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ORIGINAL RESEARCH ARTICLE

Developing a Framework of Cost Elements of Socioeconomic Burden of Rare Disease: A Scoping Review

Gillian R. Currie[1,2,3] · Brittany Gerber[2] · Diane Lorenzetti[2,4] · Karen MacDonald[2] · Susanne M. Benseler[1,3,5] · Francois P. Bernier[3,6] · Kym M. Boycott[7,8] · K. Vanessa Carias[9] · Bettina Hamelin[10] · Robin Z. Hayeems[11,12] · Claire LeBlanc[13] · Marinka Twilt[14] · Gijs van Rooijen[9] · Durhane Wong-Rieger[15] · Rae S. M. Yeung[16] · Deborah A. Marshall[2,3,17,18]

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Abstract

Background and Objective Rare diseases place a significant burden on patients, families, the healthcare system, and society. Evidence on the socioeconomic burden of rare disease is limited and mostly reflects diseases where treatments are available. We developed a framework encompassing recommended cost elements for studies of the socioeconomic burden of rare diseases.

Methods A scoping review, conducted in five databases (Cochrane Library, EconLit, Embase, MEDLINE, and APA PsycINFO), identified English language publications from 2000 to 2021 presenting frameworks developed for determining, measuring or valuing costs for rare or chronic diseases. Cost elements were extracted and used to develop a literature-informed framework. Structured feedback was gathered from experts in rare diseases, health economics/health services, and policy research to revise the framework.

Results Of 2990 records identified, eight papers were included and informed our preliminary framework; three focused on rare disease and five on chronic disease. Following expert input, we developed a framework consisting of nine cost categories (inpatient, outpatient, community, healthcare products/goods, productivity/education, travel/accommodation, government benefits, family impacts, and other), with several cost elements within each category. Our framework includes unique costs, added from the expert feedback, including genetic testing to inform treatment, use of private laboratories or out-of-country testing, family involvement in foundations and organizations, and advocacy costs for special access programs.

Conclusions Our work is the first to identify a comprehensive list of cost elements for rare disease for use by researchers and policy makers to fully capture socioeconomic burden. Use of the framework will increase the quality and comparability of future studies. Future work should focus on measuring and valuing these costs through onset, diagnosis, and post-diagnosis.

1 Introduction

Rare diseases place a significant burden on patients and their families, as well as the healthcare system and society. Estimates of the number of rare diseases range from 6000 to upwards of 8000 [1–3]. A recent analysis of Orphanet, a comprehensive database of rare diseases, reported that of the 6172 clinically unique rare diseases reviewed, 72% of the listed diseases were genetic in origin, and 70% had a pediatric onset [4]. Rare genetic diseases are unique in the patient experience of obtaining a diagnosis, which is often a lengthy and costly process requiring multiple physician visits, tests, and costs [5–7], referred to as the 'diagnostic odyssey'. Once diagnosed, treatment options are often limited as few rare diseases have treatments available [8, 9]. Where treatments do exist, they are often exceptionally expensive; in Canada 'expensive drugs for rare disease' are defined as those with a cost of >$100,000 per patient per year [10]. For patients, these diseases impact both survival and quality of life, and healthcare resource utilization among these individuals is often high. A Canadian study found that direct healthcare costs for children with genetic diseases were higher than children with chronic diseases (diabetes and asthma) and the general population [11]. Similarly, a US study reported that healthcare costs were three to five times higher among those with rare disease versus those without [12]. Outside of health care costs, the 'Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe' (BURQOL-RD) project demonstrated a significant

Extended author information available on the last page of the article

Key Points for Decision Makers

To our knowledge, our work is the first attempt to identify a comprehensive list or framework of cost elements for rare disease, to be used by researchers or policy makers to fully capture socioeconomic burden.

Our framework includes cost elements that are important and unique to rare disease, but which were not captured in existing literature we assessed, including genetic testing to inform treatment, use of private labs or travel out of the country for testing, family involvement in foundations and organizations, and advocacy costs for special access programs.

economic burden for ten rare diseases examined, with productivity costs approaching or exceeding health care and family out-of-pocket spending [13]. Societal costs are substantial due to lost productivity among individuals with rare genetic diseases and their formal/informal caregivers [14], and the economic impact on the family network is often not discussed or measured when taking a healthcare system perspective [15]. Comprehensive and standardized estimates of socioeconomic burden are needed to inform policy and funding decisions, and for full evaluation of the impact of interventions [13].

Socioeconomic burden of disease typically considers costs borne by the healthcare system, other government sectors, and by families, as well as reduced education and productivity for patients and their families [16]. The foundational step of comprehensively measuring the socioeconomic burden of rare disease is the identification of a comprehensive list of cost elements that could potentially be considered for inclusion. Currently, to identify the cost elements of socioeconomic burden, one can turn to general guidance on conducting and reporting economic evaluations, which include some examples of broad costs common to most diseases, such as hospitalization, physician services, and treatment costs (for example, see the Canadian Agency for Drugs and Technologies in Health *Guidelines for the Economic Evaluation of Health Technologies: Canada* [17]). Beyond this general guidance, there is no standardized or comprehensive list of cost elements generally for all diseases, and none specifically for rare genetic diseases.

To address the above noted gaps and the lack of available guidance on standards for measuring and reporting the socioeconomic burden, there is an urgent need for a unified and comprehensive approach to estimate the full socioeconomic burden of rare genetic diseases. Therefore, the aim of the current study is to identify any existing frameworks for measuring cost elements of socioeconomic burden of chronic or rare diseases and to draw on expertise of researchers, health economists, patient advocacy groups, and physicians to inform the development of a standardized list of costs incurred by the health system, patients, and society. This framework is intended to provide a foundational step towards the comprehensive measurement of socioeconomic burden of rare diseases, including rare genetic disease. The framework can then be adapted, modified, and refined to fit the needs of various study designs, health systems, and specific rare diseases being studied. This framework can be used to gather empirical evidence to guide our understanding of key cost drivers in rare genetic disease, allowing future research to focus on an evidence-informed core set of cost elements, and best practices for measuring and valuing these costs.

2 Methods

2.1 Scoping Review

To identify frameworks of costs, a scoping review was conducted to identify English language studies published between 2000 and 2021 reporting on frameworks for identifying, measuring, or valuing costs associated with chronic or rare (including rare genetic) diseases. Anticipating that there may be limited available frameworks or guidance related to rare genetic diseases, we also included chronic diseases that affect both children and adults in our search. We selected chronic disease given the ongoing, lifelong nature of both chronic and rare disease. The conduct and reporting of this review was guided by the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [18].

We searched the following databases to identify studies: Cochrane Library, EconLit, Embase, MEDLINE, and APA PsycINFO. Search terms included terms related to disease (e.g., rare diseases, genetic; or chronic illness), economics (e.g., burden of illness, costs, economics, SEB), and study design (e.g., best practice, design, framework, guidance, instrument, measures, models, policies, questionnaire, structure, survey, and tools). The search strategies are presented in Supplement 1 of the electronic supplementary material (ESM). The reference lists of included papers were also manually reviewed to identify relevant studies.

All search results were downloaded to Covidence (https://www.covidence.org/home) for de-duplication, study screening, and selection. 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. Studies were excluded if they were published prior to 2000, were not published in English, or did not provide a framework for identifying, measuring, or valuing costs.

Discrepancies were resolved by consensus or referred to a third member of the research team for the final decision.

For each of the included studies, study characteristics including authors, country, publication year, and disease area were extracted by a single reviewer. Separately, cost elements from each paper were extracted by a single reviewer into a list to inform the development of the literature-based framework. Consistent with scoping review methodology and the purpose of simply identifying cost elements from the literature, no quality appraisal was completed for the included studies [18, 19].

2.2 Framework Development

Members of the study team first reviewed and extracted a list of the cost elements reported in each included study. Similar cost elements were merged to account for variability in terminology from different countries and health systems. Drawing on cost categories in the CADTH guidelines for economic evaluation [17], the literature-based cost elements were preliminarily grouped into the following broad categories: healthcare system costs, costs to other government sectors, out-of-pocket costs to families or society, and education/productivity losses (Supplement 2, see ESM). The study team then further refined this into granular cost categories (e.g., hospital costs, healthcare products and goods) and cost category elements (e.g., inpatient stay and ICU were listed under hospital costs) to create the literature-informed framework.

Feedback on the literature-informed framework was gathered from our expert panel through a structured feedback exercise conducted on Zoom. The purpose of the exercise was to review what was found in the literature and then to expand on it based on their relevant expertise and experience. To capture a variety of perspectives, including clinical and advocacy/policy, the expert panel ($n = 13$) included pediatric clinicians and researchers, medical geneticists, health services researchers, health economists, and representatives from the Canadian Organization for Rare Disorders, Ontario Genomics, and Genome Alberta. The expert panel received materials about the scoping review methodology and results, the literature-informed framework, as well as questions to guide discussion and gather feedback. The framework was then revised to include cost elements not captured in the scoping review based on this feedback process (Fig. 1).

3 Results

3.1 Scoping Review

A total of 2990 records were identified. After 538 duplicates were removed, 2452 titles/abstracts were screened. Of these, 2427 were excluded and 25 papers went on to full-text screening (Fig. 2). In total, eight papers [20–27] were included: six were selected for inclusion through full-text screening, and an additional two were identified through checking reference lists (excluded studies are listed in Supplement 3, see ESM).

Three of the included papers focused on rare disease, including hereditary angioedema (HAE) [20], Down syndrome [21], and a value assessment and funding process framework in rare diseases [22]. Bygum et al. [20] aimed to contextualize the burden of HAE through interviews with patients, developing a conceptual model to illustrate the hypothesized relationships between short- and long-term health-related quality of life for patients, resource use, career/educational impacts and impairments, as well as caregiver impacts during and between acute attacks. Resource use elements included medication, treatment visits for attacks, routine care, mental healthcare, travel costs for treatment and routine care visits, along with absenteeism, decreased productivity, and loss of employment [20]. Genereaux et al. (2016) sought to understand the parental and societal costs of raising a child with Down syndrome in Canada, and developed an online costing tool by adapting two existing cost diaries to the Canadian context, which captured costs related to therapies, appointments, respite care, family service use, government benefits, transportation, and additional expenditures (e.g., medication, special equipment) as well as income loss due

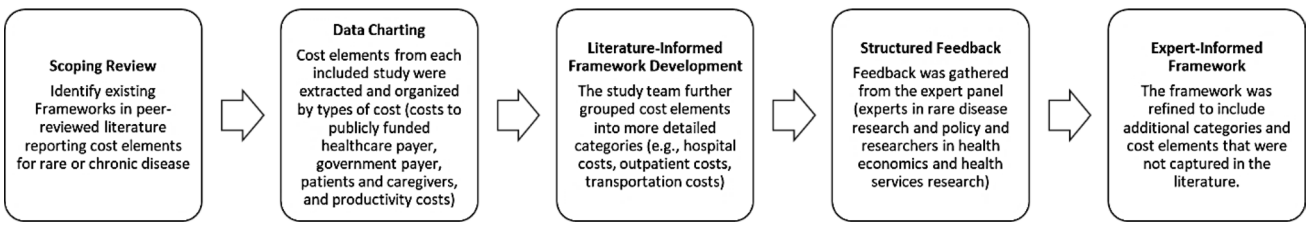

Fig. 1 Process used for developing a framework of cost elements of the socioeconomic burden of rare disease. The categories used in the data charting process were based on the types of costs presented in the CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition) [17]

to reduced work hours, paid and unpaid time off from work for parents, and care provided by friends and family [21]. Annemans et al. [22] outlined nine principles to improve the consistency of orphan medicinal products pricing and reimbursement assessment in Europe. The core elements included patient level (e.g., out-of-pocket medical costs, lost worktime, and home adaptations), healthcare system level (e.g., hospital visits, surgeries, and diagnostics), and societal level elements (e.g., out-of-pocket medical costs, lost income, and decreased productivity).

The remaining studies looked at chronic conditions, including atopic dermatitis [23], food allergies [24, 25], and arthritis [26, 27]. Boguniewicz et al. [23] developed a multiple-domain framework, including patient-reported outcomes along with clinical assessments to be used in evaluating interventions in atopic dermatitis. Elements of resource use included physician visits, prescriptions, ER and clinic visits, as well as payment and out-of-pocket costs per physician visit and expenses related to disease-specific treatments, as well as productivity/absenteeism (work or school missed) by the patient and/or their caregiver [23]. Miles et al. [24] developed a framework for assessing the cost of illness for immunoglobulin E-mediated food allergy and food intolerance. Direct costs included elements such as hospital and primary care, attendance in class, outreach and social care, informal care, and out-of-pocket expenses. Indirect costs included loss of education and income from employment, housekeeping costs, and public health campaigns. Based on the Miles et al. [24] framework, Fox et al. [25] sought to develop a questionnaire to measure costs and health utility among people living with food allergies in Europe, which included travel costs, hospital admissions, cost of medication (prescribed, over the counter, and alternative), cost of help with domestic duties, cost of food and leisure and lost earnings, lost productivity, restricted activity days, human capital reduction, time spent seeking healthcare or information, and lost leisure time [25].

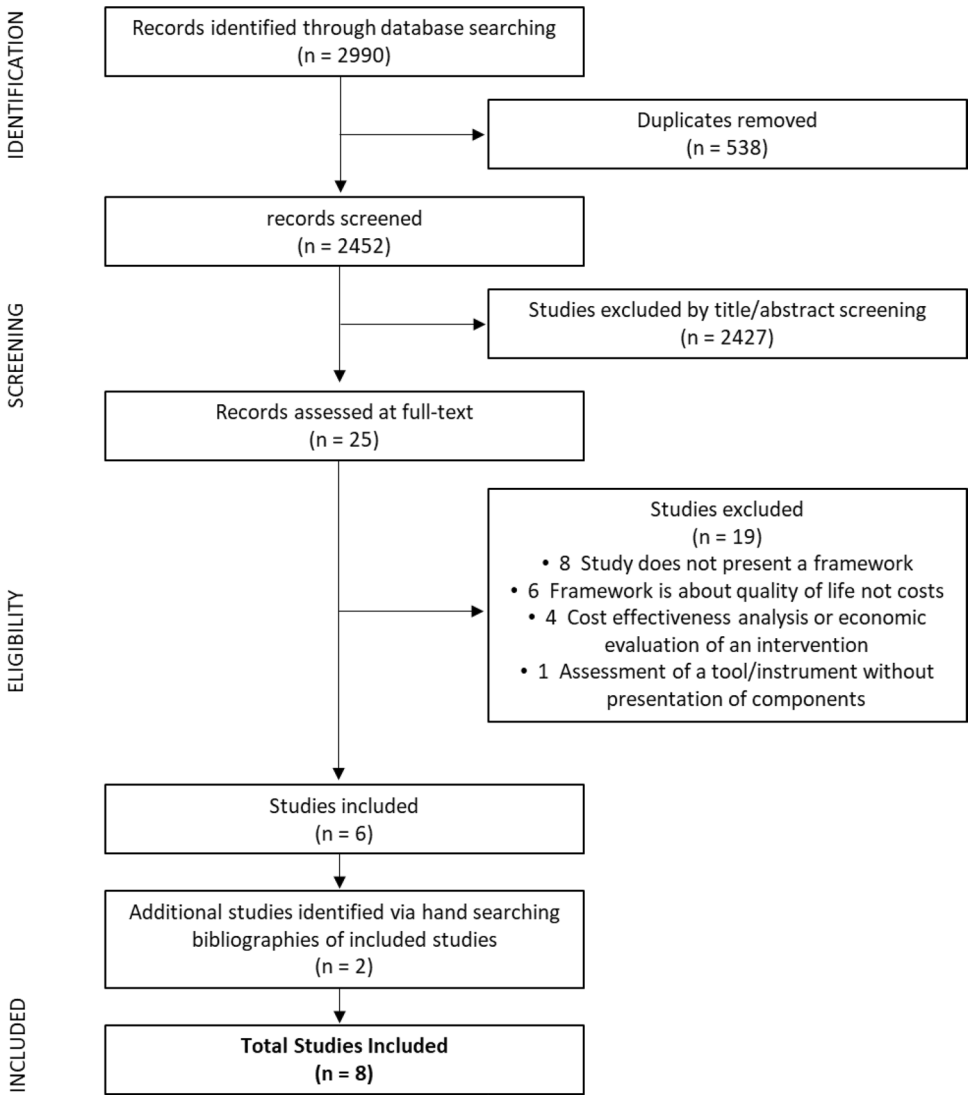

Fig. 2 Summary of the scoping review search using the PRISMA Extension for Scoping Reviews (PRISMA-ScR) diagram [18]

Merkesdal et al. [26] undertook a comprehensive literature review to develop a standardized set of cost domains to be used in economic evaluations of rheumatic diseases. Their matrix consisted of 19 domains for outpatient costs, inpatient costs, other direct disease-related costs, as well as productivity costs [26]. Lo et al. [27] conducted a systematic review of methodologies used to assess direct costs for arthritis using seven domains for healthcare costs from Merkesdal et al. [26], including visits to physicians, allied health, prescription medicine, over-the-counter medicines, and inpatient, outpatient/emergency, and diagnostic test costs.

3.2 Literature- and Expert-Informed Framework of Cost Elements

Based on the cost elements identified in this scoping review, an initial literature-informed version of the framework was developed, which was then revised based on feedback provided by experts on our research team. More specifically, as shown in Fig. 3, we refined the cost categories developed through the scoping review which included changing the 'hospital cost' and 'medical cost' categories into three more specific categories of 'inpatient', 'outpatient', and 'community' cost. These categories better account for the location of care, which also links to who bears the cost. A separate category to capture costs of Government benefits was also added.

During the structured feedback exercise, the expert panel discussed several elements that were particularly salient for rare diseases and required more detailed categorization. For instance, based on the literature, we had included 'adaptations' as a cost element, and based on expert feedback, this element was updated to also include educational adaptations (e.g., ergonomics) as well as recreational costs (e.g., use of a wheelchair for sports). Similarly, the transportation category (which captured mode of transportation) was enriched to capture other costs associated with travel for appointments, including transportation, accommodation, living costs while traveling, parking expenses, and out-of-country travel for testing or treatment. The productivity category expanded to also include loss of employment, early retirement, time spent learning about the disease and its management, and impact to siblings (who may also be absent from school due to a sick family member). Naturopathic and alternative medications and products were added to the framework. Lastly, we further refined care elements to include residential care, personal support workers, and living care arrangement costs.

During the feedback sessions, the expert panel was able to highlight additional cost elements unique to rare disease that were not captured in the literature. These additions included elements such as

- advanced testing (including genetic services, counselling or testing that would be performed after diagnosis to either further define the disease or inform treatment);
- use of private labs or travel out of the country in order to complete testing (e.g., biomarker panels) not offered through the healthcare system;
- costs associated with participation in research (such as locating studies, travel and accommodation costs) as well as families taking on research, starting foundations and organizations;
- sibling impacts (productivity and healthcare costs, such as seeing a psychologist); as well as
- administrative costs, which is unbillable time spent by physicians and their team advocating for patient access to medications (e.g., completing insurance forms, applying for special access programs); and
- costs associated with patient services and supports offered by not-for-profit and advocacy groups.

Based on the feedback provided by the expert panel, details were added to better characterize what types of costs would fall within each element by adding examples where possible to provide clarity for end users of the framework (i.e., examples were added to the allied health element to account for therapies that might fall under this element, such as occupational health or speech and language pathology).

The expert-informed framework, developed through the literature review and refined based on expert feedback, is presented in Table 1 and consists of nine cost categories: inpatient, outpatient, community, healthcare products/goods, productivity/education, travel and accommodation, government benefits, family impacts, and other costs. Within each category, we have compiled 77 cost elements for consideration. Some cost elements appear in multiple categories, which reflects that the burden of the cost may fall in various settings. For example, in Alberta, a patient may receive medications or allied health services in the hospital at the cost of the health system, while having to pay for these in the community setting.

4 Discussion

This scoping review comprehensively reviewed relevant literature to inform the development of a framework for assessing the cost elements of the socioeconomic burden of rare disease, including rare genetic disease. Of eight publications identified, notably, only three were specific to rare disease. We used the cost elements from the included papers to develop a literature-informed framework. We subsequently engaged with experts in rare disease to identify additional costs which were not captured in the literature, such as genetic services, counselling or testing to inform

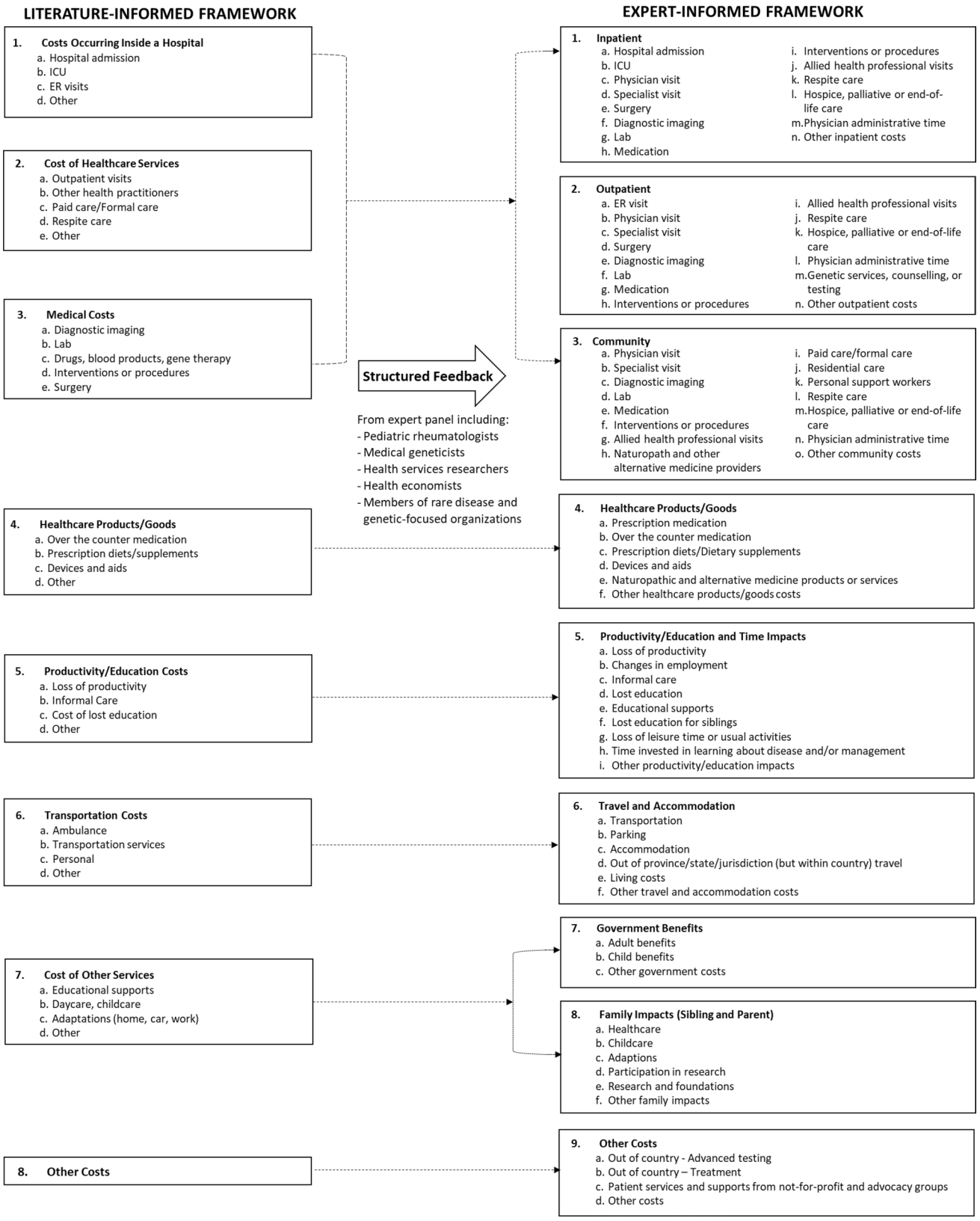

Fig. 3 Diagram illustrating changes from the literature-informed and expert-informed versions of the framework of costs elements for measuring socioeconomic burden of rare disease. *ER* emergency room, *GP* general practitioner, *ICU* intensive care unit

treatment, use of private labs or travel out of the country for testing, and family involvement in foundations and organizations, for consideration in our comprehensive list of cost elements for potential inclusion in studies of the burden of rare disease. The study team also identified the importance of what we defined as advocacy costs, which is time spent by physicians and their teams to access high-cost medications for patients with rare disease, often only available through special access programs. Our work is the first attempt to identify a comprehensive list or framework of cost elements for rare disease, to be used by researchers or policy makers to fully capture socioeconomic burden.

Despite the importance of understanding the socioeconomic burden of rare disease, the evidence from existing literature is limited. A systematic review of cost-of-illness studies of ten rare diseases included in the BURQOL-RD project found that evidence was scarce, and was aligned with treatment availability rather than the prevalence or severity of disease [13]. Given that treatments are available for very few rare genetic diseases, this results in a substantial gap in our understanding of socioeconomic burden. Another review, examining the prevalence of rare genetic diseases, associated morbidity and mortality, healthcare utilization, and orphan drugs, highlighted variations in the types of costs reported, an overall paucity of cost data related to rare genetic diseases, and significant challenges associated with estimating socioeconomic burden based on currently available data [28]. Likewise, another review demonstrated a scarcity of cost-of-illness studies and noted a lack of data to inform these estimates [29]. Studies have demonstrated gaps in costs captured outside of medical costs, such as productivity and educational impacts, non-medical costs, and out-of-pocket costs [29, 30]. For instance, a scoping review of resource use and costs in juvenile idiopathic arthritis found that productivity, educational impact, and family out-of-pocket costs were not often included despite their significant role in childhood chronic disease, further highlighting the need for a standardized list of items to be considered [30].

Measuring socioeconomic burden in rare diseases poses unique challenges, given that many costs associated with rare disease are experienced outside of the health system, by patients, their families, and society, and are difficult to measure. Appropriately capturing these costs requires attention and innovative strategies moving forward. Researchers and patient groups need to engage with health technology assessment (HTA) bodies and decision/policy makers to mitigate the challenges in estimating socioeconomic burden in the rare disease population [31], as small population sizes, limited evidence, lack of comparators, and high costs make assessing these drugs challenging under standard HTA processes [32–34]. For example, a study examining HTA recommendations for a sample of ten orphan drugs in four European countries reported diverging recommendations for six of the ten orphan drugs (list, list with restrictions, do not list) due to differences in evidence appraised, how the evidence was interpreted, and how uncertainty was managed [35]. Recent comparisons of HTA processes for drugs for rare diseases have highlighted differences in how HTA bodies assess drugs for rare disease; while some HTA bodies have not introduced separate processes for rare disease [32, 33], others have developed separate evaluation frameworks or processes for evaluating these drugs, address unique considerations for these drugs in their standard processes, or have separate funding programs and evaluation programs for these drugs [33]. The recent evaluation manual of the National Institute for Health and Care Excellence now explicitly allows committees to weight decisions based on disease severity, consider a broader evidence base, allow flexibility in accepting uncertainty in specific situations (such as rare disease or child populations), and allow for managed access programs [36]. Additionally, some novel elements of value have been presented in The International Society for Health Economics and Outcomes Research (ISPOR) value framework and may be particularly pertinent to rare disease (such as equity, severity of disease, option and insurance value [37]) and valuing drugs for rare genetic disease. While commenting on what should and should not be included in an HTA is beyond the scope of this paper, our aim is that since some HTA bodies may allow for a societal perspective (e.g., CADTH permits societal perspective as a non-reference case [17]), this framework can be used to gather the required empirical evidence of key cost drivers for rare disease which can subsequently be used to inform and guide discussions to develop a more consistent and comprehensive approach to measuring the socioeconomic burden of rare genetic disease outside of those costs typically considered by a health system perspective (e.g., hospitalizations) which are borne by patients, families, or society, to provide higher quality evidence to inform cost-effectiveness analyses.

Further research is needed to identify the normative question of what should be included in economic evaluations and HTA and the implications of modifying existing processes on downstream decision making. As noted by Sirrs et al. [38], given the high costs of drugs for rare disease, conversations regarding appropriate funding and decision making are complicated by evidentiary, economic, and ethical considerations; highlighting the need for transparency and high-quality evidence in decision making regarding drugs for rare diseases. We acknowledge that our expert panel includes individuals who study rare disease, provide care for patients with rare disease, or advocate for patients with rare diseases in Canada, and therefore, have taken a stance in advocating for the inclusion of costs borne by patients, their families, and societies, which are not traditionally captured in studies of socioeconomic burden and HTA processes. Though our

Table 1 Expert-informed framework of cost elements for measuring the socioeconomic burden of rare disease

Cost category	Additional details and examples of costs	Payer perspective[a,b] [17]
1. Inpatient (costs incurred during an acute care hospitalization, including any fees for physicians and any services performed in relation to that hospitalization, or in a post-acute hospitalization rehabilitation stay)		
a. Hospital admissions	Inpatient stay, length of stay	Public Healthcare Payer Broader Government Payer Societal
b. ICU	ICU stay, length of stay	
c. Physician visit during an inpatient stay	Physician visits during inpatient hospital stay	
d. Specialist visit during an inpatient stay	Specialist visits during inpatient hospital stay	
e. Surgery received during or requiring inpatient stay	Surgery performed during or requiring an inpatient stay	
f. Diagnostic imaging received during inpatient stay	X-ray, MRI, CT completed during inpatient stay	
g. Lab received during inpatient stay	Bloodwork, pathology, inhibitor tests completed during inpatient stay	
h. Medication received during inpatient stay	Prescription medications, infusions, gene therapy, blood products given during inpatient stay	
i. Interventions or procedures received during inpatient stay	Transfusions, joint injections performed during inpatient stay	
j. Allied health professional visits during inpatient stay	Psychologist, physiotherapist, social worker, speech and language pathologist, massage therapist, occupational therapist, respiratory therapist visits during inpatient stay	
k. Respite care received during inpatient stay	Short term period of respite for parents and/or caregivers which may be provided in various settings including in home, day programs, or overnight stays in special facilities	
l. Hospice, palliative, and end-of-life care received during inpatient stay		
m. Physician administrative time	Time spent advocating for funding for medications for patients during inpatient stay	
n. Other inpatient costs	Other costs incurred during an inpatient stay	

Table 1 (continued)

Cost category	Additional details and examples of costs	Payer perspective[a,b] [17]
2. Outpatient (costs incurred during services and treatments that do not require hospitalization)		
a. ER visit	Visit to the ER	Public Healthcare Payer Broader Government Payer Societal
b. Physician visit in an outpatient setting	Visit to physician in an outpatient setting (e.g., urgent care, ER)	
c. Specialist visit in an outpatient setting	Visit to a specialist in an outpatient setting (e.g., urgent care, ER)	
d. Surgery received in an outpatient setting	Outpatient or day surgery	
e. Diagnostic imaging in an outpatient setting	X-ray, MRI, CT	
f. Lab in an outpatient setting	Bloodwork, pathology, inhibitor tests	
g. Medication received in an outpatient setting	Prescription medications, infusions, gene therapy, blood products	
h. Interventions or procedures received in an outpatient setting	Transfusions, joint injections	
i. Allied health professional visits provided in an outpatient setting	Psychologist, physiotherapist, social worker, speech and language pathologist, massage therapist, occupational therapist visits in an outpatient setting	
j. Respite care received in an outpatient setting	Short term period of respite for parents and/or caregivers which may be provided in various settings including in home, day programs, or overnight stays in special facilities	
k. Hospice, palliative, and end-of-life care received in an outpatient setting	Services provided to patients/families with life-limiting or life-threatening illness; which may be provided in specialized facilities or the patients home	
l. Physician administrative time in an outpatient setting	Time spent advocating for funding for medications for patients (e.g., navigating special access programs for pharmaceuticals, liaising with pharmaceutical companies for patient access programs)	
m. Genetic services, counselling, or testing received in an outpatient setting	Services provided after diagnosis to further define disease or inform treatment	
n. Other outpatient costs	Other outpatient costs incurred outside of the cost elements listed above	

Table 1 (continued)

Cost category	Additional details and examples of costs	Payer perspective[a,b] [17]
3. Community setting (health professionals, non-physician health professionals and other types of care that may take place outside of hospitals)		
a. Physician visit	Family physicians seen in their community-based doctors offices	Public Healthcare Payer Broader Government Payer Private Payer Societal
b. Specialist visit	Specialist physicians seen in their community-based doctors offices	
c. Diagnostic imaging	X-ray, MRI, CT done in a community-based setting	
d. Lab	Bloodwork, pathology, inhibitor tests done in a community-based setting	
e. Medication	Prescription medications, infusions, gene therapy, blood products purchased in a community-based setting	
f. Interventions or procedures received in a in a community setting	Transfusions, joint injections done in a community-based setting (e.g., an infusion clinic)	
g. Allied health professional visits in a community setting	Psychologist, physiotherapist, social worker, speech and language pathologist, massage therapist, occupational therapist visits outside of the health system	
h. Naturopath and other alternative medicine providers seen in a community setting	Alternative medicine providers seen outside of the health system such as naturopath, osteopath, acupuncturist	
i. Paid care/formal care	Paid health services, such as home care	
j. Residential care/long-term care (community)	Long term care provided outside of the family home	
k. Personal support workers (community or home setting)	Provide help with daily tasks, may be provided in home or in long-term care settings	
l. Respite care received in the community setting	Short-term period of respite for parents and/or caregivers which may be provided in various settings including in home, day programs, or overnight stays in special facilities	
m. Hospice, palliative, and end-of-life care received in the community setting	Services provided to patients/families with life-limiting or life-threatening illness which may be provided in specialized facilities or the patients home	
n. Physician administrative time in a community setting	Time spent advocating for funding for medications for patients (e.g., navigating special access programs for pharmaceuticals, liaising with pharmaceutical companies for patient access programs)	
o. Other community costs	Other expenses incurred by the health system or patients outside of the traditional inpatient and outpatient settings	
3. Healthcare products/goods		
a. Prescription medication	Prescription medications, infusions, gene therapy, blood products	Public Healthcare Payer Broader Government Payer Private Payer Societal
b. Over-the-counter medication	Medications purchased without a prescription (e.g., pain medication, cough and cold medication)	
c. Prescription diets/dietary supplements		

Table 1 (continued)

Cost category	Additional details and examples of costs	Payer perspective[a,b] [17]
d. Devices and aids	Home CPAP machine, nebulizer, crutches	
e. Naturopathic and alternative medicine products or services	Naturopathic or alternative medicine products that patients may purchase	
f. Other healthcare products/goods costs	Vaccination, device maintenance	
4. Productivity/education and time impacts		
a. Loss of productivity (patient or parent)	Time away from work, absenteeism; presenteeism, for either the patient (of working age) or parent of a child with a rare disease	Societal
b. Changes in employment (patient or parent)	Loss of employment, change in type of job, early retirement, for either the patient (of working age) or parent of a child with a rare disease	
c. Informal care	Unpaid help from family and friends	
d. Lost education for child with rare disease	Education lost by the child with a rare disease (e.g., hours or days of school missed)	
e. Educational supports	Speech and language pathologist, special education support, education assistants	
f. Lost education for siblings	Education lost by siblings of the child with a rare disease (e.g., due to travel for appointments for child with rare disease)	
g. Loss of leisure time or usual activities for caregiver	Lost time due to caregiving responsibilities	
h. Time invested in learning about disease and/or disease management	Time spent by patients and/or their families in learning about their disease or disease management	
i. Other productivity/education costs	Other productivity, education, or time costs relevant to rare disease that are not captured by the pre-defined cost elements	
5. Travel and accommodation		
a. Transportation	Ambulance, transportation service, personal	Societal Public Healthcare Payer Private Payer
b. Parking	Parking expenses at hospitals or clinics	
c. Accommodation	Hotel costs	
d. Out of province/state/jurisdiction (but within country) travel	Expenses incurred when patients travel to other provinces/states/jurisdictions (but within their country) in search of care or treatment not available within their home jurisdiction	
e. Living costs	Living costs while traveling for medical care (e.g., food)	
f. Other travel and accommodation costs	Other travel and accommodation costs relevant to rare disease that are not captured by the pre-defined cost elements	
6. Government benefits[c]		
a. Adult benefits		Broader Government Payer
b. Child benefits		
c. Other government costs		
7. Family impacts (sibling and parent)		
a. Healthcare	Healthcare costs related to siblings and parents (e.g., psychologist for sibling or parents)	Broader Government Payer Societal
b. Childcare	Daycare, childcare, babysitting	
c. Adaptations	Adaptations required in various settings: home, education, car, workplace, travel, or recreation	

Table 1 (continued)

Cost category	Additional details and examples of costs	Payer perspective[a,b] [17]
d. Participation in research	Time spent searching for and engaging in research (e.g., questionnaires, clinical studies)	
e. Research and foundations	Family time and resources spent on research, starting foundations or organizations	
f. Other family impacts	Other impacts that families living with rare disease may experience that are not captured in the pre-defined cost elements listed above	
8. Other costs		
a. Out-of-country—advanced testing	Costs associated with travel out of the country in order to complete testing (e.g., biomarker panels) not offered through the healthcare system; includes the cost of any advanced tests themselves and related expenses	Broader Government Payer Societal
b. Out-of-country—treatment	Costs associated with travel out of the country in order to access treatments not offered through the healthcare system; including the cost of any treatments and related expenses	
c. Patient services and supports from not-for-profit and advocacy groups	Educational materials; funding for advocacy and research funding	
d. Other costs	Any other costs that are relevant for the disease of study	

The following framework is intended to provide a comprehensive list of cost categories and cost elements that may be included in studies of the socioeconomic burden of rare disease. The specific costs that are selected for inclusion may vary by 1) rare disease of interest: for example, some diseases may have large costs associated with home and car adaptations, while other diseases may not have any costs for adaptations; 2) study design: which costs and perspectives you opt to include may be influenced by whether you are conducting a cost-of-illness study or a cost-effectiveness analysis or a study of the family burden; and 3) region or country of study, as where a particular cost fits inside or outside the health system may vary by country, and in turn, who bears the burden of that cost and the perspective utilized may vary. For example, in Alberta, Canada, physiotherapy is commonly done in the community setting and the cost is borne by patients, either as an out-of-pocket expense or as an expense covered by private health insurance, rather than the health system. Several cost elements are listed across multiple settings to allow for flexibility to capture the costs where they are being incurred and for differences in health systems (e.g., diagnostic imaging may occur as part of an inpatient hospital stay, as part of an outpatient visit to an emergency room, or in a community lab with a referral from a family doctor). Please modify the list to best fit your research needs

CPAP continuous positive airway pressure, *CT* computed tomography scan, *ER* emergency room, *GP* general practitioner, *ICU* intensive care unit, *MRI* magnetic resonance imaging

[a]The costs and perspective may vary by variables such as jurisdiction (e.g., by country) or health system

[b]The perspective presented in this column is based on a Canadian perspective and has been guided by the CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition)[17]

[c]These benefits are considered transfer payments and therefore are not included in a societal perspective economic evaluation. From the perspective of individual family burden, this can be an important indicator of differences in impact and would be important to track in that context.

framework includes a comprehensive list of cost elements, we understand that it is not feasible for all cost elements to be included in all studies (e.g., cost-of-illness studies from a societal perspective may encompass a wider breadth of elements than a cost-effectiveness analysis from a health system perspective), and that expanding the costs included may have downstream implications for funding decisions and that therefore there may be disagreements regarding which costs ought to be included or excluded.

Given the heterogeneous nature of rare disease, and acknowledging that each disease is characterized by a diverse range symptoms, varying from disease to disease and person to person [39], it is imperative that future studies focus on elements of critical importance to each rare disease. For instance, one rare disease may require significant adaptations to the home to account for limited mobility, while another may require no home adaptations. To realize the potential impact of this framework, we envision researchers, working in collaboration with patients, will customize its use by selecting elements that are relevant to specific rare diseases. This foundational piece sets the stage for future research on how best to consistently measure and value the costs we have identified, including the creation of rare disease-specific resource use and costing surveys. Once studies have empirically measured costs to the health system, patients, families and society, this evidence can be used to identify key cost drivers for rare diseases and further refinement of the framework to develop a core set of cost categories and elements, along with a list of additional elements that may be considered if relevant to the disease of study.

The study has several limitations. Although it is primarily focused on the costs associated with having a disease (because the focus is on a disease, which implies having a diagnosis), some of these costs are also applicable to the diagnostic phase (i.e., when patients may be visiting physicians, hospitals, and undergoing diagnostic, laboratory, and genetic tests). However, there are additional complexities to the diagnostic odyssey, given the lengthy process and high resource utilization involved in attaining a diagnosis of a rare disease [5, 6] and to comprehensively measure the burden of rare disease, future research should focus on costs that span the full pathway of rare disease, including the cost of the research required to develop more rapid and accurate diagnostic tests and therapies. The current research was also limited to cost elements of socioeconomic burden, and therefore did not account for any quality-of-life or other outcome measures. As both the economic impact of rare disease and the loss of health-related quality of life are understudied [14], future research should encompass quality of life and outcome measures into a broader framework of the full socioeconomic burden of rare diseases. The scoping review was limited to peer-reviewed literature and given the aim of our study; we did not critically appraise the included studies. To overcome any limitations of the scoping review, our study team included an expert panel from a variety of backgrounds, including clinical researchers, health economics and health services researchers, and leaders from various genomic and rare disease organizations.

This framework is intended to address the identification component of assessing cost, and future work should focus on both measuring and valuing these costs in the context of rare disease and across the full pathway of rare disease (from onset to diagnosis, and post-diagnosis). Standard approaches to the measurement of costs include the use of administrative health data for healthcare system costs, and family/patient reports for the collection of productivity impacts and out-of-pocket costs. In the context of rare disease, use of administrative data to assess healthcare use may not be possible as many rare genetic diseases do not have ICD-10 codes meaning these patients cannot be easily identified, and we cannot systematically identify associated costs. It is also challenging to identify costs directly related to rare genetic diseases and to separate these from routine healthcare costs. Amongst patients who have not received a diagnosis, additional steps would be required to identify individuals and retrospectively review and categorize costs associated with the diagnostic odyssey and management of symptoms. Finally, in countries where healthcare is different by province, state, or region, there are often challenges with combining data and developing national estimates of disease burden. Reliance on measuring resource use from patients and parents is also limited, and families are not likely to be systematically recording costs. Sources such as the Database of Instruments for Resource Use Measurement (DIRUM; http://www.dirum.org/about) have compiled a central list of resource use instruments for health economists, however, the sheer number of instruments and differences in items considered across instruments highlights the need for consistent reporting standards. A recent study clustered methodological aspects of resource use measurement into a comprehensive framework consisting of four domains: whom to measure, how to measure, how often to measure, and additional considerations [40]; these methodological considerations can be applied by researchers to improve the measurement for economic evaluations and can be applied to the cost elements presented in our framework.

5 Conclusion

We have developed a framework which identifies key cost categories and elements, based on the literature, and further developed through feedback from experts in rare disease, to be considered in future studies of the socioeconomic burden of rare disease. The goal of this framework is to provide a comprehensive and standardized list of cost elements as

guidance for researchers when designing studies to select elements relevant to their context. Our hope is that this framework will increase the quality and comparability of future studies of the socioeconomic burden of rare disease and support relevant policy and other decision-making initiatives to address the socioeconomic burden of rare genetic diseases in both the Canadian context and more broadly. Future work should focus on both measuring and valuing these costs in the context of rare disease, across the full pathway from onset to diagnosis, and post-diagnosis. Given the unique challenges of measuring burden in this population, there is a pressing need for HTA stakeholders to acknowledge these limitations and discuss innovative approaches and non-standard solutions for assessing new technologies for rare disease.

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Authors and Affiliations

Gillian R. Currie[1,2,3] · Brittany Gerber[2] · Diane Lorenzetti[2,4] · Karen MacDonald[2] · Susanne M. Benseler[1,3,5] · Francois P. Bernier[3,6] · Kym M. Boycott[7,8] · K. Vanessa Carias[9] · Bettina Hamelin[10] · Robin Z. Hayeems[11,12] · Claire LeBlanc[13] · Marinka Twilt[14] · Gijs van Rooijen[9] · Durhane Wong-Rieger[15] · Rae S. M. Yeung[16] · Deborah A. Marshall[2,3,17,18]

✉ Gillian R. Currie
currie@ucalgary.ca

1 Department of Pediatrics, Health Research Innovation Centre, University of Calgary, Room 3C56, 3280 Hospital Drive NW, Calgary, AB T2N 4Z6, Canada

2 Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada

3 Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada

4 Health Sciences Library, University of Calgary, Calgary, AB, Canada

5 Alberta Health Services, Calgary, AB, Canada

6 Department of Medical Genetics, Alberta Children's Hospital, Calgary, AB, Canada

7 Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada

8 Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, ON, Canada

9 Genome Alberta, Calgary, AB, Canada

10 Ontario Genomics Institute, Toronto, ON, Canada

11 Child Health Evaluative Sciences, Hospital for Sick Children, Toronto, ON, Canada

12 Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada

13 Department of Pediatrics, Faculty of Medicine, McGill University, Montreal, Quebec, Canada

14 Department of Pediatrics, Cumming School of Medicine, McCaig Institute for Bone and Joint Health, and the Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada

15 Canadian Organization for Rare Disorders (CORD), Toronto, ON, Canada

16 Departments of Paediatrics, Immunology and Medical Science, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

17 McCaig Institute for Bone and Joint Health, University of Calgary, Calgary, AB, Canada

18 O'Brien Institute for Public Health, University of Calgary, Calgary, AB, Canada