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Review

Neuroscience20 (BRAIN20, SPINE20, and MENTAL20) Health Initiative: A Global Consortium Addressing the Human and Economic Burden of Brain, Spine, and Mental Disorders Through Neurotech Innovations and Policies

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INTRODUCTION

Neurological disorders cover a wide range of illnesses and substantially impact patients' daily living and world economies; they are among the leading

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Abstract. Neurological disorders significantly impact the world's economy due to their often chronic and life-threatening nature afflicting individuals which, in turn, creates a global disease burden. The Group of Twenty (G20) member nations, which represent the largest economies globally, should come together to formulate a plan on how to overcome this burden. The Neuroscience-20 (N20) initiative of the Society for Brain Mapping and Therapeutics (SBMT) is at the vanguard of this global collaboration to comprehensively raise awareness about brain, spine, and mental disorders worldwide. This paper aims to provide a comprehensive review of the various brain initiatives worldwide and highlight the need for cooperation and recommend ways to bring down costs associated with the discovery and treatment of neurological disorders. Our systematic search revealed that the cost of neurological and psychiatric disorders to the world economy by 2030 is roughly $16T. The cost to the economy of the United States is $1.5T annually and growing given the impact of COVID-19. We also discovered there is a shortfall of effective collaboration between nations and a lack of resources in developing countries. Current statistical analyses on the cost of neurological disorders to the world economy strongly suggest that there is a great need for investment in neurotechnology and innovation or fast-tracking therapeutics and diagnostics to curb these costs. During the current COVID-19 pandemic, SBMT, through this paper, intends to showcase the importance of worldwide collaborations to reduce the population's economic and health burden, specifically regarding neurological/brain, spine, and mental disorders.

Keywords: Brain20, global brain initiatives, Mental20, mental disorders cost, neurological disorders cost, Neuroscience20, Spine20, spine disorders cost

worldwide causes of disability and the second leading cause of death after cardiovascular diseases [1]. Indeed, despite a increasing population of older adults worldwide and advances in medical science, people seem to be surviving chronic disease conditions like heart disease and cancer, while unluckily, this appears to also be leading to a steep rise in neurological disorders disproportionately affecting the elderly [2]. As such, the extraordinary and rapidly increasing costs of neurological disorders (roughly approaching $800 billion a year in the United States [US]) call for a tangible strategy to reduce the burden [2]. Based on a 2016 investigation by the Information Technology and Innovation Foundation, brain disorders and diseases cost the US economy $1.5 trillion, underscoring the scale of opportunity for greater research and innovative new treatments to improve health and drive prosperity [3].

Since the 1990s, a 40% gradual increase in deaths from neurological disorders related to an aging population has occurred [1]. According to the latest report, the combined annual costs of neurological

disorders including spinal cord injury, Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD), low back pain, stroke, traumatic brain injury, amyotrophic lateral sclerosis (ALS), migraine, epilepsy, multiple sclerosis (MS), and Parkinson's disease (PD) in the US alone totals nearly $800 billion [2].

The United Nations (UN) General Assembly report of December 2017 highlighted that progress in reducing the burden of non-communicable diseases, including neurological disorders, has been insufficient to meet the UN Sustainable Development Goal targets by 2030. Strategies and programs that effectively reduce the burden of neurological disorders would help achieve these targets [4]. One of the two major global projects in which humanity has engaged in unison so far that have transformed our lives is the space program. The space program opened a plethora of global communication and facilitated businesses at a massive scale. The second, the human genome project [5], where $4 billion was spent, is giving a dividend of>$240 in return for every dollar spent. The Human Genome Project has transformed the very concept of human health. Brain Initiatives are anticipated to represent a third such project, yet without global alliance and guidelines, the enormous tasks of unraveling the brain's mysteries and ailments cannot be achieved. Lack of such initiatives would in turn prevent improvements to worldwide economies, and needlessly sustain human suffering.

The estimated cost for the nine most common neurological diseases in the US was $789 billion in 2014 [2]. The European Union's (EU) burden of neurological disorders was estimated to be $930 billion per year in 2010 [6]. Based on a published European cost model, brain disorders overall are much more costly than previously estimated constituting a major health economic challenge for EU countries [7]. These numbers illustrate the tremendous social and financial burdens neurological and mental disorders impose on nations worldwide. The growing threat of brain disorders has inspired the development of health and research policies worldwide, leading to the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative in the US, announced in April 2013 [8, 9]. The same year, the EU announced its brain research initiative, the Human Brain Project (HBP) [8, 10, 11]. Other similar initiatives have been framed across the globe in the past decade, including Japan's Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) [8, 12], Korea Brain Initiative (KBI) [8, 13], Australia Brain Alliance [8, 14], China Brain Project (CBP) [8, 15], Canadian Brain Research Strategy (CBRS) [8, 16], Latin American Brain Initiative [17], and Brain Research Africa Initiative [18]. These projects share a common aim of fostering neurological research and development through their unique approaches.

Under the current societal changes and due to the expected global increase of neuropsychiatric disorders related to the coronavirus disease 2019 (COVID-19) pandemic [19, 20], the need to update the cost estimates of neurological diseases and to develop global strategies promoting further research and collaboration is a matter of global health and security. As a response to this urgency, the Society for Brain Mapping and Therapeutics (SBMT) offers an open platform for international cooperation and partnership across G20 nations that comprise the largest economies in the world through Neuroscience-20 (N20) [21]. Since the first summit in Australia in 2014 [21], the N20 has encouraged and facilitated interaction among leaders worldwide. Over the last seven years, through the initiatives' impact, achievements, data sharing plans, and challenges, the N20 vision has heavily relied on collaboration and strategic partnerships to leverage resources and technologies. SBMT proposes that the knowledge and resources need to be shared and integrated to enable growth and progress in understanding brain mapping and function.

Neurosciences will prosper by making these advancements available internationally and freely, working for a universal benefit, and avoiding competition. This approach will lead to better management of public funds, improved development of therapeutics, and greater benefits to patients. The Brain Technology and Innovation Park (BTIP) [22], for example, is a novel research organization started by SBMT that encourages startups to focus on neuroscience by providing greater funding to neuroscience and associated projects. This paper will highlight the importance of global collaboration such as this across the brain initiatives and highlight SBMT's existing platforms and work to bolster neuroscience discovery worldwide.

LITERATURE SEARCH METHODOLOGY

We searched the available data to gather relevant information on the world's neurological disorders' economic burden, the world's brain initiatives, and the N20 initiative efforts to bring awareness of these issues and ordered them in a single article. Over

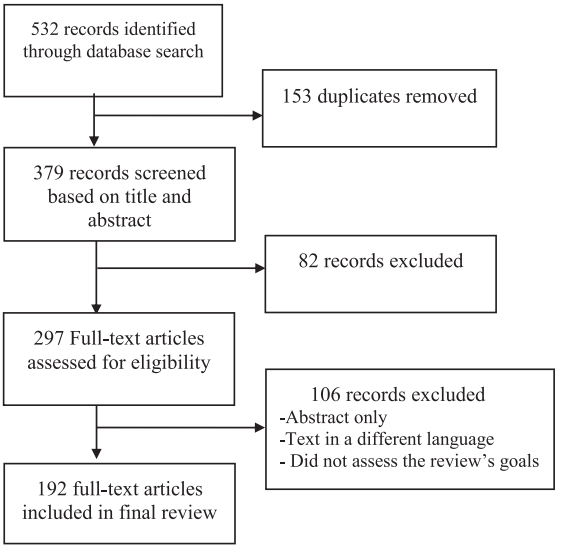

Fig. 1. Literature search strategy and flow.

465 research articles, scientific news, governmental sources, and news outlet sources with published data and information about the world's neurological disorders' economic burden were reviewed. Of the total number of articles, 183 individual references were included in this analysis. No additional items were added after screening the references (Fig. 1).

The databases used in the search for articles comprised PubMed, California Baptist University online library, Google Scholar, Brain Initiatives websites, Economic Forums, MeSH, and multiple news sources. The investigation was restricted to articles about the world's neurological disorders' financial burden, brain initiatives, and the SBMT's N20 initiative from the first brain initiative effort in 1998 to November 2020. We only contemplated articles for addition from the outlets that pertained to the subject. Each item incorporated was selected and reviewed by the individual authors, who then provided comments based on their area of expertise. The records were examined and appraised independently; those not meeting the requirement for addition were omitted. All local currencies have been converted to the standard US dollar ($) (2020).

REVIEW OF WORLDWIDE BRAIN INITIATIVES

Over the past couple of decades, independent brain initiatives have been established worldwide to bring together a more inclusive scientific collaboration in neurosciences. In the aftermath of the financial recession of 2008, the world of research, especially in the field of neurosciences, took a back seat [23]. To overcome this, the White House, in April 2013, launched the BRAIN Initiative. Organizations such as the Brain Mapping Foundation, SBMT, Paul Allen Initiative, Kavli Foundation, and other associations in the field were brought together by the Office of Science Technology and Policy at the White House to help the formulation and execution of the initiative. Under the BRAIN Initiative, $5 billion was spread equitably over ten years to develop conceptual ideas and novel technologies by integrating methods and capacity from the physical sciences into neurosciences [9]. The National Institutes of Health (NIH) convened a working group that expanded and elaborated on the initial work and put forth the BRAIN 2025 report [24, 25]. The BRAIN Initiative working group includes the NIH, Food and Drug Administration, National Science Foundation, Defense Advanced Research Projects Agency, and Intelligence Advanced Research Projects Activity, and currently involves over 300 laboratories globally. In its seventh year, the NIH BRAIN initiative is most heavily focused on psychiatric and neurological disorders, such as AD, PD, epilepsy, autism, depression, schizophrenia, and traumatic brain injury, which affects a considerable portion of the world's population. These conditions' primary causes remain elusive even after multiple neuroscience advances, partly due to the human brain's complexity [25].

The BRAIN 2025 report has come forth with seven pillars of investigation [25, 26] as mentioned below: a) Discovering diversity; b) Maps at multiple scales; c) Brain in action; d) Demonstrating causality; e) Identifying fundamental principles; f) Advancing human neuroscience; and g) From the BRAIN Initiative to the brain.

Following the launch of the Brain Initiative in the US, other countries and regions launched their own programs. Canada's neuro-ethics strategy strives to [16]: a) Harness neuroscience understandings to maximize the ability of every individual; b) Recognize and encourage aspects that increase resilience and promote recovery from brain disorders; c) Provide novel ethical and social structures necessary to catalyze and safeguard advances in neuroscience; and d) Encourage data sharing, systematic and accelerated discovery, and the execution, transformation, and democratization of technology.

Brain Canada was founded as the NeuroScience Canada Partnership and Foundation in 1998 by a group of visionary scientists and business leaders who envisioned changing brain research in Canada [27]. It led to the subsequent formation of the CBRS, whose primary focus is on four initiatives [16]: a) National Transdisciplinary Training Platform; b) Distributed Technology Development & Dissemination Platforms; c) International Neuroscience Open Data Platform; and d) Neuro-ethics Backbone.

Later in 2019, South American countries held a conference in Uruguay to formulate the Latin American Brain Initiative. Here, various neuroscience institutions from Argentina, Brazil, Chile, Cuba, and Uruguay signed a declaration of intent. They aim to ally research institutes, governments, non-governmental organizations, and policymakers to better understand and contribute to neuroscience progression. Also, the countries have, in principle, committed to better support and training of the next generation of doctors, researchers, and neuroscientists [17].

On Janurary 15, 2015, SBMT announced the African Brain initiative's formulations as part of its international Brain Initiative/Neuroscience-20 based on a series of local meetings with the South African scientists and policymakers.

In 2013, the EU started the HBP [10, 11], funded jointly by the European Commission's Future and Emerging Technologies Projects and its member countries with a $1.3 billion budget. In collaboration with research platforms such as the Alzheimer's Disease Neuroimaging Initiative, the HBP encourages industrial and scientific researchers to advance computing, neuroscience, and brain-related medicine projects [11]. Presently the HBP has collaborated with over 100 universities and research centers across Europe. The following are the research platforms of the HBP [10]: a) Neuro-informatics; b) Brain simulation; c) High-performance analytics and computing; d) Medical informatics; e) Neuromorphic computing; and f) Neurorobotics.

As per the EU Joint Program – Neurodegenerative Disease Research (JPND), current treatment for neurodegenerative diseases generally addresses the symptoms and not the cause or the progressive course of disease. JPND launched this program of investment to enable research projects on novel imaging and brain stimulation methods and technologies, which may help deliver targeted and timely prevention and therapies for neurodegenerative patients' diseases. In March 2020, Turkey's scientific and technological research council (TÜBİTAK) joined the EU JPND initiative for novel imaging and brain stimulation methods and technologies related to neurodegenerative diseases [28].

In 2008, The World Federation of Neurology (WFN) brought forth the African initiative, named Brain Africa, which resulted in a collaboration of African neurologists, scientists, and researchers to promote neuroscience research across Africa. They helped develop clinical guidelines and health policies, established best practice guidelines, and identified and promoted new leadership in neurosciences [18]. One of the limiting factors for developing neuroscience in the African continent is qualitative and quantitative training. Researchers in African countries are increasingly creating strategies to establish and expand neuroscience knowledge through education, research, and national outreach programs [29].

The Australian Brain Alliance, right from its inception in 2016, has effectively brought together scientists and researchers from all over Australia involved in brain research. They aim to promote transdisciplinary collaborations to understand the brain better and ultimately crack the brain's "code." To this end, discoveries in various areas are necessary to achieve the four grand challenges at the center of the initiative. These are outlined as [30]: a) Optimization and restoration of healthy brain function; b) Development of neural interfaces to control and record brain activity for the restoration of function; c) Understanding the neural basis of learning; and d) Delivering new understanding to brain-inspired computing.

Japan initiated the Brain/MINDS project in 2014 [12]. Three goals have been put forward using the common marmoset (Callithrix jacchus) [31]: a) To perform structural and functional brain mapping and genetic studies; b) To determine biomarkers for brain conditions; and c) To create pioneering tools to observe and operate different facets of neuronal activity.

In 2016, South Korea announced the KBI project with initial funding of $160 million [13] to employ a dual-track strategy in following objectives by creating advanced neuro-technologies and nurturing brain research. The focus is on four core areas [13, 32]: a) Construction of brain maps at multiple scales; b) Development of innovative neuro-technologies for brain-mapping; c) Reinforcing artificial intelligence-related research and development; and d) Creating personalized medicine for neurological diseases such as AD and PD.

As such, the following two strategies were devised [32]: a) Education of the general population towards brain sciences; and b) Training of neuroscientists to conduct research safely.

Initially, in the field of neuro-ethics in Korea, collective efforts were made to set up governance and proper institutionalization of the official organizations associated with KBI. These efforts need to become a part of a global collaboration [32].

The Chinese National People's Congress approved the CBP in 2016 [15]. The main target was to research the neural basis of cognitive function, improve diagnosis and prevention of brain diseases, and drive information technology and artificial intelligence projects inspired by the brain. The CBP is supported by the Chinese Academy of Sciences (CAS) Center for Excellence in Brain Science and Intelligence, a syndicate of laboratories at over twenty CAS institutes and universities, and the Chinese Institute for Brain Research. It is expected to complement similar projects worldwide with its rapidly growing cadre of top neuroscientists, the country's heavy burden of people with neurological diseases, and significant brain-imaging investment facilities [15].

The country of Iran has attempted to create its neurological projects. Establishments such as the Cognitive Science and Technologies Council have promoted neurological and technological advancements all around Iran. The team works towards creating a centralized communication network, neural mapping functions, introducing technologies, and solving ethical issues in brain and cognition research [33]. The National Brain Mapping Laboratory has provided an infrastructure for imaging and brain stimulation for cognitive research. The idea of expanding the organization in the Middle East received attention from the SBMT board of directors, thus establishing the Iranian SBMT chapter. Importantly, this initiative is meant to remain independent of political/governmental influence. The Iranian SBMT Research Accountability Group functions as an e-team at present.

THE GLOBAL ECONOMIC BURDEN OF NEUROLOGICAL DISEASES–BRAIN 20

Based on recent "Global Burden of Disease Study", the three most burdensome neurological disorders in the US were stroke, AD/other dementias, and migraine [34]. Neurological disorders cover a wide range of illnesses and have a massive impact on the patients' emotional, social, financial well-being and on society [6]. The economic cost associated with these disorders is becoming an increasingly important parameter for health and research policies; however, reliable estimates of costs are often missing. Neurological diseases that affect a significant portion of the world's population can be attributed to ADRD, MS, ALS, epilepsy, and CNS malignancies. The EU has deemed neuropsychiatric disorders one of the most significant health care challenges of the 21st century [35]. The NIH of the US alone spends almost $5.5 billion per year on neurological disorders and has not found any significant success in groundbreaking technologies or treatments for patients with brain and spinal cord disorders [35]. According to the World Health Organization (WHO), neurological conditions, such as dementia and stroke, account for 13% of the global disease burden, and dementia alone accumulated a worldwide cost of $604 billion in 2010, with around 70% of the expenses being from Western Europe and North America [35].

The current COVID-19 pandemic is also associated with neuropsychiatric complications [19]. Thus, there is an urgent need to re-evaluate and update neurological disorders' cost estimates. A study done in 2015 projected the total worldwide healthcare costs due to these disorders to exceed $2 trillion by 2030, thereby causing a massive strain on the global healthcare system [36]. A more recent report published in Lancet Commission in 2018, adjusted these figures to reflect that they could increase to over $16 trillion by 2030 [37]. Current studies reveal that neurological and mental disorders are much costlier than previously estimated [38]; for example, the cost of treating brain disorders per year was as much as $450 million in Europe [7]. According to a recent estimate, approximately one-third of Europe's population is affected by at least one brain disorder within any given year [39]. In 2010, neurological, mental, and substance use disorders accounted for 10.4% of global disability-adjusted life years (DALYs), and 28.5% of global years lived with disability [40]. As per a study in Europe in 2010, the estimated annual burden of neurological diseases was $930 billion per year, of which direct healthcare costs were $344 billion (37%), non-medical cost (nursing homes, etc.) $216 billion (23%), and the indirect cost (absenteeism from work, pensions, etc.) $367 billion (40%). The mean cost per capita per year (2010) in the EU was estimated at $21.6K including Luxembourg ($36.4K) United Kingdom (UK; $33.3K), Norway ($29.4K), Austria ($26.7K), and Germany ($26.1K) [6, 7]. There is a

considerable stigma in the community regarding neurological diseases, including ADRD, MS, ALS, and epilepsy [41].

The burden of Alzheimer's disease and related dementias

The costs of dementias are projected to increase by 85% by 2030, therefore developing countries will experience an increased economic burden. Inaction can only mean a further accumulation of debt and a potential strain on systems of care [41]. In developed countries, long-term monetary struggles come from health care costs, and 60% of dementia spending costs are on long-term care, such as social care and informal care [41, 42]. The care cost of dementia will continue to increase as the aging world population increases, estimated to reach 66 million by 2030 and up to 115 million by 2050. The expansion of the aging population will most noticeably affect low-income and middle-income countries [42].

North America

Studies calculate that AD affects an estimated 5.7 million people in the US, with a projected rise of 14 million cases in people aged 65+ years by 2050 [38]. In a study from 2015, the burden of neurodegenerative disorders like ADRD in the US were estimated to be above $277 billion annually by 2018 [43]. In Canada, the burden has been estimated to be $293 billion annually by 2040 [44]. These estimates include direct costs, indirect costs, and other expenses due to patients' lost work time [43, 44].

European Union

The total cost of dementia in the member states of the EU in 2008 was estimated to be $187 billion ($25,655 per capita per year), of which 56% (∼$14,366) represented the cost of informal care. This number's primary component includes direct costs in northern Europe and informal care in southern Europe [45]. Monthly costs based on the severity of the disease (mild, moderate, and severe) in the UK, France, and Germany are shown in Table 1 [46]. This estimate includes between 1.1–1.2 million people living with AD in France, with approximately 225K new yearly cases. The overall estimated cost of the annual treatment of AD (2015 estimate) in France was $37 billion. Medical and paramedical expenses of the health sector are $6 billion per year. The cost of informal aid is $16.6 billion per year, and medico-social costs are $15.4 billion per year [47]. Around 850K people live with dementia in the U.K., with 50–70% being AD patients. These numbers are rising and are expected to reach 1.6 million patients by 2040.

Table 1
Monthly individual cost of Alzheimer's disease in Germany, France, and the UK [41]

Country	Mild	Moderate	Severe
United Kingdom	$1957	$2216	$3300
France	$1710	$2100	$2960
Germany	$1583	$2910	$4292

The total annual cost of care for dementia in UK patients is estimated at around $41 billion. These costs include healthcare costs, social care costs, and costs of unpaid care. The largest proportion of this cost, 45%, is social care, which totals $20.6 billion. Social care costs are estimated to nearly triple over the next two decades, to $60 billion by 2040 [48]. At present, two-thirds ($29.25 billion) of the cost of dementia are paid by people with the disease and their families, either in the value of unpaid care ($18.3 billion) or in paying for private social care [46, 49]. The average individual cost of mild, moderate, and severe dementia is $32.1K, $36.2K, and $60.7K, respectively, per person per year [50]. There are currently 1.7 million people living with one or the other type of dementia in Germany, and the numbers are expected to double by 2060 [51]. The average total societal costs per year (cost data for 2010) differed significantly for patients with mild AD - $18.7K, moderate AD - $34.4K, and moderate/severe AD - $53.1K [52].

In Germany, informal care costs accounted for the largest share of total societal costs: 49% for mild, 55% for moderate, and 64% for moderate/severe AD. Dementia costs $64.2 billion, which corresponds to around $39.5K per patient annually [52]. In Italy, there are over 600K people affected by AD. The average annual cost per patient estimated, including both family costs and costs to the National Health Service and the community, amounted to $83.9K, resulting in $50.35 billion each year, of which $13.51 billion accounted for health care and assistance in the strict sense. The rest goes to the indirect expenses, which in this case, weigh almost entirely on the caregiver, that is, the family member and family members who take care of the patient [53].

Latin America

Based on a recent review [54], the lacking epidemiologic data, the need for standardizing clinical practice and improving physician training, and the existing barriers regarding resources, culture, and

stigmas are the main challenges faced by the Latin American countries with regards to the prevalence of AD. These are shown to hinder timely care and research. With respect to the health actions, many Latin American countries suffer minimal mental health facilities and do not have specific mental health policies or budgets specific to dementia [54]. As for other regions, the current increasing trend in DALYs for non-communicable disorders suggests that the prevalence of dementia is increasing in Latin America and the Caribbean [55].

There is insufficient data on the economic costs for neurological diseases in Latin America. This is despite an increasingly aging population, observed to aged more rapidly in developing countries than in developed countries [56]. As stated earlier, Latin America is lacking specific mental health policies or resources regarding dementia, unlike the EU, the US, and South Korea [57]. The World Alzheimer Report 2015 estimates the number of people living with dementia in Latin America will increase four-fold between 2015 and 2030. More than 89.28 million people with dementia are estimated to live in Latin American countries in 2020 [57]. In 2010, it was estimated that the total cost for dementia reached $235.8 billion for the Americas. The cost varied according to the socio-economic state of each country. The cost per patient ranged from $46.5K in high-income countries, $6.3K in upper-middle-income countries, $2.4K in lower-middle-income countries, and $784 in low-income countries [58].

In 2006, the total annual costs for AD patients in Buenos Aires, Argentina, were $8.1K for community-dwelling and $14.9K for institutionalized patients. The total yearly costs for patients with moderate ($6.6K) and severe ($11.2K) dementia were higher than for those with mild dementia ($5.3K) [56]. In Peru, a study from 2015 using a sample of 136 outpatients receiving treatment at a private clinic reported an average cost per trimester of $1.5K for AD, $1.8K for frontotemporal dementia, and $1.3K for vascular dementia [59]. A 2017 study in Chile used a sample of 330 informal primary caregivers who reported an average cost per patient of $943 per month [59]. In a 2018 study from Brazil, an assessment of direct and indirect costs of dementia using a sample of 156 patients with dementia being treated at an outpatient clinic showed that the costs of treatment for dementia were $1K for the mild stage, $1.7K for the moderate stage, and $1.4K for the severe stage. Also, indirect costs ranged from $536 to $545, depending on the disease's severity [60].

Table 2
Cost per capita of Alzheimer's disease and Parkinson's disease for African countries with available data. Adapted from [62]

Countries	Alzheimer's disease per capita annually ($)	Parkinson's disease per capita annually ($)
Algeria	0.05	0.02
Tunisia	1.89	1.04
Cabo Verde	3.90	7.79
Guinea Bissau	3.0	3.9
Seychelles	60	100
Sao Tome	22.93	1.0
Namibia	2.0	2.0
Swaziland	10.98	3.10

Africa

Due to low educational background and other socioeconomic factors, there is a high risk of health complications, including AD, on the African continent. The difficulty of obtaining reliable data in this region could be due to different survival rates, governmental underreporting of disease, reluctance to seek medical assistance, and/or inadequate access to medical care. The estimated prevalence of dementia in people older than 50 years in Africa in 2014 was approximately 2.4% (2.76 million people), with 76% of cases from Sub-Saharan Africa [61]. In 2015, some African countries like Niger, Nigeria, and Sierra-Leone had an annual cost per capita for AD and PD at less than $1. The data for additional African countries are shown in Table 2 [62].

Australia

In 2016, the number of people living with dementia in Australia had surpassed 413K [63]. Dementia has been the second leading cause of death in Australia, contributing to 10.6% of all deaths in females and 5.4% of all deaths in males each year. In 2016, the annual cost of dementia for Australia was $14.25 billion, with an average cost of $35.6 per person. In 2017, the total cost of dementia increased by 2.9% to $14.67 billion. The cost of dementia is predicted to grow 81% to $25.8 billion by 2036 and further to $36.8 billion by 2056, thus indicating a 2.6-fold increase in costs from 2016 [64].

Asia

Across China in 2015, the annual estimated cost per patient for AD was $19,144, and the total expenses were $167.74 billion. China predicts total yearly costs to be $507.49 billion by 2030 and $1.89 trillion by 2050 [65]. Since Japan is among the fastest aging societies globally, its sizeable elderly popula-

Table 3
Total, direct, and indirect costs associated with ADRD in Iran [67]

Iran ADRD	Mild	Moderate	Severe
Total Costs	$434	$1313	$2480
Direct Costs	$263	$641	$1257
Non-Direct Costs	$171	$672	$1223

tion inevitably creates a societal cost for dementia alone of $112 billion. Almost 90% of these costs are due to formal and informal care [66]. Most care for AD patients in Iran is received from families. The annual per-person costs of mild, moderate, and severe AD are $434, $1,313, and $2,480, respectively. Direct costs rise with the disease burden of $263, $641, and $1,257, respectively. For mild and moderate cases, most of the direct costs come from medicine, while rehabilitation is a significant cost burden in severe cases. The non-direct costs for mild, moderate, and severe levels of AD are $171, $672, and $1,223, respectively. The highest costs are from nursing services and home care for patients. The cost of AD treatment in Iran is lower than average dementia costs in upper-middle-income countries due to lower drug prices and lower wage levels [67]. Table 3 shows the total, direct and indirect costs of ADRD in Iran [67].

The burden of multiple sclerosis

The number of people living with MS increased from 2.1 million to 2.3 million worldwide between 2008 and 2013; the average cases ranged from 4.7 per 100 thousand in high-income countries to 0.04 per 100 thousand in low-income countries [69].

North America

One of the most crucial factors contributing to North America's economic cost is the high pharmaceutical cost. The estimated cost associated with treatment is directed to disease-modifying therapies (DMTs), estimated to be $70,000 per year per patient [70]. The increase in the number of patients with MS in need of clinical care in 2017 had an estimated cost of around $40 million annually in direct care-related expenses after admissions [71]. A study conducted in 2018, estimated the annual cost of MS was $1.26 billion [72]. It is vital to highlight the drug-related economic impact of MS in North American society. Creating cost-regulatory policies for the ever-increasing prices of drugs to make treatments affordable for most of the population is crucial and

Table 4
List of G20 countries and other countries with ADRD cost, estimated cost, per capita cost, and Gross Domestic Product (GDP) data. Blank boxes indicate no data is available for that country. GDP statistics are from World Bank [68]. Gray boxes indicate missing data to date

Alzheimer's Disease and Related Dementias					
	*all values USD ($)	Annual Cost ($)	Estimated Cost ($)	Per Capita cost ($)	GDP 2019 ($) (millions)
North America	United States	277 billion			21,422,226
	Canada		293 billion		1,736,426
Latin America	Total	235.8 billion			
	Mexico				1,268,871
	Argentina			6,600	445,445
	Brazil			1,700	1,839,758
	Chile			943	282,318
	Peru			1,800	226,848
European Union	EU total	187 billion		25,655	
	Germany	64.2 billion		39,500	3,861,124
	France	37 billion			2,715,518
	United Kingdom	41 billion	61 billion	36,200	2,829,108
	Italy	50.35 billion		83,900	2,003,576
Africa	South Africa				351,432
	Sub-Saharan Africa			1	448,120
Australia and Oceania	Australia	14.67 billion	25.8 billion	35,550	1,396,567
Asia	China	167.74 billion	507.49 billion	19,444	14,342,903
	Japan	112 billion	231.98 billion	56,802	5,081,770
	India				2,868,929
	Indonesia				1,119,191
	Turkey				761,426
	Saudi Arabia				792,967
	Russia				1,699,877
	South Korea				1,646,739
	Iran			1,313	453,996

Table 5
List of G20 countries and other countries with MS cost, estimated cost, per capita cost, and GDP data. Blank boxes indicate no data is available for that country. GDP statistics are from World Bank [68]. Gray boxes indicate missing data to date

Multiple Sclerosis					
	*all values USD ($)	Annual Cost ($)	Estimated Cost ($)	Per Capita cost ($)	GDP 2019 ($) (millions)
North America	United States	1.26 billion		70,000	21,422,226
	Canada				1,736,425.63
Latin America	Mexico				1,268,870.53
	Argentina				445,445.18
	Brazil			6,000	1,839,758.04
	Colombia			10,500–25,700	323,615.98
European Union	Total			17,300	
	Germany			26,700	3,861,123.56
	France			26,700	2,715,518
	United Kingdom			26,700	2,829,108.22
	Spain	1.6 billion		35,600	1,393,490.52
	Italy			26,700	2,003,576.15
Africa	South Africa				351,431.65
	Sub-Saharan			2,000–24,000	4,195.40
Australia and Oceania	Australia			68,300	1,396,567.01
Asia	China			2,800	14,342,903.01
	Japan			9,370	5,081,769.54
	India				2,868,929.42
	Indonesia				1,119,190.78
	Turkey				761,425.50
	Saudi Arabia				792,967
	Russia				1,699,876.58
	South Korea				1,646,739.22
	Iran			2,322	453,996.48

Table 6
List of G20 countries and other countries with ALS cost, estimated cost, per capita cost, and GDP data. Blank boxes indicate no data is available for that country. GDP statistics are from World Bank [68]. Gray boxes indicate missing data to date

Amyotrophic Lateral Sclerosis					
	*all values USD ($)	Annual Cost ($)	Estimated Cost ($)	Per Capita cost ($)	GDP 2019 ($) (Millions)
North America	United States	472 million		69,400	21,422,226
	Canada			32,300	1,736,425.63
Latin America	Mexico				1,268,870.53
	Argentina				445,445.18
	Brazil				1,839,758.04
European Union	Total	1.7 billion		32,600	
	Germany			93,000	3,861,123.56
	France				2,715,518
	United Kingdom				2,829,108.22
	Italy				2,003,576.15
	Switzerland	34.55 million		43,000	703082.44
	Spain			43,000	1,393,490.52
Africa	South Africa				351,431.65
Australia and Oceania	Australia		3.2 million		1,396,567.01
Asia	China			17,700	14,342,903.01
	Japan				5,081,769.54
	India				2,868,929.42
	Indonesia				1,119,190.78
	Turkey				761,425.50
	Saudi Arabia				792,967
	Russia				1,699,876.58
	South Korea				1,646,739.22

Table 7
List of G20 countries and other countries with Epilepsy cost, estimated cost, per capita cost, and GDP data. Blank boxes indicate no data is available for that country. GDP statistics are from World Bank [68]. Gray boxes indicate missing data to date

		Epilepsy			
	*all values USD ($)	Annual Cost ($)	Estimated Cost ($)	Per Capita cost ($)	GDP 2019 ($) (Millions)
North America	United States	1.7 billion		13,500	21,422,226
	Canada				1,736,425.63
Latin America	Mexico	190,500		2,600	1,268,870.53
	Argentina				445,445.18
	Brazil				1,839,758.04
European Union	Total	23.76 billion			
	Germany				3,861,123.56
	France			2,400	71,104.92
	United Kingdom				2,829,108.22
	Spain	5,200		2,500	1,393,490.52
	Italy			1,500	2,003,576.15
	Netherlands			62–421	907,050.86
Africa	South Africa			120–436	351,431.65
	Nigeria	21,900		717	448,120.43
Australia and Oceania	Australia	557.1 million			1,396,567.01
Asia	China	1 million		773	14,342,903.01
	Japan				5,081,769.54
	India	1.7 billion		344	2,868,929.42
	Indonesia				1,119,190.78
	Turkey				761,425.50
	Saudi Arabia				792,967
	Russia				1,699,876.58
	South Korea				1,646,739.22
	Iran			740	453,996.48

would reduce hospital readmissions due to patients not being able to afford medications.

European Union

In 2010, MS had an estimated total cost of $17.3K per capita in European countries. The highest costs were seen in Norway, Luxembourg, and Germany and were represented by direct healthcare expenses [7]. A study of 1,261 MS patients in five European countries showed that costs increased with advancing disease severity; for mild patients (Expanded Disability Status Scale, EDSS score ≤ 3), the costs ranged between $16.0K and $26.7K per year, per patient across countries; for moderate patients (EDSS score 4–6.5) it ran between $33.9K and $52.1K; for severe patients (EDSS ≥ 7) it ranged between $47K and $77.6K. Relapses were also associated with increased costs [73]. A literature review from Spain revealed a total value of $1.6 billion annually and a mean annual cost per MS patient of $35.6K [74].

Latin America

MS is the second most frequent neurological disorder in adults and a growing concern in Latin America, however not a health priority even though it carries a substantial economic impact. Access to therapy is generally low in these countries. There are 15 MS patient-associations integrated as a federation in Mexico, in which only the Argentinian, Brazilian, Chilean, and Uruguayan societies are full members [75]. A 2019 study from Brazil, with a sample size of 3,226 patients, reported that most patients used a public healthcare system where physicians' services, treatment, and hospitalization were accessible. The total annual cost in this sample was $6K per patient, of which direct costs represented 81% or $4.8K. The total mean annual direct costs for the payer amounted to $3K per patient. The mean out-of-pocket costs to patients were estimated at $1.2K [76]. A study predicted both direct and indirect cost in Colombia, depending on the disease's stage and its remissions and relapses, using the EDSS. The condition was segmented into four categories according to EDSS: a) Category 1 EDSS - 0 to 2.5; b) Category 2 EDSS - 3 to 5.5; c) Category 3 EDSS - 6 to 7.5; and d) Category 4 EDSS - 8 to 9.5. The study indicated that the mean yearly cost per patient varied across disease categories, with the highest price in category 2 at $25.7K and the lowest cost in category 4 at $10.5K [77]. There is a pressing need to acquire additional information about Latin America's neurological diseases and its health care system. Future research and

innovation carried out by each country will increase knowledge, create guidelines for conducting research and enable management to make better decisions to improve people's lives [77].

Some published reports from three countries (Brazil, Argentina, and Colombia) indicated the mean cost of DMT roughly at USD 35,000 per treated patient. In Brazil for instance, the cost of DMT increased from USD 14,011,700 to USD 122,575,000 only over the course of 3 years (2006–2009) [77]. As estimated by Custodio et al., owing to the demographic and health transitions in the Latin American Countries, the number of people with dementia will rise from 7.8 million in 2013 to expectedly over 27 million by 2050 [77].

Africa

A study on the epidemiology of MS in 2016 showed that Sub-Saharan Africa had the lowest prevalence rate in the world (2.1/100 thousand) [78]. Another study of the prevalence of MS from 1990 to 2016 also showed that eastern Sub-Saharan Africa and central Sub-Saharan Africa had the lowest prevalence rates, 3.3 and 2.8, respectively [79]. Data from African countries are scarce and variable [80]. The Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis was established to provide recent and updated guidelines on managing MS for the countries in this region while creating MS centers. The estimated cost of MS treatment in this region per year is $2K to $24K [81].

Australia

MS represents a significant economic burden in Australia, recognizing the direct and indirect cost of this disease. The annual expenses of MS per person grew 17% from $58.6K in 2010 to $68.3K in 2017 due to increased use of DMTs. The most significant burden was direct costs, which accounted for 44% of the annual cost, equivalent to $30.3K [82].

Asia

It is commonly thought that MS is not a prevalent disease in the Asia-Pacific region. The prevalence of MS in southern Asia and Japan is between 5 and 20 per 100K. In contrast, Hong Kong had a rate of 0.77 per 100K in 1999. Due to the high cost of surveillance and infrastructure needed, there has been a lack of data from the Asian region [83]. In Japan, as of 2015, the total monthly cost per patient with MS was $781. These costs consisted of DMT drugs (half of the overall medical expenses) and hospitalization (highest in the initial month), with drugs being the largest component (63% of overall expenditures) [84]. There was also a positive correlation between relapse frequency and medical cost [84]. China's mean price per inpatient and outpatient was $2.8K and $373, respectively [85]. In Iran, much of the costs are borne by patients with physical and neurocognitive disabilities caused by MS, thus requiring greater effort [86]. There is a significant relationship between the annual cost of disease and disease severity; an increase in degree can incur costs upwards of $194. That said, the average mean annual cost for MS in Iran is $2,322 [87].

The burden of amyotrophic lateral sclerosis

ALS is a peculiar neurodegenerative disease due to its rapid progression. Lifestyle modifications of patients and entire families due to ALS have a substantial economic impact. Costs associated with ALS treatment are significant compared to other neurological diseases, increasing the need for medical advances and financial support for patients and their families [88]. During the COVID-19 pandemic, neurological disorders cause increased mental strain more from the social environment than the virus itself. For example, ALS patients are vulnerable to both medical complications of infection and emotional distress when it comes to anxiety and depression [89].

North America

In the US, the annual financial cost in 2015 was estimated at $69.4K per patient and was in the range of $279–$472 million nationwide [88]. For 2020, the economic impact of ALS is unclear, but the financial cost was estimated to be between $64K and $200K per year, according to a recent study [90]. A Canadian study estimated the annual direct cost per patient the be $32.3K, with $19.6K (61%) paid out-of-pocket. The highest direct cost was disease-related home renovations, which received little government or non-profit organization support. Annual indirect costs (lost wages) for ALS patients and family members providing care were $56.8K [91]. The mean cost of care for ALS patients in the last year of life was estimated to be $68.3K in Canada [92].

European Union

In Europe, the estimated cost of ALS is $32.6K per capita, representing $1.7 billion in total expenses [7]. In Switzerland, this cost was even higher, with a value of $43K per capita and a total of $34.55 million in 2010 [93]. According to a Spanish study, the

mean annual cost per patient with ALS was $43K, highlighting the most important categories: informal care, early retirement, medications, and orthopedic devices [94]. The mean annual total cost of illness was $93K per patient in Germany, while the lifetime cost per patient was estimated at $292K. Nearly half of the costs were attributable to informal care [95].

Latin America

There is insufficient data from the Latin American region regarding ALS.

Africa

Insufficient data are available surrounding ALS incidence in Africa. The incidence reported in Libya was low (0.89 [0.52–1.25]/100000), but after adjustment (2.03 [1.16–2.91]/100000), the incidence was in same range as the data from Europe and North America [96].

Australia

The costs associated with formal and informal care and support services in Australia are recognized to exceed the direct health care budget. The Australian economy's loss of productivity was estimated to be $3.2 million in 2017 [97].

Asia

In Japan, the incidence is the same as in western cohorts, while a lower incidence is seen in Chinese patients. A population survey in India shows a prevalence of 4/100000, indicating a low but significant incidence [98]. China's medical patient cost ranges from $10K to $17.7K in major cities such as Guizhou, Guangdong, and Henan [99]. In Japan, because of their insurance policies, many out-of-pocket expenses drive up the economic burden for patients and their families, specifically the cost of opioids for ALS [100]. Developing countries such as Iran will see an estimated 50% increase in ALS cases from 2015 to 2040 [101]. In 2015, the developing countries including Iran, made up 71% of ALS cases, but this is estimated to drop to 67% by 2040 [101]. The cost of single-site genetic testing with repeat-primed polymerase chain reaction is about $250–$1150 [102].

The burden of epilepsy

In underdeveloped countries globally, the prevalence of epilepsy is twice that of high-income countries, most likely due to a higher risk factor incidence. However, the treatment gap for epilepsy is > 60% in lower socioeconomic areas because drug supply and quality are limited [103].

North America

The economic burden of epilepsy impacts health systems and individuals and their families. The economic costs vary according to the severity of the condition, response to treatment, and length of time since diagnosis [104]. Epilepsy's economic impact in North America is positively correlated with other neuropsychiatric disorders, such as depression, relating the disease's annual cost to the interaction between epilepsy and the comorbidity of epilepsy and depression. The yearly cost per capita in 2019 was estimated to be $13.5K in adult patients with epilepsy versus $18.8K in adult patients with epilepsy and depression. Among the almost 2 million adults suffering from epilepsy, over 675K were also diagnosed with depression. Therefore, the cost estimate for 2019 shows a total economic cost of $1.7 billion for patients with only epilepsy versus $3.5 billion for patients with comorbid epilepsy and depression. These data indicate the importance of preventing psychiatric conditions in these patients. Diminishing epileptic events to considerably reduce neuronal damage over the years, help to avoid neuro-psychiatric events [104].

European Union

At least six million people have epilepsy in the EU [105]. Epilepsy care has high misdiagnosis rates and considerable variability in organization and quality across European countries, translating into a substantial societal cost (0.2% of GDP) [106]. The total cost of epilepsy in Europe was estimated to be $18.4 billion in 2004 and $23.76 billion in 2014, with indirect costs being the dominant category [106, 107]. In Italy, the annual per capita expenditure on patients with epilepsy in 2015 was $1.5K. Spain's costs were $2.5K for outpatients, and those needing epileptic surgery cost $5.2K per year. For newly diagnosed patients in France, the cost was estimated to be $2.4K. In the Netherlands, the costs varied greatly depending on the level of care provided in general practice. The costs per person were $62. At a university hospital, it was $335, and at a more specialized epilepsy center, the cost was $421 per person [108].

Latin America

The treatment of epilepsy with a disciplined dose of medication can be affordable and accessible, with an annual cost of only $5 per person. Studies have shown

that up to 70% of people with epilepsy in developing countries with a low socio-economic background can lead everyday lives if diagnosed and treated correctly. A study in 2012 showed costs for treatment per capita varied in the public sector versus the private sector, and generic brand drugs were cheaper in the public versus the private sector by almost 30 times [109]. A study in Mexico showed the direct costs of healthcare annually for 72 patients was $190.5K, with ambulatory healthcare accounting for 76% and ancillary hospital costs 24%. Epilepsy treatment averaged $2.6K per capita. The study also showed that disease evolution or the illness's severity did not significantly alter the cost [110].

The epilepsy-related mortality in Latin America and the Caribbean is 1.04 per 100,000 inhabitants, which outweighs that of the US and Canada. Based on the reports from Latin American studies, there are around 20% of complex epilepsy cases who fail to respond to mainstream treatments [111]. That said, almost two-third of the countries of Latin America and the Caribbean are yet to develop comprehensive healthcare programs for patients with epilepsy. Nevertheless, there has been a recent program entitled epilepsy for primary health care as a cost-effective Latin American E-learning initiative since 2018 which opens more windows of hope in this respect [112].

Africa

In 2001, the annual cost of outpatient medical management per patient was $120 in South Africa, and medication costs were $436 [113]. South Africans with epilepsy living in rural areas usually consult traditional healers and biomedical caregivers for epilepsy care. The annual cost for out-of-pocket, outpatient biomedical care at a hospital was estimated to be $58.41. In contrast, the yearly cost of a traditional healer's services was $52.36 ($34.90–$87.26) [114]. In Nigeria, epilepsy is among the leading causes of neurological disorders in children. There have been very few studies done to document the costs of epilepsy in African countries. According to a Nigerian study, the total annual expenditure on treatment and care of 215 epileptic patients ranged from $155 to $21.9K, translating to $717 per capita. Of these, direct costs amounted to 72%. Since Nigeria's average annual income is significantly less than $717, the economic burden of epilepsy care is significant, with too high out-of-pocket expenditure [115].

Australia

Epilepsy carries a significant economic burden in Australia, according to a productivity-based study published recently [116]. The principal contributor to financial costs is loss of productivity costs, which account for $2.3 billion. The healthcare system costs related to treatment, which accounts for $557.1 million, the informal care costs, which account for $438.2 million, and other financial costs, like equipment, account for $8.6 million, and transport accounts for $9.9 million.

Asia

Total direct costs in Hong Kong added up to $1 million and indirect costs to $1.32 million [117]. For epilepsy in China, the cost per capita was $773. The study found that direct medical costs were $372, and non-medical expenses were $111. The indirect cost was $289, and antiepileptic drugs cost $243 [118]. The full extent of the economic burden due to epilepsy has not been thoroughly studied in developing countries such as India. A study done in 2001 assessed the direct and indirect costs of epilepsy. A total of 285 patients were part of the study. The total per-patient cost was $344. The direct cost was $93, and the indirect costs were $251. The approximate number of people with epilepsy in India was five million, leading to an estimate of the total economic costs associated with epilepsy of $1.7 billion [119]. The prevalence of epilepsy in Iran is about 1–5%, meaning that almost 840,000 individuals can be considered patients with active epilepsy [120].

Epilepsy treatment using a commonly prescribed drug such as phenobarbital costs $740 per patient annually according to the Purchasing Power Parity (PPP). This drug raises the question of cost-effectiveness, considering its many side effects. Other treatments such as topiramate can cost $674 per patient annually according to PPP, which has better cost-effectiveness but still comes at a high price [121].

The burden of CNS malignancies

The term primary brain and CNS tumors cover many pathological entities ranging from benign (WHO Grade I) to malignant (WHO Grade II - Grade IV) tumors [122]. These tumors affect all age groups and are prevalent worldwide. The following review of the epidemiology and economic burden of the brain and other CNS cancer includes all cancers coded as C70.0–C72.9 (C70, malignant neoplasm of meninges; C71, malignant neoplasm of the brain;

Table 8
List of G20 countries and other countries with incidence rate, prevalence, and mortality rate due to brain and other CNS cancers according to the GBD 2019 study results [116]. Prevalence data are crude numbers of cases per 100,000 based on 2019 global population statistics from World Bank [68]

Brain and Other CNS Cancer					
Region	Country	Incidence rate, total (per 100,000)	Prevalence, total (per 100,000)	Mortality rate, total (per 100,000)	Socio-Demographic Index (SDI)[1]
North America	United States	28,021 (8.5)	79,526 (24.2)	20,459 (6.2)	0.859 - H
	Canada	4,781 (12.7)	22,993 (61.2)	2,399 (6.4)	0.873 - H
Latin America	Mexico	3,473 (2.7)	7,611 (6.0)	3,274 (2.6)	0.649 - M
	Argentina	2,211 (4.9)	4,853 (10.8)	1,781 (4.0)	0.708 - MH
	Brazil	12,651 (6.0)	24,883 (11.8)	10,556 (5.0)	0.640 - M
European Union	Germany	7,439 (9.0)	13,158 (15.9)	6,786 (8.2)	0.898 - H
	France	8,228 (12.3)	40,335 (60.2)	4,157 (6.2)	0.834 - H
	United Kingdom	6,064 (9.1)	15,792 (23.7)	4,600 (6.9)	0.847 - H
	Spain	5,203 (11.1)	20,638 (44.0)	3,083 (6.6)	0.767 - HM
	Italy	6,056 (10.0)	18,878 (31.3)	4,169 (6.9)	0.801 - HM
	Netherlands	2,327 (13.5)	12,277 (71.1)	1,071 (6.2)	0.883 - H
Africa	South Africa	993 (1.7)	1,583 (2.7)	882 (1.5)	0.678 - M
	Nigeria	2,833 (1.4)	5,377 (2.7)	2,298 (1.1)	0.515 - LM
Australia and Oceania	Australia	1,978 (7.8)	4,537 (17.9)	1,586 (6.3)	0.839 - H
Asia	China	94,686 (6.8)	327,890 (23.5)	63,527 (4.5)	0.686 - M
	Japan	11,339 (9.0)	72,949 (57.8)	3,223 (2.6)	0.870 - H
	India	28,103 (2.1)	49,288 (3.6)	23,740 (1.7)	0.566 - LM
	Indonesia	5,659 (2.09)	9,468 (3.5)	4,988 (1.8)	0.660 - M
	Turkey	6,355 (7.8)	23,091 (28.2)	4,075 (5.0)	0.748 - HM
	Saudi Arabia	597 (1.7)	6,790 (19.8)	1,296 (3.8)	0.805 - HM
	Russia	7,570 (5.2)	10,073 (7.0)	7,171 (5.0)	0.805 - H
	South Korea	4,806 (9.3)	30,979 (59.9)	1,479 (2.9)	0.878 - H
	Iran	5,811 (7.0)	23,225 (28.0)	3,494 (4.2)	0.670 - M

[1]H, high SDI; HM, high-middle SDI; M, middle SDI; LM, low-middle SDI.

Table 9
List of G20 countries and other countries with incidence rate, prevalence, and mortality associated with brain and other CNS cancer. The data were derived from the GBD 2019 study results [126]. Countries were divided into quintiles from highest to lowest according to the socio-demographic index (SDI). The rates are crude values per 100,000 based on 2019 global population statistics from World Bank [68]

SDI[1] Quintile	SDI	Incidence per year & 100,000 (95% UI[2])	Prevalence per 100,000 (95% UI[2])	Deaths per year & 100,000 (95% UI[2])
High SDI	0.805–1	8.5 (5.8–11.2)	33.6 (21.5–43.3)	5.6 (3.8–6.3)
High-middle SDI	0.690–0.805	7.5 (4.7–9.9)	22.5 (14.0–30.3)	5.4 (3.3–6.7)
Middle SDI	0.608–0.690	5.2 (3.8–6.4)	16.0 (11.9–19.8)	3.7 (2.6–4.6)
Low-middle SDI	0.455–0.608	2.0 (1.5–2.6)	3.7 (2.7–4.8)	1.7 (1.2–2.2)
Low SDI	0–0.455	1.7 (1.1–2.4)	3.4 (2.1–5.0)	1.3 (0.9–1.9)

[1]Socio-demographic index (see text). [2]Uncertainty interval.

C72, malignant neoplasm of the spinal cord, cranial nerves, and other parts of the CNS) in the 10th edition of the International Classification of Diseases (ICD-10). According to the Global Burden of Disease (GBD) study 1990–2016 [123], the overall incidence of these cancers increased globally by 17.3% (95% confidence interval 11.4% to 26.9%) between 1990 and 2016. In 2016, the age-standardized incidence rate per 100,000 person-years was 4.63 (4.17 to 4.90).

The most common type of primary CNS cancer is diffuse glioma, including glioblastoma multiforme (GBM, grade IV), anaplastic gliomas (grade III), and low-grade diffuse gliomas (astrocytoma, oligodendroglioma, grade II). Glioblastoma, the most common primary adult CNS cancer, is almost uniformly fatal within two years despite maximal surgical, radiation, and drug therapy. Pediatric diffuse midline (brainstem) glioma is also fatal within 1-2 years of diagnosis. Non-glioma CNS cancers, e.g., grade II-IV meningiomas, are associated with significant morbidity, but long-term survival is possible with comprehensive and expensive treatment strategies [124, 125].

Tables 8 and 9 give an overview of the global patterns of incidence, prevalence, and mortality of brain and other CNS cancer for the G20 countries and various other countries presented by the GBD 2019 study group in *The Lancet* in 2020 [126]. The data

can be downloaded for analysis from the Institute for Health Metrics and Evaluation 2020 website [127]. Significant geographical and regional variations are observed, which could be due to differences in diagnostic capabilities and reporting practices combined with different age structures of the population and unknown environmental and genetic factors. A consistent association with the socio-demographic index (SDI) can be observed (Table 9). The SDI is a summary measure of development status, on a scale ranging from 0 to 1; it uses rankings of incomes per capita, average educational attainment, and fertility rates of all areas in the GBD study.

Table 9 shows that the incidence, prevalence, and mortality of brain and other CNS cancer in countries with the highest SDI is consistently higher than in countries with lower SDI. The lack of advanced imaging and medical specialists in neuro-oncology in many low- to low-middle SDI regions will affect the accuracy of registry and death certificate data. On the other hand, brain and CNS cancer incidence has steadily increased between 1990 and 2019 in the G20 and other countries shown in Table 9. For example, the growth rate of incidence in Brazil, a middle-level SDI country, accelerated during the late 1990s and then increased at the same rate as that of the US (Fig. 2). In Pakistan, a low SDI country, the incidence has increased at a similar rate as that of the US. Both Brazil and Pakistan now have a similar incidence growth rate than the US, a high SDI country. Overall, the incidence, prevalence, and mortality of brain and CNS cancer and its change over time depends on a complex interplay of socio-economic factors such as the aging pattern of the population (GBM occurs most often after age 50) and access to quality health care in CT and MRI imaging. Overall, one can expect that the number of patients with brain and CNS cancer will further grow in low- to middle SDI countries while it may slow in high SDI countries [123, 126].

Brain and other CNS cancers are a significant global economic burden because the financial costs of treatment and loss of employment are high for patients individually, and because of the substantial cost of prematurely lost or years lived with disability. Direct costs include direct medical costs paid by a third-party payer if survivors have insurance coverage or out of pocket otherwise, and non-medical direct costs covered by the cancer survivor or his family. Indirect costs to the survivor and society are related to loss of productivity due to death or disability and are measured in DALYs.

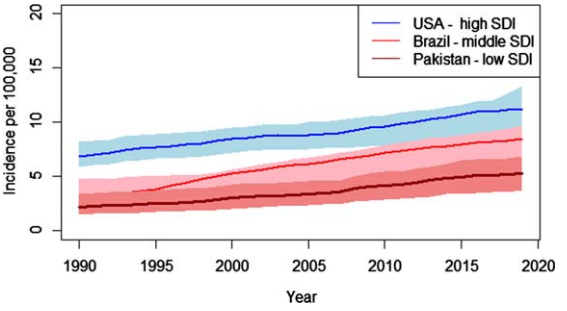

Fig. 2. Incidence of brain and other CNS cancers according to the GBD 2019 study results tool [127]. Expectation values and 95% uncertainty intervals are shown for three representative countries (USA, Brazil, Pakistan) with high, middle, and low SDI, respectively, across three world regions (North America, South America, Asia).

Only a few studies worldwide have investigated the extra direct costs associated with brain and other CNS cancer care, i.e., expenditures for a patient exceeding the expected cost of health care during a particular phase of their illness. Most of the published works have focused on the economic burden of malignant gliomas [128]. Some studies have not only estimated but forecasted the costs of cancer care, including brain and other CNS malignancies in the US [129]. Their cost estimates were based on the health care costs of Medicare beneficiaries (i.e., those aged over 65 years) during the initial period after diagnosis of cancer, the final 12 months of life, and the period between those times. The annualized mean net costs of brain cancer care were the highest among the 17 solid tumor types studied and amounted to $129,802 (2010 USD), $8,803, and $211,337 for female patients and $138,300, $9,434, and $201,366 for male patients during the initial phase, continuing phase, and 12 months before cancer death, respectively. The annual US national cost of brain and other CNS cancer care in 2010 was projected to be between $4.47 and $5.79 billion (2010 USD), rising to between $5.62 and $8.18 billion in 2020, depending on different trend scenarios for incidence and survival. Updated results of this study can be found in the 2020 publication by Mariotto et al., where brain cancer was again the most cost-intensive tumor among solid cancers with an average of $134,400, $16,700, and $169,500 (2019 USD) for medical services and $2,300 $1,400, and $1,800 for prescription drugs during the three phases of care [130], respectively. Similar a recent study in New Zealand [131] confirmed the high burden of direct medical cost in those countries. Lastly, a recent global study showed that while the heath expendi-

tures on brain and other CNS cancers is higher in high and middle-high quintile SSD countries than in the middle- to low-quintile SSD countries, the quality of care index is also much lower in the latter countries [132].

Cancer, in general, is the leading cause of death globally [133] and, therefore, has the greatest economic impact from premature death and disability of all causes of death worldwide. Table 10 summarizes the DALYs lost due to brain and CNS cancers in the G20 countries and other countries in each global region. The product of DALYs and GDP per capita allows estimating the annual cost of cancer per country around the world in 2019. The average fraction of GDP lost due to the DALYs of brain and CNS cancer was 0.14%, ranging from 0.06% for the low-SDI African countries to 0.21% for the high-SDI countries of Europe and North America [126].

North America

North America as a geographic region includes Canada with 10 Provinces and 3 Territories, the US with 50 States, Bermuda, Greenland, and Saint Pierre and Miquelon. In 2019, North America had a total population of 366.6 million [126] and a total GPD of $23.2 trillion (2019 USD) [68]. The SDIs of high-income North America, Canada, and the US were 0.860, 0.873, and 0.859, respectively [134]. The mean SDI of the 50 United States was 0.86 (ranged, 0.81 to 0.91) [134].

According to the GBD 2019 study results tool [127], 32,802 (9.0 per 100,000) patients were diagnosed with, 102,519 (28.0 per 100,000) patients lived with, and 22,861 (6.2 per 100,000) patients died from brain and other CNS cancer in North America in 2019. The number of DALYs lost due to the disease were 632,566 person life years, equivalent to a total annual cost of $40.0 billion (2019 USD).

European Union

In 2019, the EU had 28 member countries with a total population of 512.5 million [135] and a total GPD of $15.6 trillion (2019 USD) [68]. Note that the UK left the EU at the end of January 2020 but was included as a member of the EU in the 2019 GBD analysis. Geographically, Europe can be divided into Eastern, Northern, Southern, and Western Europe. However, the GBD 2019 study divided Europe into Central, Eastern, and Western regions with SDIs of 0.843, 0.788, and 0.793 [134]. The SDIs of individual countries of the EU28 included the high (18 countries) and high-middle (10 countries) SDI quintiles; the mean SDI was 0.83 with a range from 0.90 (Germany) to 0.74 (Portugal) [134].

According to the GBD 2019 study results tool [127], 55,581 (10.8 per 100,000) patients were diagnosed with, 102,519 (20.0 per 100,000) patients lived with, and 37,882 (7.4 per 100,000) patients died from brain and other CNS cancer in the EU in 2019. The number of DALYs lost due to the disease were 1,037,990-person life years, equivalent to a total annual cost of $36.2 billion (2019 USD).

Latin America

Latin America includes Central and South America, Mexico, and the Caribbean islands. In 2019, Latin America had a total population of 648.1 million [135] and a GPD of $5.7 trillion (2019 USD) [68]. Latin America, as a region, had a middle-quintile SDI of 0.633. The SDIs of Central America, South America, Mexico, and the Caribbean islands were 0.626, 0.721, 0.660, and 0.631, respectively. SDIs of individual countries ranged from high (Puerto Rico and Bermudas, 0.81) to low (Haiti, 0.43).

According to the GBD 2019 study results tool [127], 23,723 (3.7 per 100,000) patients were diagnosed with, 49,467 (7.6 per 100,000) patients lived with, and 19,407 (3.0 per 100,000) patients died from brain and other CNS cancer in Latin America in 2019. The number of DALYs lost due to the disease were 711,731-person life years, equivalent to a total annual cost of $6.3 billion (2019 USD).

Sub-Saharan Africa

The sub-Saharan Africa region includes all countries south of the Sahara. It can be further divided into Central, Eastern, Southern, and Western Africa. In 2019, the region had a total population of 1.1 billion [135] and a GDP of $1.8 trillion (2019 USD) [68]. Sub-Saharan Africa had an SDI of 0.456 (low-middle quintile) [134]. The SDIs of Central, Eastern, Southern, and Western Africa were 0.470, 0.405, 0.642, and 0.448, respectively [134]. Only the two island countries, Mauritius and Seychelles, had a middle-high-quintile SDI (0.69–0.80), South Africa and Namibia a middle quintile SDI (0.61–0.68), and the remaining 43 countries had a low- (0–0.45) or low-middle quintile SDI (0.45–0.60), which makes sub-Saharan Africa the least developed region in the word [134].

According to the GBD 2019 study results tool [127], 13,898 (1.3 per 100,000) patients were diagnosed with, 26,200 (2.4 per 100,000) patients lived with, and 11,399 (1.0 per 100,000) patients died from

Table 10
List of G20 countries and other countries with annual cost, disability-adjusted life years (DALYs) lost in 2019 and cost per capita associated with brain and other CNS cancer. Data were derived using the GBD 2019 study tool [127]. The costs for the DALYs are based on 2019 global population and GDP statistics from World Bank [68]

		Brain and Other CNS Cancer			
	*all values USD ($)	Annual Cost ($10^9$$) (95% UI[1])	DALYs[2] (2019) (95% UI[1])	Per Capita ($) (95% UI[1])	GDP 2019 ($10^6$$)
North America	United States	36.90 (29.98–40.45)	5.65 (4.59–6.20)	112.41 (91.33–123.24)	21,422,226
	Canada	3.11 (2.25–3.48)	0.67 (0.49–0.75)	82.86 (59.89–92.62)	1,736,425.63
Latin America	Mexico	1.05 (0.77–1.23)	1.05 (0.77–1.23)	8.19 (6.04–9.62)	1,268,870.53
	Argentina	0.57 (0.49–0.65)	0.57 (0.48–0.64)	12.63 (10.71–14.28)	445,445.18
	Brazil	3.73 (2.50–4.24)	3.25 (2.18–3.69)	15.41 (10.34–17.50)	1,839,758.04
European Union	Germany	1.77 (1.13–2.02)	8.23 (5.25–9.37)	99.03 (63.21–112.71)	3,861,123.56
	France	1.17 (0.66–1.39)	4.72 (2.65–5.62)	70.45 (39.58–83.79)	71,104.92
	United Kingdom	1.28 (0.88–1.39)	5.40 (3.74–5.86)	80.79 (55.91–87.75)	2,829,108.22
	Spain	0.83 (0.46–0.97)	2.47 (1.35–2.88)	52.41 (28.66–61.12)	1,393,490.52
	Italy	1.08 (0.71–1.19)	3.59 (2.36–3.95)	59.46 (39.16–65.53)	2,003,576.15
	Netherlands	0.31 (0.19–0.36)	1.61 (0.98–1.86)	92.71 (56.45–107.54)	907,050.86
Africa	South Africa	0.33 (0.23–0.38)	0.20 (0.14–0.23)	3.41 (2.37–3.91)	351,431.65
	Nigeria	1.24 (0.82–1.88)	0.28 (0.18–0.42)	1.38 (0.90–2.08)	448,120.43
Australia and Oceania	Australia	0.45 (0.33–0.50)	2.48 (1.83–2.76)	97.76 (72.02–108.75)	1,396,567.01
Asia	China	20.53 (15.84–25.25)	20.98 (16.19–25.80)	15.01 (11.58–18.46)	14,342,903.01
	Japan	0.89 (0.44–1.06)	3.57 (1.79–4.25)	28.24 (14.17–33.66)	5,081,769.54
	India	10.13 (8.03–12.42)	2.13 (1.69–2.61)	1.56 (1.23–1.91)	2,868,929.42
	Indonesia	2.02 (1.38–2.63)	0.84 (0.57–1.09)	3.09 (2.10–4.02)	1,119,190.78
	Turkey	1.33 (0.63–1.84)	1.21 (0.58–1.68)	14.54 (6.95–20.10)	761,425.50
	Saudi Arabia	0.26 (0.19–0.40)	0.61 (0.44–0.92)	17.86 (12.98–26.90)	792,967
	Russia	2.45 (1.79–2.93)	2.89 (2.11–3.45)	19.99 (14.59–23.92)	1,699,876.58
	South Korea	0.46 (0.30–0.55)	1.47 (0.95–1.76)	28.42 (18.33–34.11)	1,646,739.22
	Iran	1.29 (0.68–.54)	0.70 (0.37–0.84)	8.49 (4.47–10.14)	453,996.48

[1]Uncertainty interval. [2]Disability-adjusted life years in units of 100,000-person life years.

brain and other CNS cancer in sub-Saharan Africa in 2019. The number of DALYs lost due to the disease were 613,676-person life years, equivalent to a total annual cost of $1.0 billion (2019 USD).

Australia

Australia is the smallest continent and an independent country, comprising six states and two territories. In 2019, Australia had a total population of 25.2 million [135] and a GDP of $1.4 trillion (2019 USD) [68]. The SDI of Australia was 0.84.

According to the GBD 2019 study results tool [127], 1,978 (7.8 per 100,000) patients were diagnosed with, 4,537 (17.9 per 100,000) patients lived with, and 1,586 (6.25 per 100,000) patients died from brain and other CNS cancer in Australia in 2019. The number of DALYs lost due to the disease were 45,035-person life years, equivalent to a total annual cost of $2.5 billion (2019 USD).

Asia

Asia is the largest and most populous continent (60% of the world population). In 2019, the Asian continent had a population of 4.6 billion [135] and a GDP of $31.7 trillion (2019 USD) [136]. Geographically, Asia is divided into the following regions and countries: Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan), Northern Asia (Asian portion of Russia), Southeastern Asia (Borneo, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam), Western Asia (countries of the Middle East, Turkey, Iran, Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka), and the Far East (China and Hong Kong, Japan, Korea, Macao, Mongolia, and Taiwan).

Economically, Asia is a very diverse continent. The SDIs of Asian countries cover all quintiles, including the high quintile (e.g., South Korea, Japan, and Singapore), the high-middle quintile (e.g., Saudi Arabia, Israel, and Turkey), the middle quintile (e.g., China, Iran, and Indonesia), the low-middle quintile (e.g., India, North Korea, and Bangladesh), and the low quintile (e.g., Pakistan, Yemen, and Afghanistan) [134].

According to the GBD 2019 study results tool [127], 188,660 (4.1 per 100,000) patients were diagnosed with, 608,890 (13.2 per 100,000) patients lived with, and 129,520 (2.8 per 100,000) patients died from brain and other CNS cancers in Asia in 2019.

The number of DALYs lost due to the disease were 4,776,406-person life years, equivalent to a total annual cost of $47.8 billion (2019 USD).

In summary, brain and other CNS cancers are present worldwide. The geographical differences in incidence and prevalence are best explained by differences in the SDI, which correlates with higher life expectancy and more frequent use of advanced imaging technology to diagnose these otherwise underdiagnosed tumors. The cost of care for these brain and other CNS cancer in the high- and middle-quintile SDI countries is substantial. Many of these tumors remain incurable, and end-of-life care is expensive. Further research is needed to improve the outcome of these tumors and eventually cure them at a reasonable cost of care. The reduction of disability-adjusted life years would justify and most likely offset the use of expensive medical services and drugs.

THE GLOBAL ECONOMIC BURDEN OF MENTAL HEALTH DISORDERS–MENTAL HEALTH 20

The COVID-19 pandemic has caused significant mental health struggles due to morbidity and mortality, lack of activity, income loss, and social isolation, according to the Centers for Disease Control [137]. Past studies have suggested that > 90% of suicide victims previously suffered from a psychiatric disorder [138–140]. Expanding on social isolation, in past epidemics like the SARS outbreak, individuals' social isolation led to the pathophysiology of mental disorders and suicidal behavior [141, 142]. Mental illnesses can have measurable burdens which may be delineated through productivity losses, human capital costs, economic growth loss, statistical life approach, and massive use of resources for treatment [143, 144]. A projection in 2011 by the World Economic Forum concluded that by 2030, mental illnesses would comprise more than half of the global economic burden of non-communicable diseases at $6 trillion annually. This global financial burden is greater than cardiovascular disease, chronic respiratory disease, cancer, and diabetes [143]. Stigmatization and misconceptions of mental disorders as well as heavy use of resources for treating addictive disorders result in less effective treatment and greater spending on somatic diseases than mental disorders [144]. The economic decline during and after the COVID-19 pandemic can have harmful outcomes on individuals' mental health and increased development of psychiatric disorders and suicidal behavior [20]. One possible consequence of COVID-19, post-recovery, is a greater suicide risk, especially for individuals who suffered severe symptoms during illness [145]. In the end, unemployment, financial insecurity, precarious working conditions, inequities, lack of social interaction, and housing instability create risk factors for potential suicide ideation [145] (See Table 12).

North America

In 2013, the USA incurred a $187.8 billion spending amount on mental health costs [146]. The average Canadian medical cost per capita was $2.5K for diagnosed patients and $1.4K for undiagnosed patients. Per capita, the annual loss of employment was about $32.7K per person. In 2003, a total expenditure of $51 billion was incurred, with about 30% of the costs accounting for an undiagnosed mentally ill population [147].

European Union

Accounting for the major groups of brain disorders such as addictive disorders, affective disorders, anxiety disorders, childhood/adolescent disorders, eating disorders, epilepsy, mental retardation, migraine, Europe estimated a cost of $455 billion for the year 2004. The brain's European per capita cost of diseases was as follows: anxiety disorders $88; mood disorders $133.7; personality disorders $32; psychotic disorders $110 [6].

Latin America

Research on mental health in Latin American countries has made progress during recent years. Still, much remains to be done. The big four, namely: Brazil, Argentina, Mexico, and Chile, are ahead in resources and productivity, but more research is currently coming out of Mexico, despite a disproportionate budget compared to the other three countries (per capita $20 in Mexico versus $60 in Brazil). Eight countries have research institutes committed to research on mental health, but only Mexico has shown consistent progression in research. The other countries suffer from lacunas in policies, operational systems, and qualified personnel. The government's absence of substantial financial support seems to be at the root of this unfortunate reality [148]. In Mexico, the average cost for managing each schizophrenia case was $211, and for each depression case was

Table 11
Annual cost per capita for Mental Health in African countries with available data. Adapted from [62]

Countries	Mental health per capita annually ($)
Algeria	4
Tunisia	130
Cabo Verde	114.85
Guinea Bissau	88
Seychelles	150
Sao Tome	495.64
Namibia	72.54
Swaziland	37.81

$221 [149]. In Brazil, in 1998, expenses for psychiatric hospitalizations accounted for 95.5% of total mental health expenditures. In the ensuing period from 1995–2005, mental health expenses decreased by 26.7% per capita (from $2.66 to $1.95) [150]. Per a recent study, non-communicable diseases and mental health conditions over the period 2015–2030 are projected to cost $81.96 billion for Costa Rica, $18.45 billion for Jamaica, and $477.33 billion for Peru [151].

Africa

In the 2016/2017 financial year, the total health system costs of mental health services in South Africa were approximately $573.6 million. This total cost represented an estimated 4.6% of the total health budget and equated to $12.4 per capita on mental health expenditure. With the inclusion of non-governmental organizations' mental health services and contracted hospitals, the cost increased to $615.3 million or $13.3 per capita [152]. A study published in 2016 shows the per capita expenditure on mental health in several African countries represented in Table 11 [62]. The impact of severe mental disorders on productivity in South Africa reflected a reduction in individual income of about $4.8K per adult per year, resulting in an annual national loss of $3.6 billion. In comparison, a severe mental disorder's yearly impact on Nigeria's productivity was $463 per adult per year, totaling $166.2 million annually. Many mentally ill patients in Ghana do not have adequate access to mental health treatment [113].

Australia

There is a growth in the spectrum of brain/neurological disorders since 2017, therefore increasing the economic costs associated with them, reaching a value of over $74 billion yearly, divided into $33 billion each year for mental health disorders, $31 billion each year for neurological disorders, and $10 million each year for substance use disorders [153]. Neurological disorders' financial impact will soon comprise a higher cost to the Australian economy than heart disease, cancer, and respiratory disease combined. Mental health disorders accounted for the highest burden-of-illness (46%), followed by neurological disorders (37%) and substance disorders (16%). This report provides a proposal on how local government and scientists can help promote better care models, including new and improved interventions such as workplace interventions, strong support after a suicide attempt, and dementia support services [153].

Asia

The total direct cost of depression in Japan in 2005 was estimated at $117 billion, including outpatient care, inpatient treatment costs, and medication costs [154]. The estimated cost of depression in China was $6.2 billion in 2002. Direct costs were $ 986 million, about 16% of the total cost of depression. Indirect costs were $5.2 billion, about 84% of the total cost of depression [155]. The entire known cost of schizophrenia in Japan in 2008 was $23.8 billion. While the direct cost was $6.59 billion, the morbidity and mortality costs were $15.8 billion and $1.33 billion, respectively. Compared to other disorders, such as depression or anxiety, the direct cost accounted for a relatively high proportion of the total cost [156]. In India, the real prevalence of various mental illnesses is 10.6%, per the National Mental Health Survey (NHMS) done in 2016. India's total population is about 1300 million, putting the number of people with mental health illnesses above 130 million. The NMHS reports the average per capita monthly expenditure on treatment and care at around $15 for schizophrenia and $20 for depressive disorders [157]. The total annual costs for outpatient treatment will be about $2 billion based on the above numbers. Inpatient costs are slightly higher as the per capita cost of admission per day is $20, amounting to an annual total of $420 per capita, based on 21 days of hospitalization [158]. In Iran, the highest treatment cost reimbursement rate, by insurance services, belongs to psychiatric patients (93%). The average length of hospital stay is reported to be 23.6 days, and the average cost for each patient is estimated at $1,020. The highest cost for depression patients is attributed to hoteling (62%) and doctor's visits

(24%) [159]. The average total annual out-of-pocket expense is $ 2120.6 for those with drug use disorder and $674.6 for other mental disorders [160].

THE GLOBAL ECONOMIC BURDEN OF SPINE DISORDERS–SPINE 20

The economic burden of spine disorders is summarized in Table 13.

North America

Chronic low back pain (CLBP) is defined by symptoms lasting more than three months. The second most common cause of adult disability in the US is CLBP. Almost 80% of the population will experience acute low back pain at some point during their lives, but only a minor community will progress to CLBP. There is a prevalence rate of 10.2% for CLBP patients in the US, translating to almost 32 million people suffering from CLBP. The per-patient direct medical costs are approximately $1,843. When aggregated to the entire population, the cost totals $59 billion. Indirect costs that include the loss of work/wages are twice the direct costs at $120 billion [2].

European Union

CLBP prevalence is 19% in European adults, leading to problems in the quality of their social lives due to the physical limitations. CLBP affects healthcare systems, especially the healthcare resources for pain therapies producing a high economic burden [161]. Annual costs reach $9.4K per patient; this cost comprises 51% of healthcare and 49% societal expenses [162]. Bone metastases lead to complications, known as skeletal-related events (SREs), resulting in pain, physical disability, epidural spinal cord compression, pathologic fracture, and reduced function leading to impaired quality-of-life. These SREs are associated with high healthcare costs, up to $14.3K per SREs, noting that spinal cord decompression and bone surgery are linked with the highest costs [163].

Latin America

In Latin America, low back pain is a grievance of most working populations with an economic and social impact. A study from Mexico reports that between 10–15% of the general consultation is due to CLBP. Low back pain in Argentina takes third place among the most common disorders that cause disability and work absenteeism. In Brazil, CLBP was the diagnosis utilized for approximately 3 thousand retirement pensions in 2007 [164]. According to a Brazilian study conducted between 2012–2016, the total healthcare expenses for CLBP were $460 million [165]. In Chile in 2018, a study reports that productivity losses due to low back pain were estimated at $13.31 million per year [166].

Africa

Traumatic spine injury, a significant cause of morbidity and mortality, often affects young, salary-earning males in Africa. Many patients choose non-operative care, consisting of bed rest, due to insufficient funds and the high cost of spinal implants. The total cost of treatment via non-operative care ranged from $203 to $212. The cost of treatment per patient in Tanzania in operative care ranged from $700 to $731. Most of the cost for non-operative care was from initial x-ray imaging and hospital stays, while costs of those who had operative care were from implants, surgical fees, and postoperative imaging [167].

Australia

Chronic back problems are common in Australia, affecting 16% of the total population and causing disability in 28% of the total population CLBP affects the ability to perform daily activities, family, work, and social activities [168]. Direct costs in 2001 exceeded $500 million. Of this amount, 71% accounted for therapy by chiropractors, physiotherapists, massage therapists, general practitioners, and acupuncture. Indirect costs reached $4 billion, yielding a total cost of $4.6 billion [169].

Asia

A study of the Japanese population showed that the lifetime lower back pain prevalence was 83%, and the 4-week prevalence was 36% [170]. In terms of costs, it was estimated that the average annual direct and indirect costs per patient for chronic lower back pain were $15.2K and $12.4K, respectively. Direct costs included mostly hospital expenses, amounting to $13.3K. A study of 1.5 million individuals, where 815K were employed, reported a total economic cost of $10 billion per year due to lost productivity [171]. Moreover, China measured an age-standardized point prevalence rate for lower back pain that decreased from 5.6% to 4.2% between 1990 and 2016 [172].

Table 12
List of G20 and other countries with Mental Health Disorders cost, estimated cost, per capita cost, and GDP data. Blank boxes indicate no data is available for that country. GDP statistics are from World Bank [68]. Gray boxes indicate missing data to date

Mental Health Disorders					
	*all values USD ($)	Annual Cost ($)	Estimated Cost ($)	Per Capita Cost ($)	GDP 2019 ($) (Millions)
North America	United States	187.8 billion			21,422,226
	Canada	51 billion		2,500	1,736,425.63
Latin America	Mexico			221	1,268,870.53
	Argentina				445,445.18
	Brazil				1,839,758.04
European Union	Total	455 billion		363.7	
	Germany				3,861,123.56
	France				71,104.92
	United Kingdom				2,829,108.22
	Italy				2,003,576.15
Africa	South Africa	573.6 million		12.4	351,431.65
Australia and Oceania	Australia	33 billion			1,396,567.01
Asia	China		6.2 billion		14,342,903.01
	Japan	23.8 billion	117 billion		5,081,769.54
	India		2 billion	420	2,868,929.42
	Indonesia				1,119,190.78
	Turkey				761,425.50
	Saudi Arabia				792,967
	Russia				1,699,876.58
	South Korea				1,646,739.22
	Iran			1020	453,996.48

Table 13
List of G20 and other countries with Spine disorders cost, estimated cost, per capita cost, and GDP data. Blank boxes indicate no data is available for that country. GDP statistics are from World Bank [68]. Gray boxes indicate missing data to date

SPINE DISORDERS					
	*all values USD ($)	Annual Cost ($)	Estimated Cost ($)	Per Capita Cost ($)	GDP 2019 ($) (Millions)
North America	United States	59 billion		1,843	21,422,226
	Canada				1,736,425.63
Latin America	Mexico				1,268,870.53
	Argentina				445,445.18
	Brazil	460 million			1,839,758.04
European Union	Total			9,400	
	Germany				3,861,123.56
	France				71,104.92
	United Kingdom				2,829,108.22
	Italy				2,003,576.15
Africa	South Africa				351,431.65
	Tanzania (East Africa)			934	38796.69
Australia and Oceania	Australia	500 million			1,396,567.01
'Asia	China				14,342,903.01
	Japan			13,300	5,081,769.54
	India				2,868,929.42
	Indonesia				1,119,190.78
	Turkey				761,425.50
	Saudi Arabia				792,967
	Russia				1,699,876.58
	South Korea				1,646,739.22

NEUROSCIENCE-20 (N20) INITIATIVE OF THE SOCIETY FOR BRAIN MAPPING AND THERAPEUTICS

A comprehensive study by the WHO showed that almost 33% of the adult population have a mental health disorder such as depression, anxiety, and schizophrenia. When combined with neurological disorders, such as stroke and dementia, they account for about 13% of the global disease burden [35]. In response to the BRAIN Initiative of the White House, SBMT and Brain Mapping Foundation (BMF) initiated the N20 to form a collaboration of global research organizations by bringing them under one umbrella and helping to build on the current and upcoming brain initiatives across the G20 member nations. The goal is ultimately to unify the brightest scientists, engineers, physicians, and surgeons across the globe to introduce novel clinical solutions for neurological disorders [173].

The SBMT-2014 initiative of the G20 World Brain Mapping and Therapeutics in 2014 was developed to promote a sustainable global economy. The goals of the initiative are support and facilitation of the development of improved diagnoses and treatments for neurological disorders, job creation and the commercialization of innovative medical devices, methods, and technologies for neurological disorders, and the establishment of extensive, genuinely open, and collaborative global partnerships. The G20/N20 goals are viable due to the collaboration of national and international groups working towards the innovation, integration, translation, and commercialization of neuro-technologies, advanced diagnostics, and therapeutics.

Outcomes

Leading brain mapping experts from G20+ countries including those from China, the US, Australia, Japan, Turkey, and the Middle East, participated in the development of resolutions in each event. Below we highlight three events and their initiatives. The first G20/N20 Brain Mapping Summit was held in Brisbane, Australia (2014) [174–176], co-sponsored by SBMT, BMF, Amen Clinics, and Compumedics, bringing together neuroscientists, engineers, neurosurgeons, and policymakers. The summit established the USA-Australia Brain Mapping Initiative and the first Brain Mapping Day at the Australian Parliament (Fig. 3) [177].

Fig. 3. USA and Australian Delegates at the first brain mapping conference (USA: Drs. Babak Kateb, Mark Liker, Aaron Filler, Uttam Sinha, Brian Hemling, Katarina Novakova; Australia: Drs. Kuldip Sidhu, Kiran Sidhu, Dimity Dornan, Matthew Kiernan, Jeff Rosenfeld, Freya Ostapovitch) [177].

The second G20/N20 World Brain Mapping Summit commenced in Istanbul and Antalya, Turkey (2015) [178]. The results included establishing the Turkish Brain Mapping Initiative and six strategic points endorsed in a memorandum of understanding (Fig. 4) [177]:

a. Adoption of a consortium approach for the study of the human brain.
b. Global harmonization of related policies and the standardization of data.
c. Economic assessment of future impacts related to the prevention and diagnosis of neurological disorders.
d. Facilitating the translation, integration, and commercialization of neurotechnologies.
e. Unification of global regulations and guidelines related to clinical trials and combined drug/device discovery and development.
f. Global partnership and new funding for Brain Mapping Initiatives (basic and clinical science) encompassing academic, educational, governmental, industry, and for-profit and nonprofit organizations.

SBMT – IEEE Brain Mapping Initiative

In 2015, a joint SBMT-IEEE Brain Mapping Initiative with ten potential areas of partnerships was formulated (Fig. 5) [177]:

Fig. 4. G20/N20 in Turkey 2015. The USA, Australian, and Turkish Delegates [177].

a. Participate in the 2016 World Congress for Brain Mapping and Therapeutics.
b. Establish a potential special journal issue: IEEE-SBMT/Brain Mapping and Therapeutics.
c. Create a Kids Corner.
d. Establish a significant social media presence.
e. Standardization of neurotechnologies.
f. Partner with the SBMT and the G20 World Brain Mapping Initiative.
g. Establish fellowships and scholarships in partnership with the IEEE Foundation.
h. Establish an awards program.
i. Partner with SBMT University on Brain Mapping TV.
j. Engage IEEE-USA in Brain Policy/Brain Mapping.

National Photonics Initiative

According to the official National Photonics Initiative (NPI) website (1998), the National Research Council released a report titled Harnessing Light - Optical Science and Engineering for the 21st Century. The field of optics and photonics has a significant impact on industries like healthcare. Countries such as Germany, China, and the European Union have been at the forefront of optics and photonics sectors, while the USA did not develop a unified strategy until recently (NPI 2015). The NPI for the USA is "an umbrella organization to identify and advance areas of photonics critical to maintaining competitiveness and national security" (NPI 2015). This initiative aligned with the United States BRAIN Initiative and found itself in a partnership with the Photonics Industry Neuroscience Group (PING), NPI-PING. The initial goal of the NPI-PING was to engage US industry leaders in biomedical imaging, microscopy, lasers, advanced light sources, optical devices and components, and image analysis software. The initiative soon shifted to a collaboration of the US and international scientific societies, industry, and academia. The NPI raised awareness of the impact photonics has on our everyday lives, thus increasing cooperation and coordination among US industries, government, and academia to advance photonics-driven research. With the focus on developing and implementing advanced optical tools and strategies for the further elucidation of brain activities and structural maps, a pathway for diagnostics and treatments for serious neurological disorders such as AD and PD was made clear.

The third summit was held in Chongqing, China (2016). The summit outcome was a cooperative agreement similar to that which was established in Turkey. During this summit, a path to cure NeuroAIDS and drug addiction was highlighted [179]. Figure 6 shows members of SBMT at the 2016 N20 summit in China.

In Hamburg, Germany, in 2017, during the fourth annual summit of the N20, the primary focus was to increase global cooperation and partnership on clinical and translational neuroscience and develop a global approach to better understand and treat neurological diseases such as AD and PD using stem cell biomaterials [180]. Topics concentrated on the use of high-resolution magnetic resonance neuroimaging using innovative technology, electroencephalogram

Fig. 5. Society for Brain Mapping and Therapeutics executives (Drs. Babak Kateb, Dipin Sinha, and others) [177].

Fig. 6. G20/N20 in China 2016 Society for Brain Mapping and Therapeutics executives. (Courtesy SBMT).

(EEG) entropies [181], and innovative approaches to cancer therapeutics and advancing neuroscience innovation through the N20 [8, 182, 183]. Figure 7 shows members of SBMT at the N20 summit in Germany.

The fifth annual N20 summit in 2018 in Argentina was a revolutionary meeting where four resolutions were proposed, agreed upon, and submitted to the Sherpas of the G20 countries. This meeting was co-sponsored by SBMT, BMF, Mind-Eye Institute USA, Üsküdar University Turkey, and MEGIN-USA [184]. The North American Spine Society (NASS) was invited to be part of the N20's - SPINE20 Initiative [185]. Figure 8 shows members of SBMT at the N20 summit in Argentina. The four 2018 resolutions from the N20 in Argentina are as follows [21].

a. Account for the global economic burden of diseases and injuries of the brain, spine, retina, and peripheral nervous system.
b. Raise awareness to stop the stigmatization of neurological and neuropsychiatric diseases.
c. Close gaps in access to neurodegenerative disorders and epilepsy care.
d. Promote a whole government approach to address brain and spine disease and injury.

During the sixth N20 Summit in Japan, amendments were made to the 2018 resolutions [21, 186] that recommended harmonizing clinical trials, institutional review boards, and other fast-tracking initiatives for the introduction of therapeutics and diagnostics. These recommendations were jointly proposed by SBMT, BMF, European Spine, MEGIN, Chopra Foundation, The Japanese Society for Regeneration Medicine and Rehabilitation, Saudi Spine Society, Eurospine, Pakistan Spine Society, Japanese Spine Society, and NASS [186].

The expansion of SPINE20 was discussed and agreed upon at this meeting. Figure 9 shows members of SBMT at the N20 summit in Japan.

These recommendations are critical in the present-day world when facing the pandemic of COVID-19 [19]. There is a need for a worldwide initiative to combat the challenges in the post-COVID-19 world, as research into the different diseases and medical conditions has taken a step back due to combined efforts to find a cure for COVID-19 [187]. The pandemic's

Fig. 7. G20/N20 Summit in Germany 2017. Society for Brain Mapping and Therapeutics executives. (Courtesy of SBMT).

Fig. 8. G20/N20 in Argentina 2018. Society for Brain Mapping and Therapeutics executives. (Courtesy of SBMT).

emergence has led to a critical situation concerning individuals' mental health and well-being [188]. The G20 countries have pledged over $21 billion in the fight against COVID-19 [189].

Neuroscience-20 goals and perspectives

Given the current global situation during the COVID-19 pandemic era, SBMT has proposed 16 goals for the N20, as follows [21]:

a. Building a global alliance for brain, spine, and mental health/illness
b. Encouraging a conglomerate approach to research and development.
c. Advocating for global synchronization of policies/standardization of data.
d. Encouraging a neuro-economical assessment of the upcoming impact of COVID-19 disease, diagnostics, and prevention.
e. Encouraging simplification of translation and commercialization of technologies across all disciplines of science to swiftly identify and pioneer a new generation of therapeutics, counting stem cells, nanotechnology, device, and imaging (a nano-bio-electronic consortium/ company spinoffs).
f. Advocating global regulations and guidelines on clinical trials and drug/device - combination discovery.
g. Advocating for the advancement of innovations in brain, spine, and mental health through a global partnership and new funding initiatives

Fig. 9. G20/N20 in Japan 2019. Society for Brain Mapping and Therapeutics executives. (Courtesy of SBMT).

between academic centers, industry, non-profit organizations, and government agencies.

h. N20 is a brain and spine consortium critically important to facilitating the integration of nanotechnology, artificial intelligence, virtual reality and augmented reality, supercomputing, multimodality brain mapping/imaging (MEG), cellular therapeutics, neurophotonics, and devices that can address fast-tracking innovation, reduce the cost of healthcare delivery, and make health care delivery more efficient.
i. N20 will bring the global brain and spine initiatives together to identify the best clinical and basic science practices and create a united front to push for new effective therapeutics.
j. Setting unified standards for training, prevention, care, and advanced therapeutics related to brain, spine, and mental disorders, for physicians, engineers, surgeons, nurses, chiropractors, physical therapists, osteopaths, and physiologists' disciplines.
k. Providing capabilities at the local, regional, and national levels to advance the practice of clinical neuroscience (brain, spine, and mental health/illness) through advocacy by engaging health ministries and government programs across the globe.
l. Advocating for global research and innovation funding for brain, spine, and mental health.
m. Facilitating investment and commercialization of neuro-technologies for the brain, spine, and mental health/illness.
n. Educating professionals, patients, and families about the latest state of science, technology, innovation, and clinical neuroscience (brain, spine, and mental health/illness).
o. Providing accurate and up-to-date resources and data to the G20 nation's governments and beyond to encourage adoption of new clinical neuroscience policies.
p. Raising awareness amongst all to address mental/psychological issues such as PTSD for healthcare workers, anxiety, stress for patients, job loss, future prospect uncertainty after the pandemic and prevention of suicides in the post-COVID-19 era.

CURRENT STATUS AND FUTURE APPROACHES

There has been an expansion of research on brain and neurological disorders over the last 20 years, despite the 2008 recession, which caused havoc in global financial markets, leading to a decrease in research funding allocations. This period was critical for forming a collaborative and multidisciplinary effort to bring more funding from governmental organizations to public-private partnerships and led to several brain initiatives across the globe.

In 2013, The White House launched the NIH BRAIN Initiative. Consequently, neuroscientists worldwide have introduced several brain initiatives in various countries to create new technologies in neuroscience. Brain initiatives worldwide include those in

countries like the US, Germany, Turkey, South Korea, Australia, Japan, Argentina, Iran, and China, focusing on neurological disorders suffered by millions of individuals worldwide. Even after multiple studies and data on these disorders, the approach has resulted in little to no change for therapy and cost of these illnesses.

The primary purpose of this review paper is to highlight the importance of the global burden of neurological costs for both developed and developing countries of the G20 group. The review establishes the ever-increasing costs of illness of these disorders and the difficulty of accessing available care by patients and their caregivers. The review seeks to increase awareness of all the neurological conditions that affect patients and their families, health care providers, and health systems worldwide.

Among the many mental disorders worldwide, those that worsen the patients' quality of life, function, and surroundings take precedence. Neurological disorders, included in the current review are: AD, PD, ALS, MS, epilepsy, spine tumors, and low back pain. AD is the most common neurodegenerative disorder worldwide, affecting 5.7 million people in North America, 89.28 million in Latin America, and more than 8 million people in Europe, with cases expected to increase in the upcoming years.

There are critical geographical gaps in information, such as insufficient data and studies regarding ALS in Latin America and MS and ALS in Africa. We encourage the investment in multidisciplinary research and all continents to develop global guidelines and early screening, unifying clinical trials, drug therapies, and new technology to produce international coordination.

Another critical point is the lack of collaboration and sharing of data plans between developed and developing countries. Sharing information and communication among brain initiatives is the key to successful patient care. Regarding the Latin American brain initiative, we wish to invite all Latin American and Caribbean countries to collaborate and use the European HBP as an example and blueprint. For both the American Brain Initiative and the European Union HBP, it is essential to share acquired data, research, and resources with the brain initiatives of other developing countries. This will result in more patient-centric care and progress in neuroscience. The N20 proposes integrating knowledge and resources to better understand the brain's function and to decrease the cost of mental illnesses via early screening and prevention.

In addition to the necessary coordination among countries, more attention to novel discoveries of retinal connections to thinking, mood, posture, and sleep regulation centers might be considered as a new usage of optometric and ophthalmologic assessment. Customized eyeglasses that emphasize peripheral retinal processing rather than 20/20 central eyesight can help mitigate symptoms in some neurological and mental health problems [170]. SBMT's position is that the 20/20 assessment of the identification of stationary targets (letters on a chart) was invented in the late 1800s. Now, 160 years later, testing for navigation, orientation, and visualization needs to be included, as the world is filled with a bombardment of sensory inputs. Assessment of eye/ear connectome plays an essential role in assessing spatial awareness [190].

The suggested approach to Brain Screenings (BS) will funnel-down in the case indicated, from Level-4 to Level-1 as follow:

a. Deployment of mass-screening online and digital platforms to isolate cases with moderate to severe mental health issues needs further evaluation [Level-4 BS].
b. Performing on-demand, concise neuro-psycho-behavioral assessments and neurological examinations through telemedicine platforms or onsite visits. This can include cognitive, autoimmune, and nutritional tele-screening (Level-3 BS).
c. Onsite cognitive profiling, neuropsychological assessments (mood, affective health, emotion regulation), sensory acuity screening (visual, hearing, touch, taste, and smell) through validated tools, evaluating motor learning, balance, and coordination (Level-2 BS).
d. We suggest implementing electroencephalography (EEG), a non-invasive and low-cost assessment, as a useful tool for early detection and prevention of various neurological disorders.

Using multi-modal monitoring and neuroimaging, including EEG and quantitative EEG (qEEG), CT, functional MRI (fMRI), MEG, PET, and SPECT as standard neurodiagnostic techniques to diagnose the extent and nature of neurological, psychiatric, and cognitive issues. Timely diagnosis will mitigate these disorders' economic burden, subsequently bringing change to socio-economic status and public health policies. These disorders are chronic and debilitating, leaving the affected less able to satisfy their needs and their caregivers less productive due

to the amount of time expended on caring for the patient. The development of advanced modalities of treatment of such diseases, and at a cheaper cost compared to what is currently available, would decrease the cost of illness of such debilitating neurological disorders.

CONCLUDING REMARKS

The N20 initiative includes: BRAIN20, SPINE20, and MENTAL20 Health, covering neurological and neuropsychiatric as well as spinal column and cord health and disorders. The N20 initiative started by SBMT in 2014 has been the force behind global collaboration and partnership in the field. Since N20 2014 in Australia SBMT has held global N20 policy forums in Turkey (2015), China (2016), Germany (2017), Argentina (2018), and Japan (2019) and virtual meetings of N20 in parallel with Saudi Arabia G20 summit in 2020. This paper reviews and summarizes 6 years of global policy discussion and resolutions and concludes with comprehensive recommendations. A global unity and collaboration in the N20 missions is critical to achieve collective goals of N20/G20 members. Therefore, any efforts toward breaking the integrity of N20 initiative's separate entities, i.e., brain, spine and mental health will be confusing and counterproductive for all organizations involved.

According to data shared in last 7 years of N20, some infrastructure and models exist to guide policy intended to promote brain, spine, and mental health and prevent disorders. Bolstering prevention and early/effective diagnosis are the most important aspects of such policies. However, despite initiatives to accomplish this in several nations/regions, we still have too little information on the global costs of brain diseases to formulate sound and uniform policies on their prevention and treatment worldwide. SBMT has arrived at the following recommendations to achieve integrated improvements in brain health policies worldwide. The literature review considers the lacuna of published data regarding healthcare expenditure, especially neurological disorders across the G20 countries. Hence, we recommend to the G20 countries to make more data available and do more research to alleviate the critical lack of data. The following are steps taken by SBMT to address the global burden of brain, spine, and mental disorders:

- SBMT created the G20 country's N20-Neuroscience20 (BRAIN20, SPINE20, and MENTAL20) health initiative and Neuroscience7 (N7-BRAIN7, SPINE7, and MENTAL7) initiative in line with the G7 global infrastructure plan called Build Back Better World (B3 W) Partnership, as well as the US's Endless Frontier Act to fast track therapeutics and global partnership in neurotech innovation. N7 and N20 will facilitate innovation, translation, integration, and commercialization of neurotherapeutics and neuro-technologies to rapidly introduce a new generation of diagnostics and therapeutic tools and pharmaceuticals for neurological, spine and neuropsychiatric disorders. N20 and N7 [Neuroscience7: Brain7 (B7), Spine7 (S7), and Mental7 (M7)] will be tied into other initiatives of SBMT, including the BTIP.
- N20 and N7 will create a trustworthy collaborative environment to address exploitative behaviors often seen between organizations and individuals, which has created an environment of mistrust towards data sharing. These initiatives will also advocate for better allocation of resources across governmental agencies to consolidate resources and avoid unnecessary redundancies and exploitative activities.
- N20/N7 recognizes an urgent need for better global understanding and sustainable development, focusing on cost-utility analysis in neurological, neuropsychiatric and spine health care.
- Our data clearly demonstrate the lack of funding by the WHO for the study of neurological disorders. Therefore, we recommend proper allocation of resources to this important priority as well as developing programs for treating illiterate patients.
- N20 (Brain20, Spine20, Mental20 Health Initiative) will encourage and support consortia and initiatives across laboratories between principal investigators while maintaining intellectual property rights and incentivize such collaboration (e.g., pharmaceutical companies coming together and sharing data to better utilize resources during the COVID19 pandemic has been a good example).
- N20 (Brain20, Spine20, Mental20 Health Initiative) strongly urges G20 leaders to streamline a regulatory framework for diagnostic and therapeutic clinical trials in neurological disorders.

Specific recommendations of the N20 consortium include:

a. SBMT recommends development of Brain, Spine and Mental Health Screening (BSMHS) as a multifaceted approach for neurological disorders, which could provide necessary data towards prediction, prevention, diagnosis, and treatment of neurological and mental illnesses.
b. We should be prepared for a plethora of mental illnesses due to the COVID-19 pandemic. Thus, there is an urgent need for sharing data, resources, and for allocation of funds to curb the pandemic of mental illnesses.
c. Our recommendation is to reduce CNS cancer drug prices and fund more research on new technologies. This will cut overall costs and improve chances for cures associated with CNS cancer treatment.
d. We recognize the need for global sharing of clinical trial data to reduce total expenditures on CNS cancer treatment.
e. We propose to incentivize development of brain screening tests for early detection of dementias, including AD, and to incentivize examination of the underlying pathophysiology of such disorders.
f. N20 and BTIP will synchronize global collaborations across biotech parks, biotech agencies, non-profit organizations, and industry leaders to bridge the financial aspects of the "valley of death" in neurotech innovations.

The authors also believe the following goals of N20 will allow further collaboration and advancement in Neurotech innovation, which rapidly introduce new diagnostics and therapeutics for neurological. Spine and psychiatric disorders:

1. Build a global alliance for brain, spine and mental health/illness.
2. N20 encourages a consortium approach to research and development.
3. N20 advocates for a global harmonization of the related policies/standardization of data.
4. N20 encourages a neuro-economical assessment of the future impact of disease, diagnostics, and prevention.
5. N20 encourages facilitating translation and commercialization of technologies across disciplines of science to rapidly identify and introduce new generation of therapeutics including stem cells, nanotechnology, device, and imaging (a nanobioelectronic consortium/company spinoffs).
6. N20 advocates for unifying global regulations and guidelines on clinical trials and drug/device - combination discovery.
7. N20 advocates for advancing innovation in brain, spine, and mental health through a global partnership and new funding initiatives between academic centers, industry, non-profit organizations, and government agencies.
8. N20 is a critical brain and spine consortium to facilitate integration of nanotechnology, artificial intelligence, virtual reality/augmented reality, supercomputing, multimodality brain mapping/imaging (MEG), cellular therapeutics, neurophotonics and/or devices which could address the fast-tracking innovation, reduce the cost of the healthcare delivery, and make it more efficient.
9. N20 will be bringing the global brain and spine initiatives together to identify best clinical and basic science practices and create a united front to push for new effective therapeutics.
10. Set unified standard amongst all, for training, prevention, care, and advance therapeutics related to brain, spine and mental disorders including physicians, engineers, surgeons, nurses, chiropractors, physical therapists, osteopaths, physiologists, and other related disciplines.
11. Provide capabilities at the local, regional, and national levels to advance practice of clinical neuroscience (brain, spine, and mental health/illness) through advocacy by engaging health ministries and government programs across the globe.
12. Advocate for a global research and innovation funding for brain, spine, and mental health.
13. Facilitating investment and commercialization of neuro-technologies for brain, spine, and mental health/illness.
14. Educate professionals, patients, and families about the latest state of science, technology, innovation, and policies in clinical neuroscience (brain, spine and mental health/illness).
15. Provide accurate and up to date resources and data to the governments of G20 nation and beyond to adapt new policies for clinical neuroscience.
16. Spread awareness amongst all to address mental/psychological issues such as PTSD for healthcare workers, anxiety and stress for

patients, for those who lost jobs and about prospect of future after the pandemic and prevention of suicides in the present and post-COVID-19 era" [191].

SBMT welcomes all scientists, neurosurgeons, orthopedic surgeons, spine surgeons, rehabilitation specialists, engineers, neuroscientists, neurologists, psychiatrists, psychologists and physicists, neuroscientists, cell and molecular biologist, policymakers, philanthropists, industry and non-profit leaders to join N20 and be part of this disruptive and game changing global Neurotech innovation consortium, create a united front to confront neurological, spine and neuropsychiatric diseases and fast track therapeutics.

We strongly urge that WHO, Office of Science Technology, and Policy at the White House, NIH, G20 Ministries of Health, and G20 leaders to officially make N20 and N7 part of the annual G20 and G7 summit; they should also take concrete steps toward identifying the cost of neurological disorders to the respected economies and draft and adjust policies based on human and financial costs of such disease.

We also urge President Joseph Biden, Vice President Kamala Harris, and the US Government "Global Brain Health Act of 2019" or H. R. 2077 congressional bill introduced in 2019 and focused on galvanizing "the United States Government programs in support of brain health for global victims of autism, hydrocephalus and Alzheimer's and other forms of dementia, and for other purposes". This bill urges the US Government in general, and Secretary of the Health and Human Services, to investigate foreign assistance toward AD and other forms of dementia, which now could include the COVID-19 consequences to brain health.

The Global Brain Health Act of 2019 specifically requests the US Government to build a global corporation for neurological disorders such as AD [192–194].

SEC. 304. FOREIGN AID IMPLICATIONS

The Secretary of Health and Human Services, in collaboration with the heads of the United States Agency for International Development and other relevant Federal departments and agencies, shall:

(1) investigate the foreign aid implications of Alzheimer's disease and other forms of dementia; and

(2) inform Congress as to the need for possible changes to health care-related foreign assistance.

H.R. 2077 urges the president of the United States build a public and private partnership. SBMT has been on the forefront of building such partnership nationally and globally through N20 and N7 initiative.

SEC. 301. GLOBAL ALZHEIMER'S DISEASE AND DEMENTIA ACTION PLAN

(a) *In General*. The Secretary of Health and Human Services shall enter into negotiations with the World Health Organization to develop a plan for addressing Alzheimer's disease and other forms of dementia globally, to be known as the Global Alzheimer's Disease and Dementia Action Plan, focused on the following areas:

(1) Research, including:

(A) clinical research; and

(B) development of a stable and sustained international commitment to research.

(2) Regulatory issues.

(3) Clinical care.

(4) Supportive services for patients and caregivers, including supports using innovative technologies.

(5) Prevention and health promotion.

(6) Public awareness and education, particularly efforts aimed at reducing stigmas and increasing the inclusion of persons with Alzheimer's disease and dementia within civil society.

(b) *International Partnerships*.

(1) *In General*. In developing the plan under subsection (a), the Secretary of Health and Human Services.

(A) shall seek

(i) to enter into partnerships with other nations that have in place national plans for addressing Alzheimer's disease and other forms of dementia; and

(ii) to the greatest extent possible, ensure that the plan under subsection (a) is compatible with the plans of such other nations; and

(B) in the case of other nations that do not have such plans in place, shall encourage such nations to develop and implement such plans.

(2) *Sense of Congress*.—It is the sense of the Congress that the Group of Eight (G8) nations, working with the Group of Twenty (G20) nations, the Group of Seventy-Seven (G77) nations, and other organizations including the Organization for

Economic Cooperation and Development (OECD), should investigate systems to monitor and provide care to individuals with Alzheimer's disease and other forms of dementia in developing countries to help build care delivery capacity."

SBMT's N20 is the best vehicle for such global partnership, which has a 8 years history with major global players across the G7, G20 and G77. We have published many papers and resolutions on the cost of the neurological and neuropsychiatric and spine disorders to the world economy and have proper think-tanks in place to execute "Global Brain Health Act of 2019" in a global scale because SBMT is a global and international multi-specialty association with near 100,000 physicians, scientists, engineers, and surgeons in its network.

"Global Brain Health Act of 2019" also encourages the public-private partnership.

SEC. 305. PUBLIC-PRIVATE PARTNERSHIPS

The President shall encourage and facilitate partnerships between the Federal Government and the private sector, such as the partnerships in effect between the National Institutes of Health and pharmaceutical companies, to identify new approaches to treat Alzheimer's disease and other forms of dementia.

SBMT has established a Brain Technology and Innovation Park (BTIP), a Neurotech initiative, to be considered for of the Endless Frontier Act (S.3832) and The United States Innovation and Competition Act (S. 1260), which could fast track therapeutics and diagnostics for neurological and spinal cord/spine and neuropsychiatric disorders while creating biotech/neurotech jobs and reducing the cost of the healthcare. BTIP clearly can "identify new approaches to treat AD and other forms of dementia" as well as other neurological disorders per "Global Brain Health Act of 2019" and should be seriously considered for President Biden's healthcare, technology, and innovation agenda [192–194].

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