# Nephropathic cystinosis

Recognising ‘red flags’
to aid early diagnosis

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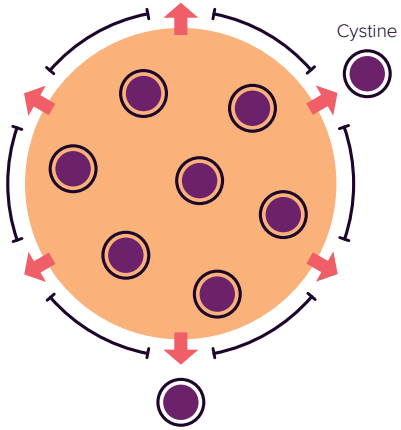
# What is cystinosis?

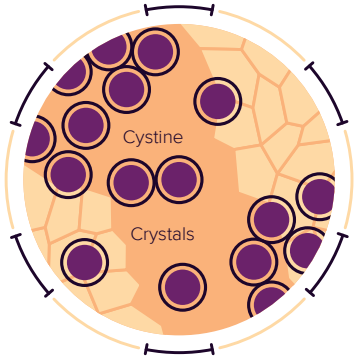
Cystinosis is an ultra-rare, progressive, lifelong, multisystemic autosomal recessive disorder with a prevalence of 1–2 people in every million.[1,2]

There are three clinically recognised forms of cystinosis, depending on the age of presentation and degree of renal disease severity.[1] The most common and severe form is nephropathic cystinosis, accounting for 95% of patients.[1]

Nephropathic cystinosis occurs as a result of mutations in the gene *CTNS*, which codes for the lysosomal cystine-proton cotransporter cystinosin.[1,3,4] In the absence of a functional transporter, cystine accumulates and crystallises inside the lysosome. Cystine accumulation leads to continuous damage in multiple organs over time.[1]




**Normal lysosome**




**Lysosome in nephropathic cystinosis**





# The importance of timely diagnosis

Owing to the rarity of nephropathic cystinosis, diagnosis is often delayed; some patients are diagnosed only when they present with end-stage renal disease (ESRD).[5]

Diagnosis of nephropathic cystinosis should be made as soon as possible, because early initiation of cystine-depleting therapy has considerable impact on the long-term prognosis. Most of the clinical manifestations of the disease can be prevented or delayed with cystine-depleting therapy.[5]

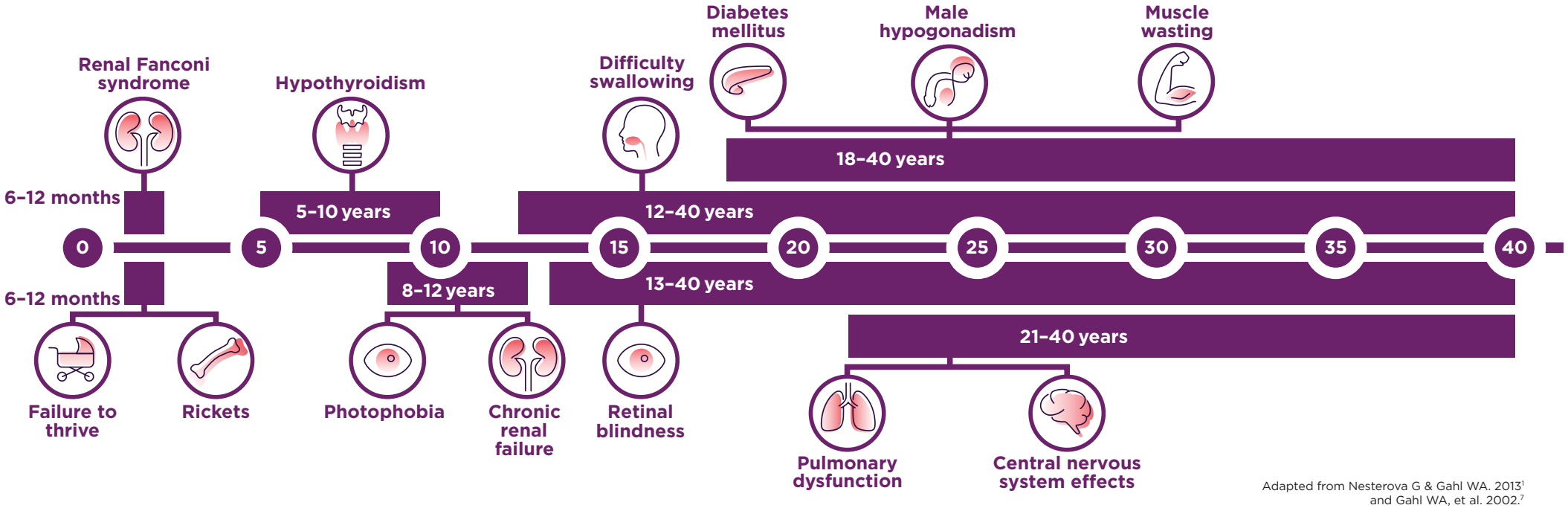
# Consequences of nephropathic cystinosis

Nephropathic cystinosis is the major identifiable cause of renal Fanconi syndrome in children, and, if untreated, leads to terminal renal failure in the first decade of life and extra-renal complications throughout life.[1]

Before treatment was available, children with nephropathic cystinosis developed advanced renal failure around age 10, and died shortly after if not treated with dialysis or kidney transplantation. Even if transplanted, multi-systemic complications continued to develop and usually resulted in death in young adulthood.[6]

Nowadays, cystine-depleting therapy has transformed this once fatal disease into a treatable disorder, allowing people with nephropathic cystinosis to live into their 40s and 50s.[1,6]

**Timeline shows age of onset of complications in patients not receiving cystine-depleting therapy**



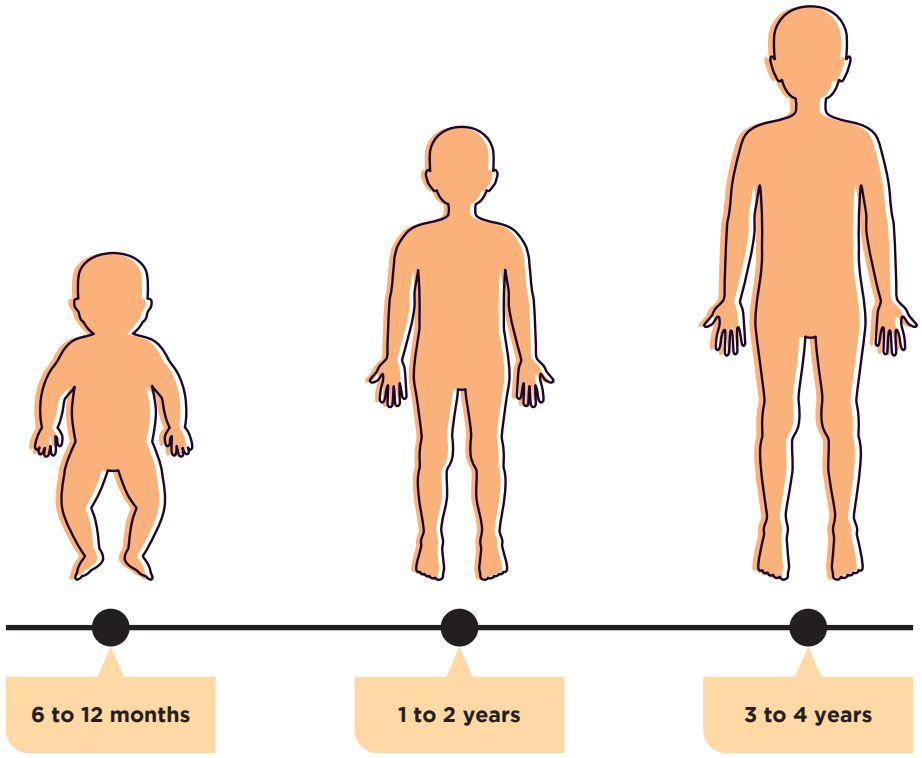

Adapted from Nesterova G & Gahl WA. 2013[1] and Gahl WA, et al. 2002.[7]



Discover Cystinosis

# Explore the early symptoms of nephropathic cystinosis

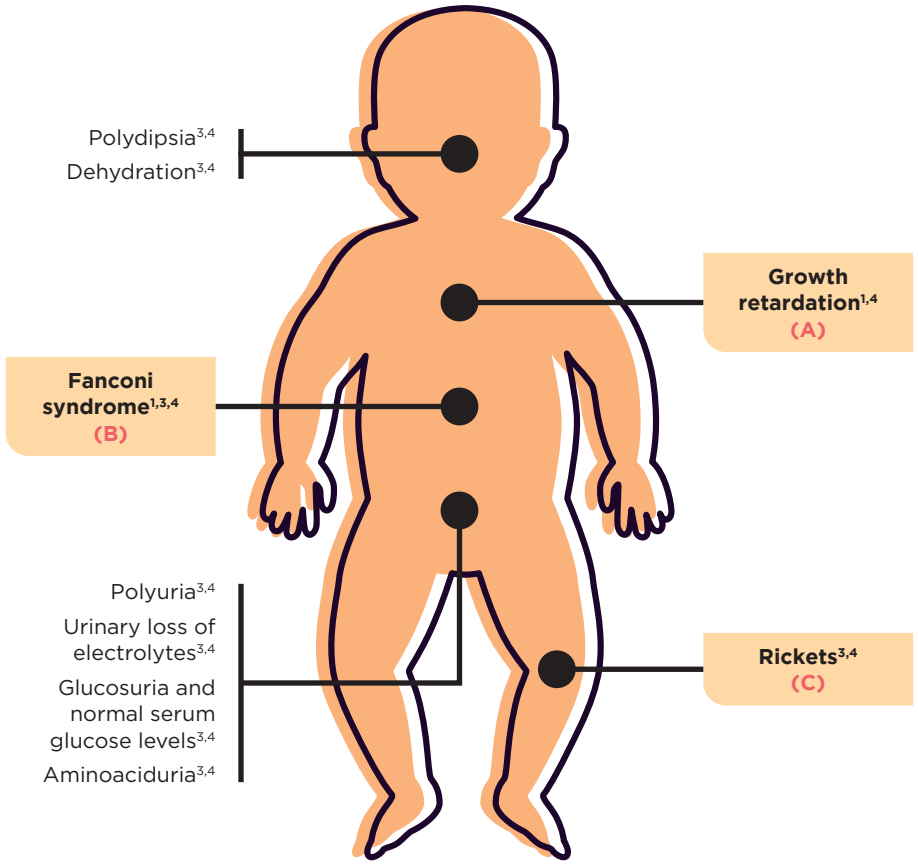
Neonates are clinically asymptomatic at birth with normal birth weight and normal length, even though cystine accumulation starts in utero.[3,4] Symptoms gradually develop during the first months of life.[3]





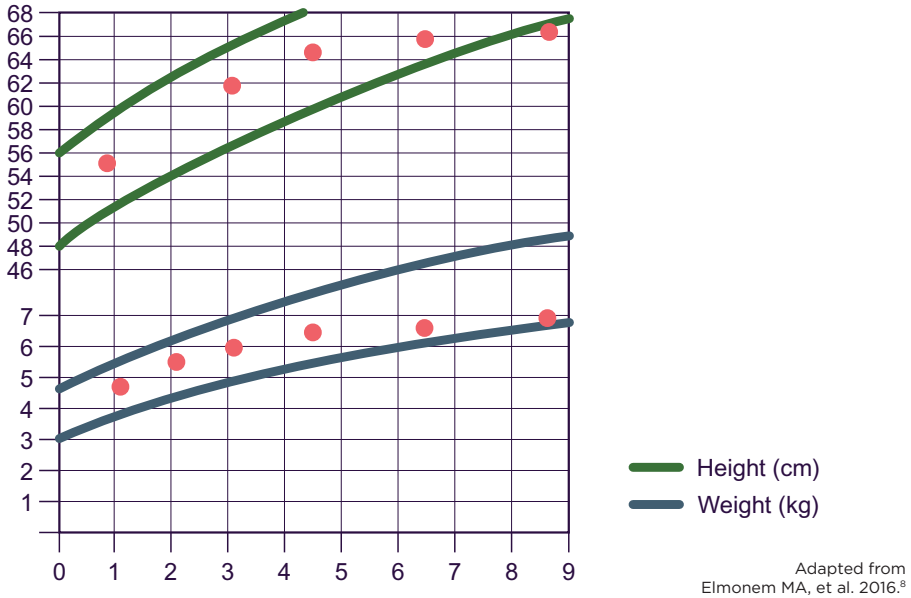



# Early symptoms: 6 to 12 months



## (A) Growth retardation

At birth, patients show normal birth length and weight parameters. By the age of 6 to 12 months, height drops to the third percentile, and further growth is restricted to less than 60% of the normal range.[8]




Adapted from Elmonem MA, et al. 2016.[8]

The graph represents the typical growth pattern of cystinosis patients if specific treatment is not started in the first year of life.[8]

**Red** markers indicate growth pattern at birth, followed by decreased growth velocity after six months.[8]

**Green** and **blue** lines represent the 3rd and the 97th percentiles for height and weight, respectively.[8]





## (B) Fanconi syndrome

Fanconi syndrome is 'a dysfunction of the proximal tubule that leads to polydipsia, polyuria, dehydration, proximal renal tubular acidosis, urinary loss of electrolytes, and growth retardation.[4]

As cystinosis is the most common reason for Fanconi syndrome at this age, this differential diagnosis should always be considered.[4]

Cystinosis should be suspected in all patients with failure to thrive and signs of renal Fanconi syndrome.[3]

Less common reasons for secondary Fanconi syndrome include:

- Dent's disease[4]
- Lowe's syndrome[4]
- Inherited fructose intolerance[4]
- Galactosaemia[4]
- Tyrosinaemia[4]

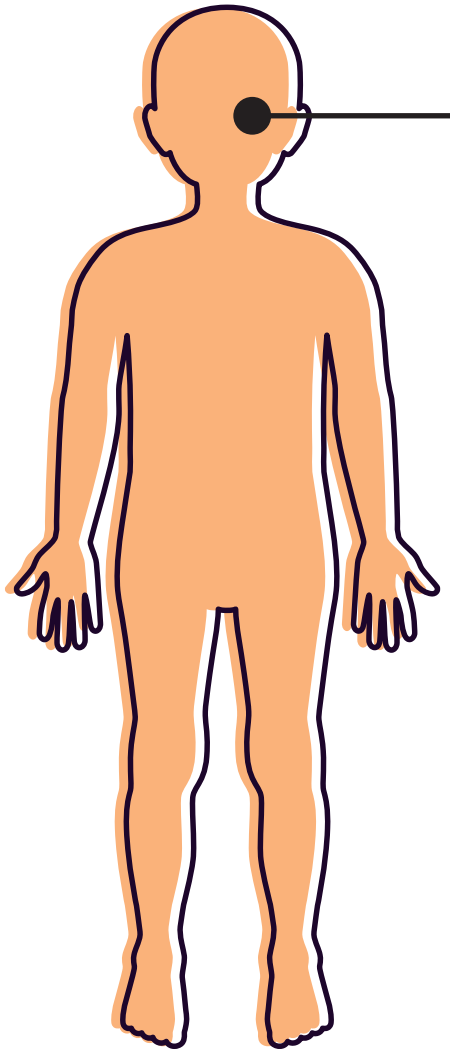
## (C) Rickets

Increased urinary loss of phosphate, calcium, and disturbances in vitamin D metabolism cause hypophosphataemic rickets in cystinosis patients.[4]

Clinical signs are:

- Genua vara[4]
- Frontal bossing[4]
- Rachitic rosary[4]
- Metaphyseal widening on skeletal X-rays[4]

# Early symptoms: 1 to 2 years



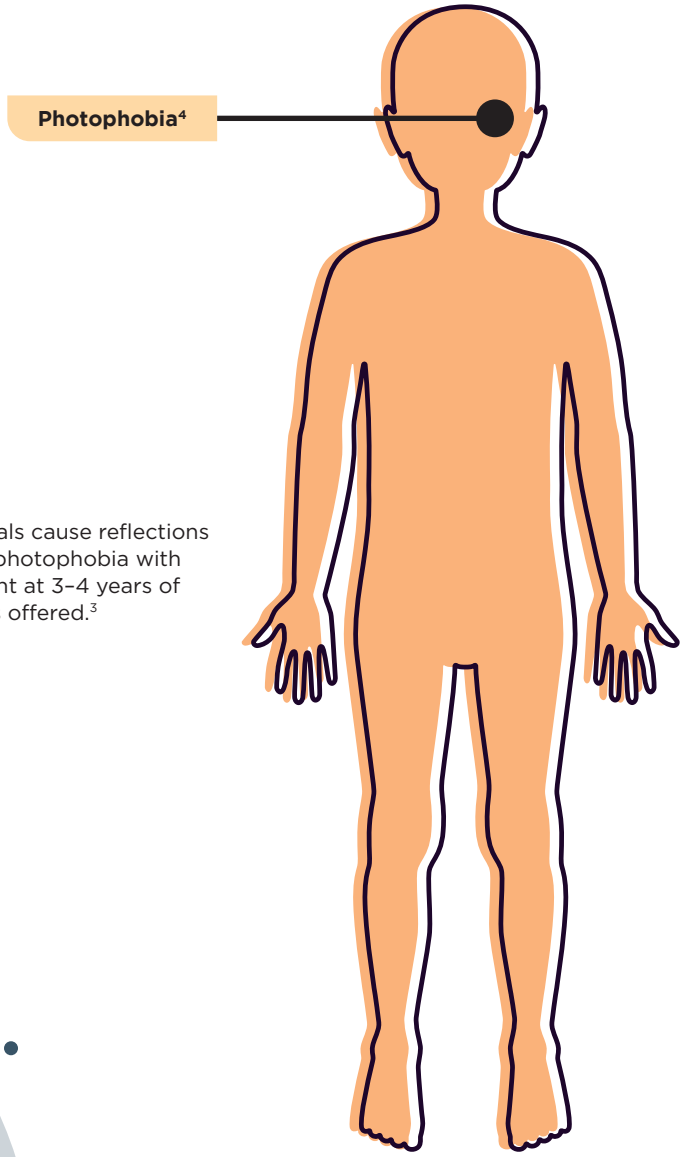

## Corneal cystine crystal accumulation

Corneal cystine crystals are absent at birth and generally can be observed by an experienced ophthalmologist with slit lamp examination starting at the age of 1.[3] Corneal crystals are always present after 16 months of age.[9]





# Early symptoms: 3 to 4 years




## Photophobia

Corneal cystine crystals cause reflections of light and result in photophobia with substantial impairment at 3–4 years of age if no treatment is offered.[3]

# Diagnostic investigations

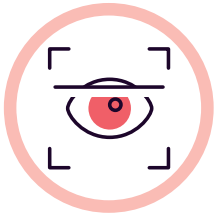
## Investigations to support a diagnosis of cystinosis

**Patient history and clinical symptoms**

- Failure to thrive and growth retardation[3]
- Polyuria, polydipsia, vomiting, constipation[3]
- Rickets[3]
- Lighter skin and hair colour (a classic but not universal finding)[8]

**Molecular testing of *CTNS* gene**

- Reveals 95% of disease-causing mutations[8]



**Slit-lamp examination**

- Corneal cystine crystals are usually visible on a slit-lamp examination, and may be the initial diagnosing criterion for late-onset patients[8]

**Tandem mass spectrometry**

- Method of WBC cystine assay^[3]
- Most sensitive and widely used[3]





**WBC cystine assay**

- Gold standard – sensitive and precise[7]
- Cystine levels can be measured in a mixed WBC preparation or in separated granulocytes (polymorphonuclear cells^)[2]
- Methods of cystine determination and threshold values vary between cell types^[10]
- Techniques may include high-performance liquid chromatography, mass spectrometry and cystine-binding protein assay^[3]

**Laboratory tests**

- Biochemical evidence that may suggest cystinosis include loss of electrolytes, minerals, glucose, amino acids, low molecular weight proteinuria and severe acidosis, elevated serum alkaline phosphatase, hypocalcaemia, hypophosphataemia, hypokalaemia[5,11]

**Other procedures**

- Imaging may help assess complications associated with cystinosis[5]
- Prenatal diagnosis can be reliably performed on DNA samples isolated from chorionic villi or amniotic fluid cells[5]

DNA = deoxyribonucleic acid; WBC = white blood cell.

# Treatment goals

Lifelong oral cystine-depletion therapy is the treatment of choice for all nephropathic cystinosis patients.[1] Therapy should be initiated as early as possible following diagnosis, and continued throughout life.[5,8]

The goal of cystine-depleting therapy is to maintain a WBC cystine level of <1 nmol hemicystine/mg protein.[4]

If adherence is consistent, cystine-depleting therapy:


Achieves leukocyte cystine depletion of up to 95% and reduces cystine levels in muscle, liver and other parenchymal tissues by up to 95%[12,13]

Delays kidney function decline and end-stage renal disease onset[14–16]

Helps prevent hypothyroidism, diabetes, neuromuscular disorders and pulmonary dysfunction, and preserves childhood growth[12,16,17]

Improves survival[16]

**Consistent adherence and early initiation is crucial to delay or prevent renal and extra-renal complications.[6,18]**

WBC = white blood cell.

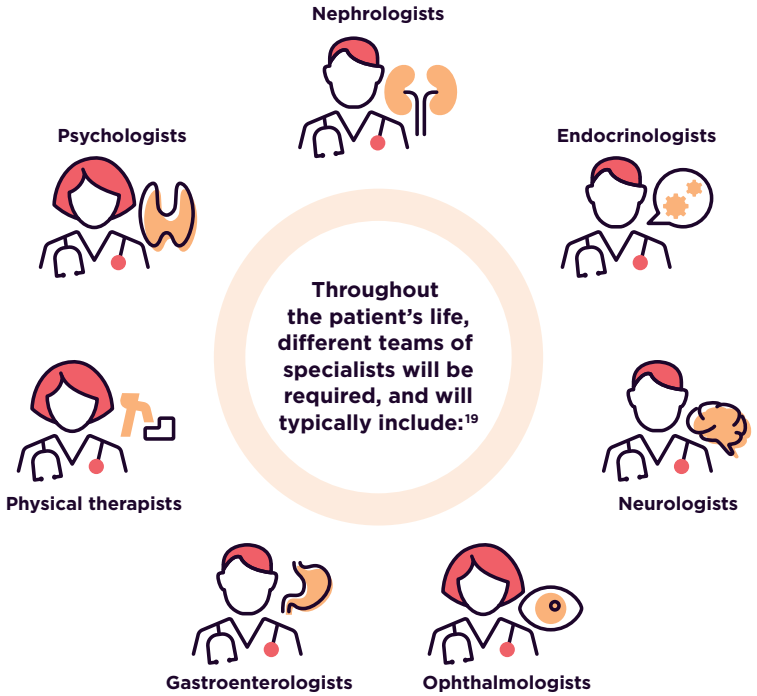




# The importance of multidisciplinary care

The transition of patients from paediatric to providers requires special attention to meet all challenges presented by adult patients with cystinosis.[5]

It is suggested that clinicians beyond the paediatric nephrologist are involved. Pubertal delay is common, although it does not affect all patients with cystinosis. Ongoing care by an endocrinologist is therefore recommended.[2]



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