Cognitive and Motor Function in Long-Duration PARKIN-Associated Parkinson Disease

RN Alcalay, Columbia University
E Caccappolo, Columbia University
H Mejia-Santana, Columbia University
MX Tang, Columbia University
L Rosado, Columbia University
MO Reilly, Columbia University
D Ruiz, Columbia University
ED Louis, Columbia University
CL Comella, Rush University
MA Nance, Struthers Parkinson’s Center

Only first 10 authors above; see publication for full author list.

Journal Title: JAMA Neurology
Volume: Volume 71, Number 1
Publisher: American Medical Association (AMA) | 2014-01-01, Pages 62-67
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1001/jamaneurol.2013.4498
Permanent URL: https://pid.emory.edu/ark:/25593/twd8z

Final published version: http://dx.doi.org/10.1001/jamaneurol.2013.4498

Copyright information:
Copyright 2014 American Medical Association. All rights reserved.
Accessed September 12, 2020 1:38 AM EDT
Cognitive and Motor Function in Long-Duration PARKIN-Associated Parkinson Disease

Roy N. Alcalay, MD, MSc; Elise Caccappolo, PhD; Helen Mejia-Santana, MSc; Ming Xin Tang, PhD; Llency Rosado, MD; Martha Orbe Reilly, MD; Diana Ruiz, BSc; Elan D. Louis, MD, MSc; Cynthia L. Comella, MD; Martha A. Nance, MD; Susan B. Bressman, MD; William K. Scott, PhD; Caroline M. Tanner, MD, PhD; Susan F. Mickel, MD; Cheryl H. Waters, MD; Stanley Fahn, MD; Lucien J. Cote, MD; Steven J. Frucht, MD; Blair Ford, MD; Michael Rezak, MD, PhD; Kevin E. Novak, PhD; Joseph H. Friedman, MD; Ronald F. Pfeiffer, MD; Laura Marsh, MD; Bradley Hiner, MD; Haydeh Payami, PhD; Eric Molho, MD; Stewart A. Factor, DO; John G. Nutt, MD; Carmen Serrano, MD; Maritza Arroyo, MD; Ruth Ottman, PhD; Michael W. Pauciulo, MBA; William C. Nichols, PhD; Lorraine N. Clark, PhD; Karen S. Marder, MD, MPH

IMPACT Importance Data on the long-term cognitive outcomes of patients with PARKIN-associated Parkinson disease (PD) are unknown but may be useful when counseling these patients.

OBJECTIVE Objective Among patients with early-onset PD of long duration, we assessed cognitive and motor performances, comparing homozygotes and compound heterozygotes who carry 2 PARKIN mutations with noncarriers.

DESIGN, SETTING, AND PARTICIPANTS Design, Setting, and Participants Cross-sectional study of 44 participants at 17 different movement disorder centers who were in the Consortium on Risk for Early-Onset PD study with a duration of PD greater than the median duration (>14 years): 4 homozygotes and 17 compound heterozygotes (hereafter referred to as carriers) and 23 noncarriers.

MAIN OUTCOMES AND MEASURES Main Outcomes and Measures Unified Parkinson Disease Rating Scale Part III (UPDRS-III) and Clinical Dementia Rating scores and neuropsychological performance. Linear regression models were applied to assess the association between PARKIN mutation status and cognitive domain scores and UPDRS-III scores. Models were adjusted for age, education, disease duration, language, and levodopa equivalent daily dose.

RESULTS Results Carriers had an earlier age at onset of PD (P < .001) and were younger (P = .004) at time of examination than noncarriers. They performed better than noncarriers on the Mini-Mental State Examination (P = .01) and were more likely to receive lower scores on the Clinical Dementia Rating (P = .003). In multivariate analyses, carriers performed better than noncarriers on the UPDRS-III (P = .02) and on tests of attention (P = .03), memory (P = .03), and visuospatial (P = .02) cognitive domains.

CONCLUSIONS AND RELEVANCE Conclusions and Relevance In cross-sectional analyses, carriers demonstrated better cognitive and motor performance than did noncarriers with long disease duration, suggesting slower disease progression. A longitudinal follow-up study is required to confirm these findings.

Published online November 4, 2013.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Roy N. Alcalay, MD, MSc, Department of Neurology, College of Physicians and Surgeons, Columbia University, 710 W 168th St, New York City, NY 10032 (rna2104@columbia.edu).
**PAR**KIN mutations are the most common genetic mutations associated with early-onset Parkinson disease (EOPD), defined by an age at onset of 50 years or younger.1 Two cross-sectional studies2,3 that examined the cognitive performance of patients with EOPD found similar neuropsychological results between homozygous and compound heterozygous (H/CH) carriers and noncarriers of PARKIN mutations. However, it has been hypothesized that H/CH carriers are less likely than noncarriers to develop dementia and that longer follow-up is required to differentiate between the cognitive performances of H/CH carriers and those of noncarriers.4 To explore this hypothesis, we repeated our cognitive performances of H/CH carriers and those of noncarriers are less likely than noncarriers to develop dementia and that longer follow-up is required to differentiate between the cognitive performances of H/CH carriers and those of noncarriers.4 To explore this hypothesis, we repeated our analyses of the Consortium on Risk for Early-Onset PD (CORE-PD) study after recruiting additional participants and restricting the analyses to those with a higher than median (>14 years) disease duration. Using cross-sectional data, we approximated long-term follow-up by examining the cognitive profiles of individuals with PD of long duration, using a larger sample of patients with EOPD than we previously reported.2

**Methods**

**Participants**

Participants with EOPD defined by an age at onset of 50 years or younger were recruited from 13 movement disorder centers participating in the CORE-PD study as previously described.6,7 Four sites (in San Juan, Puerto Rico; Albany, New York; Atlanta, Georgia; and Portland, Oregon) were later added to increase the number of H/CH carriers and noncarriers with EOPD. The institutional review boards at all the participating sites approved the protocols and consent procedures. We performed detailed examinations, including a neuropsychological battery on 178 probands with EOPD who had mutations in *PARKIN* and glucocerebrosidase (*GBA*), and on a subset of participants without known mutations.6 To approximate long-term follow-up, we examined the distribution of PD duration and selected individuals with a disease duration greater than the median duration (ie, 14 years). We excluded carriers of *GBA* and LRRK2 mutations. Because of the controversial role of heterozygous *PARKIN* mutations,6-8 heterozygous carriers were also excluded. The analyses were performed on 4 homozygotes and 17 compound heterozygotes who carry 2 mutations in *PARKIN* (ie, 21 carriers) and 23 noncarriers of mutations in *PARKIN*, *PINK-1*, *DJ-1*, LRRK2, or *GBA*.5 Of the 44 participants included in the final analysis, 38 were previously reported.2 Of the 6 new participants, 2 were carriers, and 4 were noncarriers.

**Molecular Genetic Analyses**

Participants were genotyped for *PARKIN*, *GBA*, LRRK2, *PINK-1*, and *DJ-1* as previously described.5,9,10 Beginning in 2010, we used multiplex ligation–dependent probe amplification (MLPA)7 for newly recruited probands and for all probands recruited prior to 2010 with point mutations or dosage changes. All deletions and duplications identified via MLPA were verified using real-time polymerase chain reaction. All probands with *PARKIN* mutations detected via the resequencing chip or with dosage detected via MLPA have had full sequencing of *PARKIN* exons and MLPA if not previously performed.

**Clinical and Neuropsychological Evaluation**

The clinical evaluation of CORE-PD participants has been previously described.6,11 In brief, it included the Unified Parkinson Disease Rating Scale (UPDRS),12 which was performed in the “on” state, the Mini-Mental State Examination, the Clinical Dementia Rating,13 and a neuropsychological battery. The neuropsychological battery used in our study was composed of measures corresponding to 5 cognitive domains: psychomotor speed, attention, memory, visuospatial function, and executive function (eTable 1 in Supplement). The battery included measures that could be administered in English or Spanish. Each participant was assigned a clinical consensus diagnosis based on medical history, neurological examination, neuropsychological performance, and functional impairment, without knowledge of genetic status.14 Participants were rated as being cognitively normal, as having mild cognitive impairment,16 or as being demented.11

**Statistical Analysis**

Individual neuropsychological test scores were transformed to create z scores using means and standard deviations of the entire sample of PD cases. Composite scores for each domain were computed by averaging the mean z scores from the individual tests comprising each domain.11 Demographic data, disease characteristics, Mini-Mental State Examination scores, Clinical Dementia Rating scores, and neuropsychological test performances were compared between carriers and noncarriers using the Fisher exact test, the χ2 test, and the t test as appropriate. Linear regression models were constructed to test the association between genetic status (predictor) and UPDRS Part III (UPDRS-III) and cognitive domain scores (outcomes), adjusting for age, duration of PD, education (truncated at 20 years), levodopa equivalent daily dose, and the language that the tests were administered in (ie, Spanish or English).

**Results**

The demographic and clinical characteristics of the participants stratified by *PARKIN* genetic status are shown in Table 1. The H/CH carriers had an earlier age at onset of PD and were younger at time of the examination than the noncarriers. They performed better on the Mini-Mental State Examination and were more likely to receive lower Clinical Dementia Rating scores (indicating better functional status) than noncarriers. Mean raw scores on individual neuropsychological tests are reported in eTable 2 in Supplement.

In models adjusted for age, sex, disease duration, education, levodopa equivalent daily dose, and language (Table 2), the *PARKIN* mutation status of H/CH carriers was associated with better performance on the UPDRS-III (P = .02) and on tests of attention (P = .03), memory (P = .03), and visuospatial (P = .02) cognitive domains compared with noncarriers. Better cognitive performance in each of the cognitive domains was...
highly correlated with lower UPDRS-III scores (psychomotor speed: \( r = -0.503, P = .001 \); attention: \( r = -0.541, P < .001 \); memory: \( r = -0.597, P < .001 \); visuospatial: \( r = -0.635, P < .001 \); and executive function: \( r = -0.468, P = .002 \)). Therefore, when each of the cognitive domains was included in the adjusted models with UPDRS-IIIscore as the outcome, the association between \textit{PARKIN}mutation status and UPDRS-IIIscore was not significant. Similarly, when the UPDRS-III score was included in the adjusted models, with each cognitive performance domain as the outcome, the association between \textit{PARKIN} mutation status and performance in each cognitive domain was not significant.

### Discussion

Among patients with EOPD, we have demonstrated that homozygotes and compound heterozygotes who carry \textit{PARKIN} mutations and have a long disease duration perform better than noncarriers on tests of attention, memory, and visuospatial cognitive domains and on motor examinations during the “on” state. Motor and cognitive performances were very strongly correlated, as expected. These findings are consistent with the milder motor PD previously reported in homozygotes and compound heterozygotes who carry \textit{PARKIN} mutations compared with noncarriers in cross-sectional analyses\(^6\) and with previously reported clinical observations that dementia is rare among homozygotes and compound heterozygotes who carry \textit{PARKIN} mutations.\(^1\)\(^6\)\(^\text{—}^\text{21}\) However, the differences in cognitive performance identified in the present study contrast with previous findings (including those from our own cohort) in that no significant differences in neuropsychological performance between H/CH carriers and noncarriers were shown.\(^2\)\(^3\) The possible explanations for the discrepancy are that H/CH carriers are less likely to develop the cognitive impairment and dementia that often occurs as PD advances, and that the pathology in \textit{PARKIN}-associated PD remains circumscribed to the substantia nigra, even as the disease progresses. Autopsy data also support this hypothesis. Brain autopsies from homozygotes and compound heterozygotes who carry \textit{PARKIN} mutations demonstrated nigral atrophy, but without neurodegenerative pathology in the cortex; neither Lewy bodies nor Alzheimer disease neuropathology is present in these brains, with rare exceptions.\(^2\)^\(^5\)\(^\text{—}^\text{23}\) In contrast, Lewy bodies and Alzheimer disease–like changes are the most common findings in autopsies of patients with PD dementia.\(^2\)\(^4\) We have also previously reported that homozygotes and compound heterozygotes who carry \textit{PARKIN} mutations are less likely than other

### Table 1. Clinical and Demographic Characteristics of Noncarriers and Carriers of 2 \textit{PARKIN} Mutations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Noncarriers(^a) (n = 23)</th>
<th>Carriers(^b) (n = 21)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.5 (6.4)</td>
<td>53.1 (11.5)</td>
<td>.004</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>40.2 (4.0)</td>
<td>26.6 (10.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>21.3 (4.2)</td>
<td>26.3 (9.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>15.7 (4.2)</td>
<td>13.5 (2.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Neuropsychological testing in Spanish, No. (%) of participants</td>
<td>3 (13.0)</td>
<td>5 (23.8)</td>
<td>.45</td>
</tr>
<tr>
<td>UPDRS-III score, mean (SD)</td>
<td>27.8 (10.1)</td>
<td>21.0 (7.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Levodopa equivalent daily dose, mean (SD), mg</td>
<td>811 (366)</td>
<td>650 (530)</td>
<td>.25</td>
</tr>
<tr>
<td>Ethnicity, % of participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73.9</td>
<td>61.9</td>
<td>.34</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21.7</td>
<td>38.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.3</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Female sex, No. (%) of participants</td>
<td>9 (39.1)</td>
<td>12 (57.1)</td>
<td>.37</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>27.9 (2.0)</td>
<td>29.2 (0.9)</td>
<td>.010</td>
</tr>
<tr>
<td>CDR score,(^c) No. (%) of participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (40.9)</td>
<td>16 (76.2)</td>
<td>.003</td>
</tr>
<tr>
<td>0.5</td>
<td>2 (9.1)</td>
<td>5 (23.8)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (40.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (9.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Clinical diagnosis, No. (%) of participants</td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Normal</td>
<td>5 (21.7)</td>
<td>6 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>7 (30.4)</td>
<td>13 (61.9)</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>11 (47.8)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>(z) Score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>−0.58 (1.1)</td>
<td>−0.11 (0.74)</td>
<td>.11</td>
</tr>
<tr>
<td>Attention</td>
<td>−0.64 (0.95)</td>
<td>0.00 (0.83)</td>
<td>.03</td>
</tr>
<tr>
<td>Memory</td>
<td>−0.51 (0.91)</td>
<td>−0.14 (0.79)</td>
<td>.16</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>−0.44 (1.3)</td>
<td>0.10 (0.59)</td>
<td>.08</td>
</tr>
<tr>
<td>Executive function</td>
<td>−0.53 (0.90)</td>
<td>−0.07 (0.63)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviations: CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; UPDRS-III, Unified Parkinson Disease Rating Scale Part III.\(^a\) Four noncarriers completed only portions of the neuropsychological examination.\(^b\) Four homozygotes and 17 compound heterozygotes who carry 2 mutations in \textit{PARKIN}.\(^c\) One noncarrier did not receive a CDR score.
patients with EOPD to manifest hyposmia. These clinical findings, as well as the autopsy data, suggest a “purer dopaminergic deficit” in PARKIN-associated PD.

Our findings may have important implications for genetic testing and for the counseling of homozygotes and compound heterozygotes who carry PARKIN mutations. Recent studies have demonstrated that patients with PD are interested in genetic testing results, but they may not fully understand the implications of these results or the benefits of genetic counseling. Considering that homozygotes and compound heterozygotes who carry PARKIN mutations develop PD at a younger age than noncarriers, they may be concerned about their risk for dementia and their long-term ability to work. These H/CH carriers may benefit from the assurance that they have a lower risk for dementia than patients with idiopathic PD.

The major strengths of our study include the size of our cohort, given that it represents the largest sample size of mutation carriers with long disease duration reported, to date, and the comprehensive neuropsychological battery used. Our noncarrier EOPD group is likely an appropriate comparison group, having been screened for mutations in PARKIN, GBA, LRRK2, SNCA, PINK-1, and DJ-1. We previously showed, using the same battery and a noncarrier control group, that noncarriers with EOPD perform better than GBA mutation carriers. A significant limitation of our study is its cross-sectional design. In spite of our efforts to match the genetic groups by including only patients with EOPD of long duration, noncarriers were older than H/CH carriers, and the H/CH carriers had a longer duration of disease than did the noncarriers, although we did adjust for this in the analyses. Future studies that investigate the effects of disease duration on cognitive and motor function, including those with longitudinal follow-up, will help confirm our observation that PARKIN-associated PD may progress more slowly than idiopathic PD.

**Table 2. Linear Regression Models Testing the Association Between PARKIN Mutation Status and Cognitive Domain Performance Among Patients With Early-Onset Parkinson Disease of Long Duration (>14 Years)**

<table>
<thead>
<tr>
<th>Performance</th>
<th>Noncarriers vs Carriers</th>
<th>β (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unified Parkinson Disease Rating Scale</td>
<td>4.70 (0.89-8.50)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>−0.32 (−0.75 to 0.12)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>−0.42 (−0.79 to −0.05)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>−0.36 (−0.67 to −0.05)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Visual-spatial function</td>
<td>−0.48 (−0.90 to −0.07)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>−0.28 (−0.58 to 0.01)</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

* Models are adjusted for age, sex, disease duration, education, levodopa equivalent daily dose, and language in which the tests were performed (English or Spanish). The analyses were performed on 4 homozygotes and 17 compound heterozygotes who carry 2 mutations in PARKIN (ie, 21 carriers) and 23 noncarriers of mutations in PARKIN, PINK-1, DJ-1, LRRK2, or GBA. However, 4 noncarriers completed only portions of the neuropsychological examination.
Conflict of Interest Disclosures: Dr Alcalay receives research support from the National Institutes of Health (NIH; grant KO2NS080915), the Parkinson’s Disease Foundation, the Smart Foundation, and the Michael J. Fox Foundation for Parkinson’s Research. Dr. Louis receives research support from the NIH (National Institute of Neurological Disorders and Stroke [NINDS] grants R01 NS42859, R01 NS39422, R56 NS042859, and T32 NS071568 as PI), the Huntington’s Disease Society of America, Medscape, and Augsburg College; and the Huntington Disease Society of America; Complementary and Alternative Medicine as site investigator, and the National Center for Human Genome Research RO1NS36630 as co-PI) and the Parkinson’s Disease Foundation as PI. Dr. Cornella serves on the editorial board of Clinical Neuropharmacology and Continuum: Neurology and Neuroscience-Associated Parkinson Disease. Dr. Scott is a coinventor on a patent regarding the use of genetic data for assessing risk of dementia, hypoxia, age-related macular degeneration, licensed to ArcticDx; received speaking honoraria from CHDI; and received research support from the NIH (grants EY023364, EY023394, A168804, NS071674, EY012188, HG000026, and AG090853), the BrightFocus Foundation, and the James and Esther King Biomedical Research Program. Dr. Tanner serves on the scientific advisory boards of the Michael J. Fox Foundation and the National Spasmodic Dystonia Association. She has consulted for Adamas Pharmaceuticals, Impax Pharmaceuticals, Lundbeck Pharmaceuticals, Pacific Health Research Institute (consultant for the NIH and Department of Defense [funded research]), Stanford University (consultant for the Muscular Dystrophy Association [funded research]), and NeuroHealth Research Institute (consultant for the Michael J. Fox Foundation [funded research]). She has received research support from the Michael J. Fox Foundation, the Brin Foundation, James and Sharron Clark, the NIH, the Parkinson’s Institute and Clinical Center, the Parkinson’s Disease Foundation, the Department of Defense, Panasonic, Unity Walk, and the Welding Products Manufacturer’s Group. Dr. Waters received speaking honorarium from Teva and UCB. She receives research support from the Parkinson’s Disease Foundation. Dr. Fahn reports consulting and advisory board membership with honoraria from Merz Pharma (January 2013) and Genenvon Biotechnology (he expects to receive compensation for serving as PI of a pilot clinical trial); grants and research support from the Parkinson’s Disease Foundation (no salary support); a grant from the Smart Family Foundation (December 2012); letter of thanks from the American Academy of Neurology (April 2012), Columbia University (July 2012), and Sun Pharmaceuticals India (November 2012); and editor and author honoraria from Springer for serving as coeditor of Current Neurology and Neurosurgery (annual) and Elsevier for coauthorship of the book Principles and Practice of Movement Disorders. Dr. Frucht has received research consultation fees from Lundbeck, Jazz Pharmaceuticals, and Merz. Dr. Rezak is on the speaker bureau of Teva, Medtronic, Novartis, Boehringer Ingelheim, GlaxoSmithKline, and UCB. Dr. Friedman has received speaking honorarium from Teva, General Electric, and UCB. He received research support from the Michael J. Fox Foundation, EMD Serona, Teva, Acadia, Schering-Plough, and the NIH. He has received consulting fees from Teva, Addex Pharm, UCB, Lundbeck, and Roche. He has received book royalties from Demos. Dr. Pfeiffer reports receiving honoraria from CRC Press (Taylor and Francis) and Humana Press; lecture honoraria from Teva, UCB, and US WorldMeds; honoraria for consulting from UCB; and research grants and contracts from Boehringer Ingelheim, UCB, and Phytopharm. In addition, he has received consulting fees from Tucker Ellis & West and Thomas, Thomas & Hafer. He is the editor in chief of Parkinsonism and Related Disorders (Elsevier). Dr Marsh served on the advisory board of the National Parkinson Foundation and the American Parkinson’s Disease Association. She has received consultation fees from Acadia Pharmaceutical, Ovation Pharmaceutical, Merck Serono, Boehringer Ingelheim. She has received research support from the NIH, the Forest Research Institute, Eli Lilly, the Michael J Fox Foundation, and the National Parkinson Foundation. She has received book royalties from Taylor and Francis/Informa. Dr. Payami has received funding from the NIH (grant NS36960). Dr. Molino is supported by the Riley Family Chair in Parkinson’s Disease. He has received consulting fees from US WorldMeds and Merz Pharmaceuticals. He has received research support from Merz Pharmaceuticals, Acadia Pharmaceuticals, Allergan, Prana Pharmaceuticals, Impax Pharmaceuticals, EMD Serona, NINDS grant R01 NS050118 (site investigator), and NIH grant R01 NS053024-01A1 (site investigator). Dr. Factor reports receiving honoraria from Scientific for a CME program, a University of Florida speaker program, the current Neurology and Neuroscience section editor, and UpToDate; consulting fees from Merz, Ipsen, and Chelsea Therapeutics; grant support from Caregiver Ipsen, EMD Serona, Allergan, Medtronic, the Michael J. Fox Foundation, and the NIH; and royalties from Demos and Blackwell Futura for textbooks. Dr. Nutt reports receiving research support from the National Parkinson Foundation, the NIH, the Michael J. Fox Foundation, and Ceregene. He consults for Elan Pharmaceuticals, Lunden, Bionor, Qsys Pharmaceutical, SynAgile, Presa, USA WorldMeds, and Ceregene. He received speaking honoraria from the American Academy of Neurology. Dr Serrano received research funding from the Parkinson Study Group, Boehringer Ingelheim, Teva, the Michael J. Fox Foundation, and the NIH. She has received speaker honoraria in the past from Boehringer Ingelheim and Allergan. Dr Arroyo reports receiving a speaker’s honorarium from UCB. Dr. Ottmann serves on the scientific advisory board for and holds stock options in Trigeminal Solutions; has received funding for travel from the International League Against Epilepsy, the National Institute for Mental Health, and the Correll Institute for Medical Research; has received speaker honoraria for nonindustry-sponsored lectures; serves as a consultant to Ortho-McNeil Jansen Scientific Affairs, LLC, and received research support from the NIH (grants R01 NS043472, R01 NS036319, and R03 NS065346 as PI, grant RC2 NS070344 as co-PI, and grants R01 NS036630, R01 NS039422, and R01 NS03998 as coinvestigator). Dr. Nichols reports receiving support from the NIH/National Heart, Lung, and Blood Institute (grants SROI120707-04 and S24HL10533-02). Dr. Clark received research support from the NIH (NINDS grant R01 NS060113 as PI, NINDS grants R01 NS073872, NS36630, and 2P30NS038370-11 as co-PI, and National Institute on Aging grant SPO1AG00178 [Project 3] as PI), the Parkinson’s Disease Foundation as PI, and the Michael J Fox Foundation as coinvestigator. Dr Marder served on the editorial board of Neurology: receives research support from the NIH (grant NS366630 as PI, grant T1UL1 RR024156-01 as director of Participant and Clinical Interactions Resources, and grants PO412196-G and PO412196-G as principal investigator). She received compensation for participating on the steering committee for grant U01NS052592 from the Parkinson Disease Foundation, the Huntington’s Disease Society of America, the Parkinson Study Group, CHDI, and the Michael J Fox Foundation. No other disclosures were reported.

Funding/Support: This study was funded by NIH grants NS366630 and U1L RR024156 to Dr Marder, NIH grants NS050487 and NS060113 to Dr Clark, NIH grant KO2NS080915 to Dr Alcalay, the Parkinson’s Disease Foundation (to Drs. Fahn, Marder, and Clark), grants PS0 NS039764 and PS0 NS071674 to Dr Scott, and grant NS56960 to Dr Payami.

Role of the Sponsor: The funding agencies had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Additional Contributions: We thank Paul Greene, MD, Amy Colcher, MD, Dana Jennings, MD, Andrew Siderowf, MD, MSCE, and Linda Winfield, MS, for referral of participants.
REFERENCE


