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Michael J. Fox Foundation Consortium: Geographical Differences in Returning Genetic Research Data to Study Participants

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In 2004, several mutations in the gene Leucine-rich repeat kinase 2 (*LRRK2*) were identified as a genetic cause for Parkinson's disease (PD).[1] The most common *LRRK2* mutation, G2019S, has been identified in 1% of all sporadic PD cases and 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 (AJ) 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 between 24–80%.[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*-PD brains show similar pathology to 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, by the end, 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 non-carriers, 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 a *LRRK2* mutation among PD patients are unknown and treatment is the same for carriers and non-carriers. Even so, investigators and ethics committees in different countries reached different conclusions regarding whether to inform study participants of their genetic results (Supplementary Table-1).

With regards 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 results from a non-CLIA-approved laboratory is against regulations; a minority of participants chose to pursue formal genetic counseling and clinical testing. In 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 non-manifesting *LRRK2* family member-carriers is even more complicated. Carrying a mutation is more clinically meaningful in this population than in the probands with PD as it implies a 24–80% risk for PD. However, there are no known modifying interventions that may prevent PD in this population (this is one of the major aims of this 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 this data (Supplementary Table 1).

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. In contrast, many European sites made changes allowing for increased transparency in response to the passage of laws stipulating that research participants have the right to know – or not know – their genetic status. For example, ethics committees in Trondheim and Barcelona asked researchers to change their protocols so that research subjects must be informed about the genetic testing and decide prior to participating if they wish to receive their genetic testing results.

Underscoring the importance of this issue is the recent passage of legislation, referred to above, 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 re-tested at an approved genetics lab and are required to receive genetic counseling. At least 7 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: 1. In many cases, the laboratories conducting testing uphold research rather than clinical standards 2. The information, especially without appropriate counseling, may distress participants without providing any clinical benefit. The main argument to support sharing genetic data with PD participants is the notion that this data is the participants' property, and it should therefore be their decision to receive it 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] It is likely that studies that return results to participants are more efficient. First, researchers do not need to include non-carriers in the study (to blind the participants

and researchers), and second, it is possible that participants that know their positive mutation status are amenable to participate 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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