METHODOLOGICAL APPROACH

The Value of Investing in Innovative Medicines: Socioeconomic Burden and Annual Social Impact of Roche Treatments for HER2+ Breast Cancer, Multiple Sclerosis and Retinal Disease

WifOR

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List of Abbreviations

AMD	Age-Related Macular Degeneration
DALY	Disability-Adjusted Life Year
DME	Diabetic Macular Edema
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GVA	Gross Value Added
HER2+	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
IHME	Institute for Health Metrics and Evaluation
mBC	Metastatic Breast Cancer
OCT	Optical Coherence Tomography
PR	Patients Reached
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
SI	Social Impact
SIoM	Social Impact of Medicines
SOB	Socioeconomic Burden
SoC	Standard of Care
SPC	Summary of Product Characteristics
TA	Therapeutic Area
WIOD	World Input-Output Database
YLD	Years Lived with Disability
YLL	Years of Life Lost

Glossary

Economically active person (see also "Labour force")	All persons who supply labour for the production of goods and services in a country during a specified period. This includes currently employed persons and currently unemployed persons who are available for and actively seek work.
Gross Value Added (GVA)	Gross value added (GVA) is defined as output (at basic prices) minus intermediate consumption (at purchaser prices); it contains only the added value created in the production process. GVA can be reported separately by economic entity, such as industry sector. The sum of overall GVA plus taxes on products minus subsidies on products amounts to gross domestic product (GDP).
GVA effects (direct)	Direct GVA effects are changes in the GVA creation corresponding to changes in the production of a sector. Increases in the productive activity imply increases in GVA according to the production-GVA-ratio of the respective sector (which can be derived from national accounts tables).
GVA effects (indirect)	Indirect GVA effects are changes in the GVA creation of sectors that supply goods or services to the sector where a direct effect is observed. Given the interdependence of production processes in an economy, positive direct GVA effects of increased production in one sector implicate additional GVA creation in supplier sectors. E.g. additional production in a bakery requires intermediate inputs such as flour, yeast, electricity, or machinery. Thus, additional production (and GVA creation) also takes place in the sectors supplying these goods and services.
GVA effects (induced)	Induced GVA effects are changes in the GVA creation caused by changes in consumption as a result of direct and indirect effects. Increased GVA creation implicates increased labour income. This, in turn, will be spent on consumption, inducing further production (and GVA creation).
Health Footprint	The health footprint is the incremental health benefit that a specific treatment can generate compared to an alternative treatment (usually based on clinical evidence). This benefit

	is applied to the patient population under investigation over a defined time horizon.
Health outcome	Health outcomes are used to measure the efficacy of a treatment that patients receive in addressing a health condition. Depending on the condition and the intended effect of the treatment, possible health outcomes can be specific blood test results, disease severity indicators, patient-reported outcomes, or survival probability.
Labour force	The labour force consists of all persons who supply labour to produce goods and services during a specified period, i.e., all those who are economically active. It considers people who are currently employed and people who are currently unemployed but seeking work. Unpaid workers, family workers, and students are often omitted, and some countries do not include members of the armed forces. Some definitions of the labour force additionally refer to a working age population only, e.g., to persons aged 15 and older.
Labour force participation rate	The labour force participation rate is the share of the population that is economically active. This includes all people who supply labour to produce goods and services during a specified period.
Quality Adjusted Life Years (QALY)	An outcome measure that considers both the quantity and the quality of extra life provided by the healthcare intervention. It is the arithmetic product of life expectancy and the quality of remaining life years.
Socioeconomic Footprint	The socioeconomic footprint is the sum of the economic benefits that come along with the incremental health benefits of one treatment compared to an alternative treatment. These benefits are added up for the patient population under investigation over a defined time horizon. The socioeconomic footprint is depicted as a monetary value representing labour productivity, i.e. here, gross value added (GVA) per economically active person.
Paid work	Paid work refers to work performed by an individual in the context of gainful employment.
Replacement cost approach / Proxy good approach	The market replacement cost approach, or proxy good approach, is one method to value the time spent on unpaid work. It assumes that private households would hire a

	service provider to perform the required tasks if they were unable to perform them.
Time use survey	Time use surveys measure how people on average allocate their time across different day-to-day activities in a defined time period, e.g., 24 hours.
Unpaid work	Unpaid work refers to work performed by an individual outside gainful employment. In order to distinguish unpaid work from leisure time and other activities, the third person criterion is used: unpaid work encompasses only activities which are replaceable by another person.

1 Executive Summary

1.1 Background

It is becoming increasingly evident that there is an interconnection between health and economic growth [1] (**Figure 1**). The healthcare sector is a diverse sector that contributes significantly to the Gross Domestic Product (GDP) of a country. It is also a significant source for employment opportunities, enhances productivity, and has the potential for growth. The health sector thus plays a substantial role in the overall economic health of a nation.

To acknowledge the economic interdependencies between health and the overall economy, it is essential to measure health investments and their impact on economic growth and societal well-being [2]. Metrics should be developed to answer questions such as: What is the impact of healthcare spending on GDP? How does healthcare spending contribute to the overall economic output of a country? How does healthcare spending contribute to economic growth and productivity? In what ways does it enhance the overall economic well-being of a nation?

Approaches to quantify the impact of health in the overall economy would support the necessary paradigm shift from viewing healthcare spending as a cost, to recognising it as an investment.

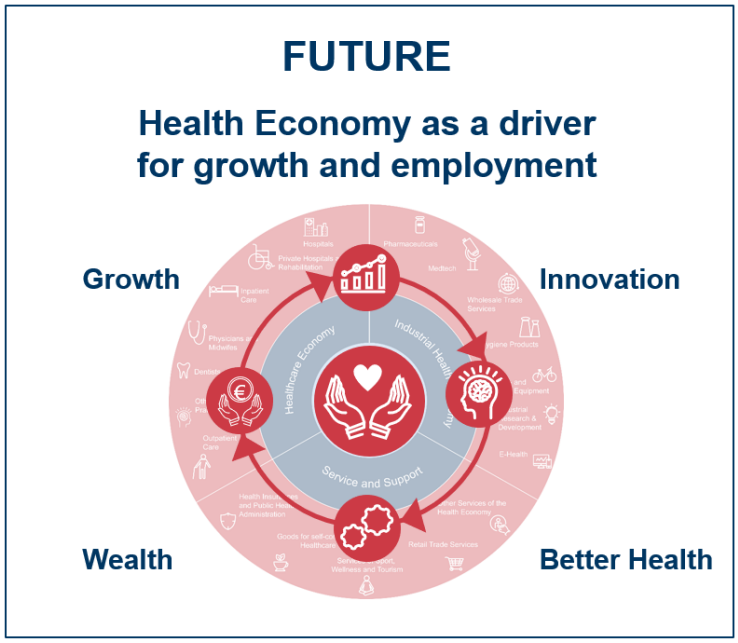

Figure 1: Health spendings are an investment which trigger a positive feedback loop.

Our approach aims to measure the downstream Social Impact of medical innovations at a macroeconomic level to demonstrate the added value brought by Roche's products to the society and to quantify this benefit in monetary terms. The Social Impact represents the benefit of the health investment brought due to and on top of the clinical health benefits and directly related costs, thus beyond the often narrowed, cost-centred, payer perspective. This methodology can be scaled up to include several products from different disease areas globally. This methodology is based on the approach published in the Value Balance Alliance white paper [3].

By additionally measuring the Socioeconomic Burden of the respective diseases these medicines treat, the above can be put into perspective.

Our goal is to demonstrate that the spendings in the healthcare sector are an investment and bring value to the society by providing evidence for return on investment differentiated by markets, regions, brands, etc. The outcomes of this analysis may form the basis to open the dialogue among various stakeholders, such as ministries of health, sick funds, and hospitals.

1.2 Social Impact of Medicines

The Social Impact of Medicines is defined as monetary value equivalent, expressed by potentially generated gross value added (GVA), of a medical innovation on a national economy and its society. The Social Impact results from health and socioeconomic modelling approaches and is affected by various input parameters and assumptions.

It quantifies not only health benefits but also the wider economic and social benefits that potentially come along with improved health. It thereby draws a connection between health gains from the use of medicines and, from an economic point of view, the important aspect of the contribution of an economic agent (such as the work force, or an industry sector) within an economy, as represented by the measures of GVA and GDP.

There are two channels through which pharmaceutical products can increase productivity potential and thus wealth to the society:

1. Prolonging life increases the time patients have for paid and unpaid work.
2. Improving health increases quality of life and leads to higher working capability.

The Social Impact consists of two complementing viewpoints to assess the effects of medicines on the Health and Socioeconomic Burden: the Health Footprint and the Socioeconomic Footprint. A multitude of inputs are required for this analysis, inducing the number of patients reached by each medicine in each country, medicine- and indication-specific QALYs, epidemiological data, and socioeconomic parameters (**Figure 2** and see relevant sections below).

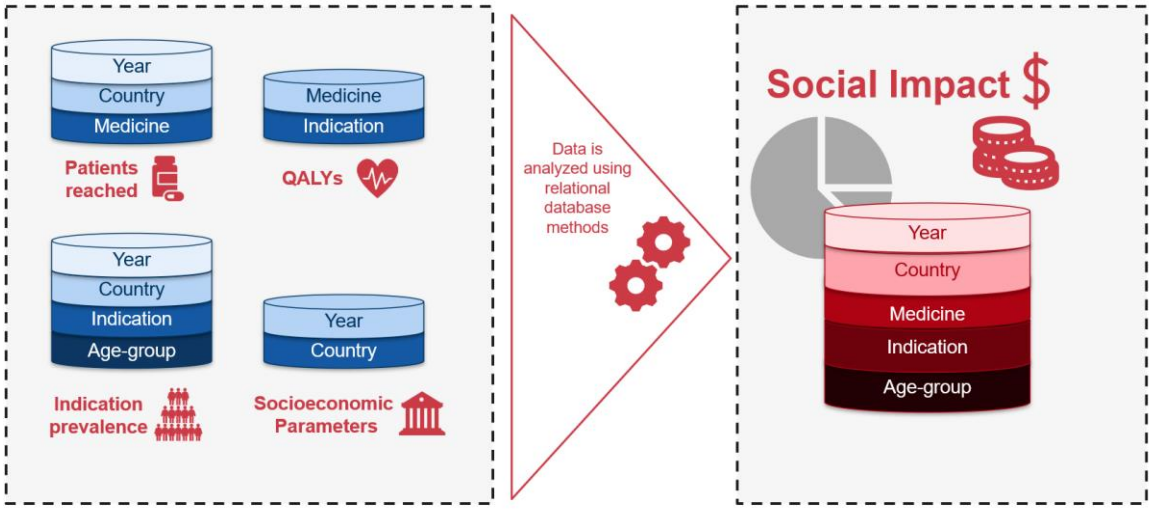

Figure 2: Our approach consists of complementing steps to evaluate the health and socioeconomic footprint of medicines.

In the Global Social Impact of Medicines approach, the Health Footprint is calculated based on the number of Quality Adjusted Life Years (QALYs) gained by treating patients with a medicine for a given indication (**Figure 3**). The annual incremental QALYs are captured; annual as this methodology calculates the yearly Social Impact of medicines, and incremental as it is based on the QALYs gained compared to the standard of care (SoC).

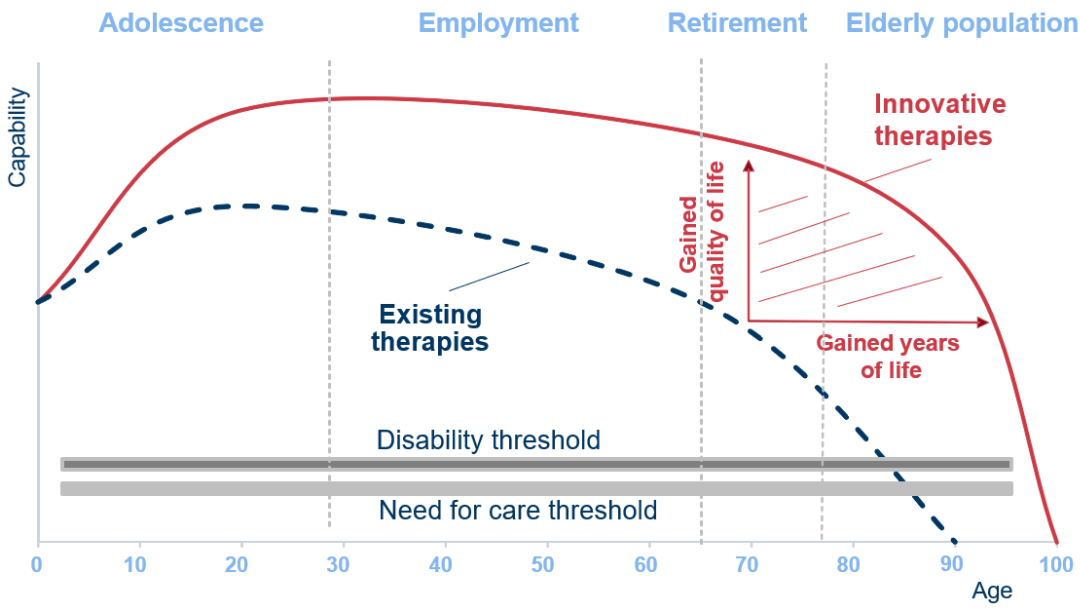

Figure 3: The Quality Adjusted Life Years (QALYs) are the starting point of our Global Social Impact of Medicines approach.

The Socioeconomic Footprint measures the socioeconomic benefits, in terms of gains in productivity, resulting from a healthier population when using a specific intervention in a chosen country and in a given year. For the purposes of this approach, it is assumed that QALYs gained lead to an increase in productive time as a patient's life expectancy and quality of life increase. Since, by definition, one QALY equals to one year in perfect health, and by assuming that one year in perfect health equals to one year of full working capability, our guiding assumption is that one QALY gained corresponds to one gained year of full productivity potential.

i.e., 1 QALY gained = 1 gained year in perfect health = 1 year gained of full work capability = 1 year of productivity gain.

In addition to paid work direct productivity gains, indirect and induced paid effects are included in the analysis to show the impact this productivity potential has along the value chain. Indirect paid effects reflect the intermediate consumption of goods and services from suppliers triggered by direct generated GVA, while induced paid effects capture the impact of spending by households receiving income based on direct and indirect generated GVA (**Figure 4**). These are calculated using multipliers from input-output analysis (for more details, see Section 5.1). This approach provides a holistic view of the overall impact of a more productive patient population on a country's economy (see Section 5).

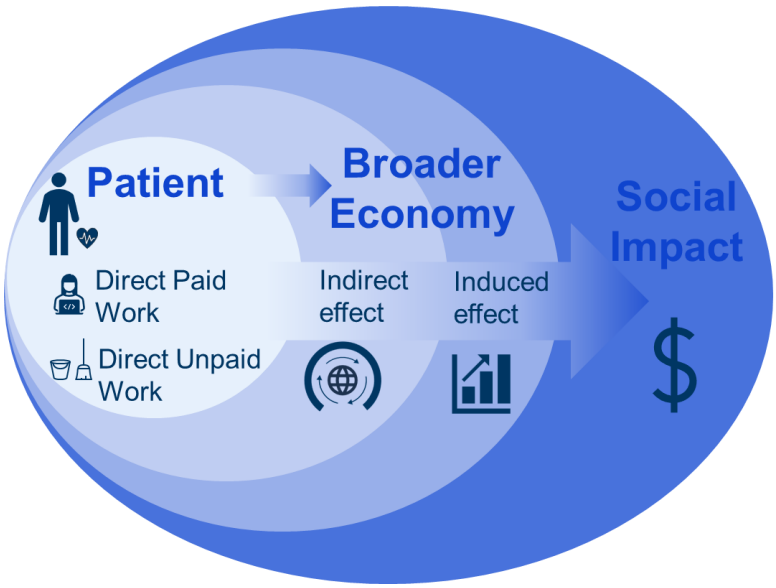

Figure 4: Illustration of the Social Impact effects captured in the study.

Furthermore, the value-added effects of unpaid work activities, such as cleaning, cooking, and childcare, that need to be outsourced by patients not able to perform them are also captured [4] **(Figure 5**). These unpaid work activities are clearly distinguished from leisure time based on Reid's third person criterion: unpaid work encompasses only the activities that can be replaced by another third person [4].

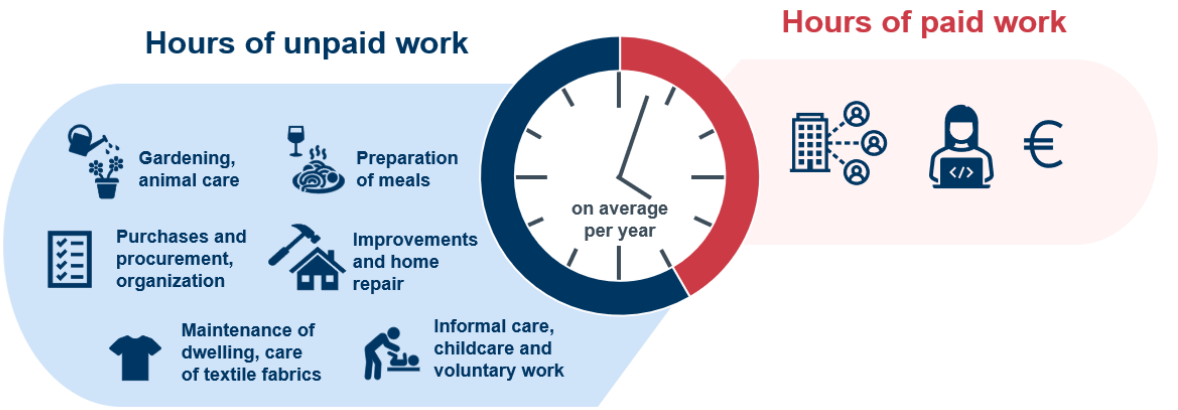

Figure 5: Unpaid work activities.

In order to measure productivity, the patients reached are divided into age groups. Patients aged between 20 and 59 contribute to productivity gains from both paid and unpaid work. Patients aged 60 and over are no longer considered part of the labour market and therefore contribute solely to productivity gains from unpaid work. Patients under the age of 20 are assumed to contribute neither to productivity gains from paid work nor to productivity gains from unpaid work (**Figure 6**).

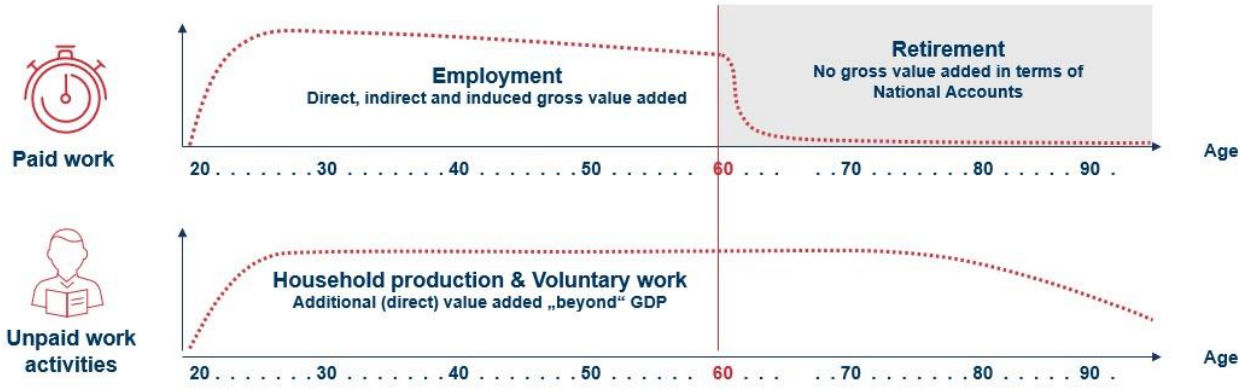

Figure 6: The contribution of the different age groups to the work paid and unpaid work.

The Social Impact is expressed in monetary terms (such as US dollars) applying GVA per economically active person within an economy as a measure of labour productivity.

In addition to performing the analysis for the base year, a forecast of the Social Impact of Medicines is performed, as well as a retrospective analysis to investigate the future and past impact that Roche's medicines in scope bring to the economy.

1.3 The Socioeconomic Burden of Diseases

The Socioeconomic Burden (SOB) aims to determine the cost that disease and disability exert upon the individual and society, considering health, social, and economic factors.

There are two channels through which diseases can decrease productivity potential and thus wealth to the society:

1. Shortening life decreases the time to spend on paid and unpaid work.
2. Adverse effects on health decrease quality of life leading to lower working capability

The SOB consists of two complementing viewpoints to assess the effects of diseases on health and economy: the Health Burden and the Socioeconomic Burden. The inputs required to calculate the SOB are summarised in **Figure 7** and described in more detail in Section 4.

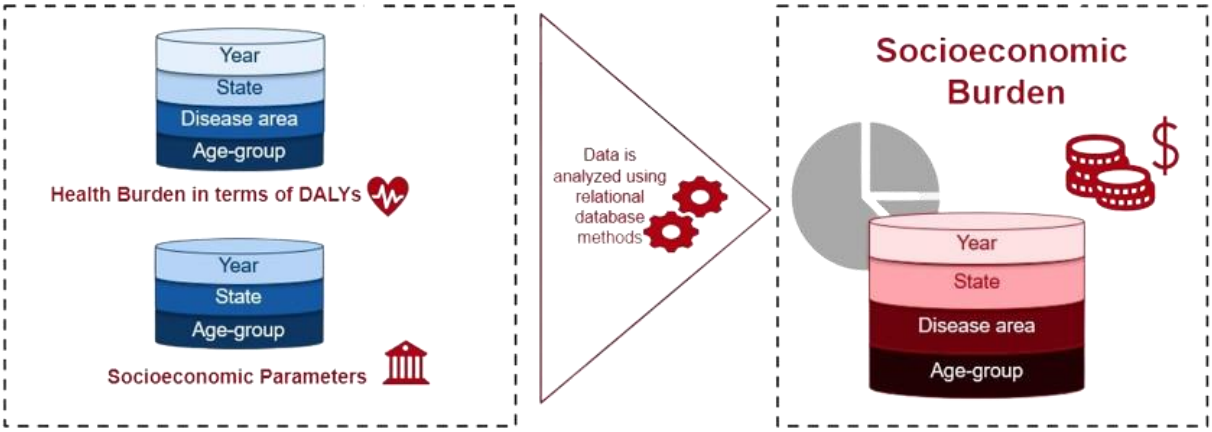

Figure 7: Our approach consists of complementing steps to evaluate the health and socioeconomic burden of a disease.

To quantify the health burden of a disease, Disability Adjusted Life Years (DALYs) are used as health outcomes. A DALY measures the overall burden of a disease and can be expressed as the cumulative number of years lost due to ill-health, disability or early death [5]. DALYs are measured by combining two different measures: a measure of life expectancy and the degree of disability during a life-threatening disease or handicap for a population (**Figure 8**).

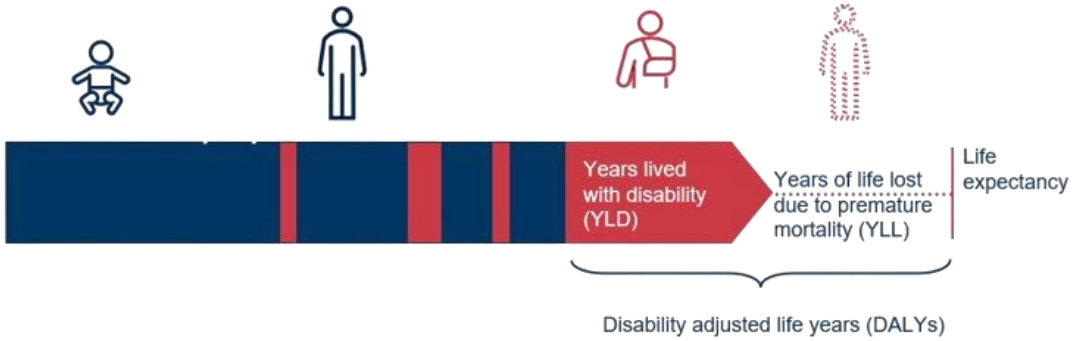

Figure 8: Visualisation of how DALYs are calculated.

To establish a link between DALYs and productivity, the following assumptions are made: first, it is assumed that one DALY equals one year of full disability; second, one year lived in full disability is translated into a full year without working capability.

i.e., 1 DALY lost = 1 year fully disabled = 1 year without productivity/work capability.

Similarly to the calculation of the Social Impact of Medicines, all four effects on productivity are captured for the Socioeconomic Burden of Diseases, namely direct paid, indirect paid, induced paid and unpaid work. For this, age-group-specific DALYs are extracted from the IHME and are monetised differently (**Figure 9**). The result is expressed in monetary terms applying GVA as a measure of labour productivity.

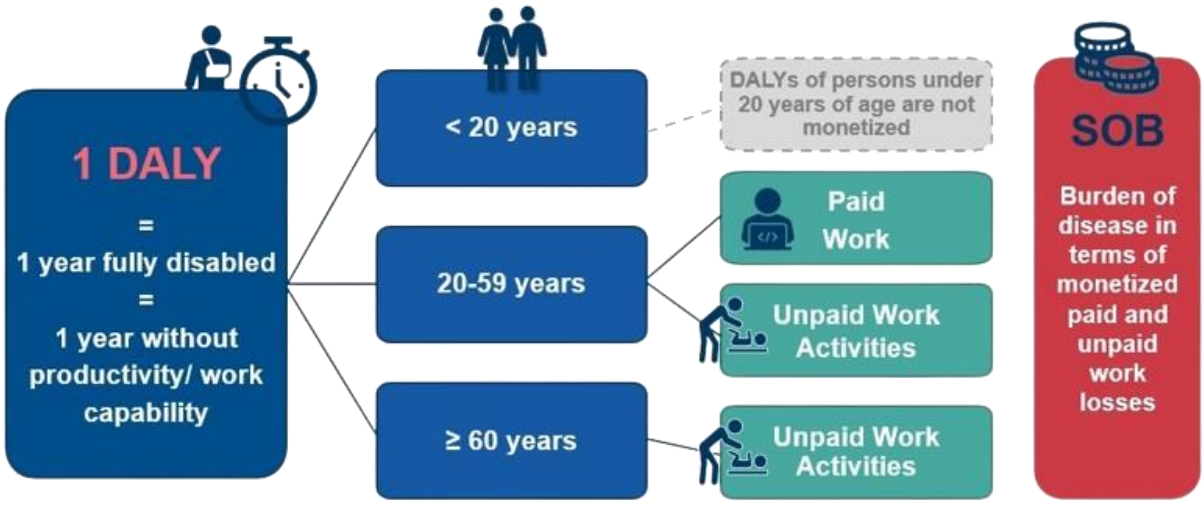

Figure 9: Monetisation of DALYs from different age groups.

1.4 Out of Scope

- Direct health benefits other than those considered to determine quality-adjusted life years (QALYs) are not included.
- Direct healthcare costs such as drug costs, physician visits, or nursing services are not included.
- Disease- or treatment-related burden for patients' contacts (i.e., informal caregivers and family members) is not included.
- System impact and process impact (e.g., implications for healthcare delivery, changes in the number of hospitalisations and potential consequences, or impact on future public health policy goals) are not included.

2 Pilot Project Scope

This is a pilot study focusing on the scope summarised in this section.

2.1 Therapy Areas

Table 1: Therapy areas in scope, as provided by Roche

Therapy Areas
Human Epidermal growth factor Receptor 2 (HER2+) breast cancer
Multiple sclerosis (MS)
Ophthalmology ▪ neovascular Age-Related Macular Degeneration (nAMD) ▪ Diabetic Macular Edema (DME)

2.2 Products and their Indications

Table 2: Product name and indications in scope, as provided by Roche

Product Name	Indications
Herceptin	HER2+ breast cancer, neo-adjuvant
	HER2+ breast cancer, adjuvant only
	1st line HER2+, HR+ and HR- metastatic breast cancer
Kadcyla	HER2+ breast cancer, adjuvant continued residual disease
	2nd line HER2+, HR+ and HR- metastatic breast cancer

Perjeta	HER2+ breast cancer, neo-adjuvant
	HER2+ breast cancer, adjuvant only
	1st line HER2+, HR+ and HR- metastatic breast cancer
Phesgo	HER2+ breast cancer, neo-adjuvant
	HER2+ breast cancer, adjuvant only
	1st line HER2+, HR+ and HR- metastatic breast cancer
Ocrevus	Primary Progressive Multiple Sclerosis (PPMS)
	Relapsing-Remitting Multiple Sclerosis (RRMS)
	Secondary Progressive Multiple Sclerosis (SPMS)
Vabysmo	Visual impairment due to Diabetic Macular Edema (DME)
	Neovascular Age-Related Macular Degeneration (nAMD)

2.3 Countries in Scope

Table 3: Countries in scope

Country Name
Brazil
Canada
China
France
Germany
Italy
Japan
Spain
United Kingdom
United States

2.4 Years in Scope

Both a retrospective and a prospective analysis were performed based on the actual or forecasted patients (PR) provided (**Table 4**).

Table 4: Years in scope

Analysis	Years in Scope	PR Captured
Retrospective analysis	2017-2023	Actual PR

Forecast analysis	2024-2032	Forecasted PR

3 Social Impact of Medicines

3.1 Health Footprint Input Parameters

The health footprint is calculated taking into account the following parameters described in this section:

- Patients reached (PR)
- Epidemiological data
- Health-related data

3.1.1 Patients Reached (PR)

The annual number of patients reached (PR) is provided by Roche per **indication**, **product** and per **country.** A forecast of the PR (for the years 2024 – 2032) is also provided as well as PR for the retrospective analysis (years 2017 – 2023). For forecasted PR data, an uncertainty range was estimated.

The effective size of the patient population depends not only on prevalence and incidence rates of a disease, but also on the rate of market penetration of a medication which might increase or decrease over time. These variations may be also due to regulatory or reimbursement reasons, but detailed additional feedback would be necessary in order to better understand these variations and eventually apply any corrections.

Careful assessment of the provided inputs is performed with WifOR's model, particularly for the brand names, product IDs, and their active molecule, as well as the countries in scope.

The validation of the PR data provided by Roche aims to check the plausibility and, if necessary, to clarify possible inconsistencies. Validation processes could be for instance:

- Make sure that all the countries and products that are in scope are included in the data sent.
- Negative PR are searched, and the plausibility is checked together with Roche.

After the plausibility is validated, the data provided is further compared to our database and the following questions are examined:

- Are there any products or indications without a QALY assigned?
- Do socioeconomic inputs exist for all countries in the PR data?
- Are prevalence data allocated for all countries?

3.1.2 Epidemiological data: Age-specific prevalence of disease indication per medicine and country

In the model, calculations are performed based on three age groups: <20, 20-59, and ≥60 years. Patients reached per medicine and indication are assigned to these age groups using official age group-specific prevalence figures (called Proportional Prevalence in our model).

The primary source of such data is the Global Burden of Disease (GBD) database [6], a database of the Institute for Health Metrics and Evaluation (IHME) which offers the possibility to extract prevalence figures per disease entity, by age group, and at a country level. No gender segregation is made. If the disease entity is not included in the GBD database, a literature search is undertaken. Proxy diseases may also be used.

For all HER2+ breast cancer indications, the proportional prevalence for 'breast cancer' is used as it is obtained from the GBD database [6]. This is because we assume the proportional prevalence for HER2+ breast cancer is similar to that for breast cancer.

For multiple sclerosis, the proportional prevalence of 'multiple sclerosis' is taken from the GBD database and used for all multiple sclerosis related indications.

The proportional prevalence of age-related macular degeneration (AMD) is also taken from the GBD database. As diabetic macular edema (DME) is not in the GBD database, 'diabetes mellitus' is used as a proxy for the proportional prevalence of the visual impairment due to this indication, as we assume the age distribution of patients with DME across the three age groups to be similar to that for diabetes mellitus. Proportional prevalence data may be found in the Appendix (**Table 7**).

3.1.3 Health-related data: QALYs

Quality-adjusted life years (QALYs) are the benefit/effectiveness measure of choice for the medicines, and respective indications, to be included in the study.

Medicine and indication-specific QALYs are shared by Roche and are extracted from health economic evaluations. QALYs are selected, as they are universal outcome measures which allow for the demonstration and comparison of health benefits across different disease areas.

The incremental undiscounted QALY, compared to the SoC (or another suitable comparator), is then calculated per patient for one year (see Section 3.2).

The QALY data used are assumed to be constant across all countries and years of analysis.

3.1.3.1 Standard of Care (SoC)

The term Standard of Care (SoC) defines established pharmaceutical treatments (or in some cases other therapeutic interventions) vs. which new products are compared in clinical and pharmacoeconomic trials. In some rare cases, the comparator may be placebo or no treatment (if no active comparison is available). We always opt for the most broadly used therapeutic approach so that we include the most widely used SoC (**Table 5**).

A challenge faced is the fact that differences between countries in terms of SoC may exist and this depends mainly on the GDP and the healthcare system. For such a global project, it is impossible to achieve uniformity or specificity of the comparator.

Table 5: SoC per product and indication

Product	Indication	SoC
Herceptin	HER2+ breast cancer, neo-adjuvant	Chemotherapy
	HER2+ breast cancer, adjuvant only	Chemotherapy
	1st line HER2+, HR+ and HR- metastatic breast cancer	Chemotherapy
Perjeta/Phesgo	HER2+ breast cancer, neo-adjuvant	Chemotherapy
	HER2+ breast cancer, adjuvant only	Chemotherapy
	1st line HER2+, HR+ and HR- metastatic breast cancer	Chemotherapy
Kadcyla	HER2+ breast cancer, adjuvant continued residual disease	Chemotherapy
	2nd line HER2+, HR+ and HR- metastatic breast cancer	Lapatinib and Capecitabine
Ocrevus	Relapsing-Remitting Multiple Sclerosis (RRMS)	Interferon beta 1-a (Avonex)
	Secondary Progressive Multiple Sclerosis (SPMS)	Interferon beta 1-a (Avonex)
	Primary Progressive Multiple Sclerosis (PPMS)	Best supportive care
Vabysmo	Visual impairment due to Diabetic Macular Edema (DME)	Ranibizumab; Aflibercept; Brolucizumab; Bevacizumab
	Neovascular Age-Related Macular Degeneration (nAMD)	Ranibizumab; Aflibercept; Brolucizumab; Bevacizumab

3.2 Health Footprint Calculation

3.2.1 Incremental Annual QALYs Gained

In our calculation of the health footprint, incremental annual undiscounted QALYs per patient, medicine and indication are used, which were provided by Roche.

- Incremental means that their value must be seen in relation to a comparator (the Standard of Care (SoC) see Section 3.1.3.1).
- Per patient means that they can be scaled up based on the patients reached provided by Roche.
- Annual is to the fact that a constant proportionality of the QALYs is assumed throughout the study's provided time horizon.
- Undiscounted means that a snapshot of the current year is captured.

The annual undiscounted QALYs gained $a\_udQALY_{m,i}$ are calculated by dividing the undiscounted total QALYs gained $udQALY_{m,i}$ by the time horizon $TH_{m,i}$:

$$a\_udQALY_{m,i} = \frac{udQALY_{m,i}}{TH_{m,i}}$$

3.2.2 QALYs Gained by Indication and Age Group

To calculate the patients per indication and age group from the patients reached provided by Roche by product and indication (and country), the following calculation is performed:

$$PR_{c,m,i,a} = PR_{c,m,i} \cdot pp_{i,a}$$

Where:

$PR_{c,m,i,a}$ are patients reached per country, medicine, indication and age group
$PR_{c,m,i}$ are patients reached per country, medicine and indication (provided by Roche)
$pp_{i,a}$ is the proportional prevalence per age group for indication i.

The total number of QALYs gained per country, medicine, indication and age group are calculated by multiplying the undiscounted QALYs per patient and year (annual QALYs gained) by the PR(country, medicine, indication, age group).

$$QALY_{c,m,i,a} = PR_{c,m,i,a} \cdot a\_udQALY_{m,i}$$

Table 6: Example to illustrate the health benefit calculation:

Product *m*	Indication *i*	Patients Reached ($PR_{m,i}$)	QALY (undiscounted) per patient year $a\_udQALY_{m,i}$	Proportional prevalence $pp_{i,a}$		
				<20	20-59	≥60
X	Indication A	29,993	0.0619	10%	17%	73%
X	Indication B	33,555	0.00212	0%	39%	61%
X	Indication C	22,888	0.00178	5%	4%	91%

e.g., QALY calculation for **X/Indication A**:

<20: 29,993 · 0.0619 · 0.1 = **185.66** QALYs gained
20-59: 29,993 · 0.0619 · 0.17 = **315.62** QALYs gained

≥60: 29,993 · 0.0619 · 0.73 = **1355.29** QALYs gained

These calculations are done for every age group, indication, product, country, and year in a Python script.

3.3 Socioeconomic Footprint Calculation

The Socioeconomic Footprint measures the socioeconomic benefits resulting from a healthier population when using a specific intervention in a chosen country and in a given year. One gained year of full working capability is translated into gained productivity.

i.e., 1 QALY gained = 1 year gained of full work capability = 1 year of productivity gain.

In addition to paid work direct productivity gains, indirect and induced paid effects are included in the analysis to show the impact this productivity potential has along the value chain. These are calculated using multipliers from input-output analysis. Furthermore, the value-added effects of unpaid work activities, such as cleaning, cooking, and childcare, that need to be outsourced by patients not able to perform them are also captured.

For the calculation of the Socioeconomic Footprint, the patients reached are divided into age groups: patients aged between 20 and 59 contribute to productivity gains from both paid and unpaid work; patients aged 60 and over are no longer considered part of the labour market and therefore contribute solely to productivity gains from unpaid work; patients under the age of 20 are assumed to contribute neither to productivity gains from paid work nor to productivity gains from unpaid work.

The Social Impact is expressed in monetary terms (such as US dollars) using GVA per economically active person within an economy.

See Section 5 below for the detailed calculations implemented for this analysis.

4 Socioeconomic Burden of Diseases

4.1 Health Burden Input Parameters

Disability Adjusted Life Years (DALYs) are the health outcomes used for the calculation of the health burden of a disease. For our analysis, DALYs by country, indication and age group are retrieved from the Institute for Health Metrics and Evaluation (IHME) using the new GBD data suite, with updated data extending to 2022 and forecasts reaching 2050 [6].

The IHME uses a hybrid approach to calculate DALYs after 2010, meaning that DALYs for the year in question are computed with the prevalence-based approach to estimate Years Lived with Disability (YLD) and the incidence-based approach to estimate Years of Life Lost (YLL).

Years of Life Lost is a measure of life expectancy and is calculated by multiplying the number of deaths due to a condition by the standard life expectancy at the age of death. The other measure is the number of YLD which is calculated by multiplying the prevalence of the condition by the disability weight of that specific condition.

$$YLL_{a,c,d} = N_{a,c,d} * L_{a,c,d}$$

$$YLD_{a,c,d} = I_{a,c,d} * DW_{a,c,d}$$

Where:

a = age, c = country, d = disease, N = number of deaths due to the condition, L = standard life expectancy at age of death, I = prevalence of a specific condition, DW = disability weight of specific condition.

The sum of YLL and YLD results in the overall DALY value for a given condition.

$$DALY_{a,c,d} = YLL_{a,c,d} + YLD_{a,c,d}$$

Where:

a = age, c = country, d = disease.

4.1.1 HER2+ Breast Cancer

DALYs for HER2+ Breast Cancer are missing from the IHME database and have therefore been estimated using a proportional allocation approach based on HER2+ prevalence among breast cancer cases.

DALYs for general Breast cancer are directly accessible from the IHME GBD database [6]. The American Cancer Society [7] reports that approximately 15% to 20% of breast tumours exhibit elevated levels of HER2. Leveraging this data, the general breast cancer DALYs were adapted to specifically capture the burden associated with HER2-positive patients. This refinement helped to approximate DALYs for HER2-positive breast cancer, which were then incorporated as a component in the overall analysis.

4.1.2 Multiple Sclerosis

DALYs for Multiple Sclerosis are directly available from the Global Burden of Diseases database, for all countries and years in scope and can be directly incorporated into the model.

4.1.3 Age-Related Macular Degeneration (AMD)

DALYs for Age-Related Macular Degeneration (AMD) are directly available from the Global Burden of Diseases database, for all countries and years in scope and can be directly incorporated into the model.

4.1.4 Diabetic Macular Edema (DME)

DALYs for Diabetic Macular Edema (DME) are missing from the IHME database and have therefore been estimated using a comparative approach based on the relationship between AMD and DME prevalence, leveraging available AMD DALYs from the IHME database.

AMD is a broad term that encompasses various stages of macular degeneration while DME is an accumulation of excess fluid in the extracellular space within the retina in the macular area.

To approximate the DALYs for DME, the approach focused on closely estimating DME prevalence by leveraging its connection to diabetes mellitus. DME is a complication that arises in individuals with diabetes, primarily due to the body's inability to regulate blood sugar levels effectively. Chronic hyperglycaemia leads to vascular damage, a key factor in the development of DME [8]. This link between diabetes and DME formed the basis for estimating DME prevalence by using data on diabetes mellitus prevalence.

Once the prevalence of DME was established, it was compared to the prevalence of AMD. Both DME and AMD are chronic, progressive eye diseases that affect the macula, resulting in similar symptoms, including central vision loss, blurriness, and distortion. Additionally, both conditions share similar treatment approaches [9], [10]. By understanding the ratio of DME to AMD prevalence within a population, it is possible to determine how frequently DME occurs relative to AMD. The ratio can be used to estimate the DALYs for DME from the DALYs for AMD.

The following is a detailed description of the systematic approach used:

1) Assignment of DME Prevalence by Income Level: Prevalence rates for DME were assigned to the different countries according to their income classification. Based on a study that calculated the prevalence of DME diagnosed via Optical Coherence Tomography (OCT) among individuals with diabetes, the prevalence was determined to be 5.81% for low-to-middle-income countries and 5.14% for high-income countries [11].
   - Country Classification by Income Level: Countries within the scope of the analysis were categorised in Upper Middle Income and High Income based on their income level.
2) Retrieval of Diabetes Mellitus and AMD Prevalences: Prevalence data for diabetes mellitus and AMD were sourced from IHME.
3) Calculation of DME Prevalences: The DME prevalence for each country was calculated by multiplying the DME prevalence rates (as determined by income level) with the corresponding diabetes mellitus prevalence in each country.

$$P_{DME,c,a} = P_{DM,c,a} * P_{DME|DM,c}$$

   Where:

   P = prevalence

   DME, c, a = prevalence of DME in a specific country and age-group

   DM, c, a = prevalence of diabetes mellitus in a specific country and age-group

   $DME \mid DM, country$ = proportion of diabetic patients who have DME, which is specific to an income level

4) Calculation of DME/AMD prevalence ratio: To assess the relative prevalence of DME compared to AMD, the DME prevalence rates were divided by the AMD prevalence rates, resulting in specific ratios for each country.

$$R_{DME|AMD,c,a} = \frac{P_{DME,c,a}}{P_{AMD,c,a}}$$

   Where:

P = prevalence

R = ratio

$DME \mid AMD, c, a$ = DME prevalence to AMD prevalence in a specific country and age-group

DME, c, a = prevalence of DME in a specific country and age-group
AMD, c, a = prevalence of AMD in a specific country and age-group.

5) Retrieval of AMD DALYs: DALYs for AMD were also obtained from IHME.
6) Estimation of DME DALYs: Finally, the DME DALYs were estimated by multiplying the calculated prevalence ratios by the AMD DALYs for each country.

$$DALY_{DME,c,a} = R_{DME|AMD,c,a} * DALY_{AMD,c,a}$$

Where:

$DALY$ = Disability-Adjusted Life Years

R = ratio

DME, c, a = DALY of DME in a specific country and age-group

$DME \mid AMD, c, a$ = DME to AMD ratio in a specific country and age-group

AMD, c, a = DALY of AMD in a specific country and age-group.

4.2 Health Burden Calculation

The health burden is quantified through total DALYs lost due to the specific disease, derived by aggregating age-specific DALYs across all relevant age groups (<20, 20-59, >60) for each country and year. This summation of age-stratified DALYs provides a comprehensive measure of the disease's impact, accounting for variations in disease burden across different age demographics of the affected population.

4.3 Socioeconomic Burden Calculation

Paid and Unpaid work are used to calculate the monetary value of productivity loss potential. Specifically for the paid work, DALYs are multiplied for the labour force participation rate obtaining the DALYs lost in economically active persons and then afterwards multiplied by the GVA per economically active person. For unpaid work, the average monetary value equivalent for unpaid work activities is estimated and then multiplied by the specific DALY value for the specific disease.

The detailed calculation steps are described in Section 5. In this analysis, DALYs are used as the multiplication factor instead of QALYs to quantify the health burden, providing a standardised measure of disease impact across populations and health conditions.

5 Socioeconomic Footprint

5.1 Background

The Socioeconomic Footprint measures the losses in productivity potential due to a disease – for the Socioeconomic Burden of diseases (SOB) – and the gains in the productivity potential associated with a healthier population due to the use of a medicine for the Social Impact of medicines (SI). This model directly builds on the results from the Health Footprint: once the health losses in terms of DALYs lost (for the SOB) or health benefits in terms of incremental QALYs gained (for the SI) are estimated stratified by year, country, medicine/indication (for the SI) or disease area (for the SOB), and age group, the Socioeconomic Footprint quantifies the productivity potential (lost or gained) linked with one DALY lost or one QALY gained, for the SOB and SI, respectively. The result is expressed in monetary terms applying GVA as a measure of labour productivity.

In this context, four different productivity effects are estimated:

1. **Direct effects of paid work:** A healthier and longer living population is able to participate in the labour market and thus contributes to economic welfare.
2. **Indirect effects of paid work:** An increase in economic activity further triggers production of intermediate goods and services in other industry sectors, creating the so-called indirect GVA effects. Indirect effects are effects arising due to the input an industry demands from other economic agents. Order placements result in an increase of economic activity at commissioned agents and their suppliers. This stimulus increases GVA and other economic figures along the value chain.
3. **Induced effects of paid work:** Additional income earned due to direct or indirect effects is in turn spent according to the propensity to consume, triggering further GVA effects along the value chain.
4. **Unpaid work:** Besides participating on the labour market, a healthier and longer living population is also able to perform unpaid work activities. While these activities are not measured in terms of national accounting, they contribute a considerable share to overall welfare ‘beyond GDP’ for the society. We approximate these welfare effects in monetary terms.

With the use of multipliers from input-output analysis, done at WifOR, to estimate indirect and induced GVA effects, the overall impact of a less productive (for the SOB) or a more productive patient population (for the SI) on a nation’s economy can be observed in a holistic way [12], [13].

To keep the estimate as robust as possible, no indirect and induced effects from unpaid work are included. Induced effects stem from direct or indirect income payments. Therefore, these effects will largely not take place in relation to unpaid work. There are some interactions between unpaid work and the economy that might be associated with indirect GVA effects, e.g., buying equipment needed to do unpaid work. However, further assumptions on the behaviour of those performing unpaid work in comparison to their market-equivalent would be necessary.

5.2 Socioeconomic Input Parameters Calculation

5.2.1 Socioeconomic Input Parameters

The socioeconomic input parameters are country specific. They are retrieved from official databases or statistical offices such as the World Bank Development Indicators [14] or the UN National Accounts Database [15]. They may need to be adjusted (e.g. convert the national currency into US dollars) or calculated for every country in the scope of the project. The following six input parameters are finally used to estimate the productivity effects:

- GVA per economically active person
- Labour force participation rate
- Indirect GVA multiplier (Economy average)
- Induced GVA multiplier (Economy average)
- Time adjustment ratio (unpaid/paid)
- GVA adjustment ratio (unpaid/paid)

When searching for inputs, different databases are queried in order of priority to minimise data gaps (missing data). In some cases, if no information is available for a country, proxy countries are used to substitute missing data.

To select the most appropriate proxy country, the data availability of the potential proxy country, geographical distance from the country under investigation, similarity in economic development (GDP per capita), and similarity in the Human Development Index (a measure of achievements in dimensions of human development, such as life expectancy at birth, education, and standard of living) are considered.

Each of the six input parameters is described in the following section and the sources from which they are drawn are specified. These inputs are used to calculate productivity effects mentioned above. Final productivity effects may be found in the Appendix (**Table 8**).

5.2.2 GVA per Economically Active Person

The average annual GVA per economically active person is used as a measure of labour productivity in a given country. To obtain this input, we divide the total GVA at basic prices measured in current USD ($GVA_{c,t}$) by the size of the labour force ($L_{c,t}$) in the respective country (c) and year (t):

$$GVA\ per\ economically\ active\ person_{c,t} = \frac{GVA_{c,t}}{L_{c,t}}$$

The following sources are used to retrieve total GVA (in descending priority):

- World Bank Development Indicators in t [14]
- World Bank Development Indicators in t-1 [14]
- UN National Accounts Database in t-1 [15]

- National statistical office of a given country c (most recent data)

The following sources are used to retrieve the size of the labour force (in descending priority):

- World Bank Development Indicators in t [14]
- National statistical office of a given country c (most recent data)

5.2.3 Labour Force Participation Rate

The following sources are used to retrieve the labour force participation rate in the respective country (c) and year (t) (in descending priority):

- World Bank Development Indicators in t [14]
- National statistical office of a given country c

The labour force participation rate may be reported separately for different age groups or as one summary measure, e.g., for people aged 15 and older as the working age population. Depending on availability, we select the data that best correspond to the included age groups and, if necessary, adjust the labour force participation rate based on additional information.

5.2.4 Total Economy Average GVA Multiplier for Indirect Effects

By means of an input-output analysis indirect GVA and direct GVA effects are determined. The indirect GVA multiplier describes the ratio of indirect to direct GVA and is used to determine average indirect GVA effects associated with paid work.

$$Total\ Economy\ Average\ multiplier\ indirect\ _c = \frac{\sum_{j=1}^{n}\left(GVA_{c,j} * indirect\ multiplier_{c,j}\right)}{\sum_{j=1}^{n} GVA_{c,j}}$$

Where:

$indirect\ multiplier_{c,j}$ is the indirect multiplier in sector j and in the corresponding country.

The following sources are used to retrieve the information to calculate the indirect GVA multiplier for the total economy (in descending priority):

- WIOD (World Input-Output Database) country c [13]
- EORA country c [12]
- WIOD proxy country
- EORA proxy country

5.2.5 Total Economy Average GVA Multiplier for Induced Effects

Similarly to the economy-wide average GVA multiplier for indirect effects, the induced GVA multiplier describes the ratio of induced to direct GVA and is used to determine the average

induced GVA effects in connection with paid labour. Similarly to direct and indirect GVA effects, induced GVA effects are also determined using an input-output analysis.

$$Total\ Economy\ Average\ multiplier\ induced\ _c = \frac{\sum_{j=1}^{n}\left(GVA_{c,j} * induced\ multiplier_{c,j}\right)}{\sum_{j=1}^{n} GVA_{c,j}}$$

Where:

$induced\ multiplier_{c,j}$ is the induced multiplier in sector j and in the corresponding country.

The following sources are used to retrieve the information to calculate the induced GVA multiplier for the total economy (in descending priority):

- WIOD country c
- EORA country c
- WIOD proxy country
- EORA proxy country

5.2.6 Time Adjustment Ratio (Unpaid / Paid Work)

No statistics or similar on the value contribution of one year of unpaid work exist. Therefore, to approximate a labour productivity value for unpaid work, the paid work productivity is adjusted by the time spent on unpaid work activities relative to paid work activities. This time adjustment ratio is calculated by dividing the gender weighted unpaid working hours by the gender weighted paid working hours:

$$Time\ use\ ratio_{c,t} = \frac{\left[\left(\frac{P_{c,t,m}}{P_{c,t}}\right) * WHU_{c,m}\right] + \left[\left(\frac{P_{c,t,f}}{P_{c,t}}\right) * WHU_{c,f}\right]}{\left[\left(\frac{P_{c,t,m}}{P_{c,t}}\right) * WHP_{c,m}\right] + \left[\left(\frac{P_{c,t,f}}{P_{c,t}}\right) * WHP_{c,f}\right]}$$

Where:

$P_{c,t,m}$ is the male (m) population in the corresponding country and year

$P_{c,t}$ is the population in the corresponding country and year

$P_{c,t,f}$ is the female (f) population in the corresponding country and year

$WHU_{c,m}$ are the unpaid working hours for males in the corresponding country

$WHU_{c,f}$ are the unpaid working hours for females in the corresponding country

$WHP_{c,m}$ are the paid working hours for males in the corresponding country

$WHP_{c,f}$ are the paid working hours for females in the corresponding country

The following sources are used to retrieve the working hours (in descending priority):

- United Nations time use survey country c [16]
- National statistical office of a given country c

- United Nations time use survey proxy country

The following sources are used to retrieve the population sizes (in descending priority):

- World Bank in t
- National statistical office of a given country c in t

Time use statistics may be reported separately for different age groups or as one summary measure, e.g., including all legal adults who do not live in communal accommodation. Depending on availability, we select the data that best correspond to the included age groups.

5.2.7 GVA Adjustment Ratio (Unpaid / Paid Work)

If only the time adjustment ratio were used, it would be assumed that one hour of unpaid work is associated with the same average labour productivity as one hour of paid work. However, as unpaid work consists of a specific set of activities that have below average labour productivity in many countries, e.g., because childcare occupations are paid less, this would not correspond to the idea of the replacement cost approach to monetise unpaid work. We thus adjust the average GVA per economically active person by setting the labour productivity of paid work activities which are comparable to unpaid work activities[1] in relation to the average labour productivity in the overall economy. This serves as a proxy of the relative value contribution of unpaid work activities and paid work activities.

We use GVA and employment data for the economic sector "Activities of households as employers" and for the overall economy from the WIOD and EORA databases. These data are available up to the year 2016.

$$GVA\ per\ employee\ sector\ HH_{c,t} = \frac{\left(\frac{GVA\ Sector\ HH_c}{\sum_{j=1}^{n} GVA_{c,j}}\right) * GVA_{c,t}}{\left(\frac{L\ Sector\ HH_c}{\sum_{j=1}^{n} L_{c,j}}\right) * L_{c,t}}$$

Where:

$GVA\ Sector\ HHc$ is the GVA in the sector representing households as employers in the corresponding country in 2016

j=1$nGVAc,j$ is the sum of GVA over all sectors (j) in the corresponding country in 2016

$GVAc,t$ is the GVA in the corresponding country and year

$L\ Sector\ HHc$ is the labour force in the sector representing households as employers in the corresponding country in 2016

$\sum_{j=1}^{n} L_{c,j}$ is the sum of the labour force over all sectors in the corresponding country in 2016

$L_{c,t}$ is the labour force in the corresponding country and year.

[1] Defined by the sector of "Activities of Households as Employers; Undifferentiated Goods and Services Producing Activities of Households for Own Use" according to the International Standard Industrial Classification revision 4 (ISIC Rev. 4) used in the WIOD database or the Eora26 sector classification used in the EORA database.

The following sources are used for the inputs to calculate the GVA adjustment ratio (in descending priority):

- WIOD country c
- EORA country c
- WIOD proxy country
- EORA proxy country

Setting this into relation to the average GVA contribution in the overall economy, we calculate a ratio indicating the estimated (hypothetical) GVA contribution of unpaid work activities relative to paid work activities:

$$GVA\ ratio_{c,t} = \frac{GVA\ per\ economically\ active\ person\ HH_{c,t}}{GVA\ per\ economically\ active\ person_{c,t}}$$

5.2.8 Economic forecast

To forecast paid and unpaid GVA effects, socioeconomic parameters for the base case year are multiplied by a growth rate for the single consecutive years. Growth rates are calculated based on country-specific data on "gross domestic product per capita, current prices". Data is obtained from the International Monetary Fund [17] and is available for 8 consecutive years (e.g., the query in October 2023 resulted in data for the years 2021 to 2028).

Growth rates always refer to a base case year and are calculated as follows:

$$Growth\ rate\ (year\ x) = 1 + \frac{GDP\ per\ capita\ (year\ x) - GDP\ per\ capita\ (basecase\ year)}{GDP\ per\ capita\ (basecase\ year)}$$

If growth rates are to be calculated for years in which no GDP-data is available from the World Economic Outlook Database, the growth rate is left constant and calculated as follows:

$$\begin{aligned} &Growth\ rate\ (year\ x) \\ &\quad = Growth\ rate\ (year\ x-1) \\ &\quad \times \left(1 + \frac{GDP\ per\ capita\ (year\ y) - GDP\ per\ capita\ (year\ y-1)}{GDP\ per\ capita\ (year\ y-1)}\right) \end{aligned}$$

Where:

$year\ x$ is the year for which the growth rate should be calculated.

$year\ y$ is the last year for which GDP per capita data are available.

Even if the base case year should be larger than the last available values, the growth rate is always calculated using the last available values for GDP per capita. The final calculated growth rates may be found in **Table 9**.

5.3 Socioeconomic Footprint Calculation

The Socioeconomic Footprint, Socioeconomic Burden (SOB) or Social Impact (SI), in the scope of this project, comprises four different productivity effects that are linked with the DALYs or QALYs gained, for the SOB or SI, respectively:

- Direct effects of paid work
- Indirect effects of paid work
- Induced effects of paid work
- Direct effects of unpaid work

These four different productivity effects are calculated for every country in scope and respective year. An overview of the final values is given in **Table 8**.

To calculate the monetary value of productivity potential in paid work (direct effects of paid work), the DALYs lost or QALYs gained are multiplied first with the labour force participation rate. These DALYs lost or QALYs gained in economically active persons are then multiplied with the average annual labour productivity (GVA per economically active person):

$$Direct\ paid\ work\ effects_{m,i,c,t,a} = DALYs\ lost_{d,c,t,a} * labor\ force\ participation\ rate_{c,t} * GVA\ per\ economically\ active\ person_{c,t}$$

$$Direct\ paid\ work\ effects_{m,i,c,t,a} = QALYs\ gained_{m,i,c,a} * labor\ force\ participation\ rate_{c,t} * GVA\ per\ economically\ active\ person_{c,t}$$

Where:

m = medicine, d = disease, i = indication, c = country, t = time, a = age group.

Subsequently, further potential productivity effects within the economy triggered along the value chain by the initial (direct) effects are estimated. These indirect and induced effects associated with paid work productivity potential are calculated by multiplying the direct effects with the respective GVA multiplier from input-output analysis.

To derive the (hypothetical) monetary value of productivity potential in unpaid work, first, the average monetary value equivalent for unpaid work activities is estimated. This is based on the average annual labour productivity of paid work (GVA per economically active person) and then adjusted to reflect differences in terms of time spent and differences in terms of GVA contribution (value creation) between paid and unpaid work activities.

- The time adjustment ratio gives an estimate of how much time is spent for unpaid work activities for each hour of paid work activities.
- The GVA adjustment ratio adjusts for the below average GVA contribution of unpaid work activities.

The estimate of the monetary value equivalent of one year of unpaid work activities is then calculated by multiplying the annual GVA per economically active person by the two adjustment factors:

$$Monetary\ value\ equivalent\ of\ unpaid\ work_{c,t} = GVA\ per\ economically\ active\ person_{c,t} * Time\ adjustment\ ratio_{c,t} * GVA\ adjustment\ ratio_{c,t}$$

Where:

c = country and t = time.

Finally, the DALYs lost or QALYs gained are multiplied with the estimated monetary value equivalent of one year of unpaid work:

$$GVA\ unpaid_{m,i,c,t,a} = DALYs\ lost_{d,t,c,a} * Monetary\ value\ equivalent\ of\ unpaid\ work_{c,t}$$

$$GVA\ unpaid_{m,i,c,t,a} = QALYs\ gained_{m,i,c,a} * Monetary\ value\ equivalent\ of\ unpaid\ work_{c,t}$$

Input data, such as the labour force participation rate or the time spent on unpaid work, are always given for a defined age group and represent an average value. However, the average age and other relevant characteristics of patients treated with Roche products may differ from the average age and characteristics of people to whom the input data relate. Therefore, the input data can only serve as an approximation in our analysis.

The monetisation of productivity potential associated with one QALY gained for (direct) paid and unpaid work is summarised in **Figure 10**.

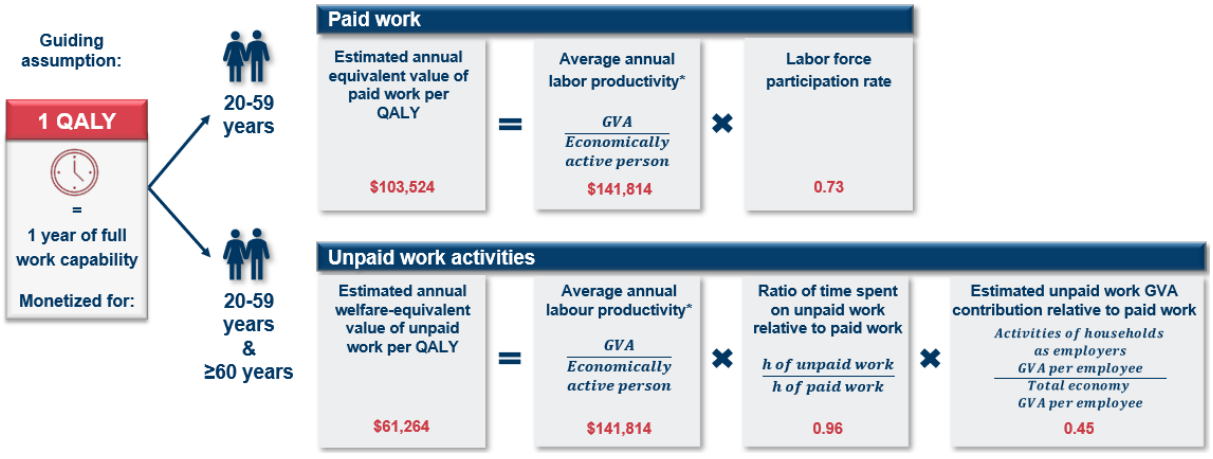

Figure 10: Illustration of the (direct) monetisation of one QALY gained. Exemplary numbers.

The total Social Impact or Socioeconomic Burden are calculated for each age group separately. The resulting $SI_{c,m,i,a}$ and $SOB_{c,d}$ are summed up by product and country to result in the $SI_{c,m}$ and $SOB_{c,d}$.

$$SOB_{c,d} = \sum_{i=1}^{n} SOB_{c,d<20} + SOB_{c,d,20-59} + SOB_{c,d,\geq 60}$$

$$SI_{c,m} = \sum_{i=1}^{n} SI_{c,m,i,<20} + SI_{c,m,i,20-59} + SI_{c,m,i,\geq 60}$$

Note: In our current methodology, any patient that may fall in the <20 age group does not contribute to the Social Impact of medicines, as this patient is assumed not to be productive.

The total QALYs gained or DALYs lost per country and product are derived accordingly:

$$DALY_{c,d} = \sum_{i=1}^{n} DALY_{c,d,<20} + DALY_{c,d,20-59} + DALY_{c,d,\geq 60}$$

$$QALY_{c,m} = \sum_{i=1}^{n} QALY_{c,m,i,<20} + QALY_{c,m,i,20-59} + QALY_{c,m,i,\geq 60}$$

6 Model Implementation

The implementation of the Socioeconomic Burden of Diseases (SOB) and the Social Impact of Medicines (SI) model consists of two parts:

a) an Excel input data collection/database that further processes and performs some of the calculations and b) a python script performing the final sets of calculation. The latter is more appropriate for large data sets, whereas the former can be easily facilitated for small amounts of data (table sizes).

The output of the python script is a granular table showing the SI per the evaluation year, the product and the country as well as the age group and the indication.

The implementation of the SOB follows the same logic and the output of the python is a granular table showing the SOB per the evaluation year, the disease area and the country as well as the age group.

A thorough quality control and multiple checks are done in all and every step of the analysis.

7 Assumptions and Limitations

The input data are always given for a defined population with certain characteristics (e.g. age distribution or country) and represent averages of that population. However, the relevant characteristics of patients treated with Roche's products may differ from the characteristics of the individuals to whom the input data refer. Therefore, the input data can only serve as an approximation in our analysis, and differences between treated and general population should be considered.

7.1 Assumptions

7.1.1 QALY-Related

- One Quality Adjusted Life-Year (QALY) is equivalent to one person-year of full work capability for both paid and unpaid work activities.
- Medicines' indications are the same in all countries. If different dosage forms exist, they are not differentiated in the analysis.
- QALY values used in the analysis are the same across countries and remain constant throughout the years.
- The comparator used for the incremental QALY calculation is the same across countries and throughout the years.

7.1.2 DALY-Related

- One Disability Adjusted Life Year (DALY) equals the loss of one year in full health. The loss of one year in full health is translated into a loss of one year of full working capability for both paid and unpaid work activities.
- Burden in the future years is assumed to be as important as in the current year. This is the reason why no discounted DALYs were used.
- HER2+ breast cancer DALY burden is directly proportional to prevalence.
- HER2+ breast cancer and other breast cancer subtypes have similar severity, progression, and health outcomes.
- Age and demographic profiles of HER2+ patients are similar to other subtypes.
- The population affected by HER2+ and general breast cancer are homogeneous meaning comparable in terms of demographic factors such as age, comorbidities, and access to care.
- HER2+ breast cancer prevalence is stable over time.
- DME and AMD contribute in a similar way to loss of mortality and morbidity on a per-case basis.
- The population affected by AMD and DME are homogeneous meaning comparable in terms of demographic factors such as age, comorbidities, and access to care.
- Disease characteristics of AMD and DME are stable and similar enough that their DALYs can be estimated based on prevalence alone.

7.1.3 PR-Related

- The Patients Reached (PR) per indication, medicine and country, as obtained, represent on-label validated figures.

- Patients under 20 years of age do not contribute to the society by neither paid nor unpaid work, whereas patients aged 60 and over only contribute through unpaid work. The patient group of 20-59 contribute to both paid and unpaid work. This is the same across all countries.
- The average patient shares the same economic profile of the population's average person, e.g., the amount of time spent working.

7.1.4 Socioeconomic Inputs-Related

- The monetary value equivalent of one year of full work capability or productivity potential in paid work is adequately represented by the average labour productivity of the economically active population in a country, expressed by GVA per economically active person.
- This analysis applies the human capital approach to measure productivity losses. The human-capital method takes the patient's perspective and counts any hour not worked as an hour lost. By contrast, the friction-cost method takes the employer's perspective, and only counts as lost those hours not worked until another employee takes over the patient's work [18].
- The monetary value equivalent of one year of full work capability or productivity potential in unpaid work is adequately represented by the average labour productivity of the economically active population adjusted by:
    - a factor indicating the amount of time spent on unpaid work activities relative to paid work activities.
    - a factor indicating the extent of GVA associated with unpaid work activities relative to paid activities.
- Certain socioeconomic inputs, such as the size of the labour force, are not available for the precise age groups of our model. It is assumed that there is no relevant difference in these input parameters for slight variations in age.

7.2 Limitations

7.2.1 QALY-Related

- QALYs gained are not directly linked to productivity gain for all diseases in the same way, as for example, a product may increase life expectancy but not QoL.
- The Social Impact of Medicines represents an annual snapshot, as all inputs pertain to the given year. Annual QALYs represent the average QALYs gained per year, thus, the difference in acute or chronic disease and of curative or therapeutic treatments is not fully captured.

- The model assumes that QALYs gained over a certain period of time is the same regardless of when patients started on therapy (i.e. QALY gains between ages 60-100 are the same in patients who start therapy at 20 as in patients who start at 60).
- The health gains reported for a studied population do not necessarily provide a perfect depiction of the target population in the country, drug and indication in question. QALY estimates per patient and year do not differ across countries.
- The strength and dosage form of the medicines are not taken into consideration.
- As the medicines' indications included are not country-specific, the outcome may not represent the actual country-specific situation.
- The choice of the comparator (SoC) is crucial. Moreover, it may change over the course of time or may be different from country to country. These are not captured in the approach. In addition, issues arise when the product is part of the current SoC.

7.2.2 DALY-Related

- DALYs are not directly linked to productivity gain for all diseases in the same way, as DALYS may be determined by a high degree of disability or, particularly in the case of fatal diseases, primarily by premature death.
- Breast cancer HER2+ prevalence might vary across countries and time.
- Treatment response, access to care, comorbidities, and demographic differences are not taken into account for the DME and HER2+ DALY calculations.
- Mortality rate of HER2+ breast cancer might differ from general breast cancer.
- DME prevalence might vary across countries.
- DME and AMD might have different disease progression, disability and mortality.
- DME and AMD might have different age and comorbidity profile.

7.2.3 PR-Related

- Patients reached estimates are performed by Roche, based on methodologies used for Periodic Benefit-Risk Evaluation Reporting to regulatory bodies. Off-label use, early access and parallel export are not taken into account.
- From one country to another the therapeutic guidelines/clinical practice and reimbursement criteria may be different, thus the use of the product across the different indications might not be the same.
- New treatment alternatives might reduce the value of established medicines, but this can only be considered, if new economic evaluations are performed.
- PR are distributed across the three age groups based on proportional prevalence that reflects disease epidemiology and not necessarily the label, therefore the Social Impact

might be overestimated if more patients treated are in the non-working age groups compared to the disease epidemiology.

7.2.4 Socioeconomic Inputs-Related

- The monetary gains are expressed in a common currency (USD) but can only hardly be compared across countries by reason of purchasing power differences.
- The average age and age distribution of patients treated with Roche products may differ from the average age of the groups of people from the input data.
- Patients treated with Roche products may differ from the groups of people from the input data in productivity-related characteristics.

8 Appendix

Table 7: Proportional prevalences per country and indication

Indication	Source	Age group		
		<20	20-59	≥60
Brazil				
Multiple sclerosis*	GBD	0.0091	0.6925	0.2983
Breast cancer**	GBD	0.0011	0.5642	0.4347
nAMD	GBD	0.0000	0.1200	0.8800
Diabetes mellitus***	GBD	0.0093	0.4845	0.5062
Canada				
Multiple sclerosis*	GBD	0.0069	0.6318	0.3613
Breast cancer**	GBD	0.0002	0.3280	0.6719
nAMD	GBD	0.0000	0.0520	0.9480
Diabetes mellitus***	GBD	0.0104	0.3386	0.6510
China				
Multiple sclerosis*	GBD	0.0197	0.7857	0.1946
Breast cancer**	GBD	0.0006	0.5641	0.4353
nAMD	GBD	0.0000	0.0962	0.9038
Diabetes mellitus***	GBD	0.0030	0.5613	0.4357
France				
Multiple sclerosis*	GBD	0.0086	0.6322	0.3592
Breast cancer**	GBD	0.0003	0.3235	0.6763
nAMD	GBD	0.0000	0.0422	0.9578
Diabetes mellitus***	GBD	0.0117	0.3154	0.6729
Germany				
Multiple sclerosis*	GBD	0.0069	0.6355	0.3576

Breast cancer**	GBD	0.0001	0.3047	0.6952
nAMD	GBD	0.0000	0.0483	0.9517
Diabetes mellitus***	GBD	0.0042	0.3257	0.6701
Italy				
Multiple sclerosis*	GBD	0.0125	0.5999	0.3876
Breast cancer**	GBD	0.0002	0.3410	0.6588
nAMD	GBD	0.0000	0.0467	0.9533
Diabetes mellitus***	GBD	0.0045	0.3027	0.6928
Japan				
Multiple sclerosis*	GBD	0.0082	0.5127	0.4790
Breast cancer**	GBD	0.0002	0.3231	0.6767
nAMD	GBD	0.0000	0.0308	0.9692
Diabetes mellitus***	GBD	0.0061	0.3057	0.6883
Spain				
Multiple sclerosis*	GBD	0.0089	0.6406	0.3505
Breast cancer**	GBD	0.0003	0.3929	0.6067
nAMD	GBD	0.0000	0.0549	0.9451
Diabetes mellitus***	GBD	0.0054	0.3409	0.6537
United Kingdom				
Multiple sclerosis*	GBD	0.0048	0.6669	0.3283
Breast cancer**	GBD	0.0002	0.3481	0.6517
nAMD	GBD	0.0000	0.0507	0.9493
Diabetes mellitus***	GBD	0.0062	0.4329	0.5608
United States				
Multiple sclerosis*	GBD	0.0077	0.6746	0.3178
Breast cancer**	GBD	0.0002	0.3143	0.6855
nAMD	GBD	0.0000	0.0484	0.9516
Diabetes mellitus***	GBD	0.0080	0.3694	0.6225

*All multiple sclerosis related indications used multiple sclerosis proportional prevalence

**All breast cancer related indications used breast cancer proportional prevalence

***Diabetes mellitus was used as a proxy of DME

Table 8: Productivity effects per country

	Direct effects of paid work	Indirect effects of paid work	Induced effects of paid work	Unpaid work
Brazil	$ 10,537.87	$ 6,647.49	$ 6,012.99	$ 1,682.12
Canada	$ 67,144.97	$ 40,357.30	$ 37,549.23	$ 41,950.32
China	$ 16,724.20	$ 26,769.99	$ 6,176.32	$ 9,190.60
France	$ 60,050.54	$ 35,541.29	$ 24,163.37	$ 26,581.84
Germany	$ 68,617.80	$ 42,779.48	$ 25,550.40	$ 11,349.55
Italy	$ 48,171.49	$ 34,792.32	$ 22,051.48	$ 11,763.56
Japan	$ 56,909.34	$ 36,960.93	$ 45,072.56	$ 24,436.23
Spain	$ 39,908.72	$ 25,410.52	$ 20,388.90	$ 13,746.74
United Kingdom	$ 62,482.94	$ 39,114.58	$ 42,465.80	$ 51,224.33
United States	$ 98,355.07	$ 63,356.95	$ 87,624.69	$ 47,685.48

Table 9: Growth rates per year and country

	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
Brazil	1.10	1.17	1.21	1.26	1.33	1.41	1.49	1.58	1.67	1.76
Canada	0.97	1.01	1.05	1.09	1.12	1.16	1.19	1.23	1.27	1.31
China	0.99	1.04	1.11	1.18	1.25	1.33	1.40	1.49	1.58	1.67
France	1.09	1.14	1.18	1.22	1.25	1.29	1.32	1.35	1.39	1.42
Germany	1.08	1.15	1.21	1.27	1.30	1.34	1.38	1.42	1.46	1.50
Italy	1.09	1.14	1.19	1.23	1.27	1.30	1.34	1.38	1.43	1.47
Japan	1.00	1.02	1.08	1.13	1.18	1.23	1.28	1.33	1.38	1.44
Spain	1.11	1.17	1.22	1.26	1.29	1.33	1.36	1.40	1.44	1.48
United Kingdom	1.08	1.15	1.23	1.30	1.38	1.46	1.54	1.63	1.72	1.82
United States	1.05	1.09	1.12	1.16	1.21	1.25	1.29	1.34	1.38	1.43

References

[1] D. E. Bloom, ‘HEALTH AND ECONOMIC GROWTH: RECONCILING THE MICRO AND MACRO EVIDENCE’. 2022. [Online]. Available: https://www.nber.org/system/files/working_papers/w26003/w26003.pdf

[2] D. A. Ostwald *et al.*, ‘If We Can’t Measure It, We Can’t Fix It - A Report to the G20 Presidency and B20 Health Taskforce’, WifOR, 2021. [Online]. Available: https://www.wifor.com/uploads/2021/05/G20_Health_Metrics_ROI_G20_B20.pdf

[3] V. H. C. VBA HEALTH CLUSTER, ‘Social Impact of Innovative Medicine’. 2024. [Online]. Available: https://www.value-balancing.com/_Resources/Persistent/0/f/c/8/0fc88eb0dd10585713d7a309ea3ba19865c7c22d/240304_VBA-Health-Cluster.pdf

[4] M. Reid, ‘Economics of Household Production’, *The ANNALS of the American Academy of Political and Social Science*, vol. 178, no. 1, pp. 213–213, Mar. 1935, doi: 10.1177/000271623517800149.

[5] ‘Disability Adjusted Life Years - an overview | ScienceDirect Topics’. Accessed: Nov. 14, 2024. [Online]. Available: https://www.sciencedirect.com/topics/medicine-and-dentistry/disability-adjusted-life-years

[6] A. J. Ferrari *et al.*, ‘Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021’, *The Lancet*, vol. 403, no. 10440, pp. 2133–2161, May 2024, doi: 10.1016/S0140-6736(24)00757-8.

[7] American Cancer Society, ‘Breast Cancer HER2 Status’. [Online]. Available: https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html

[8] D. Browning, M. Stewart, and C. Lee, ‘Diabetic macular edema: Evidence-based management’, *Indian J Ophthalmol*, vol. 66, no. 12, p. 1736, 2018, doi: 10.4103/ijo.IJO_1240_18.

[9] L. Ferro Desideri, C. E. Traverso, M. Nicolò, and M. R. Munk, ‘Faricimab for the Treatment of Diabetic Macular Edema and Neovascular Age-Related Macular Degeneration’, *Pharmaceutics*, vol. 15, no. 5, p. 1413, May 2023, doi: 10.3390/pharmaceutics15051413.

[10] E. A. Lundeen *et al.*, ‘Trends in the Prevalence and Treatment of Diabetic Macular Edema and Vision-Threatening Diabetic Retinopathy Among Commercially Insured Adults Aged <65 Years’, *Diabetes Care*, vol. 46, no. 4, pp. 687–696, Apr. 2023, doi: 10.2337/dc22-1834.

[11] J. H. B. Im, Y.-P. Jin, R. Chow, and P. Yan, ‘Prevalence of diabetic macular edema based on optical coherence tomography in people with diabetes: A systematic review and meta-analysis’, *Survey of Ophthalmology*, vol. 67, no. 4, pp. 1244–1251, Jul. 2022, doi: 10.1016/j.survophthal.2022.01.009.

[12] M. Lenzen, K. Kanemoto, D. Moran, and A. Geschke, ‘Mapping the structure of the world economy’, *Environmental Science & Technology*, vol. 46, no. 15, pp. 8374–8381, 2012.

[13] M. P. Timmer, E. Dietzenbacher, B. Los, R. Stehrer, and G. de Vries, ‘An Illustrated User Guide to the World-Input-Output Database: the Case of Global Automotive Production’, *Review of International Economics*, vol. 23, no. 3, 2015.

[14] The World Bank, ‘World Development Indicators’. [Online]. Available: https://databank.worldbank.org/source/world-development-indicators

[15] United Nations, ‘National Accounts - Analysis of Main Aggregates (AMA)’. [Online]. Available: https://unstats.un.org/unsd/snaama/index

[16] United Nations (UN), Statistics Division, ‘Time Use Data Portal. Collection of National Time Use Surveys’. [Online]. Available: https://unstats.un.org/unsd/gender/timeuse/

[17] IMF, ‘World Economic Outlook Database: October 2021’, World Economic Outlook Database. Accessed: Mar. 25, 2022. [Online]. Available: https://www.imf.org/en/Publications/WEO/weo-database/2021/October

[18] W. B. van den Hout, ‘The value of productivity: human-capital versus friction-cost method’, *Annals of the Rheumatic Diseases*, vol. 69, no. Suppl 1, pp. i89–i91, Jan. 2010, doi: 10.1136/ard.2009.117150.

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