THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Systematic Review

A systematic literature review of the impact and measurement of mobility impairment in rare bone diseases

Ther Adv Musculoskelet Dis

2025, Vol. 17: 1–36

DOI: 10.1177/1759720X251369963

Inês Alves, Ingunn Westerheim, Edward C. Hsiao, Jaymin Upadhyay, Luca Sangiorgi, Alexander Artyomenko, Kim Croskery, Juliet Johns, Emma Warnants and Gabor Barton

Abstract

Background: Although rare bone diseases (RBDs) present mobility challenges, there is little consolidated evidence on evaluated mobility measurement tools or how mobility impairments impact daily activities and quality of life (QoL).

Objectives and design: This systematic literature review investigated: (1) the impacts of mobility impairment on daily activities/QoL; (2) the suitability/comprehensiveness of tools measuring mobility.

Data sources and methods: MEDLINE/Embase databases (January 19, 2022) and Google (October 19, 2022) were searched for articles published between 2011 and 2022; conference proceedings from 2020 to 2021 were hand-searched. Included articles reported on how mobility impairments impact daily activities/QoL, or the use of tools for measuring mobility, in RBDs. A narrative analysis using descriptive statistics was conducted. Studies were assessed for risk of bias using The Alberta Heritage Foundation for Medical Research Quality Assessment Criteria and National Institute of Health Quality Assessment Tool for Case Series Studies.

Results: Inclusion criteria were met by 113 articles, investigating 39 RBDs (sample sizes: $N = 1$–959). Mobility impairments, commonly joint function/gait disturbances, negatively impacted daily activities ($n = 47$ cohorts; frequently walking (27/47; 57.4%)) and QoL ($n = 36$ cohorts; commonly pain (30/36; 83.3%; Objective 1). There were 34 functional assessments, 22 questionnaires, and 5 technologies described. Only nine functional assessments/questionnaires were reported to have good validity/reliability/responsiveness for an RBD (not reported for technologies); none comprehensively captured daily living/QoL impacts of mobility impairment. The quality of studies was moderate, though many were case studies/series, which are at inherent risk of bias.

Conclusion: Few tools comprehensively captured mobility impairments and associated impacts on daily activities/QoL. Consistent reporting of tools' validity/reliability/responsiveness would support clinicians in selecting methods for use across RBD populations. Used remotely, wearables could support understanding of real-world mobility challenges. Since searches were conducted, additional technologies (e.g., remote gait analysis) have been tested in RBDs, although validation is required.

Protocol PROSPERO registration: CRD42022311513. Sponsored by Ipsen.

Correspondence to:
Inês Alves
School of Health and Human Development, Comprehensive Health Research Centre, University of Évora, Largo dos Colegiais 2, Évora 7004-516, Portugal

National Association of Skeletal Dysplasia (ANDO Portugal), Évora, Portugal
ines.alves@uevora.pt

Ingunn Westerheim
Osteogenesis Imperfecta Federation Europe, Heffen, Belgium

Edward C. Hsiao
Division of Endocrinology and Metabolism, The UCSF Metabolic Bone Clinic, The Eli and Edythe Broad Institute for Regeneration Medicine, The Institute of Human Genetics, Department of Medicine, The UCSF Program in Craniofacial Biology, University of California San Francisco, San Francisco, CA, USA

Jaymin Upadhyay
Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA, USA

Luca Sangiorgi
Department of Rare Skeletal Disorders, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Alexander Artyomenko
Kim Croskery
Ipsen, Slough, UK

Juliet Johns
Emma Warnants
Costello Medical, London, UK

Gabor Barton
Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

Plain language summary

A review of movement challenges that impact the lives of people with rare bone diseases and an evaluation of how mobility can be measured across rare bone diseases

Rare bone diseases are a group of conditions that affect bones, cartilage, and/or muscles. People with a rare bone disease often have difficulty moving, which may stop them being able to do their usual daily activities (e.g. household chores). As a result, people may have lower quality of life. Yet there is not much research on the impact of movement difficulties across rare bone diseases. Doctors often use questionnaires or clinical assessments to measure movement. Wearable technologies worn at home might help Doctors test movement remotely and reveal day-to-day impacts on daily activities and quality of life. It is important to test and validate these technologies for people with rare bone diseases that will use them. We conducted a literature review to explore how movement difficulties affect the lives of people with rare bone diseases. The second aim was to see how different methods can measure movement across these diseases. We included literature published between 2011–2022 that provided relevant information. The literature showed that difficulty moving negatively impacts people's lives. Many experience pain and challenges with walking/personal care. There were 22 questionnaires, 34 clinical assessments, and 5 technologies used to measure movement. Some methods were not well-suited for use in particular rare bone diseases. For example, some measurements did not correspond with impacts that individuals described. Only 9 questionnaires/clinical assessments were validated. No technologies had been validated or used outside of the clinic. Researchers could do further tests to see if these tools are suitable for measuring movement in people with rare bone diseases or they could re-use existing remote technologies. These technologies would need to be validated first. The information from remote technologies used at home could help Doctors decide how best to care for people with rare bone diseases.

Keywords: burden of disease, functioning, mobility impairment, quality of life, rare bone, skeletal dysplasia

Received: 20 May 2025; revised manuscript accepted: 5 August 2025.

Background

Rare bone diseases (RBDs) are a group of conditions affecting cartilage, bones, soft tissue, and/or dentin, encompassing skeletal dysplasias and metabolic bone diseases (e.g., fibrodysplasia ossificans progressiva (FOP), osteogenesis imperfecta (OI), and X-linked hypophosphatemia (XLH)).[1,2] The list of RBDs continues to evolve; categorizations in the Nosology of Genetic Skeletal Disorders were updated in 2023, increasing the number of distinct conditions from 461 to 771.[3,4] Most individuals with RBDs have complex physical health challenges,[5,6] including substantial restriction of movement and cumulative disability.[6–9] This can negatively impact an individual's ability to perform daily activities as well as their quality of life (QoL), including emotional and social well-being.[6–9] For example, an FOP burden of illness survey demonstrated that loss of joint function, as assessed by Patient-Reported Mobility Assessment (PRMA) score, had a significant, detrimental impact on QoL for individuals with FOP, resulting in decreasing EQ-5D-5L index scores.[10] Loss of joint function also increased the proportion of individuals using assistive devices and adaptations to the home to assist with daily activities.[10]

Whilst existing research characterizes the functional, social, and physiological burden of a very limited number of RBDs,[8–10] there is a lack of consolidated evidence on the impact of mobility impairment on daily activities and QoL across different RBDs, and the related unmet needs of affected individuals. A variety of functional assessment tools and questionnaires are used in clinical practice and trials to evaluate the functional mobility of individuals with RBDs (e.g., the

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and 6-min walk test (6MWT) used as secondary endpoints in XLH clinical trials).[11] Some commonly used functional assessments correlate weakly with existing patient-reported mobility change assessments (i.e., completed without the input of a healthcare professional).[12,13] For example, individuals with hypophosphatasia (HPP) self-report greater mobility limitations than those captured by the 6MWT and 10-m walk test (10MWT).[13] Additionally, tools often measure aspects of functional mobility, but have limited use in capturing the wider impacts on daily activities and QoL that individuals experience.[14–18] A more comprehensive tool, capable of capturing multiple aspects of QoL in addition to functional mobility, may help alleviate the burden of multiple assessments,[19,20] including the need to frequently travel to a clinic for separate assessments, which may be particularly challenging for those with mobility limitations. Furthermore, many tools can only provide a snapshot of mobility challenges at a single point in time. Technological methods used remotely (e.g., wearables), have the potential to measure individuals' mobility over time in a home environment, in a manner that is more reflective of their experiences in a real-world setting.

With such a large number of RBDs, developing and validating disease-specific mobility measurement tools for every condition would be resource-intensive and costly. Clinicians caring for individuals with a particular RBD may benefit from repurposing tools used for related RBDs (e.g., with similar skeletal phenotypes), or using general mobility measurement tools that have been validated in different RBDs. However, we are not aware of any previous study that has synthesized published tools that have been used to measure mobility in RBDs, and their reported validity, reliability, or responsiveness. Such research could inform the development of more appropriate and comprehensive methods of measuring the impact of mobility impairment in RBDs.

A systematic literature review (SLR) was therefore conducted with two objectives: Objective 1 was to investigate the impacts of mobility impairment on daily activities and QoL for individuals with RBDs; Objective 2 aimed to identify existing tools or those in development for measuring mobility in RBDs, including their reported validity, reliability, or responsiveness in an RBD population. The capability of tools identified in Objective 2 to comprehensively capture the aspects of daily activities and QoL impacted by mobility impairment, as identified in Objective 1, was also synthesized. This is the first SLR, to our knowledge, that collates evidence on the impact of mobility impairment across RBDs and the tools that can measure functional mobility and wider impacts on daily activities and QoL.

Methods

This SLR was conducted in accordance with a pre-specified protocol, which was registered to PROSPERO (CRD42022311513) and written in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Search strategy

Electronic database searches were conducted on January 19, 2022, in MEDLINE and Embase, to identify relevant articles. A single search strategy was used within electronic databases, combining search terms for RBDs with terms for patient perspectives, QoL, and mobility impairment (Objective 1), and/or mobility assessment (Objective 2). The full search strategies used for each online database are provided in Supplemental Additional File 1.

Congress proceedings from the previous 2 years (January 1, 2020–December 31, 2021; Supplemental Additional File 2), and the bibliographies of relevant SLRs and (network) meta-analyses (NMAs) identified during the search of electronic databases were hand-searched to identify any additional relevant articles. Hand searches of Google were conducted on October 19, 2022, to identify any further publications not included in the databases (Supplemental Additional File 3). Database search terms were adapted for searching congress proceedings and Google; full search strategies are provided in Supplemental Additional Files 2 and 3.

Article selection

Identified articles were screened for relevance against pre-specified eligibility criteria (Table 1). Included articles were published between January 1, 2011 and January 18, 2022 (or January 1, 2020 and December 31, 2021 for congress

Table 1. Eligibility criteria used for assessing articles for inclusion in the SLR.

Domain	Inclusion criteria	Exclusion criteria
Patient population	People of any age, gender, or ethnic background, with RBDs listed in the 2019 Nosology and Classification of Genetic Skeletal Disorders[3,a]	People without RBDs
Intervention/ comparator	Any or none	NA
Outcomes (Objective 1)	Describes the perspectives of patients, physicians or researchers, or patient-reported outcomes, regarding: • Aspects of mobility impairments which impact daily activities and QoL[b] ○ Includes descriptions of mobility-related daily activities not linked to a specific mobility impairment, if the primary outcome of the study	Only describes the impact of an RBD on a mobility-related daily activity (e.g., walking or climbing stairs, without mention of a specific mobility impairment)[c] "Pain" is the only QoL impact mentioned in relation to a mobility impairment, with no other QoL or daily activities impact mentioned
Outcomes (Objective 2)	Describes the application or development of a tool that measures mobility through one or more domain, for use in studies or clinical practice[d,e] Describes the development of such a tool that can measure mobility in a preclinical setting or pilot experiments[e] Assesses the validity, reliability, or responsiveness of current tool(s) capable of measuring mobility through one or more domains	Any other outcome
Study design	Focus groups Survey/questionnaires Interviews Interventional studies (randomized and non-randomized) Observational studies (including registry studies) Case studies, case series, SLRs, NMAs,[f] health technology assessments, and economic evaluations	Narrative reviews Editorial letters
Article type	Peer-reviewed articles published from 2011 onwards Conference abstracts/posters from 2019 to 2021[g]	Peer-reviewed articles published prior to 2011 Conference abstracts/posters, and other conference proceedings (e.g., oral presentations) from before 2019[h]
Language	English language articles only	Articles in other languages
Other considerations	Studies with human participants	Animal or cell studies

Included articles were published between January 1, 2011 and January 18, 2022 (or January 1, 2020 and December 31, 2021 for congress proceedings).
[a]Or synonyms of the disease.
[b]A mobility impairment in this SLR was defined as a physiological mobility impairment that has caused an impact on daily activities or QoL.
[c]Except if the primary outcomes assessed were mobility-related daily activities.
[d]The assessment of mobility by the mobility measurement tool and not just "physical function," must have been specified within the article.
[e]With/without assessment of the validity, reliability, or responsiveness of the tool.
[f]SLRs and NMAs were considered relevant at the title/abstract review stage and hand-searched for relevant primary studies, but were excluded during the full-text review stage unless they reported primary research.
[g]See Supplemental Additional File 2 for a list of the congress proceedings that were searched.
[h]Congress proceedings published prior to 2019 identified through Google searches without a corresponding published peer-reviewed article were included.
NA, not applicable; NMA, network meta-analyses; QoL, quality of life; RBD, rare bone disease; SLR, systematic literature review.

proceedings). Articles that described individuals with RBDs listed in the 2019 Nosology and Classification of Genetic Skeletal Disorders,[3] were included if they reported on relevant outcomes. For Objective 1, relevant outcomes included the impacts of a physiological mobility impairment on daily activities and/or QoL. Mobility impairment was defined as a physiological limitation of a person's coordination or movement (encompassing gait disturbance, reduced range of joint motion, impaired limb movement, or impaired fine motor movement) or unspecified reduced mobility as reported by the study investigators. The mobility impairment could have occurred as a direct (e.g., ossification of connective tissue restricting range of motion in FOP) or indirect (e.g., bone weakening in XLH causing a gait-disturbing fracture) result of the RBD.[22,23] This broad definition was used in order to capture the wide variety of different mobility impairments people with RBDs may experience; the definition was limited to physiological limitations because wider impacts on daily activities (e.g., self-care) would be captured as impacts of mobility impairment as part of Objective 1. For Objective 2, relevant outcomes were the application or development of tool(s) capable of measuring mobility in RBDs (Objective 2). Tools including one or more domains that measure mobility were eligible.

On account of the large volume of literature identified, the eligibility criteria were tightened after the full-text review stage (final criteria shown in Table 1), to prioritize the articles of most relevance to the objectives: when assessing articles against Objective 1, if the impact of an RBD on a mobility-related daily activity was specified without mention of a specific physiological mobility impairment, the article was excluded (so included articles had to directly link a specific mobility impairment to an impact on daily activities or QoL), unless the primary study outcomes were mobility-related daily activities. Other excluded articles were those where the QoL impact mentioned was "pain" in relation to a mobility impairment, without the inclusion of any other QoL or daily activity impact. These articles were excluded because it was often not possible to ascertain if the pain was a result of the mobility impairment, or causal of reduced mobility. Additionally, pain is a more established impact of mobility impairment in RBDs and so was determined not to be an outcome of focus.[24,25]

Each abstract was reviewed against the study eligibility criteria by one reviewer (A.S., E.W., J.J.), in line with the Cochrane Handbook for Systematic Reviews and Interventions.[26] Full-text articles were reviewed by two independent reviewers (A.S., J.J.), and where necessary, a third reviewer (E.W.) was consulted to reach a final decision on whether the study eligibility criteria were met.

Data extraction and quality assessment

Data extraction was performed in line with guidelines from the University of York Centre for Reviews and Dissemination.[27] Data from included articles, such as study characteristics, patient characteristics, and outcomes related to Objectives 1 and/or 2, were extracted by a single individual (A.S., E.W., J.J.) into a pre-specified grid (Supplemental Additional File 4) and independently verified by another reviewer (A.S., J.J.). Articles reporting on the same study were linked, and the quality of included articles was assessed by one reviewer and verified by a second (A.S., J.J.). Where necessary, a third reviewer (E.W.) was consulted to reach a final decision regarding the extracted information and quality assessments (QAs). The Alberta Heritage Foundation for Medical Research (AHFMR) Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields was used to assess quality of all study types identified in Objectives 1 and 2, apart from case studies/case series (due to the number of questions in this checklist that are not applicable to this study design).[28] For case studies/series, the National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies was used to assess the quality of evidence.[29]

Data analysis

A narrative analysis was conducted whereby outcomes data were analyzed in three groups: at the study level for all included articles, for patient cohorts, and at the patient level. Where data were analyzed by article (covering all study types), descriptive statistics were calculated as the proportion or number of articles reporting each variable, with a denominator of the total number of articles (primary and secondary articles reporting on the same study population were included separately). Patient cohort data were analyzed across all study types and were presented as descriptive statistics calculated as the proportion or number

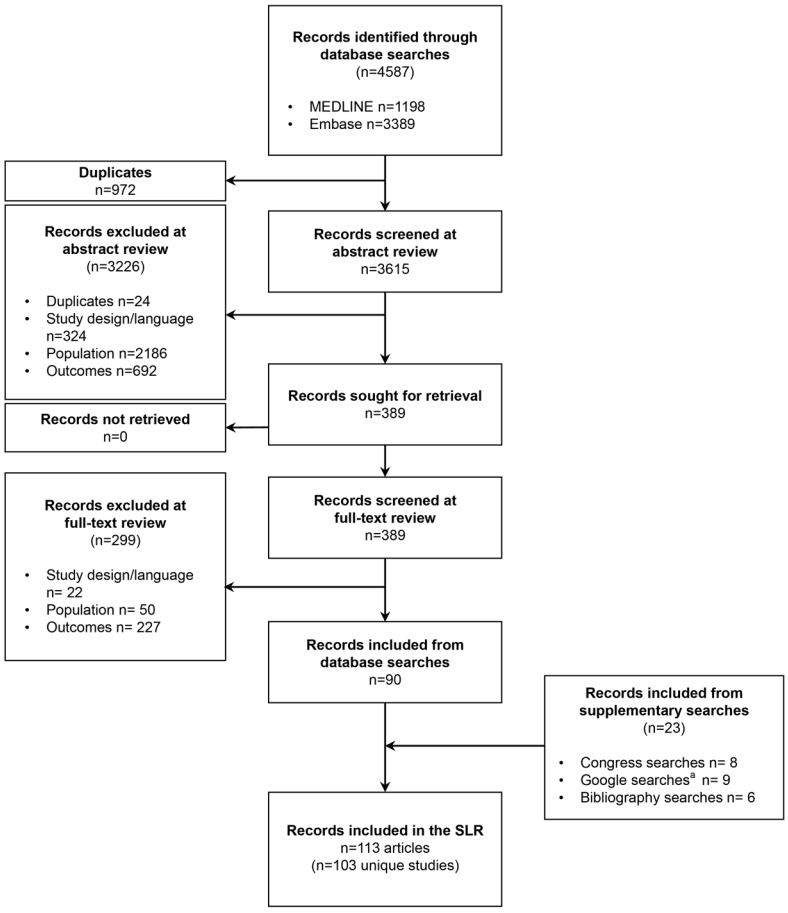

Figure 1. PRISMA flowchart of identified articles.
Included articles were published between January 1, 2011 and January 18, 2022 (or January 1, 2020 and December 31, 2021 for congress proceedings).
[a]Includes one article identified through reference linking.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SLR, systematic literature review.

of patient cohorts reporting each variable, with a denominator of the total number of patient cohorts across all articles. For patient-level data (from either cohort, cross-sectional, or case studies), descriptive statistics were calculated as the proportion or number of individuals for whom each variable was reported, with a denominator of the total number of individuals across all articles for whom patient-level data were reported.

For tools used to measure mobility, the validity, reliability, or responsiveness were extracted as reported in the article(s) and then categorized as "good," "uncertain or conflicting evidence," or "poor" (e.g., high reliability would be categorized as "good"), based on available data across articles which described that tool. If two or more articles conflicted in the reported validity, reliability, or responsiveness of the tool, or if the assessment reported in an article was unclear, the tool was categorized under "uncertain or conflicting evidence." The psychometric properties of the tools were not critically assessed as part of this SLR.

Results

Characteristics of included articles

A total of 113 articles from database searches, conference proceedings, Google searches, and bibliography searches were prioritized for extraction (Figure 1). The articles reported primarily on cross-sectional studies ($n = 35$; 31.0%), case studies ($n = 32$; 28.3%), or cohort studies ($n = 30$; 26.5%). Other study types included eight randomized controlled trials (7.1%), six single-arm interventional studies (5.3%), and two non-RCTs (1.8%). The sample size of included studies varied considerably from 1 to 959 individuals with an RBD (Supplemental Additional File 5). Across all

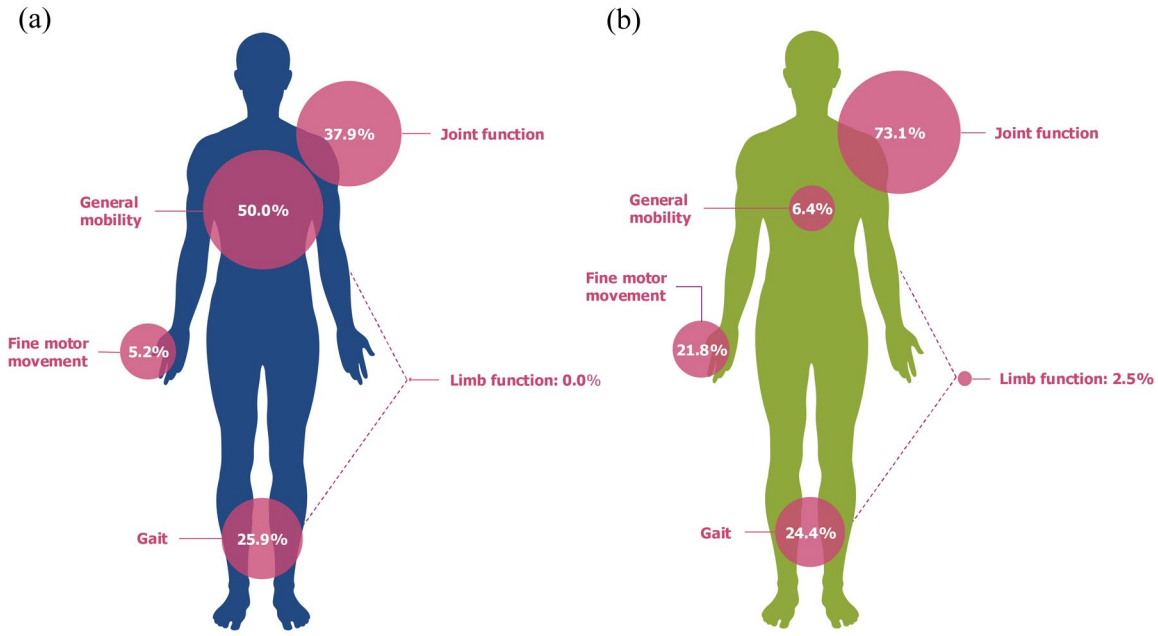

Figure 2. Proportion of individuals with RBDs with each mobility impairment. (a) Patient cohorts[a]. (b) Across articles[b].
Incorporates only individuals with RBDs for whom patient-level data were reported, from either cohort or case studies. Mobility impairments described in articles were categorized into the presented groups. "General mobility" was used when no specific details were given. "Joint function" was used when mobility impairment of a joint was specifically described, including but not limited to restricted range of motion, stiffness, function, or instability. If mobility impairment to a limb was described, without specifying the location as a joint, "limb function" was used. Circles are not proportionate to the sample size.
[a]$N = 58$.
[b]$N = 78$.
RBD, rare bone diseases.

articles, there were 84 unique individuals with an RBD for whom patient-level data were reported.

Patient characteristics

In total, 87.6% (99/113) of the included articles reported the age of the patient population, at varying timepoints. For patient cohorts ($N = 106$), the distribution of mean and median age "at the time of study" is shown in Supplemental Additional File 6; the most reported age group was 31–40 years. Age of individuals for whom patient-level data were reported are presented in Supplemental Additional File 6; the patient age "at the time of study" ranged from 17 to 63 years.

Sex was reported for 85 patient cohorts, including 6011 people, consisting of 60.8% female and 39.2% male individuals. Among the 83 individuals for whom sex was reported across articles, 48.2% (40/83) were female, and 51.8% (43/83) were male. Information regarding the race/ethnicity of included individuals can be found in Supplemental Additional File 7.

Disease characteristics

Included articles reported on 39 different RBDs; XLH was the most studied RBD ($n = 24$ articles), followed by OI ($n = 15$ articles), HPP, and FOP ($n = 13$ articles each; Supplemental Additional File 5). Disease severity was reported in 18 articles, typically based on different disease subtypes. The impact of distinct RBDs on mobility could not be compared with respect to outcomes for individuals with different disease severities.

Mobility impairment was reported for 78/84 of the individuals for whom patient-level data were available. Mobility impairments reported included issues related to joint function, gait disturbance, limb function, and fine motor movement, as well as general mobility limitations (Figure 2).

Impacts of mobility impairment on the lives of individuals with RBDs

The impact of the identified mobility impairments described above (Figure 2) on daily activities was explored in 47/113 articles, all of which described

Table 2. Daily activities reported to be negatively impacted in individuals with RBDs due to mobility impairment.

Daily activity	Articles	Individuals for whom patient-level data were reported
Walking	57.4% (27/47)	50.7% (37/73)
Personal care	31.9% (15/47)	15.1% (11/73)
Sitting/standing	23.4% (11/47)	11.0% (8/73)
Balance	14.9% (7/47)	2.7% (2/73)
Climbing stairs	10.6% (5/47)	2.7% (2/73)
Fine motor skills	10.6% (5/47)	20.5% (15/73)
Participation in school/employment	25.5% (12/47)	13.7% (10/73)
Participation in social/sporting activities	27.7% (13/47)	15.1% (11/73)

RBDs, rare bone diseases.

that mobility impairment negatively impacted daily activities. Similarly, patient-level data (from either cohort, cross-sectional, or case studies) on the impact of mobility impairment on daily activities were provided for 73 of the 78 individuals for whom mobility impairments were reported; all experienced negative effects. The activities most reported to be impacted by mobility impairment were walking and personal care (Table 2). Qualitative evidence was used more frequently than quantitative evidence for documenting an impact on daily activities, and was most commonly patient-reported ($n=14$ cohorts; $n=25$ individuals), as opposed to physician ($n=1$ cohort; $n=2$ individuals), family/caregiver-($n=1$ cohort; $n=3$ individuals), patient and family/caregiver-($n=2$ cohorts; $n=0$ individuals), or physician and patient-($n=1$ cohort; $n=0$ individuals) reported. Quantitative evidence was provided for 23 patient cohorts and 13 individuals. Figure 3 provides an overview of the quantitative tests used to evaluate the impacts of mobility impairment on daily activities, of which the 6MWT was the most frequently used (to evaluate walking across all articles). Several mobility aids were reported to have been used to support individuals with their impacted daily activities, including crutches, wheelchairs, walkers, canes, prostheses, braces, splints, orthotics, and walking aids (the type of walking aid was not specified in any of the articles; Supplemental Additional File 8).

The impact of the identified mobility impairments (Figure 2) on QoL was explored in 36/113 articles and for 42 of the 78 individuals for whom mobility impairments were reported. Nearly all articles (36/37) and patient-level data (41/42 individuals) described that mobility impairment negatively impacted QoL. Only one case study described an individual with no QoL detriment due to mobility impairment.[30] The QoL factors most reported to be impacted were pain and fatigue (Table 3). Qualitative evidence was used more frequently than quantitative evidence to document an impact of mobility impairment on QoL and was typically patient-reported ($n=12$ cohorts; $n=29$ individuals) as opposed to physician-($n=0$ cohorts; $n=0$ individuals), family/caregiver-($n=0$ cohorts; $n=1$ individuals), or patient and family/caregiver-($n=1$ cohort; $n=0$ individuals) reported. Quantitative evidence was provided for 13 patient cohorts and 1 individual with an RBD. Quantitative tests used to evaluate the impact of mobility impairment in patient cohorts are summarized in Figure 4. For one individual, the impact of mobility impairment on QoL was quantified by the 12-item Short Form Survey (SF-12); all other patient-level data included qualitative evidence only.

Tools in use or development for RBDs, which are capable of measuring mobility

Overall, 61 tools capable of measuring mobility (through one or more domain) were identified, including 22 questionnaires, 34 functional assessments, and 5 technological methods (Figure 5). These tools were mostly reported to have been used in a clinical setting (as opposed to in an individual's home; 68.9% (42/61); Figure 5).

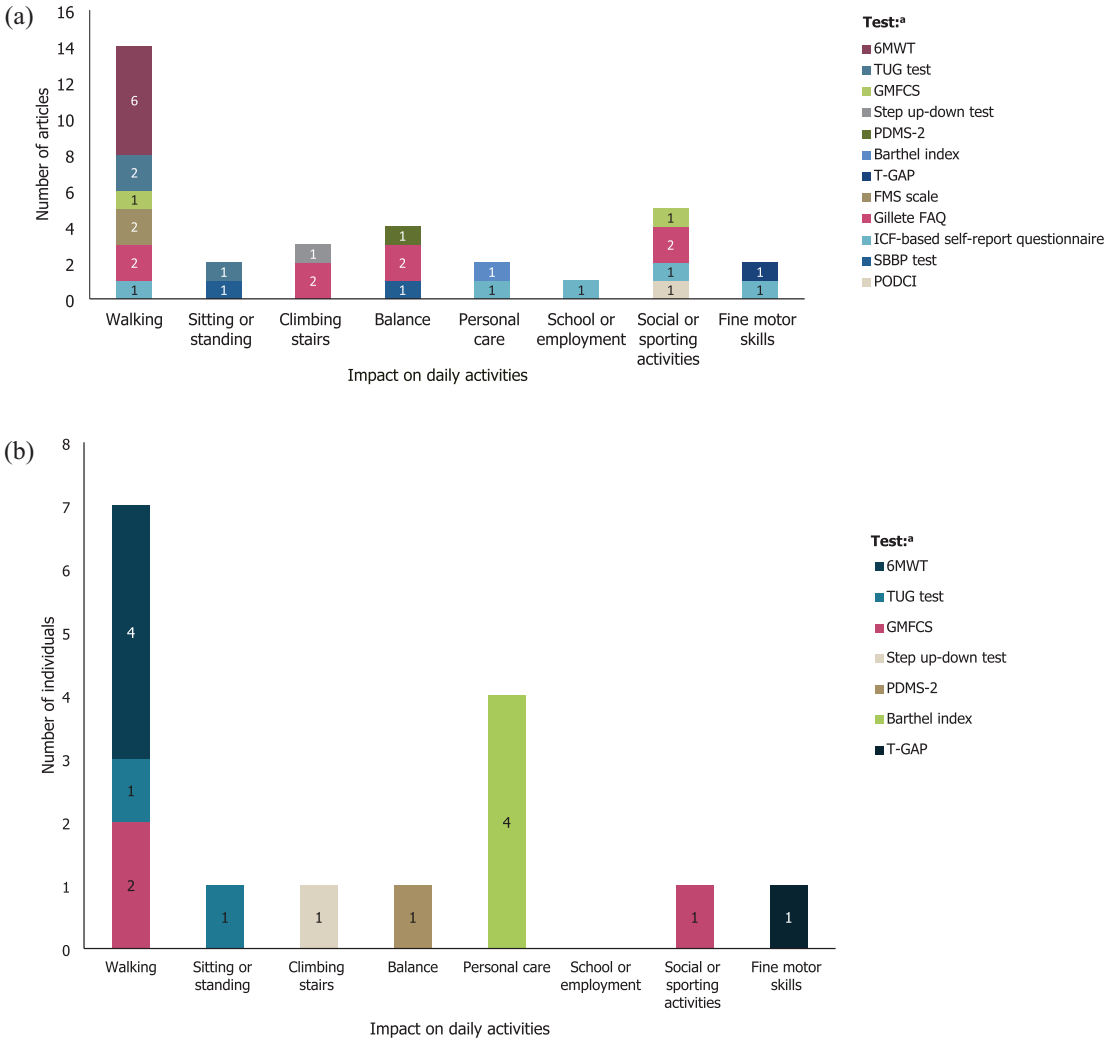

Figure 3. Tests used to quantify negative impact of mobility impairment on daily activities. (a) Across articles. (b) Individuals.
[a]All tests could quantify a positive or negative impact of mobility impairment on daily activities, however, in all identified articles, a negative impact was observed. (a) Use of LEFS, FOP-PFQ, Tegner Activity Score, Modified Lysholm Knee Score, and WOMAC in articles that did not report a specific impact on daily activities are not included in this figure. (b) Includes only individuals for whom patient-level data are reported from either cohort, cross-sectional, or case studies. Use of Tegner Activity Score, Modified Lysholm Knee Score, and WOMAC in articles that did not report a specific impact on daily activities are not included in this figure.
6MWT, 6-min walk test; FAQ, Functional Assessment Questionnaire; FMS, Functional Mobility Scale; FOP-PFQ, Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire; GMFCS, Gross Motor Function Classification System; ICF, International Classification of Functioning, Disability and Health; LEFS, Lower Extremity Functional Scale; PDMS-2, Peabody Developmental Motor Scales, second edition; PODCI, Pediatric Outcomes Data Collection Instrument; SPPB, Short Performance Physical Battery; T-GAP, Thumb Grasp and Pinch Assessment; TUG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3. QoL areas reported to be negatively impacted in individuals with RBDs due to mobility impairment.

Area of QoL	Articles	Individuals for whom patient-level data were reported
Pain	83.3% (30/36)	97.6% (40/41)
Mental health/well-being	27.8% (10/36)	9.8% (4/41)
Fatigue	13.9% (5/36)	12.2% (5/41)
Self-esteem/confidence	11.1% (4/36)	4.9% (2/41)

QoL, quality of life; RBD, rare bone diseases.

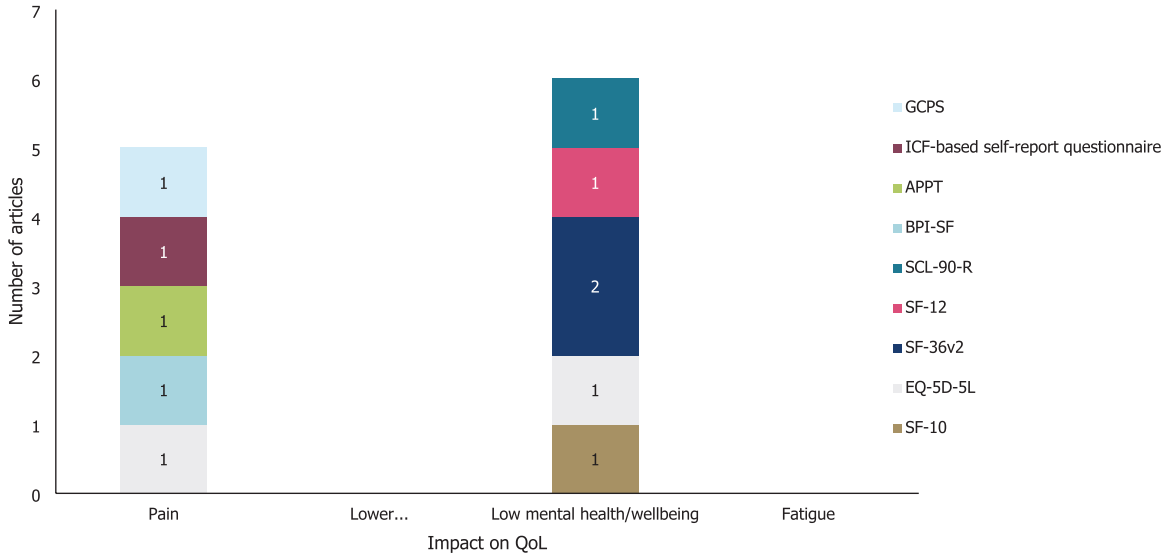

Figure 4. Number of articles using tests to report a negative impact of mobility impairment on QoL.[a]
[a]All tests could quantify a positive or negative impact of mobility impairment on QoL, however, all tests demonstrated a negative impact in all identified articles. Use of SF-10, SF-36, and PROMIS that did not report a specific impact on QoL, are not included in this figure. One study used SF-36 to assess QoL, however, this study was excluded from the analysis as SF-36 results were not provided for the individuals with evidence of impaired mobility.
APPT, Adolescent Paediatric Pain Tool; BPI-SF, Brief Pain Inventory Short Form; GCPS, Graded Chronic Pain Scale; ICF, International Classification of Functioning, Disability and Health; PROMIS, patient-reported outcome measure information system; QoL, quality of life; SCL-90-R, Symptom Checklist 90-R; SF-12, 12-item Short Form Survey; SF-36v2, 36-item Short Form Survey, version 2.

A mixture of disease-specific (27.3% (6/22)) and general (72.7% (16/22)) questionnaires were identified (Table 4), most commonly the WOMAC and EQ-5D (Supplemental Additional File 9). All but one of the disease-specific questionnaires were originally developed to assess mobility in specific RBDs, and the other (the WOMAC) had been repurposed for use in individuals with XLH and nail patella syndrome. Most questionnaires were patient-reported (86.4% (19/22); Supplemental Additional File 9).

Of the 10 questionnaires for which validity, reliability, or responsiveness were described, 7 (31.8%) were categorized as "good" (Table 4). These were the Brief Pain Inventory-Short Form, functional independence measure (FIM), FOP-physical function questionnaire (FOP-PFQ), international classification of functioning, disability, and health (ICF) self-report questionnaire, PRMA, patient-reported outcome measure information system, and WOMAC. However, these questionnaires had only been evaluated in 6 out of the 39 studied RBDs. No information on validity, reliability, or responsiveness was reported for the other 12 questionnaires.

Of the 34 identified functional assessments, the 6MWT and Cumulative Analogue Joint Involvement Scale (CAJIS) were most used (Supplemental Additional File 10). Most functional assessments of mobility were for general use across diseases (79.4% (27/34)); only three were disease-specific (8.8% (3/34)), and the specificity of four functional assessments was not reported (11.8% (4/34); Table 5). One of the disease-specific functional assessments, the modified performance-oriented mobility assessment-gait (mPOMA-G), had been modified to be relevant to HPP. The remaining two functional assessments were developed for specific RBDs (CAJIS for FOP and clubfoot assessment protocol (CAP) for idiopathic clubfoot). The operator of five assessments was specified in the included articles; three of these assessments had been operated by a physiotherapist (gross motor function measure-88, mPOMA-G, and pediatric gait, arms, legs, and spine (pGALS)) and two were operated by a physician (CAP and CAJIS). A modified CAJIS was operated by patients in one study.[46] The operator was not specified for other functional assessments (Table 5).

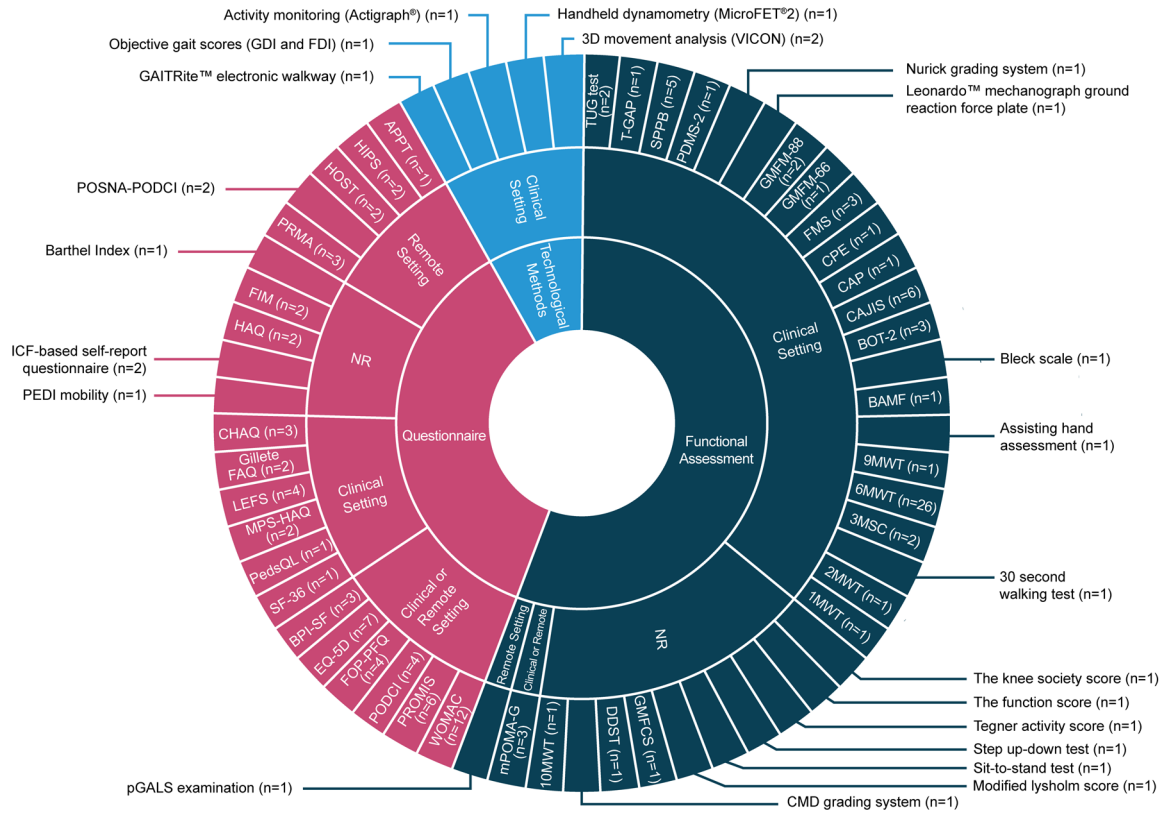

Figure 5. Identified tools capable of measuring mobility through one or more domains, by type and application setting.

"*n*" refers to the number of articles the tools were used in. Type of mobility measurement tool shown in central ring. Setting of use shown in middle ring. "Clinical" refers to any setting outside of the individual's home. Mobility measurement tool name shown in outer ring.

10MWT, 10-m walk test; 1MWT, 1-min walk test; 2MWT, 2-min walk test; 3MSC, 3-min stair climb test; 6MWT, 6-min walk test; 9MWT, 9-min walk test; APPT, Adolescent Pediatric Pain Tool; BAMF, Brief Assessment of Motor Function; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Version 2; BPI-SF, Brief Pain Inventory Short Form; CAJIS, Cumulative Analogue Joint Involvement Scale; CAP, Clubfoot Assessment Protocol; CHAQ, Childhood Health Assessment Questionnaire; CMD, Charnley Modification of the Merle d'Aubigné Postel Grading System; CPE, clinical problem evaluation; DDST, Denver developmental screening test; FAQ, functional assessment questionnaire; FDI, foot deviation index; FIM, functional independence measure; FMS, Functional Mobility Scale; FOP-PFQ, FOP-Physical Function Questionnaire; GDI, gait deviation index; GMFCS, gross motor function classification system; GMFM, gross motor function measure; HAQ, Health Assessment Questionnaire; HIPS, hypophosphatasia impact patient survey; HOST, hypophosphatasia outcomes study telephone interview; ICF, international classification of functioning, disability and health; LEFS, Lower Extremity Functional Scale; mPOMA-G, Modified Performance Oriented Mobility Assessment-Gait; MPS-HAQ, Mucopolysaccharidosis Health Assessment Questionnaire; NR, not reported; PDMS-2, Peabody Developmental Motor Scales, Second Edition; PEDI, Pediatric Evaluation of Disability Inventory; PedsQL, Pediatric Quality of Life; pGALS, pediatric gait, Arms, Legs, and Spine; PODCI, pediatric outcomes data collection instrument; POSNA-PODCI, Paediatric Orthopaedic Society of North America Paediatric Outcomes Data Collection Instrument; PRMA, patient-reported mobility assessment; PROMIS, patient-reported outcome measure information system; SF-36, 36-item Short Form Survey; SPPB, short performance physical battery; T-GAP, thumb grasp and pinch assessment; TUG, timed up and go; TUG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Only two functional assessments were reported to have "good" validity/reliability: mPOMA-G was shown to be reliable and valid in children with HPP, and pGALS demonstrated good inter- and intra-observer consistency in individuals with mucopolysaccharidoses (MPS) in the included studies (Table 5). In individuals with OI and HPP, the 6MWT and 10MWT results were reported to correlate poorly with characteristics of individuals with RBDs. There was no information on validity, reliability, or responsiveness reported for 27/34 of the functional assessments identified.

Five technological methods for assessing mobility were described across identified articles, used in a clinical setting only. These included three measuring gait (3D movement analysis assessed via VICON, objective gait scores (gait deviation index and foot deviation index), and GAITRite™ Electronic Walkway), and two assessing gross

Table 4. Identified questionnaires that measured mobility.

Questionnaire name	Number of articles reporting the use of questionnaire	Disease-specific/ general	RBD(s) assessed	Person completing questionnaire	Modifications	Domain(s)	Scoring system	Reported validity/ reliability/responsiveness of the tool
APPT[31]	1	General	Morquio A syndrome	Patient (children may have assistance from caregivers, if required)	NR	Pain	A score of 1 (no pain/ no pain interference) to 10 (the worst pain ever/complete pain interference)	NR
Barthel Index[22]	1	General	FOP	Patient	NR	Daily activities	NR	NR
BPI-SF[31–33]	3	General	Morquio A syndrome, HPP, XLH	Patient (children may have assistance from caregivers, if required)	NR	Pain intensity/pain interference	A score of 0 (no pain/ does not interfere) to 10 (the pain is as bad as you can imagine/completely interferes with daily activities)	Good: • Acceptable face and content validity in XLH • Psychometrically sound and able to distinguish differing functional statuses
CHAQ[34–36,a]	3	General	Alpha-mannosidosis, HPP, XLH	Patient	A parent-reported version may be used, where parents/ caregivers complete the questionnaire	Functional ability Pain	Functional ability: a score of 0 (no issues with functional ability) to 3 (unable to function). Limited mobility considered as a score of ⩾0.13. Pain: a score of 0–100 (higher scores indicating more limitations). VAS scores are translated to a score of 0 (no pain) to 3 (very severe pain). CHAQ Pain VAS scores: 0–1 (mild impairment), 1–2 (moderate impairment), 2–3 (severe impairment).	Uncertain or conflicting evidence
EQ-5D[31,34,37–41,a]	7	General	OI, alpha-mannosidosis, XLH, Morquio A syndrome, MPS	Patient	A parent-reported version may be used where parents/ caregivers complete the questionnaire. Different versions are available (EQ-5D-3L, EQ-5D-5L, EQ-5D-Y)	Self-care, mobility, usual activities, pain/discomfort, and anxiety/depression	5L: A score of 1 (no problems) to 5 (extreme problems) 3L: A score of 1 (no problems) to 3 (severe problems) Scores are used to create a single summary health index (range: 0–1, higher scores indicate less disability and better health)	Uncertain or conflicting evidence
FIM[42,43,a]	2	General	MPS, achondroplasia	Patient	Proxy answer (parent/ caregiver answers and an examiner verifies answer). Pediatric version (WeeFIM) for children under 7 years old. Parents/caregivers complete this version.	Self-care, mobility, and cognitive performance	Each item (18 total) is graded on a 1–7 scale, and the score is totaled. A score of 126 indicates complete independence. A score of 18 indicates complete dependence.	Good: • Acceptable to excellent consistencies between subdomains and the global score demonstrated (in MPS)

(Continued)

Table 4. (Continued)

Questionnaire name	Number of articles reporting the use of questionnaire	Disease-specific/ general	RBD(s) assessed	Person completing questionnaire	Modifications	Domain(s)	Scoring system	Reported validity/ reliability/responsiveness of the tool
FOP-PFQ[44–47,a]	4	Disease-specific; FOP	FOP	Patient	Proxy can be used for individuals aged 14 years and younger.	Daily activities	Scores expressed as a percentage of the worst possible score. Lower percentages indicate worse functioning.	Good: • Demonstrated convergent validity with CAJIS and PROMIS; FOP-PFQ scores significantly correlated with CAJIS • High reliability
Gillette FAQ[12,a]	2	General	OI	Patient	NR	Daily activities	22-item skill set questionnaire.	Uncertain or conflicting evidence
HAQ[22,32,a]	2	General	FOP, HPP	Patient	NR	Daily activities	Eight categories scored 0 (without any difficulty) to 3 (unable to perform). HAQ-DI score is derived by calculating the mean of the eight category scores.	NR
HIPS[48,49,a]	2	Disease-specific; HPP	HPP	Patient (caregivers may complete the survey on behalf of the patient)	NR	Captures patient demographics, HPP-related medical history and symptoms, mobility, and HRQoL.	NR	NR
HOST[48,49,a]	2	Disease-specific; HPP	HPP	Patient (caregivers may complete the survey on behalf of the patient)	NR	Captures patient demographics, HPP-related medical history and symptoms, mobility, HRQoL, and changes in symptoms over time.	NR	NR
ICF self-report questionnaire[50,51,a]	2	Disease-specific; skeletal dysplasias	Skeletal dysplasias	Patient	NR	Covers 86 ICF categories, including three questions for mobility.	NR	Good: • Content validity was well accepted
LEFS[52–55,a]	4	General	HPP, osteofibrous dysplasia	Patient	NR	NR	A score of 0 to 80, where a higher score indicates better lower extremity functioning.	NR
MPS-HAQ[56,57,a]	2	Disease-specific; MPS	MPS VII, Morquio A syndrome	Patient	Originally developed for patients with MPS.	Self-care, mobility, and required caregiver assistance.	Self-care and mobility domain scores range from 0 (not difficult at all) to 10 (extremely difficult). Care services domain scores range from 13 (independent) to 52 (complete assistance required).	NR

(Continued)

Table 4. (Continued)

Questionnaire name	Number of articles reporting the use of questionnaire	Disease-specific/ general	RBD(s) assessed	Person completing questionnaire	Modifications	Domain(s)	Scoring system	Reported validity/ reliability/responsiveness of the tool
PEDI mobility[58,a]	1	General	OI	Patient (physician also reviews the patient, which contributes toward the overall score)	NR	Evaluates gross motor abilities. Includes 59 mobility and self-care items reviewed	A score of 0–100; greater scores represent greater functionality.	NR
PedsQL[59]	1	General	Tibial hemimelia	NR	NR	Physical (including walking/running), emotional, social, and school functioning components.	A score of 0–100; points are assigned across questions.	NR
PODCI[36,20,60,61,a]	4	General	HPP, OI, XLH	Caregiver	NR	Six categories: upper extremity, transfers/ mobility, sports and physical functioning, pain/ comfort, happiness and satisfaction, and global functioning.	NR	NR
POSNA-PODCI[23,62,a]	2	General	XLH	Parent	English and French versions were available in one article.	Six domains: transfer and basic mobility, sports and physical function, pain/ comfort, happiness, and global functioning.	Scores are presented as normative scores (mean score in general population of healthy children is 50). Higher scores indicate better functioning.	NR
PRMA[44,63,64,a]	3	General	FOP	Patient (A surrogate (parent or caregiver) may also complete on the patient's behalf)	NR	Assesses disease burden at 15 anatomical locations based on CAJIS, and impact on daily activities.	Movement scores (for body and individual regions) from 0 (normal) to 2 (completely restricted).	Good: • PRMA scores correlate highly with physician-reported CAJIS scores
PROMIS[20,23,65–68,a]	6	General	XLH, Proetus syndrome, OI	Patient (parent/ caregiver may also complete as proxy)	Different forms are available for different ages.	Domains include physical function with mobility.	100-unit scale.	Good: • Construct validity of PROMIS in OI • Convergent validity with PODCI
SF-36[37]	1	General	OI	Patient	NR	Eight domains, including physical functioning and role limitations due to physical problems.	A score of 0–100 with higher scores indicating better musculo-skeletal function and HRQoL.	NR

(Continued)

Table 4. (Continued)

Questionnaire name	Number of articles reporting the use of questionnaire	Disease-specific/ general	RBD(s) assessed	Person completing questionnaire	Modifications	Domain(s)	Scoring system	Reported validity/ reliability/responsiveness of the tool
WOMAC[61,65,69–78,a]	12	Disease-specific; osteoarthritis	XLH, NPS	Patient	Originally used to evaluate joints in individuals with osteoarthritis.	Evaluates pain, stiffness, and physical function.	Questions measured on a 5-point Likert scale: 0 (none), to 4 (extreme). Total score is a sum of scores within each category: pain (range: 0–20), stiffness (range: 0–8), physical functioning (range: 0–68). Higher scores indicate a worse condition. Scores are normalized to a 0–100 metric scale representing the % of the maximum score.	Good: • Face and content validity acceptable in XLH

[a]Articles reported a mobility-specific domain for these questionnaires, which could include domains/questions assessing functional impairment related to activities of daily living or disability. For articles without an footnote ([a]), the questionnaire may assess additional aspects that were not captured in the included articles.
APPT, Adolescent Pediatric Pain Tool; BPI-SF, Brief Pain Inventory Short Form; CAJIS, Cumulative Analogue Joint Involvement Scale; CHAQ, Childhood Health Assessment Questionnaire; FAQ, Functional Assessment Questionnaire; FIM, functional independence measure; FOP, Fibrodysplasia Ossificans Progressiva; FOP-PFQ, FOP-Physical Function Questionnaire; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire-Disability Index; HIPS, Hypophosphatasia Impact Patient Survey; HOST, Hypophosphatasia Outcomes Study Telephone Interview; HPP, Hypophosphatasia; HRQoL, Health-Related Quality of Life; ICF, International Classification of Functioning, Disability and Health; LEFS, Lower Extremity Functional Scale; MPS, mucopolysaccharidoses; MPS-HAQ, Mucopolysaccharidoses Health Assessment Questionnaire; NPS, Nail Patella Syndrome; NR, not reported; OI, osteogenesis imperfecta; PEDI, Pediatric Evaluation of Disability Inventory; PedsQL, Pediatric Quality of Life; PODCI, Pediatric Outcomes Data Collection Instrument; POSNA, Pediatric Orthopedic Society of North America; PRMA, Patient-Reported Mobility Assessment; PROMIS, Patient-Reported Outcome Measure Information System; RBD, rare bone diseases; SF-36, 36-item Short Form Survey; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; XLH, X-linked hypophosphatemia.

Table 5. Identified functional assessment tools that measured mobility.

Assessment tool name	Aspect of mobility measured	Number of articles reporting use of mobility measurement tool	Disease-specific/ general	RBD(s) assessed	Operator	Modifications	Scoring system	Reported validity/ reliability/responsiveness of the tool
30-s Walk Test[79]	Walking ability	1	General	OI	NR	NR	Timed assessment of walking distance.	NR
1MWT[80]	Walking ability	1	General	OI	NR	NR	Timed assessment using a standardized walking course on a flat floor. Score is given in meters.	NR
2MWT[81]	Walking ability	1	General	MPS	NR	NR	Timed assessment of walking distance. Score is given in meters.	NR
6MWT[12,13,23,35,36,52,54–56,66,70,73,74,77,80,82–91]	Walking ability	26	General	HPP, MPS, OI, HME, XLH	NR	NR	Assesses the maximum distance that a patient can walk within 6 min. Score is given in meters (or feet). The percentage of predicted value (i.e., normal predicted distance walked (based on age, sex, and height)) can be calculated.	Uncertain or conflicting evidence
9MWT[92]	Walking ability	1	General	Polyostotic fibrous dysplasia	NR	NR	Endpoints are walking velocity, distance covered, ambulation endurance, and efficiency. Individuals are asked to run or walk at the fastest comfortable pace they can for nine minutes.	NR
10MWT[13]	Walking ability	1	General	HPP	NR	NR	Assessment of gait or walking speed over a fixed distance (10 m). Score is given in meters per second.	Poor: • Indicated a milder deficit compared with patient-reported limitations due to physical dysfunction
3MSC[56,88]	Ability to climb stairs	2	General	MPS	NR	NR	Score is given in number of steps or stairs per minute.	NR
AHA[93]	Fine motor function	1	NR	HOS	NR	In children with bilateral involvement, it is recommended to consider the more involved hand to be the "assisting hand" or affected side.	Quantifies frequency and quality of affected upper extremity use during bimanual tasks. Higher scores in AHA units indicate better bimanual functioning. An improvement of 5 points indicates a clinically meaningful change.	NR
BAMF[94]	Gross motor function	1	General	OI	NR	Designed specifically for children with disabilities.	Ordinal scale of 10 points (0–10). An increase in points indicates an improvement in motor function.	NR
Bleck Scale[95]	Walking ability	1	General	OI	NR	NR	5-point scale: 0 = unable to leave the bed or wheelchair or to 4 = able to walk independently or community walker.	NR
Bruininks-Oseretsky Test of Motor Proficiency (Second Edition; BOT-2)[56,85,96]	Gross motor function; fine motor function	3	General	MPS	NR	Rubric used to assign BOT-2 scoring was dependent on sex and age. Test may be modified according to individuals' needs.	Sub-tests assess motor functioning in the following areas: fine motor precision, manual dexterity, balance, running speed, and agility. Minimal important difference is defined.	NR

(Continued)

Table 5. (Continued)

Assessment tool name	Aspect of mobility measured	Number of articles reporting use of mobility measurement tool	Disease-specific/ general	RBD(s) assessed	Operator	Modifications	Scoring system	Reported validity/ reliability/responsiveness of the tool
CAJIS[45–47,64,97,98]	Restricted joint movement	6	Disease-specific; FOP	FOP	Physician (and patient for modified CAJIS score)	A modified CAJIS score based on patient-reported outcomes is available.	Degree of ankylosis is classified across 15 anatomic sites as: normal (<10% deficit, score of 0); partially impaired (10%–90% deficit, score of 1); functionally ankylosed (>90% deficit; score of 2). Maximum score is 30.	Uncertain or conflicting evidence
CAP[99]	Walking ability (often monitoring clubfoot post treatment)	1	Disease-specific; idiopathic clubfoot	Idiopathic clubfoot	Physician	NR	Subdomains include passive mobility, morphology and muscle function, and motion quality. Lower scores in the passive mobility and morphology subdomains indicate altered gait pattern.	NR
Charnley Modification of the Merle d'Aubigné Postel Grading System Grading System and VAS scores[100]	Restricted joint movement	1	General	MED	NR	NR	Assesses range of motion of the hip joint and function. Of the grading system, the maximum score is 18 points; an increase in score indicates improvement. For the VAS scores, a decrease in score indicates improvement.	NR
CPE[81]	Walking ability	1	General	MPS	NR	Study used only "walking and running" domain.	NR	NR
DDST Version II[101]	Gross motor function; fine motor function	1	NR	CODAS	NR	NR	Score is the evaluated age for the following domains, compared with real age: • Personal-social • Fine motor • Language • Gross motor	NR
FMS[12,79,87]	Walking ability	3	General	OI	Clinician	NR	10-point walking scale. Measures functional mobility including the use of assistive devices.	Uncertain or conflicting evidence
GMFCS[101]	Gross motor function	1	NR	CODAS	NR	NR	Class II score means the patient can walk indoors and outdoors, hold the rail, and climb the stairs, but running and jumping are difficult. Class III score means the patient can walk indoors or outdoors on a level surface with a walking aid.	NR
GMFM-66[94]	Gross motor function	1	General	OI	NR	NR	Points range from 0 to 100. An increase in points indicates an improvement in motor function.	NR
GMFM-88[102,103]	Gross motor function	2	General	OI, Rubinstein-Taybi syndrome	Physio-therapist	NR	Score is given as a percentage; maximum score of 100%.	NR

(Continued)

Table 5. (Continued)

Assessment tool name	Aspect of mobility measured	Number of articles reporting use of mobility measurement tool	Disease-specific/ general	RBD(s) assessed	Operator	Modifications	Scoring system	Reported validity/ reliability/responsiveness of the tool
Leonardo™ Mechanograph Ground Reaction Force Plate[35]	Balance	1	General	XLH	NR	NR	Measures: • Balance • Peak body power • Force per weight • Jumping height	NR
Modified Lysholm Score[86]	Knee joint function	1	General	HME	NR	NR	NR	NR
mPOMA-G[36,60,91]	Gait (step length, step symmetry, step continuity, trunk sway, walk stance)	3	Disease-specific; modified to be relevant to HPP	HPP	Physio-therapist	Modified for use in children with HPP	For each item, the lowest score is 0 and the highest score is 1 in most cases (can be 2 in some cases). Overall score of 0–12; 12 indicates no impairment, 0 indicates the greatest impairment.	Good: • Valid and reliable measure for detecting clinically significant impairments in children with HPP • Concurrent validity with other tools (assessing daily activities, disability, physical function)
Nurick Grading System[104]	Walking ability	1	General	Larsen syndrome	NR	The examiner used "2 to 3 scores" as other terms do not apply to the pediatric population.	Grade 2 indicates difficulty walking but fully employed or employable.	NR
PDMS-2[105]	Gross motor function	1	General	ABS	NR	Age adjusted for 7 weeks of prematurity.	Gross motor subtests are reflexes; stationary; locomotion; object manipulation; GMQ percentile. GMQ provides an estimate of a child's gross motor abilities by combining the results of the subtests that measure balance, movement, and control of the large muscle groups. Raw, standard, and age equivalent scores are reported.	NR
pGALS Examination[106]	Restricted joint movement	1	General	MPS	Physio-therapist	NR	25 assessments of specific movements of joints of the upper and lower limbs, neck, spine, and jaw. Maneuvers are classified as normal, abnormal, or not assessable. Percentage scores for the number of abnormal maneuvers calculated taking into account three separate scores per maneuver per child.	Good: • Very good consistency between observers (Kappa scores for inter-observer and intra-observer consistency)
Sit-to-Stand Test[107]	Ability to stand	1	General	CSHS	NR	NR	Score is number of sit-to-stand repetitions in set time.	NR

(Continued)

Table 5. (Continued)

Assessment tool name	Aspect of mobility measured	Number of articles reporting use of mobility measurement tool	Disease-specific/ general	RBD(s) assessed	Operator	Modifications	Scoring system	Reported validity/ reliability/responsiveness of the tool
SPPB[52,55,108–110]	Functional mobility; walking; sitting/standing	5	General	XLH, HPP	NR	NR	Assesses walking, sit-stand, and balance. Tests can include the chair rise test, tandem balance, and the 8-foot walk test. A score of <10 indicates impaired mobility.	NR
Step Up-Down Test[86]	Climbing stairs	1	General	HME	NR	NR	Patient takes 10 steps up and down. Timed assessment; score is given in seconds.	NR
Tegner Activity Score[86]	Functional mobility	1	General	HME	NR	NR	NR	NR
T-GAP[93]	Fine motor skills (grasp and pinch use patterns in children with congenital limb deficiencies)	1	NR	HOS	NR	NR	Grading scale based on sequential development of grasp patterns in infancy. More mature grasp patterns receive higher scores.	NR
The Function Score[111]	Walking; climbing stairs	1	General	Multiple epiphyseal dysplasia	NR	NR	NR	NR
The Knee Society Score[111]	Knee joint function/stability	1	General	Multiple epiphyseal dysplasia	NR	NR	NR	NR
TUG Test[52,86]	Functional mobility; walking; sitting/standing	2	General	HPP, HME	NR	NR	Measures time taken for a patient to stand up from a chair, walk a distance of 3 m at a comfortable pace, turn, walk back to the chair and sit down again. Score is given in seconds and compared with reference.	Uncertain or conflicting evidence

10MWT, 10-m Walk Test; 1MWT, 1-min Walk Test; 2MWT, 2-min Walk Test; 3MSC, 3-min Stair Climb Test; 6MWT, 6-min Walk Test; 9MWT, 9-min Walk Test; ABS, Antley-Bixler syndrome; AHA, assisting hand assessment; BAMF, Brief Assessment of Motor Function; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, Second Edition; CAJIS, Cumulative Analogue Joint Involvement Scale; CAP, Clubfoot Assessment Protocol; CODAS, Cerebral, Ocular, Dental, Auricular, Skeletal Anomalies; CPE, clinical problem evaluation; CSHS, cutaneous skeletal hypophosphatemia syndrome; DDST, Denver Developmental Screening Test; FAQ, Functional Assessment Questionnaire; FDI, functional disability inventory; FMS, Functional Mobility Scale; FOP-PFQ, Fibrodysplasia Ossificans Progressiva—Physical Function Questionnaire; GDI, gait deviation index; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure; GMQ, Gross Motor Quotient; HME, Hereditary Multiple Exostoses; HOS, Holt-Oram syndrome; HPP, hypophosphatasia; MED, multiple epiphyseal dysplasia; mPOMA-G, Modified Performance-Oriented Mobility Assessment-Gait; MPS, mucopolysaccharidosis; NR, not reported; OI, osteogenesis imperfecta; PDMS-2, Peabody Developmental Motor Scales, Second Edition; PEDI, Pediatric Evaluation of Disability Inventory; pGALS, pediatric gait, arms, legs, and spine; RBD, rare bone diseases; SPPB, short performance physical battery; T-GAP, Thumb Grasp and Pinch Assessment; TUG, timed up and go; VAS, Visual Analogue Scale; XLH, X-linked hypophosphatemia.

motor function (handheld dynamometry using MicroFET®2 and activity monitoring using Actigraph®; Table 6). These technological methods had only been used in five RBDs (OI, XLH, HPP, MPS type 1, and idiopathic clubfoot), despite all being tools intended for general use and applicable in conditions other than RBDs (e.g., use of Actigraph in sarcopenia).[112] MicroFET2 and Actigraph were operated by physiotherapists, whereas the operator was not specified for any other technological method in the included articles. None of the included articles reported on the validity, reliability, or responsiveness of these technological methods in RBDs (Table 6).

The ability of the identified tools to assess the impacts of mobility impairment on daily activities and QoL identified in Objective 1 is presented in Table 7. None of the nine tools for assessing mobility that were reported as having "good" validity, reliability, or responsiveness in RBDs comprehensively assessed the daily activity/QoL impacts of mobility impairment identified in Objective 1.

Quality assessment

The results of the AHFMR QA checklist are shown in Supplemental Additional File 11, and results of the NIH Quality Assessment Tool for Case Series Studies are shown in Supplemental Additional File 12. Results of the AHFMR checklist indicate that the quality of evidence across studies was moderate; individual QA scores for each study are provided in Supplemental Additional File 5. However, most studies only partially defined outcome measures; for example, studies using standard tools to measure outcomes such as mobility provided limited detail on the tools' use. Most notably, survey-based studies often provided incomplete descriptions of questionnaire/interview content and questionnaire response options. The quality of studies was also low with regard to controlling for confounding factors. There were 32/103 unique studies which were case studies/series; these study types are associated with inherent bias and therefore lower quality than other study designs, so were assessed separately (Supplemental Additional File 12). The quality of case studies/series was mixed. Although most studies clearly described the study objective and study population, there was varied reporting on the comparability of cases and appropriateness of outcomes; no studies clearly described any statistical methods used.

Discussion

This is the first SLR, to our knowledge, that collates evidence on the wide-ranging impacts of mobility impairments in RBDs, and tools being used or in development for RBDs to measure mobility.

In this SLR, mobility impairment was shown to negatively impact daily activities of individuals with RBDs, commonly including walking and personal care.[8,9,12,115–117] Whilst this finding is consistent with prior understanding of the impact of mobility impairment, it was author-reported, and may not have been proven in clinical practice. Other reported impacts of mobility impairment included participation in school/employment and social/sporting activities and individuals' self-esteem and mental well-being.[10,12,25,115,118] These impacts of mobility impairment are consistent with wider aspects included in the ICF Framework on Mobility.[119]

As the relationship between pain and mobility impairment is complex, pain alone was not considered sufficient as a mobility impairment for Objective 1 of this SLR; articles had to distinguish a physiological mobility impairment from pain, and pain was then extracted as an impact on QoL. Pain associated with mobility impairment was reported for nearly all individuals, highlighting the well-characterized association between pain and mobility limitations,[120–122] for example, joint restriction causing pain or pain avoidance resulting in limited mobility.

The extent of the impact of mobility impairment on daily activities and QoL was not commonly reported. Although some articles noted that individuals required mobility aids to assist with daily activities, no articles described the duration or frequency of participants' mobility aid use. In addition, identified articles did not distinguish between the use of manual and motorized mobility aids, such as wheelchairs. This is an important distinction to allow healthcare resource use and unmet needs to be properly assessed, for example, unequal access to different mobility aids (e.g., due to the higher cost of motorized vs manual wheelchairs).

Synthesis of the impacts of mobility impairment was somewhat limited by variability in how mobility was assessed, and outcomes were reported. Identified articles largely reported daily activities and QoL outcomes qualitatively, and in instances where quantified, a large variety of tests were

Table 6. Identified technological methods that assessed mobility.

Name of technological method	Aspect of mobility measured	Number of articles reporting the use of technological method	Disease-specific/ general	RBDs assessed	Operator	Methods	Outcomes
3D movement analysis (VICON)[81,113]	Gait	2	General	OI, XLH	NR	Uses spatio-temporal parameters of gait (e.g., speed, cadence, step length) derived from a 3D movement analysis with Vicon. The GDI is calculated from selected joint angles of the lower extremities and pelvis captured during the gait analysis with Vicon.	Some parameters showed significant differences among patients with different types of OI. Compared with unimpaired controls, the gait of patients with XLH deviated from normality (reduced GDI). About 50% of the patients walked with greater lateral trunk lean (waddling gait). Further factors contributing to gait deviations were higher BMI, mechanical axis deviations, and signs of enthesopathies.
Handheld dynamometry (MicroFET®2)[90]	Gross motor function	1	General	HPP	Physiotherapist	Evaluates the effects of an intervention by measuring the forces generated by knee/elbow, flexors/ extensors, and hip/ shoulder abductors. An increased score indicates improvement in motor function.	The increased forces confirmed improved muscle strength over time, contributing to improved motor function in HPP.
Activity monitoring (ActiGraph®)[90]	Gross motor function	1	General	HPP	Physiotherapist	Measures the amount of physical activity (steps taken).	Showed an increase in the number of steps taken. The increased activity was one of several indicators of improved motor function in HPP following intervention.

(Continued)

Table 6. (Continued)

Name of technological method	Aspect of mobility measured	Number of articles reporting the use of technological method	Disease-specific/ general	RBDs assessed	Operator	Methods	Outcomes
Objective gait scores (GDI and FDI)[99]	Gait	1	General	Idiopathic clubfoot	NR	Motion analysis is performed using the Helen-Hayes model and the Oxford Foot Model, and kinematic parameters of the gait pattern are used to calculate the GDI and FDI. These objective gait scores are correlated with clinical scores measured in patients with clubfoot.	NR
GAITRite™ Electronic Walkway[114]	Gait	1	General	MPS1	NR	Individuals walk for 1 min along the length of a walkway without footwear or orthosis. The walkway mat has sensor pads to measure spatial and temporal parameters of gait (cadence, gait velocity, and walking distance). Results from each patient are captured on a laptop (connected to the walkway).	Gait velocity, cadence, and walking distance increased marginally post-operatively.

No information on the validity, reliability, or responsiveness of technological methods to assess mobility in rare diseases was identified.
FDI, foot deviation index; GDI, gait deviation index; HPP, hypophosphatasia; MPS, mucopolysaccharidoses; NR, not reported; OI, osteogenesis imperfecta; RBD, rare bone diseases; XLH, X-linked hypophosphatemia.

Table 7. Tools containing at least one mobility domain capable of assessing daily activities and QoL factors impacted by mobility impairment.

Daily activities and QoL factors impacted by mobility impairment	Identified tools that can assess impacted factors	
Impaired ability to walk independently	• 1MWT • 2MWT • 3D movement analysis (VICON) • 6MWT • 9MWT • 10MWT • 30-s Walk Test • Barthel Index • Bleck Scale • BOT-2 • CAP • CPE • EQ-5D • FIM[a] • FMS • GAITRite™ Electronic Walkway	• GMFCS • HAQ • HIPS • HOST • ICF-based Self-Report Questionnaire[a] • mPOMA-G[a] • MPS-HAQ • Nurick Grading System • Objective gait scores (GDI and FDI) • PedsQL • PODCI • SPPB test • The Function Score • TUG test • WOMAC[a]
Unable to sit/stand independently	• ICF-based Self-Report Questionnaire[a] • Sit-to-Stand Test	• SPPB • TUG test
Impaired ability to climb stairs	• 3MSC • Barthel Index • Gillette FAQ • MPS-HAQ	• PODCI • Step Up-Down Test • The Function Score • WOMAC[a]
Impaired balance	• Gillette FAQ • Leonardo™ Mechanograph Ground Reaction Force Plate	• mPOMA-G[a] • PDMS-2
Impaired ability to perform personal care	• CHAQ • EQ-5D • FIM[a] • HAQ • HIPS	• HOST • MPS-HAQ • PEDI Mobility • WOMAC[a]
Impaired ability to participate in sporting activities[b]	• BOT-2 • Gillette FAQ • GMFCS • ICF-based Self-Report Questionnaire[a]	• PedsQL • PODCI • POSNA-PODCI • WOMAC[a]
Impaired fine motor skills	• AHA • BAMF • BOT-2 • CHAQ • DDST • GMFM-66	• GMFM-88 • HAQ • ICF-based Self-Report Questionnaire[a] • T-GAP
Impaired joint movement	• CAJIS • CMD Grading • FOP-PFQ[a] • HIPS • Modified Lysholm Score	• pGALS[a] • PRMA[a] • PROMIS[a] • The Knee Society Score • WOMAC[a]

(Continued)

Table 7. (Continued)

Daily activities and QoL factors impacted by mobility impairment	Identified tools that can assess impacted factors	
Pain related to mobility	• APPT • BPI-SF[a] • CHAQ • CMD Grading • HIPS	• HOST • PROMIS[a] • The Knee Society Score • WOMAC[a]
Daily activities/mobility (not specified)	• Activity monitoring (ActiGraph) • Handhold dynamometry (MicroFET®2) • LEFS	• SF-36 • Tegner Activity Score

[a]Indicates tools that are considered to have "good" validity, reliability, or responsiveness for the assessment of mobility.
[b]Tools that evaluate running have been categorized as suitable to assess the ability to participate in sporting activities.
10MWT, 10-m walk test; 1MWT, 1-min walk test; 2MWT, 2-min walk test; 3MSC, 3-min stair climb test; 6MWT, 6-min walk test; 9MWT, 9-min walk test; AHA, assisting hand assessment; APPT, Adolescent Pediatric Pain Tool; BAMF, Brief Assessment of Motor Function; BOT-2, Bruininks-Oseretsky test of motor proficiency, Version 2; BPI-SF, Brief Pain Inventory Short Form; CAJIS, Cumulative Analogue Joint Involvement Scale; CAP, clubfoot assessment protocol; CHAQ, Childhood Health Assessment Questionnaire; CMD, Charnley Modification Of The Merle D'aubigné Postel Grading System; CPE, clinical problem evaluation; DDST, Denver developmental screening test; FAQ, functional assessment questionnaire; FDI, functional disability inventory; FIM, functional independence measure; FMS, Functional Mobility Scale; FOP-PFQ, Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire; GDI, Gait Deviation Index; GMFCS, Gross Motor Function Classification System; GMFM, gross motor function measure; HAQ, health assessment questionnaire; HIPS, hypophosphatasia impact patient survey; HOST, hypophosphatasia outcomes study telephone interview; ICF, international classification of functioning, disability, and health; LEFS, Lower Extremity Functional Scale; mPOMA-G, Modified Performance Oriented Mobility Assessment-Gait; MPS-HAQ, mucopolysaccharidoses health assessment questionnaire; PDMS-2, Peabody Developmental Motor Scales, Second Edition; PEDI, pediatric evaluation of disability inventory; PedsQL, pediatric quality of life; pGALS, pediatric gait, arms, legs, and spine; PODCI, pediatric outcomes data collection instrument; POSNA-PODCI, pediatric orthopedic society of North America pediatric outcomes data collection instrument; PRMA, patient-reported mobility assessment; PROMIS, patient-reported outcome measure information system; QoL, quality of life; SF-36, 36-item Short Form Survey; SPPB, short performance physical battery; T-GAP, Thumb grasp and pinch assessment; TUG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

used, limiting comparison between studies. The sample size of included studies also ranged greatly, from 1 to 959 individuals, with larger sample sizes used in registry and survey-based studies. Though expected due to the rarity of these conditions, the very small sample size of some studies limits the conclusions that may be drawn, and the applicability of findings to the wider population of individuals with that RBD. The inclusion of case studies/series did, however, provide valuable patient-level information often not reported in large cohort studies, though utility was limited due to inconsistent reporting of outcomes between studies. Additionally, there was heterogeneity between how individuals with RBDs were reported to experience the impacts of mobility impairments, even among those with the same RBD. This is reflective of the wide range of disease severities and symptoms experienced by individuals with RBDs.[123,124]

The large number of identified tools ($N=61$) used in RBDs for measuring mobility through one or more domains is likely reflective of the heterogeneous nature of different RBDs.[4,14,15] Yet, only 9 of the 61 identified tools had been assessed through validation studies and were reported to have "good" validity, reliability, or responsiveness, and none of the technological methods had been evaluated through this lens in RBDs. Additionally, variability in methodologies used to assess reliability, validity, or responsiveness limited comparability between different functional assessments and between questionnaires. Since the time that this SLR was conducted, multiple relevant studies reporting on the same tools used to measure mobility in RBDs (e.g., 6MWT, TUG test, SPPB, HAQ-DI, VAS, WeeFIM) have been published.[125–131] Of note, only one of the identified articles reported that the tool used (6MWT) was a valid and reliable indicator of physical function in the population being studied (HPP).[130] In addition to the above, the use of a separate technological method was reported by Oder et al.,[132] which involved 3D movement analysis for assessment of upper limb movement (similar to the 3D

movement analysis used to measure gait found in this SLR)[81,113] in individuals with OI. However, consistent with the findings from this SLR, the paper did not comment on the validity, reliability, or responsiveness of this technology.[132] A recently published SLR (2025) examined the use of fully instrumented gait analysis (FGA) in individuals with RBDs; 23 of the 24 identified studies specified the motion analysis system used, which was most commonly the VICON ($n = 10$) followed by the Cleveland motion analysis protocol ($n = 6$; not identified in this SLR).[133] Though the 2025 SLR concluded that FGA may improve understanding of gait alterations in people with RBDs, the heterogeneity between studies (e.g., in test subject factors or interpretation by clinicians) and lack of reporting of accuracy/reliability of analysis systems limited the generalizability of results and conclusions that could be drawn.[133] The recent literature therefore substantiates the need identified in our SLR for high-quality studies that consistently evaluate the validity, reliability, and responsiveness of tools for measuring mobility in RBDs. This would inform selection of tool(s) to repurpose for different RBDs; for example, in a condition with the same etiology as the RBD that a tool has been previously validated.

The current SLR highlighted a range of factors that could be considered when selecting a tool for measuring mobility, including whether use of a general versus disease-specific tool is most appropriate. General tools are likely to have been used more widely than disease-specific tools and may therefore present the opportunity to modify a well-validated tool, for use in a specific RBD or population. For example, the POMA-G, a clinical gait assessment tool for adults, has already been modified to increase its sensitivity to HPP-related impairments in children, evidencing how tools may be adapted for use in a particular RBD.[60] However, given the heterogeneous nature of RBDs, disease-specific tools may more appropriately account for different etiologies, disease severities, and mobility symptoms unique to each RBD, than a general tool.[4,14,15,134]

The feasibility of using certain data collection methods in individuals with different symptoms or at different disease stages should also be considered when selecting a tool. For example, limited ambulatory status may impede individuals from participating in functional assessments, and restricted upper limb mobility may prevent someone from completing self-reported questionnaires. The status of children or people with cognitive impairments may also limit individuals' ability to complete questionnaires or use digital technologies. People with mobility impairments may also experience difficulties using public transport or traveling as a passenger (e.g., due to difficulty transferring oneself while sitting), or driving a car, and therefore struggle to attend clinical sites for assessment.[8,119,135] Therefore, mobility measurement tools that could be operated remotely by an individual with an RBD and/or caregiver, as opposed to a physician, may help to reduce the individual and healthcare system burden. Many of the functional assessments and questionnaires identified in this SLR were only able to capture individuals' mobility at one timepoint (e.g., 6MWT); consequently, the results of these assessments rarely correlate with an individual's physical characteristics.[12,13] In particular, the remote use of a simple, reproducible technological method would allow longitudinal, real-world data to be captured, and therefore would provide a more realistic picture of the difficulties an individual faces over time. Of the tools identified in this SLR that could be used in a remote setting (questionnaires and functional assessments only), none were reported to have "good" validity, reliability, or responsiveness; no technological methods had been used remotely. The lack of routine use of technologies to measure mobility in RBDs may be a result of advancements in digital capabilities being more recent, or the cost and expertise required to develop, acquire, and utilize technological methods.[136,137] Of note, since this SLR was conducted, a study by Fink et al.[15] has been published, examining built-in smartphone sensors (accelerometer and gyroscope) in a free-living environment to detect changes in gait patterns in individuals with RBDs. This readily available methodology may facilitate remote mobility assessment; however, further research into the generalizability of these findings across a wider range of RBDs and the impact of factors such as walking surface and carrying position of the smartphone was recommended by the authors.[15] Remote technological methods used to measure mobility in other conditions could also be explored to understand their appropriateness for assessing mobility impairment beyond gait in RBDs.[138,139] For example, the SV95C assessment is a qualified digital endpoint captured by a wearable device for use in place of standard walking tests in Duchenne

Muscular Dystrophy.[140] Additionally, the Mobilise-D study has validated algorithms for wrist-based gait detection (using wearable devices) in several disease areas associated with mobility limitations, such as Parkinson's disease.[141] Such wearable devices may facilitate easy data collection over time, reduce rater bias associated with judgment-based assessments, and minimize patient burden.[142,143] However, data quality should be considered due to potential inconsistencies in wearable data collection and sensor variability; clinical validation is required to regulate data quality and ensure the data are clinically relevant.[144] In addition, caution should be taken to ensure wearables are accessible to different populations, such as those with low digital literacy, with limited socio-economic resources,[144] or those who might have restricted ability to operate wearable devices (e.g., due to limited fine motor movement). Although a potentially complex and lengthy process, the validation of remote/wearable technologies for use in RBDs nonetheless presents an opportunity to better understand the extent and impacts of mobility impairment in individuals with RBDs.[145,146]

The functional limitations experienced by individuals with RBDs can be influenced both by mobility restrictions and other confounding factors such as the fatigue, reduced muscle strength, and pain seen in some RBDs.[12,48,49,147] Many individuals experience fatigue, which can impact endurance and mobility; in a recently published survey of 2312 individuals with OI, 67% of individuals reported fatigue.[18] Muscle degeneration (e.g., in FOP)[148] and reduced muscle power have been observed in individuals with RBDs; for example, diminished ankle power in individuals with XLH correlating with gait quality.[149] Additionally, motor neurons control skeletal muscle activity and can therefore influence mobility, demonstrated by the progressive loss of movement in individuals with motor neuron disease.[150] Furthermore, changes to the central nervous system structure and function have been demonstrated in relation to pain in individuals with fibrous dysplasia/McCune-Albright syndrome,[151] and the associated pain may limit mobility.[120–122] Skeletal health can also be compromised in RBDs due to abnormal muscle-bone cross-talk resulting in increased bone fragility and fracture risk.[152] Moreover, bone fragility in certain RBDs can result from reduced bone mass or defects in bone matrix composition or mineralization.[153] Such pathologies can lead to frailty characterized by weakness and slowness (e.g., slow walking speed),[8,14,133,154] which may not be captured by a single tool used to measure mobility. Mobility impairments also have widespread impacts on daily living and QoL (as demonstrated by the findings of Objective 1), which were not comprehensively captured by any of the tools identified in Objective 2 (Table 7). It may not be possible for a single tool to capture all the identified aspects of mobility, confounding physiological factors, and impacted daily activities/QoL. Nevertheless, tool(s) validated for RBDs that capture multiple mobility limitations and impacted daily activities, and characterize the relationship between them, would be beneficial to limit the burden conferred by multiple assessments and further understanding of the extent to which mobility restrictions impact individuals with RBDs.

Strengths and limitations of the SLR methodology

Consistent with the Cochrane Handbook for Systematic Reviews and Interventions,[26] this review used a pre-specified protocol, with full and transparent reporting of the eligibility criteria and review stages. Electronic database searches were supplemented by searches of reference lists of relevant SLRs and NMAs, as well as congress proceedings and Google searches, ensuring additional evidence outside of the published literature would be captured. The risk of selection bias was minimized by two reviewers independently assessing each full-text article against the SLR's eligibility criteria.

The searches were conducted in 2022, and an updated 2023 Nosology and Classification of Genetic Skeletal Disorders has since been published.[4] To ensure evidence of particular relevance published in the last 3 years on new tools capable of measuring mobility in RBDs has been captured, relevant articles were identified and incorporated in the Discussion of this publication.[15,123–131]

This SLR included a range of study designs, ensuring all available insights were captured including patient-level insights from case studies; this was particularly valuable in this SLR given the low patient numbers and limited evidence available for some RBDs. The quality of studies assessed via the AHFMR checklist (i.e.,

all studies minus case studies/series) was moderate. However, nearly a third of included studies were case studies/series, which required separate QA due to the inherent bias associated with this study design. Assessment using the NIH checklist indicated that the quality of case studies/series was moderate; however, this should be interpreted in the context of these studies being of lower quality than other study designs. A critical appraisal of the psychometric properties of the tools identified in this SLR was not independently conducted since most papers did not report the data that would be required; instead, the validity, reliability, or responsiveness of these tools was extracted if reported. Therefore, an independent critical appraisal, for example, using the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) checklist, would be beneficial to verify findings and evaluate tools for which no validation study was found.

Conclusion

Overall, this SLR collated evidence that mobility challenges in RBDs can severely limit individuals' daily activities and negatively impact their QoL. Although a large variety of tools capable of measuring mobility in RBDs were identified, only 9/61 were reported to have good validity, reliability, or responsiveness, highlighting the need for further research to modify and validate these tools for individuals with specific RBDs. None of the tools reported to have good validity, reliability, or responsiveness was capable of comprehensively capturing the range of mobility impairments and impacted daily activities and QoL factors identified, or measuring mobility remotely. Adaptable and easy-to-use tools such as wearables, that can remotely and longitudinally measure mobility and/or related daily activities in a real-world setting, would more accurately capture the challenges associated with mobility impairment, whilst conferring minimal burden on the individual with the RBD. Technologies such as smartphone sensors have recently shown promise for remotely measuring mobility challenges like gait disturbance, but would require adaptation and validation for specific RBDs.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Inês Alves: Conceptualization; Investigation; Methodology; Writing – review & editing.

Ingunn Westerheim: Conceptualization; Investigation; Methodology; Writing – review & editing.

Edward C. Hsiao: Investigation; Methodology; Writing – review & editing.

Jaymin Upadhyay: Investigation; Methodology; Writing – review & editing.

Luca Sangiorgi: Conceptualization; Investigation; Methodology; Writing – review & editing.

Alexander Artyomenko: Investigation; Methodology; Writing – review & editing.

Kim Croskery: Conceptualization; Investigation; Methodology; Writing – review & editing.

Juliet Johns: Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Emma Warnants: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Gabor Barton: Conceptualization; Investigation; Methodology; Writing – review & editing.

Acknowledgments

The authors thank Alice Slade, BSc, of Costello Medical, for medical writing support, which was sponsored by Ipsen in accordance with Good Publication Practice guidelines.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This SLR was sponsored by Ipsen.

Competing interests

I.A.: The author declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. I.W.: President of the Osteogenesis Imperfecta Federation Europe (OIFE), which from 2023 to 2025 received monetary support from: Alexion, Angitia Biopharmaceuticals, Azafaros, Mereo BioPharma, Orthopediatrics/Pega Medical, POROUS, PuREC, Quince Therapeutics, UCB Pharma, Ultragenyx; Steering Committee Member:

Sanofi; Speaker: Takeda. E.C.H.: Research support: Clementia/Ipsen, Ultragenyx, Ascendis Pharmaceuticals; Research Investigator: Clementia/Ipsen, Ascendis Pharmaceuticals; Member of the International Clinical Council on FOP, Fibrous Dysplasia Foundation Medical Advisory Board, and IFOPA Medical Registry Advisory Board (all voluntary). J.U.: Research support: Sanofi; Speaker: Orion Pharma. L.S.: The author declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. A.A.: Employee and shareholder of Ipsen. K.C.: Employee and shareholder of Ipsen. J.J.: Employee of Costello Medical. E.W.: Employee of Costello Medical. G.B.: The author declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Availability of data and materials

The data supporting the conclusions of this article are included within the article and its additional files. Full search results available on request.

ORCID iDs

Inês Alves https://orcid.org/0000-0001-8963-4736

Edward C. Hsiao https://orcid.org/0000-0001-8924-106X

Juliet Johns https://orcid.org/0009-0005-4361-2837

Emma Warnants https://orcid.org/0000-0002-6183-4143

Supplemental material

Supplemental material for this article is available online.

References

1. Maekawa H, Jin Y, Nishio M, et al. Recapitulation of pro-infammatory signature of monocytes with ACVR1A mutation using FOP patient-derived iPSCs. *Orphanet J Rare Dis* 2022; 17: 364.
2. ERN Bond. Rare bone diseases, https://ernbond.eu/bone-rare-diseases/ (2025, accessed 14 July 2025).
3. Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. *Am J Med Genet A* 2019; 179: 2393–2419.
4. Unger S, Ferreira CR, Mortier GR, et al. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet* 2023; 191: 1164–1209.
5. Eileen MS and Maurizio P. JBMRPlus: Special issue on rare bone diseases. *JBMR Plus* 2019; 3: e10218. https://doi.org/10.1002/jbm4.10218
6. Lai X, Jiang Y, Sun Y, et al. Prevalence of depression and anxiety, and their relationship to social support among patients and family caregivers of rare bone diseases. *Orphanet J Rare Dis* 2023; 18: 18.
7. Backeljauw P, Cappa M, Kiess W, et al. Impact of short stature on quality of life: a systematic literature review. *Growth Horm IGF Res* 2021; 57–58: 101392.
8. Faitos S, Inman J, Jones G, et al. *Voice of the patient report. Paper presented at the Symposium on Hypophosphatemia: Past, Present, and Future*, 23 July 2019, Baltimore, MD.
9. Seefried L, Smyth M, Keen R, et al. Burden of disease associated with X-linked hypophosphataemia in adults: a systematic literature review. *Osteoporos Int* 2021; 32: 7–22.
10. Al Mukaddam M, Toder KS, Davis M, et al. The impact of fibrodysplasia ossificans progressiva (FOP) on patients and their family members: results from an international burden of illness survey. *Expert Rev Pharmacoecon Outcomes Res* 2022; 22: 1199–1213.
11. Briot K, Portale AA, Brandi ML, et al. Burosumab treatment in adults with X-linked hypophosphataemia: 96-week patient-reported outcomes and ambulatory function from a randomised phase 3 trial and open-label extension. *RMD Open* 2021; 7: e001714.
12. Kruger KM, Caudill A, Rodriguez Celin M, et al. Mobility in osteogenesis imperfecta: a multicenter North American study. *Genet Med* 2019; 21: 2311–2318.
13. Dourrough C and Dahir K. *Addressing a knowledge gap: characterizing the physical, functional, and cognitive performance in adults with hypophosphatasia. Paper presented at the 2020 Annual Meeting of the American Society for Bone and Mineral Research (ASBMR), Virtual Event*, September 11–15, 2020, pp. S1–S349.
14. Fink S, Suppanz M, Castro M, et al. Perceived mobility challenges in rare bone diseases: how real-world gait data aligns. *J Orth Clin Res* 2024; 2: 148–161.
15. Fink SS, Oberzaucher M, Castro J, et al. Gait characterization in rare bone diseases in a real-world environment—a comparative controlled study. *Gait Posture* 2024; 112: 174–180.

16. Mayo NE and Mate KKV. Quantifying mobility in quality of life. In: Wac K and Wulfovich S (eds.) *Quantifying quality of life: incorporating daily life into medicine*. Cham: Springer International Publishing, 2022, pp. 119–136.
17. Lenderking WR, Anatchkova M, Pokrzywinski R, et al. Measuring health-related quality of life in patients with rare disease. *J Patient Rep Outcomes* 2021; 5: 1–7.
18. Westerheim IH, van Weizens T, Wekre T, et al. The IMPACT survey: a mixed methods study to understand the experience of children, adolescents and adults with osteogenesis imperfecta and their caregivers. *Orphanet J Rare Dis* 2024; 19: 1–21.
19. Basch E and Bennett AV. Patient-reported outcomes in clinical trials of rare diseases. *J Gen Intern Med* 2014; 29: 801–803.
20. Tosi LL, Floor MK, Dollar CM, et al. Assessing disease experience across the life span for individuals with osteogenesis imperfecta: challenges and opportunities for patient-reported outcomes (PROs) measurement: a pilot study. *Orphanet J Rare Dis* 2019; 14: 23.
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; 10: 89.
22. Nakahara Y, Kitoh H, Nakashima Y, et al. Longitudinal study of the activities of daily living and quality of life in Japanese patients with fibrodysplasia ossificans progressiva. *Disabil Rehabil* 2019; 41: 699–704.
23. Lim R, Shailam R, Hulett R, et al. Validation of the radiographic global impression of change (RGI-C) score to assess healing of rickets in pediatric X-linked hypophosphatemia (XLH). *Bone* 2021; 148: 115964.
24. Spencer TL, Watts L, Soni A, et al. Neuropathic-like pain in fibrous dysplasia/McCune-Albright syndrome. *J Clin Endocrinol Metab* 2022; 107: e2258–e2266.
25. Swezey T, Reeve BB, Hart TS, et al. Incorporating the patient perspective in the study of rare bone disease: insights from the osteogenesis imperfecta community. *Osteoporos Int* 2019; 30: 507–511.
26. Higgins J, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions*. Chichester: John Wiley & Sons, 2019.2019.
27. Centre for Reviews and Dissemination, University of York. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. University of York: Centre for Reviews and Dissemination, 2008.
28. Kmet LM, Cook LS and Lee R. *Standard quality assessment criteria for evaluating primary research papers from a variety of fields*. Alberta Heritage Foundation for Medical Research (AHFMR), 2004.
29. National Institutes of Health. Study quality assessment tools, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (2025, accessed 14 August 2025).
30. Martínez-Méndez JH, Gutiérrez-Acevedo MG-C, Mangual-García AA, et al. Multiple skeletal deformities in a middle-aged man. *P R Health Sci J* 2015; 34: 228–230.
31. Hendriksz CJ, Lavery C, Coker M, et al. Burden of disease in patients with Morquio A syndrome: results from an international patient-reported outcomes survey. *Orphanet J Rare Dis* 2014; 9: 1–8.
32. Seefried L, Dahir K, Petryk A, et al. Burden of illness in adults with hypophosphatasia: data from the global hypophosphatasia patient registry. *J Bone Miner Res* 2020; 35: 2171–2178.
33. Theodore-Oklota C, Bonner N, Spencer H, et al. Qualitative research to explore the patient experience of X-linked hypophosphatemia and evaluate the suitability of the BPI-SF and WOMAC® as clinical trial end points. *Value Health* 2018; 21: 973–983.
34. Borgwardt L, Guffon N, Amraoui Y, et al. Health related quality of life, disability, and pain in alpha mannosidosis: long-term data of enzyme replacement therapy with velmanase alfa (human recombinant alpha mannosidase). *J Inborn Errors Metab* 2018; 6: 1–12.
35. Högler W, Scott J, Bishop N, et al. The effect of whole body vibration training on bone and muscle function in children with osteogenesis imperfecta. *J Clin Endocrinol Metab* 2017; 102: 2734–2743.
36. Phillips D, Griffin D, Przybylski T, et al. Development and validation of a modified performance-oriented mobility assessment tool for assessing mobility in children with hypophosphatasia. *J Pediatr Rehabil Med* 2018; 11: 187–192.
37. Aubry-Rozier B, Richard C, Unger S, et al. Osteogenesis imperfecta: towards an individualised interdisciplinary care strategy to improve physical activity and quality of life. *Swiss Med Wkly* 2020; 150: w20285.
38. Cole S, Sanchez-Santos MT, Barrett J, et al. P673: patient-reported outcomes of X-linked hypophosphataemia registry participants in the UK. In: *World congress of osteoporosis, osteoarthritis and musculoskeletal diseases (WCO-IOF-ESCEO)*, virtual event, 2020.

39. Forestier-Zhang L, Watts L, Turner A, et al. Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. *Orphanet J Rare Dis* 2016; 11: 160.

40. Hu J, Zhu L, He J, et al. The usage of enzyme replacement treatments, economic burden, and quality of life of patients with four lysosomal storage diseases in Shanghai, China. *Intractable Rare Dis Res* 2021; 10: 190–197.

41. Monzo JJB, Romero LCL, Guillen E, et al. Hypophosphatemia linked to chromosome X (XLH): impact on the quality of life. *J Am Soc Nephrol* 2019; 30: 333.

42. Irving M, Savarirayan R, Arundel P, et al. *P2-284: associations between height and health-related quality of life (HRQoL) and functional independent in children with achondroplasia. Paper presented at the Annual Meeting of the European Society of Paediatric Endocrinology (ESPE), virtual event*, 2021.

43. Matos MA, Silva Lopes P, Rodrigues Corsini A, et al. Applying the functional independence measure to the assessment of patients with mucopolysaccharidosis. *Colomb Med (Cali)* 2020; 51: e213996.

44. Al Mukaddam M, Toder KS, Davis M, et al. Assessment of the impact of fibrodysplasia ossificans progressiva on quality of life for patients and their families using an international burden of illness survey. In: International Society for Pharmacoeconomics and Outcomes (ISPOR)—Europe, virtual event, 2021, p. POSA426.

45. Pignolo RJ, Baujat G, Brown MA, et al. Natural history of fibrodysplasia ossificans progressiva: cross-sectional analysis of annotated baseline phenotypes. *Orphanet J Rare Dis* 2019; 14: 98.

46. Pignolo RJ, Cheung K, Kile S, et al. Self-reported baseline phenotypes from the International Fibrodysplasia Ossificans Progressiva (FOP) Association Global Registry. *Bone* 2020; 134: 115274.

47. Pignolo RJ, Kimel M, Whalen J, et al. *P-847: validity and reliability of the Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ), a patient-reported, disease-specific measure. Paper presented at the American Society for Bone and Mineral Research (ASBMR) Annual Meeting virtual event*, 2020.

48. Rush ET, Moseley S and Petryk A. Burden of disease in pediatric patients with hypophosphatasia: results from the HPP impact patient survey and the HPP outcomes study telephone interview. *Orphanet J Rare Dis* 2019; 14: 201.

49. Weber TJ, Sawyer EK, Moseley S, et al. Burden of disease in adult patients with hypophosphatasia: results from two patient-reported surveys. *Metabolism* 2016; 65: 1522–1530.

50. Anttila H, Tallqvist S, Muñoz M, et al. Towards an ICF-based self-report questionnaire for people with skeletal dysplasia to study health, functioning, disability and accessibility. *Orphanet J Rare Dis* 2021; 16: 236.

51. Hyvönen H, Anttila H, Tallqvist S, et al. Functioning and equality according to International Classification of Functioning, Disability and Health (ICF) in people with skeletal dysplasia compared to matched control subjects—a cross-sectional survey study. *BMC Musculoskelet Disord* 2020; 21: 808.

52. Genest F, Rak D, Petryk A, et al. Physical function and health-related quality of life in adults treated with asfotase alfa for pediatric-onset hypophosphatasia. *JBMR Plus* 2020; 4: e10395.

53. Kamal AF and Ramang DS. A simple management of massive bone defect after en-bloc resection of osteofibrous dysplasia of tibial shaft: a case report. *Int J Surg Case Rep* 2021; 85: 106213.

54. Kishnani PS, del Angel G, Zhou S, et al. Investigation of ALPL variant states and clinical outcomes: an analysis of adults and adolescents with hypophosphatasia treated with asfotase alfa. *Mol Genet Metab* 2021; 133: 113–121.

55. Seefried L, Rak D, Genest F, et al. FRI-893: Physical function and health-related quality of life in adults treated with asfotase alfa for pediatric-onset hypophosphatasia. *Paper presented at the American Society for Bone and Mineral Research (ASBMR) Annual Meeting, 2019, Orlando, FL.*

56. Haller C, Song W, Cimms T, et al. Individual heat map assessments demonstrate vestronidase alfa treatment response in a highly heterogeneous mucopolysaccharidosis VII study population. *JIMD Rep* 2019; 49: 53–62.

57. Moisan L, Iannuzzi D, Maranda B, et al. Clinical characteristics of patients from Quebec, Canada, with Morquio A syndrome: a longitudinal observational study. *Orphanet J Rare Dis* 2020; 15: 270.

58. Ward LM, Rauch F, Whyte MP, et al. Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Clin Endocrinol Metab* 2011; 96: 355–364.

59. Shahcheraghi GH and Javid M. Functional assessment in tibial hemimelia (can we also save the foot in reconstruction?). *J Pediatr Orthop* 2016; 36: 572–581.

60. Phillips D, Griffin D, Przybylski T, et al. P136: a modified performance-oriented mobility assessment tool for assessing clinically relevant gait impairments and change in children with hypophosphatasia: development and validation. In: *7th International conference on children's bone health*, 2015, Salzburg, Austria.

61. Skrinar A, Dvorak-Ewell M, Evins A, et al. The lifelong impact of X-linked hypophosphatemia: results from a burden of disease survey. *J Endocr Soc* 2019; 3: 1321–1334.

62. Linglart A, Dvorak-Ewell M, Marshall A, et al. Impaired mobility and pain significantly impact the quality of life of children with X-linked hypophosphatemia. *Bone Abstracts* 2015; 4: P198.

63. Al Mukaddam M, Toder KS, Davis M, et al. POSA426: assessment of the economic impact of fibrodysplasia ossificans progressiva on patients and their families using an international burden of illness survey. *Value Health* 2022; 25: S273.

64. Kaplan FS, Al Mukaddam M and Pignolo RJ. Longitudinal patient-reported mobility assessment in fibrodysplasia ossificans progressiva (FOP). *Bone* 2018; 109: 158–161.

65. Martinez T, Schiro LM, Rodriguez P, et al. *P790: X-linked hypophosphataemic rickets: description of 16 cases in the adulthood in Argentina. Paper presented at the American Society for Bone and Mineral Research Annual Meeting (ASBMR), virtual event*, 2020.

66. Nixon A, Williams A, Skrinar A, et al. PRO153 Psychometric validation of the PROMIS physical function mobility, pain interference and fatigue in a cohort of paediatric X-linked hypophosphatemia (XLH) patients. *Value Health* 2019; 22: S870.

67. Ours CA, Sapp JC, Hodges MB, et al. Case report: five-year experience of AKT inhibition with miransertib (MK-7075) in an individual with Proteus syndrome. *Cold Spring Harb Mol Case Stud* 2021; 7: a006134.

68. Tosi LL, Oetgen ME, Floor MK, et al. Initial report of the osteogenesis imperfecta adult natural history initiative. *Orphanet J Rare Dis* 2015; 10: 146.

69. Evans R, Williams A, Nixon M, et al. POSC132: a mapping exercise and temporal extrapolation of the WOMAC index for adults with X-linked hypophosphataemia (XLH) treated with burosumab. *Value Health* 2022; 25: S113.

70. Insogna KL, Briot K, Imel EA, et al. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res* 2018; 33: 1383–1393.

71. Keen R, Insogna K, Sun W, et al. *Efficacy of burosumab in older adults with X-linked hypophosphataemia (XLH): a subgroup analysis of a randomized, double-blind, placebo controlled, phase 3 study. P-755. Paper presented at the American Society for Bone and Mineral Research (ASBMR) Annual Meeting, virtual event*, 2020.

72. Neill SCO, Murphy CG and McElwain JP. A hypoplastic patella fracture in nail patella syndrome: a case report. *J Med Case Rep* 2012; 6: 196.

73. Nixon A, Williams A and Theodore-Oklota C. PRO80 Psychometric validation of the Brief Fatigue Inventory (BFI) in adult X-linked hypophosphatemia (XLH). *Value Health* 2020; 23: S343.

74. Portale AA, Carpenter TO, Brandi ML, et al. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int* 2019; 105: 271–284.

75. Ruppe MD, Zhang X, Imel EA, et al. Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia. *Bone Rep* 2016; 5: 158–162.

76. Skrinar A, Theodore-Oklota C, Bonner N, et al. PRO152 Confirmatory psychometric validation of the Western Ontario Mcmaster Universities Osteoarthritis Inventory (WOMAC) in adult X-linked hypophosphatemia (XLH). *Value Health* 2019; 22: S870.

77. Skrinar A, Theodore-Oklota C, Bonner N, et al. PRO154 Confirmatory psychometric validation of the Brief Pain Inventory (BPI-SF) in adult X-linked hypophosphatemia (XLH). *Value Health* 2019; 22: S870.

78. Vakharia RM, Meneses ZA, Ardeljan AD, et al. Robotic-assisted lateral unicompartmental knee arthroplasty in a patient with nail-patella syndrome. *Arthroplast Today* 2021; 8: 171–175.

79. Nijhuis W, Franken A, Ayers K, et al. A standard set of outcome measures for the comprehensive assessment of osteogenesis imperfecta. *Orphanet J Rare Dis* 2021; 16: 140.

80. Hoyer-Kuhn H, Franklin J, Allo G, et al. Safety and efficacy of denosumab in children with osteogenesis imperfecta—a first prospective trial. *J Musculoskelet Neuronal Interact* 2016; 16: 24–32.

81. Graff K, Kalinowska M, Szczerbik E, et al. Spatio-temporal parameters and body of gait and body deformations in patients with osteogenesis imperfecta. *Gait Posture* 2020; 81: 113–114.

82. Belaya Z, Kalinchenko N, Grebennikova T, et al. Hypophosphatasia treatment with recombinant human TNSALP in an 18 year old patient. *J Bone Miner Res* 2019; 129: 219–227.

83. Ficicioglu C, Benedict M and Kornafel T. Impact of early diagnosis and treatment with enzyme replacement therapy for mucopolysaccharidosis IVA: a sibling control study. E-139. *J Inherit Metab Dis* 2019; 42: 365–366.

84. Ficicioglu C, Matalon DR, Luongo N, et al. Diagnostic journey and impact of enzyme replacement therapy for mucopolysaccharidosis IVA: a sibling control study. *Orphanet J Rare Dis* 2020; 15: 336.

85. Harmatz P, Whitley CB, Wang RY, et al. A novel Blind Start study design to investigate vestronidase alfa for mucopolysaccharidosis VII, an ultra-rare genetic disease. *Mol Genet Metab* 2018; 123: 488–494.

86. Kanik ZH, Gunaydin G, Sozlu U, et al. Eccentric training as an adjunct to rehabilitation program for hereditary multiple exostoses: a case report. *J Clin Diagn Res* 2016; 10: YD03–YD04.

87. Kruger KM, Caudill AC, Celin MR, et al. Mobility in osteogenesis imperfecta: a multicenter North American study. *Am J Med Genet A* 2020; 182: 697–704.

88. Lin H-Y, Chuang C-K, Chen M-R, et al. Natural history and clinical assessment of Taiwanese patients with mucopolysaccharidosis IVA. *Orphanet J Rare Dis* 2014; 9: 21.

89. McDermott M, Twomey P, Van der Kamp S, et al. X-linked hypophosphatemia patient work-up at St. Vincent's University Hospital is managed to European consensus guidelines. *Ir J Med Sci* 2021; 190: S94–S95.

90. Nishizawa H, Sato Y, Ishikawa M, et al. Marked motor function improvement in a 32-year-old woman with childhood-onset hypophosphatasia by asfotase alfa therapy: evaluation based on standardized testing batteries used in Duchenne muscular dystrophy clinical trials. *Mol Genet Metab Rep* 2020; 25: 100643.

91. Phillips D, Griffin D, Przybylski T, et al. Gait assessment in children with childhood hypophosphatasia: impairments in muscle strength and physical function. *Bone Abstracts* 2015; 4: P103.

92. Boyce AM, Kelly MH, Brillante BA, et al. A randomized, double blind, placebo-controlled trial of alendronate treatment for fibrous dysplasia of bone. *J Clin Endocrinol Metab* 2014; 99: 4133–4140.

93. Ragni LB, Zlotolow DA, Daluiski A, et al. Combined clinic and home-based therapeutic approach for the treatment of bilateral radial deficiency for a young child with Holt-Oram syndrome: a case report. *J Hand Ther* 2022; 35: 670–677.

94. Hoyer-Kuhn H, Semler O, Stark C, et al. A specialized rehabilitation approach improves mobility in children with osteogenesis imperfecta. *J Musculoskelet Neuronal Interact* 2014; 14: 445–453.

95. Atta I, Iqbal F, Lone SW, et al. Effect of intravenous pamidronate treatment in children with osteogenesis imperfecta. *J Coll Physicians Surg Pak* 2014; 24: 653–657.

96. Wang RY, da Silva Franco JF, López-Valdez J, et al. The long-term safety and efficacy of vestronidase alfa, rhGUS enzyme replacement therapy, in subjects with mucopolysaccharidosis VII. *Mol Genet Metab* 2020; 129: 219–227.

97. Al Mukaddam M, Pignolo RJ, Baujat G, et al. AEP1019: a global natural history study of Fibrodysplasia Ossificans Progressiva (FOP): 12-month outcomes. Endocr Abstr 2020; 70: AEP1019.

98. Pignolo RJ, Baujat G, Brown MA, et al. A natural history study of fibrodysplasia ossificans progressiva (FOP): 12-month outcome results. *Bone Rep* 2020; 13: P325.

99. Grin L, Wijnands S, Besselaar A, et al. The relation between clinical and objective gait scores in clubfoot patients with and without a relapse. *Gait Posture* 2022; 97: 210–215.

100. Vanlommel J, Vanlommel L, Molenaers B, et al. Hybrid total hip arthroplasty for multiple epiphyseal dysplasia. *Orthop Traumatol Surg Res* 2018; 104: 301–305.

101. Yoo SD, Han YR, Kim DH, et al. Five-year follow-up outcomes of comprehensive rehabilitation in Korean siblings with cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome: a case report. *Medicine (Baltimore)* 2019; 98: e15908.

102. Hoyer-Kuhn H, Rehberg M, Netzer C, et al. Individualized treatment with denosumab in children with osteogenesis imperfecta—follow up of a trial cohort. *Orphanet J Rare Dis* 2019; 14: 219.

103. Kovela RK, Qureshi MI, Manakandathil AS, et al. Rubinstein-Taybi syndrome: a rare case report of a female child emphasizing physiotherapy on gross motor function. *Pan Afr Med J* 2021; 40: 85.

104. Singh S, Sardhara J, Raiyani V, et al. Craniovertebral junction instability in Larsen syndrome: an institutional series and review of literature. *J Craniovertebr Junction Spine* 2020; 11: 276–286.

105. Del Rossi L. Gross motor function of a child with Antley-Bixler syndrome. *Pediatr Phys Ther* 2015; 27: 452–459.

106. Chan MO, Sen ES, Hardy E, et al. Assessment of musculoskeletal abnormalities in children with mucopolysaccharidoses using pGALS. *Pediatr Rheumatol Online J* 2014; 12: 32.

107. Carpenter T, Tabatabai L, Luca D, et al. P-788: safety and efficacy of burosumab in cutaneous skeletal hypophosphatemia syndrome (CSHS). *Presented at the American Society for Bone and Mineral Research Annual Meeting (ASBMR), virtual event*, 2020.

108. Desborough R, Nicklin P, Gossiel F, et al. Clinical and biochemical characteristics of adults with hypophosphatasia attending a metabolic bone clinic. *Bone* 2021; 144: 115795.

109. Orlando G, Clark S, Javaid MK, et al. Physical function and mobility in adults with X-linked hypophosphatemia. *Osteoporos Int* 2020; 31: S345.

110. Orlando G, Clarke S, Roy M, et al. *P191: physical function and mobility in adults with X-linked hypophosphatemia. Paper presented at the 48th European Calcified Tissue Society Congress, virtual event*, 2021.

111. Song EK, Seon JK and Agrawal PR. Single-stage corrective osteotomies for multiple angular deformities around the knee joint with patellar instability in a patient with multiple epiphyseal dysplasia: a case report. *JBJS Case Connect* 2015; 5: e82.

112. Yiu Cho Kwan R, Yat Wa Liu J, Yin Y, et al. Sarcopenia and its association with objectively measured life-space mobility and moderate-to-vigorous physical activity in the oldest-old amid the COVID-19 pandemic when a physical distancing policy is in force. *BMC Geriatr* 2022; 22: 1–11.

113. Mindler GT, Kranzl A, Stauffer A, et al. Lower limb deformity and gait deviations among adolescents and adults with X-linked hypophosphatemia. *Front Endocrinol (Lausanne)* 2021; 12: 754084.

114. Sundarapandian R, Jones S, Broomfield A, et al. Improvement in functional gait parameters following corrective thoracolumbar surgery in children affected by Mucopolysaccharidosis 1 (Hurler syndrome). *Orphanet J Rare Dis* 2020; 15: 140.

115. Struijs PAA, Kerkhoffs GMMJ and Besselaar PP. Treatment of dysplasia epiphysealis hemimelica: a systematic review of published reports and a report of seven patients. *J Foot Ankle Surg* 2012; 51: 620–626.

116. Constantino CS, Krzak JJ, Fial AV, et al. Effect of bisphosphonates on function and mobility among children with osteogenesis imperfecta: a systematic review. *JBMR Plus* 2019; 3: e10216.

117. Szabo SM, Tomazos IC, Petryk A, et al. Frequency and age at occurrence of clinical manifestations of disease in patients with hypophosphatasia: a systematic literature review. *Orphanet J Rare Dis* 2019; 14: 85.

118. Majoor BCJ, Andela CD, Bruggemann J, et al. Determinants of impaired quality of life in patients with fibrous dysplasia. *Orphanet J Rare Dis* 2017; 12: 80.

119. World Health Organisation (WHO). *International classification of functioning, disability and health*, Geneva: World Health Organization, 2001.

120. Randall ET, Smith KR, Conroy C, et al. Back to living: long-term functional status of pediatric patients who completed intensive interdisciplinary pain treatment. *Clin J Pain* 2018; 34: 890–899.

121. Merkle SL, Sluka KA and Frey-Law LA. The interaction between pain and movement. *J Hand Ther* 2020; 33: 60–66.

122. Tucker-Bartley A, Lemme J, Gomez-Morad A, et al. Pain phenotypes in rare musculoskeletal and neuromuscular diseases. *Neurosci Biobehav Rev* 2021; 124: 267–290.

123. Bacon S and Crowley R. Developments in rare bone diseases and mineral disorders. *Ther Adv Chronic Dis* 2018; 9: 51–60.

124. Van Dijk FS and Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Genet A* 2014; 164A: 1470–1481.

125. Weber TJ, Imel EA, Carpenter TO, et al. Long-term burosumab administration is

safe and effective in adults with X-linked hypophosphatemia. *J Clin Endocrinol Metab* 2023; 108: 155–165.

126. Syu Y-M, Lee C-L, Chuang C-K, et al. Functional independence of Taiwanese children with osteogenesis imperfecta. *J Pers Med* 2022; 12: 1205.

127. Dahir KK, P. Martos-Moreno, Linglart GA., A. Petryk A., et al. Impact of muscular symptoms and/or pain on disease characteristics, disability, and quality of life in adult patients with hypophosphatasia: a cross-sectional analysis from the Global HPP Registry. *Front Endocrinol* 2023; 14: 1–9.

128. Moss KE, Keen R, Fang S, et al. Mobility and quality of life in adults with paediatric-onset hypophosphatasia treated with asfotase alfa: results from UK managed access agreement. *Adv Ther* 2025; 42: 2429–2444.

129. Al Arab H, Flammier S, Espitalier M, et al. Evaluation of the benefits of adapted physical activity in children and adolescents with osteogenesis imperfecta: the MOVE-OI trial. *Orphanet J Rare Dis* 2025; 20: 175.

130. Kishnani PS, Martos-Moreno GA, Linglart A, et al. Effectiveness of asfotase alfa for treatment of adults with hypophosphatasia: results from a global registry. *Orphanet J Rare Dis* 2024; 19: 109.

131. Stepien KM, Thomas S, Hennermann JB, et al. Evolution of mobility, pain/discomfort, selfcare, and mental health in patients with alphamannosidosis: an international caregiver and patient survey. *Orphanet J Rare Dis* 2025; 20: 217.

132. Oder K, Unglaube F, Farr S, et al. Clinical, radiographic, and biomechanical evaluation of the upper extremity in patients with osteogenesis imperfecta. *J Clin Med* 2024; 13: 5174.

133. Horn J, Leardini A, Benedetti MG, et al. Fully instrumented gait analysis in rare bone diseases—a scoping review of the literature. *Gait Posture* 2025; 118: 168–177.

134. Whittal A, Meregaglia M and Nicod E. The use of patient-reported outcome measures in rare diseases and implications for health technology assessment. *Patient* 2021; 14: 485–503.

135. Lagu T, Hannon NS, Rotheberg MB, et al. Access to subspecialty care for patients with mobility impairment: a survey. *Ann Intern Med* 2013; 158: 441–446.

136. Verlinden JM. How much does it cost to build a Health Tech Application? Med Record, https://medrecord.io/cost-of-developing-healthtech-apps/ (accessed 2023, 14 August 2025).

137. APA Member Services. Using apps in clinical practice: competency considerations. American Psychological Association, https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.apa.org%2Fmembers%2Fcontent%2Fclinical-practice-apps-transcript.docx&wdOrigin=BROWSELINK (2019, accessed July 2025).

138. Mikolaizak AS, Rochester L, Maetzler W, et al. Connecting real-world digital mobility assessment to clinical outcomes for regulatory and clinical endorsement—the Mobilise-D study protocol. *PLoS One* 2022; 17: e0269615.

139. Wren TAL, Isakov P and Rethlefsen SA. Comparison of kinematics between Theia markerless and conventional marker-based gait analysis in clinical patients. *Gait Posture* 2023; 104: 9–14.

140. Servais L, Camino E, Clement A, et al. First regulatory qualification of a novel digital endpoint in Duchenne muscular dystrophy: a multi-stakeholder perspective on the impact for patients and for drug development in neuromuscular diseases. *Digit Biomark* 2021; 5: 183–190.

141. Kluge F, Brand YE, Mico-Amigo ME, et al. Real-world gait detection using a wrist-worn inertial sensor: validation study. *JMIR Form Res* 2024; 8: e50035.

142. Moore J, Goodson N, Wicks P, et al. What role can decentralized trial designs play to improve rare disease studies? *Orphanet J Rare Dis* 2022; 17: 240.

143. Chen FH, Hartman AL, Letinturier MCV, et al. Telehealth for rare disease care, research, and education across the globe: A review of the literature by the IRDiRC telehealth task force. *Eur J Med Genet* 2024; 72: 1–11.

144. Canali S, Schiaffonati V and Aliverti A. Challenges and recommendations for wearable devices in digital health: Data quality, interoperability, health equity, fairness. *PLoS Digit Health* 2022; 1: e0000104.

145. Ferrar J, Griffith GJ, Skirrow C, et al. Developing digital tools for remote clinical research: how to evaluate the validity and practicality of active assessments in field settings. *J Med Internet Res* 2021; 23: e26004.

146. Taylor KI, Staunton H, Lipsmeier F, et al. Outcome measures based on digital health technology sensor data: data- and patient-centric approaches. *NPJ Digit Med* 2020; 3: 97.

147. Behanova M, Medibach A, Haschka J, et al. Health-related quality of life and fatigue in adult

rare bone disease patients: a cross-sectional study from Austria. *Bone* 2024; 181: 117034.

148. Farid A, Golden E, Robicheau S, et al Diminished muscle integrity in patients with fibrodysplasia ossificans progressiva assessed with at-home electrical impedance myography. *Sci Rep* 2022; 12: 20908.

149. Akta C, Wenzel-Schwarz F, Stauffer A, et al. The ankle in XLH: reduced motion, power and quality of life. *Front Endocrinol* 2023; 14: 1111104.

150. National Institute of Neurological Disorders and Stroke. Motor neuron diseases, https://www.ninds.nih.gov/health-information/disorders/motor-neuron-diseases (2025, accessed 14 August 2025).

151. Golden E, van der Heijden H, Ren B, et al. Phenotyping pain in patients with fibrous dysplasia/McCune-Albright syndrome. *J Clin Endocrinol Metab* 2024; 109: 771–782.

152. Iolascon G, Paoletta M, Liguori S, et al. Neuromuscular diseases and bone. *Front Endocrinol* 2019; 10: 794.

153. El-Gazzar A and Högler W. Mechanisms of bone fragility: from osteogenesis imperfecta to secondary osteoporosis. *Int J Mol Sci* 2021; 22: 625.

154. Kubota T, Fukumoto S, Cheong HI, et al. Long-term outcomes for Asian patients with X-linked hypophosphataemia: rationale and design of the SUNFLOWER longitudinal, observational cohort study. *BMJ Open* 2020; 10: e036367.

Appendix

Abbreviations

10MWT	10-m Walk Test
1MWT	1-min Walk Test
2MWT	2-min Walk Test
3D	Three-dimensional
3MSC	3-min Stair Climb Test
6MWT	6-min Walk Test
9MWT	9-min Walk Test
AHA	Assisting Hand Assessment
AHFMR	Alberta Heritage Foundation for Medical Research
APPT	Adolescent Paediatric Pain Tool
BAMF	Brief Assessment of Motor Function
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Version 2
BPI-SF	Brief Pain Inventory Short Form
CAJIS	Cumulative Analogue Joint Involvement Scale
CAP	Clubfoot Assessment Protocol
CHAQ	Childhood Health Assessment Questionnaire
CMD	Charnley Modification of the Merle d'Aubigné Postel Grading System
CPE	Clinical Problem Evaluation
DDST	Denver Developmental Screening Test
FAQ	Functional Assessment Questionnaire
FDI	foot deviation index
FGA	full instrumented gait analysis
FIM	functional independence measure
FMS	Functional Mobility Scale
FOP	Fibrodysplasia ossificans progressiva
FOP-PFQ	Fibrodysplasia Ossificans Progressiva-Physical Function Questionnaire
GCPS	Graded Chronic Pain Scale
GDI	gait deviation index
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
HAQ	Health Assessment Questionnaire
HIPS	Hypophosphatasia Impact Patient Survey
HOST	Hypophosphatasia Outcomes Study Telephone Interview
HPP	hypophosphatasia
HRQoL	health-related quality of life
ICF	International Classification of Functioning, Disability and Health
LEFS	Lower Extremity Functional Scale
MA	meta-analysis
mPOMA-G	Modified Performance Oriented Mobility Assessment-Gait

MPS-HAQ	Mucopolysaccharidosis Health Assessment Questionnaire	PRMA	Patient-Reported Mobility Assessment
NA	not applicable	PROMIS	Patient-Reported Outcome Measure Information System
NMA	network meta-analyses		
NR	not reported	QA	quality assessment
OI	osteogenesis imperfecta	QoL	quality of life
PDMS-2	Peabody Developmental Motor Scales, second edition	RBD	rare bone disease
		SCL-90-R	Symptom Checklist 90-R
		SF-12	12-item Short Form Survey
PEDI	Pediatric Evaluation of Disability Inventory	SF-36v2	36-item Short Form Survey, version 2
PedsQL	Pediatric Quality of Life		
pGALS	Pediatric Gait, Arms, Legs, and Spine	SLR	systematic literature review
PODCI	Pediatric Outcomes Data Collection Instrument	SPPB	short performance physical battery
POSNA-PODCI	Paediatric Orthopaedic Society of North America Paediatric Outcomes Data Collection Instrument	T-GAP	thumb grasp and pinch assessment
		TUG	timed up and go
		WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	XLH	X-linked hypophosphatemia