ARTICLE

Health-related quality of life in patients with diverse rare diseases: An online survey

Anoushka Rao[1] [iD], Megan Yabumoto[1,2], Eliana Ward-Lev[1], Emily G. Miller[1], Hetanshi Naik[3], Meghan C. Halley[1],*[iD]

[1]Center for Biomedical Ethics, Stanford University School of Medicine, Stanford, CA; [2]Division of Genetic Medicine, Seattle Children's Hospital, Seattle, WA; [3]Department of Genetics, Stanford University School of Medicine, Stanford, CA

A B S T R A C T

Purpose: Rare diseases substantially contribute to population morbidity and mortality. Understanding rare disease health-related quality of life (HRQL) is essential for evaluating platform-based interventions that aim to tackle multiple rare diseases at a time. However, most HRQL studies focus on single or select group of rare diseases, often in a single country. Our study aimed to identify patient- and disease-specific correlates of HRQL across diverse rare diseases.

Methods: We conducted an international online survey of rare disease patients and caregiver proxies affected by a systematically identified sample of rare diseases. We calculated EQ-5D scores and conducted multivariate linear regression to examine sociodemographic and disease predictors of EQ-5D-5L visual analog scale (VAS) and utility scores (United States only).

Results: A total of 1053 individuals affected by 103 different rare diseases participated, including 660 patients and 393 caregiver proxies. Disability status and disease prevalence correlated with poorer HRQL across models ($P < .05$). Increased pain and decreased ability to perform usual activities also correlated with lower VAS for both adult patients and caregiver proxies ($P < .05$). Being unemployed approached significance as a correlate of both lower caregiver proxy VAS and lower patient utility scores.

Conclusion: Our results suggest that across rare diseases, lower HRQL is associated with a reduced rare disease prevalence and disability status, among other predictors. Understanding the key correlates of HRQL is essential for developing interventions for improving health care delivery and quality of life for rare disease patients and families.

Introduction

An estimated 10,000 rare diseases affect over 300 million people around the world.[1] Although definitions vary, internationally a rare disease is one affecting approximately 40 per 100,000 individuals.[2] The majority (70%) of these diseases present in childhood and have a suspected or confirmed genetic origin.[3] Although individually rare,

collectively these diseases are responsible for an estimated 28% of deaths in the neonatal intensive care unit,[4] and over half of these diseases are associated with a reduced lifespan.[5] Patients with rare diseases also have significant health care needs, with rare diseases collectively accounting for an estimated 25% of all admissions to the neonatal intensive care unit[6] and pediatric intermediate care units,[7] more than 30% of admissions to pediatric long-term care facilities, and more than 40% of pediatric comfort care patients.[8] Studies in a range of countries also suggest that the collective economic burden of rare disease care, including direct medical costs to the health care system and out-of-pocket health care costs to families, is immense.[9,10]

Although the manifestation of individual rare diseases varies widely, patients with rare diseases and their caregivers report many similar challenges in navigating the health care system and society. Patients and caregivers report significant delays in diagnosis, limited treatment options, and a lack of providers with sufficient knowledge of their unique condition.[11] Other reported challenges include poor doctor-patient communication and feelings of uncertainty, especially for those who have yet to receive a diagnosis.[12] Outside of the clinic, rare disease patients report stigma, social exclusion, and a lack of social and emotional support from others who understand their unique challenges.[13] The shared health care and social support needs of the rare disease community suggest the opportunity to develop interventions to improve quality of life for patients with a range of rare diseases.[14]

Recent advances in the therapeutic landscape for rare disease also are increasingly breaking down distinctions between individual rare diseases.[14] Advances in multi-omics and other approaches to functional genomics suggest that phenotypically distinct rare diseases may share underlying pathophysiology at the cellular level.[15] These shared mechanisms open the door for platform-based approaches to therapeutic development that explicitly attempt to address more than one rare disease at a time. Examples of such approaches include the use of umbrella or basket trials to evaluate a single therapy in multiple rare diseases, as in a recent trial evaluating a monoclonal antibody in three different rare diseases with shared molecular pathophysiology.[16] Platform-based approaches also include development of innovative therapeutic delivery mechanisms that can be repeatedly modified to target different disease-causing mutations.[17] The expansion of these approaches suggests movement away from a "one disease at a time" approach to therapeutic development for rare diseases.[14]

Despite growing recognition of both the shared challenges and opportunities to improve health care and outcomes for rare diseases, with few exceptions,[18,19] much of the peer-reviewed literature measuring patient-reported outcomes has focused on a single disease, or select group of well-known rare diseases (eg, cystic fibrosis).[10] Systematically capturing the perspectives of patients across a broad range of rare diseases is challenging; not only are patients few in number and spread across the globe, but also the large number of rare diseases and highly diverse phenotypes makes sampling a challenge. The lack of integrated, systematic data across rare diseases limits our ability to compare outcomes across different rare diseases, identify factors that may exacerbate poor outcomes, or evaluate interventions targeting diverse rare diseases.[14,20]

Research that seeks to systematically understand the impacts of a range of different rare diseases on general outcomes, such as health-related quality of life (HRQL), is essential to fill this gap.[14] To this end, we sought to identify patient- and disease-specific characteristics associated with differences in HRQL in a systematically selected international sample of diverse rare diseases.[21,22]

Materials and Methods

Overview

To assess HRQL and characteristics associated with variation in HRQL, we administered an anonymous, online survey to rare disease patients and caregivers from October to December of 2021. Participants were identified from Facebook support groups for systematically identified rare diseases. A preliminary version of these results and analyses were presented at the ISPOR Conference in 2023.[21,22] This study protocol was reviewed and approved by the Stanford University School of Medicine Institutional Review Board, Protocol #61783.

Sampling and recruitment

We first identified a stratified random sample of 1200 rare diseases from the Orphanet database.[18] Because only 4% of rare diseases with relatively high prevalence account for an estimated 80% of rare disease patients, our sample was constructed such that 40% of diseases selected were these more common rare diseases (ie, those with a point prevalence 1-9 in 1,000,000 or greater). This sampling strategy was designed based on (1) the estimated percentage of rare diseases with a genetic etiology; (2) the distribution of point prevalence for rare diseases in Orphanet,[3] (3) recent data on the emergence of rare disease support groups on Facebook by disease prevalence,[23] and (4) anticipated response rates based on prior studies using this recruitment method.[24] After identifying the initial sample, the list of diseases was reviewed, and any rare diseases without a known or suspected genetic etiology were removed by a trained genetic counselor (M.Y.) based on the existing evidence available in the scientific literature (eg, GeneReviews).[25]

After identifying our sample of rare diseases, we utilized a study-specific Facebook account to search for support groups for each of the 1200 diseases in our sample. Identified groups were included based on group size (only the single largest group was included if multiple groups were identified for a disease) and disease-specific focus (the

specific disease was listed in the group name and/or in the public description). To recruit individual participants for the survey, a member of our research team contacted up to three moderators of each identified Facebook group with Institutional-Review-Board-approved language to share with the group participants. Individuals were eligible to participate if they were (1) 18 years of age or older, (2) able to write and read in English, and (3) self-identified as either a patient with, or a caregiver of a patient with, a rare or undiagnosed disease. Additional details of our approach for sampling rare diseases and Facebook group identification have been published in Yabumoto et al[26] (2022).

Data collection and measures

Data were collected electronically using Qualtrics. Measures were drawn from validated instruments whenever possible or were adapted from existing instruments and piloted with an outside group of rare disease patients and caregivers before use.

Outcome measure

To measure HRQL, we utilized the EQ-5D-5L.[27] We selected this measure because of its rigorous development and testing and use in over 17,000 registered studies around the world for over 30 years.[28] It is also generic (as opposed to condition-specific) and brief, assessing five dimensions of HRQL (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression), as well as a global question using a visual analog scale (VAS). The VAS asks respondents to self-rate their health on a scale of 1 to 100, in which 1 is the "worst health you can imagine," and 100 is the "best health you can imagine."[23] Each question block in the EQ-5D-5L corresponds to a single dimension and elicits a value from 1 to 5 that describes the severity of impairment in each of the dimensions (5 being most impaired). For both the EQ-5D-5L and VAS, patients were asked to self-report HRQL, and caregivers were asked to report on the HRQL of the patient they are caring for by proxy (referred to here as "caregiver proxy").

Additionally, and unlike many other commonly used HRQL measures (eg, Patient-Reported Outcomes Measurement Information System measures,[29] and The World Health Organization Quality of Life measure[30]), the EQ-5D-5L is a preference-based measure with associated value sets. This allows its use in the calculation of location-specific utility values to inform value assessments in policy and health care decision making, of which there is a critical lack of data in rare diseases. Value sets are typically country/region specific collections of index values, which indicate how severe a given 5 number code is relative to the population in that region. To calculate utility scores, the resulting 5 number "code" (eg, 11345) summarizing the respondent rating on each of the 5 EQ-5D dimensions is converted into a single utility score, which ranges from 0 to 1, in which 1 is the best HRQL.[31]

Predictor variables

We collected data on a range of sociodemographic and disease characteristics, including role (patient/caregiver), age, gender, self-reported race and ethnicity, location, urbanicity, education, employment, household income, and social media connectedness.[20] We applied the Office of Management and Budget standards when asking about race, ethnicity, and gender.[32] Although a more granular categorization of race was included in the original survey (15 categories), our multivariate model included the five Office of Management and Budget racial categories because of very small sample sizes in some racial groups. Survey questions about disease characteristics included disability status, having prior genetic testing, having a confirmed genetic diagnosis (defined as having an identified genetic mutation known to cause the patient's rare disease), age of symptom onset, and rare disease (clinical) diagnosis.

Data analysis

All data were analyzed in R (version 4.1.1). Descriptive statistics were calculated as means and standard deviations for normally distributed data, or medians and interquartile ranges for nonnormal data. Nominal variables were dichotomized when possible and included role (caregiver vs patient), gender (male vs female), location (United States vs outside the United States), community type (urban vs rural), employment (employed vs unemployed), disability identity (disabled vs not disabled), and genetic diagnosis (diagnosed vs undiagnosed). Because our participant sample included demographic characteristics of both patients and caregivers inside and outside the United States, we divided the sample into four groups for analysis: (1) patients in the United States, (2) patients outside the United States, (3) caregivers in the United States, and (4) caregivers outside the United States.

We modeled VAS and utility scores as outcomes, assessing predictors of each. We first conducted univariable analyses (t test, χ^2, or analysis of variance) between predictor variables and outcomes in each of the four analytic groups. Predictor variables for which univariable analyses were significant at $P < .20$ were then included in four initial multivariate linear regression models: (1) all patients (United States and non-United States) with VAS as the outcome variable, (2) all caregivers (United States and non-United States) with VAS as the outcome variable, (3) United States patients with the utility score as the outcome variable, and (4) United States caregivers with the utility score as the outcome variable. Predictor variables were assessed in each model manually until the most parsimonious models were identified. A significance level of 0.05 was used for all analyses. Additionally, we completed a Spearman's rank correlation to determine interdimensional-correlation in the EQ-5D domains.

Conducting separate multivariate regression analyses for patients and caregivers with the VAS as the primary outcome allowed us to investigate causal mechanisms in VAS

heterogeneity without the confounder of reporting mechanism (self vs proxy). Because utility values are based on location-specific utility weights, comparing utility measures across countries may lead to erroneous conclusions about utility score differences. To account for this, only United States participants were included in models with utility score as the primary outcome. In addition, although we collected data on race, ethnicity, and income from all participants, our analysis suggested inconsistent interpretation of these questions by international participants. Therefore, these variables were only included in the utility score model, which included only United States participants.

Results

Sample characteristics

A total of 1053 participants, including 660 (63%) patients and 393 (37%) caregivers, from 103 disease groups participated in the survey. The median Facebook group size was 1400 individuals (IQR = 765-2800).[26] The mean age of adult patients was 44.60 years old (SD 13.00), whereas that of caregivers was 43.10 years old (SD 10.30).

Among adult patients, 81% ($n = 532$) were female, 62% ($n = 406$) were employed, 81% ($n = 535$) reported having some college education or greater, 44% ($n = 287$) reported living in a rural community, and 35% ($n = 232$) reported having a genetic diagnosis. Among caregivers, 86% ($n = 336$) were female, 67% ($n = 262$) were employed, 84% ($n = 329$) reported having some college education or greater, 45% ($n = 175$) reported living in a rural community, and 48% ($n = 190$) reported that their care recipient had received a genetic diagnosis.

Among United States-based participants only, 94% ($n = 578$) identified as White, 44% ($n = 268$) reported a household income greater than $100,000, and 71% ($n = 434$) reported that they (or their care recipient) had private insurance. Among United States adult patients, 94% ($n = 360$) identified as White, 39% ($n = 150$) reported a household income greater than $100,000, and 69% ($n = 262$) reported having private insurance. Among United States caregivers 94% ($n = 218$) identified as White, 51% ($n = 118$) reported a household income of $100,000 or greater, and 74% ($n = 172$) reported that their care recipient had private insurance. Additional details can be found in Table 1.

VAS, utility scores, and EQ-5D domains

The mean VAS score (scored from 1 to 100, with 100 indicating best HRQL) was 68.10 (SD = 21.40) across all participants. The mean VAS score was 66.87 (SD 19.66) among all patients (United States and non-United States) compared with 70.40 (SD = 24.20) as reported by caregiver proxies. Among United States participants only, the mean utility score (scored from 0 to 1, with 1 indicating best HRQL) was 0.71 (SD 0.22). For only United States patients, the mean utility score was. 0.74 (SD = 0.16) compared with 0.67 (SD = 0.28) as reported by United States caregiver proxies.

Within each of the 5 EQ-5D domains (scored from 1 to 5, with 1 indicating the best outcome in that dimension), responses provided by all (United States and non-United States) adult patients versus those provided by all caregiver proxies were divergent in many cases. Caregivers tended to report higher self-care deficits for their care recipient, with 21% of caregivers scoring a 5 (total deficit) for their care recipient on the Self-Care dimension, whereas only one patient scored the same for themselves. Similar increases in caregiver-reported deficiencies were observed in the Mobility and Usual Activities dimensions. Additionally, caregivers tended to report fewer anxiety deficits for their care recipient, with 46% of caregivers scoring a 1 (no deficit) for their care recipient on the Anxiety/Depression dimension, as opposed to only 28% of adult patients scoring the same. Across all participants, self-care had the highest reported proportion of "no deficit" responses (70%, $n = 636$). The distribution of responses for each EQ-5D domain is depicted in Figure 1.

Within the 5 EQ-5D dimensions, the strongest correlation was between Usual Activities and Mobility ($r = 0.66$). There was also a moderate correlation between Self-Care and Mobility ($r = 0.58$), Self-Care and Usual Activities ($r = 0.56$), and Pain and Usual Activities ($r = 0.46$) (Supplemental Table 1).

Multivariate regression analysis

VAS—All patients

Significant univariable predictors of lower patient VAS included identifying as male ($P = .04$), living in an urban community ($P = .003$), being affected by a lower prevalence rare disease ($P = .006$), being unemployed ($P < .001$), identifying as disabled ($P < .001$), and scoring more poorly for each of the 5 EQ-5D dimensions (Self-Care, Mobility, Usual Activities, Anxiety/Depression, and Pain/Discomfort) ($P < .001$, Supplemental Table 2). The final multivariate regression model, including all adult patients, explained 39% of the variability observed in VAS scores in this population and included gender, location, community type, disease prevalence, disability status, and each of the 5 EQ-5D domain scores as predictors. In the final model, living in an urban community ($P = .04$), identifying as disabled ($P = .006$), and reporting poorer scores for Mobility ($P = .02$), Usual Activities, Anxiety, and Pain ($P < .001$ for each) were significant predictors of poorer HRQL (lower VAS). In addition, identifying as male ($P = .08$), living in a country other than the United States ($P = .09$) and being affected by

Table 1 Demographic characteristics of rare disease patients and caregivers

Respondent Characteristics	N, Patient (%)	N, Caregiver (%)	Total N (% of All Responses)
Number of Respondents	660 (63)	393 (37)	1053
Age (Median, IQR)	44 (35-54)	41 (36-49)	43 (35-52)
Missing (n, %)	21 (3.20)	8 (2.00)	29 (2.80)
Gender	660	393	1053
Female	532 (80.60)	336 (85.50)	868 (82.40)
Male	106 (16.10)	47 (11.90)	153 (14.50)
Non- binary	6 (0.90)	0 (0.00)	6 (0.60)
Transgender Male	4 (0.60)	0 (0.00)	4 (0.40)
Prefer to self-describe	0 (0.00)	1 (0.30)	1 (0.10)
Prefer not to say	1 (0.10)	1 (0.30)	2 (0.20)
Missing	11 (1.70)	8 (2.00)	19 (1.80)
Location	660	393	1053
United States (US)	382 (57.90)	233 (59.30)	615 (58.40)
Non-United States	189 (28.60)	98 (24.90)	287 (27.30)
North America	49 (25.90)	15 (15.30)	64 (22.30)
South America	4 (2.10)	0 (0.00)	4 (1.40)
Europe	90 (47.60)	53 (54.10)	143 (49.80)
Australia	24 (12.70)	12 (12.20)	36 (12.50)
Asia	7 (3.70)	6 (6.10)	13 (4.50)
Africa	5 (2.60)	5 (5.10)	10 (3.50)
Other	10 (5.30)	7 (7.10)	17 (5.90)
Missing	89 (13.50)	62 (15.80)	151 (14.30)
Race (select all that apply, US only)	382	233	615
American Indian or Alaskan Native	10 (2.60)	3 (1.30)	13 (2.10)
Asian or Asian American	12 (3.10)	10 (4.30)	22 (3.60)
Black or African American	12 (3.10)	6 (2.60)	18 (2.90)
Native Hawaiian or other Pacific Islander	1 (0.30)	0 (0.00)	1 (0.20)
White	360 (94.20)	218 (93.60)	578 (940)
Other	4 (1.00)	5 (2.10)	9 (1.50)
Missing	9 (2.40)	6 (2.60)	15 (2.40)
Hispanic Ethnicity (US only)	382	233	615
Hispanic/Latino	20 (5.20)	16 (6.90)	36 (5.90)
Not Hispanic/Latino	361 (94.50)	216 (92.70)	577 (93.80)
Missing	1 (0.30)	1 (0.40)	2 (0.30)
Community Type	660	393	1053
Rural	287 (43.50)	175 (44.50)	462 (43.90)
Urban	356 (53.90)	206 (52.40)	562 (53.40)
Missing	17 (2.60)	12 (3.10)	29 (2.70)
Employment Status	660	393	1053
Employed	406 (61.50)	262 (66.70)	668 (63.40)
Not Employed	230 (34.90)	117 (29.80)	347 (33.00)
Missing	24 (3.60)	14 (3.50)	38 (3.60)
Education Level	660	393	1053
Less than high school	6 (0.90)	5 (1.30)	11 (1.00)
High school or GED	86 (13.00)	43 (10.90)	129 (12.20)
Some college or associate degree	178 (27.00)	87 (22.20)	265 (25.20)
Bachelor's degree	169 (25.60)	131 (33.30)	300 (28.50)
Advanced or graduate level coursework or degree	188 (28.50)	111 (28.20)	299 (28.40)
Missing	33 (5.00)	16 (4.10)	49 (4.70)
Household Income (US only)	382	233	615
<$25,000	29 (7.60)	6 (2.60)	35 (5.70)
$25,001-$50,000	63 (16.50)	26 (11.20)	89 (14.50)
$50,001-$100,000	100 (26.10)	61 (26.20)	161 (26.10)
$100,001-$200,000	150 (39.30)	118 (50.60)	268 (43.60)
>$200,000	0 (0.00)	0 (0.00)	0 (0.00)
Prefer not to say/don't know	29 (7.60)	22 (9.40)	51 (8.30)
Missing	11 (2.90)	0 (0.00)	11 (1.80)

Table 1 Continued

Respondent Characteristics	N, Patient (%)	N, Caregiver (%)	Total N (% of All Responses)
Patient Disability Status[a]	660	393	1053
Not disabled	238 (36.10)	197 (50.10)	435 (41.30)
Disabled	378 (57.30)	173 (44.00)	551 (52.30)
Missing	44 (6.60)	23 (5.90)	67 (6.40)
Patient Insurance Status (US only)[a]	382	233	615
Public insurance	111 (29.00)	57 (24.50)	168 (27.30)
Private insurance	262 (68.60)	172 (73.80)	434 (70.60)
Missing	9 (2.40)	4 (1.70)	13 (2.10)
Patient Disease Prevalence[a]	660	393	1053
Unknown	94 (14.20)	61 (15.50)	155 (14.70)
<1 in 1,000,000	46 (7.00)	32 (8.20)	78 (7.40)
1-9 in 1,000,000	80 (12.10)	92 (23.40)	172 (16.30)
1-9 in 100,000	307 (46.50)	111 (28.20)	418 (39.80)
1-9 in 10,000	133 (20.20)	84 (21.40)	217 (20.60)
1-9 in 1000	0 (0.00)	13 (3.30)	13 (1.20)
Social Connectedness (Median, IQR)	3.70 (3.30-4.30)	4.00 (3.30-4.30)	3.70 (3.30-4.30)
Missing (n, %)	127 (19.20)	91 (23.20)	218 (20.70)
Patient Diagnosis[a]	660	393	1053
Genetic diagnosis	232 (35.20)	190 (48.30)	422 (40.10)
No genetic diagnosis	367 (55.60)	165 (42.00)	532 (50.50)
Missing	61 (9.20)	38 (9.70)	99 (9.40)
Patient VAS (Mean, SD)[a]	66.87 (19.66)	70.40 (24.20)	68.10 (21.40)
Patient Utility Score (Mean, SD)[a]	0.74 (0.16)	0.67 (0.28)	0.71 (0.22)
Patient EQ-5D Scores by Dimension (Mean, SD)[a]	660	393	1053
Self-Care	1.29 (0.66)	2.30 (1.62)	1.65 (1.21)
Mobility	1.74 (0.96)	2.09 (1.42)	1.87 (1.16)
Usual Activities	1.92 (0.95)	2.23 (1.32)	2.03 (1.11)
Anxiety	2.21 (1.01)	1.88 (1.00)	2.09 (1.02)
Pain	2.35 (1.01)	1.85 (0.93)	2.17 (1.01)

VAS, visual analog scale.

[a]Data refer to the patient and were provided either by self-report or by the caregiver by proxy.

a lower prevalence disease ($P = .07$) were each correlated with poorer HRQL but did not reach statistical significance at $P < .05$ (Table 2).

VAS—All caregivers
Significant univariable predictors of lower proxy VAS score included older caregiver age ($P < .001$), identifying their care recipient as disabled ($P < .001$) and as affected by a lower prevalence rare disease ($P < .001$), and reporting greater deficits for each of the 5 EQ-5D dimensions (Self-Care, Mobility, Usual Activities, Anxiety/Depression, and Pain/Discomfort) ($P < .001$, Supplemental Table 2. The final multivariate regression model with all caregiver proxies explained 40% of the variability observed in VAS scores in this population and included age, employment status, disease prevalence, and 2 EQ-5D Domains (Activities and Pain) as predictors (Table 2). In this model, older caregiver age ($P = .007$), having a care recipient affected by a lower prevalence rare disease ($P = .02$), and reporting greater deficits in the domains of Usual Activities and Pain ($P < .001$ for each) were significantly correlated with poorer HRQL (lower VAS). In addition,

caregivers who reported being unemployed also reported lower HRQL for their care recipient ($P = .09$), although this association did not reach statistical significance at $P < .05$ (Table 2).

Utility score—United States patients
Significant univariable predictors of lower utility scores included reporting a lower education level ($P = .002$), having public insurance ($P = .001$), being unemployed ($P < .001$), having a lower household income ($P < .001$), and identifying as disabled ($P < .001$, Supplemental Table 2). The final multivariate regression model with all patients and utility score as the primary outcome explained 27% of the variability observed in utility scores in this population and included employment status, education level, household income, social connectedness, disability status, and insurance status as predictors. In multivariate analysis, identifying as disabled was significantly correlated with poorer HRQL (lower utility score, $P < .001$). In addition, patients who reported being unemployed also reported lower HRQL (lower utility score, $P = .08$), although this association did not reach statistical significance at $P < .05$ (Table 2).
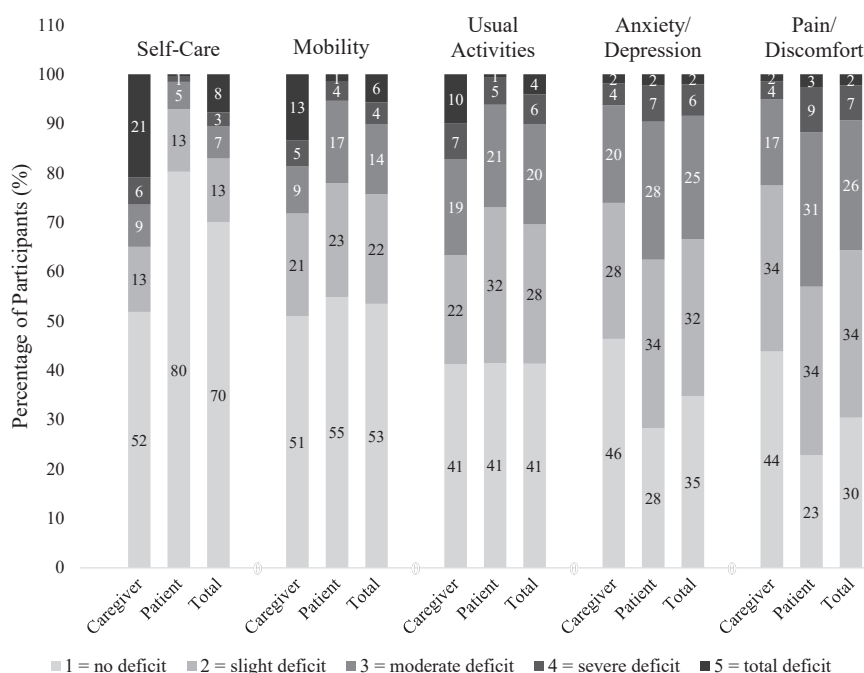
Figure 1 Percentage distribution of the five EQ-5D dimension scores (Self-Care, Mobility, Usual Activities, Anxiety/Depression, and Pain/Discomfort) as reported by caregiver-proxies, patients, and all participants. A score of 1 indicates "no deficit," 2 indicates "slight deficit," 3 indicates "moderate deficit," 4 indicates "severe deficit," and 5 indicates "total deficit" for a dimension.

Utility score—United States caregivers

Significant univariable predictors of lower proxy utility score included identifying their care recipient as disabled ($P < .001$), lower social connectedness of the caregiver ($P < .01$), and having a care recipient affected by a lower prevalence rare disease ($P < .001$, Supplemental Table 2). The final multivariate regression model with all United States caregivers and utility score as the primary outcome explained 24% of the variability observed in utility scores in this sample and included patient disability status and patient disease prevalence as predictors (Table 2). In multivariate analysis, having a care recipient affected by a lower prevalence rare disease ($P < .001$) and who identified as disabled ($P < .001$) were significantly correlated with poorer HRQL (lower utility score, Table 2).

Analysis of the residual plots for the multivariate linear regression models revealed a nonrandom distribution of residuals (eg, residuals clustering in two main locations) for the models in which utility score was the primary outcome. Additional models were constructed to further evaluate if there was a better model to use for our predictors and outcome variable, which included generalized linear model and generalized additive model, resulting in no notable change in the nonrandom distribution of residuals.

Discussion

This study of HRQL in an international sample of patients and caregiver proxies affected by 103 different rare diseases

(Supplemental Table 3) identified multiple correlates of HRQL. In particular, identifying as disabled and being affected by a lower prevalence disease (or having a care recipient as such) were significantly correlated with poorer HRQL in 3 of 4 models. Increased pain and decreased ability to perform usual activities also were significantly correlated with lower VAS for both patients and caregiver proxies, and being unemployed approached significance as a correlate of both lower caregiver proxy VAS and lower patient utility scores. Additional correlates of lower VAS or lower utility scores that warrant further investigation include decreased mobility, increased anxiety, urban location, older caregiver age, living in a country other than the United States, and identifying as male.

Our findings extend the rapidly growing literature focused on HRQL specifically for rare disease patients. Although the literature examining HRQL across diseases using the EQ-5D is extensive, many have focused on comparison between rare diseases as a group and other common diseases (eg, diabetes mellitus and asthma).[33,34] Although others have examined variation in HRQL across different rare diseases, many of these efforts have been limited geographically.[35,36] A notable exception is the work of Bogart et al,[18,19] which examined correlates of HRQL (assessed using NIH Patient-Reported Outcomes Measurement Information System measures) in a sample of patients with diverse rare diseases in the United States. Their analyses identified additional correlates of poorer HRQL, including in specific disease subtypes (rare systemic and rheumatologic, neurological, and immune diseases), those

having multiple rare diseases, longer symptom duration, and lower income. On the other hand, Bogart et al[19] found that having had a formal diagnosis for a longer period was associated with better HRQL. Although our study did not include all of the correlates explored by Bogart et al[18,19] (eg, disease classification and number of rare diseases), our results also identified a link between indicators of low socioeconomic status (specifically being unemployed) and

Table 2 Full multivariate linear regression analysis for variables associated with proxy and self-reported VAS and EQ-5D utility scores

All Patients, VAS Outcome ($R^2 = 0.39$ $N = 465$)		
Variable	Beta Estimate	P Value[a]
(Intercept)	94.96	<.001***
Gender	−3.55	.08
Female		
Male		
Location	2.61	.09
US		
Non-US		
Community Type	−2.95	.04*
Rural		
Urban		
Patient Disease Prevalence	1.02	.07
Patient Disability Status	−4.91	.006**
No Disability		
Disability		
EQ-5D Domains		
Mobility	−3.36	.02*
Usual Activities	−4.65	<.001***
Anxiety	−2.83	<.001***
Pain	−3.24	<.001***

All Caregivers, VAS Outcome[b] ($R^2 = 0.40$ $N = 312$)		
Variable	Beta Estimate	P Value
(Intercept)	109.20	<.001***
Age	−0.28	.007**
Employment Status	−3.84	.09
Employed		
Not Employed		
Patient Disease Prevalence	1.77	.02*
EQ-5D Domains		
Usual Activities	−4.79	<.001***
Pain	−10.33	<.001***

US Patients, Utility Score Outcome ($R^2 = 0.27$ $N = 276$)		
Variable	Beta Estimate	P Value
(Intercept)	0.77	<.001***
Employment Status	−0.03	.08
Employed		
Not Employed		
Education Level	0.01	.19
Household Income	0.007	.35
Social Connectedness	−0.003	.76
Patient Disability Status	−0.15	<.001***
No Disability		
Disability		

(continued)

Table 2 Continued

US Patients, Utility Score Outcome ($R^2 = 0.27$ $N = 276$)		
Variable	Beta Estimate	P Value
Patient Insurance Status	−0.003	.89
Private		
Public		

US Caregivers, Utility Score Outcome[b] ($R^2 = 0.24$ $N = 199$)		
Variable	Beta Estimate	P Value
(Intercept)	0.63	<.001***
Patient Disability Status	−0.19	<.001***
No disability		
Disability		
Patient Disease Prevalence	0.01	<.001***

VAS, visual analog scale.
[a]Significance codes: <0.001 (***); <0.01 (**); <0.05 (*); <0.1 (.).
[b]As a note, VAS and utility scores reported by caregivers are proxy scores for the patients they are caring for.

poorer HRQL, consistent with Bogart et al. Our study also adds disease prevalence and disability (which were not included by Bogart et al), among other correlates, to our still nascent understanding of correlates of HRQL across diverse rare diseases[18,19] (see Supplemental Table 4 for descriptive information on disease classification HRQL outcomes).

Studies also have examined HRQL in rare diseases as a group and have focused on comparisons between rare and other common diseases, or with population norms. Results indicate that patients with rare diseases report lower HRQL as a group, even when compared with common chronic diseases.[33,34] For example, one study comparing HRQL in patients with rare diseases, breast cancer, rheumatoid arthritis, rare cancers, and multiple sclerosis found that rare disease patient groups reported the lowest overall VAS and EQ-5D-5L utility score.[34] These findings point to the urgent need to develop interventions to address HRQL in rare disease that, although individually rare, collectively affect hundreds of millions of patients worldwide.[1]

Researchers in the European Union have taken a more systematic approach to examining HRQL in rare diseases. The recently completed Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe (BURQOL-RD) project focused on developing a set of harmonized instruments (including the EQ-5D-5L used here) to examine HRQL in different rare diseases.[10] Although valuable for the insights it provides, this effort only included 10 rare diseases, each with a relatively high prevalence (eg, cystic fibrosis, epidermolysis bullosa, and hemophilia), and analyses focused on outcomes by individual rare disease.[37-45] Our results further expand the literature examining HRQL across a broad range of rare diseases through the use of a systematic sampling procedure to ensure the inclusion of diseases with varying prevalence. In addition, our findings suggest that disease prevalence may be an important predictor of HRQL, with patients with lower prevalence diseases at higher risk of poor outcomes. Patients with more common rare diseases may have greater access to therapies, better

informed clinicians, and/or greater access to a patient community for social support, which may contribute to better HRQL. Given that patients with very low prevalence rare diseases (classified here as having a point prevalence of 1-9 in 1,000,000 or fewer) represent 1 in every 5 rare disease patients and that 96% of all diseases classified as rare fall into this category, improving outcomes for these patients one disease at a time is neither sustainable nor efficient.[3,14] Developing interventions to addresses common barriers to health care and therapeutic interventions that can treat multiple rare diseases will be essential to improving outcomes for patients affected by ultra-rare diseases.

Of note, our examination of the distribution of EQ-5D dimension scores reported by patients and caregiver proxies revealed lower anxiety deficits and higher self-care deficits reported by caregiver proxies for their dependents than by adult patients. This may indicate differences in pediatric versus adult rare disease patients' HRQL. However, past research on proxy bias in HRQL estimates also has shown caregiver underestimation of HRQL in EQ-5D utility scores generally[46] and specifically in caregiver underestimation of anxiety deficits and overestimation of self-care deficits,[47] suggesting that such findings should be interpreted cautiously.

In addition, although our results suggest a consistent association between disability status and lower HRQL, this finding should be interpreted within the context of known limitations of the EQ-5D and similar HRQL measures. Past research suggests that the EQ-5D may not accurately represent the health of disabled populations because of its conflation of disability with poor HRQL.[48] Particularly in countries that utilize cost-effectiveness analyses in health resource allocation decision making, the use of utility scores may lead to resources directed toward disabled communities being deemed less "efficient" and thus increase barriers to accessing care.[49] At a minimum, our findings provide further evidence relevant to the extensive debate around the use of such measures as they relate to disability status.

Limitations

Our study has several limitations. This was a cross-sectional survey; therefore, association between variables cannot be interpreted as inferring causality. As is common in online survey research,[50] our response rate cannot be empirically determined, nor can the diagnoses of respondents be confirmed. The majority of participants in our study were high income, White, and female, a documented pattern in studies conducted using social media.[24,51] Although we recruited participants internationally, the survey was only available in English; thus, the sample is limited to those proficient in reading and writing English. Additionally, we limited our analysis of utility scores and a number of predictor variables (eg, race, ethnicity, and income) to only United States participants because of challenges in collecting consistent sociodemographic data across international contexts and wide variation in the locations of non-United States

participants. We also collected geographic region but not individual country for each participant. However, expanding our participant pool to an international context provided the benefit of including more patients with each rare disease and partially addressing a longstanding challenge in understanding the shared experiences of the global rare disease community.[52] Future studies including more diversity of income, race, and gender will be particularly important for examining disparities in access to health care at the intersection of socioeconomic status and disease prevalence.

Our models did not explain much of the variation in our primary outcomes. Analysis of the residuals from the multivariate analyses revealed a non-random distribution, suggesting that a linear model was not the model of best fit. Apart from there being confounders not accounted for, there are a variety of factors that may have contributed to this outcome. Our survey was not exhaustive in its inclusion of all possible predictors of HRQL, which may have led to the lower R^2 values across all models. For example, questions not included on the survey that may have provided interesting insight into outcome variables include availability of and access to treatment(s) and the multisystemic vs isolated nature of the rare disease. Further, we observed a noticeable increase in variability explained across models with EQ-5D dimensions included as predictor variables, calling into question the validity of the utility score. Past research in other contexts has shown that variability in VAS scores can be explained by changes in EQ-5D domain scores.[53] This provides insight into the divergence of R^2 values between models with outcome variables of VAS versus the EQ-5D utility score and may add weight to the argument that the VAS has a larger predictive validity compared with the EQ-5D utility score on HRQL.[53]

Conclusion

This study addresses an essential gap in knowledge of HRQL across an international sample of rare diseases. Our findings suggest that, even in a diverse sample of rare diseases, lower HRQL is associated with self-identified disability status and reduced rare disease prevalence among other predictors. In addition, overall HRQL in our participant sample is substantially lower than patients with common chronic conditions.[21,22] Given the shared challenges faced by rare disease patients in the health care system, understanding key predictors associated with poorer HRQL is essential to developing policies and funding priorities for research to improve health care delivery and quality of life across the thousands of identified rare diseases.

Data Availability

The data sets generated and/or analyzed during the current study are not publicly available because of privacy concerns with small numbers of patients with certain rare diseases.

The data may be made available from the corresponding author on request if the specific quest does not raise additional privacy concerns.

Author Contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: M.C.H., M.Y., A.R., E.G.M.; Data Curation: M.C.H., M.Y., A.R., E.G.M.; Formal Analysis: M.C.H., M.Y., A.R., E.W.-L., H.N.; Funding Acquisition: M.C.H.; Methodology: M.C.H., M.Y., A.R., E.G.M.; Supervision: M.C.H., H.N.; Writing-original draft: A.R., H.N., M.C.H.; Writing-review and editing: A.R., M.Y., H.N., M.C.H., E.G.M., E.W.-L.

Ethics Declaration

This study was approved by an Institutional Review Board (Program for the Protection of Human Subjects at Stanford University School of Medicine), and all participants provided informed consent.

Conflict of Interest

Meghan C. Halley serves as chair of the board of directors of the Undiagnosed Diseases Network Foundation (uncompensated). All other authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2024.101889) contains supplemental material, which is available to authorized users.

References

1. Haendel M, Vasilevsky N, Unni D, et al. How many rare diseases are there? *Nat Rev Drug Discov.* 2020;19(2):77-78. http://doi.org/10.1038/d41573-019-00180-y

2. Richter T, Nestler-Parr S, Babela R, et al. Rare disease terminology and definitions-a systematic global review: report of the ISPOR rare disease Special Interest Group. *Value Health.* 2015;18(6):906-914. http://doi.org/10.1016/j.jval.2015.05.008

3. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet.* 2020;28(2):165-173. http://doi.org/10.1038/s41431-019-0508-0

4. Wojcik MH, Schwartz TS, Yamin I, et al. Genetic disorders and mortality in infancy and early childhood: delayed diagnoses and missed opportunities. *Genet Med.* 2018;20(11):1396-1404. http://doi.org/10.1038/gim.2018.17

5. Ferreira CR. The burden of rare diseases. *Am J Med Genet A.* 2019;179(6):885-892. http://doi.org/10.1002/ajmg.a.61124

6. Malam F, Hartley T, Gillespie MK, et al. Benchmarking outcomes in the Neonatal Intensive Care Unit: cytogenetic and molecular diagnostic rates in a retrospective cohort. *Am J Med Genet A.* 2017;173(7):1839-1847. http://doi.org/10.1002/ajmg.a.38250

7. Soneda A, Teruya H, Furuya N, et al. Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a Children's Hospital. *Eur J Pediatr.* 2012;171(2):301-305. http://doi.org/10.1007/s00431-011-1534-2

8. O'Malley M, Hutcheon RG. Genetic disorders and congenital malformations in pediatric long-term care. *J Am Med Dir Assoc.* 2007;8(5):332-334. http://doi.org/10.1016/j.jamda.2007.02.008

9. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. *Orphanet J Rare Dis.* 2022;17(1):163. http://doi.org/10.1186/s13023-022-02299-5

10. López-Bastida J, Oliva-Moreno J, Linertová R, Serrano-Aguilar P. Social/economic costs and health-related quality of life in patients with rare diseases in Europe. *Eur J Health Econ.* 2016;17(suppl 1):1-5. http://doi.org/10.1007/s10198-016-0780-7

11. Garrino L, Picco E, Finiguerra I, Rossi D, Simone P, Roccatello D. Living with and treating rare diseases: experiences of patients and professional health care providers. *Qual Health Res.* 2015;25(5):636-651. http://doi.org/10.1177/1049732315570116

12. Bryson B, Bogart K, Atwood M, et al. Navigating the unknown: a content analysis of the unique challenges faced by adults with rare diseases. *J Health Psychol.* 2021;26(5):623-635. http://doi.org/10.1177/1359105319828150

13. Munro M, Cook AM, Bogart KR. An inductive qualitative content analysis of stigma experienced by people with rare diseases. *Psychol Health.* 2022;37(8):948-963. http://doi.org/10.1080/08870446.2021.1912344

14. Halley MC, Smith HS, Ashley EA, Goldenberg AJ, Tabor HK. A call for an integrated approach to improve efficiency, equity and sustainability in rare disease research in the United States. *Nat Genet.* 2022;54(3):219-222. http://doi.org/10.1038/s41588-022-01027-w

15. Tambuyzer E, Vandendriessche B, Austin CP, et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. *Nat Rev Drug Discov.* 2020;19(2):93-111. http://doi.org/10.1038/s41573-019-0049-9

16. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med.* 2018;378(20):1908-1919. http://doi.org/10.1056/NEJMoa1706314

17. Lekstrom-Himes J, Brooks PJ, Koeberl DD, et al. Moving away from one disease at a time: screening, trial design, and regulatory implications of novel platform technologies. *Am J Med Genet C Semin Med Genet.* 2023;193(1):30-43. http://doi.org/10.1002/ajmg.c.32031

18. Bogart K, Hemmesch A, Barnes E, et al. Healthcare access, satisfaction, and health-related quality of life among children and adults with rare diseases. *Orphanet J Rare Dis.* 2022;17(1):196. http://doi.org/10.1186/s13023-022-02343-4

19. Bogart KR, Irvin VL. Health-related quality of life among adults with diverse rare disorders. *Orphanet J Rare Dis.* 2017;12(1):177. http://doi.org/10.1186/s13023-017-0730-1

20. von der Lippe C, Diesen PS, Feragen KB. Living with a rare disorder: a systematic review of the qualitative literature. *Mol Genet Genomic Med*. 2017;5(6):758-773. http://doi.org/10.1002/mgg3.315

21. Rao A, Yabumoto M, Ward-Lev E, Naik H, Halley M. PCR225 predictors of health-related quality of life across rare diseases: an online survey. *Value Health*. 2023;26(6):S354. http://doi.org/10.1016/j.jval.2023.03.2767

22. Rao A, Yabumoto M, Ward-Lev E, Naik H, Halley M. PCR225 predictors of health-related quality of life across rare diseases: an online survey. *Value Health*. 2023;26(6):S354. http://doi.org/10.1016/j.jval.2023.03.2767

23. Titgemeyer SC, Schaaf CP. Facebook support groups for rare pediatric diseases: quantitative analysis. *JMIR Pediatr Parent*. 2020;3(2):e21694. http://doi.org/10.2196/21694

24. Miller EG, Woodward AL, Flinchum G, Young JL, Tabor HK, Halley MC. Opportunities and pitfalls of social media research in rare genetic diseases: a systematic review. *Genet Med*. 2021;23(12):2250-2259. http://doi.org/10.1038/s41436-021-01273-z

25. Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed June 14, 2024. http://www.ncbi.nlm.nih.gov/books/NBK1116/

26. Yabumoto M, Miller E, Rao A, Tabor HK, Ormond KE, Halley MC. Perspectives of rare disease social media group participants on engaging with genetic counselors: mixed methods study. *J Med Internet Res*. 2022;24(12):e42084. http://doi.org/10.2196/42084

27. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208. http://doi.org/10.1016/0168-8510(90)90421-9

28. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. *Appl Health Econ Health Policy*. 2017;15(2):127-137. http://doi.org/10.1007/s40258-017-0310-5

29. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 suppl 1):S3-S11. http://doi.org/10.1097/01.mlr.0000258615.42478.55

30. The World Health Organization Quality of Life (WHOQOL). World Health Organization. Accessed April 18, 2023. https://www.who.int/publications-detail-redirect/WHO-HIS-HSI-Rev.2012.03

31. Pickard AS, Law EH, Jiang R, et al. United States valuation of EQ-5D-5L health states using an international protocol. *Value Health*. 2019;22(8):931-941. http://doi.org/10.1016/j.jval.2019.02.009

32. Office of Management and Budget (OMB). Standards. Office of Research on Women's Health. Accessed March 24, 2024. https://orwh.od.nih.gov/toolkit/other-relevant-federal-policies/OMB-standards

33. Zhou T, Guan H, Wang L, Zhang Y, Rui M, Ma A. Health-related quality of life in patients with different diseases measured with the EQ-5D-5L: a systematic review. *Front Public Health*. 2021;9:675523. http://doi.org/10.3389/fpubh.2021.675523

34. Efthymiadou O, Mossman J, Kanavos P. Differentiation of health-related quality of life outcomes between five disease areas: results from an international survey of patients. *Int J Technol Assess Health Care*. 2018;34(5):498-506. http://doi.org/10.1017/S0266462318000557

35. Ng YNC, Ng NYT, Fung JLF, et al. Evaluating the health-related quality of life of the rare disease population in Hong Kong using EQ-5D 3-level. *Value Health*. 2022;25(9):1624-1633. http://doi.org/10.1016/j.jval.2022.04.1725

36. Xu RH, Ng SSM, Luo N, Dong D, Zhang S. Measurement of health-related quality of life in individuals with rare diseases in china: nationwide online survey. *JMIR Public Health Surveill*. 2023;9(1):e50147. http://doi.org/10.2196/50147

37. López-Bastida J, Linertová R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with Prader-Willi syndrome in Europe. *Eur J Health Econ*. 2016;17(suppl 1):99-108. http://doi.org/10.1007/s10198-016-0788-z

38. López-Bastida J, Linertová R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with scleroderma in Europe. *Eur J Health Econ*. 2016;17(suppl 1):109-117. http://doi.org/10.1007/s10198-016-0789-y

39. Iskrov G, Astigarraga I, Stefanov R, et al. Social/economic costs and health-related quality of life in patients with histiocytosis in Europe. *Eur J Health Econ*. 2016;17(suppl 1):67-78. http://doi.org/10.1007/s10198-016-0790-5

40. Chevreul K, Gandré C, Brigham KB, et al. Social/economic costs and health-related quality of life in patients with fragile X syndrome in Europe. *Eur J Health Econ*. 2016;17(suppl 1):43-52. http://doi.org/10.1007/s10198-016-0784-3

41. Angelis A, Kanavos P, López-Bastida J, et al. Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe. *Eur J Health Econ*. 2016;17(suppl 1):31-42. http://doi.org/10.1007/s10198-016-0783-4

42. Chevreul K, Michel M, Brigham KB, et al. Social/economic costs and health-related quality of life in patients with cystic fibrosis in Europe. *Eur J Health Econ*. 2016;17(suppl 1):7-18. http://doi.org/10.1007/s10198-016-0781-6

43. Cavazza M, Kodra Y, Armeni P, et al. Social/economic costs and quality of life in patients with haemophilia in Europe. *Eur J Health Econ*. 2016;17(suppl 1):53-65. http://doi.org/10.1007/s10198-016-0785-2

44. Cavazza M, Kodra Y, Armeni P, et al. Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe. *Eur J Health Econ*. 2016;17(suppl 1):19-29. http://doi.org/10.1007/s10198-016-0782-5

45. Kuhlmann A, Schmidt T, Treskova M, et al. Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe. *Eur J Health Econ*. 2016;17(suppl 1):79-87. http://doi.org/10.1007/s10198-016-0786-1

46. Arons AMM, Krabbe PFM, Schölzel-Dorenbos CJM, van der Wilt GJ, Rikkert MGMO. Quality of life in dementia: a study on proxy bias. *BMC Med Res Methodol*. 2013;13:110. http://doi.org/10.1186/1471-2288-13-110

47. Griffiths AW, Smith SJ, Martin A, Meads D, Kelley R, Surr CA. Exploring self-report and proxy-report quality-of-life measures for people living with dementia in care homes. *Qual Life Res*. 2020;29(2):463-472. http://doi.org/10.1007/s11136-019-02333-3

48. Taylor WJ, Lord SL, McPherson KM, McNaughton HK. EuroQol EQ-5D may not adequately describe the health of people with disabilities. *Disabil Rehabil*. 2001;23(7):281-285. http://doi.org/10.1080/096382801750143607

49. Nielsen L. Disability discrimination and patient-sensitive health-related quality of life. *Camb Q Healthc Ethics*. 2023;32(2):142-153. http://doi.org/10.1017/S0963180122000202

50. Nelson LM, Simard JF, Oluyomi A, et al. US public concerns about the COVID-19 pandemic from results of a survey given via social media. *AMA Intern Med*. 2020;180(7):1020-1022. http://doi.org/10.1001/jamainternmed.2020.1369

51. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. *Qual Life Res*. 2021;30(3):803-816. http://doi.org/10.1007/s11136-020-02650-y

52. Nestler-Parr S, Korchagina D, Toumi M, et al. Challenges in research and health technology assessment of rare disease technologies: report of the ISPOR rare disease Special Interest Group. *Value Health*. 2018;21(5):493-500. http://doi.org/10.1016/j.jval.2018.03.004

53. Whynes DK, TOMBOLA Group. Correspondence between EQ-5D health state classifications and EQ VAS scores. *Health Qual Life Outcomes*. 2008;6(1):94. http://doi.org/10.1186/1477-7525-6-94