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CHRONIC HYPOPHOSPHATEMIA:
DIFFERENTIAL DIAGNOSIS IN CHILDREN AND ADULTS

AN INDEPENDENT HUB SESSION

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THIS PROGRAMME HAS BEEN DEVELOPED BY TWO EXPERTS

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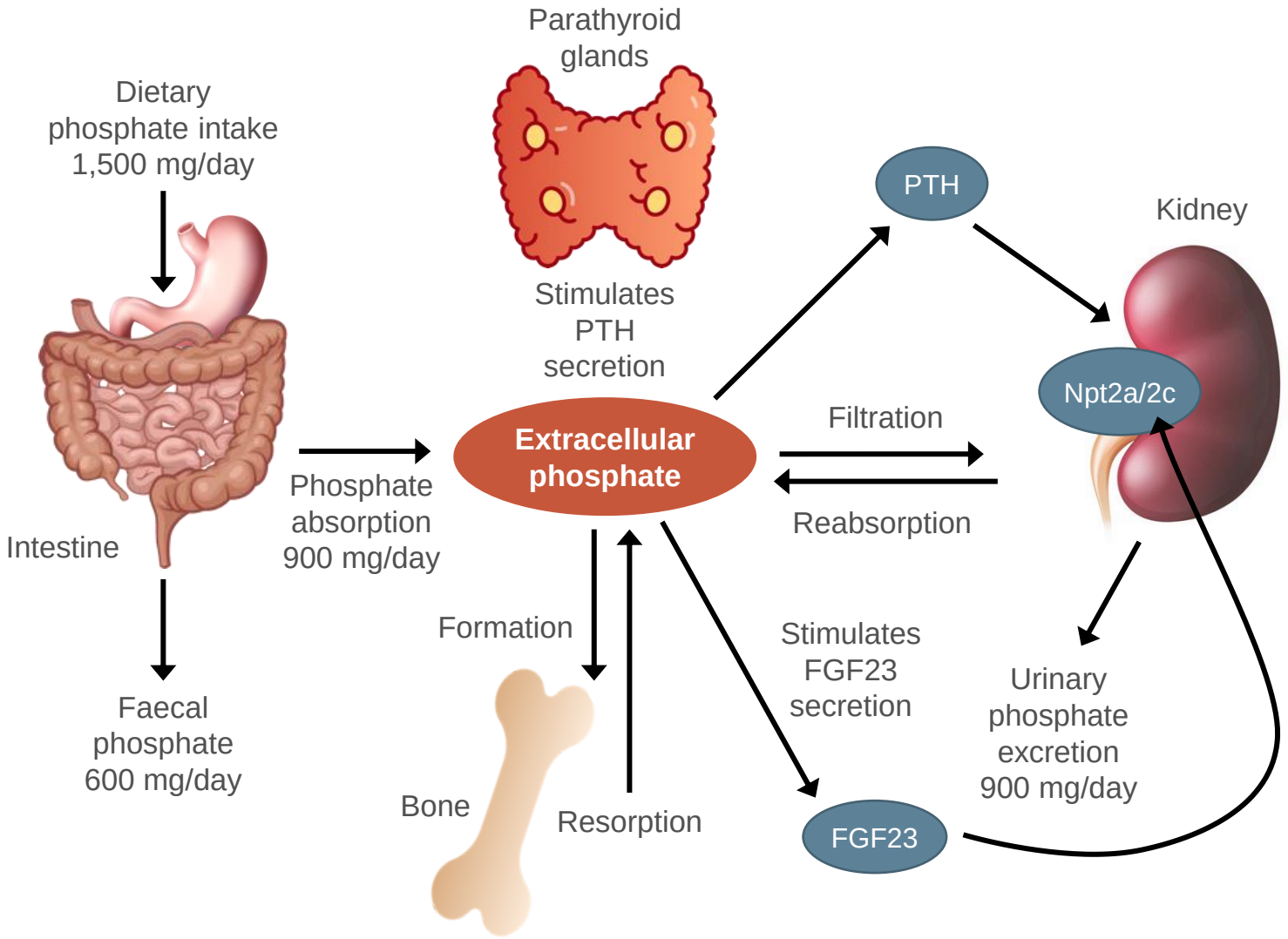
CHRONIC HYPOPHOSPHATEMIA:
DIFFERENTIAL DIAGNOSIS IN CHILDREN AND ADULTS

INTRODUCTION AND COMMON CHALLENGES

PHOSPHATE HOMEOSTASIS

KEY PLAYERS



FGF23, fibroblast growth factor 23; Npt2a/2c, sodium-dependent phosphate transport protein 2a/2c; PTH, parathyroid hormone

Adapted from: Komaba H and Fukagawa M. Kidney Int. 2016;90:753-63

HYPOPHOSPHATEMIA IN CHILDREN AND ADULTS
UNDERSTANDING THE CONDITION

What is it?

- A condition characterised **by abnormally low levels of phosphate** in the blood, resulting from **impaired phosphate regulation**, **renal dysfunction** or **genetic disorders**

- **Hypophosphatemia has broad origins:**
  - **FGF23 mediated:**
    - X-linked hypophosphatemia (XLH): Genetic disorder leading to excessive FGF23 production
    - Tumour-induced osteomalacia (TIO): Overproducing FGF23 leading to phosphate wasting
  - **Non-FGF23 mediated:**
    - Dietary: Inadequate phosphate intake or malnutrition
    - Renal tubular effects: Causing phosphate wasting
    - Soft tissue: Alkalosis leading to phosphate shifts

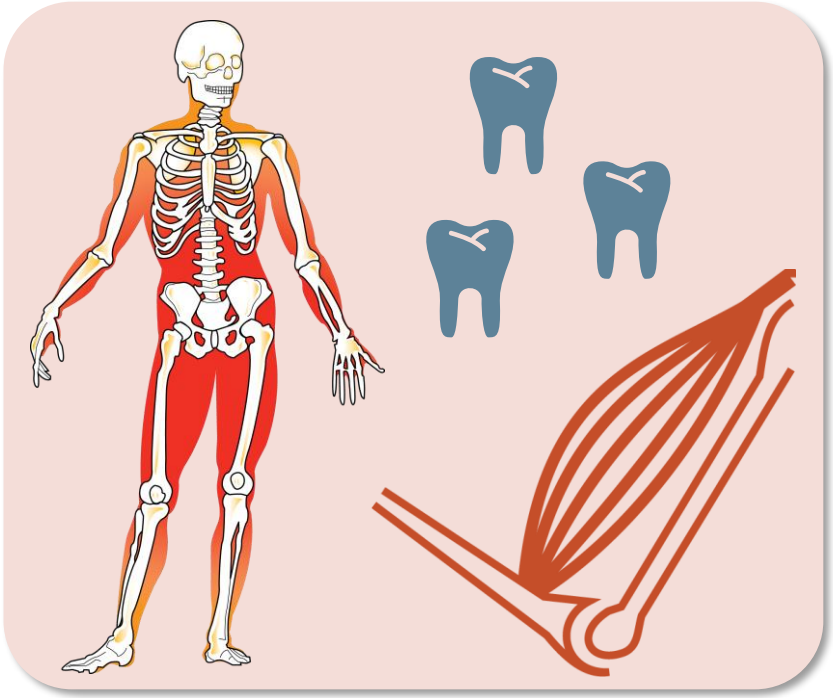
FGF23, fibroblast growth factor 23; TIO, tumour-induced osteomalacia; XLH, X-linked hypophosphatemia

HYPOPHOSPHATEMIA IN CHILDREN AND ADULTS
UNDERSTANDING THE CONDITION

What is it?

- A condition characterised **by abnormally low levels of phosphate** in the blood, resulting from **impaired phosphate regulation**, **renal dysfunction** or **genetic disorders**

- **Chronic hypophosphatemia has a negative impact on[1,2]:**
  - Bone growth and quality
  - Muscle structure and function
  - Dental mineralisation



1. Glorieux FH, et al. Orphanet J Rare Dis. 2022;17:30; 2. Larsson A, et al. Front Oral Health. 2023;4:1087761

CHRONIC HYPOPHOSPHATEMIA IN CHILDREN AND ADULTS
CHALLENGES IN DIAGNOSIS

Diagnostic challenges

- Chronic hypophosphatemia can be difficult to diagnose[1]:
  - Non-specific symptoms
  - Overlap with other metabolic disorders

Differential diagnosis is important[2]

- To ensure accurate identification of the primary aetiology and provide the best possible care for the patient

Presentation of two patient cases, including polling questions

1. Villa-Suárez JM, et al. Int J Mol Sci. 2021;22:4303; 2. Goyal R and Jialal I. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available at https://www.ncbi.nlm.nih.gov/books/NBK551586/

PATIENT CASE 1

PATIENT CASE 1

7-year-old girl

SYMPTOMS

- Slow growth, otherwise healthy
- Limping and difficulty in running
- Several dental abscesses, 10 teeth extracted

LAB

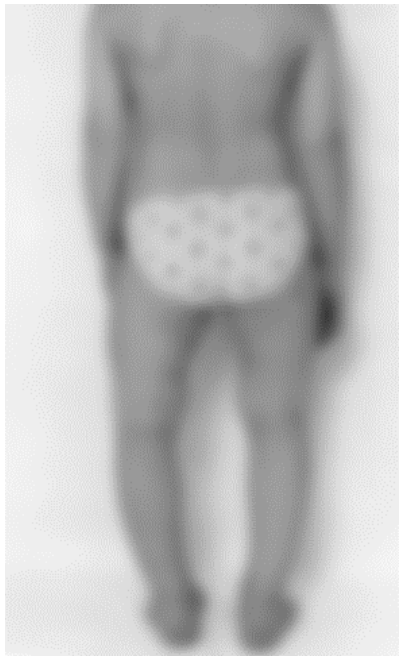
- Basic laboratory work normal, including complete blood count and Ca, 25-OHD and PTH

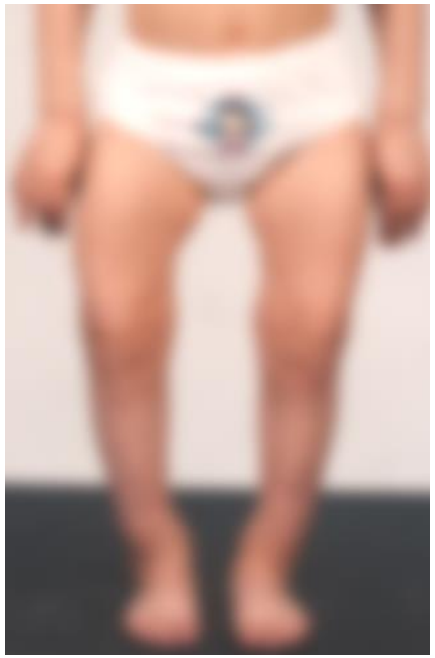
Referred to diagnostic evaluation at 7 years

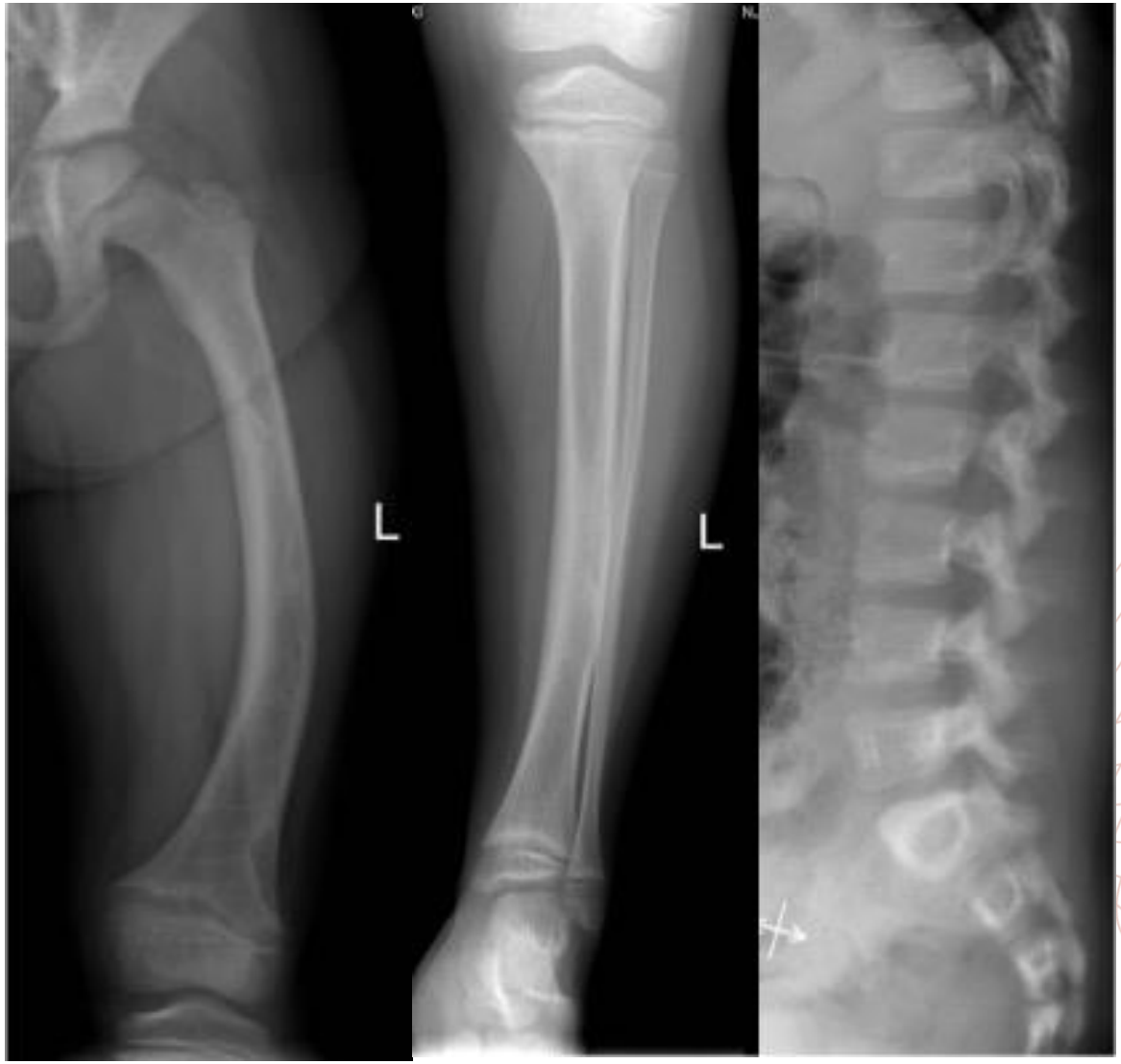
Ca, calcium; 25-OHD, 25-hydroxyvitamin D; PTH, parathyroid hormone

Information courtesy of Prof. Mäkitie

PATIENT CASE 1







- Short stature (height – 2.9 SDS)
- Lower limb deformities
- Wide wrists and ankles
- Rickets confirmed by radiography

SDS, standard deviation score

Information courtesy of Prof. Mäkitie

LABORATORY WORK

Biochemistry

- Normal S-Ca, 25-OHD
- Low S-Pi, high U-Pi
- High ALP
- Normal PTH
- Normal $1,25(OH)_2D$

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; S-Ca, serum calcium; S-Pi, serum phosphate; U-Pi, urinary phosphate

Information courtesy of Prof. Mäkitie

POLLING QUESTION 1

WHICH LABORATORY PARAMETER SUGGESTS THAT RICKETS IS NOT CAUSED BY CALCIUM OR VITAMIN D DEFICIENCY?

A. Normal S-Ca
B. High ALP
C. Low S-Pi
✓ D. Normal PTH

ALP, alkaline phosphatase; PTH, parathyroid hormone; S-Ca, serum calcium; S-Pi, serum phosphate

PATIENT CASE 1
LABORATORY RESULTS

Biochemistry

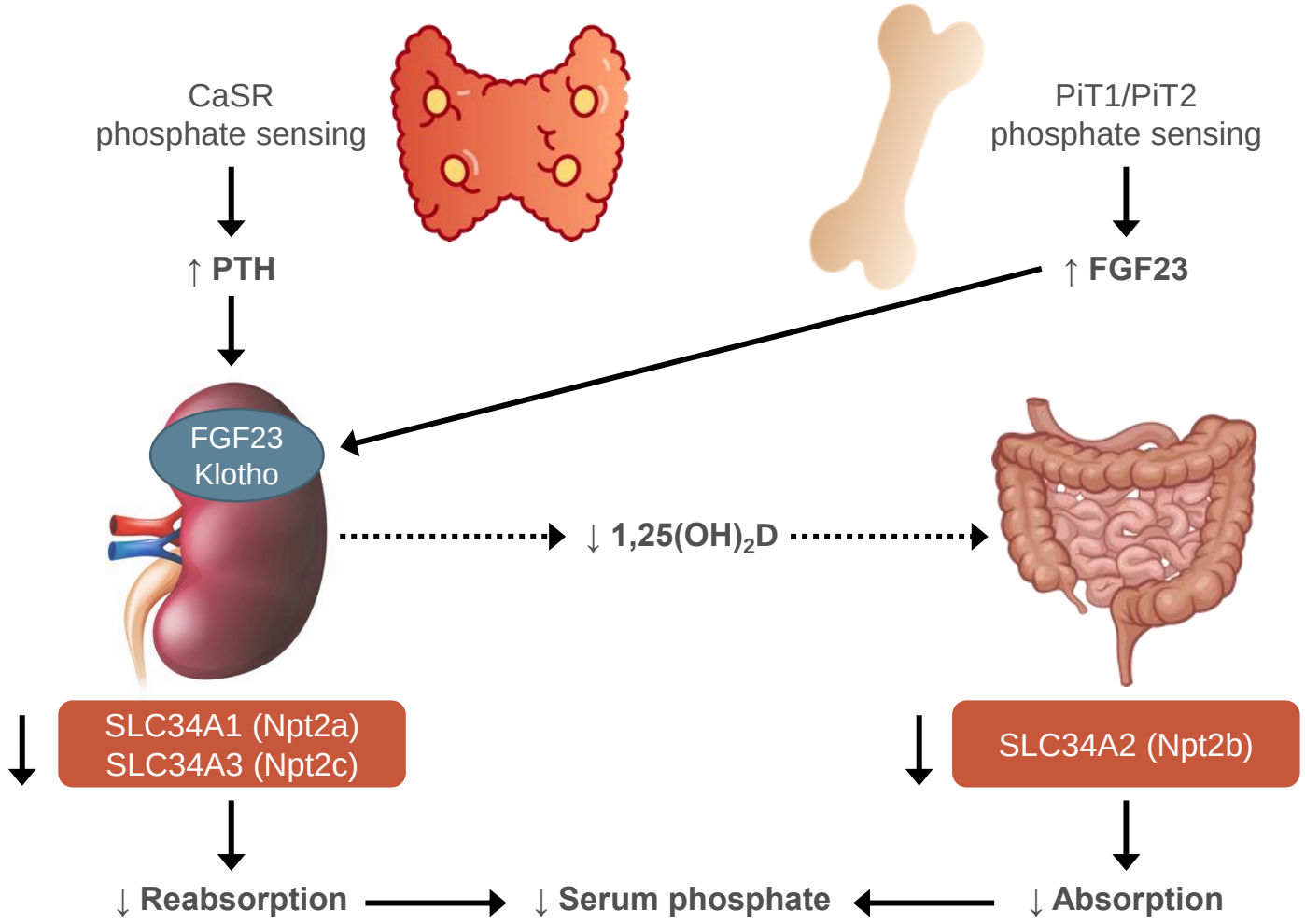
- Normal S-Ca, 25-OHD
- Low S-Pi, high U-Pi ← Reduced tubular reabsorption
- High ALP
- Normal PTH
- Normal $1,25(OH)_2D$
- Increased serum FGF23 ←

1,25(OH)2D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; S-Ca, serum calcium; S-Pi, serum phosphate; U-Pi, urinary phosphate

Information courtesy of Prof. Mäkitie

MAINTENANCE OF NORMAL PHOSPHATE BALANCE

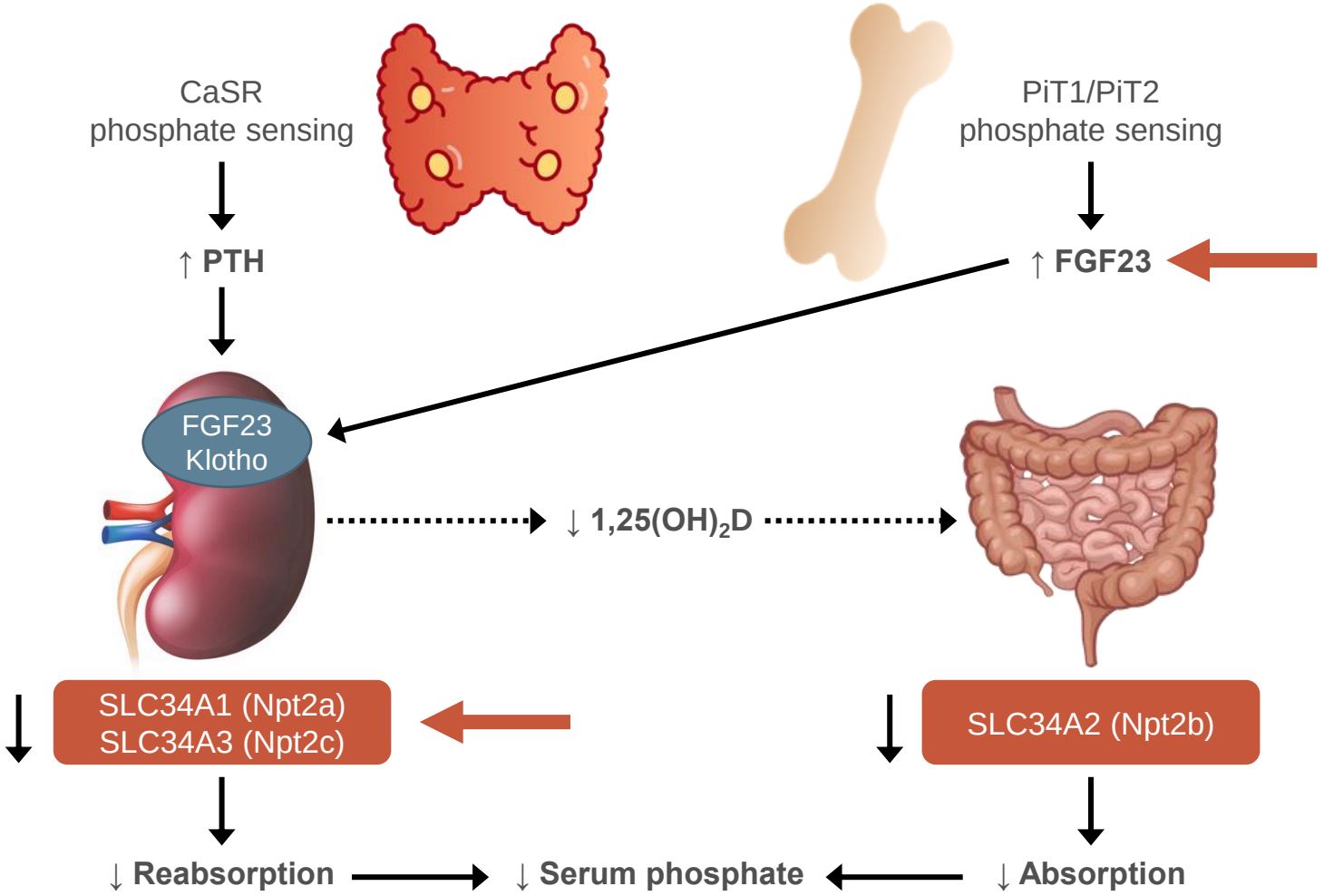
HIGH SERUM OR HIGH DIETARY PHOSPHATE



$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; CaSR, calcium sensing receptor; FGF23, fibroblast growth factor 23; Npt2a/b/c, sodium-dependent phosphate transport protein 2a/b/c; PiT1/2, sodium-dependent phosphate transporter 1/2; PTH, parathyroid hormone

Adapted from: Hernando N, et al. Physiol Rev. 2021;101:1-35

GENETIC DISORDERS LEADING TO HYPOPHOSPHATEMIA



Disorders with:

- **Excessive FGF23 production**
- Inadequate urinary Pi reabsorption

1,25(OH)2D, 1,25-dihydroxyvitamin D; CaSR, calcium sensing receptor; FGF23, fibroblast growth factor 23; Npt2a/b/c, sodium-dependent phosphate transport protein 2a/b/c; Pi, inorganic phosphate; PiT1/2, sodium-dependent phosphate transporter 1/2; PTH, parathyroid hormone

Adapted from: Hernando N, et al. Physiol Rev. 2021;101:1-35

PATIENT CASE 1

PATIENT WAS DIAGNOSED WITH X-LINKED HYPOPHOSPHATEMIA (XLH)

	XLH	AD	AR
Prevalence	+++	+	+
Genes	*PHEX*	*FGF23*	*DMP1, ENPP1, FAM20C*
FGF23	↑↑	↑↑	↑↑

- A gene panel including these genes and several others confirmed a **heterozygous PHEX mutation**
- **No family history**, the parents were mutation negative

AD, autosomal dominant; AR, autosomal recessive; DMP1, dentin matrix acidic phosphoprotein 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FAM20C, family with sequence similarity 20, member C; FGF23, fibroblast growth factor 23; PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome;

X-LINKED HYPOPHOSPHATEMIA (XLH)
SYMPTOMATOLOGY AND PATHOPHYSIOLOGY IN CHILDREN

OVERVIEW[1]

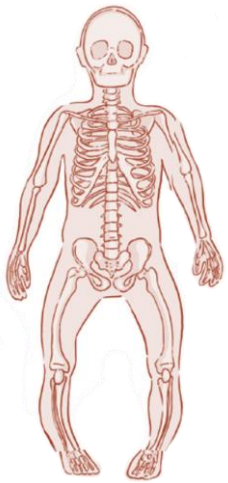
PAEDIATRIC

Delayed and disproportionate growth

Craniosynostosis

Rickets

Delayed motor development and gait abnormalities



Short stature

Deformity of weight-bearing limbs

Tooth abscesses

Excessive dental caries

Osteomalacia

Bone and joint pain

Joint stiffness

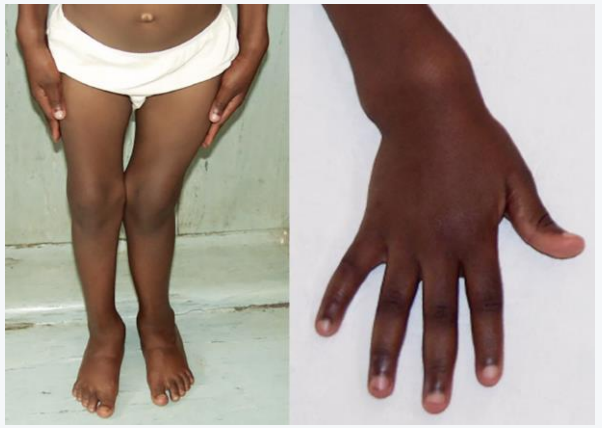
Muscle pain and weakness

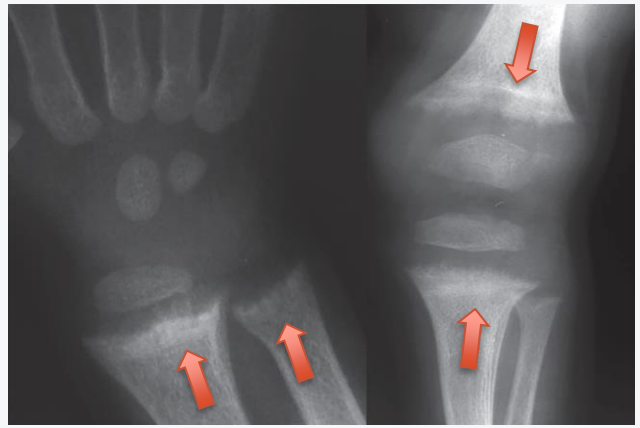
Chiari malformation

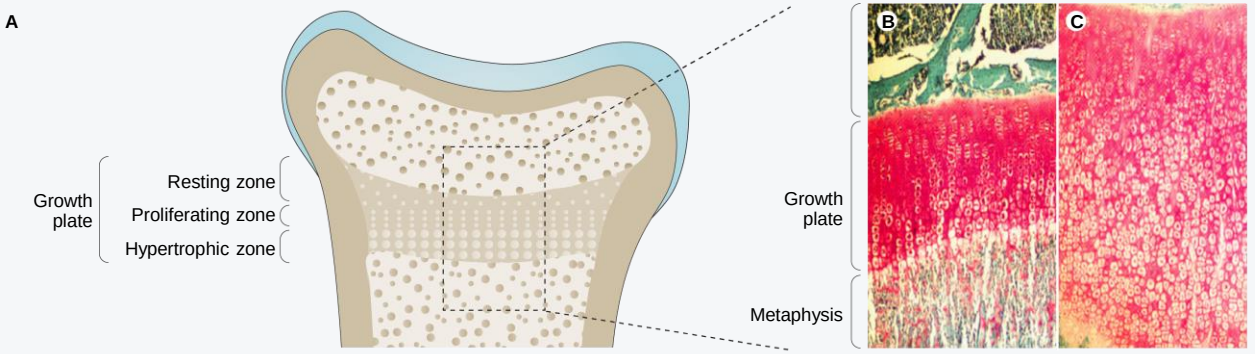
Gait abnormalities

Diminished quality of life including psychosocial impact

EXAMPLES[2]







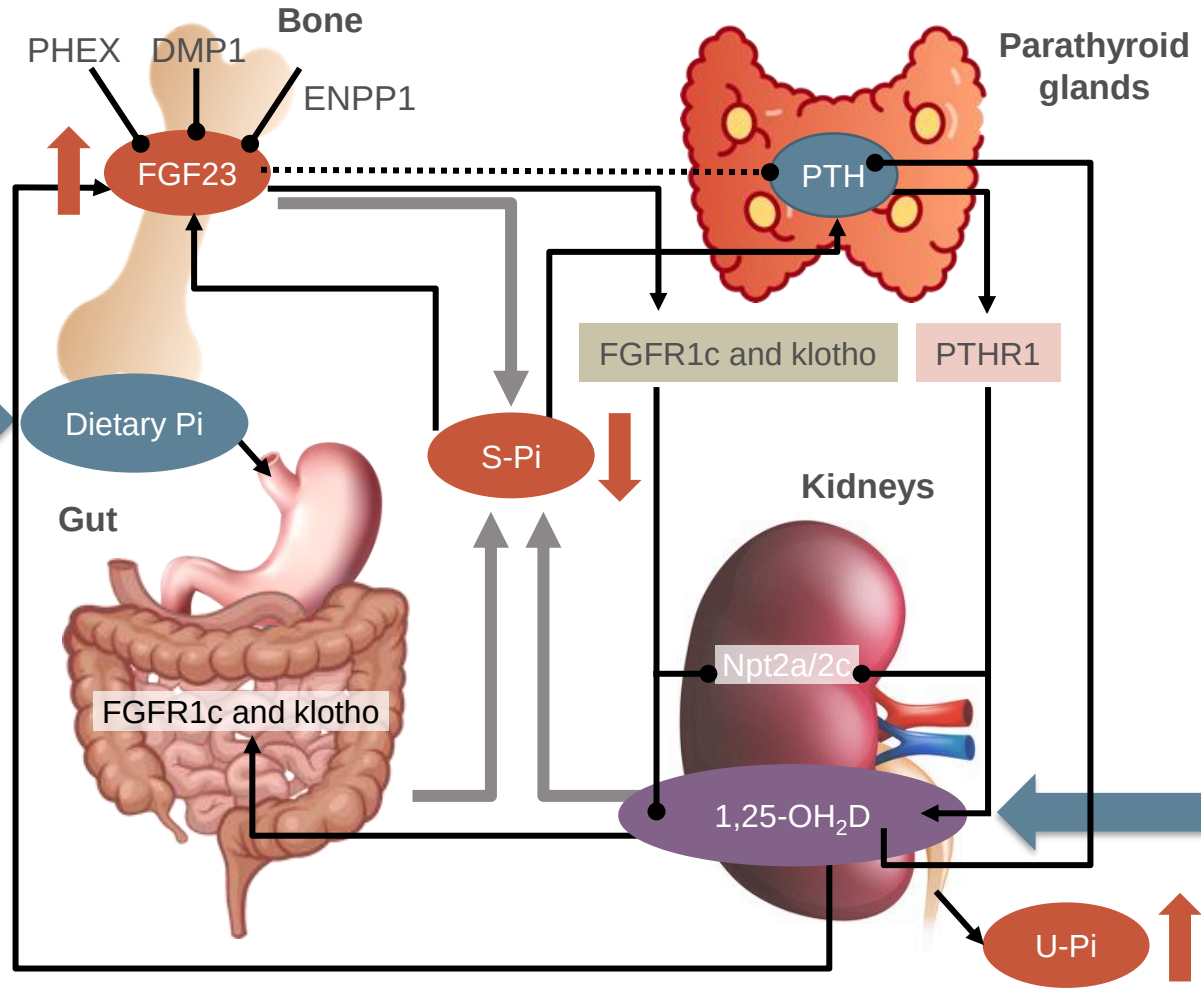
1. Beck-Nielsen SS, et al. Orphanet J Rare Dis. 2019;14:58; 2. Carpenter TO, et al. Nat Rev Dis Primers. 2017;3:17101

X-LINKED HYPOPHOSPHATEMIA (XLH)

CONVENTIONAL TREATMENT: NORMALISE MINERALISATION

Oral phosphate[1]:

- 20-60 mg/kg/d in 3-5 doses



Active vitamin D[1]:

- alfacalcidol 30-50 ng/kg

1,25(OH)2D, 1,25-dihydroxyvitamin D; d, day; DMP1, dentin matrix acidic phosphoprotein 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23, fibroblast growth factor 23; FGFR1c, fibroblast growth factor receptor 1 isoform c; Npt2a/2c, sodium-dependent phosphate transport protein 2a/2c; PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; Pi, inorganic phosphate; PTH, parathyroid hormone; PTHR1, PTH receptor 1; S-Pi, serum phosphate; U-Pi, urinary phosphate

Figure adapted from Bergwitz C, et al. N Engl J Med. 2011;365:1625-35; 1. Haffner D, et al. Nat Rev Nephrol. 2019;15:435-455

POLLING QUESTION 2

WHAT IS THE MAIN BIOCHEMICAL TREATMENT GOAL WITH CONVENTIONAL TREATMENT OF XLH?

A. Normalise U-Pi
B. Normalise S-Pi
✓ C. Normalise ALP
D. Normalise PTH

ALP, alkaline phosphatase; PTH, parathyroid hormone; S-Pi, serum phosphate; U-Pi, urinary phosphate; XLH, X-linked hypophosphatemia

X-LINKED HYPOPHOSPHATEMIA (XLH)

CONVENTIONAL TREATMENT: NORMALISE MINERALISATION

Conventional treatment[1,2]

- Oral phosphate: 20–60 mg/kg/d in 3–5 doses
- Active vitamin D: alfacalcidol 30–50 ng/d
- Targets in biochemistry
- **Normalise ALP**
- Avoid:
  - Secondary hyperparathyroidism
  - Hypercalciuria
- Accept hypophosphatemia

Impact of treatment[3,4,5]

- Conventional treatment is challenging
- Complications
  - Nephrocalcinosis
  - Secondary and tertiary hyperparathyroidism
- Incomplete treatment response
  - Partial healing of rickets
  - Often no catch-up growth
  - Residual deformities
  - Less frequent dental problems

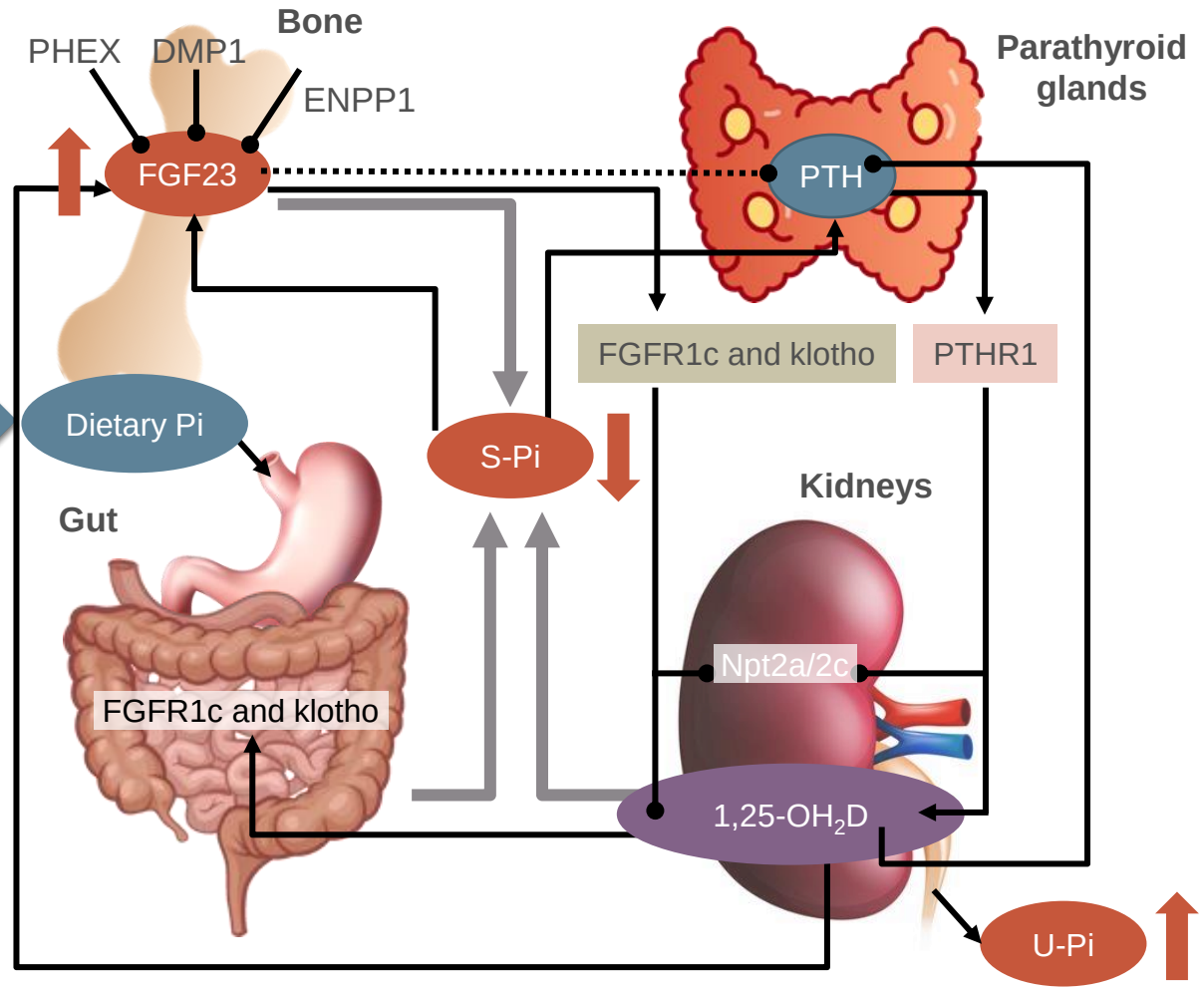
ALP, alkaline phosphatase; d, day;

1. Bergwitz C, et al. N Engl J Med. 2011;365:1625-35; 2. Haffner D, et al. Nat Rev Nephrol. 2019;15:435-455; 3. Eddy MC, et al. Bone. 1997;21:515-20; 4. Park E and Kang HG. Clin Exp Pediatr. 2024;67:17-25; 5. Mao M, et al. J Clin Endocrinol Metab. 2020;105:3243-3249;

X-LINKED HYPOPHOSPHATEMIA (XLH) TREATMENT: NORMALISE MINERALISATION

FGF23 antibody:

- Subcutaneous injection every two weeks



1,25(OH)2D, 1,25-dihydroxyvitamin D; DMP1, dentin matrix acidic phosphoprotein 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23, fibroblast growth factor 23; FGFR1c, fibroblast growth factor receptor 1 isoform c; NaPi-IIa/c, sodium-phosphate cotransporter type IIa/c; PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; Pi, inorganic phosphate; PTH, parathyroid hormone; PTHR1, PTH receptor 1; S-Pi, serum phosphate; U-Pi, urinary phosphate

Figure adapted from Bergwitz C, et al. N Engl J Med. 2011;365:1625-35

X-LINKED HYPOPHOSPHATEMIA (XLH)
A LIFE-LONG DISEASE

XLH **disease burden** progresses from childhood to adulthood[1]

- The symptoms of XLH **accumulate** over time
- Adults **transitioning** from paediatric to adult health care are at risk of poor outcomes
  - A well-supported transition is needed

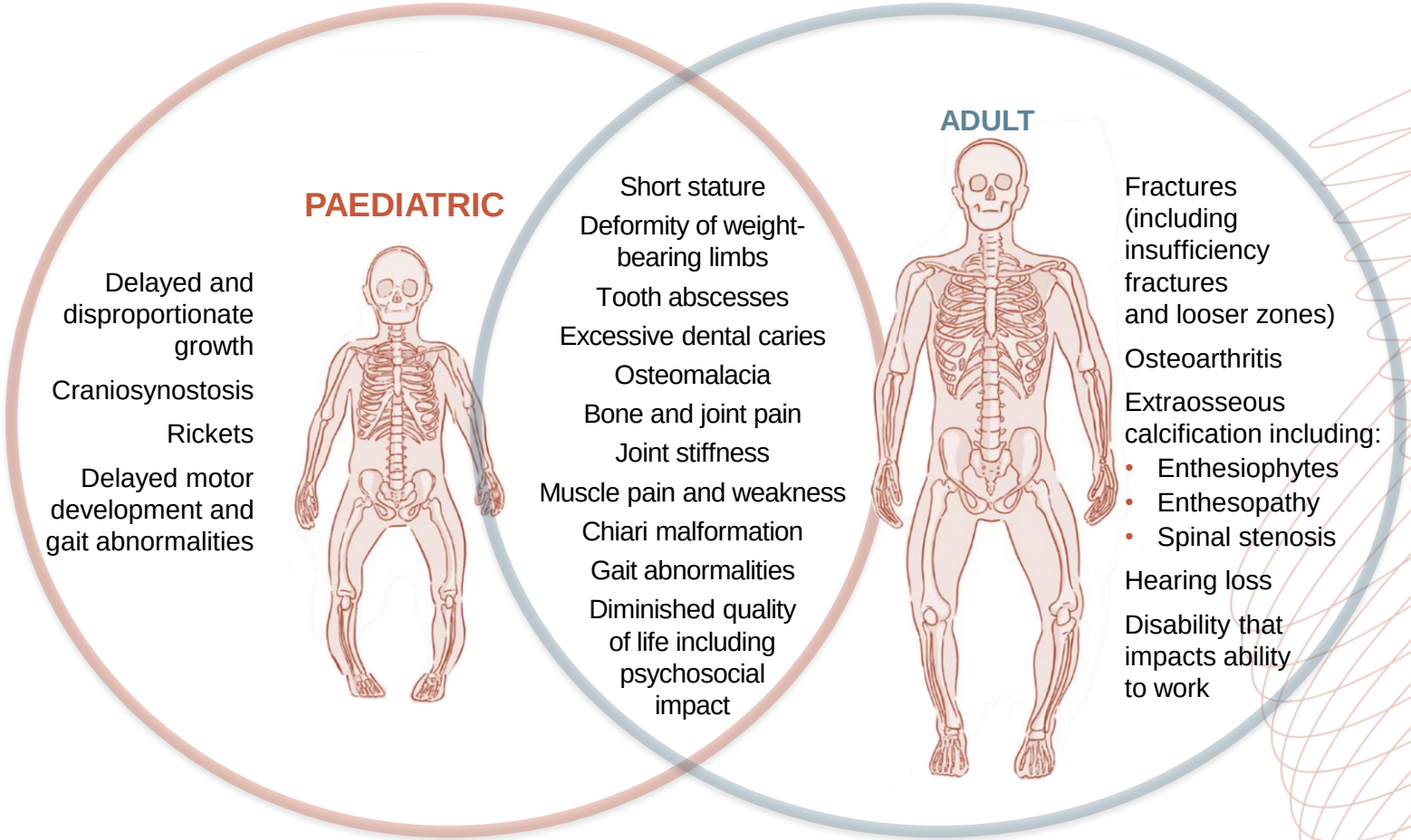


Figure adapted from Beck-Nielsen et al.[2]

1. Giannini S, et al. Osteoporos Int. 2021;32:1937-1949; 2. Beck-Nielsen SS, et al. Orphanet J Rare Dis. 2019;14:58

PATIENT CASE 1
SUMMARY AND LEARNING POINTS

- Phosphate homeostasis is tightly regulated
- Genetic defects may lead to hypo- or hyperphosphatemia
  - The hormone FGF23 is the main player in pathogenesis
- XLH is the most common genetic form of hypophosphatemia
  - Conventional treatment
  - FGF23 antibody treatment
- XLH is a life-long disease

FGF23, fibroblast growth factor 23 ; XLH, X-linked hypophosphatemia

PATIENT CASE 2

POLLING QUESTION 1

WHAT CLINICAL HISTORY FINDINGS SHOULD PROMPT URGENT REFERRAL TO A METABOLIC BONE SPECIALIST FOR FURTHER INVESTIGATION IN A PATIENT SUSPECTED OF HAVING TUMOUR-INDUCED OSTEOMALACIA (TIO)?

A. History of recurrent infections

✓ B. Sudden onset of bone abnormalities and fractures without history of trauma in a previously healthy individual

C. History of chronic back pain with no improvement despite conservative treatment

D. History of travel to endemic areas for bone diseases

PATIENT CASE 2

55-year-old male

- No family history of bone fragility

DISEASE PRESENTATION

- Multiple vertebral and axial fragility fractures over the last 4 years
- No apparent trauma

MEDICAL AND SOCIAL HISTORY

- Healthy and physically active as a young man
- No major clinical problems and surgeries prior to the last 4 years
- Lawyer and father of two healthy children

Information courtesy of Prof. Brandi

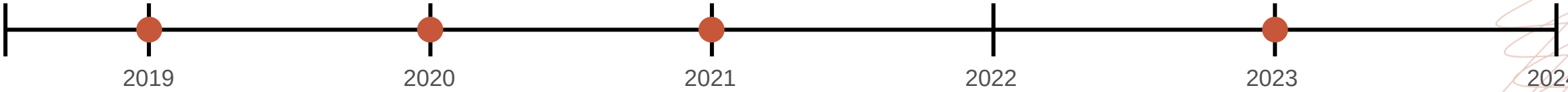
PATIENT CASE 2

HISTORY OF PRESENT ILLNESS

Age 51 years
Pain in left femur with diagnosis of bone oedema and recommendation to rest

Age 53 years
Fracture of left femoral neck required an osteosynthesis

December 2023: Age 55 years
Presentation



Age 52 years
Extension of oedema to right femur; injectable bisphosphonates prescribed

- 2021-2023
  - Fractures in right femur and nine vertebrae (with no trauma)
  - 13 cm loss in height

- 2019-2023
  - Loss of 30 kg in weight, predominantly muscle mass

Information courtesy of Prof. Brandi

PATIENT CASE 2
BIOCHEMICAL AND BONE ASSESSMENTS

Biochemistry at first examination: Dec 2018

Test, unit	Reference range	Value
Serum Ca, mg/dL	8.2-10.6	9.7
24-hr urine Ca, mg/day	100-300	**45**
Serum Pi, mg/dL	2.5-4.5	**1.69**
24-hr urine Pi, mg/day	400-1,300	**2,256**
25(OH)D, ng/mL	30-100	42.5
PTH, pg/mL	11-67	**86.8**
Bone ALP, µg/mL	6-30	**89**
β-CTx, ng/mL	0.115-0.748	**1.280**

Additional biochemistry at follow-up due to abnormal serum and urine levels

Test, unit	Reference range	Value
$1,25(OH)_2D$, pg/mL	15.2-90.1	**8.9**
FGF23, pg/mL	23.2-95.4	**312**

Bone densitometry

DEXA: L1-L4 T-score = **−3.5**

Text in red indicates a value outside the reference range

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; β-CTx, carboxy-terminal cross-linked telopeptide of type I collagen ALP, alkaline phosphatase; Ca, calcium; DEXA, dual-energy X-ray absorptiometry; FGF23, fibroblast growth factor 23; hr, hour; L, lumbar; Pi, inorganic phosphate; PTH, parathyroid hormone

Information courtesy of Prof. Brandi

PATIENT CASE 2
INITIAL TREATMENT

Pharmacological therapy:

- Oral phosphate
- Calcitriol
- Aminobisphosphonates

→ **Modest improvement in pain and muscle symptoms**

Clear suspicion of tumour-induced osteomalacia (TIO):

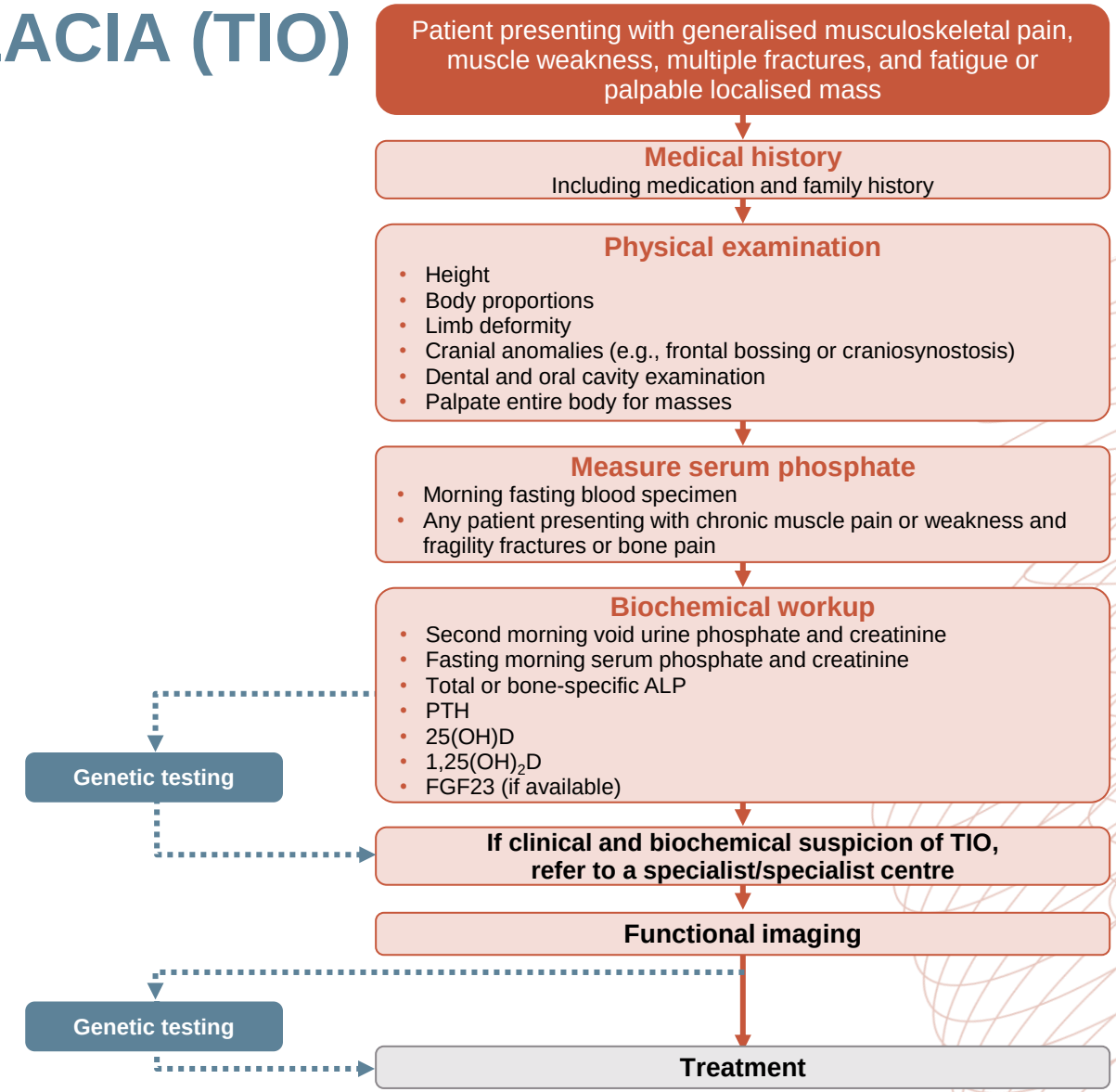
- No family history of bone fragility
- Sudden onset of bone abnormalities and fractures without a history of trauma
- Hypophosphatemia and elevated serum FGF23

→ **How to localise the tumour?**

FGF23, fibroblast growth factor 23; TIO, tumour-induced osteomalacia
Information courtesy of Prof. Brandi

TUMOUR-INDUCED OSTEOMALACIA (TIO)
DIAGNOSTIC ALGORITHM

- Rare paraneoplastic syndrome
  - Overproduction of phosphaturic hormones, as FGF23, by tumours (associated with tumours that are mesenchymal in nature)[1]
- Different than XLH, TIO is usually diagnosed in the adult patient[2]
- Algorithm for its management has been published



Adapted from Jan de Beur et al. [3]

1,25(OH)2D, 1,25-dihydroxyvitamin D (calcitriol); 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; XLH, X-linked hypophosphatemia

1. Alonso G and Varsavsky M. Endocrinología y Nutrición (English Edition). 2016;63:181-186; 2. Laurent MR, et al. GeneReviews® [Internet]. Adam MP, Feldman J, Mirzaa GM, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at https://www.ncbi.nlm.nih.gov/books/NBK83985/; 3. Jan de Beur, SM, et al. J Intern Med. 2023;293:309-328

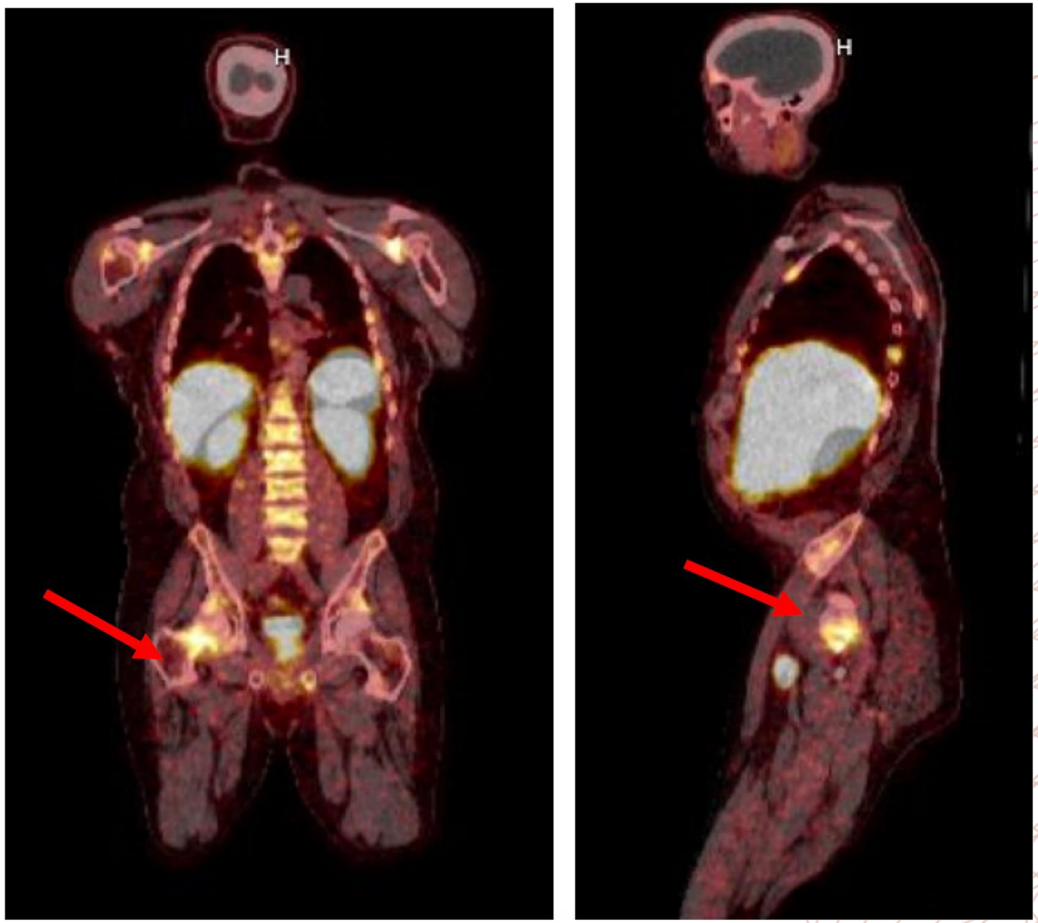
TUMOUR LOCALISATION PROCESS (3 MONTHS)
ASSESSMENT RESULTS

Negative

- CT scan
- MRI scan
- FDG-PET/CT scan
- SPECT/CT (^{111}Indium-octreotde-scinti) scan

Positive

- PET/CT (^{68}Gallium-DOTANOC) scan (X-ray negative) at level of right femoral trochanter
- Selective venous catheterisation revealed **higher FGF23** at the level of the right common femoral vein compared with the left common femoral vein (644.6 pg/mL and 325.6 pg/mL, respectively)



Example of a positive PET/CT scan demonstrating marked tracer uptake[1]

CT, computed tomography; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/CT; FGF23, fibroblast growth factor 23; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography

1. Chen DW, et al. Clin Diabetes Endocrinol. 2020;6:12

Information courtesy of Prof. Brandi

POLLING QUESTION 2

WHAT IS THE SUGGESTED NEXT STEP AFTER LOCALISATION OF THE TUMOUR IN A PATIENT WITH TIO?

A. Stop treatment with oral phosphate and calcitriol

B. Perform a biopsy of the localised tumour for histological diagnosis

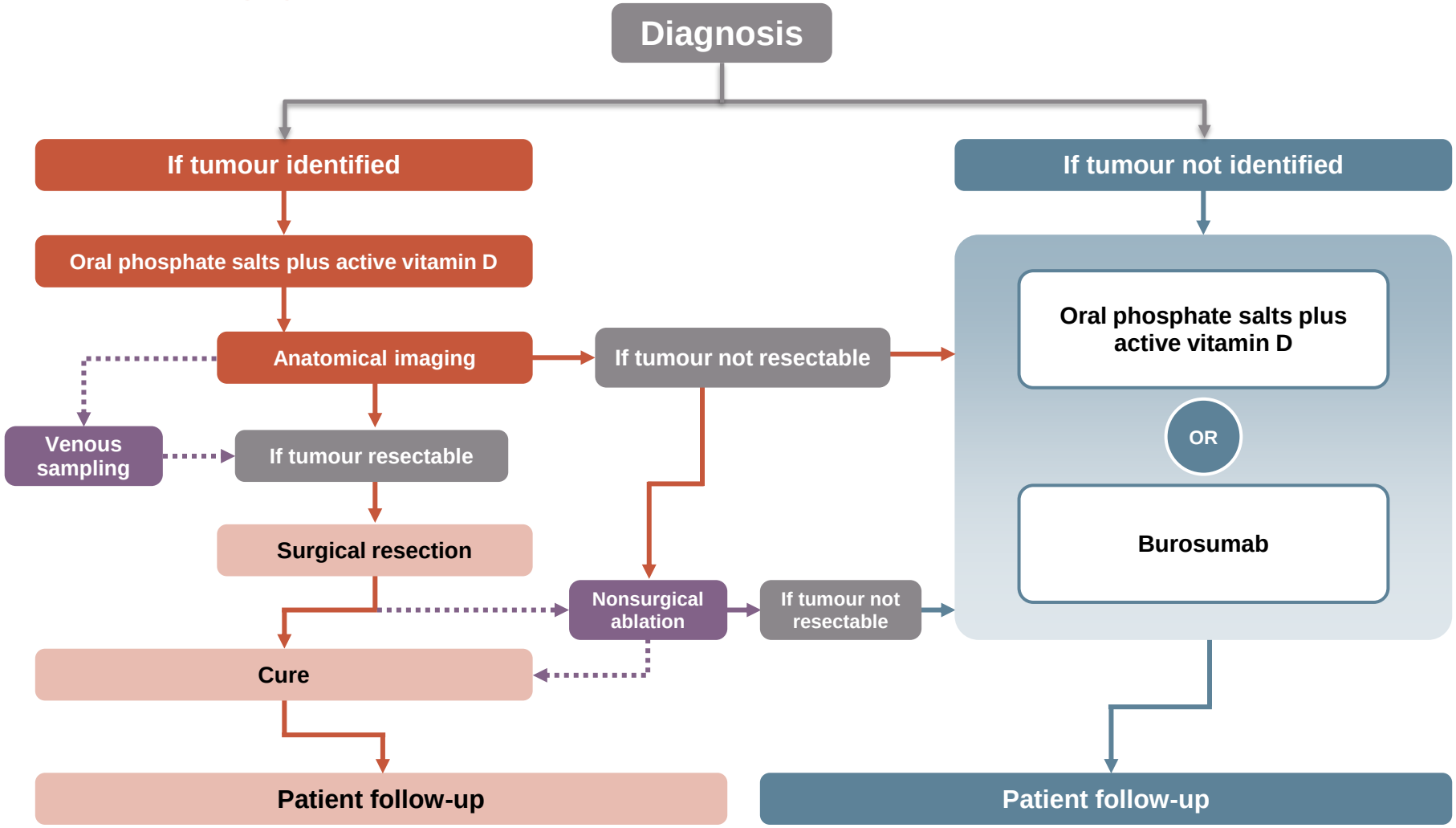
✓ C. Schedule the patient for surgical removal of the tumour

D. Conduct a follow-up imaging study to monitor tumour growth

TIO, tumour-induced osteomalacia

TUMOUR-INDUCED OSTEOMALACIA

TREATMENT ALGORITHM



Adapted figure

Jan de Beur, SM, et al. J Intern Med. 2023;293:309-328

DEFINITIVE MANAGEMENT
TUMOUR REMOVAL

The tumour was successfully removed from the right femoral trochanter:

- Histologically diagnosed as an osteoblastoma, positive for FGF23 peptide with staining
- 24 hours post-surgery, FGF23 values dropped to 16.4 pg/mL
- Shortly after surgery, the patient was able to walk without help and went back to skiing

Following surgery, the patient made good clinical recovery

FGF23, fibroblast growth factor 23;
Information courtesy of Prof. Brandi

PATIENT CASE 2
SUMMARY AND LEARNING POINTS

- This patient suffered multiple vertebral and axial fragility **fractures** without an apparent cause **for 4 years before being diagnosed** and undergoing successful surgical treatment
- A clinical history of **sudden onset of bone abnormalities and fractures** without history of trauma in a previously healthy individual should prompt **urgent referral** to a metabolic bone specialist for further investigation
- A full **clinical examination**, **biochemical investigation** and **specialised imaging** may be required to make a **final diagnosis of TIO** and to localise the tumour(s)
  - **Many patients suffer for years** because their tumour is not localised, is not amenable to surgery or is in an inaccessible location
- **PET/CT (^{68}Gallium-DOTANOC)** may reveal tumour(s) even if not detected by other imaging techniques

CT, computed tomography; PET, positron emission tomography; TIO, tumour-induced osteomalacia; XLH, X-linked hypophosphatemia

Information courtesy of Prof. Brandi

KEY CLINICAL TAKEAWAYS

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DIFFERENTIAL DIAGNOSIS OF CHRONIC HYPOPHOSPHATEMIA IN CHILDREN AND ADULTS

- **Phosphate homeostasis is tightly regulated.** FGF23 plays a key role in the mechanisms involved in disorders linked to phosphate wasting
- Hypophosphatemia can have genetic or physiological causes. Genetic causes continue throughout the life of the patient and **transition of care** from childhood to adulthood is crucial
- **Skeletal deformities** in childhood and **sudden onset of bone abnormalities and fractures** without a history of trauma in a previously healthy adult should prompt suspicion of rare bone disorders, such as **XLH and TIO**
- **Several guidelines** on the management of chronic hypophosphatemia exist (XLH and TIO). Updates are expected to be published soon

FGF23, fibroblast growth factor 23; TIO, tumour-induced osteomalacia; XLH, X-linked hypophosphatemia

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