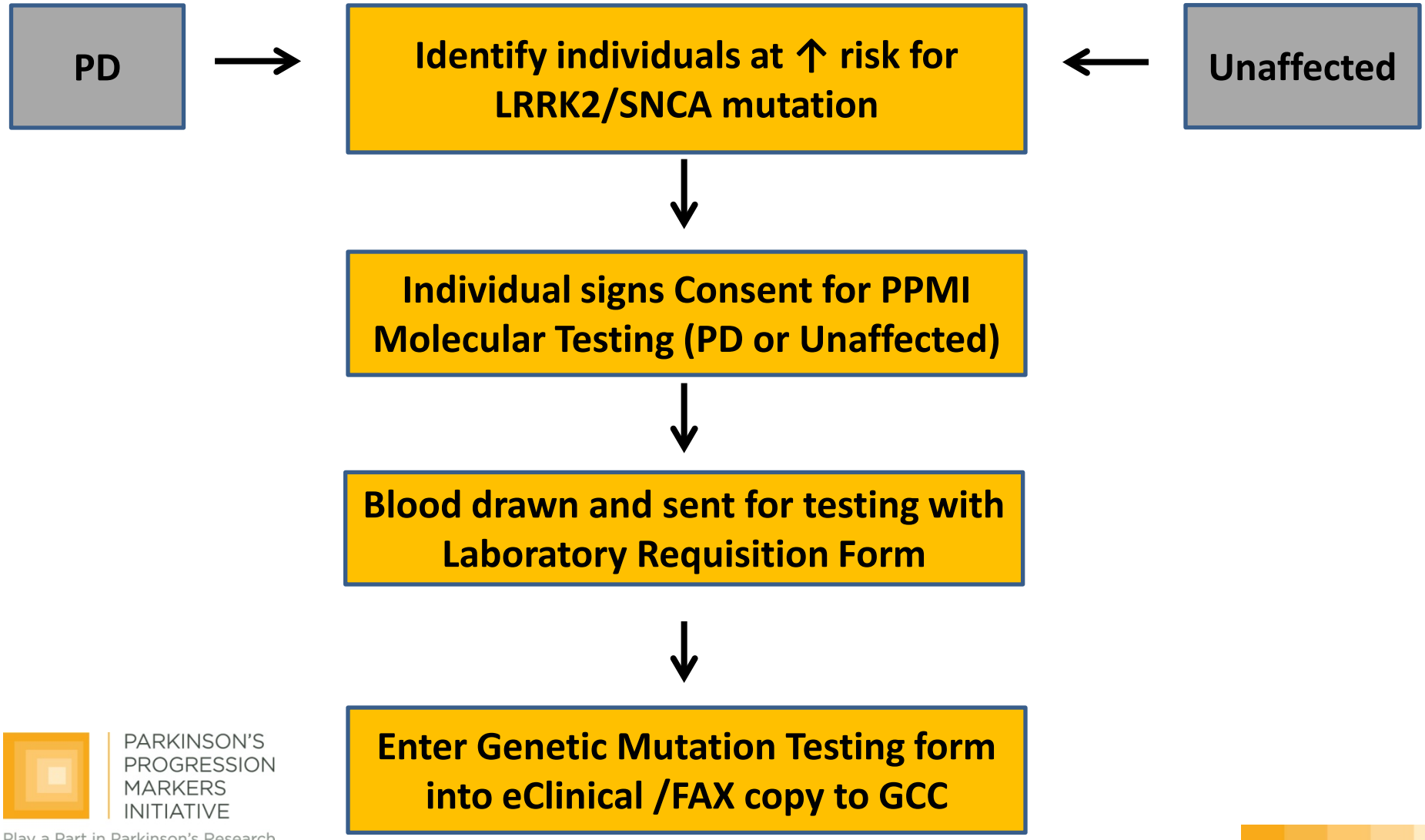
Family Members and PPMI

- PPMI site is contacted by an individual who identifies themselves as a relative of a PPMI subject
- PPMI site schedules an appointment for the individual to come to the site and learn about PPMI

Family Member of a LRRK2/SNCA+ (No previous testing)



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Family Members

- Recruiting family members is critical
  - They provide the greatest opportunity to enroll individuals who carry a mutation but are not affected
- We want to be sure we maximize all the potential for family members for each and every PPMI study subject

LRRK2 Genetic Testing in South Florida

Stuart Isaacson, MD
PDMDC of Boca Raton
September 17, 2013

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Play a Part in Parkinson's Research

Ashkenazi Jewish Heritage

- Ethnoreligious individuals who trace their origins to the indigenous Hebrew speaking people of Canaan in the Middle East
- Migration along the Rhine in Germany from Alsace in the south to Rhineland in the north during the Middle Ages
- Later established communities throughout Eastern Europe
- Migration to United States, especially Northeast and later SE Florida

AJ 2012

- Ashkenazim migrated up Rhine, to Poland, Romania, Ukraine
- ISR 6m, US 5.5m, Fr .5m, UK .3m, Rus/Arg .2m, Ger/AUS/BRZ .1m
- Many entered US thru Ellis Island, to NE and other areas: ~200 J communities >1000ppl
- >95% AJ, not Sephardic
- Many ID as Jews/Jewish, not AJ/origin

AJ South Florida

- Miami Beach to West Palm Beach
- 600k, D-125k, Br-150k, PBC-300k, with 75% in BR/DR/BB
- In PBC, 65% >65yo, 40% >75yo
- In So FL, 78% of all elderly are AJ (180k)
- i.e., BB, CV, KP (14,000,95% AJ)

Some challenges

- “not Ashkenazi”
- Cultural
- Ref/Cons, but Orth/Has
- History of antisemitism, holocaust
- Why now?
- What can be done about it?
- PCP/GC: 52%brca ref, 14%lrrk2 ref
- Insurance: LTC, disability

Some solutions

- Anonymous, de-ID
- No med record created
- No letter unless requested
- Cultural
  - Preserve life
  - Generation-to-Generation
  - “For the kinder”
  - a bissel

Why study people who carry the LRRK2 mutation?

- The majority of people who have LRRK2 mutation **do not** develop PD

- Studying individuals who have the LRRK2 gene but don't have PD, would be very valuable to assist researchers to better understand:
  - Who will develop PD and who will not
  - What early subtle symptoms predict the diagnosis of PD
  - How to develop treatments for people with LRRK2 and PD
  - When will PD develop in people with LRRK2 gene
  - How to slow or stop progression of preclinical disease in people with LRRK2
  - Does LRRK2 gene play a role in other neurologic conditions

A unique opportunity to get involved!

- The Michael J. Fox Foundation has invested over $50M to date to better understand LRRK2's role in PD

- In 2010, MJFF launched the Parkinson's Progression Markers Initiative (PPMI) to identify biomarkers of Parkinson's disease progression
  - Biomarkers are abnormalities found in blood, urine, spinal fluid, or brain scan imaging
  - Biomarkers are crucial to test PD medications and to understand why PD progresses slowly over decades
  - PDMDC of Boca Raton is one of 20 world-wide sites

- MJFF has recently announced additional funding to identify Ashkenazi Jews who have the LRRK2 mutation but do not have PD
  - Focus on the Ashkenazi Jewish population in southeast Florida
  - Volunteers who choose to be tested can be evaluated at the Boca Raton site

What does participation involve?

- Anyone of Ashkenazi Jewish heritage can be tested for LRRK2 at no cost
- PPMI is an observational trial – participants do not receive any treatment
- Volunteers undergo brain scans, clinical tests, and collection of biological specimens (blood, urine, cerebrospinal fluid)
- Why do you need me?
  - Approximately 400 individuals of Ashkenazi Jewish heritage will need to be tested and choose to participate in this ground-breaking study

What does participation involve?

- The first step is to identify whether you carry the LRRK2 mutation
  - Genetic counseling and testing is provided at no cost at the Parkinson's Disease and Movement Disorders Center of Boca Raton
  - If an individual already knows his/her genetic status, can also contact the Boca Raton site for further screening
- If testing indicates a person has LRRK2+, then that individual will be invited to join the pre-PPMI Clinical Research Study
- Will undergo further screening tests, which may lead to ongoing participation in the pre-PPMI research program

How to play a part in this important PD genetics program

- Let us know you are interested:
  - Write your contact information on the back of your nametag and turn it
  - Sign up sheets being passed around or provide your name on a sheet at the check-in desk
  - Contact the Parkinson's Disease and Movement Disorders Center of Boca Raton to register for the genetic counseling and testing process
    - Call (561) 392-1818 ext. 6
    - email PDgenestudy@ParkinsonsCenter.org (see postcards provided)
- Share this information with your friends and family
- Take extra postcards to bring home and hand out at your clubhouse, community center, synagogue, friends, and family
- Visit www.michaeljfox.org/ppmi/genetics to learn more or share information online

THANK YOU FOR BEING A PARTNER IN THIS RESEARCH!!!

Some dilemmas

- Explaining AJ, no FH, part-J
- Cohort vs. Registry
- Older vs. younger yield
- GBA
- What if +FH, -lrrk2/gba
- Implications for children >50

Strategies for recruitment

- AJ with FH, but no PD:
  - Ones that call are motivated
  - How to reach ones that don't
  - Outreach symposia
  - Cards placed in sr comm, pool, bagels, deli, kosher
  - Newspaper, but beware lexicon
  - J newspapers, mags
  - Synagogues (but >75 in PBC)

Strategies for recruitment

- AJ with PD in community:
  - Outreach symposia
  - Cards placed in sr comm, pool, bagels, deli, kosher
  - Newspaper, but beware lexicon
  - J newspapers, mags
  - Support groups, exercise, newsletters

Strategies for recruitment

- AJ with PD in clinic:
  - 1-2 routine, 3-4 plan, 5-10 infrastruct
  - Sign in waiting room, exam room
  - Discussion lengthens visit
  - Discussion can diminish/impact care
  - “Anyone in the family have PD or are Jewish?”

LRRK2 Genetic Testing in South Florida

Stuart Isaacson, MD
PDMDC of Boca Raton
September 17, 2013

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

The G209A SNCA cohort in Greece: Recruitment efforts

Leonidas Stefanis, MD, PhD
Maria Stamelou, MD, PhD
Second Department of Neurology
University of Athens Medical School
September 16, 2013

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Background

- **The G209A SNCA mutation identified in the seminal publication of Polymeropoulos et al., 1997, in Italian and Greek families**
- **Greek families resided in the Peloponese**
- **Participation of the Medical School of the Univ. of Patras (Drs. Papapetropoulos and Athanassiadou)**
- **A series of other cases subsequently reported by this and other groups in Greece**
- **However, no systematic analysis of the frequency of the mutation and no systematic follow-up of these families**

Background: My involvement

- Return from the US to Greece in 2003, at BRFAA
- Established a lab on pathogenesis of PD
- In 2006 started working in Attikon Hospital, Second Dept. of Neurology
- Establishment of Movement Disorders Clinic and DNA biobank of Greek PD patients
- In 2007 I saw patient IM, 62 yo, with incipient PD
- Three of her brothers had died in their 40s and 50s with PDD

Background

- **In 2007 started performing specific testing for the G209A SNCA mutation in the lab**
- **IM, her niece and a few other unrelated patients from the evolving Biobank tested positive**
- **All except IM, with EOPD**
- **All with clear autosomal dominant pattern of inheritance**

Recruitment as part of MEFOPA

- **MEFOPA: Mendelian Forms of Parkinson's Disease**
- **EU/FP7 Health Collaborative Project**
- **2010-2013**
- **PI: Thomas Gasser**
- **Aim to record subjects, either carriers or patients, with PD Mendelian traits in Europe**
- **Obtain clinical information**
- **Obtain biological samples in two sets**

MEFOPA: An opportunity

- **An opportunity to reexamine the «lost» G209A cohorts in Greece**
- **An opportunity to collect biological samples from this defined genetic cohort**

Results of MEFOPA recruitment efforts in Greece

- 30 subjects with the G209A SNCA mutation enrolled in the study
- 22 symptomatic, 8 asymptomatic
- Two visits for most of them
- Three have died during this period
- Demographic, Clinical information and variable biospecimens from all
- Only in one case was CSF obtained due to atypical presentation
- Fibroblasts in 11 subjects

Symptomatic carriers

N	M/F	Age of onset Mean± SD (Range)	Disease duration Mean± SD (Range)	H&Y Mean± SD (Range)
22	10/12	44.8±10.3 (30-65 years)	7.1± 4.3 (0.5-18 years)	2.4 ±1.2 (1-5)

Symptomatic carriers
Disease duration < 7 years

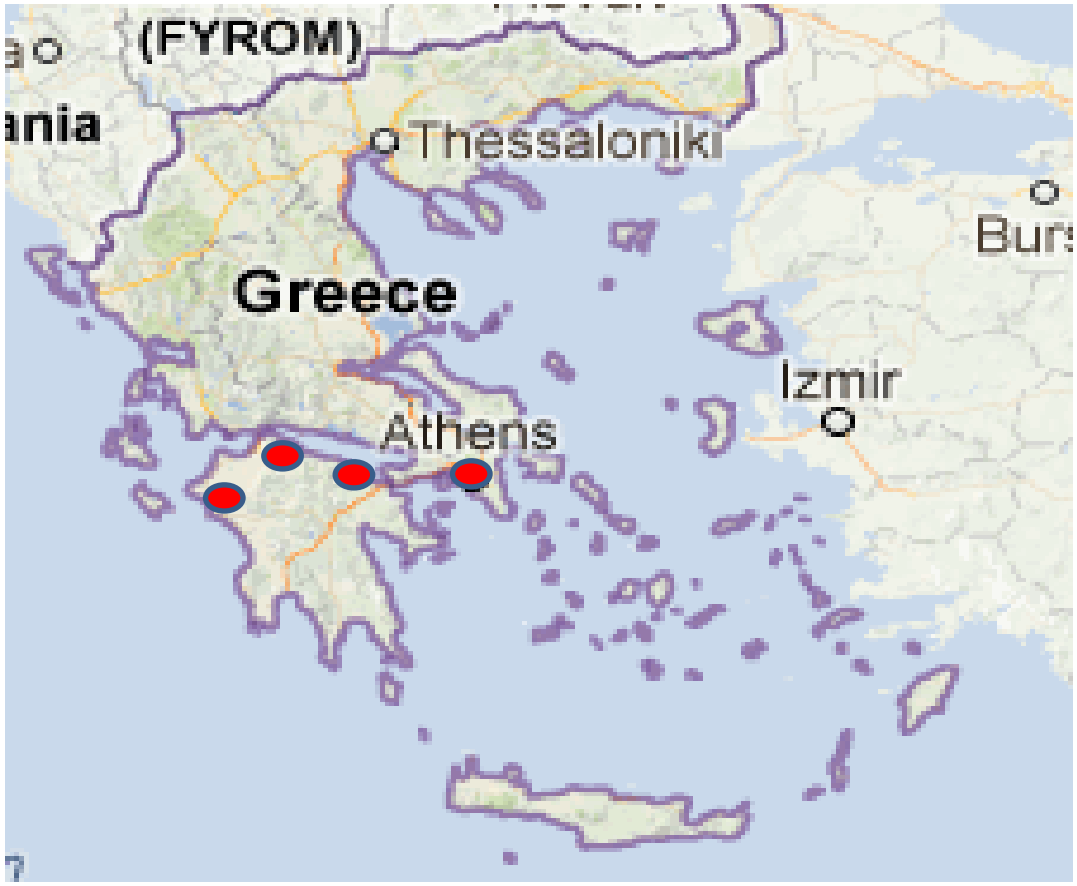
N	M/F	Age of onset Mean± SD (Range)	Disease duration Mean± SD (Range)	H&Y (Range)
13	6/7	46.3±11.8 (30-65 years)	4.4± 1.7 (0.5-7 years)	1-3

- **Phenotypic variability between families and members of the same family**

Asymptomatic carriers

N	M/F	Age (Range)
8	1/7	51.4 ± 19.1 (35-90 years)

Areas were most of the current subjects and families are located



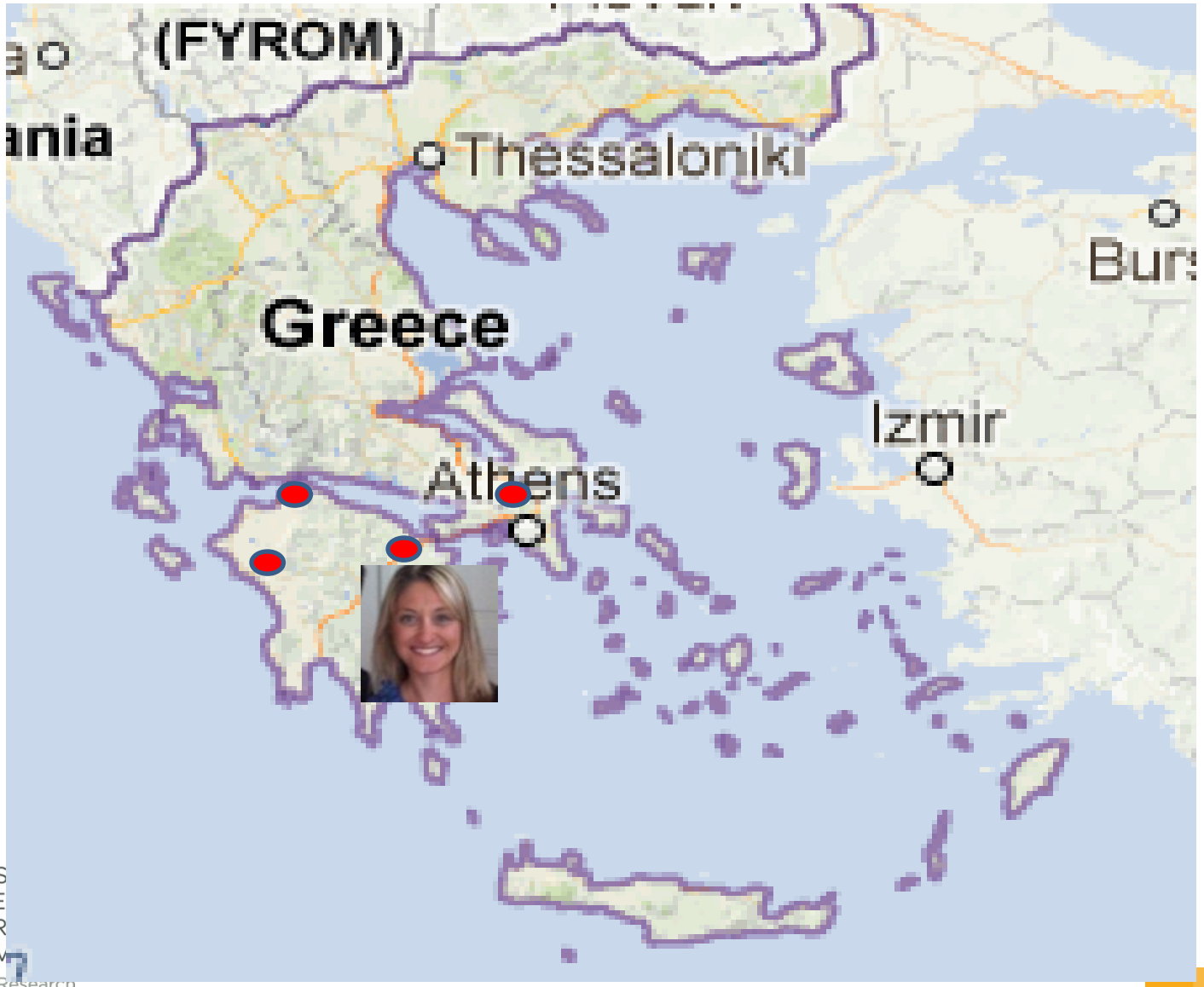
Strategy for recruitment

- **We enlisted the help of all groups who had previously published work on G209A SNCA families**
- **Especially crucial was the participation of A. Athanasiadou and A. Papadimitriou**
- **Interrogation within the families for additional affected or non-affected relatives**
- **We informed colleagues working in Movement Disorders Clinics in the Athens area about the study**
- **Continuous flow of subjects to our outpatient clinic, where, in a study we have performed (Bozi et al., in press), in a sample enriched for genetic load (AAO<50 and/or Mendelian PD), about 4% of PD patients carry the mutation**

Further recruitment efforts within PPMI

- **Build on subjects and families already enrolled in MEFOPA (2 more symptomatic subjects recently identified from unrelated families)**
- **Inform Neurologists throughout Greece through the Hellenic Neurological Association**
- **Present results from MEFOPA at National Neurology meetings**
- **Organize meetings for local physicians in Hospitals and Health Centers where clusters of cases appear**
- **Enlist the assistance of the Neurology Dept of the Univ of Patras**
- **Inform the public at large about our ongoing work, through the media**

Areas were most of the current subjects and families are located



Keys for successful recruitment

- **Establishing a good relationship with affected families**
- **Word of mouth through families**
- **Having a good network of colleagues willing to refer patients**
- **Having a flow of patients in one's own Clinic**
- **Ability to perform relevant genetic test rapidly and on site**
- **Advertising at the local level if geographical concentration exists**
- **Convincing subjects that this is worthwhile**

Recruiting LRRK2 Subjects in Norway

Bjørg Johanne Warø, MD
Norwegian University of Science and Technology
St. Olav's Hospital
Trondheim, Norway
September 17, 2013

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The Trondheim PD cohort

- Started 1997 by Dr. Aasly
- Biosamples, on:
  - >900 iPD patients
  - >150 family members with PD
  - >150 siblings
  - >150 children
  - > 100 spouses
  - > 1000 healthy controls

The LRRK2 PD cohort

- In 2004: 8 LRRK2 families were identified.
- In 2013: 15 LRRK2 families, ca. 100 mutations carriers (1/3 of whom have PD).
- 2 mutations:
  - G2019S
  - N1437H

About us

- Too many cooks spoil the broth.
- PD patients are followed by the same doctor over years.
- Nurse specialist on PD.
- Same doctor, JAa, does all LPs.
- Flexibility

The Ashkenazi Jewish LRRK2 Study

Anat Mirelman, PhD
Tel Aviv Medical Center
September 16, 2013

The *LRRK2* Ashkenazi Jewish Consortium

- Established in 2009 and includes 3 centers:
  - Tel Aviv Medical Center, Israel
  - Beth Israel Medical Center, NY
  - Columbia University Medical Center, NY
- Aim: to examine the clinical characteristics and genetic modifiers of families of PD probands with and w/o G2019S mutations.

The *LRRK2* Ashkenazi Jewish Consortium

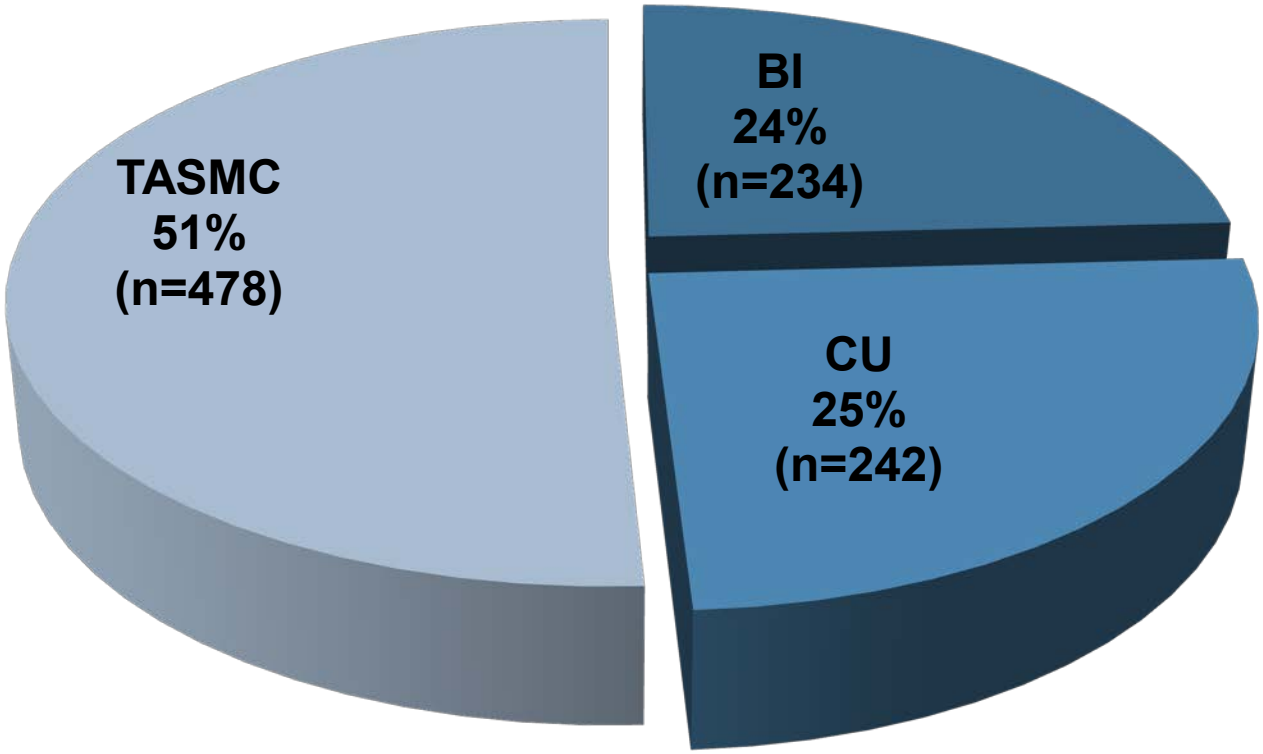
- The study included different procedures:

  1) Screening evaluation of PD probands
  2) In-depth evaluation of carriers, and subset of non-carriers and all willing first-degree family members
  3) A supplement study: Longitudinal follow up on those recruited to the in-depth evaluation

Domain	Tool
Genotype	DNA sample from blood
Medical history	life habits and environmental questionnaires
Neurological examination	UPDRS, H&Y, S&E
Autonomic function and sleep	SCOPA-AUT, PD NMS, RBDQ, Epsworth
Olfaction	UPSIT
Mood and affect	BDI, GDS, STAI
Neuropsychological evaluation	MoCA, FAS, Digit span, Stroop test, TMT, HVLT, JLo
Motor features	Finger taping, BBS, TUG, gait , spirals
Brain activation	Rest MRI and fMRI- cognitive, motor and emotional , tasks
Dopaminergic neuronal integrity	DaT scan and FDG PET

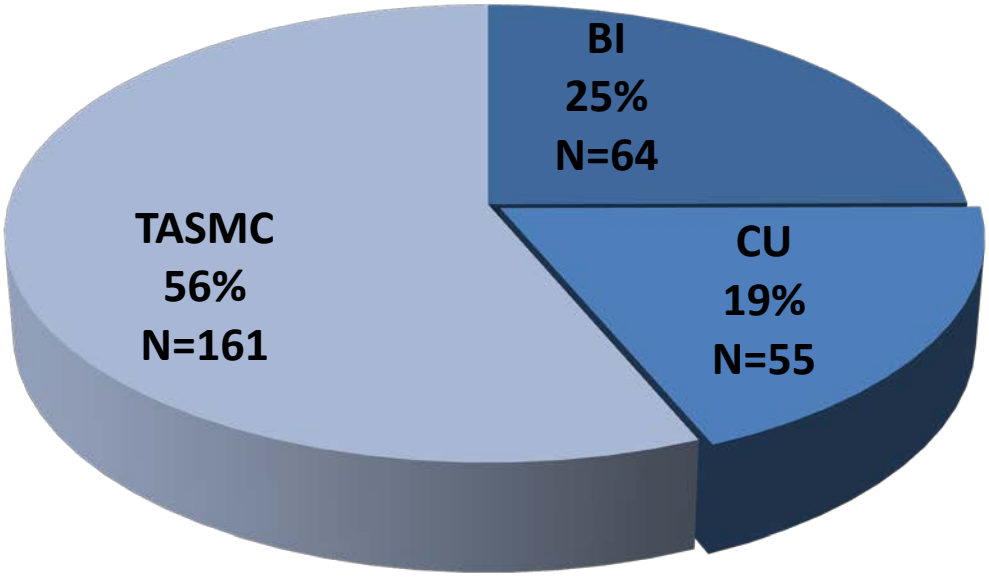
AJ consortium Total Enrolled

N=954



The AJ consortium First degree relative cohort

N=280



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Recruitment 7/09 – 9/13

	PD	1st degree	Control	Total
Enrolled in cross sectional	643	280	47	954
G2019S +	191	146	1	334
G2019S -	452	134	---	574
DAT (in TA)	57	67	---	124
fMRI (in TA)	4	112		116

Recruitment Process- TA

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

A collaborative effort

- Open door policy
- Benefits for the participants
- NOT test subjects!
- Counseling

Clinical Counseling

- Discuss clinical assessment
- Discuss imaging findings
- Discuss potential neuroprotection
- Genetics counseling if subjects insist
  - Clinical genetic testing
  - Genetic counseling

- 93 first degrees went through clinical counseling
  - 6 wanted genetic status

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Fighting the risk of developing Parkinson's disease; clinical counseling for first degree relatives of patients with Parkinson's disease

Nir Giladi [a,c], Anat Mirelman [a,d,*], Avner Thaler [a], Anat Bar-Shira [b], Tanya Gurevich [a,c], Avi Orr-Urtreger [b,c]

[a] Movement Disorders Unit, Department of Neurology, Tel-Aviv University, Tel-Aviv, Israel
[b] Genetic Institute Tel-Aviv Medical Centre, Tel-Aviv University, Tel-Aviv, Israel
[c] Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[d] Ben Gurion University, Beer Sheba, Israel

Movement Disorders Unit, Tel Aviv Medical Center

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Play a Part in Parkinson's Research

Recruitment experience RBD cohort

Tanya Simuni, MD

Northwestern University

September 16, 2013

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

One center experience

- Contact Sleep MDs
- Present study outline
- Request list of established RBD patients
- Biweekly reminders
- Request list of referring MDs
- Email study information to the larger MD group

Recruitment tree

- PSG database search
- Clinical records database
- Establish protected slots for these patients to be seen

PPMI Communications, Incidents and Notifications

Irina Lazurenko
Clinical Trials Coordination Center/
Center for Human Experimental Therapeutics
University of Rochester Medical Center

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

UNIVERSITY of ROCHESTER MEDICAL CENTER

Study Contacts
CTCC TEAM

- Irina Lazurenko
  Lead Project Manager
  Phone: (585) 273-4239
  Fax: (585) 461-3554
  Email: irina.lazurenko@chet.rochester.edu

  – Assist with all site communications
  – Primary contact for Global sites

Study Contacts
CTCC TEAM

- Alice Rudolph

  Project Manager

  Phone: (585) 275-0556

  Fax: (585) 461-3554

  Email: alice.rudolph@chet.rochester.edu

  – Primary contact for U.S. sites
  – Back up to Lead PM

Study Contacts
CTCC TEAM

- Sue Bennett

  Information Analyst

  Phone: (585) 273-4234

  Fax: (585) 461-4594

  Email: susan.bennett@chet.rochester.edu

    - Data Management
      - eCRF Issues
      - Query Management
      - Missing Forms Reports
      - Study Closeout

Site Personnel

- One Primary Investigator
  - Sub-investigators accepted as approved by sponsor and study team
  - Subjects screened/enrolled by a sub-I should be followed by same individual throughout for consistency of assessments and evaluations
- One Primary Coordinator
  - Co-coordinators accepted as approved by sponsor and study team
- Investigator is responsible for seeing *all* subjects at *all* visits and conducting Investigator required assessments
- Any change in primary Investigator must be preapproved by the PPMI Steering Committee

Site Personnel

- Report staff changes to the CTCC as soon as possible
  - Complete the New/Change Staff form
- Update Delegation Log (fax copy to CTCC)
- Update 1572, U.S. sites only (if applicable)

Site Activation

Each site must receive confirmation of site activation from the CTCC before any potential subject is consented to participate.

- Requirements include:
  - IRB/Ethics approval
  - Subcontract in place
  - Imaging technical site approval (from Imaging core)
  - Regulatory documents completed
  - PI and Coordinator protocol training completed
  - Additional site staff training completed (as applicable)
  - EDC training (if not previously done) for PI, Coordinator and Data Entry staff

Incidents and Notifications

Reportable Events (Incidents)

- The following events are considered reportable events (**incidents)** and must be reported to the CTCC project manager as soon as possible and within 24 hours of site awareness:
  - Initiation of PD medication
  - Change of diagnosis
  - Participation in any other clinical trial or study
  - Premature withdrawal (e.g., withdrawal of consent)
  - Serious adverse event (SAE)
  - Pregnancy
  - Death

Incident Reports

- Summary of the event as reported to CTCC
- Sites to review and verify information upon receipt
- Print copy for study file

Notifications

- Purpose: To report noteworthy and relevant clinical or data management information that might influence the interpretation of the study data
- May be a general site issue as well as subject specific
- Notifications should be communicated by telephone or email to the CTCC as soon as possible

Notifications

- Examples of issues requiring notification:
  - Protocol violations
  - Blood sample not collected or shipped to Coriell
- Include with the report to CTCC:
  - Site number
  - Staff code of reporting Investigator or Coordinator
  - Subject ID number
  - Date of event or observation

Notification Reports

- Generated as a summary of the event as reported to the CTCC
- Sites to review and verify information upon receipt
- Print copy for study file

Activity Reports

Enrollment Status Report

09/13/2013 21:49 *Clinical Trials Coordination Center*

PPMI
Enrollment Status Report

Center	Consented				Excluded/ Declined				Pending SC/BL				Enrolled				Withdrawn				Active			
	PD	HC	SW	Total	PD	HC	SW	Total	PD	HC	SW	Total	PD	HC	SW	Total	PD	HC	SW	Total	PD	HC	SW	Total
Total:	*487*	*241*	*83*	*811*	*64*	*45*	*19*	*128*	*0*	*0*	*0*	*0*	*423*	*196*	*64*	*683*	*10*	*8*	*2*	*20*	*413*	*188*	*62*	*663*
034 INSTITUTE FOR NEURODEGENERATIVE DISORDERS	62	18	8	**88**	4	4	2	**10**	0	0	0	**0**	58	14	6	**78**	1	1	0	**2**	57	13	6	**76**
289 UNIVERSITY OF TUEBINGEN	27	13	7	**47**	2	1	1	**4**	0	0	0	**0**	25	12	6	**43**	0	1	1	**2**	25	11	5	**41**
032 EMORY UNIVERSITY SCHOOL OF MEDICINE	23	15	5	**43**	1	1	2	**4**	0	0	0	**0**	22	14	3	**39**	0	1	0	**1**	22	13	3	**38**
057 UNIVERSITY OF ALABAMA AT BIRMINGHAM	22	16	7	**45**	5	3	1	**9**	0	0	0	**0**	17	13	6	**36**	1	0	0	**1**	16	13	6	**35**
006 OREGON HEALTH & SCIENCE UNIVERSITY	22	15	3	**40**	2	3	0	**5**	0	0	0	**0**	20	12	3	**35**	0	0	0	**0**	20	12	3	**35**
290 PARACELSUS-ELENA KLINIK	23	11	5	**39**	2	0	2	**4**	0	0	0	**0**	21	11	3	**35**	0	1	0	**1**	21	10	3	**34**
088 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL	25	12	7	**44**	6	3	1	**10**	0	0	0	**0**	19	9	6	**34**	0	1	0	**1**	19	8	6	**33**
096 UNIVERSITY OF WASHINGTON/VA HEALTH CARE SYSTEM	24	15	1	**40**	2	3	1	**6**	0	0	0	**0**	22	12	0	**34**	0	0	0	**0**	22	12	0	**34**
012 THE PARKINSON'S INSTITUTE	24	13	4	**41**	6	2	1	**9**	0	0	0	**0**	18	11	3	**32**	0	0	0	**0**	18	11	3	**32**
120 CLEVELAND CLINIC	25	11	4	**40**	3	5	1	**9**	0	0	0	**0**	22	6	3	**31**	2	1	0	**3**	20	5	3	**28**
018 UNIVERSITY OF PENNSYLVANIA	23	15	0	**38**	3	4	0	**7**	0	0	0	**0**	20	11	0	**31**	0	1	0	**1**	20	10	0	**30**
007 BAYLOR COLLEGE OF MEDICINE	25	9	1	**35**	2	2	0	**4**	0	0	0	**0**	23	7	1	**31**	0	0	0	**0**	23	7	1	**31**
040 BOSTON UNIVERSITY MEDICAL CENTER	18	13	2	**33**	3	0	0	**3**	0	0	0	**0**	15	13	2	**30**	0	0	0	**0**	15	13	2	**30**
019 UNIVERSITY OF SOUTH FLORIDA	21	14	5	**40**	3	6	3	**12**	0	0	0	**0**	18	8	2	**28**	0	0	0	**0**	18	8	2	**28**
028 JOHNS HOPKINS UNIVERSITY	20	7	6	**33**	3	2	2	**7**	0	0	0	**0**	17	5	4	**26**	0	0	0	**0**	17	5	4	**26**
001 UNIVERSITY OF ROCHESTER	19	10	1	**30**	2	2	0	**4**	0	0	0	**0**	17	8	1	**26**	3	0	0	**3**	14	8	1	**23**
023 UNIVERSITY OF CALIFORNIA, SAN DIEGO	13	9	1	**23**	1	0	0	**1**	0	0	0	**0**	12	9	1	**22**	1	0	0	**1**	11	9	1	**21**
291 INNSBRUCK MEDICAL UNIVERSITY	8	8	6	**22**	0	0	1	**1**	0	0	0	**0**	8	8	5	**21**	1	0	0	**1**	7	8	5	**20**
089 UNIVERSITY OF CINCINNATI	15	1	2	**18**	0	0	0	**0**	0	0	0	**0**	15	1	2	**18**	0	0	0	**0**	15	1	2	**18**

/home/study/ppmi/prod/main/reports/enroll_status.sas sid=p1 prj=PRJ0101B

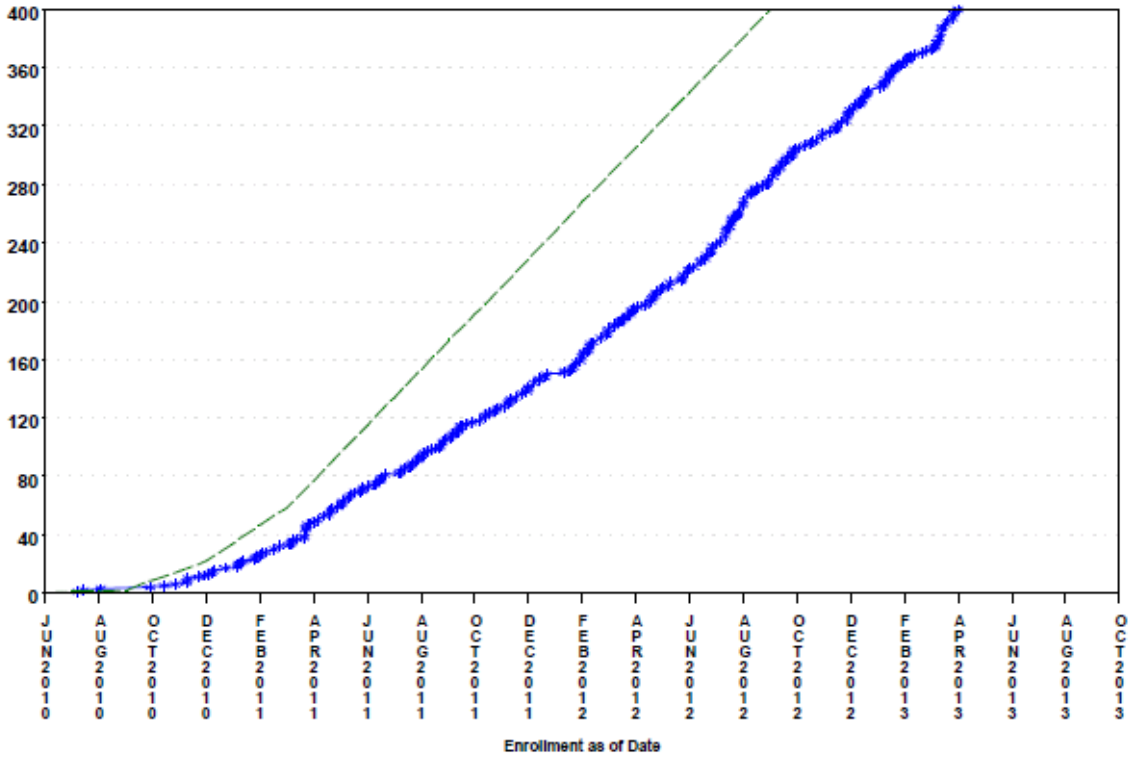
Enrollment Graph

21:52 Friday, September 13, 2013 1

PPMI Cumulative Enrollment - PD Subjects

Fri, Sep 13, 2013: 423 Enrolled for PD Subjects (106%)

* = Actual, --- = Target



PARKINSON' PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Activity Report

09/13/2013 21:55 *Clinical Trials Coordination Center*

PPMI
Activity Report

			Incidents					
Center	Enrolled	Active	Start PD Meds	Change Diagnosis	Another Study	SAE	Pregnancy	Death
TOTAL	685	662	204	33	8	1	0	5
001 UNIVERSITY OF ROCHESTER	26	23	8	2	0	0	0	0
006 OREGON HEALTH & SCIENCE UNIVERSITY	35	35	16	2	2	0	0	0
007 BAYLOR COLLEGE OF MEDICINE	31	31	15	0	0	0	0	0
012 THE PARKINSON'S INSTITUTE	32	32	6	3	1	0	0	0
018 UNIVERSITY OF PENNSYLVANIA	31	30	13	0	0	0	0	1
019 UNIVERSITY OF SOUTH FLORIDA	28	28	7	2	0	0	0	0
023 UNIVERSITY OF CALIFORNIA, SAN DIEGO	22	21	7	1	0	0	0	1
028 JOHNS HOPKINS UNIVERSITY	26	26	4	1	0	0	0	0
032 EMORY UNIVERSITY SCHOOL OF MEDICINE	39	38	7	4	0	0	0	1
034 INSTITUTE FOR NEURODEGENERATIVE DISORDERS	79	77	38	6	3	0	0	1
040 BOSTON UNIVERSITY MEDICAL CENTER	30	29	9	2	0	0	0	0
057 UNIVERSITY OF ALABAMA AT BIRMINGHAM	37	35	16	0	0	0	0	0
088 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL	34	33	13	4	2	0	0	0
089 UNIVERSITY OF CINCINNATI	18	18	5	1	0	0	0	0
096 UNIVERSITY OF WASHINGTON/VA HEALTH CARE SYSTEM	34	34	14	0	0	0	0	0
120 CLEVELAND CLINIC	31	28	9	1	0	0	0	0
154 SUN HEALTH RESEARCH INSTITUTE / ARIZONA PD CONSORTIUM	16	13	3	1	0	1	0	0
196 PD AND MOVEMENT DISORDERS CTR OF BOCA RATON	7	7	0	0	0	0	0	0
289 UNIVERSITY OF TUEBINGEN	43	40	0	0	0	0	0	1
290 PARACELSUS-ELENA KLINIK	35	34	11	3	0	0	0	0
291 INNSBRUCK MEDICAL UNIVERSITY	21	20	3	0	0	0	0	0

Questions

PPMI Financial Overview

Vanessa Arnedo
The Michael J. Fox Foundation

September 17th 2013

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Subcontracts

- The Michael J Fox Foundation will contract with all sites directly
- Agreements for Genetic Cohort were sent to all sites in June
- Goal is to have all agreements fully executed by end of September

Site Budget

1) Each PPMI Site receives fixed CTS Support each year
2) Site is paid per subject, per assessment/biospecimen collected
3) Subject travel/accommodation reimbursement -> can be pooled across subjects

Payment Schedule & Process

- Site payments are issued on a quarterly basis
- CTCC will generate a report at the end of each quarter based on completed assessments/ biospecimens entered into e-clinical database:
  - *No missing pages*
  - *Investigator e-Signatures are applied to Signature Forms for all completed visits*
  - *Entry Complete status is checked on each eCRF page*

Other payment notes

- DaTScan ligand is provided to sites by GE
  - Questions, contact Susan Mendick at smendick@mnimaging.com
- Travel reimbursement for some sites will be more than other sites depending on geography – will revaluate by site based on need
- Payment/reimbursement for recruitment or retention related promotions or events are separate from site budget

Meeting Reimbursement

- Email sent by Kathy Vestuto last week included the *Expense Reimbursement Form*
- Please fill this out and attach original receipts and mail to Kathy
- MJFF can only reimburse items accompanied with a receipt

PPMI
Ancillary Studies
& Protocol Amendments

Carlie Tanner

September 17, 2013

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Play a Part in Parkinson's Research

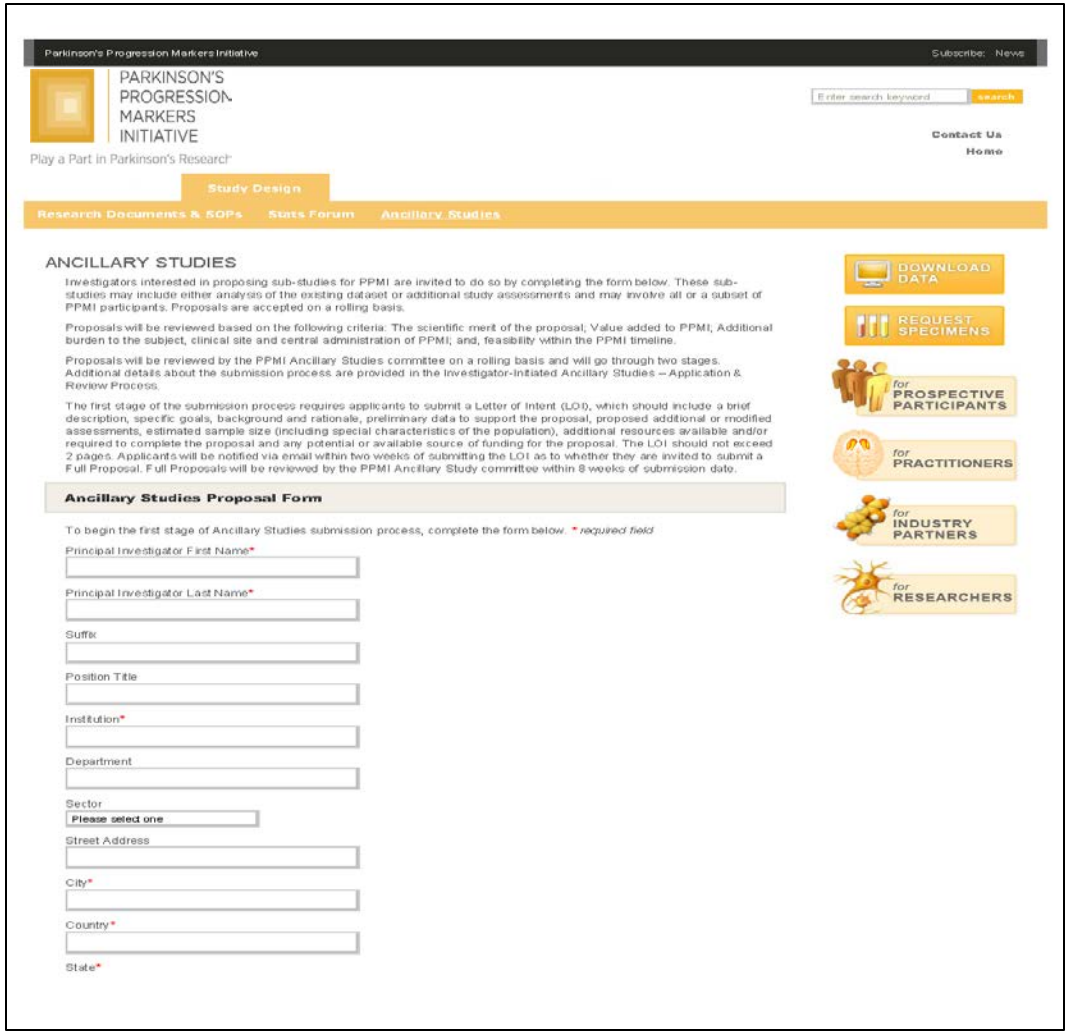
PPMI Ancillary Study Proposals

- PPMI was designed to have the ability to review and incorporate new assessments that could be beneficial to the overall goal of the study

- Ancillary study Proposals are generated from different sources
  - PPMI Steering Committee
  - PPMI Ancillary Study proposal process
  - PPMI Cores
  - PPMI Working Groups
  - ISAB

PPMI Ancillary Study Proposals

- Easy access e-Form located on PPMI study website
- Preliminary 2 page proposal
- Screening review
- Full proposal by invitation
- Review by Ancillary Studies Committee, other committee as appropriate



PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

PPMI Ancillary Study Proposal *Review Criteria*

- Scientific Merit of the proposal
- Consistent with & furthers the overall PPMI goals of developing biomarkers for the progression, prognosis or diagnosis of PD?
- Sufficient preliminary data to justify using PPMI cohort?
- Does not add undue subject burden or detract from the main PPMI protocol
- Expertise, resources and environment of investigator(s)
- Willing to comply with PPMI policies including Publication and Intellectual property
- Data generated from analyses of PPMI data returned; public access

PPMI Ancillary Studies & PPMI Protocol Amendments

Amendment Number	Date	Change
3	15-JUL-2011	Longitudinal follow-up of screen failures due to scans with evidence of dopaminergic deficit (SWEDDs) Feasibility & reliability of in-home testing with the OPDM-dexterity measure (TAP-PD)
4	30-MAR-2012	18F-AV-133 VMAT-2 PET imaging Addition of cognitive categorization Resting state MRI sequences
5	27-NOV-2012	Added prodromal cohort - hyposmic, LRRK2, RBD Added Olfactory and RBD Cores Assessment of Physical Activity (measured using PASE)
6	28-MAY-2013	Added Genetic Cohort & Genetic Registry (PD & unaffected subject with LRRK2 or SNCA mutations)

PPMI Amendment-7 & Beyond

New proposals & expanding current study

- Beta amyloid imaging – Flutemetamol & possibly other β-Amyloid agents
  - PET imaging 200 subjects at select sites
- NY Stem Cell Foundation collaboration
  - Pilot study: IND collection of skin biopsies from 20 PD, 5 control subjects. Biopsies to NYSCF to generate iPS and fibroblast lines which will be stored at Coriell.
- Pathology Core
  - Discussions regarding developing central facility
- Broader screening for LRRK2 affected individuals
  - Add new ICF to allow for screening of high risk individuals without a relative with PD at all sites; - ability to re-contact?

PPMI Amendment-7 & Beyond

New proposals & expanding current study

- Objective Measurements of Motor Function (Prodromal & Unaffected Genetic cohorts):
  - In-office assessments of finger tapping (e.g., Objective Parkinson's Dexterity Monitoring devices) &/or gait devices
- Neuro-ophthalmology spectral domain optical coherence tomography [SD-OCT] and multifocal electroretinograpy [mERG]
  - Following up with investigator – proposal pending
- Other Imaging Approaches Under Consideration:
  - Imaging inflammation?
  - Tau imaging?

PPMI Data Analyses

Christopher S. Coffey
The University of Iowa

PPMI Genetics Cohort Kickoff Meeting
September 17, 2013
New York, NY

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

OVERVIEW

Source of data for this presentation:

- All data comes from a data freeze based on data obtained from the LONI website on 09/09/13

ENROLLMENT

Group	Consented	Enrolled	Withdrawn	Active	Complete
PD Subjects	487	423	10	413	0
Healthy Controls	241	196	8	188	0
SWEDD Subjects	83	64	2	59	3
Prodromal Cohort	20	1	0	1	0

684 Total Subjects Enrolled

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

BASELINE CHARACTERISTICS

Comparison of Baseline Characteristics Among Various Subsets:

- Early PD
- Healthy Controls
- SWEDD Subjects
- Prodromal Subjects
- *PD with and without LRRK2 or SNCA mutation*
- *Unaffected LRRK2 or SNCA mutation carriers*

BASELINE CHARACTERISTICS

Group	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)
Males	277 (65%)	126 (64%)	40 (63%)
Age (mean)	62	61	61
Education < 13 yrs	77 (18%)	29 (15%)	18 (28%)
Hispanic/Latino	9 (2%)	3 (2%)	2 (3%)
Caucasian	391 (92%)	182 (93%)	61 (95%)
Family Hx of PD	102 (24%)	10 (5%)	21 (32%)

BASELINE CHARACTERISTICS

Group	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)
MDS-UPDRS Score			
- Total Score	32.4 (13.1)	4.6 (4.5)	28.2 (17.4)
- Part I	5.6 (4.1)	2.9 (3.0)	8.3 (6.5)
- Part II	5.9 (4.2)	0.5 (1.0)	5.7 (5.1)
- Part III (Motor Exam)	20.9 (8.9)	1.2 (2.2)	14.3 (9.4)
Hoehn & Yahr			
- Stage 0	0 (0%)	193 (99%)	0 (0%)
- Stage 1	186 (44%)	2 (1%)	37 (58%)
- Stage 2-5	237 (56%)	0 (0%)	27 (42%)
Modified Schwab	93.2 (5.9)	N/A	94.8 (6.0)
Duration of Disease (months)	6.7 (6.5)	N/A	7.4 (7.9)

BASELINE CHARACTERISTICS

Group	PD Subjects (N = 423)	Healthy Controls (N = 196)	SWEDD Subjects (N = 64)
MOCA Total Score	27.1 (2.3)	28.2 (1.1)	27.1 (2.4)
GDS Total Score	2.3 (2.4)	1.3 (2.1)	3.3 (3.6)
SCOPA AUT Score	9.5 (6.2)	5.9 (3.7)	13.8 (8.8)
State Trait Anxiety Score	65.3 (18.3)	57.1 (14.1)	69.8 (18.1)
QUIP	0.3 (0.6)	0.3 (0.7)	0.6 (1.0)
UPSIT Raw Score	22.4 (8.2)	34.0 (4.9)	31.4 (6.2)
Epworth Sleep. Scale (Sleepy = 10 or above)	66 (16%)	24 (12%)	21 (33%)
REM Sleep Disorder (Positive = 5 or above)	160 (38%)	39 (20%)	26 (41%)

BASELINE CHARACTERISTICS

Group	PD Subjects (N = 419)	Healthy Controls (N = 192)	SWEDD Subjects (N = 62)
Contralateral Caudate	1.84 (0.56)	3.10 (0.65)	2.86 (0.60)
Ipsilateral Caudate	2.15 (0.60)	2.87 (0.61)	2.82 (0.57)
Contralateral Putamen	0.70 (0.27)	2.26 (0.58)	2.08 (0.53)
Ipsilateral Putamen	0.96 (0.38)	2.03 (0.55)	2.05 (0.50)

NOTE: For Healthy Controls and PD subjects with symmetrical presentation, 'Ipsilateral' is defined as the lower of the left and right values.

BASELINE CHARACTERISTICS

Group	PD Subjects (N = 63)	Healthy Controls (N = 39)	SWEDD Subjects (N = 4)
A-Beta	228.7 (45.6)	242.8 (50.0)	276.0 (23.0)
T-Tau	46.1 (24.7)	53.9 (19.3)	55.0 (25.4)
P-Tau	21.0 (7.8)	24.9 (8.5)	23.5 (8.4)
Alpha-Synuclein	1082 (611.1)	1264 (425.8)	1413 (750.6)

BASELINE CHARACTERISTICS

Other Baseline Papers in Progress:

- Cognitive (Weintraub)
- DaTSCAN (Marek / Seibyl)
- DTI (Schuff)
- Biologics (Shaw / Trojanowski)
- Urate (Radu)
- Sleep (Simuni)

VISIT COMPLIANCE

Group	6 Months # Expected (% Seen)	1 Year # Expected (% Seen)	2 Year # Expected (% Seen)	3 Year # Expected (% Seen)
PD Subjects	357 (92%)	256 (91%)	89 (87%)	2 (100%)
Healthy Controls	166 (95%)	149 (97%)	70 (83%)	2 (100%)
SWEDD Subjects	55 (80%)	38 (95%)	7 (57%)	N/A

PRIMARY OBJECTIVES

Primary Objective #1: Estimate mean rates of change and variability of clinical, imaging, and biomic outcomes at study intervals ranging from baseline to 36 months in various subsets:

- Early PD
- Healthy Controls
- SWEDD Subjects
- Prodromal Subjects
- *PD with and without LRRK2 or SNCA mutation*
- *Unaffected LRRK2 or SNCA mutation carriers*

PRIMARY OBJECTIVES

Specific examples of outcomes for consideration:

- MDS-UPDRS
- Dopamine transporter imaging striatal uptake
- Vesicular monoamine transporter-2 uptake
- Serum & CSF alpha-synuclein

PRIMARY OBJECTIVES

PD patient subsets may be defined by:

- Baseline assessments
- Genetic mutations
- Progression milestones
- Rate of clinical, imaging, or biomic change

PRIMARY OBJECTIVES

Primary Objective #2: Comparison between rates of change in mean of clinical, imaging, and biomic outcomes at study intervals ranging from 3 to 36 months in various subsets:

- Early PD vs. Healthy Controls
- Early PD vs. SWEDD
- Early PD vs. Prodromal Subjects
- *PD with LRRK2 or SNCA mutation vs. PD without LRRK2 or SNCA mutation*
- *Unaffected LRRK2 or SNCA mutation carriers vs. Healthy Controls*

SECONDARY OBJECTIVES

Secondary Objective #1: Examine predictive value of early clinical non-motor features, imaging, and biomic outcomes for future course of disease.

- Examine short-term change during first six months / 1 year for each progression endpoint using mixed model (continuous endpoints) or logistic regression (dichotomous endpoints)
- Initial model will consider all baseline characteristics, and all possible two-way interactions
- Will utilize backwards selection to build a model for each progression endpoint

SECONDARY OBJECTIVES

Secondary Objective #1: Examine predictive value of early clinical non-motor features, imaging, and biomic outcomes for future course of disease.

- Consider progression endpoints that show short-term differences between subgroups
- Primary focus on long-term change in UPDRS score – additional long-term endpoints may be considered as well
- If successful, final model will provide subset of short-term progression endpoints predictive of change in long-term endpoints – suggest biomarkers for future studies of interventions in PD patient populations

SECONDARY OBJECTIVES

Secondary Objective #2: Examine proportion of SWEDD subjects that have a change in diagnosis over 24 month evaluation period

- Percentage and 95% confidence interval will be reported
- Other possible diagnoses will be further divided into 2 categories:
  - Other parkinsonian syndrome with a dopamine transporter deficit
  - Other condition with a dopamine transporter deficit

SECONDARY OBJECTIVES

Secondary Objective #3: Examine proportion of prodromal subjects who phenoconvert within two years.

- Percentage & 95% confidence interval will be reported
  - Overall, and by specific type of prodromal subject (all must have baseline DaTSCAN binding showing minimal to moderate DAT deficit):
    - Hyposmia (<10th percentile by age & gender)
    - RBD
    - *LRRK2 or SNCA mutation*

SECONDARY OBJECTIVES

Secondary Objective #4: Exploratory analyses to examine whether baseline DaTSCAN binding or progression of clinical, imaging, or biospecimen biomarkers predict those subjects likely to phenoconvert.

- Percentage & 95% confidence interval will be reported
- Examine whether short-term change in progression endpoints are predictive of phenoconversion
- Will involve fitting a logistic regression model for phenoconversion, with each progression endpoint serving as a covariate

SECONDARY OBJECTIVES

Secondary Objective #5: Exploratory analyses to compare Genetic Cohort & Genetic Registry.

- *Comparison of baseline characteristics*
- *Comparisons of changing in potential progression endpoints across two groups*

SAMPLE SIZE JUSTIFICATION

Because of exploratory nature of the planned analyses, it is very difficult to provide a formal sample size justification for the entire model building process.

However, we examined the ability of proposed sample size (400 PD patients/200 healthy controls) to detect meaningful effects of interest.

SAMPLE SIZE JUSTIFICATION

Total Sample Size	Detectable Correlation	Detectable Difference in Prevalence	Detectable Difference in Means (Standardized)
300	0.16	17%	0.33
400	0.14	14%	0.28
450	0.14	15%	0.28
600	0.11	13%	0.24

Last two rows correspond to first set of comparisons (PD patients vs. healthy controls)

First two rows correspond to second set of comparisons (among PD subsets)

SAMPLE SIZE JUSTIFICATION

Other planned sample sizes less justified:

- SWEDD sample size based on estimated % of SWEDD subjects observed during recruitment period
- Prodromal cohort sample size based primarily on prior exploratory studies
  - Will allow estimating phenoconversion rate with a 95% CI width of +/- 10%
- *LRRK2 & SNCA sample size based primarily on exploratory studies and considerations regarding availability of subjects with PD & family members with these specific genetic mutations*

PPMI Publication Policy and Plan

Ken Marek
The Institute for Neurodegenerative Disorders

Genetic Kickoff Meeting
Sept 16, 2013
New York, NY

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

Publication Policy

Goals-

- High quality, rapid publication
- Consistent with the broad PPMI collaboration
  - SC, Cores, Sites, Working Groups
- Credit PPMI investigators
- Encourage non-PPMI community

Publication Policy

- **Key Primary and Primary**
- **Others**
- **Abstracts for meetings**
- **Role of DPC**

Publication Policy-Key Primary

Key Primary Publications - *Key Primary Publications* are defined as those reports, analyses and publications identified by the PPMI Steering Committee as fulfilling the primary objectives of the study. Examples of these reports include publications detailing the baseline or yearly data-cuts

The SC will be primarily responsible for completion of all Key Primary Publications. Key Primary publications will be authored by the Steering Committee, Investigators, Study Cores and Working Groups reflecting the contribution of those authors.

Publication Policy - Key Primary

For KEY primary publications

"And The Parkinson's Progression Markers Initiative*" will be written on the author line of the manuscript with an asterisk referring to the list of names of individuals identified on the PPMI author list. The author list must be included as an appendix to ensure that all authors may be cited. The complete list of PPMI Study Investigators can be found at www.ppmi-info.org/Authorslist

Sent to both the PPMI Steering Committee and the PPMI Data & Publications Committee (DPC) for review prior to journal submission.

Publication Policy-Primary

Primary Publications - Primary publications are defined as reports, analyses and publications that are initiated by PPMI study members that utilize PPMI data, but which do not address the primary objectives of the study. Examples of these studies include a focus on specific biomarkers of disease progression, study infrastructure or recruitment.

Publications developed by study investigators, cores, working groups and authorship will reflect the contribution of those authors. In addition to the authors, "And The Parkinson's Progression Markers Initiative*" will be written on the author line of the manuscript with an asterisk referring to the list of names of individuals identified on the PPMI author list. The author list must be included as an appendix to ensure that all authors may be cited. The list of PPMI Study Investigators can be found at www.ppmi-info.org/Authorslist

Publication Policy-Primary

Primary Publications - Sent to both the PPMI Steering Committee and the PPMI Data & Publications Committee (DPC) for review prior to journal submission

Publication Policy-Other

Other Publications - It is expected that investigators outside of the study will conduct research and seek to publish analyses using PPMI data and specimens. These individuals are encouraged to publish novel scientific findings that result from their research using PPMI. Authorship of such a publication will not include PPMI in the author line,

Publication Policy-Other

PPMI personnel and PPMI funding support will be acknowledged by including the following within the manuscript:

"Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org."

"PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including [list the full names of all of the PPMI funding partners found at www.ppmi-info.org/fundingpartners]."

Make link to webpage

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Publication Policy-Other

All other publications must be sent to the PPMI DPC for administrative review prior to journal submission. To submit to the DPC, please upload the publication for review via the PPMI website

Publication process - Primary

- Authors should develop data analysis plan in collaboration with Stats
- Authors should develop time-line for drafts and completion of report
- Goal is to identify authors for primary publications.

Source and Cut of Data

- Source should be LONI data so need to submit all data
- Timing of Data cuts - Data cuts to be published by SC
    - Baseline, 6 months, 1 year, then yearly
- Definition of full data set

Publication and Analysis plans

Baseline data Papers

Paper #	Description	Contact	Status	Date of Most Recent Change to List
1	Overall Baseline Paper	Ken Marek	Preliminary Tables Reviewed	24 Apr 2013
2	Cognitive Paper	Dan Weintraub	Building Tables with Data	18 Apr 2013
3	DATSCAN Paper	John Seibyl / Ken Marek	Tables Sent to John and Ken / Feedback Pending	18 Apr 2013
4	DTI Paper	Norbert Schuff	-	24 Apr 2013
5	Biologics Paper	Les Shaw / John Trojanowski	-	18 Apr 2013
6	Urate Paper	Constantinescu Radu	Tables for an abstract sent to Radu / Feedback Pending	18 Apr 2013

Baseline data

- Primary baseline
- Subsets
- Cognitive – domains, compare UPDRS
- Imaging - DAT, AV133, DTI, Resting state
- Biologics -CSF analytes, Urate, Genetics
- Process - Recruitment, Imaging, CSF
- Ancillary - Tap
- SWEDD

ANALYSES

- TD vs PIGD
- Meds vs no Meds
- Comparison cognitive with imaging/CSF
- Sleep assessments
- Enrollment/recruitment
- Comparison of DAT and DTI
- UPDRS vs cognitive measures

PLANNED ANALYSES

Planned Analysis #1: Comparison of Baseline Characteristics Among Healthy Subjects and PD Subjects.

- Continuous variables assessed using t-test
- Dichotomous variables assessed using chi-square test
- Appropriate assumptions will be assessed for each comparison and any necessary adjustments (i.e., transformations) will be made prior to analysis

12 month data

- Primary baseline
- Subsets
- Cognitive – domains, compare UPDRS
- Imaging - DAT, AV133, DTI, Resting state
- Biologics -CSF analytes
- Process – Retention,CSF
- Ancillary - Tap
- SWEDD

PLANNED ANALYSES

Planned Analysis #2: Comparison of Short-Term Change in Progression Endpoints.

- Examine short-term change during first six months for each progression endpoint using mixed model (continuous endpoints) or logistic regression (dichotomous endpoints)
- Initial model will include all baseline characteristics, indicator for whether healthy control of PD patient, and all possible two-way interactions
- Will utilize backwards selection to build a model for each progression endpoint

PLANNED ANALYSES

Planned Analysis #3: Examination of Whether Short-Term Change in Progression Endpoints is Predictive of Change in Long-Term Endpoints

- Consider only progression endpoints that show differences between healthy subjects and PD patients
- Primary focus on long-term change in UPDRS score – additional long-term endpoints may be considered as well
- Ten-fold cross-validation procedure will be used to test predictive validity of each model
- If successful, final model will provide subset of short-term progression endpoints predictive of change in long-term endpoints – suggest biomarkers for future studies of interventions in PD patient populations

PLANNED ANALYSES

Planned Analysis #4: Examination of PD Subsets

- Each of first three sets of analyses will be repeated comparing subsets of PD patients
- If successful, final model will determine whether some short-term progression endpoints are more predictive of long-term endpoints for some subsets of PD patients and less predictive for other subsets

PLANNED ANALYSES

Planned Analysis #5: Proportion of SWEDD subjects that have a change in diagnosis over 24 month evaluation period

- Percentage and 95% confidence interval will be reported
- Other possible diagnoses will be further divided into 2 categories:
  - Other parkinsonian syndrome with a dopamine transporter deficit
  - Other condition with a dopamine transporter deficit

PLANNED ANALYSES

Planned Analysis #6: Exploratory analysis of SWEDD subjects

- Important changes over time found in planned analyses 1-3 will be assessed in the SWEDD subjects
- Will help to assess whether changes over time in SWEDD subjects are similar or dissimilar to PD subjects

PLANNED ANALYSES

Baseline

Tabulate and compare for all subjects Demographics by diagnostic category (PD, HC, SWEDD; Compare PD vs HC; PD vs SWEDD)

- Age
- Gender
- Education
- Ethnicity
- Race
- Family history of PD

(From tables 3 and 4 – monthly)

PLANNED ANALYSES

Baseline

Tabulate and compare for all subjects Summary clinical scores by diagnostic category (PD, HC, SWEDD; Compare PD vs HC;PD vs SWEDD)

- UPDRS Total and subscore
- Hoehn and Yahr
- Schwab and England
- Dur of Dis
- MOCA total
- GDS Total
- SCOPA AUT total
- State Anxiety
- QUIP
- UPSIT
- Epworth

(From tables 4 and 5)

PLANNED ANALYSES

Baseline

Tabulate and compare for all subjects DAT imaging SBR
by diagnostic category (PD, HC, SWEDD; Compare PD vs HC;PD vs SWEDD)

- Mean striatal
- Mean putamen
- Mean caudate
- Ipsilateral Caudate
- Contralateral Caudate
- Ipsilateral Putamen

Contralateral Putamen

PLANNED ANALYSES

Baseline

Tabulate and compare for all subjects CSF synuclein, amyloid, Tau by diagnostic category (PD, HC, SWEDD; Compare PD vs HC;PD vs SWEDD)

- $A\beta_{1-42}$ (pg/mL)
- t-tau (pg/mL)
- $p\text{-}tau_{181}$ (pg/mL)
- t-tau/$A\beta_{1-42}$ ratio
- $p\text{-}tau_{181}/A\beta_{1-42}$ ratio
- $p\text{-}tau_{181}$/t-tau ratio
- A-syn (pg/mL)

Should we include hemoglobin data?

PLANNED ANALYSES

Baseline

UPDRS as an anchor: relationship between baseline UPDRS with non-motor, imaging, biologic at baseline (PD, HC, SWEDD; Focus on PD) – See Ravina et al. *Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease*

Adjusted for age, gender, duration of disease

To be compared

- MOCA total
- GDS Total
- SCOPA AUT total
- State Anxiety
- QUIP
- UPSIT
- Epworth
- DAT
- $A\beta_{1-42}$ (pg/mL)
- t-tau (pg/mL)
- p-tau_{181} (pg/mL)
- t-tau/$A\beta_{1-42}$ ratio
- p-tau_{181}/$A\beta_{1-42}$ ratio
- p-tau_{181}/t-tau ratio
- A-syn (pg/mL)

PLANNED ANALYSES

Baseline

DAT scan as anchor: relationship between baseline DAT with motor, non-motor biologics at baseline (PD, HC, SWEDD; Focus on PD) See Ravina et al. *Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease*

Adjusted for age, gender, duration of disease

To be compared

- UPDRS
- MOCA total
- GDS Total
- SCOPA AUT total
- State Anxiety
- QUIP
- UPSIT
- Epworth
- $A\beta_{1-42}$ (pg/mL)
- t-tau (pg/mL)
- p-tau_{181} (pg/mL)
- t-tau/$A\beta_{1-42}$ ratio
- p-tau_{181}/$A\beta_{1-42}$ ratio
- p-tau_{181}/t-tau ratio
- A-syn (pg/mL)
- Urate

Timeline

PPMI - Genetic Timeline

Draft Amendment 6 – Complete
Site visits and Approvals – Complete

Site Contract July /Nov 2013
Site submission to IRB/Ethical committee –July/Nov 2013

Subject enrollment August 2013
All sites enrolling – Nov-Dec 2013

Enrollment complete – Dec 2015

Completion of 3 year f/u on all subjects – Dec 2018