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# Evaluation of the Societal Burden of Rare Diseases in the United States

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# Abstract

Background

Most patients with rare diseases have no effective treatment or cure available to them. However, scarcity of data and disease complexity mean the full extent of the patient, family and social burden of rare diseases remains undocumented. Understanding the cost drivers and the economic impact that a lack of treatment poses is critical for highlighting the unmet need to inform future investments and policymaking.

Methods

We selected five priority therapeutic areas (TAs; metabolic, neurological, congenital, hematological and immunological) encompassing 227 well documented rare diseases. Discussions with patients and physicians identified the 24 most relevant (highest unmet need) diseases within the five TAs. We assessed direct (costs associated with medical care), indirect (costs related to productivity losses) and mortality (costs associated with loss of life) costs. We also assessed these costs for 24 chronic mass-market (MM) diseases. Based on the overall cost burden per patient per year (PPPY) for the rare diseases, a scenario analysis was conducted to assess the average cost if treatments were not available. Lastly, the findings from the initial 24 rare diseases were extrapolated to 227 rare diseases in the five TAs.

Results

The average cost burden of the 24 diseases analyzed ranged from $121 000 to $334 000 PPPY compared with $26 000 PPPY for MM diseases. Averaging across selected rare diseases, lack of treatment was associated with a 21.2% increase in total costs, from $198 000 to $240 000 PPPY. When these results were extrapolated to 227 rare diseases belonging to the five TAs, similar results were obtained: the average cost of rare diseases was approximately 10 times higher ($266 000 PPPY vs $26 000 PPPY) than for the MM diseases.

Conclusions

Our findings demonstrate that rare diseases impose substantial economic burden, which remains high even when treatments are available. However, the cost composition shifts towards medical care and away from other types of burden. To the extent that new treatments provide clinical benefit for patients and their families, these shifts in burden are likely productive. Accelerated progress in the development of diagnostic methods, treatments and updated regulatory frameworks for rare diseases are recommended.


# Introduction

In the United States (US), rare diseases are defined as those affecting fewer than 200 000 people [1]. Collectively, it is estimated that approximately 30 million patients in the US are affected by more than

7000 rare diseases [2]. 70% of rare diseases are pediatric onset, and it is estimated that 95% of rare diseases have no specific treatment or curative options.

Because of the rarity of each disease, very little is known about the underlying causes and natural history of the diseases. Indeed, an international working group of experts identified lack of familiarity with rare diseases, the heterogeneous nature of the diseases themselves, non-specific diagnostic criteria, and geographic variation as key challenges in disease recognition and diagnosis [3]. Furthermore, disease rarity is also a challenge when recruiting patients for clinical trials, which hampers the generation of robust evidence for treatment guideline development and reimbursement assessments [3]. Overall, this lack of information on the natural progress of these diseases results in a lack of effective treatment options, corroborated by the fact that disease-specific treatments are only available for ~5–7% of patients [4, 5].

The US, European Union member countries and others have established legislation and policies to incentivize development of new drugs for rare diseases that have none and for those rare diseases that do not respond to current treatments [6-8]. The first of these approaches was the Orphan Drug Act of 1983 (ODA), a set of policies intending to resolve market failures in for profit companies wanting to invest in these treatments due to low market size and therefore low expected revenue [9]. The ODA fueled the development of ~400 drugs between 2010 and 2018 for rare disease indications [10]. Despite the rapid increase in the number of new orphan drugs over the last 10 years [11], many important therapy areas remain underserved. Indeed, some of these designations are for drugs that are predominantly used to treat non-orphan conditions [12]. Furthermore, a significant proportion of new orphan indications granted between 2015 and 2019 were for rare cancer treatments [13]. Finally, a previous analysis of pediatric indications revealed that in a sample of 31 pediatric orphan indications for drugs exclusively for the treatment of rare diseases, 25 were for age- or biomarker-based subsets of rare diseases for which the drug was already approved [10].

To better understand the current economic burden of rare diseases, empirical studies are needed. A recent report from the Every Life Foundation discussed the social costs of rare diseases based on insurance claims information and a survey that explored patient and family burden [14]. This report estimated that the total economic burden associated with rare diseases in the US was approximately $1 trillion in 2019 [14]. Importantly, this study did not include an estimate of the costs associated with mortality.

Here we present an estimate of direct (costs directly attributable to patient care), indirect (patients and caregivers' loss of productivity and lost resource value as a result of disease morbidity) and mortality-related costs for 24 rare diseases and evaluate burden of care both when treatment is available and when no treatment exists. We also compared these costs with chronic mass market (MM) diseases to highlight the need to better serve individuals with rare diseases.

# Methods

# Identification of rare diseases

The identification of rare diseases for inclusion in this analysis required the synthesis of top-down and bottom-up evidence generation approaches. In the top-down approach, a database was created based on a review of more than 500 published articles and lists in relevant databases including: Orphanet, the Genetic and Rare Diseases Information Center, the National Organization for Rare Diseases (NORD) and the National Institutes of Health. The selections were also directly discussed with the IQVIA centers of excellence, several patient advocacy groups, and therapy area experts from 15 institutions (Additional file 1: Table S1). This top-down approach yielded a list of 373 rare diseases, covering approximately 8.4 million patients with rare diseases, which served as the basis for the analysis (Fig. 1).

Owing to time and data constraints, it was not possible to evaluate 373 rare diseases in detail. Therefore, we augmented the top-down approach with a bottom-up approach to identify priority therapeutic areas (TAs) and indications according to patient advocacy groups and scientific experts engaged in the development of new treatments for rare diseases. This assessment was augmented by information from IQVIA and external expert interviews. Based on this work, 24 diseases were prioritized for our analysis. Some of the criteria used for selecting these diseases included:

- degree of unmet need
- relative importance to patient advocacy groups
- interest in the scientific community
- prevalence
- apparent burden of disease

These 24 diseases belonged to five TAs: metabolic, neurological, congenital, hematological and immunological, and included diseases that have therapies and those with no current treatments (beyond symptomatic treatments). Given the criteria used, our assessment was biased toward high unmet need diseases. This final group of 24 high unmet need rare diseases impacts approximately 584 000 patients in the US (Fig. 1; Additional file 2: Table S2).

# Cost sources

This analysis employed a medical care and societal perspective. The overall cost burden of rare diseases was inclusive of costs related to direct medical expenses, indirect costs attributed to the rare disease and mortality costs derived from the annualized value of statistical life (VSL). The US Department of Health and Human Services 2016 defines VSL as the rate at which the individual substitutes money for reductions in current mortality [15]. The 2021 base case estimate for VSL was used to generate a VSL of $130 000 per year out of the $10.3 million VSL for the 79-year average lifespan in the US [15].

# Calculation of overall disease cost burden associated with the selected 24 rare diseases

The cost per patient and prevalence for each of the 24 high unmet need diseases identified across the five TAs was based on primary (i.e., interviews with physicians, specialists, and key opinion leaders) and secondary (i.e., published data sources) market research. Three cost dimensions were quantified (Additional file 3: Table S3): direct costs (cost of treatment [including prescription drugs], medical procedures, hospitalizations [including inpatient, intensive care unit, and outpatient], physician visits, home health care, and other medical costs), indirect costs (patient and caregiver productivity loss, work loss, home changes, travelling and accommodation for medical visits), and mortality costs based on the difference in average life expectancy between patients with a given rare disease and the 79 years used to calculate VSL.

Published estimates of the total cost burden associated with 24 MM diseases (including diabetes, cardiovascular, Alzheimer's disease, arthritis and back pain, cancers, and others) were used for the purpose of benchmark comparisons with the rare disease burden across TAs [16]. Data on direct and indirect costs were obtained from the 2018 Milken Institute report on the cost of chronic diseases [16]. Mortality costs were estimated using VSL in the same way as described for the rare diseases.

# Scenario analysis assessing lack of treatment impact

Based on the overall cost burden per patient per year (PPPY) for the 24 rare diseases, a scenario analysis was conducted to assess the average cost PPPY under conditions when treatments were available compared with when treatments were not available (no treatment scenario).

# Extrapolation of cost burden

For diseases with high unmet need, direct and indirect costs were extrapolated using a weighted average (based on number of patients) of each TA based on the 24 selected rare diseases (Fig. 1). For diseases with medium or low unmet needs, the direct and indirect costs per patient were based on sources identified during a targeted review of the literature where data were available. In the absence of evidence in the literature, the cost of the remaining diseases was estimated using a weighted average based on the costs of diseases determined to have a similar unmet need. Mortality costs were estimated based on the life expectancy identified for each of the diseases; where not available, this was based on the average life expectancy for diseases in the TA. The mortality cost was estimated for each disease based on the difference in life expectancy between patients with a given disease and the 79 years used to calculate VSL. The overall burden was calculated by extrapolating a weighted average based on the 227 rare diseases in the five TAs to the remaining number of patients with rare diseases that remained in our initial database of 373 diseases.

# Results

## Economic burden of 24 rare diseases measured on a per patient per year basis

Based on analysis of the 24 rare diseases with high unmet need across five TAs (Fig. 1; Additional file 2: Table S2), the cost burden ranged from $121 000 to $334 000 PPPY (average overall cost of $213 000 PPPY; Fig. 2). The overall burden was highest for metabolic ($334 000 PPPY) and neurological disorders ($317 000 PPPY) and these TAs were also associated with the highest proportion of costs associated with mortality (39% and 43%, respectively). Direct costs contributed the highest proportion of the overall burden for hematological (74%), immunological (71%), metabolic (51%), and congenital (47%) diseases, while direct and indirect costs were split almost evenly in the congenital diseases (29% and 28%, respectively; Fig. 2). Overall, burden was generally driven by treatment and mortality costs for rare diseases. Indirect costs were the smallest proportion of cost burden except for in congenital (43%) and immunological diseases (16%; Fig. 2).

## The burden of rare diseases is higher than the burden of MM diseases when measured on a per patient per year basis

The average burden of rare diseases ($213 000 PPPY) was higher than that of the MM diseases ($26 000 PPPY; Fig. 2). Even for indirect costs, which contributed more to the cost profile of MM diseases than for rare diseases (18% for rare diseases vs 61% for MM diseases; Fig. 2), the cost PPPY was higher for rare diseases than for MM diseases (~$38 000 vs ~$16 000).

## Lack of treatment for rare diseases is associated with increased disease burden

Fig. 3 shows the average burden PPPY and associated cost drivers across the five TAs of interest under scenarios in which treatments do or do not exist. Summaries of the individual diseases within each TA are provided in Additional file 4: Fig. S1.

Based on selected diseases across the five TAs, lack of treatment was associated with average increases in other direct costs ($63 000 PPPY with treatment vs $118 000 PPPY without treatment), indirect costs ($40 000 PPPY with treatment vs $73 000 PPPY without treatment) and mortality costs ($36 000 PPPY with treatment vs $49 000 PPPY without treatment; Fig. 3). Importantly, across all the TAs assessed, access to treatment effectively shifts burden relating to indirect and mortality costs into direct costs (treatment and other direct costs).

Increases in the average total cost burden PPPY were observed for all TAs (Fig. 3). The percentage increases in total burden ranged from a 2.2% increase for congenital diseases to an increase of 51.8% for metabolic diseases.

## Extrapolation of the results from 24 rare diseases to the overall rare disease patient population in this analysis

When the results were extrapolated to include the 227 known rare diseases across the five TAs of interest, the average overall cost for rare diseases was 10 times higher ($266 000 PPPY vs $26 000 PPPY) than for the MM diseases (Fig. 4). The cost profiles for neurological, metabolic and hematological diseases were similar to those generated by the deep-dive analysis of the 24 representative rare diseases (Fig. 4 and Fig. 2).

There were however some distinctions noted in how the cost profiles changed following extrapolation. The profile for congenital diseases changed substantially with the proportion of mortality costs increased from 9% (for the four diseases selected for deep-dive analysis; Fig. 2) to 60% (for the 41 congenital diseases in the extended list; Fig. 4) and both direct and indirect costs halving while this TA became the most costly (average burden of $602 000 PPPY; Fig. 4). This is explained by a reduced availability of treatments and reduced life expectancy for the congenital diseases in the extended list of 41 diseases. Similarly, across the 36 immunological diseases included in the extended list, direct costs decreased from 71% (for the five diseases selected for deep-dive analysis) to 55% (for the 36 immunological diseases in the extended list) and mortality costs increased from 13% (for the five diseases selected for deep-dive analysis; Fig. 2) to 33% (for the 36 immunological diseases in the extended list; Fig. 4). Analogous changes were observed to differing degrees in the other TAs.

Finally, when our findings were extrapolated to the total of 8.4 million patients covered by the 373 rare diseases in our analysis, the overall cost of rare diseases in the US is estimated to be $2.2 trillion compared with $3.4 trillion for 133 million patients with MM diseases. Current estimates suggest that are as many as 30 million patients with rare diseases in the US [17], meaning that the overall burden is likely to be much larger than our results.

## Discussion

Our analysis highlights the substantial societal cost burden associated with rare diseases, which ranged from $121 000 to $334 000 PPPY (average overall cost of $213 000 PPPY) across the five TAs (including 24 diseases that were extensively analyzed). Notably, the overall cost burden was highest for metabolic and neurological diseases and with the exception of the neurological diseases, direct costs contributed the highest proportion to overall costs across the TAs. Furthermore, when our results were extrapolated to all rare diseases in our TAs of interest, the average burden of rare diseases was 10 times higher than that associated with the MM diseases (on a per patient basis). Overall, our findings suggest that the total

burden associated with rare diseases is $2.2 trillion for 8.4 million patients, rising to between $7 trillion to $8 trillion depending on prevalence estimates of 25 or 30 million patients with rare diseases in the US [17].

Beyond our analysis, we speculate that, as more diseases are taken into consideration, less information may be available about them, meaning they are less likely to have safe and effective therapies. This opinion is supported by findings from a previous study that systematically reviewed cost of illness evidence for 10 rare diseases [18]. This study observed a correlation between data availability and the existence of available therapies rather than severity or rarity of the diseases [18]. Overall, these considerations indicate that our cost of mortality estimate might be an underestimation in the context of the entire population of rare diseases. However, this interpretation cannot be supported by data because complete knowledge and description of all rare diseases (~7000) would be required to assess this fully. It is also important to note that our overall findings may represent an underestimate because social costs (including impact on health-related quality of life; HRQoL) were not part of this analysis. A previous systematic literature review of qualitative research suggested that living with a rare disease is associated with a substantial psychological and social impact [19]. These observations highlight the need to consider as many aspects of healthcare costs as possible to gain a full picture of the overall burden of rare diseases.

Our scenario analysis highlights the societal value that rare disease therapies can provide. Based on selected top diseases within the 24 diseases extensively evaluated in this study, lack of treatment was associated with a 21.2% increase in the average total PPPY costs, from $198 000 to $240 000. Interestingly, for some of the TAs assessed (neurological and congenital) the costs were similar irrespective of treatment availability. This is likely because the treatments typically improve the HRQoL of patients and such intangible costs were not part of this analysis, leading to the similar overall costs observed. This comparison shows the substantial beneficial impact made by rare disease treatments. To illustrate this point further, if we consider the 24 rare diseases selected for our deep-dive analysis, we note that the total cost to society is approximately $125 billion (based on the 584 000 patients included here), or 10 times the cost associated with MM diseases on a PPPY basis ($266 000 vs $26 000) [16]. Furthermore, our scenario analysis demonstrated that in addition to overall reductions in burden when treatments are available, mortality costs as well as indirect costs were converted to direct costs. These costs are more likely to be financed by private and public payers. These findings highlight that, generally speaking, providing access to rare disease treatments generates substantial value for society because it lowers the associated economic burden [20, 21].

A major strength of this study is that it presents an economic tool for analysis of the impact of rare disease on society. It also provides scenarios so that policymakers can understand the benefit of investing in innovation and policy reforms to accelerate the availability of, and access to, rare disease treatments.

The overall methodology and the diseases selected were validated by key stakeholders; however, some limitations remain. To maximize accuracy of the initial cost estimates, a sample of 24 diseases was selected based on unmet need, but the directional extrapolations performed to encompass larger sets of diseases required the use of some proxies and assumptions. Selecting diseases that are the most burdensome means that potentially those with the highest profile may not be representative of the entire TA. This limitation was mitigated by the subsequent extrapolations, which meant that information on diseases not initially selected was accounted for. Additionally, by not including estimates of intangible costs from our analysis, the results potentially represent an underestimate of the overall burden of rare diseases in the US. Finally, the geographical scope of this work is limited to the US and does not include any consideration of other regions of the world where economic considerations might be different, such as Europe or China. Future work could overcome these limitations by allowing for in-depth investigations of all rare diseases for which proxies and approximations were used in this analysis, by including estimates of intangible costs, and by extending the work to other countries and regions.

# Policy considerations and a path forward

Our analyses underline the substantial societal burden that rare diseases represent in the US. While legislative changes like the ODA have resulted in an increasing number of orphan drug designations [13], more needs to be done to accelerate this progress. State and Federal policy must recognize the distinct characteristics of developing and commercializing rare disease treatments and that the value assessment and pricing of rare diseases greatly differ from MM diseases [22, 23]. This consideration must be attended as policymakers pursue the need to manage and predict drug spending with improving patient outcomes.

Moving forward, we suggest steps to facilitate patient-centric progress:

1. Rare diseases should be considered a public health crisis commanding a governmental response to maximize treatment availability. Given the substantial burden that rare diseases represent on a per patient basis compared with market conditions, funding for rare diseases should be allocated on par with MM diseases to reduce the associated societal burden.
2. Investments should be encouraged by policymakers to nurture and sustain innovation based on the positive economic return from rare disease therapies. One potential approach is a shared responsibility framework, which ensures that all stakeholders work collaboratively to expedite research of, and access to, new therapies for rare diseases. Existing incentives for rare disease drug development such as the Orphan Disease Grant Program [24] and the Rare Pediatric Disease Priority Review Voucher Program [25] should be expanded and extended indefinitely, while also advancing new incentives that will accelerate treatment options.
3. Policymakers must support the necessity for a long-term approach to research and its challenges and think in terms of a fostering a cooperative dynamic with industry. Industry shares the

responsibility to respond and should consider rare disease application of its innovations in its business strategy and research and development allocations.

4. Changes are required to recognize the economic burden faced by the rare disease patient population. There should be an increase in caregiver resources and relief for families affected by rare diseases, because they bear high indirect or non-reimbursed expenses. Indeed, 75% of NORD survey respondents reported experiencing financial strain as a result their rare disease or the rare disease of a family member [5].
5. Increased access to diagnoses could potentially be stimulated in a number of ways, including the reauthorization and modernization of newborn screening, expansion of state newborn screening panels and other opportunities to diagnose rare diseases, as well as enabling funding for genetic screening for infants in neonatal intensive care units. A fundamental challenge that remains for several patients with rare diseases is the time taken to reach a diagnosis and optimal clinical management [2]. Information from a 2019 NORD survey suggests that 28% of respondents had waited seven or more years for a diagnosis, increasing severity of illness and patient healthcare debt [5]. Looking forward, ongoing advancement in molecular science aimed at more precise identification of endpoints and improved diagnostics will require ongoing modernization of these programs.
6. We advocate for an amendment to the Pediatric Research Equity Act to require pediatric testing across rare diseases when a drug intended to treat an adult has a common molecular target in pediatric diseases. This will increase screening and inclusion in trials.
7. State Rare Disease Advisory Boards should be considered a major strategic partner with State governments helping ensure expeditious access to therapies and preventing individual states from blocking or delaying access to rare disease innovations. Following diagnosis, challenges relating to potentially having to relocate to areas with specialist centers and barriers accessing treatment have also been reported, which add to financial strains [5]. State Rare Disease Advisory Boards could play a major role in collaborating to address these challenges.

# Conclusions

Our findings demonstrate the substantial economic burden that rare diseases represent in the US. This economic burden remains high even when treatments are made available, but its composition shifts towards medical care and away from indirect and mortality costs. To the extent that new treatments provide clinical benefit for patients and their families, these shifts in burden are likely productive. These findings support the view that the development of safe and effective treatments for rare diseases generate substantial value for society. We conclude that urgent policy changes could help ensure accelerated progress in the development of diagnostic methods for rare diseases as well as treatment options.

# Abbreviations

HRQoL, health-related quality of life

ODA, Orphan Drug Act of 1983

NORD, National Organization for Rare Disorders

PPPY, per patient per year

TA, therapeutic area

VSL, value of statistical life

## Declarations

# Ethics approval and consent to participate

Not applicable.

# Consent for publication

Not applicable.

# Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

# Competing interests

GC and GC are full-time employees of Chiesi Global Rare Diseases. IQVIA, the employer of PA, JK and CC received consulting fees from Chiesi Global Rare Diseases for this analysis.

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# Authors’ contributions

All authors contributed to the study design, data interpretation, and critical review of manuscript content. PA, JK and CC performed and reviewed the initial data analyses.

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# Figures

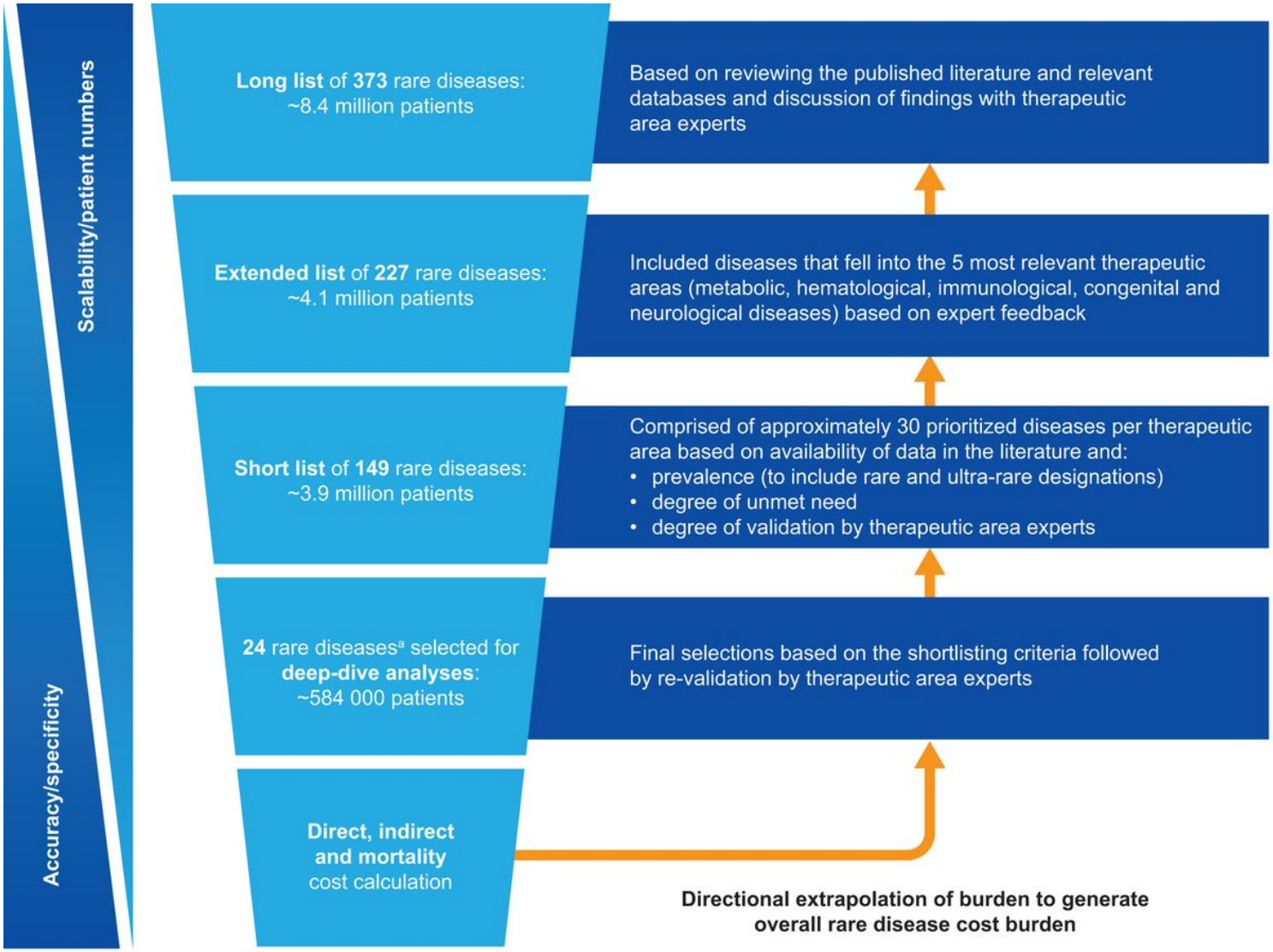
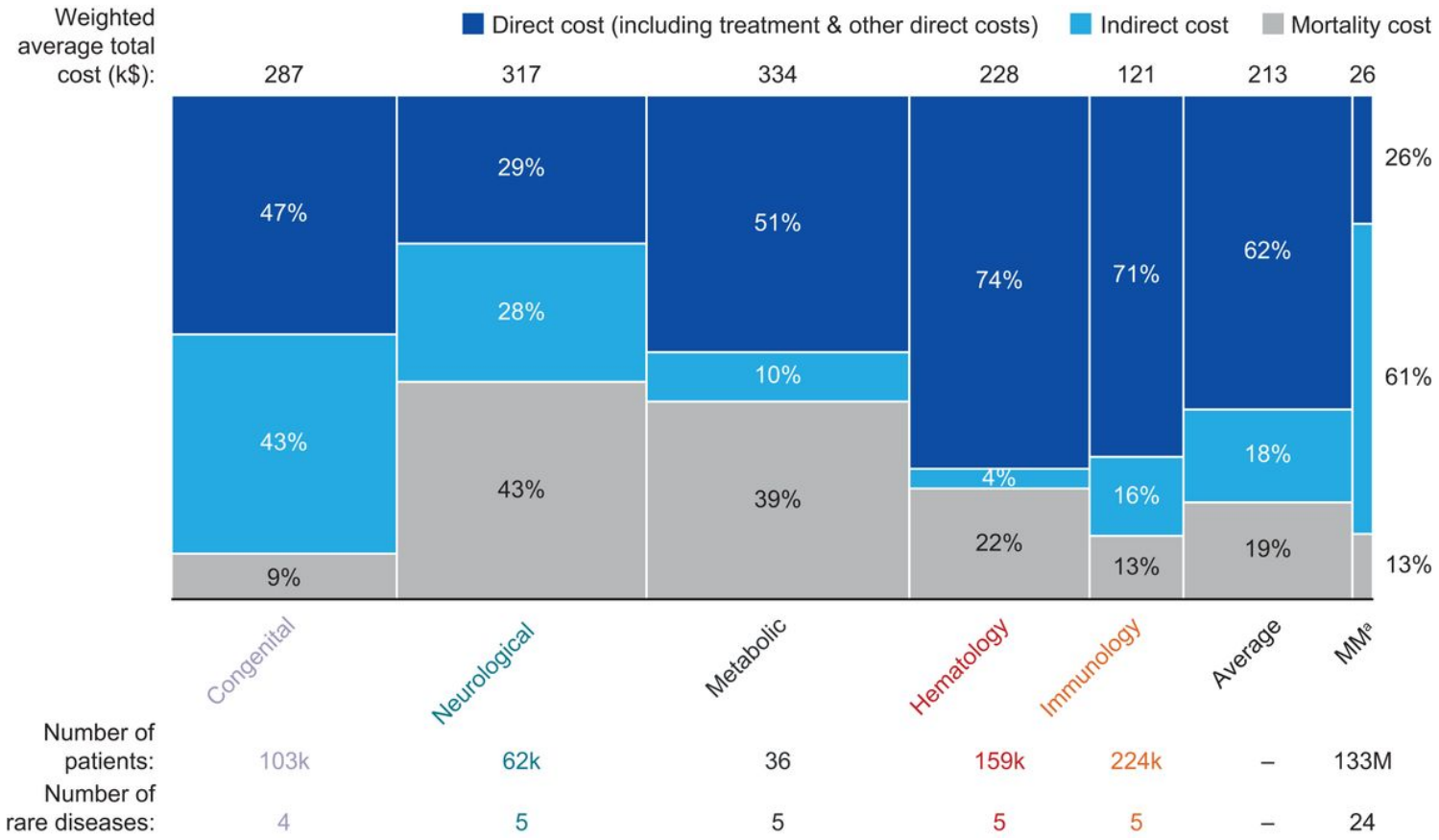


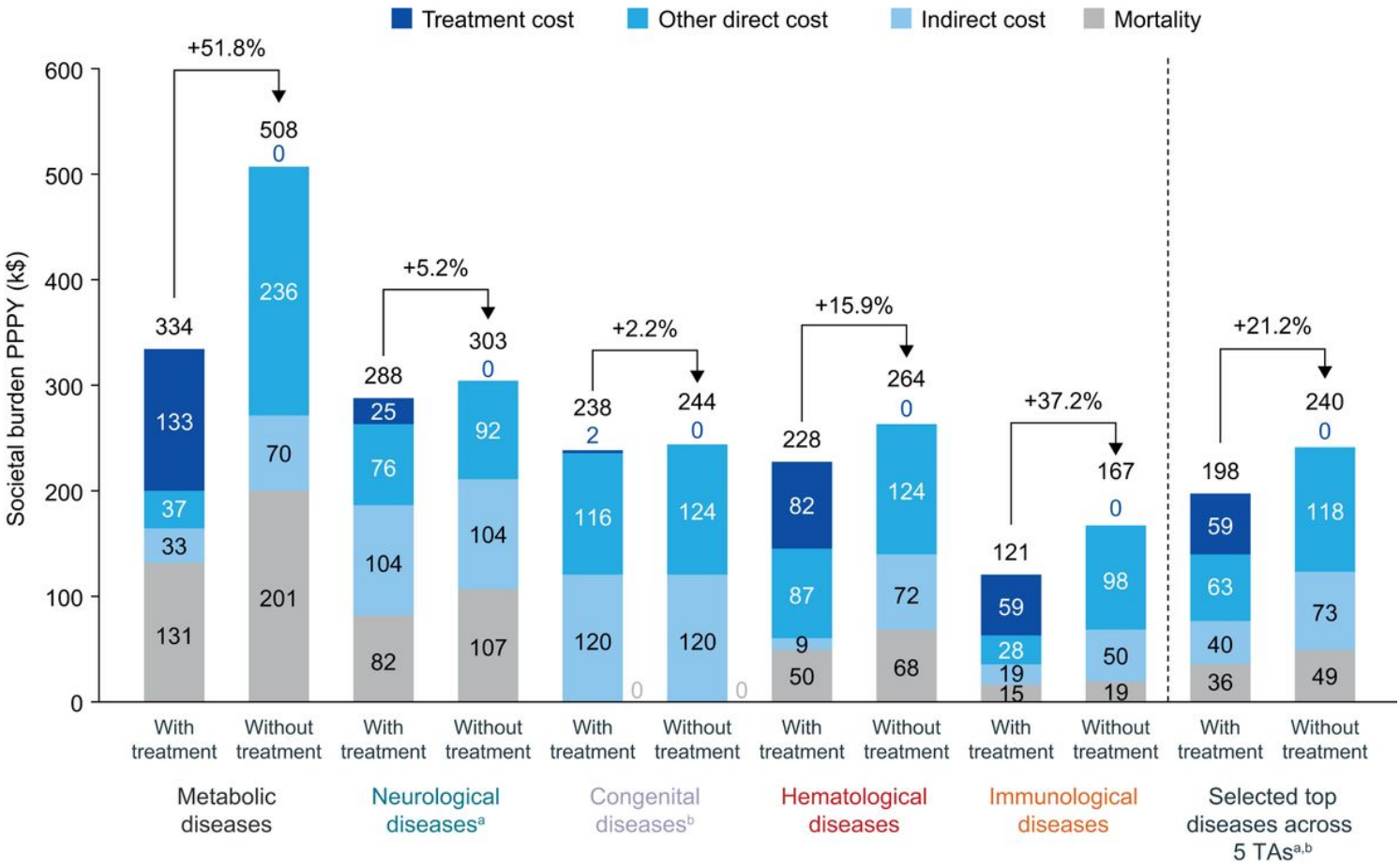

**Figure 1**

Overview of process to determine rare disease burden. aFabry disease, Gaucher disease type I, mucopolysaccharidosis (Hunter, Hurler), ornithine transcarbamylase deficiency, phenylketonuria, acquired aplastic anemia, acute intermittent porphyria, atypical hemolytic uremic syndrome, beta thalassemia major, sickle cell disease, autoimmune encephalitis, common variable immune deficiency, juvenile idiopathic arthritis, myasthenia gravis, pemphigus vulgaris, Angelman syndrome, Christianson syndrome, deletion 5p, fragile X syndrome, amyotrophic lateral sclerosis, ataxia telangiectasia, Duchenne muscular dystrophy, early-onset familial Alzheimer's disease and spinal muscular atrophy type I (proximal).




## Figure 2

Average burden of rare disease therapeutic areas PPPY across 24 rare diseases. Mean total costs based on a weighted average (by number of patients) of the top five diseases across neurological, metabolic, hematology and immunology diseases, top four congenital diseases and 24 comparator MM diseases. Column widths are weighted based on the average total cost per group. aMM diseases included diabetes, cardiovascular, Alzheimer's disease, arthritis and back pain, cancers and others. MM, mass-market; PPPY, per patient per year.




## Figure 3

Burden of disease PPPY (k$) across top rare diseases with and without treatment. Bars show the average burden PPPY (broken down by cost driver) associated with TAs as well as the average of selected diseases across the TAs. aExcludes spinal muscular atrophy because it was an outlier in this space. bFrom the selected top diseases in congenital TA; Christianson and Deletion 5P were excluded because no treatment exists for these diseases; hence, no difference in cost magnitude. PPPY, per patient per year; TA, therapeutic area.

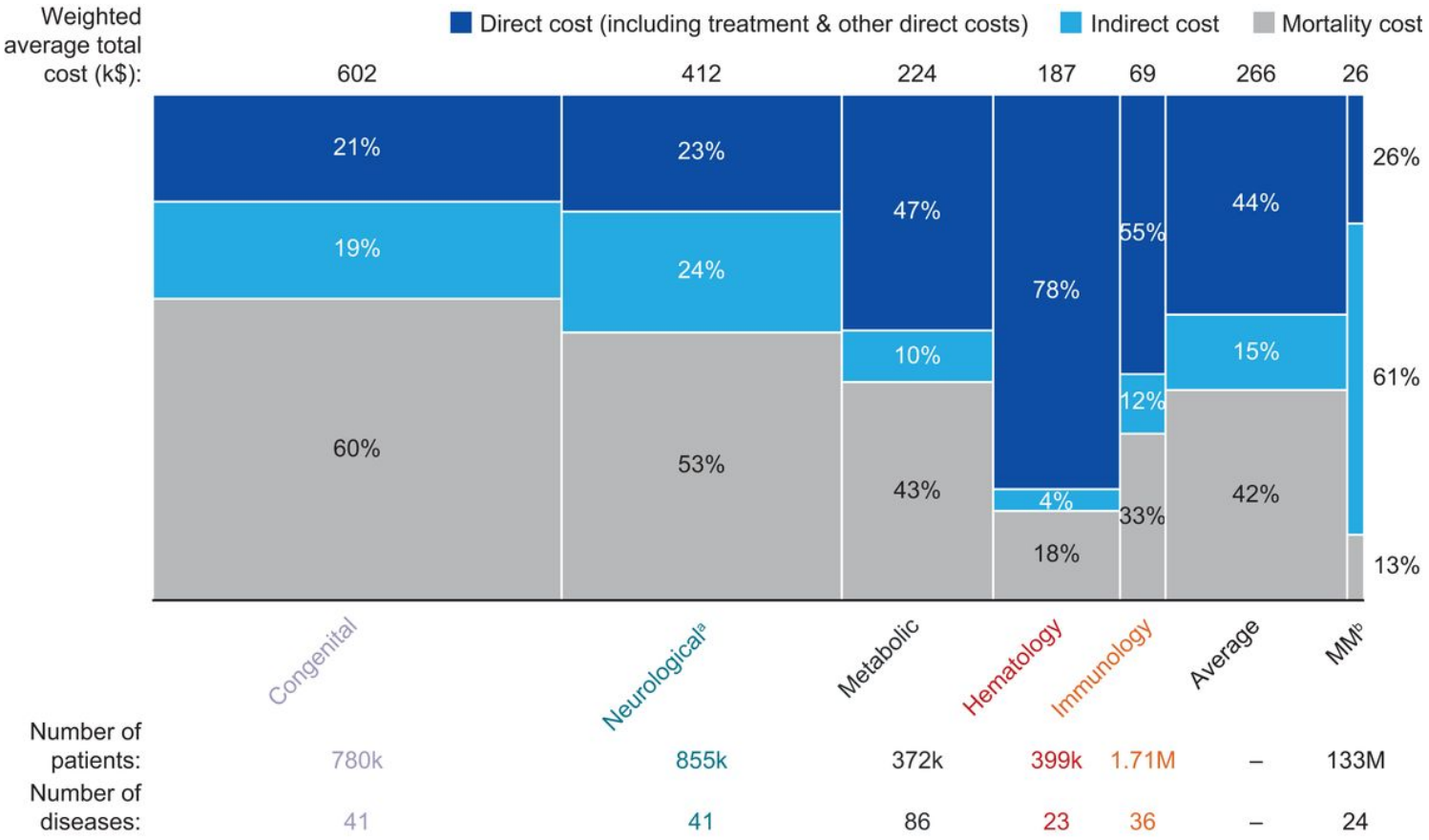



**Figure 4**

Extrapolated average burden of rare disease therapeutic areas PPPY across 227 rare diseases. Mean total costs based on a weighted average (by number of patients) of the 227 included diseases across neurological, metabolic, hematology, immunology, and congenital TAs and 24 comparator MM diseases. aSpinal muscular atrophy was excluded from the weighted average of representative disease to determine the average % of direct and indirect costs because it is an outlier, since it has a curative treatment. bMM diseases included diabetes, cardiovascular, Alzheimer's disease, arthritis and back pain, cancers, and others. MM, mass-market; PPPY, per patient per year.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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