

# The Importance of Evaluating Potential Underlying Causes of Kidney Stones: A Survey of Physician Experiences in Diagnosing Primary Hyperoxaluria Type 1

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## Background and Objective:

### Primary Hyperoxaluria Type 1 (PH1)<sup>1</sup>:

#### Pathophysiology

- Defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- AGT deficiency leads to overproduction of oxalate; results in insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course may ultimately lead to multi-organ damage from systemic oxalosis

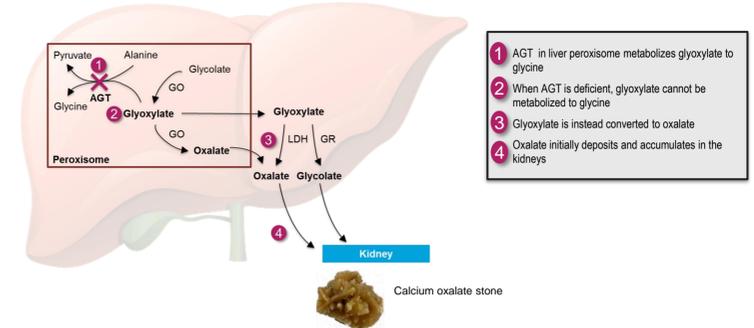
#### Diagnostic Challenges

- Clinical phenotype of PH1 is heterogeneous: wide spectrum of clinical manifestations, variable age of presentation, and unpredictable rate of progression
- These factors often lead to delayed diagnosis increasing disease burden

### Objective:

To identify triggers that raised suspicion of disease and factors that contributed to diagnostic delays throughout the PH1 patient journey

### Oxalate Synthesis in PH1<sup>2</sup>:

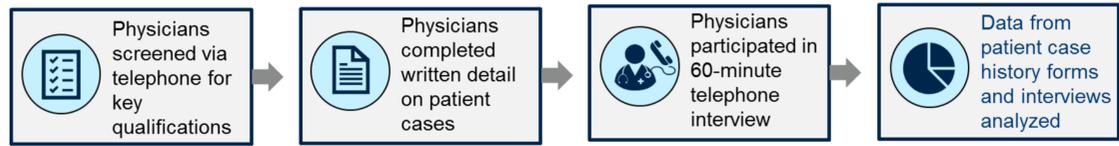


## Methods

### Physician Research Interviews

#### A series of case-based physician interviews

- Key inclusion criteria: physicians in practice for 2+ years; active role in diagnosing, treating, or managing 1+ PH1 patient within last 5 years; spend ≥50% of time in direct patient care; see 100+ total patients per year; able to review PH1 patient medical records



## Results

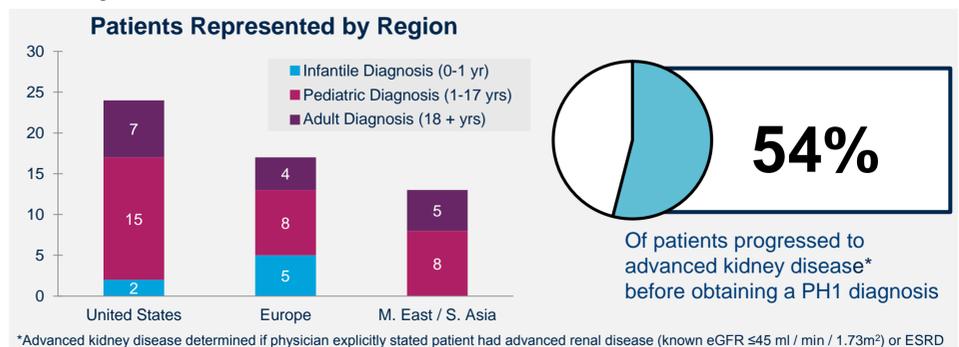
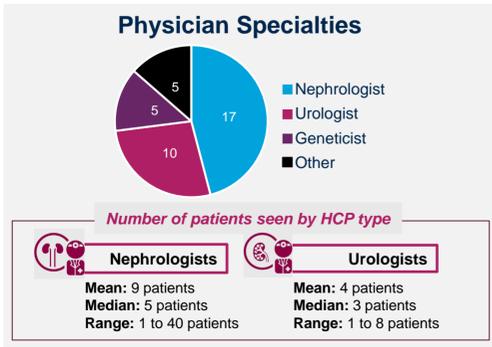
### Physician and Patient Characteristics

#### Physician Characteristics

- 37 physician interviews were conducted between November 2018 and March 2019
- Physicians were from the United States (N=17), Europe (N=13), and Middle East / South Asia (N=7)

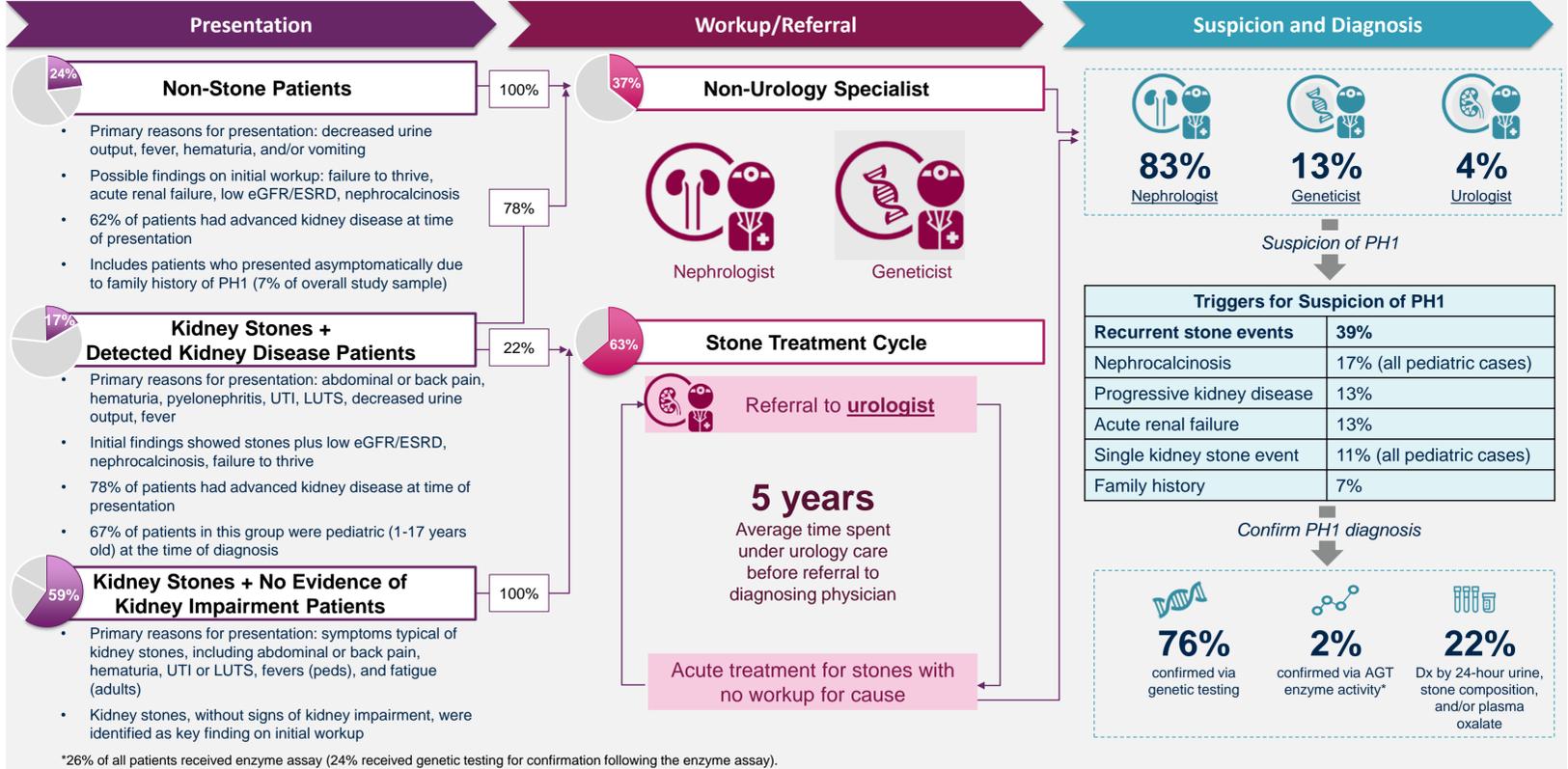
#### Patient Characteristics

- A total of 54 PH1 patient cases were reported by the physicians interviewed
- Age of diagnosis ranged from 1 month – 48 years (median 7.5 years)
  - By the time of interviews, patients were a median of 9.5 years (range: 0.5 – 25 years) post-diagnosis



### Patient Journey from Presentation to Diagnosis

- Kidney stones were the disease manifestation which most commonly triggered suspicion of PH1; however, in many cases, kidney stones were treated acutely without further evaluation, leading to significant diagnostic delay
- Majority of patients presented with stones and remained under urology care for treating stones for several years with no metabolic evaluation (stone treatment cycle); these patients spent an average of 5 years in this cycle
- Recognition of kidney impairment was critical to appropriately evaluate patients and obtain diagnosis of PH1 when kidney stones were the main disease manifestation

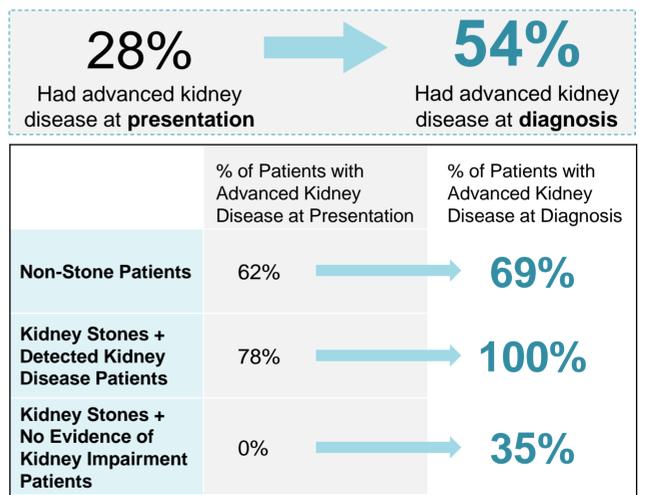
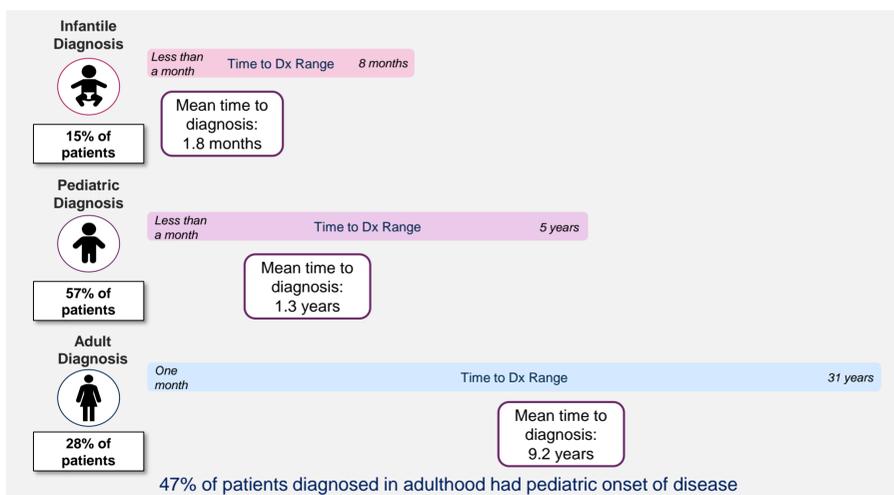


### Diagnostic Delay

- Time from first symptoms to diagnostic confirmation was shorter in infant and pediatric patients compared to adults; infant and pediatric patients tended to have more overt symptoms that drove urgency to diagnose
- In many cases, due to diagnostic delay, patients – particularly adults – had already progressed to advanced kidney disease by the time of diagnosis

### Disease State At Diagnosis

- Majority of patients (54%) were not diagnosed until they reached advanced kidney disease
- Includes 35% of the patient group with only kidney stones at diagnosis, all of whom had intact kidney function at the time of initial presentation



## Discussion & Summary

- Kidney stones were the most common symptom triggering PH1 suspicion; interviewees also most commonly mentioned kidney stones (a single event in children and recurrent events in adults) when asked what, in retrospect, should have triggered suspicion in these cases
- Despite this, a number of patients with PH1 experienced long times to diagnosis following initial onset of disease manifestations, which often included kidney stones
  - In many cases, patients initially presented with minimal or no renal impairment, but progressed to advanced kidney disease before diagnosis; this delay in diagnosis prevented the opportunity to modify the course of the disease
- Key factors that contributed to diagnostic delay: patients remaining in the stone treatment cycle with no further evaluation/workup completed for a while after initial presentation with stones and/or lack of awareness/suspicion of PH1

**Conclusion:** Although all patients with kidney stones should be evaluated according to existing stone management guidelines<sup>3-4</sup>, many patients in this study remained in the stone treatment cycle without evaluation for extended periods of time. A single stone event in children and recurrent events in adults should immediately trigger suspicion and evaluation for an underlying genetic cause, such as PH1, to provide an opportunity to modify the disease course

