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# Six Action Steps to Address Global Disparities in Parkinson Disease
## A World Health Organization Priority

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**IMPORTANCE** The Global Burden of Disease study conducted between 1990 and 2016, based on a global study of 195 countries and territories, identified Parkinson disease (PD) as the fastest growing neurological disorder when measured using death and disability. Most people affected by PD live in low- and middle-income countries (LMICs) and experience large inequalities in access to neurological care and essential medicines. This Special Communication describes 6 actions steps that are urgently needed to address global disparities in PD.

**OBSERVATIONS** The adoption by the 73rd World Health Assembly (WHA) of resolution 73.10 to develop an intersectoral global action plan on epilepsy and other neurological disorders in consultation with member states was the stimulus to coordinate efforts and leverage momentum to advance the agenda of neurological conditions, such as PD. In April 2021, the Brain Health Unit at the World Health Organization convened a multidisciplinary, sex-balanced, international consultation workshop, which identified 6 workable avenues for action within the domains of disease burden; advocacy and awareness; prevention and risk reduction; diagnosis, treatment, and care; caregiver support; and research.

**CONCLUSIONS AND RELEVANCE** The dramatic increase of PD cases in many world regions and the potential costs of PD-associated treatment will need to be addressed to prevent possible health service strain. Across the board, governments, multilateral agencies, donors, public health organizations, and health care professionals constitute potential stakeholders who are urged to make this a priority.

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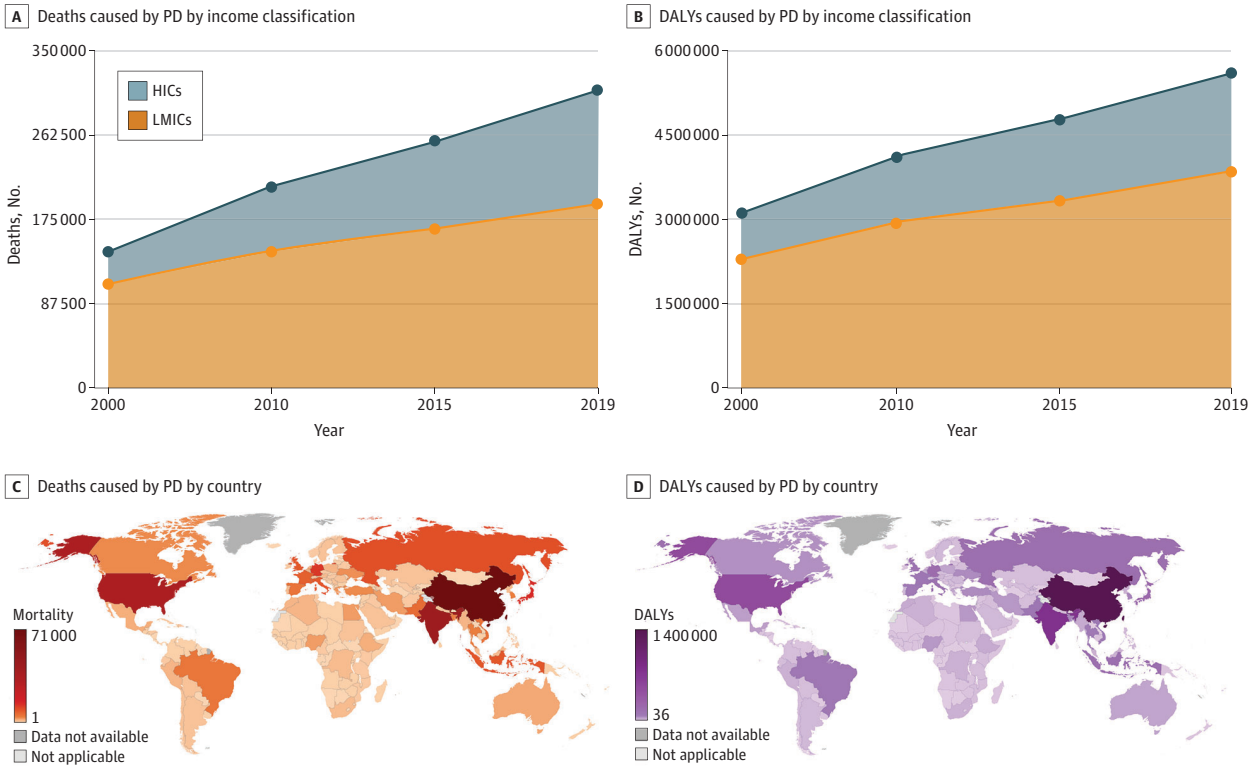
The Global Burden of Disease study identified Parkinson disease (PD) as the fastest growing neurological disorder between 1990 and 2016 in terms of death and disability. This calculation was based on a global study with estimates of prevalence, deaths, and disability-adjusted life-years (DALYs) in 195 countries and territories.[1] Current estimates suggest that in 2019, PD resulted in 5.8 million DALYs, increasing by 81% since 2000. Moreover, it is estimated that PD caused 329 000 deaths in 2019, an increase of more than 100% since 2000 (**Figure 1**).[2]

The rise in cases is thought to be multifactorial and is likely affected by factors such as aging populations, improved research methods, advanced technologies, better education, and an increased awareness of the disease.[3] Higher prevalence rates could also be a result of increasing life expectancy.[3] A link tying PD to specific environmental exposures is supported by expanding evidence.[4] The available evidence may possibly explain the unusual finding that in PD, DALY rates increase with Sociodemographic Index rather than decrease, as with most other health conditions. This principle has been demonstrated in China, for example, which has undergone large-scale industrial growth and observed a doubling of age-adjusted prevalence rates since 1990.[3]

PD is a disorder with a wide range of motor and nonmotor manifestations that result in, among others, mental health disorders, impaired mobility, sleep disturbance, mood and cognition issues, autonomic dysfunction, and a markedly decreased quality of life. Irrespective of geographical location, people with PD and their caregivers face tremendous difficulties and suffering. Given the large inequalities in access to neurological care across different parts of the world, vulnerable populations frequently bear a higher disease burden and stigma.

A European study estimated that PD associated costs reached €13.9 billion (US $14.9 billion) in 2010.[5] In the US, recent estima-

Figure 1. Deaths and Disability-Adjusted Life-Years (DALYs) Caused by Parkinson Disease (PD) by Income Classification and Country




HIC indicates high-income country; LMIC, low- and middle-income country.

tions of the total cost of PD (including direct and indirect medical costs and nonmedical costs) was $51.9 billion in 2017.[6] Rigorous economic studies for PD in LMICs are lacking. A systematic review in 2016 failed to identify a single study in an LMIC within the prior decade.[7]

According to World Health Organization (WHO) Atlas for Neurological Disorders,[8] the available resources for neurological disorders, including PD, within most countries are grossly insufficient, with large inequalities existing across regions, income levels, and countries. This has been reinforced by a recent study demonstrating the consistent scarcity and unaffordability of PD therapies and resources in most African countries.[9] Likewise, in low-income countries, the total neurological workforce is 0.1 per 100 000 population compared with a global median of 3 per 100 000 population.[8] A strong recognition of the growing effect, high numbers, and contrasting lack of resources and treatment for people with PD needs to be addressed, particularly in LMICs. As the world's population ages and the number of people with PD continues to grow, there is a pressing need for a concerted and robust public health response. Across the board, governments, multilateral agencies, donors, public health organizations, and health care professionals constitute potential stakeholders who are urged to make this a priority.

In April 2021, a multidisciplinary, sex-balanced, international WHO consultation workshop identified 6 workable avenues for action with emerging themes and a focus on LMICs and resource-limited settings. An overview of the discussion topics and multiple strategies that emerged from these discussions included the domains of disease burden; advocacy and awareness; prevention and risk reduction; diagnosis, treatment, and care; caregiver support; and research (**Table**).

## Disease Burden

PD affects all racial and ethnic groups and sexes, with both incidence and prevalence rising with age.[10] Prevalence varies among regions and populations, with limited data in LMICs and even less on other parkinsonian disorders. For instance, in sub-Saharan Africa, a lack of reported PD case studies has led to the belief that PD is less common in Africa than the rest of the world.[11] However, current evidence suggests that, in reality, people with PD in Africa and other resource-limited areas often have poor access to health care and are thus often unidentified.[11]

Data based on race and ethnicity are inconsistent, although a family history can be found more frequently in certain populations.[12] Globally, PD characteristics may be different as well. For instance, in the Western Pacific region, it has been reported that differences in characteristics of nonmotor PD symptoms and lower rates of dyskinesias were present compared with Europe and with North America.[13] With 1.8 billion people in the Western Pacific region, more studies will be needed to further elucidate the racial and ethnic differences within this and other large populations. Across the globe, better-standardized epidemiological data will be needed to determine the actual prevalence and incidence of PD.

Table. Challenges and Proposed Solutions for Advancing Best Practices and Expanding Resources for Parkinson Disease (PD)

| Challenges identified | Proposed solutions |
|---|---|
| Lack of quality epidemiological data | Generate better-standardized epidemiological and economic data, with equitable representation (by race, ethnicity, geography, sex, and gender) |
| Lack of awareness | Public education and training of health workforce as well as change in legislation and policy to address PD |
| Lack of risk reduction and prevention strategies | Generate harmonized approaches for PD risk reduction based on existing evidence, with both individual-level and population-level interventions |
| Lack of access to diagnosis, treatment, and care | Develop culturally and socioeconomically acceptable models of care that are interdisciplinary, replicable, affordable, and accessible to those who need them most and integrate a continuum of services to include wellness, neurorehabilitation, and palliative care at the earliest stages of diagnosis through the implementation of universal health coverage |
| Lack of caregiver support | Provide an accurate and timely diagnosis, accompanied by training and education to caregivers as well as psychosocial, financial, and community-based support |
| Lack of research coordination and investment | Improve coordination, reduce redundancies, provide appropriate funding to conduct and implement research, and build research capacity where needed |

Lack of appropriate management because of the inaccessibility of drugs and specialized care also contributes to increased disease burden. Access to a neurologist is associated with lower risks of sustaining hip fractures, being admitted to a long-term care facility, or dying. These findings emphasize the importance of adequate care.[14]

Government expenditure on health is inadequate in all resource-limited countries, with patients relying heavily on out-of-pocket expenses even for basic health care.[9] Governmental insurance does not cover most PD therapies across many countries. For example, insurance coverage of levodopa was only partial in 44% and not covered in 16% of 28 African countries responding to surveys.[9] The reality in many cases is that people with PD in these countries are forced to prioritize their more basic needs over PD care.

## Advocacy and Awareness

Increased awareness of PD and improved clinical diagnostic skills are possible contributing factors to the rise in PD incidence and prevalence.[15] Advocacy and awareness are particularly important, as factors such as young age at onset of PD and sex and race differences can factor into a potential for disparate care and delays in diagnosis.[16] Diagnostic delays are particularly common in people with young-onset PD because of the incorrect perception that this disorder only affects older individuals. There are slow improvements in LMICs owing to improved training of the health care workforce, screening questionnaires,[17] and the additional effect of patient-driven and family-driven advocacy groups. A growing number of outreach and educational programs targeted at neurologists, non-neurologist physicians, and allied health practitioners (including nurse specialists and physiotherapists) in Africa have been implemented and supported by professional organizations.[18] Integrated media has also proved to be an excellent method of combatting the associated stigma and discrimination of PD. An example of a low-cost, effective public educational campaign strategy that could be used in other LMICs was conducted in Thailand. Videos of people with PD in everyday situations (such as gait freezing in the middle of the road) were dispersed through social media and on digital billboards in front of department stores. This effort was aimed at spreading awareness of PD. The campaign was viewed almost 1 million times and was an effective way to create community awareness about PD.[19]

There are few existing policy priorities specifically addressing PD globally. However, policies relating to disability, workplace rights, and governance of financing and insurance of health care have cross-cutting themes that are relevant to PD. Mandated by the 73th World Health Assembly 2020, the Brain Health Unit at WHO has prepared an intersectoral global action plan on epilepsy and other neurological disorders to address the challenges and gaps that exist worldwide in providing care and services for people with neurological disorders and to ensure a comprehensive, coordinated response across sectors.[20] Given that PD often affects individuals in their working years, with many motor symptoms limiting mobility, disability rights prohibiting discrimination based on disability in areas such as employment and transportation are particularly relevant. Public education, policy and legislation change, and the awareness of existing workplace antidiscrimination policies available in different languages will be crucial to improving the lives of people living with PD.

## Prevention and Risk Reduction

Many factors have been examined as risk factors for PD, and causal inferences can be challenging. A substantial need remains to specifically identify clear risks for PD, particularly the modifiable ones. An increased risk has been reported among those with exposure to pesticides.[21-24] Amphetamine or methamphetamine, lack of physical activity, heavy metals, air pollution, traumatic brain injury, and industrial solvents, such as trichloroethylene (TCE), have also been implicated but all will require more study.[24,25]

Evidence linking the exposure to pesticides with the risk of developing PD is substantial and supported by multiple meta-analyses.[21,22] Some of the most commonly used pesticides, such as paraquat and chlorpyrifos, have been associated with an increased risk of PD and are banned in many countries (although not in the US).[26] Applying protective measures might decrease this risk; however, it is often the case that measures to protect users, such as personal protective equipment, are not readily available or are ineffective in LMICs (for example, personal protective equipment may be too expensive or may be impractical to wear in hot climates).[27]

Importantly, the risk of developing PD as a result of exposure to pesticides or other toxic chemicals in our environment is not restricted to those with occupational exposure but is also increased for individuals living in the immediate vicinity of farmlands and rural communities. Alarmingly, pesticides and herbicides are increasingly being deployed in LMICs.[28] For hazardous pesticides that pose high risks that cannot effectively be prevented, often the case in LMICs, the most effective option to mitigate the risks will be to end the use of the pesticide through regulatory action. It is generally the case that less hazardous alternatives for effective pest management will be available.[29]

It is particularly concerning in the context of preventing PD that current procedures deployed to screen for toxic effects of pesticides before release to market do not specifically focus

on potential toxic effects for dopaminergic neurons in the substantia nigra, from which arise the main symptoms of PD. Another issue of concern is that pesticides are typically screened for toxic effects in isolation, whereas the reality is that citizens are exposed to potentially interacting cocktails of different pesticides, sometimes simultaneously or through different time periods, which could have synergistic effects.[30] This means that combined risk assessments should be undertaken whenever possible; internationally applied procedures to test for potential neurotoxic effects of any existing pesticide should be updated, and any potentially hazardous combination of pesticides should be replaced by safer alternatives.

The industrial solvent TCE has also been linked to PD,[31] although to our knowledge, no large meta-analyses have been performed.[32] Exposure to TCE could be widespread because TCE is found in many common household products, such as paint removers, glue, stain removers, carpet cleaner, and as a spot-cleaning agent in dry cleaning.[4]

Protective factors for PD showing potential as possible secondary prevention tools include caffeine, physical activity, and possibly uric acid. Caffeine not only decreases the risk of developing PD but may potentially also slow progression once the disease has started.[33] Uric acid also holds possible potential for uses in secondary prevention, as high uric acid levels may be linked to a delay of PD progression.[34] However, a recent phase 3 clinical trial that tested the disease-modifying potential of inosine, which aims to elevate uric acid levels, showed no effect on disease progression in patients with PD.[35] Studies are also ongoing to attempt to elucidate the as yet undetermined mechanism of the low risk of PD among people who use tobacco and/or nicotine products.[36] However, given the many risks and detrimental effects of smoking and tobacco use,[37] the public health guidance and evidence not to smoke is clear.[36] Converging evidence from epidemiological studies, work in rodents with experimental parkinsonism, and clinical trials in individuals with manifest PD suggest that physical activity may slow down the process of neurodegeneration in PD and perhaps even in the prodromal phase. Enhancing the volume of physical activity appears to be a particularly attractive way to possibly prevent PD, particularly for LMICs, where an exercise intervention could be readily deployed at a low cost.

Although proof of causality is incomplete because of the paucity of trials in humans and the etiologic studies alluded to are observational, many provide consistent enough evidence to warrant investigation into the potential for secondary prevention strategies and are considered sufficiently strong by some workshop participants to promote physical activity and, arguably, moderate doses of caffeine for primary and secondary prevention of PD.[24]

## Diagnosis, Treatment, and Care

### Strengthening Health and Social Systems and Building Capacity

The diagnosis of PD is principally made by clinical evaluation, making it potentially suitable to be targeted for widespread improvement at the primary care level. Appropriately trained nonphysician health care workers could potentially diagnose PD in rural clinics. This approach has already made headway, with PD specialist courses for health care professionals in countries such as Tanzania, Ghana, South Africa, and Ethiopia and also online in 2021.[18]

Screening questionnaires can also be helpful in nonspecialized settings and have been validated for PD in different languages in Cameroon, Egypt, and Nigeria.[17] In cases where the diagnosis is not straightforward, protocols are needed whereby more complex cases could be referred for specialist opinion, possibly using telemedicine. Thus, education and training of primary health care professionals, promoting and increasing the neurological workforce, and optimizing the use of digital technology, such as telemedicine, to provide specialist support to remote areas will be key components in improving diagnosis and in providing sustainable care. Clinical telemedicine capabilities have already expanded dramatically as a result of the COVID-19 pandemic.[38] Continued promotion and expansion of telemedicine into high-quality educational courses for neurologists and nonspecialists has proven feasible in sub-Saharan Africa[39] and should be considered a priority.

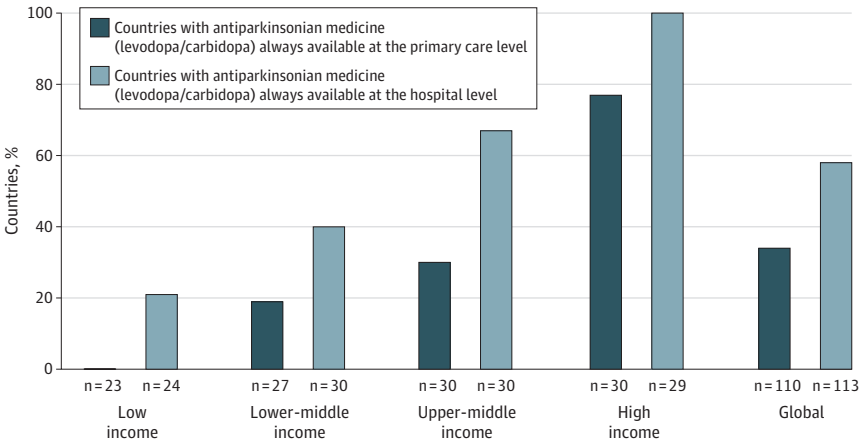
### Ensuring the Availability of Essential Drugs, Diagnostics, and Interdisciplinary Therapies

A large treatment gap exists for many neurological disorders, including PD. A major contribution to the wide gap is reduced access to effective medications and, when available, associated high cost. According to the WHO Atlas for Neurological Disorders, only 37 of 110 countries had levodopa/carbidopa consistently available in primary care settings (**Figure 2**).[8] A continent-wide survey of 28 African countries further documented the unavailability and high cost of PD therapies in most of surveyed countries.[9] Although limited by a lack of standardized manufacturing, *Mucuna pruriens*[40] (velvet beans) and the *Vicia faba* (broad bean) contain measurable and clinically active levodopa levels and have been shown to have dopaminergic effects in patients with PD, thus having the potential to serve as a substitute for levodopa in resource-limited countries. Similar to surgery for epilepsy in LMICs, the availability of neurosurgical treatments such as deep brain stimulation and ablative surgery is limited not only because of the small or nonexistent numbers of neurosurgeons practicing[8] but also because of associated high device costs and the paucity of imaging modalities, such as magnetic resonance imaging.

As with many degenerative neurological disorders, nonpharmacological management might offer affordable symptomatic relief of motor, nonmotor, and mental health symptoms in PD. Rehabilitation, aerobic and resistance exercise, physiotherapy, and exercises such as tai chi and yoga are gaining increasing attention and have the advantages of being enjoyable for individuals, economically feasible, and culturally integrated within communities.[41] Counseling on sleep, diet, and mind-body approaches, such as meditation, should be explored as well as engagement in community or research, where available. However, very few patients are referred to therapists who have the skills for these types of multidisciplinary interventions.[42] Despite this, even the most rudimentary educational information about PD—for example, resources describing the benefits of nonpharmacological management—are unavailable to people with PD, their families, and even physicians globally, particularly in local languages.

The impact and harm of loneliness and social isolation, already an issue in patients with PD, have become increasingly important and relevant during the COVID-19 pandemic.[43] Interruption of rou-

Figure 2. Availability of Antiparkinsonian Medication at the Primary Care and Hospital Levels




Reproduced from World Health Organization, 2017.[8]

tine treatment and health care support has further contributed to these social challenges.[44] Considering the lack of all levels of care in low-resource settings, the goal remains to develop culturally and socioeconomically acceptable models of care that are interdisciplinary, replicable, affordable, and accessible and to integrate a continuum of services, including neurorehabilitation and palliative care, at the earliest stages of diagnosis through the implementation of universal health coverage.

## Caregiver Support

PD has specific factors that contribute to increased caregiver burden, including the progressive nature of the disease and timing of onset. As the disease advances, the development of cognitive impairment, psychiatric manifestations, and sleep disruption contribute to an even higher rate of caregiver burden. Caregivers can experience limitations in social interactions, frustrations with medication administration, and limitation in their capabilities to provide care as the disease progresses, which may ultimately catalyze the difficult decision to consider an alternative living facility.

As care partners age, their own health issues can also develop.[45] This can profoundly affect care in situations of only 1 caregiver as well as affect already changing family support, structure, and dynamics from urbanization and population shifts.[46] Given that effective caregiving has associated health benefits for both the caregiver and the person with PD and can lead to delays in institutionalization, caregiver support must include and address the needs of the invisible patient—the caregiver.[45]

Factors that improve caregiver burden in the early stages of the disease include provision of a timely diagnosis; effective communication and education about caregiver roles, medications, and adverse effects; and rehabilitation and palliative care strategies, including governmental entitlements and discussions of decision-making capacity.[47] Social workers, patient support groups, and community-based support provide effective resources. Finally, in addition to caregiver burden, it is important to recognize and to treat demoralization in the patient and, potentially, in the caregiver, which may be present even if depression and mood disorders are absent.[48] Other conditions, such as dementia, can offer wide resources for caregivers, such as WHO's iSupport program.[49]

## Research

Because of increased funding and a greater number of initiatives in the past 2 decades, the amount of basic, translational, and clinical research in the field of PD has grown. These types of research studies can be paired with global population health and epidemiological data to better inform the public health perspective. Epidemiological data are critical to identifying population variations and needs, designing targeted policy changes and interventions, and allocating research and health care resources. This, in turn, would inform health care professional training and allow for systematic improvements in care and treatment gaps, including the availability of medications. Moreover, promoting research in LMICs is crucial to investigate cultural and population differences of variable risk factors, genetics, and phenomenology of PD.

Ensuring that countries have appropriate funding to conduct and implement research as well as building research capacity where needed will be a critical next step to achieving progress. In addition to the incredible examples set by HIV, tuberculosis, and malaria funding,[50] successful neurological examples include epilepsy research initiatives in sub-Saharan Africa, such as the National Institute for Health and Care Research's Research and Innovation for Global Health Transformation (RIGHT) program[51] and the Davos Alzheimer Collaborative.[52] Both provide approaches that have been successful at increasing LMIC investment in epilepsy and dementia. Productive research involves improving infrastructure in LMICs, ensuring appropriate ethical procedures, and growing global collaborations among investigators and research consortia. Moreover, the inclusion of civil society organizations, people with PD, and their support networks is vital to increasing the success and impact of research and to ensure that locally relevant issues are addressed.

## Global and Regional Health Policies to Implement the PD Strategies

The adoption of the intersectoral global action plan on epilepsy and other neurological disorders[20] will be paramount to coordinating efforts and leveraging momentum to advance the agenda of neurological conditions, such as PD, in all settings. With global targets being set by the action plan and proposed actions translated by governments into national plans, it is hoped that countries' actions will improve access to care and treatment, recovery, well-being, and participation of people living with neurological disorders, while reducing mortality, morbidity, and disability associated with neurological conditions. Emphasis is also given to preventing neurological disorders and promoting brain health and development across the life course and addressing stigma and discrimination through multidisciplinary and multisectoral approaches.

The overarching global action plan will also aid in addressing the challenges, strategies, and priorities that differ by geographic region, country, and socioeconomic status. For example, most data published are based on populations within high-income countries in Europe and North America. Many other regions, such as the Middle East, North Africa, and South Asia, have different cultural and socioeconomic situations, such as large families, high rates of consanguinity, and strong community support.[53] Identified needs within these countries include those outlined in the Table as well as an increased neurological workforce (specifically movement disorder specialists), availability of medication, and advanced therapies.[53]

The Western Pacific region, which includes China, is projected to grow to more than half of the world's PD population by 2030.[3] Differences between the Western Pacific region and Europe and Americas include variations in genetic variants, distinctive Asian parkinsonism variants, and lower rates of dyskinesias.[13] The challenges and priorities in this region mirror those in other regions (Table) and include increased research, neurological workforce, and awareness.[13]

Disparities also exist in high-income countries with gaps existing in diagnosis, treatment, and deep brain stimulation interventions—particularly among women and underrepresented populations.[16,54] In terms of research, diversity in clinical research beyond White populations has been low. Solutions to addressing some of these gaps could follow funding strategies such as those offered by the Michael J. Fox Foundation.[55]

## Conclusions

PD presents a formidable public health challenge. There is a pressing need for a global public health response to address health and social requirements for people with PD. There is also a need for effective preventive actions to slow or arrest the rising incidence before the costs of treatment overwhelm country health services. The lack of prevention, awareness, services, therapies, treatments, and care for PD has created barriers to building an integrated system of interdisciplinary care, particularly in low-resource settings. PD must be emphasized on public health agendas and key actions must be taken and coordinated to generate strategies, programs, policies, and services that can be effective for people with PD, their families, and their caregivers. This coordination will require a global effort, involving the sharing of knowledge, advancing best practices, increasing advocacy efforts, and expanding resources. Here, we have highlighted 6 workable avenues for action in the domains of disease burden; advocacy and awareness; prevention and risk reduction; diagnosis, treatment, and care; caregiver support; and research. It is now more important than ever to work collaboratively, before the burden of PD overwhelms our ability to effectively respond to these critical needs.

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