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SCOPING REVIEW

Are We Capturing the Socioeconomic Burden of Rare Genetic Disease? A Scoping Review of Economic Evaluations and Cost-of-Illness Studies

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Abstract

Background and Objectives Rare diseases have a significant impact on patients, families, the health system, and society. Measuring the socioeconomic burden is crucial to valuing interventions for rare diseases. Healthcare system costs are significant, but so are costs to other government sectors, patients, families, and society. To understand the breadth of costs captured in rare disease studies, we examined the cost categories and elements of socioeconomic burden captured in published studies.

Methods A scoping review was conducted using five electronic databases to identify English language economic evaluations and cost-of-illness studies of interventions for rare diseases (2011–21). We mapped costs using a previously developed evidence-informed framework of socioeconomic burden costs for rare disease.

Results Of 4890 studies identified, 48 economic evaluations and 22 cost-of-illness studies were included. While 18/22 cost-of-illness studies utilized a societal perspective, only 7/48 economic evaluations incorporated societal costs. Most reported cost categories related to medical costs, with medication and hospitalizations being the most common elements for both study designs. Costs borne by patients, families, and society were reported less among economic evaluations than cost-of-illness studies. These included: productivity (10% vs 77%), travel/accommodation (6% vs 68%), government benefits (4% vs 18%), and family impacts (0% vs 50%).

Conclusions Contrary to cost-of-illness analyses, most of the included economic evaluations did not account for the hidden burden of rare diseases, that is, costs borne by patients, families, and societies. Including these types of costs in future studies would provide a more comprehensive picture of the burden of disease, providing empirical data to inform how we value and make decisions regarding rare disease interventions, health policy, and resource allocation.

1 Introduction

Rare genetic diseases are those affecting only a small proportion of the population, often defined as those affecting fewer than 1 in 2000 people [1], and include inherited diseases that are passed from one generation to the next as well as de novo mutations that are not passed from one's parents. Rare genetic diseases affect children, adults, and future generations as genetic changes are carried forward [2]. While individually rare, with an estimated 7000–8000 identified rare diseases, collectively, rare diseases impact a large portion of the population [1, 3, 4].

Rare diseases collectively contribute significantly to morbidity, mortality, and healthcare costs, and have a significant impact on patients, their families, and society. Patients with rare genetic diseases often experience a prolonged and expensive diagnostic odyssey, requiring multiple tests and consultations with various healthcare practitioners to reach a diagnosis [5, 6]. Moreover, more than half of patients with rare genetic diseases are undiagnosed and most rare genetic diseases are currently untreatable, creating a tremendous burden on the individual, their families, and society [7]. Studies of the socioeconomic burden of rare disease in the USA and Europe have demonstrated the considerable burden attributed to costs to the healthcare system, productivity loss, and out-of-pocket costs to families, with costs to patients, their families, and society accounting for a large proportion of the overall burden [8–10].

A study of medicines approved by the European Medicines Agency with an orphan drug designation from 1 January, 2015 to 31 March, 2020 found that Canadians had less frequent and timely access to therapies for rare disease, reporting that fewer therapies for rare disease were submitted to Health Canada than to the European Medicines Agency or to the US Food and Drug Administration, and

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Key Points for Decision Makers

Earlier scoping reviews focused on cost-of-illness studies in rare disease have highlighted that there is a piecemeal approach to measuring the socioeconomic burden of rare disease and that costs to the medical system are more often captured than costs to patients, families, or society.

Our paper adds to this knowledge base by also including economic evaluations and highlighting the gap in costs considered by economic evaluations, which were largely conducted from a payer perspective and focused on health system costs. The hidden burden of rare disease, that is, costs borne by patients, families, and societies, are not often considered in economic evaluations of interventions for rare diseases.

Measuring and reporting these costs would better inform a comprehensive understanding of the burden of rare disease, which may impact health policy decisions and resource allocation and how we value interventions for rare disease.

that among those submitted, less than half were listed on public provincial formularies [11]. However, in the past decade, Canada has experienced an increase in the number of orphan medicines, or medicines used to treat rare diseases and conditions, which have received approvals, including approvals of 'expensive drugs for rare disease,' or those drugs with a cost exceeding CAD$100,000 per patient per year. By the end of 2020, 104 'expensive drugs for rare disease' had received approval in Canada [12].

When it comes to deciding which interventions should be funded given the finite resources for health spending, economic evaluations can provide decision makers with data on trade-offs between the costs and effects of interventions (e.g., treatments, devices, procedures). Studies of socioeconomic burden often explore and estimate costs to the healthcare system, costs to other government sectors, costs to families, as well as reduced productivity and education [13]. Economic evaluations are often conducted from the perspective of the healthcare payer, meaning they focus on costs to the healthcare system. However, economic evaluations may also adopt a private payer perspective (which considers costs to private payers such as drugs or medical devices), a broader government payer perspective (which considers costs to the publicly funded healthcare payer as well as other sectors, such as social services), or a societal perspective, which accounts for costs to patients and informal caregivers (e.g., out-of-pocket expenses) and productivity costs [14, 15]. Conversely, cost-of-illness studies are economic studies that aim to measure all costs of a disease, often considering costs to patients, their families, and society, along with costs to the health system.

Rare diseases, like chronic disease, are often ongoing in nature; however, rare diseases are unique in that they have a lengthy diagnostic odyssey [5, 6], with costs both to health systems and families [16], and once diagnosed, healthcare costs for children with genetic diseases are higher than children with chronic diseases (diabetes and asthma) and the general population [17]. In addition to these healthcare system costs, costs to families (e.g., out-of-pocket expenses and informal care costs) and society (e.g., lost productivity) represent a key component of burden in rare disease [8–10]. Highlighting the importance of these costs, the United Nations resolution on rare disease has committed to addressing the catastrophic out-of-pocket health expenditures for families [18]. However, the economic impact on the family network is often not discussed or measured when taking a healthcare system perspective [19]. To better understand the extent to which studies capture the socioeconomic burden of rare diseases, the aim of this scoping review is to examine which costs are included in economic evaluations of interventions for rare diseases compared to costs included in cost-of-illness studies for rare diseases.

2 Methods

We conducted a scoping review to identify economic evaluations and health technology assessments of interventions for rare genetic diseases or cost-of-illness studies of rare genetic diseases. We conducted and reported this review following the Preferred Reporting Items for Scoping Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidance [20]. The search was conducted in the following databases: Cochrane Library, EconLit, Embase, MEDLINE, and PsycINFO. The search strategy, designed in collaboration with a medical research librarian, can be found in the Electronics Supplementary Material (ESM). The search combined terms (subject headings and keywords) from two concepts: (i) rare genetic diseases that would be investigated in genetics clinics (e.g., hereditary, heredodegenerative, inborn, genetic, orphan, rare, ultra-rare, names of specific rare diseases) and (ii) socioeconomic burden (e.g., cost, cost-analysis, economic, socio-economic, socioeconomic, SEB, SES, societal, productivity, education, social supports, disability supports, family costs).

All search results were downloaded to Covidence (https://www.covidence.org/) for de-duplication, study screening, and selection. Studies were included if they were an economic evaluation or health technology assessment (with a cost-effectiveness component, measuring costs associated with a rare disease) or a cost-of-illness study, and published in English, from 2011 to 2021. To improve comparability

across the included studies, we limited included studies to those from Canada and peer countries utilized in comparisons by the Canadian Institute of Health Information, including Australia, France, Germany, the Netherlands, New Zealand, Sweden, the UK, and the USA [21]. We employed the European definition of rare disease as a condition affecting fewer than 1 in 2000 people to ascertain rare disease [1]. To check eligibility, each disease was searched in Orphanet (which utilizes the European definition of a disease affecting not more than 1 person per 2000 in the European population) to confirm it was a rare disease based on this definition [22]. Because our focus was on diagnosed rare diseases, screening and diagnostic tests were excluded from this scoping review. Title/abstract screening and full-text review were completed in duplicate by two members of the research team, who independently screened all identified abstracts against established inclusion and exclusion criteria (Table 1). Discrepancies were resolved by consensus or referred to a third member of the research team for a final decision.

Study characteristics, including country of study, study design, study perspective, and rare disease were extracted for each included study. Economic evaluations were classified using the Drummond et al. taxonomy, based on whether there was a comparison of two or more alternatives and whether costs and consequences of the alternatives were examined; studies characterising costs of a disease were categorized as cost-of-illness studies [13].

To characterize and compare the types of costs included, we applied a current evidence-informed framework of proposed cost elements for studying the socioeconomic burden of rare disease that was developed based on the literature and supplemented by expert input [23]. The framework consisted of several cost categories including: inpatient costs (e.g., hospitalization), outpatient costs (e.g., emergency room visits), community costs (e.g., paid care), healthcare products or goods (e.g., over-the-counter medications), productivity or education costs, travel and accommodation (e.g., transportation), government benefits, family impacts (e.g., adaptations), and other costs relevant to rare disease (e.g., out-of-country travel for advanced testing or treatment); see ESM. Given challenges of categorizing costs as inpatient, outpatient, or community, as few studies explicitly reported the setting(s) in which costs were incurred, for the purposes of this scoping review, an additional category, 'uncategorized medical costs,' was created to capture several of the cost elements from the 'inpatient, outpatient and community' cost categories. This category captured cost elements such as diagnostic imaging, laboratory tests, interventions or procedures, surgery, allied healthcare, genetic services, physician administration time, respite care, and palliative care.

For each included study, two reviewers independently compared costs identified in the study to the costs captured in the evidence-informed framework. For each cost element of the framework, the reviewers noted whether a cost had been included or not (yes or no); any additional costs falling outside of the categories and elements from the framework were captured using open-text fields to ensure all costs were considered. Costs were extracted in duplicate, and discrepancies were resolved by consensus or referred to a third member of the research team for a final decision.

Table 1 Inclusion and exclusion criteria for our scoping review of cost-of-illness studies of rare diseases and economic evaluations of interventions for rare diseases

Inclusion	Exclusion
The study focuses on a rare disease that is inherited/genetic and listed in Orphanet[a]	The study is about a common chronic disease
The primary study is measuring costs (SEB) associated with a rare disease	The study is about a rare but not inherited disease (i.e., childhood cancers, retinopathy) or was not in Orphanet
Economic evaluations of treatment, intervention, or care	The study does not address the cost portion of SEB
Cost-effectiveness or full economic evaluation	Cost of intervention only, no comparative aspect (e.g., costing of intervention or technology)
Cost analysis (comparative)	Cost effectiveness of treatment for event/complication of disease
Budget impact analyses that look at drug costs along with other costs	Studies on diagnostic testing
Health technology assessments with a cost-effectiveness component	Non-English studies
Cost-of-illness or burden of disease study	Study design (not an economic evaluation, cost-of-illness study, or a primary study)
English	
From Canada, Australia, France, Germany, the Netherlands, New Zealand, Sweden, the UK, and the USA[b]	From a country other than Australia, France, Germany, the Netherlands, New Zealand, Sweden, the UK, and the USA
Published from 2011 to 2021	Published prior to 2011

SEB socioeconomic burden

[a]Orphanet uses the European definition of a rare disease, as defined by the European Union Regulation on Orphan Medicinal Products (1999), of being a disease that affects not more than 1 person per 2000 in the European population (https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN)

[b]These countries were selected to align with countries defined as peer countries, those with similar resources to devote to healthcare, by the Canadian Institute for Health Information (https://www.cihi.ca/en/oecd-interactive-tool-international-comparisons-peer-countries-canada)

3 Results

A total of 4890 records were identified. After 658 duplicates were removed, 4232 titles/abstracts were screened. Of these, 3527 were excluded and 705 went on to full-text screening. In total, 48 economic evaluations [24–71] and 35 cost-of-illness [72–106] publications were included (Fig. 1).

Given that 14 of the cost-of-illness publications identified were related to the 'Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe' (BURQOL-RD) study (http://www.burqol-rd.com), which sought to quantify the burden of ten rare diseases (cystic fibrosis, Prader–Willi syndrome, hemophilia, Duchenne muscular dystrophy, epidermolysis bullosa, Fragile X syndrome, scleroderma, mucopolysaccharidosis, juvenile idiopathic arthritis, and histiocytosis) from eight member countries, including Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, and the UK [72–74, 77, 78, 80–84, 93, 96, 97, 99], we will report the cost elements of these publications collectively as the BURQOL-RD study, rather than individual publications, to avoid overinflating the number of studies reporting certain cost elements. Therefore, the cost categories and cost elements will be reported for 22 studies. Characteristics of included studies, including country of study, study design, study perspective, and rare disease considered are presented in Table 2.

3.1 Cost Categories

The breadth of costs varied greatly across studies, though cost-of-illness studies were more likely to capture costs across several cost categories, with 7 of 22 (32%) studies reporting one to five cost categories and 15 studies (68%) reporting six or more cost categories. Conversely, most of the economic evaluations included only a few cost categories, with most (41 of 48 studies, 85%) reporting between one and five cost categories and seven (15%) reporting six or more cost categories (Table 2).

Among the 48 economic evaluations, the most reported costs were to the health system, including inpatient costs (35 studies, 73%), outpatient costs (24 studies, 50%), community costs (11 studies, 23%), healthcare products and goods (45 studies, 94%), and uncategorized medical costs (33 studies, 69%). Given that few of these studies were conducted from a societal perspective, costs to patients and society were less commonly captured. Only five studies (10%) reported productivity or education costs, three studies (6%) reported travel or accommodation costs, and two studies (4%) reported government benefits. Notably, no economic evaluation studies reported family impacts (e.g., childcare), Fig. 2.

By comparison, among the 22 cost-of-illness studies, the majority captured costs to the health system, with 18 studies (82%) reporting inpatient costs, 20 (91%) reporting outpatient costs, 13 (59%) reporting community costs, 21 (95%) including uncategorized medical costs from inpatient, outpatient, or community settings (e.g., medical tests, therapeutics), and 21 studies (95%) reporting costs of healthcare products or goods. These studies more commonly incorporated costs borne by patients, their families, and society: 17 (77%) reported productivity or education costs, 15 (68%) reported costs related to travel and accommodation, 11 studies (50%) reported family impacts, and four studies (18%) reported government benefits, Fig. 2.

3.2 Most Reported Cost Elements

Overall, 24 cost elements from the evidence-informed framework were reported in one or more of the economic evaluations, compared with 33 cost elements reported in one or more of the cost-of-illness studies. Table 3 provides a summary of the cost elements reported in the included studies.

As shown in Fig. 3, the most reported cost elements among all included studies were medications (62 studies in total or 89% of studies) and hospital admissions (53 studies in total, 76%). Other commonly reported cost elements were medical tests (reported in 43% of all studies), outpatient visits (provider unspecified, 37%), surgery (37%), devices and aids (36%), lost productivity (29%), emergency room visits (26%), informal care (24%), and specialist visits (24%). The remaining cost elements were reported in less than 20% of included studies.

The five most reported elements among the economic evaluations were medications (41 studies, 85%), hospitalizations (35 studies, 73%), surgery (20 studies, 42%) medical tests (16 studies, 33%), and outpatient visits (provider unspecified,16 studies, 33%). The five most reported elements in the cost-of-illness studies were medications (21 studies, 95%), hospitalizations (18 studies, 82%), devices and aids (15 studies, 68%), lost productivity (15 studies, 68%), and allied health (15 studies, 68%).

3.3 Least Reported Cost Elements

Given the large proportion of economic evaluations employing a health system payer perspective, few costs elements pertinent to patients, their families, or society were included in these studies (Fig. 3). Only five (10%) of the economic evaluations included loss of productivity. Fewer than five studies included costs for paid/formal care, transportation, informal care, prescription diets/dietary supplements, government benefits, over-the-counter medication, genetic

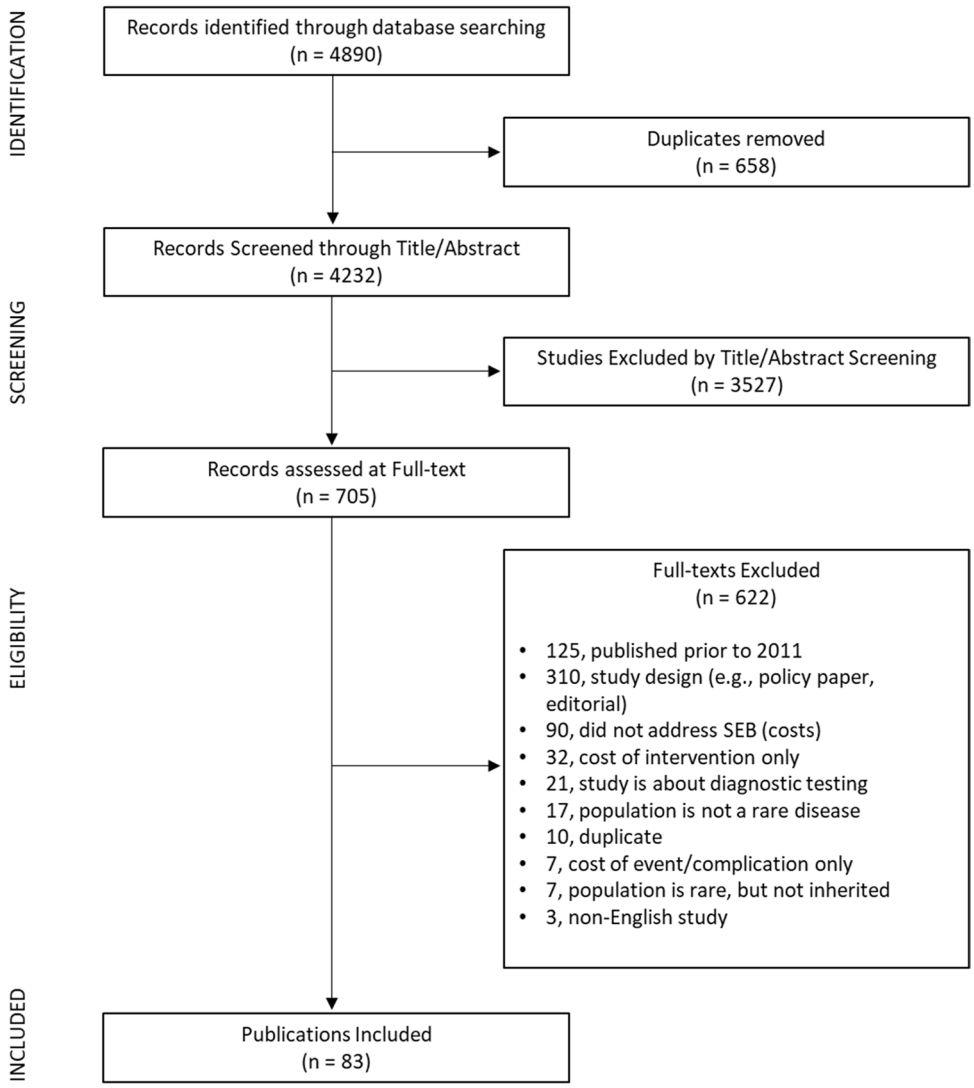

Fig. 1 Study selection using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidance [20]. *SEB* socioeconomic burden

services, counseling or testing, educational supports, naturopathic or alternative medicine products or services, and palliative, respite, or residential care. Several other costs included as part of the evidence-informed framework of costs relevant for rare diseases were not included in the economic evaluations (e.g., adaptations, parking, accommodation, loss of leisure time or usual activities).

Among the cost-of-illness studies, costs reported in ten or fewer studies included outpatient visits (unspecified), paid/formal care, transportation, general practitioner visits, adaptations, emergency room visits, respite care, surgery, and interventions or procedures. Cost elements reported in five or fewer studies included genetic services, counseling or testing, over-the-counter medication, naturopathic/alternative medicine providers or products/services, changes in employment, childcare, educational supports, intensive care unit, prescription diets/supplements, residential care, parking, accommodation, loss of leisure time or usual activities, living costs, social support, and physician advocacy time. Costs not reported largely fell in the 'other' category, such as out-of-country travel for advanced testing or treatment, participation in research, or research and foundations (Fig. 3).

4 Discussion

To better understand the breadth of socioeconomic burden being assessed in studies of rare genetic disease, our scoping review aimed to examine reported costs in economic evaluations of interventions for rare diseases and in cost-of-illness studies for rare disease to identify any gaps in costs captured. In this scoping review, 48 economic evaluations and 22 cost-of-illness studies were considered. While most of the cost-of-illness studies (18, 82%) were conducted from a societal perspective, incorporating costs to patients, their families, and society, only seven of the included economic evaluations

Table 2 Study characteristics of all studies included in the scoping review

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Cost-of-illness studies ($n = 22$)												
Baker, 2021 [75] Australia Cost of illness	Societal	Multiple: Prader–Willi syndrome, Angelman syndrome, chromosome 15q duplication and Fragile X syndromes	✓	✓		✓	✓	✓	✓	✓	✓	
Brown, 2020 [76] Australia Cost of illness	Societal	Hemophilia	✓	✓	✓	✓	✓	✓	✓	✓		
Chambers, 2020 [79] Australia Cost of illness	Patient, caregiver, and societal	SMA	✓	✓	✓	✓	✓	✓	✓		✓	
Geelhoed, 2011 [89] Australia Cost of illness	Health system	Down syndrome	✓	✓	✓	✓	✓					
Teoh, 2016 [104] Australia Cost of illness	Societal	DMD	✓	✓	✓	✓	✓	✓			✓	
Genereaux, 2016 [90] Canada Cost of illness (pilot)	Parental and societal costs	Down syndrome			✓	✓	✓	✓	✓	✓		
Price 2015 [100] Canada Cost of illness	Not specified	Hemophilia		✓			✓	✓	✓		✓	
Heimeshoff, 2012 [92] Germany Cost of illness	Societal	CF	✓	✓		✓	✓	✓	✓			✓

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Karl, 2017 [94] Germany Cost of illness	Not specified	Alpha-1-antitrypsin-deficient COPD	✓	✓		✓	✓	✓				
Schorling, 2019 [101] Germany Cost of illness	Societal	Charcot–Marie–Tooth	✓	✓	✓	✓	✓	✓	✓		✓	✓
Schreiber-Katz, 2014 [102] Germany Cost of illness	Societal	Duchenne and Becker muscular dystrophies	✓	✓	✓	✓	✓	✓	✓		✓	✓
BURQOL-RD studies [72–74, 77, 78, 80–84, 93, 96, 97, 99] Multiple Cost of illness	Societal	CF, Prader–Willi syndrome, hemophilia, DMD, epidermolysis bullosa, Fragile X syndrome, scleroderma, mucopolysaccharidosis, juvenile idiopathic arthritis, histiocytosis	✓	✓	✓	✓	✓	✓	✓			
Eriksson, 2017 [88] Multiple Cost of illness	Societal	ADPKD	✓	✓	✓	✓	✓	✓	✓			
Giunti, 2013 [91] Multiple Cost of illness	Health sector and societal	Friedreich Ataxia	✓	✓	✓	✓	✓	✓			✓	
Landfeldt, 2014 [95] Multiple Cost of illness	Societal	DMD	✓	✓		✓	✓	✓	✓		✓	✓

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
O'Hara, 2017 [98] Multiple Cost of illness	Societal and participant/ family	Hemophilia	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Eljamel, 2018 [86] UK Cost of illness	Service provider (National Health Service)	Congenital hyperinsulinism	✓	✓		✓	✓					
Eljamel, 2019 [87] UK Cost of illness	Service provider (National Health Service)	Wolfram syndrome	✓	✓	✓	✓	✓					✓
Weidlich, 2016 [105] UK Cost of illness (cost description)	UK National Health Service	Thalassemia major, beta		✓		✓	✓					✓
Wyatt, 2012 [106] UK Cost of illness	National Health Service, social care and other publicly funded care and support services	Lysosomal storage disorders	✓	✓	✓	✓	✓	✓	✓		✓	
Cloutier, 2020 [85] USA Cost of illness	Societal	ADPKD				✓		✓	✓			✓
Skalicky, 2018 [103] USA Cost of illness	Not specified	Tuberous sclerosis complex	✓	✓		✓	✓		✓		✓	

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Economic evaluations (n = 48)												
Brown, 2020 [27] Australia Budget impact analysis (set within a cost-of-illness framework)	Societal	Hemophilia	✓	✓	✓	✓	✓	✓	✓	✓		
Windegger, 2020 [71] Australia Cost-utility analysis	Australian healthcare system	Primary immunodeficiency disease	✓	✓		✓	✓					✓
Coyle 2014 [31] Canada Cost-effectiveness analysis	Publicly funded healthcare system	Paroxysmal nocturnal hemoglobinuria					✓					✓
Health Quality Ontario, 2016 [40] Canada HTA (cost-effectiveness analysis; budget impact analysis)	Ontario Ministry of Health and long-term care	Retinitis pigmentosa		✓	✓	✓	✓					✓
Health Quality Ontario, 2017 [41] Canada HTA (cost-effectiveness analysis; budget impact analysis)	Ontario Ministry of Health and long-term care	Retinitis pigmentosa		✓	✓	✓	✓					✓
Lillquist, 2011 [53] Canada Cost-benefit analysis	Not specified	CF	✓				✓					

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
McGirr, 2017 [56] Canada Cost-effectiveness analysis	Canadian healthcare payer	CF	✓	✓		✓	✓					
Simoncelli, 2015 [63] Canada Cost-consequence analysis	Quebec healthcare system	Hereditary tyrosinemia type I	✓	✓		✓	✓					
Polack, 2021 [59] France Cost-effectiveness analysis, cost-utility analysis	Collective (including all direct medical costs)	Hemophilia	✓	✓			✓					✓
Berger, 2013 [25] Germany Cost-effectiveness analysis	German statutory health insurance	Hemophilia	✓				✓					
Koeberlein-Neu, 2018 [50] Germany Cost-utility analysis; cost-effectiveness analysis	Societal	Hemophilia	✓	✓		✓	✓	✓	✓			✓
Castro-Jaramillo, 2012 [28] Multiple cost-effectiveness analysis	Health system	Pompe disease	✓			✓	✓					✓

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Farrugia, 2013 [36] Multiple cost-utility analysis	UK National Health Service/US third-party payer	Hemophilia				✓	✓					
Vaidya, 2014 [68] Multiple cost-effectiveness analysis	Healthcare payer	Retinitis pigmentosa		✓	✓	✓	✓			✓		✓
Henry, 2018 [42] Sweden Cost-utility analysis	Swedish health system	Hemophilia					✓					
Bentley, 2013 [24] UK Cost-utility analysis	UK National Health Service	Thalassemia, beta				✓	✓					✓
Karnon, 2012 [46] UK Cost-effectiveness analysis	UK health service	Thalassemia			✓		✓					✓
Landfeldt, 2017 [51] UK Cost-effectiveness analysis	Healthcare system and societal	DMD	✓	✓	✓	✓	✓	✓				✓
Tappenden, 2014 [65] UK Cost-effectiveness analysis	National Health Service	CF	✓				✓					

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Tappenden, 2017 [66] UK Cost-utility analysis; cost-effectiveness analysis	UK National Health Service and Personal Social Services	CF	✓			✓	✓					✓
Whiting, 2014 [70] UK Health technology assessment (cost-effectiveness; budget impact)	UK National Health Service	CF	✓	✓	✓	✓	✓					✓
Bernstein, 2020 [26] USA Cost-effectiveness analysis	US commercial payer	Hereditary angioedema	✓	✓	✓		✓					
Clark, 2017 [29] USA Cost-effectiveness analysis	Not specified	ADPKD				✓	✓					✓
Cook 2020 [30] USA Cost-effectiveness analysis	US health system	Hemophilia				✓	✓					✓
Dilokthornsakul, 2016 [32] USA Cost-utility study	US payer	CF	✓	✓		✓	✓					
Earnshaw, 2015 [33] USA Costing analysis	US third-party payer	Hemophilia	✓			✓	✓					

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Erickson, 2013 [34] USA Cost-effectiveness analysis	Societal	ADPKD		✓		✓	✓					✓
Fallah, 2016 [35] USA Cost-utility analysis	US third-party payer	Tuberous sclerosis complex	✓	✓		✓	✓					
Gibbons, 2019 [37] USA Cost-effectiveness analysis	Societal and third-party payer	Fuchs endothelial dystrophy		✓		✓	✓	✓	✓			✓
Hay, 2011 [38] USA Cost-minimization model	US third-party payer	Hemophilia	✓				✓					
Hay, 2013 [39] USA Cost-effectiveness analysis	US third-party payer	Hemophilia	✓			✓	✓					
Joish, 2018 [43] USA Cost-effectiveness analysis	US third-party payer	Carcinoid syndrome in patients with neuroendocrine tumors	✓	✓			✓					
Kacker, 2014 [45] USA Cost-effectiveness analysis	Hospital transfusion service	Sickle cell disease	✓			✓						
Kacker, 2014 [44] USA Economic evaluation	Hospital transfusion service	Sickle cell disease	✓			✓						

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Kazi, 2020 [47] USA Cost-effectiveness analysis	US healthcare sector	Transthyretin amyloid cardiomyopathy	✓	✓			✓					
Kim, 2019 [48] USA Cost-effectiveness analysis	US payer	Hemophilia	✓				✓					
Kim, 2020 [49] USA Cost-effectiveness analysis	US payer	Hemophilia	✓			✓	✓					
Li, 2015 [52] USA Cost-effectiveness analysis	Societal	Propionic acidemia and classical methylmalonic acidemia	✓		✓		✓	✓				✓
Machin, 2018 USA [54] Cost-effectiveness analysis	US third-party payer	Hemophilia	✓			✓	✓					✓
Malhotra, 2019 [55] USA Cost-effectiveness analysis	Societal	ADPKD				✓						✓
Neufeld, 2018 [57] USA Cost analysis	US healthcare payer	Hemophilia	✓				✓					
Panguluri ,2017 [58] USA Cost-effectiveness analysis	US healthcare	CF	✓	✓		✓	✓					✓
Rueda, 2020 [60] USA Budget impact analysis	Third-party payer	Alpha-1 antitrypsin deficiency	✓	✓	✓	✓	✓					✓

Table 2 (continued)

Author, year Country Study design	Perspective (as described by author)	Rare disease(s)	Inpatient	Outpatient	Community	Uncategorized Medical Costs[a]	Healthcare products or goods	Productivity/ education Costs	Travel and accommodations	Government benefits	Family impacts	Other[b]
Schechter, 2015 [61] USA Cost-utility analysis; cost-effectiveness analysis	US third-party payer	CF	✓	✓		✓	✓					✓
Sharma, 2018 [62] USA Cost-effectiveness analysis	US payer	CF	✓	✓		✓	✓					✓
Skornicki, 2014 [64] USA Budget impact analysis	Private healthcare payer	Lennox–Gastaut syndrome	✓	✓			✓					
Vadagam, 2018 [67] USA Cost-effectiveness analysis; budget impact analysis	US healthcare payer	CF	✓	✓		✓	✓					
Wherry, 2020 [69] USA Cost-effectiveness analysis	US payer	CF	✓		✓	✓	✓					✓

ADPKD autosomal dominant polycystic kidney disease, *CF* cystic fibrosis, *DMD* Duchenne muscular dystrophy, *SMA* spinal muscular atrophy

[a]Uncategorized medical costs include medical costs from the framework that were unable to be categorized as occurring in an inpatient, outpatient, or community setting, including costs for: diagnostic imaging, laboratory tests, interventions/procedures, surgery, allied health, genetic services, physician administration time, respite care or palliative care

[b]Other costs included: out of country (advanced testing), out of country (treatment), and patient services/supports from not-for-profit and advocacy groups as well as any reported costs that did not fit into a pre-defined cost element or where the setting was unclear (e.g., annual medical costs)

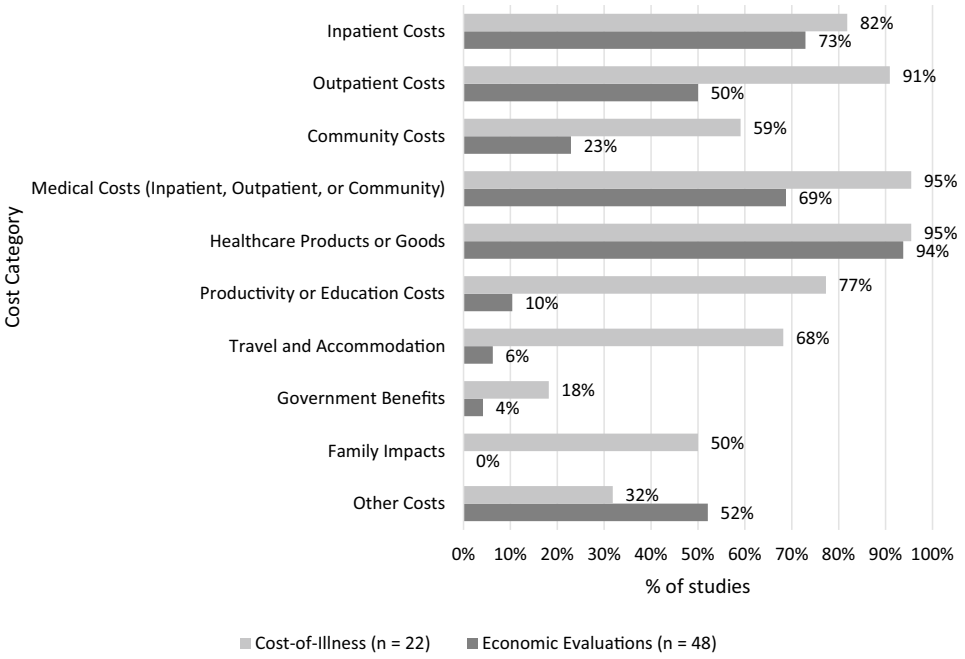

Fig. 2 Comparison of the cost categories represented by the costs reported in the included economic evaluations ($n = 48$) and cost-of-illness ($n = 22$[a]) studies. [a]Though we identified 35 cost-of-illness publications, only 22 studies are considered in the reporting of cost elements and cost categories, as 14 of the publications identified were part of the BURQOL-RD program and are collectively considered here as the BURQOL-RD study, rather than individual publications, to avoid overinflating the number of studies reporting certain cost elements

incorporated societal costs (though one only reported health system costs). Generally, the cost-of-illness studies captured a wider breadth of cost elements than the included economic evaluations, including productivity (77% vs 10%), travel and accommodation (68% vs 6%), government benefits (18% vs 4%), and family impacts (50% vs 0%).

Previous literature characterizing the types of costs included in studies of socioeconomic burden, including a scoping review of cost-of-illness studies in rare diseases [107], a scoping review of measuring healthcare resource use and costs in juvenile idiopathic arthritis [108], and a systematic review of costs reported in studies of children with medical complexity [109], all noted that costs incurred by patients, their families, and caregivers are less frequently reported [107–109]. García-Pérez et al. reported 100% of studies included medical costs, 60% included non-medical costs, 68% included lost productivity costs, and 43% included informal care costs [107]. Kip et al. reported that healthcare resource use items, such as medications, inpatient and outpatient visits, laboratory tests, and medical visits were most reported, productivity losses of caregivers were more commonly reported than future productivity losses of patients, and family-borne costs were less commonly reported [108]. Sidra et al. found that the majority of the included studies (24 studies, 89%) reported on healthcare service costs while only three studies (11%) reported on costs from a family perspective [109]. Our findings build on this knowledge base by utilizing an evidence-informed framework of costs, previously developed to inform a standardized approach to measuring the socioeconomic burden of rare diseases [23], to enable us to compare and highlight differences in the breadth of costs considered by economic evaluations and cost-of-illness studies. A consistent finding across our review and earlier reviews is that the costs captured, especially among the included economic evaluations, are largely focused on medical costs.

Research from the USA and Europe has highlighted the magnitude of costs incurred by patients, their families, and society. In the USA, a study estimated the total economic burden of 379 rare diseases in 2019 to be $997 billion, noting that only 45% of this total burden was attributed to direct medical costs ($449 billion), with the remainder attributed to indirect costs due to productivity loss ($437 billion, 44% of the total burden), non-medical costs, such as home or vehicle adaptations ($73 billion, 7% of the total burden), and non-covered costs, such as acupuncture or massage therapy ($38 billion, 4% of the total burden) [8]. Likewise, the BURQOL-RD program in Europe has also highlighted the magnitude of costs incurred by patients, their families, and societies, demonstrating that these costs represent an important and substantial component of the burden of rare disease [9, 10]. A systematic review of the cost-of-illness literature for the ten diseases of interest in the BURQOL-RD program reported that though limited information on productivity costs (they referred to as indirect costs) was available, authors note that they may account for a significant portion of overall costs [10]. These findings suggest that while health costs do attribute a large portion of the burden, focusing on only these costs does not provide a comprehensive understanding of the burden of these diseases, as much of the burden is hidden, in that it is borne by patients, their families, and society. Our scoping review and others have

Table 3 Cost elements from an evidence-informed framework of costs as reported in included studies, overall ($n = 70$), in economic evaluations ($n = 48$) and in cost-of-illness studies ($n = 22$[a])

Cost category, cost elements	Number of studies reporting element ($N = 70$) n (%)			References
	Overall ($n = 70$)	Economic evaluations ($n = 48$)	Cost of illness ($n = 22$[a])	
Inpatient				
Hospital admission	53 (76%)	35 (73%)	18 (82%)	[25–28, 32, 33, 35, 38, 39, 43–45, 47–54, 56–64, 66, 66, 67, 69–71, 75, 76, 79, 86–89, 91, 92, 94, 95, 98, 101–104, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
ICU	6 (9%)	4 (8%)	2 (9%)	[28, 48, 49, 63, 79, 98]
Other inpatient costs (e.g., physician fees, inpatient medical costs)	8 (11%)	4 (8%)	4 (18%)	[35, 38, 39, 56, 86, 92, 94, 102]
Outpatient[b]				
ER visit	18 (26%)	10 (21%)	8 (36%)	[26, 27, 43, 50, 51, 58, 60, 63, 64, 71, 75, 76, 94, 95, 103, 104, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
GP visit	14 (20%)	5 (10%)	9 (41%)	[50, 51, 58, 60, 71, 75, 76, 79, 89, 94, 95, 102, 104, 106]
Specialist visit	17 (24%)	6 (13%)	11 (50%)	[27, 50, 51, 58, 60, 71, 75, 76, 79, 87, 89, 94, 95, 98, 102, 104, 105]
Outpatient visit (provider not specified)	26 (37%)	16 (33%)	10 (45%)	[26, 30, 32, 37, 40, 41, 43, 47, 59, 61–63, 67, 70, 75, 86–88, 91, 92, 101, 103, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Other outpatient costs (e.g., outpatient pharmacy, outpatient administration, outpatient care)	29 (41%)	17 (35%)	12 (55%)	[26, 27, 34, 35, 37, 40, 41, 43, 47, 51, 58–60, 63, 68, 70, 71, 76, 86–88, 91, 92, 95, 100–102, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Community				
Naturopath and other alternative medicine providers	2 (3%)	0 (0%)	2 (9%)	[98, 106]
Paid care/formal care	14 (20%)	4 (8%)	10 (45%)	[27, 46, 68, 70, 76, 79, 88, 89, 91, 98, 101, 104, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Residential care	3 (4%)	1 (2%)	2 (9%)	[27, 75, 76]
Personal support workers	0 (0%)	0 (0%)	0 (0%)	
Other community costs (e.g., community services, in home treatment, community mental healthcare)	14 (20%)	7 (15%)	7 (32%)	[26, 40, 41, 51, 52, 60, 69, 87, 89–91, 95, 102, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Uncategorized medical costs (inpatient, outpatient, or community setting)[c]				
Tests (e.g., laboratory or diagnostic imaging)	29 (41%)	16 (33%)	13 (59%)	[24, 27, 30, 33, 34, 39, 44, 45, 49, 51, 55, 56, 58, 60, 67, 71, 76, 79, 86–88, 91, 92, 95, 98, 103–105], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Intervention or procedures (e.g., transfusion, joint injection)	11 (16%)	5 (10%)	6 (27%)	[31, 44, 45, 55, 60, 86–88, 98, 103, 105]
Surgery	26 (37%)	20 (42%)	6 (27%)	[24, 27, 30, 32, 33, 36, 37, 40, 41, 54, 61–63, 68–70, 86–88, 91, 98, 103]
Genetic services/counseling/testing	6 (9%)	1 (2%)	5 (23%)	[54, 75, 86, 87, 104, 105]
Allied health professional	23 (33%)	8 (17%)	15 (68%)	[27, 40, 41, 50, 51, 58, 63, 70, 75, 76, 79, 87, 89–92, 94, 95, 98, 101, 102, 104, 106]
Physician advocacy time	1 (1%)	0 (0%)	1 (5%)	[85]

Table 3 (continued)

Cost category, cost elements	Number of studies reporting element ($N = 70$) n (%)			References
	Overall ($n = 70$)	Economic evaluations ($n = 48$)	Cost of illness ($n = 22$[a])	
Respite care	8 (11%)	1 (2%)	7 (32%)	[51, 75, 76, 79, 89–91, 95]
Palliative care	1 (1%)	1 (2%)	0 (0%)	[28]
Health products and/or goods				
Medication	62 (89%)	41 (85%)	21 (95%)	[24–39, 42, 43, 46–51, 54, 56–67, 69–71, 75, 76, 79, 86–92, 94, 95, 98, 100–105, 105, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Medication, over the counter	7 (10%)	2 (4%)	5 (23%)	[27, 50, 75, 76, 79, 91, 98]
Prescription diets/dietary supplements	5 (7%)	3 (6%)	2 (9%)	[35, 52, 56, 76, 102]
Devices and aids	25 (36%)	10 (21%)	15 (68%)	[27, 40, 41, 46, 50, 58, 59, 68, 70, 75, 76, 79, 86, 87, 89–91, 95, 95, 98, 100–102, 104], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Naturopathic or alternative medicine products/services	6 (9%)	1 (2%)	5 (23%)	[59, 76, 89, 98, 102, 103]
Other healthcare products/goods costs (e.g., vaccinations, device maintenance, medical supplies)	23 (33%)	16 (33%)	7 (32%)	[24, 31, 32, 35, 40, 41, 52, 56, 59, 60, 62, 65, 67, 68, 70, 71, 79, 86, 89, 90, 100, 105] , BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Productivity and education costs				
Cost of loss of labor productivity (e.g., lost earnings/income/wages)	20 (29%)	5 (10%)	15 (68%)	[27, 37, 50–52, 76, 79, 85, 88, 90–92, 94, 95, 98, 101, 102, 104, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Changes in employment	5 (7%)	0 (0%)	5 (23%)	[75, 91, 94, 98], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Informal care	17 (24%)	3 (6%)	14 (64%)	[27, 50, 51, 75, 76, 79, 85, 88, 90, 91, 95, 98, 101, 102, 104, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Cost of lost education	0 (0%)	0 (0%)	0 (0%)	
Educational supports	4 (6%)	1 (2%)	3 (14%)	[52, 75, 90, 91]
Lost education for siblings	0 (0%)	0 (0%)	0 (0%)	
Loss of leisure time or usual activities	1 (1%)	0 (0%)	1 (5%)	[79]
Time invested in learning about disease/disease management	0 (0%)	0 (0%)	0 (0%)	
Other productivity/education costs (e.g., absenteeism, presenteeism)	6 (9%)	3 (6%)	3 (14%)	[27, 37, 51, 76, 92, 100]
Travel and accommodation costs				
Transportation	13 (19%)	3 (6%)	10 (45%)	[27, 37, 50, 75, 76, 85, 88, 90, 95, 98, 100, 106], BURQOL-RD [72–74, 77, 78, 80–84, 93, 96, 97, 99]
Parking	2 (3%)	0 (0%)	2 (9%)	[100, 106]
Accommodation	2 (3%)	0 (0%)	2 (9%)	[100, 106]
Out of province/state/jurisdiction (but within country) travel	0 (0%)	0 (0%)	0 (0%)	
Living costs	1 (1%)	0 (0%)	1 (5%)	[100]
Other travel and accommodations costs (e.g., mileage, travel expenses)	6 (9%)	0 (0%)	6 (27%)	[79, 92, 101–103, 106]

Table 3 (continued)

Cost category, cost elements	Number of studies reporting element ($N = 70$) n (%)			References
	Overall ($n = 70$)	Economic evaluations ($n = 48$)	Cost of illness ($n = 22$[a])	
Government benefits				
Adult benefits	0 (0%)	0 (0%)	0 (0%)	
Child benefits	0 (0%)	0 (0%)	0 (0%)	
Other government costs (e.g., disability support, social benefits)	6 (9%)	2 (4%)	4 (18%)	[27, 68, 75, 76, 90, 98]
Family impacts				
Healthcare	0 (0%)	0 (0%)	0 (0%)	
Childcare	4 (6%)	0 (0%)	4 (18%)	[95, 100, 103, 106]
Adaptations	9 (13%)	0 (0%)	9 (41%)	[75, 79, 91, 95, 98, 100–102, 104]
Participation in research	0 (0%)	0 (0%)	0 (0%)	
Research and foundations	0 (0%)	0 (0%)	0 (0%)	
Other family impacts (e.g., other professional services, self-help group)	5 (7%)	0 (0%)	5 (23%)	[91, 95, 101, 102, 106]
Other costs				
Out of country, advanced testing	0 (0%)	0 (0%)	0 (0%)	
Out of country, treatment	0 (0%)	0 (0%)	0 (0%)	
Patient services/supports from not-for-profit and advocacy groups	0 (0%)	0 (0%)	0 (0%)	
Other costs not captured elsewhere in the framework (e.g., total healthcare costs, annual mean costs, other expenditures, intangible costs)	32 (46%)	25 (52%)	7 (32%)	[24, 28–31, 34, 37, 40, 41, 46, 50–52, 54, 55, 58–62, 66, 68–71, 85, 87, 92, 95, 101, 102, 105]

ER emergency room, *GP* general practitioner, *ICU* intensive care unit

[a]Though we identified 35 cost-of-illness publications, only 22 studies are considered in the reporting of cost elements and cost categories, as 14 of the publications identified were part of the BURQOL-RD program and are collectively considered here as the BURQOL-RD study, rather than individual publications, to avoid overinflating the number of studies reporting certain cost elements

[b]Physician costs captured in the outpatient category may include physician or specialist visits occurring in both outpatient or community setting, as it was not always possible to distinguish the setting in which this care was occurring

[c]Uncategorized medical costs include medical costs from the framework that were unable to be categorized as occurring in an inpatient, outpatient, or community setting, including costs for: diagnostic imaging, laboratory tests, interventions/procedures, surgery, allied health, genetic services, physician administration time, respite care, or palliative care

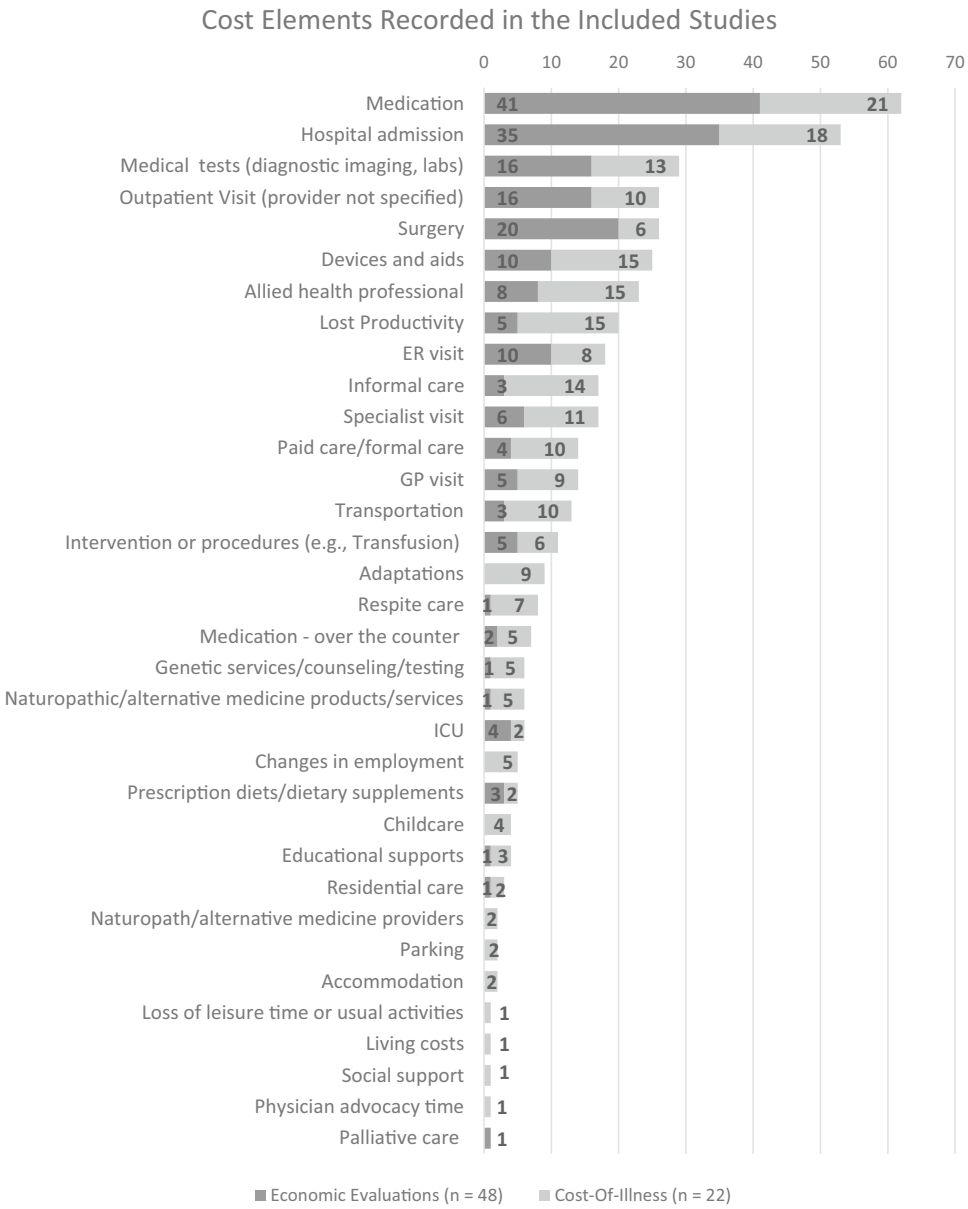

Fig. 3 Cost elements reported in the included studies: economic evaluations ($n = 48$) versus cost-of-illness studies ($n = 22$[a]). [a]Though we identified 35 cost-of-illness publications, only 22 studies are considered in the reporting of cost elements and cost categories, as 14 of the publications identified were part of the BURQOL-RD program and are collectively considered here as the BURQOL-RD study, rather than individual publications, to avoid overinflating the number of studies reporting certain cost elements. *ER* emergency room, *GP* general practitioner, *ICU* intensive care unit, *labs* laboratory tests. Some cost elements were not captured in any studies and are not included in this figure, including: personal support workers, cost of lost education, lost education for siblings, time spent learning about the disease/disease management, out of province or country travel, government benefits (adult or child), family healthcare impacts, out-of-country travel or advanced testing or treatment, participation in research, or research and foundations

highlighted that these costs are often overlooked in studies of rare disease [107–109]. However, the hidden burden of disease is not limited to rare disease, for example, both patients with rheumatoid arthritis and patients with Alzheimer's disease have significant costs beyond direct healthcare costs. A US study of people living with rheumatoid arthritis reported annual excess healthcare costs at $8.4 billion, costs of other rheumatoid arthritis consequences at $10.9 billion, along with intangible costs associated with quality-of-life loss at $10.3 billion and premature mortality at 9.6 billion [110]. Among patients with Alzheimers disease in the USA, the total cost of care in 2022 was estimated to be $321 billion, including $81 billion, or 25% of the total cost, in out-of-pocket costs and $34 billion, or 11%, in other costs (e.g., private insurance, health maintenance organizations, managed care organizations, or uncompensated care); this does not include the cost of informal caregiving [111]. An ISPOR spotlight highlighted that much of the burden of Alzheimer's disease is born by patients, their families, and society, costs traditionally not included in cost-effectiveness analyses, arguing that "*it may be necessary to expand the cost per QALY framework to include new elements of burden and value, or to develop a novel framework that is better suited to those dynamics*" [112].

Another finding of our scoping review was reporting inconsistencies among the studies captured in our review, which has been noted in earlier reviews [108, 109]. One finding was poorly defined cost elements, for example, referencing costs such as 'patient care' or 'background medical costs' or 'annual costs' without a clear definition of what

is included; this made it challenging to determine what costs were included or to which setting these costs should be attributed (inpatient, outpatient, or community medical costs). We found that in most instances the authors did not report the setting (inpatient, outpatient, or community) for cost elements such as surgery, diagnostic imaging, laboratory tests, or medications, making it difficult to determine who would bear the brunt of that cost (i.e., healthcare system, private payer, or out-of-pocket cost). Kip et al. also noted that details were often missing, such as clearly stating the type of medical professional being consulted in a medical professional visit [108]. Similarly, many of the studies included in our review referenced outpatient visits without specifying the type of visit or healthcare provider being seen. We also found variability in the terms used, perhaps because of the country of study or in data sources (e.g., studies from the USA often include costs related to physician fees). Challenges in comparing costs given the variability in studies of socioeconomic burden of rare disease (country, disease, what costs were included, how cost data were collected), along with inconsistencies in reporting, highlight the need for a unified approach to measuring the socioeconomic burden to facilitate making comparisons across diseases and countries, which would enhance our ability to fully understand the socioeconomic burden of rare disease. To ensure that pertinent costs are being incorporated and the full burden of disease is being captured, future studies should engage with patients and their families to bring the patient and his/her family voice to the measurement of socioeconomic burden of rare diseases. Though estimating the socioeconomic burden of rare diseases is uniquely challenging, given that many of the costs associated with rare disease are experienced outside of the health system, by excluding these costs, studies are underestimating the full impact of rare diseases on patients, their families, and society.

While most health technology assessment (HTA) bodies focus on health system costs, some do allow for other costs to be submitted as additional analyses. For example, in Canada the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluations [14] note that the reference case should adopt a public healthcare payer perspective, accounting for costs incurred by the public payer, while non-reference cases can vary in perspective, including private payer, broader government payer, or societal payer perspectives, to account for various types of costs and types of outcomes that fall outside of the perspective of the publicly funded healthcare payer. Furthermore, in an effort to broaden the view of 'value' in healthcare, in 2018, an ISPOR Special Task Force Report introduced novel elements of value for consideration in cost-effectiveness analyses, beyond the traditional elements of net costs and quality-adjusted life-years gained, and commonly used productivity and adherence-improving factors, including: reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers [113]. However, how HTA bodies deal with societal costs and proposed novel elements of value varies. A review of HTA guidelines by Breslau et al. examined whether, and to what extent, various HTA bodies had adopted societal costs (defined as: consumption, economic activity, education, environment, family spillover, healthcare system capacity, housing, legal, social services, transportation) and novel elements of value (adherence-improving factors, equity, fear of contagion, genericization, insurance value, productivity, real option value, reduction of uncertainty, scientific spillover, severity of disease, value of hope) in guidelines for conducting economic evaluations ($n = 53$). They report that the number and type of elements mentioned varied, and that when mentioned, elements were infrequently recommended for inclusion in the base case (some recommended they be included in sensitivity analyses or qualitative discussions) [114].

In addition to differences in the perspectives considered and how societal costs and value elements are considered by HTA bodies, there is variation in how HTA bodies evaluate drugs for rare diseases as highlighted in recent studies comparing the processes for evaluating drugs for rare diseases [115, 116]. A 2023 report by CADTH reviewed international HTA processes for evaluating drugs for rare diseases, they found that while some HTA bodies have separate evaluation frameworks or process specific to drugs for rare diseases (e.g., the National Institute for Health and Care Excellence), others did not have separate evaluation frameworks or processes, but rather, addressed the unique needs for assessing drugs for rare diseases through their standard processes, and that other countries or organizations have separate funding programs and evaluation frameworks for drugs for rare diseases [116].

These differences have important implications for drugs for rare diseases. A study examining recommendations for ten orphan drugs appraised by HTA bodies in England, Scotland, Sweden, and France reported that six of the ten drugs received diverging recommendations (i.e., a positive review in on country, but rejected in another), and concluded this was because of differences in evidence appraised by the HTA bodies (e.g., different evidence included by some), how the evidence was interpreted, and how uncertainty was managed [117]. Within Canada, there is variance in drugs accessible across the provinces as there is no national policy for drugs for rare diseases (though funding has been allocated to developing a National Strategy for Drugs for Rare Disease) and funding recommendations made by CADTH do not necessarily translate to which drugs are funded by the provinces (e.g., some drugs may be funded by a province though special access programs), with a recent study showing only fair agreement between CADTH's reimbursement

recommendations and coverage in Ontario, with 78% of drugs with a positive CADTH recommendation and 52% of drugs with a negative recommendation being funded by the province [118].

Taken together, these variations highlight that there is a need for a comprehensive and consistent measurement of the burden of rare diseases. Though economic evaluations have traditionally been limited to health system costs, the additional elements of value proposed by ISPOR, along with our increased understanding of the hidden burden of disease to patients, their families, and society, highlight the need for HTA bodies to work together to determine how to adapt to this changing landscape and how best to address the burden of disease, including costs incurred beyond the health system. Though these discussions are beyond the scope of our current paper, we would argue that a first step would be to consistently incorporate costs to patients, their families, and societies into studies of burden to provide empirical evidence of the key cost drivers of disease, which can then be used to inform future discussions regarding how to address this burden (whether this be through incorporating such costs into HTA decision making, or using this to inform government allocation of funding and supports). Sirrs et al. have highlighted the need for high-quality evidence to inform decision making, noting that "*Without high-quality evidence to assess value, we inadvertently prioritize patients with rare diseases over those with common diseases, creating conflict among ethical principles such as social utility, justice and the rule of rescue. Lack of transparency over what is being funded and for whom makes it hard to mitigate challenges through effective policy development*" [119]. To this end, future research and policy work should address questions of creating operationalizable criteria for when and how costs to patients, their families, and society should be considered in reimbursement decisions, as including these costs in some HTA decisions and not in others creates potential inequities across disease areas and this needs to be reconciled.

The current review was limited to English language peer-reviewed literature from electronic databases, and no gray literature searching or hand searching was conducted. In line with the scoping review methodology, and our aims of investigating the state of the literature examining what costs were collected in economic evaluations of interventions for rare diseases and in cost-of-illness studies, no quality appraisal was conducted for included studies. Because of reporting, it was difficult to categorize medical costs as occurring in an inpatient, outpatient, or community setting, and therefore, we created an additional category for uncategorized medical costs for the purposes of this scoping review; however, despite challenges in defining the setting of these costs, our results still highlight a focus on medical costs.

5 Conclusions

Our scoping review of economic evaluations of interventions in rare diseases and cost-of-illness studies of rare diseases has provided insights into the type and breadth of costs reported in these study designs, highlighting variability in both the types of costs and the breadth of costs considered across studies. Notably, our study demonstrated that most economic evaluations are conducted from a healthcare system or payer perspective, and therefore, largely consider only medical expenses. While cost-of-illness studies more routinely capture costs to patients, their families, and society, with few of the economic evaluations utilizing a societal perspective, the hidden burden of rare diseases borne by patients and their families may be undercounted in these types of studies. The inclusion of productivity and educational costs, travel and accommodation costs, government benefits, family impacts, and other costs in future studies would provide a more comprehensive picture of the full burden of disease, which in turn will provide evidence regarding key cost drivers of disease that can be used to inform future discussions of assessing value for new health technologies.

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Declarations

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Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Code availability Not applicable.

Authors' contributions All authors contributed to the study conception and design. Acquisition of data was performed by GC, BG, RJB and DL. All authors were involved in the analysis and/or interpretation of data. The first draft of the manuscript was prepared by GC, BG, RJB and DM, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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