Health Disparities in Parkinson's Disease:

Improving Care for America's Most Vulnerable Populations

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I. Introduction

Health disparities are differences in disease states and health conditions that exist among specific population groups and limit their ability to achieve their full health potential. While health status disparities refer to differences in the incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups, *healthcare disparities* classically refer to differences in healthcare access, quality, and outcome. [1]. However, there are more nuanced definitions depending on the time and context. For example, in its landmark report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* published in 2003, the Institute of Medicine (IOM), now called the National Academy of Medicine, defined healthcare disparities as "group differences in the quality of health care that are not due to access-related factors or clinical needs, preferences, and appropriateness of interventions" [2]. The term health disparity often overlaps with the term *health inequity*, a specific type of *health inequality* that denotes an immoral or unjust difference in health based on political, economic, or societal factors [1,3]. Health disparities are thought

to represent the metric by which progress toward achieving health equity is measured, such that a reduction in health disparity contributes to greater health equity [4]. In the remainder of this report, we use the term health disparity inclusive of health inequities given its more common usage in the United States (U.S.).

Researchers have observed health disparities among members of different racial and ethnic groups. Race and ethnicity are overlapping concepts that are often used synonymously. *Race* refers to physical differences that groups consider socially significant, while *ethnicity* refers to shared cultural characteristics like language, ancestry, practices, or beliefs [5,6]. Although healthcare disparities are frequently described in the context of racial or ethnic differences, disparities can exist in the delivery of care to individuals based on age, gender, sexual orientation or gender identity, disability, socioeconomic status, or geographic location. In the U.S., several groups are formally designated as health disparity populations by the National Institutes of Health, including American Indians/Alaska Natives, Asian Americans, Blacks/African Americans, Hispanics/Latinos, Native Hawaiians and Pacific Islanders, sexual and gender minorities, socioeconomically disadvantaged populations, and underserved rural populations [7]. The terminology used to describe race/ethnicity is highly variable in the medical literature. One systematic review exploring all primary research articles published in four leading journals from 1999-2003 found 116 different terms to describe various racial/ethnic groups [8]. In this review, we describe racial and ethnic groups using the following terms unless otherwise specified: Alaska Native, Asian, Black, Hawaiian Native, Latino, Native American, and White.

The relationship between race, ethnicity, and health is complex. Because there is more genetic variation between members of the same race than between members of different racial groups, race is increasingly recognized as a social rather than biological construct. In addition, racism, racial segregation, and racial discrimination directly impact the ability of minoritized groups to access and receive quality health care. In the U.S., race and ethnicity are closely associated with socioeconomic

status (SES) and may serve as a proxy for other social and environmental factors [9,10]. These factors, often known as the *social determinants of health*, have a profound impact on health and health outcomes and include variables such as education, housing, access to transportation, proximity to quality care, and exposure to racism and other discriminatory health practices, among others [11]. It is essential for policy makers and community leaders to understand the intricate relationship between race, SES, and the social determinants of health in order to identify and eliminate racial and ethnic disparities at the individual, community, state, and national levels.

Since the IOM's initial report, numerous studies have explored widespread differences in disease states and health care services based on race and ethnicity in the U.S. [12]. A growing body of research in Parkinson's disease (PD) suggests that significant differences exist in the incidence, prevalence, diagnosis, and treatment of PD across racial and ethnic minority groups. For example, Blacks are less likely to be diagnosed with PD [13,14], more likely to have delays in diagnosis [15] and, once diagnosed, are undertreated when compared to their White counterparts [16–18]. Diagnostic and treatment delays also translate into higher rates of morbidity and mortality [19,20], and these disparities can persist after accounting for insurance status and access to health care based on provider availability and geographic location [21]. The exact relationship between race and PD risk is unknown and prior research efforts have failed to identify discrete causes of health disparities in PD [21]. In addition to healthcare disparities, there is a lack of minority involvement in PD research. Of the clinical trials published between 1985 and 2007, only 17% reported participation by race/ethnicity [22,23]. Of the studies that did report this demographic variable, less than 8% of participants were non-White [22,23]. Lack of racial and ethnic diversity in clinical research adversely impacts our understanding of PD outcomes and limits our ability to provide quality, evidence-based care, further exacerbating health disparities [23].

To confront healthcare disparities in PD, we must: 1) recognize them, 2) understand their underlying causes, 3) identify modifiable risk factors, and 4) develop interventions and policies to improve care for all persons with PD. In this report, we review existing research on racial and ethnic disparities in PD and describe the current state of knowledge regarding the epidemiology, etiology, phenotype, diagnosis, and treatment of PD in persons from diverse backgrounds, including data related to military veterans from racial and ethnic minority groups. We also identify important gaps in knowledge and propose strategies to not only reduce racial inequities in PD diagnosis, treatment, and clinical research, but also improve care quality and care delivery for America's most vulnerable populations.

II. Historical Context

To understand the origin of racial and ethnic disparities in the U.S., we must first understand the historical context in which they arose. During the colonization of North America, Native Americans experienced significant mortality in the setting of communicable diseases brought by European settlers, such as smallpox, measles, influenza, and malaria [24]. As European migration increased, health disparities were further exacerbated by displacement, warfare, and governmental policies. The reservation system imposed between the 1830s and 1870s transformed patterns of morbidity and mortality and fueled the spread of tuberculosis, among other diseases [24]. Despite attempts to reduce health disparities through economic development and the creation of the Indian Health Service (IHS) in 1955 [25], mortality rates among Native Americans and Alaska Natives still remain high compared to the general population due to chronic liver disease and cirrhosis, diabetes mellitus, unintentional injuries, assault/homicide, intentional self-harm/suicide, and chronic lower respiratory diseases [26]. The current life expectancy among Native Americans and Alaska Natives is 5.5 years less than all races combined

[26]. These longstanding disparities in disease burden and life expectancy are attributed in part to inadequate education, disproportionate poverty, and health care discrimination [26].

During the nineteenth and early twentieth centuries, modern American medicine was rooted in the practice of scientific racism and eugenics [12]. Scientific racism reinforced the concept of race as an innate biologic and genetic attribute, and American scientists like Dr. Samuel Morton used anatomical features such as skull size to categorize races and promote White superiority [27,28]. Advocates of the eugenics movement also influenced laws that led to the forced sterilization of "undesirable" racial groups in an effort to create a more intelligent, Whiter society [27]. During these eras, Blacks were cast as innately diseased by physicians who used pseudoscientific methods to support theories of biological White superiority, primarily to justify the enslavement and brutal treatment of Africans. For example, enslaved Africans who attempted to escape captivity were deemed to have a mental illness called "drapetomania" based on the assertion that Africans needed and benefited from enslavement and bondage [29]. In the aftermath of the Civil War, rates of illness and death rose among newly emancipated Blacks, and poor health conditions plagued segregated cities as a legacy of African enslavement [30]. Racialized conceptions of disease susceptibility still persist today, and other communities of color have been targeted by scientific racism [12].

In the 1960s, the term "model minority" was coined to describe Asians as an educated, hard-working, and economically successful group [31]. Critics of this term suggest the stereotype was developed during the Civil Rights era to deny the existence of structural racism and instead attribute racial inequality to underperformance among other racial/ethnic groups [31,32]. The "model minority" stereotype is classically applied to all Asian subgroups; however, ethnic subgroups differ with regard to culture, language, immigration patterns, and level of acculturation within the U.S. [31]. These subgroups include East Asians (e.g., Chinese, Japanese, Korean), South Asians (e.g., Bangladeshi, Indian, Pakistani), Southeast Asians (e.g., Filipino, Cambodian, Thai, Vietnamese), and Pacific Islanders (e.g., Native

Hawaiians, Chamorros, Marshallese) [31]. In healthcare, disparities among Asian subgroups are often minimized and Asians are underrepresented in national surveys and health databases. Those that do include information on Asians often collect data in aggregate, which can mask health disparities and create challenges when addressing public health concerns across Asian subgroups [31].

In recent decades, persons of Hispanic/Latino origin have become the largest minority group and fastest growing segment of the U.S. population [33]. This growth is largely attributed to immigration and fertility, and immigrants from the Caribbean and Latin America comprise over half of the Latino population [33]. Immigration poses unique health challenges. Immigrants can encounter educational barriers and menial and unstable employment opportunities that contribute to poverty [34]. In addition, Latino individuals are less likely to seek or receive healthcare services than the general U.S. population due to language barriers and lower rates of health insurance [35]. Certain health conditions are also more common among Latino individuals, who experience greater disparities in diabetes risk, cervical cancer, liver disease, and deaths from work-related injuries [36]. Interestingly, foreign-born Latino individuals have a longer life expectancy at birth and experience better health outcomes than native-born Latino individuals, a phenomenon coined the "Hispanic Mortality Paradox" [37]. While controversial, this paradox is attributed in part to a "healthy migrant effect" which involves cultural patterns and health behaviors among first generation Latinos [37]. Although the implementation of the Affordable Care Act has improved access to medical care for those without insurance, barriers to access still persist, and significant differences in health outcomes among Hispanic/Latino subgroups are not reflected in national aggregate data.

As a consequence of historical, scientific, and structural racism, racist cultural beliefs and practices contribute to issues of stereotyping, mistrust, and unconscious bias among patients and providers. *Bias* has been used to describe both implicit stereotypes and prejudice in healthcare and is defined broadly as "the negative evaluation of one group and its members relative to another" [38],

often on the basis of nationality, race, sex, gender identity, or sexual orientation [39]. In one systematic review exploring implicit racial/ethnic bias among healthcare professionals in 15 studies, low to moderate levels of implicit racial/ethnic bias were found in all studies but one [40]. Most health care providers demonstrated positive attitudes toward Whites and negative attitudes toward people of color, and this *implicit* bias associates with *explicit* actions, such as inappropriate treatment decisions, negative patient–provider interactions, and poor treatment adherence, resulting in worse patient health outcomes [40].

Health experiences and outcomes in the U.S. have historically differed between members of the White majority and members of racial and ethnic minority groups [1]. In 1985, the U.S. Department of Health and Human Services released the *Report of the Secretary's Task Force on Black and Minority Health*, also known as the Malone-Heckler Report, that used substantive data to describe prominent and growing health disparities within the Black community [1,41]. In 2003, the IOM report concluded that bias, prejudice, and stereotyping contributed to widespread differences in health care based on race and ethnicity [2,12]. More recently, the 2018 National Healthcare Quality and Disparities Report documented that Black, Native American and Alaska Native, and Hawaiian Native and Pacific Islander patients received poorer care than their White counterparts on 40% of quality metrics, with little to no improvement from prior decades [12,42]. Health disparities have been increasingly recognized among racial/ethnic groups in the diagnosis and treatment of chronic diseases like PD.

III. PD Epidemiology

1. Background

PD is the second most common neurodegenerative disorder that affects over one million Americans in the U.S. Among all racial groups, the prevalence of PD in the U.S. has been estimated at 572 per 100,000 persons [43], and the incidence rate has been estimated at 37.55 per 100,000 person-years for women

and 61.21 per 100,000 person-years for men [44]. State-level differences in prevalence also exist. In a recent study of U.S. Medicare beneficiaries in 2014, crude prevalence varied from 845 per 100,000 persons in Minnesota to 1,781 per 100,000 persons in New York [45]. The top five states contained 20.7% of all Medicare beneficiaries diagnosed with PD, including New York, Connecticut, Florida, Pennsylvania, and Rhode Island. After adjusting for baseline differences in race, age, and sex, the District of Columbia, New York, Illinois, Connecticut, and Florida had the highest prevalence [45] [**Figure 1A**].

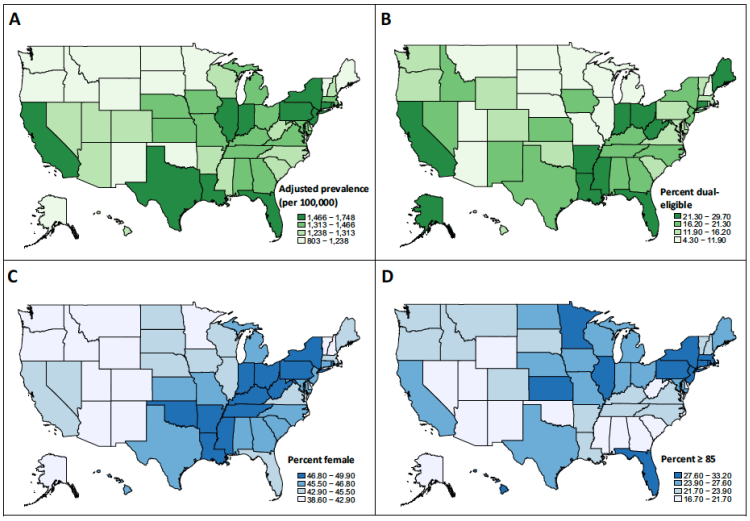


Fig. 1 Prevalence of Parkinson's disease and characteristics of individuals with PD by state. **a** Prevalence of Parkinson's disease (per 100,000), adjusted for age, race, and sex, among Medicare beneficiaries in 2014. **b** Percentage of Medicare PD population that is dual-eligible. **c** Percentage of Medicare PD population that is female. **d** Percentage of Medicare PD population aged 85 years and older. Data are shown in quartiles

Despite the heterogeneity of symptoms across racial and ethnic groups, current diagnostic criteria and clinical recommendations are based on studies that were conducted using patients of European descent, making it more difficult to understand PD epidemiology in non-White populations [46]. Because early data on health disparities in smaller racial and ethnic minority groups are limited, initial studies that specifically explored racial disparities in the incidence and prevalence of PD are largely based on the Black experience, while more recent studies have explored disparities in more diverse cohorts.

2. Incidence and Prevalence (Historical Studies 1970-2000)

Differences in the prevalence of PD between Blacks and Whites were recognized as early as the 1960s-1970s [47–49]. In a study exploring all hospital discharges in Baltimore, Maryland between 1965-1967, Kessler noted that rates of PD were much lower in Black patients of all ages than White patients, hypothesizing that increased melanin pigmentation in Blacks may reduce the risk of depigmentation in the substantia nigra, a characteristic finding in PD patients at autopsy [47]. Lower PD prevalence among Blacks was also corroborated by results from a community survey conducted in Baltimore during the same time period in which local physicians referred patients with parkinsonism for home interviews [48]. Of the 127 patients surveyed, only 17 (7.5%) were non-White, less than half of their proportion in the general population at that time [48]. In another study, all medical records from patients admitted to Charity Hospital in New Orleans, Louisiana were reviewed between 1959-1969 [49]. PD prevalence was 147 per 100,000 Whites and 22 per 100,000 Blacks [49]. Unfortunately, hospital and clinic-based studies have inherent biases. They fail to include individuals who do not receive medical attention, and given the possibility of hospitalization bias, provider bias, and the underrepresentation of Blacks in medical research, additional studies sought to confirm these early findings.

In a landmark study published in 1985, Schoenberg and colleagues studied the prevalence of PD in Copiah County, Mississippi, a community that contained equal numbers of White and Black residents [50]. During this study, research staff conducted door-to-door surveys at every home and institution to identify persons with symptoms that could be consistent with PD or other disorders of interest. Participants were then invited to undergo a brief neurological examination at a public health clinic to confirm diagnosis. Researchers found no significant difference in the age-adjusted prevalence ratios of PD in Blacks and Whites: 338 versus 353 per 100,000 inhabitants 40 years and older, respectively [50]. With regard to incidence, 42% of PD cases were newly diagnosed and disproportionately Black; these individuals would not have been captured in prevalence studies restricted to hospital records or physician report [50]. In 1988, Schoenberg and colleagues expanded on this study and compared

findings with similar door-to-door surveys conducted in Igbo-Ora, Nigeria, as West Africa was thought to represent the ancestral origin of Blacks residing in Mississippi [51]. In Nigeria, researchers found a lower age-adjusted PD prevalence ratio of 59 per 100,000 inhabitants 40 years and older. Thus, the 5-fold increase in PD prevalence among Blacks in Mississippi was hypothesized to represent a difference in incidence rate rather than survival, possibly due to an environmental exposure among U.S. residents.

In a later study, Mayeux and colleagues explored the frequency of idiopathic PD by age, ethnic group, and sex between 1988-1991 in Washington Heights-Inwood, a culturally diverse neighborhood of New York City [52]. Data were gathered from a community registry of PD cases using inpatient and outpatient records and information gathered from health agencies and senior centers, along with a random sample of Medicare beneficiaries residing in the same community. Researchers found that age-adjusted prevalence rates were lower for Blacks than for Whites and Latinos, and lower for women than men. However, incidence rates were also highest among Black men [52]. Although these discordant incidence and prevalence rates among Blacks could be attributed to shorter survival times that can lower disease prevalence in certain populations, diagnostic delays due to insurance status or limited access to health services may also have contributed to findings [52]. Thus, in an attempt to remove insurance status as a confounding variable in calculating incidence, all patients within the Kaiser Permanente Medical Care Program (KPMCP) of Northern California were screened for PD between 1994-1995 [53]. In descending order, the age- and gender-adjusted incidence rate was highest among Hispanics (16.6/100,000), followed by non-Hispanic Whites (13.6/100,000), Asians (11.3/100,000), and Blacks (10.2/100,000), suggesting that PD incidence does vary by race/ethnicity [53]. However, these results have limited generalizability given that patients in the Kaiser system have higher SES than the general population. Other studies have explored PD incidence in race-specific cohorts. Morens and colleagues determined age-specific and age-adjusted PD incidence in men of Japanese or Okinawan descent enrolled in the Honolulu Heart Study between 1965-1994 [54]. PD incidence rates and age-

incidence patterns were similar to rates previously published for White men in Europe and the U.S., and were higher than rates published for Asian men residing in Asia [54]. Similar to the work conducted in Igbo-Ora, Nigeria [51], these data suggest that environmental factors may contribute to observed risk differences rather than country of origin.

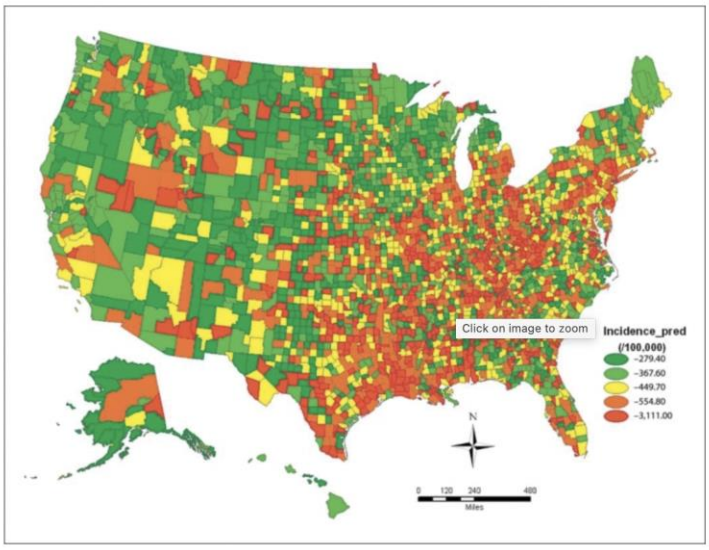
3. Incidence and Prevalence (Modern Studies: 2000-Present)

More recently, PD incidence and prevalence have been explored using large national datasets, including Medicare and Medicaid, which allow for the study of other racial and ethnic groups. Medicare is a government subsidized healthcare system in the U.S. for disabled persons and those age 65 and older, while Medicaid is a federal and state healthcare program for persons with limited income. Using Medicare data from 1995 and 2000-2005, Willis and colleagues calculated the prevalence and annual incidence of PD by race, age, sex, and county [55]. Age-standardized PD prevalence was greatest in White men (2,168/100,000) and lowest in Asian women (964/100,000). The incidence ratio in Blacks compared to Whites (0.74, 95% CI 0.73-0.75) was higher than the prevalence ratio (0.58, 95% CI 0.57-0.58), again suggesting that lower survival among Blacks may decrease the prevalence of PD. Age-adjusted PD prevalence and annual incidence per 100,000 Medicare beneficiaries are listed below by ethnic group [55]. [**Table 1**]:

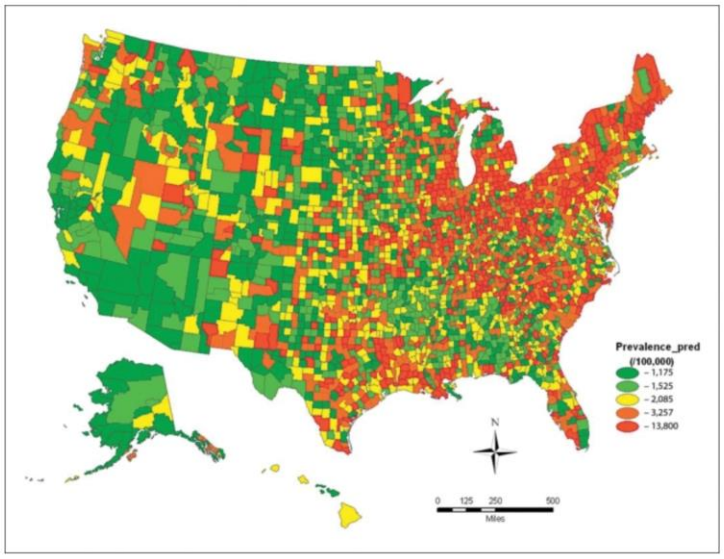
Race	1995	2000	2001	2002	2003	2004	2005	Mean (SD)	Ratio (CI)
White									
Prevalence	1,505.46	1,723.43	1,715.86	1,703.34	1,693.74	1,675.62	1,683.99	1,671.63 ± 75.18	
Incidence				450.57	454.63	450.24	452.03	451.87 ± 2.00	
Black									
Prevalence	848.86	1,042.10	1,041.59	1,068.18	1,072.28	1,069.63	1,112.27	1,036.418 ± 6.01	0.58 (0.575–0.581)
Incidence				354.10	354.64	361.93	377.02	361.92 ± 10.68	0.74 (0.732–0.748)
Hispanic									
Prevalence	1,356.59	1,513.07	1,511.76	1,562.38	1,581.16	1,608.43	1,671.32	1,543.53 ± 99.33	0.89 (0.881–0.896)
Incidence				462.9	486.92	468.14	486.29	476.06 ± 12.36	1.07 (1.047–1.084)
Asian									

Prevalence	1,113.23	1,085.96	1,080.69	1,144.22	1,173.45	1,171.76	1,200.61	1,138.56 ± 46.47	0.62 (0.617–0.631)
Incidence				338.34	338.60	332.69	346.94	339.14 ± 5.87	0.69 (0.657–0.723)

PD prevalence and incidence were also greater in urban than rural counties, and Bayesian mapping of PD revealed a non-random distribution of incident [**Figure 2**] and prevalent [**Figure 3**] PD cases in the Midwest and Northeast regions of the U.S. [55].



County level age- and race-standardized incidence (per 100,000) of Parkinson disease among Medicare beneficiaries in the United States (year = 2003).



County level age- and race-standardized prevalence (per 100,000) of Parkinson disease among Medicare beneficiaries in the United States (year = 2003).

Similar to studies of care access, this study supported the finding that the incidence and prevalence of PD is substantially higher in Whites than Blacks or Asians. Using Pennsylvania Medicaid claims from 1999-2003, Dahodwala and colleagues identified newly diagnosed cases of PD among 182,271 Medicaid beneficiaries age 40-65 [13]. The 4-year cumulative incidence of PD was 45 per 100,000 persons: 54 per 100,000 Whites, 40 per 100,000 Latinos, and 23 per 100,000 African Americans. These observed racial differences in PD incidence were not explained by age, sex, income, insurance, or healthcare utilization, and authors hypothesized that differences could be explained by biological differences, social determinants of health, or other cultural factors [13].

The incidence and prevalence of PD has also been extrapolated from pharmacology studies. In one large cohort from the Geographic and Racial Differences in Stroke (REGARDS) study, only 0.51% of Black patients were on PD medications compared to 0.97% of White patients [56]. Older age and gender were associated with higher likelihood of PD medication use, but there was no association between medication use and income, education level, or geographic area of residence. Although PD diagnosis was not included in the study, data suggested a lower prevalence of PD within the African American

population, though racial inequities in PD diagnosis and treatment may have contributed [56]. Accordingly, a study of Medicare Part D files from 2007-2010 described the prevalence of anti-Parkinson drug use among Medicare beneficiaries with PD [57]. Blacks with PD were less likely than Whites to be prescribed PD medication, along with patients who were not seen by a neurologist for care [57].

Although the majority of epidemiologic data from the U.S. describes the incidence and prevalence of PD in White, Black, Latino, and Asian populations, smaller studies have also explored PD among Native Americans. Members of 573 federally recognized American Indian and Alaska Native Tribes are eligible for services provided by the IHS, a comprehensive agency within the Department of Health and Human Services that provides health services to approximately 2.56 million Native Americans who live on or near reservations in the Western U.S. and Alaska [26]. Gordon and colleagues have published three epidemiological studies on PD in Native Americans and Alaska Natives [58–60]. First, using inpatient and outpatient records from the IHS between 2002-2009, the crude and overall prevalence of PD was determined by age, sex, and region. Of the 2 million Native Americans and Alaska Natives who received medical care from the IHS, 2,613 patients met inclusion criteria for PD, yielding an overall crude period prevalence rate of 143.8/100,000 persons and age-adjusted rate of 355.7/100,00 persons [58]. These rates were higher among men and varied by geographical region, with the highest overall prevalence observed in the Southwest, Alaska, and Southern Plains. Although figures were not directly comparable to other populations, prevalence rates were higher than those documented in minority groups from Northern Manhattan [52].

In subsequent studies, Gordon and colleagues also explored the period prevalence of PD in the Navajo Nation, the largest reservation in the U.S. that contains 200,000 inhabitants and comprises 25,000 square miles of land in northeastern Arizona, southeastern Utah, and northwestern New Mexico [59,60]. In their first study, researchers used the Shiprock Service Unit IHS database from 2005-2009 [59]. Among 61,853 patients who sought medical care in New Mexico, 126 had PD, yielding a crude

period prevalence rate of 203.7/100,000 persons and age-adjusted prevalence rate of 335.9/100,000 persons [59]. These figures were consistent with their initial study suggesting that PD prevalence is highest in the Southwest where the Navajo reside. Expanding on this research, a follow-up study determined the annual incidence and point prevalence rates of PD among Navajo patients receiving health care between 2001-2011 at all service units [60]. Among 524 Navajo with incident PD, the average annual crude incidence rate was 22.5/100,000 persons. The average age-adjusted annual incidence rate was 35.9/100,000: 47.5/100,000 men and 27.7/100,000 women. While these figures are greater than those reported for all race/ethnicities in the KPMCP study [53], the crude incidence is lower than that reported in Medicare data for other racial/ethnic groups. In addition, the crude point prevalence rate was 145.5/100,000 persons and the overall age-adjusted prevalence rate was 261.0/100,000 persons [60]. When compared to national Medicare data, the crude and age-adjusted prevalence rates are also lower than rates seen in other minority populations, though figures are not directly comparable and Native Americans may have lower rates of PD diagnosis due to limited access to specialty care.

Overall, the majority of studies suggest that the incidence and prevalence of PD differs by racial and ethnic group, with highest rates in Whites, followed by Latinos, Blacks and Asians, and Native Americans who have the lowest reported rates of disease. Although European ancestral groups have been reported to have the highest prevalence of monogenic risk factors or genetic traits associated with early-onset PD, several factors limit our ability to clearly understand whether there is any association between ancestry or social risk factors with polygenic or late-onset PD. Typical case ascertainment methods have relied on clinical records from academic medical centers which are disproportionately accessed by persons with high income, advanced education, and quality primary care. The current PD diagnostic criteria are drawn from such cohorts. PD epidemiology studies (both medical record- and administrative data-based) may therefore be limited in their ability to capture or reflect PD occurring in

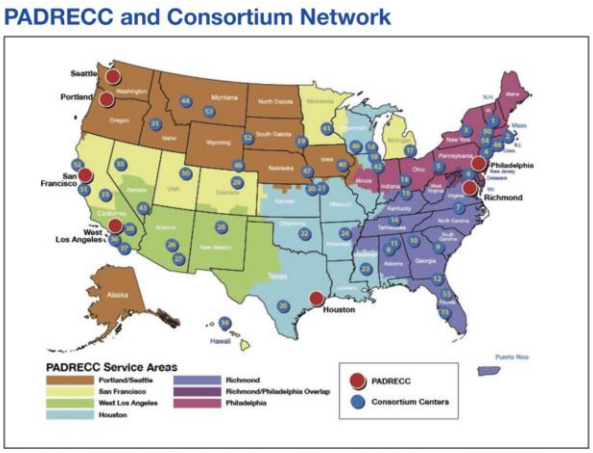
persons who experience complications from co-morbid diseases (e.g., diabetes, cerebrovascular disease), or have language, insurance, geographical, or socioeconomic barriers to receiving a PD diagnosis. Second, persons living with PD from minoritized groups are often undiagnosed even when they present with typical symptoms due to implicit bias. In addition, differences in prevalence may be impacted by misclassification bias from studies using diagnostic codes [12] and racial disparities in life expectancy [14]. The degree to which racial and ethnic differences in the incidence and prevalence of PD stem from sampling bias due to health disparities or differences in PD genetic susceptibility, environmental exposure, or phenotype are currently unknown and remain a major gap in the field.

4. Mortality

Several studies have reported racial differences in PD mortality [61] and the reporting of PD on death certificates [62]. A search of mortality files from the National Center for Health Statistics and Bureau of the Census in 1988 found that Whites were more likely to die with an International Classification of Diseases (ICD)-9 diagnosis of PD compared to Blacks, though it is unknown whether PD severed as a primary or contributing cause of death [61]. A 2005 study explored disparities in the reporting of PD on death certificates using a national population-based survey linked to death certificate data [62]. Among decedents with clinically diagnosed PD, only 54.8% had PD recorded on their death certificate. Reporting also differed by SES: nearly 70% of persons in higher income categories had PD recorded at time of death compared to 35.4% of those earning $10,000 or less, suggesting the possibility of underlying bias in PD reporting [62]. Unfortunately, this study population was 90% White, limiting further analysis in racial/ethnic groups with lower SES. Lack of knowledge regarding racial/ethnic differences in PD death documentation remains a significant barrier to identifying and addressing health disparities in PD mortality.

5. Veteran Statistics

Veterans are a unique population who receive care through the Department of Veterans Affairs (VA), a government-run network of health facilities that provides care to over 6 million military veterans, approximately 23% of whom are from racial or ethnic minority groups [63]. Because eligible veterans have access to the same medical services, VA studies have examined health disparities without confounding from racial differences in insurance coverage [64]. Between 1997-1999, 55,637 veterans carried a diagnosis of PD [65]; however, more recent data suggests this number may exceed 100,000 [66]. To improve care for this population, the VA established the Parkinson's Disease Research, Education, and Clinical Center (PADRECC) in 2001. Six centers are currently located in Philadelphia, Pennsylvania, Richmond, Virginia, Houston, Texas, Los Angeles, California, San Francisco, California, and a combined center in Portland, Oregon and Seattle, Washington [65] [**Figure 4**].



Abbreviation: PADRECC, Parkinson's Disease, Research, Education, and Clinical Centers.

Although no formal studies have assessed the incidence and prevalence of PD among the VA population, one study explored racial and ethnic differences in PD care at the Los Angeles PADRECC between 2001-2002 [18]. Of 374 patients with PD, 309 (82.6%) were White, 30 (8.0%) were Hispanic/Latino, 23 (6.2%) were Black, 11 (2.9%) were Asian, and 1 (0.3%) was Native American [18].

While PD was more common in Whites and Latino individuals compared to those from other racial/ethnic minority groups, these figures are consistent with demographics in the greater Los Angeles area, where Latino individuals comprise a greater segment of the population.

6. Predictors of Survival

Race/ethnicity may also influence survival. In one retrospective cohort study, 138,000 Medicare beneficiaries with incident PD were identified in 2002 and followed through 2008 [20]. Hispanics (HR 0.72, 95% CI 0.65-0.80) and Asians (HR 0.86, 95% CI 0.82-0.91) had a lower adjusted risk of death than White males. Black patients have also been shown to have a higher risk of death than White patients in several studies [20,52]. However, few studies have investigated mortality among Asians, Latinos, and Native Americans, and the role to which other factors, including comorbidities, culture, health care access, genetics, or environmental risk, contribute to survival is currently unknown. Epidemiological data from different PD populations are important not only to define disease burden, but also to identify clues that allow for further exploration of underlying etiologies and diseases trajectories.

IV. PD Etiology

1. Ancestry and Genetics

While the etiology of PD is largely unknown, researchers have identified several gene mutations and environmental factors that contribute to disease risk. Numerous familial and genetic studies have explored the role of ancestry and gene mutations in PD risk. Below, we summarize existing knowledge of these risk factors by race/ethnicity.

Familial Studies

Since the first documented familial cluster of PD in 1880 [67], genetic factors have been implicated in its development, leading to multiple twin and kindred studies from the late 1970s-1990s. The majority of early studies were conducted in predominantly White populations. In one example from 1995, Tanner

and colleagues identified monozygotic (MZ) and dizygotic (DZ) twins with PD enrolled in the National Academy of Sciences/National Research Council World War II Veteran Twins Registry [68]. Researchers hypothesized that if genetic factors were implicated, disease concordance in genetically-identical MZ twins would exceed that of DZ twins. After recruiting 71 MZ and 90 DZ pairs with complete diagnostic data, MZ concordance exceeded DZ concordance among patients with disease onset <50 years, suggesting a possible genetic component to early-onset disease. However, pairwise concordance was similar among patients with disease onset >50 years, inconsistent with a purely genetic cause. Unfortunately, this cohort was limited to White men residing in the U.S., making it difficult to generalize findings to women or other communities of color. To our knowledge, no data has been collected on twins from different racial and ethnic groups.

In contrast, some kindred studies have offered insight into the role of ancestry among smaller minority groups. For example, Denson and colleagues explored eight large kindreds from North America between 1987-1993 [69]. Although the majority of PD cases occurred in families of English, Danish, and German descent, one kindred was Native American and contained 52 family members over five generations. Four individuals developed PD over two generations, and symptom onset ranged from 52-62 years of age characterized by levodopa-responsive parkinsonism and dementia [69]. Another case-control study explored familial PD aggregation using data from Kaiser Permanente in Northern California to compare the incidence of PD among first-degree relatives of PD patients and controls from different racial groups [70]. Between 1994-1995, the cumulative incidence of PD was significantly higher among relatives of PD patients than controls (RR 3.4, 95% CI 1.9-5.9), and familial aggregation was stronger among siblings (RR 5.4, 95% CI 1.8-16.0) than parents (RR 2.75, 95% CI 1.3-5.2) of PD patients. Interestingly, familial aggregation was also higher among first-degree relatives of Hispanic/Latino PD patients (RR 8.5, 95% CI 1.0-68.9), non-Hispanic White PD patients (RR 2.7, 95% CI 1.5-5.1), and Asian PD patients (RR 2.1, 95% CI 0.2-20.1) compared to controls [70]. These data overlap with the initial

epidemiologic study at KPMCP suggesting that Hispanics have the highest PD incidence rate [53] and warrants further study of genetic risk factors in the Latino population. Notably, while this study observed familial aggregation of PD, it could not determine if this aggregation was due to shared environmental exposures among family members or the interaction of genetic and environmental risk factors [70].

Young-Onset PD

In addition to familial aggregation, there is increasing evidence that genetics may influence early PD development. Young-onset PD (YOPD) is defined as PD onset before age 40 or 50. Over the last 25 years, several pathologic genes have been identified in YOPD patients, including alpha-synuclein (*SNCA*), parkin (*PRKN*), PTEN-induced putative kinase 1 (*PINK1*), *DJ-1,* leucine-rich repeat kinase-2 (*LRRK2*)*,* and glucocerebrosidase (*GBA*). While *PRKN* mutations are thought to represent the most common genetic cause of YOPD [71], the prevalence of these genetic mutations may also vary by racial or ethnic group [72]. In a multicenter study from the Consortium on Risk For Early-Onset PD (CORE–PD), researchers explored the presence of *SNCA*, *PRKN*, *PINK1*, *DJ-1*, *LRRK2* and *GBA* mutations among 956 patients with PD onset ≤ 50 years of age [71]. In this sample, 14.7% of patients reported a family history of PD in a first-degree relative and 6.7% patients had *PRKN* mutations. Although no *PRKN* mutations were identified among 12 Black PD patients, 12 of the 77 Hispanic/Latino PD patients were identified as *PRKN* carriers, including 7 Puerto Rican, 2 Mexican, 1 Cuban, 1 Dominican, and 1 Peruvian patient. Compared to non-Hispanic Whites, Hispanic/Latino patients were significantly more likely to carry any *PRKN* mutation (OR 2.7, 95% CI 1.3-5.7) or carry a heterozygous *PRKN* mutation (OR 2.8, 95% CI 1.1-7.2), suggesting elevated risk of YOPD among Hispanic/Latino individuals, particularly those of European descent [71]. In a follow-up study using the CORE-PD sample, researchers also reported the frequency and clinical characteristics of YOPD patients with other genetic mutations [72]. Of 953 individuals, 158

(16.6%) carried a known gene mutation: 64 were *PRKN* carriers, 35 were *LRRK2* G2019S carriers, 64 were *GBA* carriers, and 1 had a single A104T *DJ-1* mutation. No *SNCA* or *PINK1* carriers were identified. Similar to the initial study, Hispanic/Latino individuals were more likely to be *PRKN* carriers than non-Hispanic Whites (15.6% versus 5.9%, p=0.003). In addition, mutations were more common in individuals of Ashkenazi Jewish ancestry than in those without (32.4% versus 13.7%, p<0.001), likely driven by the increased frequency of *LRRK2* G2019S and *GBA* mutations in this population. Given the greater likelihood of genetic mutations among Latino and Jewish patients with YOPD, genetic counseling was recommended [72].

Interestingly, one study showed that people with melanoma, which is strongly linked to red hair in early adulthood, fair skin, and polymorphisms in the *MC1R* (melanocortin 1 receptor) gene, are at higher risk of PD [73], suggesting that Whites may have a higher genetic risk of PD than persons of color. Unfortunately, few studies have explored genetic mutations in Black or African YOPD patients and samples sizes are too small to make definitive conclusions. In a recent study from Zambia, all *PRKN*, *PINK1*, *DJ-1, SNCA*, and *LRRK2* exons were sequenced in 12 PD patients with disease onset prior to age 50 [74]. Two heterozygous *PRKN* deletions (exons 2 and 4) were detected in one early-onset case, along with a novel missense *LRRK2* variant (p.Ala1464Gly). Pathogenic mutations were not detected in *SNCA*, *PINK1*, *DJ-1*, or *LRRK2* G2019S despite its prevalence in North Africa [74]. Another review of PD-associated genetic factors in sub-Saharan Africa reported *PRKN* mutations in 2 Black patients from South Africa without other known genetic mutations [75]. Despite these data, each study enrolled fewer than 50 Black PD patients. Although known PD mutations in sub-Saharan Africa may play a minor role in PD risk, the true prevalence of pathogenic gene mutations among U.S. Blacks is currently unknown and represents a major gap in current literature.

Late-Onset PD

Genetic studies in late-onset PD, characterized by disease onset after age 50, have also provided insight into PD pathogenesis in different racial/ethnic groups. Two genes are commonly implicated in late-onset disease: *GBA* and *LRRK2* mutations [**Table 2**].

Table 2.

Gene Mutation	Allelic Variants	Populations
GBA	84insGG R496H	Ashkenazi Jewish
LRRK2	G2019S	Ashkenazi Jewish Basque North African Berber/Arab
	R1441G	Hispanic/Latino (Spanish origin) European Asians residing in Western nations
	Q1111H	Hispanic/Latino (Amerindian origin)
	rs1491942	Hispanic/Latino (Spanish and Amerindian origin)
	A419V R1628P G2385R	East Asians
SNCA	Rs356225	Hispanic/Latino (European, Amerindian and African origin)

Homozygous recessive *GBA* mutations cause Gaucher's disease, while heterozygous carrier status is one of the strongest genetic risk factors for PD. The prevalence and penetrance of *GBA* mutations vary by

ethnicity, and 84insGG and R496H variants can increase the risk of PD in Ashkenazi Jewish populations [76,77].

In addition, *LRRK2* mutations are recognized as the most frequent monogenic cause of PD to date and are typically inherited in an autosomal dominant fashion. *LRRK2* mutations are most common in patients of Basque, Ashkenazi Jewish, and Northern African origin [78]. Although several *LRRK2* allelic variants have been implicated in PD, two amino acid mutations are the most frequent *LRRK2* mutations, including G2019S and R1441C/G/H [78]. The G2019S mutation, in particular, is the most common genetic cause of PD worldwide and accounts for 1% of sporadic PD and 4% of familial PD [79]. In a study that explored *LRRK2* variants among diverse PD patients at the Baylor College of Medicine in Houston, Texas, 6 patients were heterozygous for the G2019S mutation: 3 Ashkenazi Jewish, 2 White, and 1 Hispanic patient [78]. In addition, 1 Hispanic female was heterozygous for the R1441G mutation. While the R1441C/G/H mutation occurs at a relatively low frequency in North Americans, the R1441G mutation is more common in PD patients of Hispanic origin [78]. Another *LRRK2* mutation, Q1111H, was recently identified among two Hispanic brothers but not among White patients [80]. Researchers then screened for this variant in 1150 PD patients and 310 healthy controls from Peru, Chile, Uruguay and Argentina. Interestingly, this gene variant was thought to originate from individuals of Amerindian rather than pure Spanish origin [80]. Given the potential for *LRRK2* variants in patients of mixed ancestry, a more recent study also explored differences in genetic mutations among 311 Mexican Mestizos [81]. Researchers found a significant risk association for the variant rs1491942 in individuals with a higher percentage of Native American ancestry [81]. Given the growing population of Hispanic/Latino individuals in the U.S. of Central and Latin American origin, further studies in Latino subpopulations are needed to explore the role of *LRRK2* variants in PD risk. To this end, the Latin American Research Consortium on the Genetics of Parkinson's Disease (LARGE-PD) was created in 2005 to help determine new susceptibility genes for PD in these populations and identify subgroups of

individuals at high-risk for PD [82]. The LARGE-PD team recently published their findings after genotyping 807 Latinos with PD and 690 controls [83]. They found that the *SNCA* locus was associated with PD risk in both the discovery and replication cohorts. In exploratory analyses, there were also specific risk loci based on ancestry – *STXBP6* on chromosome 14 among Latinos with Native American ancestry and *RPS6KA2* on chromosome 6 among Latinos with African ancestry.

In addition to genetic risk variants among Hispanic/Latino individuals, other studies have explored *LRRK2* variants in other minority groups. In one example, DNA samples from 22 Black PD patients with disease onset from 27-65 years of age were obtained from the Coriell Cell Repository collection [84]. Researchers identified 16 exonic variants, including three novel changes, but no known common variants (>5%) were identified as the sample size was too small to make conclusions [84]. A more recent meta-analysis explored overall population differences in *LRRK2* variant distribution in 94 articles that included 49,299 cases and 47,319 controls [85]. Subgroup analyses were performed for Africans, Europeans and West Asians (defined as Asians residing in Western nations), Hispanic/Latinos, East Asians, and mixed populations. In the absence of obvious heterogeneities and bias among included studies, researchers concluded that *LRRK2* G2019S, R1441C/G/H, A419V, R1628P, and G2385R variants were significantly associated with increased PD risk in all populations, while R1398H was associated with decreased risk. In East Asian populations, A419V, R1628P, and G2385R increased risk of PD, while R1398H decreased risk. In contrast to the Baylor study, R1441C/G/H also increased PD risk in European/West Asian populations, though may be more common in Latino patients of Spanish origin. These findings support the notion that *LRRK2* variant distribution differs by racial/ethnic group and should be used to inform future genetic screening strategies and gene therapy development in diverse PD populations [85]. To our knowledge, no multi-ethnic genome-wide association studies have been conducted in the U.S. [76]. There are many other studies reporting ethnic variation in PD gene mutations, though describing ethnic variation in the prevalence and penetrance of each mutation is

beyond the scope of this report. Genetic variation likely contributes to the heterogeneity of PD symptoms, and these data support the inclusion of diverse populations in genetics research including sampling from large geographic regions. Future studies should aim to recruit larger samples of racial/ethnic minorities, particularly Blacks with PD.

2. Environmental Factors

Researchers have explored the role of ancestry/genetics and environmental factors in PD risk by studying persons with PD who reside in the East (Asia and Middle East) and West (Russia, Europe, Americas, Australia, and New Zealand) [86]. The incidence and prevalence of PD is greater in Western nations, consistent with prior studies suggesting that PD is more common in 1) African Americans compared to Nigerians [51] and 2) American men of Japanese or Okinawan descent compared to Asian men [54]. Although gene mutations may overlap within certain communities, these studies support the role of environmental factors in PD causation Geographic location is often a stronger determinant of PD risk than ethnicity [76], and PD risk has been associated with the following: residence in a rural community, occupational exposures, and service in the U.S. Armed Forces. Because certain risk factors may disproportionately affect persons of color, environmental and occupational exposures may contribute to racial/ethnic disparities in PD.

Rural Residence

The association between PD and environmental exposures was not considered until the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, or MPTP, a synthetic street narcotic that caused a clinical syndrome resembling PD in the early 1980s [87,88]. Due to this chemical's resemblance to common herbicides, investigations into rural living, well water consumption, and pesticide use were also conducted [87]. In 1986, Tanner and colleagues surveyed 95 PD outpatients and found significantly greater well water consumption among PD patients with disease onset before age 47 [89]. Early case-

control studies also cited rural living as a possible risk factor for PD. In 1990, researchers at the University of Kansas evaluated agricultural exposures among 150 PD patients and 150 age- and sex-matched controls [90]. PD patients had significantly more years of rural residence and well water consumption; however, there were no differences in farming history or pesticide/herbicide use [90]. In contrast, Hancock and colleagues examined exposure to well water, farming, and pesticides among 319 PD patients and 296 controls matched for age, sex, cigarette smoking, and caffeine consumption in the North Carolina Research Triangle [91]. Self-reported pesticide exposure with dose-response effects was associated with PD (specifically organochlorines and organophosphorus compounds), but not farm living or well water consumption. Unfortunately, data were not presented by race/ethnicity, making it difficult to explore associations in communities of color.

In 1998, Marder and colleagues at Columbia University explored environmental risk factors among White, Black, and Latino individuals in New York City [92]. Among 89 PD cases, 53 were White, 31 were Latino, and 5 were Black. Rural living, area farming, and well water consumption were associated with PD in Black patients only. Interestingly, area farming was also protective in Latino individuals from developing countries, suggesting that urban living may be a greater risk factor for PD in recently industrialized countries [92]. Data regarding rural residence are inconsistent and some researchers have suggested that rurality may not be a useful research variable in PD epidemiology because many definitions of rurality are based on economic and political variables and involve few quantifiable or specific risk factors linked to PD pathogenesis [55]. While most environmental studies do not specifically explore racial/ethnic differences in rural residence and associated exposures, they support the notion that location of residence and environmental factors may increase PD risk. These data are particularly important because certain racial/ethnic groups may be more likely to reside in affected areas, including migrant workers from Central and Latin America that reside in U.S. farming communities.

Occupational Exposures

Unlike studies that explored pesticide exposure as a result of rural living and non-occupational exposure, the Agricultural Health Study explored the incidence of PD among licensed pesticide applicators in Iowa and North Carolina [93]. Incident PD was significantly associated with cumulative pesticide exposure (OR 2.3, 95% CI 1.2-4.5) and personally applying pesticides (OR 1.9l, 95% CI 0.7-4.7).

Exposure to heavy metals has also been implicated in PD risk. In one population-based case-control study, 144 PD patients and 464 age, sex, and race-matched controls were enrolled at the Henry Ford Health System in Detroit, Michigan [94]. Participants received an extensive questionnaire detailing worksite conditions of all jobs held for more than six months from age 18 onward [94]. A blinded industrial hygienist then rated the occupational exposure to each metal of interest. When adjusted for sex, race, age, and smoking status, those with 20 or more years of exposure to the following metals had a significantly increased risk of PD: manganese (OR 10.61, 95% CI 1.06-105.83), copper (OR 2.49, 95% CI 1.06-5.89), lead-copper (OR 5.24, 95% CI 1.59-17.21), lead-iron (OR 2.83, 95% CI 1.07-7.50), and iron-copper (3.69, 95% CI 1.40-9.71). These findings suggest that chronic exposure to heavy metals, either alone or in combination, is associated with PD, and welding remains a significant PD risk factor [94]. Few, if any, studies have explored these exposures in different racial and ethnic groups.

In addition to pesticides and heavy metals, occupational exposure to other materials may increase risk of PD, including paper, sawdust, engine fumes, paint, and other chemicals. Because these associations are less understood, the Centers for Disease Control and Prevention (CDC) evaluated associations between usual occupations and PD mortality using data from the CDC's National Institute for Occupational Safety and Health (NIOSH) National Occupational Mortality Surveillance program, a population-based surveillance system that includes approximately 12.1 million deaths from 30 U.S. states with reported occupations [95]. Occupation codes were grouped into 26 categories based on similar job duties and ordered from high SES (e.g., management, business operations) to low SES (e.g.,

construction, transportation) positions. In this sample, PD patients were older and more likely to be White and male than decedents with other diagnoses. In addition, authors found that patients with higher SES occupations had elevated PD mortality [95]. This finding contrasts with prior studies that explored exposures to chemicals or toxicants that occur more frequently in lower SES occupations. These data could be explained by the aggregation of occupational groups, failure to account for the duration of employment, or the underreporting of PD on death certificates among individuals of racial and ethnic minority groups given known disparities in PD death documentation [62].

Finally, because vitamin D may reduce the risk of PD, one study examined the hypothesis that working outdoors is associated with a decreased risk of PD [96]. Using participants enrolled in Group Health Cooperative, a health maintenance organization in the Puget Sound region of Washington and the University of Washington Neurology Clinic, 447 non-Hispanic PD patients diagnosed between 1992-2008 and 578 age-, sex-, and race-matched controls completed self-reported occupational histories. Interestingly, outdoor work was inversely associated with PD (OR 0.74, 95% CI 0.44-1.23), suggesting that sunlight exposure and other correlates of outdoor work may not play a substantial role in PD risk [96]. This finding is particularly important for individuals who work indoors, including factory workers, mine workers, and others who do not have access to natural light.

Military Exposures

Several environmental exposures have been linked to elevated PD risk among U.S. veterans. First, PD is associated with Agent Orange (AO) exposure during the Vietnam War from 1961-1975. AO is a powerful dioxin-containing chemical that was used as a herbicide and defoliant in Vietnamese forests [97,98]. Toxic AO byproducts, including 2,3,7,8-tetrachlorodibenzodioxin, induce free radical formation and have been implicated in PD and other health conditions [98]. Idiopathic PD is currently a VA service-connected condition in patients with documented AO exposure. AO has also been associated with an increased risk of dementia after controlling for demographic variables [98]. Although many studies have

explored the health effects of AO, few have stratified data by race/ethnicity. However, Black Americans were more likely than White Americans to be drafted for the Vietnam War and comprised 16.3% of all draftees in 1967 despite only comprising 11% of the U.S. population [99]. Future studies should explore whether PD outcomes in affected veterans differ by racial/ethnic group.

Between August 1990 and July 1991, approximately 700,000 American troops were deployed to the Persian Gulf [100]. During this time, Gulf War servicemen and women were exposed to potentially hazardous chemicals, including smoke from oil well fires, chemical and biological warfare compounds, depleted uranium, and pesticides, among other agents [101]. Although these agents have not been directly linked to PD, one prior study assessed whether Gulf War veterans displayed PD-like symptoms that were associated with deployment-related exposures [101]. Researchers enrolled 293 veterans who underwent MRI scans of the brain and completed symptom and exposure questionnaires. Compared to healthy veterans, Gulf War veterans with chronic multi-symptom illness, previously known as Gulf War syndrome [102], self-reported more PD-like motor and non-motor symptoms, more war-related exposures, and had smaller basal ganglia volumes. Although little is known about the long-term consequences of deployment-related exposures, findings from this study suggest that Gulf War veterans may be at higher risk of PD, though a more recent study of 621,902 Gulf War veterans and 746,248 non-Gulf War veterans found no difference in PD mortality rate ratios after more than a decade of follow-up [100]. Longitudinal studies are needed to determine absolute PD risk as veterans age.

Between August 1, 1953 and December 31, 1987, environmental contaminants were present in the water supply at Camp LeJeune, a U.S. Marine Corps Base in North Carolina [103]. Certain diseases have been associated with exposure to trichloroethylene and perchloroethylene [66]. In addition, there is strong evidence of a potentially causal relationship between these contaminants and PD, as these solvents may interfere with mitochondrial function and lead to oxidative stress and apoptosis of

nigrostriatal neurons [66,104,105]. Similar to AO, idiopathic PD is considered a VA service-connected condition in former residents of Camp LeJeune [103].

Finally, military service is also associated with an increased risk of head injury, and several studies have evaluated whether traumatic brain injury (TBI) is associated with an increased risk of PD, particularly among veterans from Operation Enduring Freedom in Iraq and Afghanistan [66]. In one nationwide study, all patients with TBI from the VA database were identified between October 2002 and September 2014 and age-matched to patients without TBI [106]. Among 325,870 total patients, 1,462 were diagnosed with PD during follow-up. Mild TBI was associated with a 56% increased risk of PD, even after adjusting for demographics and medical/psychiatric comorbidities. In addition, TBI patients with PD were 1) diagnosed at a significantly younger age than non-TBI patients with PD, 2) more likely Black or Hispanic/Latino, and 3) more likely to have medical and psychiatric comorbidities [106]. Racial differences in TBI and PD risk warrant further study, particularly because parkinsonism and PD were recently recognized as VA service-connected conditions for veterans with service-related moderate or severe TBI [66,107].

V. PD Phenotype and Diagnosis

1. Phenotype

In addition to racial differences in genetic risk factors for PD and potential exposure to environmental contaminants, research suggests that PD may be underrecognized and underreported in persons of color. Unlike other neurological conditions, PD is a clinical diagnosis based on a physician's interpretation of a patient's self-reported history and physical exam. Many patients are unaware of their symptoms, and comorbid cognitive impairment can reduce awareness of PD [108]. In some circumstances, non-neurologists and other practitioners may not recognize the signs and symptoms of the disease. To diagnose PD, the current Movement Disorder Society (MDS) clinical diagnostic criteria

require the presence of bradykinesia, or slowness or movement, and either rigidity or resting tremor in the absence of atypical features [109]. These clinical symptoms, known as a patient's phenotype, can vary significantly between individuals. Unfortunately, the MDS and other consensus diagnostic criteria were primarily based on the evaluation of White PD patients. Because PD symptoms may differ by race and ethnicity, it is unknown whether current guidelines contribute to diagnostic delays [13]. In most patients, PD symptoms can be grossly divided into three categories: prodromal symptoms, motor symptoms, and non-motor symptoms.

Prodromal Symptoms

Although diagnostic criteria are based on visible motor symptoms such as bradykinesia, rigidity, or tremor, PD pathology is thought to begin decades before the development of motor symptoms. Prodromal PD is defined by the MDS as "the stage wherein early symptoms or signs of PD neurodegeneration are present, but classic clinical diagnosis based on fully evolved motor parkinsonism is not yet possible" [110]. Prodromal symptoms often herald the diagnosis of PD and include olfactory impairment, constipation, mood changes, and rapid eye movement (REM) behavior disorder. While treatment remains symptomatic, accurate identification of patients with prodromal, or preclinical, PD could allow for earlier prognostic counseling or earlier enrollment in clinical trials that offer potentially disease-modifying therapies. Few studies have explored phenotypic differences by race/ethnicity in prodromal PD. However, three studies have explored racial differences in olfactory function [111–113]. The first study used data from two community-based projects to determine the prevalence of anosmia in Whites and Blacks: 1) the Atherosclerosis Risk in Communities (ARC) study that used the 12-item Sniffin' Sticks test, and 2) the Health, Aging, and Body Composition (HABC) study that used the 12-item Brief Smell Identification Test [111]. In the pooled analysis, the overall prevalence of anosmia was 22.3% among Blacks and 10.4% among Whites. This racial difference remained significant after controlling for

age, sex, education, cognition, *ApoE* status, daytime sleepiness, general health status, body mass index, and PD diagnosis [111]. In a second study also using the HABC cohort, researchers identified 42 incident PD cases among 30 White and 12 Black participants with hyposmia over 9.8 years of follow-up [112]. In contrast to the initial study, the association between baseline olfactory impairment and the development of PD was stronger in Whites (HR 4.9, 95% CI 2.3-10.5) than Blacks (HR 2.5, 95% CI 1.7-10.8). Finally, a third study also examined the association between olfactory dysfunction and PD development in the Honolulu-Asia Aging Study [113]. Among patients with hyposmia, researchers identified 35 cases of incident PD over 8 years of follow-up that were most common in patients from the lowest quartile of odor identification after 4 years of follow-up. These findings suggest that impaired olfaction can pre-date clinical PD in Asian men by at least 4 years, though data were not directly compared to other racial and ethnic minority groups. More work is needed to explore racial differences in other prodromal symptoms and subsequent risk of PD.

Motor Symptoms

After passing through the prodromal phase, a formal diagnosis of PD is typically based on the presence of cardinal motor features: bradykinesia, resting tremor, rigidity, and postural instability. Three PD subtypes have also been identified based on the predominant motor symptom, including tremor-dominant, akinetic-rigid, and postural instability and gait difficulty (PIGD) PD. In a study that examined the motor features of early PD in rural patients from central California, 49% were akinetic-rigid, 39% were tremor-dominant, and 12% had mixed phenotypes [114]. Unfortunately, the majority of current data has been collected in White patients, and few studies have compared motor symptoms and PD subtypes in an ethnically diverse sample. In one study that did explore racial differences in PD motor symptoms, Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) scores were higher in Blacks after adjusting for age, cognitive function, and years since diagnosis [115]. A subsequent smaller study

compared 24 Black and 25 White patients with PD at a single clinic and found no difference in UPDRS-III score, but did find worse gait and balance function on quantitative testing among Blacks with PD [116]. Another recent study also examined the frequency of parkinsonism and PD in three Chicago-based community cohorts consisting of 1272 Black and 3335 White Americans [117]. Blacks were less likely to have parkinsonism compared to Whites, suggesting lower rates of PD in the Black community that are still largely unexplained. One review also compared proportions of motor subtypes in several mono-ethnic studies from around the world [76]. While the prevalence of PD subtypes did differ between studies, it was difficult to determine patterns or correlations due to lack of standardized research methodology and differences in inclusion and exclusion criteria [76].

Non-Motor Symptoms

While not included in the formal diagnostic criteria for PD, non-motor symptoms (NMS) are also common and contribute to significant morbidity and mortality. These symptoms include constipation, urinary dysfunction, orthostasis, mood disorders, cognitive impairment, hallucinations, and psychosis, among others. Similar to motor symptoms, few studies have compared these symptoms across ethnically diverse samples. A small study compared Blacks and Whites with PD as an exploratory outcome and found no differences in sleep, fatigue, or olfaction [116]. But, the study did find that Blacks with PD may have greater symptoms of pain and depression. The Non-Motor Symptom Questionnaire (NMSQ) was designed and validated in 2006 and has been used in different populations, showing that all patients suffer from a high burden of NMS regardless of ethnicity [76,118]. For example, one study explored non-motor symptoms among Hispanic/Latino patients with PD in Mexico City using the NMSQ [119]. The most frequent NMS were nocturia, urinary urgency, feelings of sadness, constipation, and insomnia [119]. Authors found no differences in the total number or frequency of NMS based on gender or age of PD onset, though the total number of symptoms did increase with disease progression. These

NMS were similar to reports from other countries, suggesting that overlap exists between racial/ethnic groups. A more recent review also explored the prevalence of NMS in Asian populations using both the NMSQ and Non-Motor Symptoms Scale (NMSS) [120]. Symptoms of memory impairment, constipation, and nocturia were most commonly self-reported on the NMSQ, while the domains of sleep/fatigue, attention/memory, and mood/apathy were most prevalent on the provider-completed NMSS. Phenotypic variability also existed within subgroups from different Asian and Western countries and may be influenced by diet, nutritional status, exercise, comorbidities, and prescribing practices/medical side effects. For example, anticholinergic drugs are used to treat PD in Asia due to their low cost and may contribute to higher rates of cognitive and/or memory impairment [120]. These results suggest that NMS are common in Asian populations and that phenotypic heterogeneity among subgroups would benefit from further study.

As referenced above, cognitive impairment is one of the most frequent and disabling non-motor symptoms in PD, which frequently co-occurs with neuropsychiatric disorders, including depression, anxiety, and hallucinations, and contributes to overall mortality. Some studies suggest that Black patients with PD have higher rates of cognitive decline and progression to dementia than other racial/ethnic groups [20,76]. Black PD patients are also more likely to be prescribed dementia medications compared to White PD patients [76,121]. Similar findings have been observed among Hispanic/Latino patients who may have more severe PD dementia or behavioral symptoms [20,76,121]. Data is conflicting regarding cognitive impairment in Asian PD patients and neuropsychological tests have not been validated in many non-English languages. While Asians have the lowest odds of being diagnosed with dementia in the Medicare cohort, Asian PD patients also report higher levels of subjective cognitive impairment than White patients [122]. The incidence and prevalence of PD dementia among Asian patients is currently unknown, and future studies are needed to explore racial differences in other NMS.

There is limited evidence for ethnic variation in the motor and non-motor features of PD, and significant gaps in the literature remain [76]. Phenotypic differences may be explained by genetic determinants, cultural factors, healthcare inequalities, or comorbid conditions such as Alzheimer's disease or vascular disease that may also vary by race/ethnicity [76].

2. Diagnosis

One hypothesis for lower rates of PD diagnosis among racial and ethnic minority groups is that the diagnosis of PD in these groups may be missed or delayed in those exhibiting typical symptoms. In the only population-based door-to-door study of PD prevalence in the U.S., researchers found that about 40% of individuals identified with parkinsonism through the study had been previously undiagnosed. Furthermore, Blacks were twice as likely to be undiagnosed as Whites with parkinsonism [50]. Dahodwala and colleagues conducted a retrospective chart review of veterans with newly diagnosed PD at the Philadelphia VAMC to explore whether Blacks presented for care at a later PD stage, a proxy for delayed diagnosis [15]. Compared to their White counterparts, Blacks presented for care at more advanced PD stages (H&Y 2.5 vs. 2.0) and reported less disability at the same level of motor impairment. Additionally, under-reporting of disability accounted for a significant portion of the racial difference in PD stage at diagnosis [15]. Similarly, in a study of new visits to a specialty movement disorders clinic, Blacks and those with lower educational attainment and low income presented with worse motor scores and greater disability [115]. These findings could be influenced by differences in health literacy or mistrust of the healthcare system, prompting individuals to be less vocal about their symptoms or seek care at a later time [123].

Because health literacy and attitudes about PD may play a role in unexplained diagnostic delays, Pan and colleagues conducted a mixed-methods study involving focus groups at 10 senior centers in Philadelphia serving older White, Black, and Chinese Americans [123]. Overall, there was a low level of

knowledge about PD among community members. During qualitative focus groups, there were also several racial/ethnic differences in response to a question about reasons for not seeking medical care. While Blacks identified lack of insurance, religious concerns, and mistrust as barriers, Chinese Americans identified language barriers and lack of knowledge on where to seek treatment. Both groups are also subject to explicit bias and receipt of lower quality care from health care providers. More studies are needed to evaluate perceptions of PD and care-seeking behaviors among diverse populations. It is especially important to note that data on PD incidence, prevalence, and mortality will be biased if there are substantial rates of undiagnosed PD, particularly among those from racial and ethnic minority groups.

VI. Access to Care and Care Delivery

After PD diagnosis, racial differences also exist in access to care and care delivery. The most common problems with care access include cost of services, inadequate insurance coverage, transportation limitations, lack of family support, and lack of access to specialty care and support resources [124,125]. This is particularly problematic in PD, as multidisciplinary care provided by a movement disorders specialist, nurse, and social worker has been associated with improvements in motor function and quality of life [126]. When patients are unable to seek care from a PD specialist, they must choose whether to seek care from a general neurologist. their primary care provider, or forgo PD-specialized healthcare altogether. In one study exploring care access among Medicare beneficiaries between 2002-2005, only 58% of Medicare patients with PD received neurologist care [19]. Sex and race were significant predictors of neurologic treatment, and women (OR 0.78, 95% CI 0.76-0.80) and non-Whites (OR 0.83, 95% CI 0.79-0.87) were less likely to be treated by a neurologist. When exploring data by demographic group, Black female patients with PD were least likely to receive neurologist care during the study period (AOR 0.67, 95% CI 0.62-0.71), followed by Black male and White female patients after

adjustment for medical comorbidities and SES [19]. [**Table 3**]

Table 3 Referral rates and adjusted odds of receiving neurologist treatment (2002–2005) among Medicare beneficiaries with incident Parkinson disease

Model 2 variables: Race-sex pairs	Referred, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	*p*
White male	31,520 (55.1)	Reference	Reference	
White female	29,627 (46.7)	0.72 (0.70–0.73)	0.76 (0.74–0.78)	<0.001
Black male	1,529 (44.7)	0.67 (0.63–0.72)	0.68 (0.63–0.73)	<0.001
Black female	1,982 (45.4)	0.61 (0.57–0.64)	0.67 (0.62–0.71)	<0.001
Hispanic male	704 (51.7)	0.80 (0.70–93)	1.19 (0.95–1.48)	0.122
Hispanic female	726 (47.4)	0.65 (0.56–75)	0.79 (0.63–0.98)	0.036
Asian male	359 (50.0)	0.88 (0.80–0.98)	0.92 (0.81–1.05)	0.210
Asian female	327 (44.1)	0.74 (0.67–0.82)	0.85 (0.75–0.95)	0.006

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Model includes race-sex pairs, age, modified comorbidity index, and socioeconomic deprivation score.

In another study that evaluated racial and ethnic differences in the utilization of neurologic care in patients with self-identified PD using the Medical Expenditure Panel Survey between 2006-2013, only 56% of patients saw a neurologist [127]. After controlling for age, sex, activity limitation, self-reported health status, health insurance coverage, family income, education, and region, Black and Hispanic/Latino patients with five neurologic conditions (PD, multiple sclerosis, epilepsy, headache, and cerebrovascular disease) were significantly less likely to receive outpatient neurology care, particularly those with less education, income, and no health insurance [127]. Consequently, Blacks also had higher neurology-related ED visit rates, inpatient admissions, and hospitalization costs than White patients. These acute care utilization patterns may pose challenges for PD patients from communities of color, as hospital staff can lack the knowledge necessary to treat PD motor symptoms, non-motor symptoms, and associated medical complications [128].

For military veterans, the Veterans Health Administration (VHA) is charged with providing specialty care to all persons with PD regardless of their background or insurance status, making it an ideal system in which to study access to medical care, education, and support services. As noted above,

the VHA created six PADRECCs in 2001 to improve the delivery of healthcare to persons with PD [65]. All veterans are eligible for PADRECC services, though details regarding racial/ethnic differences in PADRECC access are currently unknown. When comparing PD care in PADRECCs vs. other VA clinics, PADRECC patients received PD education and support services more frequently that non-PADRECC PD patients [129]. PADRECC patients also reported higher satisfaction and received a broader range of educational materials [129] suggesting that PADRECC specialty care is superior to general care. Unfortunately, many VA patients do not live in close proximity to a PADRECC site, and persons with PD who reside in rural communities often have more difficulty seeking subspecialty care due to limited provider availability and longer wait times. To improve care for persons with PD residing in rural locations, advancing technology such as telehealth platforms have been increasingly utilized. PD patients are particularly good candidates for telemedicine given their restricted mobility and the ease of visual assessment [130]. Because some patients of lower SES may not have access to a smartphone or computer, persons with PD in the VHA are eligible for a VA-issued iPAD to facilitate home telehealth visits. Other veterans can use telehealth services at local community clinics that virtually connect to larger PADRECCs. Teleneurology has successfully delivered care to veterans in both rural and urban settings with high levels of patient and provider satisfaction [131,132]. These services have also expanded in the wake of the COVID-19 pandemic. Health care access is a complex concept that can be influenced by organizational and socio-cultural factors [12]. Further work is needed to improve healthcare access and deliver equitable care to all vulnerable PD populations.

VII. Treatment Disparities

1. Medical Treatment

Treatment disparities have been well-documented in the PD literature and involve medical and surgical therapies. Symptomatic treatment in PD involves a variety of medications, including

carbidopa/levodopa, dopamine agonists, monoamine B inhibitors (MAOBi), catechol-O-methyl-transferase inhibitors (COMTi), and amantadine to improve clinical outcomes. Dopaminergic medications are the mainstay of treatment; however, only 33-66% of patients start medication at time of diagnosis [16,57]. The choice and utilization of anti-Parkinson drugs may vary based on clinical and non-clinical factors, including motor symptoms, comorbidities, patient preference, and provider characteristics. Patient characteristics, including race/ethnicity and SES, are also independently associated with treatment differences in numerous diseases [2]. In an early study using Medicaid claims data from 1999-2003, 307 newly diagnosed cases of PD were identified, of which 14% were Black and 86% were White [16]. In unadjusted analyses, Black patients were less likely than White patients to receive any medication or physical therapy (12% vs 38%). Black patients were also less likely to receive medication alone (12% vs 33%). In adjusted analyses, Blacks remained significantly less likely to be started on medication or referred for physical therapy after controlling for other demographic and clinical factors, including age, sex, geography, initial visit with a neurologist, and reason for Medicaid eligibility [16], suggesting that racial disparities exist in medical treatment [133]. More recently, Dahodwala and colleagues described the prevalence of anti-Parkinson drug use among Medicare Part D beneficiaries with PD from 2007-2010. Over 81% of PD patients were treated with anti-Parkinson drugs; however, Black patients and those without a neurologist were significantly less likely to be treated [57]. Black nursing home residents with PD are also less likely to receive anti-Parkinson drugs [134].

In the veteran population, one study explored dopamine agonists (e.g., bromocriptine, pergolide, pramipexole, ropinirole) as monotherapy for PD motor symptoms. In contrast to their White counterparts, non-White veterans were significantly less likely to be titrated to therapeutic range [18]. In 2007, members of the Parkinson Study Group also assessed the safety, tolerability, and efficacy of adjunctive pramipexole in 149 PD patients of African, Asian, or Hispanic heritage treated with levodopa [135]. Patients were randomized to pramipexole or placebo, and the main outcome measure included

the change in UPDRS-II (motor experiences of daily living) and UPDRS-III (motor symptoms) scores from baseline to week 10. Overall, members of each racial/ethnic group responded similarly to pramipexole suggesting no differences in response to therapy, though non-significant differences were noted in the rate of adverse effects. For example, asthenia (fatigue) was more common in patients of Asian heritage, confusion was reported more frequently by Black patients, and hallucinations were nearly 3-fold higher in Black patients compared to Hispanic/Latino patients. In addition, insomnia and dyskinesias were more common in pramipexole-treated Hispanic/Latino patients [135]. Thus, the need for anti-Parkinson medications with a favorable side effect profile is crucial for patients from racial and ethnic minority groups.

With regard to levodopa-induced side effects, racial/ethnic differences may also exist in the development of dyskinesias or "wearing off" that could stem from prescribing practices or differential response to dopaminergic therapies. Unfortunately, these motor complications of PD treatment have not been extensively studied in diverse patient populations [76]. Some studies suggest that Asian patients may be more likely to experience dyskinesia, resulting in lower recommended doses of dopaminergic drugs [122,136]. Racial/ethnic differences may also exist in drug metabolism. For example, racial variations in the COMT enzyme suggest that patients of African descent may metabolize levodopa faster than patients of European descent [137].

Racial disparities also exist in prescribing practices for medications that treat non-motor symptoms, such as cognitive impairment and depression. In one study exploring patterns of dementia treatment and frank prescribing errors among Medicare beneficiaries with PD, Mantri and colleagues found that dementia drugs were more likely to be prescribed to Black (AOR 1.33, 95% CI 1.28-1.35) and Hispanic/Latino (AOR 1.28, 95% CI 1.22-1.35) beneficiaries and less likely to be prescribed to Native American beneficiaries (AOR 0.62, 95% CI 0.51-0.74) [121]. These data call into question whether unique PD trajectories exist across demographic groups if cognitive impairment is indeed more prevalent

among Black and Hispanic/Latino patients. However, Black Medicare beneficiaries with PD are at greater risk than their White counterparts for both vascular dementia and Alzheimer disease, and thus, the increased odds of dementia medication use may be explained by coexisting vascular dementia, PD dementia, or a mixed neurocognitive disorder. Lower cross-cultural validity of cognitive testing may also overestimate dementia severity in some Hispanic/Latino patients for whom English is a second language [121]. Data also suggest that prescribing errors may be more common among certain demographic groups. For example, among patients receiving an acetylcholinesterase inhibitor for dementia, such as donepezil, rivastigmine, or galantamine, Hispanic/Latino (AOR 1.11, 95% CI 1.00-1.23) and female (AOR 1.30, 95% CI 1.25-1.35) beneficiaries had greater odds of being co-prescribed an anticholinergic drug, a frank prescribing error that can exacerbate cognitive impairment [121]. Finally, racial disparities in antidepressant treatment have also been studied among U.S. veterans. In a retrospective study of 309 non-Hispanic White and 65 non-White veterans with PD at the Los Angeles PADRECC, Cheng and colleagues detected disparities in depression treatment among non-Whites [18]. Further research is needed to identify risk factors that contribute to treatment disparities, along with any group-specific associations or drug-drug interactions.

2. Surgical Treatment

In addition to medical therapies, racial disparities also exist in procedural interventions, such as deep brain stimulation (DBS) surgery [138,139]. An early study exploring predictors of DBS placement in 71 non-federal U.S. hospitals from 1996-2000 found that younger age, White race, private insurance, residence in higher income areas, and hospital teaching status were associated with DBS surgery after adjusting for year of surgery [17]. 85.9% of patients who underwent DBS were White, while only 0.6% of DBS patients were Black [17]. Another study of more than 657,000 Medicare beneficiaries from 2007-2009 also demonstrated racial differences in the likelihood of DBS placement: for every 1 Black patient

who received DBS, 5 White patients underwent the procedure [140]. A third study of more than 2 million PD discharges from U.S. hospitals also revealed that Blacks were 8 times less likely to undergo DBS surgery than Whites after controlling for patient and hospital-level factors [140].

Lower utilization of DBS among Black patients has been attributed to several factors, including a higher prevalence of concomitant dementia which may be a contraindication for DBS placement, increased medical comorbidities, lower SES, patient distrust, and inadequate patient–physician communication [139,140]. Medicaid coverage may also predict DBS placement. White Medicaid patients with PD received significantly more DBS surgeries the Black non-Medicaid patients, which supports that notion that race, rather than SES alone, may contribute to these disparities [141]. There is also significant cost associated with DBS surgery [141,142]. In one study exploring healthcare utilization and cost among U.S. veterans with and without DBS after 5 years of follow-up, average total healthcare costs, including DBS procedures and complications, were $77,131 higher per person for patients who received DBS than patients who received medical management [143]. It is also unknown to what degree patient preferences may contribute to perceived disparities. For example, in a retrospective chart review of the University of Miami DBS database, women were less likely to undergo DBS compared to men, largely based on preferences [144].

3. Therapies and Palliative Care

While exercise and physical activity have been shown to slow PD progression, racial/ethnic disparities also exist in referral patterns for therapies. For example, Hispanic/Latino PD patients are less likely than their White counterparts to receive physical therapy, occupational therapy, and speech therapy [145,146]. Hispanic/Latino PD patients are also less likely than Asian PD patients to receive therapy services despite having the second highest PD incidence and prevalence rate [146]. In contrast to therapies, racial/ethnic disparities were not found in referral patterns for inpatient palliative care

services in one study, though women, patients with Medicare/Medicaid, and those with lower income were less likely to be referred to palliative care [147]. Disparities in access to rehabilitation services and palliative care may result in lower functional outcomes and poorer quality of life. Future studies that explore the reasons underlying treatment disparities are crucial to promote equitable access to medical care, DBS surgery, and support services.

4. Outcomes

Disparities in PD treatment ultimately lead to worse outcomes. Individuals who do not receive care from a neurologist are more likely to have hip fractures, visit the ED, be hospitalized and placed in skilled nursing facilities, and, ultimately, die [19].

VIII. Research Disparities

Despite significant advances in PD research, the majority of published studies come from the U.S. and Europe, where patient populations are predominantly White and racial/ethnic minorities are underrepresented in both observational studies and clinical trials. In one review that assessed minority participation in PD trials between January 1, 1985 and December 31, 2007, only 41 of 239 (17%) publications representing 33 distinct studies reported racial/ethnic participation [22]. Of these 33 studies, 7,481 participants were enrolled, of whom 8% were non-White. In addition, only 9 of 32 studies reported detailed racial/ethnic composition other than the percentage of "White/Caucasian" patients enrolled. These 9 studies enrolled a total of 1,009 participants, including 17 Black and 13 Hispanic/Latino participants that represented 1.7% and 1.3% of total enrollment, respectively. In comparison, non-Whites represented 20% of the U.S. population over age 60 in 2009 [148]. A more recent meta-analysis reviewed the participation of racial and ethnic minorities in PD trials that evaluated the treatment of neuropsychiatric symptoms [149]. Similar to the initial review, only 11 of 63 studies reported racial/ethnic composition. Of the studies that included data on race/ethnicity, only 5 (0.2%) Black, 16

(0.64%) Hispanic, and 539 (21.44%) Asian patients were enrolled, while a total of 1,908 (75.8%) White patients were included. Failure to enroll diverse populations exacerbates PD disparities and limits our ability to detect differences in disease outcomes, response to interventions, and therapeutic benefit [23]. In addition, failure to include non-White patients limits the generalizability of research findings to communities of color.

Several barriers may explain the underrepresentation of different racial groups in PD research. In the U.S., clinical trials are conducted at a limited number of academic medical centers that can pose barriers to recruitment and research participation [23]. First, patients residing in rural regions may have difficulty accessing these centers. In addition, patients are largely referred for studies by their neurologist or movement disorders specialist. However, in one study of Medicare beneficiaries with PD, 42% of patients did not see a neurologist [19], which may disproportionately affect persons of color. Barriers to research participation may also affect those of lower SES, as participation in clinical trials can have a significant financial burden on patients and their family members who are responsible for other PD-associated medical expenses [23]. Financial burden includes both direct costs of travel and lodging near a participating research site and indirect costs incurred through missed days of work and potential loss of employment. In one study, 30% of participants with PD reported that financial commitments were a burden to trial participation [150]. Thus, the PD trial referenced above that studied pramipexole in levodopa-treated PD patients of African, Hispanic, and Asian descent had success in recruiting a diverse sample after reimbursing participants for direct and indirect study expenses, such as transportation and child or dependent care [135]. In communities of color, delays in diagnosis and presentation for clinical care at more advanced stages of disease may also prevent enrollment in early-stage neuroprotective trials [21]. Finally, language barriers can pose major challenges to research enrollment, as the majority of trials do not permit the recruitment of non-English speaking patients.

Despite these barriers, a survey of PD patients found no racial differences in willingness to participate in clinical research [151]. For example, one study at the University of Miami enrolled 113 PD patients and 49 caregivers to evaluate their willingness to participate in genetic studies [152]. Although Hispanic/Latino and non-Hispanic/Latino patients were equally motivated to participate in genetic research for PD, Hispanic/Latino patients were less likely to be influenced by the promise of scientific advancements "*To help future generations with PD*". This lack of scientific interest correlated with lower education levels, and authors attributed the underrepresentation of Hispanic/Latino individuals in PD research to a reduced invitation to participate. There are also perceived facilitators of participation among racial minorities, including benefits of participation (e.g. medical services, monetary compensation) and altruism (i.e. helping another in need) [153].

Lack of diversity in clinical trials has important implications. First, because PD is a heterogeneous disorder with complex etiologies, risk factors, and outcomes, our understanding is limited when only certain subpopulations are studied. Second, underserved minority groups receive substandard PD care when compared to Whites, and lack of available data from clinical trials limits our ability to provide more effective, evidence-based care [16,18,140]. As the number of research opportunities increases, expanding access to clinical trials and ensuring equitable enrollment are exceedingly important.

To this end, several initiatives were recently developed to improve minority recruitment and combat racial disparities in clinical research. In 2019, the Michael J. Fox Foundation for Parkinson's Research (MJFF) and the Community Access, Recruitment, and Engagement (CARE) Research Center at Massachusetts General Hospital partnered on a study called Fostering Inclusivity in Research Engagement for Underrepresented Populations in Parkinson's Disease, or FIRE-UP PD [154]. This initiative will establish outreach programs at four academic sites to develop community-focused interventions and develop culturally relevant messaging and materials to educate patients on PD research [154]. These sites include Boston Medical Center, Cleveland Clinic Florida (Weston), University

of Colorado, and Northwestern University. To ensure diversity in basic science research and genetic studies, the Aligning Science Across Parkinson's (ASAP) Initiative also developed the Global Parkinson's Program to fund international multidisciplinary teams that are dedicated to exploring the underlying causes of PD [155]. A subset of this initiative, known as the Global Parkinson's Genetics Program, or GP2, will genotype >150,000 volunteers worldwide to explore genetic PD risk factors [156]. On a national level, the NIH has also expanded minority recruitment. Despite these advances, lack of diversity in PD research remains a significant limitation in the medical literature.

IX. Summary of Gaps in Knowledge

Although research exploring racial and ethnic disparities in PD has grown in the last decade, many gaps in knowledge still remain.

1. Epidemiology

Between the 1960s and 1990s, several community-based studies explored the incidence and prevalence of PD in communities of color. While these studies explored the epidemiology of PD among White, Black, and Latino patients, few studies have explored the incidence and prevalence of PD in other minority populations, including Asians and Native Americans. In addition, sample sizes in these early studies were relatively small. Since the early 2000s, epidemiologic studies involving large national datasets have improved the generalizability of PD data. However, large organizations, such as the Centers for Medicare and Medicaid Services, commonly present data in aggregate form and fail to capture data from racial/ethnic subgroups or from those who are uninsured or undocumented. In addition, detailed sociodemographic information is limited. Thus, the perceived impact of social determinants of health on PD incidence, prevalence, morbidity, and mortality is largely unknown. Because race/ethnicity is often considered a proxy variable for SES, there is a significant need to understand the role of social determinants in PD epidemiology and health outcomes.

Gaps:

- Studies exploring PD among Asians, Native Americans, and racial and ethnic subgroups
- Studies exploring PD among undocumented and uninsured patients
- Studies that explore the impact of social determinants on PD epidemiology

2. Etiology

The etiology of PD is currently unknown and may represent a combination of genetic and environmental risk factors that disproportionately affect individuals from different racial and ethnic groups. Unfortunately, the majority of early familial studies and genetic analyses were conducted among patients of European descent. In the last 25 years, the identification of PD-associated gene mutations, including alpha-synuclein (*SNCA*), parkin (*PRKN*), PTEN induced putative kinase 1 (*PINK1*), *DJ-1,* leucine-rich repeat kinase-2 (*LRRK2*)*,* and glucocerebrosidase (*GBA*), have allowed for genetic studies in more diverse populations. Despite technological advancements, genetic testing in communities of color is lacking and few studies have explored genetic mutations in Black or African YOPD patients. In addition to genetic risk factors, prior research suggests that geographical location may be a stronger determinant of PD risk than ethnicity, further supporting an environmental cause [76]. To this end, many studies have explored rural residence, occupational exposures, and service in the U.S. Armed Forces as potential risk factors for PD. Unfortunately, few studies stratify data by race/ethnicity which may aggravate or mitigate PD risk in certain environments. To address health disparities, there is a critical need to understand the role of genetic and environmental risk factors in diverse racial/ethnic and socioeconomic groups.

Gaps:

- Studies exploring PD gene mutations and gene penetrance in communities of color, particularly among Black patients
- Multi-ethnic genome-wide association studies in the U.S.
- Studies exploring rural, environmental, and occupational risk factors that may disproportionately affect a specific racial or ethnic group

3. Phenotype and Diagnosis

Several studies have detected racial disparities in the diagnosis of PD, which may be under-recognized and under-reported in communities of color. In addition, PD phenotype, including prodromal, motor, and non-motor symptoms, may vary by racial/ethnic group. Because the majority of studies highlight diagnostic disparities in Black populations, more studies are needed to detect racial differences in the presentation and diagnosis of PD among Hispanic, Asian, and Native American patients in the U.S. Such differences may prompt further revision of the current MDS diagnostic criteria that were developed based on evaluation of White patients.

Gaps:

- Studies exploring racial differences in symptom onset and diagnosis
- Studies exploring racial differences in prodromal, motor, and non-motor symptoms
- Studies exploring comorbid disease burden or cultural factors/preferences that could contribute to phenotypic differences or influence the recognition of these differences in minority populations

4. Access to Care/Care Delivery

In addition to differences in PD diagnosis, disparities exist in care access and delivery. These disparities likely stem from racial/ethnic differences in health-seeking behaviors, provider bias, and social

determinants of health, including insurance coverage, cost of services, transportation limitations, and limited specialty care and support resources based on geographic location that can influence an individual's ability to access and navigate the healthcare system. In one study of Medicare beneficiaries, women and non-Whites were less likely to be treated by a neurologist [19]. Despite these differences, further research is needed to characterize more detailed racial differences in access to specialty (neurology) and subspecialty (movement disorders) care and their underlying causes. In addition, future studies should explore barriers to care in patients from other designated health disparity populations, including LGBTQ individuals and those from resource-limited settings.

Gaps:

- Studies exploring differences in care access among different racial/ethnic groups
- Studies detailing racial/ethnic and socioeconomic barriers to PD care access and delivery
- Studies exploring barriers to care among individuals from designated health disparity populations, including LGBTQ patients and those from socioeconomically disadvantaged and underserved rural populations
- Interventions to improve specialty or subspecialty care access
- Interventions to improve care delivery, including translation services

5. Treatment

Disparities in both medical and surgical treatment and referral for support therapies have been documented in the PD literature. Black patients, for example, are less likely to be started on anti-Parkinson medication and less likely to undergo DBS surgery [16,139,141]. Other studies have explored differences in prescription drug usage and surgery referral among White, Black, and Hispanic/Latino patients. Hispanic/Latino patients are also less likely than White and Asian patients to receive therapy

services [145,146]. Despite these data, little information exists regarding treatment patterns among Asians, Native Americans, and racial and ethnic subgroups. In addition, few studies have explored treatment preferences among these groups that may influence care decisions, along with sociodemographic factors such as income, insurance coverage, or family support.

Gaps:

- Studies exploring racial/ethnic differences in prescribing practices for medications that treat both motor and non-motor symptoms
- Studies exploring racial/ethnic differences in medication efficacy, tolerability, and adverse reactions
- Studies exploring racial/ethnic differences in DBS referral patterns
- Studies exploring the influence of patient preferences and social determinants on treatment plans
- Interventions to reduce disparities in medical and surgical treatments

6. Research

The majority of observational and clinical trial data come from published studies in the U.S. and Europe. As a result, the majority of research participants are White and few studies publish data collected from patients of color. Failure to include diverse research subjects further limits the generalizability of PD research and exacerbates PD disparities. Thus, more research is needed to determine specific barriers to participation among diverse patients with PD. Further research is also needed to determine what outreach efforts or accommodations (e.g. reimbursement of transportation costs or study materials in languages other than English) are most appropriate to encourage participation among minority groups. The scarcity of race-specific data remains a significant barrier to identifying disparities and ultimately overcoming them.

Gaps:

- Studies exploring barriers to study recruitment and participation among diverse PD patients
- Studies exploring the efficacy of outreach efforts and incentives to improve enrollment
- Interventions to improve research participation and clinical trial enrollment among racial and ethnic minority groups

X. Strategies to Reduce Inequities and Improve Care

Racial and ethnic disparities are pervasive in PD and increasingly important, not only because racial and ethnic minority groups will represent half of the U.S. population by 2040, but because all Americans should have equitable access to health care regardless of their age, race/ethnicity, sex, gender identity, geographic location, or financial resources [127]. Healthcare disparities exist at all levels of PD care, from diagnosis to treatment and participation in clinical research. Thus, to confront healthcare disparities in PD, we must first *recognize them*. Because diagnostic delays exist among members of racial and ethnic minority groups, and persons of color are less likely to be cared for by neurologists [13,19], educational campaigns are needed to improve both individual knowledge and community awareness of PD symptoms and care. In addition, there is a significant need for improved translation services and written translated materials for non-English speaking patients to improve PD recognition and promote care-seeking behaviors.

Following PD diagnosis, many racial/ethnic minorities are also undertreated when compared to their White counterparts [16–18]. However, little is known about the factors that contribute to these diagnostic and treatment disparities, making it important to *understand their underlying causes*. For example, individual preferences or community-based differences may influence care-seeking behaviors and medical decision making, along with patient mistrust rooted in historical racism. Racism and discrimination are powerful forces that prevent minority groups from receiving necessary care and

should be acknowledged. Physician-level factors also include conscious and unconscious provider bias, provider-held beliefs or stereotypes about the behavior or health of minorities, and greater clinical uncertainty regarding the PD symptoms experienced by minority patients [20,157]. Finally, inequality within the healthcare system itself also contributes to care disparities, particularly for patients without insurance coverage and those who live in medically-underserved communities. Further research is needed to understand patient, provider, and community-level factors that guide health behaviors. To explore these factors, targeted programs are needed to identify perceived barriers to care and cues to action among rural residents and persons of color. In one study exploring rural health needs among a PD community in Wyoming, focus groups identified PD complications, lack of coordinated care and community/financial support, and stigma of diagnosis as the largest barriers to health and wellbeing [158]. Participants recommended the use of technology to provide educational programming and support telehealth clinical visits with specialists. Partnership with community groups and church or other spiritual organizations can also provide support for those living with PD. Next, culture-centered care should be implemented in all physician practices to build patient trust, and physicians should consider including the entire family unit or designated decision maker at all appointments [139]. Finally, health services research that explores healthcare outcomes in large administrative datasets are needed to define the scope and severity of PD disparities at the state and national levels.

Through the process of improving and reorganizing our understanding of the underlying causes of health disparities, we must next *identify modifiable risk factors.* Are certain etiologies (i.e., genetic risk factors or environmental exposures) more common among patients from certain racial/ethnic groups? Can we improve access to medical and subspecialty care? Can we improve minority enrollment in clinical trials to enhance our understanding of PD care? Although the majority of research participants are White, the composition of PD research participants should ideally mirror the demographics of PD patients in certain communities. Researchers have proposed several potential reasons for disparities in

research participation. First, delays in diagnosis and presentation to clinical care at more advanced stages of disease may prevent enrollment in more early, neuro-protective trials [23]. Second, the majority of clinical trials occur at specialty movement disorder centers that are not accessible to all patients. Thus, recruiting a higher proportion of minority patients for clinical research will require access to participants outside of the traditional model of movement disorders center-based recruitment [23]. One of the most successful studies to recruit diverse participants involved the use of pramipexole in levodopa-treated Parkinson's disease patients of African, Asian, and Hispanic heritage conducted by the Parkinson Study Group [135]. This study successfully recruited patients from communities of color by reimbursing participants for travel expenses and dependent care to reduce financial barriers. Another study tested a recruitment methodology in order to improve minority patient participation in PD trials by providing partial funding for a recruitment coordinator, continuing medical education for physicians serving underserved populations, and outreach to community-based referring physicians [159]. Unfortunately, this study was stopped early for lack of efficacy, but sites that were most successful in recruiting a diverse sample had stronger relationships with community physicians. Partnerships with community health workers or trusted laypeople from underrepresented communities can help build relationships with minority patients [160]. While uncertainty remains surrounding efforts to increase diversity in clinical trial participation, Vaswani and colleagues suggest several barriers and mitigation strategies [23] [**Table 4**]:

Table 2 Barriers and potential mitigation strategies to improve trial participation

Trial stage	Barrier	Potential mitigation strategy
Recruitment	Lack of racial and ethnic diversity	Prespecified goal for recruitment of minority subjects Translate recruitment material into other languages, use of plain language in health literacy materials, tailoring research to community needs Make in-person translators available Build an ethnic and racially diverse recruitment team Partner with community health workers or trusted laypeople Expand recruitment to sites that serve a high proportion of minorities and have had prior success recruiting diverse populations
	Limited comprehension or trust of research	Identify community research advocates or navigators Develop opportunities for learning about research Engage communities in the development process Crowdsourcing for study design, recruitment tactics, consent format Delivery of material via print and video or multimedia format Educational opportunities for potential participants Provide participants their own research data when possible
	Geographic location	Provide or reimburse for transport, accommodations Develop community physician partnerships
	Concerns over research integrity	Electronic and passive data capture Use of biochemical and imaging markers as outcomes Blockchain data monitoring
Screening/enrollment	Burdensome requirements	Simplified study design Short double-blind phase Provide telephone/text/electronic reminders of visits Coordinate medical and research visits Alter study design to reduce inefficiency/waste of participant time via adaptive designs and pragmatic trials
	Concern of receiving placebo	Active treatment comparison Cross-over to treatment after placebo-controlled phase Open-label design
	Limited pool of potential participants	Registries of research-interested PD patients Electronic medical record screening tools Opt-out research consent for whole clinic
	Lack of racial and ethnic diversity	Establish relationships with community groups Identify community research advocates
	Geographical location	Partnering/networking with nonacademic physicians to expand access to research Remote screening via telephone or video conference Enhanced records access through electronic medical records
Retention	Loss of income due to trial participation	Compensation strategies tailored to participants needs (travel, lodging, parking, child/adult care, work leave reimbursement) Reward payments for timely completion of study requirements
	Home/life obligations	Limit in-person evaluations, consider telehealth or virtual research visits Decrease research burden by limiting unnecessary data collection, increasing remote data capture Flexible time of visits, including evenings and weekends

The use of thoughtful and novel trial designs, technology, financial incentives, careful attention to the burdens of trial participation, and recognition of disparities in healthcare access and delivery can help address common barriers [23]. Most importantly, in addition to targeting modifiable risk factors, we must also *develop interventions and policies* to improve care for all PD patients. What guidelines can we implement to reduce variability in treatment due to unconscious bias? What governmental policies can

we put in place to improve affordability and access to care? To combat racial disparities in PD, we must think creatively about solutions that will not only reduce disparities, but also improve quality of care for all PD patients. To this end, we propose the following health policy action steps:

1. Develop a national plan for Parkinson's disease

The prevalence of PD is rising. Policies to improve PD diagnosis and treatment should be implemented at a population level to confront and reduce inequities in care. To ensure timely diagnosis, public health campaigns are needed to improve awareness and recognition of PD symptoms. To identify at-risk populations, a national registry should be created to collect epidemiologic data and determine geographic trends in PD incidence and prevalence, as PD registries currently exist in select states only (e.g., California, Nebraska) and clusters may cross state lines. In addition, government insurance programs like Medicare should guarantee coverage for specialty drugs and advanced therapies regardless of patient income. Because implicit bias, structural racism, and patient mistrust in the healthcare system are barriers to developing national health policies, the initiatives outlined below may also serve as incremental steps toward achieving a national PD plan.

2. Establish an advisory council within the Department of Health and Human Services on PD care, services, and research

In the process of developing a national agenda, an advisory council should help set the standard for PD care and oversee collaborative efforts between government agencies, private foundations, healthcare systems, and grassroots organizations to reduce health disparities in PD. An advisory council could also coordinate efforts across federal research agencies, ensure the proper allocation of funding for PD-related research and health initiatives, and catalyze private sector research through tax credits and the efficient dissemination of results from federally-funded studies to private sector organizations that are developing interventions to combat racial disparities. Finally, this council could help recruit and invest in

PD workforce from minority and immigrant-serving communities to improve engagement among persons of color.

3. Invest in community, patient, family, and provider PD education

There is a pressing need for greater community awareness of PD symptoms to ensure timely diagnosis and treatment. Public health campaigns at the local, state, and national levels are needed to educate the public and health care providers on recognizing (and screening for) common prodromal, motor, and non-motor symptoms. Improved translation services in clinical settings will help promote health-seeking behaviors among non-English speaking patients. In communities without a practicing neurologist or PD specialist, continuing medical education courses could also teach general practitioners about the nuances of PD diagnosis and treatment and could be offered virtually or in-person at professional conferences.

4. Invest in PD disparities research

Because research participation in PD trials disproportionately occurs among White individuals, we must also develop innovative strategies for diverse clinical trial recruitment to strengthen the science underlying PD etiology and treatment. Grant proposals that address PD health disparities and encourage diverse research participation should be prioritized in the review process. Additional research money is also needed to ensure these projects are funded. Financial incentives, like student loan forgiveness, could be awarded to research teams that enroll a certain percentage of research participants from different racial/ethnic groups. Conversely, if pharmaceutical companies or other study groups fail to enroll minorities, they could face harsher penalties, such as withheld approval from the US Food and Drug Administration for study drugs. [139]

5. Invest in the care of military service personnel and Veterans at elevated risk of PD

Non-White populations were disproportionately recruited for military service during the Vietnam War, which may place Veterans from racial and ethnic minority groups at elevated risk of PD through unique exposures (e.g., Agent Orange, trichloroethylene and perchloroethylene, TBI). To reduce racial disparities and improve health outcomes, we must invest in the care of active service members and Veterans. Environmental exposures to chemicals and other contaminants should be limited when possible, and annual screening for PD should be offered free of charge to those with and without formal service connection.

6. Support nationwide teleneurology initiatives and insurance reimbursement

There is a national shortage of neurologists in the US, and many persons with PD do not have access to neurology specialty care. To improve care access in underserved and rural communities, teleneurology initiatives are needed. State and national laws should be implemented to allow neurologists and PD specialists to conduct virtual visits with all patients regardless of their state of residence. Insurance reimbursement for virtual visits should also be commiserate with in-person visits to avoid de-incentivizing or penalizing providers for expanding care coverage to those most in need.

Strategies to reduce inequities and improve care in PD are a public health priority for America's most vulnerable populations.

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