Genetic testing in adults with unexplained cholestasis

Patient Checklist

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Consider genetic testing in adults with unexplained cholestasis when **one or more** of the following apply:

- ☐ **Unexplained cholestasis after exclusion of specific causes, including:**
  - viral hepatitis
  - alcohol-related and drug-induced* liver injury
  - biliary obstruction (except in people meeting LPAC criteria; see below
  - autoimmune liver disease

- ☐ **Recurrent or episodic cholestasis: discrete attacks with symptom-free intervals between episodes**

- ☐ **Personal or family history of intrahepatic cholestasis of pregnancy (ICP):** including cholestasis that persists postpartum rather than resolving

- ☐ **Early-onset, recurrent, or low phospholipid-associated cholelithiasis (LPAC):**
  - biliary symptoms before age 40 years
  - recurrence after cholecystectomy
  - intrahepatic micro- or macrolithiasis

- ☐ **Cholestasis with a normal or low GGT:** disproportionately low relative to the degree of biochemical/clinical cholestasis

- ☐ **Prolonged or atypical drug-induced cholestasis:** DILI that fails to resolve within the expected time frame, or recurs with exposure to unrelated drugs

- ☐ **Consanguinity or a family history of liver disease, including:**
  - unexplained cirrhosis
  - early liver-related death
  - biliary malignancy
  - similar presentations in siblings, parents, or extended family members

- ☐ **Extrahepatic features suggestive of Alagille syndrome, including:**
  - cardiac (murmur, peripheral pulmonary stenosis)
  - vertebral (butterfly vertebrae)
  - ocular (posterior embryotoxon)
  - characteristic facies
  - renal anomalies

*Genetic variants in cholestasis-associated genes may also be associated with a DILI phenotype.

Presence of any item above supports referral for hepatology-led genetic evaluation, ideally with pre-test counseling on the possibility of variants of uncertain significance.

Abbreviations: DILI, drug-induced liver injury; GGT, gamma-glutamyl transferase; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholelithiasis.

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Audience: This resource is intended for healthcare professionals outside the United States only.

Faculty disclosures and more resources can be found here:

bit.ly/rare-liver-diseases