Introduction

Parkinson Disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer disease, and it is characterized by several motor and non-motor symptoms [1]. Although oral therapy provides good control of motor symptoms during the initial stage of the disease, in some patients the onset/worsening of levodopa-resistant symptoms, complications and motor fluctuations in the advanced stage of the disease lead to increased disability and decreased quality of life, demanding the implementation of device assisted therapies [1]. Device assisted therapies, encompassing continuous levodopa/carbidopa intestinal gel (LCIG) infusion, deep brain stimulation (DBS) and apomorphine infusion, reduce some of the troublesome complications that are poorly managed with pharmacological therapy in advanced PD [2–4]. LCIG provides continuous levodopa infusion directly into the proximal jejunum by way of percutaneous endoscopic gastrostomy with jejunal extension tube (PEG-J) connected to a portable infusion pump. The administration of a gel suspension of levodopa/carbidopa directly in the duodenum allows continuous uptake of the drug while bypassing the gastric emptying -a potential cause of suboptimal response to levodopa: this leads to less variability in plasma levels of levodopa with fewer motor fluctuations compared to oral levodopa [3]. Both clinical studies and real-life experience have demonstrated the efficacy of LCIG in relieving both motor and non-motor symptoms and improving activities of daily living and quality of life; however, complications related to both the device and to the therapy have been reported [5–9].

Even though the aetiology of PD in most patients remains unknown, genetic mutations/variants are identified in approximately 5-10% of cases: they can be either high-penetrance (e.g. *SNCA*, *VPS35*, biallelic *PRKN/PINK1/DJ1*, rarer *LRRK2* variants), intermediate penetrance (e.g. *LRRK2* G2019S), low penetrance genetic risk factors (e.g. *GBA1* variants) and in other cases non pathogenetic polymorphisms that have been linked with specific clinical features (e.g. *BDNF* variants) [1]. Among genetic mutations/variants, glucocerebrosidase (*GBA1*) are the most frequently found in idiopathic PD and are associated with clinical features, depending on the specific mutation/variant [10–13]. In the perspective of a tailored and personalized medicine for PD, whether the genetic status influences the outcome of device assisted therapies is a question of great interest, also considering the importance of patients' selection for optimal outcome of these treatments. Several features must be considered: age, frailty, cognitive status, phenotype (motor and non-motor symptoms), response to levodopa, side effects or complication profile, the patient's comfort with invasive therapy options, and the caregiver's support [14, 15]. Some data is available regarding the effectiveness of DBS in patients with PD and different genetic background: although the efficacy of DBS was confirmed in all groups, differences among different genetic groups were found [16]. Indeed, a recent study suggested that the combined effects of *GBA1* mutations/variants and STN-DBS in PD negatively impact cognition [17]. To our knowledge, besides of a meeting abstract reporting no difference

between GBA-PD and other LCIG patients [18], genetic features and their relationship with clinical outcome and complications have not been extensively investigated in LCIG cohorts.
The aim of this study was to evaluate motor and cognitive outcomes in a series of LCIG-patients with genetic mutations/variants.

Methods

Patients

All patients underwent LCIG and were followed up at our institution between 2008 and 2018. They underwent a cross-sectional neurological evaluation and blood samples collection between 2017 and 2019. Patients underwent neuropsychological follow-up, those who were evaluated within 2±1 years after the LCIG start were included in the analysis. All baseline data were retrospectively extracted from the data system of the Movement Disorders Centre of the University of Turin, Italy. Follow-up assessment was performed during clinical outpatient visits. Inclusion criteria were: diagnosis of idiopathic PD [19], fulfilment of inclusion criteria for the LCIG therapy (including clinical evaluation with levodopa and/or naso-intestinal tube infused levodopa challenge, neuropsychological tests, psychological assessment, motivational assessment, caregiver consultation, absence of comorbidities) and the treatment with LCIG delivered by PEG-J, as previously described [20]. All patients gave their informed consent for genetic testing and participation in the study. The study was performed in agreement with the principles of the Declaration of Helsinki and in compliance with Italian legislation on retrospective studies and was approved by the local Ethics Committee.

Outcome measures

All the available demographic and clinical variables at the time of LCIG start (baseline) were collected and analysed: gender, age, disease duration, duration of motor fluctuations, Levodopa Equivalent Daily Dose (LEDD) [21], stage of PD as per the Hoehn and Yahr score, Unified Parkinson's Disease Rating Scale (UPDRS) part I-IV or Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I-V [22], Schwab and England score (SE) [23]. A validated formula was used to convert MDS-UPDRS II and III into UPDRS II and III scores, when needed [24]. The part III at baseline was assessed in 2 dopaminergic treatment conditions: "OFF" (after ≥ 12 hours withdrawal from antiparkinsonian medication) and "ON" (45 minutes after the administration of levodopa); at follow up patients were assessed while in "ON" condition with their habitual therapy ("daily ON").
In patients with UPDRS III at baseline, 4 composite motor scores from UPDRS-III were calculated: (1) akinesia (sum of the face item 19; hands items 23, 24, 25; feet item 26; and global akinesia item 31, range 0–40); (2) rigidity (items 22, range 0–20); (3) tremor (items 20, 21, range 0–28); and (4) axial (speech item 18; arising from a chair item 27; posture item 28; gait item 29; and postural stability item 30, range 0–20) as previously described [25].

Cognitive and behavioural assessments were performed in the best clinical "ON" condition at baseline and at follow-up visit. Patients were submitted to an extensive neuropsychological battery assessing reasoning, memory, frontal executive functions, phonemic and category verbal fluency tasks as previously described [26]; mild cognitive impairment (MCI) was defined as moderate or severe impairment on at least two neuropsychological tests, when cognitive deficits are not sufficient to interfere significantly with functional independence, in accordance with the Level-I of MDS criteria for MCI [27]. PD-Dementia (PD-D) was defined according to the MDS criteria [28].
The following behavioural measures were also collected [26]: depression, assessed by means of the Beck Depression Inventory (BDI); apathy, assessed by means of the Apathy Scale (AS). Quality of life (QoL) was assessed through the Parkinson's Disease Questionnaire (PDQ-39).
In addition, all patients were evaluated at baseline and follow-up for peripheral neuropathy (PNP), defined as symmetric alteration of action potential amplitudes or velocities in at least two motor or sensory nerves at the nerve conduction studies (NCS), either clinical or subclinical, as previously described [29].

Genetic testing

Patients were tested for nine PD related genes using next-generation sequencing (NGS) approach (see Supplementary Table 1 for the complete list of genes included in the panel). A custom panel was designed with the HaloPlex online design tool (SureDesign, Agilent Technologies) and sequenced on MiSeq platform (Illumina, Inc., San Diego, CA, USA). Exon dosage changes were investigated by ligation-dependent probe amplification method (MLPA) using P051 kit (MRC Holland, Amsterdam, the Netherlands) (GBA1 was not included in the MLPA analysis). Samples were additionally genotyped for *GBA1* variants by Sanger sequencing, *BDNF* polymorphisms were assessed, among other variants, using the Neurochip, as described elsewhere [30].

Statistical analysis

Descriptive statistics (mean, standard deviation, and range) were used for continuous variables and frequency for categorical data. Shapiro-Wilk test was used to test normality. Independent samples t-test (continuous variables with normal distribution), the Mann-Whitney U test (continuous variables without normal distribution) or Fisher exact test (categorical variables) were used to compare demographic and clinical data between the groups of LCIG patients: patients with mutations/variants vs all other patients, *GBA1* variants vs all other patients, *BDNF* Val66Met vs all other patients. Wilcoxon signed-rank test was used to compare outcomes at different time point within the same group. ANOVA repeated measures was used to compare the evolution of clinical measures between the different groups (patients with mutations/variants vs all other patients, *GBA1* mutations/variants vs all other patients, *BDNF* Val66Met vs all other patients); the analyses were covaried for age, duration of PD, length of follow-up, Bonferroni correction was applied. All p-values reported are two-

tailed, and a $p < 0.05$ was considered statistically significant. Data were analysed using the Statistical Package for the Social Sciences (SPSS 26 for Windows, Chicago, IL).

Results

Patients

Data from 56 consecutive PD patients who underwent LCIG were analysed. The mean age of patients at the onset of PD symptoms was 54.3 ±7.9 years, disease duration was 12.6±4.1 years and LCIG treatment duration at last follow-up was 4.9±2.6 years (Table 1). Nine patients (15%) had at least 1 variant in any PD-associated gene, 13 (23%) had *BDNF* Val66Met polymorphism. There was no significant difference in the time of follow up between the groups, except for the *SNCA* group (which had a shorter follow up, Table 1). There was a significant difference in age at LCIG between patients with no mutations/variants and patients with *BDNF* Val66Met polymorphism (*BDNF* Val66Met= 71.5±4 years old, no-mutation patients=66.9±7.5 years old, $p<0.005$) (Table 1); there was no significant difference in other variables within these groups. Demographic and clinical features of all the patients are detailed in Table 1 and 2. Information on each patient, including the specific mutation/variant, are summarized in Table 3.

Motor outcome

Compared to baseline, the whole groups showed a significant worsening in SE, HY, UPDRS II and III and LEDD and a significant reduction in motor complications (UPDRS IV) at follow-up (Table 1). Compared with baseline, there was a significant reduction of UPDRS IV in the *BDNF* Val66Met subgroup at follow-up (Table 1). Changes of motor outcome during follow-up did not reach significance in other subgroups (Table 1).

At baseline and follow-up, there was no significant difference in motor assessment between patients with vs patients without mutations/variants and between patients with *GBA1* mutations/variants vs all other patients (Table 1). ANOVA repeated measures did not show any significant difference in the change of motor symptoms during the follow-up between different groups.

Neuropsychological outcome

The baseline neuropsychological assessment, performed on 49 patients, showed the following cognitive profiles: normal cognitive profile in 22 patients, MCI in 24 patients, dementia in 3 patients; these latter cases received LCIG therapy due to the severe motor picture and high reliability of their caregivers. Thirty-two patients underwent neuropsychological follow-up after 1.9±1 year; in this subgroup, 25 had no mutations, 4 carried *GBA1* variants, 2 carried *SNCA* mutations, 1 carried *PRKN* mutations, 9 carried the Val66Met *BDNF* variant. There were no significant differences in the time of follow-up between the groups (table 4, supplementary table 2 and 3). ANOVA repeated measures

did not show any significant difference in the change of neuropsychological assessments during the follow-up between different groups.

Treatment-related adverse events

At baseline, neuropathy was observed in 5 patients in the no-mutations/variants group, 3 in the *BDNF* Val66Met group, 1 in the *GBA1* group, 1 in the *SNCA* group, 0 in the *PRKN* group and 1 in the *LRRK2* group. At follow up, 6 patients in the no-mutations/variants group, 6 in the *BDNF* Val66Met group, 2 in the *GBA1* group, 1 in the *SNCA* group, 1 in the *PRKN* group and 1 in the *LRRK2* had polyneuropathy. 10 patients in total underwent removal of the LCIG device due to complications: 6 patients in the no-mutations/variants group, after a mean of 1.14 years (2 due to abdominal pain, 1 due to neuropathy, 2 due to lack of benefit 1 due to excessive dyskinesias); 1 in the *BDNF* Val66Met group (after 2 years due to neuropathy in a concomitant haematological disease); 2 patients in the *GBA1* group (1 patient immediately after the LCIG start due to delirium and 1 patient after 8 years due to global worsening), 1 patient in the *PRKN* group (after 6 years due to bumper syndrome).

Discussion

Besides of improving our understanding of the pathophysiological mechanisms of PD, the increasing knowledge of genetics of the disease offers the possibility of improving treatments, not only by designing new target-directed drugs, but also through a better classification of PD populations.

The identification of specific clinical feature associated to genetic markers and the characterization of response to treatment can be a fundamental tool to implement a personalized approach in the treatment of PD; this is particularly relevant in the field of device assisted therapies, as these are directed to patients with a more complex clinical picture, are more invasive than standard pharmacological therapy and require a greater commitment of the patients and their caregivers. Selection of patients is the cornerstone of success in device assisted therapies, and the identification of genetic criteria might add important information in this process. Hence, we aimed to analyse our LCIG cohort to determine if specific genotypes are associated with different outcomes.

Currently, together with subcutaneous apomorphine infusion and DBS, LCIG represents a therapeutic option for patients with fluctuating symptoms, unresponsive to optimal oral treatment. Current evidence suggests that genetic background may influence the clinical picture, the natural progression of the disease and the individual responsiveness to treatments in PD [9]. Some genetic mutations/variants have been associated with some specific features in PD; for example, *GBA1* variants have been associated with earlier onset, more rapid motor deterioration, and a higher risk of cognitive impairment (for a review, see [10]); while the *BDNF* polymorphism Val66Met has been associated with milder motor symptoms, a slower rate of progression and a higher risk of levodopa-

induced complications, cognitive impairment and psychiatric symptoms [31]. However, it is still unclear how genetic factors influence the outcome of device assisted therapies for PD.

In our LCIG cohort, we observed a prevalence of 15% of PD-related mutations/variants, 5 *GBA1* (8.7%), 2 *SNCA* (3.5%), 1 *LRRK2* (1.7%), 1 *PRKN* (1.7%); 13 (23%) carried the *BDNF* Val66Met polymorphism. We did not find any significant differences in motor and cognitive outcome among patients with and without mutations/variants. Patients carrying mutations/variants showed a satisfactory response to LCIG and did not report more adverse events than patients without mutations/variants, except for one patient carrying complex GBA1 mutations/variants and with psychiatric comorbidities who developed infectious complications and delirium after initiation of LCIG, leading to its withdrawal. As in other PD cohorts, *GBA1* variants were the most frequent (8.7% of patients). The percentage of patients with genetic variants in our cohort reflects that reported in general unselected PD populations, in contrast to data on DBS cohorts in which genetic mutations/variants are over-represented, probably due to the selection of younger patients with good prognostic factors for DBS (i.e., absence of cognitive impairment and comorbidities) [32]. In DBS cohorts, some differences have been noted in GBA-PD patients: they tend to undergo DBS earlier than other patients [32], possibly because of a more aggressive disease course and -despite of motor improvement- they tend to show more complications, specifically cognitive impairment [16]. Indeed, GBA-PD is associated to a greater risk of dementia depending on the variants/mutations [12] and STN-DBS seems to increase this risk: GBA-PD patients show more cognitive impairment after DBS than PD patients without GBA1 mutations/variants who underwent DBS and they also show a worse cognitive outcome after STN-DBS compared with GBA-PD patients who did not undergo DBS -also when stratified according to the mutation/variant type. Accordingly with what observed in non-DBS cohorts, cognitive decline after STN-DBS is faster in subjects carrying neuronopathic mutations/variants [17]. In our cohort, we have not observed significant differences between GBA-PD patients and other groups in terms of motor and non-motor symptoms and complications of LCIG; it must be considered that the small size of the sample might account for these results.

Several studies have linked the *BDNF* Val66Met with the susceptibility, incidence, and clinical features of several neurodegenerative disorders, including PD [31]. In our cohort, there was no difference in motor or neuropsychological outcome between patients carrying this polymorphism and others. Patients with the *BDNF* Val66Met polymorphism tended to undergo LCIG at an older age than patients without mutations, possibly a reflection of a slighter older age at onset than the other groups (this difference did not reach statistical significance).

The follow-up of our cohort as a whole showed a significant increase in SE, HY, UPDRS II and III and LEDD reflecting the progression of the disease, but a significant reduction in motor complications (UPDRS IV), as a confirmation of the effectiveness of LCIG therapy on motor complications. Although the trend was similar in subgroups, these differences did not always reach significance, likely due to the smaller sample size.

Overall, we observed no cognitive worsening at follow-up among four *GBA1* patients, with a concomitant significant benefit in terms of motor symptoms. However, due to the small sample and limited number of patients carrying genetic mutations/variants, statistical analyses were underpowered: this is a limitation of this study, hence no definitive conclusions can be drawn yet on the genotype impact on LCIG outcome.

Although it has been suggested by some authors that LCIG should be the preferred advanced therapy in severe GBA1 phenotypes, [33] due to the scarcity of data available in GBA-PD who underwent LCIG, it is our opinion that patients carrying such variants/mutations should be assessed independently following the indications for patients' selection in LCIG. The final decision on the most appropriate device-assisted therapy for PD (such as DBS, LCIG, or apomorphine infusion) should be based on clinical evaluation, assessment of patients' needs, as well as on the potential risk and benefits that are associated with each procedure. Moreover, the role of the caregiver is particularly important when addressing patients for LCIG. We have previously reported that cognitive impairment is the main determinant of mortality in LCIG patients: considering the greater risk of cognitive impairment in GBA-PD, these patients might identified as more vulnerable after LCIG [20]. This study has several limitations that hinder the possibility of drawing definitive conclusions , such as the small sample size, the crossover design and the limited number of genes included in our panel (which does not include other genes that have been associated with atypical forms of Parkinson's disease e.g. PLA2G6, ATP13A2, FBXO7, DNAJC6, SYNJ1, VPS13C, RAB39B). Prospective, long-term studies on infrequent genotypes should be performed by multinational collaboration in order to reliably decipher genotype-related differences in device assisted therapies outcome and offer new insights to customize the treatment of PD; moreover, a prospective study design would provide more reliable and controlled data. While waiting for more data on the influence of the genetic background on LCIG outcome, we further stress the importance of a careful selection of patients, and we recommend a cautious use of LCIG in patients with cognitive, alterations regardless of the genetic background, given the impact of cognitive deficits on device management and survival[20].

References

1. Balestrino R, Schapira AHV (2020) Parkinson disease. Eur J Neurol 27:27–42. https://doi.org/10.1111/ene.14108

2. Deuschl G, Schade-Brittinger C, Krack P, et al (2006) A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. N Engl J Med 355:896–908. https://doi.org/10.1056/NEJMoa060281

3. Fernandez HH, Odin P (2011) Levodopa–carbidopa intestinal gel for treatment of advanced Parkinson's disease. Current Medical Research and Opinion 27:907–919. https://doi.org/10.1185/03007995.2011.560146

4. Katzenschlager R, Poewe W, Rascol O, et al (2018) Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. The Lancet Neurology 17:749–759. https://doi.org/10.1016/S1474-4422(18)30239-4

5. Poewe W, Bergmann L, Kukreja P, et al (2019) Levodopa-Carbidopa Intestinal Gel Monotherapy: GLORIA Registry Demographics, Efficacy, and Safety. J Parkinsons Dis 9:531–541. https://doi.org/10.3233/JPD-191605

6. Dafsari HS, Martinez-Martin P, Rizos A, et al (2019) EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. Mov Disord 34:353–365. https://doi.org/10.1002/mds.27626

7. Martinez-Martin P, Reddy P, Katzenschlager R, et al (2015) EuroInf: AMulticenter Comparative Observational Study of Apomorphine and Levodopa Infusion in Parkinson's Disease: Apomorphine and Levodopa in PD. Mov Disord 30:510–516. https://doi.org/10.1002/mds.26067

8. Standaert DG, Aldred J, Anca-Herschkovitsch M, et al (2021) DUOGLOBE : One-Year Outcomes in a REAL-WORLD Study of Levodopa Carbidopa Intestinal Gel for Parkinson's Disease. Mov Disord Clin Pract 8:1061–1074. https://doi.org/10.1002/mdc3.13239

9. Tsunemi T, Oyama G, Saiki S, et al (2021) Intrajejunal Infusion of Levodopa/Carbidopa for Advanced Parkinson's Disease: A Systematic Review. Mov Disord 36:1759–1771. https://doi.org/10.1002/mds.28595

10. Balestrino R, Schapira AHV (2018) Glucocerebrosidase and Parkinson Disease: Molecular, Clinical, and Therapeutic Implications. Neuroscientist 24:540–559. https://doi.org/10.1177/1073858417748875

11. Filippi M, Balestrino R, Basaia S, Agosta F (2022) Neuroimaging in Glucocerebrosidase-Associated Parkinsonism: A Systematic Review. Movement Disorders mds.29047. https://doi.org/10.1002/mds.29047

12. Cilia R, Tunesi S, Marotta G, et al (2016) Survival and dementia in GBA-associated Parkinson's disease: The mutation matters: Survival in PD-GBA. Ann Neurol 80:662–673. https://doi.org/10.1002/ana.24777

13. Iwaki H, Blauwendraat C, Leonard HL, et al (2019) Genetic risk of Parkinson disease and progression:: An analysis of 13 longitudinal cohorts. Neurol Genet 5:e348. https://doi.org/10.1212/NXG.0000000000000348

14. Abbruzzese G, Barone P, Bonuccelli U, et al (2012) Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson's disease: efficacy, safety and patient selection. Funct Neurol 27:147–154

15. Siddiqui J, Aldaajani Z, Mehanna R, et al (2018) Rationale and patient selection for interventional therapies in Parkinson's disease. Expert Review of Neurotherapeutics 18:811–823. https://doi.org/10.1080/14737175.2018.1535902

16. Rizzone MG, Martone T, Balestrino R, Lopiano L (2019) Genetic background and outcome of Deep Brain Stimulation in Parkinson's disease. Parkinsonism & Related Disorders 64:8–19. https://doi.org/10.1016/j.parkreldis.2018.08.006

17. Pal G, Mangone G, Hill EJ, et al (2022) Parkinson Disease and Subthalamic Nucleus Deep Brain Stimulation: Cognitive Effects in *GBA1* Mutation Carriers. Annals of Neurology 91:424–435. https://doi.org/10.1002/ana.26302

18. Thaler A, Hillel A, Shabtai H, et al (2017) Assessing the response to L-dopa/carbidopa intestinal gel infusion based on genetic status. In: Movement Disorders. Vancouver, pp S1–S627

19. Postuma RB, Berg D, Stern M, et al (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30:1591–1601. https://doi.org/10.1002/mds.26424

20. Artusi CA, Balestrino R, Imbalzano G, et al (2020) Beyond 10 years of levodopa intestinal infusion experience: Analysis of mortality and its predictors. Parkinsonism & Related Disorders 76:98–103. https://doi.org/10.1016/j.parkreldis.2019.10.004

21. Tomlinson CL, Stowe R, Patel S, et al (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease: Systematic Review of LED Reporting in PD. Mov Disord 25:2649–2653. https://doi.org/10.1002/mds.23429

22. Goetz CG, Tilley BC, Shaftman SR, et al (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results: MDS-UPDRS: Clinimetric Assessment. Mov Disord 23:2129–2170. https://doi.org/10.1002/mds.22340

23. Schwab RS, England AC (1968) Projection techniques for evaluating surgery in Parkinson's Disease. Royal College of Surgeons in Edinburgh

24. Goetz CG, Stebbins GT, Tilley BC (2012) Calibration of unified Parkinson's disease rating scale scores to *Movement* Disorder Society-unified Parkinson's disease rating scale scores: Calibration of UPDRS Scores to MDS-UPDRS Scores. Mov Disord 27:1239–1242. https://doi.org/10.1002/mds.25122

25. Lau B, Meier N, Serra G, et al (2019) Axial symptoms predict mortality in patients with Parkinson disease and subthalamic stimulation. Neurology 92:e2559–e2570. https://doi.org/10.1212/WNL.0000000000007562

26. Zibetti M, Merola A, Rizzi L, et al (2011) Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease: 9 Years of STN-DBS in PD. Mov Disord 26:2327–2334. https://doi.org/10.1002/mds.23903

27. Litvan I, Goldman JG, Tröster AI, et al (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: *Movement* Disorder Society Task Force guidelines: PD-MCI Diagnostic Criteria. Mov Disord 27:349–356. https://doi.org/10.1002/mds.24893

28. Emre M, Aarsland D, Brown R, et al (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22:1689–1707. https://doi.org/10.1002/mds.21507

29. Merola A, Romagnolo A, Zibetti M, et al (2016) Peripheral neuropathy associated with levodopa–carbidopa intestinal infusion: a long-term prospective assessment. Eur J Neurol 23:501–509. https://doi.org/10.1111/ene.12846

30. Blauwendraat C, Faghri F, Pihlstrom L, et al (2017) NeuroChip, an updated version of the NeuroX genotyping platform to rapidly screen for variants associated with neurological diseases. Neurobiology of Aging 57:247.e9-247.e13. https://doi.org/10.1016/j.neurobiolaging.2017.05.009

31. Shen T, You Y, Joseph C, et al (2018) BDNF Polymorphism: A Review of Its Diagnostic and Clinical Relevance in Neurodegenerative Disorders. Aging and disease 9:523. https://doi.org/10.14336/AD.2017.0717

32. Pal GD, Hall D, Ouyang B, et al (2016) Genetic and Clinical Predictors of Deep Brain Stimulation in Young-Onset Parkinson's Disease. Mov Disord Clin Pract 3:465–471. https://doi.org/10.1002/mdc3.12309

33. Salles PA, Mata IF, Fernandez HH (2021) Should we start integrating genetic data in decision-making on device-aided therapies in Parkinson disease? A point of view. Parkinsonism & Related Disorders 88:51–57. https://doi.org/10.1016/j.parkreldis.2021.05.013