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 consequences[2-4]

Alnylam® PHARMACEUTICALS

Any unusual presentation among stone formers merits further investigation[1]

CHILD OR ADOLESCENT

- Any stone[1,5]
- Family history of stones[1]

ADULT

- Recurring stones[1]
- Multiple or bilateral stones[1]
- Stones that may be larger, on average, such as staghorn stones[1,6-9]
- Family history of stones[1]
- Stones with unusual biochemical composition[1]

When patients present with kidney stones, a metabolic stone disease may be the cause[1,2]

34% of stones in pediatric patients were linked to a metabolic condition*[10]

11% 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
- Primary hyperoxaluria type 2 (PH2)
- Primary hyperoxaluria type 3 (PH3)
- Cystinuria
- Absorptive hypercalciuria
- Xanthinuria
- Dent disease
- Renal hypouricemia
- Renal hypomagnesemia
- 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™

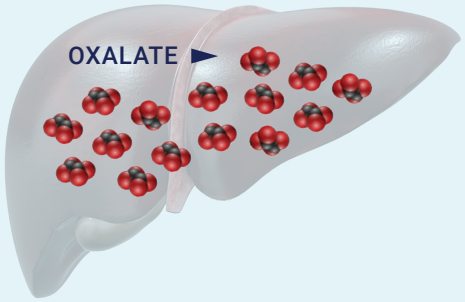
PH1 is a progressive, life-threatening, inherited disease that often presents with kidney stones[2-4]

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]

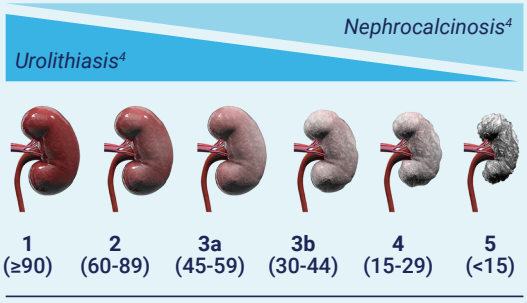
PH1: A METABOLIC DEFECT IN THE LIVER[3,4,19]

- *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 excreted[4]
- 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) stages[20]
(estimated glomerular filtration rate [eGFR] range [mL/min/1.73m²])

AGT=alanine:glyoxylate aminotransferase.
AGXT=alanine glyoxylate aminotransferase.

BEHIND THE STONE

PH1 can present in children and adults[3]

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 infancy[3]

Nephrocalcinosis[2-4,8]

Progressive kidney function decline[2,4]

Systemic oxalosis may lead to the following[23]:

- **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.

BEHIND THE STONE

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]

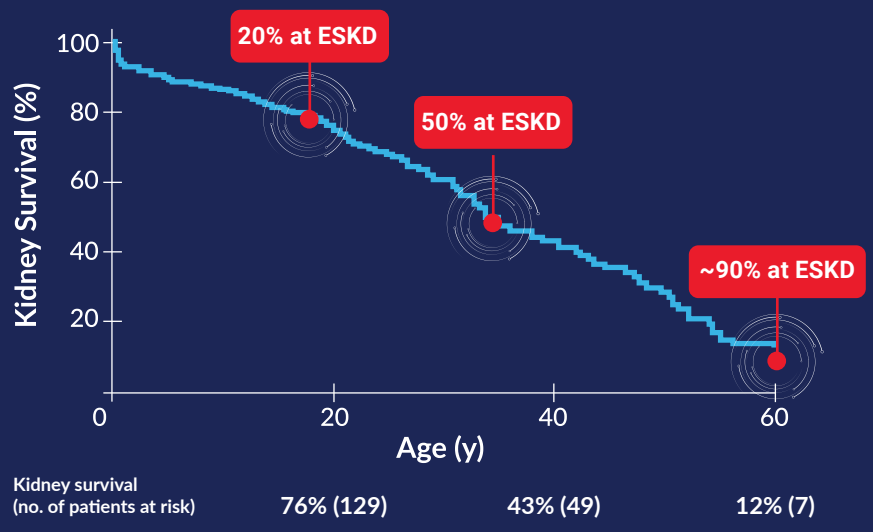
Historically, PH1 has a low index of suspicion due to:

- Its rarity[15]
- 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 symptoms[8]

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 ESKD[27]
- 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 function[28]

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]

BEHIND THE STONE

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 m^2/24 hours[2]

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 m^2. Levels >50 µmol/L are suggestive of PH1.[3]

GENETIC TESTING[31]

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 m^2/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]

Alnylam Act® is one option for genetic testing and counseling

AlnylamAct®

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.

BEHIND THE STONE

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

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