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# Disclosure of Research Results in Genetic Studies of Parkinson Disease Due to *LRRK2* Mutations

**Claustre Pont-Sunyer**[1], **Susan Bressman**[2],[3], **Deborah Raymond**[2], **Amanda Glickman**[2], **Eduardo Tolosa**[1], and **Rachel Saunders-Pullman**[2],[3]

[1]Parkinson disease and Movement Disorders Unit, Neurology Service, IDIBAPS, CIBERNED, Universitat de Barcelona, Hospital Clínic, Barcelona, Catalonia, Spain

[2]Department of Neurology, Mount Sinai Beth Israel Medical Center, New York, NY, USA

[3]Department of Neurology, Icahn School of Medicine, Mount Sinai Medical Center, New York, NY, USA

## Abstract

With the advent of large genetic studies examining both symptomatic and asymptomatic individuals, whether and how to disclose genetic research results have become pressing questions. The need is particularly acute in the case of *LRRK2* research: Movement centers worldwide are recruiting cohorts of individuals with PD and their family members, including asymptomatic carriers, clinical features and treatment are complex and evolving, and disclosure policies vary at different sites and have been modified during the course of some studies. Herein, we present the major ethical principles of autonomy, beneficence, non-maleficence, and honesty that should guide disclosure policies in studies of families with *LRRK2* mutations. We make recommendations regarding: genetic counseling, policies of either active or passive disclosure, responsibilities of funders to budget for genetic counseling, clinical genetic testing where locally required for disclosure, and aspects of study design to avoid mandatory disclosure whenever feasible.

### Keywords

Parkinson disease; *LRRK2* mutation; ethics; disclosure; genetic counseling; clinical research

Correspondence to: Claustre Pont-Sunyer; Rachel Saunders-Pullman.

**Authors' roles:**

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C.P-S 1A, 1B, 1C, 3A, 3B
S.B. 1B, 3B
D.B. 1B, 3B
A.G. 1B, 3B
R.M. 1B, 3B
E. T. 1B, 3B
R. S-P. 1A, 1B, 1C, 3A, 3B

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## INTRODUCTION

Full disclosure of *clinical* results to patients is the standard procedure in medical care. However, release of *research* results to study participants, in particular those from genetic research, is less straightforward. Questions of whether and how to disclose genetic research results have become especially relevant in the study of Parkinson disease (PD) due to Leucine-rich repeat kinase 2 (*LRRK2*) mutations. Mutations in *LRRK2* represent the most frequent monogenetic cause of PD worldwide[1]; the protein is a druggable target; and clinical movement disorder centers around the world are studying *LRRK2* PD patients and their family members.

The two extreme positions on research disclosure are “complete non-disclosure” and “complete full disclosure.” Complete non-disclosure prohibits release of status, even in life-threatening situations, and complete full disclosure is difficult to maintain given the dynamic nature of scientific advances. Complete non-disclosure is not readily applicable to *LRRK2*, and complete full disclosure is not possible because scientific understanding of the implications of harboring a *LRRK2* mutation continues to evolve. A more practical position is **qualified disclosure**[2], which discloses results if certain conditions are met. Within the qualified disclosure model, a *passive* approach allows for disclosure only at a participant’s request, while an *active* approach provides full information and genetic counseling prior to study enrollment, with disclosure inherent to the study design.

Reported disclosure practices vary widely between countries. These differ with regard to whether research results must be confirmed in a certified laboratory and whether disclosure is mandatory for different groups of subjects (e.g. those with PD vs. those without). For example, in the US (Clinical Laboratory Improvement Amendments)[3], Germany (Genetics Diagnostics Act) [4], and Israel (Genetic Information Law) [5] federal law dictates that results may be disclosed only if performed through a certified or accredited laboratory. In Spain, results can be disclosed from research laboratories without necessarily being confirmed by an accredited clinical lab, although usually a separate sample is drawn. Even among study sites of the Michael J Fox Foundation (MJFF) funded LRRK2 Consortium Study, disclosure policies varied[6]. For example, Israeli ethics committees required active disclosure of status to PD patients and deemed non-disclosure to participants with PD unethical. In Barcelona, Spain, whereas asymptomatic relatives of LRRK2 PD patients’ results were initially not disclosed, following interpretation of the Ley de Investigación Biomédica[4], all participants were eventually determined to have the right to know research results. At the New York Mount Sinai Beth Israel site, passive disclosure was performed for both PD and non-PD participants, with additional clinical testing necessary to determine gene status.

This evident lack of consensus necessitates that researchers, study participants, ethics boards and funders confront the complex issues surrounding the disclosure of *LRRK2* research results, guided by the ethical principles of autonomy, beneficence, non-maleficence, and honesty. Herein we review these principles in relation to *LRRK2* PD and present guidelines for counseling and disclosure.

## AUTONOMY

Subjects exercising autonomy in obtaining individual research results first gained momentum in HIV and AIDS studies[8] and, in recent years, direct-to-consumer testing has made highly complex genetic information accessible through private companies[9].

Preferences regarding receipt of results in *LRRK2* studies vary with subjects' PD symptoms, age, medical knowledge, education and other factors[10]. Among 13 MJFF *LRRK2* Consortium sites, 10 reported that "many" or "some" subjects were interested in receiving results. In contrast, 7 of 11 sites reported that "few" at-risk family members were interested[3]. In a study of genetic attitudes limited to the subgroup of participants at the New York Ashkenazi Jewish (AJ) *LRRK2* Consortium sites, older individuals with PD (*LRRK2* carriers and non-carriers) were less likely to "definitely/probably" want to pursue genetic testing than younger subjects. Across demographic groups, subjects were more likely to want testing if they perceived results as influencing early prevention, treatment, or medication response [11]. At Tel Aviv Sourasky, only five out of 46 AJ first-degree relatives of affected *LRRK2* carriers wished to pursue testing after undergoing clinical genetic counseling [12].

Genetic counseling to provide education in a non-directive manner is essential to preserve autonomy[13]. Information covered should include: i) Transmission, incomplete penetrance, and PD risk in *LRRK2* mutation carriers; ii) The meaning of a negative or positive test for participant and family members, and iii) the availability of *LRRK2*-specific treatments or research studies for affected individuals or carriers (Table 1).

Ideally, a specially trained counselor and/or clinician should perform genetic counseling. Remote counseling, in the telemedicine setting, could lower costs and aid uniformity across multi-site studies, but also raises privacy concerns and could impair a counselor's ability to assess coping and provide support. Education and disclosure should occur in two separate sessions so that subjects can process facts, options, and feelings before making a decision about testing.

Implicit in the principle of autonomy is the right of a participant *not* to receive results. This is protected by international[14, 15] and, in many countries, national legislation[5]. At Tel Aviv Medical Center, subjects with PD who do not want results can opt out of learning their *LRRK2* G2019S mutation status, and family members only receive results if specifically requested [12]. At Mount Sinai Beth Israel Medical Center and Hospital Clinic in Barcelona, subjects opt in to testing by signing a separate consent form authorizing disclosure (Barcelona) or requesting confirmatory clinical testing (MSBI). It is also possible to preserve autonomy in clinical trials: protocols for the Alzheimer's Prevention Initiative (API) and Genentech study include enrollment of standard-risk volunteers to receive placebo so that learning their carrier status is not a pre-requisite for participation [16].

## BENEFICENCE AND NON-MALEFICENCE

The major argument for restricted disclosure is that it limits the potential for harmful consequences, including anxiety and depression. This is of particular concern to *LRRK2*

researchers because anxiety and depression are increased in PD overall, and depression is believed to be increased in *LRRK2* carriers prior to the development of motor symptoms of PD [17]. In addition, a study of individuals who underwent testing for familial adenomatous polyposis indicated that the anxiety associated with a positive test varied with the information given about the disease [18]. These considerations are especially relevant as risk estimates of *LRRK2* mutation carriers developing PD are variable and highly debated, ranging between 14–100% at age 80 [19,20, 21].

While both anxiety and depression have been studied in genetic counseling for neurodegenerative disorders such as Huntington and Alzheimer disease, few studies specific to PD patients and their family members have been performed [22, 23]. In a study of asymptomatic individuals at risk for familial Alzheimer disease or fronto-temporal-dementia (FTD), nine out of twelve reported wanting testing for "relief from worry and anxiety." After disclosure, one individual with positive and two with negative results had moderate anxiety, and one with negative results and a past history of depression had moderate depression, indicating that risk of adverse psychological effects can be associated with both positive and negative test results[18]. Among 49 sibling pairs who underwent *BRCA1*/*BRCA2* genetic testing, siblings with different test results reported more interpersonal strain than those with the same test result, either positive or negative[24]. Studies of the psychological effects of disclosure in *LRRK2* PD are needed.

While there are currently no pharmacogenomic approaches to *LRRK2* PD, knowledge of *LRRK2* mutation status could have benefits including enhanced understanding of disease prognosis and more rapid enrollment in novel randomized clinical trials (RCTs) focused on *LRRK2* carriers. Molecular testing for *LRRK2* mutations, especially G2019S, is simple, inexpensive, highly specific, and a helpful diagnostic tool [25]. Researchers should inform participants prior to study enrollment whether G2019S only, other pathogenic variants, or the entire *LRRK2* gene will be sequenced.

Predictive testing of asymptomatic *LRRK2* mutation carriers is particularly complex. Genetic discrimination is prohibited in the European Union [5] and in Israel [6]. While, in the US, the Genetic Non-Discrimination Act (GINA) protects individuals from discrimination in obtaining health coverage[10], it does not extend to long-term care or life insurance coverage. Among the *LRRK2* AJ Consortium, 28.6% of relatives of an affected *LRRK2* carrier reported being "somewhat" or "very" worried about losing insurance due to genetic results[11]. On the other hand, informed unaffected carriers, not generally under the care of a movement disorder physician or neurologist, may benefit from greater awareness of new clinical trials targeted toward them.

Researchers must further resolve what threshold of relative risk is worthy of disclosure and whether disclosure of PD-specific mutations should be limited to *LRRK2* mutations in ethnic populations where other PD genes are also at increased frequency. *LRRK2* mutations in Ashkenazi Jews likely account for approximately 10–15% of all PD (both sporadic and familial), while another 15% is attributable to glucocerebrosidase (*GBA)* mutations, raising the question as to whether these mutations should also be evaluated and disclosed [26]. However, the relative risk of developing PD associated with single or double *GBA* mutations

is smaller than with *LRRK2*, and the frequency of a single mutation in *GBA* in this population is much greater [27]. In *LRRK2* studies, policies should be determined regarding a) the type of screening performed and reported and b) the disclosure of mutation data discovered in addition to the mutation of interest. The latter could include both mutations screened that are of interest to the disease (such as *GBA* mutations in Ashkenazi Jews with PD) or incidental genetic variants as may be found from a genome-wide association study.

## HONESTY AND OBLIGATIONS OF RESEARCHERS

The therapeutic misconception is defined as a subject's belief that inclusion in a study will benefit his or her short-term treatment. In the context of *LRRK2* research, awareness of mutation status would not currently alter treatment. However, participation in clinical research may have indirect benefits such as increasing the amount of time the physician spends with the patient and facilitating access to new scientific findings. There is also concern that researchers may be motivated for subjects to learn their status, as it may increase recruitment: relatives of a known mutation carrier may be more motivated to participate than those of a PD subject with no known genetic cause of PD. To avoid the therapeutic misconception and preserve autonomy, researchers should ensure that subjects are fully informed and understand all aspects of participation prior to study enrollment.

The obligations of researchers should be clear. The language of the consent should describe the duration over which contact will be maintained and whether updates will be provided or must be requested. The consent form should clarify whether subjects agree to participation in unrelated studies (as a control). If additional genetic data is determined, e.g. for genetic modifiers such as *MAPT*, results that currently have no clinical significance might in the future be relevant to treatment or disease prevention [28]. Therefore participants should be informed of the circumstances in which genetic results might be forthcoming, and be given the choice to opt out of learning possibly relevant results including incidental genetic findings. Practical challenges, such as fluctuations in research funding, may cause most centers to limit information provided to that available at the time of the study. In these cases, centers may want to stipulate that subjects will not be informed of new findings in the future.

Finally, confirmatory clinical testing may incur additional costs. These may be borne by the study funder, the research site or the subject, and the decision must be made who shoulders this burden.

## RECOMMENDATIONS AND CONCLUSIONS

While specifics will vary based on national and local requirements, we recommend that for *LRRK2* mutation studies:

1. Genetic counseling be made available to all study participants whenever disclosure is considered. The method and content of counseling will vary by site but should include at minimum information regarding heritability, the meaning of having/not having a mutation (see Table), and the type of results, covering i) specific mutations are tested (e.g. G2019S or R1441G/C) or complete *LRRK2* sequencing is

performed and ii) incidental pathogenic findings, including the time period over which additional data may be returned and the choice to opt out of future disclosure.

2. A policy of qualified disclosure should be used, whereby subjects may receive research results in the context of genetic counseling and reserve the right not to receive results. Site-specific policies, such as whether to use active or passive qualified disclosure, will depend on multiple factors including whether a participant is symptomatic, study design and feasibility, and emerging therapies. Future *LRRK2*-specific studies of disclosure may further inform efforts to uphold ethical principles in research. Sites may also consider whether to actively or passively disclose non-*LRRK2* mutations or variants that are risk factors at increased frequency in a population.
3. Genetic testing of asymptomatic minors is not recommended.
4. Funders provide for costs related to disclosure, including genetic counseling, clinical laboratory testing where legally required[4], and logistics of study design to allow participation without mandatory disclosure.

In conclusion, subjects wishing to receive individual research results must be well informed about the meaning of those results for themselves and their families. This goal is best accomplished through education and counseling. While decisions regarding disclosure will change as scientific understanding and treatment evolve, the ethical principles do not change, and the models described herein remain relevant.

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## TABLE

Information about *LRRK2* mutation to be included in the disclosure to research participants

| **Inheritance** | **Autosomal dominant** |
|---|---|
| Transmission | 50% |
| Penetrance | Incomplete; and variable, with a lifetime range from 14%–100% by age 80, depending on the series and the ethnic background [19–21, 29–34]; for example penetrance of G2019S mutation in Ashkenazi Jews is approximately 24–30% [19, 32].<br>No current method to predict whether and when carriers will develop the disease or the progression of disease. |
| The meaning of a negative test | For asymptomatic relatives a negative test for *LRRK2* mutations means lower risk for developing PD than if they had the mutation. However, it is not zero, as a small percentage of *LRRK2* negative PD (phenocopies) have been described in families with a *LRRK2* positive proband[35, 36]. Other genetic and environmental factors are considered causative in these cases. |
| The meaning of a positive test | In PD patients, harboring the mutation supports the diagnosis and arguably may confer slightly better prognosis. Prognostication may differ, although current knowledge suggests that the typical course of *LRRK2* PD is usually slowly progressive levodopa responsive parkinsonism, [30] and atypical phenotypes are rare, especially for G2019S carriers.[37–39]<br>Unaffected carriers who harbor a *LRRK2* mutation have a predisposition to develop PD. However, many, even most, as in the case of Ashkenazi Jews, will not. There are other factors that determine whether a *LRRK2* carrier will develop PD which we do not yet understand. This is an important reason to remain engaged in research. |
| Current lifestyle or medical prevention recommendations for *LRRK2* carriers | Development of *LRRK2* targeted drugs studies is promising, and enrollment in future clinical trials may be focused on *LRRK2* carriers. Currently there are no *LRRK2* specific medical, diet or lifestyle recommendations that can be given to carriers. |

Abbreviation key: DBS, Deep Brain Stimulation; *LRRK2*, Leucine-rich repeat kinase 2; PD, Parkinson's disease.