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Choice of Implantable Pulse Generators for Deep Brain Stimulation: An Overview of Clinical Practice

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Keywords

Deep brain stimulation · Movement disorders ·
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Abstract

Introduction: The success of deep brain stimulation (DBS) treatment depends on several factors, including proper patient selection, accurate electrode placement, and adequate stimulation settings. Another factor that may impact long-term satisfaction and therapy outcomes is the type of implantable pulse generator (IPG) used: rechargeable or non-rechargeable. However, there are currently no guidelines on the choice of IPG type. The present study investigates the current practices, opinions, and factors DBS clinicians consider when choosing an IPG for their patients. **Methods:** Between December 2021 and June 2022, we sent a structured questionnaire with 42 questions to DBS experts of two international, functional neurosurgery societies. The question-

naire included a rating scale where participants could rate the factors influencing their choice of IPG type and their satisfaction with certain IPG aspects. Additionally, we presented four clinical case scenarios to assess preference of choice of IPG-type in each case. **Results:** Eighty-seven participants from 30 different countries completed the questionnaire. The three most relevant factors for IPG choice were “existing social support,” “cognitive status,” and “patient age.” Most participants believed that patients valued avoiding repetitive replacement surgeries more than the burden of regularly recharging the IPG. Participants reported that they implanted the same amount of rechargeable as non-rechargeable IPGs for primary DBS insertions and 20% converted non-rechargeable to rechargeable IPGs during IPG replacements. Most participants estimated that rechargeable was the more cost-effective option. **Conclusion:** This present study shows that the decision-making of the choice of IPG is very individualized. We identified the key factors influencing the physician’s choice of IPG. Compared to patient-centric studies, clinicians may value different aspects. Therefore, cli-

nicians should rely not only on their opinion but also counsel patients on different types of IPGs and consider the patient's preferences. Uniform global guidelines on IPG choice may not represent regional or national differences in the health-care systems.

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Introduction

Deep brain stimulation (DBS) is an acknowledged treatment for several movement disorders. Studies have shown that DBS can also be an effective treatment for other diseases, such as epilepsy [1] and obsessive-compulsive disorder (OCD) [2]. Ongoing research and innovation in the industry result in more options for implantable pulse generators (IPGs), such as IPGs with rechargeable capacity, sensing possibilities, visualized programming options, or teleprogramming capacity.

Two different types of IPGs for DBS exist. Primary cell IPGs were first available, have a fixed battery capacity, and therefore need to be surgically replaced once their battery power is drained. The battery life for a primary cell IPG depends on individual stimulation settings, impedances, and the IPG model [3]. Although there are limited data comparing IPGs from different manufacturers, several studies have found that newer generation IPGs from one manufacturer have a significantly shorter lifespan. The lifespan of the newer IPGs ranges from 35.6 to 53.3 months, whereas the lifespan of the older, non-rechargeable IPGs ranges from 51.3 to 70.4 months [3–5].

Rechargeable-cell IPGs are smaller and have a longer expected lifetime of up to 25 years. These IPGs require regular observance and frequent inductive recharging to maintain battery levels. Rechargeable IPGs are more expensive than non-rechargeable IPGs. However, they may offer long-term cost efficiency due to the lack of replacement surgeries and fewer surgical complications [6].

The success of deep brain stimulation (DBS) treatment depends on proper patient selection, accurate electrode placement, and adequate stimulation settings. The choice of IPG can also affect long-term satisfaction and therapy outcomes. We may consider the choice of IPG as a minor detail in DBS surgery, but it can impact the overall experience and success of treatment. Currently, no formal protocols or guidelines exist to assist clinicians and patients in making the most appropriate decision on the type of IPG. We commonly mention several patient and caretaker factors as relevant, but we have no standard approach for determining the best IPG type for a given pa-

tient. Also, there needs to be more documentation on what factors influence a physician's choice of IPG.

The choice of IPG can be based on technical parameters. Converting to another type of IPG may cause a difference in impedances [7], requiring different parameter settings [8], and not all current available IPGs have the same longevity as the previous version [3]. Another important factor in the choice of IPG may be national or center-specific agreements on reimbursement [9]. Besides financial and technical reasons, motor and cognitive functions, patient capability to monitor and operate the device, the size of the IPG [10], and patient preference may be determining factors. The complexity of IPG choice is increased further by combining implants from different medical device manufacturers to enable new stimulation options with already implanted DBS electrodes by creating so-called hybrid DBS systems [11, 12]. From the patient's perspective, the convenience of recharging was rated as "easy," with high levels of user satisfaction (93.8%) and willingness (93.3%) to recommend the rechargeable IPG [13]. DBS indication may also be an important factor for patient satisfaction, as several studies reported that this was higher for patients with dystonia than those with Parkinson's disease [13, 14]. In this paper, we aimed to assess the clinical practice of physicians with a survey to create an overview of the international landscape on this topic and identify the most common factors and opinions on IPG choice.

Materials and Methods

We conducted a structured, electronic, and cloud-based questionnaire on the online service Momentive™ (formerly SurveyMonkey®). Participants were recruited by email. In December 2021 and June 2022, we invited all members of the European Society for Stereotactic and Functional Neurosurgery (ESSFN) and the European Association of Neurological Surgeons (EANS) to participate in our study. Informed consent was given in a digital way. After clicking on a link, email recipients were prompted to an informed consent page. Before making the questionnaire accessible, participants needed to state that the informed consent statement was read and that they agreed to data collection and analysis by clicking on another link that led to the first question. Clinical experts, such as neurologists and neurosurgeons with expertise in movement disorders and DBS, were included. Participants from the industry were excluded from data analysis to focus this survey on clinical practice. We asked participants if we could contact them if further clarifications were needed.

Questionnaire

The questionnaire (online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000529495) consisted of 42 questions. We asked for the participant's profession and

Fig. 1. Four clinical case scenarios to consider implantation of a rechargeable IPG.

Case 1 A 75-year-old male with bilateral DBS and a non-rechargeable IPG for Parkinson's disease was admitted to the hospital with an empty battery. His wife recently passed away. He has some problems with short-term memory and taking care of himself. His BMI is 19. His children are considering moving him into a nursing home. <i>Would you recommend a rechargeable IPG?</i>
Case 2 A 39-year-old female with young-onset Parkinson's disease presented herself on the outpatient clinic. She is working as a journalist and travelling around the world. She has a BMI of 21. Your stereotactic team indicates bilateral DBS in the STN after careful evaluation. <i>Would you recommend a rechargeable IPG?</i>
Case 3 A 50-year-old male with essential tremor presents himself on the outpatient clinic. He never finished elementary school. He was working on a construction site but is currently unemployed due to his motor symptoms. He lives with his wife, and they are illiterate. He gained 10 kg in the last year and his BMI is currently 30. Your stereotactic team indicates unilateral DBS in the Vim after careful evaluation. <i>Would you recommend a rechargeable IPG?</i>
Case 4 A 48-year-old female with cervical dystonia present herself on the outpatient clinic. She is teaching on an elementary school and living on her own. She has a wide social network and is self-conscious about her body. She has a BMI of 22. Your stereotactic team indicates unilateral DBS in the GPi after careful evaluation. <i>Would you recommend a rechargeable IPG?</i>

country they work in for background variables and local existing reimbursement strategies and regulations. Questions were closed with two or more possible answers, and the participant had to choose the most appropriate or multiple answers whenever possible. Satisfaction was rated on an ordinal scale from zero to 10 (0 = totally unsatisfied, 10 = totally satisfied). We presented four clinical case scenarios and asked participants if they would recommend a rechargeable or non-rechargeable IPG for each case (Fig. 1).

Statistical Analysis

All questions with categorical answers are descriptively reported with percentages. We checked the questions with numerical answers for normal distribution, and depending on the distribution, we reported the mean and, if applicable, the median and quartiles. The significant difference between the mean satisfaction of the current size of the rechargeable IPG and the non-rechargeable one was measured by paired *t* test, with $\alpha < 0.05$. The Pearson χ^2 test was used to determine a significant difference between the answers of the question "How long do non-rechargeable IPGs realistically last?" and "How long should non-rechargeable IPGs realistically last?"; between the answers of the question "How much time do you think patients need to invest each week into charging?" and "What do you think is an acceptable time for patients need to invest into charging?"; and between percentages of patients who present to the hospital with a fully depleted rechargeable IPG and a fully depleted non-rechargeable IPG, with $\alpha < 0.05$. Statistical analysis was performed using SPSS version 28 (IBM Corp., released in 2021; IBM SPSS Statistics for Windows, Version 28.0, Armonk, NY: IBM Corp.). Participants were asked for 13 aspects regarding their importance when counseling a patient on the

choice of IPG. We dichotomized the ratings into relevant (fairly important, important, very important) and non-relevant (slightly important, not at all important, I do not consider this aspect at all) factors.

Results

The online survey was sent to a total of $n = 323$ recipients. 114 participants gave informed consent (35.3% of recipients). Ten participants were excluded due to preliminary exiting the survey or due to duplicate participation. Five participants worked for the industry and were therefore excluded. The total of included participants for this survey was 87 (26.9% of recipients). The professions of the participants were neurosurgeon (71, 81.6%), neurologist (6, 6.9%), researcher (4, 4.6%), DBS nurse (4, 4.6%), neuropsychologist (1, 1.1%), and physicist (1, 1.1%). The participants worked in 30 different countries. 74.7% (65 of the participants) were from Europe. There were also participants from America, Asia, and Australia (Fig. 2).

Expert Opinion

The three factors that were rated as most relevant in the decision-making for the type of IPG were "existing

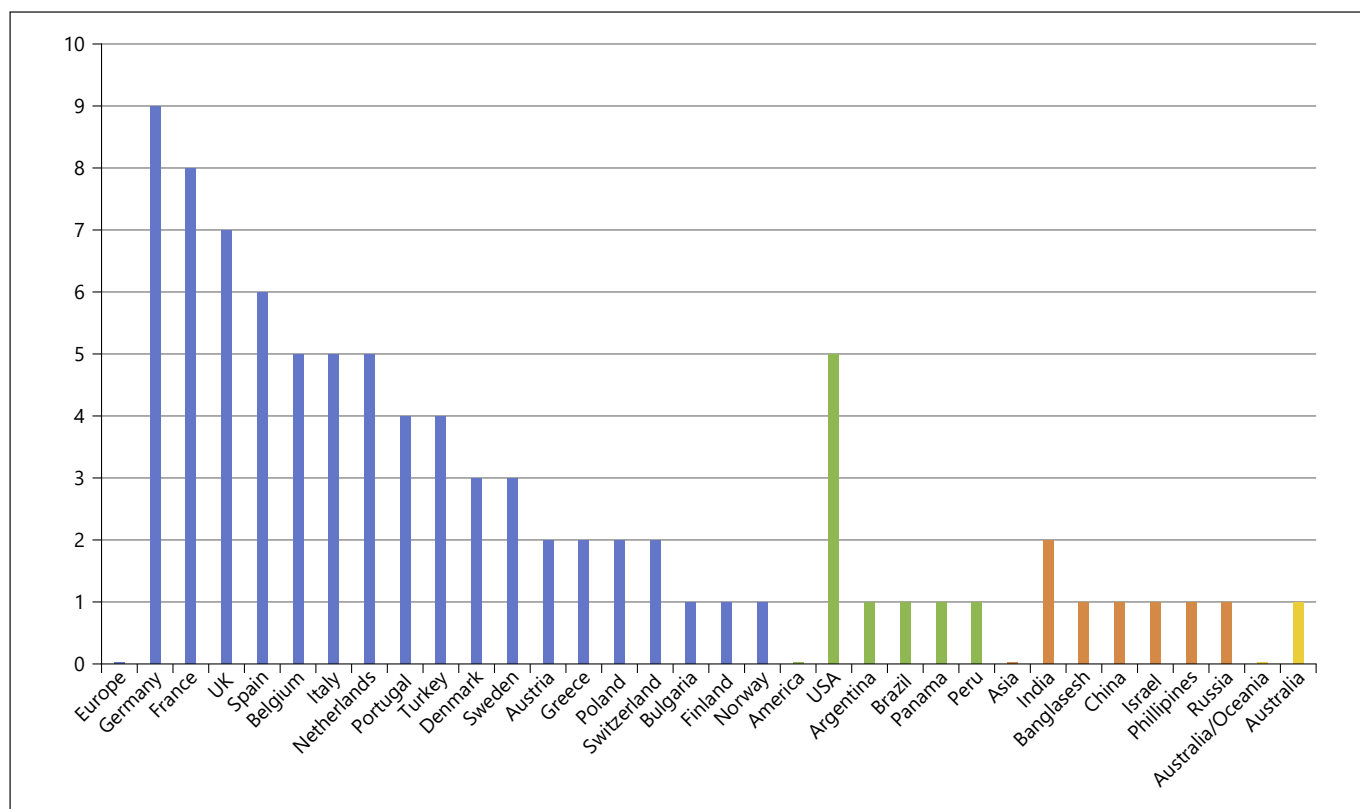


Fig. 2. Participants' countries of residence.

social support" (96.6%), "cognitive status of the patient" (91.9%), and "patient age" (82.7%). The three factors which were regarded as the least relevant for IPG choice were "financial aspects" (39.0%), "personal clinician preference" (38.3%), and "research" aspects (37.9%) (Fig. 3).

Figure 4 shows the preferences for choosing a specific type of IPG depending on the indication, the setting of IPG replacement surgery, the body location for implantation, and reimbursement. The most notable preference was the choice of a rechargeable IPG for dystonia patients (65, 74.7%). There was no clear consensus on which type of IPG had the most preference for the other aspects considered.

Strategies

Forty-one participants (47.1%) had a standardized approach to determine whether to implant a rechargeable or non-rechargeable IPG in their DBS center. Three of the 30 countries have specific regulations on what type of IPG can be implanted. Sixty-two percent ($n = 54$) always and 22% ($n = 19$) usually counsel the patient on both types of IPG. An interdisciplinary involvement of both neurolo-

gists and neurosurgeons in the choice of IPG was present in 63% of cases. For all participants, the neurosurgeon (85%) was most commonly involved in the choice of IPG, even more common than the patients themselves and partners/family combined (77%). Neurologists were involved in IPG choice in 70%.

Implantable Pulse Generators

Fifty-four percent of the participants ($n = 47$) had the general strategy to always start with a non-rechargeable IPG. The mean percentage of actual primary IPG implantation with rechargeable IPGs was 51% (standard deviation [SD] 31.9). Sixty-three percent ($n = 55$) believed that avoiding repetitive replacement surgeries was valued higher by patients than the burden of regularly investing time in recharging the IPG.

Seventy-two percent ($n = 61$) estimated the initial costs of a rechargeable IPG to be higher compared to a non-rechargeable IPG. Fifty percent estimated that the rechargeable IPG becomes more cost-effective than a non-rechargeable IPG with the first replacement surgery. The median percentage of converting a non-rechargeable IPG

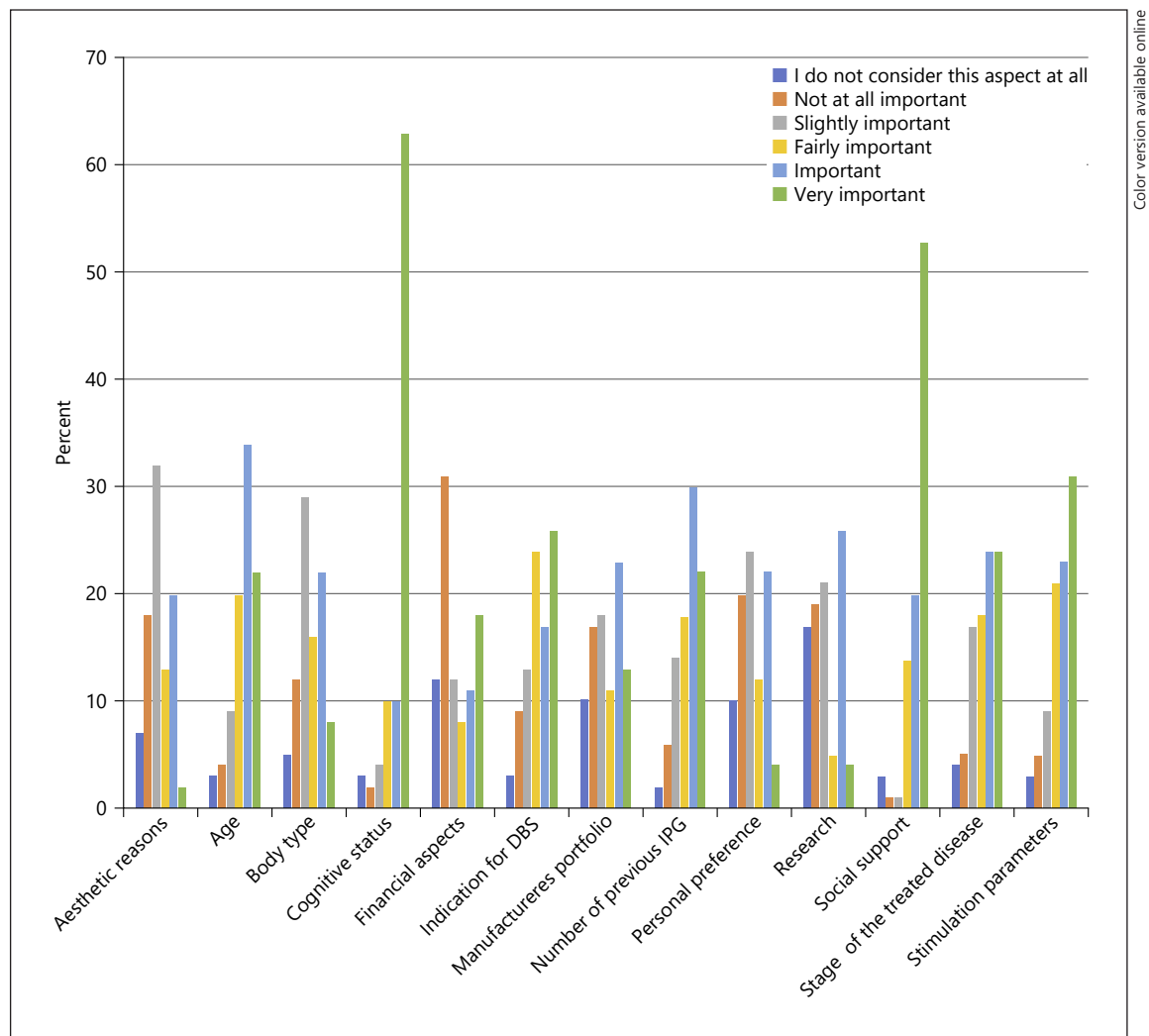


Fig. 3. Relevance of aspects on the choice of IPG type when counseling patients.

to a rechargeable one was 20%. Eighty percent ($n = 67$) of the participants have never or rarely needed to convert a patient from a rechargeable IPG (back) to a non-rechargeable IPG. The most common reason to convert was the patient's capability (38.1%) (Table 1).

There was disagreement among the participants about the expected lifespan of non-rechargeable IPGs. Eighty-two percent of the participants ($n = 71$) estimated that a non-rechargeable IPG lasts between 2 and 5 years. However, 64% of the participants ($n = 56$) believed that non-rechargeable IPGs should realistically last between 5 and 10 years (Table 2).

Thirty-three percent ($n = 29$) thought that a reasonable amount of time for patients to charge their IPG would be

less than 1 h per week, and 44% ($n = 38$) found 1–2 h per week acceptable. Sixty percent ($n = 52$) estimated that patients need to spend less than 2 h per week recharging their IPG (Table 3). Sixty-seven percent ($n = 58$) advised patients to develop a fixed charging route, e.g., once a week on a given day at a specific time. Sixty-three percent ($n = 55$) had a standardized protocol, often facilitated by the industry, in their DBS center on how to train patients to charge their rechargeable IPG. Forty-nine percent ($n = 43$) taught their patients how to charge the IPG with more than one training session. Forty percent ($n = 35$) would advise patients with a non-rechargeable IPG to check the battery once a month (Table 4). Forty-three percent ($n = 37$) experienced that less than 5% of their patients with a

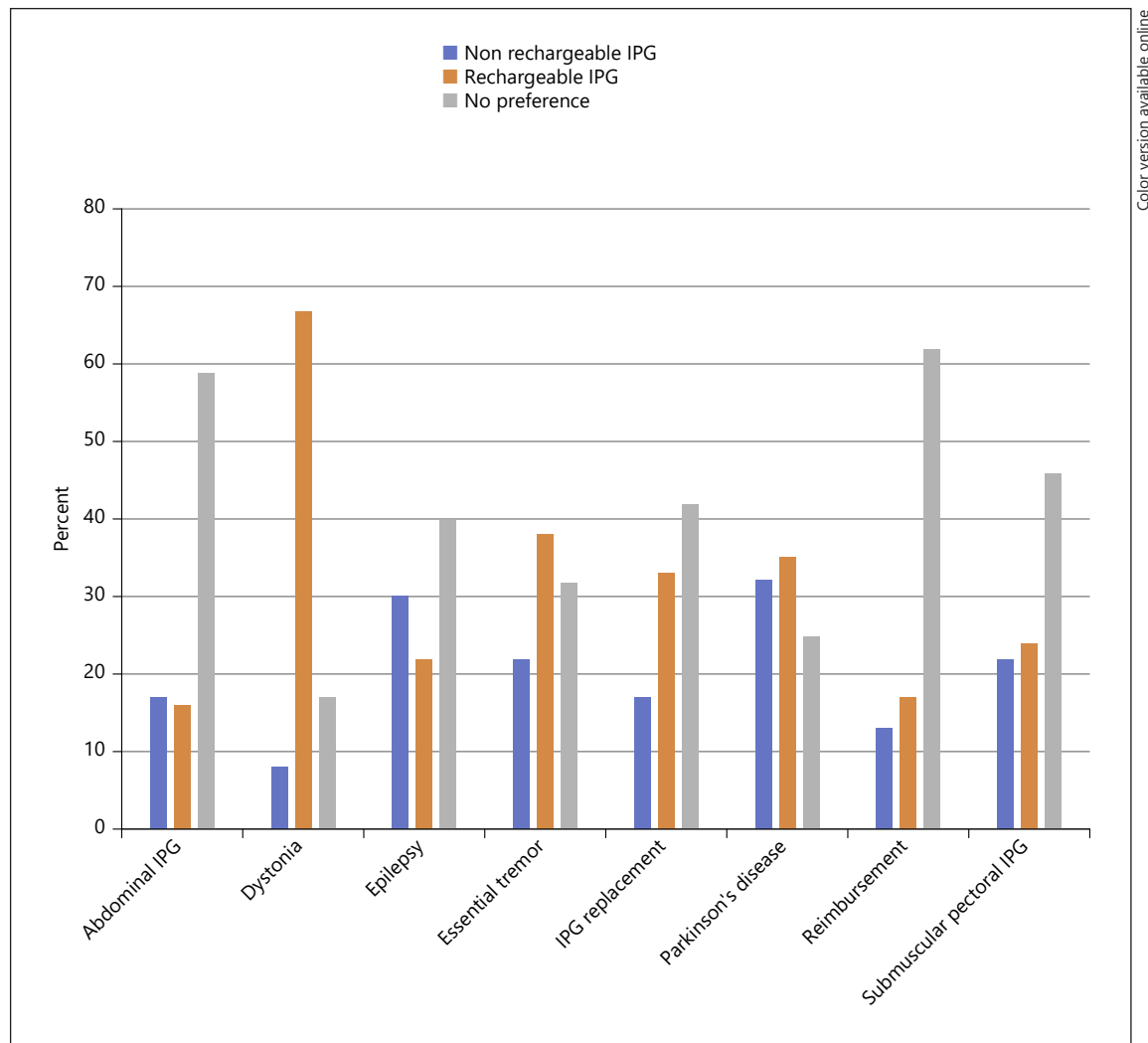


Fig. 4. Preference of IPG type for certain factors.

non-rechargeable IPG presented to the hospital with a fully depleted battery. Fifty-three percent ($n = 46$) experienced this for patients with fully discharged rechargeable IPGs. These rates were not significantly different ($p = 0.208$) (Table 5).

On a scale from 1 to 10, the mean satisfaction of the current size of non-rechargeable IPGs is 4.61 (SD 2.4). The rechargeable IPGs were rated significantly better at 7.64 (SD 2.1; $p < 0.001$).

Reimbursement

The national health care system covers the cost of DBS surgery in 27 of the 30 countries. In 5 out of 30 countries, rechargeable IPGs were reported by participants not to be readily available for implantation.

Forty-six percent ($n = 40$) of the participants responded that there was no additional reimbursement for implanting a rechargeable IPG to accommodate the increased cost. Still, the hospital often compensated for the price difference. Seven participants (8%) responded that they needed to propose implanting a rechargeable IPG to the health insurance before surgery. Seven participants (8.0%) from 6 different countries have had an insurance claim because they implanted a rechargeable IPG rather than a non-rechargeable IPG. Twenty-three percent of the participants ($n = 20$) are concerned that manufacturers will stop producing rechargeable IPGs for financial reasons.

Table 1. Need to convert a patient from a rechargeable IPG to a non-rechargeable IPG: reasons and total percentages

	Patient's capability, n (%)	Technical/hardware issues, n (%)	Recharging time, n (%)	Total, n (%)
Never				30 (35.7)
Rarely	32 (38.1)	4 (4.8)	1 (1.2)	37 (44)
Sometimes	6 (7.1)	2 (2.4)	1 (1.2)	9 (10.7)
Usually	2 (2.4)	1 (1.2)	0	3 (3.6)
Always	2 (2.4)	0	0	2 (2.4)
I don't know	2 (2.4)	0	1 (1.2)	3 (3.6)

Table 2. Opinion of clinicians about longevity of IPGs

	How long do non-rechargeable IPGs realistically last?, n (%)	How long should non-rechargeable IPGs realistically last?, n (%)	How long should rechargeable IPGs last?, n (%)
1–2 years	4 (4.7)	0	2 (2.3)
2–5 years	71 (81.6)	18 (20.7)	
5–10 years	8 (9.2)	56 (64.4)	5 (5.7)
10–15 years	2 (2.3)	11 (12.6)	19 (21.8)
15–20 years			30 (34.5)
20–25 years			15 (17.2)
Lifelong	–	–	13 (14.9)
Missing data	2 (2.3)	2 (2.3)	3 (3.4)

χ^2 test for expected versus actual lifetime of non-rechargeable IPGs, $p = 0.062$.

Table 3. Opinion about time to invest in charging the IPG

	How much time do you think patients need to invest each week into charging?, n (%)	What do you think is an acceptable time for patients need to invest into charging?, n (%)
<1 h/week	14 (16.1)	29 (33.3)
1–2 h/week	38 (43.7)	38 (43.7)
2–4 h/week	22 (25.3)	14 (16.1)
>4 h/week	6 (6.9)	1 (1.1)
I don't know	4 (4.6)	2 (2.3)
Missing data	3 (3.4)	3 (3.4)

χ^2 test expected versus actual time patients must invest in recharging, $p = 0.923$.

Clinical Case Scenarios

Scenario 1 presented an older patient with Parkinson's disease and an impaired cognitive status who is not able to take care of himself. Ninety percent of the participants would not recommend a rechargeable IPG for the replacement of the IPG (Fig. 5a). Seventy-three percent of the participants would recommend a rechargeable IPG as the first IPG placement for scenario 2: a young woman with Parkinson's disease with a traveling lifestyle (Fig. 5b). Scenario 3 illustrated an obese, illiterate patient with essential tremor. Sixty-six percent of the participants would

Table 4. Advised interval to check the battery of a non-rechargeable IPG

	n (%)
Once a week	9 (10.3)
Once a month	35 (40.2)
Once every 3 months	25 (28.7)
Once every 6 months	16 (18.4)

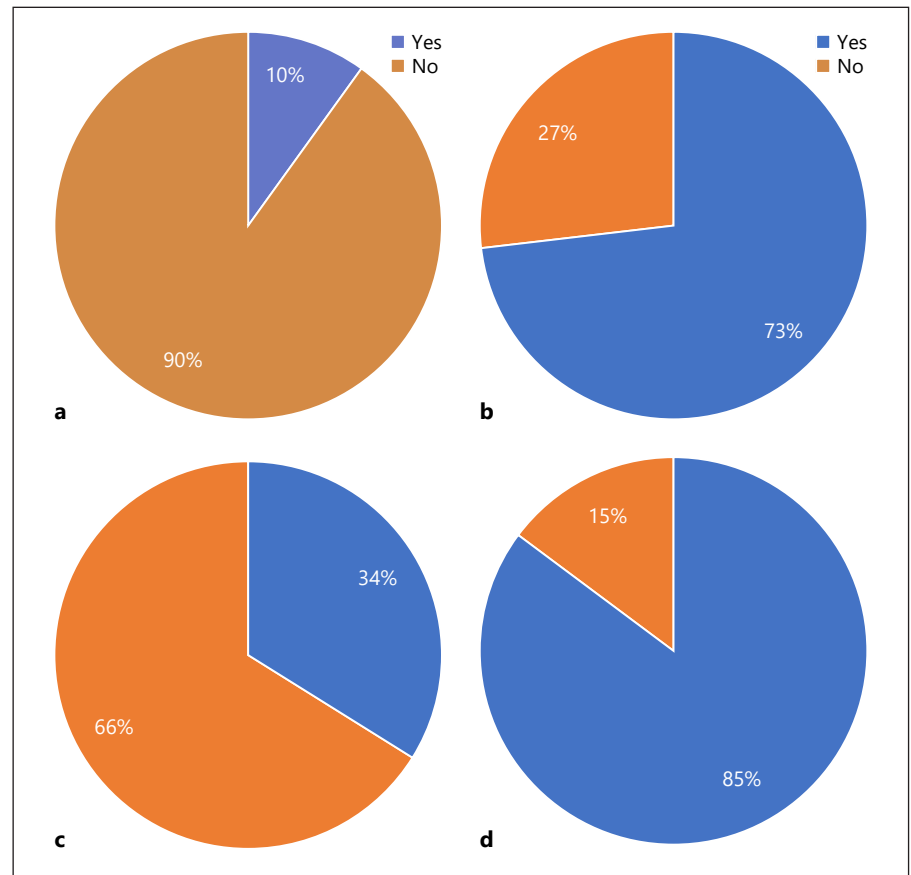


Fig. 5. Question: Would you recommend a rechargeable IPG? **a** Case 1. **b** Case 2. **c** Case 3. **d** Case 4.

Table 5. Percentage of patients presenting to the hospital with a fully depleted battery

	Depleted battery of non-rechargeable IPG, n (%)	Depleted battery of rechargeable IPG, n (%)
<5% patients	37 (42.5)	46 (52.9)
5–9% patients	19 (21.8)	13 (14.9)
10–24% patients	10 (11.5)	6 (6.9)
25–50% patients	7 (8.0)	3 (3.4)
>50% patients	5 (5.7)	1 (1.1)
I don't know	7 (8.0)	15 (17.2)
Missing data	2 (2.3)	3 (3.4)

χ^2 test non-rechargeable versus rechargeable IPGs, $p = 0.208$.

not recommend a rechargeable IPG as the first implant (Fig. 5c). Eighty-five percent of the participants would recommend a rechargeable IPG as the initial neurostimulator for scenario 4, a well-educated young woman with cervical dystonia (Fig. 5d).

Discussion

The three factors rated as most important for the choice of IPG were age, the cognitive status of the patient, and existing social support. A slight majority of participants thought that the patients value not having to undergo repetitive replacement surgeries more than the burden of regularly investing time in recharging the IPG. However, fewer participants would start with a rechargeable IPG as a general strategy and implant a rechargeable IPG as the primary IPG only on a case-dependent decision. Only a small percentage would convert a non-rechargeable IPG to a rechargeable IPG. However, at least half of all the participants estimated that a rechargeable IPG was more cost-effective than a non-rechargeable IPG after the first replacement. These results highlight discrepancies between expected patient preference or cost-effectiveness and actual clinical practice.

The size of the non-rechargeable IPG showed a lower score on satisfaction than the size of the rechargeable IPG. Furlanetti et al. [10] concluded that the concern about

IPG size in patients that received a non-rechargeable IPG rose from 6.7% preoperatively to 60% on long-term post-operative follow-up. Size could be a determining factor, especially in patients with IPG discomfort, pocket pain, or low BMI. The actual longevity of the rechargeable IPG did match the expected longevity. The true and expected longevity of the non-rechargeable IPG did differ, although not significantly. While some manufacturers offer rechargeable IPGs of up to 25 years of lifetime, the products have yet to be on the market for this long. Therefore, no long-term data on battery capacity reduction over time are available. The industry's innovation may focus on improving the size and longevity of the non-rechargeable IPG to improve patient satisfaction in the future, especially for patients for whom a rechargeable IPG is not a realistic option.

Rechargeability is crucial, as newer non-rechargeable IPGs have shorter battery life than older models [3–5]. DBS experts in this survey expect a 5- to 10-year longevity but only perceive 2–5 years. Additionally, it is known that the risk of wound infections grows exponentially with the third IPG replacement [15]. Combined, these factors may prevent patients from being considered for rechargeable IPGs, as non-rechargeable alternatives are currently limited.

Patients and their families were counseled for both types of IPGs by most participants and involved in the decision-making process. Besides the opinion of the neurosurgeon or neurologist, the patient's preference should also be considered an essential factor. There is no clear consensus on what is determinant in the choice of type of IPG. Therefore, clinicians counseling patients on the different IPGs should reflect and elaborate on the patient's preference and offer the option of the kind of IPG rather than relying on personal experience and opinions.

The four clinical case scenarios were designed to illustrate the variety of clinical practice cases. There is no unanimous correct answer for the choice of type of IPG. The majority, as expected, did not recommend converting to a rechargeable IPG for an older patient with impaired cognitive status in line with the most relevant factors "age," "existing social support," and "cognitive status." However, a small group of 10% would still recommend it. The Multi Recharge Trial showed that patients did not need to recharge the battery themselves to successfully maintain therapy. Caregivers like family members or a nursing home can perform the recharging [13].

Most participants would recommend the initial placement of a rechargeable IPG for the traveling, high-func-

tioning woman in scenario 2. The Multi Recharge trial [13] showed that most of their patients with rechargeable IPG also traveled and had recharged the device while traveling, implying that the need to travel would not be a disadvantage. Interestingly, a third of the participants would still recommend a rechargeable IPG for an obese patient with limited education and illiteracy. Changes in weight and the amount of soft tissue between the battery and the patient programmer can influence recharging. A large percentage of the participants recommend a rechargeable IPG for the young patient with dystonia. This corresponds with the general preference of the participants to give a rechargeable IPG to patients with dystonia and the fact that dystonia patients usually require higher stimulation parameters, must recharge longer, and rate the recharging easier compared to Parkinson's patients [13].

Reimbursement only significantly affects the decision-making process if rechargeable IPGs are unavailable in a specific country or a proposal must be submitted first. Regulations with insurance could influence the decision-making process, as several participants from different countries received insurance claims.

A strength of this survey was the significant response of participants from multiple DBS centers worldwide. It shows the opinions and strategies of the experts compared to the clinical practice. However, this survey has the limitation that we cannot verify the actual objective percentages but must rely on estimates, e.g., of implanted rechargeable IPGs or patients with depleted non-rechargeable IPGs presenting to the hospitals. For some aspects of reimbursement, some conflicting information was given, which could not be fully resolved by approaching individuals for clarification. The return rate of 26.9% was on the lower end of similar online surveys. However, this may be due to the global scope of the survey, representing very diverse situations regarding DBS and IPG implants. Furthermore, this study may have a selection bias as active members of functional neurosurgery societies tend to be located at larger academic centers. Therefore, the study may miss reaching DBS experts at smaller and non-academic centers.

The variable sample sizes regarding the profession of the DBS experts do not allow for adequately assessing whether, e.g., neurosurgeons and neurologists have different clinical practices or preferences regarding IPG choice. In addition, some participants were also from professions that are not directly involved with IPG implants. However, these participants consistently did neutrally answer questions on IPG implants (e.g., "I don't

know”). While the rate of dropouts (<10%) was comparatively low for a more comprehensive survey like ours, a future survey can likely be shortened and focus more on DBS experts who are currently active and directly involved in IPG choice and implants.

Conclusion

The choice of which type of IPG should be implanted varies across different countries and centers. Varieties of answers were given, and other strategies were mentioned. As the varieties of answers in this survey showed that the ideal type of IPG for the patient depends on multiple factors and is highly individualized. We must be cautious about the influence of insurances that solely focus on financial aspects. We may also reconsider the usefulness of uniform global guidelines for all DBS centers, as national differences seem to be large.

Acknowledgments

The authors thank the European Society for Stereotactic and Functional Neurosurgery (ESSFN) and the European Association of Neurological Surgeons (EANS) for distributing the survey among their members.

Statement of Ethics

This study was conducted in accordance with the current version of the World Medical Association’s Declaration of Helsinki. This study was granted an exemption from requiring an ethics approval by the Ethics Committee of the University of Heidelberg because of the nature of the study on collecting data of healthcare professionals on clinical practice without collecting any personal or patient-specific health-related information. The potential size of the group of participants (global collective of DBS experts) and data anonymization were factored in to avoid identification of individual participants.

Due to the nature of the study as an email-distributed questionnaire, obtaining written informed consent was waived by the

Ethics Committee of the University of Heidelberg. However, participants were required to give digital informed consent before participating in this study. Participants needed to read and agree to an informed consent form and state both by clicking on a digital confirmation button before being forwarded to the questionnaire.

Conflict of Interest Statement

Martin Jakobs received speaking honoraria from Boston Scientific and research grants from Abbott and is a consultant for Efinger Instruments. Marie Therese Krüger is a consultant for Boston Scientific and Brainlab. She has received speaking honoraria from Elekta and consultancy and travel fees from Medtronic. Yara Rosalie Willems, Niels Anthony van der Gaag, Kuan Hua Kho, and Øystein Vesterli Tveiten report no conflicts of interest.

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Author Contribution

Yara Rosalie Willems was involved with data analysis and interpretation, writing the first manuscript draft, creating tables and figures, and manuscript proofreading. Niels Anthony van der Gaag was involved in the conceptualization of the study, data analysis and interpretation, writing the first manuscript draft, and manuscript proofreading. Kuan Hua Kho, Øystein Tveiten, and Marie Therese Krüger were involved in the conceptualization of the study and manuscript proofreading. Martin Jakobs was involved in conceptualization of the study, data analysis and interpretation, writing the manuscript draft and revision, and manuscript proofreading.

Data Availability Statement

All data generated and analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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