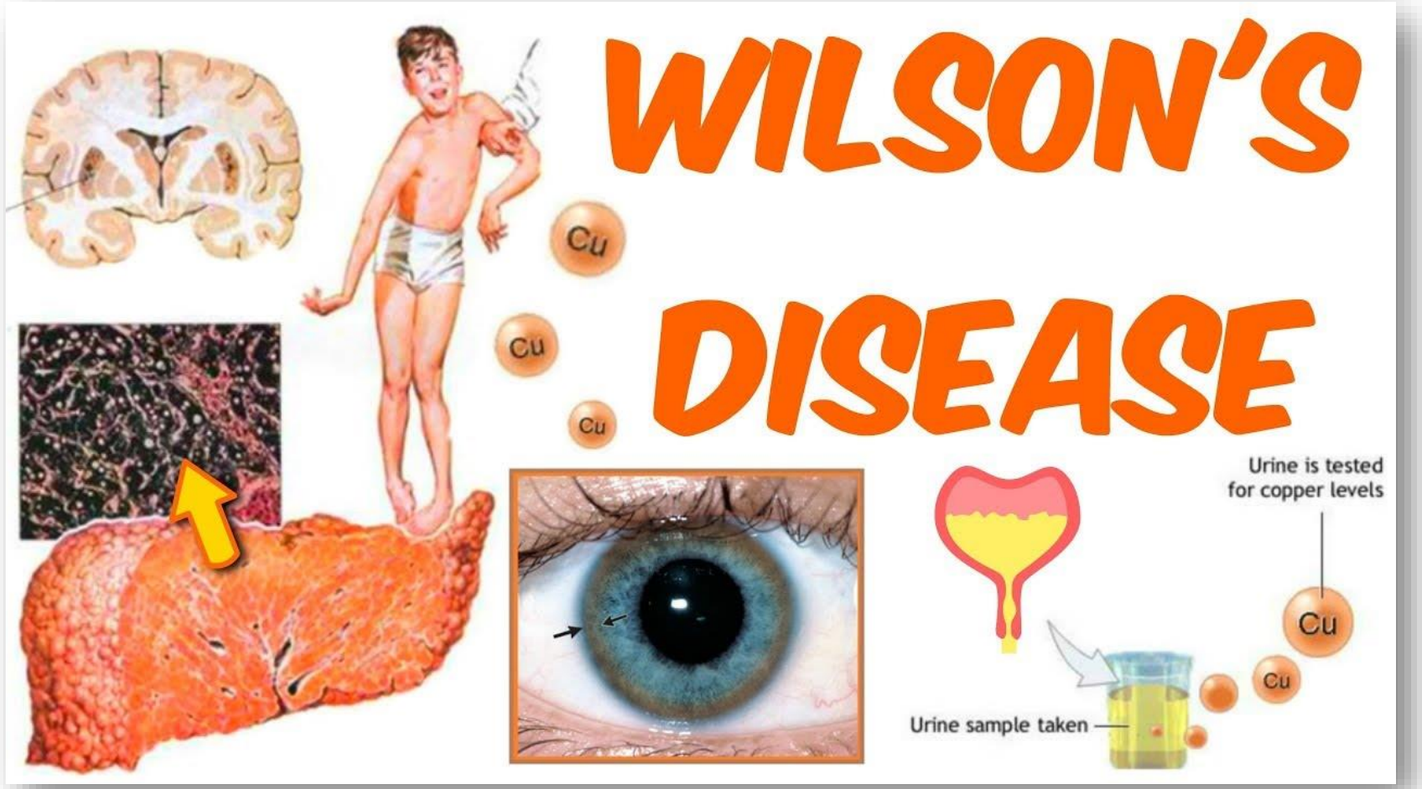
In the Name of God



Diagnostic tests

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Importance of Early Diagnosis

1 Prevent Liver Failure

Early diagnosis and treatment can prevent irreversible liver damage and potentially fatal consequences.

2 Neurological Protection

Treatment can mitigate neurological complications and improve the long-term quality of life for children with Wilson's disease.

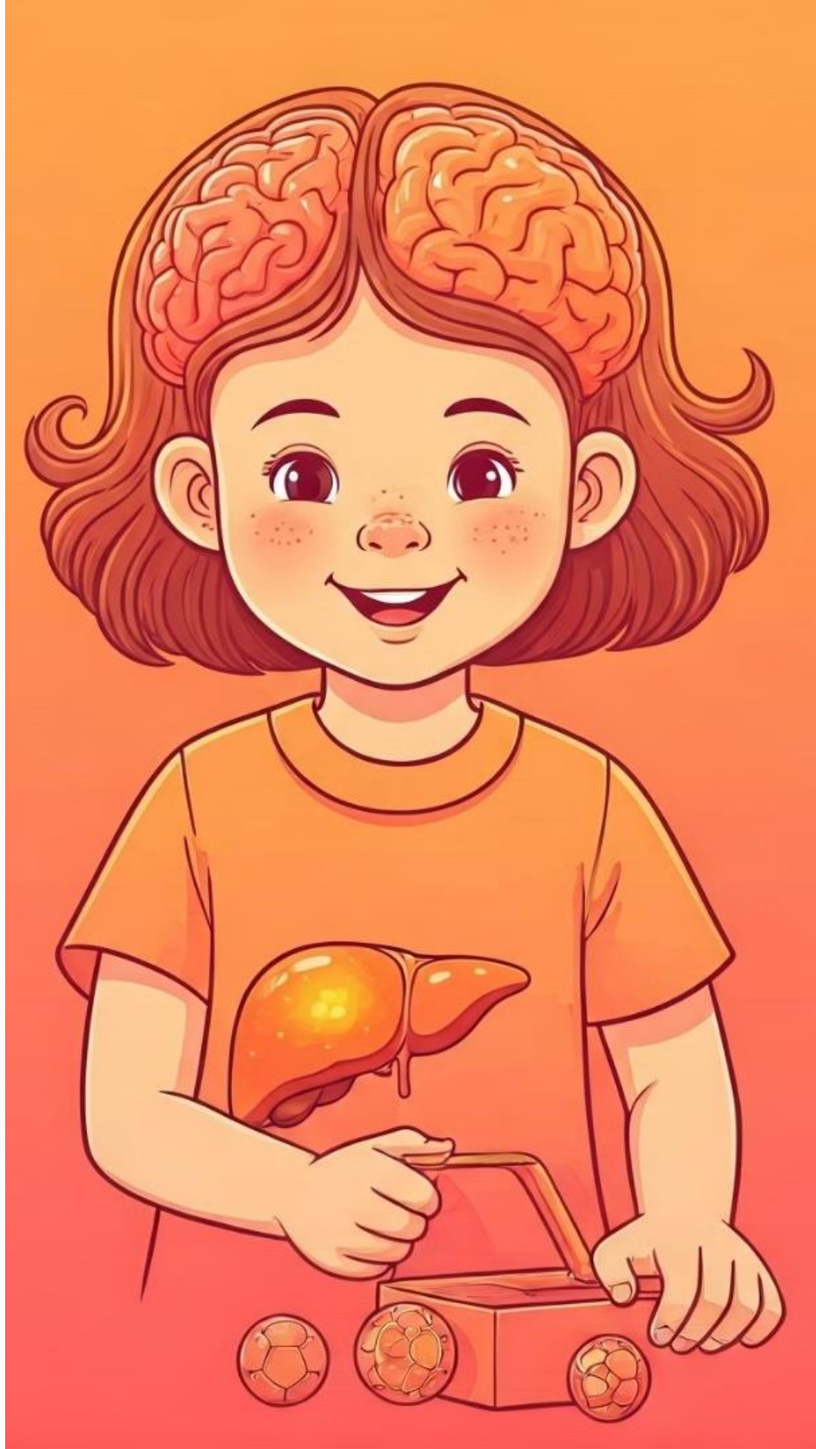
Diagnostic Tests in Ped. Wilson's Disease

In patients with clinical features suggestive of Wilson disease:

Start by liver biochemical tests

- a complete blood count
- Serum ceruloplasmin
- copper levels
- ocular slit-lamp examination (or optical tomography)
- 24-hour urinary copper excretion.

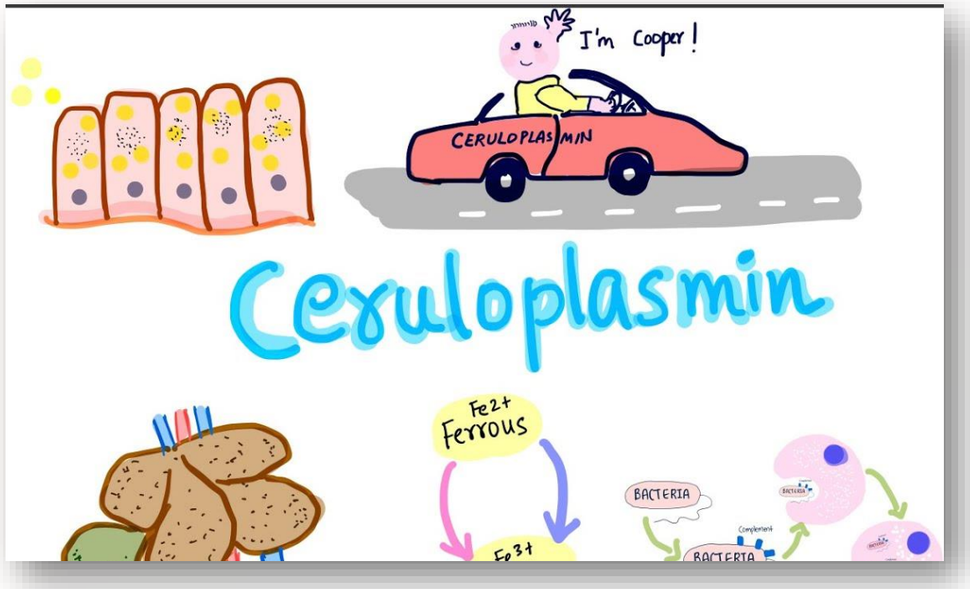
- ➢ The results of these tests may be sufficient to make a diagnosis of Wilson disease
- ➢ In patients with indeterminate results: additional testing:



Biochemical Tests:

1- Ceruloplasmin

- 85-90 % of pts with WD have ↓ ceruloplasmin (<20 mg/dL).
- Serum ceruloplasmin near 20 + KF ring: diagnostic of WD
- A very low ceruloplasmin <5: strong evidence for WD.
- Normal values for serum ceruloplasmin vary by age



A low ceruloplasmin level is not sufficient to make a diagnosis of Wilson disease, and a normal level does not exclude a diagnosis of Wilson disease.

Serum ceruloplasmin may be low in patients without WD:

- 10-20% of asymp heterozygous carriers:
  - serum ceruloplasmin < 10- 20
- Acute viral hepatitis
- Chronic hepatitis
- Drug-induced liver disease
- Alcohol-induced liver disease
- Malabsorption
- Marked renal or enteric protein loss:
  - nephrotic syndrome or protein-losing enteropathy.
- End-stage liver disease of any cause
- Rare diseases: Menkes disease & aceruloplasminemia
- Copper deficiency (parenteral nutrition, excessive Zn admin)

Serum ceruloplasmin may be normal or elevated in patients with WD:

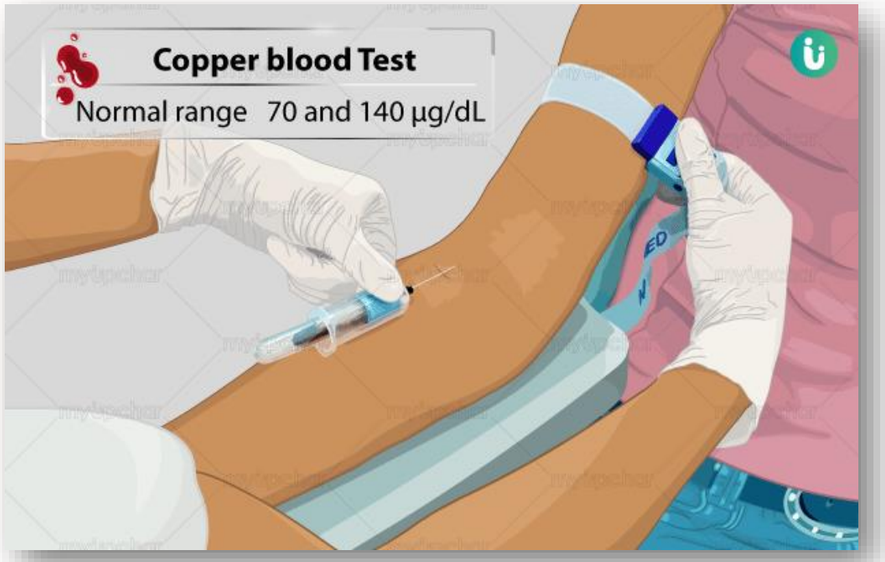
- Acute hepatitis
- Pregnancy
- Estrogen suppl/use of oral contraceptives
- Inflammation and tissue injury: acute phase reactant

Biochemical Tests:

2- Copper Levels

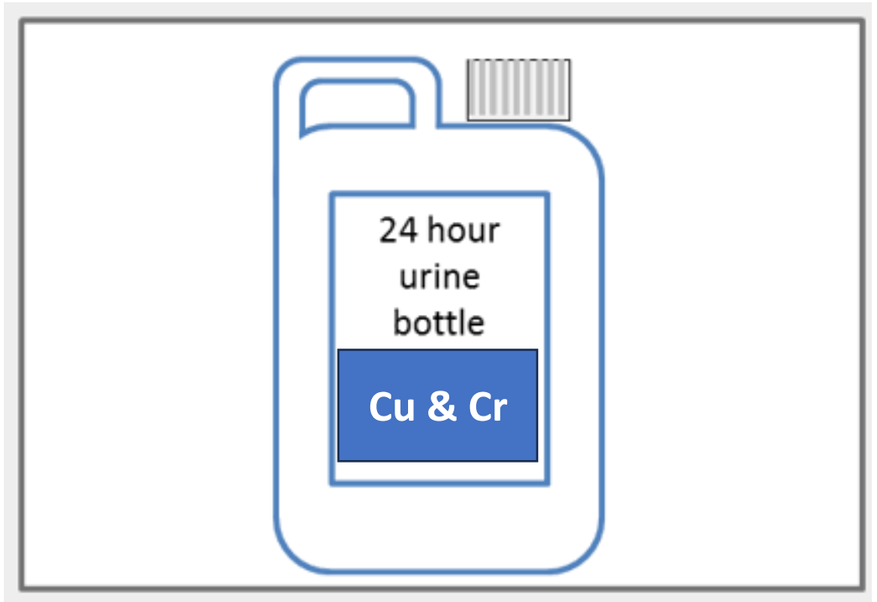
Measures the amount of copper in the blood and urine.

Elevated levels indicate copper accumulation.



- In WD, the serum copper is ↓ in proportion to the ↓ in ceruloplasmin, despite the presence of copper overload
- EXCEPTION : : marked ↑ of serum copper in the setting of acute liver failure due to WD > 200 mcg/dL.
- serum non ceruloplasmin-bound copper ? as a diagnostic test for WD:
  - better for therapeutic monitoring of treatment

- Urinary copper: diagnosis of WD and for monitoring therapy.
- In WD: typical: 24-hour urinary copper excretion of >100 mcg
- >40 mcg/24-hours: suggestive: further evaluation.
- ↑ urinary copper in:
  - other forms of chronic active liver disease
  - heterozygotes for Wilson disease
  - but most often levels are below 100 mcg per 24 hours
- The 24-hour collection is begun at the time the pt awakens.
- The 1st void is discarded and the exact time noted. Subsequently, all urine voids are collected, with the last void timed to finish the collection at exactly the same time the next morning.
- The 24-hour urine creatinine: 15-20 mg/kg body weight.
- The test should not be used in patients with renal failure.
- Spot urine: not reliable
- Avoid copper contamination of the urine containers.



Penicillamine challenge test:

- As a means to increase sensitivity and specificity of the 24-hour urine study for diagnosing WD.
- Penicillamine greatly increases urinary copper in pts with WD, and to a lesser extent, in pts with other forms of liver disease.
- The penicillamine challenge is rarely used because:
  - unreliable for excluding WD in asymptomatic siblings
  - not been evaluated for differentiating heterozygous carriers from affected homozygotes
  - not been well-standardized in adults
- Has been standardized in children, but as an adjunctive test
- a 500 mg dose of penicillamine (regardless of the pt's weight) at the beginning of the 24-hour urine collection and then again at 12 hours.
- Urinary copper > 1600 mcg per 24 hours is much more likely in WD compared with other types of liver disease.

Give your child the first dose of 500mgs of Penicillamine (for example at 9am)

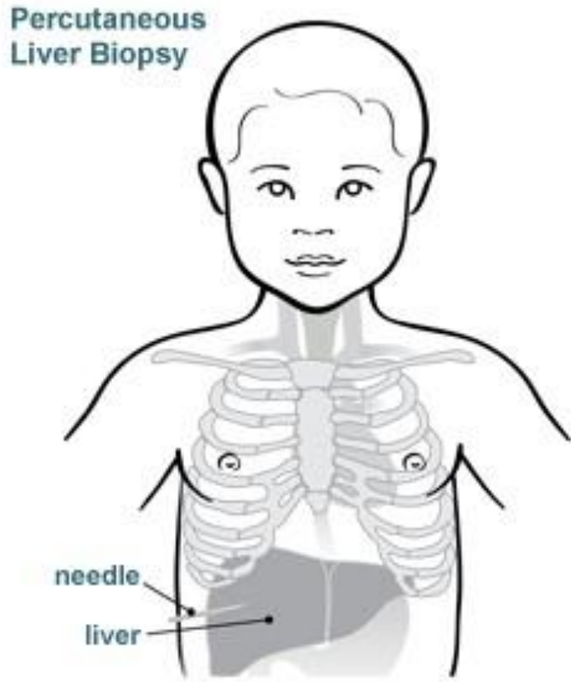
Give the second dose of 500mgs of Penicillamine 12 hours after the first dose (for example at 9pm).

TABLE 4. Diagnostic score in Wilson's disease, agreed at a consensus meeting (64)

Score	−1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of WD (or typical brain MRI)		Absent		Present	
Coombs negative hemolytic anemia + high serum copper		Absent	Present		
Urinary copper (in the absence of acute hepatitis)		Normal	1–2 × ULN	>2 × ULN, or normal but >5 × ULN 1 day after challenge with 2 × 0.5 g D-penicillamine	
Liver copper quantitative	Normal		<5 × ULN (<250 μg/g)	>5 × ULN (>250 μg/g)	
Rhodanine positive hepatocytes (only if quantitative Cu measurement is not available)		Absent	Present		
Serum ceruloplasmin (nephelometric assay)		>0.2 g/L	0.1–0.2 g/L	<0.1 g/L	
Disease-causing mutations detected		None	1		2

Total score	evaluation
0-1	unlikely
2-3	probable
4 or more	Highly likely

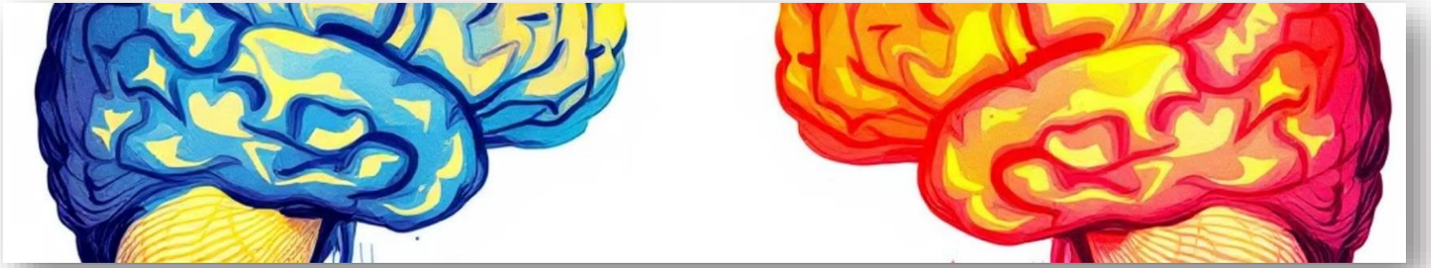
- While a diagnosis of Wilson disease is established in patients with ↓ serum ceruloplasmin levels, KF rings, and ↑ urinary copper, additional testing is required in patients with indeterminate results (a Leipzig score of three or less).



Gene
Sequencing

- Typically, the next step: liver biopsy to determine the hep cu concentration and to look for histologic changes suggestive of WD, especially in patients with abnormal liver tests.

- Genetic testing: an increasing role in the diagnosis of WD
- for whom a diagnosis cannot be established in other ways
- to identify mutations within a family to screen asymptomatic members.
- approximately 900 mutations within the ATP7B
- can distinguish healthy heterozygote carriers from affected presymptomatic WD patients, and confirm the diagnosis of WD.
- next-generation sequencing in 95% of affected subjects



Imaging Techniques: MRI and Slit-lamp Examination:

MRI

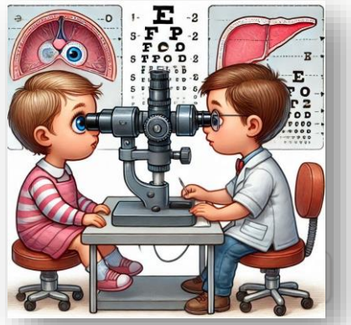
- Often shows abnormalities in neuropsychiatric involvement, may be normal when the presentation is solely with hepatic.
- MRI findings for Wilson disease: abnormal T-2 signals in the basal ganglia, brainstem, and white matter.

1

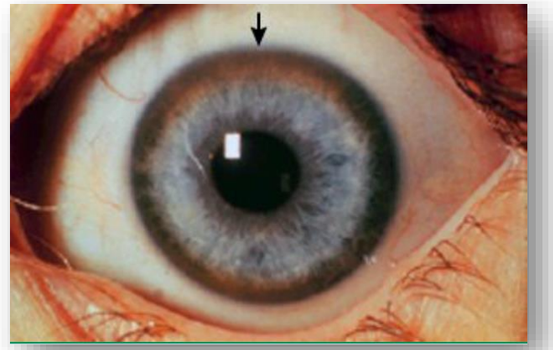
2

Slit-lamp Exam

- Kayser-Fleischer rings: a characteristic copper deposition in the cornea
- Sun flower cataract: copper deposits in the lens

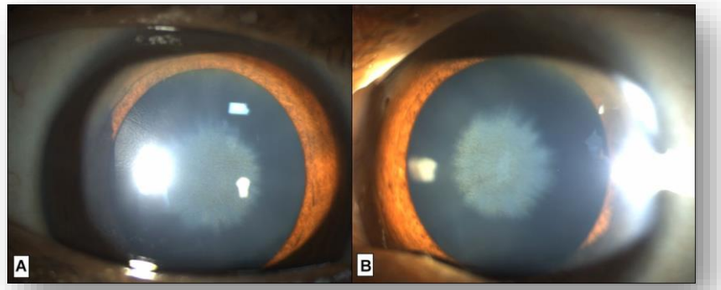


Kayser-Fleischer rings: copper deposit in the Descemet membrane

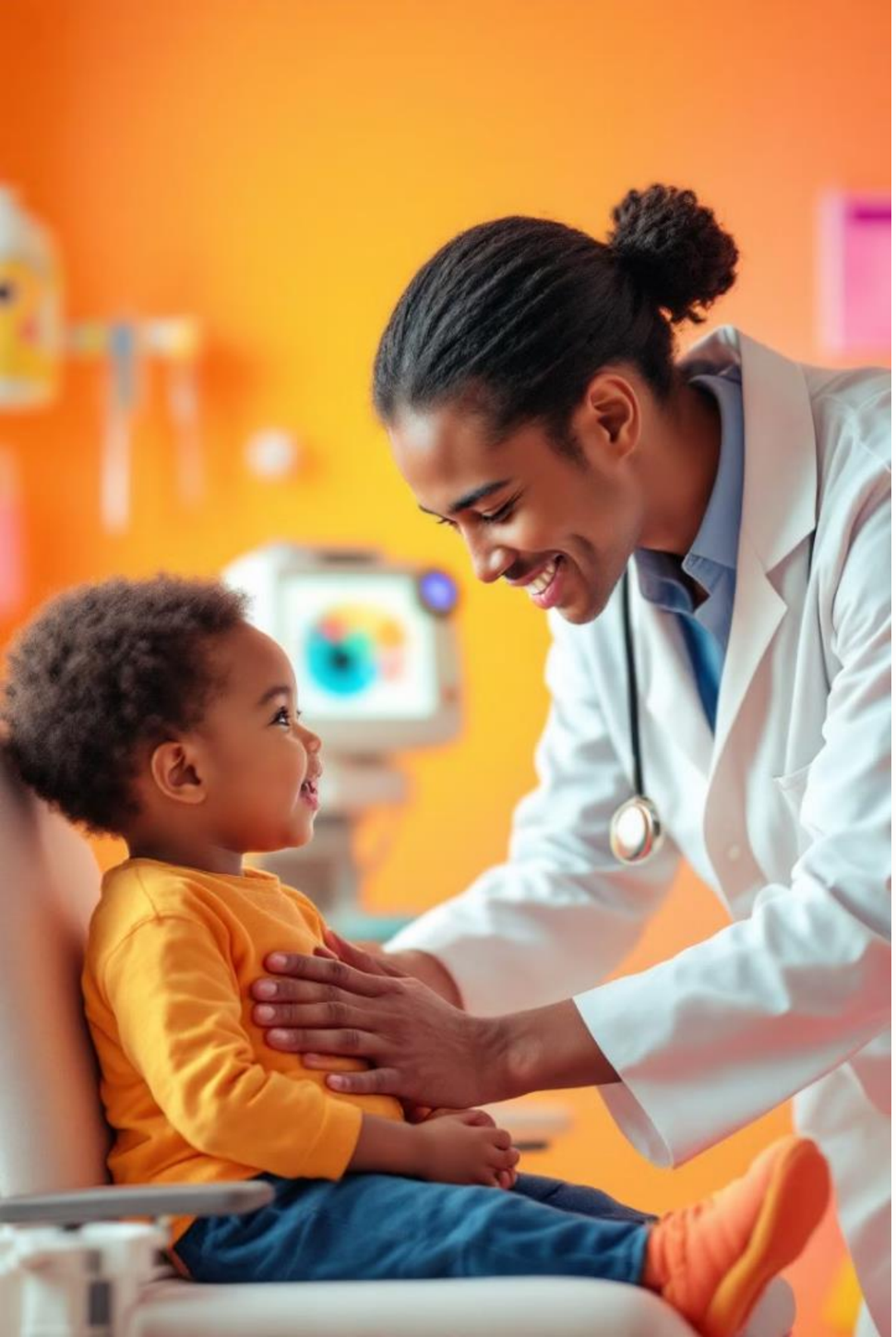


- In 50-60 % of patients with isolated hepatic WD and in over 90% of patients with clinical neurologic involvement
- Among patients presenting with ALF, KF rings are present in approximately half.
- While highly suggestive of Wilson disease, KF rings are not specific for WD.
  - rarely been reported in other chronic cholestatic diseases
- They are usually most pronounced at the inferior and superior poles of the cornea (Kayser-Fleischer rings gradually disappear with effective medical treatment for Wilson disease or following liver transplantation. Their reappearance suggests noncompliance with therapy.
- Generally asymptomatic, appearing bilaterally, with the upper portion of the cornea being the first to be affected.
- Over time, these rings spread circumferentially

Sunflower cataracts: copper deposits in the lens



- prevalence in Wilson disease is not well established,
- not appear to interfere with vision.
- Like Kayser-Fleischer rings, the cataracts gradually disappear with treatment.



Combination of Tests for Accurate Diagnosis

1

Biochemical Tests

Initial screening for abnormal copper metabolism.

2

Genetic Confirmation

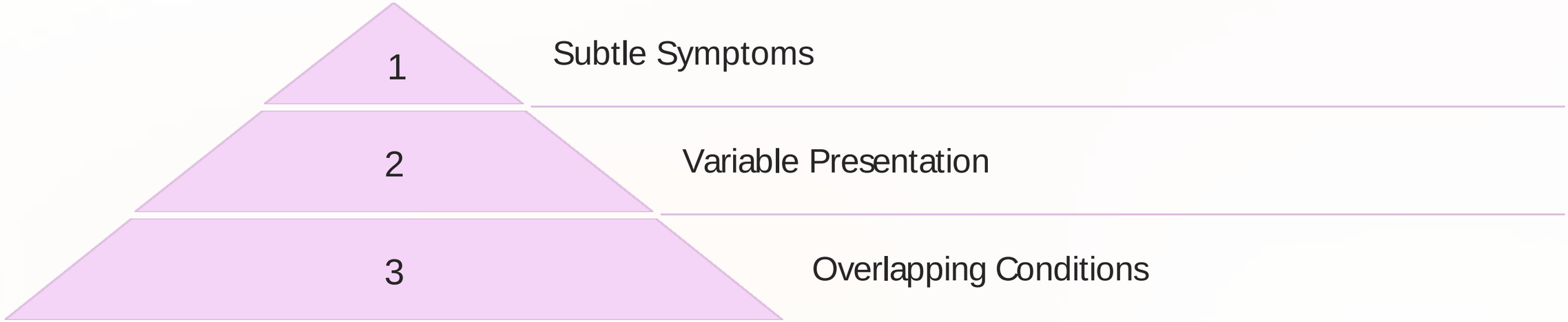
Confirms the presence of ATP7B gene mutations.

3

Imaging Assessment

Identifies neurological and ocular abnormalities.

Challenges and Limitations of Diagnostic Approaches




THANK YOU
Any Questions?