Prediction of cognition in Parkinson’s disease with a clinical-genetic score: longitudinal analysis of nine cohorts

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Summary

**Background.** While Parkinson’s disease (PD) is thought of as a movement disorder, cognitive impairment has an outsized influence on patients’ well being. Accurate forecasts of cognitive function have the potential to be of great benefit for clinical trials and care. We aimed to develop a prediction algorithm that could be applied to prospective studies of recently diagnosed patients.

**Methods.** We developed an algorithm to predict global cognitive impairment (defined as Mini Mental State Exam (MMSE) ≤25) using data from 1,350 patients with 5,165 longitudinal visits over 12·8 (median, 2·8) years. Age at onset, MMSE, education, motor exam score, gender, depression and GBA mutations, machine selected through stepwise Cox’ hazards analysis and Akaike’s information criterion, were used to compute the multivariable predictor. Independent validation was performed in another 1,132 patients with 19,127 visits over 8·6 (median, 6·5) years.

**Findings.** The clinical-genetic score accurately predicted cognitive impairment within ten years of disease onset with an area under the curve (AUC) of >0·85 in both the discovery (95% CI, 0·821-0·902) and independent validation populations (95% CI, 0·779 - 0·913). 72·6% of patients scoring in the highest quartile were cognitively impaired by ten years vs. 3·7% in the lowest quartile (hazard ratio, 18·4, 95% CI, 9·4 - 36·1). Dementia or disabling cognitive impairment was predicted with an AUC of 0·877 (95% CI 0·788-0·943) and high negative predictive value (0·920, 95% 0·877-0·954) at the predefined cutoff (0·196). Performance was stable in 10,000 randomly resampled subsets.

**Interpretation.** Our predictive algorithm provides a potential test for future cognitive health or impairment in patients with Parkinson’s. It could improve trials of cognitive interventions and inform health care planning.
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Research in context

Evidence before this study

Cognitive decline is one of the most debilitating manifestations of disease progression in Parkinson’s and a key determinant of a patient’s quality of life and independence. The development of disabling cognitive impairment or dementia in PD is associated with a two-fold increased mortality risk, higher health care burden, and frequently leads to institutionalization. We searched PubMed with the terms “Parkinson’s disease”, “dementia”, “cognitive impairment” for reports published before October, 2015. Previous studies identified individual clinical risk factors associated with cognitive deficits in PD. Recently, mutations in the Gaucher’s disease-associated gene β-glucocerebrosidase (GBA) were associated with cognitive impairment in PD and with dementia with Lewy bodies. The user-friendly Framingham Cardiovascular Risk Score has benefitted cardiology and is part of standard care and trials. Based on user-entered age, gender, and cardiovascular risk factors, this model estimates a patient’s 10-year risk of having a heart attack. For PD, however, no integrated and widely applicable assessment tool for predicting the risk of cognitive decline has been established.

Added value of this study

First, we built and validated a first clinical-genetic cognitive risk score. This predicts the risk of global cognitive decline in patients with PD based on the analysis of a discovery population of 1,350 and a validation population of 1,132 participants. Areas under the curve for predicting global cognitive decline were 0.863 (95% CI, 0.821-0.902) for discovery and 0.854 (95% CI, 0.779 - 0.913) for validation. Adjusting for the prevalence of cognitive impairment among patients with PD of 26.7% yielded a substantial negative predictive value of 0.884 (95% CI 0.818-0.923). 72.6% of patients scoring in the highest quartile were cognitively impaired by ten years compared to only 3.7% in the lowest quartile (hazard ratio, 18.4, 95% CI, 9.4 - 36.1).
Second, dementia is characterized as a loss of cognitive ability severe enough to interfere with normal activities of daily living. Going beyond cognitive impairment, the AUC for predicting dementia within ten years from onset was 0.877 (95% CI 0.788-0.943) --- even higher than for global cognitive decline. Third, patients with high scores (>0.196) had a much steeper decline in serial Montreal Cognitive Assessments over time compared to individuals with lower scores in longitudinal random and fixed effects model analyses (p < 0.0001). This may be of particular use for enriching clinical trials designed for disease modification or to ameliorate cognitive decline. Our statistical power estimate indicates that the sample size required for such a hypothetical trial can be reduced by as much as 6-fold, if only high risk patients are included, compared to an equally powered trial of “all comers”.

Fourth, a clinical variables-only version of the risk score can be used in clinical settings, where GBA genotyping is not easily obtained, while the clinical-genetic score provides superior prediction where GBA status is available. Finally, prediction accuracies were highly stable in 10,000 randomly resampled subsets and downloadable cognitive risk calculators (beta-versions) of both the clinical-genetic and the clinical variables-only predictive score were implemented.

**Implications of all the available evidence.**

A cognitive risk score for patients with PD that integrates replicated clinical and genetic predictors into a single survival statistic predicts the risk of developing global cognitive decline within ten years from disease onset with high accuracy (with an AUC greater than 0.85 and CI 95% of 0.779-0.913). The score will enable trialists to enrich their populations with participants most likely to experience cognitive decline and, more generally, may help with health planning by identifying patients most likely to experience excellent cognitive health during ten years from disease onset. Further studies are needed to identify and validate additional clinical, genetic, and biological risk factors that could be seamlessly integrated into this versatile risk assessment tool.
Introduction

Although Parkinson’s disease (PD) is thought of as a movement disorder, recently, it has become clear that impaired cognition in PD has an outsized impact on quality of life and survival\textsuperscript{1}. The ability to predict and manage this complication is necessary to better provide reassurance and inform care planning. It is also highly relevant for recruitment and stratification of clinical trials, particularly those designed to slow disease progression and to prevent dementia. While a multitude of Parkinson’s medications is available to improve motor aspects of the disease, these do not have a major effect on cognitive decline.

Demographic and clinical risk factors for cognitive decline in PD are emerging. Age-at-onset\textsuperscript{2,3}, depression\textsuperscript{2}, and education\textsuperscript{2,4} have been nominated as predictors of dementia in multiple small or medium-sized cohorts (e.g. the largest published study examined 400 subjects for several years)\textsuperscript{2-4}. Measures of baseline disease severity using motor and cognitive scores are linked to an increased risk of developing future dementia\textsuperscript{2-5}. Complementing these clinical clues, mutations in the β-glucocerebrosidase gene (\textit{GBA}; found in about 10% of patients with gene sequencing) are linked to accelerated cognitive decline in PD\textsuperscript{6-9}. Other progression loci have been nominated, but remain controversial (e.g. \textit{MAPT} Refs.\textsuperscript{10} vs.\textsuperscript{11}; \textit{APOE} Refs.\textsuperscript{12} vs.\textsuperscript{13}) and await further replication.

Here we develop a clinical-genetic score predictive of global cognitive impairment in a discovery set of 1,350 participants with PD followed in six longitudinal cohorts and validated in 1,132 participants from three independent, well phenotyped longitudinal cohorts. The validated user-friendly and versatile cognitive risk calculator for PD can be downloaded and used to calculate a patient’s risk estimate.
Methods

Study Design and Participants

Figure 1 shows a summary of our workflow. Table 1 describes the cohorts and further details are available in the appendix. 3,200 patients with PD were longitudinally assessed with 27,022 study visits in nine longitudinal cohorts from North America and Europe between 1986 and 2016 (table 1 and appendix figure 1). Written informed consent for each cohort was obtained from the participants under the supervision of each local ethics committee. The Institutional Review Board of Partners HealthCare approved the current analyses. 96.3% of study visits occurred within 12 years of longitudinal follow-up from disease onset with a median follow-up time of 6.4 years from onset (interquartile range, 4.6 years) (appendix figure 2). We thus focused our primary analysis on the 12-year time frame from disease onset. Serial Mini Mental State Exam (MMSE) scores were longitudinally collected in seven cohorts. Montreal Cognitive Assessment (MoCA) scores were collected in two cohorts and converted to MMSE scores according to a published formula. To ensure consistency across studies, an MMSE score with the cut-off of ≤25 was defined as an indicator of significant global cognitive impairment as recommended by the International Parkinson and Movement Disorders Society (MDS) Task Force. Cohort-specific definitions of Parkinson’s disease dementia were used (appendix table 1). For seven cohorts operationalized level 1 diagnostic criteria for Parkinson’s disease dementia (PDD) of the Movement Disorders Society Task Force (appendix table 1) were available; PreCEPT and DATATOP used distinct definitions. PreCEPT defined PDD as a score of 4 on the MDS-UPDRS subscale 1 item 1 defined as “cognitive dysfunction [that] precludes the patient’s ability to carry out normal activities and social interactions”. For DATATOP published criteria for cognitive impairment leading to functional impairment were used. The MDS-Unified PD Rating Scale (UPDRS) part II and III scores were obtained from four cohorts, and estimated for the five remaining cohorts using the UPDRS or SPES/SCOPA-motor scales based on published conversion formulas (table 1). Hoehn and Yahr scales (HY) were longitudinally collected in all cohorts. Ethnicity was
self-reported. GBA mutations were defined as in Ref.\textsuperscript{8}. For several cohorts this analysis evaluated previously collected longitudinal phenotypic data; for the active HBS, PPMI, PDBP, DIGPD cohorts both retro- and prospectively collected longitudinal data elements were included.

**Statistical Analysis**

The appendix includes further details of the statistical methods, including a step by step calculation of the predictive score and the hypothetical power estimate. 3,200 patients with PD from nine cohorts were screened for eligibility. 235 patients were excluded because they had a MMSE ≤ 25 at baseline and 135 were excluded because their first study visit occurred more than 12 years after disease onset. Six cohorts representing 1,350 patients (after exclusion of an additional 334 patients with missing covariates) with 5,165 longitudinal visits over 12·8 (median, 2·8; interquartile range (IQR) 3·1) years were assigned to the discovery population (Figure 1): HBS, CamPalGN, PICNICS, PROPARK, DIGPD and PDBP. Because stratification of patients in clinical trials is a potential application of the risk score, we \textit{a priori} assigned the two trial cohorts, DATATOP and PreCEPT, to the validation population. The PPMI study is designed for validation and was therefore also assigned to the validation population (Figure 1). Cochran's Q-test and the I\textsuperscript{2} index\textsuperscript{29,30} were used to test for heterogeneity across studies (appendix table 2).

The discovery population was used to evaluate candidate clinical and GBA risk factors and to build the risk score (Figure 1). Nine clinical and genetic risk factors previously associated with dementia in PD were considered for evaluation based on prior evidence\textsuperscript{2,3,5} and applicability to our datasets: GBA mutation status, age at onset of PD, gender, years of education at baseline, baseline MMSE, MDS-UPDRS II, MDS-UPDRS III scores, Hoehn & Yahr stage, and baseline depression status. GBA was included because of unequivocal evidence from multiple, large\textsuperscript{6,7,9} and smaller longitudinal studies (e.g. Ref.\textsuperscript{31}), consistently confirming an association with pace of cognitive decline. Other candidate progression loci are still controversial (e.g. \textit{MAPT} Refs.\textsuperscript{10} vs.\textsuperscript{11}; \textit{APOE} Refs.\textsuperscript{12} vs.\textsuperscript{13}).
The Cox proportional hazards statistic was used to estimate the influence of these risk factors on time (years from PD onset) to reaching the endpoint of global cognitive impairment (i.e., duration of diagnosed PD illness at point of cognitive impairment) during longitudinal follow-up in the discovery population. The Cox regression coefficients, which were incorporated into the cognitive risk score, each index the hazard rate throughout the time period analyzed, which is assumed to be constant throughout that period. For each predictor separately, we tested the validity of the latter assumption, commonly referred to as the “proportional hazard assumption” and found it to be true for all predictors except the MDS-UPDRS II, which was discarded for this reason. The eight remaining risk factors were entered into a multivariable Cox model and a backward elimination was performed to remove uninformative variables from the model based on the lowest Akaike’s information criterion (AIC). Hoehn & Yahr stage was eliminated from the model during this process (AIC of 2,088·2 without HY vs. 2,089·5 with HY). The final multivariable Cox regression model then included the remaining seven risk factors (Figure 1). To adjust for differences among the seven cohorts, a “cohort” term was included as a random effect (using a “frailty” Cox model). Regarding “cohort” as a random term permits inferences about cohort level variance among a hypothetical universe of studies in the referent population. We built a risk score for global cognitive impairment in PD with a technique similar to that used to compute the Framingham Cardiovascular Risk score. A step by step calculation of the score is included in the appendix table 3, figure 6. The score was then validated in 1,132 patients with 19,127 follow-up visits over 8·6 (median, 6·5; IQR 3·1) years. In all analyses, p values less than or equal to 0·05 were considered statistically significant. Detailed methods, downloadable risk calculators, and illustrative case studies can be found in the appendix.
Results

Clinical-genetic score and prediction of cognitive decline in the discovery population. The proportional variance in the cognitive risk scores accounted for by the model as a whole was 97.4%. Each of the seven predictors included into the model significantly contributed to the information content of the clinical-genetic score. Age at PD onset was responsible for 56.5% of the variance, followed by MMSE at enrollment (7.7%), years of education (5.4%), MDS-UPDRS part III score at enrollment (4.7%), gender (2.6%), depression at enrollment (1.9%), and GBA carrier status (1.5%). Our clinical-genetic score showed high accuracy (quantified by AUC estimates) for predicting, whether a patient will develop global cognitive impairment within ten years from disease onset. In the discovery population, the AUC was 0.863 (95% CI 0.821-0.901; figure 2A); with a specificity of 0.717 (95%CI 0.652-0.775) and a sensitivity of 0.865 (95%CI 0.802-0.918) at the optimal cutoff (0.196). Patients with cognitive risk scores in the highest (fourth) quartile had a dramatically increased hazard ratio (HR) for global cognitive impairment of 21.6 (95% CI, 10.9 - 42.9) compared to those in the lowest risk quartile (the reference quartile; p < 0.0001, table 2). Kaplan-Meier survival curves of subjects in the highest and lowest risk quartiles, respectively (figure 2C), revealed that 95.8% (95% CI 92.7%-99.1%) of patients in the lowest quartile of risk scores survived for ten years without global cognitive impairment in contrast to only 34.9% (95% CI 26.5%-46.2%) in the highest quartile (a 60.9% difference; p < 0.0001 log-rank test; figure 2C).

Prediction of cognitive decline in the validation population. Importantly, the cognitive risk score built in the discovery study (consisting of the seven predictors and \( \beta \) coefficients from the discovery study) was locked-in and applied “as is” to the new patients of the independent validation population. Similarly, the quartile ranges and the optimal cutoff identified in the discovery study were rigorously applied to the validation population. The predictive score was highly accurate in the validation population with an AUC of 0.854 (95% CI 0.779-0.913) (figure 2B). Specificity was 0.744 (95% CI 0.604-0.868) and sensitivity was 0.733 (95% CI 0.617-0.831) at the pre-set cutoff of a score of 0.196.
Adjusting for a 26.7% prevalence of Mild Cognitive Impairment in non-demented patients with PD patients yielded a negative predictive value of 0.884 (95% CI 0.818-0.923) with a positive predictive value of 0.510 (95% CI 0.400-0.639). Patients with risk scores in the highest (fourth) quartile had a substantially increased HR for global cognitive impairment of 18.4 (95% CI, 9.4 - 36.1) compared to those in the lowest risk quartile (table 2). Kaplan-Meier survival curves of subjects in the highest and lowest quartile of risk scores, respectively, in the validation population are shown in figure 2D. 96.3% (95% CI 94.1% - 98.6%) of patients in the lowest quartile of risk scores survived for ten years without global cognitive impairment while only 27.4% (95% CI 12.6%-59.8%) of patients in the highest quartile of risk scores survived for ten years without global cognitive impairment in the validation population (a 68.9% difference; p < 0.0001 log-rank test; figure 2D).

**Prediction of dementia.** Global cognitive impairment is not dementia, as dementia is characterized as a loss of cognitive ability severe enough to interfere with normal activities of daily living. We tested how the cognitive risk score performs in predicting risk of dementia in individuals with PD without global cognitive impairment at enrollment. To avoid issues of circularity, we conservatively tested dementia prediction in the independent validation population that was not used to build the predictive score. 1,122 patients with 19,081 longitudinal study visits were available for this analysis. Cohort-specific definitions of a clinical diagnosis of PD dementia (PDD) were employed as described in the Methods section. The AUC for predicting dementia within ten years from onset was 0.877 (95% CI 0.788-0.943) --- even higher than for global cognitive decline (figure 3). At the cutoff of 0.196, dementia was predicted with a sensitivity of 0.861 (95% CI 0.716-0.944) and specificity of 0.721 (95% CI 0.594-0.841). The negative predictive values for dementia ranged from 0.920 (95% 0.877-0.954) to 0.941 (95% CI 0.919 - 0.961) based on systematic estimates of prevalence of dementia amongst patients with PD ranging from 31.1% (high quality studies) to 24.5% (all studies). Patients with risk scores in the highest (fourth) quartile had a substantially increased HR for dementia of 21.9 (95% CI, 6.5 - 73.1) compared to those scoring in the lowest quartile (table 3). 98.9 (95% CI 97.6% -
99.9%) of patients in the lowest quartile of risk scores survived for ten years without dementia while only 48.3% (95% CI 21·3%-62.8%) of patients in the highest quartile of risk scores survived for ten years without dementia (a 50.6% difference; p < 0.0001 log-rank test).

**Stable prediction accuracy in 10,000 re-sampled training and test sets.** A stable classifier will achieve a consistently high prediction accuracy independent of which patients are arbitrarily assigned to the discovery or validation sets. To test the stability of the predictive score we rebuilt and retested the score in 10,000 training and test sets randomly generated from the entire study population. In each iteration the entire population of patients was randomly split into a training and a test set (with sample sizes equal to the sample sizes of the discovery and validation sets used in the original analysis). In each iteration, we repeated the original analysis procedure starting with rebuilding the cognitive risk score *ab initio* in the training set from the eight variables qualifying for possible inclusion (including HY stage) and using backward stepwise pruning based on the Akaike information criterion. Each rebuilt score was then applied to the corresponding test sets. In 10,000 iterations, age at onset, enrollment MMSE score, and years of education remained in the model after stepwise pruning in 100% of iterations, enrollment MDS-UPDRS III in 98.30%, GBA carrier status in 91.79%, depression in 90.61%, and gender in 78.52% (figure 4A). HY stage (which did not make it into our clinical-genetic score) was added to the model in 34.86% of iterations. Across the 10,000 re-sampled test sets, the mean AUC was 0.833 (95% CI, 0.785-0.876) consistent with stable performance. Moreover, the score also stably and accurately predicted dementia across the 10,000 re-sampled training and test sets with an average training AUC of 0.879 (95% CI 0.837-0.916) and an average testing AUC of 0.872 (95% CI 0.817-0.920) (figure 4B).

**Prediction of longitudinal trajectories in Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA) scores.** To evaluate longitudinal trajectories of serial MMSE scores in the patients with high (> 0.196) vs. low enrollment cognitive risk scores (≤ 0.196) at enrollment, we performed a generalized mixed random and fixed effects longitudinal meta-analysis adjusting for
disease duration at enrollment. We conservatively conducted these analyses in the validation population that was not used to build the risk score. PD patients with high enrollment risk scores had a significantly more rapid longitudinal decline in MMSE scores over time with \( p < 0.0001 \) compared to the patients with low enrollment risk scores (figure 5A). Furthermore, the Montreal Cognitive Assessment (MoCA) test may be more sensitive than the MMSE for detecting cognitive change in patients with PD\textsuperscript{23}. We thus analyzed the longitudinal trajectories of MoCA scores in PPMI and PreCEPT, two of the validation cohorts, which have included this scale into their assessment battery. Patients with high risk scores at enrollment had a much steeper decline in MoCA scores over time compared to patients with low risk scores with \( p < 0.0001 \) (figure 5B).

**Power analysis for a hypothetical clinical trial enriched for patients with high cognitive risk scores.** We performed a power analysis to estimate sample size requirements for a personalized, three-year clinical trial of a hypothetical drug designed to halt cognitive decline (as measured by serial MoCA or MMSE, respectively) in a targeted trial of patients predicted to be at high risk of cognitive decline based on enrollment cognitive risk scores at or above the cutoff of 0.196. Sample sizes of 137 (152) per placebo and 137 (152) per drug group were sufficient in order to yield 80% power for serial MoCA (or MMSE assessments). By contrast, if instead unselected patients with PD were enrolled to test the same experimental drug (over the same time period, assuming the same \( \alpha \), same standard deviation, and same test-retest correlations), 801 (802) patients would need be enrolled for each of the active treatment and placebo arms to achieve 80% power for serial MoCA (or MMSE assessments) (figure 5C). Detailed methods as well as two illustrative case studies are shown in the appendix.

Medications inhibiting acetylcholine esterase activity (AChE) can be used to enhance cognitive function in patients with PD and could conceivably inflate MMSE scores. However, we found no statistically significant influence of AChE inhibitors (rivastigmine, donepezil and galantamine) on MMSE scores in the three cohorts with pertinent medication information (PPMI, PDBP, HBS), neither at enrollment nor during longitudinal follow-up.
For longitudinal analyses, examining the performance and stability of the prediction accuracy for various time frames (not just the ten-year time frame) using time-dependent ROC curves is of interest. For our score, the time-dependent prediction accuracy (as measured by the incident/dynamic average iAUC\textsuperscript{35}) was stable at various time points (from 1 to 11 years from disease onset; appendix figure 4). It somewhat degraded during year 12, likely due to the relatively low number of patients who completed 12 years of follow-up.

Collectively, the clinical-genetic cognitive risk score was robustly associated with both binary and continuous longitudinal cognitive outcomes, including global cognitive impairment, level 1 dementia, and decline in MMSE and MoCA scores over time.

**A clinical variables-only version of the risk score can be used in settings, where GBA genotyping is not easily obtained, while the clinical-genetic score provides superior prediction where GBA status is available.** Because GBA genotyping requires specific laboratory expertise and is not ubiquitously available to the clinician, we explored a variation of the score comprising the six clinical features only (without GBA). This clinical score was informative and predicted global cognitive decline with high accuracy in both the discovery population with an AUC of 0·859 (95% CI, 0·816 - 0·898) and the validation population with an AUC of 0·827 (95% CI, 0·741 - 0·893) (appendix figure 5A,B). Similar to the clinical-genetic score, in 10,000 randomly resampled training and testing subsets, the clinical variables-only score was a stable predictor of both cognitive impairment and dementia (appendix figure 5D). The negative predictive value for dementia in the test sets ranged from 0·875 (95% CI, 0·812-0·926) to 0·906 (95% C.I., 0·872-0·937) based on estimates of prevalence of dementia amongst patients with PD ranging from 31·1% (high quality studies)\textsuperscript{34} to 24·5% (all studies)\textsuperscript{34}. In a head-to-head comparison with the clinical-genetic score, however, the prediction accuracy of the clinical-only score significantly underperformed compared to that of the clinical-genetic score with p < 0·0001 (appendix figure 5E). Thus, the informative clinical-only score allows facile implementation in
settings where \textit{GBA} status is not easily obtained, while the clinical-genetic score can provide superior prediction where \textit{GBA} status is available.
Discussion

We have developed a clinical-genetic risk score that is an informative predictor of global cognitive impairment and dementia in patients with PD as evidenced using discovery and validation populations consisting of 2,830 patients and 25,069 longitudinal clinical assessments. The area under the curve for accurately predicting global cognitive impairment within ten years of disease onset was greater than 85% in both the discovery and validation populations (with 95% CIs of 0.821-0.902 and 0.779 - 0.913, respectively). The AUC for predicting the development of dementia within ten years from disease onset was 87.7% (95% CI, 0.788 - 0.943) in the validation population. The cognitive risk score was associated with the binary outcomes of future cognitive impairment and dementia as well as continuous longitudinal measures such as a steeper decline in MMSE and MoCA scores tracked over time.

In addition to the clinical-genetic risk factors here evaluated, reduced levels of Aβ42 in cerebrospinal fluid have also been reported to be a predictor of dementia in patients with PD and this is supported by neuroimaging studies with Amyloid PET. Our cognitive risk score offers the advantage that it is non-invasive, without the risks associated with lumbar puncture and without the significant costs and restricted availability of PET imaging. The clinical variables-only version is portable and can be nearly universally implemented. The clinical-genetic version can be implemented in any setting with access to a certified gene testing lab.

The predictive algorithm we have developed has considerable strengths. It was built starting from a small set of variables each already individually and separately linked to cognitive decline or dementia in PD by prior evidence. This enhances the validity of the variables in the score. Consistent with previous evidence we confirmed the age at onset, male gender, baseline cognitive and motor function, as well as depression as statistically significant individual predictors of cognitive impairment adjusting for covariates (appendix figure 3). GBA mutation status conferred a 58% increased risk of cognitive impairment extending previous observations. However, our composite score as a whole is
more informative than the individual components. The parameters were winnowed down through machine learning driven by Akaike’s information criterion, which is designed to parsimoniously reduce the number of features in a model to only those carrying independent information. The predictor was built (as well as tested) in longitudinal cohorts, a superior study design compared to time-static, cross-sectional studies. The cohorts included vary in their design, recruitment, and assessments. Importantly, while PICNICS, CamPaIGN, and PROPARK are population-based cohorts designed to represent a community, other cohorts include the biomarkers studies HBS, PDBP, and PPMI; and clinical trial cohorts, DATATOP and PreCEPT. These cohorts are not representative of the PD patient population as a whole, however, they are similar to “typical” clinical trial populations in the US and the EU. Moreover, the fact that the score was highly stable and informative across these varying cohorts is a testament to its robustness and should allow for it to be used in other similar cohorts and most importantly, trial populations. Consistently, the cognitive risk score was informative in predicting multiple indicators of the construct of cognitive impairment.

The score includes clinical as well as protein-coding mutations (not simply tag SNPs) in the GBA gene. In future work we plan to weigh distinct types of GBA mutations included in the score according to their emerging differential contributions to the speed of cognitive progression in PD. Particularly mutations linked to neuropathic Gaucher’s disease associate with accelerated cognitive decline, but are found in just 1-4% of patients with PD. Moreover, a major ongoing effort in our consortium is to identify, validate, and fine map progression variants and to include them into future, improved versions of the risk score.

The score has the potential to facilitate clinical trials of experimental treatments designed to ameliorate or reduce the pace of cognitive decline. Therapeutic trials in PD are hampered by the slow and highly varied rate of progression of clinical endpoints. Because some participants with PD on placebo will experience minimal decline in cognition, it is difficult to demonstrate a therapeutic effect of the experimental therapeutic over a reasonable sample size and time course. The predictive score
represents a simple tool for stratifying and enriching the trial with patients most prone to more rapid cognitive decline, which can be taken as a surrogate marker of advancing pathology --- as such agents that arrest or slow down the cognitive decline leading to dementia are likely to be disease modifying. Our power analysis estimated that recruiting patients with high risk scores >0·196 into such a trial will reduce the required samples size by as much as 6-fold (figure 5C). Thus, our model should translate into more cost-effective trials, allow for “more shots on target”, and overall increase chances of successful drug trials. Indeed, there is very active interest in trials addressing cognitive decline in PD. According to the ClinicalTrials.gov database there are currently more than 100 trials registered exploring pharmacological or non-pharmacological interventions designed to improve cognition in PD. Moreover, potentially disease-modifying GBA-directed therapeutics are expected to enter clinical trials over the next months.

The utility of the cognitive risk score in clinical practice will require adaptation to the care setting and prospective evaluation. Our cognitive risk score yields substantial negative predictive values of 88·4% for cognitive impairment and 92·0% for dementia within ten years from disease onset. A low score could be reassuring for some patients and their families. It could help to allay worries and guide health and home planning decisions. On the other hand, a high risk score, while likely of great benefit for enriching a research trial population, has a limited positive predictive value for specific patient (in part due to the modest prevalence of cognitive impairment in the general PD population). Moreover, the absence of a specific treatment or proven risk factor modification raises difficult ethical questions, but will allow the family to plan more realistically for the future needs of the affected individual. All of this is not unique to PD as similar issues have been raised by ApoE4 testing in mild cognitive impairment41, and more recently, with clinical exome sequencing. The Framingham Cardiovascular Risk score (which inspired this work) includes cholesterol, smoking, and hypertension, which have effective interventions. For the cognitive risk score, it is as yet unknown, whether modification of any of the risk factors comprising the score will impact on cognitive outcome. Education for example is per
definition modifiable, but no ready made interventions have been delineated for PD. *GBA*-directed therapeutics are not available yet for PD, although much progress has been made in treating peripheral manifestations of Gaucher’s disease. As with any medical advance pushing beyond current practice paradigms, the appropriate medical and ethical framework for considering the cognitive risk score in practice settings will have to be carefully outlined by the stakeholders, including patients and clinicians. This conversation will evolve when disease-modifying medications (that could be used to delay the onset of dementia in patients with PD) emerge from clinical trials.

In the DATATOP and PreCEPT cohorts, DNA was collected several years after enrollment for a subset of participants\(^{17}\). Thus, they may underrepresent patients with more rapidly progressive disease, but it is unlikely that this would yield a spurious association between the cognitive risk score and cognitive decline. The Cochran's Q-test for heterogeneity of effects across cohorts indicated that any differences in disease progression between studies (due to sampling or selection effects) should not bias the test of interest. Moreover, we found no evidence that so-called memory enhancing medications or drop outs materially influenced the results of this study.

The frequency of global cognitive impairment (within ten years from disease onset) among patients with PD in the discovery and validation populations was highly consistent, 24.7\% and 26.0\%, respectively, based on Kaplan-Meier estimates. These estimates are also consistent with reported prevalence estimates, ranging from 18.9\%\(^{42}\) to 57.1\% for mild cognitive impairment\(^{43}\) and from 8.3\%\(^{44}\) to 41\%\(^{45}\) for dementia among patients with PD; with rigorous door-to-door surveys calculating a frequency of 16\%\(^{34}\). Furthermore, natural history studies have attempted to capture the frequency of cognitive impairment in PD, but due to major design differences, the range of estimates is rather wide, from 26\%\(^{2}\) to as high as 83\% among twenty-year survivors\(^{46}\). A definite view has not crystallized due to small sample sizes, variable follow-up lengths, and fundamental differences in the analytical methods used in each of the various studies.
Going forward, we hope that the accuracy of this score will be further improved and its applications extended. Major ongoing efforts in mapping the genome, epigenome, transcriptome, and other big data spaces of Parkinson’s should highlight and validate further clinical, genetic, and biological predictors in the near future. Such data can, in theory, be seamlessly integrated into the versatile risk assessment tool we have here developed.
### Table 1: Overview of study cohorts.

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>N (% male)</th>
<th>Age at Enrollment (years, SD)</th>
<th>Years of Education (years, SD)</th>
<th>Study Years (years, range)</th>
<th>GBA Mutation no. of subjects (%)</th>
<th>Mutations Screened</th>
<th>Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBS (USA)</td>
<td>556 (64.2%)</td>
<td>66-1 (9.8)</td>
<td>15-1 (1-9)</td>
<td>1.8 (0-8.0)</td>
<td>42 (7.6%)</td>
<td>Targeted Sequencing or N370S, E326K, T369M Genotyping</td>
<td>MMSE, H, UPDRS I-IV</td>
</tr>
<tr>
<td>DATATOP (USA, Canada)</td>
<td>437 (66.6%)</td>
<td>60-1 (9-0)</td>
<td>14-3 (3-4)</td>
<td>6-3 (0-7.8)</td>
<td>39 (8.9%)</td>
<td>Targeted Sequencing</td>
<td>MMSE, HY, UPDRS I-III</td>
</tr>
<tr>
<td>DIGPD (France)</td>
<td>409 (57.0%)</td>
<td>69-4 (9-9)</td>
<td>11-5 (3-3)</td>
<td>6-9 (0-12.8)</td>
<td>15 (13.2%)</td>
<td>Sanger Sequencing</td>
<td>MMSE, HY, MDS-UPDRS I-IV</td>
</tr>
<tr>
<td>CamPaIGN (UK)</td>
<td>129 (65.9%)</td>
<td>66-1 (9-2)</td>
<td>12-1 (2-9)</td>
<td>3-1 (0-6-7)</td>
<td>8 (6.2%)</td>
<td>Sanger Sequencing</td>
<td>MMSE, HY, MDS-UPDRS I-IV</td>
</tr>
<tr>
<td>PICNICS (UK)</td>
<td>327 (66.1%)</td>
<td>59-6 (10-7)</td>
<td>12-0 (4-2)</td>
<td>4-6 (0-6-3)</td>
<td>53 (16.2%)</td>
<td>Targeted Sequencing or Whole Exome Sequencing</td>
<td>MMSE, HY, SPES/SCOPA-motor scale</td>
</tr>
<tr>
<td>PreCEPT (USA, Canada)</td>
<td>332 (66.6%)</td>
<td>60-5 (9-4)</td>
<td>16-1 (3-2)</td>
<td>6-7 (0-8-6)</td>
<td>32 (9.6%)</td>
<td>Targeted Sequencing</td>
<td>MMSE, HY, UPDRS I-III</td>
</tr>
<tr>
<td>PDBP (USA)</td>
<td>499 (61.9%)</td>
<td>64-9 (9.2)</td>
<td>15-6 (2-7)</td>
<td>0-7 (0-3-1)</td>
<td>46 (9.2%)</td>
<td>NeuroX Genotyping</td>
<td>MoCA, HY, MDS-UPDRS I-IV</td>
</tr>
<tr>
<td>PPMI (USA, Europe)</td>
<td>396 (64.9%)</td>
<td>61-6 (9.7)</td>
<td>15-5 (3-0)</td>
<td>3-2 (0-5-1)</td>
<td>41 (10.4%)</td>
<td>Whole Exome Sequencing</td>
<td>MoCA, HY, MDS-UPDRS I-IV</td>
</tr>
</tbody>
</table>

The studies included are the Harvard Biomarkers Study (HBS)\(^{14,15}\); Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP)\(^{16}\); Parkinson Research Examination of CEP-1347 Trial/A Longitudinal Follow-up of the PRECEPT Study Cohort (PreCEPT/PostCEPT)\(^{17}\); Cambridgeshire Parkinson’s Incidence from GP to Neurologist (CamPaIGN)\(^{8,10,47}\), Parkinsonism: Incidence, Cognition and Non-motor heterogeneity in Cambridgeshire (PICNICS)\(^{19}\), Drug Interaction with Genes in PD (DIGPD)\(^{48}\), PROfiling PARKinson’s disease (PROPARK) study\(^{49}\), Parkinson’s Disease Biomarkers Program (PDBP)\(^{21}\) and Parkinson’s Progression Markers Initiative (PPMI)\(^{20}\). HBS was examined in two parts: for 173 individuals targeted sequencing of the entire GBA locus was performed; for 383 participants three GBA mutations were genotyped. UPDRS subscale II, III scores were converted into MDS-UPDRS II, III scores according to the conversion formula developed by Goetz et al.\(^{27}\). The SPES/SCOPA-motor scale was converted into MDS-UPDRS III score according to Ref.\(^{28}\). The MoCA from PDBP and PPMI was converted into MMSE score according to Ref.\(^{24}\).
Table 2: Patients with high cognitive risk scores have a substantially increased hazard ratio for global cognitive impairment compared to those with scores in the lowest quartile.

<table>
<thead>
<tr>
<th></th>
<th>Quartile</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>0 to &lt;0.0954</td>
<td>0.0954 to &lt;0.1958</td>
<td>0.1958 to &lt;0.3789</td>
<td>0.3789 to ≤1</td>
</tr>
<tr>
<td><strong>Discovery population</strong></td>
<td>Parkinson’s disease (N)</td>
<td>338</td>
<td>337</td>
<td>337</td>
</tr>
<tr>
<td>Cognitive risk scores (range)</td>
<td>0.0076-0.0954</td>
<td>0.0954-0.1955</td>
<td>0.1951-0.3789</td>
<td>0.37891-0.0000</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>2.7 (1.2-5.9)</td>
<td>6.0 (2.9-12.5)</td>
<td>21.6 (10.9-42.9)</td>
</tr>
<tr>
<td>p value</td>
<td>0.013</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Validation population</strong></td>
<td>Parkinson’s disease (N)</td>
<td>375</td>
<td>320</td>
<td>281</td>
</tr>
<tr>
<td>Cognitive risk scores (range)</td>
<td>0.0089-0.0951</td>
<td>0.0955-0.1951</td>
<td>0.1951-0.3776</td>
<td>0.3809-0.9729</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>3.2 (1.6-6.7)</td>
<td>8.3 (4.2-16.2)</td>
<td>18.4 (9.4-36.1)</td>
</tr>
<tr>
<td>p value</td>
<td>0.0015</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Hazard ratio (HR) and confidence intervals (CI) were calculated using Cox regression models.*
Table 3: Patients with high cognitive risk scores have an increased hazard ratio for dementia compared to those with scores in the lowest quartile.

<table>
<thead>
<tr>
<th>Quartile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to &lt;0·0954</td>
<td>0·0954 to &lt;0·1958</td>
<td>0·1958 to &lt;0·3789</td>
<td>0·3789 to ≤1</td>
</tr>
</tbody>
</table>

**Validation population**

<table>
<thead>
<tr>
<th>Parkinson’s disease (N)</th>
<th>372</th>
<th>317</th>
<th>279</th>
<th>154</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive risk scores (range)</td>
<td>0·0089-0·0951</td>
<td>0·0955-0·1951</td>
<td>0·1959-0·3376</td>
<td>0·3809-0·9729</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1</td>
<td>3·1 (0·8-11·9)</td>
<td>8·8 (2·6-30·0)</td>
<td>21·9 (6·5-73·1)</td>
</tr>
<tr>
<td>p value</td>
<td>0·091</td>
<td>0·0005</td>
<td>&lt;0·0001</td>
<td></td>
</tr>
</tbody>
</table>

*Hazard ratio (HR) and confidence intervals (CI) were calculated using Cox regression models.
Figure legends

Figure 1: Flow chart of study design.

HBS=Harvard Biomarkers Study, DATATOP=Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; PreCEPT=Parkinson Research Examination of CEP-1347 Trial/A Longitudinal Follow-up of the PRECEPT Study Cohort; CamPalGN=Cambridgeshire Parkinson’s Incidence from GP to Neurologist; PICNICS=Parkinsonism Incidence, Cognition and Non-motor heterogeneity in Cambridgeshire; DIGPD=Drug Interaction with Genes in PD; PROPARK=PROfiling PARKinson’s disease study; PDBP=Parkinson’s Disease Biomarkers Program; PPMI=Parkinson’s Progression Marker Initiative (PPMI). AUC=area under the curve.

Figure 2: Prediction of global cognitive impairment.

(A,B) The clinical-genetic score showed high accuracy (quantified by AUC estimates) for predicting, whether a patient will develop global cognitive impairment within ten years from disease onset in the discovery and the validation populations. (A) In the discovery population, 1,350 patients with PD and MMSE > 25 at baseline were followed with 5,165 visits for up to 12.8 (median, 2.8) years. (B) In the independent validation population, 1,132 patients with PD and MMSE > 25 at baseline were followed with 19,127 visits for up to 8.6 (median, 6.5) years. Sensitivity and specificity at the cutoff score of 0.196 (the optimal cutoff identified in the discovery population) are shown for both populations. (C,D) Covariate-adjusted Kaplan-Meier curves for survival free of global cognitive impairment. (C) In the discovery population, 95.8% (95% CI 92.7%-99.1%) of patients with PD in the lowest (first) quartile of scores survived for ten years without global cognitive impairment compared to 34.9% (95% CI 26.5%-46.2%) of those scoring in the highest (fourth) quartile. (D) In the validation population, 96.3% (95% CI 94.1% - 98.6%) of patients in the lowest quartile of scores survived for ten years without global cognitive impairment compared to 27.4% (95% CI 12.6%-59.8%) of patients scoring in the highest quartile scores. To ensure consistency across studies, an MMSE score with the cutoff of ≤ 25
was taken as an indicator of significant global cognitive impairment as recommended by the International Parkinson and Movement Disorders Society (MDS) Task Force.  

**Figure 3: Prediction of dementia.**

Beyond cognitive decline, the clinical-genetic score predicts risk of dementia in individuals with PD in validation population. 1,122 patients (without global cognitive impairment at baseline) with 19,081 longitudinal study visits were available for this analysis. The accuracy of the clinical-genetic score for predicting dementia was high with an AUC of 0.877 (95% CI 0.788-0.943). Sensitivity and specificity for predicting dementia at the cutoff (0.196; as predefined in the discovery population based on Figure 2A).

**Figure 4: Stability of the score.**

To test the stability of the predictive score, we rebuilt and retested the score model in 10,000 randomly generated training and test subsets. In each iteration the entire population of patients was randomly split into a training and a test set pair. In each iteration, we rebuilt the predictive score ab initio in the training set, eliminated predictor variables based on the Akaike information criterion, and used it to predict global cognitive decline in the corresponding test set. (A) In 10,000 iterations, age at onset, enrollment MMSE score, and years of education remained in the score model after stepwise pruning in 100% of iterations, enrollment MDS-UPDRS III in 98.30%, GBA carrier status in 91.79%, depression in 90.61%, and gender in 78.52%. HY stage (which did not make it into our clinical-genetic score) was included in 34.86% of iterations. (B) Across the 10,000 re-sampled test sets, the mean AUC was 0.833 (95% CI, 0.785-0.876) for predicting global cognitive impairment and, even higher, 0.872 (95% CI, 0.817-0.929) for dementia. These data indicate stable variable selection and score performance.
Figure 5: Prediction of longitudinal trajectories of Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA) scores.

(A) To evaluate longitudinal trajectories of serial MMSE scores in the patients with high (> 0.196) vs. low enrollment cognitive risk scores (≤ 0.196) at enrollment, we performed a generalized mixed random and fixed effects longitudinal meta-analysis adjusting for disease duration at enrollment. These analyses were conservatively restricted to the validation population. PD patients with high enrollment risk scores had a significantly more rapid longitudinal decline in MMSE scores over time with p < 0.0001 compared to the patients with low enrollment risk scores. Illustrative mean MMSE scores across time predicted from the estimated fixed effect parameters in the mixed random and fixed effects model analysis are shown for Parkinson’s patients with low clinical-genetic risk scores (blue) and those with high scores at enrollment (red). Patients with high scores (measured at enrollment) had a more rapid decline in cognitive function (as measured by serial MMSE) compared to those with low scores with p < 0.0001 adjusting for duration of PD at enrollment. Illustrative MMSE values for a mean disease duration at enrollment are shown. CRS=global cognitive impairment risk score.

(B) Illustrative mean MoCA scores across time predicted from the estimated fixed effect parameters in the mixed random and fixed effects model analysis in Parkinson’s patients with low clinical-genetic risk scores (≤ 0.196; blue) and those with high scores at enrollment (> 0.196; red). Patients with high clinical-genetic scores at enrollment had a more rapid decline in MoCA scores compared to those with low scores with p < 0.0001 adjusting for disease duration at enrollment. The analysis of MoCA scores was restricted to PPMI and PreCEPT, the two validation cohorts, which had included this scale into their assessment battery. MoCA scores were not collected in DATATOP. Illustrative MoCA values for a mean disease duration at enrollment are shown.

(C) Improved power for clinical trials in populations with elevated clinical-genetic scores. Enriching populations based on the clinical-genetic score >0.196 for trials of therapeutics designed to address cognitive impairment in PD will reduce the required sample size by 6-fold compared to an equally
powered trial without enrichment. In this hypothetical power estimate, required sample sizes were 137 for the placebo and 137 for the experimental treatment group in order to achieve 80% power. A traditional clinical trial of any PD patients (not enriched based on the clinical-genetic score) would require 801 patients per group to achieve the same power (over the same three-year time period, assuming same $\alpha$, standard deviation, and test-retest correlations). $\alpha = 0.05$ for detecting the difference in trajectories for MoCA across time for the placebo vs. the treatment group (group $\times$ time interaction), MoCA scores predicted by our study were used.
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PreCEPT/PostCEPT Study. PreCEPT/PostCEPT Steering Committee: University of Rochester: David Oakes, Ira Shoulson; University of Toronto: Anthony E. Lang; Parlinson’s Institute: Caroline Tanner; Institute for Neurodegenerative Disorders: Kenneth Marek; Voyager Therapeutics: Bernard Ravina; Brigham and Women’s Hospital: Clemens Scherzer, University of Ottawa: Michael Schlossmacher, Avid Radiopharmaceuticals: Andrew Siderowf, We thank the Parkinson Study Group (PSG) PreCEPT/PostCEPT investigators for the acquisition of high-quality clinical data, careful follow up of study subjects and collection of blood samples.

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Author contributions
GL integrated data, performed statistical analysis, wrote the manuscript, reviewed and edited manuscript; JJL interpreted data, wrote the statistical analysis section, reviewed and edited manuscript; JCC, AB, FC, designed, enrolled study participants in DIGPD study, reviewed and edited manuscript; AE collected data in DIGPD study, reviewed and edited manuscript; BB integrated data, provided funding, reviewed and edited manuscript; ZL, KP processed biospecimens and performed quality-control, reviewed and edited manuscript; DF, KB performed patient assessments, obtained and processed biospecimens of HBS; reviewed and edited manuscript; IEJ processed data in the PROPARK study, reviewed and edited manuscript; AT-L assisted with overseeing organization and execution of HBS, reviewed and edited manuscript; SW-R contributed to GBA sequencing in CamPAIGN and PICNICS study, reviewed and edited manuscript; SE processed data in PreCEPT/PostCEPT study, reviewed and edited manuscript; CMT served on the Steering Committee of PPMI, reviewed and edited manuscript; IS was principal investigator of DATATOP, and reviewed and edited manuscript; AEL served on the Steering Committees for the DATATOP and PreCEPT
studies, reviewed and edited manuscript; GM processed biospecimens of the DIGPD cohort for GBA sequencing, reviewed and edited manuscript; BR designed and served on the Steering Committee of PPMI, reviewed and edited manuscript; PH; JJvH, JM designed and directed PROPARK study, reviewed and edited manuscript; RAB, CHW-G designed, and the recruitment and assessment of patients and DNA sample collection and preparation in CamPAIGN and PICNICS study, reviewed and edited manuscript. CRS conceived, directed, supervised, and interpreted the study, wrote the manuscript, provided funding, designed and directed HBS, and designed and served on their Steering Committees of PPMI and PDBP.

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