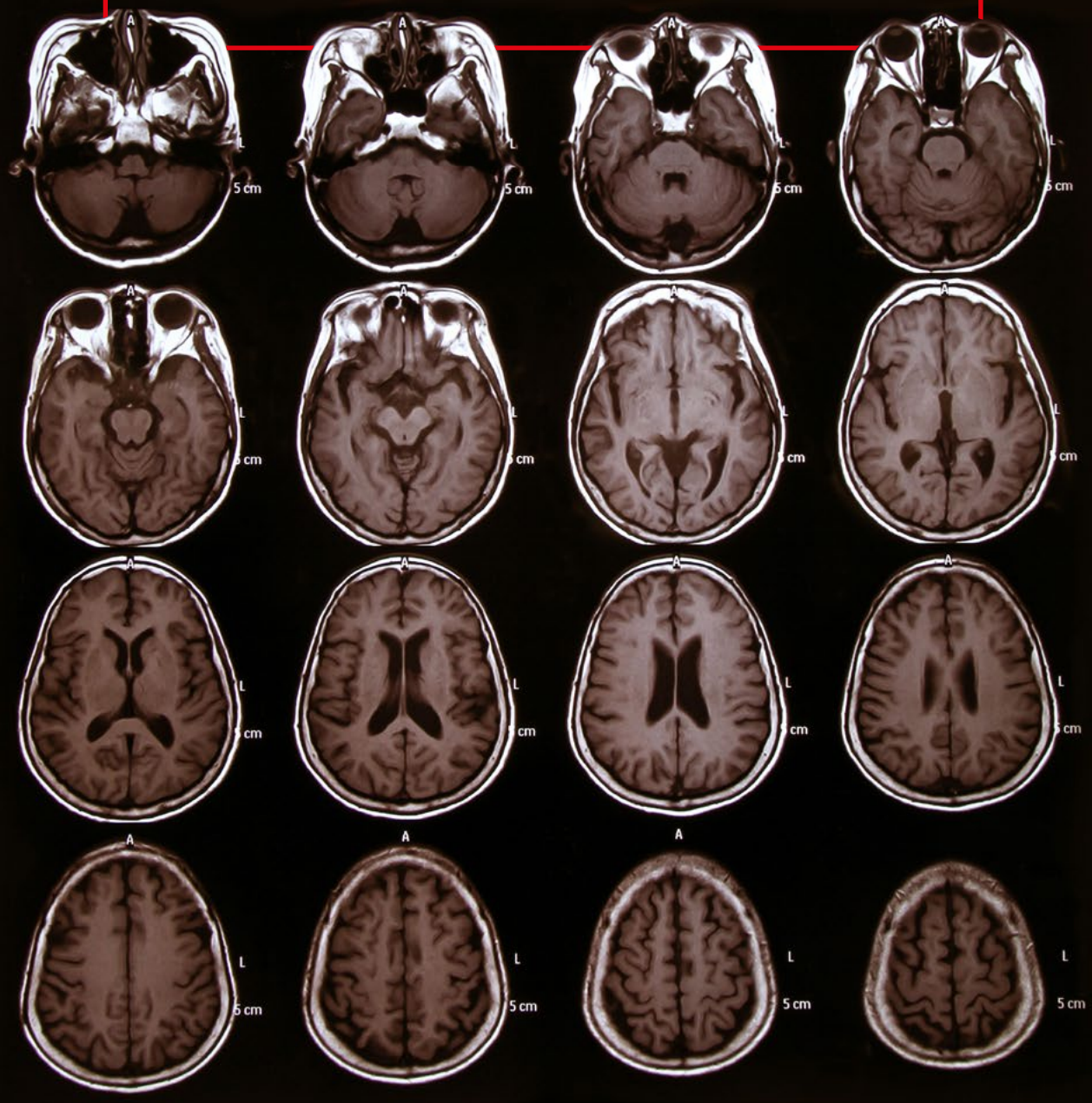
ECONOMIST IMPACT

The value of action

Mitigating the global impact of neurological disorders

Methodology appendix



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Contents

Research objectives

Neurological conditions are the leading cause of disability worldwide.[1] Strategies and programmes that reduce the burden from neurological disorders are in great demand. Progress so far, as well as reducing inequalities in health and social care support for patient with neurological conditions, has been insufficient in terms of meeting the UN Sustainable Development Goal targets by 2030.[2] Changing demographics, including ageing populations, is expected to increase the burden of neurological disorders in coming years, representing a significant threat to health systems and national economies.[3] In order to play a part in focusing efforts to reduce the burden from neurological conditions, Economist Impact sought to develop research to stimulate a multidimensional debate which showcases the value of action on neurological conditions from three angles: the epidemiological impact, the economic impact and the current policy landscape with reference to where urgent changes are required.

Specific overarching objectives of the research included:

- Raising the overall awareness of neurological conditions and neuroscience using a selection of global markets and neurological conditions;
- Capture a more nuanced view of the multifaceted impacts of neurological conditions, including what degree of the impact is amenable to preventive, therapeutic, rehabilitative or political action;
- Partnering constructively with a wide range of stakeholders to capture the evolving nature of the landscape of neurological disorders;
- Develop an engaging and practical set of outputs to be shared in the public domain for multi-stakeholder consumption that establish the value of policies and best practices for neurological conditions.

This Methodology Appendix was commissioned and funded by F. Hoffman La Roche. Roche have had no input into the content of this appendix apart from the input of the Roche advisor which was that of their own expertise and not of the company. Roche conducted a factual accuracy check prior to publication but any decisions to incorporate comments were made solely at the discretion of Economist Impact.

This research was led by Chrissy Bishop. Analysis was led by Triangulate Health Ltd, in collaboration with Economist Impact. Data collection and analysis were led by Towo Babayemi and Camilo Gutierrez, with input from Bernardo Dias de Aquino Nascimento. This appendix and accompanying deliverables were written and edited by Chrissy Bishop, Towo Babayemi and Amanda Stucke. All members of the research team were employed by or contracted by Economist Impact. The Findings Report can be found on the Economist Impact website.

Methodology overview

This study applied a cross-sectional approach to estimate the economic burden of neurological conditions at the national level in the 11 markets of focus. Unidirectional, compartmental estimates were developed to show the economic burden of each condition by country, age and severity level in 2019 (chosen based on most recent Global Burden of Disorder (GBD) data).[4] **Table 1** highlights the key parameters for the analysis.

Table 1

Key input parameters examined for the analysis

Parameter	Data Points
Epidemiology	For each combination of disorder/severity:
	Number of patients or prevalence of disorder at age N / Age of disorder onset
	Risk of mortality from disorder at age N
	Remaining life expectancy at premature death
Productivity	For each combination of disorder/severity:
	Absenteeism fraction (age group, severity level)
	Percent days off work
	Percent reduced working capacity while at work
	Unemployment rate
	Proportion of patient population in premature retirement/Retirement age
	Informal caregiver time
Outcomes	For each combination of disorder/severity:
	Number of deaths / mortality rate by age
	DALY burden: Disability weight
Costs	For each combination of disorder/severity:
	Direct health care costs for all services provided
	Disability related pensions
	Productivity Loss: GDP per capita
	Direct healthcare costs to be a combination of:
	Primary care visits
	Medication
	Preventative services.
	Specialist services
	Surgery
	Hospitalization
	Rehabilitation
	Long-term care
	Disability aids (walking aids, home remodelling, etc.)

Source: Economist Impact analysis, 2022.

Assumptions and limitations

In creating a pragmatic analytical model for the purposes of health policy, analysis is typically either designed to cover broad topic areas at a high level, or dive deeply into a subset of more specific quantitative questions. This analysis is intentionally broad in scope, as the core aim of the program includes the desire to engage stakeholders in a conversation around neurological conditions as a whole. While it provides a valuable platform to recognise similarities and differences in the burden of neurological conditions, it does mean that detailed estimates unique to each disorder area are limited.

As is true of most analyses of this sort, the ability to establish high-quality estimates is limited to the quality, depth and timeliness of data inputs, and relies upon a number of assumptions to generate results. Accurate estimates of disorder burden are pivotal for driving neurological policy agendas. The unfortunate truth about the burden of neurological disorders globally is that it is largely unknown. Data is scarce even in high income countries, which is the primary barrier to effectively planning neurological healthcare services. The Institute for Health Metrics and Evaluation has attempted to bridge data gaps by providing the best possible estimates of prevalence, but the reality is that registries and standardised approaches to data collection are inconsistent and highly variable by country.[4]

Furthermore due to limited data available, the model assumed homogeneity across age groups for various inputs (i.e. Disability Adjusted Life Years [DALYs], cost of care, productivity loss). To adjust for this, we applied discounts and adjustments to the extent possible to ensure estimates are conservative (see Analysis section for details). However, this may still impact the ability to account for longer term, demographic impacts on the analysis results. Similarly, among the 11 neurological conditions featured, some have widely variable impacts across gender groups. Again due to limited availability of data and scope of the analysis, we did not use sex-disaggregated data which can hide important patterns within the analysis.

There are also limitations in the cross-sectional design of this model. A model can always be improved and run over a longer period. However, to do that, more parameter values are required that are often too expensive and challenging to collect and maintain across broad populations. Additionally, we would need to include demographic dynamics into the model which is complex. The analysis also relies upon national averages for a number of inputs, which may prevent true reflection of the wide variety of experiences in accessing quality care within countries. Also, while the research takes broad impacts of different types of actions into account, it does not consider the efficacy of specific treatments.

A subset of 10 countries was selected for this analysis which represent a diverse set of geographies, economic statuses, health systems, etc. The attributes of the countries selected may have impacts on overall conclusions of the study, and may mean that results have limited generalisability geographically.

Finally, this analysis places a monetary value on health as the lost value of economic productivity due to ill health, disability or premature mortality. In reality, there are secondary costs such as transportation, secondary mental and physical health effects, impacts on loved ones, etc. that are not possible to capture in this kind of analysis.

Despite these considerations, this type of analysis is designed to drive forward progress and debate urgently needed to tackle the impacts of neurological conditions globally, and provides a useful quantitative basis to do so.

Initial research

Country selection

The first step of the research engagement was to select a representative set of countries for analysis. We sought to ensure wide representation across a set of core criteria to maximise applicability of the research and results.

Four core criteria underpinned country selection:

- Epidemiological burden of selected neurological disorders
- Maturity and structure of health systems, including policy and clinical approaches to neurological disorders
- Socioeconomic status
- Geographic diversity, including representation from all major global regions

Final selected markets for the research include: Brazil, China, Colombia, Germany, Italy, Japan, Kenya, Lebanon, Romania, UK and USA.

Condition selection

The GBD, the core reference dataset for this work, includes fifteen neurological disorders: stroke, Alzheimer's disorder, Parkinson's disorder, motor neuron disorders (e.g., ALS), multiple sclerosis, brain and central nervous system cancers, meningitis, encephalitis, tetanus, idiopathic epilepsy, migraine, tension-type headaches, traumatic brain injury, spinal cord injury, and other neurological disorders.[5] Due to the scope of this study, we have excluded infectious disorders and focused on the following ten conditions:

- Stroke
- Alzheimer's disorder
- Parkinson's disorder
- Spinal muscular atrophy
- Multiple sclerosis
- Brain and nervous system cancers
- Epilepsy
- Migraine and tension headaches
- Traumatic brain injury
- Spinal cord injury

In this report, we made an intentional decision not to focus on mental conditions in order to shift the conversation beyond mental health and increase global policy response to neurological disorders more widely.

Evidence search and review

A multi-pronged approach was adopted, beginning with a focused database search to review evidence pertaining to relevant MeSH terms. The initial results were reviewed and sifted by a member of the Economist Impact research team. Based on the results of the first sift, a main search of indexed databases (Medline, Embase, Cochrane Library and Epistemonikos), grey literature sources and final Google Scholar/Google advanced search of title/ relevant for additional studies was conducted.

Initial key search terms included:

- Neurological disorders
- Stroke
- Alzheimer's disorder
- Dementia
- Parkinson's disorder
- Multiple sclerosis
- Guidelines and prevention

Additional search terms were added to the final search based on selected geographies and chosen set of 10 conditions highlighted in the study.

The search was limited to English language sources published within the last ten years at the time of the search (2012-2021). The search yielded 1227 initial results, of which 290 sources were included after titles and abstracts were reviewed for duplication and relevance. While not all may be cited in this document, all 290 references underwent more extensive review in the creation of the background evidence review.

Expert consultation

We consulted more than 15 globally representative experts in the neurological field to validate our approach. Experts were identified and selected based on their contributions to the neurology field, including presence of publications in our informal and formal research for the project. Experts included those who represent the following areas: academia, medicine, patient organisations, policy, health economics, rehabilitation and industry. Individual and collective diversity were considered in the recruitment of experts. Economist Impact conducted due diligence to exclude any experts with potential conflicts of interest, including any pre-existing relationships with the study sponsor.

Semi-structured interviews were conducted, alongside two structured expert panel meetings in the summer of 2021. Meetings were recorded and transcribed by the Economist Impact team. Meeting transcripts were used as an input in forming the findings report and other deliverables from this research.

An alphabetical list of consulted experts can be found in the Findings Report.

Analysis

Analysis approach

As stated, this study applied a cross-sectional approach to estimate the economic burden of 10 neurological conditions at the national level in the 11 markets of focus. Unidirectional, compartmental estimates were developed for the economic burden of each condition by country, age and severity level in 2019 (this year was chosen based on most recent GBD data).[4] Unless stated otherwise, severity levels for each condition were included based on sub-condition data from the GBD dataset. Each estimate began with a population at risk derived from the World Population Prospects demographic dataset and the prevalence of each condition based on GBD epidemiological data.[4, 6]

Once the subset of the population from each country who would develop each condition was isolated, the average likelihood of mortality, specific care needs, DALYs[1], productivity losses and the productivity losses of their informal caregivers were estimated over a one-year time horizon for different hypothetical scenarios.

The analysis reports the impact of each scenario on the following costs:

- Direct cost of medical care
- The cost of patient productivity losses due to absenteeism, presenteeism, unemployment and early retirement
- The cost of informal caregiver productivity losses due to caring for the patient
- DALYs resulting from each scenario, where DALYs averted reflect a positive effect on health outcomes

Scenario development

Data to parameterise the condition-specific estimates and scenarios were extracted from published literature in consultation with experts. Within each scenario chosen for each of the 10 conditions (usually baseline, prevention, treatment and rehabilitation), the baseline parameter values were changed to simulate the effect of the hypothetical scenario on patients with each disorder.

Because of the significant financial burden reported in the literature, in this report we wanted to establish, and where possible quantify, what degree of this burden is amenable to preventive, therapeutic, rehabilitative or political action. By taking a global approach, we wanted to identify which neurological disorders and which countries require more action than others, to broadly inform resource allocation.

For each neurological condition, we estimated the total costs, including direct medical costs, costs of productivity losses for patients (including absenteeism, presenteeism, unemployment, and early retirement), and costs of productivity losses for caregivers. Costs by level of severity of disorder were calculated across age groups by establishing the annual cost of unemployment, total annual cost of absenteeism for patients, total annual cost of presenteeism for patients, total annual cost of early retirement, total annual cost of productivity lost for informal caregivers to care for patients and the total annual cost of productivity losses.

1 DALYs are a sum of the years of life lost due to premature mortality from disorder and years lives with disability. In this analysis, a lower DALY value indicates better health in the population while a higher DALY value indicates more years of life lost, and years lived with disability.

To examine the impact of interventions to improve clinical outcomes, four primary scenarios were established across all 10 disorder areas:

1. Baseline or no treatment – The baseline costs are defined as the current status of care for each disorder, including the prevalence, treatment cost, productivity loss due to presenteeism and absenteeism, and cost of informal care as of 2019
2. Prevention – Captures the proportion of the disorder burden amenable to effective public health prevention policies (some of the conditions highlighted are not preventable so for consistency, we did not assess impact of prevention for each disorder in the scenarios)
3. Treatment – The costs and impact associated with scaling up treatments for each condition to all eligible members of the population according to guidelines or recommended best practice
4. Rehabilitation – The costs and impact of scaling up rehabilitation for each condition to all eligible members of the population

The scenarios were built to allow for changes in the disorder prevalence, disorder mortality, care cost, patient's productivity losses, informal caregiver productivity losses and disability weightings. Consistent with a cross-sectional approach, patients did not transition between severity states within this study, and the same population was used as the baseline scenario.

Generating results and projections

The impact of scenarios on the economic burden of neurological conditions have been estimated using incremental changes in total costs and DALYs. For every intervention scenario, we assumed that both treatment and rehabilitation reduced a patient's disorder-related disability by 10% based on primary and secondary research conducted in this study. This means we could account for the change in a person's disability (DALYs) with or without intervention. If a prevention scenario involved a treatment (such as in the case of epilepsy and migraine) we also reduced the patient's disorder-related disability by 10%. **Table 2** shows which variables were modified in each of the 10 disorder areas of focus given intervention.

The outcomes of the analysis are presented for each condition by country and scenario in 2019. The outcomes included direct medical costs, costs of productivity losses for patients (including absenteeism, presenteeism, unemployment and early retirement), costs of productivity losses for caregivers and DALYs (disability-adjusted life years).

Lastly, the total cost of each scenario was projected beyond 2019. As the benefit of many interventions for neurological disorders are gleaned long after implementation, these future costs provide more insight as to when the return on investment in these disorder areas could be realised.

Table 2
Variables modified for intervention scenarios by disorder (prevention, treatment, and rehabilitation, where relevant)

	Disorder									
Variables modified for scenario	Alzheimer's disease	Brain cancer	Epilepsy	Migraine	Multiple sclerosis	Parkinson's disease	Spinal cord injury	Spinal muscular atrophy	Stroke	Traumatic brain injury
Prevalence of the mild classification of neurological disorder	●		●						●	
Prevalence of the moderate classification of neurological disorder	●		●						●	
Prevalence of the moderate classification of neurological disorder	●		●						●	
Death due to the mild classification of neurological disorder		●							●	
Death due to the moderate classification of neurological disorder		●							●	
Death due to the severe classification of neurological disorder		●							●	
Death due to the terminal classification of neurological disorder		●								
Average age of retirement among the general country population										
Proportion of general country population actively participating in the workforce										
Proportion of working time lost from absenteeism among people with neurological disorders due to their disorder		●		●	●				●	
Proportion of working time lost from presenteeism among people with neurological disorders due to their disorder			●	●	●				●	
Proportion of people with neurological disorders who are unemployed due to their disorder					●		●		●	●
Proportion of people with neurological disorders who retire early due to their disorder		●			●				●	
Average age of early retirement due to neurological disorder										
Proportion of informal caregiver's working time lost due to care for a person with a neurological disorder (or mild Alzheimer's disease)	●	●	●		●	●	●	●	●	●
Proportion of informal caregiver's working time lost due to care for a person with moderate or severe Alzheimer's disease	●									
DALY weight, a value used to quantify health losses from living with a disorder		●			●		●			
DALY weight for mild classification of neurological disorder	●		●			●		●	●	●
DALY weight for moderate classification of neurological disorder	●		●	●		●			●	●
DALY weight for severe classification of neurological disorder	●		●			●			●	●
Baseline cost of care adjusted by country healthcare spend per head for neurological disorder (or mild Alzheimer's disease)	●	●	●	●	●	●	●	●	●	●
Baseline cost of care for moderate Alzheimer's disease	●									
Baseline cost of care for severe Alzheimer's disease	●									
Disability adjusted life-years, a measure of overall burden of disease represented as years lost due to disability, premature death or poor health										

Source: Economist Impact analysis, 2022.

Inputs, assumptions and data sources by disorder area

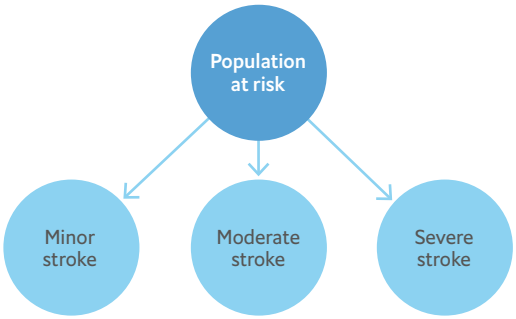
Stroke

Figure 1 illustrates the stroke analysis, which was run for four different scenarios – baseline, prevention, treatment, and rehabilitation. The composition of the scenarios for stroke are displayed in **Table 3**.

In the prevention scenario, the stroke prevalence was reduced by 90% according to evidence which suggests primary prevention and reduction of modifiable risk factors (by adapting lifestyle factors and taking blood pressure lowering treatments), will reduce the risk of stroke by 90%.[7, 8] The analysis also assumes the cost of stroke will also reduce by 90% if 90% of cases are avoided.

In the treatment scenario, we estimated the impact of thrombolysis on stroke outcomes for all eligible patients.[9-11] Firstly the cost of care from baseline increased with the addition of thrombolysis.[12] The evidence suggests thrombolysis increases independence (or disability free survival) by 9% for acute ischemic stroke but increases mortality by 2.5% in the first 7 days after thrombolysis.[13] We therefore estimated a possible increase in mortality, but a reduction in disability. This also has indirect implications on days lost from work, unemployment, early retirement and informal caregiver productivity losses. The evidence suggests timely stroke treatment can reduce days lost from work by 20%.[14] Due to the absence of data on the impact of thrombolysis on unemployment and early retirement, we used a data on the proportion of people who were employed (35.3%) following a stroke. We assumed those that survived and were employed (35.3%) had received timely stroke treatment.[15] A rehabilitation scenario was added as stroke patients receiving physical and cognitive rehabilitation experience lower disability.[16] Although physiotherapy support in the first 12 months after discharge will increase the cost of care by 37%, it can reduce patient unemployment and productivity losses for the informal caregiver by 47%.[17, 18]

Figure 1
Stroke analysis structure



Source: Economist Impact analysis, 2022.

Table 3
Stroke analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses	Change in DALY weights
Prevention	Reduce by 90.00%								
Treatment		Increase by 0.05%	Refer to adjusted cost in parameter values	Reduce by 20.00%	Reduce by 20.00%	Reduce by 35.00%	Reduce by 35.00%	Reduce by 20.00%	Reduce by 10.00%
Rehabilitation			Increase by 37.00%			Reduce by 47.00%	Reduce by 47.00%	Reduce by 47.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

To calculate the total cost from 2019-2030, it was assumed that the costs of care was only incurred in 2019 for the prevention and treatment scenarios. Beyond 2019, only indirect costs were incurred for these treatments. The cost of care for rehabilitation was incurred in all years. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%. Even while the costs of rehabilitation are incurred in each year, the indirect benefits continue to grow over time which generate savings.

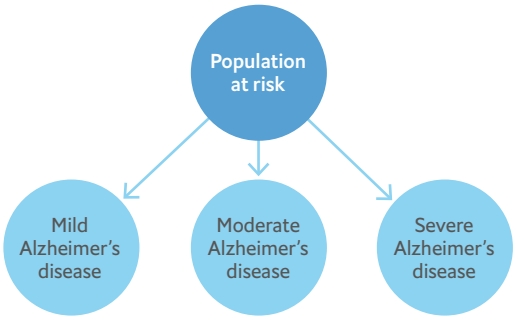
Alzheimer's disorder

Figure 2 illustrates the Alzheimer's disorder analysis, which was run for two different scenarios – baseline and treatment. Only Alzheimer's disorder was included in the estimate, and other dementias were excluded. This is partly because 60-70% of dementia cases are diagnosed as Alzheimer's[19] and because the evidence suggests treatments are currently only effective in Alzheimer's disorder.

The composition of the scenarios for Alzheimer's are displayed in **Table 4**.

The scenarios in **Table 4** were built to allow for changes in the care cost, informal caregiver productivity losses and disability weightings.

Figure 2
Alzheimer's disease analysis structure



Source: Economist Impact analysis, 2022.

Table 4
Alzheimer's disease analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiveR productivity losses for patients with mild disease	Change in informal caregiver productivity losses for patients with moderate or severe disease	Change in DALY weights
Prevention	Reduce by 40%									
Treatment			Increase by 13.00%					Reduce by 32.00% in HICs; reduce by 52% in LMICs	Reduce by 32% in HIC and Reduce by 52.00% in LMICs	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

In the prevention scenario, the prevalence of Alzheimer's is reduced according to a study by the Lancet Commission which suggests preventing 12 risk factors for dementia accounts for around 40% of cases (including alcohol consumption, smoking obesity, depression etc.).[20] Treatment for Alzheimer's disorder includes Alzheimer's specific medications, treatment of vascular risk factors, sleep and mood disorders as well as treatments for relevant co-morbid conditions. For the purposes of the analysis, we only included the impact of acetyl cholinesterase inhibitors, which was in 2019, the data year of this study, the primary evidence based pharmacological treatment for Alzheimer's disorder.[21-24] In one study which itemised the cost of Alzheimer's disorder including medical care, social care and informal care, medications accounted for 13% of the total costs of care. We therefore increased the baseline cost of care by 13% in the estimate for the treatment scenario.[25]

Acetyl cholinesterase inhibitors do not slow progression of the disorder, but do reduce symptoms, which may enable patients to stay at home longer and decrease the burden faced by formal and informal caregivers.[26, 27] Randomised controlled trials have found acetyl cholinesterase inhibitors to reduce cognitive and functional symptoms in mild and severe Alzheimer's disorder, but not in mild cognitive impairment (which is excluded from the analysis). One study states treatments for Alzheimer's disorder (cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists) were associated with a 32% decrease in informal care costs.[28] Therefore the significance of acetyl cholinesterase inhibitors is realised through their impact on reducing informal caregiver time, especially when many studies refer to informal care costs accounting for 50% to 62% of the total cost of Alzheimer's care.[25, 29] The productivity losses for informal caregiving time were reduced by 32% in HICs. Because of poor access to healthcare in LMICs, more informal care for people with Alzheimer's disorder is provided in LMICs. We therefore assumed the impact of treatment on informal caregiving time to be higher in LMICs (52%).

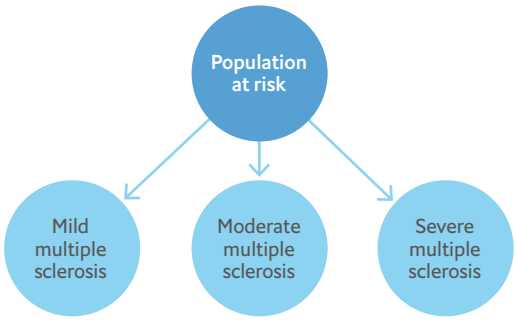
To calculate the total cost from 2019-2030, it was assumed that the treatment costs of Alzheimer's care were incurred in each year. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%. Even while the costs of care are incurred in each year, the indirect benefits continue to grow over time which generates savings.

Multiple sclerosis

Figure 3 illustrates the MS analysis, which was run for three different scenarios – baseline, treatment and rehabilitation. The composition of the scenarios are displayed in **Table 5**.

The scenarios were built to allow for changes in the care cost, patient's productivity losses, informal caregiver productivity losses and disability weightings. A prevention scenario was omitted from this analysis as MS is currently not preventable. In the treatment scenario, we estimated the effect of disorder modifying therapies (DMTs), which slow the progression of MS and reduce the frequency of relapses but do not prevent the disorder which means medications have no impact on prevalence.[30]

Figure 3
Multiple sclerosis analysis structure



Source: Economist Impact analysis, 2022.

In the treatment scenario, the cost of care was increased from baseline. It is estimated that DMTs will change the baseline cost of care by 50% in high income countries. In Brazil, DMTs account for almost 100% of the total costs of care.[31, 32] Another study states DMTs account for 70% of health care costs, for patients with commercial insurance in the US.[33] To account for changes in the cost of this in the analysis, we increased the cost of disorder modifying therapies by 60% in HIC and 30% in LMIC.

Treatment has a considerable effect on the productivity of the individual and on caregivers. In mild cases of MS, DMTs can enable a reduction in days missed from work of 42%.[34] In a study with a larger sample size including mild and moderate cases of MS, 68% of patients who started a high efficacy DMT achieved "No Evidence of Disorder Activity" after one year of treatment.[35] We therefore assumed that after one year, DMTs enabled maintenance of independence levels increasing the likelihood that the patient would be able to work, and reducing the impact on caregivers by 68%. This scenario is only applied to those who are able to work, thus excludes severe cases of MS.

In the rehabilitation scenario which in the case of MS largely relates to Physiotherapy and Occupational Therapy, the cost of care was increased from baseline. This increase is based on data which states rehabilitation will increase

Table 5
Multiple sclerosis analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses	Change in DALY weights
Treatment			Refer to adjusted cost in parameter values	Reduce by 68.00%	Reduce by 68.00%	Reduce by 68.00%	Reduce by 68.00%	Reduce by 68.00%	Reduce by 10.00%
Rehabilitation			Refer to adjusted cost in parameter values	Reduce by 8.00%	Reduce by 8.00%	Reduce by 8.00%	Reduce by 8.00%	Reduce by 8.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

baseline cost of care by 7%.[36] Another paper looked at the costs of different components of care for MS relapses, reporting the cost for Physiotherapy, Occupational Therapy and rehabilitation at 10%.[37] Therefore the costs of rehabilitation could increase the costs of care from between 7-10%.

In terms of impact on productivity levels, outpatient exercise programmes have been shown to improve muscle tone in patients with MS in several RCTs. Berg balance scales improved by 4.33 points in exercise groups over non-exercise groups. An increase of 4.33 Berg balance points is attributable to a 7.7% increase in function (total score berg balance is 56. 4.33/56 = 0.77*100).[38] We therefore assumed an increase in patient productivity of 8% and a reduction in informal caregiver burden by 8% following rehabilitation. Again we do not apply this scenario to severe cases of MS who we assume will not be working.

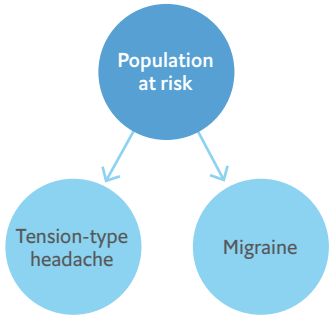
The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%. To calculate the total cost from 2019-2030, it was assumed that the costs of care were incurred in each year. Even while the costs of care are incurred in each year, the indirect benefits continue to grow over time which generates savings.

Migraine

Figure 4 illustrates the migraine analysis, which was run for three different scenarios – baseline, preventative treatment, and symptomatic treatment. The composition of the scenarios for migraine are displayed in **Table 6**.

Prevention of migraine (i.e., behavioural interventions, acupuncture, Roboflavin) may reduce frequency, severity and duration of migraine attacks.[39] Prevention does not cure migraines it only reduces the frequency, which means it has no impact on prevalence for the analysis.[40] Prevention does however have an impact on patient productivity. In the preventive treatment scenario, the cost of care was increased from baseline and patient productivity losses were reduced. The cost of preventative treatments makes up around 73.8% of the total direct costs of care according to

Figure 4
Migraine analysis structure



Source: Economist Impact analysis, 2022.

Table 6
Migraine analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses	Change in DALY weights
Preventative treatment			Increase by 64%	Reduce by 3.9%	Reduce by 3.9%				Reduce by 10%
Symptomatic treatment			Increase by 11.3%	Reduce by 2%	Reduce by 2%				Reduce by 10%

Source: Economist Impact analysis, 2022.

the evidence.[41] Productivity losses were reduced according to evidence which suggests severe migraines result in 3.9% absenteeism.[42]

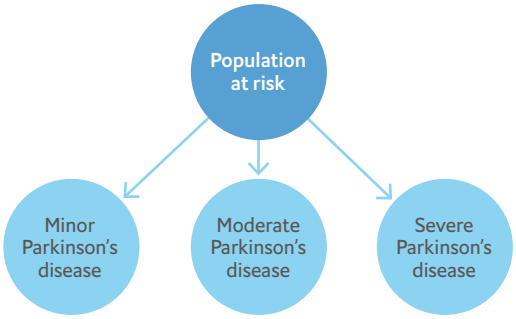
In the symptomatic treatment scenario, the cost of care was increased from baseline according to evidence which suggests the cost of acute or symptomatic medications makes up 11.3% of the direct costs of care.[41] We assumed symptomatic treatment would have less of a positive impact on absenteeism given a person is likely to take time off work every time they experience a migraine episode and have to take symptomatic medication. We assumed symptomatic treatment would have 50% less impact on absenteeism than preventative treatment.

Parkinson's disorder

Figure 5 illustrates the Parkinson's disorder analysis, which was run for three different scenarios – baseline, treatment, and rehabilitation. The composition of the scenarios for Parkinson's disorder are displayed in **Table 7**.

The scenarios were built to allow for changes in the care cost, informal caregiver productivity losses and disability weightings. A prevention scenario was omitted from the Parkinson's disorder analysis as it is not currently possible to prevent the disorder. In the treatment scenario, the effect of levodopa was estimated, as there is fairly strong evidence that identifies this as the most widely used and effective treatment for Parkinson's Disorder.[43] Levodopa enables the management of symptoms such as uncontrolled, involuntary movements and remains effective across severity levels. However, this treatment becomes less

Figure 5
Parkinson's disease analysis structure



Source: Economist Impact analysis, 2022.

Table 7
Parkinson's Disease analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses for patients with mild disease	Change in DALY weights
Treatment			Increase by 22.00%					Reduce by 31.00%	Reduce by 10.00%
Rehabilitation			Increase by 21.7%					Reduce by 13%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

effective as the disorder progresses.

According to expert opinion, levodopa is a fairly cheap drug. The evidence base suggests that the costs of prescription medications for Parkinson's is likely to increase the baseline cost of care by between 14 to 22%.[44] While this increase will include other prescription drugs, we assumed levodopa would accrue a large proportion of these costs.

We did not estimate the effect of levodopa on patients employment levels as the majority of patients with Parkinson's disorder will not be working. We did account for levodopa's effect on caregiver time.[43, 44] One study suggests that levodopa treatment resulted in a 31% lower annual decline in Unified Parkinson's Disorder Rating Scale-III scores.[45-47] We therefore assumed that a greater level of independence would also reduce informal caregiver burden by 31%.

For the rehabilitation scenario, physiotherapy had the strongest evidence base in terms of its success rates in Parkinson's disorder. Rehabilitation using physiotherapy and light exercises has been shown to improve levels of independence and reduce caregiver burden by a third. Around 40% of caregivers indicated that their health had suffered as a result of caregiving, a third of which would be around 13%.[48] Rehabilitation is estimated to increase the cost of care by 21.7% from baseline.[49]

Spinal muscular atrophy

Figure 6 illustrates the SMA analysis, which was run for two different scenarios – baseline and treatment. The composition of the scenarios for SMA are displayed in **Table 8**. We only included SMA Type I in the analysis, which accounts for around 60% of all SMA cases.[50] Type IIs and Type IIIs were excluded. The main reason for only including Type I is due to the complexity of modelling SMA and, people with Type I are a more homogenous group in terms of treatment response according to expert opinion. Consequently, the estimate only includes children up to the age of 5 as overall, about 68% of children with SMA type I die before their second birthday and 82% die before their fourth birthday.[51]

The treatment scenario was built to allow for changes in the care cost, informal caregiver productivity losses and disability weightings. Prevention was omitted from the analysis as SMA is currently not preventable. Rehabilitation was

Figure 6
Spinal muscular atrophy analysis structure

Source: Economist Impact analysis, 2022.

Table 8
Spinal muscular atrophy analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses for patients with Type I	Change in DALY weights
Treatment			Increase by 68%					Reduce by 34.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

also omitted from the analysis, as most patients with SMA Type I will require physiotherapy and specialist equipment to survive and it was too difficult to disentangle these costs from baseline costs of care. In the treatment scenario, we only estimated the impact of nusinersen, as it has a robust evidence base supporting its effectiveness in slowing the progression of SMA and was the only oral drug widely available to treat SMA in 2019, the data year of this study. In an economic study looking at the cost effectiveness of SMA, nusinersen accounted for around 79% of the total costs of care.[52] The other 21% is attributable to ventilation, inpatient visits, consultant care and informal caregiving.[53] One study found that use of nusinersen can also decrease inpatient costs by 27% but increase outpatient costs by 16.1%.[54] To capture the impact of nusinersen on the direct costs, we reduced the cost impact of treatment by 11%. Our treatment scenario therefore increased the costs of care by 79%-11%=68%.

In terms of treatment effects, nusinersen slows the progression of the disorder and can reduce the risk of death or progression to full-time ventilation for infants with SMA Type I by 47%.[55] All patients with Type I SMA require permanent assisted ventilation within 2 years of life.[56] Treatment with nusinersen therefore means fewer patients require full-time ventilation over a 6 month - 12 month time period. As caregivers report more hours of care for ventilated patients (12.39 hours per day) compared to patients who did not need breathing support (8.17 hours per day), treatment with nusinersen could reduce daily caregiving hours by 4.22 hours or 34%.[55, 57] Therefore in the analysis, we reduced informal caregiver productivity loss accordingly.

To calculate the total cost from 2019-2030, it was assumed that the costs of care were incurred in each year. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%.

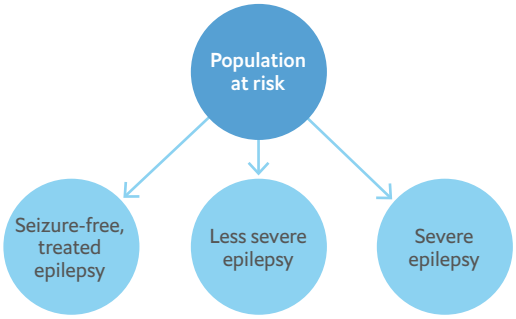
Epilepsy

Figure 7 illustrates the epilepsy analysis, which was run for three different scenarios – baseline, preventative treatment and symptomatic treatment. The evidence for the effectiveness of rehabilitation for epilepsy is inconclusive therefore a rehabilitation scenario was omitted from this analysis. The composition of the scenarios for epilepsy are displayed in **Table 9**.

According to the World Health Organization (WHO) with appropriate access to healthcare, it is possible to prevent 25% of seizures in high-income countries (HIC) and 15% of seizures in middle and low-income countries (LMICs).[58] In LMICs there is generally a low availability of anti-seizure medication. A recent study found the average availability of generic anti-seizure medicines in the public sector of low-and middle-income countries to be less than 50%.[58] Similarly, WHO also estimates a greater reduction of the prevalence of seizures in HIC and lower in LMICs with appropriate access to symptomatic treatment.[58] Thus for the preventative and symptomatic treatment scenarios, the change in the prevalence of seizures was differentiated by income status to represent different levels of access to epilepsy treatment. Evidence also suggests that up to 70% of people living with epilepsy could become seizure free with appropriate use of anti-seizure medicines.[58] Adequate treatment can improve quality of life, mental health and productivity as well as employment status in 70% of cases.[59] We therefore assumed that people with controlled epilepsy are 70% more likely to be able to work, and less likely to retire early (**Table 9**).

To calculate the total cost from 2019-2030, it was assumed that the costs of treatment were incurred in each year as epilepsy treatment is ongoing rather than a one off acute event. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%. Even while the costs of treatment are incurred in each year, the indirect benefits continue to grow over time which generates savings.

Figure 7
Epilepsy analysis structure



Source: Economist Impact analysis, 2022.

Table 9
Epilepsy analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses	Change in DALY weights
Preventative treatment	Reduce by 25% in HICs; Reduce by 15% in LMICs								
Symptomatic treatment	Reduce by 70% in HICs; Reduce by 50% in LMICs		Refer to adjusted cost in parameter values	Reduce by 70.00%	Reduce by 70.00%	Reduce by 70.00%	Reduce by 70.00%	Reduce by 70.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

Spinal cord injury

Figure 8 illustrates the spinal cord injury analysis, which was run for two different scenarios – baseline and rehabilitation. The composition of the scenarios for spinal cord injury are displayed in **Table 10**.

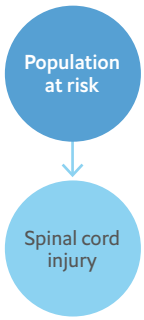
For each of the scenarios in **Table 10**, the baseline parameter values were changed to simulate the effect of the hypothetical scenario on patients with spinal cord injury. The scenarios were built to allow for changes in the care cost, patient's productivity losses, informal caregiver productivity losses and disability weightings.

Similarly to traumatic brain injury, the only scenario we could realistically estimate was rehabilitation. In the rehabilitation scenario, the cost of care was increased from baseline by 15.12% (same as the increase in costs for traumatic brain injury as we were unable to find data for spinal cord injury) and patient unemployment and productivity losses for the informal caregiver were reduced by 43%. Again we took a value from traumatic brain injury research to determine the impact of rehabilitation on unemployment (the average of mild and severe unemployment rates from TBI). We also did not have the data to adjust this according to the severity (in terms of prevalence by severity level or cost) therefore assumed a standard cost across all spinal cord injuries.

The analysis was run over a one-year time horizon to estimate the 2019 costs and outcomes of each scenario. The analysis estimated the following costs for each scenario: direct cost of medical care; cost of patient productivity losses due to absenteeism, presenteeism, unemployment and early retirement; and cost of informal caregiver productivity losses due to care for the patient. The analysis estimated the disability-adjusted life years (DALYs) resulting from each scenario, where DALYs averted reflect a positive effect on health outcomes.

To calculate the total cost from 2019-2030, it was assumed that the costs of care were incurred in each year. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%. Even while the costs of care are incurred in each year, the indirect benefits continue to grow over time which generates savings.

Figure 8
Spinal cord injury analysis structure



Source: Economist Impact analysis, 2022.

Table 10
Spinal cord injury analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment	Change in patient's early retirement	Change in informal caregiver productivity losses	Change in DALY weights
Rehabilitation			Increase by 15.12%			Reduce by 43.00%		Reduce by 43.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

Traumatic brain injury

Figure 9 illustrates the traumatic brain injury analysis, which was run for two scenarios – baseline and rehabilitation. The composition of the scenarios for traumatic brain injury are displayed in **Table 11**.

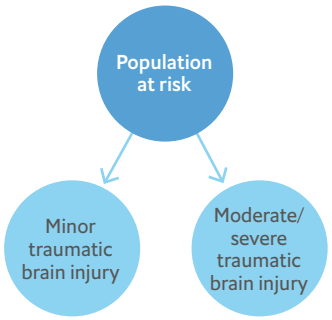
For each of the scenarios in **Table 11**, the baseline parameter values were changed to simulate the effect of the hypothetical scenario on patients with traumatic brain injury. The scenarios were built to allow for changes in the care cost, patient's productivity losses, informal caregiver productivity losses and disability weightings.

We only included a rehabilitation scenario for traumatic brain injury as treatment (mostly emergency inpatient care) is too variable (dependent on the injury) to realistically estimate. Furthermore, emergency treatment was largely covered in the baseline treatment costs so its inclusion in the scenarios would risk double counting. We included a rehabilitation scenario as the evidence base is fairly robust on the impact of vocational rehabilitation (VR). One study suggests that VR enables a return to work (RTW) rate of 17% in moderate to severe cases.[60] A further study found 69% of people with mild TBI returned to employment following VR.[61] Another randomised controlled trial found a rate of 14% RTW in moderate to severe cases.[62] We therefore assumed a higher RTW for mild cases and a lower RTW for severe cases. Accordingly, we assumed an increase in patient productivity and decrease in caregiver burden by 69% for mild cases and by 17% for moderate/severe cases.

The cost of care was also increased from baseline to account for the cost of VR. Due to a lack of evidence, this cost was estimated by taking the cost of VR as a proportion of the total costs associated with traumatic brain injury.

To calculate the total cost from 2019-2030, it was assumed that the costs of care were incurred in each year. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%. Even while the costs of care are incurred in each year, the indirect benefits continue to grow over time which generates savings.

Figure 9
Traumatic brain injury analysis structure



Source: Economist Impact analysis, 2022.

Table 11
Traumatic brain injury analysis scenarios

	Change in disease prevalence	Change in disease mortality	Change in disease cost	Change in patient's absenteeism	Change in patient's presenteeism	Change in patient's unemployment for mild disease	Change in patient's unemployment for moderate to severe disease	Change in patient's early retirement	Change in informal caregiver productivity losses with mild disease	Change in informal caregiver productivity losses with moderate to severe disease	Change in DALY weights
Rehabilitation			Increase by 15.12%			Reduce by 69.00%	Reduce by 17.00%		Reduce by 69.00%	Reduce by 17.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

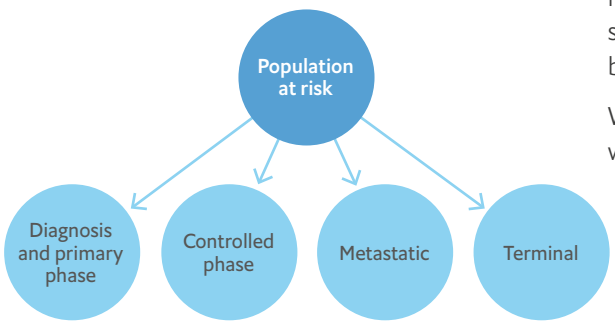
Brain and nervous system cancers

Figure 10 illustrates the cancer analysis, which was run for three different scenarios – baseline, surgery, and chemotherapy. The composition of the scenarios for cancer are displayed in **Table 12**. Prevention was omitted from the analysis as brain cancer is currently not preventable.

For each of the scenarios in **Table 12**, the baseline parameter values were changed to simulate the effect of the hypothetical scenario on patients with brain cancer. The scenarios were built to allow for changes in the disorder mortality, care cost, patient's productivity losses, informal caregiver productivity losses and disability weightings.

We estimated the impact of surgery and chemotherapy separately. For low grade glioma, surgery is typically the only treatment needed.

Figure 10
Brain cancer analysis structure



Source: Economist Impact analysis, 2022.

In some cases of low grade glioma and generally for higher grade gliomas, radiation therapy and chemotherapy are the next line of treatment after surgery.[63] Due to the complexity of treatment, there was an insufficient evidence base to estimate the economic impact of treatment with surgery and chemotherapy together so we did not include this as a scenario. Despite the evidence trying to separate and measure the effects of each treatment separately, we also know that at some point in the patient's treatment cycle they will have received both. We therefore view the figures in the analysis scenarios for chemotherapy and surgery as a range. Rehabilitation is not supported by a significant evidence base and also omitted. In the surgery scenario, brain cancer mortality was reduced by 30% (only in year 1). This figure was based on literature which states tumour resection can improve median survival of patients by 30% for patients with grade IIII gliomas.[64] To make this figure realistic for low grade gliomas we further reduced mortality by 50%. In the chemotherapy scenario the brain cancer mortality was reduced by 16.3% for all patients.[65]

We increased the cost of care from baseline with the inclusion of chemotherapy and surgery by 61% and 5.7% respectively.[66] Surgery eliminated seizures in at least 43% of patients with low grade glioma and glioneuronal tumours.[67] We assumed the reduction in seizures may enable people to work and reduce absenteeism by 43%.

Table 12
Brain cancer analysis scenarios

	Change in disease prevalence	Change in disease mortality for Stage 1 and 2	Change in disease mortality for Stage 3 and 4	Change in disease cost	Change in patient's absenteeism stage 1 and 2	Change in patient's presenteeism	Change in patient's unemployment stage 1 and 2	Change in patient's early retirement	Change in informal caregiver productivity losses stage 1 and 2	Change in DALY weights
Surgery		Reduce by 50.00%	Reduce by 30.00%	Increase by 5.70%	Reduce by 43.00%		Reduce by 52.00%		Reduce by 43.00%	Reduce by 10.00%
Chemotherapy		Reduce by 16.30%	Reduce by 16.30%	Increase by 61.00%	Reduce by 59.00%		Reduce by 70.30%		Reduce by 59.00%	Reduce by 10.00%

Source: Economist Impact analysis, 2022.

Chemotherapy reduced seizure frequency by 59% in patients with low grade glioma, which also impacts caregiver burden. This study explicitly states the patients had not received surgery.[68] We therefore assumed that informal caregiver burden will decrease by 59%.[68]

Surgery may enable a return to work rate of 52% in the year following diagnosis (for stages I and II).[69] Surgery and adjuvant treatment (chemo & radiotherapy) may enable a return to work rate of 70.7% for stage II and III gliomas.[70] We were not able to remove the effect of radiotherapy from this scenario. For metastatic and terminal gliomas, we assumed no RTW as no one would be employed. We assumed however there would be an impact on caregivers.

To calculate the total cost from 2019-2030, it was assumed that the costs of care was only incurred in 2019 for each scenario. The total costs were calculated from 2019-2030 and discounted at a rate of 3.5%.

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