Neonatal and Adult Cholestasis: Sequencing Panel

Test Code: MM340
Turnaround time: 3 weeks
CPT Codes: 81223 x1, 81330 x1, 81332 x1, 81404 x1, 81405 x1, 81406 x1

Condition Description

Neonatal cholestasis is often clinically defined as the prolonged occurrence of conjugated hyperbilirubinemia in the newborn period, due to impairments in the flow of bile. It is caused by a diverse group of hepatobiliary diseases with overlapping clinical presentations, supporting a need for multi-gene diagnostic panel.

The incidence of neonatal cholestasis is estimated to be 1 in 2500 live births. Genetic and metabolic causes account for at least 25-30% of all cases of neonatal cholestasis, generally due to impairments of hepatobiliary transport, intermediary metabolism, storage disorders, or bile duct dysgenesis. Several of these disorders are life-threatening and benefit from early diagnosis and intervention, yet diagnosing the specific cause via routine serum chemistries or by evaluation of liver biopsies is not as definitive as direct genetic testing. Moreover, several cholestatic entities develop in adults that are caused by variants in these same genes.

Highlights for pediatricians, internists, gastroenterologists, and hepatologists include:

- PFICs, Alagille syndrome, A1AT, bile acid synthetic disorders, CF, etc., all on one platform
- Extremely rare cholangiopathies, (nephronophthises, ARPKD) as well as causes of neonatal liver failure (DGUOK and others)
- Opportunities to diagnose adult-onset cholestatic syndromes, including BRIC, LPAC, and ICP
- Evaluation of hyperbilirubinemia: Crigler-Najjar and Dubin-Johnson syndromes

Reference:


Genes

- ABCB11, ABCB4, ABCG5, ABCG8, AKR1D1, ALDOB, AMACR, ATP8B1, BAAT, CC2D2A, CFTR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCDC2, DGUOK, DHC7, EHHD4, FAH, GBP2, HPRT1, HNF1B, HSD17B4, HSD3B7, INVS, JAG1, LIPA, MTS1, MPV17, NOTCH2, NPC1, NPC2, NPHS1, NPHS2, NPHP4, NR1H4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX20, PEX21, PEX26, PEX3, PEX5, PEX6, PEX7, PKHD1, POLG, SCP2, SERPINA1, SLC10A1, SLC10A2, SLC25A13, SLC27A5, SMPD1, TMEM216, TRMU, UGT1A1, VIPAS39, VPS33B

Indications

This test is indicated for:

- Newborns and adults with chronic liver disease.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot
provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Whole Blood (EDTA)**

**Specimen Requirements:**
- EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Related Tests**
- Neonatal and Adult Cholestasis: Deletion/Duplication Panel