

Bile acid synthesis disorders represent a distinct category of metabolic liver disease characterized by a deficiency in the activity of one of the 17 enzymes responsible for the conversion of cholesterol to the primary bile acids, cholic and chenodeoxycholic acids. Mutations in any of the genes encoding these enzymes result in a failure to synthesize the normal primary bile acids, which are essential for maintaining bile flow and normal liver function. When there is a deficiency in enzyme activity the liver produces high concentrations of atypical bile acids that contribute to liver injury.

Bile acid synthesis defects are autosomal recessive traits that may account for cases of intrafamilial progressive cholestatic liver disease. The phenotype manifests as a broad spectrum and can be the cause of late-onset cholestasis in children and adolescents, while also presenting in adults.

The diagnosis of a bile acid synthetic disorder is achieved using mass spectrometry by detecting the presence of unique and specific atypical bile acids and intermediates associated with each genetic defect and by a lack of normal primary bile acids. Early diagnosis is important to avoid the progression to end-stage liver disease, or liver transplantation. Primary bile acid therapy with oral cholic acid was recently approved by the FDA for the treatment of bile acid synthetic disorders.

## Indications/Utility:

Diagnostic testing in pediatric and adult patients presenting with conditions of cholestatic liver disease, neurological disease, or fat-soluble vitamin malabsorption of unknown etiology. Urine FAB-MS analysis provides a rapid and cost-effective means of diagnosing the most common of the genetic defects in the metabolism of cholesterol to the primary bile acids. Mass spectrometry testing may be used to monitor the biochemical response to primary bile acid therapy and to help in decisions on dose adjustments, where compliance should lead to a reduction in levels of atypical bile acids.

## Genetic Defect (Enzyme Deficiency):

Genetic defects in bile acid synthesis causing liver disease, fat-soluble vitamin malabsorption, or neurological disease diagnosed by urine fast atom bombardment ionization mass spectrometry (FAB-MS) analysis.

- $3\beta$ -Hydroxy- $\Delta^5$ - $C_{27}$ -steroid oxidoreductase (HSD3B7) deficiency, formerly called  $3\beta$ -hydroxy- $\Delta^5$ - $C_{27}$ -steroid dehydrogenase/isomerase (also referred to as  $3\beta$ -HSD or HSD3B7)
- Oxosteroid  $5\beta$ -reductase deficiency (AKR1D1) deficiency (sometimes referred to as  $5\beta$ -reductase deficiency)
- Sterol 27-hydroxylase (CYP27A1) deficiency, presenting as CTX
- Oxysterol  $7\alpha$ -hydroxylase (CYP7B1) deficiency
- 2-Methylacyl-CoA racemase (AMACR) deficiency
- Bile acid conjugation defects:
  - ◆ Bile acid-CoA ligase (BACL) deficiency
  - ◆ Bile acid-CoA:N-acyl amino acid transferase (BAAT) deficiency
- Generalized peroxisomal  $\beta$ -oxidation disorders

## Sample Type:

Urine, random

## Volume:

5 – 25 mL  
1 mL (minimum)

## Specimen Preparation:

Collect in a sterile container. Label the tube with the patient's name, birth date, and date of urine collection. Freeze ASAP. **Note:** if the patient is being treated with the bile acid Ursodeoxycholic Acid (Urso<sup>®</sup>, Actigall<sup>®</sup>), this treatment should be interrupted for 5 days before collection of the urine sample.

## Unacceptable Specimens:

Do not collect in or on diapers or cotton balls.

## Stability:

**Frozen:** Greater than 10 years

*This test was developed and its performance characteristics were determined and validated by the Clinical Mass Spectrometry Laboratory at Cincinnati Children's Hospital Medical Center. It has not been cleared or approved by the U.S. Food and Drug Administration. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88) as qualified to perform high-complexity laboratory testing.*

## Testing Schedule:

Weekly. **Turnaround Time:** Typically 7 – 10 days. For urgent testing, call the lab at (513) 636-4203.

## CPT Code:

83789

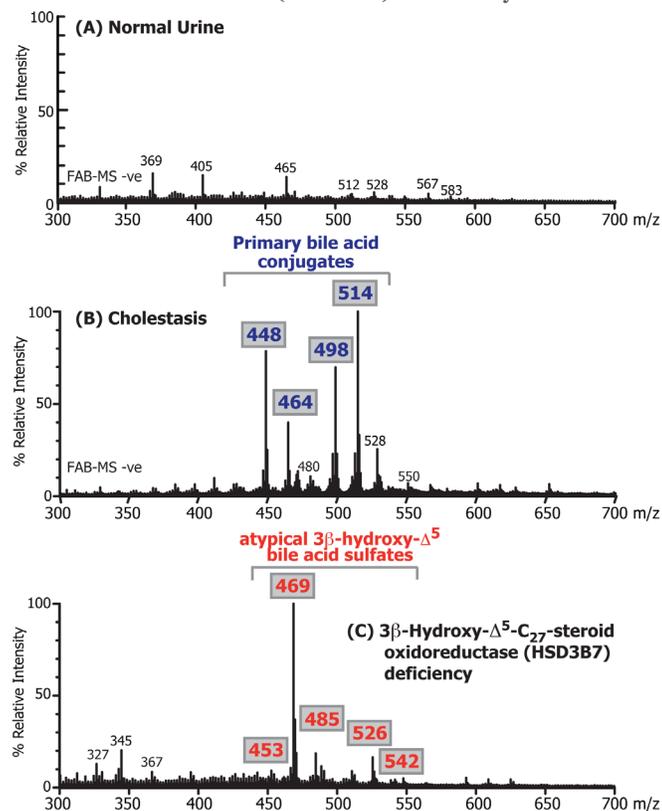
## Costs:

Please contact (513) 636-0120 for pricing or for billing questions.

## Methodology:

Application of liquid secondary ionization mass spectrometry using fast atom bombardment (FAB-MS) ionization to detect the negative ions associated with the presence of increased concentrations of atypical bile acids in urine resulting from the loss of activity of one of the key enzymes that catalyze the production of normal primary bile acids by the liver. Each enzyme defect yields a distinct and specific mass spectrum that permits the diagnosis of the genetic defect.

Examples of typical negative ion mass spectra obtained from the analysis of urine from, (A) a healthy normal infant, (B) a patient with idiopathic cholestasis in which primary bile acid synthesis is not impaired, and (C) a patient with a bile acid synthetic disorder due to a  $3\beta$ -Hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid oxidoreductase (HSD3B7) deficiency:



## Shipping Instructions:

Please enclose the Test Requisition Form with the sample. All information must be completed, including an indication of any drug therapies the patient may be taking. Place samples in a Styrofoam box and ship frozen on dry-ice to arrive Monday through Friday.

## Shipping Address:

Clinical Mass Spectrometry Facility, MLC 7019  
Department of Pathology and Laboratory Medicine  
Cincinnati Children's Hospital Medical Center  
240 Albert Sabin Way  
Cincinnati, Ohio 45229-3039

## Contact Information:

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## References:

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