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Systematic Review of Race/Ethnicity in Parkinson's Disease

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SYSTEMATIC REVIEW OF RACE/ETHNICITY IN PARKINSON'S DISEASE

By

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ABSTRACT

A Systematic Review of Race/Ethnicity in Parkinson's Disease

(Under the Direction of Dr. Toshikazu Ikuta)

The goal of this study was to examine race/ethnicity with an emphasis on African Ancestry in Parkinson's Disease (PD) through a systematic review. Out of 448 scholarly articles that were originally extracted from the search, 445 were excluded due to their irrelevance regarding race/ethnicity and African ancestry in PD. Three scholarly articles were obtained through a PubMed/MEDLINE search for the review. Amongst the three sources that were chosen, there were more than 450,000 participants with PD that ranged in ages 40-65+; each case of PD within these studies were reported from 1993-2005. The varying races/ethnicities of White/non-Hispanic White, Black/African American, Asian, and Hispanic/Latino were included in these three studies. During the systematic review of the studies, the first study concluded that the PD rate per 100,00 was highest in Whites with 2,168.18, Asians with 1,138.56, and lowest in Blacks with 1,036.41. In the second article, Whites also had the highest rate of PD with 54 cases per 100,000, Latinos following with 40, and lastly, African Americans with 23. In the third and final study, contrastingly, Hispanics had the highest incidence rate per 100,000 of 16.6 while non-Hispanic White rates followed with 13.6. In the same study, Asians had a rate of 11.3 per 100,000, and lastly, Blacks with a rate of 10.2. Based on the systematic review of the three sources, PD varies by race/ethnicity, and it is less common in Blacks/African Americans. Further research and closer examinations of PD regarding the influences of biological and social factors will enhance future discoveries of Parkinson's Disease.

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Introduction

Parkinson's disease is a chronic, neurodegenerative disease common in older individuals with a median age at onset of 60 years old [1]. Parkinson's Disease causes degeneration of the central nervous system, particularly the dopaminergic neurons in the midbrain substantia nigra. This part of the brain stem contains dopamine responsible for reward, motivation, memory, attention, and regulation of bodily movements. Once these cells die or become impaired, they produce less dopamine which affects all of the aforementioned responsibilities and especially results in movement problems. These movement problems include uncontrollable shaking or tremors, stiffness, bradykinesia, or slowness of movement, loss of automatic movement, and difficulty with walking, balance, and coordination. Because Parkinson's Disease impacts neurons in the brain, symptoms associated with speech and cognition, such as speech or writing changes are also likely to occur. Based on the Hoehn and Yahr rating scale to classify severity of Parkinson's Disease symptoms, there are five stages of this disease. The first stage consists of a mild form. In this stage, only mild symptoms, such as unilateral tremors and changes in posture, walking, and facial expressions, occur, but no overall interference with daily activities. In stage two, symptoms begin to progress. Tremors and other movement problems become bilateral, and daily tasks become more difficult and lengthy. Mid-stage is the third stage that consists of increased balance problems, so more accidental falls occur; activities such as dressing and eating become significantly impaired. The fourth stage embodies decreased independence; a walker may be needed to aid in walking and standing, and help is required for daily activities. The fifth stage, the final stage, is the most advanced stage of Parkinson's Disease. Due to stiffness in legs during this stage, a wheelchair is required; aid with all daily activities is also required. Along

with physical impairments, a person with stage five Parkinson's Disease may also experience hallucinations and delusions. Since PD is a progressive disorder that continues to worsen overtime, there is not an overall cure for the disease, but there are forms of treatments, such as physical rehabilitation, surgical procedures, and oral medications, that may help with some symptoms.

The exact pathophysiology of Parkinson's Disease remains unknown [2]. This puzzling presumption can relate to numerous factors that hinder the research of Parkinson's Disease, such as variation of survival rates since it is a disease of the elderly, healthcare disparities within the African American community, or the lack of diversity amongst previous studies of Parkinson's Disease [3, 4]. While researchers have shown the influence sex has on Parkinson's Disease, concluding that it is more common in men than women, studies pertaining to race/ethnicity remain conflicting between researchers. Many believe that the cause of PD is likely connected to both race/ethnicity and genetic influences of mutations and polymorphisms. In addition to the aforementioned factors, healthcare disparities in the treatment of African Americans or individuals with African ancestry have also heightened the interest of researchers as another subcomponent in the influences of race/ethnicity.

Race/Ethnicity in Parkinson's Disease

While there are no explicit studies concluding that the cause of Parkinson's Disease is directly related to race/ethnicity, there have been numerous studies showing that these factors contribute to the influence of Parkinson's Disease. In one investigation of a total of 20 case-control studies, 8 studies of Caucasian population and 12 studies of Asian, with 6,354 subjects, researchers Liu, Wang, and Zhang concluded that both races/ethnicities within this

study contained a high risk of Parkinson's Disease due to a common polymorphism [5]. According to this same source, the incidence of Parkinson's Disease is high within Caucasians and Asians due to a shared common pattern that could possibly be a direct linkage to their race/ethnicity. The authors explicitly explained that "significant relationships with Parkinson's Disease risk in these populations were observed" [5]. Because this study has a limitation of only comparing two races/ethnicities, further research pertaining to this matter was conducted. A similar study compared Young Onset of Parkinson's Disease (YOPD) in the United States, similar to Older Onset of Parkinson's Disease (OOPD) with the exception that YOPD occurs in ages 21-49 [6]. In this study a diverse range of ethnic groups or races were included; the race/ethnicity of participants were either White, Black, Hispanic, or Asian. Of the 14,354 participants identified with Young Onset of Parkinson's Disease, white men and women comprised the majority of cases with a combined percentage of 83.6%. The researchers of this study, Willis, Schootman, Kung, and Racette concluded that "YOPD is most common among white males" further alluding to the notion that race/ethnicity influences Parkinson's Disease. While many of these studies are regarding race/ethnicity, varying genetic influences are commonly included in the forenamed articles due to correlations between the two factors.

Genetic Influences

Along with the influences of race/ethnicity, genetics also play a vital role in research regarding the pathophysiology of Parkinson's Disease. The studies include a wide variety of genes and polymorphisms, such as *SNCA* rs356220 studied amongst Caucasians and Asians and *LRRK2* Gly2385 Arg studied in Malaysians, Indians, Singaporeans, Chinese, and Taiwanese [7, 8]. In a specific study regarding individuals of European, West Asian, East Asian, Hispanic, and

Mixed descent, researchers conducted a meta-analysis of 50 studies consisting of 20,267 Parkinson's Disease patients and 24,807 controls [9]. Zhang, et al. (2018) analyzed the impacts of *GBA* mutations on Parkinson's Disease which has a distinct genetic feature of "ethnic heterogeneity in different regions," meaning these mutations appear across a mixture of ethnic groups [9]. Within the aforementioned descents researchers found that eleven out of eighteen variants increased the risk of Parkinson's Disease in the total populations [9]. More specifically, Zhang, et al. (2018) concluded that the variants L444P, N370S, H255Q, D409H, RecNicI, E326K increased the risk of PD in European/West Asians while L444P increased the risk of PD in Hispanics, East Asians and Mixed populations [9]. Due to this discovery of a correlation between *GBA* mutations and increased risk of PD in a diverse population, the researchers gathered that this relationship could be "essential in genetic screening in PD patients from different populations with different ethnic backgrounds" [9]. Furthermore, experimenters of a similar study explained that even though Parkinson's Disease usually occurs sporadically in patients, there is still a "strong genetic basis for this disease" due to approximately 10%-15% of PD cases exhibiting a family history of the disease [5]. To justify this notion, researchers of this source Liu, Wang, & Zhang (2014) analyzed Monoamine Oxidase B (MAOB) A644G polymorphism, enzymes involved in metabolism regulation in neurotransmitters such as dopamine; due to biological properties of MAOB experimenters inferred that this variant could be utilized as a "disease marker of PD" [5]. Using the methodology of a meta-analysis, researchers yielded results that exemplified a significant relationship between MAOB A644G polymorphism and PD risk. The correlation between the influences of genetics and race/ethnicity

on PD are two of the more commonly studied topics, whereas studies on healthcare disparities are limited.

Influences of Healthcare Disparities

Based on empirical research of scholarly articles, there have been fewer analyses of healthcare disparities in Parkinson's Disease and African ancestry compared to any other race/ethnicity especially Caucasians/Whites/non-Hispanic Whites. This is exemplified in a PD study that consisted of varying races and ethnicities, including Europeans, East and West Asians, and Hispanics. This study sought to explore the relationship between *GBA* variants and Parkinson's Disease; the researchers of this study explained how they failed to conduct a quantitative analysis in Africa due to an insufficient amount of original studies [9]. Because the impacts of healthcare disparities especially amongst individuals of African descent with PD have limited examinations, researchers Hemming, Gruber-Baldini, Anderson, et al (2011) conducted a study to deduce further information pertaining to this topic. In this study of analyzing racial and socioeconomic disparities in PD of 1,090 participants with parkinsonism, researchers yielded profound results. The outcomes of this study reported that African Americans had greater disability and disease severity than their White counterparts, and African Americans were reported to be diagnosed half as likely as having PD as Whites [4]. This suggests that "Parkinson's Disease is underdiagnosed in African Americans" [4]. This idea relates to the notion that the incidence ratio, or newly diagnosed cases of PD, is higher in Blacks, but the prevalence ratio, or *actual number* of PD cases, is higher in Whites [2]. In addition to fewer reports of PD, African Americans also experience disproportionate forms of distributions in treatment for Parkinson's Disease. According to the results from Hemming, Gruber-Baldini,

Anderson, et al (2011), African Americans were four times less likely to receive treatment for PD while Whites were twice as likely to receive medications for Parkinson's Disease [4]. In a study comparing Parkinson's Disease pain in Indian versus Caucasian participants, it was concluded that PD Caucasians were eighty times more likely to report aching pain and dull pain by 108 times more compared to PD Indians [10]. There are an enumerating amount of factors that could contribute to these conclusions, but for the purpose of relevancy to healthcare disparities these results exemplify that there are more common reports of pain in PD Caucasians which possibly yields higher treatment probabilities. Hemming, Gruber-Baldini, Anderson, et al (2011) further noted in their study that African Americans were prescribed fewer antiparkinsonian medications, yet the administration of antipsychotic medications were higher in this same race [4]. In a study analyzing life expectancy of PD patients in the United States, researchers found that out of 138,728 participants with Parkinson's Disease, African Americans had the highest frequency of dementia at 78.2% with the highest crude death rate of 66.4% [11]. This provides an indirect correlation between higher administration of antipsychotics and increased dementia and death rates in African Americans. According to Weintraub, Chen, Ignacio, et al. (2011), diagnosis of Parkinson's Disease and dementia were associated with antipsychotic drug use and worsening of parkinsonism [12]. Overall, evidence of healthcare disparities based on socioeconomic status and race is growing rapidly. Further research regarding this matter is pertinent to additional discoveries of influences on Parkinson's Disease.

As previously mentioned, the exact influence that race/ethnicity has on Parkinson's Disease remains controversial due to an enumerating amount of reasons, ranging from healthcare disparities to studies with a lack of diversity and large numbers of participants [4, 13]. With this

research, I plan to discover whether race/ethnicity has any influence on Parkinson's disease and its contributions to the pathophysiology of PD. I also anticipate discovering if African Americans are more or less likely to suffer from Parkinson's Disease compared to their nonblack counterparts.

To address these aforementioned issues, we conducted a systematic review to obtain a more conclusive understanding of race/ethnicity and incidence of Parkinson's Disease. The outcomes of the systematic review will be described in the results section. For a better understanding, interpretations of the retrieved data will then be incorporated into the discussion section. Lastly, recommendations for implementations of better research methods concerning race/ethnicity specifically amongst African ancestry in Parkinson's Disease will be discussed in the conclusion.

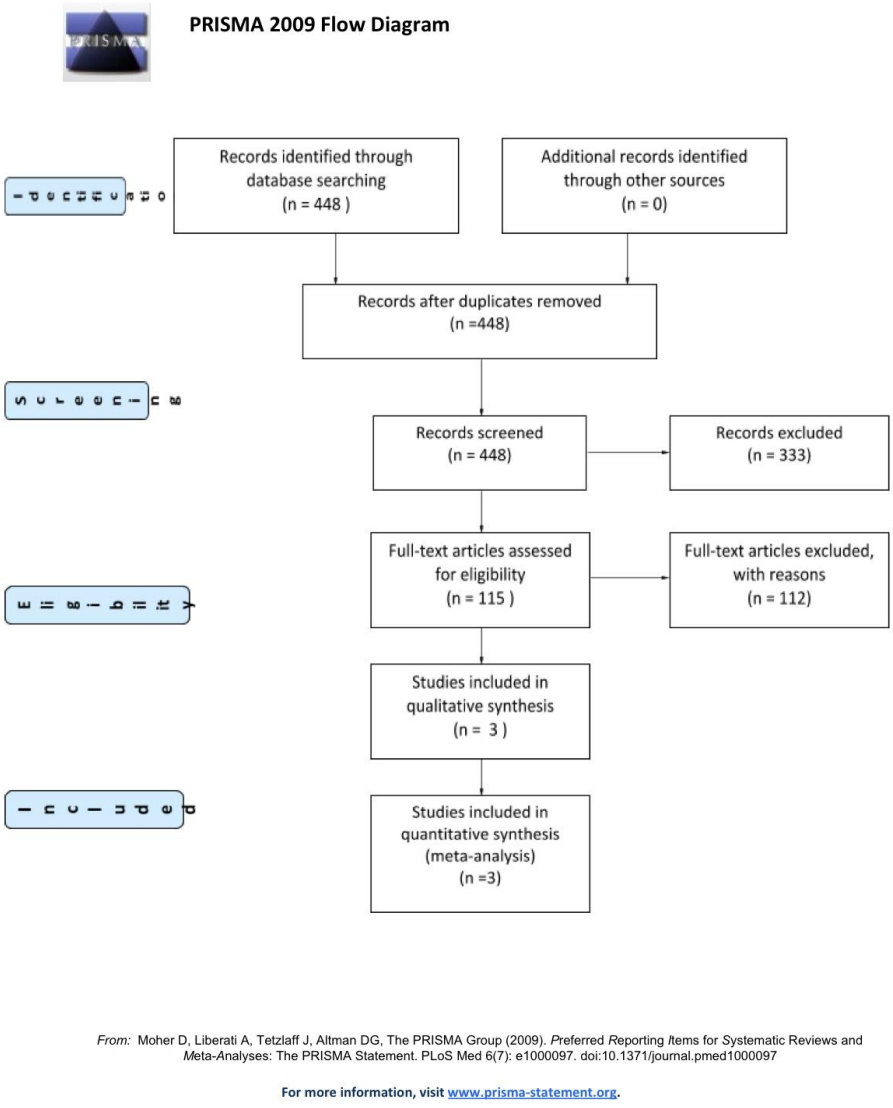
Methods

A meta-analysis based on a systematic review was the initial goal of this study, but in order to combine all sources into one single statistical analysis we needed to obtain more information directly from the authors as the sources were composed of contrasting numbers. Instead, we performed a systematic review. In order to determine eligible studies for the systematic review, a MEDLINE (PubMed) search was performed for publications available on May 30, 2020. The following search terms were used [[(race OR ((ethnicity)) AND (parkinson)]. Searches in Google Scholar and Cochrane Library databases were also conducted to supplement the MEDLINE search. Studies impertinent to Parkinson's Disease and race/ethnicity were first excluded, and then studies that did not include specifically Parkinson's Disease and African ancestry were excluded. From the remaining studies, sources that had the incidence of African ancestry and Parksinson's Disease were selected. Also, studies were excluded if potentially confounding biases in subject selection were involved, such as studies of one particular race or ethnicity. Studies were included whether or not they included randomized interventions. No other exclusion criterion was employed. Remaining studies were categorized by incidence rate and risk ratio of Parkinson's Disease in order to allow analyses on each subgroup independently.

Results

As seen in Figure 1, 448 scholarly articles were initially analyzed. 333 scholarly articles were then excluded due their irrelevance to Parkinson's Disease and race/ethnicity which left 115 articles. 112 more sources were further excluded since they did not pertain to the specific topic of Parkinson's Disease, race/ethnicity, and African ancestry which left the final three sources that were used for the systematic review. Within the three sources, there were more than 450,000 participants with Parkinson's Disease that were composed of four different races/ethnicities of White/Caucasian, Black/African American, Asian, and Hispanic/Latino. Participants ranged from ages 40-65+, and each case of PD within these studies were reported from 1993-2005 [2, 13, 3].

Figure 1. *Methodology Numbers*



Three scholarly articles were obtained through a PubMed/MEDLINE search for the review; the comprehensive, numerical results of these three sources are shown in Table 1. The first study pertains to the geographic and ethnic variation of individuals 65 years and older with Parkinson's Disease in 1995, and 2000-2005 [2]. Through the methodology of a cross-sectional study of over 450,000 Medicare beneficiaries with Parkinson's Disease in the United States, the PD prevalence and incidence rate was calculated by age, race, sex, and county. The results concluded that the PD rate per 100,00 was highest in Whites with 2,168.18, Asians with 1,138.56, and lowest in Blacks with 1,036.41 [2]. Researchers of this article further gathered that "the mean age-standardized prevalence of Parkinson's Disease in Blacks and Asians was approximately 50% lower than the prevalence in Whites" [2]. In the second article, racial differences in the diagnosis of PD was analyzed among 319 cases of Parkinson's Disease in adults ages 40-65 from

Table 1. *Incidence Ratios in PD by Race/Ethnicity of Systematic Review Studies*

	Study 1*	Study 2**	Study 3***
	Prevalence Rate (no., per 100,000)	Incidence Rate (no., per 100,000)	Incidence Rate (no., per 100,000)
Race/ Ethnicity			
White/non-Hispanic White	2,168.18	54	13.6
Black/African American	1,036.41	23	10.2
Asian	1,138.56	---	11.3
Hispanic/ Latino	---	40	16.6

* Wright Willis, A., Evanoff, B., Lian, M., Criswell, S., & Racette, B. (2010). Geographic and ethnic variation in Parkinson disease: A population-based study of US Medicare beneficiaries. Retrieved July 01, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2865395/

**Dahodwala, N., Siderowf, A., Xie, M., Noll, E., Stern, M., & Mandell, D. S. (2009). Racial differences in the diagnosis of Parkinsons disease. *Movement Disorders, 24*(8), 1200-1205. doi:10.1002/mds.22557

***Eeden, S. K. (2003). Incidence of Parkinsons Disease: Variation by Age, Gender, and Race/Ethnicity. *American Journal of Epidemiology, 157*(11), 1015-1022. doi:10.1093/aje/kwg068

1999-2003 [13]. The overall cumulative incidence during this four year period was 45 cases per 100,000 [13]. Specifically, Whites had the highest rate of PD with 54 cases per 100,000, Latinos following with 40, and lastly, African Americans with 23 [13]. This means that the four year comprehensive risk of PD was 0.21% for Whites, 0.08% for African Americans, and 0.15% for Latinos [13]. In the third and final study, contrastingly, Hispanics had the highest incidence rate per 100,000 of 16.6 while non-Hispanic White rates followed with 13.6 [3]. In the same study, Asians had a rate of 11.3 per 100,000, and lastly, Blacks with a rate of 10.2 [3]. This study aimed to estimate the incidence of Parkinson's Disease by varying factors, such as gender, age, and ethnicity in 588 participants with PD through 1994-1995 [3].

Discussion

This systematic review investigated the influences that race/ethnicity has on PD and if African Americans were more or less likely to suffer from PD. Three sources with more than 450,000 PD participants were analyzed to collect information about prevalence and incidence of PD in African Americans compared to other races. In the overall analysis, it appeared that race/ethnicity does influence PD, and all three studies reported significantly less incidence/prevalence in African Americans. Although exact reasonings for these results remain controversial and unspecified, it can be implied that social and economic contributions, such as healthcare disparities and biological mechanisms, such as neuromelanin, are possible attributes.

The healthcare disparity in African American communities is a notable, yet predominately neglected topic. Relating to Parkinson's Disease, a recent study proved that African Americans were diagnosed at half the rate of Whites which further exemplifies that African American PD patients are underrepresented in Parkinson's Disease data [13]. Causes of these observed racial disparities can be linked to three general factors: patients, physicians, and the overall healthcare system [13]. Factors concerning patients could be based on their personal beliefs, education level, and culture. For example, studies have shown that African Americans and other minorities may dismiss common medical conditions as normal symptoms of increasing in age that do not require medical attention [4]. Similarly, physicians may intentionally or obliviously contribute to healthcare disparities through factors such as clinician biases, medical uncertainty, and stereotyping. Socioeconomic status, race, and education level are all possible factors physicians may take into consideration when determining specialist referrals; they may also be prompted by unconfirmed reports that PD is less common in African Americans [4].

Lastly, the accessibility, health coverage, and financing of the overall healthcare system are components that possibly contribute to the healthcare disparities in African Americans [13]. Accompanying these socioeconomic determinants is a more biological component that can further explain the results of this study.

The biological mechanism of neuromelanin and its relationship to PD is a recently studied topic in the discovery of PD pathophysiology. Neuromelanin is a dark brown intracellular pigment that is primarily associated with PD. In humans, neuromelanin contents increase with age which, consequently, is the main risk factor for Parkinson's Disease. Because natural PD development and substantial levels of neuromelanin are unique to humans, extensive research on PD and neuromelanin is limited. Despite this limitation, though, it is understood that increased levels of intracellular neuromelanin may introduce dopaminergic cell death and degradation in PD [16]. The presence of neuromelanin is a normal component of the human brain as it accumulates with age, but once these levels of neuromelanin surpass a certain threshold of buildup, death of intracellular neurons occurs. This phenomenon triggers neuronal dysfunction and PD-related symptoms [16]. Since neuromelanin is newly researched, its correlation to other possible influences of PD, such as race/ethnicity, remains unknown. However, the relationship between PD and cutaneous melanoma has been vaguely explored. Vila (2019) explained that PD patients have an increased risk of developing cutaneous melanoma, a skin cancer in pigment producing cells, and contrariwise. Loss-of-function variants in the melanocortin I gene, which have a direct relation to fair skin and red hair, are linked to a higher risk of developing both cutaneous melanoma and PD [16]. This relationship exhibits a positive association between

neuromelanin levels and the production of hair and skin pigmentation. Additionally, this provides a possible explanation for lower rates of Parkinson's Disease in African Americans.

There are possible limitations within this systematic review. The first limitation is in regards to the systematic review itself. A meta-analysis was the initial form of methodology for this study, but the chosen sources did not have like numbers that could be combined into a single statistical analysis without supplemental information directly from the authors. Furthermore, the small number of chosen sources, 3, poses a possibility of underrepresentation with race/ethnicity in PD. The few numbers of studies directly relevant to African ancestry and PD are other possible limitations. Out of the 448 sources analyzed for the systematic review, less than 10 involved the previously mentioned terms. Third, the years of the sources used for the review dates back to 1993-2005. The procedures and equipment researchers used for those studies may be currently outdated. Lastly, my biases from personally experiencing a family member with Parkinson's Disease are prospective limitations, but these biases were mitigated through the information obtained from scholarly articles.

Despite the limitations, the three sources used for the systematic review exemplified strengths that are not illustrated in comparing studies. One strength includes the substantial participants size of all the studies combined. The population of more than 450,000 PD participants provides an opportunity to "quantify the impact of ethnic risk factors in PD" [13]. Moreover, all of the sources included at least three racial and ethic groups to accurately compare and contrast patterns in the various groups. Additionally, the data within these sources explicitly examined racial differences in PD incidence and prevalence. Contrastingly, many other studies

have only been on one race/ethnicity [14, 15]. These strengths contribute to the validity and diversity of the results from this systematic review.

Conclusion

The information gathered from this systematic review suggests that race/ethnicity has some influence on Parkinson's Disease, and incidence/prevalence of Parkinson's Disease is significantly lower in African Americans. Although reasons that explain these results remain controversial and unconfirmed, they can be linked to impacts of healthcare disparities in the African American community and the presence of increased intracellular neuromelanin contents in the brain. In order to validate these possibilities, further research and closer examinations of Parkinson's Disease regarding the influences of biological and socioeconomic factors must be administered. Additionally, more research studies pertaining to this topic should be conducted with more diverse populations. These advancements into future research will be beneficial to Parkinson's Disease patients and family members, physicians, and neuroscientists because of enhanced healthcare and preventative measures for Parkinson's Disease.

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