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INTERNATIONAL FEDERATION OF MUSCULOSKELETAL RESEARCH SOCIETIES

XLH RESOURCE TOOLKIT

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X-Linked Hypophosphatemia: diagnosis, management and monitoring across the lifespan

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Purpose

Why XLH

XLH is a rare genetic disorder that requires specialized knowledge for early intervention and long-term management. Currently, there is a significant need for centralized, high-quality educational resources, particularly for clinicians in Low- and Middle-Income Countries (LMICs).

The XLH Resource Toolkit addresses these gaps by providing:

- **Diagnostic Support**
  - Basic knowledge and tools to support reaching an accurate XLH diagnosis
- **Clinical Management**
  - Insights into optimizing care for both children and adults

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For more information, visit ifmrs.org/xlh-hub

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01

Understanding XLH

What it is, how it affects the body, and the burden it carries across a lifetime

What is X-linked hypophosphatemia?

In plain language

XLH is an inherited condition in which the kidneys let too much phosphate escape into the urine.

Phosphate is a mineral that bones and teeth need to harden. Without enough of it, children's bones bend and grow poorly (rickets) and adults' bones stay soft (osteomalacia) — leading to pain, deformity, fractures, stiffness and tooth abscesses.

XLH is present from birth and lifelong. It is not caused by diet or lack of sunlight, and ordinary vitamin D does not correct it.

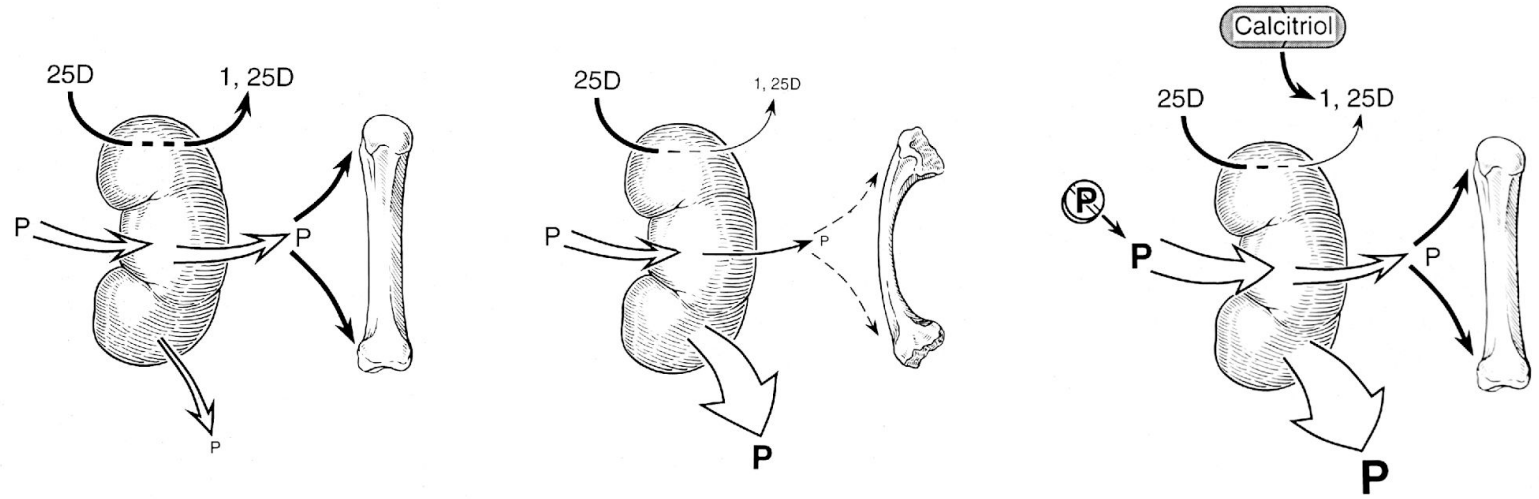
Clinical definition

- **Most common inheritable cause of rickets** — historically called X-linked hypophosphatemic rickets or vitamin D–resistant rickets
- **Cause:** inactivating variants in the PHEX gene → excess FGF23 → renal phosphate wasting, low $1,25(OH)_2D$ and reduced gut phosphate absorption
- **Inheritance:** X-linked dominant — an affected father passes XLH to all daughters and no sons; an affected mother to 50% of children
- **About one-third** of patients have no known family history (de novo variants)
- **Suspected** when serum phosphate is low because phosphate leaks into the urine

A lifelong, multisystem disorder — not just a childhood bone disease

Source: Carpenter TO. "The New XLH International Guidelines: Sharing patients' and experts' perspectives" – IFMRS Workshop. Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

How XLH disrupts phosphate balance



Healthy

Kidney retains phosphate (P); adequate P reaches bone; inactive vitamin D (25D) is converted to active 1,25D — bones are strong and resist deformity.

XLH

Large amounts of P are lost in the urine; too little reaches bone, which becomes undermineralized and deformed; conversion of 25D to 1,25D is impaired.

Treatment

Oral phosphate plus calcitriol (active vitamin D) partly replace what is lost — but renal phosphate wasting continues, so doses must be given several times daily.

Source: Carpenter TO. "The New XLH International Guidelines: Sharing patients' and experts' perspectives" – IFMRS Workshop.

Manifestations across the lifespan

Children
Rickets

- Rickets — softening and bowing of growing bones
- Lower-limb deformity and disproportionate short stature
- Dental abscesses from poorly mineralized teeth
- Craniosynostosis (skull sutures close too early)

Adults
Osteomalacia

- Osteomalacia, fractures and pseudofractures
- Bone and joint pain, early osteoarthritis, stiffness
- Enthesopathies and osteophytes; spinal stenosis
- Muscle weakness and fatigue
- Dental infections and periodontal disease
- Tinnitus and hearing loss
- Hyperparathyroidism; renal disease with excess therapy

Biochemical hallmarks

- Low serum phosphate
- Reduced tubular phosphate reabsorption (TRP, TmP/GFR)
- Low or inappropriately normal $1,25(OH)_2D$
- High or inappropriately normal FGF23
- Normal or high ALP — reflects rickets/osteomalacia

Complications accumulate with age — calling for comprehensive, lifelong management

Source: Carpenter TO. "The New XLH International Guidelines: Sharing patients' and experts' perspectives" – IFMRS Workshop. Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. (Table 1)

The burden of disease in adults

75.9%
report dental abscesses
XLH Registry

71.8%
report skeletal symptoms
XLH Registry

43–47%
have a history of fracture, rising with age
n = 336

21–42%
have nephrocalcinosis
published series

34.6%
report tinnitus
XLH-DMP, n = 364

29.1%
report hearing loss
XLH-DMP, n = 364

18.4%
have spinal stenosis
XLH-DMP, n = 364

25–30%
develop tertiary hyperparathyroidism
adults with XLH

Impact on quality of life

- Health-related quality of life is lower than in the general population — the physical component most consistently
- Pain, stiffness, fatigue and impaired mobility interfere with daily life and worsen with age
- Affects work, travel, physical and mental health, and family and social life
- Osteoarthritis requiring hip or knee replacement as young as 30

Psychological support is an unmet need — patient organizations can help locate community resources.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

02

Diagnosis and initial assessment

Recognizing XLH, excluding its mimics, and establishing a baseline

Making the diagnosis

THE PANEL PROPOSES · non-GRADEd

1. Diagnose XLH in the presence of chronic hypophosphatemia, in the absence of other conditions that cause renal phosphate wasting
2. The diagnosis is supported by an X-linked inheritance pattern in the family
3. Where XLH is suspected without a family history, genetic testing is suggested to confirm a disease-causing *PHEX* variant
4. If DNA testing is negative or finds a variant of uncertain significance (VUS), the diagnosis relies on clinical and biochemical findings

Key facts

- A pathogenic / likely pathogenic *PHEX* variant confirms XLH but is not necessary for the diagnosis
- No variant is identified in up to 10% of patients with XLH
- About one-third have no recognized family history
- FGF23 measurement and DNA analysis help, where available
- Exclude tumor-induced osteomalacia and Fanconi syndrome (aminoaciduria, glycosuria, acidosis, LMW proteinuria)

Diagnosis integrates clinical evaluation, renal phosphate wasting and skeletal imaging

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Typical biochemistry in XLH

Parameter	Typical result in XLH	Comment
Serum phosphate (fasting)	↓ Low	The key laboratory finding
Serum calcium	Normal	
PTH	Normal or ↑	Rises further with high-dose phosphate therapy
25(OH)D	Normal or ↓	
1,25(OH)$_2$D	↓ or inappropriately normal	
FGF23	↑ or inappropriately normal	Helpful, but not necessary to establish the diagnosis
ALP / bone-specific ALP	↑ or normal	Biochemical marker of rickets and osteomalacia
Urine calcium / creatinine	Normal or ↓	
TmP/GFR	↓ Low	Confirms renal phosphate wasting

Measuring TmP/GFR

- Use a fasting second-void or 2-hour morning urine
- Measure phosphate and creatinine in serum and urine at the same time
- A low value indicates renal phosphate wasting
- Interpret results against age-specific reference ranges

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. Carpenter TO. "The New XLH International Guidelines: Sharing patients' and experts' perspectives" – IFMRS Workshop.

DIAGNOSIS · DIFFERENTIAL

Other causes of hypophosphatemia to exclude

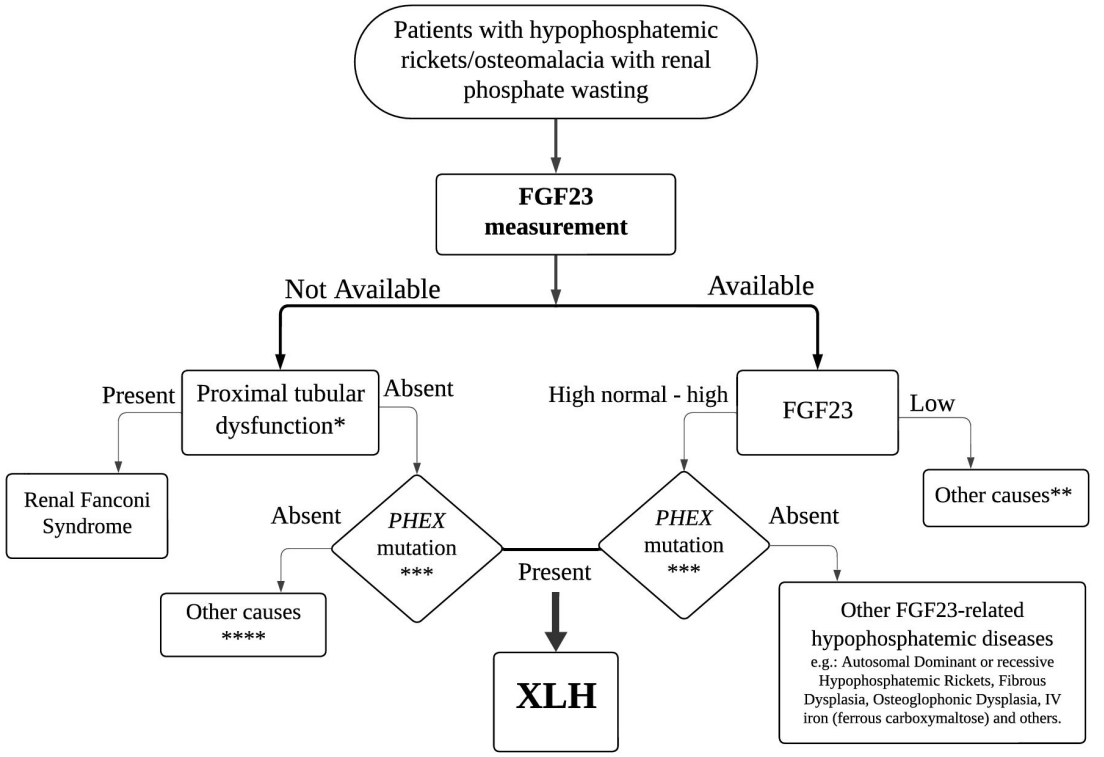
FGF23-dependent	
X-linked hypophosphatemia (XLH)	*PHEX*
Autosomal-dominant hypophosphatemic rickets	*FGF23*
Autosomal-recessive hypophosphatemic rickets	*DMP1, ENPP1, FAM20C*
Hypophosphatemic rickets with hyperparathyroidism	*KLOTHO*
Osteoglophonic dysplasia	*FGFR1*
Opsismodysplasia	*INPPL1*
Cutaneous skeletal hypophosphatemia syndrome	*RAS*
Fibrous dysplasia	*GNAS*
Tumor-induced osteomalacia	Acquired
Autoimmune Osteomalacia (AIO)	Acquired
IV iron (especially ferric carboxymaltose)	Acquired

FGF23-independent	
Hereditary hypophosphatemic rickets with hypercalciuria	*SLC34A3*
Hypophosphatemia and nephrocalcinosis	*SLC34A1*
Dent disease (X-linked recessive)	*CLCN5*
Nephropathic cystinosis	*CTNS*
Hypophosphatemia, nephrolithiasis, osteoporosis	*NHERF1*

Also consider: vitamin D–related disorders (CYP27B1, CYP2R1, VDR) and Fanconi syndrome. Bone histomorphometry showing peri-osteocytic “halo” lesions favors XLH over tumor-induced osteomalacia.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. (Table 2)

Diagnostic pathway for suspected XLH



*Low molecular weight proteinuria, aminoaciduria, renal glycosuria, renal tubular acidosis.
**Proximal tubular dysfunction, vitamin D deficiency, HHRH.
***It is recognized that DNA testing may not be available and it is possible that not all variants in *PHEX* can be detected.
****Other FGF23-related hypophosphatemic diseases besides XLH, HHRH and vitamin D deficiency

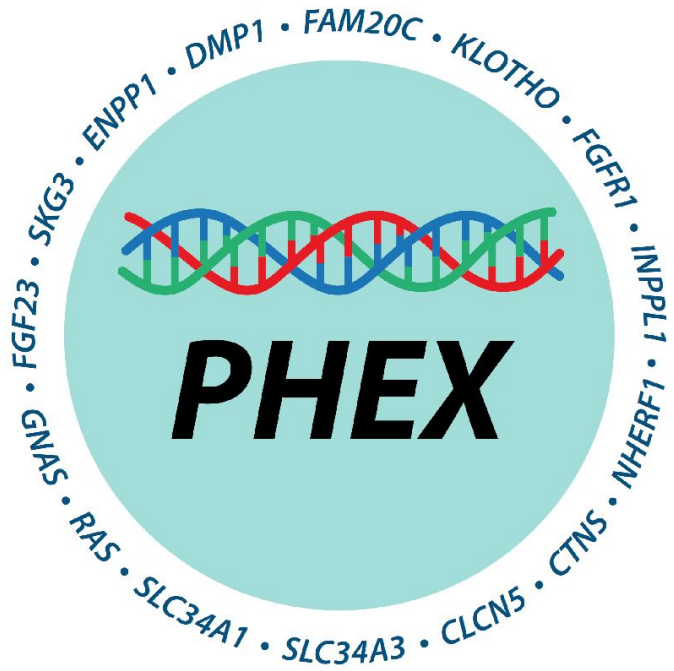
Abbreviations: FGF23: fibroblast growth factor 23; HHRH: hereditary hypophosphatemic rickets with hypercalciuria; PHEX: phosphate-regulating endopeptidase homolog, X-linked (PHEX) gene; XLH: X-Linked Hypophosphatemia
Normal range: TmP/GFR: Female 0.96 – 1.44, Male 0.9-1.35; Serum Phosphorus: 0.8 – 1.45 mmol/L

Reading the pathway

- Start from hypophosphatemia with renal phosphate wasting
- Use FGF23 (where available) to split FGF23-dependent from independent causes
- Confirm with *PHEX* testing if there is no X-linked family history
- No pathogenic variant is found in up to 10% of XLH patients
- A positive family history may be absent with a de novo variant (occurring sporadically)

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. (Figure 1)

Genetics: when PHEX testing is negative



Testing options

Any method that sequences *PHEX* can support the diagnosis — single-gene sequencing, gene panels, whole-exome or whole-genome sequencing. Next-generation panels are not yet accessible in many countries.

What conventional sequencing can miss

Pathogenic mosaicism, deep intronic variants and chromosomal rearrangements — whole-genome approaches may be needed.

Variants of uncertain significance

Classifications change as knowledge grows: consider re-interpretation later, or referral to a variant-interpretation laboratory or specialist.

When genetics is inconclusive

The diagnosis rests on clinical and biochemical findings. Bone histomorphometry (peri-osteocytic lesions) can support an “XLH-like” phenotype.

A negative genetic test does not rule out XLH

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

INITIAL ASSESSMENT · ADULTS

Baseline assessment for every adult with XLH

WE SUGGEST · weak / conditional *Weak recommendations, very low-certainty evidence (80/80/80 expert practice survey)**

1 History

Family history of XLH or X-linked dominant hypophosphatemia; fractures or pseudofractures; dental abscesses or periodontitis

2 Body measurements

Standing height, weight and BMI

3 Blood pressure

Baseline blood pressure

4 Musculoskeletal exam

Bony tenderness and range of motion

5 Laboratory tests*

Serum P, corrected Ca, ALP, 25(OH)D, creatinine/eGFR, PTH, TmP/GFR; 24-h (or spot) urine Ca & Cr; 24-h urine P & Cr

6 Genetic testing

Panel for hypophosphatemia-associated genes, including *PHEX*

7 Bone density

Baseline BMD — interpret with care (see next slide)

8 Dental assessment

Periapical X-rays or orthopantomogram for enlarged pulp chambers, pulp necrosis and periapical bone loss

*Specimens preferably morning and fasting (≥2–3 h), with serum and urine collected together or within 2 hours of each other.
*80/80/80: practice adopted when 80% of experts performed it 80% of the time in 80% or more of their patients attending an initial assessment.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. (Figure 2)

Imaging and bone density in adults

THE PANEL PROPOSES · non-GRADEd

Skeletal imaging

- **At initial assessment:** skeletal survey with plain X-rays to detect asymptomatic pseudofractures
- **If radiographs are inconclusive:** bone scintigraphy to evaluate further
- **What to look for:** pseudofractures (Looser zones) at high-stress sites; early degenerative disc disease; hip and knee joint damage; enthesopathies; spinal ligament calcification, which can cause spinal stenosis
- **Workup:** evaluate other causes of hypophosphatemia (differential diagnosis)

Interpreting DXA in XLH

Lumbar spine	Often falsely HIGH — ligamentous ossification, enthesopathy, lamina thickening, larger bone area
Hip and 1/3 radius	Tend to be LOW
Still useful	With cautious interpretation, for fracture risk — e.g. postmenopausal women and men over 50 with superimposed osteoporosis or hypogonadism

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

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03

Managing XLH in adults

Treatment, evidence, medications, complications, surgery, dental care, monitoring and pregnancy

Who to treat — and what treatment should achieve

THE PANEL PROPOSES · non-GRADEd

- **Treat when there is osteomalacia:** symptoms or biochemical/histological evidence — bone pain, stiffness, weakness, osteomalacic fractures, elevated ALP, or osteomalacia on bone biopsy
- **Before surgery:** optimize medical therapy (burosumab, or phosphate + active vitamin D if burosumab is unavailable) before orthopedic or dental-implant surgery
- **Young adults:** continue medical therapy for at least several years after growth-plate closure, to optimize peak bone mass (~20–25 years) even when asymptomatic
- **Ongoing care:** weigh the benefits and risks of therapy and the patient's capacity for ongoing monitoring
- **Asymptomatic adults:** individualize treatment based on symptoms and comorbidities

Treatment goals in adults

1. **Normalize alkaline phosphatase**
2. **Heal fractures and pseudofractures**
3. **Improve bone pain and physical function**

Normalizing fasting serum phosphate is NOT in itself a goal of active vitamin D and oral phosphate.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

ADULT MANAGEMENT · GRADED

Treatment recommendations in adults

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1

WE RECOMMEND · strong

Adults WITH fractures or pseudofractures

We recommend burosumab therapy over no therapy

Strong recommendation · moderate certainty

2

WE SUGGEST · weak / conditional

Adults WITHOUT fractures or pseudofractures

We suggest burosumab therapy over no therapy

Conditional recommendation · low certainty

3

WE SUGGEST · weak / conditional

Adults WITH fractures or pseudofractures

We suggest burosumab therapy over active vitamin D and phosphate salts

Conditional recommendation · low certainty

If burosumab is not available, symptomatic adults should be treated with active vitamin D and oral phosphate

The IWG recognizes there may be limitations to drug-therapy accessibility. Wording follows the recommendation box and Figure 5 of the guideline. The abstract phrases the conditional burosumab-vs-conventional recommendation as applying 'in the absence of fractures or pseudofractures' — worth confirming with the guideline authors before external use.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. (Figure 5)

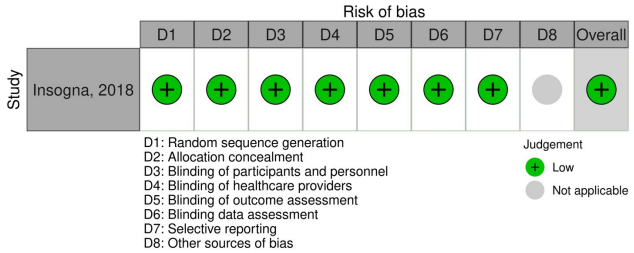
The pivotal trial: burosumab vs placebo in adults

134 adults with XLH were randomized to burosumab or placebo; outcomes were assessed at 24 weeks.

Study	Insogna 2018 — randomized, double-blind, placebo-controlled
Sites	USA, France, UK, Ireland, Italy, Japan, South Korea
Participants	68 burosumab · 66 placebo · aged 18–65
Follow-up	24 weeks (open-label extension to 48 and 96 weeks)

Inclusion
XLH confirmed by DNA or family history; serum P < 2.5 mg/dL (0.81 mmol/L); low TmP/GFR; BPI worst pain ≥ 4

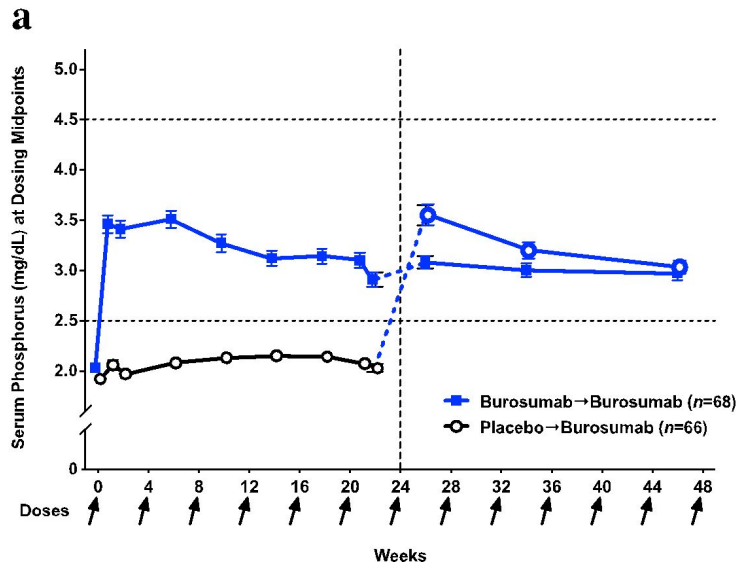
Exclusion
Corrected Ca > 10.8 mg/dL; PTH > 2.5× ULN or recent PTH-suppressing drugs; traumatic fracture or orthopedic surgery in past 6 months



Risk of bias: LOW
across all assessed domains

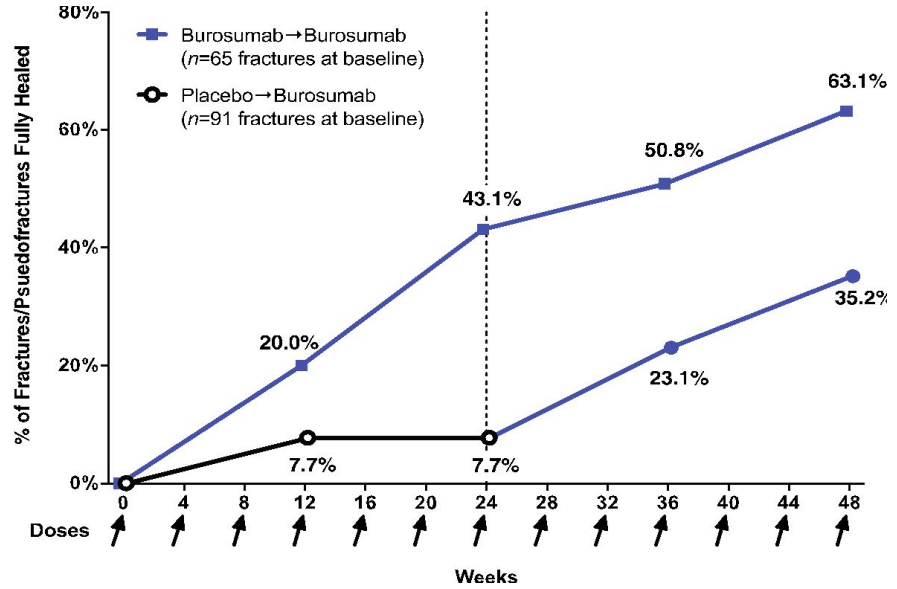
Source: Insogna KL, et al. J Bone Miner Res. 2018;33(8):1383–1393. Ali DS, et al. Systematic Review: Efficacy of Medical Therapy on Outcomes Important to Adult Patients with X-Linked Hypophosphatemia. J Clin Endocrinol Metab. 2024.

Burosumab raised phosphate and healed fractures



Serum phosphorus

Rose into the normal range on burosumab; placebo patients stayed low until crossing over to burosumab at week 24.



Fractures / pseudofractures fully healed

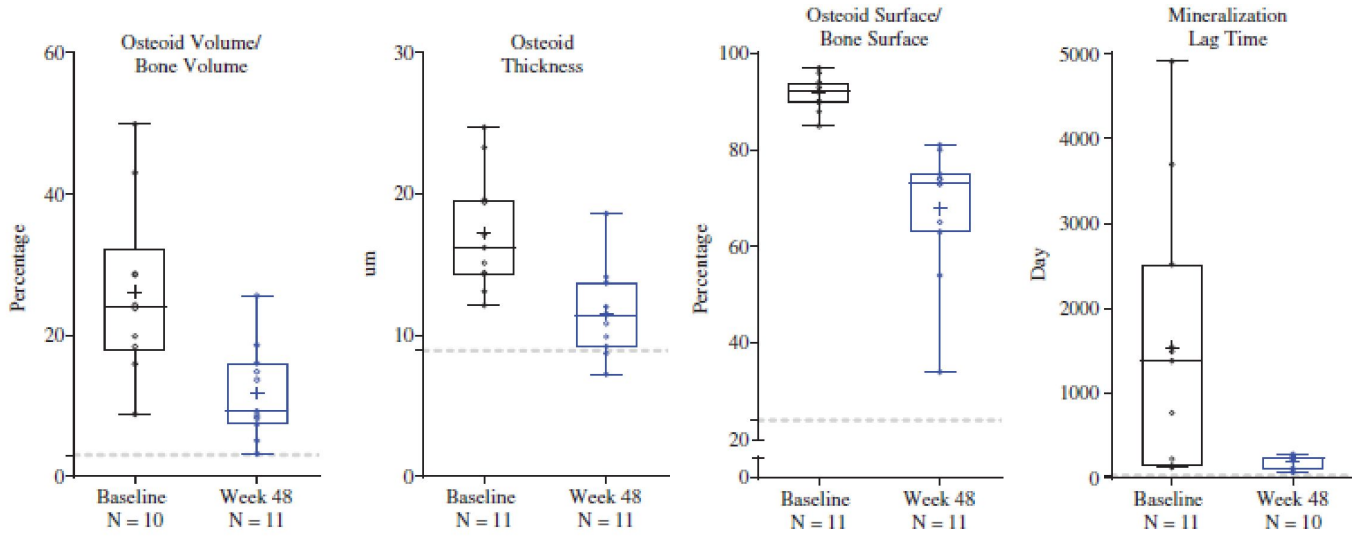
~50% of participants had fractures at baseline. Healed: 43.1% at 24 weeks (63.1% at 48) on burosumab vs 7.7% on placebo.

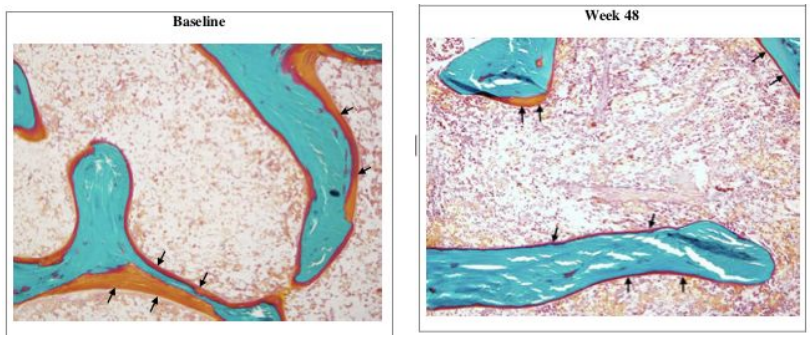
Fracture and pseudofracture healing was 16.8-fold greater with burosumab than placebo (P < .001)

Source: Insogna KL, et al. J Bone Miner Res. 2018. Portale AA, et al. Calcif Tissue Int. 2019. Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Burosumab improved osteomalacia on bone biopsy

Paired iliac-crest biopsies in 14 adults showed improved osteoid and mineralization after 48 weeks of burosumab.





Baseline **Week 48**

Osteoid (unmineralized bone, shown in red-pink) is visibly thinner after 48 weeks of treatment.

Histomorphometry improved substantially — but was not completely normalized after 1 year

Source: Insogna KL, et al. J Bone Miner Res. 2019. Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Summary of findings: burosumab vs no treatment

Outcome	No treatment	Burosumab	Difference (95% CI)	Certainty	What it means
Fracture / pseudofracture healing (radiographic)	8 per 100	43 per 100	35 more per 100 (22 to 49 more)	Moderate	Burosumab probably improves healing — and pain from fractures
Worst pain (BPI-SF, 0–10)			MD 0.46 lower (0.53 to 0.38 lower)	Moderate	Little or no effect on directly measured pain
Worst fatigue (BFI, 0–10)			MD 0.27 lower (0.36 to 0.17 lower)	High	Little or no effect on fatigue
Adverse events (restless legs, limb discomfort, cramps, headache)	8 per 100	12 per 100	—	Low	May make little or no difference
Treatment-related serious adverse events	0 per 100	0 per 100	0 fewer (3 fewer to 3 more)	Low	May not increase serious adverse events
Dental abscesses	8 per 100	13 per 100	5 more per 100 (5 fewer to 16 more)	Low	No reduction shown; dental outcomes were not a trial endpoint

Strongest benefit: fracture and pseudofracture healing. Effects on pain scores and fatigue were small.

Source: Ali DS, et al. Systematic Review: Efficacy of Medical Therapy on Outcomes Important to Adult Patients with X-Linked Hypophosphatemia. J Clin Endocrinol Metab. 2024. Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

The evidence shows:

Active vitamin D and oral phosphate raises FGF23

Prospective observational study (Imel, JCEM 2010)

- 5 patients (18–41 y) elected no treatment; 10 (7 children, 3 adults; 2–30 y) took calcitriol + phosphate
- Follow-up 14.4 ± 11.7 months (treated) vs 25 ± 32 months (untreated)
- Treatment was associated with increases in FGF23, related to phosphate dose
- Concern: conventional therapy may contribute to complications

Bone density and bone markers

6-year prospective cohort (Shanbhogue, CTI 2018)

- 27 adults (18–73 y): 11 on alfacalcidol + phosphate, 16 untreated
- Spine and hip BMD did not differ significantly
- PTH[1], FGF23[2], 1,25D[3] and P1NP[4] unchanged in both groups
- CTX[5] increased with conventional therapy (p = 0.044); trend to lower Ca, P and TmP/GFR[6]

Guideline summary Conventional therapy improves bone mineralization, is likely useful for fracture healing and for preventing and treating dental complications — but may decrease rather than eliminate abscesses and fractures. Complications include secondary/tertiary hyperparathyroidism, nephrocalcinosis and reduced kidney function. Evidence is insufficient to judge its effect on quality of life.

[1]Parathyroid hormone. [2]Fibroblast growth factor 23. [3]1,25-dihydroxyvitamin D. [4]Procollagen type 1 N-terminal propeptide. [5]C-terminal telopeptide of type 1 collagen. [6]Tubular maximum phosphate reabsorption per glomerular filtration rate.

Source: Imel EA, et al. J Clin Endocrinol Metab. 2010. Shanbhogue VV, et al. Calcif Tissue Int. 2018. Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

How to treat

THE PANEL PROPOSES · non-GRADEd

Burosumab

Anti-FGF23 monoclonal antibody

- Use the recommended starting dose: 1 mg/kg every 4 weeks (approved maximum 90 mg every 4 weeks)
- Titrate to serum P in the low–mid normal range at peak (~7 days post-dose) and just below / low-normal at trough
- Avoid hyperphosphatemia at any point in the dosing cycle
- Interpret every lab result relative to the timing of the last dose
- Contraindicated with eGFR < 30 mL/min or acute kidney injury; use cautiously with eGFR 30–60

Active vitamin D and oral phosphate

Active vitamin D ± phosphate salts

- Use when burosumab is unavailable in symptomatic adults
- Never use phosphate salts as monotherapy
- Do NOT target fasting serum phosphate — high phosphate loads drive severe hyperparathyroidism
- Adjust doses to avoid hypercalcemia and hypercalciuria
- Use ALP (total or bone-specific) as the biochemical marker of osteomalacia
- Separate calcium intake from phosphate doses by 1 hour

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Medications used to treat adults with XLH

Medication	Role	Typical adult dosing in the guideline	Label / status notes
Burosumab	Anti-FGF23 antibody; preferred therapy where available	1 mg/kg SC every 4 weeks; max 90 mg / 4 weeks	Approved for XLH. Dosing every 2 weeks or > 90 mg per 4 weeks is off-label
Phosphate salts	Replace phosphate — always with active vitamin D	750–2000 mg/day in 3–4 divided doses	Conventional therapy; GI intolerance common
Calcitriol	Active vitamin D; dampens PTH	0.5–1 µg/day (twice daily)	Conventional therapy
Alfacalcidol	Active vitamin D (alternative to calcitriol)	0.75–1.5 µg/day (once daily)	Conventional therapy
Cinacalcet	Tertiary (hypercalcemic) hyperparathyroidism	Specialist-directed; monitor serum calcium	Off-label in XLH; not recommended in pregnancy
Hydrochlorothiazide / potassium citrate	Persistent hypercalciuria	Specialist-directed	Adjunct; stop thiazides before conception

Approval, reimbursement and labelling of all agents vary by country — confirm locally. Doses are those quoted in the guideline; individualize and adjust to response and complications. Lower maintenance doses of conventional therapy may minimize long-term complications.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Recognizing and managing complications

THE PANEL PROPOSES · non-GRADEd

Tertiary hyperparathyroidism

Affects 25–30% of adults; may appear years after stopping therapy

- Off-label calcimimetic (cinacalcet) to lower PTH; monitor Ca to prevent hypocalcemia
- If uncontrolled → consider subtotal parathyroidectomy

Hypercalciuria and nephrocalcinosis

Nephrocalcinosis in 21–42%; can progress to CKD

- Reduce active vitamin D dose first
- Persistent: hydrochlorothiazide or potassium citrate
- Sodium < 1500 mg/day; fluids up to 3 L/day
- Renal ultrasound for surveillance

Kidney disease and hypertension

Linked to over-treatment, hypercalcemia, sodium phosphate salts

- Treat CKD and hypertension per regional guidelines (incl. ACEi / ARB)
- Estimate eGFR with CKD-EPI using creatinine and cystatin C
- Burosumab may lower blood pressure

Neurologic and hearing

Spinal stenosis 18%, cord compression 10%, hearing loss up to 34%

- Neurologic and fundoscopic exam if headache or neuro symptoms
- Spinal imaging and surgical referral for nerve or cord compression
- Impact of treatment on hearing is not yet known

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Orthopedic care, spine and rehabilitation

Complete fractures

- Soft, under-mineralized bone: nailing is preferable to plating
- Burosumab supports healing (35 more healed per 100 vs placebo)
- Consult a specialized orthopedic team for multi-planar deformity

Pseudofractures

- If at high risk of progressing to full fracture or deformity → start burosumab (conventional therapy if unavailable)
- Healing can be slow — 63% of active fractures healed after 48 weeks
- Refer for surgery if deformity or severe pain persists despite medical therapy

Deformity and joints

- Intramedullary rods spanning the whole bone for realignment osteotomies
- Coordinate surgery with the metabolic bone specialist; optimize medical therapy first
- Advanced joint disease may need arthroplasty — sometimes by age 30

Spine and rehabilitation

- Scoliosis: early referral to the spinal team with physiotherapy
- Surgical fixation if Cobb angle > 30°, depending on progression and curve location
- Monitor for spinal stenosis; laminectomy and fusion may be required

Coordinate every surgery between the surgical team and metabolic bone specialists

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Dental and oral care in adults

THE PANEL PROPOSES · non-GRADEd

- **Dental visits at least annually** to screen for infection, with periodontal supportive care (twice-yearly in adults) tailored to each patient
- **Active oral problems:** treat with medical therapy (active vitamin D and oral phosphate or burosumab) to reduce dental infections and periodontitis severity
- **Clinical and radiological assessment** for spontaneous pulp infection — colour change, fistula, swelling, abscess, cellulitis, pain, periapical bone loss — and periodontitis
- **Orthopantomogram**, complemented or replaced by cone-beam CT, after recent oral manifestations; repeat as needed
- **Orthodontics:** start medical therapy before treatment begins

Dental implants: timeline

1. **3–6 months**
   of medical therapy before surgery
2. **Implant surgery**
   never in the absence of medical treatment
3. **≥ 6 months**
   continue therapy after surgery; allow up to 6 months to heal

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Follow-up monitoring in adults

WE SUGGEST · weak / conditional *Weak recommendations, very low-certainty evidence (expert practice survey)*

At least once a year

- Pain assessment
- Fracture / pseudofracture history and exam for tenderness
- Weight, standing height, BMI; blood pressure
- History of dental infections
- Fasting serum P, Ca, ALP, creatinine/eGFR, PTH, 25(OH)D; spot urine P/Cr and Ca/Cr

Every 6–12 months

- Dental assessment
- Exam for skeletal deformity, osteoarthritis and joint restriction

When indicated

- Neurologic deficit → comprehensive neurologic exam
- Bone pain → skeletal survey or X-rays yearly
- Renal ultrasound annually or less often

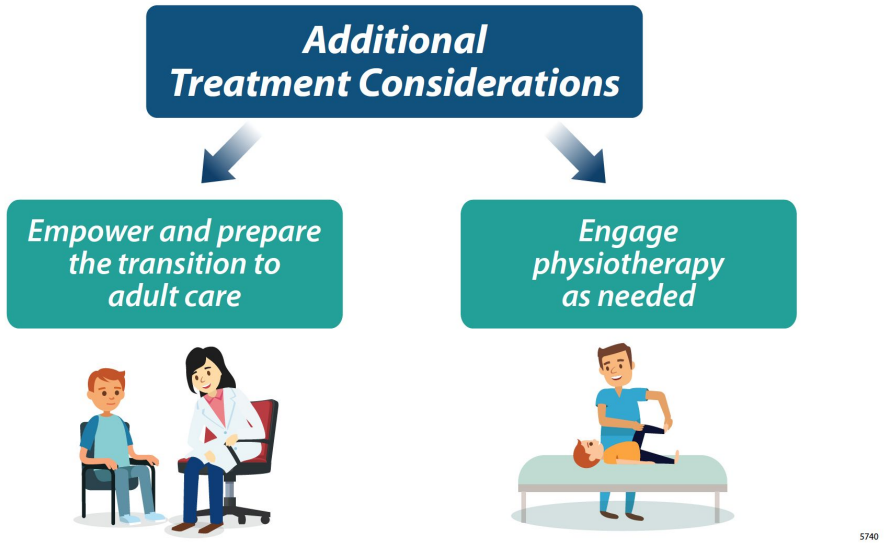
Not routinely required (discretionary): sitting-height measurement; formal quality-of-life assessment.

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. (Figure 4)

Transition from pediatric to adult care

THE PANEL PROPOSES · non-GRADEd

- **Expert, multidisciplinary care:** ongoing care by a metabolic bone disease expert who uses multidisciplinary services — with patient support groups — to address disease-related comorbidities
- **Keep treating through peak bone mass:** continue medical therapy (burosumab, or phosphate + active vitamin D) for at least several years after epiphyseal closure, as peak bone mass is reached at ~20–25 years
- **Individualize:** consider benefits and risks of treatment and the person's ability to engage with ongoing monitoring
- **Prepare early:** empower young people to manage their own care; engage physiotherapy as needed



Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Pregnancy and lactation (1): planning and monitoring

WE SUGGEST · weak / conditional

- Genetic counseling for all women of childbearing age, including adolescents, on inheritance and transmission risk
- Counsel women on burosumab or active vitamin D and oral phosphate about the limited evidence on risks and benefits in pregnancy
- Comprehensive neurologic exam if neurologic deficits are present
- Serum calcium (corrected or ionized) every trimester; creatinine/eGFR monthly if on therapy; fasting phosphate at least once
- Not routinely needed: 6-minute walk test, QoL assessment, renal ultrasound for nephrocalcinosis

THE PANEL PROPOSES · non-GRADEd

- **Preconception planning:** multidisciplinary counseling on inheritance and possible complications; a genetic counselor is useful; prenatal or preimplantation genetic testing may be options
- **Medication review before conception:** stop thiazides, ACE inhibitors and ARBs; cinacalcet not recommended in pregnancy
- **Burosumab:** safety in pregnancy and lactation is not established and it crosses the placenta — data are inadequate for a recommendation; discuss risks and benefits
- **Tertiary hyperparathyroidism:** consider surgery before conception

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

Pregnancy and lactation (2): managing therapy

THE PANEL PROPOSES · non-GRADEd

During pregnancy

- Optimize serum calcium and vitamin D before and throughout pregnancy and breastfeeding
- Ideal fasting phosphate target in pregnancy is unknown
- Phosphate in 4–5 daily doses, always with active vitamin D (calcitriol twice daily; alfacalcidol once daily)
- Lower doses may suffice as placental $1,25(OH)_2D$ rises — monitor closely
- Normalize bone-specific ALP with adequate calcium, active and native vitamin D

Monitoring

- Laboratory checks every 1–2 months: phosphate, calcium, eGFR, bone-specific ALP
- Blood pressure at every visit; treat hypertension with the obstetrician, per regional guidance
- No evidence yet that treating maternal XLH benefits the fetus

Lactation and the infant

- Monitor serum calcium closely — hypercalcemia may worsen with PTHrP rises
- Adjust active vitamin D in secondary / tertiary hyperparathyroidism
- Check phosphate in breastfed infants of affected mothers
- See babies early when there is a family history

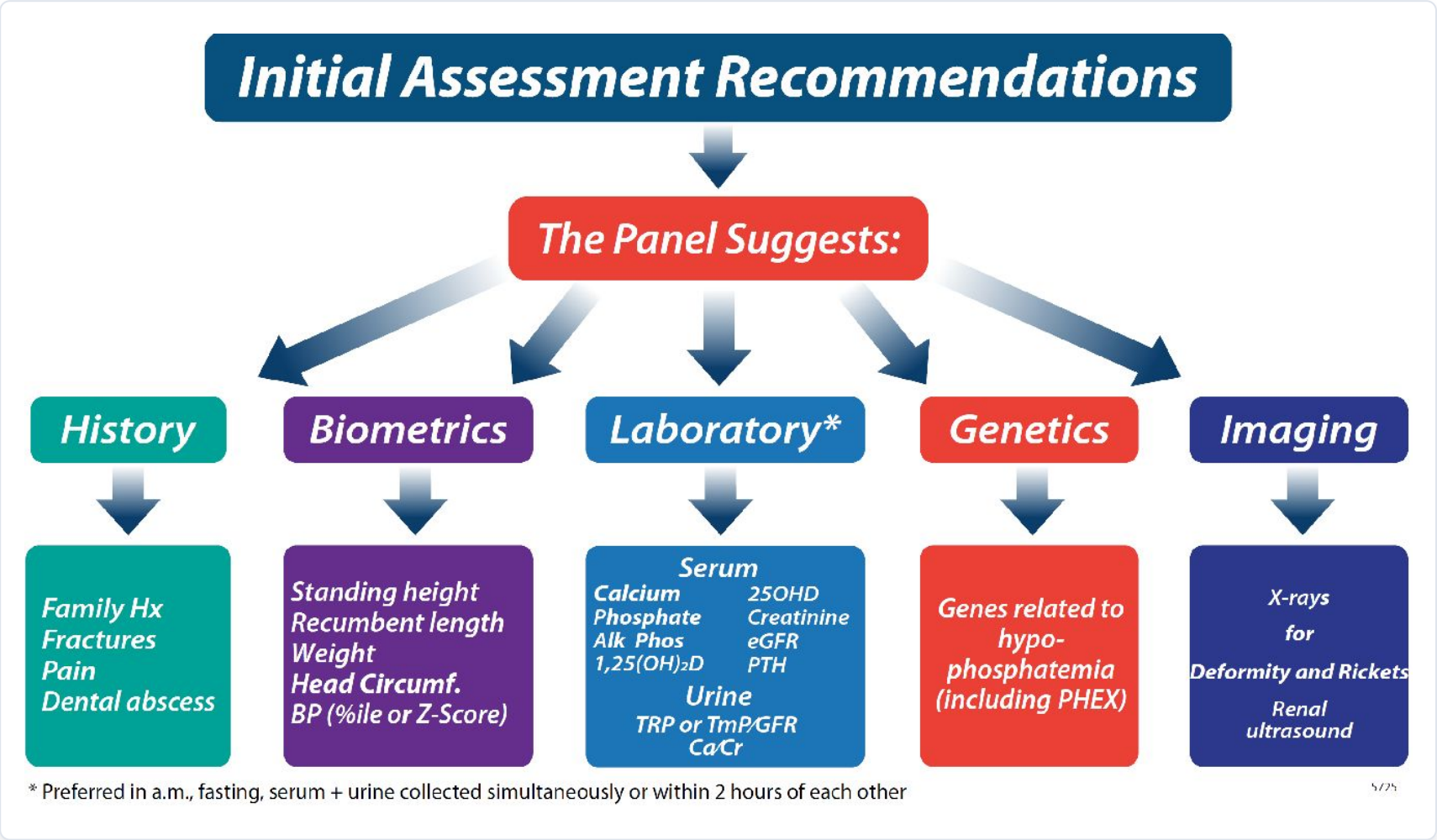
Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370.

04

Managing XLH in children

Highlights from the international pediatric guideline (Ali DS et al., JCEM 2025)

Initial assessment in children

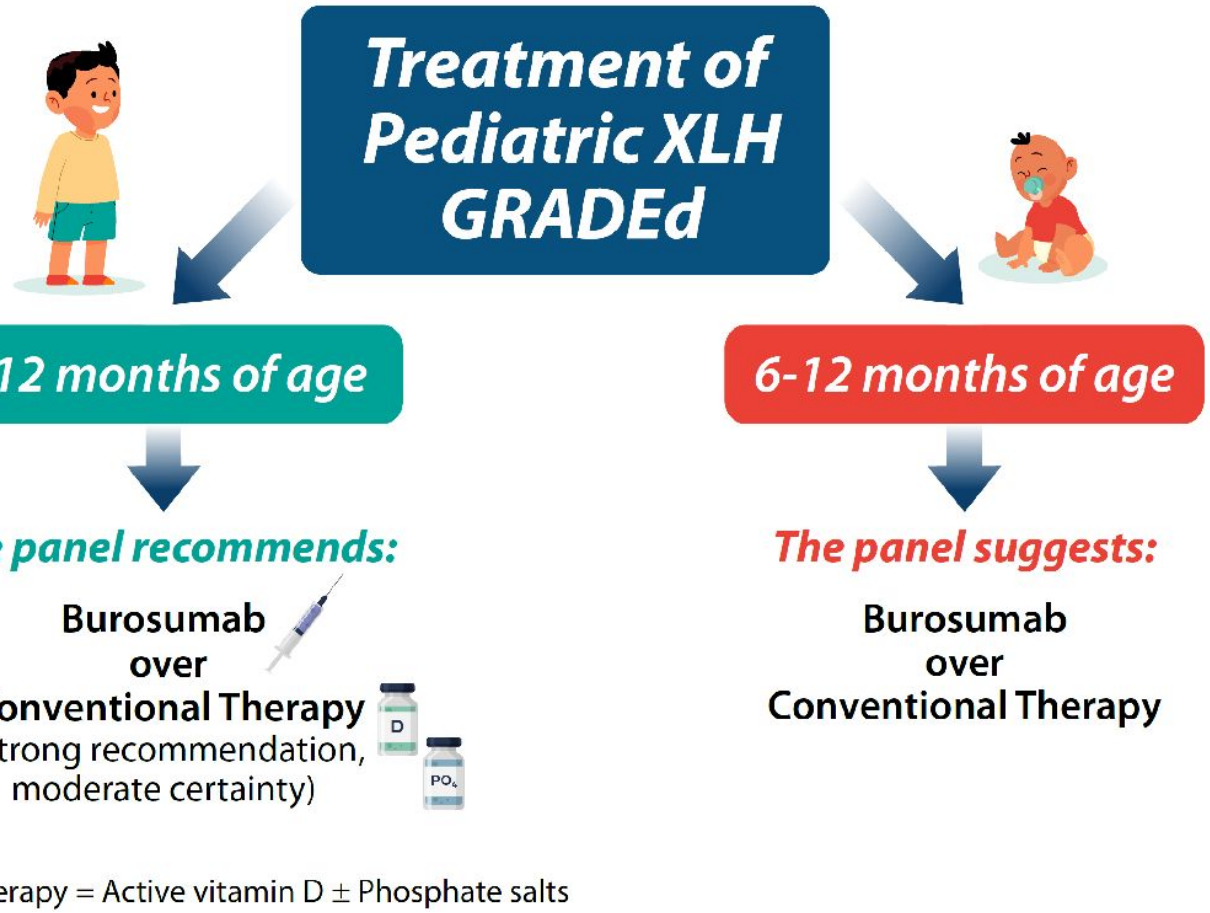


Five domains

- History — family history, fractures, pain, dental abscesses
- Biometrics — standing height / recumbent length, weight, head circumference, BP (as Z-scores)
- Laboratory — fasting serum and urine
- Genetics — hypophosphatemia gene panel incl. *PHEX*
- Imaging — X-rays for deformity and rickets; renal ultrasound

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Treatment recommendations in children

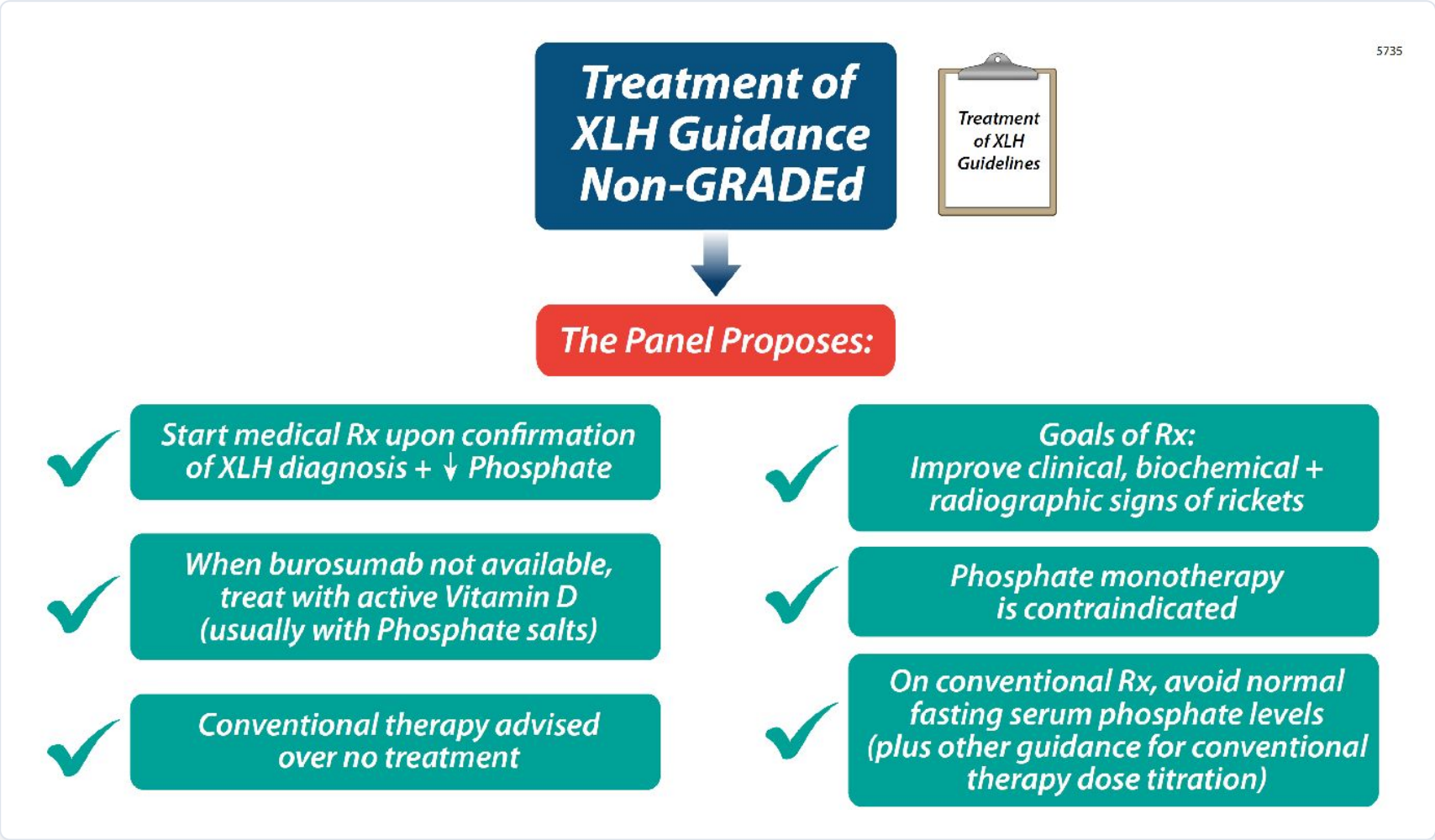


At a glance

- ≥ 12 months of age: burosumab is recommended over active vitamin D and oral phosphate (strong recommendation, moderate certainty)
- 6–12 months of age: burosumab is suggested over active vitamin D and oral phosphate

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Treatment guidance in children: starting and goals

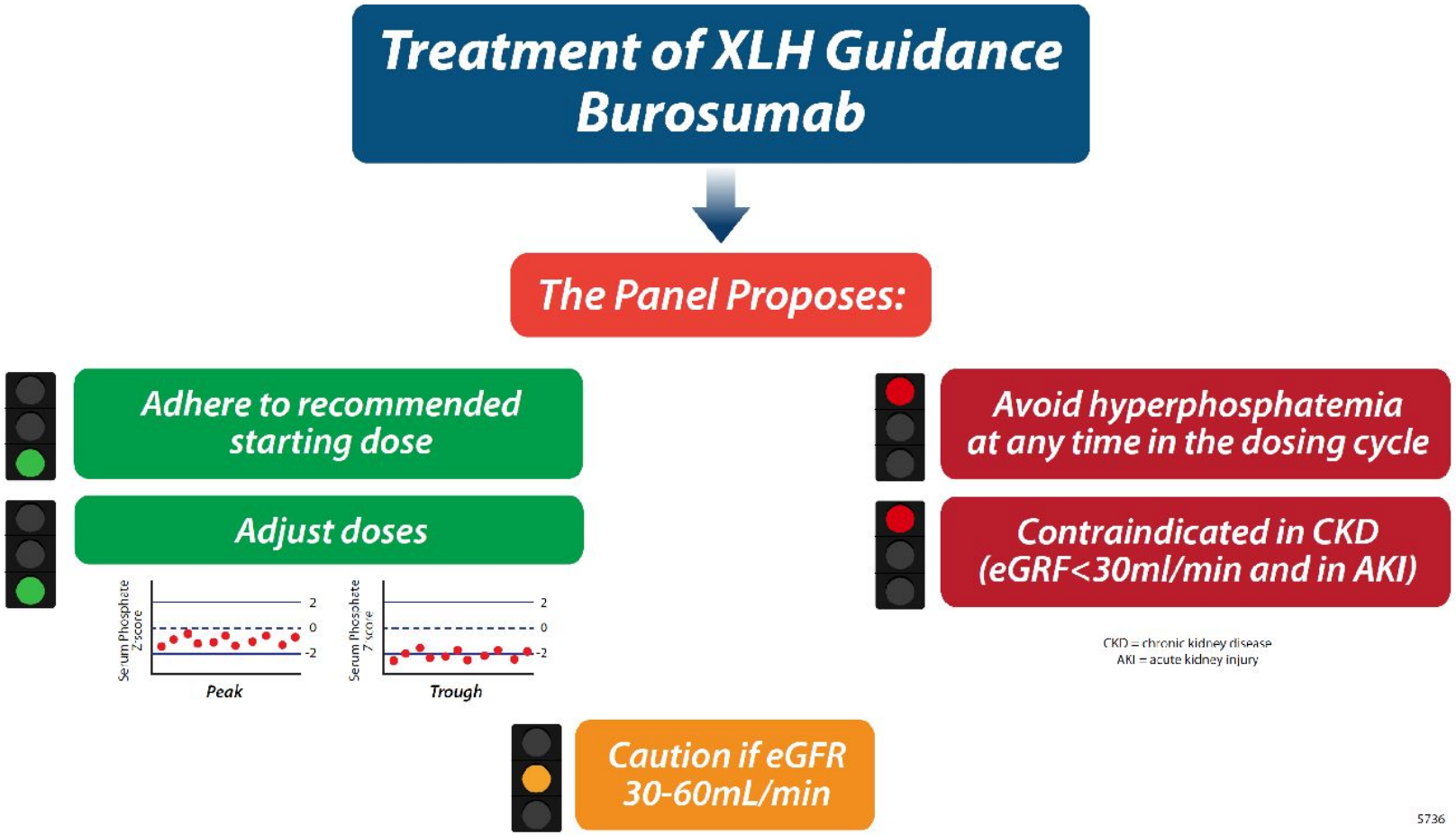


Key points

- Start treatment once XLH is confirmed and phosphate is low
- See babies early when there is a family history
- Goals: improve clinical, biochemical and radiographic signs of rickets
- If burosumab is unavailable, use active vitamin D (usually with phosphate) — preferred over no treatment
- Phosphate monotherapy is contraindicated
- Do not target normal fasting phosphate

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Treatment guidance in children: using burosumab

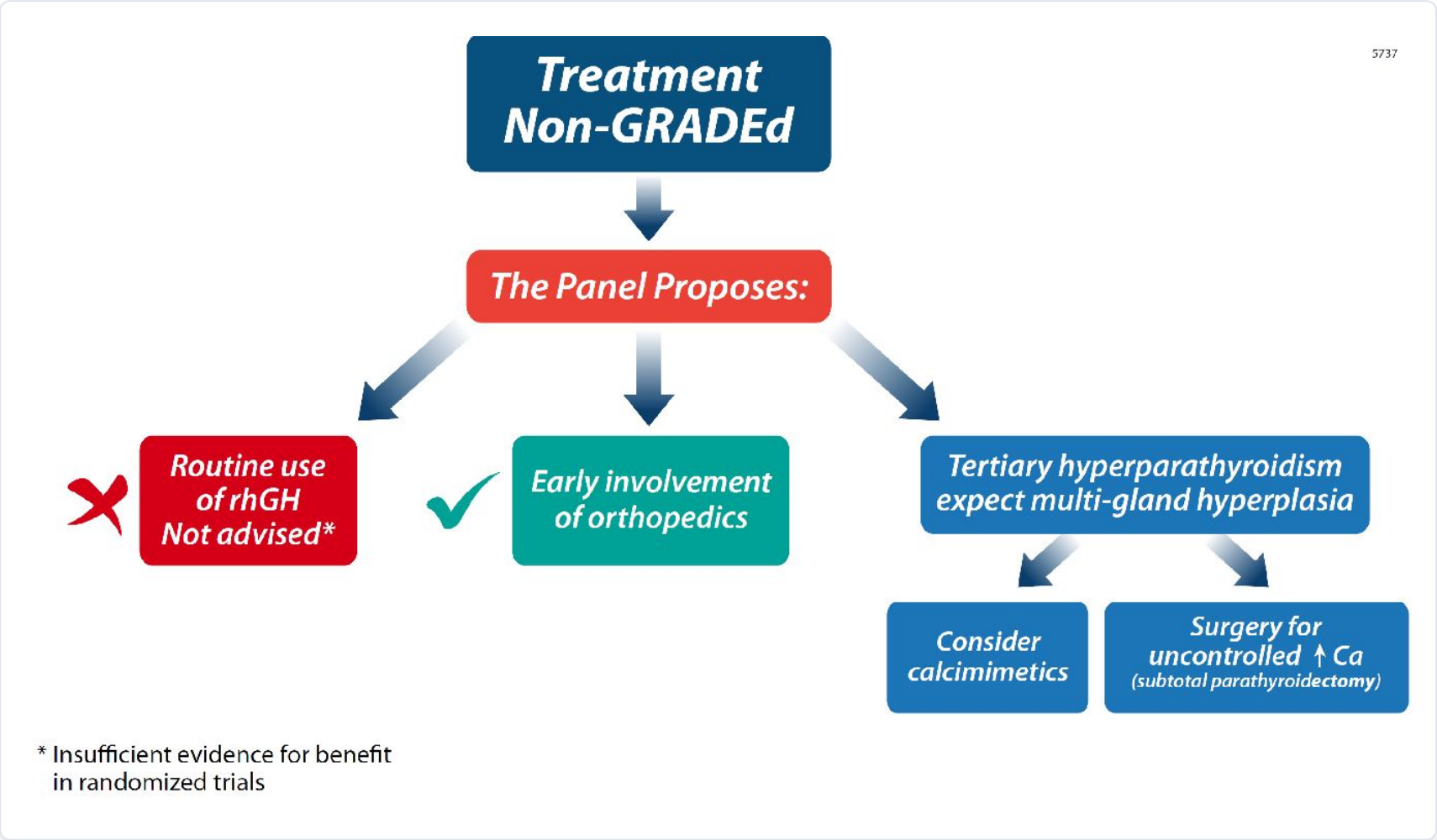


Key points

- Adhere to the recommended starting dose, then adjust
- Avoid hyperphosphatemia at any time in the dosing cycle
- Contraindicated in CKD (eGFR < 30) and acute kidney injury
- Use with caution at eGFR 30–60 mL/min

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Treatment guidance in children: other therapies



Key points

- Routine growth hormone (rhGH) is not advised — insufficient evidence of benefit in trials
- Involve orthopedics early
- Expect multi-gland disease in tertiary hyperparathyroidism: consider calcimimetics, or surgery if uncontrolled

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

CHILDREN · MONITORING

Follow-up monitoring in children

WE SUGGEST · weak / conditional *From infancy to adolescence · all weak recommendations, very low-certainty evidence*

Growth

Every 3–6 months

- Standing height (recumbent length ≤ 2 y)
- Weight, head circumference, BP
- Expressed as age/sex percentile or Z-score

Skeleton

Every 3–6 months

- Exam for deformity from 6 months: genu varum/valgum, tibial torsion, spinal curvature
- Growth velocity until adult height

Teeth

3–6 / 6–12 months

- Record dental infections or cellulitis every 3–6 months
- Dental visit every 6–12 months from age 1 (after eruption)

Laboratory

Every 3–6 months

- Serum P, Ca (corrected or ionized), ALP, creatinine, eGFR, PTH
- Spot urine Ca/Cr; morning spot urine P/Cr
- 25(OH)D at least yearly

Imaging

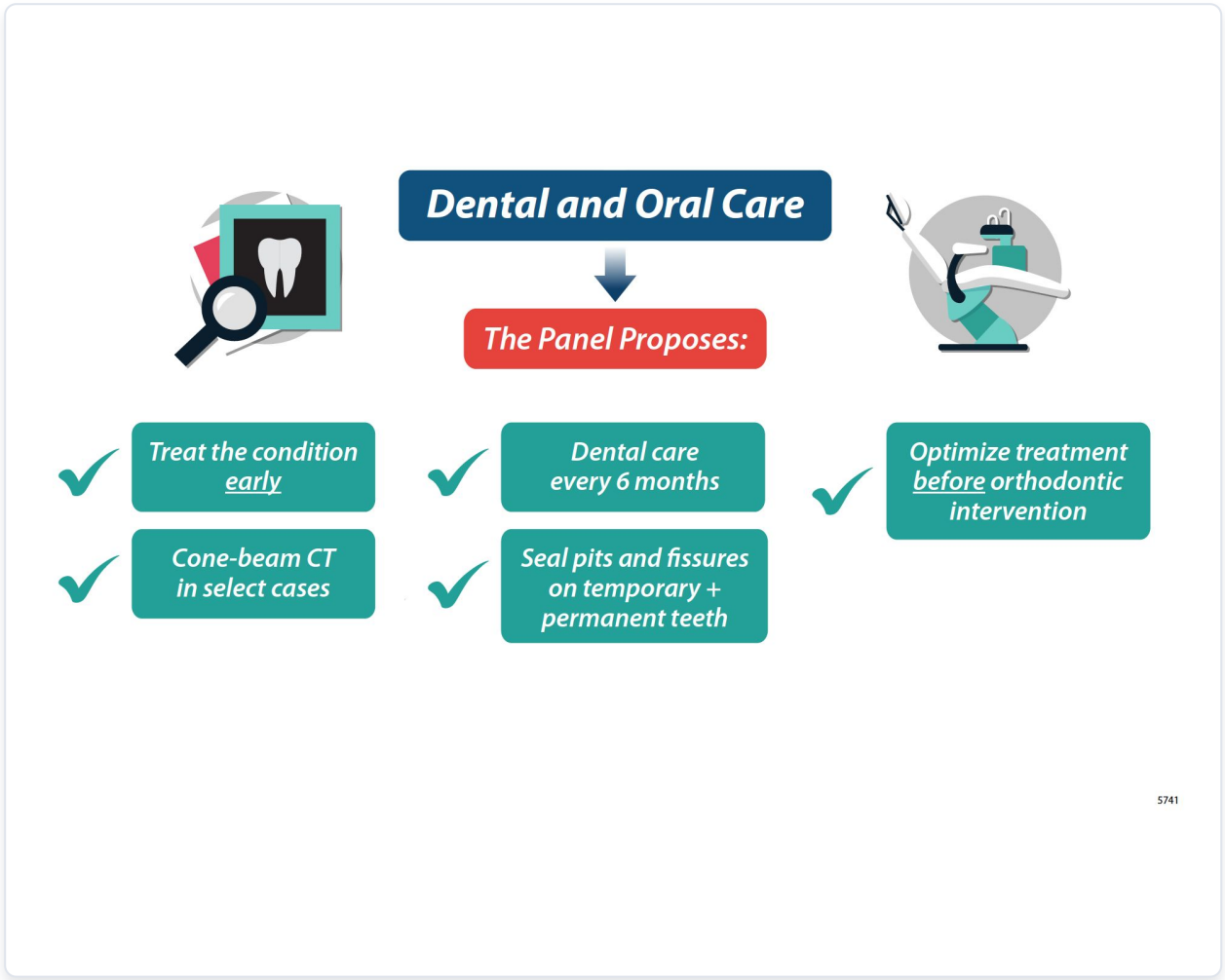
Periodic

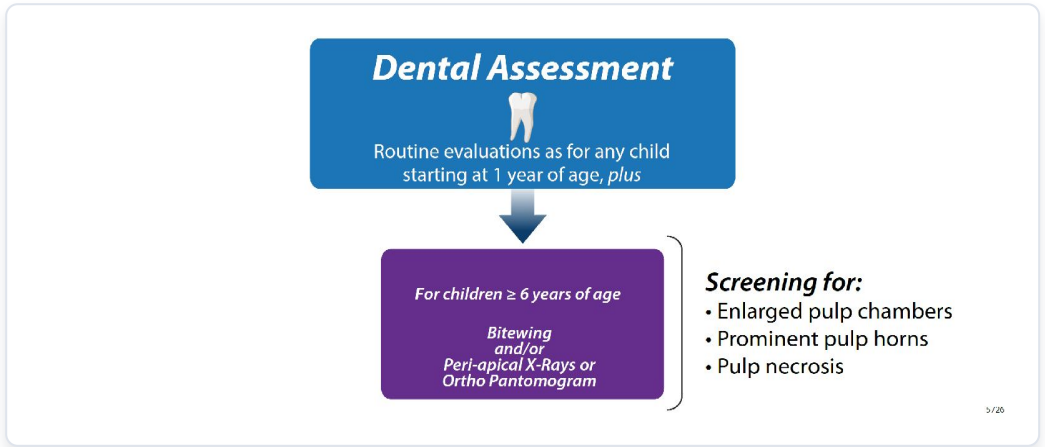
- Renal ultrasound yearly or less often
- Knee / hand-wrist X-rays for rickets
- Targeted X-rays for localized pain

Not routinely required: 6-minute walk test (unless symptomatic) · QoL assessment · fundoscopy ≤ 2 years · 24-h urine Ca/Cr · RGI-C scoring · BMD in children. Labs: morning, fasting ≥ 2–3 h, serum and urine within 2 h.

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Dental and oral care in children

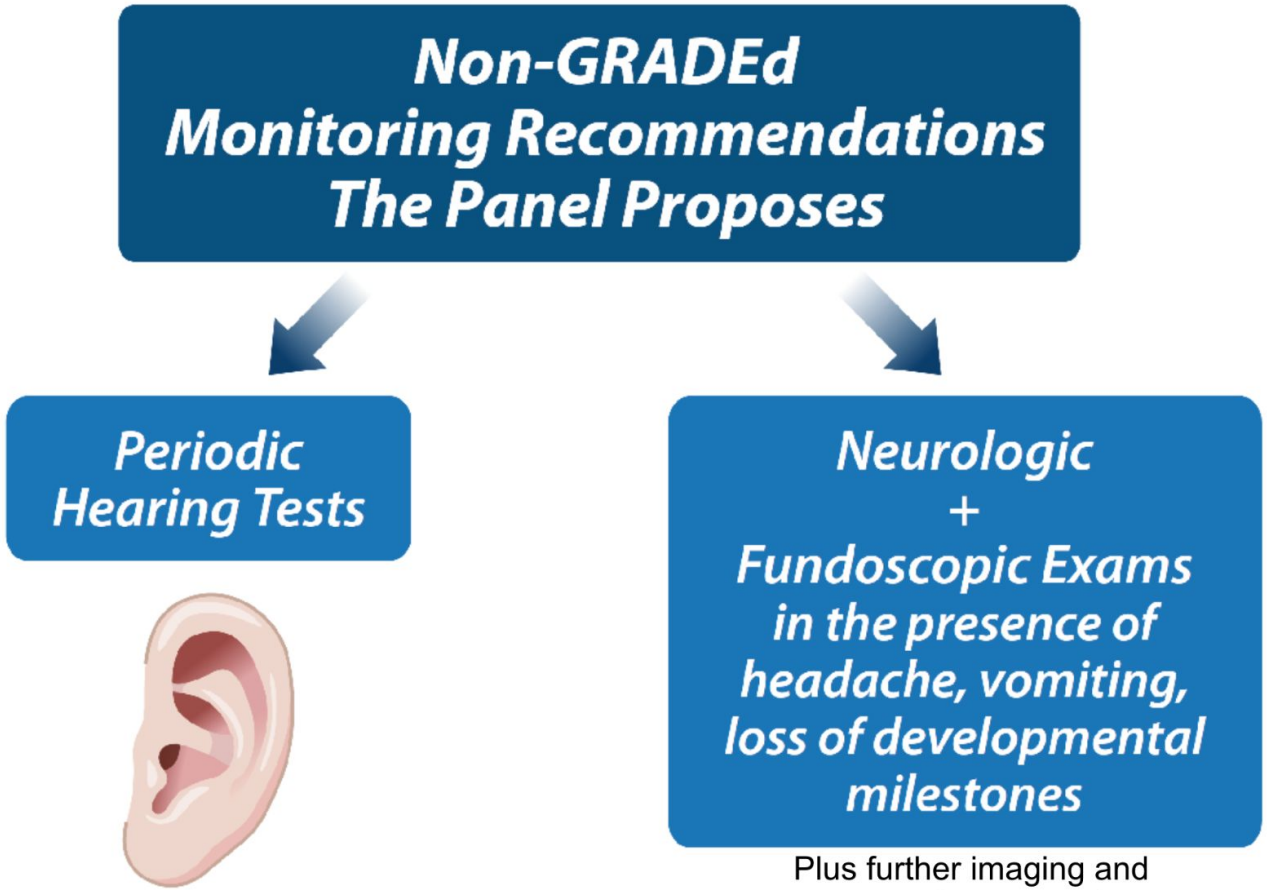




- Routine dental evaluation from age 1, plus XLH-specific screening
- From age 6: bitewing and/or periapical X-rays or orthopantomogram for enlarged pulp chambers, prominent pulp horns and pulp necrosis
- Treat early; dental care every 6 months; seal pits and fissures; optimize treatment before orthodontics

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

Hearing and neurologic monitoring in children



Key points

- Periodic hearing tests
- Neurologic and fundoscopic exams if headache, vomiting or loss of developmental milestones
- Further imaging and referral as appropriate

Source: Ali DS, Carpenter TO, Imel EA, Ward LM, et al. X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110:2055–2070. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

IFMRS
INTERNATIONAL FEDERATION OF MUSCULOSKELETAL RESEARCH SOCIETIES

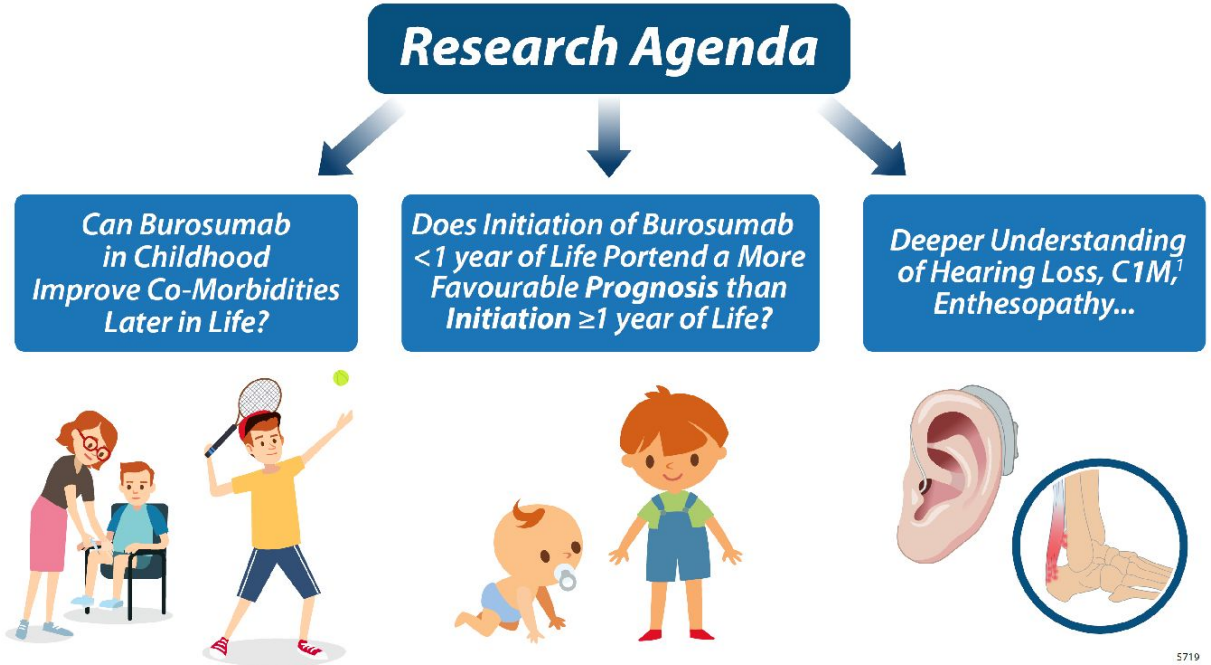
05

Research, resources and next steps

Open questions, where to find support, and what is still to be added to this toolkit

RESEARCH AGENDA

What we still need to learn



Priority gaps in adult XLH

- Which features are driven by low phosphate, and which by *PHEX* loss or excess FGF23 directly
- Whether long-term FGF23 inhibition fully normalizes bone histology
- Causes of arthritis and enthesopathy — and whether they can be prevented
- Treatment response of dental disease, hearing loss, craniosynostosis and CNS complications
- Optimal burosumab dosing intervals — symptoms often recur near the end of the 28-day cycle
- True burden: health-related quality of life, lost productivity and economic cost; functional outcomes beyond the 6-minute walk

[1]*Chiari 1 malformation (a complication of craniosynostosis)*

Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. Slide content courtesy of Leanne M. Ward, MD FRCPC FASBMR.

RESOURCES

Regional guidelines and consensus statements

UK	Padidela R, et al. Clinical guidelines for burosumab in the treatment of XLH in children and adolescents: British paediatric and adolescent bone group recommendations. Endocr Connect. 2020;9:1051–1056.
Belgium	Laurent MR, et al. Consensus recommendations for the diagnosis and management of XLH in Belgium. Front Endocrinol. 2021;12:641543.
Spain	González-Lamuño D, et al. Clinical practice recommendations for the diagnosis and treatment of XLH: a consensus based on the ADAPTE method. Med Clin (Barc). 2022;159:152.e1–e12.
International	Haffner D, et al. Rickets guidance: part II — management. Pediatr Nephrol. 2022;37:2289–2302.
Australia	Sandy JL, et al. Clinical practice guidelines for paediatric XLH in the era of burosumab. J Paediatr Child Health. 2022;58:762–768.
Europe	Mughal MZ, et al. Burosumab for XLH in children and adolescents: opinion based on early experience in seven European countries. Front Endocrinol. 2023;13:1034580.
Asia-Pacific	Munns CF, et al. Asia-Pacific consensus recommendations on XLH: diagnosis, multidisciplinary management, and transition from pediatric to adult care. JBMR Plus. 2023;7:e10744.
International	Haffner D, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2025;21:330–354.
Italy	Baroncelli GI, et al. Experts' consensus on the management and treatment of individuals with XLH across lifespan. J Endocrinol Invest. 2025;48:2199–2228.
International	Ali DS, Carpenter TO, Imel EA, Ward LM, Appelman-Dijkstra NM, Chaussain C, et al. X-linked hypophosphatemia management in children: An International Working Group clinical practice guideline. J Clin Endocrinol Metab. 2025;110(7):2055–2070. doi:10.1210/clinem/dgaf093.
International	Khan AA, Ali DS, Appelman-Dijkstra NM, Carpenter TO, Chaussain C, Imel EA, et al. X-linked hypophosphatemia management in adults: An International Working Group clinical practice guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. doi:10.1210/clinem/dgaf170.
Middle East	Seefried, L., Alzahrani, A.S., Alsaffar, H. *et al.* Expert guidance on X-linked hypophosphatemia in adults and adolescents in the Gulf region. *Orphanet J Rare Dis* (2026). https://doi.org/10.1186/s13023-026-04640-8
Japan	Hoshino Y, Ito N. Autoimmune osteomalacia: a novel FGF23-related hypophosphatemic osteomalacia. J Bone Miner Metab. 2026 Mar;44(2):269-275. doi: 10.1007/s00774-026-01697-0. Epub 2026 Feb 14. PMID: 41691126; PMCID: PMC13152884.

RESOURCES

Patient organizations and the XLH Hub

Why patient organizations matter

- Resources, education, community and peer-to-peer support for patients of all ages
- Guidance on disease management, self-care and the transition from pediatric to adult care
- Help finding specialized multidisciplinary care and navigating the healthcare system
- A route to psychological and community support — and a platform for advocacy

IFMRS XLH Information Hub

ifmrs.org/xlh-hub/



Source: Khan AA, Ali DS, Appelman-Dijkstra NM, et al. X-Linked Hypophosphatemia Management in Adults: An International Working Group Clinical Practice Guideline. J Clin Endocrinol Metab. 2025;110(8):2353–2370. IFMRS XLH Information Hub.