PUBLICATIONS

Manuscripts

1. Shneider BL, Magee JC, Karpen SJ, Rand EB, Narkewicz MR, Bass LM, Schwarz K, Whitington PF, Bezerra JA, Kerkar N, Haber B, Rosenthal P, Turmelle YP, Molleston JP, Murray KF, Ng VL, Wang KS, Romero R, Squires RH, Arnon R, Sherker AH, Moore J, Ye W, Sokol RJ, Childhood Liver Disease Research Network Chi L.**Total Serum Bilirubin within 3 Months of Hepatoportoenterostomy Predicts Short-Term Outcomes in Biliary Atresia.** J Pediatr. 2016;170:211-7 e2. PubMed PMID: 26725209.

   There is significant value in the early prediction of clinical outcomes after the Kasai hepatoportoenterstomy (HPE) for biliary atresia (BA). This study was designed based upon prior retrospective work from ChiLDReN (*J. Pediatr.* 2006;148:467-474). In these prospective investigations, a successful HPE was defined by the ability to achieve a total bilirubin less than 2 mg/dl in the first three months after HPE. Fifty percent (69/137) of infants did not have a successful HPE according to these criteria. These infants were at greater risk for subsequently developing ascites, low serum albumin levels and abnormal blood clotting studies. In addition, these infants were at 12-fold increased risk of requiring liver transplantation in the first two years of life and a 16-fold increased risk of dying or requiring liver transplantation in the first two years of life. We suggest that clinicians follow total bilirubin levels on a monthly basis for the first six months after HPE for BA. In those infants where total bilirubin does not drop below 2 mg/dl, careful attention should be paid to nutritional status, anticipatory guidance should be provided for the potential for development of progressive liver disease and consideration should be given to evaluation for liver transplantation.

2. Karjoo S, Hand NJ, Loarca L, Russo PA, Friedman JR, and Wells RG. **Extra-Hepatic Cholangiocyte Cilia are Abnormal in Biliary Atresia.** Journal of Pediatric Gastroenterology and Nutrition. 2013; 57(1): 96-101.

   In this manuscript, the authors report their findings of abnormal extrahepatic cholangiocyte cilia in both human biliary atresia and in the rhesus rotavirus mouse model. These results suggest that the abnormalities of bile duct cilia may be part of the pathophysiology of biliary atresia.

3. Karjoo S, Wells RG. **Isolation of Neonatal Extrahepatic Cholangiocytes.** Journal of Visualized Experiments. 2014; 5(88): video.

   In this publication, the authors report an optimized technique for the isolation of a pure population of extrahepatic cholangiocytes from neonatal mouse liver. These cell populations will be very useful for studies of bile duct disease, such as biliary atresia.

4. Wang KS, Moss RL, Caty MG, Davidoff A, Fallat ME, Heiss KF, Holcomb G 3rd, Meyers RL, Watterberg KL, Aucott S, Benitz WE, Cummings JJ, Eichenwald EC, Goldsmith J, Poindexter BB, Puopolo K, Stewart DL, Wang KS, Kerkar N, Karpen SJ, Sokol RJ, Schwarz KB, Mogul DB, Harpavat S. **Newborn Screening for Biliary Atresia.** Pediatrics. 2015 Dec; 136(6):e1663-9. doi: 10.1542/peds.2015-3570.

   Given that earlier diagnosis of biliary atresia predicts better outcome following surgery, screening of infants for biliary atresia has been considered by many. It has even been implemented in a number of countries, but not in the United States. This paper is collaborative report on the state of the art feasibility of screening newborns for biliary atresia in the US. This was put together as a collaborative effort between the American Academy of Pediatrics Committee on Fetus and Newborn and Section on Surgery and ChiLDReN.

5. Leung D, Ye W, Molleston J, Weymann A, Ling S, Paranjape S, Romero R, Schwarzenberg SJ, Palermo J, Alonso E, Murray K, Marshall B, Sherker A, Siegel M, Krishnamurthy R, Harned R, Karmazyn B, Magee J C, Narkewicz MR on behalf of the Cystic Fibrosis Liver Disease Network (CFLD NET). **Baseline ultrasound and clinical correlates in children with Cystic Fibrosis.** J Pediatrics. 2015 Oct; 167(4): 862-868.

   This multicenter, prospective study investigated the relationship between abdominal ultrasound findings and demographic, historical, and clinical features in children, 3-12 years, with cystic fibrosis (CF) through the North American Cystic Fibrosis Liver Disease Network (CFLD NET) to predict hepatic fibrosis. Unsuspected cirrhotic pattern was seen in 3.3% of young patients with CF, and heterogeneous pattern in 8.9%. Abnormal ultrasound and ursodeoxycholic acid use was associated with CF-related diabetes, and early P aeruginosa associated with normal ultrasound. Prospective assessment of these risk factors may identify potential interventional targets.

6. Kamath BM, Chen Z, Romero R, Fredericks EM, Alonso EM, Arnon R, Heubi J, Hertel PM, Karpen SJ, Loomes KM, Murray KF, Rosenthal P, Schwarz KB, Subbarao G, Teckman JH, Turmelle YP, Wang KS, Sherker AH, Sokol RJ, Magee JC; Childhood Liver Disease Research Network (ChiLDReN). **Quality of Life and its Determinants in a Multi-Center Cohort of Children with Alagille Syndrome.** J Pediatrics. 2015 Aug;167(2):390-396.

   This is an analysis of quality of life in children and their parents with Alagille syndrome, in comparison to children with other chronic liver diseases. Children with Alagille syndrome clearly have reduced quality of life. Growth failure appears to be the major determinant of impaired quality of life in Alagille syndrome. This is significant because poor growth is a potentially treatable cause of poor quality of life.

7. Ogawa M, Ogawa S, Bear CE, Ahmadi S, Chin S, Li B, Grompe M, Keller G, Kamath BM, Ghanekar A.**Directed differentiation of cholangiocytes from human pluripotent stem cells.** Nat Biotechnol. 2015 Aug; 33(8):853.61.

   Induced pluripotent stem cells (iPSCs) are stem cells that are derived from mature cells (a skin sample or blood). iPSCs can be made to develop into many different cell types in order to study disease. In this study, we describe a method to differentiate bile duct cells (cholangiocytes) from iPSCs. We demonstrate how this technology can be used to study cystic fibrosis liver disease. This platform will be useful to study many other biliary diseases.

8. Teckman JH, Rosenthal P, Abel R, Bass LM, Michail S, Murray KF, Rudnick DA, Thomas DW, Spino C, Arnon R, Hertel PM, Heubi J, Kamath BM, Karnsakul W, Loomes KM, Magee JC, Molleston JP, Romero R, Shneider BL, Sherker AH, Sokol RJ. **Baseline Analysis of a Young Alpha-1-AT Deficiency Liver Disease Cohort Reveals Frequent Portal Hypertension.** JPGN. 2015 (epub ahead of print).

   This is the first report of the patients with alpha-1-antitrypsin deficiency enrolled in the LOGIC study of the ChiLDREN Network. Enrollment began in 2008 and includes patients with both mild and severe liver disease, as well as a group who have already received liver transplants. The results show that in most cases the growth and development of all the children are normal, regardless of the severity of their disease. The quality of life is also generally high. Studies of the routine medical care of these patients indicates that detailed follow up is needed to appropriately identify and to treat the most severe patients, as many routine liver blood tests do not effectively differentiate the mild from the severe liver disease patients. Enrollment into this study will continue and further analysis of the data will continue.

9. Coughlin CR, Scharer GH, Friederich MW, Yu HC, Geiger EA, Creadon-Swindell G, Collins AE, Vanlander AV, Coster RV, Powell CA, Swanson MA, Minczuk M, Van Hove JL, Shaikh TH. **Mutations in the mitochondrial cysteinyl-tRNA synthase gene, CARS2, lead to a severe epileptic encephalopathy and complex movement disorder.** J Med Genet. 2015 (epub ahead of print).

    Mitochondrial disease is often suspected in cases of severe epileptic encephalopathy especially when a complex movement disorder, liver involvement and progressive developmental regression are present. Although mutations in either mitochondrial DNA or POLG are often present, other nuclear defects in mitochondrial DNA replication and protein translation have been associated with a severe epileptic encephalopathy.

10. Tsai EA, Grochowski CM, Falsey AM, Rajagopalan R, Wendel D, Devoto M, Krantz ID, Loomes KM, Spinner NB. **Heterozygous Deletion of FOXA2 Segregates with Disease in a Family with Heterotaxy, Panhypopituitarism, and Biliary Atresia** Human Mutation. 2015; 36(6): 631-7.

    Biliary atresia (BA) is a pediatric cholangiopathy with unknown etiology occurring in isolated and syndromic forms. Laterality defects affecting the cardiovascular and gastrointestinal systems are the most common features present in syndromic BA. We identified a child with BA, malrotation, and interrupted inferior vena cava whose father presented with situs inversus, polysplenia, panhypopituitarism, and mildly dysmorphic facial features. Chromosomal mucroarray analysis demonstrated a 277 kb heterozygous deletion on chromosome 20, which included a single gene, FOXA2, in the proband and her father. This deletion was confirmed to be de novo in the father. Further genetic screening revealed that the proband carried an additional protein-altering polymorphism in the NODAL gene that is not present in the father, and this variant has been shown to decrease expression of the gene. As FOXA2 can be a regulator of NODAL expression, we propose that haploinsufficiency for FOXA2 combined with a decreased expression of NODAL is the likely cause for syndromic BA in this proband.

11. Lorent K, Gong W, Koo AK, Waisbourd-Zinman O, Karjoo S, Sealy I, Kettleborough RN, Stemple DL, Ueno Y, Windsor PA, Whittaker SJ, Porter JR, Wells RG, Pack M. **Identification of a Plant Isoflavonoid that Causes Biliary Atresia.** Sci Trans Med. 2015; 7(286):286ra67.

    We used a biliary secretion assay in zebrafish to isolate a previously undescribed isoflavonoid, biliatresone, from Dysphania species implicated in a recent BA outbreak. This compound caused selective destruction of the extrahepatic, but not intrahepatic, biliary system of larval zebrafish. A mutation that enhanced biliatresone toxicity mapped to a region of the zebrafish genome that has conserved synteny with an established human BA susceptibility locus. The toxin also caused loss of cilia in neonatal mouse extrahepatic cholangiocytes in culture and disrupted cell polarity and monolayer integrity in cholangiocyte spheroids. Together, these findings provide direct evidence that BA could be initiated by perinatal exposure to an environmental toxin.

12. Wen Ye, Phil Rosenthal, John Magee and Peter Whitington. **Factors Determining Delta-Bilirubin Levels in Biliary Atresia Infants.** JPGN. 2015; 60(5):659-63.

    δ-Bilirubin (Bδ) forms when bilirubin conjugates covalently bind to albumin by way of nonenzymatic transesterification in patients with cholestasis. Infants with cholestasis with biliary atresia form Bδ. The aim of the present study was to investigate the factors determining serum Bδ concentrations in infants with biliary atresia.

13. Venkat VL, Shneider BL, Magee JC, Turmelle Y, Arnon R, Bezerra JA, Hertel PM, Karpen SJ, Kerkar N, Loomes KM, Molleston J, Murray KF, Ng VL, Raghunathan T, Rosenthal P, Schwartz K, Sherker AH, Sokol RJ, Teckman J, Wang K, Whitington PF, Heubi JE; Childhood Liver Disease Research and Education Network.**Total serum bilirubin predicts**

fat-soluble vitamin deficiency better than serum bile acids in infants with biliary atresia. JPGN. 2014; 59(6):702-7.

Fat soluble vitamin (FSV) deficiency is a consequence of cholestatic liver disease. A reliable biomarker could provide a method of screening for patients who should be aggressively monitored for FSV deficiency. We studied infants enrolled in the Trial of Corticosteroid Therapy in Infants with Biliary Atresia (START) after hepatoportoenterostomy receiving standardized FSV supplementation and monitoring of total bilirubin (TB), serum bile acids (SBA) and FSV levels. Our findings suggest that serum TB in infants with biliary atresia is a robust biomarker of FSV insufficiency and that it is superior to SBA.

14. Ng, Vicky Lee; Haber, Barbara H; Magee, John C; Miethke, Alexander; Murray, Karen F; Michail, Sonia; Karpen, Saul J; Kerkar, Nanda; Molleston, Jean P; Romero, Rene; Rosenthal, Philip; Schwarz, Kathleen B; Shneider, Benjamin L; Turmelle, Yumirle P; Alonso, Estella M; Sherker, Averell H; Sokol, Ronald J; Childhood Liver Disease Research and Education Network (CHiLDREN). **Medical status of 219 children with biliary atresia surviving long-term with their native livers: results from a North American multicenter consortium.** J Pediatr. 2014; 165(3):539-546.

    To examine the medical status of children with biliary atresia (BA) with their native livers after hepato-portoenterostomy (HPE) surgery.

15. Heubi JE, Setchell KD, Jha P, Buckley D, Zhang W, Rosenthal P, Potter C, Horslen S, Suskind D. **Treatment of bile acid amidation defects with glycocholic acid.** Hepatology. 2015; 61(1):268-74.

    The final step in the production of bile acids before they leave the liver is the attachment of an amino acid, taurine or glycine, to them. Bile acid conjugation defects were predicted to present with fat/fat soluble vitamin malabsorption with minimal cholestasis. We treated 5 patients from 4 families with defective bile acid conjugation using the conjugated bile acid, glycocholic acid, under an investigational new drug license from the FDA. Treatment with glycocholic acid resulted in increases in bile acids in bile that were conjugated with glycine to 60% from almost none before treatment. To test the effects of treatment and the increase in conjugated bile acids on fat soluble vitamin absorption, we measured vitamin D2 and tocopherol absorption using test doses and demonstrated improvement in both. Growth improved in 3/3 growth-delayed prepubertal patients. There were no reported adverse effects from glycocholic acid therapy in over 25 patient years of therapy. Conclusions: Oral glycocholic acid therapy is safe and effective in improving growth and fat-soluble vitamin absorption in children and adolescents with inborn errors of bile acid metabolism due to conjugation defects.

16. Bessho, Kazuhiko; Mourya, Reena; Shivakumar, Pranavkumar; Walters, Stephanie; Magee, John C; Rao, Marepalli; Jegga, Anil G; Bezerra, Jorge A. **Gene expression signature for biliary atresia and a role for interleukin-8 in pathogenesis of experimental disease.** Hepatology. 2014; 60(1):211-23.

    The investigators analyzed the genes in livers of children with biliary atresia to determine if they differ from other types of pediatric liver disease. They found the livers in biliary atresia have greater level of activation of inflammation genes. Among these genes, interleukin-8 (IL-8) was particularly interesting because it was increased in biliary atresia as well as in a mouse model of experimental biliary atresia. In this mouse, the inactivation of IL-8 decreased inflammation and obstruction of bile ducts, and improved long-term survival. These findings suggest that liver gene studies may aid in diagnosis of disease, and that IL-8 pathways may be treatment targets in future studies.

17. Bezerra, Jorge A; Spino, Cathie; Magee, John C; Shneider, Benjamin L; Rosenthal, Philip; Wang, Kasper S; Erlichman, Jessi; Haber, Barbara; Hertel, Paula M; Karpen, Saul J; Kerkar,

Nanda; Loomes, Kathleen M; Molleston, Jean P; Murray, Karen F; Romero, Rene; Schwarz, Kathleen B; Shepherd, Ross; Suchy, Frederick J; Turmelle, Yumirle P; Whitington, Peter F; Moore, Jeffrey; Sherker, Averell H; Robuck, Patricia R; Sokol, Ronald J; Childhood Liver Disease Research and Education Network (ChiLDREN). **Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized clinical trial.** JAMA. 2014; 311(17):1750-9.

The investigators carried out a clinical trial to determine whether the use of high dose corticosteroids after the Kasai surgery improves biliary drainage and survival with the native liver. The trial was called Steroids in Biliary Atresia Randomized Trial (START) and was conducted in 140 infants with an average age of 2.3 months in several centers of the Network. The trial design included high doses of methylprednisolone/oral prednisolone or placebo initiated within 72 hours of surgery. They found that corticosteroids did not improve bile drainage at 6 months after surgery or transplant-free survival when compared to the placebo group at 24 months of age. They also found that participants receiving steroids had earlier time of onset of their first serious adverse when compared to placebo. They concluded that high dose steroid therapy following the steroid treatment was associated with earlier onset of serious adverse events in children with biliary atresia.

18. Sambrotta, Melissa; Strautnieks, Sandra; Papouli, Efterpi; Rushton, Peter; Clark, Barnaby E; Parry, David A; Logan, Clare V; Newbury, Lucy J; Kamath, Binita M; Ling, Simon; Grammatikopoulos, Tassos; Wagner, Bart E; Magee, John C; Sokol, Ronald J; Mieli-Vergani, Giorgina; University of Washington Center for Mendelian Genomics; Smith, Joshua D; Johnson, Colin A; McClean, Patricia; Simpson, Michael A; Knisely, A S; Bull, Laura N; Thompson, Richard J. **Mutations in TJP2 cause progressive cholestatic liver disease** Nat Genet. 2014; 46(4):326-8.

19. Tsai EA, Grochowski CM, Loomes KM, Bessho K, Hakonarson H, Bezerra JA, Russo PA, Haber BA, Spinner NB, Devoto M. **Replication of a GWAS signal in a Caucasian population implicates ADD3 in susceptibility to biliary atresia** Hum Genet. 2014; 133(2):235-43.

In the study by Tsai et al. 2013, we carried out a Genome-Wide Association Study (GWAS) in 171 Caucasian patients with biliary atresia and 1,630 control individuals. We focused on a region of chromosome 10 that had previously been implicated as a possible disease locus for biliary after a GWAS study in a Chinese population. We were able to further fine-map the previously identified signal that had been near the XPNPEP1 and ADD3 genes, localizing it within an intron of the ADD3 gene.

20. Cui, S., Leyva-Vega, M., Tsai, E. A., EauClaire, S. F., Glessner, J. T., Hakonarson, H., Devoto, M., Haber, B. A., Spinner, N. B., Matthews, R. P. **Evidence from human and zebrafish that GPC1 is a biliary atresia susceptibility gene.** Gastroenterology. 2013; 144(5):1107-15.

21. K. D. Setchell, J. E. Heubi, S. Shah, J. E. Lavine, D. Suskind, M. Al-Edreesi, C. Potter, D. W. Russell, N. C. O'Connell, B. Wolfe, P. Jha, W. Zhang, K. E. Bove, A. S. Knisely, A. F. Hofmann, P. Rosenthal and L. N. Bull.**Genetic defects in bile acid conjugation cause fat-soluble vitamin deficiency.** Gastroenterology. 2013; 144(5):945-55.

The final step in bile acid synthesis involves conjugation with glycine and taurine, which serves to promote fat and fat soluble vitamin absorption. We described the clinical, biochemical, molecular and liver biopsy features of a genetic defect in bile acid conjugation in 10 infants/children who presented with fat-soluble vitamin deficiency, often growth failure, and in some, transient neonatal cholestatic liver disease. Urinary bile acids were elevated and predominantly unconjugated. Glycine or taurine conjugates were absent in the urine, bile and serum. Unconjugated bile acids accounted for all but 4% of the bile acids in duodenal bile with concentrations too low for efficient fat and fast soluble vitamin absorption. The biochemical profile was consistent with a defect in bile acid conjugation with 4 different

homozygous mutations in 8 patients tested. These findings suggest that patients with neonatal cholestasis of unknown cause and later onset unexplained fat-soluble vitamin deficiency should be screened for defects in bile acid conjugation.

22. Mealer M, Kittelson J, Thompson BT, Wheeler AP, Magee JC, Sokol RJ, Moss M, and. Kahn MG. **Remote source document verification in two national clinical trials networks: A pilot study.** PLoS One. 2013; 8(12).

    This paper describes a study testing whether it was feasible to use remote electronic monitoring for verification of data from clinical trials, instead of in-person monitoring, which is one of the major costs of doing clinical trials. Data from the START (Steroids in Biliary Atresia Trial) as well as other clinical trials in adults were used to compare remote monitoring to in-person monitoring. The study showed that more than 99% of data could be monitored remotely and that this was a feasible way to reduce costs of monitoring during clinical trials.

23. Mack CL, Anderson KM, Aubrey MT, Rosenthal P, Sokol RJ and Freed BM. **Lack of HLA predominance and HLA shared epitopes in biliary Atresia.** SpringerPlus. 2013; 2(1):1-13.

    This study encompasses the largest HLA analysis for BA in the United States and is the first study to perform shared epitope analysis. When controlling for multiple comparisons, no HLA allele or shared epitope association was identified in BA. Therefore, future studies of genetic links to BA that involve alterations of the immune response should include investigations into defects in regulatory T cells and non-HLA factors.

24. Molleston JP, Sokol RJ, Karnsakul W, Miethke A, Horslen S, Magee JC, Romero R, Squires RH and Van Hove JL for Childhood Liver Disease Research and Education Network. **Evaluation of the child with suspected mitochondrial liver disease** J Pediatr Gastroenterol Nutr. 2013; 57(3):269-276.

    This paper outlines a tiered approach to the evaluation of the child with suspected mitochondrial liver disease. A detailed table summarizes clinical presentations and underling gene defects in recognized mitochondrial hepatopathies.

25. Schwarz KB, Haber BH, Rosenthal P, Mack CL, Moore J, Bove, K, Bezerra JA, Karpen SJ, Kerkar N, Shneider BL, Turmelle YP, Whitington PF, Molleston JP, Murray KF, Ng VL, Romero R, Wang KS, Sokol RJ and Magee JC for Childhood Liver Disease Research and Education Network. **Extra-hepatic anomalies in infants with biliary atresia: results of a large prospective North American multi-center study.** Hepatology. 2013; 58(5):1724-31.

    In all, 289 infants who were enrolled in the prospective database prior to surgery at any of 15 participating centers were evaluated for major birth defects. Eighty-four percent of the total (242/289) infants) had no major defects. Ten percent of the infants (30/289) had what used to be called “fetal embryonal” syndromic defects or laterality defects with a classical pattern of abnormalities known to be associated with each other: malformation or absence of the spleen, switching of the organs from one side of the body to the other (“situs inversus”) and certain heart defects known to be associated. The new information in this report was that six percent of the infants (17/289) had multiple malformations not classically considered laterality defects: cardiovascular (71%), gastrointestinal (24%) and genitourinary anomalies (47%). These three groups of infants suggest that BA may have multiple causes.

26. Sundaram SS, Alonso EM, Haber B, Magee JC, Fredericks E, Kamath B, Kerkar N, Rosenthal P, Shepherd R, Limbers C, Varni JW, Robuck P and Sokol RJ for Childhood Liver Disease Research and Education Network. **Health related Quality of Life in patients with biliary atresia surviving with their native liver.** J Pediatr. 2013; 163(4):1052-7.

Health related quality of life (HRQOL) looks at physical, psychological (including emotional and cognitive), and social health and is important in understanding the effect of a chronic disease on children and their families. In this study from the ChiLDReN network, we measured HRQOL in 221 children with biliary atresia (BA) who had not undergone liver transplant and in 151 following liver transplant. HRQOL in emotional and psychosocial functioning were poorer in the BA children than healthy children. There were no HRQOL differences in BA patients who had undergone liver transplant compared to those who had not had a liver transplant. An elevated serum bilirubin level and black race were associated with lower HRQOL in BA. This study identified important opportunities to improve overall health of children with biliary atresia.

27. Brindley SM, Lanham AM, Karrer FM, Tucker RM, Fontenot AP and Mack CL. **Cytomegalovirus-specific T-cell reactivity in biliary atresia at the time of diagnosis is associated with deficits in regulatory T cells.** Hepatology. 2012; 55(4):1130-1138.

Liver T-cell responses to CMV were identified in the majority of BA patients at diagnosis, suggesting perinatal CMV infection as a plausible initiator of bile duct damage. Deficiency of Tregs in BA patients implies decreased inhibition of inflammation and autoreactivity, leading to exaggerated bile duct injury.

28. Chu AS, Russo PA and Wells RG. **Cholangiocyte cilia are abnormal in syndromic and non-syndromic biliary atresia.** Mod Pathol. 2012; 25(5):751-757.

Isolated cases of syndromic biliary atresia have been shown to result from abnormalities in proteins associated with motile cilia. Cholangiocytes have primary cilia, which are solitary, non-motile cilia. In this study, liver tissue samples from patients with syndromic or non-syndromic biliary atresia, or with unrelated liver diseases, were stained to examine the number and morphology of the primary cilia on cholangiocytes. Compared to livers not affected by biliary atresia, livers with either form of biliary atresia demonstrated cholangiocytes with significantly decreased numbers of primary cilia, and those cilia present were morphologically abnormal. This suggests that cellular changes resulting in abnormal cilia could be a common mechanism in syndromic and non-syndromic biliary atresia.

29. Kamath BM, Bauer RC, Loomes KM, Chao G, Gerfen J, Hutchinson A, Hardikar W, Hirschfield G, Jara P, Krantz ID, Lapunzina P, Leonard L, Ling S, Ng VL, Hoang PL, Piccoli DA and Spinner NB. **NOTCH2 mutations in Alagille syndrome.** J Med Genet. 2012; 49(2):138-144.

30. Mack CL, Feldman AG and Sokol RJ. **Clues to the etiology of bile duct injury in biliary atresia.** Semin Liver Dis. 2012; 32(4):307-316.

This review details the plausible role of virus infection, autoimmunity and a dysregulated immune response in the pathogenesis of biliary atresia.

31. Kamath BM, Piccoli DA, Magee JC, and Sokol RJ for Childhood Liver Disease Research and Education Network. **Pancreatic insufficiency is not a prevalent problem in Alagille syndrome.** J Pediatr Gastroenterol Nutr. 2012; 55(5):612-614.

Alagille syndrome affects many different parts of the body in addition to the liver. Older research suggested that the pancreas can be affected in Alagille syndrome. The pancreas is an organ near the liver and intestine that has several functions, including producing enzymes which travel to the intestine where they are essential for breaking down fat in the diet. We wanted to evaluate this enzyme function of the pancreas in patients with Alagille syndrome. We tested the stools of 42 children with Alagille syndrome for a pancreatic enzyme known as fecal elastase. This is a very good test of pancreatic function. In our study none of the patients had an abnormal fecal elastase measurement. This indicates that pancreatic problems are not a significant problem in Alagille syndrome and testing of the pancreas should not be performed routinely.

32. Penton AL, Leonard LD and Spinner NB. **Notch signaling in human development and disease.** Semin Cell Dev Biol. 2012; 23(4):450-457.

In Notch Signaling in Human Development and Disease, Penton et al. review the evidence for involvement of mutations in NOTCH signaling pathway genes in human developmental disease. The review the evidence for mutations in Notch pathway ligands JAG1 (Alagille syndrome and cardiac disease), Delta-like 3 (spondylocostal dysostosis); and Notch receptors NOTCH1 (cardiac disease) and NOTCH2 (Alagille syndrome and Hajdu Cheney Syndrome. Other Notch signaling pathway members HES7, lunatic fringe, and MESP2 have also been associated with vertebral defects seen in spondylocostal dysostosis.

33. Sheridan RM, Gupta A, Miethke A, Knisely AS and Bove KE. (Letter to the editor) **Multiple dysplastic liver nodules in PFIC2 underscore risk for neoplasia associated with functional BSEP deficiency.** Am J Surg Pathol. 2012; 36(5):785-786.

This letter to the editor describes a liver explant with multiple small, well-differentiated dysplastic nodules in a previously reported older patient with progressive relatively indolent cholestatic liver disease, who is a compound heterozygote for ABCB11 mutation. This extends previous observations in clinically more severe BSEP deficiency and supports the proposition that risk for HCC in ABCB11 disease is elevated in association with functional BSEP deficiency as well as with complete loss of BSEP expression.

34. Shneider BL, Abel RB, Haber B, Karpen SJ, Magee JC, Romero R, Schwarz K, Bass LM, Kerkar N, Miethke AG, Rosenthal P, Turmelle Y, Robuck PR and Sokol RJ for Childhood Liver Disease Research and Education Network. **Portal hypertension in children and young adults with biliary atresia.** J Pediatr Gastroenterol Nutr. 2012; 55(5):567-573.

Biliary atresia in most circumstances leads to scarring of the liver that may progress to a severe form of scarring referred to as cirrhosis. In the setting of cirrhosis, blood from the intestines and spleen cannot flow through the liver normally and pressure builds up in the blood vessels leading into the liver. This build up of pressure is called portal hypertension. The pressure in these blood vessels is not typically measured directly and therefore clinical findings are used as markers of portal hypertension. Portal hypertension can lead to serious medical problems including bleeding into the intestines, accumulation of fluid in the abdomen, low oxygen levels in blood and build up of toxins. This study looked at portal hypertension in 163 children with biliary atresia who had not had a liver transplant and who were being cared for at centers involved in the Childhood Liver Disease Research and Education Network. The average age of children in this study was 9 years. Portal hypertension was present in about two thirds of the children. Growth was near normal in the children with biliary atresia both with and without portal hypertension. Blood tests were looked at to determine how well the liver functioned. In general liver function was slightly below normal in these children whether they had portal hypertension or not. As would be expected, white blood cell and platelet counts were lower in children with portal hypertension. Overall, children with biliary atresia often have evidence of portal hypertension but are growing well and have a mild reduction in liver function. These children are continuing to be followed by the Childhood Liver Disease Research and Education Network. Future reports will tell us if and when portal hypertension leads to problems for these children.

35. Shneider BL, Magee JC, Bezerra JA, Haber B, Karpen SJ, Raghunathan T, Rosenthal P, Schwarz K, Suchy FJ, Kerkar N, Turmelle Y, Whitington PF, Robuck PR and Sokol RJ for Childhood Liver Disease Research and Education Network (ChiLDREN). **Efficacy of fat**

soluble vitamin supplementation in infants with biliary atresia: a prospective multi-center analysis. Pediatrics. 2012; 130(3):e607-614.

Intestinal absorption of fat-soluble vitamins (e.g. vitamins A, D, E and K) is dependent upon the presence of bile acids in the intestine. Infants with biliary atresia may be at risk for fat-soluble vitamin insufficiency due to a potential reduction in bile that is secreted from the liver into the intestine. A multivitamin preparation (ADEKs® or AquADEKs®) that contains a form of vitamin E that is absorbed independent of bile acids is used as a supplement in infants with biliary atresia because it has been presumed to be efficacious. The ChiLDREN consortium prospectively assessed the efficacy of this multivitamin preparation in infants with biliary atresia. Infants with biliary atresia whose total bilirubin was greater than 2 mg/dl in the first 6 months after a Kasai procedure were at high risk of having at least one vitamin insufficiency (either vitamin A, D or E) when standard doses of this multivitamin preparation were utilized. Individual fat-soluble vitamin supplementation and monitoring is necessary to provide optimal fat-soluble vitamin blood levels in infants with biliary atresia who have a total bilirubin greater than 2 mg/dL.

36. Zahm AM, Hand NJ, Boateng LA and Friedman JR. **Circulating microRNA is a biomarker of biliary atresia.** J Pediatr Gastroenterol Nutr. 2012; 55(4):366-369.

The lack of reliable noninvasive diagnostic biomarkers of biliary atresia (BA) results in delayed diagnosis and worsened patient outcome. We examined the ability of serum miRNAs to distinguish BA from other forms of neonatal hyperbilirubinemia. We found that circulating levels of the miR-200b/429 cluster are elevated in infants with BA and have promising diagnostic clinical performance.

37. Bessho K and Bezerra JA. **Biliary atresia: will blocking inflammation tame the disease?** Annu Rev Med. 2011; 62(X):171-185.

The investigators analyzed the genes in livers of children with biliary atresia to determine if they differ from other types of pediatric liver disease. They found the livers in biliary atresia have greater level of activation of inflammation genes. Among these genes, interleukin-8 (IL-8) was particularly interesting because it was increased in biliary atresia as well as in a mouse model of experimental biliary atresia. In this mouse, the inactivation of IL-8 decreased inflammation and obstruction of bile ducts, and improved long-term survival. These findings suggest that liver gene studies may aid in diagnosis of disease, and that IL-8 pathways may be treatment targets in future studies.

38. Chu AS, Diaz R, Hui JJ, Yanger K, Zong Y, Alpini G, Stanger BZ and Wells RG. **Lineage tracing demonstrates no evidence of cholangiocyte epithelial-to-mesenchymal transition in murine models of hepatic fibrosis.** Hepatology. 2011; 53(5):1685-1695.

Some investigators believe that epithelial cells such as cholangiocytes and hepatocytes in the injured liver undergo an epithelial-to-mesenchymal transition (EMT), such that they lose their epithelial identity and become myofibroblasts, a form of mesenchymal cell that can secrete collagens and other matrix proteins making up scar tissue (fibrosis). In this study, all cholangiocytes and hepatocytes were genetically modified so that they and cells derived from them could be traced. When the livers from mice with these labeled cells were injured, there was no evidence that any of the cells involved in making scar tissue were derived from epithelial cells. In combination with two studies from another group, this strongly suggested that, at least in mouse models, EMT is not an important process in the generation of fibrosis.

39. Evason K, Bove KE, Finegold MJ, Knisely AS, Rhee S, Rosenthal P, Miethke AG, Karpen SJ, Ferrell LD and Kim GE. **Morphologic findings in Progressive Familial Intrahepatic Cholestasis 2 (PFIC2): Correlation with genetic and immunohistochemical studies.** Am J Surg Path. 2011; 35(5):687-696.

Twelve children with PFIC2 had light and electron microscopy of liver biopsies as well as genetic evaluation of the BSEP gene, ABCB11.The age at presentation, pace of progressive liver disease and specific genetic mutations were highly varied. Indolent course was noted in two patients with mutations who had demonstrable BSEP in liver canaliculi. Possible linkage was observed between mutations that ended BSEP transcription and severity of hepatocellular injury

(necrosis and fibrosis). However, no definitive correlation between specific mutations and histopathology was established in this small series of well-studied patients.

40. He M, Pei Z, Mohsen AW, Watkins P, Murdoch G, Van Veldhoven PP, Ensenauer R and Vockley J. **Identification and characterization of new long chain acyl-CoA dehydrogenases.** Mol Genet Metab. 2011; 102(4):418-429.

    Long-chain fatty acids are an important source of energy in muscle and heart where the acyl-CoA dehydrogenases (ACADs) participate in consecutive cycles of beta-oxidation to generate acetyl-CoA and reducing equivalents for generating energy. However, the role of long-chain fatty acid oxidation in the brain and other tissues that do not rely on fat for energy is poorly understood. Here we characterize two new ACADs, ACAD10 and ACAD11, both with significant expression in human brain.

41. Li J, Bessho K, Shivakumar P, Mourya R, Mohanty SK, Dos Santos JL, Miura IK, Porta G and Bezerra JA. **Th2 signals induce epithelial injury in mice and are compatible with the biliary atresia phenotype.** J Clin Invest. 2011; 121(11):4244-4256.

    Using a mouse model of experimental atresia, the investigators found that the type-2 cytokine interleukin-13 (IL-13) played a key role in pathogenesis of bile duct injury. Quantifying this cytokine in serum of children at the time of diagnosis of biliary atresia, IL-13 and other type-2 cytokines increased in a subset of children. This is the first study to show a link between type-2 cytokines in biliary atresia.

42. Russo P, Magee JC, Boitnott J, Bove KE, Raghunathan T, Finegold M, Haas J, Jaffe R, Kim GE, Magid M, Melin-Aldana H, White F, Whitington PF, Sokol RJ for the Biliary Atresia Research Consortium. **Design and validation of the Biliary Atresia Research Consortium histologic assessment system for cholestasis in infancy.** Clin Gastroenterology and Hepatol. 2011; 9(4):357-362.

    The BARC histological assessment system (for studying liver biopsies) identified features of liver biopsies from jaundiced infants, with good agreement between liver pathologists who read the biopsies that might be used in diagnosis and determination of future medical course. The system diagnosed biliary atresia (BA) quite well and identified infants with biliary obstruction with reasonable agreement between pathologists. However, distinguishing between BA and disorders such as total parenteral nutrition associated liver disease and alpha-1-antitrypsin deficiency is not possible without adequate clinical information.

43. Saxena V, Shivakumar P, Sabla G, Mourya R, Chougnet C and Bezerra JA. **Dendritic cells regulate natural killer cell activation and epithelial injury in experimental biliary atresia.** Nature Rev Gastroenterol Hepatol 2011;8:660. Sci Transl Med. 2011; 3(102):102ra194.

    The investigators studied the number and function of dendritic cells in the livers of mice and children with biliary atresia. They found increase in the number of activated dendritic cells, and the removal of the cells prevented the disease in mice. These findings identified dendritic cells as key cellular triggers of biliary injury.

44. Shin S, Walton G, Aoki R, Brondell K, Schug J, Fox A, Smirnova O, Dorrell C, Erker L, Chu AS, Wells RG, Grompe M, Greenbaum LE and Kaestner KH. **Foxl1-Cre-marked adult**

hepatic progenitors have clonogenic and bilineage differentiation potential. Genes Dev. 2011; 25(11):1185-1192.

This study examined the function of a specific set of cells in the liver, cells expressing the transcription factor Foxl1. Foxl1 is thought to be a progenitor cell marker, and this study showed that Foxl1-expressing cells could differentiate into both hepatocytes and cholangiocytes, depending on the culture conditions, consistent with their being progenitor cells.

45. Superina R, Magee JC, Brandt ML, Healey PJ, Tiao G, Ryckman F, Karrer FM, Iyer K, Fecteau A, West K, Burns RC, Flake A, Lee H, Lowell JA, Dillon P, Colombani P, Ricketts R, Li Y, Moore J and Wang KS. for Childhood Liver Disease Research and Education Network (ChiLDREN). **The anatomic pattern of biliary atresia identified at time of Kasai Hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival.** Ann Surg. 2011; 254(4):577-585.

46. Leyva-Vega M, Gerfen J, Thiel BD, Jurkiewicz D, Rand EB, Pawlowska J, Kaminska D, Russo P, Gai X, Krantz ID, Kamath BM, Hakonarson H, Haber BA and Spinner NB. **Genomic alterations in biliary atresia suggest region of potential disease susceptibility in 2q37.3.** Am J Med Genet A. 2010; 152A(4):886-895.

Leyva-Vega et al. screened a cohort of 35 patients with biliary atresia using a genome-wide SNP based chromosomal microarray (CMA) analysis test to look for deletions and duplications that might be associated with the disorder. They identified two patients with large, overlapping deletions on chromosome 2, suggesting that there might be a BA susceptibility locus in this region of the chromosome. There was a 1.76 Mb overlapping regions at the intersection of the 2 deletions, that contained 30 genes, that can be considered BA candidate genes.

47. Matte U, Mourya R, Miethke A, Liu C, Kauffmann G, Moyer K, Zhang K and Bezerra JA. **Analysis of gene mutations in children with cholestasis of undefined etiology.** J Pediatr Gastroenterol Nutr. 2010; 51(4):488-493.

The investigators screened for genetic mutations in the genes SERPINA1A, ATP8B1, ABCB11, ABCB4 and JAG1 in 51 children with chronic intrahepatic cholestasis of undefined etiology. Sequence analysis assigned a molecular diagnosis in 27% of the patients based on the presence of variants likely to cause disease phenotypes.

48. Moyer K, Kaimal V, Pacheco C, Mourya R, Xu H, Shivakumar P, Chakraborty R, Rao M, Magee JC, Bove K, Aronow BJ, Jegga AG and Bezerra JA. **Staging of biliary atresia at diagnosis by molecular profiling of the liver.** Genome Med. 2010; 2(5):33.

The investigators analyzed the human genome to determine whether the expression of gene groups can provide insight into the stages of liver disease at the time of diagnosis. To this end, they scored the degree of inflammation and fibrosis (scarring) in the liver biopsies from 47 infants with biliary atresia. They also quantified the expression of all human genes in the liver biopsies using a gene chip. The investigators found that about 1/3 of the patients had either inflammation or fibrosis in the livers at the time of diagnosis using standard anatomical criteria. In contrast, using a new method to classify the patients based on the pattern of gene expression (also known as molecular profiling), they were able to stage the disease into inflammation or fibrosis in a greater percentage of the patients and to link fibrosis with poor outcome. The implication of the findings is that the liver disease of babies with biliary atresia has variable degrees at diagnosis. Future studies will examine whether the use of molecular profiling will aid the monitoring of patients and the design of clinical trials.

49. Pawlikowska L, Strautnieks S, Jankowska I, Czubkowski P, Emerick K, Antoniou A, Wanty C, Fischler B, Jacquemin E, Wali S, Blanchard S, Nielsen IM, Bourke B, McQuaid S, Lacaille F, Byrne JA, van Eerde AM, Kolho KL, Klomp L, Houwen R, Bacchetti P, Lobritto S, Hupertz V, McClean P, Mieli-Vergani G, Shneider B, Nemeth A, Sokal E, Freimer NB, Knisely AS, Rosenthal P, Whitington PF, Pawlowska J, Thompson RJ and Bull LN. **Differences in presentation and progression between severe FIC1 and BSEP deficiencies.** J Hepatol. 2010; 53(1):170-178.

50. Sokol RJ. **Reloading against rare liver diseases.** J Pediatr Gastroenterol Nutr. 2010; 50(1):9-10.

A discussion of bile acid synthesis defects and their challenges as an example of a rare cholestatic childhood liver disease is presented. An argument is provided supporting the benefits of collaboration among centers, countries and continents in unraveling the causes, modifying factors and the conduct of clinical trials in rare liver diseases. The challenges ahead will be to obtain sustainable resources and funding, to develop robust national and international registries and annotated tissue/DNA repositories for rare diseases, to capitalize on the implementation of electronic medical records, and to formulate and disseminate best practices to practitioners.

51. Van Hove JLK, Saenz MS, Thomas JA, Gallagher RC, Lovell MA, Fenton LZ, Shanske S, Myers SM, Wanders RJ, Ruiter J, Turkenburg M and Waterham HR. **Succinyl-CoA ligase deficiency: a mitochondrial hepatoencephalomyopathy.** Pediatr Res. 2010; 68(2):159-164.

52. Wang H, Malone JP, Gilmore PE, Davis AE, Magee JC, Townsend RR and Heuckeroth RO. **Serum markers may distinguish biliary atresia from other forms of neonatal cholestasis.** J Pediatr Gastroenterol Nutr. 2010; 50(4):411-416.

53. Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K and Merkel PA.**Clinical research for rare disease: opportunities, challenges, and solutions.** Mol Genet Metab. 2009; 96(1):20-26.

Over 7000 rare diseases affect nearly 30 million people in the United States. Furthermore, for the 10% of people with a rare disease and for their families, these disorders no longer seem rare. Molecular genetics have characterized the cause of many rare diseases and provide unprecedented opportunities for identifying patients, determining phenotypes, and devising treatments to prevent, stabilize, or improve each disease. The U.S. Orphan Drug Act of the U.S. FDA has stimulated industry investment in clinical trials to develop treatments for rare diseases. For trainees interested in finding a treatment for a rare disease, a commitment to longitudinal care of patients allows one to establish the phenotype and natural history of the disease and the creation of a collaboration scientific team is critical. The ability to conduct clinical research for rare diseases has changed dramatically in the past two decades resulting in increased understanding of the basis of these disorders leading to direct benefit to patients.

54. Sokol RJ. **Biliary atresia screening: why, when, and how?** Pediatrics. 2009; 123(5):e951-952.

This commentary describes various approaches to screening infants for biliary atresia, the potential advantages of these approaches, and the need for a newborn screening test that would be appropriate for North America

55. Swigonova Z, Mohsen AW and Vockley J. **Acyl-CoA dehydrogenases: Dynamic history of protein family evolution** J Mol Evol. 2009; 69(2):176-193.

The acyl-CoA dehydrogenases (ACADs) are enzymes that catalyze the alpha,beta-dehydrogenation of acyl-CoA esters in fatty acid and amino acid catabolism. Eleven ACADs are now recognized in the sequenced human genome. We performed a systematic comparative genomic study, integrating homology searches with methods of phylogenetic reconstruction, to investigate the evolutionary history of this family. Our finding that eukaryotic ACAD species are more closely related to bacterial ACADs is consistent with endosymbiotic origin of ACADs in eukaryotes and further supported by the localization of all nine previously studied ACADs in mitochondria.

56. Strautnieks SS, Byrne JA, Pawlikowska L, Cebecauerova D, Rayner A, Dutton L, Meier Y, Antoniou A, Stieger B, Arnell H, Ozcay F, Al-Hussaini HF, Bassas AF, Verkade HJ, Fischler B, Nemeth A, Kotalova R, Shneider BL, Cielecka-Kuszyk J, McClean P, Whitington PF, Sokal E, Jirsa M, Wali SH, Jankowska I, Pawlowska J, Mieli-Vergani G, Knisely AS, Bull LN and Thompson RJ. **Severe bile salt export pump deficiency: 82 different ABCB11 mutations in 109 families.** Gastroenterology. 2008; 134(4):1203-1214.

57. Sundaram SS, Bove KE, Lovell MA and Sokol RJ. **Mechanisms of disease: inborn errors of bile acid synthesis.** Nat Clin Pract Gastroenterol Hepatol. 2008; 5(8):456-468.

Bile acids work as natural detergents to help the body break down and use the fats and vitamins taken in as food. They are chemicals made by the liver that start as cholesterol and are converted to their final form through a progressive series of steps. Each step in this path requires a special protein, or enzyme, to occur correctly. An inborn error of bile acid synthesis, an inherited condition, occurs if one of these enzymes is defective. There are 9 known errors of bile acid synthesis, which can cause abnormal liver tests, jaundice, neurologic problems, and severe vitamin deficiencies. If diagnosed early, patients may respond well to medical therapy. This paper carefully reviews the chemical pathway of bile acid synthesis, along with the clinical presentation, diagnosis and treatment of each known error of bile acid synthesis.

58. DeRusso PA, Ye W, Shepherd R, Haber BA, Shneider BL, Whitington PF, Schwarz KB, Bezerra JA, Rosenthal P, Karpen S, Squires RH, Magee JC, Robuck PR and Sokol RJ. for Biliary Atresia Research Consortium. **Growth failure and outcomes in infants with biliary atresia: a report from the Biliary Atresia Research Consortium.** J Hepatol. 2007; 46(5):1632-1638.

Malnutrition is a significant clinical problem in infants with biliary atresia. The natural history of poor growth and its potential association with early need for transplantation or death in children with biliary atresia was determined. Growth velocity was significantly slower in infants with poor bile flow compared to those with good bile flow after the Kasai procedure.

59. He M, Rutledge SL, Kelly DR, Palmer CA, Murdoch G, Majumder N, Nicholls RD, Pei Z, Watkins PA and Vockley J. **A new genetic disorder in mitochondrial fatty acid beta-oxidation: ACAD9 deficiency.** Am J Hum Genet. 2007; 81(1):87-103.

The acyl-CoA dehydrogenases are a family of multimeric flavoenzymes that catalyze the alpha,beta -dehydrogenation of acyl-CoA esters in fatty acid beta -oxidation and amino acid catabolism. Genetic defects have been identified in most of the acyl-CoA dehydrogenases in humans. Acyl-CoA dehydrogenase 9 (ACAD9) is a recently identified acyl-CoA dehydrogenase that demonstrates maximum activity with unsaturated long-chain acyl-CoAs. We now report the first three cases of ACAD9 deficiency.

60. Heubi JE, Setchell KD and Bove KE. **Inborn errors of bile acid metabolism.** Semin Liver Dis. 2007; 27(3):282-294.

Nine recognized inborn errors of bile acid metabolism have been identified which lead to enzyme deficiencies and impaired bile acid synthesis in infants, children and adults. Patients may present with neonatal jaundice due to liver disease, neurologic disease, or fat and fat soluble vitamin malabsorption. This review focuses on a description of the disorders of bile acid synthesis that are directly related to single defects in the metabolic pathway and summarizes the clinical, biochemical, liver biopsy findings, clinical course and response to oral bile acid with either cholic acid or glycocholic acid.

61. Lee WS and Sokol RJ. **Liver disease in mitochondrial disorders.** Semin Liver Dis. 2007; 27(3):259-273.

Liver involvement is a common feature in childhood mitochondrial disorders, particularly those that present in the newborn period and in infants. Nervous system, muscle and heart involvement are common and a key finding is the presence of elevated blood lactate levels.. The liver disease usually progresses and is not infrequently fatal. Current medical therapy of mitochondrial liver disorders is largely ineffective. The role of liver transplantation in patients with mitochondrial diseases is not clear because features outside of the liver do not respond to transplantation. Recent advances have led to discovery of new genetic causes of these diseases, including the following genes: SCO1, BCS1L, POLG, DGUOK, and MPV17 and deletion or rearrangement of mitochondrial DNA. Large multicenter studies will be needed to address the gaps in our knowledge in these rare liver diseases.

62. Liu C, Aronow BJ, Jegga AG, Wang N, Miethke A, Mourya R and Bezerra JA. **Novel resequencing chip customized to diagnose mutations in patients with inherited syndromes of intrahepatic cholestasis.**Gastroenterology. 2007; 132(1):119-126.

The authors report the development of a high-throughput re-sequencing chip that efficiently reads SERPINA1, JAG1, ATP8B1, ABCB11 and ABCB4, with a high call rate and accuracy. Bench-testing of the chip in normal and diseased subjects identified disease-causing mutations.

63. Mack CL, Falta MT, Sullivan AK, Karrer F, Sokol RJ, Freed BM and Fontenot AP. **Oligoclonal expansions of CD4+ and CD8+ T-cells in the target organ of patients with biliary atresia.** Gastroenterology. 2007; 133(1):278-287.

Biliary atresia is associated with oligoclonal expansions of CD4+ and CD8+ T cells within liver and extrahepatic bile duct remnant tissues, indicating the presence of activated T cells reacting to specific antigenic stimulation. Future studies entail identifying the specific antigen(s) responsible for T-cell activation and bile duct injury.

64. Shneider BL, Bezerra JA, Sokol RJ and Whitington PF. **Reply to: 'Multicenter Biliary Atresia Outcome Studies: the importance of surgical aspects by Petersen, et. al.** J Pediatr. 2007; 150(6):e89-e90.

Letter to the Editor.

65. Sokol RJ, Shepherd RW, Superina R, Bezerra JA, Robuck P and Hoofnagle JH. **Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop.** J Hepatol. 2007; 46(2):566-581.

This report summarizes a National Institutes of Health workshop held on September 12 and 13, 2006 in Bethesda, MD, that addressed the issues of outcomes, screening and pathogenesis of biliary atresia.

66. Setchell KD and Heubi JE. **Defects in bile acid biosynthesis - diagnosis and treatment.** J Pediatr Gastroenterol Nutr. 2006; 43(Suppl 1):S17-22.

67. Shneider BL, Brown MB, Haber B, Whitington PF, Schwarz K, Squires R, Bezerra J, Shepherd R, Rosenthal P, Hoofnagle JH and Sokol RJ. **A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000.** J Pediatrics. 2006; 148(4):467-474.

The objective of the study is to determine the prognostic factors and optimal approaches to the diagnosis and management of biliary atresia, the leading indication for liver transplantation in children. The outcome in the study centers was equivalent to that reported in other countries. Total bilirubin in early follow-up (3 months) after hepatoportoenterostomy was highly predictive of outcome. Efforts to improve bile flow after hepatoportoenterostomy may lead to improved outcome in children with biliary atresia.

68. Hoofnagle JH. **Biliary Atresia Research Consortium (BARC).** J Hepatol. 2004; 39(4):891.

69. Sokol RJ. **New North American research network focuses on biliary atresia and neonatal liver disease**[News and Views]. J Pediatr Gastroenterol Nutr. 2003; 36(1):1.

The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health of the United States (NIDDK) has initiated funding of a 5-year, multicenter study of biliary atresia, neonatal hepatitis, and related neonatal liver diseases. The overall goal of this consortium is to gather clinical and biochemical data and adequate numbers of serum, tissue and DNA samples in a prospective manner to facilitate research and generate new hypotheses and test existing hypotheses on the pathogenesis and optimal diagnostic and treatment modalities of these disorders.

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1. Vicky Lee Ng, Lisa G. Sorensen, Estella M. Alonso, Emily M. Fredericks, Wen Ye, Saul J. Karpen, Benjamin L. Shneider, Jorge A. Bezerra, Jean P. Molleston, Karen F. Murray, Philip Rosenthal, Kaspar S. Wang, Kathleen Loomes, Paula M. Hertel, Nanda Kerkar, Kathleen B. Schwarz, Yumirle Turmelle, Barbara H. Haber, Averell H. Sherker, John C. Magee, Ronald J. Sokol for the ChiLDReN Network. **Neurodevelopmental Outcomes in Patients with Biliary Atresia and Native Liver at Ages 1 and 2 Years: Results from ChiLDReN.** American Association for the Study of Liver Diseases (AASLD) 66th Annual Meeting, San Francisco, CA: November 13-17, 2015. Hepatology 62(S1):78A.

2. Kathleen M. Loomes, Catherine Spino, Nate Goodrich, Thomas Hangartner, Amanda Marker, James E. Heubi, Binita M. Kamath, Benjamin L. Shneider, Philip Rosenthal, Paula M. Hertel, Saul J. Karpen, Nanda Kerkar, Jean P. Molleston, Karen F. Murray, Kathleen B. Schwarz, Jeffrey Teckman, Yumirle P. Turmelle, Peter F. Whitington, Averell H. Sherker, John C. Magee, Ronald J. Sokol for the Childhood Liver Disease Research Network

(ChiLDReN). **DXA Bone Density in Alagille Syndrome Correlates with Fracture History and Degree of Cholestasis.** American Association for the Study of Liver Diseases (AASLD) 66th Annual Meeting, San Francisco, CA: November 13-17, 2015. Hepatology 62(S1):174A.

3. Benjamin L. Shneider, John Magee, Nanda Kerkar, Jeffrey Moore, Wen Ye, Saul Karpen, Peter Whitington, Jorge Bezerra, Paula Hertel, Jean Molleston, Kasper Wang, Henry Lin, Robert Squires, Philip Rosenthal, Vicky Ng, Yumirle Turmelle, Kathleen Schwarz, Averell Sherker, Ronald Sokol for ChiLDReN. **Prospective Analysis of Presenting Features of Neonatal Cholestasis – Limitations in Predictive Models of Biliary Atresia.**Presented at North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) 29th Annual Meeting, Washington, DC: October 7-11, 2015.

4. Vicky Lee Ng, Lisa G. Sorensen, Estella M. Alonso, Emily M. Fredericks, Wen Ye, Saul J. Karpen, Benjamin L. Shneider, Jorge A. Bezerra, Jean P. Molleston, Karen F. Murray, Philip Rosenthal, Kaspar S. Wang, Kathleen Loomes, Paula M. Hertel, Nanda Kerkar, Kathleen B. Schwarz, Yumirle Turmelle, Barbara H. Haber, Averell H. Sherker, John C. Magee, Ronald J. Sokol for the ChiLDReN Network. **Neurodevelopmental Outcomes in Patients with Biliary Atresia and Native Liver at Ages 1 and 2 Years: Results from ChiLDReN.** American Association for the Study of Liver Diseases (AASLD) 66th Annual Meeting, San Francisco, CA: November 13-17, 2015. Hepatology 62(S1):78A.

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6. Benjamin L. Shneider, John Magee, Nanda Kerkar, Jeffrey Moore, Wen Ye, Saul Karpen, Peter Whitington, Jorge Bezerra, Paula Hertel, Jean Molleston, Kasper Wang, Henry Lin, Robert Squires, Philip Rosenthal, Vicky Ng, Yumirle Turmelle, Kathleen Schwarz, Averell Sherker, Ronald Sokol for ChiLDReN. **Prospective Analysis of Presenting Features of Neonatal Cholestasis – Limitations in Predictive Models of Biliary Atresia.**Presented at North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) 29th Annual Meeting, Washington, DC: October 7-11, 2015.

7. Loomes KM, Tsai EA, Underkoffler LA, Grochowski C, Falsey A, Kamath BM, Lin H, Hankenson KD, Devoto M, Spinner NB. **A genome-wide association study identifies THBS2 as a candidate modifier of liver disease severity in Alagille syndrome.** American Association for the Study of Liver Diseases (AASLD) 65th Annual Meeting, Boston, MA: November 10, 2014. Hepatology 60(S1):252A.

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(ChiLDREN). **High-dose corticosteroid therapy following portoenterostomy in infants with biliary atresia does not improve outcome: The multi-center, randomized, double-blind, placebo-controlled START Trial.** American Association for the Study of Liver Diseases (AASLD) 64th Annual Meeting, Washington, D.C.: November 1, 2013. Hepatology 58(S1):263A.

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11. Molleston J, Sokol RJ, Karsakul WW, Miethke AG, Magee JC, Squires RH, VanHove JL for the Childhood Liver Disease Research and Education Network. **Evaluation guidelines for suspected mitochondrial hepatopathies.** World Congress Ped Gastro, Hep & Nutrition, Taipei, Taiwan: November 14, 2012.

12. Dexheimer P, Connor J, Karns R, Miethke A, Aronow B, Zhang K and Bezerra J. **High-throughput mutation screen identifies high frequency of double and triple heterozygous gene variants in patients with idiopathic cholestasis.** Presented at American Association for the Study of Liver Diseases (AASLD) 63rd Annual Meeting, Boston, MA: November 9-13, 2012. Hepatology 56(S1):204A.

13. Jericho H, Westfall E, Knisely A, Verkade H and Whitington P. **Bile salt kinetics in children with genetic cholestasis and bile diversion therapy.** Presented at American Association for the Study of Liver Diseases (AASLD) 63rd Annual Meeting, Boston, MA: November 9-13, 2012. Hepatology 56(S1):208A-209A.

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15. Karjoo S, Pack M, Porter JR and Wells R. **A toxin that induces biliary atresia causes disruption of microtubules and loss of primary cilia.** Presented at American Association for the Study of Liver Diseases (AASLD) 63rd Annual Meeting, Boston, MA: November 9-13, 2012. Hepatology 56(S1):725A.

16. Kamath BM, Chen Z, Romero R, Fredericks E and Magee J for the Childhood Liver Disease Research and Education Network. **Quality of Life in Alagille syndrome is associated with growth failure and cardiac defects.** Presented at American Association for the Study of Liver Diseases (AASLD) 63rd Annual Meeting, Boston, MA: November 9-13, 2012. Hepatology 56(S1):732A-733A.

17. Molleston J, Sokol RJ, Karsakul WW, Miethke AG, Magee JC, Squires RH, VanHove JL for the Childhood Liver Disease Research and Education Network. **Evaluation guidelines for suspected mitochondrial hepatopathies.** Presented at World Congress of Pediatric Gastroenterology, Hepatology and Nutrition 4th Annual Meeting, Taipei, Taiwan: November 14-18, 2012.

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