



Diagnostic Resource

DIAGNOSTIC ASSESSMENT OF PATIENTS WITH SUSPECTED HYPOPHOSPHATASIA (HPP)

HPP is caused by deficient alkaline phosphatase (ALP) activity. It is an inherited, multisystemic metabolic disease that can progress.^{1-3*}

The impact of deficient ALP activity in HPP can be significant. Early detection and assessment of disease burden may help avoid years of potential misdiagnosis, incorrect therapies, and disease progression.⁴⁻⁷

This assessment is based on published International Working Group (IWG) consensus HPP diagnostic criteria and is not a substitute for a physician's clinical judgment or expertise.

*HPP is a rare disease; the true prevalence is unknown.⁸

HPP *diagnosis overview*

To diagnose hypophosphatasia (HPP), look for persistently low ALP alongside clinical signs and symptoms, such as impaired physical function, musculoskeletal and joint pain, bone fractures, or chronic fatigue.^{1,3,9-17}

Persistently low ALP levels are the hallmark of HPP. Persistently low ALP can be defined as 2 or more ALP levels below normal range in intervals of more than 30 days.^{8,16-23}

If you see an ALP value of ~40 U/L or below* in adults or ~160 U/L or below*† in children, look for a pattern of low ALP levels adjusted for patient age and sex. The value of 160 U/L can be used for screening for HPP and should not be considered a diagnostic marker for evaluating pediatric patients.^{8,16-23}

Adults

~≤40 U/L

Children

~≤160 U/L

Refer to your lab for appropriate age- and sex-adjusted reference range.*

ALP activity should be interpreted using age- and sex-adjusted reference ranges, after other causes of low ALP have been excluded. ALP levels that are normal for adults could represent pathological levels for children.^{5,23,24}

Recommended Lower Limit of Normal Range of ALP Based on Age and Sex ^{23‡}			
Age range (years)	ALP activity (U/L)		
	Male		Female
0 to 14 days	<90		
15 days to <1 year	<134		
1 to <10 years	<156		
10 to <13 years	<141		
13 to <15 years	<127		<62
15 to <17 years	<89		<54
17 to <19 years	<59		<48

ALP activity persistently below these values could be a sign of HPP.²³



Signs and symptoms of HPP can appear at any age and often resemble more common conditions, such as osteoporosis, arthritis, fibromyalgia, pseudogout, or other rheumatic conditions. Check for low ALP and consider HPP in the differential diagnosis of these conditions.^{1,4,9-11,15,25-31}

*These values serve as general guidelines to prompt further investigation; however, evaluation should always be based on persistently low readings relative to the specific age- and sex-adjusted reference ranges of the performing laboratory.³²

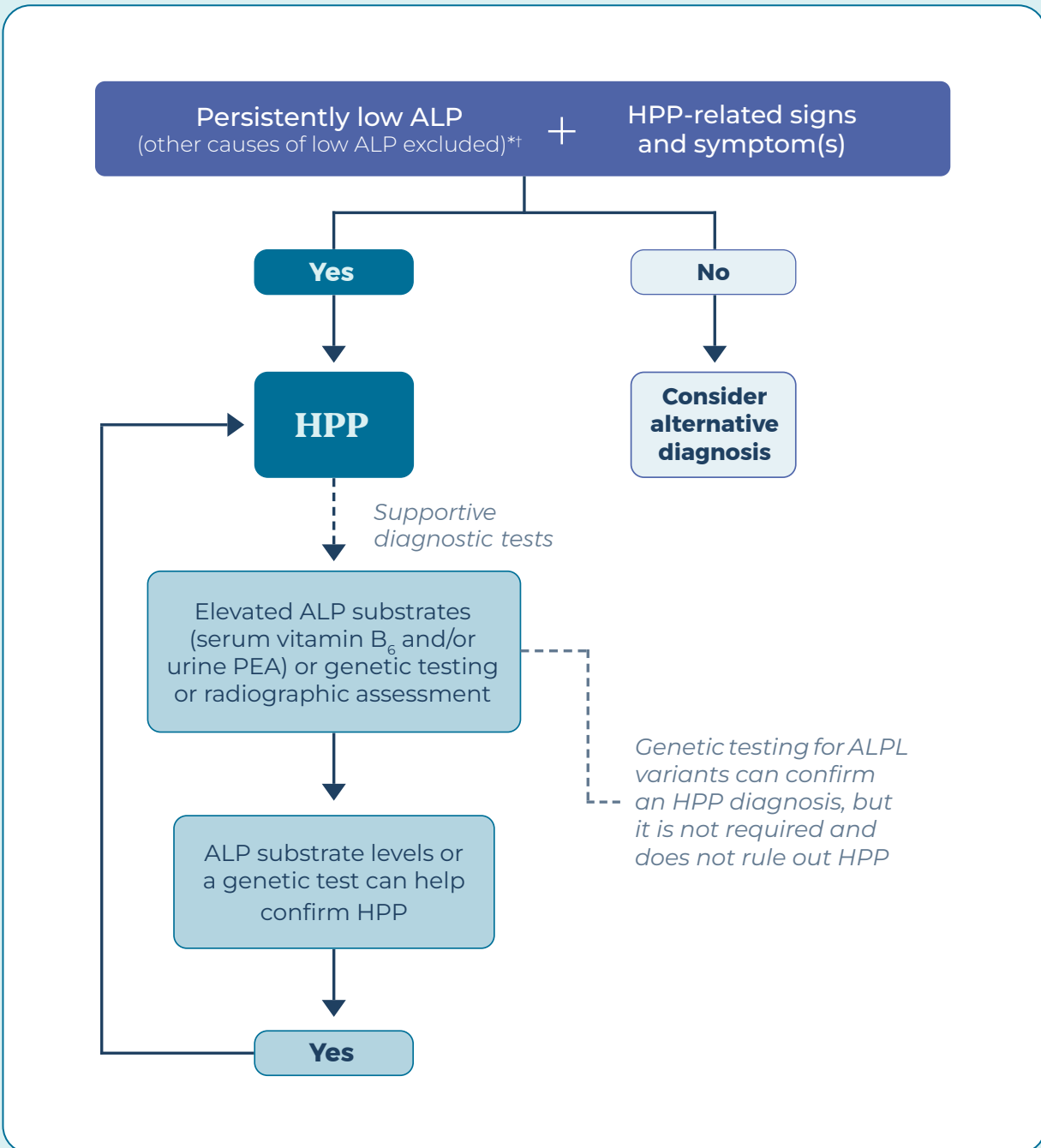
†The value of ~160 U/L or below is based on the Associated Regional and University Pathologists (ARUP) Reference Laboratory (Utah, USA) online test directory, with ~160 U/L being the highest level of the low range of ALP for male and female patients aged 1 to 13 years old. It is important to note that normal ranges for serum ALP activity are higher in infants, children, and adolescents than they are in adults.^{22,23}

‡Table adapted from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project. CALIPER samples from 1072 male and 1116 female participants (newborn to 18 years) were used to calculate age- and sex-specific reference intervals. No variation in ALP based on ethnic differences was observed. Check with your lab for their appropriate age- and sex-adjusted reference range.²³

ALP, alkaline phosphatase.

An approach for diagnosing a patient with suspected HPP^{16,17}

Adapted from the IWG-recommended diagnostic criteria for HPP in children and adults.



*Adjusted for age/sex (obligate criterion).

†Conditions that lead to transiently elevated ALP activity, such as healing fractures or certain infections, should also be excluded in patients with HPP.³³

ALP, alkaline phosphatase; ALPL, alkaline phosphatase, biomineralization-associated; HPP, hypophosphatasia; IWG, International Working Group; PEA, phosphoethanolamine.

Patient *medical history*

Since hypophosphatasia (HPP) symptoms and their intensity can change, **the impact of the disease may not always be obvious.** Ask your patients about how symptoms may have impacted their ability to learn, work, and live independently.^{13,14,34-36}

Ask your patients about their history with any of these symptoms:

 Rheumatic^{36,37}	Do they have any joint pain or stiffness? • Joints feeling stiff or sore when they first get up or after sitting for a while • Joint pain or swelling that makes it hard to reach, bend, or get dressed comfortably
 Skeletal^{9,29,37-39}	Do they have a history of fractures, including slow-to-heal fractures, rickets (weak/soft bones), bone pain, craniosynostosis, or osteomalacia? • Bone pain or pain that gets worse with movement • Getting stress fractures when doing something routine, such as stepping off a curb or lifting a box • Skull surgery, bowed legs, or rickets
 Muscular^{9,37}	Do they have muscle pain or weakness, fatigue, difficulty walking, or waddling gait? • Feeling fatigued or muscles aching or feeling weak on days when they have been inactive • Exerting a lot of effort or swaying when doing simple activities, such as walking around
 Neurologic^{37,40,41}	Do they experience neuropathic pain, headaches, fatigue, anxiety, or depression? • Feeling shooting pain, tingling, or numbness, especially in hands and feet • Getting headaches frequently • Having trouble concentrating, experiencing brain fog, or feelings of being down or easily irritated • Seizures, either currently or in the past
 Growth/Development^{9,37}	Did they miss motor milestones and/or show evidence of failure to thrive as a child? • Seeming smaller or slower to hit physical milestones (children) • Finding it hard to keep up physically with peers, family, or friends
 Dental^{9,29,37}	Do they have a history of premature tooth loss, poor dentition, or periodontal disease? • Cavities or teeth falling out with the root still intact • Needing more dental visits than normal, even with oral hygiene and regular care
 Renal^{34,36,41}	Do they have any signs/symptoms of renal disease suggestive of hypercalcemia and/or renal stones/calcification? • Kidney stones or pain in their back or sides without a clear cause • Urine looking red or different than normal
 Gastrointestinal⁴²	Have they experienced any gastrointestinal issues? • Nausea, vomiting, and feeding difficulties (in infants) • Gastrointestinal dysfunction (in adults)

This list is not exhaustive. Patients may present with other signs and symptoms.

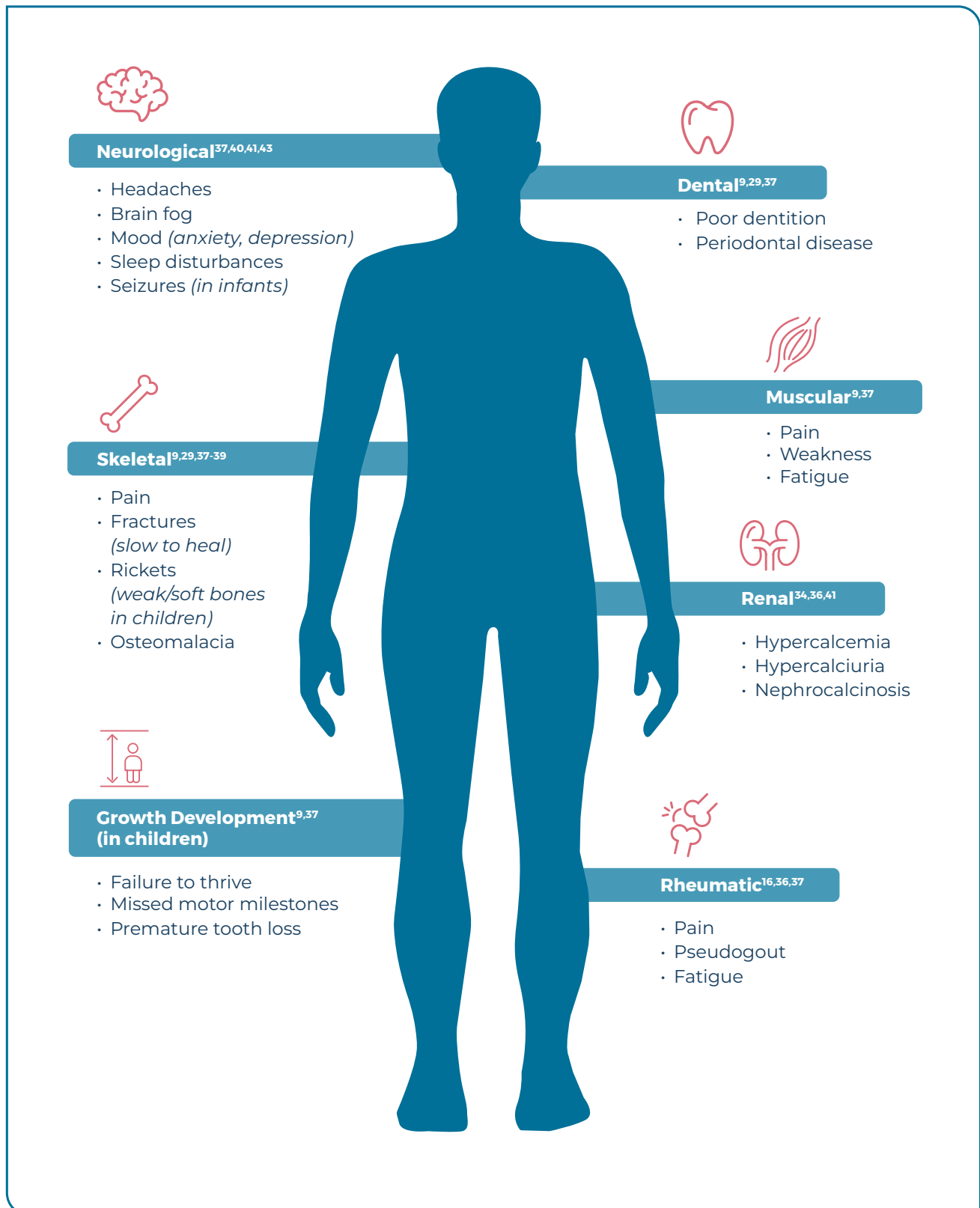


Family history may also be relevant. If these symptoms are known to exist in biological family members, this information may be clinically relevant since HPP can be inherited.

HPP *signs and symptoms*

Hypophosphatasia (HPP) can present as a broad range of multisystemic manifestations.

Since HPP can present at any age, evaluating current symptoms and possible overlooked symptoms from childhood is important for an accurate diagnosis.^{2,13,42}



ALP enzymatic activity

Persistently low ALP* levels are the hallmark of HPP. If you see an ALP value of **~40 U/L or below† in adults or ~160 U/L or below‡ in children**, look for a pattern of low levels adjusted for patient age and sex.^{8,16-18,20-23}

ALP activity should be interpreted using age- and sex-adjusted reference ranges, after other causes of low ALP have been excluded. ALP levels that are normal for adults could represent pathological levels for children.^{5,23,24}

Scan the QR code to learn more about ALP



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Substrate levels

Low ALP activity can cause elevation of its natural substrates, vitamin B₆ (PLP) and PEA.⁴⁴

Patients with HPP may present with^{3,44}:

↓ Persistently low ↑ Elevated

ALP[‡]

PLP[¶] PEA* PPI**

Urine PEA⁴⁵

0-30 days	1.04–54.23 mmol/mol creatinine
31 days-35 months	4.30–58.00 mmol/mol creatinine
3-6 years	3.54–28.32 mmol/mol creatinine
7-17 years	1.22–14.12 mmol/mol creatinine
≥18 years	0.59–7.25 mmol/mol creatinine

- Elevated PEA: supports a diagnosis of HPP^{42,44}
- Low or normal PEA: does not rule out a diagnosis of HPP^{16,17}
- Check with your lab for their appropriate age-adjusted reference range for Urine PEA

Serum vitamin B₆ (PLP)

Vitamin B₆ reference range (µg/L)⁴⁶

5–50

- Elevated vitamin B₆: supports a diagnosis of HPP^{42,44}
- Low or normal vitamin B₆: does not rule out a diagnosis of HPP^{16,17}
- Check with your lab for their appropriate reference range for serum PLP

KEEP IN MIND

*Persistently low ALP can be defined as 2 or more ALP levels below normal range in intervals of more than 30 days.^{5,16,17,19}

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¶Look for a pattern of persistently low ALP levels if you see an ALP value of ~40 U/L or below in adults or ~160 U/L or below in children.^{8,16-18,20-23}

¶Pyridoxal 5'-phosphate (PLP) levels may be elevated in individuals taking supplements containing vitamin B₆. PLP levels may also appear as normal or low in patients with HPP. This does not invalidate the HPP diagnosis.⁴¹

¶Phosphoethanolamine (PEA) levels may be normal in some patients with HPP. PEA results may be elevated in other bone diseases.^{47,48}

**Inorganic pyrophosphate (PPI) tests are done in research settings only and are not commercially available.³⁸

ALP, alkaline phosphatase; HPP, hypophosphatasia.

HPP

genetic testing

While a positive *ALPL* genetic test may help to confirm if your patient has hypophosphatasia (HPP), it is NOT required for diagnosis, and a negative test does not rule out HPP.⁴⁹

Possible test results*

Positive	A variant is reported as pathogenic or likely pathogenic, and the results may be consistent with an HPP diagnosis. ⁵⁰⁻⁵²
Inconclusive	A variant was found, but its significance to the disease is uncertain (variant of unknown significance or VUS). Inconclusive results <i>do not</i> rule out HPP. The variant's classification may change with additional research or publications in the future. ⁵¹⁻⁵⁴
Negative	The test did not identify a variant or a variant of likely relevance to the disease; this <i>does not</i> rule out HPP, and additional genetic testing may be conducted if desired. ^{29,49,53-55}

A clinical geneticist is recommended to interpret results and understand if other family members may be affected.

Family mapping

Since HPP can be inherited, a diagnosis should prompt ALP testing and evaluation of any signs or symptoms in the patient's family.^{17,56,57}



HPP can be inherited in an autosomal dominant or autosomal recessive manner, with dominant inheritance being the most frequently observed.²⁹



Intrafamilial clinical variability is common among patients with HPP. Clinical investigation may reveal related individuals who present with a different phenotype to the proband.²⁹

*Additional genetic test results may include "Likely Benign" and "Benign," which refer to variants that are not expected to be associated with disease.

ALP, alkaline phosphatase; *ALPL*, alkaline phosphatase, biomineralization associated.

Hypophosphatasia (HPP)
may feel different for every
patient, but it should **never**
feel unimportant.^{13,14,34,35}

Since HPP symptoms and their intensity can change over time, the impact of the disease may not always be immediately apparent.

Ask your patients about how symptoms may have impacted their ability to work, learn, and live independently.^{13,14,34-36}

See how HPP and its multisystemic symptoms can impact patients' quality of life.



To learn more, visit hypophosphatasia-hcp.com

References: 1. Injean P, Tan J, Lee S, Downey C. *ACR Open Rheumatol.* 2023;5(10):524-528. 2. Villa-Suárez JM, García-Fontana C, Andújar-Vera F, et al. *Int J Mol Sci.* 2021;22(9):4303. 3. Conti F, Ciullini L, Pugliese G. *Clin Cases Miner Bone Metab.* 2017;14(2):230-234. 4. Szabo SM, Tomazos IC, Petryk A, et al. *Orphanet J Rare Dis.* 2019;14(1):85. 5. Khan AA, Brandi ML, Rush ET, et al. *Osteoporos Int.* 2024;35(3):431-438. 6. Cao Y, Zhang F, Huang X, Jiang A, Jiang S, Wu M. *Front Oral Health.* 2025;6:1585188. 7. Sutton RA, Mumm S, Coburn SP, Ericson KL, Whyte MP. *J Bone Miner Res.* 2012;27(5):987-994. 8. Kishnani PS, Seefried L, Ozono K, et al. *Orphanet J Rare Dis.* 2025;20(1):626. 9. Rockman-Greenberg C. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. 10. Bishop N, Munns CF, Ozono K. *Arch Dis Child.* 2016;101(6):514-515. 11. Hoff P, Mann A, Steinmüller M, Aliluev A. *BMJ Open.* 2025;15(7):e097235. 12. Larsen PB, Skausig OB, Jensen EA. *Pract Lab Med.* 2018;11:19-22. 13. Durrrough C, Colazo JM, Simmons J, et al. *Bone.* 2021;142:115695. 14. Pierpont EI, Simmons JH, Spurlock KJ, Shanley R, Sarafoglou KM. *Orphanet J Rare Dis.* 2021;16(1):80. 15. Lefever E, Witters P, Gielen E, et al. *J Clin Densitom.* 2020;23(3):340-348. 16. Brandi ML, Khan AA, Rush ET, et al. *Osteoporos Int.* 2024;35(3):439-449. 17. Rush E, Brandi ML, Khan A, et al. *Osteoporos Int.* 2024;35(1):1-10. 18. Adeli K, Higgins V, Nieuwesteeg M, et al. *Clin Chem.* 2015;61(8):1049-1062. 19. Vieira LHR, Peixoto KC, Flósi CL, de Farias MLF, Madeira M. *Arch Endocrinol Metab.* 2021;65(3):289-294. 20. Quest Diagnostics. Accessed April 14, 2026. <https://testdirectory.questdiagnostics.com/test/test-detail/234/alkaline-phosphatase?cc=MASTER> 21. Labcorp. Accessed April 14, 2026. <https://www.labcorp.com/tests/001107/alkaline-phosphatase> 22. ARUP Laboratories. Accessed April 14, 2026. <https://ltd.aruplab.com/Tests/Pub/0021020> 23. Colantonio DA, Kyriakopoulou L, Chan MK, et al. *Clin Chem.* 2012;58(5):854-868. 24. Kurihara M, Tajima H, Ishii R, Matsumoto T, Migita M. *Pediatr Int.* 2025;67(1):e70260. 25. Tsang T, Raghuwanshi MP. *J Endocr Soc.* 2021;5(suppl 1):A201-A202. 26. Yoshida H, Murakami T, Ogawa A, et al. *Endocrinol Diabetes Metab Case Rep.* 2025;2025(1):e240121. 27. Feurstein J, Behanova M, Haschka J, et al. *Orphanet J Rare Dis.* 2022;17(1):435. 28. Bangura A, Wright L, Shuler T. *Cureus.* 2020;12(6):e8594. 29. Nunes ME. In: Adam MP, Mirzaz GM, Pagon RA, et al, eds. *GeneReviews®*. Seattle (WA):University of Washington, Seattle; 1993-2026. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1150/> 30. Mornet E, et al. In: Pagon, et al, eds. *GeneReviews®*. Accessed April 14, 2026. <http://www.ncbi.nlm.nih.gov/books/NBK1150> 31. Rodziewicz M, et al. *Rheumatol Adv Pract.* 2018;2(suppl 1). 32. Adeli K, Higgins V, Trajcevski K, White-Al Habeeb N. *Crit Rev Clin Lab Sci.* 2017;54(6):358-413. 33. Tournis S, Yavropoulou M, Polyzos SA, Doulgeraki A. *J Clin Med.* 2021;10(23):5676. 34. Weber TJ, Sawyer EK, Moseley S, Odrliin T, Kishnani PS. *Metabolism.* 2016;65(10):1522-1530. 35. Dahir KM, Seefried L, Kishnani PS, et al. *Orphanet J Rare Dis.* 2022;17(1):277. 36. Högl W, Langman C, Gomes da Silva H, et al. *BMC Musculoskelet Disord.* 2019;20(1):80. 37. Kishnani PS, Rush ET, Arundel P, et al. *Mol Genet Metab.* 2017;122(1-2):4-17. 38. Hypophosphatasia. NORD. Updated February 16, 2021. Accessed April 14, 2026. <https://rarediseases.org/rare-diseases/hypophosphatasia/> 39. Whyte MP. Hypophosphatasia. In: Bilezikian JP, et al, eds. *Principles of Bone Biology*. 3rd ed. Academic Press; 2008:1573-1598. 40. Colazo JM, Hu JR, Dahir KM, Simmons JH. *Osteoporos Int.* 2019;30(2):469-480. 41. Bianchi ML, Bishop NJ, Gunañabens N, et al. *Osteoporos Int.* 2020;31(8):1445-1460. 42. Seefried L, Genest F, Hofmann C, Brandi ML, Rush E. *Calcif Tissue Int.* 2025;116(1):46. 43. Kim SM, Korkmaz F, Sims S, Ryu V, Yuen T, Zaidi M. *Osteoporos Sarcopenia.* 2023;9(4):115-120. 44. Khan AA, Rush ET, Wakeford C, Staub D, Brandi ML. *Adv Ther.* 2025;42(9):4270-4299. 45. Quest Diagnostics. Accessed April 14, 2026. <https://testdirectory.questdiagnostics.com/test/test-detail/14168/phosphoethanolamine-pea-urine-with-creatinine?cc=MASTER> 46. Mayo Clinic Laboratories. Test ID: PLP. [Accessed April 14, 2026] <https://www.mayocliniclabs.com/test-catalog/overview/42359#Overview> 47. Shajani-Yi Z, Ayala-Lopez N, Black M, Dahir KM. *Bone.* 2022;163:116504. 48. McKiernan FE, Dong J, Berg RL, et al. *Osteoporos Int.* 2017;28(8):2343-2348. 49. Mornet E. *Metabolism.* 2018;82:142-155. 50. Shapiro JR, Lewiecki EM. *J Bone Miner Res.* 2017;32(10):1977-1980. 51. US National Library of Medicine. MedlinePlus. Updated July 28, 2021. Accessed April 14, 2026. <https://medlineplus.gov/download/genetics/understanding/testing.pdf> 52. Richards S, Aziz N, Bale S, et al. *Genet Med.* 2015;17(5):405-424. 53. Rehm HL, Bale SJ, Bayrak-Toydemir P, et al. *Genet Med.* 2013;15(9):733-747. 54. Hoffman-Andrews L. *J Law Biosci.* 2018;4(3):648-657. 55. Lefever E, Witters P, Gielen E, et al. *J Clin Densitom.* 2018;23(3):340-348. 56. Mornet E, Taillandier A, Domingues C, et al. *Eur J Hum Genet.* 2021;29(2):289-299. 57. Peroutka C, Beck NM, Gough E, Marzinke M, Hoover-Fong J. Published online February 26, 2021.