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Corresponding author: Gian Pal, MD, MS, Rutgers-Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, NJ 08901, Phone: (732) 235-7733, gian.pal@rutgers.edu.

AUTHORS' ROLES

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Daniel Corcos	
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Gaps and Controversies: Cognitive Effects of STN-DBS in

Leo Verhagen Metman	
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Parkinson's disease with *GBA1* pathogenic variants

Gian Pal, MD MS[1], **Daniel M. Corcos, PhD**[2], **Leo Verhagen Metman, MD PhD**[3], **Zvi Israel, MD**[4,5], **Hagai Bergman, MD PhD**[4,6,7], **David Arkadir, MD PhD**[4,8]

[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, United States

[2]Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, Illinois, United States

[3]Parkinson's Disease and Movement Disorders Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[4]Faculty of Medicine, The Hebrew University and Hadassah, Jerusalem, Jerusalem, Israel

[5]Department of Neurosurgery, Hadassah Medical Center, Jerusalem, Israel

[6]Department of Medical Neurobiology, Institute of Medical Research Israel–Canada (IMRIC), The Hebrew University–Hadassah Medical School, Jerusalem, Israel

[7]The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University, Jerusalem, Israel

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[8]Department of Neurology, Hadassah Medical Center, Jerusalem, Israel

Abstract

Genetic subtyping of patients with Parkinson's disease (PD) may assist in predicting the cognitive and motor outcomes of subthalamic deep brain stimulation (STN-DBS). Practical questions were recently raised with the emergence of new data regarding suboptimal cognitive outcomes after STN-DBS in individuals with PD associated with pathogenic variants in *glucocerebrosidase* gene (*GBA1*-PD). A variety of gaps and controversies, however, remain including: (1) Does STN-DBS truly accelerate cognitive deterioration in *GBA1*-PD? If so, what is the clinical significance of this acceleration? (2) How should the overall risk-to-benefit ratio of STN-DBS in *GBA1*-PD be established? (3) If STN-DBS has a negative effect on cognition in *GBA1*-PD, how can this effect be minimized? (4) Should PD patients be genetically tested prior to STN-DBS? and (5) How should *GBA1*-PD patients considering STN-DBS be counseled? We aim to summarize the currently available relevant data and detail the gaps and controversies that exist pertaining to these questions. In the absence of evidence-based data, all authors strongly agree that clinicians should not categorically deny DBS to PD patients based solely on genotype (*GBA1* status). We suggest that PD patients considering DBS may be offered genetic testing for *GBA1*, where available and feasible, so the potential risks and benefits of STN-DBS can be properly weighed by both the patient and clinician.

Keywords

Parkinson's disease; deep brain stimulation; glucocerebrosidase; cognition

INTRODUCTION

Currently, clinicians tailor treatment for each individual Parkinson's disease (PD) patient based on information collected by detailed anamnesis and findings on physical examination. Data regarding the patient's age, lifestyle, cognitive state, severity of different PD symptoms, medical treatment and potential side effects of different interventions are all integrated into the treatment plan. Incorporation of genetic information into this treatment plan could lead to further "personalization." There is accumulating evidence that the future success of disease modification in PD will require a personalized, biomarker-based approach, e.g., *LRRK2* inhibitors for carriers of relevant pathogenic variants.[1] The role of personalized medicine in symptomatic therapies for PD, previously suggested by some researchers[2], is less clear. A recent study[3] raised concern that subthalamic deep brain stimulation (STN-DBS) may accelerate cognitive deterioration in PD associated with pathogenic variants in the *GBA1* gene (*GBA1*-PD), thereby challenging the current practice of being agnostic to genetic data when recommending symptomatic (surgical) treatment.

The *GBA1* gene codes for glucocerebrosidase (GCase), a lysosomal enzyme with reduced activity in carriers of pathogenic variants[4]. The degree of GCase activity reduction depends upon the specific type of variant present, and whether individuals are homozygous or heterozygous variant carriers[5]. PD associated with *GBA1* does not follow a strict Mendelian inheritance with variable penetrance[6]. Thus carriers of pathogenic variants are at increased

risk of PD, and based on the variant type and population studied, penetrance may be as high as 29.7% by age 80[7, 8]. Another study found that risk of PD associated with *GBA1* pathogenic variants was 10% at 60 years, 16% at 70 years, and 19% at 80 years of age.[9] Heterozygous pathogenic variants in *GBA1* are associated with an increased risk of PD, whereas homozygous variants are associated with Gaucher disease (GD) and an increased PD risk[7]. *GBA1*-PD has, on average, a more aggressive disease course. *GBA1*-PD patients suffer from a disease with an earlier age of onset[10, 11], experience faster motor deterioration[11, 12], earlier neuropsychiatric symptoms including dementia[11, 13] and probably have earlier mortality[11].

Patients with *GBA1*-PD are more likely to receive device-aided therapies[11], including DBS[14]. Studies have shown that between 12 and 17% of those undergoing DBS, regardless of ethnicity, are carriers of *GBA1* pathogenic variants, [14, 15] whereas estimates in the European non-Ashkenazi Jewish population range from 2.9-12%[16]. Those who opt for DBS tend to be younger, have clear levodopa responsiveness, and obvious clinical features that qualify them for DBS, such as dyskinesia and motor fluctuations, which may explain this genetic enrichment[14, 15]. Patients with *GBA1*-PD who undergo STN-DBS experience a good motor outcome, similar to patients without *GBA1* pathogenic variants (non-*GBA1*-PD).[15] This improvement enables a significant reduction in anti-parkinsonian medication burden. Are these clinical advantages marred by accelerated cognitive impairment possibly induced by STN-DBS in *GBA1*-PD?

Three decades after STN-DBS was established as a therapy for advanced PD[17], the attempts to optimize selection criteria for this procedure are still ongoing. The presence of a *GBA1* mutation in an STN-DBS candidate is the new potential player in this selection process. Here, we aim to summarize the available data and obstacles that remain in deciding whether and how to integrate GBA1 genetic status in the selection process of candidates for STN-DBS.

WHAT WE KNOW

As this paper aims to address possible long-term, procedure-induced, cognitive outcomes of STN-DBS in *GBA1*-PD, we will briefly summarize current knowledge regarding the cognitive outcomes of non-operated *GBA1*-PD patients, available data regarding long-term cognitive and quality of life (QoL) outcomes of STN-DBS in non-genotyped PD, and the long-term cognitive outcomes of STN-DBS in *GBA1*-PD.

Cognitive decline in *GBA1*-PD without DBS:

GBA1-PD is associated with a more rapid cognitive decline and increased risk for dementia[11, 18]. In the first decade that follows PD diagnosis patients with *GBA1*-PD lose 0.5 points annually on the Mini-Mental State Examination (MMSE), twice the rate found in idiopathic PD[19]. The rate of cognitive decline is partially determined by the specific mutation. Pathogenic variants that lead to type I GD in their bi-allelic form (e.g., p.N370S) are considered mild, or non-neuronopathic, while variants that cause neuronopathic Gaucher (type II or type III) in their bi-allelic form (e.g., p.L444P, 84GG) are considered severe. Both mild and severe pathogenic variants are associated with increased rate of cognitive

deterioration relative to non-*GBA1*-PD. When compared to non-*GBA1*-PD patients, the cumulative risk for dementia among carriers of a mild *GBA1* mutation is two-fold, while this risk increases to greater than five-fold in those with severe variants[11]. Data regarding dementia risk is less clear for individuals carrying the polymorphism *p.E326K* which does not cause Gaucher disease in the bi-allelic form. It has been suggested that the *p.E326K* variant may increase the risk for dementia to the same magnitude as severe variants[12, 13].

Cognitive deterioration following STN-DBS in non-genotyped PD:

The short-term effect of STN-DBS on cognition has been the focus of investigation in a relatively large number of studies. While some controlled studies did not find intervention-dependent cognitive impairment during the first year after the intervention[20] others documented a moderate impairment in verbal fluency as well as milder impairments in other domains, mainly executive function[21]. A meta-analysis[22] summarizing data from 28 methodologically heterogeneous, relatively small (median number of participants 17) and mostly uncontrolled studies, showed a moderate deterioration in verbal fluency, and a small deterioration in executive function and verbal learning and memory, in the first year after surgery. The clinical significance of these changes was not estimated.

Knowledge regarding the long-term cognitive effects of STN-DBS, which is more relevant to the purpose of this manuscript, is limited. The absence of proper control groups, that would enable the separation of the intervention effect from the natural history of disease, makes the interpretation of results difficult. Two five-year prospective studies[23, 24] demonstrated a similar yearly reduction in the Mattis Dementia Rating Scale (MDRS) in non-genotyped PD following STN-DBS. This reduction was statistically significant in one study (from 140.2±3.9 at baseline to 134±8.7) but not in the other (136±10 to 131±18). It is important to note that the decline in both groups was very similar – 6 points versus 5 points but the variability was much higher in the second study. Both studies demonstrated a statistically significant drop in the Frontal lobe assessment scores (43.2±7.2 to 36.3±10.8 and 40.4±9.2 to 37.3±11.2 respectively). These results were replicated by retrospective studies that documented a similar rate of decline in MDRS after five to six[25, 26] or even eight years[26] post-DBS.

The decline in MDRS score does not necessarily reflect daily difficulties experienced by the patient and their surroundings. Dementia, a diagnosis that considers the patient's functional cognitive disability, was reported by one of the prospective studies[24] to occur in 11.6% of the participants 5 years after STN-DBS. The long-term cumulative rates of dementia in STN-DBS patients were reported also by several retrospective studies. These studies, however, suffer from high dropout rates that may contribute to biases (likely underestimation) when evaluating the true prevalence of dementia. The frequency of post-STN-DBS dementia in these studies ranges from 5% (1/20 patients) after 8 years[27] and 53% (29/55 patients) at 10 years[28]. A relatively large study with a high dropout rate (28.6%) reported dementia in 4/175 (2.2%) patients after a year, in 12/142 (8.4%) patients after five years, and in 31/104 (29.8%) after ten years[29]. Based on the natural history of the disease[30], the prevalence of dementia in this study was lower than expected, possibly due to a younger age at PD onset in this population. In this study, predictors of dementia included

lower frontal scores and hallucinations at baseline in addition to male sex, older age, and perioperative cerebral bleeding. Importantly, the incidence and prevalence of dementia in PD patients with DBS is reported to be comparable to the general PD population (non-DBS).[29]

QoL following STN-DBS in non-genotyped PD:

Patient-centered outcomes are at the core of establishing the benefit of symptomatic interventions. Several studies have documented improvement in QoL, using the Parkinson's Disease Questionnaire (PDQ-39), in the first years following STN-DBS surgery[31, 32]. Patients who were operated relatively early in their disease course experienced an even larger improvement in QoL compared with patients on best medical-therapy[32] over a 24-month period.

Improvement in the PDQ-39 is partially lost three years after surgery[33] and returns to pre-operative value within five years after the procedure[26, 34]. Six years after surgery the score in the PDQ-39 scale is higher than the pre-DBS score, likely reflecting increased disease burden on QoL[25]. As expected, *GBA1*-PD patients reported significantly worse quality of life compared with their counterparts 7.5 years after STN-DBS with the greatest deficits in mobility, activities of daily living, cognition, and communication.[35] Unfortunately, in the absence of a control group of non-operated PD patients, these data are difficult to interpret, especially in the light of the motor benefit of STN-DBS that has been shown to last for over a decade[36].

Cognitive deterioration in *GBA1*-PD following DBS:

The cognitive decline in *GBA1*-PD following DBS has been assessed only in retrospective studies. Interpreting the results of these studies is limited by the absence of a control group of non-operated *GBA1*-PD patients at comparable stages of disease.

It has been shown that in the first year following surgery the cognitive decline in *GBA1*-PD is significantly more pronounced (MDRS 138.1±4.2 at baseline and 135.0±7.1 at one year) than in other forms of monogenic PD or in PD without a known genetic cause[37]. Two retrospective studies[15, 35] with longer follow-up (87.5% with STN and 12.5% with GPi-DBS), demonstrated that although *GBA1*-PD patients were operated at a younger age, their cognitive (and motor) capabilities deteriorated faster compared to operated non-*GBA1*-PD patients. Five years post-DBS the average decline in MDRS was 4.4 ± 7.3 points per year in the *GBA1*-PD group compared with only 0.5 ± 0.9 points per year in the non-*GBA1*-PD group[15]. Only 3/10 (30%) of the patients in the *GBA1*-PD group were cognitively intact 7.9±1.6 years post-surgery compared with 13/16 (81%) in the non-*GBA1*-PD group[35].

The largest study of the cognitive outcome of patients with *GBA1*-PD following STN-DBS analyzed pooled retrospective data from 12 datasets (follow up of up to 5 years post-surgery)[3]. The rate of post STN-DBS cognitive deterioration in 58 individuals from this group was compared with the rates of cognitive deterioration in three control groups. These included non-operated *GBA1*-PD patients (82 individuals), and of operated (98 individuals) and non-operated (128 individuals) non-*GBA1*-PD patients. For this comparison, results of other cognitive tests (MMSE and Montreal Cognitive Assessment) were converted to MDRS scores. As expected, operated patients with *GBA1* pathogenic variants deteriorated

cognitively faster than operated patients without pathogenic variants. The more concerning finding, which has the potential to affect our clinical practice, was that operated *GBA1*-PD patients deteriorated 1.71 points / year faster than non-operated *GBA1*-PD patients ($p < 0.0001$) (Figure 1). This finding was also valid when *GBA1*-PD patients were sorted into carriers of non-neuronopathic (mild) or neuronopathic (severe) types of *GBA1* pathogenic variants. It is also important to note that operated non-*GBA1*-PD patients also deteriorated faster relatively to their non-operated non-*GBA1*-PD counterparts but the difference between these groups was smaller, although significant (0.53 points / year, $p < 0.0004$).

The main criticism on this study[38] was that half of the non-operated *GBA1*-PD patients were in a earlier stage of disease, mainly from the Parkinson's Progression Markers Initiative (PPMI) cohort[39]. The operated group, on the other hand, were patients with longer PD duration who were referred for STN-DBS. Since the rate of cognitive decline in PD may not be linear, with a slower rate in the early phase of the disease and possible acceleration in advanced phases[40], to a certain degree, a faster cognitive decline in the operated group may be expected even if STN-DBS was avoided.

GAPS AND CONTROVERSIES

The outcomes of DBS are difficult to generalize since they may be dependent on multiple factors. Major factors include the patient and target selection process by a multidisciplinary team, surgical and anesthesia methods, and accuracy of electrode placement in the operating room, and the DBS programming that is done in parallel with a reduction in oral medications. Estimation of the clinical benefit of this procedure is, therefore, more complex than evaluating the efficacy of oral drug which can be given according to a precise protocol. In addition, long-term studies suffer from high drop-out rates that lead to biases. These factors limit our knowledge of the long-term cognitive effects of the procedure and the stimulation on cognition. The possibility that STN-DBS may accelerate cognitive decline in a sub-population of patient calls for an urgent effort to answer the following issues.

Controversy: Does STN-DBS truly accelerate cognitive deterioration in *GBA1*-PD? If so, what is the clinical significance of this acceleration?

Pooled multi-center data raised concerns regarding accelerated dementia in *GBA1*-PD patients following STN-DBS[3]. This observation requires verification using systematic, thorough and rigorous data collection procedures. Moreover, estimating the overall benefit of STN-DBS should consider factors such as motor benefit, independence in activity of daily living, reduced side effects of anti-parkinson medications, risk of psychosis, depression, anxiety, and other non-motor symptoms. Ideally, a prospective and randomized study comparing cognitive outcomes of *GBA1*-PD patients with and without STN-DBS would be needed to establish the overall risk-to-benefit ratio of STN-DBS in *GBA1*-PD patients.

Gap: If STN-DBS has a negative effect on cognition in *GBA1*-PD, how can this effect be minimized?

The choice of operation timing, DBS target, anesthesia method, programming, and post-surgical regimen of anti-parkinsonian medication, and exercise which has been shown to

improve cognition,[41] are all modifiable parameters that could potentially minimize negative effects of DBS in case these exist.

Pre-operative cognitive impairments are a risk factor for accelerated post-operative cognitive deterioration[30]. On average, *GBA1*-PD patients receive lower scores on cognitive tests at the time of operation[42]. Would an earlier referral of these patients to STN-DBS minimize the possible cognitive side effect of the procedure?

Based on anecdotal observation from two *GBA1*-PD patients, it has been suggested that the GPi may serve as a cognitively safer target for DBS[43]. This observation is in-line with some, but not all,[44] studies demonstrating slightly reduced risk for cognitive decline in non-genotyped PD with GPi-DBS as compared to STN-DBS[45] and with the systematic review and evidence based guideline from the Congress of Neurological Surgeons.[46] Clinicians favoring GPi-DBS over STN-DBS in *GBA1*-PD, however, should consider that STN-DBS enables greater reduction of medication burden compared with GPi-DBS[44, 47]. Medication reduction may be of potential benefit in *GBA1*-PD patients in cases where high dopaminergic burden is contributing to psychosis and orthostatic hypotension, both of which are more prevalent in *GBA1*-PD[48, 49]. Which of these targets is better suited for *GBA1*-PD patients? The answer to this question is still pending.

In non-genotyped PD patients, it has been suggested that the long term neuropsychiatric negative effects of DBS could be, at least partially, attributed to the reduction of anti-parkinsonian medications[50]. However, increased apathy, anxiety, or depression could all contribute to lower performance on cognitive tests[51]. Should a more moderate reduction in anti-parkinsonian medication be considered post-operatively in *GBA1*-PD?

Controversy: Should PD patients be genetically tested prior to STN-DBS?

Knowledge regarding the genetic status and mutation type (i.e. severity) of the patient is crucial to establish the effect of any pathogenic variants on the outcomes of STN-DBS. Only such knowledge would allow us to establish better criteria for patient selection and to build gene-based ‘personalized’ protocols for DBS management.

A point of controversy between the authors of this manuscript is whether such genetic tests should be performed as part of routine clinical practice, outside of clinical trials. On the one hand, it could be argued that knowledge regarding *GBA1* status is not ‘actionable’ since recommendations cannot be consolidated based on present data. The counterpoint to this argument is that patients with *GBA1* pathogenic variants have a right to be aware of their genetic status. Also, such patients should be made aware of the knowledge and gaps summarized above so that an informed decision can be made. We agreed that a good compromise between these approaches is to inform patients regarding this controversy before performing genetic testing.

Gap: How should *GBA1*-PD patients considering STN-DBS be counseled?

Patients who are already aware of their genetic status, either through clinical trials or following clinical test, should be presented with lack of a definitive answer to the question of the effect of STN-DBS on cognition, and overall risk-to-benefit ratio in *GBA1*-PD. They

should be presented with the lack of complete answers regarding the effect of STN-DBS on cognition, and the associated risk-benefit ratio in *GBA1*-PD. Patients should also be aware of the possibility of GPi-DBS, infusion therapies such as continuous intestinal infusion of levodopa-carbidopa[52], as well as continuous subcutaneous dopaminergic infusions that are becoming available.

Controversy: How should the overall risk-to-benefit ratio of STN-DBS in *GBA1*-PD be established?

Several challenges exist when considering the type of data and resources required to execute such a study and the authors of the present work have conflicting opinions on whether some of the following obstacles can be overcome.

First, screening PD patients considering STN-DBS for *GBA1* pathogenic variants would require coordination of timely genetic testing and counseling as part of the DBS pre-operative process. Second, the ethics of randomizing subjects to a treatment (STN-DBS) with the goal of determining whether it will worsen cognition must be considered, and whether patients would be willing to participate in such a program must also be weighed before embarking on such a study. The authors of the present work have conflicting opinions also on whether the current data constitute equipoise and the ease of recruiting for such a study. Third, all *GBA1* pathogenic variants are not equivalent, and a randomized study would require matching of *GBA1*-PD patients with and without DBS based at-least on mutation severity to definitively determine if there is a difference between groups. Cognitive tests performed in such a study should be sensitive enough to detect early cognitive impairments that may be expected in *GBA1*-PD and are predictors for post-DBS dementia. Information regarding other predictors of dementia in *GBA1*-PD, such as CSF glucocerebrosidase activity (can be taken during the surgery)[53] and APOE status[19], should also be collected, though collection of such data raises additional challenges regarding recruitment and associated sample size. Fourth, such a randomized-controlled trial would likely offer an option for the patients assigned to the best medical treatment group to switch over to get DBS after 1-2 years. This timeframe may not be long enough to fairly evaluate cognitive outcomes. In addition, such a study should not be just focused on neuropsychological tests (e.g., MDRS) but would include patient-centered outcomes such as quality of life, non-motor symptom burden, prevalence of psychosis, caregiver strain, as well as other objective outcomes, such as falls and fractures, transition to a nursing facility, hospitalizations, and mortality. Such a prospective study would require great financial resources and, since the long-term outcome is the main interest, will yield results after at least a decade. As such, we do not foresee such a study being conducted. Monitoring the trajectory of cognitive decline of *GBA1*-PD patients in the years leading up to DBS may also be considered, but this approach would not determine whether DBS directly impacts cognition.

An alternative and more feasible approach would be through the development of a repository of PD patients with and without DBS, with long-term longitudinal follow-up and high-quality surgical data. DBS device manufacturers have established registries to collect prospective data (NCT04071847, NCT02071134, NCT00959296), but there is

limited financial incentive to collect and analyze genetic data from the manufacturer's perspective, and these registries do not include patients without DBS. One specific dataset, the Registry for the Advancement of DBS in Parkinson's Disease (RAD-PD), is currently collecting prospective clinical and imaging data in DBS subjects, but not genetic data. Other longitudinal studies, such as PPMI[39] study and the Accelerating Medicines Partnership (AMP-PD)[54] are high quality studies with long-term follow-up, but data regarding details of DBS are limited. Thus, a concerted effort is needed to develop new registries and/or expand existing studies to include genetic data and high-quality DBS data. Such studies could be leveraged to not only examine outcomes in *GBA1*-PD patients, but also DBS outcomes of other monogenic subtypes of PD, such as, but not limited to, *LRRK2* and *PRKN*,[55] in addition to single nucleotide polymorphisms derived from genome wide association studies.[56] The other significant benefit of such an approach is that the registries would be open to all sites performing DBS and this would provide a more representative set of outcomes than a randomized design which would almost certainly focus on very experienced major medical centers.

A complementary approach would be to design a Patient Centered Outcomes Research Initiative (PCORI) study that would promote comparative effectiveness (CER) research to inform patient decisions. An alternative strategy would be to compare STN-DBS to other therapies that address motor fluctuations, namely continuous infusion therapies, which would allow for comparison of subjects at comparable stages of disease severity. The expected approval of subcutaneous continuous carbidopa/levodopa[57], or their prodrugs[58], may be an opportunity for the movement disorders community to conduct a randomized controlled trial that would identify the best symptomatic therapy, DBS vs. infusion, for *GBA1*-PD patients. Future studies comparing the outcome of STN-DBS and continuous infusions should only target participants who are cognitively preserved to avoid current biases in patient selection for device-aided therapies.

Finally, using existing datasets from well-conducted clinical trials that compare the outcomes of patients with STN-DBS with those on best medical therapies may also yield valuable insights. In several studies, longitudinal data such as MDRS and PDQ-39 exist for these groups[59, 60]. Close to 10% of these who participate in these trials are expected to carry a mutation in *GBA1*[14], an effort to genotype living participants in these studies (following approval by the relevant ethics committees) would yield important knowledge. When considering the above options, leveraging existing data seems to be the most feasible, efficient, and practical approach to better understand the effects of DBS in *GBA1*-PD patients.

CLINICAL PRACTICE: EXPERT OPINION

As reviewed here, limited data exist regarding the risk-to-benefit ratio of performing STN-DBS in patients with *GBA1*-PD. Open questions discussed here warrant careful additional study and will take time to fully answer. Clinicians in the field face the challenge of deciding how to move forward with their PD patients considering DBS. We therefore decided to share our expert opinion which is based on our experience and understanding of existing data and its limitations.

All authors strongly agree that clinicians should not categorically deny DBS to PD patients based solely on genotype (*GBA1* status). As discussed above, *GBA1*-PD patients clearly benefit motorically from DBS implantation. Given the heterogeneous clinical profile of *GBA1* patients, and based on our own personal experience, there are cases of *GBA1* patients who obtain significant benefit from DBS without cognitive problems. The challenge lies in our ability to accurately predict who may suffer from potential cognitive problems after implantation and further work is needed in this area as described above. Therefore, when considering a *GBA1* patient, the potential benefits and risks of implantation need to be carefully weighed and discussed thoroughly with the patient.

We suggest that PD patients considering DBS may be offered genetic testing for *GBA1*, where available and feasible, and pre-test counseling should be performed by the clinician, genetic counselor, or other qualified team member. Genetic status could provide the clinician and patient with a more complete picture regarding the potential risks and benefits of STN-DBS. If patients opt for genetic testing, it should be confirmed whether they would like to receive the results. Finally, if the patient agrees to receive results, we recommend post-test counseling by the clinician, genetic counselor, or other qualified professional. The clinician and patient may then together decide the most optimal plan and consider the potential benefits of interventions such as DBS, and weigh the potential cognitive risk which may be associated with STN-DBS. Cases where the risk of cognitive decline is outweighed by the motor benefits of DBS exist, and ultimately should be decided by the patient and clinician together.

Lastly, based on our experience, we suggest that stimulation increments and medication decrements are performed with even more caution than usual, as *GBA1*-PD patients may not tolerate the same aggressive reduction of the LEDD as their non-*GBA1* counterparts. It is important to remember that the desired outcome is the overall improvement of quality of life for patients and their families, and each case must be considered according to its individual characteristics.

CONCLUSIONS

While the long-term motor benefit of STN-DBS is well established, data regarding the possible long-term effect of the procedure on cognition are limited. Concern regarding possible accelerated cognitive impairment in *GBA1*-PD following STN-DBS should be considered in the light of these limited data. While further investigations (as outlined above) are being conducted, we will continue to base decisions regarding DBS and the associated target according to each individual's symptoms.

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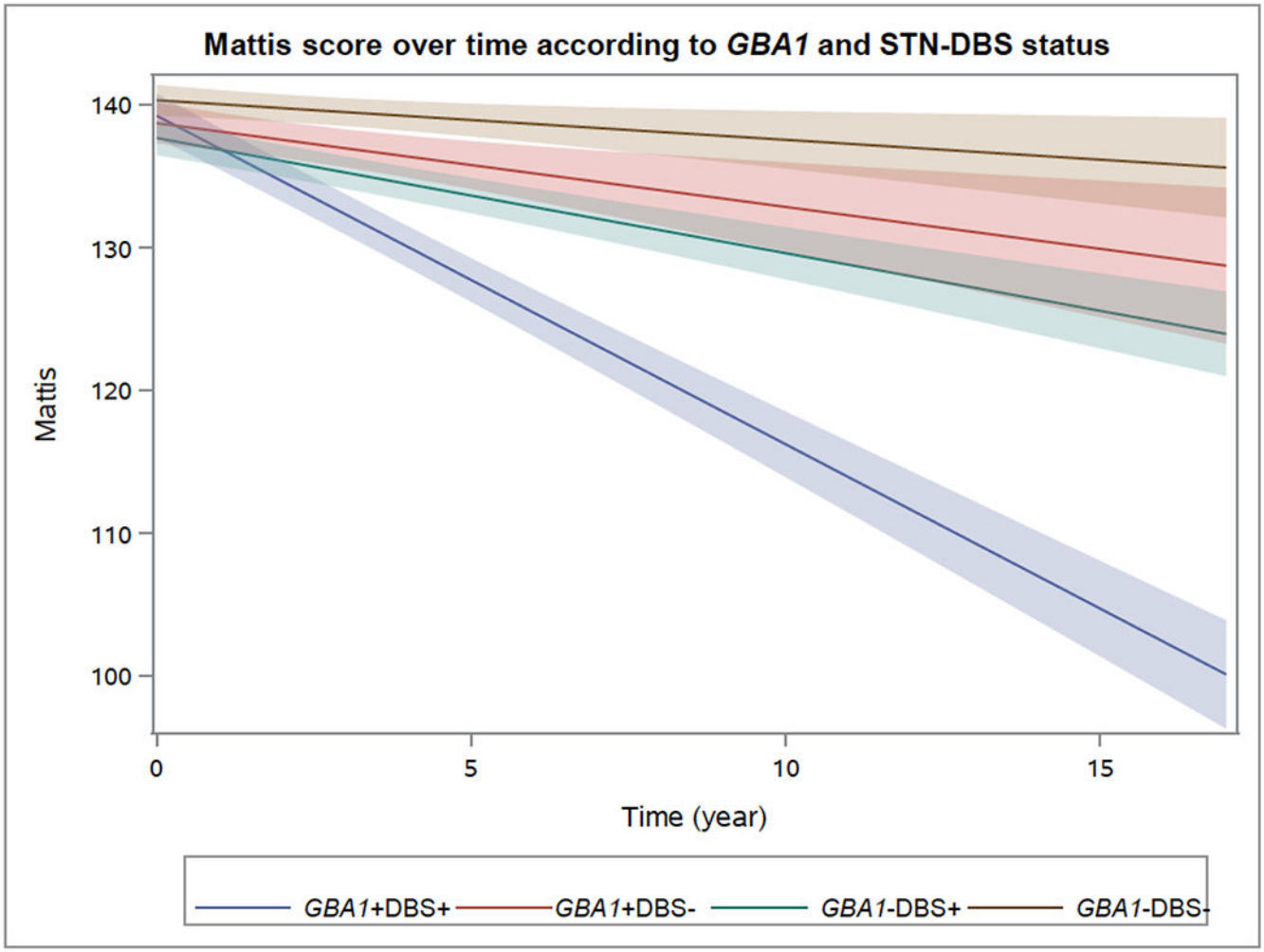

Figure 1:
Parkinson's patient with mutation in *GBA1* (*GBA*-PD) cognitively deteriorated faster following subthalamic deep brain stimulation (STN-DBS) compared to non-operated *GBA*-PD patients. Linear fit with 95% confidence interval bands is shown. Figure modified from Pal et al. 2022[30] with permission.