



Patient-reported experiences of XLH can guide the selection of meaningful trial endpoints and ensure a patient-centric drug development programme



Living with XLH affects nearly every aspect of life, for both patients and their families.



Adults with XLH report significant impairments on quality of life.



Pain is reported as the most burdensome symptom for adults with XLH.

# Understanding XLH's Impact: Incorporating patient perspectives to develop a comprehensive conceptual disease model (CDM) to drive patient engagement and the generation of meaningful patient experience data

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## BACKGROUND & AIMS

- X-linked hypophosphatemia (XLH) is a rare genetic disorder with a prevalence of 3.9-5 in 100,000 live births.<sup>1</sup>
- A mutation in the phosphate-regulating gene causes elevated serum levels of fibroblast growth factor 23 (FGF23), limiting renal phosphate re-absorption resulting in hypophosphatemia.<sup>1</sup>
- XLH can cause musculoskeletal, neurological, auditory, and dental complications, and can have a significant impact on quality of life.<sup>1</sup>
- A 2018 study published a conceptual model summarizing concepts reported in interviews with patients with XLH in the United States.<sup>2</sup>
- The study presented here aimed to develop an updated CDM to synthesize important concepts from the literature more broadly.

## CONCLUSIONS

- XLH affects nearly all body systems and has a significant impact on patients' quality of life.
- The draft CDM provides the foundation for a comprehensive clinical outcome assessment strategy to drive further patient-centred research.
- Subsequent qualitative research, such as concept elicitation interviews, will be conducted in the next phase of research to gain further insight into the experiences of people with XLH and refine the CDM.

## METHODS

- A targeted literature review (TLR) was conducted, prioritizing qualitative, patient experience data published since 2018.
- Due to the scarcity of recent qualitative studies, findings from gray literature, including market research insights, supplemented scientific data.
- Patient-reported signs, symptoms and impacts of XLH were extracted from the literature and synthesised in the revised CDM.

## RESULTS

- 16 articles meeting eligibility criteria were included in the data extraction (Figure 1) and informed the development of the draft XLH CDM (Figure 2).
- The model summarizes published and unpublished literature, building on findings from the 2018 CDM<sup>2</sup>.
- 29 signs and 34 symptoms were reported
  - Symptoms were often reported as progressive.
  - Chronic pain was reported as the most burdensome symptom and occurs in several areas of the body.
- XLH has widespread impacts on daily life, affecting emotional well-being, work, finances, physical functioning, relationships and sleep. The impacts of XLH also extend to the family.

Figure 1 PRISMA flow diagram for TLR

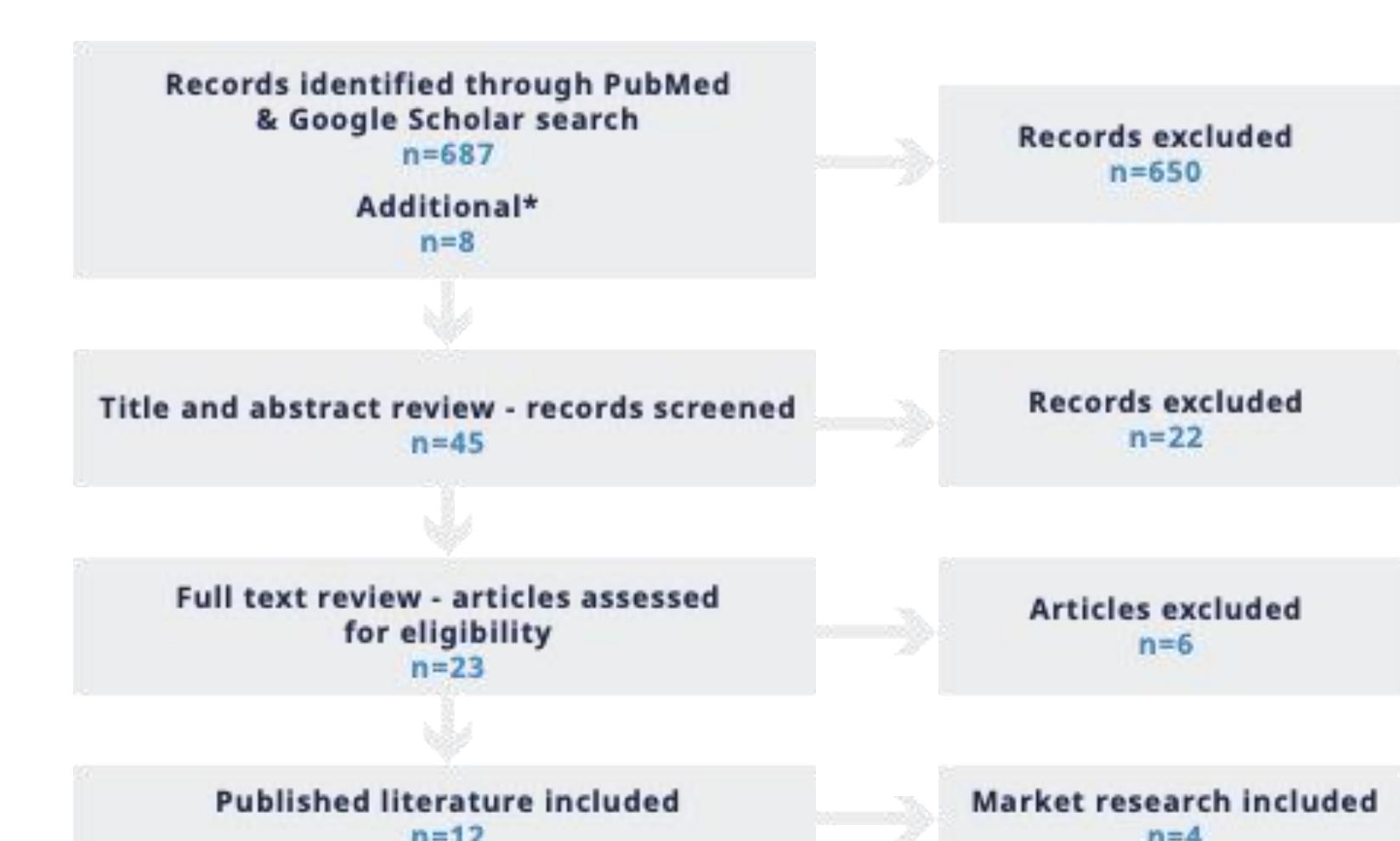


Figure 2 Draft conceptual disease model of XLH signs, symptoms and impacts in adults

MODEL KEY:

\* New concepts added by our study

† Mentioned in 3 or more studies (including model by Theodore-Okiota et al 2018)

Described as most burdensome in 13 sources

Signs

Dental

- Abscesses
- Dental necrosis \*
- Endodontic infections \*
- Malocclusion \*
- Maxillofacial cellulitis \*
- Periodontal disease \*
- Tooth loss \*
- Excessive dental cavities \*

Neurological

- Spinal cord compression \*
- Spinal stenosis †
- Chiari 1 malformation

Musculoskeletal

- Malformation of joints
- Pseudo-fractures \* /fractures \*
- Bone bowing
- Calcifications
- Craniosynostosis \*
- Enthesopathy \*
- Limb deformities
- Osteomalacia † / soft bones/bone weakness
- Osteopenia
- Osteoporosis \*
- Osteoarthritis \*
- Osteophytes/bone spurs
- Short stature †
- Skeletal deformities \*
- Bursitis

Other

- Obesity and metabolic \* dysfunction
- Renal complications \*
- Hypertension \*

### Symptoms

Multifaceted, multi-system, progressive, debilitating, and heterogeneous across individuals with XLH.

Auditory

- Hearing loss \*
- Tinnitus \*

Dental

- Poor dental health/ dental complications \*
- Difficulty swallowing

Musculoskeletal

- Poor muscle function \*
- Stiffness/difficulty bending limbs or joints † (worsens from adolescence to adulthood)
- Muscle spasms
- Swelling/inflammation
- Cramping
- Muscle fatigue
- Muscle weakness †

Sensory

- Loss of balance/vertigo
- Loss of sense of smell

Neurological

- Headaches
- Numbness
- Tingling

Physical

- Gait abnormalities \*

Fatigue

- Low energy \*
- Exhaustion \*
- Tiredness/fatigue
- Weakness

Pain

- Acute pain \*
- Bone pain †
- Chronic pain \*
- Dental/tooth pain \*
- Joint pain †
- Knee pain \*
- Muscle pain †
- Neurological/nerve pain \*
- Nociceptive pain \*
- Pain from syringomyelia \*
- Spinal pain \*

Other

- Sinus issues
- Anemia

### Impacts on patients

Most negative impact on daily lives is from chronic pain and problems with mobility. Impacts occur across lifetime and are progressive.

Medical management

- Downplaying pain leading to delays in treatment/ symptom management \*
- Self managing due to lack of clinician experience in XLH \*
- Disengagement with medical system due to inexperienced clinicians \*

Sleep

- Sleep disturbances due to pain † (e.g., waking in the night due to pain)

Use of assistive devices and adaptations

- Modified home and equipment
- Using walking aids

Emotional/Psychological

- Anxiety \*
- Anger
- Being bullied \*
- Being stared at \*
- Catastrophizing thoughts \*
- Concerns/feelings about passing on XLH \*
- Depression †
- Development of coping strategies (resilience, acceptance) \*
- Impatience
- Needing care from family members \*
- Negative impact on enjoyment of life \*
- Fear of becoming incapacitated \*
- Feeling 'different' to others \*
- Frustration † (regarding treatment, awareness, ability)
- Lack of/reduced independence \*
- Low self-confidence \*
- Low self-esteem \*
- Positive outlook
- Self-consciousness
- Reduced psychological wellbeing \*
- Self-doubt \*
- Stress \*
- Worries about being a burden \*
- Worries about the future †
- Worries about the wellbeing of affected children

Career/Financial

- Cost of care \*
- Excessive and costly dental work \*
- Early retirement \*
- Negative impacts on professional interactions from hearing difficulties \*
- Needing to give up work/work reduced hours \*
- Career options limited by mobility, pain, fatigue \*
- Limited professional activities \*

Daily activities

- Reduced ability to do shopping \*
- Reduced ability to do household chores †
- Reduced ability to look after children/doing things with children †
- Difficulty getting dressed
- Clothing
- Doing laundry
- Getting in and out of a car
- Getting in and out of the bath or shower
- Difficulty chewing
- Difficulty driving
- Gardening

Physical function

- Balance
- Difficulties walking
- Difficulty sitting
- Difficulties standing for long periods of time †
- Difficulty bending
- Difficulty arising
- Difficulty reaching things
- Difficulty gripping
- Difficulty crossing legs
- Difficulty lying down
- Getting on and off the bus
- Problems with physical exertion \*
- Problems with balance \*
- Reduced mobility †
- Reduced range of motion (e.g., in hips)
- Sport/exercise
- Slow movement
- Trouble with stairs

Relationship/Social

- Difficulties in intimate relationships and family planning \*
- Sexual functioning
- Limited motivation to go out \*
- Social isolation
- Reduced ability to participate in social and athletic activities \*
- Social activities
- Lack of support

### Family Impacts

Emotional/ Psychological

- Sadness/frustration that multiple generations have XLH \*
- Moral anguish around family planning \*
- Unwanted attention from others \*

Family activities

- Impact on 'normal' family activities, e.g., holidays \*
- Children dealing with XLH challenges \*
- Impact on non-affected siblings \*

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<sup>1</sup>Laurent MR, Harvengt P, Mortier GR, et al. X-Linked Hypophosphatemia. 2012 Feb 9 [Updated 2023 Dec 14]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK83985/>

<sup>2</sup>Theodore-Okiota, C., Bonner, N., Spencer, H., Arbuckle, R., Chen, C. Y., & Skrinar, A. (2018). 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 in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 21(8), 973-983. <https://doi.org/10.1016/j.jval.2018.01.013>