The economic and health impact of rare diseases: A meta-analysis

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Abstract

Objective: Lack of medical and scientific knowledge on rare diseases (RD) often translates into limited research on them and a subsequent lack of understanding of their economic impact. This meta-analysis aims to fill this gap by evaluating the economic impact of RDs and exploring potential factors associated with the societal burden of RD.

Methods: Studies published between January 2010 and February 2017 were identified by searches in the PubMed platform. Thirty eligible studies were identified for inclusion, and nineteen studies were included in the meta-analysis and outcomes were explored. The cost categories include direct healthcare costs, direct non-healthcare formal costs, and direct non-healthcare informal costs. The patients' health-related quality of life (QoL) dimensions examined include EQ-5D scores, VAS scores and Barthel index, and the carers' utility outcomes include EQ-5d scores, VAS scores and Zarit scale. Random effects meta-regression models were used for modelling the impact of study and societal characteristics on cost.

Results: Across all RDs, mean direct healthcare (DH) costs ($16,513) account for the majority of direct costs (mainly driven by drug costs), followed by mean direct healthcare informal (€15,557) and mean direct healthcare formal (€4,579) costs. Body system affected by the RD, Gross Domestic Product (GDP) per capita and public health expenditure in country of study were the most significant determinants in predicting cost. In regards to QoL outcomes, patients with musculoskeletal diseases seem to have the lowest quality

of life across EQ-5D scores, VAS scores and Barthel index. The burden on caregivers seemed to be associated with Autoimmune, followed by Musculoskeletal and Respiratory conditions.

Conclusions: This meta-analysis highlights the significant burden of RDs on the health care system and explicitly provides evidence for the magnitude of this impact. Such estimates are necessary to further the debate on priority setting around RDs and their comparison with other chronic diseases. Nevertheless, the large degree of cost variability across RDs might suggest that the use of umbrella terms to raise awareness around RDs' societal impact might not be warranted.

Introduction

Rare diseases (RDs) are conditions or disorders commonly of genetic origin and often chronic, progressive and hereditary in nature (1). About 80% of RDs are genetic in origin, while (auto) immunological, oncological and toxicological causes are found in only 10%, 4% and 3%, respectively (2). Many rare diseases appear early in life, affecting children with about 30% of children with RDs not surviving past their fifth birthday (3). RDs can be asymptomatic early on, with over 50% of rare diseases appearing later during adulthood (4). To date, there are 6,000 to 8,000 known rare diseases, with a prevalence of RDs unevenly distributed geographically. While individual RDs may be rare, many people suffer from some type of RD, with 30 million people in the US (5), 30 million in Europe (6), 2 million in Australia (7) and an overall figure of 350 million people world-wide (5). Yet, the accuracy of prevalence figures is hard to gauge, often due to lack of population based epidemiological research.

Lack of medical and scientific knowledge also means that most rare diseases currently having no cure with available treatments targeting improved quality of life and extending life expectancy. About a quarter of patients diagnosed with a rare disease can have a diagnostic delay of between 5 and 30 years and 95 % of rare diseases are still without specific treatments (8). Available treatments are expensive (e.g. treatment for Fabry and Pompe diseases cost up to €200,000 and €700,000 per patient per year, respectively) (9),

with sharp pricing strategies by pharmaceuticals acting as a cost recovering mechanism in a market with limited consumers (i.e. patients) and exponentially increasing research and development costs (10).

The limited existing scientific knowledge, the difficulties in expanding knowledge- base, high costs of drug development and associated pricing suggest that standard efficiency principles would be difficult to be applied and, if possible, would likely consider RD drugs highly cost-ineffective. As such, either due their circumstances or cost-ineffectiveness, RDs are rendered low priority and are often overlooked by health care systems.

On the other side, cost-effectiveness approaches have been criticised for its comparison analysis comparing between a specific treatment and no treatment choices (9). Therefore, equity arguments have often been put forward for the prioritization of rare diseases. Others have argued for the patient's right to health care (11) or that doctors have an ethical obligation to treat patients with the best drug available and restricting access based on cost arguments is potentially violating the patient–doctor agency relationship (1).

Much of the discussion in the literature is based upon the premise of accurate accounting of the costs of rare diseases. The present study works towards that goal by contributing to the body of knowledge on the economic burden of RDs by examining the same conditions across a number of jurisdictions and using the same costing categories. We perform a systematic literature review and a meta-regression analysis to understand the economic impact of rare diseases from a societal perspective and to identify the factors affecting this impact. The findings of this paper highlight the economic burden of RD to patients, carers and health system, and contribute to the policy discussion on how health systems can balance health equity and responsiveness.

Materials and methods

Search strategy

Given the focus of the paper on costs of rare disease, the electronic search was based on the following search terms: ("rare diseases"[All Fields] OR "orphan disease"[All Fields]) AND (impact[Title/Abstract] OR cost[Title/Abstract] OR costs[Title/Abstract] OR burden[Title/Abstract]). Quality of life (QoL) terms were not

explicitly included as such outcomes were of secondary interest and only if costs were present within a study. The search was run in the PubMed platform and was carried out in February 2017. We restricted our search to studies published between January 2010 and January 2017, as the exponential increase of health care costs and rapid medical and technological developments would render obsolete and uninformative cost and social impact estimates from earlier studies. In addition to publications in English, studies published in Portuguese, Spanish, Greek, French and Italian were also included. References were downloaded in Zotero, a web-based cross-platform open source research tool developed at George Mason University, USA. Authors were contacted for further information if additional clarification was needed. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used as a basis for the overall study approach (12).

Inclusion and exclusion criteria

Studies were eligible if they explored the economic impact of rare diseases on individuals, relationships (caregivers/family) and society and reported collected cost data. Studies investigating projected or predicted costs, treatment trial results, genomics, drug development, orphan drug policies, and disease profiles were excluded from this review. Editorials, reviews and studies for which the full text could not be retrieved or only an abstract was available were also excluded.

Data extraction

Data extraction was carried out by two investigators (EM and ARS). After duplicates were removed, titles and abstracts were scanned by one researcher (ARS) to identify studies suitable for a full-text review. The process was checked by a second researcher (EM) on a random subsample of 300 studies of the retrieved references. The full text was subsequently retrieved for the identified studies, and they were reviewed by two researchers (EM and ARS), with disagreements resolved by discussion. Overall, 30 studies fulfilled all inclusion criteria and were therefore included in the analysis (Figure 1). Data extraction for these studies was carried out using a pre-defined extraction table.

Determinants and outcomes

The primary outcomes of the study are: direct healthcare costs (DH) which includes expenses with drugs, medical tests and visits and hospitalizations; direct non-healthcare formal costs (DNHF) relates to costs such as professional carer, social services and non-healthcare transport; and direct non-healthcare informal costs includes informal carer provided by the main carer and other carer (DNHI). Secondary outcomes of QoL were extracted whenever present in the reviewed studies. Specifically, three patient utility outcomes (i.e. EQ-5D score, VAS score, Barthel index) and three caregiver utility outcomes (i.e. EQ-5D score, VAS score, Zarit scale) were examined.

Each reviewed study is classified over a number of dimensions. First, due to few studies per disease we focused on body systems affected with five categories identified, namely Cognitive (i.e. Fragile X syndrome, Prader-Willis), Respiratory (i.e. Cystic Fibrosis, generic rare lung diseases, Idiopathic Pulmonary Fibrosis, Pulmonary Arterial Hypertension), Autoimmune (i.e. Juvenile Idiopathic Arthritis, Systemic sclerosis, Scleroderma, Myelofibrosis disease), Musculoskeletal (i.e. Duchenne muscular dystrophy, Becker muscular dystrophy, Pompe, Osteogenesis Imperfecta, X-linked Hypophosphatemia, Fibrous Dysplasia, Sternocostoclavicular Hyperostosis, Myasthenia Gravis) and Other (i.e. Alport (kidney), Amyotrophic Lateral Sclerosis (Neurodegenerative), Epidermolysis bullosa (skin), Haemophilia (blood), Gaucher disease (metabolism), phenylketonuria (metabolism), Acromegaly (hormonal), Histiocytosis, Myelofibrosis disease, Hereditary Angioedema, Tuberous Sclerosis Complex (multisystem)). Second, we examined whether values presented in a study refer to children or general patient populations. Third, we classified the health care system of each country within the studies to Insurance (i.e. Bulgaria, Hungary, Italy, Spain, Sweden, UK) or Tax based (i.e. France, Germany, Netherlands, China). Given that the breakdown allowed by the health care system classification is too coarse in drawing inference on cost variation, we further matched our dataset (by country and year) for the meta-regressions with data from the World Bank database (13). In doing so we expanded our data to contain information on countries' public health expenditure (as percentage of Gross Domestic Product (GDP)), GDP per capita (Purchasing Power Parity (PPP) at constant 2011 international dollars) and life expectancy at birth. All three variables are standardized and along with the study characteristics are used to explain variations in cost and QoL across studies.

Statistical analysis

For the estimations we fitted random-effects (variance-weighted) meta-regression models for each cost and QoL outcome. The known large degree of heterogeneity suggests that fixed effects specification was not appropriate and as such was omitted. Model specifications are gradually build starting from a baseline set of covariates and in turn adding new covariates to test whether they capture or explain new variation in outcomes. Given the variance weights regression models, only studies that provided information on the uncertainty around their average outcome values (i.e. standard deviation or confidence intervals) are included in the estimation. All costs were transformed in 2014 Euro values.

Results

Review of the literature

Initially, the literature search yielded a total of 782 titles. Of these 782 studies, 713 articles were deemed irrelevant, with the remaining 69 articles assessed for further analysis and full-text downloading and reading. Of these, 30 publications discussed the social and economic impact of rare diseases and were incorporated in this review. Table 1 lists the studies eligible for synthesis along with some of their qualitative characteristics. Of the 30 eligible studies, relevant data for quantitative analysis and meta-regressions were available in a subset of 19 papers (14–32). The 11 papers not included in the meta-regressions are grey-shaded in Table 1 (33–43). In the present meta-analysis we first offer a descriptive overview of the results of the systematic review, followed by the meta-regression findings.

Populations and outcomes

The majority of studies collected information on the costs of illness of rare diseases (Table 1). A societal perspective approach was employed in most cases, while six studies implemented a health care system or health plan approach and one focused on the pharmaceutical industry (Table 1). Some of the studies not only captured patients' burden and health services responsiveness, but also the burden of caregivers and families. Only a few studies focused their analysis on caregivers and families enhancing understanding of the social, financial and emotional effects of rare diseases. These psychosocial and contextual realities can

be examined as part of the quality of life approaches, that go beyond the advancements in medical treatment by integrating what Cohen and Biesecker (44) classify as “the next frontier in healthcare for individuals living with rare genetic conditions” (p. 2).

Regional distribution

Most studies were conducted in Europe, many of them as part of the ‘‘Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe’’ - BURQOL-RD- project. This project included Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the UK and data collection spanned 3 years (2011-2013). Of the remaining studies, ten were carried out in individual European countries, three in China, three in the USA, two in Australia and one in Canada (Table 1).

Data sources

The majority of studies relied on questionnaires for data collection. Studies often identified study participants (adult and children) from patients receiving outpatient care or through disease centres, patients’ associations (19,34,39,43) and national registries (16). Self-administered surveys were used by the BURQOL-RD project, as well as two out of three studies conducted in China (14,28). Of the many studies administering questionnaires, some relied solely on web-based surveys (8,19,27), questionnaires sent by mail (26,29,35), the combination of the two (16,17,20–23,25,29–31,34,35,45,46) or face to face (28,43) administration.

Using administrative datasets, two studies published in 2016 analysed hospital utilisation data in Western Australia (36) and Germany (37) to understand demand and costs in the case of general rare diseases (Western Australia) and lung diseases (Germany), respectively. Further, two studies utilized health databases (one used the European Orphanet database (15) and the other used the IMS Health MIDAS database (33) and finally one study used the RUDY (Rare and Undiagnosed Diseases Study) web-based registry data (27). Other studies focused on qualitative research by conducting interviews (40) and focus groups (26).

Overall, amongst the studies estimating the economic impact of the rare disease, the largest sample comes from Schreiber-Katz et al. (16) who collected information on 363 patient/parent pairs in Germany. The second largest sample size comes from Chevreul et al. (21) that collected 240 and 193 surveys from French and Spanish respondents, respectively, out of 905 respondents across 8 countries.

Diseases and body systems

Rare diseases in general were examined in five cases (14,33–36) with three studies focusing on more than one rare disease (15,16,27). Further, three studies included or focused on Duchenne Muscular Dystrophy (15–17), two on Haemophilia (18,19,47,47) and two on Juvenile Idiopathic Arthritis (20,25) with several other rare diseases addressed just once in the remaining studies.

Patients' direct costs of rare diseases

Looking at the raw values collected from the studies included in this meta-analysis, Table 2 presents descriptive statistics with mean, median (10th and 90th) and percentage of total for the overall sample and by body and health care system types for each of the three patients' cost outcomes. Mean direct healthcare costs (DH, €16,513) account for a large part of all direct costs (mainly driven by drug costs), followed by mean DNHI costs (€15,557) and mean DNHF costs (€4,579). Patterns are similar for median values with DNHI now possessing the largest share. To explore the links between these three cost types, we calculated overall correlation coefficients and plotted them in pairs (colour coded by health care system type) to identify any observable patterns. Figure 2 suggests very low correlations, all nonsignificant at the 5% level, something also verified by the plots with little dependence among them and no consistent cost patterns overall or by body system.

Looking at heterogeneity across body and health care systems, Table 2 further presents mean values for various sub-samples, namely by body system (i.e. these are averages across all other dimensions apart from body system) and health care systems types. Diseases classified under the "Other" category possess the highest DH costs, a result mainly driven by haemophilia. Haemophilia accounts for the highest cumulative economic impact (€464,762) in 2012. This total average annual cost per patient is mainly due

to prescription drugs, which account for approximately 90% of the total cost (€174,712/year). Turning to median values, the highest burden is observed for Respiratory diseases. Using both mean and median values, Cognitive diseases occupy the highest direct non-healthcare formal and informal costs with Fragile X syndrome (€8,607) and Prader-Willi syndrome (€23,547), respectively. Looking at individual diseases with respect to total direct costs, Haemophilia ranks first, followed by Myelofibrosis, Histiocytosis, Prader-Willi syndrome and Cystic fibrosis. Finally, insurance based systems seem to have higher mean and median values across all three cost outcomes, with sizeable differences mainly for DH, although not statistically significant due to the very large variances.

Table 3 presents descriptive statistics for the three patients' QoL outcomes. Overall, musculoskeletal diseases seem to have the lowest quality of life across all three outcomes both for mean and median values. In regards to the body systems that have recorded higher mean and median outcomes, some variation was found across the instruments used. Respiratory, Other and Autoimmune seem to have higher mean and median outcomes based on EQ-5D score, VAS and Barthel index, respectively. As expected, differences in the patient experience are negligible by health care system types. Again, to explore correlations, we plot patient costs against patient EQ-5D observing significant negative correlation between QoL and DNHF and DNHI but not DH (Figure 3). Table 4 gives descriptive statistics for the three caregivers' QoL outcomes. Autoimmune, followed by Musculoskeletal and Respiratory disease seem to put the most burden on caregivers, while again there is little difference in values between system types.

Quantitative synthesis: Health and economic determinants of costs of rare diseases

Table 5 presents the results of the meta-regressions for three patient cost outcomes. The overall predicted means and standard errors for each outcome are given at the bottom two rows of the table. All mean predicted values are statistically significant at the 5% level. Mean direct healthcare costs vary between €13,137 and €17,624 depending on the specification, mean direct non-healthcare formal costs between €884 and €1,076 and mean direct non-healthcare informal costs between €11,766 and €13,308.

For direct health care costs (DH), compared to other rare disease, conditions affecting cognitive and autoimmune systems are associated with €23,688 and €19,120 lower costs, respectively. Increasing public health expenditure by one standard deviation lowered costs by €29,832 or more depending on the specification, while a corresponding increase in GDP per capita increased costs by €31,239. For DNHF, costs did not vary by disease type but are lower by around €1,500 or more for insurance based health care systems compared to tax based systems. An and increased life expectancy at birth by one standard deviation is associated with an increased mean cost in our meta-regression of between €406 and €645. For DNHI costs, cognitive, respiratory and musculoskeletal rare conditions showed higher costs of €9,028, €8,028 and €9,245, respectively and autoimmune lower by €6,109 compared to Other RD. No link between costs and health system or life expectancy was observed, but a one standard deviation increase in public health expenditure was associated with a drop in mean cost of €9,508 (although effect was not consistent across specifications), whereas the opposite effect was found for higher GDP per-capita with an increase of €11,544.

Estimation results from meta-regressions of patient and caregivers EQ-5D QoL outcomes are given in Table 6, Overall, musculoskeletal disease seems to put the highest burden on both patients and their caregivers. As expected, higher burden for patients translates to higher burden for caregivers, while the older the patient the worse the EQ-5D for caregivers. None of the remaining factors have any significant association with the outcome for patients, whereas for caregivers increased public health and GDP per capita expenditure is linked to lower and higher utility scores, respectively.

Discussion

This study draws its findings from a systematic review and meta-analysis of 19 studies published on the economic burden of RDs, focusing on reported costs collected from patients and carers, health plans and hospital data sets.

Mean direct healthcare costs account for the majority of all direct costs, mainly driven by drug costs. Among body systems, the residual “Other” category, led by Haemophilia, features the highest costs. Respiratory

RDs account for the greatest burden and represent the second highest direct healthcare costs, while rare musculoskeletal conditions account for the second lowest.

The findings from this study build on published evidence of the economic burden of rare diseases and highlight some of the highest mean annual costs per capita for a RDs population cohort estimated at 6% to 10% of the population (48) – €11,780 for healthcare costs, €4,143 for formal non-healthcare costs, and €17,511 for informal non-healthcare costs. Nevertheless, significant variation in these figures opens opportunities for reviewing clinical pathways and health services responsiveness and diseases that have low expenditures and better health utilities. Putting those costs into perspective, studies (49,50) on the annual costs for rheumatoid arthritis and asthma reported a mean annual healthcare cost of €4,737 and €4,934, respectively, which represent less than 50% of the mean annual healthcare costs per patient reported in our study, while lifetime costs of colorectal cancer, driven by drug therapies, have been reported at €23,688 for patients diagnosed in the stage I phase and €48,835 for stage III patients (51).

Further, our findings on the highest total direct cost of individual diseases, such as Haemophilia, Myelofibrosis, Histiocytosis, Prader-Willi syndrome and Cystic fibrosis raises attention to the affordability of orphan drugs and the role of the government in driving co-payment assistance policies to address high expenditure with drugs.

The meta-analysis shed light on the breakdown of the cost of rare disease, and its variability, offering evidence for the place of RDs to be reconsidered by exploring RDs patients' journeys and associated expenditure, as well as opportunities for decision-makers to improving the health services capabilities, which include the diagnosis services, the integration and coordination of care, the expansion of the training of medical and clinical practitioners, and the establishment of care and clinical pathways (38,42,52,53). Such argument is reinforced when considering evidence on cost of co-morbidities (not part of our meta-analysis) with past work, for instance, on Cushing's disease (a rare endocrine disorder) suggesting annual costs of comorbidities among controlled patients to be $13,236 and lifetime costs at $397,091 (54). Nevertheless, two studies examining health claims data concluded drug costs may offset administration and adverse events management costs (55), while also expected to reduce the costs associated with

comorbidities (56). Future research on the relationship between treatment costs and prevented comorbidities might offer some rationale for further investment in R&D.

Overall, the marked heterogeneity of diseases, their biological complexity and phenotype and the available clinical means of treatment, it is apparent that a unified approach to cost estimation and subsequent resource allocation is not suitable. This review serves to underline the importance of this variation in the manner in which these diseases affect different systems and how they are expressed and treated.

The relevance of public health expenditure and GDP per capita as determinants of cost but working in opposite directions is potentially related to an underlying story of healthcare system structure and drug prices. However, our meta-analysis is not powered to provide more evidence on the causal pathways behind such findings.

Besides pure economic impact, the social cost on health-related quality of life of patients (HRQoL) and caregivers is a crucial aspect of RD burden. A large number of the retrieved studies used quality of life measures as indicators of disease burden, yet they were outside the scope of the review and hence not examined in detail. In the studies collected, we observed that musculoskeletal conditions were associated with lower HRQoL mainly driven by Duchenne muscular dystrophy, while countries with higher public health expenditure were linked with significantly lower mean HRQoL. Overall, integration of patient-reported health outcomes and HRQoL measures in the delivery of care and research with RD patients is likely to improve their place in priority setting exercises, while promoting a value-based medicine will potentially harness the development of social care and clinical pathways focusing on the wellbeing of the patients, and the physical and life dimensions RDs patients' value (57). Consistent with the position of the European Organization for Rare Diseases (EURODIS) on rare disease research infrastructure, development, and governance, the inclusion of patients as full and equal partners is a central recommendation set forth by the Canadian Organization for Rare Disorders (CORD).

Studies and patient's heterogeneity

A number of challenges has been identified during collection of studies reporting cost of RDs, among which are difficult diagnosis, small patients' numbers, lack of evidence with regard to efficient and validated models of organisation. High heterogeneity among patients, health systems and in the evolution of disease for each different RD and patient are the most relevant challenges in assessing total costs of treatments for rare diseases, and quality of life outcomes. Moreover, RD definitions vary widely among countries, even among countries with well-established plans and strategies.

In Europe, in all the ERN ReCONNET countries (European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases) are in place national plans for rare diseases. Additionally, a common definition of rare disease, based on the proportion of cases in the population, and their rare disease activities operate under multinational legislation called the Orphan Medicinal Product Regulation (EC) No. 141/2000 is applied. However, heterogeneity exists in the reimbursement of Orphan Drugs, direct provision by the healthcare system, involvement of patients' associations in decision making and implementation of clinical practice guidelines. While several countries have regulations specific to orphan drugs that are designed to accelerate the authorization process, streamlined processes do not necessarily expedite drug approval. While the number of Orphan Medicinal Product (OMPs) available in European markets is increasing, as seen in the growth in designations and authorisations, the level of access to these medicines varies significantly across different health systems. Despite receiving a marketing authorisation from the European Medicines Agency, not all OMPs are launched in different markets nor the time it takes for each country's health technology system to make a decision is the same. There is an even greater difference in the number of medicines actually receiving funding. In Germany, reimbursement is automatic so nearly all OMPs launched are available, while in France, more OMPs are reimbursed than those that have received a national Health Technology Assessment (HTA) decision, while in Italy and England, the proportion of OMPs receiving reimbursement is significantly lower. The nature of the disease also influences funding and reimbursement, where for instance in England, a higher proportion of oncology OMPs receive an HTA appraisal and are reimbursed when compared to non-oncology OMPs. There may be various explanations for this discrepancy, including the existence of a dedicated conditional approval process for oncology products through the Cancer Drugs Fund (58).

Based on these large differences, traditional approaches could not be appropriate for assessing the cost as experienced in rare diseases. To improve the comparison of studies and obtain more information from

analysis and meta-analysis, a fundamental direction for HTA in rare diseases is the creation of an EU standard that encourages researchers and scientists to adopt the same criterion for selecting the more appropriate methodologies for the analysis. Big data and international registries could improve our knowledge on the field, and heterogeneity could be a resource only in case of homogeneous or comparable methods of analysis (59).

Rare disease policies thus require a global approach in addition to the national one, for example, through international research platforms for both fundamental and translational research. This would facilitate sharing derived knowledge and developments in screening methods and standards of care and diagnosis. Health authorities should join national and international efforts to improve the visibility of rare diseases in medical information systems to fill this appalling void. In this sense the inclusion of rare diseases in the revised version of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) will significantly help decide policy and monitor spending. In collaboration with several partners, including OrphaNet, ICD-11 has incorporated all rare diseases. Only a few of these have an individual code, but all have their own Uniform Resource Identifier (URI), allowing rare disease Registries and researchers access to detailed epidemiological data on conditions of interest (60).

Variations in disease definitions, could be an obstacle to the integration of national plans into larger international plans. Researchers on rare diseases have emphasized the need for the integration of rare disease plans and studies into international consortiums. This would replace the fragmented approach currently in place with a more coordinated effort that would include larger numbers of patients and caregivers.

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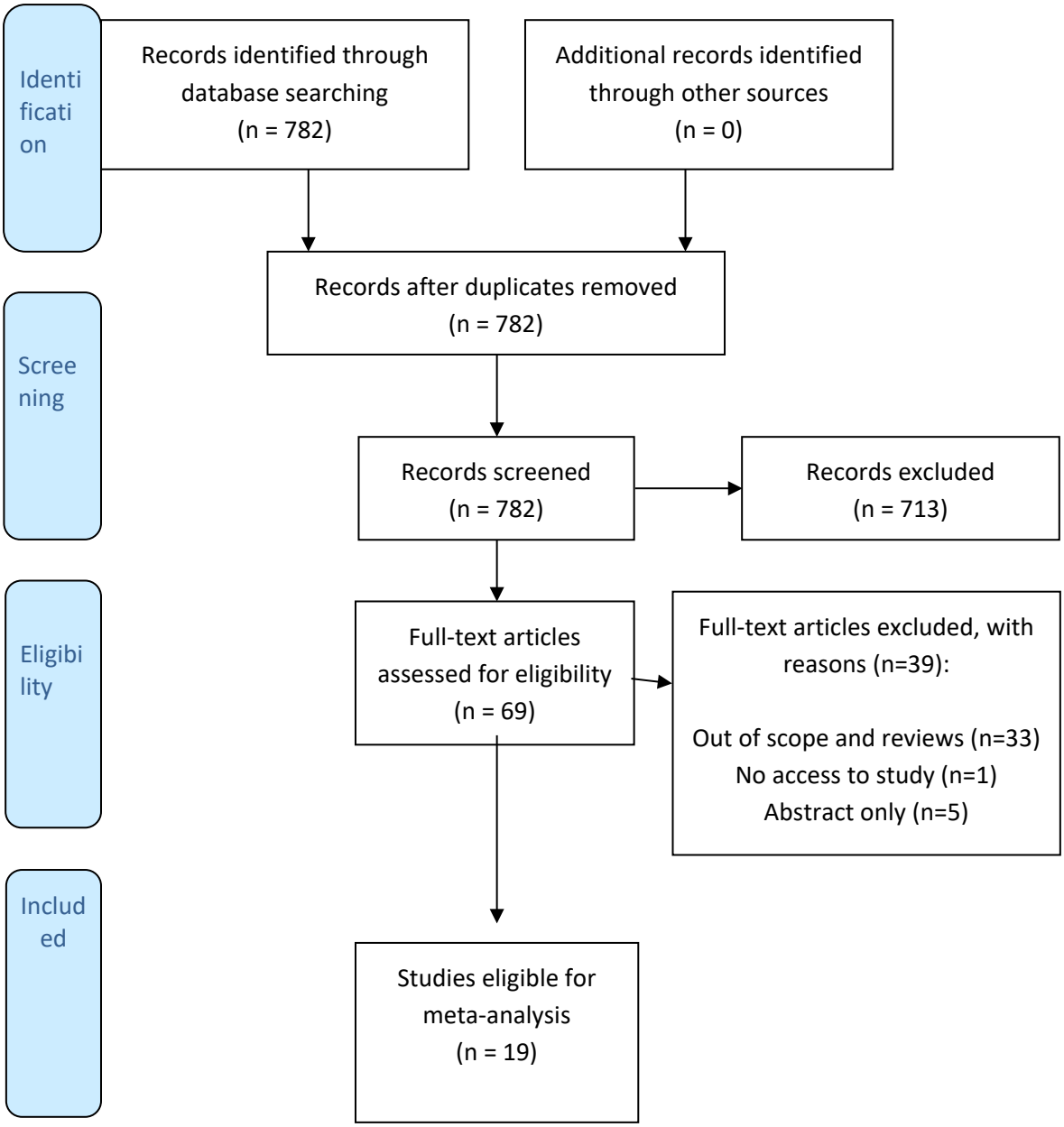

Figure 1. PRISMA flowchart (12) of literature

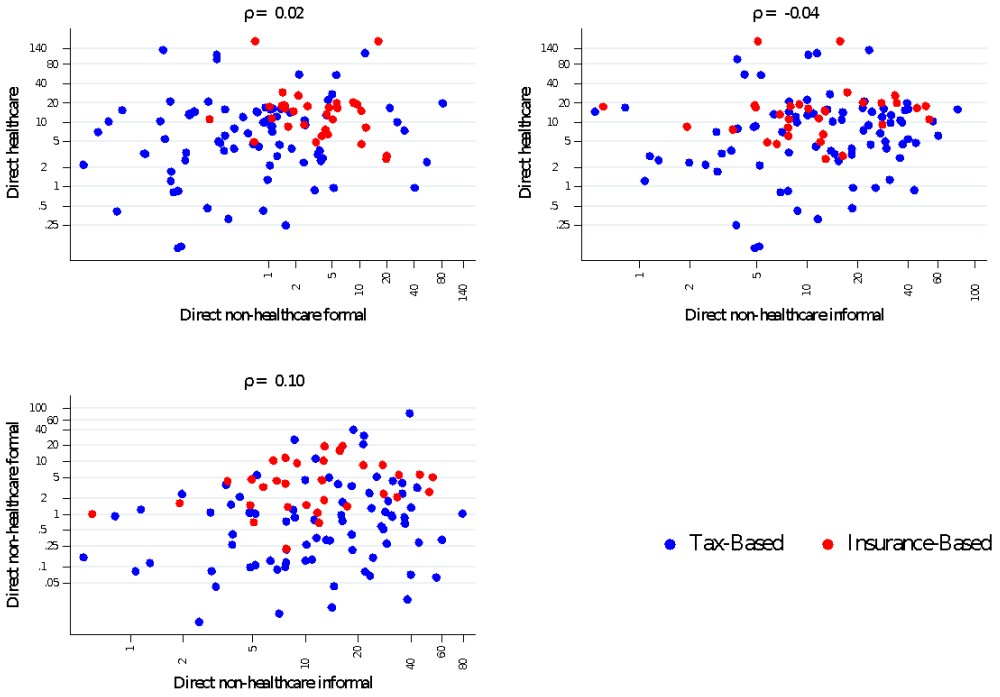

Figure 2: Mean patients' costs outcomes plotted in pairs by health care system type. For better illustration both axes are expressed in logarithmic scale. Pairwise correlations are given at the top of each graph panel.

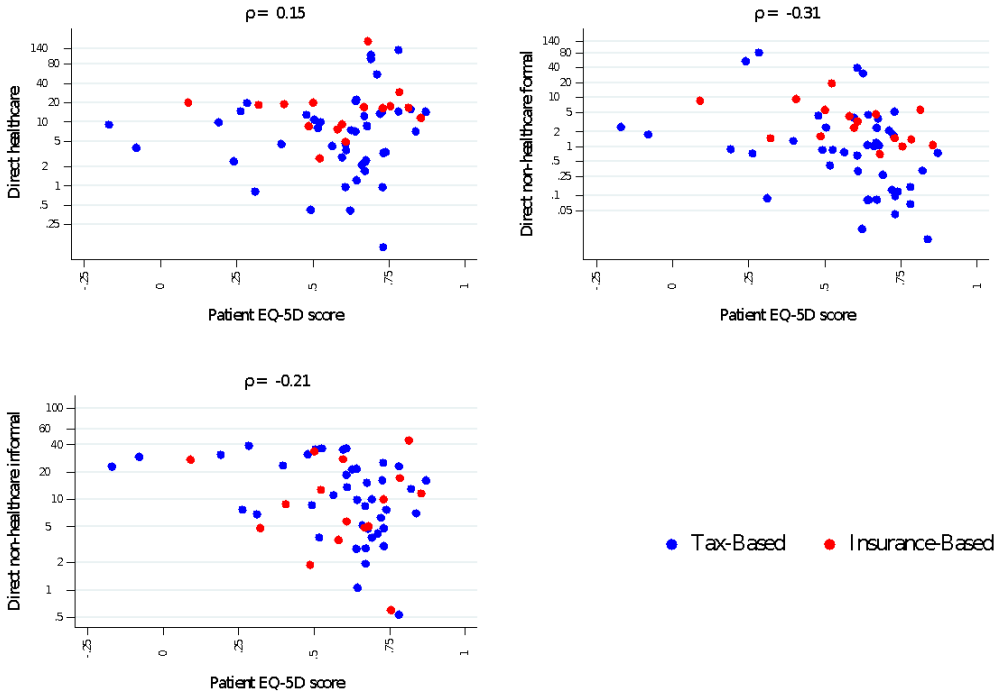

Figure 3 : Patients' costs and Patients' utility outcomes plotted in pairs by health care system type. For better illustration we have dropped one outlier value (i.e. Sweden EQ-5D value for Duchenne Muscular Dystrophy at -0.71) and the cost axis is expressed in logarithmic scale. The full graph in given in the Appendix. Pairwise correlations are given at the top of each graph panel.

Table 1. Study Characteristics with qualitative parameters

Authors	**Year (horizon)**	**Disease**	**Country**	**Participants and Sample Size range**	**Methods**	**Publication Year**	**Costing approach**
Divino et al. [15]	2007-2013	General RD	Canada	174 orphan drugs	IMS Health MIDAS database	2016	Pharmaceutical expenditures for rare diseases-Future trend analysis
Molster et al (34)	2014	General RD	Australia	810 Patients	Online survey	2016	N/A
Silibello et al. [16]	2010-2013	General RD	Italy	154 Caregivers	Questionnaire	2016	N/A
Walker et al. [9]	1999-2010 & 2010	General RD	Australia	61,279 One RD code patients	Admin Hospital data	2016	Total discharge cost estimation-Health care system perspective
Xin et al. [40]	2015	General RD	China	982 Patients	Questionnaire	2016	Bottom-up approach. Out-of-pocket Societal approach.

Xin, Guan & Shi [45]	2014	Duchenne Muscular Dystrophy, Alport Syndrome, Tuberous Sclerosis Complex, Amyotrophic Lateral Sclerosis, Idiopathic Pulmonary Fibrosis, Pulmonary Arterial Hypertension, Gaucher disease	China	10 Panel experts	Delphi method and calculation of the catastrophic expenditure and impoverish expenditure through annual per capita income	2016	Catastrophic and impoverishment approaches (societal perspective)
Schreiber-Katz et al. [32]	2013	Duchenne and Becker muscular dystrophies	Germany	363 Patients	Questionnaire	2014	Societal perspective; Micro-costing method.
Cavazza et al. [22]	2011-2013	Duchenne muscular dystrophy	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Patients [2-87] Caregivers [2-61]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach

Cavazza et al. [49]	2011-2013	Haemophilia	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Patients [2-89] Caregivers [1-9]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach
Kodra et al. [36]	2012	Haemophilia	Italy	Patients 89 Caregivers 17	web-based cross-sectional survey	2014	Societal perspective - Bottom-up approach-For indirect: Human Capital Approach
Vogl & Leidl [11]	2006-2012	Lung Diseases (including rare lung diseases)	Germany	N/A	Hospital data	2016	Sum up method and Forecasting approach-health care perspective
Angelis et al. [20]	2013	Juvenile Idiopathic Arthritis	UK	Patients 23	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach

Zhang et al. [13]	2008-2012	Acromegaly	USA	43 patients	Registry data	2016	Disease attributing costing-Health care system perspective
Chevreul et al. [19]	2011-2013	Cystic fibrosis	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Patients [5-240] Caregivers [3-56]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach
Angelis et al. [21]	2011-2013	Epidermolysis bullosa	Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK	Patients [6-54] Caregivers [1-26]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach
Chevreul et al. [23]	2011-2013	Fragile X syndrome	Bulgaria, France, Germany, Hungary,	Patients [2-95] Caregivers [1-56]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-

			Italy, Spain, Sweden, UK				Indirect cost: Human capital Approach
Aygören-Pürsün et al. [38]	2011	Hereditary Angioedema	Spain, Germany, Denmark	111 Patients	Questionnaire	2016	N/A
Iskrov et al. [18]	2011-2013	Histiocytosis	France, Germany, Italy, Spain, Bulgaria, UK, Sweden	Patients [2-35] Caregivers [1-9]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach
Kuhlmann et al. [24]	2011-2013	Juvenile idiopathic arthritis	Germany, Sweden, Italy, UK, France, Bulgaria	Patients [1-67] Caregivers [1-16]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach
Somanadhan and Larkin [34]	N/A	Mucopolysaccharidosis (MPS) disorder	Ireland	8 Caregivers	Interviews	2016	N/A

Guptill et al. [12]	2008-2010	Myasthenia gravis	USA	1288 patients	Claims datasets	2011	Health care system perspective-Sum up costing approach
Rose et al. [14]	2013-2016	Neuroendocrine tumours of gastrointestinal or lung origin	USA	66 patients	Registry data	2016	Health care system/pharmacy perspective-prevalence approach-Sum up costing approach
Gimenez et al. [42]	2013	Myelofibrosis disease	Spain	33 Patients	Questionnaire	2014	Sum all medical approach; Societal perspective-Prevalence approach
Forestier-Zhang et al. [10]	2014-2016	Osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia	UK	109 Patients	Questionnaire – RUDY platform	2016	Willingness to pay from a health system perspective
Wang et al. [39]	2014-2015	Phenylketonuria	China	127 Patients and caregivers	Questionnaire and Interview	2016	Bottom-up method-out-of-pocket Societal approach

Kanters et al	2005-2009	Pompe disease	Netherlands	80 Patients	Questionnaire	2011	Societal perspective-sum-up direct cost method, shadow price method for informal care estimation and friction cost method for productivity losses
López-Bastida et al. [25]	2011-2013	Prader-Willi syndrome	Spain, Bulgaria, Hungary, Germany, Italy, the UK, Sweden, France	Patients [5-61] Caregivers [2-41]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach
López-Bastida et al. [26]	2011-2013	Scleroderma	Germany, Italy, Spain, France, the UK, Hungary, Sweden	Patients [23-147] Caregivers [3-17]	Questionnaire	2016	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach

van der Kloot et al. [37]	N/A	Sternocostoclavicular hyperostosis	Netherlands	52 Patients	Interviews and Questionnaires	2010	N/A
López-Bastida et al. [29]	2011-2012	Systemic sclerosis	Spain	147 Patients	Questionnaire	2014	Bottom-up method-societal perspective-prevalence approach-Indirect cost: Human capital Approach

Table 2: Descriptive statistics for all three cost outcomes for the Overall sample, by Body system and by Health care system type

		DH (€)			DNHF (€)			DNHI (€)		
	# of Obs	Mean (SD)	Median (10^{th} ; 90^{th})	% of Total	Mean (SD)	Median (10^{th} ; 90^{th})	% of Total	Mean (SD)	Median (10^{th} ; 90^{th})	% of Total
Overall	122	16,513 (30,045)	9,579 (1,237; 21,229)	0.400	4,579 (10,645)	1,072 (84; 10,435)	0.120	16,557 (15,070)	11,519 (1,968; 38,004)	0.490
Body System										
Cognitive	27	5,653 (6,272)	2,814 (317; 16,862)	0.210	6,981 (10,450)	3,191 (109; 21,416)	0.160	22,094 (13,765)	19,990 (4,828; 44,219)	0.660
Respiratory	16	16,008 (5,322)	14,553 (11,048; 26,143)	0.460	1,188 (1,410)	812 (82; 4,332)	0.0400	20,043 (12,012)	16,732 (6,295; 38,004)	0.500
Autoimmune	20	13,125 (6,687)	12,521 (4,977; 21,860)	0.670	1,106 (1,358)	735 (116; 3,176)	0.0500	6,181 (4,203)	7,738 (302; 11,789)	0.280
Musculoskeletal	12	9,050 (7,481)	7,657 (865; 20,153)	0.250	5,773 (7,282)	3,168 (101; 10,435)	0.170	17,441 (11,319)	15,001 (6,538; 31,189)	0.590
Other	47	26,270 (46,099)	7,712 (2,201; 111,745)	0.420	5,527 (14,434)	1,079 (44; 11,712)	0.140	16,496 (18,328)	10,098 (1,146; 44,154)	0.460
HC system										
Insurance-Based	33	23,609 (41,570)	14,912 (4,940; 26,143)	0.460	5,331 (5,332)	3,816 (708; 11,712)	0.150	15,567 (13,781)	11,673 (4,832; 34,019)	0.390
Tax-Based	89	13,881 (24,227)	7,145 (865; 21,229)	0.380	4,300 (12,049)	735 (69; 7,583)	0.110	16,928 (15,585)	11,445 (1,292; 39,177)	0.530

Table 3: Descriptive statistics for three patient utility outcomes for the Overall sample, by Body system and by Health care system type

		EQ-5D score		VAS		Barthel index	
	# of Obs	Mean (SD)	Median (10^{th} ; 90^{th})	Mean (SD)	Median (10^{th} ; 90^{th})	Mean (SD)	Median (10^{th} ; 90^{th})
Overall	68	0.560	0.640	62.21	62.50	70.51	83.78
		(0.26)	(0.26; 0.78)	(11.43)	(49.00; 76.70)	(30.48)	(16.80; 97.50)
Body System							
Cognitive	12	0.600	0.610	66.45	64.55	64.21	80.40
		(0.13)	(0.41; 0.73)	(11.69)	(56.20; 82.50)	(30.01)	(14.70; 86.67)
Respiratory	8	0.710	0.690	61.19	62.95	74.26	93.70
		(0.11)	(0.52; 0.87)	(8.26)	(46.00; 69.70)	(34.41)	(16.90; 98.90)
Autoimmune	12	0.580	0.640	59.08	59.65	81.62	93.44
		(0.17)	(0.26; 0.73)	(5.45)	(49.00; 64.80)	(27.17)	(19.27; 97.50)
Musculoskeletal	11	0.250	0.310	51.85	55.60	44.06	49.25
		(0.44)	(-0.17; 0.66)	(14.01)	(30.00; 64.10)	(25.45)	(6.60; 80.00)
Other	25	0.630	0.670	66.76	66.70	75.78	86.43
		(0.16)	(0.32; 0.78)	(10.07)	(53.25; 77.50)	(27.12)	(19.33; 97.50)
HC system							
Insurance-Based	16	0.590	0.600	60.14	61.10	89.45	93.40
		(0.20)	(0.32; 0.81)	(9.05)	(53.25; 67.60)	(10.71)	(81.15; 97.50)
Tax-Based	52	0.560	0.650	62.86	62.80	64.09	80.40
		(0.28)	(0.26; 0.74)	(12.09)	(49.00; 77.50)	(32.34)	(15.70; 97.20)

Table 4: Descriptive statistics for three caregiver utility outcomes for the Overall sample, by Body system and by Health care system type

		EQ-5D score		VAS		Zarit scale	
	# of Obs	Mean (SD)	Median (10^{th} ; 90^{th})	Mean (SD)	Median (10^{th} ; 90^{th})	Mean (SD)	Median (10^{th} ; 90^{th})
Overall	63	0.740 (0.15)	0.760 (0.61; 0.88)	72.36 (9.22)	72.50 (60.00; 83.10)	30.86 (7.60)	30.91 (21.70; 40.89)
Body System							
Cognitive	12	0.780 (0.05)	0.770 (0.73; 0.85)	77.41 (5.19)	76.40 (71.30; 82.50)	36.12 (6.58)	36.96 (27.00; 44.13)
Respiratory	8	0.800 (0.11)	0.840 (0.63; 0.92)	74.94 (11.28)	79.20 (53.30; 84.90)	26.85 (2.96)	27.85 (21.70; 29.30)
Autoimmune	13	0.690 (0.12)	0.670 (0.59; 0.80)	68.39 (9.81)	69.80 (50.00; 78.30)	28.16 (8.35)	26.74 (22.90; 33.67)
Musculoskeletal	8	0.670 (0.08)	0.690 (0.51; 0.78)	71.38 (9.60)	73.50 (56.00; 81.50)	29.13 (8.36)	31.90 (14.50; 37.30)
Other	22	0.740 (0.21)	0.800 (0.49; 0.93)	71.39 (8.99)	70 (61.67; 83.10)	31.41 (7.23)	32.30 (18.50; 40.89)
HC system							
Insurance-Based	17	0.720 (0.14)	0.740 (0.49; 0.87)	68.55 (8.20)	69.20 (59.44; 79.00)	32.96 (8.27)	33.80 (23.36; 41.74)
Tax-Based	46	0.740 (0.16)	0.780 (0.61; 0.88)	73.77 (9.26)	75.68 (61.50; 83.70)	29.80 (7.13)	29.75 (21.50; 38.60)

Table 5: Estimation results from random-effects meta-regressions for patient cost outcomes

	HC	HC	HC	HC	DNHF	DNHF	DNHF	DNHF	DNHI	DNHI	DNHI	DNHI
Patient utility score			15,682				-760.1**				-7,600	
			(14,511)				(361.1)				(5,752)	
Mean patient age				-1,069				53.16				-426.0
				(636.3)				(69.12)				(501.1)
Body System (ref: Other)												
Cognitive		-23,688***				514.4				9,028***		
		(7,727)				(407.8)				(2,914)		
Respiratory		-12,583				157.8				8,028***		
		(8,086)				(347.5)				(2,866)		
Autoimmune		-19,120**				-141.9				-6,109**		
		(8,435)				(370.7)				(2,961)		
Musculoskeletal		-19,759*				592.1				9,245**		
		(10,089)				(546.1)				(3,794)		
HC system (ref: Insurance Based)												
Tax-Based	-7,759	-7,137	-6,605	-228.0	-1,448***	-1,651***	-2,200***	-1,413**	3,129	3,546	1,272	3,617
	(7,500)	(7,102)	(10,105)	(5,450)	(396.0)	(429.9)	(347.2)	(603.8)	(3,553)	(2,869)	(3,972)	(4,341)
Public health expenditures (% GDP)	-29,832***	-28,098***	-34,617**	-11,068	755.9	1,016*	1,054***	1,151	-8,050	-9,508**	-10,181*	-7,318
	(10,724)	(10,174)	(14,280)	(7,787)	(499.0)	(553.6)	(301.6)	(851.8)	(4,985)	(4,007)	(5,598)	(6,096)
GDP per capita	31,239**	29,957**	36,058**	12,943	-1,147*	-1,379**	-1,862***	-1,343	9,096*	11,544***	9,443	10,062
	(12,150)	(11,545)	(16,148)	(8,387)	(575.5)	(628.9)	(411.7)	(902.3)	(5,126)	(4,042)	(5,764)	(6,188)
Life expectancy at birth	2,496	2,782	4,203	1,185	405.8**	488.7**	645.3***	308.5	3,095	3,087*	3,662	1,659
	(5,048)	(4,782)	(6,771)	(3,631)	(199.0)	(223.8)	(116.0)	(352.8)	(2,232)	(1,767)	(2,476)	(2,683)
Constant	20,334***	34,237***	12,124	18,815***	1,942***	2,052***	3,056***	1,829***	10,824***	6,278**	15,181***	12,691***
	(6,604)	(7,950)	(12,892)	(4,967)	(363.5)	(467.2)	(438.0)	(558.4)	(2,902)	(2,916)	(5,101)	(3,890)
Observations	75	75	58	41	75	75	58	41	71	71	54	40
I-squared	97.30	94.70	97.20	97.90	77	77.70	59.10	75.30	90.50	82.80	89.20	90.40
Predicted Mean	14936	17624	17483	13137	934.1	1076	884.7	1045	13001	11766	12562	13308
Predicted Mean SE	6708	8393	8933	4697	292.4	431.2	194.7	474.8	3026	3150	3356	3583

Standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1

Table 6: Estimation results from random-effects meta-regressions for patient and caregivers utility outcomes

	Patient EQ-5D	Patient EQ-5D	Patient EQ-5D	Caregiver EQ-5D	Caregiver EQ-5D	Caregiver EQ-5D	Caregiver EQ-5D
Body System (ref: Other)							
Cognitive		-0.0250			-0.0236		
		(0.0833)			(0.0307)		
Respiratory		0.0781			0.00435		
		(0.0893)			(0.0329)		
Autoimmune		-0.0460			-0.0993***		
		(0.0791)			(0.0320)		
Musculoskeletal		-0.408***			-0.123***		
		(0.0855)			(0.0398)		
Patient utility score						0.127**	
						(0.0478)	
Mean patient age			0.0276				-0.0125**
			(0.0232)				(0.00603)
HC system (ref: Insurance-Based)							
Tax-Based	-0.0774	-0.00581	-0.273	-0.00828	0.00460	0.00960	-0.0176
	(0.0906)	(0.0735)	(0.182)	(0.0338)	(0.0289)	(0.0329)	(0.0439)
Public health expenditures (% GDP)	-0.0905	-0.189*	-0.179	-0.125**	-0.138***	-0.103**	-0.128**
	(0.126)	(0.103)	(0.254)	(0.0470)	(0.0402)	(0.0462)	(0.0596)
GDP per capita	0.0410	0.176	-0.0600	0.0994*	0.123***	0.0920*	0.0801
	(0.141)	(0.115)	(0.281)	(0.0526)	(0.0453)	(0.0508)	(0.0682)
Life expectancy at birth	0.00196	-0.0281	0.102	0.0255	0.0252	0.0221	0.0336
	(0.0622)	(0.0505)	(0.118)	(0.0220)	(0.0188)	(0.0211)	(0.0275)
Constant	0.628***	0.646***	0.571***	0.776***	0.805***	0.690***	0.860***
	(0.0814)	(0.0760)	(0.184)	(0.0294)	(0.0295)	(0.0430)	(0.0445)
Observations	58	58	29	54	54	52	31
I-squared	99.20	97.10	99.50	93.50	87.60	92	91
Predicted Mean	0.574	0.593	0.488	0.770	0.775	0.772	0.779
Predicted Mean SE	0.0814	0.0856	0.159	0.0303	0.0339	0.0289	0.0384

Standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1