Gretchen MacCarrick, MS, CGC[1], Bart Loeys, MD, PhD[2] and Harry C. Dietz III, MD[1,3]

[1]Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland, USA; [2]Center for Medical Genetics, University of Antwerp, Antwerp, Belgium; [3]Howard Hughes Institute, Chevy Chase, Maryland, USA. Correspondence: Gretchen MacCarrick (goswald1@jhmi.edu)

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Michael J. Fox Foundation *LRRK2* Consortium: geographical differences in returning genetic research data to study participants

In 2004, several mutations in the gene encoding leucine-rich repeat kinase 2 (*LRRK2*) were identified as being a genetic cause for Parkinson disease (PD).[1] The most common *LRRK2* mutation, G2019S, has been identified in 1% of all sporadic PD cases and in 4% of all familial PD cases.[2] Among selected populations, the frequency of the G2019S mutation is much higher. Up to 18% of all Ashkenazi Jewish PD cases[3] and 40% of North African Berbers with familial PD carry the G2019S mutation.[4] PD penetrance is age dependent and very controversial, with estimates ranging between 24 and 80%.[5] Clinically, *LRRK2*-related PD is indistinguishable from idiopathic PD on an individual patient level.[2] As a group, mutation carriers may have less tremor and more postural and gait difficulties.[6,7] Most autopsies of *LRRK2*-related PD brains show pathology similar to that seen in idiopathic PD, including the presence of Lewy bodies in the substantia nigra and cortex.[8,9]

In 2008, the Michael J. Fox Foundation established an international consortium to investigate *LRRK2*, which, eventually, included nine countries across four continents (Canada, China, France, Germany, Israel, Norway, Spain, Tunisia, and the United States). The methodology for subject recruitment is similar in most centers; PD participants are examined and screened for *LRRK2* mutations, and a more thorough investigation is performed on those with mutations (and a subset of those without mutations). All willing family members are then recruited so that *LRRK2* carriers with and without PD, as well as noncarriers, may be examined.

The study design raised an ethical question: should the genetic testing results be reported to participants? Currently, the clinical implications of carrying an *LRRK2* mutation among PD patients are unknown, and treatment is the same for carriers and noncarriers. Even so, investigators and ethics committees in different countries reached different conclusions regarding whether to inform study participants of their genetic test results.

With regard to PD participants, none of the centers in the United States offered the results of genetic testing performed for research purposes to participants. In New York state, reporting of results from a laboratory not approved per the Clinical Laboratory Improvement Amendments is against regulations; a minority of participants chose to pursue formal genetic counseling and clinical testing. By contrast, review committees in Israel concluded that it would be unethical not to provide the data to study participants with PD, and, as a result, all participants who requested results (the vast majority) received them.

The ethical dilemma among nonmanifesting *LRRK2* carrier family members is even more complicated. Carrying a mutation is more clinically meaningful in this population than in the probands with PD because it implies a 24–80% risk for PD. However, there are no known modifying interventions that may prevent PD in this population (developing such interventions is one of the major aims of the Michael J. Fox Foundation Consortium). Therefore, most centers chose, at the start of recruitment, not to reveal mutation status to non-PD participants, unless they first received genetic counseling and clinical testing. Most centers have reported that only a handful of non-PD participants were interested in receiving these data.

In many centers, the protocol for sharing genetic results with all participants was changed partway through the study. After initially reporting genetic data (if requested), the Toronto research team obtained ethics committee approval to stop revealing these results because they felt that the participants were confused by the information and/or did not understand how to interpret it. By contrast, the ethics committee in Trondheim asked researchers to alter the protocol so that study participants who were told of the risks associated with having a mutation could be notified of their genetic status. As a result,

approximately 20% of nonmanifesting carriers expressed interest in learning these results (most of the participants with PD that were recruited in Trondheim were already aware of their mutation status).

Underscoring the importance of this issue is the recent passage of legislation to regulate the acquisition and sharing of genetic information in specific countries. As an example, in 2010 Germany enacted the Genetic Diagnostics Act, which requires individuals to clearly indicate their preference for receiving—or not receiving—their genetic testing results; research participants who elect to be informed of their genetic status in Germany must be retested at an approved genetics laboratory and must receive genetic counseling. At least seven other countries in Western Europe alone (Austria, France, Norway, Portugal, Spain, Sweden, and Switzerland) have also established legal precedents for the handling of genetic information.[10]

The main arguments against sharing genetic results with participants are the following: (i) In many cases, the laboratories conducting testing uphold research rather than clinical standards. Moreover, (ii) the information, especially without appropriate counseling, may distress participants without providing any clinical benefit. The main argument to support sharing genetic data with participants is the notion that these data are the participants' property, and it should therefore be their decision to receive the results or not. Indeed, most centers that offer the genetic information have indicated that the vast majority of participants with PD are interested in receiving genetic data.[11] In addition, it is likely that studies that return results to participants are more efficient. First, researchers do not need to include noncarriers in the study (to blind the participants and researchers), and second, it is possible that participants who know their positive mutation status are amenable to participation in more demanding protocols.

The nature of this report is descriptive. We have not studied the causes for geographical differences in these reporting policies; however, the dramatic discrepancies between what is permitted and/or deemed ethical in different centers suggests an urgent need for researchers in the field to arrive at an informed consensus regarding best practices for the sharing of genetic data with participants.

The ethical questions raised by this study are pertinent to disorders—neurodegenerative and otherwise—with complex genetic etiology, incomplete penetrance, and typical onset past middle age, for which no disease-modifying treatment currently exists. Collecting data on what patients and families know and understand about genetics and about the kind of data they would like to receive will help guide future policy making.

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DISCLOSURE

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Roy N. Alcalay, MD, MS[1], Jan Aasly, MD[2], Daniela Berg, MD[3], Susan Bressman, MD[4], Alexis Brice, MD[5], Kathrin Brockmann, MD[3], Piu Chan, MD, PhD[6], Lorraine Clark, PhD[1], Florence Cormier, MD[5], Jean-Christophe Corvol, MD, PhD[5], Alexandra Durr, MD, PhD[5], Maurizio Facheris, MD, MS[7], Matthew Farrer, PhD[8], Tatiana M. Foroud, PhD[9], Thomas Gasser, MD[3], Nir Giladi, MD[10], Cheryl Halter, MS[9], Anthony Lang, MD, FRCPC[11], J. William Langston, MD[12], Connie Marras, MD, PhD[11], Jose-Felix Marti-Masso, MD, PhD[13], Javier Ruiz Martinez, MD, PhD[13], Helen Mejia-Santana MS[1], Anat Mirelman, PhD[10], Claustre Pont-Sunyer, MD[14], Avi Orr-Urtreger, MD, PhD[10], Deborah Raymond, MS[4], Rachel Saunders-Pullman, MD, MPH[4], Birgitt Schüle, MD[12], Caroline Tanner, MD, PhD[12], Eduardo Tolosa, MD[14], Alison Urkowitz, MPA[7], Dolores Vilas, MD[14], Adina Wise, MA[1] and Karen Marder, MD, MPH[1]

[1]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, USA; [2]Department of Neurology, St Olavs University Hospital, Trondheim, Norway; [3]Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany; [4]Department of Neurology, Beth Israel Medical Center and St. Luke's and Roosevelt Hospitals, Mount Sinai School of Medicine, New York, New York, USA; [5]Centre de Recherche de l'Institut du Cerveau et de la Moelle Épinière, INSERM U1127, Paris, France; [6]Department of Neurology and Neurobiology, Xuanwu Hospital Capital Medical University, Beijing, China; [7]The Michael J. Fox Foundation for Parkinson's Research, New York, New York, USA; [8]Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; [9]Department of Medical and Molecular Genetics, Indiana University, Indianapolis, Indiana, USA; [10]Tel Aviv Sourasky Medical Center, and Sackler Faculty of Medicine, Tel Aviv, Israel; [11]Morton and Gloria Shulman Movement Disorders Centre and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital, Toronto, Ontario, Canada; [12]The Parkinson's Institute and Clinical Center, Sunnyvale, California, USA; [13]Neurology Service, Hospital Universitario Donostia, Biodonostia, Basque Country University (UPV/EHU), San Sebastián, Spain; [14]Neurology Service, Hospital Clínic de Barcelona, Universitat de Barcelona, IDIBAPS, Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas, Barcelona, Catalonia, Spain. Correspondence: Roy N. Alcalay (rna2104@columbia.edu)

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