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Original research

Disease burden by *ALPL* variant number in patients with non-life-threatening hypophosphatasia in the Global HPP Registry

Priya S Kishnani ,[1] Lothar Seefried,[2] Kathryn M Dahir,[3] Gabriel Á Martos-Moreno,[4] Wolfgang Högler,[5] Cheryl R Greenberg,[6] Shona Fang,[7] Anna Petryk,[7] William R Mowrey,[7] Agnès Linglart,[8] Keiichi Ozono[9]

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[1]Duke University Hospital, Durham, North Carolina, USA
[2]University of Würzburg, Würzburg, Germany
[3]Vanderbilt University Medical Center, Nashville, Tennessee, USA
[4]Hospital Infantil Universitario Niño Jesús, IIS La Princesa, Universidad Autónoma de Madrid, CIBERobn, ISCIII, Madrid, Spain
[5]Johannes Kepler University Linz, Linz, Austria
[6]University of Manitoba, Winnipeg, Manitoba, Canada
[7]Alexion, AstraZeneca Rare Disease, Boston, Massachusetts, USA
[8]Paris-Saclay University, AP-HP and INSERM, Bicêtre Paris Saclay Hospital, le Kremlin, Bicêtre, France
[9]ISEIKAI International General Hospital, Osaka, Japan

Correspondence to
Dr Priya S Kishnani;
priya.kishnani@duke.edu

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ABSTRACT

Background Hypophosphatasia (HPP) is a rare metabolic disease caused by autosomal dominant or recessive inheritance of *ALPL* variants resulting in low alkaline phosphatase activity. The objective of this analysis was to compare HPP disease burden between patients with non-life-threatening disease in the Global HPP Registry who have one *ALPL* variant versus two or more *ALPL* variants.

Methods Patients were included if they had one or more *ALPL* variants identified through genetic testing and first HPP manifestations after 6 months of age. Assessments included history of HPP manifestations, Brief Pain Inventory-Short Form (BPI-SF), Health Assessment Questionnaire-Disability Index (HAQ-DI), 6-Min Walk Test (6MWT), Paediatric Quality of Life Inventory (PedsQL) and 36-Item Short-Form Survey V.2 (SF-36v2).

Results Of 685 included patients, 568 (82.9%) had one *ALPL* variant, 116 (16.9%) had two variants, and one (0.1%) had three variants. Patients with two or more *ALPL* variants had higher proportions of skeletal (52.1% vs 32.6%), dental (73.5% vs 56.0%), muscular (36.8% vs 23.6%) and neurological (22.2% vs 8.8%) manifestations at last assessment. BPI-SF, HAQ-DI, PedsQL and SF-36v2 scores were similar between groups. Distances walked on the 6MWT were similar between groups for children. Distance walked was lower among adults with two or more variants (293 m (n=8)) than adults with one variant (466 m (n=103)), although the former group was very small.

Conclusion HPP disease burden is high in patients with HPP, regardless of *ALPL* variant number. While prevalence of HPP-specific manifestations was higher in patients with two or more variants than those with one variant, patient-reported outcomes were similar between groups.

Trial registration number NCT02306720; EUPAS13514.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with life-threatening disease who first manifest signs and symptoms of hypophosphatasia (HPP) before 6 months of age typically have two *ALPL* variants and their disease burden is well characterised.

WHAT THIS STUDY ADDS

⇒ Patients who first manifest signs and symptoms of HPP after 6 months of age may have one or multiple *ALPL* variants.

⇒ This study shows that disease burden can be high in both groups, although the frequency of HPP-specific signs and symptoms is higher among patients with two or more variants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The significant burden of disease across Global HPP Registry participants with HPP suggests that access to effective treatments, such as enzyme replacement therapy, should not be conditional on number of *ALPL* variants but rather the clinical status of the patient.

INTRODUCTION

Hypophosphatasia (HPP) is a rare, inherited metabolic disorder caused by deficient tissue-non-specific alkaline phosphatase (ALP) enzyme activity due to variants in *ALPL*.[1 2] Tissue-non-specific ALP is a cell surface phosphohydrolase expressed in multiple tissues and cell types.[1–3] Reductions in tissue-non-specific ALP activity within tissues are reflected in reduced circulating ALP activity.[4] Low ALP activity can lead to extracellular accumulation of its substrates, including inorganic pyrophosphate (PPi), a strong inhibitor of bone mineralisation; pyridoxal 5′-phosphate (PLP), the active form of vitamin B_6 and phosphoethanolamine (PEA), which has poorly defined biologic activity in HPP.[4]

ALP deficiency and the resulting accumulation of its substrates result in a broad spectrum of HPP clinical manifestations. HPP in infants <6 months of age typically is associated with life-threatening clinical manifestations and poor survival, especially in the absence of enzyme replacement therapy (ERT); patients develop respiratory failure, craniosynostosis, hypercalcaemia, hyperphosphataemia, nephrocalcinosis, vitamin B_6-responsive seizures and failure to thrive.[3 5–7] Patients may experience premature loss of deciduous teeth, rickets, bone deformity, delayed motor milestones, difficulty walking, craniosynostosis, osteomalacia, pseudofractures, recurrent and poorly healing fractures (particularly atypical femoral and metatarsal fractures), chondrocalcinosis, fatigue, muscle

weakness, musculoskeletal pain, among other manifestations, and reduced quality of life (QoL).[3 5 8–17]

A clinical diagnosis of HPP may be made based on low age-adjusted and sex-adjusted ALP activity (obligate criterion), clinical signs and symptoms and radiological findings.[14] However, many factors and diagnoses beyond HPP can also cause low serum ALP activity and should be excluded.[13 14 18] Additional biochemical confirmation, including assessment of the ALP substrates PLP, PPi or PEA, can be used to confirm diagnosis, although not all patients with HPP present with elevated PLP.[14 19] An additional very important strategy to confirm HPP diagnosis is genetic testing of *ALPL*. Genetic confirmation is highly recommended when available, although causative genetic variants can remain elusive using current diagnostic methods.[14] More than 450 *ALPL* variants have been reported to the Johannes Kepler University *ALPL* Gene Variant Database, including pathogenic and benign variants along with variants of uncertain clinical significance.[20 21]

The vast majority of patients who manifest life-threatening symptoms before 6 months of age inherit HPP in an autosomal recessive manner (two *ALPL* variants *in trans*).[6 22] For those who first manifest symptoms after 6 months of age, the youngest are more likely to inherit HPP in an autosomal recessive manner rather than an autosomal dominant manner (one *ALPL* variant), although adults diagnosed with HPP may have two *ALPL* variants as well.[15 22 23] Less is known about disease burden in patients without life-threatening disease, who are typically patients with first HPP symptom manifestation after 6 months of age.

The current analysis was performed using data from patients enrolled in the Global HPP Registry to evaluate the relationship between HPP disease burden and *ALPL* variant number (one vs two or more variants) in patients who manifest the disease after 6 months of age. Patients with two variants likely inherited one variant on each allele, which means that they would be biallelic. However, since phasing was not known, referring to these patients as having one variant or two or more variants was deemed more accurate than assuming a monoallelic versus biallelic variant state. Measures of disease burden included pain, disability, impaired physical function and reduced QoL.

METHODS

Study design

The Global HPP Registry is an observational, prospective, multinational registry (NCT02306720; EUPAS13514) that was initiated in 2014 and began enrolling patients with HPP in 2015 regardless of treatment with asfotase alfa (Strensiq; Alexion, AstraZeneca Rare Disease, Boston, Massachusetts, USA), the first-generation ERT.[10] The registry collects data on the natural history of HPP and the effectiveness and safety of long-term treatment with asfotase alfa.[24] The registry design and data collection techniques were previously described.[8]

Study population

Inclusion criteria

This analysis included patients diagnosed with HPP at any age, including patients diagnosed in utero through genetic screening. Diagnosis in utero does not predict clinical manifestations at birth, since genetic screening typically cannot distinguish between prenatal benign and perinatal HPP.[25] To be included in the analysis, patients must have presented with signs and symptoms of HPP after reaching 6 months of age, have had ALP enzyme activity below the age-adjusted and sex-adjusted lower limit while not receiving treatment and have had *ALPL* genetic testing with a documented *ALPL* pathogenic or likely pathogenic variant or variant of uncertain significance according to American College of Medical Genetics and Genomics guidelines.[26] Patients with two *ALPL* variants were assumed to be biallelic, because inheritance *in trans* could not be established.

Exclusion criteria

Patients were excluded if they first presented with signs and symptoms of HPP before 6 months of age, as HPP disease burden is well characterised in these patients[5 27]; if they did not have a documented age at first disease manifestation, age at enrollment or date of birth; if they discontinued from the registry because they received an alternative diagnosis; or if they did not have a known ERT start date (for those patients who had ever received treatment). Patients with ambiguous or incomplete data were cleared through consultation with the individual sites and with expert geneticists.

Summary of assessment measures

Among patients who had never received asfotase alfa treatment, the most recently obtained assessment for all outcome measures was used. Among patients who had ever received asfotase alfa treatment, only data from before treatment initiation were included in the analysis. Registry data were reviewed for history of HPP signs and symptoms, including skeletal, muscular, dental, neurological, constitutional/metabolic, respiratory, renal,

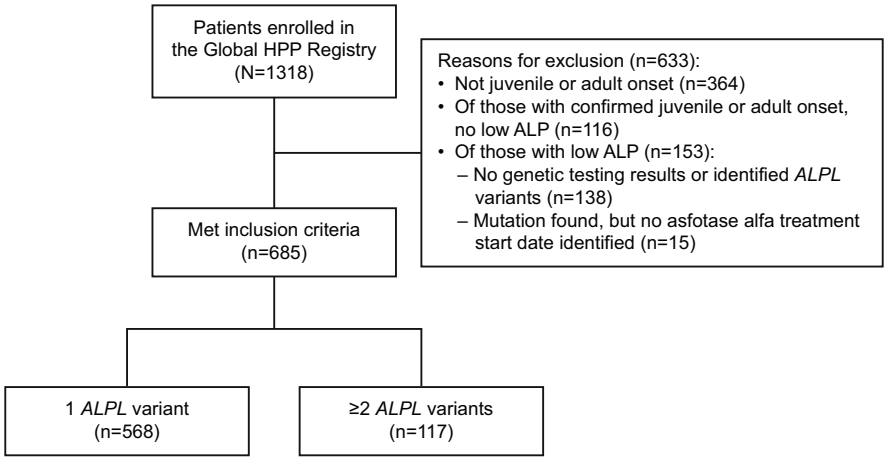

Figure 1 Patient flow chart. ALP, alkaline phosphatase; HPP, hypophosphatasia.

Table 1 Patient demographics

	Total (N=685)	1 Variant (n=568)	≥2 Variants (n=117)*
Sex, n (%)			
Female	446 (65.1)	381 (67.1)	65 (55.6)
Male	239 (34.9)	187 (32.9)	52 (44.4)
Race, n (%)			
White	511 (74.6)	439 (77.3)	72 (61.5)
Asian	56 (8.2)	33 (5.8)	23 (19.7)
Other/Multiple†	19 (2.8)	13 (2.3)	6 (5.1)
Not reported	99 (14.5)	83 (14.6)	16 (13.7)
Age at HPP diagnosis, years	(n=661)	(n=550)	(n=111)
Mean (SD)	29.5 (23.0)	31.7 (22.3)	18.6 (23.2)
Median (range)	29.5 (–0.5, 75.3)	32.6 (0.0, 75.3)	3.9 (–0.5, 74.7)
Age at last follow-up‡	(n=684)	(n=567)	(n=117)
Mean (SD), years	35.3 (22.7)	36.8 (22.3)	28.0 (23.5)
Median (range), years	36.5 (0.2, 85.1)	39.3 (1.6, 85.1)	16.4 (0.2, 77.3)
<18 years, n (%)	230 (33.6)	169 (29.8)	61 (52.1)
≥18 years, n (%)	454 (66.3)	398 (70.1)	56 (47.9)
Ever received ERT, n (%)	237 (34.6)	162 (28.5)	75 (64.1)

*One patient had three variants.
†Other races include two patients who reported as Native Hawaiian or other Pacific Islander, both of whom had one variant; one patient who reported as Black or African American who had one variant; and one patient who reported as Native American or Alaska Native who had two or more variants.
‡For patients who ever received ERT, this time point represents the last assessment before initiation of ERT.
ERT, enzyme replacement therapy; HPP, hypophosphatasia.

rheumatological manifestations and pain. In patients who ever received ERT, the manifestation must have occurred before ERT initiation. The classification of signs and symptoms is described in more detail in online supplemental table 1.[5 8] The Brief Pain Inventory-Short Form (BPI-SF) and the Health Assessment Questionnaire-Disability Index (HAQ-DI) were used to measure pain and patient-reported functional status in adults.[28–30] The 6-Min Walk Test (6MWT) was conducted by a trained healthcare provider to assess physical functioning in adults and children with HPP. For unknown reasons, not all patients eligible for this analysis performed the 6MWT. Health-related quality of life (HRQoL) was assessed using the Paediatric Quality of Life Inventory (PedsQL)[31 32] among children (aged ≥2 to <18 years) and using the 36-Item Short-Form Health Survey V.2 (SF-36v2) among adults (aged ≥18 years).[33]

Description of assessment measures

Brief Pain Inventory-Short Form

The BPI-SF has two domains: pain intensity and pain interference.[28 29] Pain intensity is measured using four items (worst pain, least pain, average pain over the past 24 hours and pain right now) rated on a scale of 0 (no pain) to 10 (worst pain imaginable). Pain interference is measured using seven items (general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life) rated on a scale of 0 (no interference) to 10 (complete interference). Scores on each of these domains range from 0 to 10, where lower scores indicate less pain.

Health Assessment Questionnaire-Disability Index

The HAQ-DI measures the degree of difficulty a person has with accomplishing 20 tasks across eight categories of daily living (dressing/grooming, arising, eating, walking, hygiene, reach, grip and regular activities) in the week before assessment.[30] Each task is assessed on a scale of 0 (without difficulty) to 3 (unable to perform). A total score is computed by calculating the mean of each of the eight category scores, using the highest task score in each category. Total scores range from 0 to 3, with lower scores indicating less disability.

6-Min Walk Test

The 6MWT is a validated and reliable measure of physical function in patients with HPP aged 5 years or older.[34] 6MWT is used to measure the distance a person can quickly walk on a hard flat surface for 6 min and the per cent of predicted distance walked.[35] The per cent of predicted distance walked is based on sex, age and, in adults, height.[36 37]

Paediatric Quality of Life Inventory

The PedsQL comprises 23 items across the four domains of physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school functioning (five items).[31 32] The questionnaire involves parallel child self-report and parent proxy-report formats, each of which uses developmentally appropriate language and first-person or third-person tense in age intervals 2–4, 5–7, 8–12 and 13–18 years; parents or caregivers completed the survey for children aged 2–4 years. Scores for each domain are expressed as transformed scores on a scale of 0–100, with higher scores indicating better HRQoL.

36-Item Short-Form Survey V.2

The SF-36v2 is a general health survey containing 36 items covering eight domains: general health perceptions, physical functioning, physical role functioning, emotional role functioning, social functioning, bodily pain, vitality and mental health.[33] Scores across these domains are aggregated to calculate the mental component summary and physical component summary (PCS) scores. Scores are compared with the general adult population norm (mean 50; SD 10) on each domain, based on a 2009 general US population sample.[33] Higher scores indicate better HRQoL.

Statistical analysis

This analysis used registry data collected from first patient enrollment in the Global HPP Registry in 2015 through 30 June 2023. For all outcome measures, the most recently obtained assessment was used. For patients who had been treated with asfotase alfa at any time, only data from before the treatment start date were included in the analysis. Patients or their caregivers completed the assessments of pain, disability and HRQoL during routine clinic visits per standard of care. All analyses were performed using SAS Life Science Analytics Framework V.5.4a (SAS Institute, Cary, North Carolina, USA). Data were summarized using descriptive statistics: counts and percentages for categorical variables and mean, SD, median, range and IQR for continuous variables, as appropriate. Values for the SF-36v2, PedsQL and 6MWT were compared between patients with one versus two or more *ALPL* variants by calculating differences in means and 95% CIs. Because of the skewness of the data, differences in medians and 95% CIs were calculated to compare HAQ-DI and BPI-SF pain severity and pain interference scores. Age-adjusted least squares mean values obtained from a general linear model were assessed but showed no differences from the unadjusted data; therefore, unadjusted values are reported for SF-36v2, PedsQL, BPI-SF and HAQ-DI.

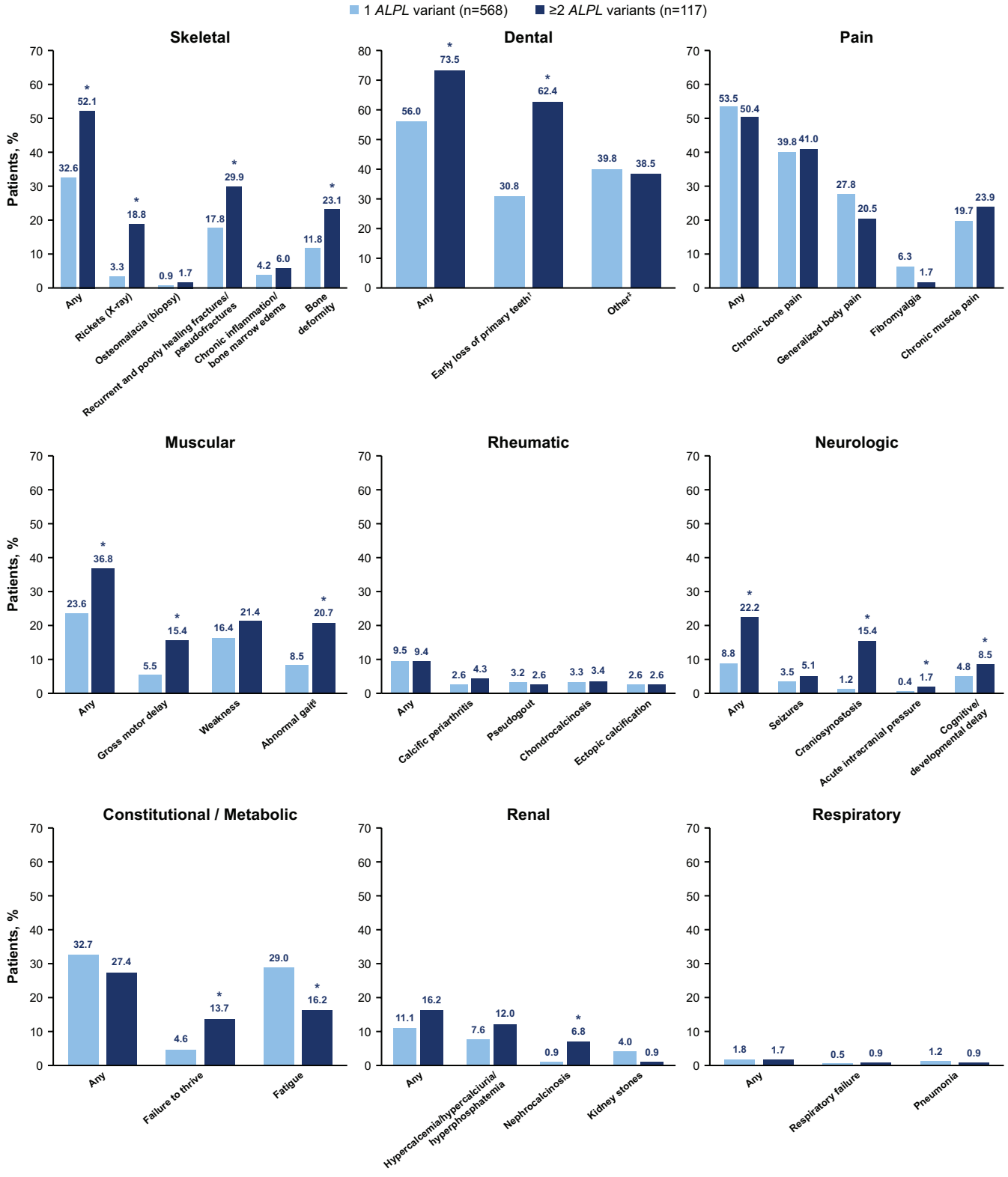

Figure 2 Reported history of baseline signs and symptoms of HPP by number of *ALPL* variants. Patients may have more than 1 sign and symptom within each category. *Prevalence ratio is statistically significant based on 95% CI of prevalence ratio not overlapping 1. †Excludes patients <6 months of age at enrolment. ‡Includes loss of permanent teeth, loose teeth, poor dentition, hypodontia, dental implants, dental bridges and dentures. §Excludes patients <2 years of age at enrolment. HPP, hypophosphatasia.

RESULTS

Patient characteristics

As of 30 June 2023, 1318 patients were enrolled in the Global HPP Registry, of whom 685 met the inclusion criteria for this analysis (figure 1). A total of 568 patients (82.9%) had one *ALPL* variant, 116 patients (16.9%) had two variants and one patient (0.01%) had three variants. Of 568 patients with one *ALPL* variant, 183 (32.2%) had a dominant-negative variant,

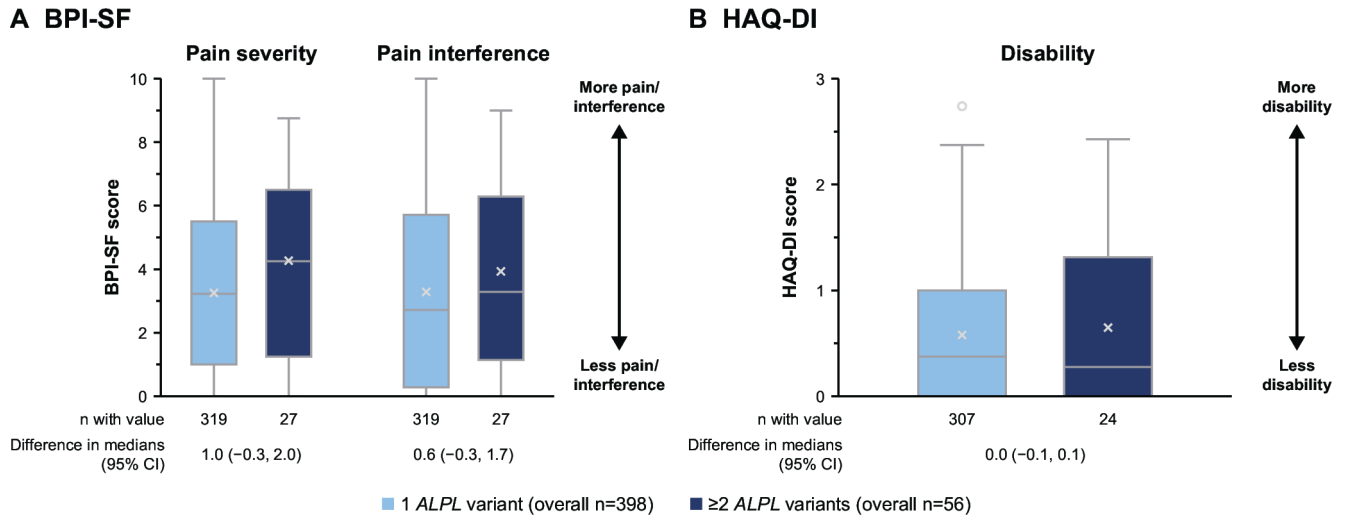

Figure 3 BPI-SF scores (A) and HAQ-DI scores (B) in adults by number of *ALPL* variants. Box plots show median and IQR with whiskers representing 95% CIs; x denotes mean value. BPI-SF, Brief Pain Inventory-Short Form; HAQ-DI, Health Assessment Questionnaire-Disability Index.

218 (38.4%) did not have a dominant-negative variant and 167 (29.4%) had a variant not yet tested for dominant-negative effects according to the *ALPL* Gene Variant Database.[20 21]

Patient demographics are shown in table 1. Patients with two or more variants versus one variant were comparable with respect to sex (female: 55.6% vs 67.1%) but differed slightly with respect to race (White: 61.5% vs 77.3%; Asian: 19.7% vs 5.8%). The median age at HPP diagnosis was 3.9 years (range: −0.5 to 75 years) among patients with two or more variants and 32.6 years (range: 0 to 75 years) among patients with one variant. Age at diagnosis may precede age at first disease manifestation through genetic screening in utero. The median age at time of last follow-up was 16.4 years among patients with two ore more variants and 39.3 years among patients with one variant, with a higher proportion of adults with one variant (age ≥18 years: 47.9% vs 70.1%). More patients with two or more variants than patients with one variant had ever received ERT (64.1% and 28.5%).

History of HPP signs and symptoms

Patients with two or more variants had a higher baseline proportion of skeletal (52.1% vs 32.6%; prevalence ratio (95% CI) 1.6 (1.4, 1.8); p<0.001), dental (73.5% vs 56.0%; 1.3 (1.2, 1.4); p<0.001), muscular (36.8% vs 23.6%; 1.5 (1.3, 1.8); p=0.004) and neurological (22.2% vs 8.8%; 2.5 (2.1, 2.9); p<0.001) manifestations versus patients with one variant. Pain (50.4% vs 53.5%; prevalence ratio (95% CI) 0.9 (0.7, 1.1); p=0.405), rheumatic (9.4% vs 9.5%; 1.0 (0.4, 1.6); p=0.927) and constitutional/metabolic (27.4% vs 32.7%; 0.82 (0.51, 1.1); p=0.201) manifestations were not significantly different between the two variant groups (figure 2). Among the constitutional/metabolic manifestations of HPP, fatigue was less prevalent among patients with two or more variants than among patients with one variant (16.2% vs 29.0%; prevalence ratio (95% CI) 0.55 (0.12, 0.98)). Among the renal symptoms of HPP, nephrocalcinosis was more prevalent among patients with two or more variants than patients with one variant (6.8% vs 0.9%; prevalence ratio (95% CI) 7.6 (6.5, 8.7)) and hypercalcaemia/hypercalciuria/hyperphosphataemia followed a similar trend (12.0% vs 7.6%; 1.6 (1.0, 2.1)).

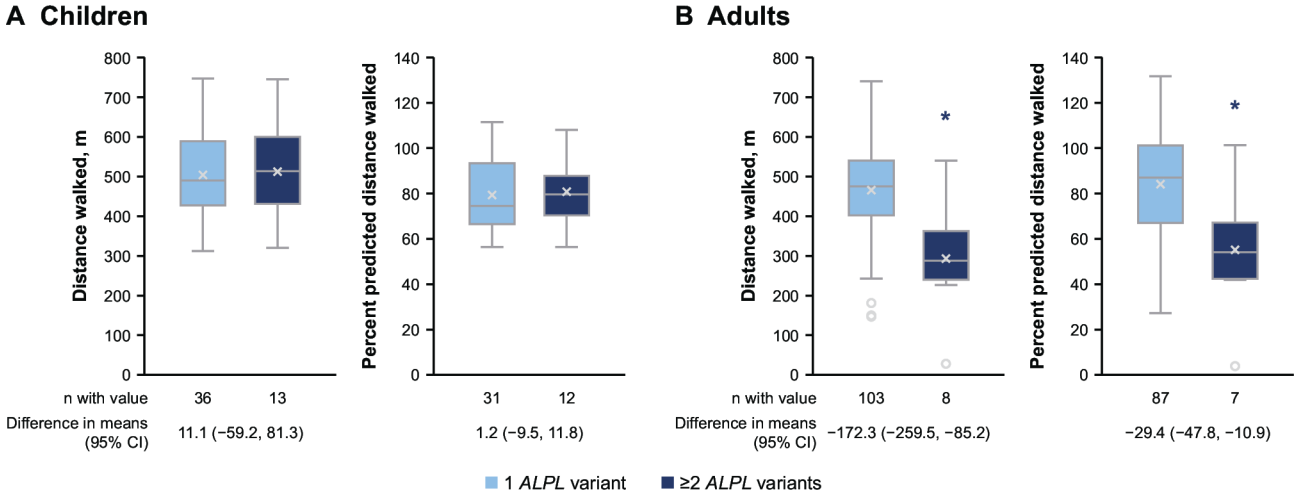

Figure 4 6MWT results in (A) children and (B) adults with disease onset >6 months of age by number of *ALPL* variants. Box plots show median and IQR with whiskers representing 95% CIs; x denotes mean value. 6MWT, 6-Min Walk Test. *p<0.005.

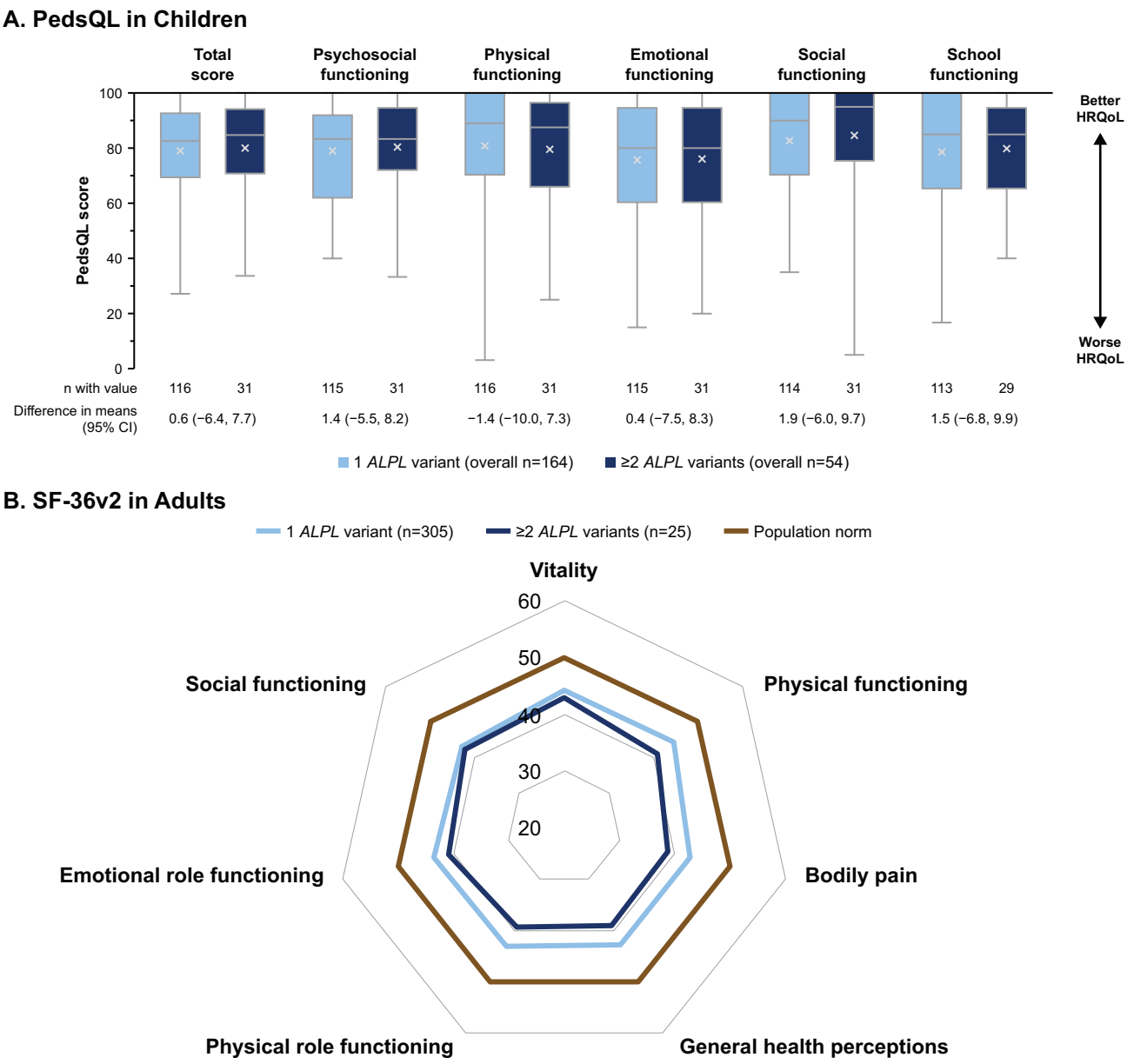

Figure 5 Quality of life in (A) children and (B) adults by number of *ALPL* variants. (A) PedsQL in children. Box plots show median and IQR with whiskers extending from minimum to maximum value; x denotes mean value. Per data from the California State Children's Insurance programme, means (parent report) in general population are 81.34 for total score, 83.26 for physical health, 80.22 for psychosocial health, 80.28 for emotional functioning, 82.15 for social functioning and 76.91 for school functioning.[32] HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory. (B) SF-36v2 in adults. Mean scores are shown. Higher scores indicate a more favourable health status; 50 is average for the general population. SF-36v2, 36-Item Short-Form Health Survey V.2.

Pain and disability

Among adults, median (IQR) BPI-SF pain severity scores were not significantly different between patients with two or more variants (n=27; 4.3 (1.3, 6.5)) and patients with one variant (n=319; 3.3 (1.0, 5.5); p=0.129) (figure 3A, online supplemental table 2). Median (IQR) BPI-SF pain interference scores also were not significantly different between patients with two or more variants (n=27; 3.3 (1.1, 6.3)) and patients with one variant (n=313; 2.7 (0.3, 5.7); p=0.257) (figure 3A, online supplemental table 2). In assessments of patient-reported disability, median (IQR) scores on the HAQ-DI were comparable between patients with two or more variants (n=24; 0.3 (0.0, 1.3)) and patients with one variant (n=307; 0.4 (0.0, 1.0); p=0.861) (figure 3B, online supplemental table 2).

Walking ability

Among children who performed the 6MWT, mean (SD) age was similar between patients with two or more variants vs one variant (10.6 (3.4) years vs 9.6 (3.1) years). Mean (SD) distances walked on the 6MWT were comparable between children with two or more variants (n=13; 514 (121) m) and children with one variant (n=36; 503 (103) m; p=0.753). Mean (SD) per cent predicted distances walked were also similar between children with two or more variants (n=12; 80.5% (14.0%)) and children with one variant (n=31; 79.3% (16.0%); p=0.824) groups (figure 4A, online supplemental table 2). Two (15.4%) children with two or more variants and one (2.8%) child with one variant used assistive devices to complete the test.

Mean (SD) ages were similar between adults with two or more variants (46.8 (11.9) years) and adults with one variant (48.7 (15.6) years) who performed the 6MWT. Among adults with two or more variants, the mean (SD) 6MWT distance walked was 293 (148) m (n=8) and the mean (SD) per cent predicted distance walked was 55.1% (29.3%; n=7). Among adults with one variant, the mean (SD) 6MWT distance walked was 466 (118) m (n=103), with substantial variation in mobility across the cohort, and the mean (SD) per cent predicted distance walked was 84.5% (23.3%; n=87) (figure 4B, online supplemental table 2). Adults with two or more variants showed significantly lower per cent predicted distance walked than adults with one variant (difference in means: −29.4 (95% CI −47.8, –10.9); p=0.002). One (12.5%) adult with two or more variants and five (4.9%) with one variant used assistive devices to complete the test.

Quality of life

Among children, mean (SD) PedsQL total scores were comparable between groups, with no apparent association with *ALPL* variant state (two or more variants (n=31): 80.1 (17.4); one variant (n=116): 79.5 (17.8); p=0.859). Patient scores on the psychosocial, physical, emotional, social and school functioning domains were also comparable between groups (figure 5A, online supplemental table 3). There was no difference in mean (SD) age between children with two or more variants (9.8 (4.4) years) and children with one variant (9.0 (3.8) years).

Among adults who completed the SF-36v2 assessment, patients with two or more variants were significantly younger (mean age (SD) 41.6 (13.5) years (n=25)) than those with one variant (49.1 (15.1) years (n=305); p=0.018). Mean SF-36v2 scores were consistently lower—indicating worse HRQoL—than the survey-defined general population mean (50)[38] in both groups. No statistically significant association between number of *ALPL* variants and SF-36v2 scores was found for any domain; however, values trended lower among adults with two or more variants than among those with one variant for the composite PCS score (p=0.055) and scores on the individual physical functioning (p=0.097) and bodily pain (p=0.084) domains (figure 5B, online supplemental table 4).

DISCUSSION

This is the first study to examine the burden of illness specifically among patients with HPP with first disease manifestation after 6 months of age. The findings of this analysis indicate a high level of disease burden in patients with HPP regardless of number of *ALPL* variants, although patients with two or more variants demonstrated higher disease burden in some respects. For example, patients with two or more variants were more likely to report skeletal, neurological, muscular and dental signs and symptoms at baseline, and adults with two or more variants had worse mobility than adults with one variant, although the sample size for the former group was very small. Measures of pain, disability and QoL were generally comparable, with some domains showing numerically more favourable outcomes for patients with one variant than for those with two or more variants.

Patients with two or more *ALPL* variants versus one *ALPL* variant were comparable with respect to sex; however, they differed with respect to age at diagnosis and race. The median age at time of diagnosis was markedly lower among patients with two or more variants than among those with one variant (3.9 vs 32.6 years), suggesting that patients with two or more variants had high disease burden at a young age that brought them to medical attention. In addition, a greater percentage of patients in the group were Asian with two or more variants, which may suggest geographic variability in HPP inheritance.[39]

A greater proportion of patients with two or more variants demonstrated HPP signs and symptoms in several body systems (skeletal, dental, muscular or neurological manifestations) compared with patients with one variant. The higher rate of dental signs and symptoms among patients with two or more variants was driven in part by a higher proportion of patients in this group reporting early loss of primary teeth compared with patients with one variant. The higher prevalence in this group may be related to the younger median age of these patients and may be subject to recall bias among older patients with one variant. Nephrocalcinosis and hypercalcaemia/hypercalciuria/hyperphosphataemia were also reported in higher proportions of patients with two or more variants; both manifestations are frequently reported in children with HPP.[5 40] Fatigue was more common among patients with one variant, potentially owing to the older median age at last follow-up of patients with one variant vs those with two or more variants (39.3 vs 16.4 years). Fewer patients with one variant had received treatment with asfotase alfa, which may have also contributed to their higher prevalence of fatigue; further investigation is needed to determine what factors underpin this finding. Finally, it is noteworthy that several signs and symptoms were still common among patients with one variant, with more than half reporting dental symptoms and pain, and about one-third reporting skeletal and constitutional/metabolic manifestations. There were no differences in respiratory signs and symptoms between the two groups, likely because of the low prevalence in both groups and exclusion of patients who first manifest symptoms of HPP before 6 months of age.

In the current analysis, reported levels of pain and disability were high in both groups, and this did not significantly differ by variant number. These findings are consistent with those of a previous study in which a substantial burden of illness was observed among adults and adolescents with HPP independent of inheritance pattern (autosomal recessive or autosomal dominant).[23] In published literature, the percentage of patients with HPP who report pain ranges from 34% to 95%,[12 40 41] supporting pain as a frequent manifestation in this population. Mean scores on the HAQ-DI in this study were higher than an estimated population HAQ-DI mean of 0.25 among adults in Finland, indicating greater disability.[42] Furthermore, in a survey of 125 patients with HPP, use of canes (25%), crutches (30%), walkers (18%) and wheelchairs (30%) as adaptive tools for improving mobility were commonly reported.[41]

The median 6MWT distance walked and median per cent predicted distance walked were significantly lower among adults with two or more variants than adults with one variant, although only eight patients with variants completed this assessment. Only mobile patients could perform the 6MWT, limiting the data interpretation to those who were ambulatory. Patient age was similar between groups. Distance walked was highly variable in both variant groups, with predicted distances walked as low as 27.3% among those with one variant and as low as 4.2% among those with two or more variants, consistent with high disease burden and disability in patients with HPP. The median distance walked, median per cent predicted distance walked and patient age did not differ by *ALPL* variant number among children with 6MWT data. A previous study reporting 6MWT results among patients with HPP enrolled in two clinical trials of asfotase alfa found a median distance walked of 401 m among adults and 491 m among adolescents at baseline.[34] These reported distances are similar to distances walked in the present

study and are within the lower range of 6MWT values found in healthy individuals (400–700 m).[43]

Among adults, mean SF-36v2 scores were similar between groups, although patients with one variant were on average older. In both groups, SF-36v2 scores were lower than the general adult population mean of 50, indicating poor HRQoL regardless of variant number.[38] In a cohort of 8836 healthy children, the mean total PedsQL score was 83.9.[32] Among children in this study in either group, scores on the PedsQL physical functioning domain fell below established score thresholds, consistent with patients meeting criteria for a moderate to major chronic condition.[44] Other published reports of QoL in patients with HPP have similarly shown scores below the general population average.[9 40] Collectively, paediatric and adult patients with HPP report poor QoL compared with healthy populations, regardless of *ALPL* variant number.

Among the limitations in this study, complete and consistent data capture was difficult because information was collected during real-world clinical practice with potential differences in standard of care across many sites globally. Patient-reported data captured by the registry were subject to recall bias. There may also have been some degree of selection bias associated with registry enrollment, in that symptomatic patients were more likely to seek medical attention and be enrolled; however, the registry also includes untreated patients and thus was likely to represent a broad spectrum of the disease. The 6MWT data reported in this study also should be interpreted with caution as data were available for a small subset of adults with two or more variants. Previous literature has described greater disease burden among heterozygotes who carry a variant that exerts a dominant-negative effect compared with heterozygotes with no dominant-negative effect.[45] Assessment of outcomes among patients with specific variants and genotype-phenotype pairs was beyond the scope of this analysis; however, further analysis of specific *ALPL* variants among patients in the Global HPP Registry is the subject of future investigation.

CONCLUSION

This is the first analysis to investigate the burden of disease among patients with HPP who have one *ALPL* variant vs those with two or more *ALPL* variants. Among patients who manifest HPP after 6 months of age, those with one variant had fewer skeletal, dental, neurological and muscular signs and symptoms compared with patients with two or more variants. However, patients with one variant still exhibited considerable signs and symptoms; more than half reported dental symptoms and pain and about one-third reported skeletal and constitutional/metabolic manifestations. Patients in both groups reported lower HRQoL and greater disability than the general population.

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Competing interests PSK, KMD, GÁM-M, AL, CRG, KO, WH and LS consult for/have received research funding/honoraria from Alexion, AstraZeneca Rare Disease. AP, WRM and SF are employees of and may own stock/options in Alexion, AstraZeneca Rare Disease. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics approval This study was approved by the Duke University Health System Institutional Review Board (approval no. Pro00059370; IRB of PSK, principal investigator) and by the institutional review board or its equivalent at all local participating study sites. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

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Data availability statement Data are available on reasonable request. Data may be obtained from a third party and are not publicly available. Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymisation or anonymisation (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://alexion.com/our-research/research-and-development. Link to Data Request Form: https://alexion.com/contact-alexion/medical-information.

ORCID iD

Priya S Kishnani http://orcid.org/0000-0001-8251-909X

REFERENCES

1 Weiss MJ, Cole DE, Ray K, *et al*. A missense mutation in the human liver/bone/kidney alkaline phosphatase gene causing a lethal form of hypophosphatasia. *Proc Natl Acad Sci U S A* 1988;85:7666–9.
2 Villa-Suárez JM, García-Fontana C, Andújar-Vera F, *et al*. Hypophosphatasia: a unique disorder of bone mineralization. *Int J Mol Sci* 2021;22:4303.
3 Whyte MP. Hypophosphatasia - aetiology, nosology, pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol* 2016;12:233–46.
4 Salles JP. Hypophosphatasia: biological and clinical aspects, avenues for therapy. *Clin Biochem Rev* 2020;41:13–27.
5 Martos-Moreno GÁ, Rockman-Greenberg C, Ozono K, *et al*. Clinical profiles of children with hypophosphatasia prior to treatment with enzyme replacement therapy: an observational analysis from the Global HPP Registry. *Horm Res Paediatr* 2024;97:233–42.
6 Leung ECW, Mhanni AA, Reed M, *et al*. Outcome of perinatal hypophosphatasia in Manitoba Mennonites: a retrospective cohort analysis. *JIMD Rep* 2013;11:73–8.
7 Whyte MP, Rockman-Greenberg C, Ozono K, *et al*. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. *J Clin Endocrinol Metab* 2016;101:334–42.
8 Dahir KM, Seefried L, Kishnani PS, *et al*. Clinical profiles of treated and untreated adults with hypophosphatasia in the Global HPP Registry. *Orphanet J Rare Dis* 2022;17:277.
9 Dahir KM, Kishnani PS, Martos-Moreno GÁ, *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;14:1138599.
10 Högler W, Langman C, Gomes da Silva H, *et al*. Diagnostic delay is common among patients with hypophosphatasia: initial findings from a longitudinal, prospective, global registry. *BMC Musculoskelet Disord* 2019;20:80.

11 Rauf MA, Kotecha J, Moss K. Reducing diagnostic delay in hypophosphatasia: a case series of 14 patients presenting to general rheumatology. *Osteoporos Int* 2023;34:1647–52.
12 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.
13 Khan AA, Josse R, Kannu P, *et al*. Hypophosphatasia: Canadian update on diagnosis and management. *Osteoporos Int* 2019;30:1713–22.
14 Khan AA, Brandi ML, Rush ET, *et al*. Hypophosphatasia diagnosis: current state of the art and proposed diagnostic criteria for children and adults. *Osteoporos Int* 2024;35:431–8.
15 Genest F, Seefried L. Subtrochanteric and diaphyseal femoral fractures in hypophosphatasia--not atypical at all. *Osteoporos Int* 2018;29:1815–25.
16 Harper MC. Metabolic bone disease presenting as multiple recurrent metatarsal fractures: a case report. *Foot Ankle* 1989;9:207–9.
17 Iqbal U, Anwar H, Chaudhary A, *et al*. Recurrent metatarsal fractures in postmenopausal woman with low serum alkaline phosphatase: a rare diagnosis not to miss. *J Investig Med High Impact Case Rep* 2017;5:2324709617718851.
18 Schmidt T, Schmidt C, Amling M, *et al*. Prevalence of low alkaline phosphatase activity in laboratory assessment: is hypophosphatasia an underdiagnosed disease? *Orphanet J Rare Dis* 2021;16:452.
19 Whyte MP, May JD, McAlister WH, *et al*. Vitamin B_6 deficiency with normal plasma levels of pyridoxal 5′-phosphate in perinatal hypophosphatasia. *Bone* 2021;150.
20 Farman MR, Rehder C, Malli T, *et al*. The Global *ALPL* gene variant classification project: Dedicated to deciphering variants. *Bone* 2024;178.
21 JKU Faculty of Medicine. The *ALPL* gene variant database [OMIM *171760]. 2023. Available: https://alplmutationdatabase.jku.at/ [Accessed 03 Jan 2024].
22 Whyte MP, Zhang F, Wenkert D, *et al*. Hypophosphatasia: validation and expansion of the clinical nosology for children from 25 years experience with 173 pediatric patients. *Bone* 2015;75:229–39.
23 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;133:113–21.
24 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;35:2171–8.
25 Sperelakis-Beedham B, Taillandier A, Domingues C, *et al*. Utility of genetic testing for prenatal presentations of hypophosphatasia. *Mol Genet Metab* 2021;132:198–203.
26 Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24.
27 Kishnani PS, Martos-Moreno GÁ, 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.
28 Cleeland CS. The brief pain inventory user guide. Houston, TX The University of Texas M. D. Anderson Cancer Center; 2009.
29 Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap* 1994;23:129–38.
30 National Institute of Environmental Health Sciences. Instructions for the health assessment questionnaire. 2024. Available: www.niehs.nih.gov/sites/default/files/research/resources/assets/docs/haq_instructions_508.pdf [Accessed 04 Mar 2024].
31 Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001;39:800–12.
32 Varni JW, Burwinkle TM, Seid M, *et al*. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003;3:329–41.
33 Maruish ME. User's Manual for the SF-36v2 Health Survey 3rd Ed. Lincoln, RI: QualityMetric, Inc, 2011.
34 Phillips D, Tomazos IC, Moseley S, *et al*. Reliability and validity of the 6-Minute Walk Test in hypophosphatasia. *JBMR Plus* 2019;3:e10131.
35 American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
36 Geiger R, Strasak A, Treml B, *et al*. Six-minute walk test in children and adolescents. *J Pediatr* 2007;150:395–9.
37 Chetta A, Zanini A, Pisi G, *et al*. Reference values for the 6-min walk test in healthy subjects 20-50 years old. *Respir Med* 2006;100:1573–8.
38 Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)* 2000;25:3130–9.
39 Kishnani PS, Seefried L, Dahir KM, *et al*. New insights into the landscape of *ALPL* gene variants in patients with hypophosphatasia from the Global HPP Registry. *Am J Med Genet A* 2024;194:e63781.
40 Rush ET, Moseley S, 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.
41 Weber TJ, Sawyer EK, Moseley S, *et al*. Burden of disease in adult patients with hypophosphatasia: results from two patient-reported surveys. *Metab Clin Exp* 2016;65:1522–30.
42 Krishnan E, Sokka T, Häkkinen A, *et al*. Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. *Arthritis Rheum* 2004;50:953–60.
43 Enright PL. The six-minute walk test. *Respir Care* 2003;48:783–5.
44 Huang I-C, Thompson LA, Chi Y-Y, *et al*. The linkage between pediatric quality of life and health conditions: establishing clinically meaningful cutoff scores for the PedsQL. *Value Health* 2009;12:773–81.
45 Mornet E, Taillandier A, Domingues C, *et al*. Hypophosphatasia: a genetic-based nosology and new insights in genotype-phenotype correlation. *Eur J Hum Genet* 2021;29:289–99.