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Review

A Review on Response to Device-Aided Therapies Used in Monogenic Parkinsonism and *GBA* Variants Carriers: A Need for Guidelines and Comparative Studies

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Abstract. Parkinson's disease (PD) is in some cases predisposed-or-caused by genetic variants, contributing to the expression of different phenotypes. Regardless of etiology, as the disease progresses, motor fluctuations and/or levodopa-induced dyskinesias limit the benefit of pharmacotherapy. Device-aided therapies are good alternatives in advanced disease, including deep brain stimulation (DBS), levodopa-carbidopa intestinal gel, and continuous subcutaneous infusion of apomorphine. Candidate selection and timing are critical for the success of such therapies. Genetic screening in DBS cohorts has shown a higher proportion of mutation carriers than in general cohorts, suggesting that genetic factors may influence candidacy for advanced therapies. The response of monogenic PD to device therapies is not well established, and the contribution of genetic information to decision-making is still a matter of debate. The limited evidence regarding gene-dependent response to device-aided therapies is reviewed here. An accurate understanding of the adequacy and responses of different mutation carriers to device-aided therapies requires the development of specific studies with long-term monitoring.

Keywords: Parkinson's disease, parkinsonian disorders, genetic disorders, apomorphine, levodopa, infusion pumps, deep brain stimulation

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative condition after Alzheimer's disease and is the fastest-growing neurodegenerative disorder, with a projected prevalence of 12 million by 2040 [1]. The incidence ranges from 5 to 25 annual cases per 100,000, with the mean age of onset in the seventh decade [2].

There is still a knowledge gap in our understanding of the molecular basis for neurodegeneration in PD. Several environmental and genetic risk factors have been identified, including rare monogenic disorders [3].

A broad genotype-phenotype correlation can be recognized for certain variants [4]. Besides, monogenic PD may benefit from gene-specific treatment

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strategies (i.e., *LRRK2* and *GBA*) [5]. However, it remains to be seen whether this applies to device-aided therapies such as deep brain stimulation (DBS), levodopa-carbidopa intestinal gel infusion (LCIG), or continuous subcutaneous apomorphine infusion (CSAI) [6, 7]. These therapies are potential options for individuals with PD with complications such as refractory "wearing-off" and levodopa-induced dyskinesias [8].

Surprisingly, genetic screening has demonstrated an overrepresentation of specific genetic variants in DBS cohorts (up to 29%) compared to the overall PD population (estimated at 5–10%). *GBA*, *LRRK2,* and *PRKN* variants are the most frequent [9].

This association raises whether individuals with certain genetic variants represent better candidates for specific device-aided therapies and whether these genetic factors affect the response to such therapies. We suggest reading a previous publication addressing the phenotype-genotype relationship in decision-making on device-aided therapies [10]. The latter issue, how genetic factors affect treatment response, is addressed below.

DEVICE-AIDED THERAPIES

The success of device-aided therapies depends on selecting the suitable device for the right patient. Key eligibility features include: (I) $\geq$1 hour of troublesome dyskinesia per day, or $\geq$ 2 hours "off" symptoms per day and need to take levodopa $\geq$ 5-times per day; (II) no more than mild dementia and absence of troublesome hallucinations; and (III) significant difficulty with activities of daily living. Patients demonstrating good levodopa response who are emotionally stable, physically healthy, cognitively intact, and younger (preferably < 70 years of age) are ideal candidates for CSAI, LCIG, or DBS [11]. While these therapies seem to provide a similar improvement in reducing "off" time by around 40–60%, their effects on dyskinesia and non-motor symptoms are heterogeneous, and their side effects and complications can be quite different [12]. Table 1 summarizes their main indications, advantages, disadvantages, and contraindications.

In terms of selecting which device therapy is most appropriate, DBS is favored with younger patients and minimal non-levodopa-responsive motor symptoms (except for tremor) [13, 14]. DBS may be contraindicated if there is dementia, hallucinations, uncontrolled depression, marked postural and gait problems, severe brain atrophy, or suspected atypical parkinsonism.

LCIG can still be considered for patients with mild-to-moderate dementia or age > 70 years, even with severe depression [15]. However, patients with dopamine dysregulation, punding, or pre-existent peripheral neuropathies may be less favorable candidates.

CSAI can be considered if there are mild hallucinations or moderate cognitive impairment. Moreover, it might improve neuropsychological performance [16, 17]. In addition, this device may ameliorate depression, apathy, "off" pain, and slowness of thinking [18]. However, it seems less favorable in patients with impulse control disorders (ICD), marked psychosis, daytime somnolence, and troublesome orthostatic hypotension [19].

We caution against dogmatism since there is also favorable evidence for device therapies in some of these reported contraindications. For example, there are cases where LCIG and CSAI improve ICD, and where LCIG decreases dopamine dysregulation syndrome [20–22]

A relevant factor in decision-making for device-aided therapies is the long-term outcome expectancy. Chronic STN-DBS can cause dysarthric speech, problems in verbal fluency, worsening freezing of gait, and axial symptoms. These are important determinants of quality of life [23–25]. Severe pre-operative gait difficulties might predict limited long-term DBS benefits [23, 24]. Moreover, motor outcomes one year after bilateral STN-DBS are inversely correlated with the rate of progression of motor symptoms [26].

The leading causes of discontinuation of LCIG therapy in long-term follow-up include worsening cognition, dyskinesias, chronic polyneuropathy, weight loss, and hallucinations. Eventually, LCIG may become ineffective [27, 28].

Like LCIG, long-term CSAI may worsen cognition, dyskinesias, postural instability, and hallucinations. CSAI also causes sedation and orthostatic hypotension. These factors may obscure the long-term benefits in some patients [29–32]. Furthermore, a decrease in therapeutic effect may become an important reason for discontinuation within the first four years [33].

In conclusion, it is essential to recognize patient heterogeneity and, if possible, identify biomarkers of short and long-term outcomes. Understanding phenotype-genotype relationships and how variants predict the risk of significant disease milestones [34]

Table 1
Comparison between different device-aided therapies

Ideal clinical Indications	Advantages	Disadvantages	Relative Contraindications
Deep Brain Stimulation			
⇒ **PD>5 y (>4 y in EARLY Stim)** ⇒ **<75 y** ⇒ **Motor improvement > 30% with Levodopa** ⇒ **Significant motor fluctuations and dyskinesia** ⇒ **Medication-resistant tremor** ⇒ Ref. [7, 13, 111–114]	⇒ 25–68% reduction in "off" periods ⇒ 40–60% reduction in dyskinesias ⇒ Significant benefit on tremor, bradykinesia, rigidity, dystonia, dyskinesia. ⇒ Potential reduction on total LEDD (STN-DBS) ⇒ Symptoms that may respond includes, truncal deviations, fatigue, inner restlessness, anxiety, depression, ICD, freezing of gait, urinary and gastrointestinal symptoms, weight loss ⇒ Ref. [19, 111, 115–118]	⇒ **Procedural**: Invasive neurosurgery with uncommon but serious peri-operative complications (e.g., intracranial hemorrhage, postoperative wound or hardware infection, transient postoperative delirium) ⇒ **Described AE**: Balance and gait problems, freezing, depression, anxiety, apathy, suicide committed, psychosis, ICD, cognitive decline, dysarthria, swallowing problems, eyelid apraxia, dyskinesia, pain, weight gain. ⇒ **Nonresponding symptoms**: Autonomic dysfunction, dysphagia, dysphonia, cognition or verbal fluency, postural instability, RBD, excessive daytime sleepiness. ⇒ Ref. [19, 111, 117–120]	⇒ Poor cognition ⇒ Troublesome hallucinations ⇒ Poor social support ⇒ Target/most bothersome symptoms are not responsive to Levodopa (except tremor) ⇒ Severe depression ⇒ Dopamine dysregulation or punding ⇒ Poor operative candidate, severe brain atrophy or intracranial lesions affecting surgical approach ⇒ Severe systemic disease ⇒ Lack of compliance at follow-up ⇒ Ref. [7, 111–114]
Levodopa–carbidopa intestinal gel infusion			
⇒ **Advanced PD** ⇒ **with significant motor fluctuations** ⇒ **Troublesome "off" periods > 3 h per day** ⇒ Ref. [7, 111, 121, 122]	⇒ 47–59% reduction in "off" periods ⇒ 49–64% reduction in time with dyskinesias ⇒ Potential benefit on NMS: anxiety episodes, sleep, irritability, urinary and orthostatic symptoms, pain, constipation, attention and fatigue, delusions, mood disorders and ICD. ⇒ May be effective as monotherapy ⇒ Ref. [19, 111, 121–126]	⇒ **Procedural:** Invasive procedure with less common but serious peri-operative complications; PEG-J tube blockage or failure; PEG-J tube or skin infection ⇒ Infusion device thought large and cumbersome ⇒ Aesthetics, excessive granulation tissue ⇒ **Described AE:** Abdominal pain, nausea, flatulence, constipation, diarrhea, orthostatic hypotension, peak-dose dyskinesias, diphasic dyskinesias, insomnia, sleep attacks, anxiety. ⇒ Rarely reported AE include peripheral neuropathy, weight loss ⇒ **Nonresponding symptoms**: Freezing and festination with no response to levodopa, postural instability, dysphagia, and dysarthria ⇒ Ref. [19, 111, 124, 126]	⇒ Poor cognition ⇒ Troublesome hallucinations ⇒ Poor social support ⇒ Poor fine motor skills ⇒ Contraindications for PEG procedural ⇒ Conditions that interfere with kinetic of the drug ⇒ pre-existing peripheral neuropathy ⇒ Dopamine dysregulation syndrome or punding ⇒ Severe systemic disease ⇒ Ref. [7, 111]

(*Continued*)

Table 1
(*Continued*)

Ideal clinical Indications	Advantages	Disadvantages	Relative Contraindications
Continuous subcutaneous infusion of apomorphine			
⇒ **PD of > 3 y (TOLEDO study)** ⇒ **Advanced PD, with motor fluctuations, troublesome "off" time, and dyskinesias** ⇒ **Good response to levodopa** ⇒ **Effective rescue doses of apomorphine but either needed too frequently or are associated with increasing dyskinesia** ⇒ Ref. [7, 18, 111, 124, 127]	⇒ 25–85% reduction in motor fluctuations ⇒ 43–64% reduction in time with dyskinesias ⇒ Older age, slight to moderate dementia and depression are not absolute contraindications ⇒ Potential benefit on NMS, such as pain (related to dystonia), restless legs, panic attacks, depression, apathy, insomnia, slowness of thinking, swallowing, micturition disorders. ⇒ Ref. [18, 19, 111, 128–134].	⇒ **Related to device:** skin complications and nodules from subcutaneous injections ⇒ Requirements for placement of subcutaneous line daily. ⇒ **Described AE:** weight gain, neuropsychiatric side effects, daytime somnolence, nausea, orthostatic hypotension, coombs antiglobulin positive hemolytic anemia. ⇒ Risk of ICD ⇒ Potential benefit on dyskinesias may be delayed by weeks. ⇒Ref. [19, 111]	⇒ Poor social support ⇒ Poor fine motor skills ⇒ Presence of dopamine dysregulation, punding or ICD ⇒ Severe hallucinations or dementia ⇒ Orthostatic hypotension ⇒ Severe fatigue syndrome ⇒ Severe systemic disease ⇒ Anticoagulation ⇒ Ref. [7, 18, 111, 124]

DBS, deep brain stimulation; LCIG, Levodopa-carbidopa intestinal gel; CASI, continual apomorphine subcutaneous infusion; iPD, idiopathic Parkinson's disease; NMS, non motor symptoms; PEJ, percutaneous endoscopic Jejunostomy; AE, adverse effects; ICD, impulse control disorders; LEDD, Levodopa equivalent daily dose.

may affect the timing, appropriateness, expected outcome, and expectations for device-aided therapies [10].

CLINICAL FEATURES OF CAUSAL MUTATIONS AND GENETIC RISK FACTORS FOR PARKINSONISM

Most PD cases are sporadic, associated with genetic, epigenetic, and environmental risk factors [35]. The most frequent genetic risk factors for sporadic PD are *GBA*, *SNCA*, *LRRK2,* and *MAPT* [36]. In addition, PD-causal monogenic variants account for 5 to 10% of cases [35, 37].

The severity and risk associated with *GBA* depend on the variant [38]. Overall, the *GBA* motor phenotype resembles idiopathic PD, possibly with faster progression, more bradykinesia, and levodopa-induced dyskinesias [39, 40]. Cognitive changes appear earlier and tend to be more prominent, particularly in memory and visuospatial domains [41–44]. The dementia risk with a severe *GBA* variant is 2.9 times higher than for mild variants and 5.6 times higher than for idiopathic PD [38]. Severe *GBA* variants may also have more neuropsychiatric and autonomic disturbances [45]. Bi-allelic carriers have faster disease progression and higher mortality than idiopathic PD [42, 46, 47].

Autosomal dominant (AD) PD includes *SNCA*, *LRRK2*, and *VPS35*. *LRRK2* variants are the most frequent cause of monogenic PD, with p.G2019S, p.R1441C, and p.R1441G being the most common. The phenotype resembles idiopathic PD, with atypical signs rarely reported [48]. A more uniform disease course regardless of the age of onset [51] and a higher likelihood to develop dystonia and dyskinesias earlier have been reported [49]. Like iPD, *LRRK2*-PD most likely manifests PIGD phenotype with disease progression [50]. Remarkably, *LRRK2* p.G2019S carriers with a PIGD phenotype have a lower risk of dementia than observed in non-carriers with this phenotype [51]. Overall, LRRK2-PD have a lower risk of dementia [48, 52–54], manifests less olfactory impairment [49, 55], and RBD [56, 57] than non-carriers with PD.

SNCA variants include duplications or triplications and missense mutations, with p.A53T as the most frequent. Some *SNCA* variants (p.A53T and p.E46K) are more likely to develop dementia [58]. Depression, psychosis, and autonomic compromise are also more common for certain *SNCA* variants compared to idiopathic PD [5, 48, 52, 59–62]. For *VPS35*, the most common point mutation p.D620N presents with classical PD features with minimal atypical signs, although postural instability and daytime sleepiness may be more common [48, 63, 64].

Autosomal recessive (AR) PD, such as *PRKN*, *PINK1,* and *DJ1,* present with a phenotype similar to idiopathic PD but with younger age of onset. Patients with *PRKN* variants can respond dramatically to low doses of dopaminergic agents [65]. In addition, it can present with exercise-induced lower extremity dystonia [66] and gait compromise associated with diphasic dyskinesias [67]. Variants of these three genes are uncommonly associated with atypical parkinsonian features [68].

On the other hand, *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, *SYNJ1*, and *VPS13C* represent AR forms that often manifest with juvenile parkinsonism, faster progression, and atypical features including supranuclear gaze palsy, oculomotor or eyelid apraxia, intellectual disability, facial-faucial-finger mini-myoclonus, ataxia, dysarthria, dysphagia, pyramidal signs, seizures, psychosis and dysautonomia [69–77].

Because of scarce evidence, how these causal or risk-modifying variants affect outcomes is debatable. Currently, decision-making for advanced therapies is based on clinical features, which are unreliable for inferring the underlying genetics. Incomplete penetrance (i.e., *LRRK2*, *GBA*), phenotype variability, and environmental factors affect clinical features [34]. At the same time, there is evidence that genetics affect outcomes in ways that would affect decision-making. This is reviewed in the next section.

CURRENT EVIDENCE FOR DEEP BRAIN STIMULATION IN MONOGENIC PARKINSONISM AND GBA VARIANTS CARRIERS

Pal et al. analyzed the Consortium On Risk for Early-onset PD (CORE-PD) cohort, emphasizing *PRKN*, *LRRK2,* and *GBA*. Ninety-nine individuals who received DBS, and 684 without DBS, were identified. Carriers of pathogenic (or "risk" variants for *GBA*) were more common in the DBS vs. non-DBS groups (26.5% vs. 16.8%, respectively) [78]. Performing genetic screening in a cohort of 94 DBS-treated PD patients, Angeli et al. found that 26% had *PRKN*, *LRRK2* p.G2019S, or *GBA* variants. No pathogenic variants were found in *SNCA*

[9]. Likewise, De Oliveira et al. reported that in addition to *GBA* variants, *PRKN and LRRK2* were the most common monogenic forms in DBS cohorts [79]. Interestingly, the response to DBS seems to be related to the variants. Tables 2–5 summarize the evidence for outcomes obtained with device-aided therapies in monogenic parkinsonism and *GBA* carriers.

Various authors have proposed different categories for motor outcomes. In their systematic review, de Oliveira et al. defined a mean UPDRS-III change of 50% or more as a marked response, a mean change of 30% to 50% as a satisfactory response, and less than 30% change as an unsatisfactory response [79]; on the other hand, Kuusimäki et al., defined an improvement of 30% or more in the UPDRS-III score as a favorable outcome; 20–30% a moderate outcome; and < 20% a poor/mild result [80].

DBS in carriers of genetic variants that modify the risk for developing PD or influence PD-related outcomes (GBA)

GBA carriers have DBS earlier in the disease course compared to *LRRK2, PRKN,* or non-mutation carriers [9, 78]. Most *GBA* carriers have marked or satisfactory short-term (<2 years) outcomes to STN-DBS [79]. Data for longer-term follow up are scarce, but outcomes tend to worsen over time. The authors hypothesized that because STN-DBS carries additional cognitive risk over GPi-DBS, the latter target may be preferable for *GBA* carriers, who are already at increased risk for cognitive impairment [79]. A separate study showed *GBA* carriers developed cognitive impairment and stimulation-resistant symptoms within 2 to 7 years after surgical treatment [81] (see Table 2). Thus, the overall benefit of DBS may be compromised due to the rapid progression of cognitive and neuropsychiatric symptoms [80].

A recent study screening for *LRRK2*, *GBA,* and *PRKN* mutations evaluating cognition at baseline and one-year post-DBS showed that high-risk or severe *GBA* variant was associated with pronounced post-operative cognitive decline [82]. The motor benefit was similar among groups.

Modeling different datasets, Pal et al. examined global cognition using the Mattis Dementia Rating Scale to compare the rate of change between *GBA* variant carriers and non-carriers with and without STN-DBS in PD. *GBA* carriers with DBS declined on average 2 points/year more than non-carriers with no DBS, 1.7 points/year more than *GBA* carriers with no DBS, and 1.5 points/year more than non-carriers with DBS [83]. Authors proposed that although non-randomized, this study suggests that *GBA* variants and STN-DBS's combined effect negatively impact cognition, advising that *GBA* variant carriers should be counseled regarding potential risks associated with STN-DBS and alternative options may be considered [83].

Finally, the GPi target may be preferable for *GBA* carriers with dystonia and dyskinesia [79].

Both GPi-DBS and STN-DBS have similar outcomes on motor function measured by the UPDRS-III in the "on" and "off" medication state [84–86], and both targets have a beneficial effect on levodopa-induced dyskinesias [87]. STN-DBS achieves this goal mainly by a greater reduction in medication dosages [87, 88]; but also, stimulation of the area above the STN can directly suppress levodopa-induced "on"-dyskinesia [86]. In contrast, GPi-DBS may provide greater anti-dyskinetic effects possibly by a direct mechanism [84, 85, 87]. Hence, clinical guidelines recommend GPi as the target, especially when reduction of medication is not anticipated, and there is a goal to reduce the severity of "on" medication dyskinesias [84, 89].

On the other hand, although it seems relatively safe concerning cognitive function, chronic stimulation of STN has been associated with a subtle decline in cognitive domains, exceptionally verbal fluency, and executive function [90, 91]. Despite little data is supporting that STN-DBS has a worse cognitive outcome than GPi-DBS [92], more published information is required for validation [93]; if there is significant concern about cognitive decline, particularly regarding verbal fluency, processing speed, and working memory in a patient undergoing DBS, GPi has been recommended [84, 89].

DBS in autosomal dominant PD (SNCA, LRRK2, VPS35)

A systematic review showed that *LRRK2* p.R1441G had poorer outcomes than other *LRRK2* variants [79]. Overall, the response of *LRRK2* p.G2019S carriers to STN-DBS was comparable to idiopathic PD [81]. There are reports of another variant, p.T2031S developing neuropsychiatric problems 5–7 years after DBS [80].

Thus far in the literature, five individuals carrying a *VPS35* p.D620N variant have undergone DBS (STN = 3, unreported target = 2) and were followed for 1 to 8 years. The motor outcome was favorable in 3, moderate in 1, and poor in 1 who developed

Table 2
Available evidence of outcomes for different device-aided therapies in GBA variants carriers

Device	Best evidence available	Number of cases	Age at onset (y)	Disease duration till advanced therapy	Follow-up period	Outcome	Complications
LCIG	**Case series** (abstract) [105]	**11**	Mean about 54	13.54 (7.78)	Not specified (After titration and stabilization of LCIG treatment)	Higher UPDRS-III scores compared to idiopathic PD (44.3 vs. 29), possibly because of a more severe phenotype.	GBA carriers were treated on lower doses (1476 vs. 1702) due to higher rates of hallucinations (71.4% vs. 63.6%) and lower cognitive scores (MoCA 18 vs. 23.3), compared to idiopathic PD
DBS	**Systematic Review** [80]	**50** (STN $n=33$, GPi-DBS $n=4$, Vim-DBS $n=1$, NA $n=12$)	21 to 58		1.6 to 7.5 y	Favorable long term motor outcome in 18. Moderate benefit in 3. Poor outcome in 9. One study reported better outcomes with STN-DBS and Vim-DBS than with GPi-DBS.	Cognitive impairment faster than non-carriers
STN-DBS	**Systematic Review and Meta-analysis** [81]	**33** 31 heterozygous and 2 homozygous	Mean 41.4 – 49-7	11.2 (5)– 17.3 (5.5)	24–90 mo	UPDRS-III score improved by 49% (20 points: 95% CI, 4.5–35.5; $p=0.01$) ($n=33$). LEDD was reduced by 22% (269.2 mg/d; 95% CI, 226.8–311.5 mg/d; $p<0.001$) ($n=30$). UPDRS-IV score improved by 37 to 80% ($n=16$)	Progressive cognitive decline, in 3 studies with a mean follow-up of 72.2 [21.1] mo ($n=26$)
DBS	**Systematic Review** [79]	**19** STN-DBS ($n=16$) Gpi-DBS ($n=2$) Vim-DBS ($n=1$)	35.6–54	6.2–21 y	1–10 y	STN-DBS at 2–6-y responses were marked in 1, satisfactory in 1 and unsatisfactory in 1. After > 6 y, two had satisfactory improvement. LEDD decreased. Motor complications improved from 37% to 100%. Two GPi-DBS cases had 24.8% improvement, and 1 Vim-DBS case showed 42.9% improvement (both at 1-y follow-up)	All the studies showed cognitive decline in GBA patients who underwent STN or GPi-DBS

LEDD, levodopa equivalent daily dose.

Table 3
Available evidence of outcomes for different device-aided therapies in autosomal dominant monogenic parkinsonism

Gene	Device	Best evidence available	Number of cases	Age at onset (y)	Disease duration till advanced therapy	Follow-up period	Outcome	Complications
SNCA *Duplication*	**DBS**	**Systematic Review** [79]	**2** STN-DBS	35 and 41	5 and 6 y	One and 2 y	UPDRS III improved 43% and 52% LEDD decreased by 29.7% ($n=1$). Motor complications improved by 87.5% ($n=1$). Stable cognition. ICD resolved ($n=1$) Depression scores improved or remained stable	Stimulation-induced right foot dystonia relieved by modulating stimulation parameters ($n=1$)
		Systematic Review [80]	**4** STN-DBS ($n=3$) GPi-DBS ($n=1$)	18 to 40 (mean 33.5)	5 to 8 y (mean 6.25)	From 1 mo to 2 y	Favorable motor outcome	Cognitive deterioration ($n=2$)
		Systematic Review [135]	**3** STN-DBS ($n=2$) GPi-DBS ($n=1$)			From 1 mo to 3 y	Improvement in motor features and reduction in LEDD	Foot dystonia, decline in verbal fluency and attention ($n=1$). MMSE worsened from 26 to 23 ($n=1$)
		Systematic Review and Meta-analysis [81]	**1** STN-DBS	41	5 y	12 mo	43% motor improvement 63% LEDD reduction	MMSE worsened from 30 to 29 points.
SNCA *missense*	**STN-DBS**	**Case report** [136]	**1** p.A53E Heterozygous	42	5 y	NR	Reduced fluctuations and increased "on" time.	NR
LRRK2	**LCIG**	**Case report** [103]	1	49	19 y	2 y	Effective treatment up until his death	Deceased after 24 mo (colon cancer)
		Case series (**Abstract**) [105]	**16** *p.*G2019S in Ashkenazi Jewish	NR	NR	NR	Similar motor outcomes to non-carriers LCIG dose 1622 (vs. 1702 in non-carriers)	Dyskinesia in 93.3% (vs. 90.6% in non-carriers) Hallucinations 42.8% (vs. 63.6% in non-carriers)
	CSAI	**Case report** [108]	**1**	42	14 y	NR	NR	NR
	DBS	**Systematic Review** [135]	**72**	NR	NR	3 mo to 7 y	No significant differences compared to non-carriers	A single p.N1437H carrier with significant psychiatric comorbidity committed suicide after 6 mo

		Systematic Review [80]	**87** STN-DBS ($n=79$) Target NR ($n=8$)	29 to 62		0.25 to 7 y	Outcome reported in 73 (83.9%) Poorer outcome in p.R1441G carriers compared to p.G2019S carriers	Two p.T2031S carriers developed neuropsychiatric problems after 5–7 y
		Systematic Review [79]	**50** p.G2019S ($n=44$)	34 to 55	5 to 18 y	Intermediate follow-up (2–6 y) in 29 (58%)	At Intermediate follow-up all had marked or satisfactory improvement. Three of four p.R144G carriers had < 30% improvement. Motor complications improved from 33.3% to 75% LEDD decreased from 17.5% to 75%	Two p.T2031S carriers experienced behavioral disorders p.R1441G carriers had significantly less improvements in UPDRS II (22%) when compared with the LRRK2 negative group
		Systematic Review and Meta-analysis [81]	**46 STN-DBS**	43.4 (3.7)	13.4 (1.6) y	6–24 mo	UPDRS-III improved by 46% in LRRK2 ($n=46$) vs. 53% in iPD LEDD was reduced by 61% ($n=27$) vs. 55% in iPD UPDRS-II improved 45.2% to 66.7% in p.G2019S carriers ($n=10$). UPDRS-IV Improved by 50% to 75% ($n=15$)	UPDRS-II deteriorated 10% in p.R1441G carriers ($n=4$) Stable postsurgical Mattis dementia rating scale score ($n=9$)
VPS35	**DBS**	**Systematic Review** [79]	**3** p.D620N STN-DBS	42, 45 and 49	13 and 19 y. NR in 1 case	1, 5, and 8 y	LEDD was reduced 30 to 76.5% UPDRS-III improved 36 to 43.8%	One patient had episodes of FOG and falls after the drastic reduction of LEDD, which improved after medication adjustment and stimulation.
		Systematic review [80]	**5** p.D620N STN-DBS ($n=3$) NR ($n=2$)	42 to 49 (mean 45.75) ($n=4$)	10 to 13 y (mean 11.33) ($n=3$)	1–8 y ($n=3$)	Favorable in 4, minor motor benefit in 1 UPDRS-III improvement of 69% (8 y), 36% (1 y) and 37% ($n=3$)	FOG and falls after surgery, which improved with levodopa and stim ($n=1$) Significant dysarthria ($n=1$)
		Systematic Review [135]	**6** p.D620N ($n=5$) p.R524W ($n=1$)	37 to 49 (mean 46.6)	7 to 21 y (mean = 12.8) ($n=4$)	1 to 8 y ($n=3$)	Good outcome ($n=2$) 76% improvement in UPDRS-III (8 y post-operative) 36% improvement in UPDRS-III (1 y) ($n=1$) 37% improvement in UPDRS-III and decrease of peak-dose dyskinesia ($n=1$) Modest effect ($n=1$)	Dysarthria ($n=1$) Increase frequency of falls and FOG ($n=1$)

NR, not reported; LEDD, levodopa equivalent daily dose.

Table 4
Available evidence of outcomes for different device-aided therapies in monogenic autosomal recessive parkinsonism

PRKN	**LCIG**	**Case report** [106]	**1** heterozygous *PRKN* p.T240M	10	14 y	83 mo	88% improvement in UPDRS III 74% improvement in NMSS 79% improvement in PDQ-8	NR
		Case series [103]	**2**	28 and 43	35 and 22 y	3 mo and 5 mo	NR	One case deceased 3 mo after
	CSAI	**Case series** [109]	**2**	7 and 29	25 and 18 y	Case 1: NR Case 2:2 y	Case 1: NR; Case 2: "with motor benefit"	Case 1: NR (severe motor and psychiatric features before starting CSAI). Case 2: Psychotic symptoms resolved after stopping CSAI.
	DBS	**Systematic Review** [80]	**67** STN-DBS ($n = 51$) GPi-DBS ($n = 5$) Zona inserta ($n = 1$)	7 to 52		0.5 to 7 y	Favorable long-term motor outcome in 76.1% Modest improvement in 4 patients (6.0%) Poor benefit in 2 cases (3.0%)	Like non-carriers
		Systematic Review [135]	**27** Homozygous/ compound heterozygous			3 mo to 8 y	No difference compared to non-carriers. DBS efficacy in cases with disease duration up to 45 y, with sustained response for many years.	
		Systematic Review [79]	**25** STN-DBS ($n = 22$) GPi-DBS ($n = 3$) (homozygotes/ compound heterozygotes			STN-DBS 18/22 had < 2 y follow-up 7/22 had a 2–6 y follow-up outcomes GPi-DBS cases had 12 mo follow-up	At 2–6 y of STN-DBS follow-up 2/7 had marked responses, 4/7 Satisfactory responses, and 1/7 Unsatisfactory responses The mean LEDD change range from 2.1% to 91.7% Improvement in UPDRS IV raged from 20% to 100% GPi Unsatisfactory motor response (21% of improvement)	3 of 4 homozygous STN-DBS with slightly worsened of UPDRS-I after surgery worsening of parkinsonian hypophonia was observed in 1 PRKN patient 3 patients experienced ballistic dyskinesias after surgery
		Systematic Review and Meta-analysis **STN-DBS** [81]	**36** 18 homozygotes, and 18 heterozygotes	10 to 45	4 to 45 y. Mean = 23.9 (3.6) y	3 mo to 6 y	UPDRS-IV improved by 70% UPDRS-III improved by 43 % LEDD was reduced by 61% ($n = 23$) UPDRS-II improved by 62% to 81.8% ($n = 4$) UPDRS-IV improved by 20% to 100% ($n = 13$)	PRKN carriers ($n = 8$) showed no or minimal undesired effects

PINK-1	**LCIG**	**Case report** [107]	**1** homozygous	29	26 y	4 y	Excellent response to low-moderate infusion rates (30–60 mg/h, LEDD 600–900). After 3 y, she required higher infusion rates plus 3–4 bolus of 40 mg/day (LEDD *1,200 mg/24 h). She developed dyskinesias and the hourly rate was reduced.	Sensory axonal polyneuropathy. Vitamin B6 deficit. 4 y after starting LCIG therapy she developed dopamine dysregulation syndrome, marked dyskinesias, ICD, punding behavior and psychosis
	DBS	**Case reported in a series** [96]	**1** Homozygous STN-DBS	30	30 y	3–6 y	Favorable motor outcome comparable to patients without mutations. A 43.7% change in UPDRS-III in the long term	NR
		Case report [97]	**1** Homozygous GPi-DBS	30	19 y	2 mo	Improvement of gait, dystonia, and dyskinesia No difference in UPDRS-III score on-medication, but reduction in UPDRS IV-score and LEDD.	NR

NR, not reported; LEDD, levodopa equivalent daily dose.

Table 5
Available evidence of outcomes for different device-aided therapies in monogenic autosomal recessive parkinsonism presenting with atypical feature

ATP13A2	**STN-DBS**	**Case report** [102]	**1** Heterozygous *ATP13A2* p.R449Q, and two *Parkin* variants—a deletion of exons 3 and 4, and duplications of exons 7 to 12	36	14 y	NR	Favorable	Postural instability and depression.
PLA2G6	**CSAI**	**Case report** [110]	**1**	27	3 y	1 y	Motor benefit with gait recovery	Intermittent visual hallucinations
	DBS	**Case report** [98]	**1** GPi-DBS and Vim-DBS Atypical neuroaxonal dystrophy (NAD) phenotype.	Childhood	About 10 y	9 mo	Good control of dystonic storm, oculogyric crises, and tremors	
FBXO7	**CSAI**	**Case report** [99]	**1**	16	4 y	6 mo	50% reduction of daily “off” time	Severe dyskinesias after 6 mo
	GPi-DBS	**Case report** [99]	**1**	16	5 y	6 mo	Good response (Not detailed)	Permanent anarthria
DNAJC6	**STN-DBS**	**Case report** homozygous [100]	**1** *DNAJC6* p.T741=	31	15 y	Not reported	Marked improvement	Not reported
VPS13C	**STN-DBS**	**Case report** [101]	**1** *VPS13C* compound heterozygous canonical splice-site	39		2.5 y		Severe dysarthria and mild aphasia.

NR, not reported; LEDD, levodopa equivalent daily dose.

gait impairment, dysarthria, behavioral changes, and cognitive decline a few years later [80].

In a meta-analysis of *SNCA* duplications, three individuals had bilateral STN-DBS with good results. Two did not have cognitive decline at four-year follow-up. However, the third individual developed dementia [94]. Another individual with mosaicism of *SNCA* duplication, with motor complications, mild cognitive impairment, hallucinations, and an impulse control disorder, had bilateral GPi-DBS eight years after symptom onset. Good motor benefit was reported 1 month after surgery [95] (Table 3).

In summary, outcomes appear favorable for the most common *LRRK2* pathogenic variant, p.*G2019S*, but may be poor for p.*R1441G* due to rapid cognitive decline and worsening of neuropsychiatric symptoms. The evidence remains very limited for *SNCA* and *VPS35,* with heterogeneous outcomes.

DBS in autosomal recessive PD (PRKN, PINK-1, DJ1)

PRKN carriers tend to have earlier disease onset yet longer disease duration at DBS surgery [9, 78]. After DBS, most of them have sustained motor improvement and in activities of daily living comparable to idiopathic PD [81]. Data for GPi-DBS are scarce. One *PINK1* homozygous patient had satisfactory motor improvement after STN-DBS, but long-term results are not available, and nonmotor outcomes were not described [96, 97]. We found no published data on *DJ1* variants undergoing DBS (see Table 4).

DBS in autosomal recessive parkinsonism with atypical features

Bilateral GPi-DBS and ventralis intermediate nucleus (Vim)-DBS has been successfully utilized for dystonic storm treatment in a 15-year-old girl with atypical neuroaxonal dystrophy (NAD) phenotype, a subgroup of *PLA2G6*-associated neurodegeneration (PLAN). She had a complex clinical picture characterized by progressive generalized dystonia, spasticity, myoclonus, intentional tremor, oculogyric crises, seizures, and poor cognition. She achieved good control of dystonic storm symptoms, oculogyric crises, and tremors at a 9-month follow-up [98]. The use of DBS for the *PLA2G6*-associated dystonia-parkinsonism phenotype has not been reported.

A female carrier of a *FBXO7* homozygous variant with juvenile parkinsonism associated with postural instability, dysarthria, hypophonia, marked motor fluctuations, and levodopa-induced dyskinesias was reported to have satisfactory motor control with multiple device-aided therapies. At age 21, five years after symptoms onset, CSAI reduced daily "off" time by 50%. However, within 6 months, the patient developed severe "on"-period generalized chorea-dystonic dyskinesias. Bilateral GPi-DBS was implanted and achieved good control of those symptoms at a 6-month follow-up. However, severe dysarthria progressed to permanent anarthria [99].

In a cohort of early-onset sporadic or familial PD, a 46-year-old homozygous *DNAJC6* p.T741 = female carrier with levodopa-responsive parkinsonism since age 31, who developed severe motor complications, underwent bilateral STN-DBS with marked improvement. However, the follow-up time and details were not reported [100].

A Caucasian woman with parkinsonism since age 39 had severe dyskinesias under dopaminergic treatment, dysarthria, tremor, mild dementia, hallucinations, dystonia, gait, and gastrointestinal tract problems. She had compound heterozygous canonical splice-site variants in *VPS13C* (p.Lys639Aspf sTer14, p.Leu678GlufsTer26, p.Ala1072GlufsTer14, p.Ala1072_Gln1110del, p.Ser1076ArgfsTer4). She had initial benefit from STN-DBS but developed severe dysarthria and mild aphasia after 2.5 years. Rapid progression of symptoms was reported at a 4-year follow-up [101].

A Persian male bearing a p.R449Q heterozygous mutation in *ATP13A2*, who was also known to carry two Parkin mutations—a deletion of exons 3 and 4 and duplications of exons 7 to 12, was reported to have parkinsonian symptoms, including rest tremor and a good response to levodopa, since the age of 36. At 50, a favorable response to STN-DBS stimulation was reported, with mild postural instability and depression but no atypical neurological signs [102].

EVIDENCE ON THE USE OF LEVODOPA CARBIDOPA INTESTINAL GEL

Autosomal dominant PD and GBA mutations

In a cohort of 12 PD patients on LCIG in the UK, the authors reported one patient with *LRRK2*. This carrier had a 19-year history of PD and died 24 months after LCIG initiation because of colon cancer [103]. In a study in Tel Aviv, where 44 PD patients underwent LCIG, five were LRRK2 carriers, four were *GBA* heterozygotes, two were *GBA* homozygotes, and another was a carrier of both GBA

and LRRK2. No significant differences were found between the carrier versus non-carrier group [104]. The same study group published an abstract of the data from 69 Ashkenazi Jewish patients with known *GBA* (11 cases) or *LRRK2* p.G2019S mutations (16 cases) and 42 idiopathic PD. Motor UPDRS scores were significantly higher, and levodopa equivalent daily doses (LEDD) were lower among GBA-PD than in the two other groups. Although not statistically significant, *GBA*-PD had a higher rate of hallucinations and lower cognitive scores. The latter could explain the lower LEDD in this group [105] (see Tables 2 and 3).

Autosomal recessive PD with homogeneous presentations

A juvenile PD patient carrying a *PRKN* p.T240M variant in a heterozygous state had a marked improvement in motor and non-motor scores on LCIG in a long follow-up period [106]. A 63-year-old *PRKN* carrier with a history of 35 years of parkinsonism died 3 months after introducing LCIG from unspecified causes [103].

A woman with homozygous *PINK1* variants with parkinsonism since age 29 underwent LCIG at age 55 for motor fluctuations and dyskinesias. For three years, the motor response was satisfactory, but she required B6 vitamin replacement for sensory axonal polyneuropathy. Four years after LCIG, she developed marked dyskinesias, dopamine dysregulation syndrome, ICD, and punding [107].

EVIDENCE FOR CONTINUOUS APOMORPHINE SUBCUTANEOUS INFUSION

Autosomal dominant PD

In a case series of British *LRRK2* patients, a 42-year-old man was reported to have a CSAI pump 14 years after disease onset for severe drug-induced dyskinesias. Before CSAI, he had depression, obsessive and hypomanic behavior, excessive alcohol drinking, and dopamine dysregulation syndrome. Outcomes were not specified [108].

Autosomal recessive PD with homogeneous presentations

Two *PRKN* patients have been reported with CSAI. The first case was a 32-year-old man with 25 years of progressive parkinsonism-dystonia syndrome, with deterioration of laryngeal dystonia on levodopa and severe neuropsychiatric symptoms. No outcomes were reported. The second case was a 57-year-old with a previous thalamotomy started on CSAI at age 47 with benefit. However, he developed psychosis with paranoid delusions that resolved after stopping apomorphine [109].

Autosomal recessive parkinsonism presenting with atypical features

A Turkish woman with homozygous *PLA2G6* p.R747W and heterozygous *LRRK2* p.W1295R variants developed parkinsonism at age 27. By age 29, she had severe parkinsonism with bilateral tremors, hypophonia, dysarthria, postural instability, and cognitive impairment. She had a good response to combined antiparkinsonian medications but developed irritability, restlessness, and ICD. By age 30, she was unable to stand or walk independently. After CSAI (5 mg/hour), she could walk for at least a 1-year follow-up. She developed intermittent visual hallucinations [110].

As mentioned above, a female *FBXO7* homozygous variant carrier with juvenile parkinsonism was reported to have a transient motor benefit with CSAI. After 6 months, the patient developed severe "on" dyskinesias, requiring bilateral GPi-DBS [99].

DISCUSSION

The cumulative evidence for device-aided therapies in monogenic-PD and *GBA* carriers is still scarce.

Along with a regional difference in the prevalence of specific variants, the availability of advanced therapies is critical. Device-aided therapies offered in different countries may vary through healthcare systems, local experience, and center preferences. For instance, we have observed that publications on infusion therapies (i.e., LCIG and CSAI) in monogenic parkinsonism come predominantly from the UK and Middle Eastern countries (Israel, Saudi Arabia, and Turkey), and LCIG in GBA-PD from Israel. On the other hand, DBS-related publications are more widely distributed (i.e., North America, Europe, Middle East, Asia, South America, Australia), possibly because of increasing access to this therapy. Unfortunately, decision-making on device selection is not explicit in most reports from countries where more than one device-aided therapy is available (e.g., Italy, UK, Israel, Turkey, USA). Future reports should

explain the selection of a specific device-aided therapy, especially when other alternatives are available.

Systematic reviews and a meta-analysis constitute the best evidence for DBS in monogenic PD. However, these are limited by small sample size, short follow-up, and incomplete data.

Moreover, several investigators have used different categories and cut-off values when defining DBS responses in gene-related PD populations; because of this heterogeneity, the same percentage of change in UPDRS-III would be qualified differently by distinct authors. An explicit limitation of this approach is the lack of consensus, adding difficulties when interpreting the literature. In addition to arbitrariness in establishing cut-off values, the effectiveness of these therapies has been firmly focused on the change in UPDRS-III scores, in our opinion lacking adequate emphasis on non-motor symptoms or changes in quality of life, which can be decisive in decision-making and in establishing the benefits of these therapies. Further, with some exceptions, reports on LCIG or CSAI lack objective and detailed results making a similar analysis difficult.

Mutation carriers seem to be overrepresented in DBS-cohorts compared to non-carrier PD populations. *LRRK2* p.G2019S, homozygous or compound heterozygous *PRKN,* and *GBA* were the most frequent variants. This may be attributed to an overlap of the phenotype with criteria for device eligibility. However, this is not necessarily equivalent to suitableness in the selection. For instance, these all had motor outcomes comparable to patients with idiopathic PD, at least in the short term, with STN-DBS as the most frequent target. However, the motor benefit of STN-DBS in *GBA*-PD may be countered by a faster cognitive decline and axial symptoms following DBS than non-carriers. On the other hand, even if carriers may have poorer outcomes than non-carriers, this is not equal to absent benefit (e.g., motor benefit vs. cognitive decline). Future randomized studies should consider the quality of life as a primary outcome to better understand the risk-benefit ratio in *GBA*-PD.

This should be kept in mind when discussing prognosis, timing, and expectations for DBS.

Publications on DBS in autosomal recessive variants with atypical features are mainly limited to individual cases. Some patients have reported benefits, but outcomes are incompletely reported, and long-term data is scarce. Dysarthric speech, swallowing disturbances, freezing of gait, and balance problems are frequent features of atypical autosomal recessive parkinsonism (e.g., *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, *SYNJ1*, and *VPS13C*). On the other hand, these symptoms can occur using DBS parameters optimal for improving tremor, rigidity, and bradykinesia. Therefore, data is insufficient to differentiate device therapies outcomes (i.e., adverse effects) from disease progression or therapy non-responsiveness. At this point, in select cases, DBS seems to be a reasonable palliative therapy or a rescue treatment in emergencies such as dystonic storms.

Small genetic screening studies are the primary source of evidence for LCIG. There is no significant difference in motor outcomes between *LRRK2* p.G2019S or *GBA*-carriers and non-carriers. *GBA* carriers in the LCIG studies had lower cognitive scores and higher scores for hallucinations.

CSAI has the most limited evidence of the three therapies in monogenic PD and *GBA* carriers. As expected, available cases tend to include individuals with very advanced diseases, given the typical patient selection criteria. CSAI may be a helpful alternative in recessive parkinsonism with atypical features, with some efficacy, as shown in the *FBOX7* and *PLA2G6* case reports.

The available information regarding individual monogenic variants and device-aided therapies is far from comprehensive. The data are limited to small numbers of patients, short follow-ups, and observational reports. Multicenter prospective cohort studies are needed to guide our knowledge and improve decision-making for device-aided therapies and PD-related variants.

In addition, we recommend that several key elements be included when reporting outcomes from device-aided therapy amongst genetic PD populations (Fig. 1).

First, when discussing the genetic variant, the type of variant, its pathogenicity, and its homozygote or heterozygote state should be included. When using panels, all the genes studied should be mentioned, especially in patients belonging to ethnicities at risk for more than one type of variant (for example, *LRRK2* p.G2019S and *GBA* variants in Ashkenazi Jews).

Second, when discussing phenotype, characterization must be rigorous, including the age at symptom onset, age at diagnosis, disease duration, initial clinical manifestation, presence of falls, freezing of gait, cognitive profile, neuropsychiatric manifestations, and other non-motor symptoms. The absence of unreported features should be specified. Individuals may be classified according to the MDS-UPDRS-III score (i.e., tremor dominant, intermediate, or postural insta-

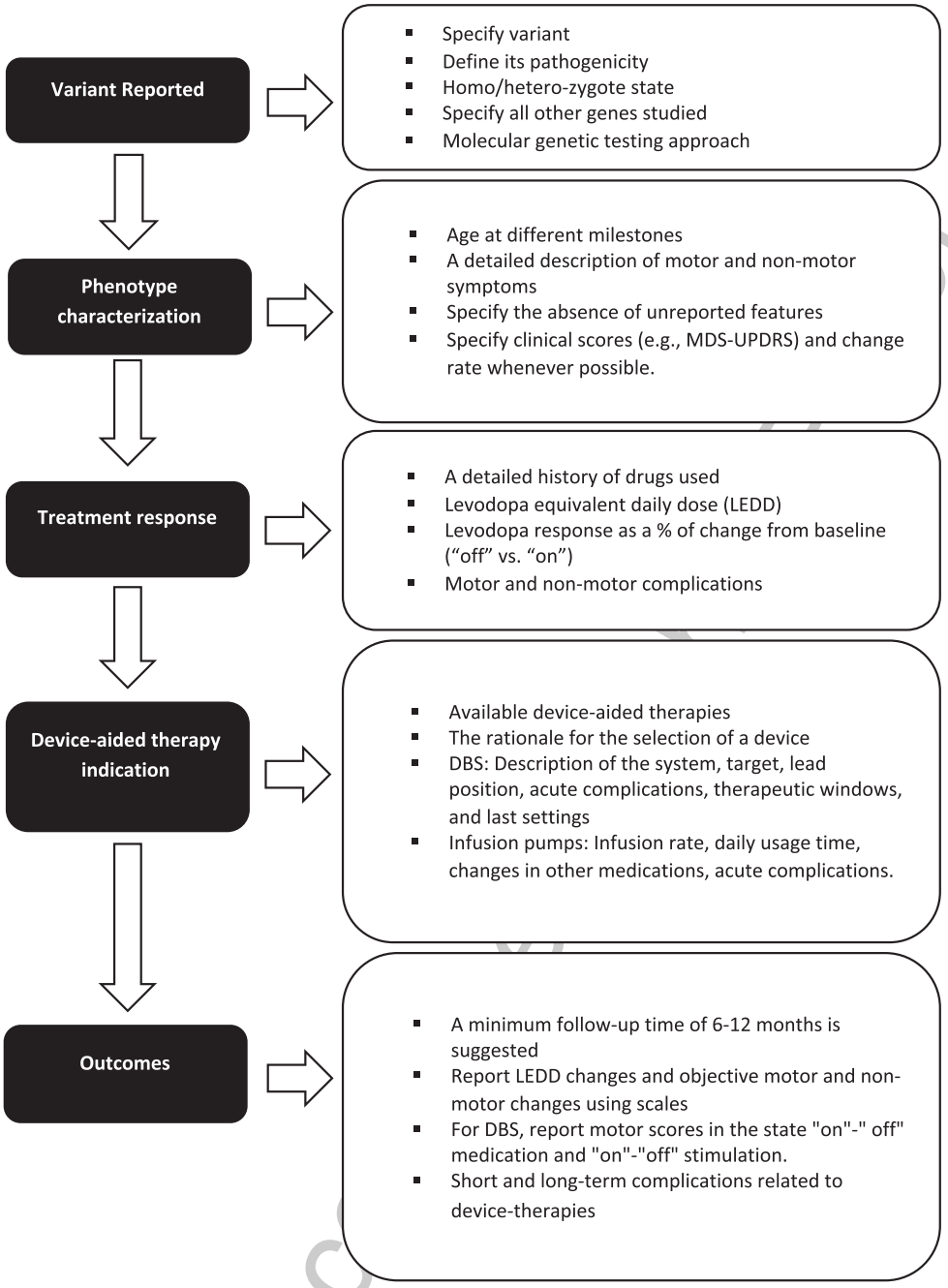

Fig. 1. Key elements to consider when reporting the response to device-aided therapies in patients with monogenic parkinsonism or GBA variants carriers.

bility/gait difficulty). Levodopa response should be described as % of change from baseline. Whenever possible, the rate of progression of motor and non-motor symptoms (i.e., cognitive decline) in the pre- and post-device-aided therapy stage should be included. A detailed history of the drugs used, related side effects and levodopa equivalent daily dose should also be included.

Third, the indication and rationale for each specific advanced device-aided therapy should be documented. In addition, for DBS, it is essential to define whether the surgery is uni- or bilateral, which

commercial device was implanted, the target, lead position information, therapeutic window, and final stimulation parameters. The infusion rate, daily usage time, and changes in other medications should be indicated for infusion pumps.

Finally, long-term motor and non-motor outcomes should be measured objectively using, for example, the MDS-UPDRS scale administered at multiple time points. In the case of DBS, it is essential to report motor scores in the state "on"-" off" medication and "on"-"off" stimulation. Follow-up time should be sufficient for the device settings to reach a steady-state and assess disease progression, treatment efficacy, and long-term adverse effects. While there is no specific time, a reasonable minimum follow-up time would be greater than 6–12 months.

CONCLUSION

Based on current studies, it is unfeasible to establish evidence-based decision-making guidelines for device-aided therapies in monogenic parkinsonism. So far, an added prognostic value of genetic testing beyond a careful clinical assessment when patients are evaluated for device-aided therapies is yet to be demonstrated for monogenic parkinsonism. Large prospective cohorts combining genetic profiling with deep phenotyping, and randomized studies, can provide relevant data to address this question.

Although no randomized trials are available, based on accumulated evidence on the natural history and probable deleterious cognitive outcomes after STN-DBS in carriers of pathogenic variants in *GBA*, several authors have proposed that candidates for this device therapy should be screened for *GBA* mutations as part of the pre-surgical assessment. Carriers should be counseled regarding potential risks associated with STN-DBS, considering alternative options [83]. Comparative studies of different device-aided therapies in this population are pending.

We call for the development of guidelines that allow us to improve the quality and number of reports and randomized clinical studies that optimize our decision-making on device-aided therapies in monogenic parkinsonism and *GBA* carriers.

CONFLICT OF INTEREST

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Royalty: Dr. Fernandez has received royalty payments from Demos Publishing and Springer for serving as a book author/editor.

Contractual Services: The Cleveland Clinic has a contract with Teva for Dr. Fernandez's role as a Co-Principal Investigator in Deutetrabenazine for Tardive Dyskinesia global studies.

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