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Published in:
Parkinsonism & Related Disorders

DOI:
10.1016/j.parkreldis.2006.04.006

2006

Link to publication

Citation for published version (APA):
Hjelmgren, J., Ghatnekar, O., Reimer, J., Grabowski, M., Lindvall, O., Persson, U., & Hagell, P. (2006). Estimating the value of novel interventions for Parkinson's disease: An early decision-making model with application to dopamine cell replacement. *Parkinsonism & Related Disorders*, *12*(7), 443-452. https://doi.org/10.1016/j.parkreldis.2006.04.006

Total number of authors:
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Download date: 18. Dec. 2025

This is an author produced version of a paper published in Parkinsonism and Related Disorders. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:
Hjelmgren J, Ghatnekar O, Reimer J, Grabowski M, Lindvall O, Persson U and Hagell P.
"Estimating the value of novel interventions for Parkinson's disease: An early decision-making model with application to dopamine cell replacement."
Parkinsonism and Related Disorders. 2006 Jun 21
doi:10.1016/j.parkreldis.2006.04.006

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Estimating the value of novel interventions for Parkinson's disease: An early decision-making model with application to dopamine cell replacement

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Key words: Parkinson's disease, cost-effectiveness, outcomes, modeling, cell therapy

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ABSTRACT

A long-term cost-effectiveness model for early decision-making and estimation of outcomes of novel therapeutic procedures for Parkinson's disease (PD) was developed based on the Hoehn and Yahr (HY) stages of PD. Results provided support for model validity. Model application to a future dopamine cell replacement therapy indicated long-term cost offsets and gains in quality-adjusted life years in early onset PD (HY III-IV), as compared to standard drug therapy. The maximum price premium (i.e., profit or compensation for developmental costs) for the intervention to remain cost-effective was estimated to €12 000-€64 000 according to cost-per-QALY thresholds of €38 000-€70 000 and depending on whether all or only medical direct costs are considered. The study illustrates the value of early health economic modeling and the described model shows promise as a means to estimate outcomes and aid decision-making regarding novel interventions for PD.

1. Introduction

Available therapies offer major symptomatic relief during the initial stages of Parkinson's disease (PD), and approaches such as deep brain stimulation and continuous drug delivery systems can offer relief from disabling complications during later stages [1,2]. None of the therapeutic options clinically available for PD today has unequivocally been shown to modify the underlying disease process. However, advances in experimental animal PD models have raised the possibility of novel interventional approaches that go beyond the symptomatic paradigm available hitherto. Such emerging interventions include, e.g., in vivo gene delivery by viral vectors [3], ex vivo gene therapy through implantation of encapsulated genetically engineered cells [4], and local intraparenchymal administration of neurotrophic factors [5] aimed at counteracting neurodegeneration and halting symptom progression. Alternatively, to use stem cell-based approaches in order to replace dead neurons with healthy ones, restore deficient transmitter release and reconstruct neuronal circuitries [6]. Interventions such as these depend on advanced biomedical technologies and expertise, which most probably will render them relatively costly. In order to gain acceptance, they will thus need to offer long-term gains beyond those offered by currently available therapies, not only in terms of efficacy and effectiveness but also regarding the disease-related societal burden [2]. It is currently unknown if or to what extent this can be reasonably expected to be achieved with novel candidate interventions for PD.

The cost-effectiveness of a new therapy can be simulated early in its development through health economic models using assumptions about efficacy, adverse events, quality of life and costs. Early outcome modeling is important for a variety of reasons [7-9]. First, it provides initial guidance in priority settings and decision-making for the further development of interventions. Secondly, it allows for estimates regarding the cost limits of a therapy from a cost-effectiveness perspective. Thirdly, it is helpful in estimating outcomes in

a longer term than what is possible in clinical trials. Information derived from such models can be used to improve the design of future clinical trials.

The objectives of this study were to develop a health economic simulation model for early decision-making and estimation of long-term outcomes of novel interventions for PD and, as an example of early decision-making modeling, to apply this model to assess the cost-effectiveness of a future dopamine cell replacement therapy for PD.

2. Methods

2.1. Model design

Our approach was to build a state transition model that structures patients' disease progression from diagnosis to end of life, where each state represents specific treatment patterns and health levels. Such a model allows (i) combination of data from several sources, which simplifies analysis of relevant economic perspectives and costs not collected in a clinical trial; (ii) extension of the time horizon beyond that of a clinical trial, thus covering time perspectives that are more relevant for policy decisions; and (iii) early decision-making analyses where the modeled intervention may be altered by changing the parameters put into the model. The model described here regards disease progression as a continuous temporal function. Each state was defined by the Hoehn and Yahr (HY) stage of PD [10].

2.2. Disease progression and costs

Approval was obtained from the Research Ethics Committee, Faculty of Medicine, Lund University, Sweden. Disease progression was estimated from 79 PD patients (48 men, 31 women) randomized from the Department of Neurology, Lund University Hospital, Sweden. Data regarding age, "off"-phase HY stage, and time since diagnosis were collected (Table 1). Because it was assumed that novel interventions primarily aim at

modifying the underlying disease progression and/or pathology, "off"-phase HY stages were used [11]. Change in HY stage between the first and most recent visit was used to estimate disease progression (*DP*), the HY stage at diagnosis was used to estimate *DP* as a function of disease severity (*HY*), the difference in time between the first and most recent visit was used to estimate the annual disease progression (*t*), and age at diagnosis was used to estimate the impact of age on *DP*. All variables were included as covariates in a multivariate ordinary least square regression model (equation 1), where u_t denotes the unobservable error term.

$$DP = \beta_0 + \beta HY + \beta t + \beta age + u_t. \quad (1)$$

Statistical calculations were performed in SPSS 11.5 for Windows (SPSS, Inc., Chicago, IL). Parameters from these calculations were used to develop a simulation model using Excel 2000 (Microsoft Corp., Redmond, WA).

None of the patients in the clinical cohort died during the follow-up period. However, the probability of surviving during a defined period of time will have an impact on the number of years a person will spend in a particular health state. To obtain the mortality-adjusted life years, the accumulated probability of surviving *t* years was multiplied by *t* number of years. Since the probability of surviving the first and subsequent *t*-1 years is greater for younger individuals we calculated mortality-adjusted life years for individuals in the age groups <64 and ≥64, respectively. Data on survival probabilities were obtained from Swedish life tables [12]. Most studies indicate a somewhat increased mortality in PD compared to the general population [2]. To account for this, we used data from a study by Hely et al. [13] who estimated the excess mortality of PD using standardized mortality ratios (SMR). The mortality-adjusted life years for PD patients were derived by multiplying the

SMR (1.8 and 1.5 for ages <64 and ≥64, respectively) with the annual hazard rate for the general population.

In order to estimate the number of quality-adjusted life years (QALYs) during the natural history of disease we used health state utilities by HY stages according to the generic EuroQol (EQ-5D) scale (Table 2) [14,15]. The EQ-5D is a pre-scored health status classification system including five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each attribute has three levels (no, some, and major problems), thus defining 245 (3^5) possible health states. Utilities for each health state (range: -0.594 to 1.0, indicating worst possible and full health, respectively) were measured by the time trade-off method [16]. The number of QALYs during a defined period of time was obtained by multiplying the number of mortality adjusted life-years in each HY stage with its health utility weight.

PD related costs were derived from an earlier study on costs and resource use in PD, as estimated by "off"-phase HY stages (Table 2) [17]. Costs associated with the respective HY stages included those related to co-morbidities and complications such as depression, motor fluctuations and dyskinesias under standard pharmacological therapy. Calculations were made in Euros (€) according to the price level of 2002, using the average 2002 exchange rate to the Swedish krona (€1 = SEK 9.19). The perspective presented here includes direct costs, i.e., medical (in- and outpatient care, pharmaceuticals and investigations) and other direct (transportations and home help) costs. All calculations (costs and QALYs) in the base case analysis are based on a discount rate of 3%, which is the recommended rate in Sweden [18].

2.3. Model application

We estimated the cost-effectiveness of a future cell-based therapy for PD that aims to provide striatal dopaminergic reinnervation. For this purpose we used clinical data on

the outcomes following neural transplantation in a series of 14 patients (12 men, 2 women) with idiopathic PD who had received intrastriatal grafts of dopamine-rich human embryonic ventral mesencephalic tissue (Table 1) [19]. Data included age, "off" phase HY, drug treatment, motor fluctuations, and adverse events [19-21]. Data were collected preoperatively (n=14) and at 2, 5, and 10 years following transplantation (n=14, 8 and 1, respectively).

The two-year post-operative data on grafted patients showed that clinical disease progression, in terms of HY stages, had ceased in 8 patients and was reversed in 6 patients. Patients who had been followed for five years after surgery either experienced a further improvement (n=2) or stayed in the two-year post-operative disease stage (n=6). In the base case model of disease progression for transplanted patients, we assumed an initial progressive improvement during two years, followed by a stationary period up to five years after grafting, after which disease progression was assumed to follow its preoperative path (Fig. 1A). Since the efficacy of a future cell therapy for PD is unknown, we altered the efficacy assumption in the sensitivity analyses (see below) in order to test the robustness of the results (Fig. 1B).

Intervention costs were calculated as the sum of the surgical procedure itself and intervention-related care. Based on estimates from our neural transplantation trials, intervention costs were thus estimated to €32 644 per patient for bilateral implantations. Since there is always a risk for complications in connection with surgery the expected costs of complications were also valued. A literature review of clinical transplantation trials in PD [21] revealed that the most frequent significant complications, with possible or probable relation to the procedure, are hematoma and dyskinesias. The former has been reported in approximately 5% of grafted patients and clinically significant graft-induced dyskinesias in about 15% of patients. For costing purposes, we assumed that a hematoma requires the same amount of care as a stroke. Therefore, the expected cost of a hematoma was assumed to be equal to the probability (i.e., 0.05) of getting a hematoma multiplied by the average four-year

cost of stroke (€31 361) [22]. Furthermore, it was assumed that approximately a third of the patients who develop significant graft-induced dyskinesias would require additional neurosurgery. The cost of such additional surgery was estimated to €20 000 [23]. The remaining two-thirds of dyskinetic patients were assumed to receive treatment with amantadine, estimated to an annual cost of €540 (the cost of a daily dose of 200 mg amantadine in Sweden). Due to uncertainties regarding the incidence of adverse events, these assumptions were altered in the sensitivity analyses (see below).

Since the transplanted patients in our series were relatively young (mean age, 52) and the majority (10 out of 14) was diagnosed as HY III and IV at the time of transplantation, the cost-effectiveness of transplantation was evaluated for HY III-IV patients aged <64 years. The time horizon in the base case scenario was 25 years.

2.4. The value of the intervention

By adding the total intervention cost (i.e., procedure + complications costs) to medical and other direct costs of illness, the total cost (TC) for cell therapy (TC_{cellRx}) is obtained. To evaluate the cost-effectiveness, expressed as cost-per-QALY gained, the difference in total costs between grafted (TC_{cellRx}) and non-grafted ($TC_{control}$) patients is divided by the difference in QALYs (equation 2).

$$\textit{Cost-per-QALY gained} = (TC_{cellRx} - TC_{control}) \,/\, (QALYs_{cellRx} - QALYs_{control}) \qquad (2)$$

As long as the cost-per-QALY gained falls below what the society is willing to pay for a QALY (i.e., the cost-per-QALY threshold) the intervention is regarded as cost-effective.

The price premium is any excess cost additional to the actual intervention costs, such as profit or compensation for intervention developmental costs. In the base case analysis the price premium is assumed to be zero. By adding a price premium, the total cost for the intervention will increase. We therefore estimated how large the maximum price premium could be in order for the intervention to be equivalent to or fall below two suggested cost-per-QALY thresholds: €38 000 and €70 000. The first is based on a retrospective analysis of policy decisions at the National Institute for Clinical Excellence in the UK [24], and the latter has recently been suggested as an acceptable cost-per-QALY threshold in Sweden [25].

2.5. Sensitivity analyses

To assess the model's robustness to a number of key assumptions, sensitivity analyses were performed regarding the time horizon (10-20-30 years), discount rate (0-5%), treatment efficacy (+/- 50%; Fig. 1B), and the occurrence of hematoma and dyskinesias (+/- 100%). The analytic perspective was also varied from direct medical costs to also include other direct costs. Furthermore, EQ-5D based health state utilities were altered from the time trade-off to the visual analog scale (VAS) method.

3. Results

3.1. Disease progression model

All variables included in the model were significant predictors of disease progression ($p<0.05$). However, model fit (adjusted R^2) improved from 0.423 to 0.452 when time and age ≥64 were regarded as interaction variables. The model was therefore revised to include separate progression rates for individuals <64 and ≥64 years ($t_{<64}$ and $t_{\geq 64}$), and HY stages at diagnosis (*HY*), as explanatory variables. Equation 3 shows the annual progression rate (*DP*) in terms of HY stages.

$$DP = 0.850 - 0.263HY + 0.112\ t_{<64} + 0.199\ t_{\geq 64} + u_t \qquad (3)$$

While HY stages are discrete steps in the I-V interval, the model counts HY units that are positioned between the discrete steps. Thus, HY values in the 0.5-1.49 interval indicate HY stage I, HY values of 1.5-2.49 indicate HY II, etc. Individuals in the age groups <64 and ≥64 progress 0.112 and 0.199 HY steps per year, respectively. This means that it takes 8.93 (1/0.112) and 5.13 (1/0.199) years for patients in the age group <64 and ≥64 to progress one HY step, respectively, when the impact of the constant term (0.850 steps at t_0) and baseline HY stage (-0.263 steps per initial HY stage) is not taken into account. Table 3 illustrates the unadjusted and mortality-adjusted disease progression during a 25-year period for patients starting in HY II when the effects of the constant term and baseline HY stage are included in the model.

Table 4 illustrates the modeled present value of total direct costs and QALYs according to initial age and HY stage. The total costs during 25 years are higher for patients with more advanced PD at baseline. As a consequence of a longer expected survival, total costs are also higher for patients <64 years.

3.2. Model application

We found that the two-year post-operative treatment effect was dependent on the preoperative HY stage (p=0.002); patients in HY stages III and IV improved by an average of 0.552 and 0.736 HY steps, respectively. This is equivalent to 4.7 and 6.2 mortality-adjusted years in less advanced disease stages for patients in HY III and IV, respectively.

Table 5 shows the present value of total direct costs for non-grafted and grafted patients in HY III and IV. As a result of the procedure related costs, overall direct medical costs are higher for grafted than for non-grafted patients. However, cost savings in home help,

inpatient care and pharmaceuticals are achieved, which compensate for this. Since grafted patients are less costly and have a higher number of QALYs, the model indicates that cell therapy would yield cost savings in both HY III and IV patients.

Figure 2 gives the modeled estimated maximum price premium according to two cost-per-QALY thresholds. In order not to overestimate the price premium these estimates were derived for HY stage III patients. Results indicate that there is room for a price premium to compensate developmental costs according to both cost-per-QALY thresholds. Due to savings in direct costs that fall outside the hospital sector, the maximum price premium is higher if all direct costs are considered rather than direct medical costs only.

The model's sensitivity to base case assumptions is displayed in Table 6. It can be seen that the result in the base case scenario is sensitive for patients in HY III concerning changes in time horizon, discount rate, treatment effect and health utility method, whereas the results are generally stable for patients in HY IV.

4. Discussion

In this study, we developed a health economic simulation model for estimation of cost effectiveness and early decision-making in the development of novel therapeutic approaches for PD. Application of the model to a future cell-based therapy, as applied to the Swedish health care system, suggests long-term cost-effectiveness and room for a price premium in HY III-IV patients with early onset PD.

The model described here is capable of analyzing novel therapeutic technologies that are expected to alter the clinical disease progression rate. Assumptions regarding improvements, stationary periods, and slower/faster progression rates can be evaluated. Similarly to a majority of previous cost-effectiveness models for PD [11], our model is a mathematical decision model that enables analysis of the incremental cost-per-QALY gained, based on progression according to a clinical surrogate endpoint (HY). Also similar to other

model applications, we do not report either internal or external validity tests. Based on experiences from existing decision-models, it has been recommended [11] that PD models should cover a long time horizon, include a full spectrum of clinically relevant outcomes and PD-specific mortality, and separate disease progression from symptomatic treatment effects in order to avoid structural bias. Our model fulfils all these requirements.

A unique advantage of the present model, not found in other PD models [11], is that it can estimate a maximum price premium allowed for the intervention to fall below a specific cost-per-QALY threshold. The maximum price premium should be interpreted as the maximum acceptable profit to cover developing costs of the new technology. Cost-per-QALY thresholds are becoming increasingly public as more countries are regulating reimbursement and issuing treatment guidelines for new interventions [26]. Our model was based on the Swedish health care system, but devised to be applicable to available data on treatment costs and health state utilities for different HY stages. Such data are now available from a variety of countries (see, e.g., Refs 17, 27-30).

In contrast to the majority of models used to assess cost-effectiveness in PD [11], disease progression and cost data in the model presented here were derived from real life clinical practice and not a randomized clinical trial (RCT). Whereas RCTs are regarded gold standard for evaluating efficacy, they are also artificial. For example, the frequent use of placebo as the comparator and explicit inclusion and exclusion criteria, as well as the extra attention given to RCT patients (regardless of group assignment) may all contribute to non-representative outcomes [7,31,32]. Using real life observations as the basis for modeling is also less restricting and enables hypothetical comparisons between standard therapy and a variety of alternative strategies. This is a particularly important feature in early decision-making modeling, where assumptions typically need to be varied and re-iterated as new data become available [9,33].

The natural disease progression model was based on a clinical sample of 79 PD patients. While it is acknowledged that this somewhat restricted sample size leads to increased variance and decreased precision in estimates, resulting model fit was acceptable and model output were in general accordance with previously published experiences (see below). Resource use and cost data for the model were derived from an earlier cost-of-illness study, expressing costs (including those related to co-morbidities and complications) by "off"-phase HY stages under standard therapy [17]. Recent data indicate that dyskinesias may contribute to PD-related costs also after controlling for the effects of HY stages [34]. However, the extent to which this applies to the model presented here is not completely evident due to methodological discrepancies. As opposed to our baseline cost-of-illness study [17], but similarly to other decision models for PD [11], Péchevis et al. [34] based their estimates on "on"-phase HY stages and excluded costs associated with co-morbidities. This point to a need for further descriptive studies to clarify whether complications such as dyskinesias need to be accounted for in future model revisions and applications or if such practice will result in double-accounting, as compared to our current model.

Since our model is based on a cohort of patients who did not die, we used national Swedish survival probabilities [12] to adjust for mortality, and excess mortality due to PD was also accounted for [13]. The resulting disease progression estimates were similar to those in earlier clinical studies [10,13,35,36]. The model indicated more rapid progression for older than younger individuals. While the reason(s) for an age-related difference remains speculative, this result is in agreement with previous observations where older patients (mean age at onset >65 years) have shown more severe symptomatology than younger patients (mean age at onset ≤55 years) with the same disease duration, also after controlling for co-morbidities [37,38]. Taken together, these similarities with previous clinical studies support the validity of the model presented here.

The number of patients used in the model application was small. However, given that the model was devised for early decision-making purposes in the development of novel therapeutic interventions, this type of sample is likely to be representative of future model applications. As such, the application presented here supports the usefulness of the model and illustrates the value of early modeling in the development of novel interventions.

Although the present model-application supports further development towards a future cell-based therapy for PD, it is important to underscore that the results are based on open-label transplantation trials using primary human embryonic tissue. A recent RCT demonstrated no differences in symptomatic relief between grafted and sham-operated patients [39], and a previous double-blind RCT also failed to meet its primary end-point (a global retrospective patient self-assessment), although grafted patients did significantly better than controls on measures of motor function [40,41]. Because of the many practical, biological and ethical limitations associated with this procedure, as well as the high variability in clinical outcomes, efforts are now directed at identifying alternative sources of graft tissue, in particular stem cells [6,21,42,43]. A clinically competitive cell-based therapy has to yield better and more reliable outcomes in the absence of significant complications, as compared to the transplantation trials performed to date [6,19,21,39,42,43].

Thus, because the modeling results were based on a suboptimal procedure, they probably underestimate the cost-effectiveness of a future cell replacement therapy for PD. Nevertheless, results suggest favorable long-term outcomes among early onset PD patients in HY stages III-IV. According to available cost-per-QALY thresholds [24,25], sensitivity analyses also indicate cost-effectiveness or cost savings in a majority of instances. Altering health state utility estimation from the time trade-off to the VAS method increased the cost-per-QALY for HY III patients beyond that suggested for Sweden [25]. However, the VAS method is not recommended for utility weighting either in Sweden [18] or elsewhere [44].

The graft tissue used in the clinical trials that provide the input variables was obtained at no cost from elective abortions. It is therefore of interest to consider the potential price premium, i.e., how much the costs can be allowed to increase before exceeding certain cost-per-QALY thresholds. Our estimates thus indicate room for a price premium of a future cell therapy with similar efficacy to the example with embryonic tissue used here. For example, long-term cost-effectiveness would be achieved given that all direct costs are considered and that the price premium stays below €36 000 to 64 000 (UK and Swedish cost-per-QALY thresholds, respectively). These estimates can be seen as tentative approximations of the value of a future cell replacement therapy for PD and correspond to a maximum total intervention cost of €72 000-100 000.

In conclusion, we present an early decision-making model for estimation of long-term outcomes of novel therapies for PD that enables hypothetical comparisons between standard treatment and a variety of alternative strategies. While refinements will be necessary to optimize the model, initial comparisons with clinical data regarding disease progression support its validity. Application of the model to the case of a future cell-based therapy indicates potential for cost-effectiveness and room for a price premium. This health economic simulation model shows promise as a means of estimating outcomes and aiding decision-making regarding novel interventions for PD.

Acknowledgements

This study was supported by the Swedish Research Council, the Skane County Council's Research and Development Foundation, the Kock, Söderberg, and Rut and Erik Hardebo Foundations.

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Legends to figures

Figure 1:

The assumed base case pattern of efficacy following cell therapy is illustrated in (A) by a progressive downward shift in HY stage (ΔHY) from t_0 (time of grafting) to t_1 followed by a stationary phase (t_1 to t_2), after which clinical disease progression continues at an unaltered rate, as compared to preoperatively. Grafted patients (DP_G) will thus reach the most advanced stage of the disease (HY V) at a later time point (t_4) compared to non-grafted (DP_{NG}) patients (t_3). To test the robustness of the results, disease progression paths were altered (B) under the assumption that the effect is reduced (DP_{G*}) and increased (DP_{G**}) compared to the base case assumption (DP_G).

HY, Hoehn & Yahr stage of Parkinson's disease; DP, disease progression for grafted (DP_G) and non-grafted (DP_{NG}) Parkinson's disease patients.

Figure 2:

Model estimated maximum price premium for a cell therapy for Parkinson's disease (costs in Euro 2002). The y-axis illustrates cost-effectiveness, expressed as cost-per-QALY gained (i.e., the ratio of the difference in costs and difference in QALYs between grafted and non-grafted patients; see Methods). The x-axis illustrates the size of the price premium (i.e., cost additional to the actual intervention costs, e.g., profit or compensation for developmental costs), which is 0 in the base case. Horizontal lines represent suggested cost-per-QALY thresholds [24,25] and dashed lines are costs-per-QALY gained according to whether direct medical costs only or medical + other direct costs are considered. If the cost-per-QALY gained falls below an established threshold the treatment is considered as cost-effective. According to the two cost-per-QALY thresholds, A and B indicate maximum acceptable price

premiums of €12 000 and €40 000 when only medical costs are considered, whereas A^* and B^* indicate maximum acceptable price premiums of €36 000 and €64 000 when also other direct costs are considered.

[The size of a potential price premium (PP) is determined as follows: $PP=(TC_{cellRx}-TC_{control})/(QALY_{cellRx}-QALY_{control})$ - cost-per-QALY threshold, where TC_{cellRx} (PC+CC+other costs) denotes total costs for cell therapy and $TC_{control}$ denotes total costs for non-grafted patients.]

HY, Hoehn & Yahr stage of Parkinson's disease; QALY, quality-adjusted life years.

Table 1. Sample characteristics

Clinic sample (n=79):	
Age at onset	56.8 (12.3) [1]
Age at PD diagnosis	58.6 (11.9) [1]
Age at time of survey	69.2 (11.3) [1]
PD duration at first neurological assessment	4.3 (4.0) [1]
PD duration at time of survey	12.4 (6.1) [1]
Initial"off"-phase HY stage	2 (1-3) [2]
HY stage I	27 (34.2) [3]
HY stage II	25 (31.6) [3]
HY stage III	18 (22.8) [3]
HY stage IV	8 (10.1) [3]
HY stage V	1 (1.3) [3]
"Off"-phase HY stage at time of survey	4 (2-5) [2]
HY stage I	2 (2.5) [3]
HY stage II	20 (25.3) [3]
HY stage III	16 (20.3) [3]
HY stage IV	18 (22.8) [3]
HY stage V	23 (29.1) [3]
Grafted patients (n=14) [19]: [4]	
Age	52.0 (7.0) [1]
PD duration	11.9 (2.2) [1]
"Off"-phase HY stage	3.25 (3-4.25) [2]
HY stage I	0 [3]
HY stage II	1 (7.1) [3]
HY stage III	6 (42.9) [3]
HY stage IV	4 (28.6) [3]
HY stage V	3 (21.4) [3]

[1] Mean (standard deviation).
[2] Median (25^{th}-75^{th} percentile).
[3] n (%).
[4] At the time of grafting.
PD, Parkinson's disease; HY, Hoehn & Yahr stage of Parkinson's disease.

Table 2. Input parameters used in the early decision-making model of Parkinson's disease by Hoehn & Yahr (HY) stages.

	Annual Costs [17] [a]									Health state utility [14,15] [b]	
	Direct health care costs					Other direct costs					
HY stage	Inpatient care	Out-patient care	Pharmaceuticals	Investigations	Sum	Transport	Home help	Sum	Total cost	EQ-5D$_{TTO}$	EQ-5D$_{VAS}$ [d]
I	115	503	1 072	60	**1 745**	55	132	**188**	**1 936**	0.90	0.785
II	248	952	966	32	**2 198**	62	1 193	**1 255**	**3 453**	0.60	0.668
III	536	909	1 400	120	**2 965**	85	6 128	**6 213**	**9 178**	0.30	0.538
IV	2 323	637	1 569	162	**4 690**	65	2 381	**2 446**	**7 136**	0.20 [c]	0.520 [c]
V	2 015	503	2 405	195	**5 119**	73	10 132	**10 205**	**15 324**	0.11 [c]	0.430 [c]

[a] Costs are in Euros 2002.
[b] According to the EQ-5D as estimated using the time trade-off (EQ-5D$_{TTO}$) and visual analog scale (EQ-5D$_{VAS}$) methods.
[c] Due to few HY IV and V patients (n = 3 and 4, respectively) these were originally pooled to yield health utility values of 0.20 (EQ-5D$_{TTO}$) and 0.52 (EQ-5D$_{VAS}$) for stages IV+V [14]. Separate values for stage IV and V were 0.19 and -0.21 (EQ-5D$_{TTO}$) and 0.80 and 0.317 (EQ-5D$_{VAS}$), respectively [15]. Because of the small numbers of patients and large uncertainties, utilities for modeling purposes were derived by extrapolation from earlier stages.
[d] EQ-5D$_{VAS}$ was only used in the sensitivity analyses of the model application.

Table 3. Unadjusted and mortality-adjusted disease progression (in years) for Parkinson's disease patients with Hoehn & Yahr (HY) stage II according to age for a 25-year horizon.

	HY II	HY III	HY IV	HY V	Total duration
Unadjusted disease progression:					
Age <64	1.47	8.93	8.93	5.67	25.00
Age ≥64	0.83	5.03	5.03	14.11	25.00
Mortality-adjusted disease progression:					
Age <64	1.44	8.02	6.90	3.87	20.23
Age ≥64	0.78	3.90	2.77	4.20	11.65

Table 4. Treatment costs (in 2002 Euros) and quality-adjusted life years (QALYs) during a 25-year horizon for patients with Parkinson's disease initiating treatment at different Hoehn & Yahr (HY) stages and ages. Costs and outcomes discounted at 3%.

	HY II <64	**HY II ≥64**	**HY III <64**	**HY III ≥64**	**HY IV <64**	**HY IV ≥64**
Direct medical costs						
Inpatient care	18 107	11 959	27 038	15 783	31 872	17 992
Out-patient care	11 163	6 483	9 753	5 548	8 259	4 651
Pharmaceuticals	22 311	14 860	27 544	16 559	31 631	18 100
Investigations	1 937	1 264	2 464	1 459	2 746	1 563
Sum	**53 517**	**34 566**	**66 799**	**39 349**	**74 508**	**42 306**
Other direct costs						
Transport	1 080	717	1 088	635	1 055	599
Home help	72 946	52 190	91 055	57 236	110 717	64 383
Sum	**74 026**	**52 907**	**92 144**	**57 871**	**111 772**	**64 982**
Total costs	**127 543**	**87 473**	**158 943**	**97 220**	**186 279**	**107 288**
Cumulative QALYs	3.936	2.210	2.880	1.607	2.183	1.219

Table 5. Treatment costs (in 2002 Euros), quality-adjusted life years (QALYs), and cost-effectiveness during a 25-year treatment period for standard (control) and cell therapy in Parkinson's disease according to preoperative Hoehn & Yahr (HY) stage of disease.

	HY III Control (A)	**HY III Cell therapy (B)**	**Cost difference (B-A)**	**HY IV Control (C)**	**HY IV Cell therapy (D)**	**Cost difference (D-C)**
Direct medical costs						
Transplantation[1]	n/a	36 004	36 004	n/a	36004	36004
Inpatient care	27 038	17 630	-9 408	31 872	22 660	-9 212
Out-patient care	9 753	11 544	1 791	8 259	10 512	2 253
Pharmaceuticals	27 544	21 046	-6 498	31 631	22 946	-8 685
Investigations	2 464	1 953	-511	2 746	2 138	-608
Sum	**66 799**	**88 177**	**21 378**	**74 508**	**94 260**	**19 752**
Other direct costs						
Transport	1 088	1 108	20	1 055	1 063	8
Home help	91 055	67 182	-23 873	110 717	68 235	-42 482
Sum	**92 144**	**68 290**	**-28 853**	**111 772**	**69 298**	**-42 474**
Total costs	**158 943**	**156 467**	**-2 476**	**186 279**	**163 558**	**-22 721**
Cumulative QALYs	2.880	3.753	0.873	2.183	3.316	1.133
Cost-per-QALY gained[2]		**Cost saving**			**Cost saving**	

[1] Includes procedure costs (€ 32 644), expected cost of hematoma (€ 1 568) and dyskinesias (€1 792).

[2] ΔCosts/ΔQALYs

Table 6. Univariate sensitivity analysis of key variables for cell therapy initiated at Hoehn & Yahr (HY) stages III and IV, respectively. Cost per quality-adjusted life year (QALY) gained in Euro 2002.

		Cost-per-QALY gained	
Time horizon:	**10 years**	**20 years**	**30 years**
HY III	66 192	19 793	cost saving
HY IV	24 103	cost saving	cost saving
Discount rate:		**0%**	**5%**
HY III		cost saving	10 578
HY IV		cost saving	cost saving
Treatment effect (ΔHY)[1]:		**-50%**	**+50%**
HY III		929	cost saving
HY IV		cost saving	cost saving
Treatment effect (post-operative disease progression) :		**-50%[2]**	**+50%[3]**
HY III		Cost increasing[4]	2 461[5]
HY IV		69 870	Cost saving
Treatment effect (duration of stationary period):		**0 years**	**10 years**
HY III		2 334	8 600[5]
HY IV		cost saving	cost saving
Incidence of post-operative dyskinesias[6]:		**-100%**	**+100%**
HY III		cost saving	cost saving
HY IV		cost saving	cost saving
Incidence of hematoma[6]:		**-100%**	**+100%**
HY III		cost saving	cost saving
HY IV		cost saving	cost saving
Analytic perspective:		**Direct medical costs only**	**All direct costs[7]**
HY III		24 473	3 476[5]
HY IV		17 433	cost saving
Health utility weighting method:		**VAS (EQ-5D)** [8]	
HY III		92 216	
HY IV		31 080	

[1] Percentage improvement in HY compared to base case (Fig. 1).

[2] 50% increased postoperative progression rate.

[3] 50% decreased postoperative progression rate.

[4] A 50% increased postoperative disease progression rate results in more costs and less QALYs gained compared to non-grafted patients.

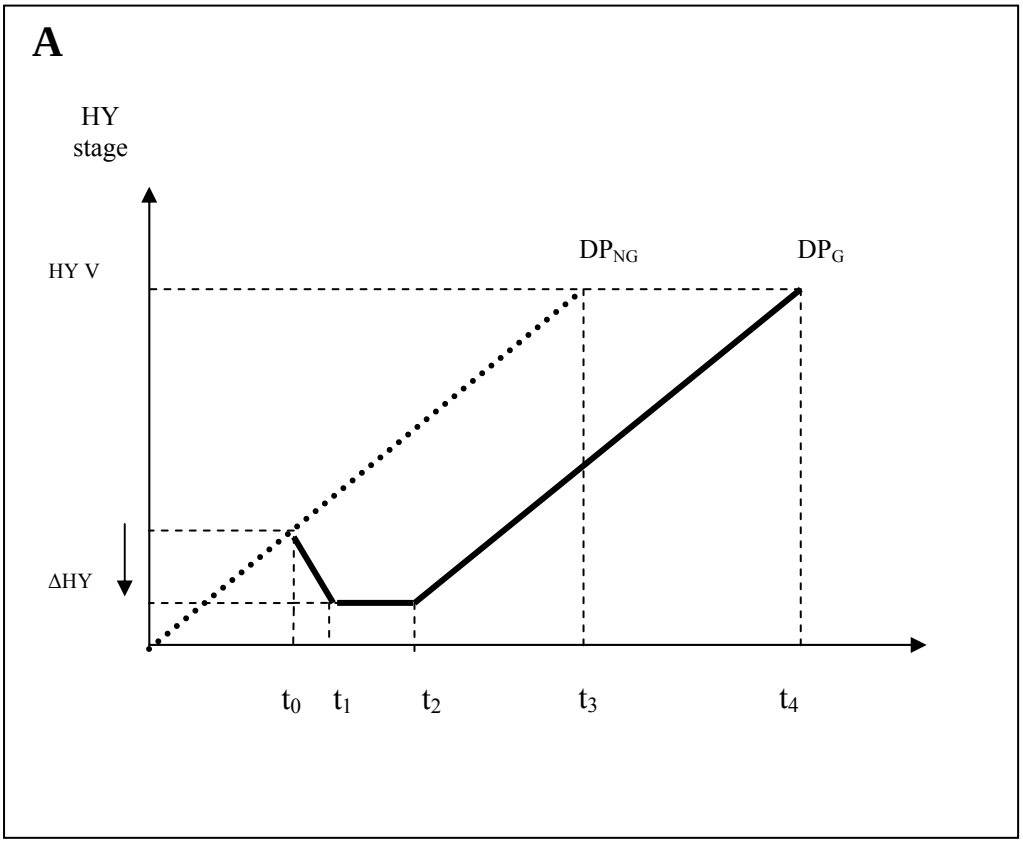
[5] Increase in cost-per-QALY in both directions of the sensitivity analysis despite cost saving in the base case are due to non-linear cost development across HY stages [17].

[6] Only differences in costs are regarded.

[7] Direct medical costs and other direct costs (transportation and home care).

[8] Accumulated QALYs gained for HY III and HY IV patients amount to 0.233 and 0.559, respectively.

Fig. 1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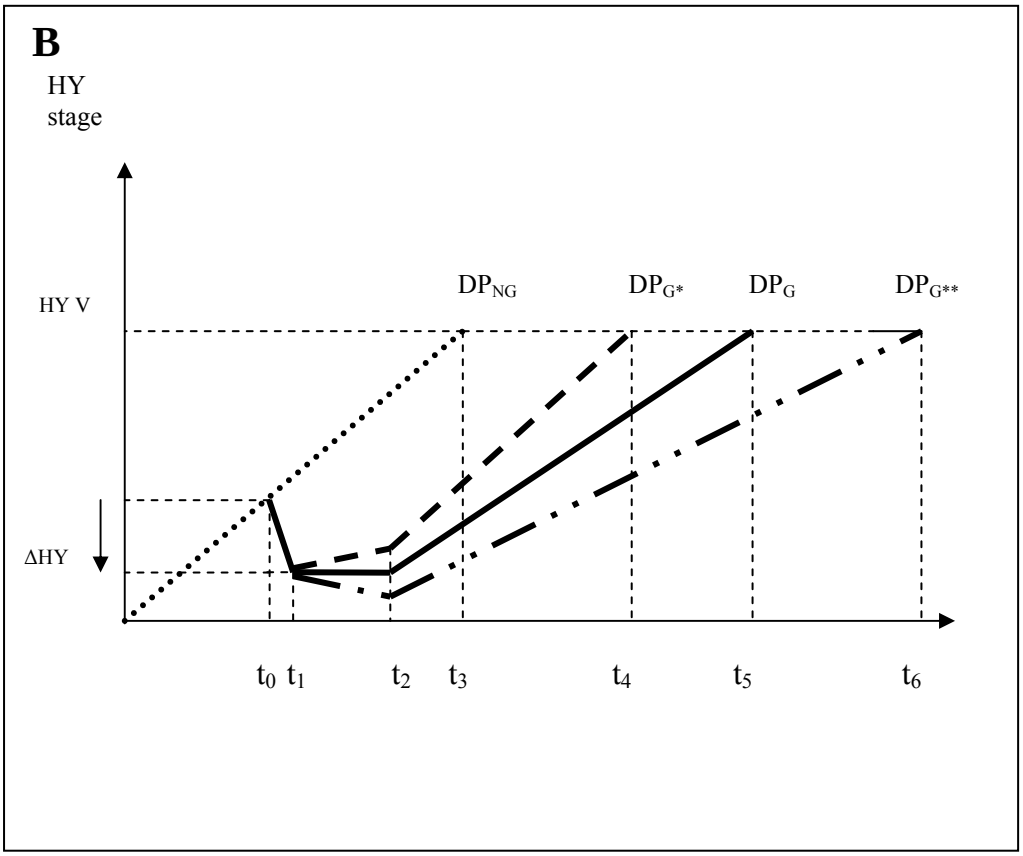
B
HY
stage
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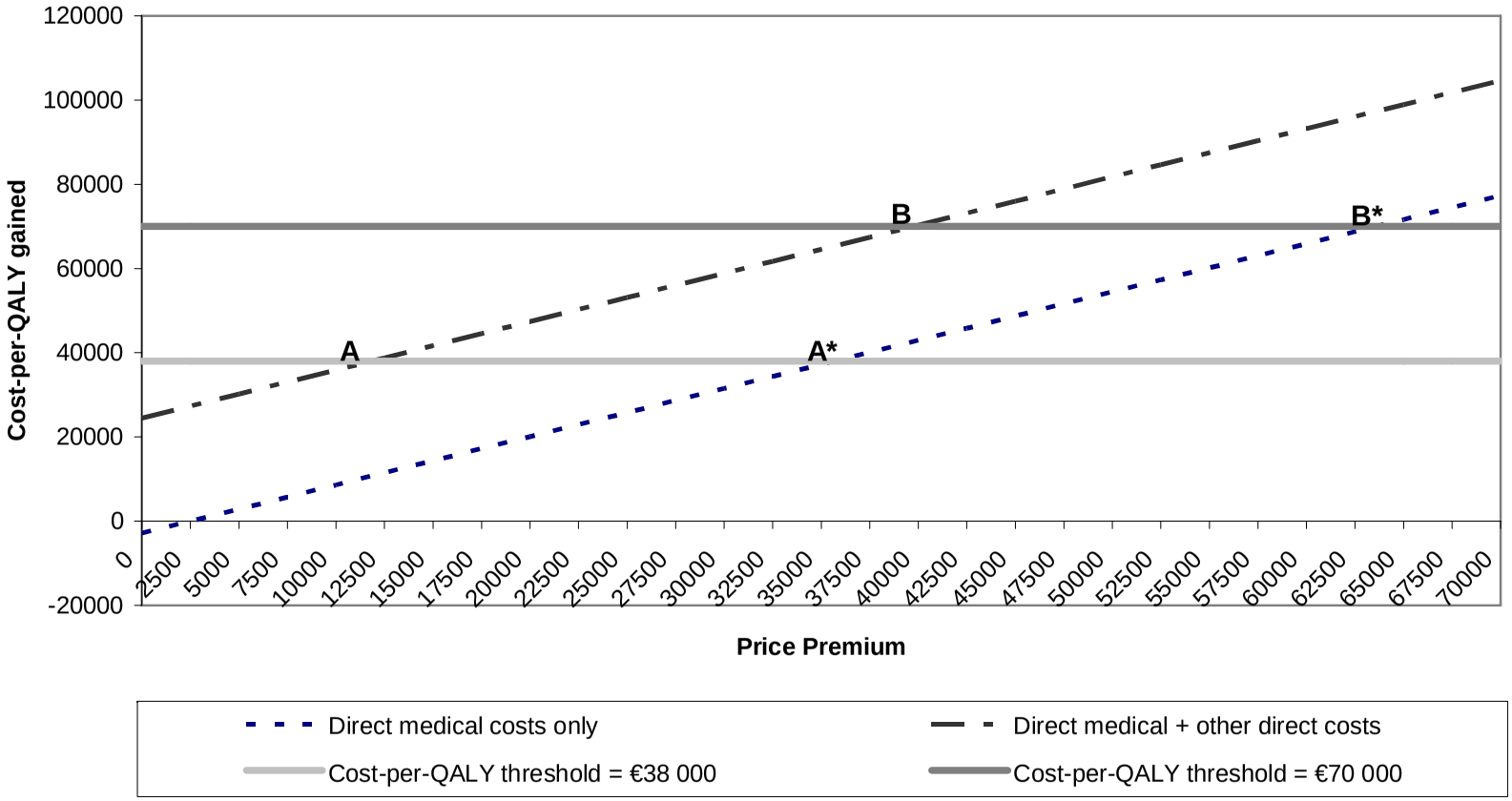
Fig. 2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Cost-per-QALY gained
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A*
B
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2500
5000
7500
10000
12500
15000
17500
20000
22500
25000
27500
30000
32500
35000
37500
40000
42500
45000
47500
50000
52500
55000
57500
60000
62500
65000
67500
70000
Price Premium
Direct medical costs only
Direct medical + other direct costs
Cost-per-QALY threshold = €38 000
Cost-per-QALY threshold = €70 000