

Consider PH1 Early As Disease Progression in PH1 May Lead to Kidney Failure

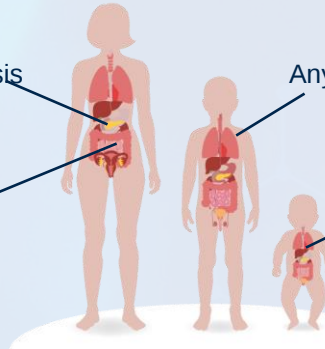
Click on **+** symbols throughout to learn more

PH1 severity is variable and the disease presents differently in different age groups¹⁻⁴

It is important to suspect PH1 in individuals with common symptoms, which include:^{1,4}

Nephrocalcinosis or recurrent nephrolithiasis

Reduced kidney function or kidney failure with history of kidney stones or nephrocalcinosis



Any kidney stone

Poor weight gain or linear growth and impaired kidney function

+ Click for more PH1 symptoms

+ Click to explore the **characteristics of kidney stones** indicative of PH1



Primary Hyperoxaluria Type 1 (PH1) is a rare, **genetic**, metabolic disorder characterized by the **overproduction** of oxalate by the liver^{5,6}

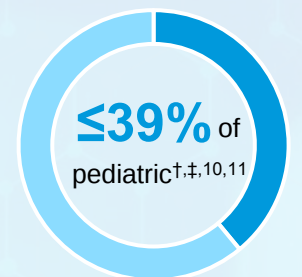
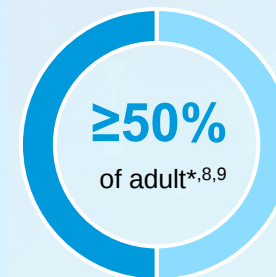


Diagnostic delay is a key challenge in PH1⁷
The median delay is 5.5 years in adults⁸



Delayed diagnosis may lead to significant morbidity and mortality. Oxalate accumulation may lead to progressive kidney damage and systemic oxalosis^{1,12,13}

% patients with **ESKD** at diagnosis



Overview of the diagnostic recommendations for the identification of PH1¹⁴⁻¹⁶

+ Click for the PH diagnostic algorithm

Suspect PH1 in:

Patients with kidney stones and **relatively preserved kidney function**¹⁴⁻¹⁶

Patients with **CKD stage 3 and beyond** or on dialysis¹⁴⁻¹⁶

With nephrocalcinosis or CaOx stones¹⁴⁻¹⁶

Measure UOx and metabolites^{§,14-16}

Measure POx and/or UOx^{¶,14-16}

Tests for PH¹⁴⁻¹⁶

- +** Urinary oxalate (UOx)
- +** Plasma oxalate (POx)

Genetic testing to help confirm a diagnosis of PH¹⁴⁻¹⁶



This information is being provided for educational purposes only and is not intended to replace the independent medical judgment of any healthcare professional. *Based on a population of 10 patients who were diagnosed with PH1 as adults in a cohort study;⁸ †Based on a retrospective review of 18 children with PH1;¹⁰ ‡Based on a retrospective study of 526 adult and pediatric patients with PH1;¹¹ §For patients, especially children, who are unable to provide a 24-h UOx, consider measuring spot UOx:Cr;^{14,15} ¶For use in patients with residual urine output.¹⁶

+ Click for references and abbreviations

Intended for US HCPs

Scan the QR code to learn more on the RNAi Science website



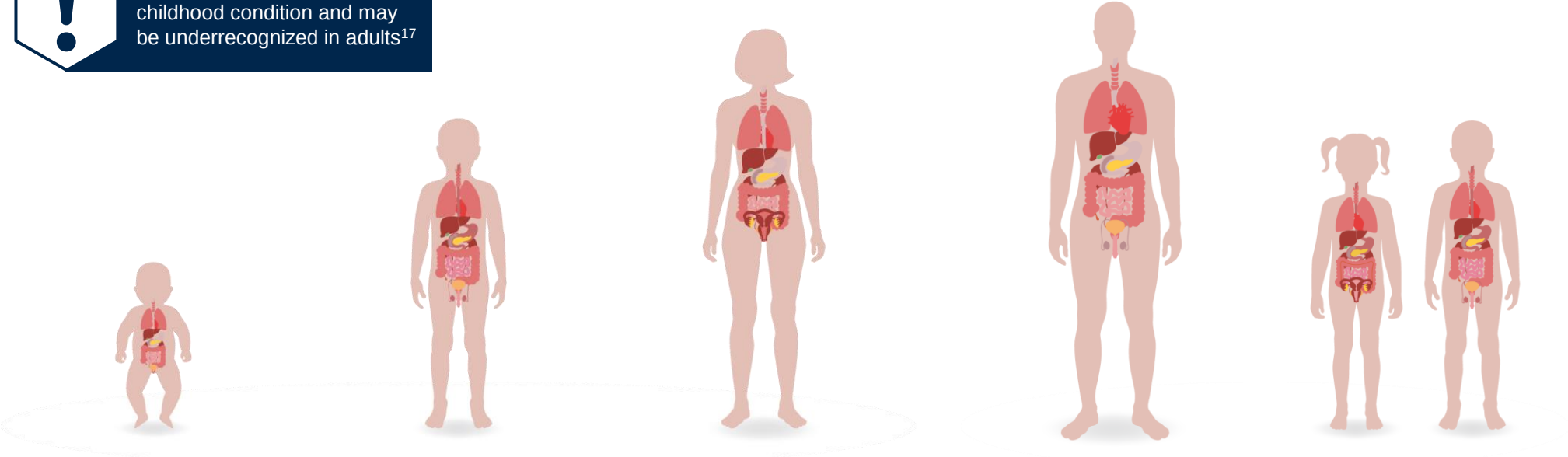
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Primary Clinical Manifestations of PH1 Can Look Different in Different Populations¹⁻⁴

Relative Incidence (%) and Typical Features of PH1 Phenotypes at Initial Presentation

! PH1 may be perceived as a childhood condition and may be underrecognized in adults¹⁷



Age ¹⁻⁴		
Infancy (~10%)	Childhood (~60%)	Adulthood (<10%)

Post-KTx ¹	Screening ¹
Disease recurrence (~10%)	PH1 family history (<10%)

- | | | |
|---|---|---|
| <ul style="list-style-type: none">• Nephrocalcinosis• Kidney impairment/failure• Poor weight gain• UTI | <ul style="list-style-type: none">• Kidney colic• Hematuria• UTI• Recurrent urolithiasis• Nephrocalcinosis• Acute kidney failure | <ul style="list-style-type: none">• Mild to moderate decline in kidney function• Acute kidney failure• Nephrocalcinosis• Recurrent kidney stones• CKD |
|---|---|---|

- | | |
|---|---|
| <ul style="list-style-type: none">• Subsequent increase in serum creatinine• CaOx crystals on biopsy• Graft failure | <ul style="list-style-type: none">• Diagnosis in a symptomatic sibling• Diagnosis in a presymptomatic individual due to family history |
|---|---|

These are not all the signs and symptoms of PH1.

+ Click for references and abbreviations

PH1 Is the Most Common and Severe Form of PH Worldwide and Is Caused by AGXT Gene Variants^{2,18}

PH constitutes a group of rare, metabolic disorders caused by recessive genetic variants^{5,6}

PH arises from inherited enzyme deficiencies that lead to the accumulation of oxalate, the end product of glyoxylate metabolism. Each PH type is caused by a different gene variant and enzyme deficiency.^{5,6,19}

Causes of PH types^{6,18}

- **PH1 (~70% of PH cases):** AGXT gene variants
- **PH2:** GRHPR gene variants
- **PH3:** HOGA1 gene variants

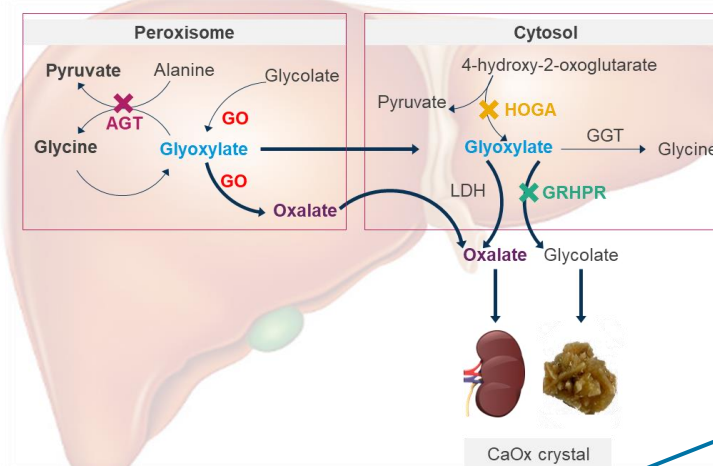
PH1, the **most severe** type of PH, arises from a deficiency of liver-specific peroxisomal **AGT**^{6,18}

PH1 is likely underdiagnosed due to heterogeneous clinical presentation¹⁸

The prevalence of **diagnosed PH1** in North America and Europe is estimated to be **1–3 patients per million people**^{5,19}

PH1 is caused by a deficiency of liver-specific peroxisomal AGT, leading to oxalate accumulation^{6,18}

PH1 pathophysiology and the role of oxalate^{5,20}

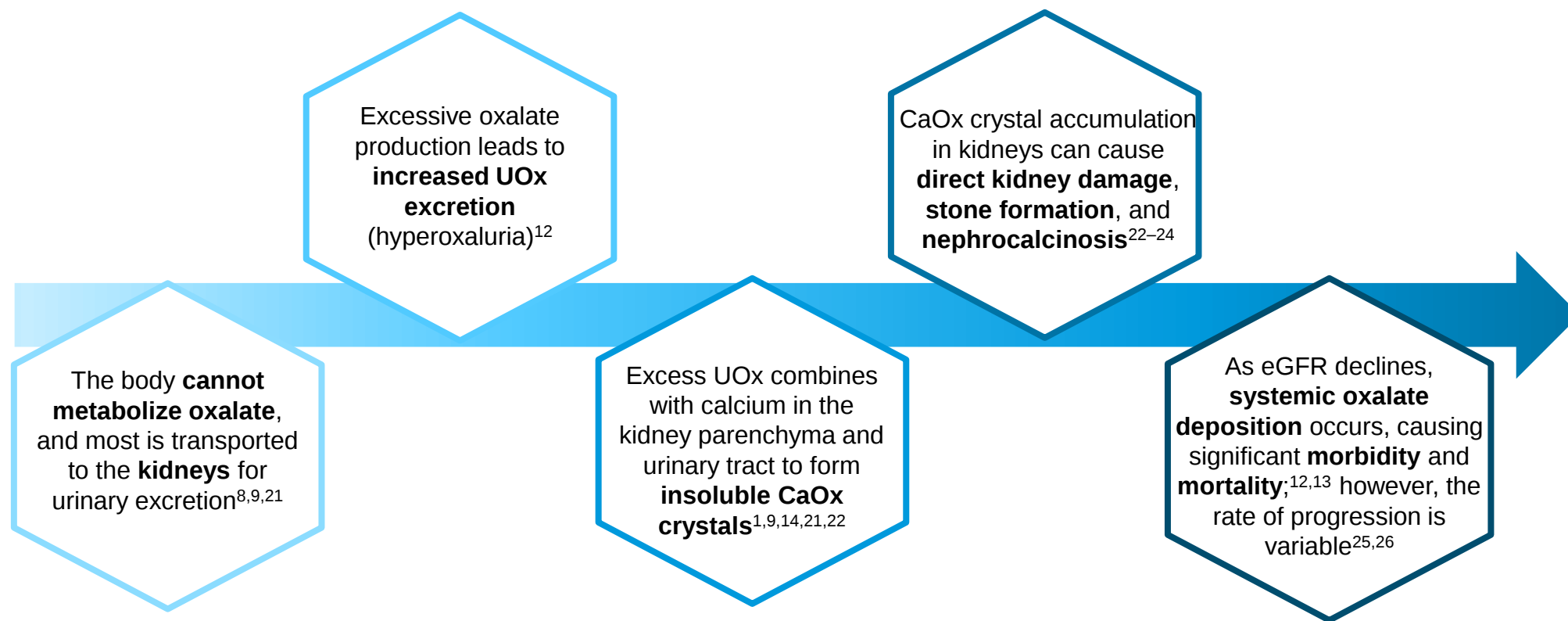


Click for references and abbreviations

Identify PH1 Early in Diagnostic Workup: Oxalate Overproduction May Lead to ESKD and Systemic Oxalosis¹⁻³



The Role of Oxalate in PH1 Pathophysiology

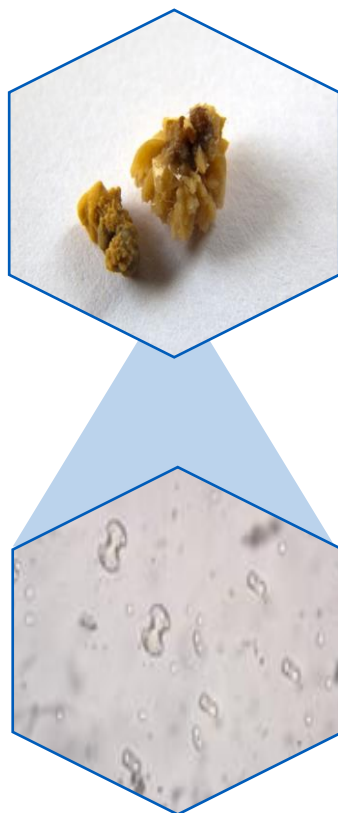


Diagnostic delay may be avoided by being aware of the signs and symptoms of PH1 and facilitating testing of appropriate patients^{9,22}



Click for references and abbreviations

Analyses in Patients With PH1 Have Identified Kidney Stone Characteristics



Magnified image

Kidney Stone Characteristics¹⁶

- Typically, **calcium oxalate monohydrate** (whewellite) stones
- **Peculiar morphology** reflecting speed of formation
 - White or pale yellow instead of brown
 - Disorganized internal structure
 - Radiating inner structure

Kidney stones are one of the most common symptoms of PH1; however, not all patients with PH1 are stone formers^{16,19,27}



Click for references and abbreviations

Diagnostic Algorithm: Published Recommendations for the Diagnosis of Patients with Suspected PH^{14–16}

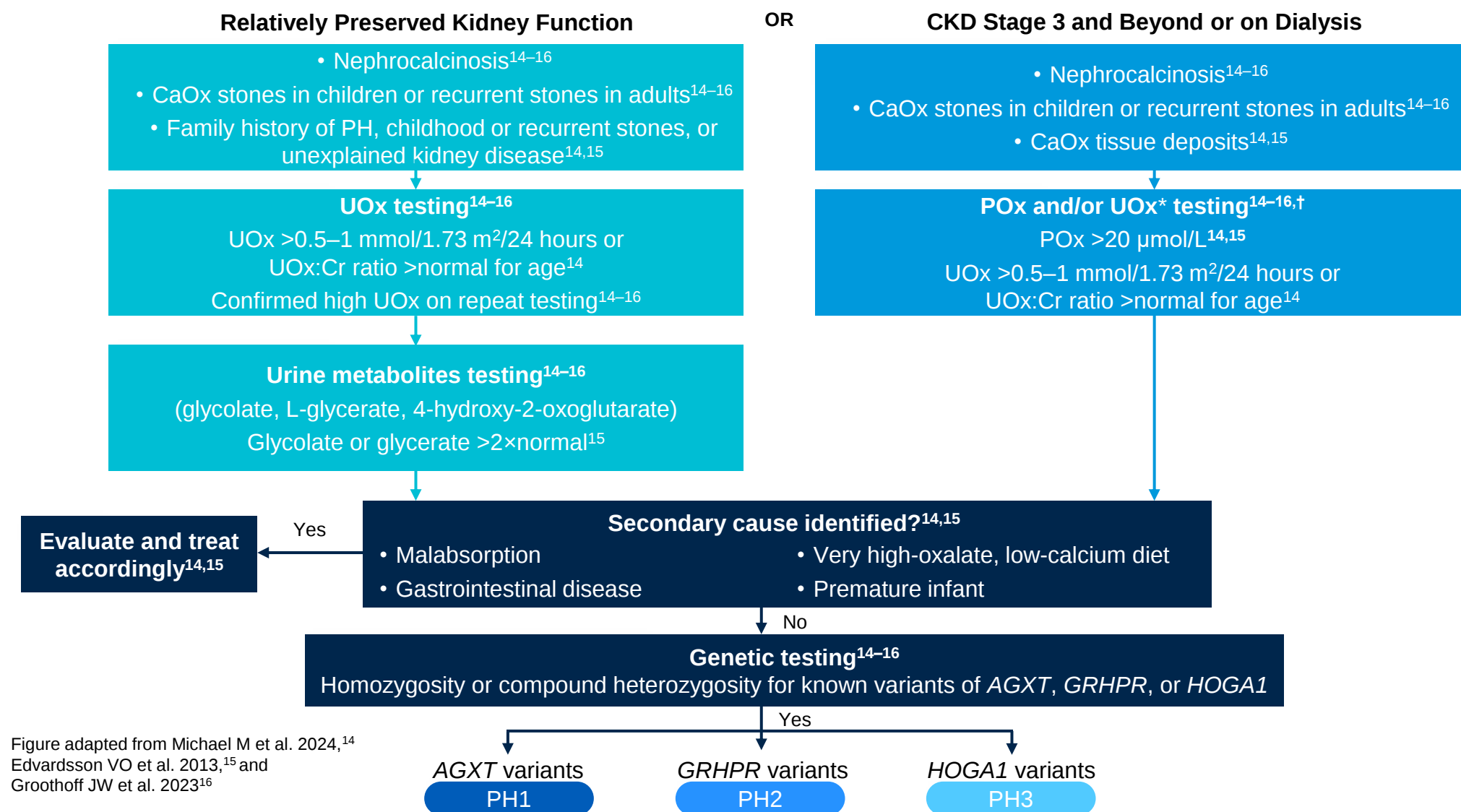


Figure adapted from Michael M et al. 2024,¹⁴
 Edvardsson VO et al. 2013,¹⁵ and
 Groothoff JW et al. 2023¹⁶

This information is being provided for educational purposes only. It is not intended to replace the independent medical judgment of any healthcare professional. Note that PH includes three types: PH1, PH2, and PH3. *For use in patients with residual urine output;¹⁶ †As patients on dialysis without PH can have average POx levels between 50 and 60 μmol/L, patients on dialysis with PH may have even higher values.¹⁶

+ Click for references and abbreviations

UOx Testing is Recommended in Patients with Relatively Preserved Kidney Function as a Key Measure of PH1 Diagnosis¹⁴



UOx

POx

Measuring UOx in Patients with Relatively Preserved Kidney Function

Collect 24-hour urine sample¹⁴



Repeat test to confirm UOx elevation¹⁴



Suggestive of PH: UOx levels above 0.5–1 mmol/1.73 m² per day*,^{14,16,28}



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*Utilize lab with experience measuring plasma and urine oxalate.¹⁶



Click for references and abbreviations

UOx Testing is Recommended in Patients with Relatively Preserved Kidney Function as a Key Measure of PH1 Diagnosis¹⁴



UOx

POx



Measuring UOx in Patients with Relatively Preserved Kidney Function

Age Considerations¹⁴

- The results of 24-hour UOx should be corrected to 1.73 m² BSA
- A random UOx:Cr can be used if there are challenges with timed urine collection
- **Suggestive of PH:** Random UOx:Cr higher than normal*

Differential Diagnosis^{14,16}

- Exclusion of secondary causes of hyperoxaluria is required before genetic investigations



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*Random UOx:Cr vary significantly by age. Consult pediatric reference tables for interpretation.¹⁴



Click for references and abbreviations

In Patients with CKD Stage 3 and Beyond or on Dialysis, POx is Recommended as a Main Measure of PH1 Diagnosis^{*,14,16}



UOx



POx



Practical Considerations for Measuring POx

Blood sample **must be placed on ice** and sent to the laboratory **immediately** as plasma has to be separated rapidly from cells^{16,29}

- Variations in POx levels due to **differences in assays and reference laboratories can cause confounding when interpreting results**¹⁴ therefore utilization of the same laboratory is recommended for POx tests³⁰

Measuring POx in Patients with CKD Stage 3 and Beyond^{14,16}

- POx should be corrected for eGFR, as POx increases with decreasing eGFR¹⁶

Suggestive of PH: POx levels above 20 $\mu\text{mol/L}$ ¹⁴



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*UOx can be considered for use in patients with residual urine output.¹⁶



Click for references and abbreviations

In Patients with CKD Stage 3 and Beyond or on Dialysis, POx is Recommended as a Main Measure of PH1 Diagnosis^{*,14,16}



UOx



POx



Measuring POx in Patients on Dialysis^{14,16}



As patients on dialysis **without PH can** have average POx levels between 50 and 60 micromols/L, patients on dialysis with PH may have even **higher values**

Suggestive of PH: POx levels >50–60 $\mu\text{mol/L}^\dagger$



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*UOx can be considered for use in patients with residual urine output;¹⁶ [†]Utilize lab with experience measuring plasma and urine oxalate.¹⁶



Click for references and abbreviations



Genetic Testing can Help Confirm the Diagnosis of PH1*



A presumptive diagnosis of PH by UOx or POx can be confirmed by molecular testing of *AGXT* gene for PH1¹⁴

Genetic confirmation of PH1 is important because:

- Elevated biochemical parameters may be due to various etiologies¹⁶
- It has a direct impact on clinical management³¹
- It can have implications for family planning^{16,31}



Ideally, after biochemical testing and clinical assessment leads to suspicion of PH, **genetic testing** should be performed as **early as possible**¹⁶

PH1 is an autosomal recessive disease¹⁴

It is recommended to offer genetic counseling to **patients with PH1 and their families**^{14,16}



- Screening of **all at-risk relatives** (symptomatic or not)^{14,16}
- Also important for:^{14,16}
 - Carrier testing
 - Prenatal testing

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*After excluding secondary causes of PH1.¹⁶



Click for references and abbreviations



Abbreviations and References

AGT, alanine-glyoxylate transaminase; AGXT, alanine-glyoxylate aminotransferase; BSA, body surface area; CaOx, calcium oxalate; CKD, chronic kidney disease; Cr, creatinine; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; GO, glycolate oxidase; HCP, healthcare professional; KTx, kidney transplant; PH, primary hyperoxaluria; PH1, PH type 1; PH2, PH type 2; PH3, PH type 3; POx, plasma oxalate; UOx, urinary oxalate; UOx:Cr, urinary oxalate to creatinine ratio; UTI, urinary tract infection.

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