

WHEN KIDNEY STONES MAY BE A SIGN OF SOMETHING MORE SERIOUS^{1,2}



Primary hyperoxaluria type 1 (PH1):
A metabolic stone disease with
potentially devastating consequences²⁻⁴

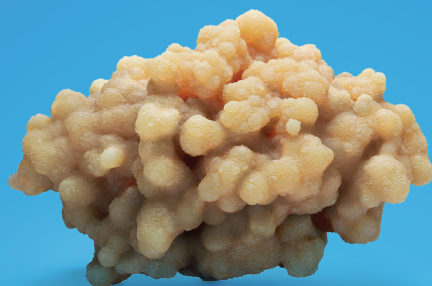
 **Alnylam**
PHARMACEUTICALS

Any unusual presentation among stone formers merits further investigation¹



CHILD OR ADOLESCENT

- Any stone^{1,5}
- Family history of stones¹

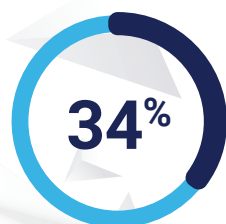


ADULT

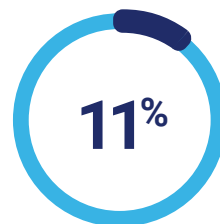


- Recurring stones¹
- Multiple or bilateral stones¹
- Stones that may be larger, on average, such as staghorn stones^{1,6-9}
- Family history of stones¹
- Stones with unusual biochemical composition¹

When patients present with kidney stones, a metabolic stone disease may be the cause^{1,2}



of stones in pediatric patients were linked to a **metabolic condition**^{*10}



of adults presenting with kidney stones or nephrocalcinosis had a **causative mutation**^{†11}

^{*}Based on data from a retrospective review of 511 children at a single UK center collected between 1993 and 2015.¹⁰

[†]Based on data from a cohort of 166 adult patients seen at tertiary centers in the UK.¹¹

EXAMPLES OF METABOLIC STONE DISEASES^{1,12,13}

- | | |
|--------------------------------------|---------------------------------|
| • PH1 | • Xanthinuria |
| • Primary hyperoxaluria type 2 (PH2) | • Dent disease |
| • Primary hyperoxaluria type 3 (PH3) | • Renal hypouricemia |
| • Cystinuria | • Renal hypomagnesemia |
| • Absorptive hypercalciuria | • Distal renal tubular acidosis |

The American Urological Association (AUA) recommends metabolic testing through 24-hour urine collection analysis in high-risk and interested first-time stone formers for substances including oxalate and stone-forming salts.¹⁴

BEHIND THE
STONE



PH1 is a progressive, life-threatening, inherited disease that often presents with kidney stones²⁻⁴



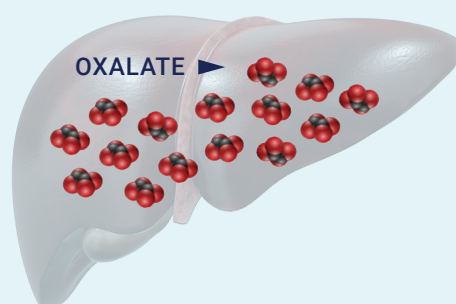
PH1 is caused by autosomal recessive mutations in the *AGXT* gene.^{3,4}



PH1 is rare and remains underdiagnosed in clinical practice.^{8,15-18}

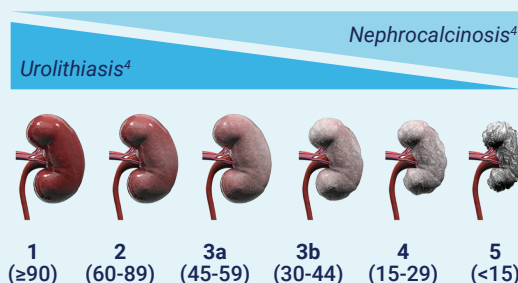
PH1: A METABOLIC DEFECT IN THE LIVER^{3,4,19}

- *AGXT* gene mutations impair the function of a liver enzyme called AGT^{4,19}
- Oxalate, a toxic metabolite, is continuously overproduced as a result^{3,4}



EXCESS OXALATE DAMAGES THE KIDNEYS^{2,4}

- Oxalate is primarily renally excreted⁴
- Oxalate forms calcium oxalate crystals that can aggregate to form kidney stones or be deposited into kidney tissue and lead to nephrocalcinosis^{3,8}
- Over time, oxalate overproduction can lead to progressive kidney function decline^{2,4}



Chronic kidney disease (CKD) stages²⁰
(estimated glomerular filtration rate [eGFR] range [mL/min/1.73m²])

AGT=alanine:glyoxylate aminotransferase.

AGXT=alanine glyoxylate aminotransferase.

PH1 can present in children and adults³

PH1 patients with identical genotypes, and even members of the same family, can have variable disease presentations.²

SIGNS AND SYMPTOMS OF PH1 TO LOOK FOR



Kidney stones are the most common clinical manifestation and the one that most often leads to a diagnosis of PH1, though not all patients with PH1 may be stone formers.^{8,21,22}

CHILDREN/ADOLESCENTS	ADULTS	ALL AGES
Any stone ^{1,3,4}	Unusual* and/or recurrent stones ^{1,2}	Family history of stones ¹

*Including multiple, bilateral, and/or large stones.^{1,2}

Other possible signs and symptoms



Failure to thrive in infancy³



Nephrocalcinosis^{2-4,8}



Progressive kidney function decline^{2,4}

Systemic oxalosis may lead to the following²³:

 Bone disorders	 Cutaneous and vascular manifestations	 Cardiac manifestations	 Ophthalmologic manifestations	 Neurologic manifestations
--	---	--	---	---

These are not all the possible signs, symptoms, or complications of PH1, and not all patients exhibit them at the same time.⁴

In a study, children with PH1 were characterized by presentation before adolescence, nephrocalcinosis, decreased eGFR and calcium oxalate monohydrate stone composition*†—awareness of these characteristics could help with earlier diagnosis, which is crucial given the progressive nature of the disease.²⁴

*Compared to controls of children with kidney stones not caused by PH1 in a study conducted using the PEDSnet database, a clinical research network of 8 US pediatric health systems, including 37 patients with PH1 and 147 controls (clinical characteristics of the PH1 group vs the control group that were statistically significant [$P < 0.05$]).²⁴

†The case-control study used electronic health record data collected between 2009 and 2021 from 8 US health systems.

‡Most control patients did not have genetic testing; urine chemistries were not performed on all patients; diagnostic coding errors may exclude some patients with PH1.



PH1 is often undiagnosed and continues to cause progressive damage due to oxalate overproduction^{8,16}



5.5 years

is the **median delay** in adults between onset of clinical manifestations and diagnosis.¹⁶

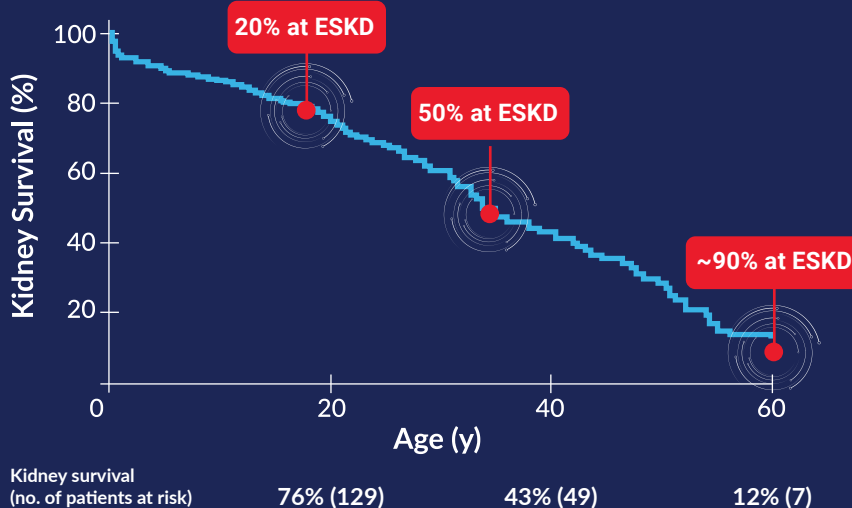
Historically, PH1 has a low index of suspicion due to:

- Its rarity¹⁵
- The nonspecific nature and lack of follow-up on kidney stone events^{8,17}
- The fact that nephrocalcinosis and declining kidney function may occur without symptoms⁸

PH1 can lead to a progressive decline in kidney function with eventual advancement toward end-stage kidney disease (ESKD), though the rate is variable.^{3,8,18,25,26}

- Patients with higher urinary oxalate (UOx) excretion progress more quickly to ESKD²⁷
- In some instances, kidney function can decline after a single incident of dehydration due to acute illness or intense physical activity^{9,28,29}
 - This can occur even in patients with previously stable kidney function²⁸

PATIENTS TYPICALLY PROGRESS TO ESKD*¹⁸



*Based on retrospective kidney survival data from 247 patients with PH1 from the Rare Kidney Stone Consortium Registry.¹⁸

Figure adapted from Hopp K, et al. J Am Soc Nephrol. 2015;26:2559-2570.

As kidney function declines, the kidneys are unable to excrete oxalate effectively, and systemic oxalosis can occur.^{8,30}

Oxalate spreads and forms crystals throughout the body—including in the bones, joints, retina, and heart.^{8,30}

Given the progressive, unpredictable nature of PH1, early diagnosis is critical^{3,8}

If PH1 is suspected, common methods seen in clinical practice to test for the disease include (but are not limited to):

MEASURING OXALATE LEVELS

In patients with **preserved kidney function**³¹:

24-HOUR URINE TEST^{*14,19,32}

Normal UOx level (all ages):
<0.50 mmol (<45 mg)/1.73 m²/24 hours²

Spot testing can be used when 24-hour urine test is not possible.⁸

In PH1, UOx levels are often between 2 to 5 times higher than the upper limit of normal.³³

In patients with **impaired kidney function**³¹:

PLASMA OXALATE MEASUREMENT^{8,19,34}

Normal plasma oxalate level: ≤2 μmol/L^{†35}

Substantially elevated levels are typical when eGFR is <30 mL/min/1.73 m². Levels >50 μmol/L are suggestive of PH1.³

GENETIC TESTING³¹

Identifying AGXT gene mutations with genetic testing can help confirm a PH1 diagnosis with high sensitivity and specificity.^{19,36}

It is recommended to screen family members of a patient with PH1, especially siblings.^{8,19}

The AUA recommends genetic testing to confirm a PH1 diagnosis in any patient with UOx excretion exceeding 0.85 mmol/1.73 m²/day (75 mg/day).^{†14}

A diagnosis of PH1 is based on the independent medical judgment of the treating physician.

*Values of UOx are laboratory- and method-dependent.

†Reference values have not been established for patients under 18 years of age or greater than 87 years of age.³⁵

‡In adults without bowel dysfunction.¹⁴

Management options for PH1 range from lifestyle changes, hyperhydration, supplements (alkali citrate and vitamin B6), and prescription medications (RNA interference therapies) to dialysis and transplant surgery.³¹

This testing information is provided for educational purposes only and is not intended to replace the independent medical judgment of any healthcare professional.

**BEHIND THE
STONE**

Alnylam Act[®] is one option for genetic testing and counseling



The Alnylam Act[®] program was created to provide access to genetic testing and counseling to patients as a way to help people make more informed decisions about their health.

- While Alnylam provides financial support for this program, tests and services are performed by independent third parties
- Healthcare professionals must confirm that patients meet certain criteria to use the program
- Alnylam receives de-identified patient data from this program, but at no time does Alnylam receive patient-identifiable information. Alnylam may use healthcare professional contact information for research purposes
- Both genetic testing and genetic counseling are available in the US and Canada
- Healthcare professionals or patients who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Alnylam product
- No patients, healthcare professionals, or payers, including government payers, are billed for this program



For more information about these third-party programs, visit AlnylamAct.com.

KNOW THE SIGNS, AND IDENTIFY PH1 EARLIER



PH1 is a progressive, life-threatening, inherited disease that often presents with **kidney stones**.²⁻⁴



Oxalate overproduction from the liver **primarily damages the kidneys**, with eventual advancement toward ESKD.²⁻⁴



PH1 remains underdiagnosed. **Metabolic testing** can raise suspicion of PH1, and **genetic testing** can help confirm a diagnosis.^{8,14-17}

Alnylam Act® is one option for genetic testing.

For more information, visit AboutPH1.com



References: 1. Ferraro PM, D'Addessi A, Gambaro G. *Nephrol Dial Transplant*. 2013;28(4):811-820. 2. Hoppe B. *Nat Rev Nephrol*. 2012;8(8):467-475. 3. Milliner DS, Harris PC, Cogal AG, Lieske JC. <https://www.ncbi.nlm.nih.gov/books/NBK1283/>. Updated November 30, 2017. Accessed September 17, 2018. 4. Cochat P, Rumsby G. *N Engl J Med*. 2013;369(7):649-658. 5. Hoppe B, Kemper MJ. *Pediatr Nephrol*. 2010;25:403-413. 6. Jendeberg J, Geijer H, Alshamari M, Cierznia B, Lidén M. *Eur Radiol*. 2017;27(11):4775-4785. 7. Carrasco A Jr, Granberg CF, Gettman MT, Milliner DS, Krambeck AE. *Urology*. 2015;85(3):522-526. 8. Hoppe B, Beck BB, Milliner DS. *Kidney Int*. 2009;75(12):1264-1271. 9. Leumann E, Hoppe B. *J Am Soc Nephrol*. 2001;12:1986-1993. 10. Issler N, Dufek S, Kleta R, Bockenhauer D, Smeulders N, van't Hoff W. *BMC Nephrology*. 2017;18(36):1-8. 11. Halbritter J, Baum M, Hynes AM, et al. *J Am Soc Nephrol*. 2015;26(3):543-551. 12. Sperling O. *Mol Genet Metab*. 2006;89(1-2):14-18. 13. Worcester EM, Coe FL. *Prim Care*. 2008;35(2):369-viii. 14. Pearle MS, Goldfarb DS, Assimos DG, et al. *J Urol*. 2014;192(2):316-324. 15. Harambat J, Fargue S, Acquaviva C, et al. *Kidney Int*. 2010;77:443-449. 16. van der Hoeven SM, van Woerden CS, Groothoff JW. *Nephrol Dial Transplant*. 2012;27:3855-3862. 17. Hulton SA. *Int J Surg*. 2016;36:649-654. 18. Hopp K, Cogal AG, Bergstralh EJ, et al. *J Am Soc Nephrol*. 2015;26:2559-2570. 19. Cochat P, Hulton SA, Acquaviva C, et al. *Nephrol Dial Transplant*. 2012;27(5):1729-1736. 20. Drawz P, Rahman M. *Ann Intern Med*. 2015;162(11):ITC1-ITC16. 21. Edvardsson VO, Goldfarb DS, Lieske JC, et al. *Pediatr Nephrol*. 2013;28(10):1923-1942. 22. Hoppe B, Langman CB. *Pediatr Nephrol*. 2003;18:986-991. 23. Garrelfs SF, Oosterveld MJ, Hulton S-A, et al. In: Abstracts of the 50th Anniversary ESPN Meeting, Glasgow; September, 2017. *Ped Nephrol*. 2017;32:1643-1834. 24. Tasian GE, Dickinson K, Park G, et al. *J Pediatr*. 2024;20:88.e1-88.e9. 25. Jamieson NV. *Am J Nephrol*. 2005;25:282-289. 26. Tintillier M, Pochet JM, Cosyns JP, Delgrange E, Donckier J. *Clin Nephrol*. 2004;62(2):155-157. 27. Zhao F, Bergstralh EJ, Mehta RA, et al. *Clin J Am Nephrol*. 2016;11:119-126. 28. El-Reshaid K, Al-Bader D, Madda JP. *Saudi J Kidney Dis Transpl*. 2016;27(3):606-609. 29. Harambat J, Fargue S, Bacchetta J, Acquaviva C, Cochat P. *Int J Nephrol*. <https://www.ncbi.nlm.nih.gov/pubmed/21748001>. Published June 16, 2011. Accessed November 15, 2018. 30. Falk N, Castillo B, Gupta A, McKelvy B, Bhattacharjee M, Papasozomenos S. *Ann Clin Lab Sci*. 2013;43(3):328-331. 31. Groothoff JW, Metry E, Deesker L, et al. *Nat Rev Nephrol*. 2023;19:194-211. 32. Ben-Shalom E, Frishberg Y. *Pediatr Nephrol*. 2015;30(10):1781-1791. 33. Bhasin B, Ürekli HM, Atta MG. *World J Nephrol*. 2015;4(2):235-244. 34. Raju DL, Cantarovich M, Brisson ML, Tchervenkova J, Lipman ML. *Am J Kidney Dis*. 2008;51(1):e1-e5. 35. Mayo Clinic Laboratories. https://www.mayocliniclabs.com/test-catalog/download-setup.php?format=pdf&unit_code=606472. Accessed July 13, 2020. 36. Williams EL, Bagg EA, Mueller M, Vandrovicova J, Aitman TJ, Rumsby G. *Mol Genet Genomic Med*. 2015;3(1):69-78.