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DOI: https://doi.org/10.1002/jimd.12777

Received: 21 February 2024 | Revised: 14 June 2024 | Accepted: 24 June 2024

DOI: 10.1002/jimd.12777

ORIGINAL ARTICLE

JIMD SSIEM WILEY

The PompeQoL questionnaire: Development and validation of a new measure for children and adolescents with Pompe disease

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Abstract

Genetic disorders pose great challenges for affected individuals and their families, as they must cope with the irreversible nature of the disease and a life-long dependence on medical assistance and treatment. Children and adolescents dealing with Pompe disease (PD) often struggle to keep up with their peers in physical activities. To gain valuable insights into their subjective experiences and better understand their perception and coping related to daily challenges linked to their condition and treatment, the use of standardized questionnaires is crucial. This study introduces the novel PompeQoL 1.0 questionnaire for children and adolescents with PD, designed for comprehensive assessment of both disease-specific FDH and HRQoL through self- and proxy reports. Content validity was ensured through patients' and parents' involvement at the initial stages of development and in subsequent cognitive debriefing process. Participants found the questionnaire easy to understand, answerable, relevant, and comprehensive. Adjustments based on feedback from patients and their parents improved its utility as a patient- and observer-reported outcome measure. After careful item examination, 52 items were selected, demonstrating moderate to excellent test–retest reliability for most scales and initial evidence for satisfactory construct validity. The PompeQoL questionnaire stands as a valuable screening instrument for both clinical and research purposes. Future research should prioritize additional revisions and larger validation studies, focusing on testing the questionnaire in clinical

We present the PompeQoL, the first disease-specific questionnaire for children and adolescents with PD, addressing both FDH and HRQoL. This comprehensive measure is designed for application in clinical practice and research.

Moritz Ilan Truninger and Helene Werner shared first authorship (equal contributions).

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Funding information
Sanofi

Communicating Editor: Jaak Jaeken

practice and trials. Nevertheless, the PompeQoL 1.0 stands out as the first standardized measure providing insights into disease-specific FDH and HRQoL among children and adolescents with various forms of PD.

KEYWORDS
functioning, disability, and health; health-related quality of life; Instrument; observer-reported outcome; patient-reported outcome; pediatric patients; proxy report; self-report

1 | INTRODUCTION

Genetic disorders entail the challenge for affected individuals and their families to cope with the irreversible nature of the disease and life-long dependence on medical assistance and treatment. Pompe disease (PD; OMIM#232300, Online Mendelian Inheritance in Man, OMIM®[1]), also known as glycogen storage disease type II, is a rare, progressive genetic muscle disorder caused by a deficiency of the enzyme acid alpha-glucosidase required to break down glycogen stored in lysosomes. Depending on the genotype, it can manifest either as infantile-onset form (IOPD) with symptoms appearing typically within the first few months of life or as late-onset form (LOPD), appearing later in life with a typically milder progression and usually without heart involvement. The most prominent symptom of both forms is profound muscle weakness, which can affect activities such as sitting, standing, crawling, as well as vital functions like breathing, drinking, and swallowing. Untreated, progressive cardiac muscle weakness in IOPD eventually leads to heart failure.[2] With advancing muscle weakness, many individuals require a wheelchair or mechanical ventilation.[3,4] Since 2006, the mortality rate has been significantly reduced due to implementation of an enzyme replacement therapy (ERT) which positively influences the symptoms but is costly and time-consuming.[5]

Children and adolescents with PD often struggle to keep up with their peers in physical activities. To gain valuable insights into their subjective experiences, and to better understand their perception and coping with daily challenges related to their condition and treatment, it is crucial to utilize standardized questionnaires for assessing functioning, disability, and health (FDH), as well as health-related quality of life (HRQoL), as emphasized by Fayed et al.[9] Compared to generic HRQoL questionnaires, disease-specific measures are typically more sensitive and effective in tracking individual changes over time.[6] In the existing literature, the distinction between FDH and HRQoL is not always clear, primarily due to the development of many patient-reported outcomes (PROs) occurring before a consensus emerged regarding their differences.[7–10] FDH and HRQoL may cover similar health-related domains; however, FDH items focus on self-reports regarding the objective state of these domains (e.g., "Can you walk?"), whereas HRQoL items explore a more subjective perspective (e.g., "How do you feel about your current walking capacities?").

Until now, only one disease-specific measure for children and adolescents with PD exist, the "Pompe-Pediatric Evaluation of Disability Inventory" (Pompe-PEDI).[11] This instrument assesses two FDH aspects (i.e., mobility and self-care) through parental reports only. It lacks a self-report measure capturing both FDH and HRQoL. Such an instrument is particularly relevant for personalized patient care and assessment of treatment effectiveness. We have therefore developed a novel measure, the PompeQoL 1.0 questionnaire, uniquely addressing both FDH and HRQoL.

This study outlines the development of the new PompeQoL 1.0 questionnaire, including results regarding a cognitive debriefing process ensuring content validity. Furthermore, we present the results of an initial field test, which involves a comprehensive psychometric evaluation. This assessment examines item characteristics, test–retest reliability, and construct validity to ensure the robustness of the PompeQoL 1.0 questionnaire.

2 | METHODS

2.1 | Participants

2.1.1 | Overall project

This study is part of an international data collection in Switzerland, Germany, and Austria, aiming to develop a disease-specific HRQoL and FDH questionnaire for children and adolescents with PD, following established guidelines.[6,12,13] The study was approved by the review boards of all participating hospitals and conducted in full accordance with the Declaration of Helsinki. Recruitment involved six children's hospitals/departments: Zurich, Giessen, Mainz, Salzburg, Vienna and Bregenz.

Affected individuals were excluded if they were <8 years (minimum age for self-report) or <5 years (minimum age for proxy reports by parents) or >18 years at inclusion, if they had insufficient command of the German language, or were incapable to follow study procedures (e.g., due to severely reduced health status).

2.1.2 | Present study

This study describes the cognitive debriefing, wherein qualitative feedback on items was obtained, and psychometric evaluation of the PompeQoL 1.0 questionnaire. For the cognitive debriefing, a small group of five children and adolescents with PD and five mothers of affected individuals were recruited. For the psychometric evaluation of the self- respectively proxy report versions of the questionnaire, 16 children and adolescents and 35 parents (20 mothers, 15 fathers) were recruited. All debriefing participants were part of the evaluation sample. In the test–retest evaluation, 45 participants took part, including 14 out of 16 children and adolescents (87.5%), 18 out of 20 mothers (90%), and 13 out of 15 fathers (86.7%).

2.2 | Procedures and analyses

2.2.1 | Overall project

Participation was voluntary. After obtaining written and verbal consents from children and adolescents, and their parents, a very first draft of the questionnaire was developed. Socio-demographic and medical characteristics were collected through parent-reports. In order to identify core topics with high content validity, qualitative interviews with children, adolescents, and their parents were conducted; details of the procedure and results are reported elsewhere.[14] Questionnaire items were constructed based on insights of these interviews, clinical expertise, information of existing disease-specific questionnaires for adults with PD (i.e., "Pompe Disease Symptom Scale"[15]; "Pompe Disease Impact Scale"[15]; "Rasch-built Pompe-Specific Activity scale"[16]; and "IPA/Erasmus MC Pompey Survey", www.erasmusmc.nl/en/research/projects/ipa-erasmus-mc-pompe-survey), and for pediatric male patients with Duchenne muscular dystrophy (e.g., DMD-QoL[17]), a disease with some similar symptoms.

2.2.2 | Present study

After completing the first draft of the PompeQoL questionnaire, consisting of 59 items, structured one-to-one online interviews were conducted and comprehensibility, answerability, appropriateness, and relevance were assessed by using a guide adapted from previous templates.[17,18] After completing a section, participants were asked if they found all questions easy to understand and to answer, and whether they considered them appropriate and relevant. Any reported or observed issues (e.g., long hesitation) were addressed. At the very end, important missing topics were also inquired about. Interviews were video recorded and each aspect (e.g., comprehensibility) was evaluated on a 3-point Likert scale (e.g., easy—moderate—difficult to understand). Subsequently, two authors (M.T., H.W.) discussed evaluations and comments, and adjusted items which resulted in a second draft of the questionnaire with again 59 items used in psychometric evaluation. An online questionnaire booklet was created using RedCap,[19,20] including the PompeQoL 1.0 questionnaire and other questionnaires. Children and adolescents >8 years of age completed the questionnaires during structured online interviews with M.T., while parents completed it independently. About 2 weeks later (average of 16.76 days, SD = 4.45, range 7–31), participants were asked to complete the PompeQoL 1.0 questionnaire again for a test–retest assessment.

For item selection, we examined the distribution of item responses as recommended by Fayers and Machin.[12] Specifically, we looked at mean, standard deviation, range, selectivity, item intercorrelation within a scale, and missing data percentage. Items were evaluated for exclusion based on unfavorable characteristics in both self- and proxy-reported data. For item selection regarding physical problems, only responses from participants reporting any physical problems were considered. The final decision involved discussion among four authors (M.T., H.W., M.L., M.H.). Items were retained in the questionnaire if their content was essential for addressing key disease-related issues. This item selection process led to the final version of the questionnaire, comprising 52 items. Table 1 presents the items of the PompeQoL 1.0 questionnaire, including response options and scale affiliation. Detailed item descriptives and the selection process are shown in Table S1.

2.3 | Measures

2.3.1 | Sociodemographic and medical characteristics

Sex, age, children's mother tongue, and whether parents were born in another country (yes/no) were assessed. Mother tongue was dichotomized into German vs. non-German. PD types were classified as IOPD and LOPD.

TABLE 1 Items included in the PompeQoL 1.0 questionnaire for self-report.[a]

Nr.	Items	Response options type	Scale
1	Do you have difficulties doing the following things because of your muscle weakness?		
1a	...holding your arms above your head, for example, when putting on or taking off a pullover	Intensity I	FDH-muscle
1b	...holding objects in your hand, such as a glass of water	Intensity I	FDH-muscle
1c	...writing or drawing with a pencil for a longer period of time	Intensity I	FDH-muscle
1d	...sitting unassisted on a chair (without leaning)	Intensity I	FDH-muscle
1e	...speaking clearly and distinctly (pronunciation)	Intensity I	FDH-muscle
1f	...sitting up from lying down, for example, on a bed	Intensity I	FDH-muscle
1g	...standing up from sitting, for example, from a chair	Intensity I	FDH-muscle
1h	...standing unassisted for a longer period of time (without holding on)	Intensity I	FDH-muscle
1i	...walking around the house or apartment (without climbing stairs)	Intensity I	FDH-muscle
1j	...going outside, for example, walking to school or taking a walk	Intensity I	FDH-muscle
1k	...fast running/ sprinting, for example, when playing games and in physical education classes	Intensity I	FDH-muscle
1l	...walking up several flights of stairs	Intensity I	FDH-muscle
1m	...riding a bike up a slope, for example, up a hill	Intensity I	FDH-muscle
2	Do you use the following aids outside of your home? For example, at school or in your free time.	Qualitative	
3[b]	Do the difficulties you have because of your muscle weakness bother you?	Intensity II	HrQoL-physical
4	Do you need breathing support?	Qualitative	
5[b]	What kind of breathing support do you use?	Qualitative	
6	Compared to others of your age, do you have difficulties breathing when you do the following things?		
6a	...when lying down, when you are awake (without using breathing support)	Intensity I	FDH-other
6b	...during light physical exertion, for example, walking or driving a wheelchair for short distances	Intensity I	FDH-other
6c	...during heavy physical exertion, for example, jogging, running, or driving a wheelchair fast	Intensity I	FDH-other
7[b]	Do your difficulties in breathing bother you?	Intensity II	HrQoL-physical
8	Do you have pain?		
8a	...in your back	Frequency I	FDH-other
8b	...in your neck/ head	Frequency I	FDH-other
8c	...in your legs/ feet	Frequency I	FDH-other
9[b]	Does your pain bother you?	Intensity II	HrQoL-physical
10	Do you get tired and exhausted quickly after activities? For example, after school or after sports.	Frequency I	FDH-other
11[b]	Does it bother you that you get tired and exhausted quickly after activities?	Intensity II	HrQoL-physical
12	Do you have difficulties hearing? (in spite of hearing aids/ surgery)?	Intensity I	FDH-other
13[b]	Do your difficulties in hearing bother you?	Intensity II	HrQoL-physical
14	Do the following things bother you?		HrQoL-physical
14a[b]	...when you can't do some things as well as others your age	Intensity II	HrQoL-physical
14b[b]	...when you need help to do something	Intensity II	HrQoL-physical
14c[b]	...when you can't do some things at all that you would like to do	Intensity II	HrQoL-physical
15	Are you worried that your physical problems and difficulties might get worse in the future?	Frequency I	HrQoL-physical
16	Are you satisfied with what you can do physically?	Intensity II	HrQoL-physical

TABLE 1 (Continued)

Nr.	Items	Response options type	Scale
17	Are you satisfied with how well you can take part in activities with others? For example, doing things with friends in your free time, going on school trips, or participating in clubs.	Intensity II	HrQoL-psychosocial
18	Do you feel that your parents and your family support you well (or would support you well)? For example, if you have or had problems with your disease.	Intensity II	HrQoL-psychosocial
19	Do you feel that your friends support you well (or would support you well)? For example, if you have or had problems with your disease.	Intensity II	HrQoL-psychosocial
20	Do you feel that others exclude you because of your disease?	Frequency I	HrQoL-psychosocial
21[b]	Does it bother you if your parents or others in your family are especially concerned about you because of your disease?	Intensity II	HrQoL-psychosocial
22	Are you angry because you have Pompe?	Frequency I	HrQoL-psychosocial
23	Are you sad because you have Pompe?	Frequency I	HrQoL-psychosocial
24	Are you uncomfortable with other people knowing you have Pompe?	Frequency I	HrQoL-psychosocial
25	Are you satisfied with your life?	Intensity II	HrQoL-psychosocial
26[c]	Are you worried about how you'll come across to girls (if you're interested in girls), or how you'll come across to boys (if you're interested in boys), because of Pompe?	Frequency I	HrQoL-psychosocial
27[c]	Are you worried about how attractive others find you, because of Pompe?	Frequency I	HrQoL-psychosocial
28[b,c]	Does it bother you that you are less able to realize your plans or wishes for the future because of Pompe, or that you have already had to adjust them?	Intensity II	HrQoL-psychosocial
29	Do the following things bother you?		
29a	...the enzyme replacement therapy	Intensity II	HrQoL-treatment
29b	...the injection for enzyme replacement therapy. For example, because you are afraid of it or because it hurts.	Intensity II	HrQoL-treatment
29c	... that you sometimes can't do certain things because of enzyme replacement therapy. For example, doing something with friends, going to school, going on vacation for a longer period of time.	Intensity II	HrQoL-treatment
29d	That you have other regular appointments because of Pompe. For example, medical check-ups, physiotherapy, and speech therapy.	Intensity II	HrQoL-treatment
30	Where do you do enzyme replacement therapy?	Qualitative	
31	Do you think it's good that you do enzyme replacement therapy at this place?	Intensity II	HrQoL-treatment

Note: Following response options types are used: Intensity I: no/ none, a little, some, a lot, not able to do; Intensity II: not at all, a little, somewhat, quite a lot, very much; Frequency I: no/never, rarely, sometimes, often, always; Qualitative: For item 2: orthotic braces, walker/walking sticks, manual wheelchair, electric wheelchair; for item 4: at night, during the day; for item 5: breathing mask, ventilator (tracheostoma), other support; for item 30: at the hospital, at home, at school, somewhere else.

Abbreviations: FDH, Functioning, Disability, and Health; FDH-muscle, Scale "Muscle Weakness"; FDH-other, Scale "Other Physical Problems"; FDH-total, FDH index; HRQoL, health-related quality of life; HRQoL-physical, Scale "Experience of Physical Difficulties"; HRQoL-psychosocial, Scale "Experience of Psychosocial Impacts"; HRQoL-total, HRQoL index; HRQoL-treatment, Scale "Experience of Treatment".

[a]The proxy report contains parallel rephrased items (e.g., Does it bother your child that...?).

[b]Items only needed to be answered if there are difficulties in these areas (as explained in instructions).

[c]Items only needed to be answered if child >12 years of age or if parents of a child >12 years of age (as explained in instructions).

2.3.2 | Online questionnaire booklet

Included in this booklet was the PompeQOL 1.0 questionnaire, as well as two well-established and validated questionnaires, taht is, PedsQL and DISABKIDS.[21–23]

2.3.3 | PompeQoL

Disease-specific HRQoL and FDH over the past 4 weeks were assessed using the German version of the 52-item PompeQoL 1.0 questionnaire. It comprises a self-report version for children and adolescents aged 8–21 years and a parallel proxy report version for caregivers of those aged 5–21. The items were originally in German and translated into English using a forward-and-backward translation process (for presentation in this paper).

Forty-eight of the 52 items are included in the scale scores and divided into two sections. The first section establishes a total FDH index (FDH-total) with "Muscle Weakness" (13 items, FDH-muscle) and "Other Physical Problems" (8 items, FDH-other). The latter covers various symptoms, including breathing difficulties, pain, fatigue, and hearing difficulties. The second section focuses on a total HRQoL index (HRQoL-total) with three scales: "Experience of Physical Difficulties" (10 items, HRQoL-physical), "Experience of Psychosocial Impact" encompassing themes on social environment, emotional impact, and themes for adolescents and young adults (9–12 items, HRQoL-psychosocial), and "Experience of Treatment" (5 items, HRQoL-treatment). Each scale follows a formative model, except the scale "FDH-muscle," which can be considered to be based on a reflective model.[12,24] Most questions use a 5-point Likert intensity scale (ranging from "not at all" to "very much" or "no/none" to "not able to do"), while some use a 5-point frequency scale (ranging from "no/never" to "always"). Negatively phrased items are reverse-scored. Scores are linearly transformed into values from 0 to 100, with higher values indicating better FDH or HRQoL, and then averaged to scale scores respectively indices scores. Scale or index scores are calculated only when 80% or more of the corresponding items are completed. Four qualitative items (item 2, 4, 5, and 30) are not included in scale scores (see Table 1).

2.3.4 | PedsQL and DISABKIDS

To assess the construct validity of the PompeQoL 1.0 questionnaire, we utilized the German versions of the Pediatric Quality of Life (PedsQL), predominantly evaluating generic FDH, and DISABKIDS-37, focusing on generic HRQoL.[9]

The Pediatric Quality of Life (PedsQL) 4.0 Generic Core Scales is a widely used 23-item measure covering a 4-week recall period, employing a 5-point Likert frequency response scale.[22] Proxy reports can be collected for children, adolescents, and young adults aged 2–25 years, while self-reports can be obtained for those aged 5–25 years. This instrument comprises 4 scales: "Physical Functioning" (8 items), "Social Functioning" (5 items), "Emotional Functioning" (5 items), and "School Functioning" (5 items). The "Physical Health Summary" score (PHS) is determined by the "Physical Functioning" scale, while the "PsychoSocial Health Summary" score (PSHS) is computed as the sum of items over the number of items answered in the "Emotional", "Social" and "School Functioning" scales. Items are reverse-scored and linearly transformed to a 0–100 scale, with higher scores indicating better health.

The DISABKIDS Chronic Generic Measure (DCGM-37) is suitable for all chronic health conditions and is validated for children and adolescents aged 4–16 years, with both proxy and child versions available, covering a 4-week recall period.[23] The answering format comprises 5-point Likert frequency response options. The questionnaire includes six scales representing three main dimensions of HrQoL: (a) Mental dimension: "Independence" (IND, 6 items) and "Emotion" (EMO, 7 items); (b) Social dimension: "Social Exclusion" (EXCL, 6 items) and "Social Inclusion" (INCL, 6 items); and (c) Physical dimension: "Physical Limitation" (LIM, 6 items) and "Treatment" (MED, 7 items). Scores can be transformed to a range of 0–100.

2.4 | Statistical analyses and hypotheses

Data were analyzed using RStudio version 4.3.1. Two-tailed and one-tailed tests, specifically for testing a priori hypotheses, were conducted at a significance level of $p < 0.05$. Due to non-normal distribution of many variables and a relatively small sample, non-parametrical methods were employed. To test differences between IOPD versus LOPD groups on PompeQoL scales, Mann–Whitney U-tests were conducted, with effect sizes computed using Cliff's d (small effect >0.15; medium effect >0.33; large effect >0.47).[25,26] Test–retest reliability, an adequate measure for scales based on formative and reflective models,[27] was measured using Kendall's rank correlation coefficients. Construct validity was evaluated through three types of a priori hypotheses, as outlined in the COSMIN guidelines.[13] Hypotheses included group differences, scale intercorrelations within the PompeQoL, and associations with scales of other questionnaires, tested using (one-sided) Mann–Whitney *U*-Tests and

TABLE 2 Overview of a priori-defined hypotheses to assess the construct validity of the PompeQoL 1.0 questionnaire.

Type of hypotheses	Specific hypotheses			
Group differences between IOPD and LOPD on PompeQoL scales	1	FDH-Total Scores for LOPD	>	FDH-Total Scores for IOPD
Intercorrelations among PompeQoL scales	2	Association of FDH-total with... - HrQoL-Physical	>	Association of FDH-total with... - HrQoL-psychosocial; HrQoL-treatment
Associations between PompeQoL and PedsQL scales	3a	Association of FDH-total with... - PHS	>	Association of FDH-total with... - PSHS
	3b	Association of HrQoL-total with... - PSHS	>	Association of HrQoL-total with... - PHS
Associations between PompeQoL and DISABKIDS scales	4a	Association of HrQoL-treatment with... - MED	>	Association of HrQoL-treatment with... - IND; EMO; EXCL; INCL; LIM
	4b	Association of HrQoL-physical with... - LIM	>	Association of HrQoL-physical with... - IND; EMO; EXCL; INCL; MED
	4c	Association of FDH-total with... - LIM	>	Association of FDH-total with... - IND; EMO; EXCL; INCL; MED
	4d	Association of HrQoL-psychosocial with... - IND; EMO; EXCL; INCL	>	Association of HrQoL-psychosocial with... - LIM; MED

Abbreviations: EMO, emotion; EXCL, social exclusion; FDH, functioning, disability, and health; HRQoL, health-related quality of life; INCL, social inclusion; IND, independence; IOPD, infantile-onset Pompe disease; LIM, physical limitation; LOPD, late-onset Pompe disease; MED, treatment; PHS, physical health summary; PSHS, PsychoSocial Health Summary.

Kendall's rank correlation coefficients. A detailed overview of our a priori hypotheses is presented in Table 2. The rationale for hypothesis 1 is that individuals with the more severe form, IOPD, would score lower on "FDH-total" due to increased physical difficulties. Other hypotheses were based on the assumption of greater similarities in health-related constructs between specified scales (e.g., "FDH-total" and "PHS" vs. "PSHS", hypothesis 3a).

3 | RESULTS

3.1 | Sociodemographic and medical characteristics

3.1.1 | "Cognitive Debriefing" sample

The five children and adolescents with PD had an average age of 12.80 years (SD = 4.09; range eight to 19; 40% females, all German speakers), with three (60%) having IOPD. Five mothers (average age 41.60 years, SD = 4.28, range 38–48) reported on three daughters and two sons (average age 9.80 years, SD = 3.63, range 6–15). Most of their children (80%) had IOPD, while one had LOPD. In two cases, paired child–mother data were available.

Four of the five self-reporting patients (80%) reported three or more PD symptoms (muscle weakness, breathing difficulties, pain, and fatigue), while one patient reported none. Two children required assistance: one with a walker, the other with both manual and electric wheelchairs. One child required breathing support with a mask. In addition, three received ERT at home, and two at other locations (e.g., school). Among those with mother-reported information, for two patients (40%) one to two PD symptoms were reported, while for three patients (60%) three or more symptoms were reported. Three did not use any assistance, while one used a walker, and another an electric wheelchair. Only one child needed continuous breathing support over a tracheostoma. Two children received ERT at home, and three at other respectively multiple locations.

3.1.2 | "Psychometric Evaluation" sample

The PompeQoL 1.0 questionnaire underwent testing with 23 families, comprising 16 children's self-reports and 35 parental proxy reports (20 mothers, 15 fathers). Reporting sources varied across families: Three families provided both self-reports and mother-reports, 10 involved responses from all three sources, and five featured reports from both mothers and fathers without self-reports. Three families provided self-reports exclusively, and two cases involved reports solely from mothers.

The 16 self-reports from children and adolescents averaged 14.30 years (SD = 4.00; range 8–20; 31.25% females, 93.75% German mother tongue), with six

(37.5%) having IOPD. Ten out of 15 patients (62.5%) reported three or more PD symptoms, two (12.5%) one or two symptoms, and four (25%) none. None used an electric wheelchair; two required a manual wheelchair, with one also needing orthotic braces. Orthotic braces were also utilized by two other children, one alongside a walker. Four children and adolescents required breathing support (75% via a mask, 25% missing), with one using it exclusively during the day, two at night, and one both day and night. Additionally, 68.75% received ERT at home, 6.25% at hospital, and 25% at other respectively multiple locations.

The 20 mothers (average age of 43.1, SD = 5.7, range 35–54, 15% born abroad) reported five daughters and 15 sons (average age 12.50 years, SD = 4.00, range 8–20). Half had IOPD, and half had LOPD. Mothers reported for 16 out of the 20 patients (80%) three or more PD symptoms and for four (20%) one or two symptoms. Seven children required assistance: three with electric wheelchairs (one also with a manual wheelchair and a walker), two needed a manual wheelchair (one also with orthotic braces), and two with orthotic braces (one also with a walker). In total, six children and adolescents required breathing support, via mask ($n = 3$), via tracheostoma ($n = 2$), and via other ($n = 1$). Additionally, 55% received ERT at home, 5% at the hospital, and 40% at other respectively multiple locations.

The 15 fathers (average age of 46.1 years, SD = 6.8, range 36 to 56, 6.67% born abroad) reported on 2 daughters and 13 sons (average age = 11.80 years, SD = 3.80, range 8–20). Six children (40%) were affected by IOPD. Fathers reported three or more PD symptoms for 10 of the 15 patients (66.7%), one or two symptoms for two (13.3%), and no symptoms for three patients (20%). Four children required assistance: two with electric wheelchair (one also with a manual wheelchair and a walker), two with a manual wheelchair (one also with orthotic braces), one solely with orthotic braces. In total, four children and adolescents required breathing support, via mask ($n = 3$), and via other ways ($n = 1$). Additionally, 53.3% received ERT at home and 46.7% at other respectively multiple locations.

3.2 | Cognitive debriefing (content validity)

Overall, patients and parents found the PompeQoL 1.0 questionnaire easy to understand and complete. All items were found appropriate by most participants, with participants acknowledging their relevance. In terms of comprehensibility and answerability, the following adjustments were made: Six items were removed due to difficulty in understanding or answering, and four items were split into two or three items each to address mixed topics. Additionally, one item was added to address the lack of a question on participation in social activities, maintaining the overall number of items at 59. Furthermore, about half of the items were rephrased, mainly through minor adjustments such as single-word replacements or small additions to enhance clarity, answerability, and relevance. General modifications to instructions and examples aimed for more detailed guidance. Uniformity across the questionnaire was enhanced and recall period reminders were included in response to observations made in interviews. Finally, response options for three questions were changed from frequency to intensity and "No" was included in the response options "none" and "never."

3.3 | Psychometric evaluation

3.3.1 | Psychometric properties and test–retest reliability

Psychometric properties of the PompeQoL 1.0 questionnaire are shown in Table 3. Means and skewness were higher for self-reported scales than for proxy-reported scales. While floor effects were not present, ceiling effects were more prevalent in self-reports than in proxy reports. All Kendall correlation coefficients between the first and the second assessment points were significant (self-reports: $r = 0.61$–0.95; proxy reports: $r = 0.61$–0.96).

3.3.2 | Construct validity

IOPD vs. LOPD group differences

Table 4 presents group differences for the PompeQoL scales between children and adolescents affected by IOPD vs. LOPD. Medium to strong effect sizes were observed for the "FDH-muscle" and "FDH-total" scales, indicating higher scores for children affected by LOPD (in self- and proxy-reported data). Our hypothesis (1) was met.

Scale intercorrelations

Table 5 shows PompeQoL scale intercorrelations. Significant intercorrelations were noted among the two FDH scales for both self- and proxy reports (ranging from $r = 0.51$–0.68). Our hypothesis (2) of a higher correlation coefficient between FDH-total and HRQoL-physical compared to FDH-total and HRQoL-psychosocial or HRQoL-treatment was confirmed in proxy reports, and partially confirmed in self-reports.

TABLE 3 Psychometric properties of the PompeQoL 1.0 questionnaire.

Scale	*N* items	Mean			SD			Median			IQR			Skewness			% Ceiling			Test–retest reliability[a]		
		Self	ProxyM	ProxyF	self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF
FDH-muscle	13	77.64	62.87	70.90	19.09	30.66	28.18	77.88	71.15	73.08	34.13	48.56	38.46	−0.33	−0.58	−0.78	25.00	20.00	20.00	0.87***	0.92***	0.91***
FHD-other	8	85.74	73.36	81.46	17.19	20.26	15.60	90.62	78.12	81.25	21.09	28.12	31.25	−1.95	−1.12	−0.09	31.25	0	20.00	0.91***	0.78***	0.96***
FDH-total	21	80.73	66.85	74.92	17.01	25.11	22.06	80.36	68.45	72.62	29.17	32.14	36.90	−0.77	−0.75	−0.38	25.00	0	20.00	0.95***	0.93***	0.91***
HrQoL-physical	10	76.88	64.60	74.52	26.12	25.53	20.42	90.00	66.25	77.50	42.50	41.88	40.00	−0.84	−0.24	−0.15	31.25	5.00	6.67	0.81***	0.76***	0.87***
HrQoL-psychosocial	9-12	82.38	70.91	78.70	14.65	19.28	16.24	85.42	73.96	79.17	22.57	32.99	27.08	−0.76	−0.41	−0.52	6.25	0	6.67	0.73***	0.82***	0.82***
HrQoL-treatment	5	83.75	65.31	71.67	13.10	25.83	16.76	87.50	72.50	75.00	23.75	38.75	20.00	−0.25	−0.80	−0.37	18.75	5.00	6.67	0.61**	0.72***	0.61**
HrQoL-total	24-27	80.68	67.43	75.84	17.26	19.35	14.91	89.81	68.63	75.00	29.51	33.05	26.16	−0.70	−0.35	−0.17	0	0	0	0.70***	0.80***	0.86***

Note: Sample sizes, excluding test–retest reliability, were $n = 16$ (self), $n = 20$ (proxyM; except FDH-other, $n = 19$), and $n = 15$ (proxyF). For test–retest reliability, the sample sizes were $n = 14$ (self), $n = 18$ (proxyM; except FDH-muscle, FDH-other, and FDH-total, $n = 17$), and $n = 13$ (proxyF; except FDH-other, $n = 12$).

Abbreviations: IQR, interquartile range; proxyF, proxy reports of fathers; proxyM, proxy reports of mothers.

[a]Kendall rank correlation coefficient (τ).

**$p \leq 0.01$; ***$p \leq 0.001$.

Correlations with PedsQL and DISABKIDS

Table 6 shows correlation coefficients between scales of the PompeQoL 1.0 and PedsQL or DISABKIDS. As hypothesized (3a), a stronger correlation was found between the FDH-total and PHS score compared to PSHS score in both self- and proxy-reported data. Regarding hypothesis 3b, the association between HRQoL-total and PSHS was stronger than with PHS only in paternal-reported data, not in self- or maternal-reported data.

Analyzing PompeQoL and DISABKIDS scale correlations, our results show a stronger correlation between HRQoL-treatment and MED than with any other DISABKIDS scale. Thus, our hypothesis 4a was confirmed in both self- and proxy-reported data. Similarly, the association between HRQoL-physical and LIM was stronger than with (almost) any other DISABKIDS scale. Hypothesis 4b was fully confirmed for self-reported data and largely confirmed in proxy-reported data.

Hypothesis 4c proposed a stronger association between FDH-total and the DISBKIDS scale LIM compared to any other DISBAKIDS scale. This was partially confirmed in self-reported data, largely confirmed in maternal-reported data, and fully confirmed in paternal-reported data. Regarding hypothesis (4d), anticipating a stronger association between HRQoL-psychosocial and IND, EMO, EXCL, INCL of the DISBKDIS than with LIM, and MED of the DISBAKIDS, this was largely fulfilled in paternal-reported data, but incompletely observed in self- or maternal-reported data.

4 | DISCUSSION

This study introduces the PompeQoL 1.0, a novel questionnaire for children and adolescents with PD, designed for comprehensive assessment of both disease-specific FDH and HRQoL through self- and proxy reports. Content validity was ensured through patients' and parents' involvement at the very beginning of the development process and in a cognitive debriefing process. Participants found the questionnaire easy to understand, answerable, relevant, and comprehensive. Adjustments based on feedback from patients and their parents improved its utility as a patient- and observer-reported outcome measure. After careful item examination, 52 items were selected, demonstrating moderate/good to excellent reliability for most scales and initial evidence for satisfactory construct validity, despite some ceiling effects.

Our item analysis revealed ceiling effects in most scales, both self-reports and proxy reports, without floor effects. While this may suggest positive aspects such as overall well-being or that some children and adolescents are quite well-managed under current treatment

TABLE 4 Group differences between IOPD and LOPD for the PompeQoL 1.0 scales.

	Self				ProxyM				ProxyF			
	IOPD	LOPD			IOPD	LOPD			IOPD	LOPD		
	Median (IQR)	Median (IQR)	*p*	Cliff's d	Median (IQR)	Median (IQR)	*p*	Cliff's d	Median (IQR)	Median (IQR)	*p*	Cliff's d
FDH-muscle	69.23 (20.67)	92.31 (34.62)	0.11	−0.50	41.35 (44.15)	79.81 (28.85)	0.001***	−0.89	49.04 (46.15)	98.08 (27.88)	0.02*	−0.78
FHD-other	90.62 (11.72)	92.19 (27.34)	1	−0.02	75.00 (42.19)	82.81 (29.69)	0.25	−0.32	71.88 (20.31)	93.75 (32.81)	0.29	−0.35
FDH-total[a]	75.60 (12.80)	92.26 (31.85)	0.10	−0.40	54.17 (39.61)	80.95 (29.17)	0.004**	−0.71	55.36 (29.76)	96.43 (29.76)	0.009**	−0.76
HrQoL-physical	80.00 (31.88)	95.00 (61.25)	0.74	−0.12	57.50 (36.25)	72.50 (46.67)	0.17	−0.37	61.25 (40.00)	95.00 (37.50)	0.10	−0.54
HrQoL-psychosocial	80.56 (21.88)	89.58 (23.96)	0.62	−0.17	73.96 (27.95)	74.72 (44.79)	0.91	−0.04	79.17 (23.44)	79.17 (35.07)	0.77	0.11
HrQoL-treatment	80.00 (27.50)	90.00 (23.75)	0.70	−0.13	75.00 (37.50)	70.00 (46.25)	0.65	0.13	77.50 (25.00)	65.00 (22.50)	0.37	0.30
HrQoL-total	80.44 (25.64)	92.59 (34.26)	0.51	−0.22	68.63 (34.11)	70.00 (38.48)	0.58	−0.16	68.75 (26.50)	80.43 (29.03)	0.69	−0.15

Note: Sample sizes (IOPD vs. LOPD) were $n = 6$ versus 10 (self), $n = 10$ versus. 1 (proxyM; except FDH-other for IOPD, $n = 9$) and $n = 6$ versus 9 (proxyF).

Abbreviations: IOPD, infantile-onset Pompe disease; IQR, interquartile range; LOPD, late-onset Pompe disease; proxyF, proxy reports of fathers; proxyM, proxy reports of mothers.

[a]For this score, we had a priori hypothesis (1, see Table 2) and conducted a one-tailed Mann–Whitney *U* test. In all other cases, two-tailed Mann–Whitney *U* tests were utilized.

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

TABLE 5 Scale intercorrelations of the PompeQoL 1.0 questionnaire.

	FDH-muscle			FDH-other			FDH-total			HrQoL-physical			HrQoL-psychosocial			HrQoL-treatment		
	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF
FDH-muscle	-	-	-															
FHD-other	0.62**	0.51**	0.68***	-	-	-												
FDH-total	0.92***	0.84***	1***	0.71***	0.71***	0.69***	-	-	-									
HrQoL-physical	0.47*	0.53**	0.66***	0.76***	0.66***	0.73***	0.54**	0.63***	0.66***	-	-	-						
HrQoL-psychosocial	0.47*	0.20	0.21	0.67***	0.42*	0.28	0.53**	0.32	0.20	0.75***	0.52**	0.39*	-	-	-			
HrQoL-treatment	0.07	−0.13	0.05	0.29	0.05	0.10	0.15	−0.05	0.04	0.40*	0.17	0.19	0.26	0.47**	0.41*	-	-	-
HrQoL-total	0.43*	0.31	0.46*	0.65***	0.51**	0.53**	0.49**	0.43**	0.45*	0.88***	0.69***	0.66***	0.77***	0.79***	0.70***	0.47*	0.46**	0.51*

Note: Kendall correlation coefficients (τ) are depicted. Sample sizes were $n = 16$ (self), $n = 20$ (proxyM; except FDH-other, $n = 19$), and $n = 15$ (proxyF).
Abbreviations: FDH, functioning, disability, health; HRQoL, health-related quality of life; proxyF, proxy reports of fathers; proxyM, proxy reports of mothers.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

TABLE 6 Correlation between PompeQoL 1.0 and the PedsQL/DISABKIDS scales.

	PedsQL						DISABKIDS																	
	PHS			PSHS			IND			EMO			EXCL			INCL			LIM			MED		
PompeQoL	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF	Self	ProxyM	ProxyF
FDH-muscle	0.87***	0.72***	0.89***	0.45*	0.28	0.50*	0.52*	0.41*	0.62**	0.28	0.14	0.28	0.35	0.22	0.40	0.23	−0.03	0.21	0.36	0.45**	0.79***	−0.06	0.03	−0.04
FHD-other	0.64**	0.70***	0.61**	0.50*	0.46**	0.57**	0.55*	0.56**	0.55**	0.48*	0.39*	0.36	0.57*	0.40*	0.41*	0.42	0.21	0.34	0.66**	0.61***	0.78***	0.23	0.30	0.03
FDH-total	0.79***	0.83***	0.91***	0.45*	0.43*	0.49*	0.45*	0.53**	0.61**	0.32	0.23	0.27	0.42	0.28	0.39	0.19	0.04	0.22	0.42	0.55**	0.80***	−0.01	0.17	−0.05
HrQoL-physical	0.51*	0.68***	0.61**	0.43*	0.50**	0.62**	0.57**	0.71***	0.67***	0.64**	0.51**	0.40	0.55*	0.57**	0.46*	0.36	0.08	0.34	0.80***	0.73***	0.69***	0.46*	0.42*	0.11
HrQoL-psychosocial	0.49*	0.44**	0.20	0.50*	0.35*	0.46*	0.63**	0.59***	0.52**	0.77***	0.70***	0.84***	0.74***	0.65***	0.60**	0.28	0.32	0.54**	0.68**	0.53**	0.34	0.34	0.57**	0.43*
HrQoL-treatment	0.09	0.15	−0.05	0.17	0.20	0.06	0.22	0.21	0.19	0.36	0.52**	0.49*	0.29	0.41*	0.38	0	0.07	0.24	0.41	0.24	0.12	0.74**	0.68***	0.86***
HrQoL-total	0.45*	0.57***	0.37	0.45*	0.44**	0.51**	0.59**	0.63***	0.60**	0.68**	0.67***	0.67**	0.58**	0.57***	0.47*	0.32	0.19	0.48*	0.79***	0.64***	0.53**	0.49*	0.59***	0.41*

Note: Kendall correlation coefficients (τ) are depicted. Sample sizes regarding correlations between PompeQoL and PedsQL scales: $n = 14$ (self), $n = 20$ (proxyM), and $n = 15$ (proxyF); and between PompeQoL and DISABKIDS: $n = 13$ (self), $n = 19$ (proxyM, except FDI-other, $n = 18$), and $n = 15$ (proxyF).
Abbreviations: EMO, emotion; EXCL, social exclusion; INCL, social inclusion; IND, independence; LIM, physical limitation; MED, treatment; PHS, physical health summary; proxyF, proxy reports of fathers; proxyM, proxy reports of mothers; PSHS, PsychoSocial Health Summary.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

procedures, it also raises concerns about the questionnaire's sensitivity to detect variations, particularly at the higher end. Notably, in our preceding qualitative interview study, some participants also reported no physical limitations in response to open-ended questions.[14] This poses a challenge in sensitively engaging with them, as potential physical problems may only be detectable through clinical testing. However, ceiling effects are quite common in generic and disease-specific HRQoL and FDH questionnaires.[21,28,29] Our experiences also showed that it is extremely challenging to involve physically or emotionally severely affected children and adolescents with PD in the development process of a questionnaire due to limited communication abilities.

Test–retest reliability analysis demonstrated good to excellent stability of the PompeQoL 1.0 questionnaire. All scales showed significant positive, moderate to strong correlations between the first and second assessment points, with slightly higher correlations for the "FDH-total" index compared to the "HRQoL-total." This could be because disease-specific symptoms, like muscle weakness may be perceived as relatively consistent over 2 weeks under stable therapy conditions. In contrast, psychosocial impacts could vary to a greater extent based on recent events, such as someone being unable to participate in a social activity like playing football with friends. The scale "HRQoL-treatment" showed slightly lower reliability, likely due to its lowest number of items (i.e., five items), making it more sensitive to random fluctuations. Additionally, actual changes might have occurred between the two time points, such as for example the ERT being perceived as more burdensome due to a recent painful injection. Nevertheless, our results suggest that the questionnaire reliably measures FDH and HRQoL in children and adolescents with PD.

Construct validity of the PompeQoL 1.0 questionnaire was evaluated through various hypotheses. As anticipated, in terms of group differences between LOPD versus IOPD patients, "FDH-total" scores were lower for children with IOPD in both self- and proxy-reported data. This suggests that physical symptoms and related difficulties are perceived to be more pronounced in this patient group, aligning with its clinical characterization of a more severe and rapidly progressing disease course. Intercorrelations between the PompeQoL scales showed stronger correlations for "FDH-total" and "HRQoL-physical" compared to "HRQoL-psychosocial" or "HRQoL-treatment." This supports our reasoning that the "FDH-total" should be more like the "HRQoL-physical" than the other HRQoL subscales. Furthermore, associations between PompeQoL scales and two external measures (PedsQL and DISABKIDS) were explored. Consistent with our hypothesis (3a in Table 2), a stronger correlation between "FDH-total" and the "PHS" compared to "PSHS" was found in both self- and proxy reports. This supports good construct validity, indicating that the information assessed by the FDH index aligns more closely with aspects of the PHS scale from the PedsQL than with the PSHS scale, which also covers items related to emotional, social, and school functioning. In contrast, our next hypothesis (3b, Table 2) was not met. One possible explanation for this could be that the themes assessed by the "HrQoL-total" and the "PSHS" are less similar than anticipated. For example, the "HrQoL-total" scale lacks questions on school functioning, while five items in the "PSHS" specifically address this aspect. The reason for not including questions about school functioning in the PompeQoL was that topics such as concentration issues or problems with academic tasks did not come up in the qualitative interviews.[14] Good construct validity was further supported by the finding that the "HRQoL-treatment" scale correlated highest with the DISABKIDS subscale "MED" (self- and proxy reports; 4a in Table 2), which indicates that our new scale successfully addresses the experienced impact of taking medication, receiving injections, and related aspects. Additionally, our findings showed a stronger correlation between "HRQoL-physical" and "LIM" compared to all other DISABKIDS scales, supporting our hypothesis (4b in Table 2) in self- and largely in proxy-reported data. The results for the last two hypotheses (4c and 4d, Table 2) were mixed and did largely not confirm our initial hypotheses. This discrepancy may be attributed to substantial differences in content and topics covered between the two instruments. Upon reviewing the DISAKBIDS scales, we came to the assumption that physical limitations might be included in the "IND" scale, despite its conceptual classification as part of the mental domain. When examining correlations in the DISABKIDS validation study, we found that the "IND" scale correlated similarly with both "EMO" (0.63) and "LIM" (0.62), supporting this assumption (see DISABKIDS manual[23]). This might explain part of the mixed results for hypotheses 4c and 4d.

Overall, it is worth noting that self-reported data showed less consistency with our a priori expectations, possibly due to poorer psychometric properties leading to lower precision and greater susceptibility to random fluctuations. Additionally, children who self-reported seemed to be in better physical condition than those for whom parents provided proxy reports. The mode of data collection, either through interviews or online questionnaires, may have influenced these findings as interviews could encourage socially desirable answers. This aspect may be worth investigating in future studies.

The strengths of our study are the multicenter, international data collection, adding robustness to the study. The study employed a mixed methods approach

combining qualitative cognitive debriefing with psychometric evaluation for a comprehensive understanding of the questionnaire's properties.[6,9] The PompeQoL questionnaire underwent a rigorous development process, including qualitative interviews, expert input, and consideration of existing disease-specific questionnaires, enhancing its content validity. In addition, we specifically addressed both FDH and HrQoL, a differentiation often lacking in the literature.[9] The inclusion of a test–retest evaluation demonstrated the reliability of the questionnaire, with a high participation rate. That is, scores remained fairly to very stable over a short time period where no significant change was expected. Notably, it is worth noting that our sample had a relatively high proportion of fathers compared to other studies.[28,30] Nevertheless, the following limitations merit note: Firstly, the relatively small sample size and the use of an opportunity sample may impact generalizability and limit the ability to detect smaller effects. This was due to the rarity of PD, which limits the number of available participants, although our recruitment involved six centers in three countries. To increase the generalizability of future findings and to increase sample size, future studies should include more centers. This could be achieved by translating the PompeQoL into multiple languages and using the translation validation process to gather further data on reliability and validity. Secondly, we could not assess the construct validity of the FDH-index with objective tests like a 6-min walk test or conduct a structural validity analysis (e.g., confirmatory factor analysis) for the "FDH-muscle" scale, which is based on a reflective model. This should be done in future studies. Thirdly, cross-cultural validity may be constrained, as our development process focused exclusively on a German-speaking sample. The generalizability of the findings to other cultural contexts may be influenced by variations in social, linguistic, and cultural factors not represented in the tested population. Fourthly, we have not examined responsiveness of the PompeQoL questionnaire, thus, it is yet unclear if the questionnaire can accurately detect and measure meaningful changes over time, especially in response to treatment or interventions.[31] Although there is evidence that disease-specific instruments are more sensitive to detect changes over time than generic instruments,[32] this property should be tested in the context of future interventional studies. Such studies would involve longitudinal data collection and could provide a better understanding of how the questionnaire performs in detecting changes in FDH and HRQoL in pediatric patients with PD. Finally, the PompeQoL questionnaire is specifically tailored to pediatric patients with PD. While this specificity is one of its strengths, it restricts its use to pediatric patients with PD and is therefore not suitable for comparisons with other conditions or the general population. For such comparisons, generic or chronic generic instruments are required. Given the advantages and disadvantages of both disease-specific and generic instruments, a combined use is often suggested.[33] Thus, we recommend that for studies aiming to compare PD with other conditions or control groups, a combination of generic questionnaires, such as the PedsQL or DISABKIDS, along with a disease-specific questionnaire may be most appropriate.

The PompeQoL 1.0, the first psychometrically evaluated questionnaire addressing the impact of PD on children and adolescents in terms of both FDH and HRQoL, stands as a valuable screening instrument for clinical and research purposes. Future research should prioritize additional revisions and larger validation studies, focusing on testing the questionnaire in clinical practice and trials, for example to examine responsiveness. In addition, it is crucial to further develop the instrument to counteract the described ceiling effects. This could be done, for instance, through testing shifted response options or creating separate versions for mild and severe cases of PD in children and adolescents. It is noteworthy that many severely affected individuals struggle with paper questionnaires, necessitating innovative methods to facilitate their participation and gain valuable insights into their perceptions and experiences.

AUTHOR CONTRIBUTIONS

Moritz I. Truninger was involved in designing the study, made substantial contributions to acquisition of data, carried out data analysis and interpretation, and revised the manuscript critically for intellectual content. Helene Werner was involved in designing the study, supervised data acquisition and analysis, made contributions to data interpretation, and drafted the manuscript. Markus A. Landolt contributed to the study conception, carried out data interpretation, and revised the manuscript critically for intellectual content. Andreas Hahn, Julia Hennermann, Florian B. Lagler, Dorothea Möslinger, Charlotte Pfrimmer, and Marianne Rohrbach were involved in recruitment and acquisition of patient data. Martina Huemer provided the original study concept, made substantial contributions to study design, coordinated the study, contributed patient data, carried out data interpretation, and revised the manuscript critically for intellectual content. All authors read and approved the final version.

ACKNOWLEDGEMENTS

We thank all children and adolescents with PD and their parents who participated in the study and shared their experiences with us. Many thanks go to Flavio

Mariano Heller for setting up the online questionnaire booklet in Redcap and providing technical support, Simply Language Switzerland association for assistance in finalizing the German version of the questionnaire in simple and understandable language, Simon Milligan, Ellen Russon, and Alexandra Vogt for careful forward and backward translation of the final version of the questionnaire, Thea Abele for supporting recruitment of participants in Giessen, and Anja Bomba for supporting the EC submission in Salzburg. We thank Sanofi for the financial support of the project.

FUNDING INFORMATION

The project was supported financially by Sanofi. There was no influence on the content of the project work, the study processes, or on the content and preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

Moritz I Truninger, Helene Werner, Markus A. Landolt, Andreas Hahn, Dorothea Möslinger, Charlotte Pfrimmer, and Marianne Rohrbach declare that they have no conflict of interest. Martina Huemer has received unrestricted research grants from Nutricia Metabolics and SOBI, and consultancy honoraria or travel support from Aeglea, Chiesi, Nutricia Metabolics, Sanofi, Recordati, and Immedica Pharma, all unrelated to this work. Julia B. Hennermann has received consulting fees/honoraria and/or travel expenses from Chiesi, Amicus, Takeda, and Sanofi, all unrelated to this work. Florian B. Lagler has received unrestricted research grants from Sanofi, Takeda, and Chiesi and honoraria as speaker and consultant from these companies plus Biomarin and Amicus, all unrelated to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

INFORMED CONSENT

Informed consent was obtained from all participants for being included in the study. Caregivers gave informed consent for their/their child's participation. Adolescent patients gave informed consent for participation. Ethical approval for this study was given by the local review boards of all participating hospitals.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Truninger MI, Werner H, Landolt MA, et al. The PompeQoL questionnaire: Development and validation of a new measure for children and adolescents with Pompe disease. *J Inherit Metab Dis*. 2024;1-15. doi:10.1002/jimd.12777