# Liver Panels by Next-Generation Sequencing

**Description:** The Liver Panels are specifically designed for comprehensive analysis of genes associated with inherited liver diseases in children. The six Liver Panels are described below:

| Liver Panels NGS Panels | Genes included |
|---|---|
| Cholestasis Panel | *ABCB11, ABCB4, ABCC2, AKR1D1, ATP8B1, BAAT, CLDN1, CYP7B1, EPHX1, HSD3B7, JAG1, NOTCH2, SERPINA1, SLC10A1, SLC25A13, TJP2, VIPAS39, VPS33B* |
| Jaundice Panel | *ABCB11, ABCB4, ATP8B1, JAG1, TJP2* |
| Bile Acid Defects Panel | *AKR1D1, CYP7B1, HSD3B7* |
| Cystic Disease of the Liver/Kidney Panel | *PKHD1, PRKCSH* |
| Gilbert/Crigler-Najjar Syndrome | *UGT1A1* |
| Wilson Disease | *ATP7B* |

## Genes Included:

Inherited liver diseases are a genetically heterogeneous group of conditions which may be inherited in an autosomal dominant or recessive manner.

| Gene | Condition | Inheritance |
|---|---|---|
| *ABCB11* | Progressive familial intrahepatic cholestasis 2<br>Benign recurrent intrahepatic cholestasis 2 | AR |
| *ABCB4* | Progressive familial intrahepatic cholestasis 3<br>Benign recurrent intrahepatic cholestasis 3 | AR |
| *ABCC2* | Dubin-Johnson syndrome | AR |
| *AKR1D1* | Congenital bile acid synthesis defect 2 | AR |
| *ATP7B* | Wilson Disease | AR |
| *ATP8B1* | Progressive familial intrahepatic cholestasis 1<br>Benign recurrent intrahepatic cholestasis 1 | AR |
| *BAAT* | Familial hypercholanemia | AR |
| *CLDN1* | Ichthyosis, Leukocyte Vacuoles, Alopecia, and Sclerosing Cholangitis | AR |
| *CYP7B1* | Congenital bile acid synthesis defect 3<br>Spastic paraplegia 5A | AR |
| *EPHX1* | Familial hypercholanemia | AR |
| *HSD3B7* | Congenital bile acid synthesis defect 1 | AR |
| *JAG1* | Alagille syndrome | AD |
| *NOTCH2* | Hajdu-Cheney syndrome<br>Alagille syndrome | AD |
| *PKHD1* | Polycystic kidney and hepatic disease | AR |
| *PRKCSH* | Polycystic liver disease | AD |
| *SERPINA1* | Emphysema Due To AAT Deficiency | AR |
| *SLC10A1* | NTCP deficiency | AR |
| *SLC25A13* | Citrullinemia type II | AR |
| *TJP2* | Progressive familial intrahepatic cholestasis 4<br>Familial hypercholanemia | AR |
| *UGT1A1* | Crigler-Najjar syndrome | AR |
| *VIPAS39* | Arthrogryposis, Renal Dysfunction, and Cholestasis 2 | AR |
| *VPS33B* | Arthrogryposis, Renal Dysfunction, and Cholestasis 1 | AR |

Key: AD= autosomal dominant, AR= autosomal recessive

Cincinnati Children's

Human Genetics

Cytogenetic and Molecular Genetics Laboratory
CLIA#: 36D0656333
Phone: (513) 636-4474
Fax: (513) 636-4373
Email: moleculargenetics@cchmc.org
www.cincinnatichildrens.org/genetics

## Indications:

**NGS Panels:**

- Genetic diagnosis in a patient with a clinical diagnosis of inherited liver disease
- Carrier identification in individuals with a family history of inherited liver disease of unknown genetic basis

**Deletion/ duplication analysis of liver panel genes:**

- Completion of the diagnostic evaluation in a patient with a clinical diagnosis of inherited liver disease who is either negative for mutations or heterozygous for a mutation in a gene associated with an autosomal recessive condition through an NGS panel

**Gene Specific Sequencing:**

- Genetic diagnosis in a patient with inherited liver disease for whom clinical symptoms/ ancillary testing suggest a specific genetic diagnosis

**Mutation Specific Analysis:**

- Carrier testing of parents and other relatives for recurrence risk assessment
- Presymptomatic testing of at-risk siblings for medical management
- Prenatal diagnosis of an at-risk fetus, after confirmation of mutation(s) in the parent(s) and by prior arrangement only

## Specimen:

At least 3 mls of whole blood in a lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection.

**Note:** Saliva samples are also acceptable. Please call 513-636-4474 for a free saliva collection kit.

## Testing Methodology:

This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5' and 3') of the genes specified above using TruSeq Custom Amplicon (TSCA) followed by next-generation sequencing with >20 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

## Analytical Sensitivity:

The sensitivity of DNA sequencing is over 98% for the detection of nucleotide base changes, small deletions, and insertions in the regions analyzed. Analytical sensitivity may be compromised by rare primer site mutations. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic variants have been reported in many of these genes and will not be identified using this test methodology. If the patient has received a liver transplant or recent blood transfusion, donor DNA may be present in the blood along with the patient DNA (chimerism). In this case, additional testing may be required to rule out chimerism.

Of note, exons 1, 2 and 4 of *NOTCH2* gene are not covered by this test due to homology issues with primer design.

## Note:

Reflex to the Cholestasis Panel is available after testing is completed through one of the other Liver Panels by NGS.

Single gene sequencing is available for all genes on the panel. Deletion and duplication analysis by targeted CGH is available for all genes on this panel except *ABCC2, AKR1D1, CLDN1, CYP7B1, EPHX1, HSD3B7, NOTCH2, PKHD1, SLC10A1, VIPAS39, VPS33B.*

## Turn-Around Time:

- 28-42 days for the Cholestasis Panel and up to 28 days for Jaundice Panel, Bile Acid Defects Panel, Cystic Disease (Liver/Kidney) Panel, Gilbert/Crigler-Najjar Syndrome and Wilson Disease
- 28-84 days for single gene sequencing
- 28 days for deletion and duplication analysis by targeted CGH

## Costs:

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

## CPT Codes:

- **Cholestasis Panel:** 81407, 81479x17
- **Jaundice Panel:** 81407, 81479x4
- **Bile Acid Defects Panel:** 81479x3
- **Cystic Disease (Liver/Kidney) Panel:** 81408, 81479
- ***UGT1A1,* Gilbert/Crigler-Najjar Syndrome:** 81479
- ***ATP7B,* Wilson Disease:** 81406
- **Single gene sequencing of any gene on the Liver Chip except *JAG1, PKHD1* and *ATP7B:*** 81479
- **Single gene sequencing of *JAG1:*** 81407
- **Single gene sequencing of *PKHD1:*** 81408
- **Single gene sequencing of *ATP7B:*** 81406
- **Deletion and duplication analysis of any gene on a Liver Panel except *JAG1:*** 81479
- **Deletion and duplication analysis of *JAG1:*** 81406

## Shipping Instructions:

Please enclose **test requisition** with sample.
**All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

## Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

## Results:

Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for the clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

## References:


*Aggarwal, A. and M. Bhatt (2013) "Update on Wilson Disease." International Review of Neurobiology 110: 313-48.*

*Bals, R. (2010) "Alpha-1-Antitrypsin Deficiency." Best Practice & Research. Clinical Gastroenterology 24(5): 629–33.*

*Canu, G., A. Minucci, et al. (2013) "Gilbert and Crigler Najjar Syndromes: An Update of the UDP-Glucuronosyltransferase 1A1 (UGT1A1) Gene Mutation Database." Blood Cells, Molecules & Diseases 50(4): 273-80.*

*Carey, E.J., A.H. Ali, et al. (2015) "Primary Biliary Cirrhosis." Lancet (London, England) 386(10003): 1565-75.*

*Carlton, V.E.H., B.Z. Harris, et al. (2003) "Complex Inheritance of Familial Hypercholanemia with Associated Mutations in TJP2 and BAAT." Nature Genetics 34(1): 91–6.*

*Devictor, D., P. Tissieres, et al. (2011) "Acute Liver Failure in Children." Clinics and Research in Hepatology and Gastroenterology 35(6-7): 430-7.*

*Drenth, J.P., R.H. te morsche, et al. (2003) "Germline mutations in PRKCSH are associated with autosomal dominant polycystic liver disease." Nature Genetics 33(3): 345-7.*

*Erlinger, S. (2015) "NTCP Deficiency: A New Inherited Disease of Bile Acid Transport." Clinics and Research in Hepatology and Gastroenterology 39(1): 7-8.*

*Gissen, P., L. Tee, et al. (2006) "Clinical and molecular genetic features of ARC syndrome." Hum Genet, 120(3): 396-409.*

*Guay-Woodford, L.M. (2014) "Autosomal Recessive Polycystic Kidney Disease: The Prototype of the Hepato-Renal Fibrocystic Diseases." Journal of Pediatric Genetics 3(2): 89–101.*

*Guegan, K., K. Stals, et al. (2012) "JAG1 Mutations Are Found in Approximately One Third of Patients Presenting with Only One or Two Clinical Features of Alagille Syndrome." Clinical Genetics 82(1): 33-40.*

*Komatsu, M., M. Yazaki, et al. (2008) "Citrin Deficiency as a Cause of Chronic Liver Disorder Mimicking Non-Alcoholic Fatty Liver Disease." Journal of Hepatology 49(5): 810–20.*

*Morotti, R.A., F.J. Suchy, et al. (2011) "Progressive Familial Intrahepatic Cholestasis (PFIC) Type 1, 2, and 3: A Review of the Liver Pathology Findings." Seminars in Liver Disease 31(1): 3–10.*

*Shah, I. and S. Bhatnagar (2010) "NISCH Syndrome with Hypothyroxinemia." Annals of Hepatology 9(3): 299-301.*

*Turnpenny, P.D. and S. Ellard (2012) "Alagille Syndrome: Pathogenesis, Diagnosis and Management." Eur J Hum Genet 20(3): 251–7.*

*Václavíková, R. et al. (2015) 'Microsomal Epoxide Hydrolase 1 (EPHX1): Gene, Structure, Function, and Role in Human Disease', Gene 571 (1): 1-8.*

*Van der Woerd, W.L., S.W.C. van Mil, et al. (2010) "Familial Cholestasis: Progressive Familial Intrahepatic Cholestasis, Benign Recurrent Intrahepatic Cholestasis and Intrahepatic Cholestasis of Pregnancy." Best Practice & Research. Clinical Gastroenterology 24(5): 541–53.*

*Van Mil, S.W.C., R.H.J. Houwen, et al. (2005) "Genetics of Familial Intrahepatic Cholestasis Syndromes." Journal of Medical Genetics 42(6): 449–63.*

*Zhou, Y. and J. Zhang (2014) "Arthrogryposis-Renal Dysfunction-Cholestasis (ARC) Syndrome: From Molecular Genetics to Clinical Features." Italian Journal of Pediatrics 40: 77.*