Neonatal cholestasis Introduction and diagnostic approach

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Objectives

- Discuss the **diagnostic work-up** of the cholestatic infant
- Discuss **triage** of liver specimens
- Review the **salient histologic features of the developing liver** and their relationship to findings in the liver biopsies of cholestatic infants
- Discuss the **major histologic patterns** observed in liver biopsies from **cholestatic infants** and their differential diagnosis.

Pediatric Liver Disease

- Children are not little adults
- Many adult liver diseases are also seen in pediatric patients
  - Hepatitis B
  - Hepatitis C
  - Autoimmune hepatitis
  - Non-alcoholic Steatohepatitis (NASH)
- However, some are unique to pediatric hepatology or have onset mainly in the pediatric age group
  - **Neonatal cholestasis**
  - Developmental/metabolic disorders

Definitions

- Jaundice:
  - Elevated unconjugated or conjugated bilirubin
  - Clinically evident when total bilirubin > 2.5 – 3.0 mg/dl
- Cholestasis: reduction of bile flow from the liver, resulting in retention of biliary substances within the liver.
  - Cholestasis = conjugated (or direct) bilirubin
- Conjugated hyperbilirubinemia: > 1.0 mg/dl (17 µmol/ L) (NASPGHAN Guideline, JPGN 2017)
- Hepatitis: inflammation of the liver

15% of neonates develop jaundice

Physiologic versus pathologic jaundice

Physiologic jaundice

- Common and nearly never dangerous.
- Unconjugated hyperbilirubinemia.

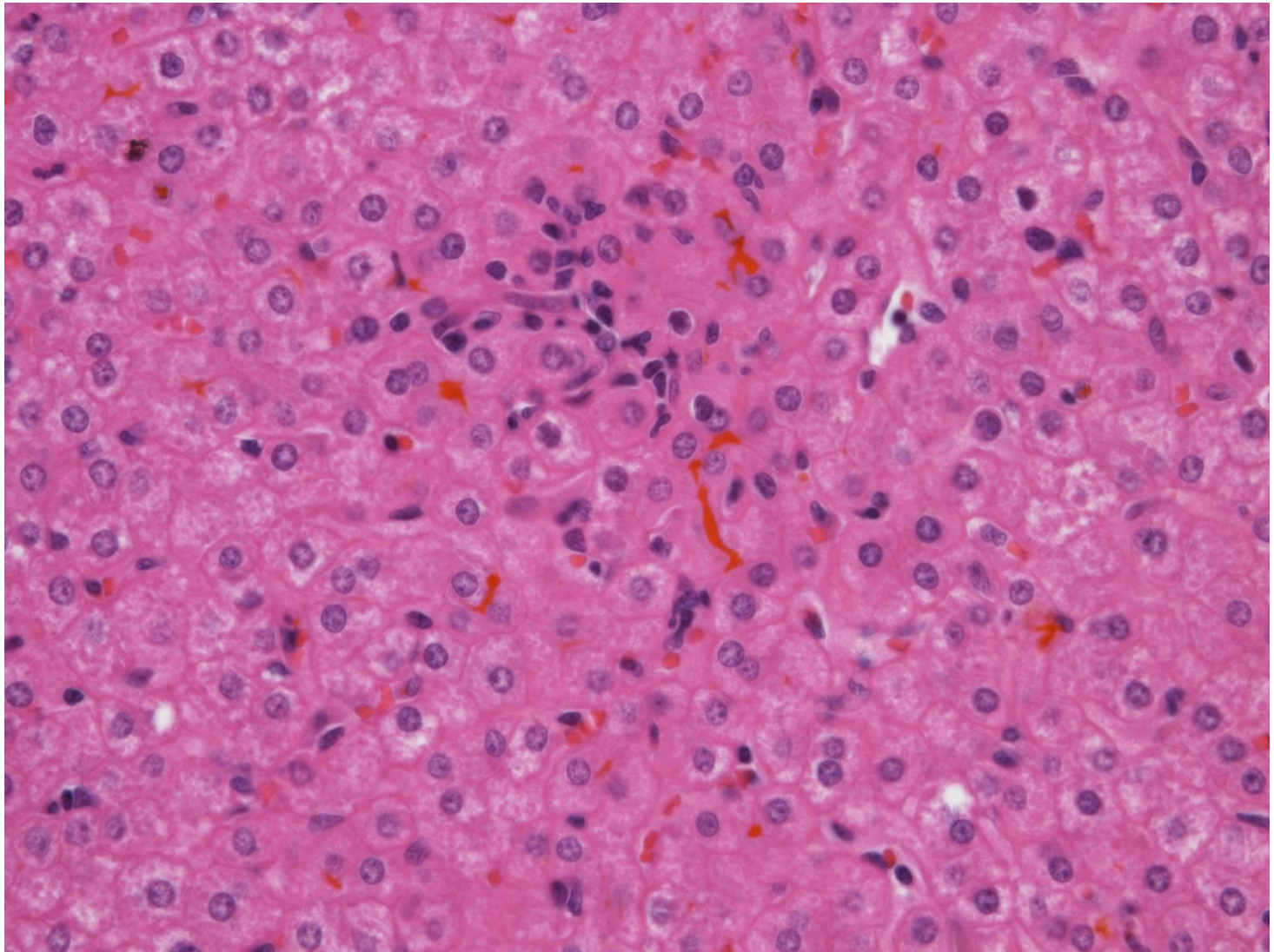
Pathologic jaundice

- An emergency with potential for fatal outcome and chronic disease. It is never normal.
- Conjugated hyperbilirubinemia (cholestasis, with a few exceptions).

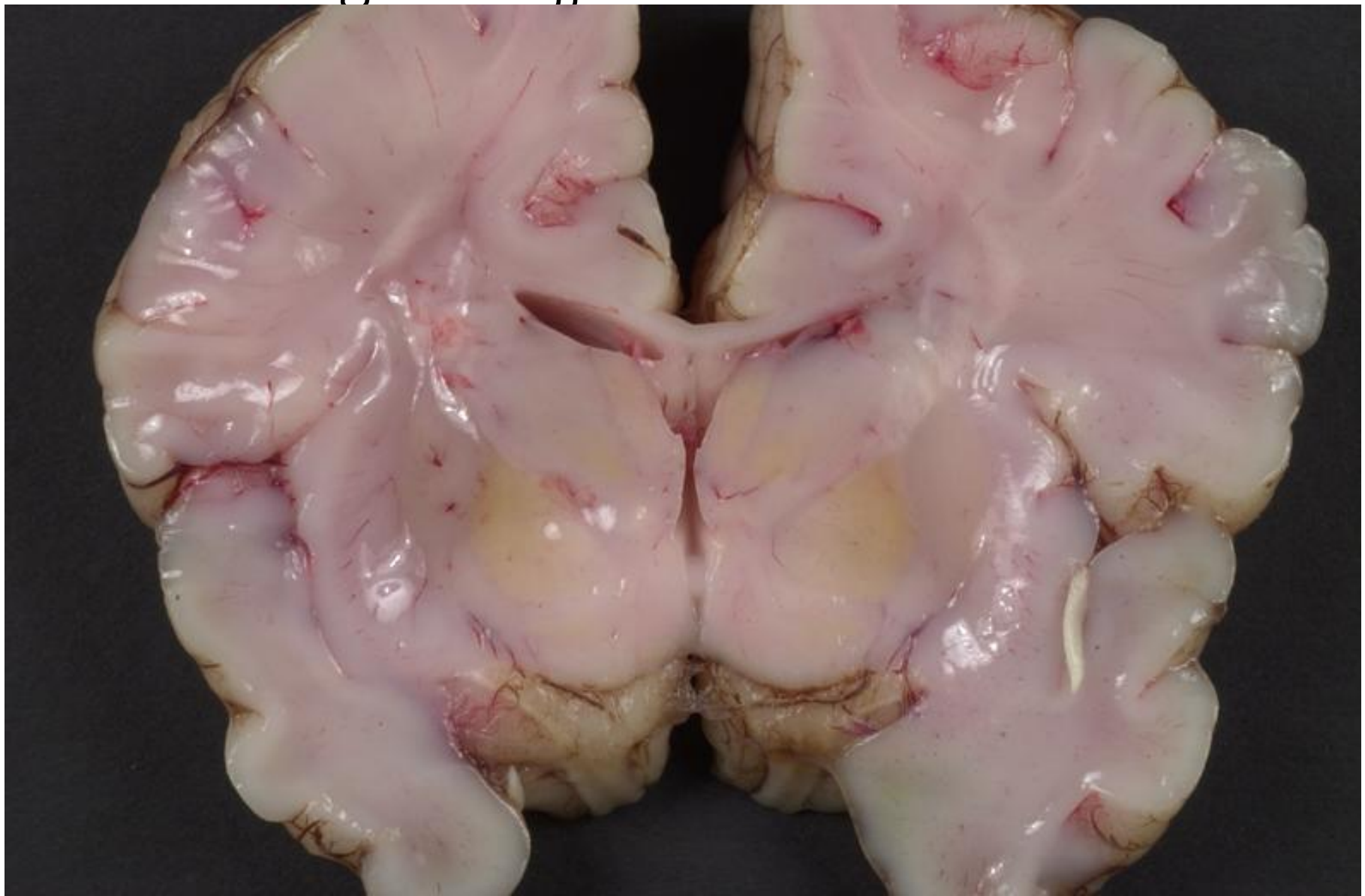
Differential diagnosis of Unconjugated Hyperbilirubinemia

- Physiologic jaundice
- Bilirubin overproduction - hemolysis, hematomas, dyserythropoiesis
- Diminished bilirubin uptake – sepsis, right heart failure
- Inherited disorders
  - UGT1A1 (uridine diphosphate glycosyltransferase)
    - Crigler-Najjar types I and II
    - Gilbert syndrome (promoter gene)

Unconjugated hyperbilirubinemia – Crigler-Najjar



Kernicterus – Crigler-Najjar



Differential diagnosis of Neonatal cholestasis

Neonatal Hepatitis

- Idiopathic NH
- Viral NH
  - CMV
  - Herpes
  - Rubella
  - Reovirus
  - Adenovirus
  - Enteroviruses
  - Parvovirus B19
  - Paramyxovirus
  - Hepatitis B
  - HIV
- Bacterial and parasitic
  - bacterial sepsis
  - UTI
  - Syphilis
  - Listeriosis
  - Toxoplasmosis
  - Tuberculosis
  - Malaria

Bile duct obstruction

- Cholangiopathies
  - Biliary atresia
  - Choledochal cysts
  - Nonsyndromic Paucity
  - Alagille syndrome
  - Sclerosing Cholangitis
  - Spontaneous duct perforation
  - Caroli disease
  - Congenital hepatic fibrosis
  - Bile duct stenosis
- Other
  - Inspissated bile/mucus
  - Cholelithiasis
  - Tumors
  - Masses

Intrahepatic Cholestatic syndromes

- Progressive familial intrahepatic cholestasis (PFIC)
  - Type 1 Byler P-type ATPase
  - Type 2 Canalicular Bile Acid Tx
  - Type 3 MDR3 deficiency
- Aagenaes cholestasis lymphedema
- N. Am. Indian Cholestasis
- Nielsen Greenland Eskimo cholestasis
- Benign Recurrent Intrahepatic cholestasis
- Dubin Johnson MRP2 cMOAT deficiency
- Rotor syndrome

Metabolic disorders

- a1-antitrypsin deficiency (A1AT)
- Cystic fibrosis
- Neonatal iron storage disease
- Endocrinopathies
  - Hypopituitarism
  - Hypothyroidism
- Amino acid disorders
  - Tyrosinemia
  - Hypermethionemia
  - Mevalonate kinase deficiency
- Lipid disorders
  - Niemann-Pick A, B
  - Niemann-Pick C
  - Gaucher
  - Wolman
  - Cholesterol ester storage ds
- Urea cycle disorders
  - Arginase deficiency
- Carbohydrate disorders
  - Galactosemia
  - Fructosemia
  - Glycogen storage IV
- Mitochondrial disorders
  - Oxidative phosphorylation
- Peroxisomal disorders
  - Zellweger
  - Infantile Refsum
  - Other enzymopathies
- Bile acid synthetic disorders (BASD)
  - 3b-hydroxysteroid dehydrogenase/i
  - D4-3-oxosteroid 5b-reductase
  - Oxosterol 7a-hydroxylase

Toxic

- Drugs
- Parenteral alimentation
- Aluminum

Miscellaneous associations

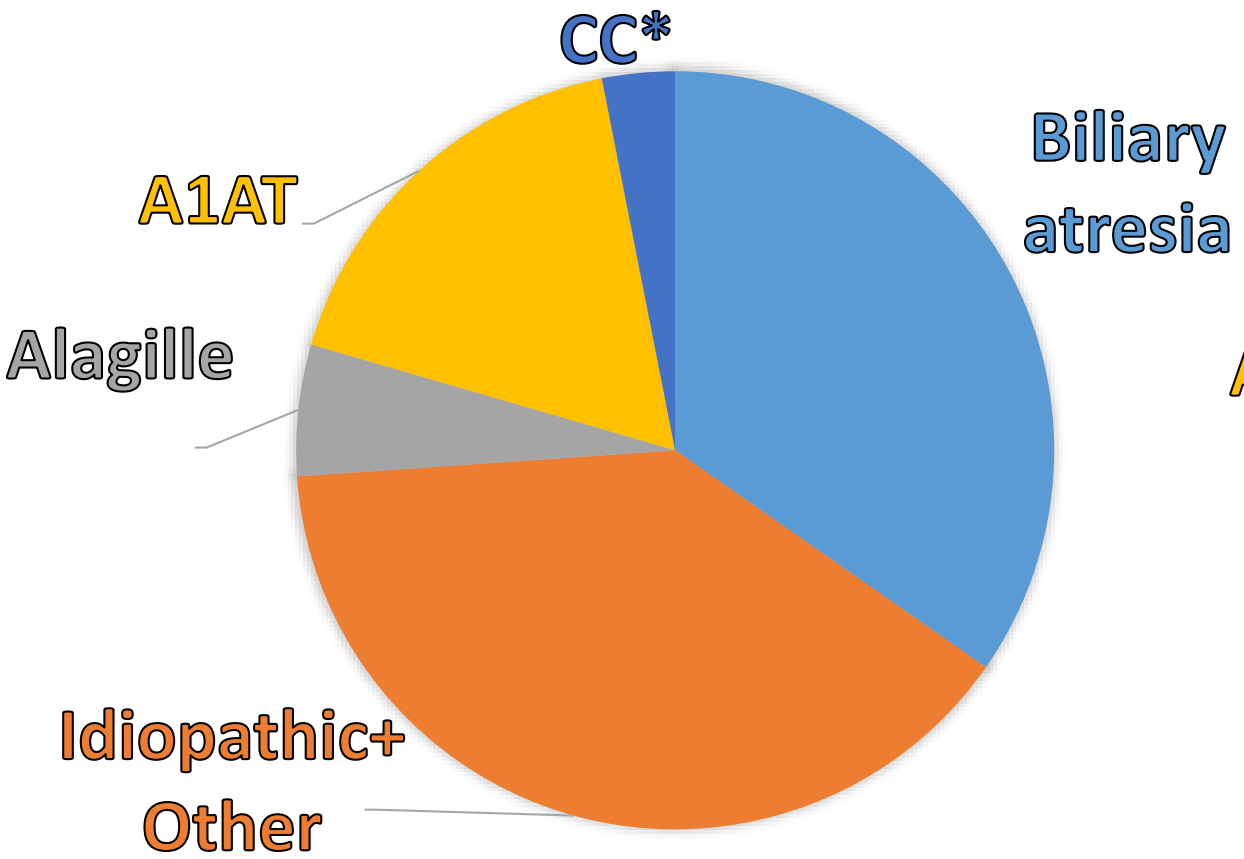
- Shock/hypoperfusion
- Histiocytosis X
- Neonatal lupus erythematosus
- Indian childhood cirrhosis
- Autosomal trisomies 17, 18, 21
- Graft v host disease
- Erythrophagocytic lymphohistiocytosis
- ECMO
- Veno-occlusive disease
- Donahue leprechaunism
- Arthrogryposis cholestasis
- Erythroblastosis fetalis

Guiding principles for evaluation

- There are over 100 etiologies
- Many complex, rare metabolic diseases some of which have new and effective therapies
- Design initial evaluation according to:
  - What is dangerous and treatable?
  - What is common?
  - What patterns provide clues for specific etiologies?

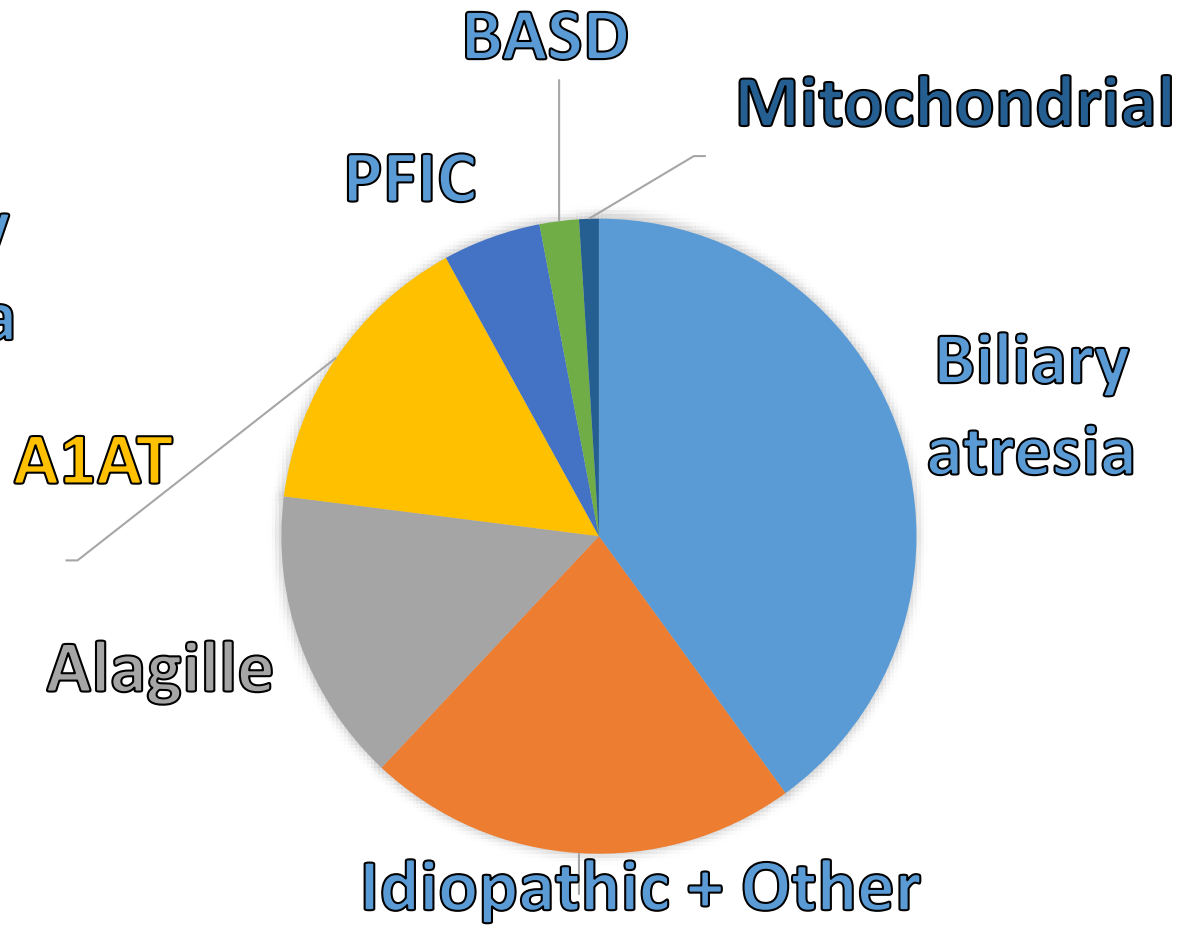
Etiologies of Neonatal Cholestasis

Lancet 1989: King's College Hospital(n= 1096)



*CC – Choledochal cyst

ChiLDReN Network 2001-17 (n=3096)



Important Critical Etiologies: Early Treatment Improves Outcome

- **Biliary atresia** → **Kasai portoenterostomy**
- Extrahepatic obstruction → Surgery
- Galactosemia → Lactose restriction
- Tyrosinemia → NTBC (Nitisinone)
- Hypopituitarism → Cortisol, thyroxine
- Bile acid synthetic defects → Cholic acid
- Sepsis and urinary tract infection → Antibiotics
- Syphilis → Antibiotics

Clinical Evaluation

History

Physical exam

- Dysmorphism
- Eye findings
- Heart murmur
- Liver size
- Spleen size

Tier 1 studies

- Fractionated bilirubin
- Enzymes: ALT, AST, GGT, Alkaline Phosphatase
- Albumin, PT, PTT
- Cultures, blood and urine for viruses / bacteria
- Urine reducing sugar
- Serologies (TORCHS)
- Newborn screen results
- Sweat test
- Alpha 1-antitrypsin level & phenotype
- Serum amino acids
- Urine organic acids

Tier 2 Studies

- Imaging
  - Ultrasound
  - DISIDA scintigraphy
  - Cholangiogram
- Specific metabolic investigations
- Genetic testing – Gene Panel/Exome
- Liver biopsy

Clues from Gamma glutamyl transferase (GGT) Levels

- **Low/normal GGT with cholestasis**
  - Bile acid synthetic disorders
  - Progressive familial intrahepatic cholestasis (PFIC)
    - *ATP8B1* (PFIC I)
    - *ABCB11* (PFIC II)
    - *TJP2*
    - *MYO5B*
    - *NRIH4* (farnesoid-X receptor)
- **High GGT cholestasis (practically everything else)**
  - Extrahepatic disorders
  - Biliary atresia
  - Choledochal cyst
  - Intrahepatic duct disorders
  - Alagille syndrome
  - MDR3 deficiency... Etc..

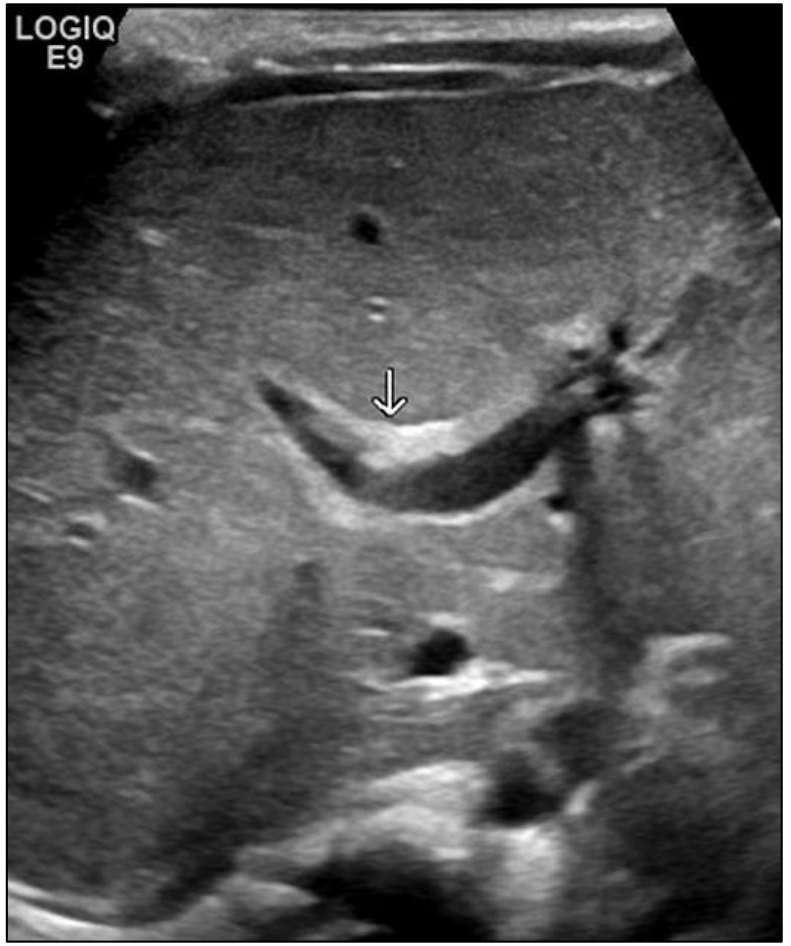
Ultrasound

Useful in the identification of abnormalities

- Choledochal cyst
- Bile duct stones
- Spontaneous perforation of the common bile duct
- Abnormal findings that can point to BA Splenic Malformation (BASM)
  Polysplenia, heterotaxy, preduodenal portal vein

Potentially misleading findings

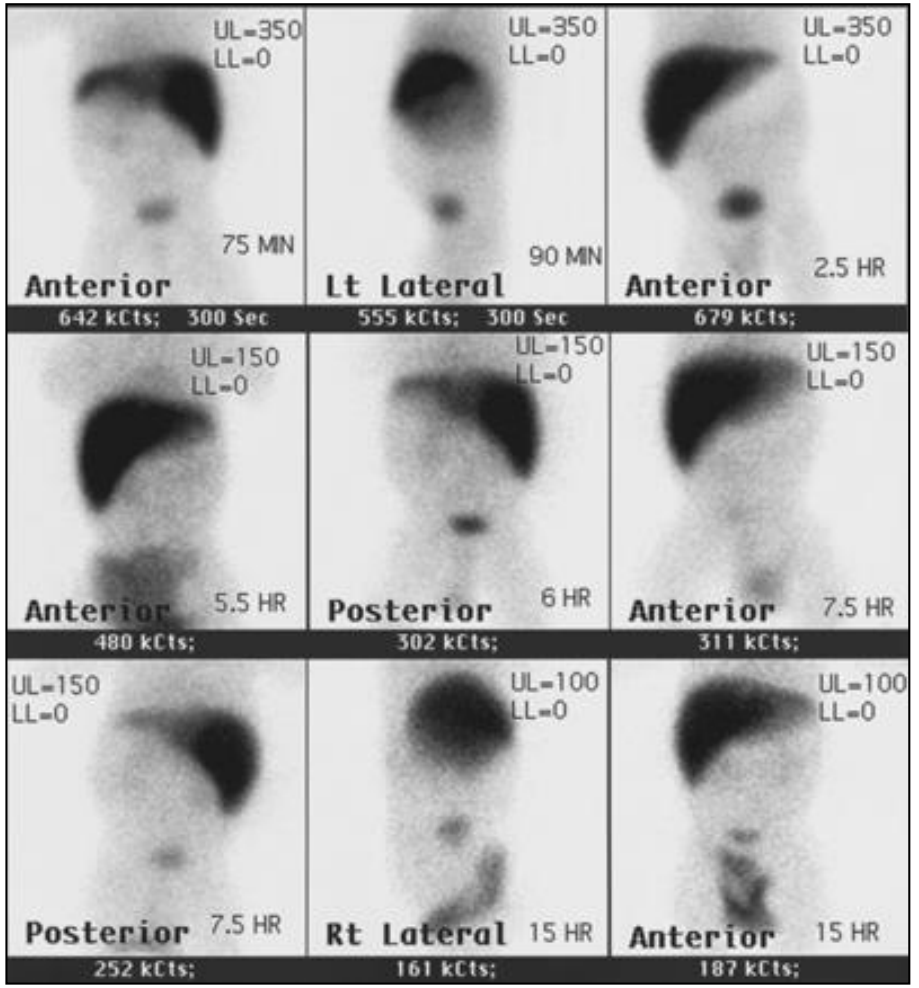
- Echogenicity or lack of echogenicity
- Diminished size or absent gallbladder
- Lack of duct dilatation



"triangular cord" sign, present in only 40% of BA cases (*Cho et al Eur J Radiol 2016 85:1045*)

Hepatobiliary scintigraphy (HIDA/DISIDA Scintiscan)

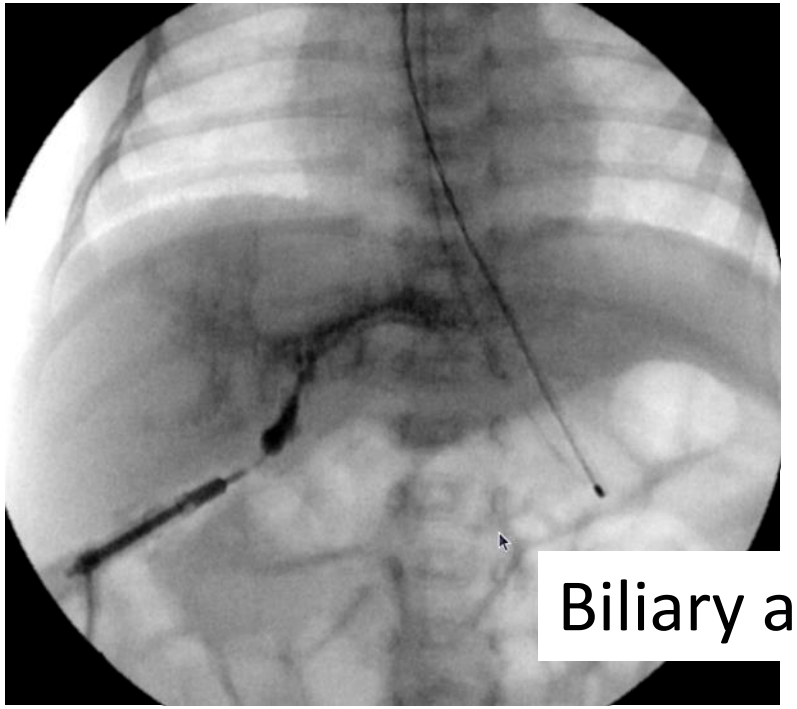
- **Useful when excretion is present (within 20-30 mins of uptake)**
  - Eliminates BA
- **Never diagnostic**
- **Potentially misleading**
  - Neonatal hepatitis
  - Alagille syndrome



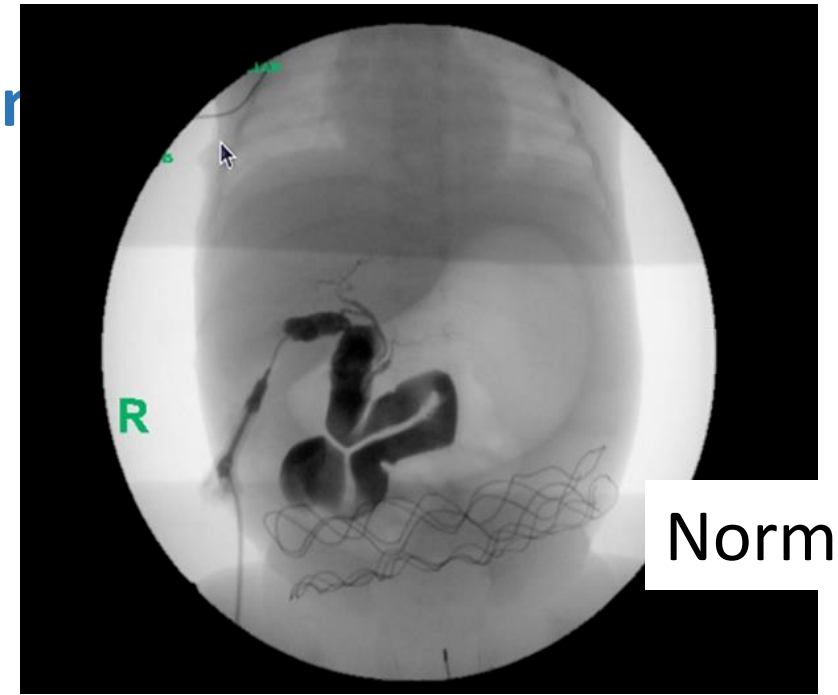
Good uptake, absent excretion

Operative and Endoscopic Cholangiography

- **Operative cholangiogram**
  - Gold standard
  - Difficult in Alagille syndrome
- **Endoscopic retrograde cholangiogram**
  - Not widely available
  - Technically difficult
  - Expensive
  - Rarely therapeutic



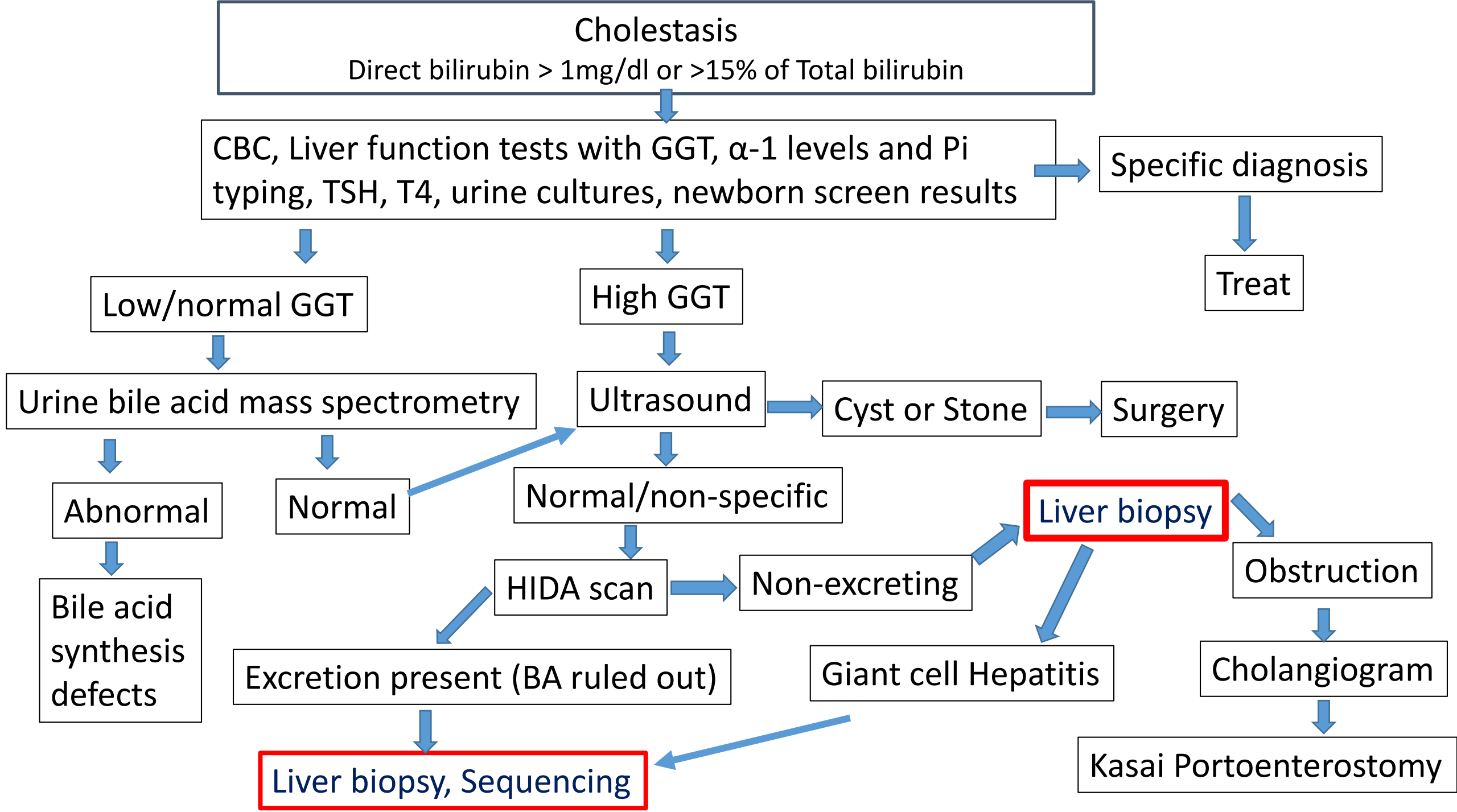
Biliary atresia



Normal

The changing genetic landscape of pediatric liver disease

- **1997-recently**
  - 5 main genes of interest (*JAG1, NOTCH2, ATP8B1, ABCB11, ABCB4*)
  - Single gene testing or limited panels
- **Current era of genomic diagnostics**
  - Increased yield with new technologies (Gene Panel and Exome)
  - Identification of new disease-causing genes; fewer “idiopathic” cases
  - Need for correlation with clinical and histologic phenotypes
  - Identification of genes as disease modifiers (*SERPINA1 Z* allele in chronic liver disease, i.e. Cystic fibrosis)

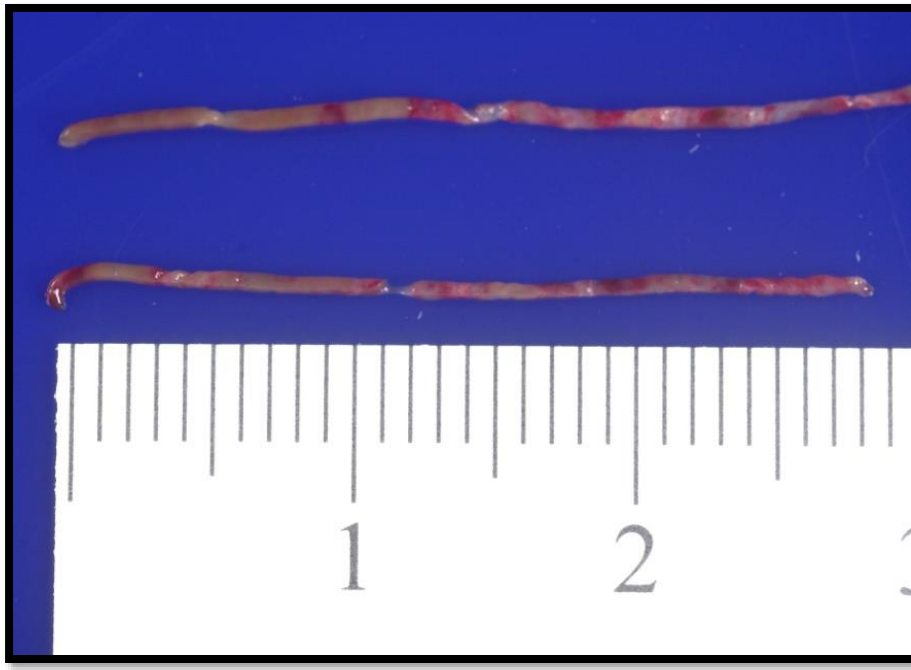

Cholestasis
Direct bilirubin > 1mg/dl or >15% of Total bilirubin
CBC, Liver function tests with GGT, α-1 levels and Pi typing, TSH, T4, urine cultures, newborn screen results
Specific diagnosis
Treat
Low/normal GGT
High GGT
Urine bile acid mass spectrometry
Ultrasound
Cyst or Stone
Surgery
Abnormal
Normal
Normal/non-specific
Liver biopsy
Obstruction
Bile acid synthesis defects
HIDA scan
Non-excreting
Excretion present (BA ruled out)
Giant cell Hepatitis
Cholangiogram
Liver biopsy, Sequencing
Kasai Portoenterostomy

Liver biopsy – why and when?

- Remains the most accurate of the available diagnostic tests for biliary atresia with the best sensitivity/specificity (*Lee et al, J Ped Surg 2016*)
- Recommended procedure and mandatory in *most* pediatric hospitals prior to taking an infant to the operating room (*Guidelines for the Evaluation of Cholestatic Jaundice in Infants, NASPGHN, JPGN 2017*)
- Balance timely diagnosis versus invasiveness and risk of biopsy
  - Is anesthesia required? – risk not negligible in infants
  - Complication rate 1.7% in children, up to 4.6% in infants (bleeding requiring intervention)

Handling of liver specimens

- Needle core biopsies – percutaneous (or transjugular, more rarely)
  - 16G, 1.6 mm diameter
  - 18G, 1.2 mm diameter
  - 20G, 1mm
    - Not recommended due to fragmentation
- Wedge biopsies
  - Usually at laparotomy
- Partial hepatectomies
  - Usually for local lesions (tumors)
- Explants (transplants, autopsies)



Handling of liver specimens

- Biopsy triage
  - One 16G core 20 mm length = 15 mg of tissue
  - Electron microscopy- most cases
  - Snap-freeze – larger specimens, when metabolic disease suspected (Glycogen storage disease require ~ 100 mgs)
  - Cultures (rarely; if cholangitis suspected clinically)
  - Fe^{++}/Cu^{++} one 10 mm core, fresh or formalin fixed paraffin embedded, metal-free container
- Cores placed in biopsy cassettes
- Overnight routine processing for cores; can be compressed to 6 hours in an emergency

Routine stains and Immunohistochemistry in liver biopsies in Cholestatic infants

Routine

- Hematoxylin and Eosin x 3 (sections 1, 4, 8)
- Trichrome (Gomori or Masson)
- Periodic Acid–Schiff (PAS)and

  PAS with diastase
- Reticulin
- Iron
- Copper

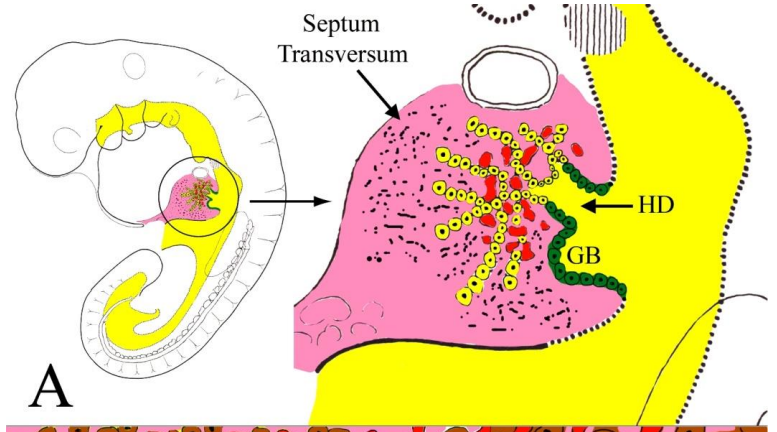
Immunohistochemistry

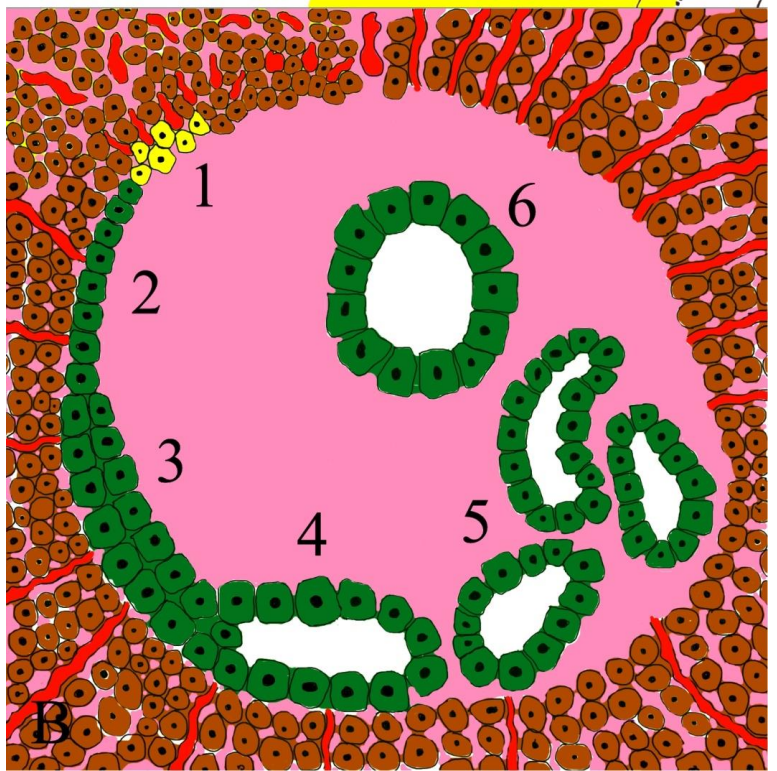
- Biliary markers
  - Cytokeratin 7 and 19
- Canalicular transporter proteins
  - cMOAT (*ABCC2/MRP2*)
  - BSEP (*ABCB11*)
  - MYO5B
  - MDR3 (*ABCB4*)
- Intercellular junction proteins
  - TJP2
  - Claudin-1

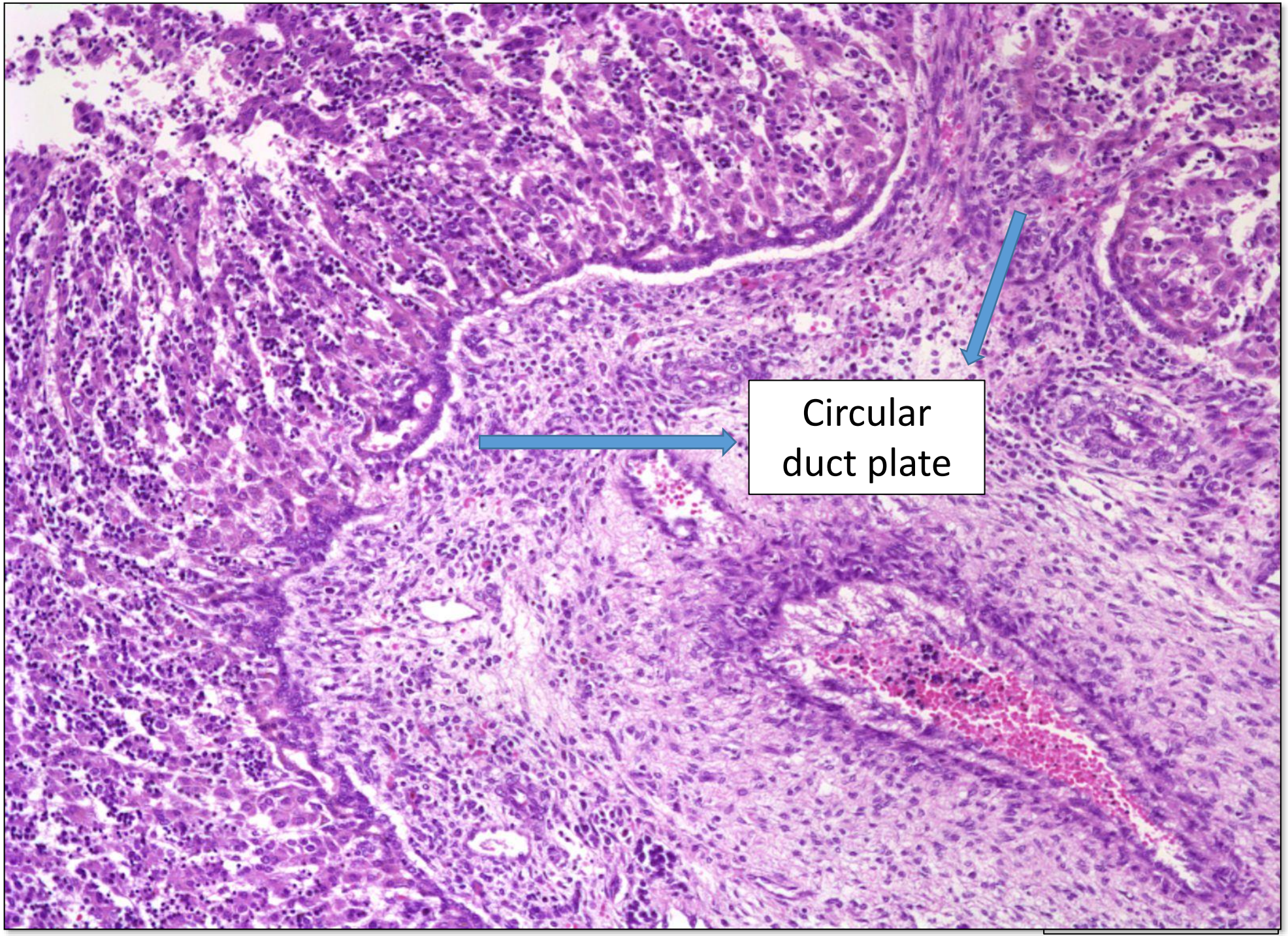
Liver developmental changes

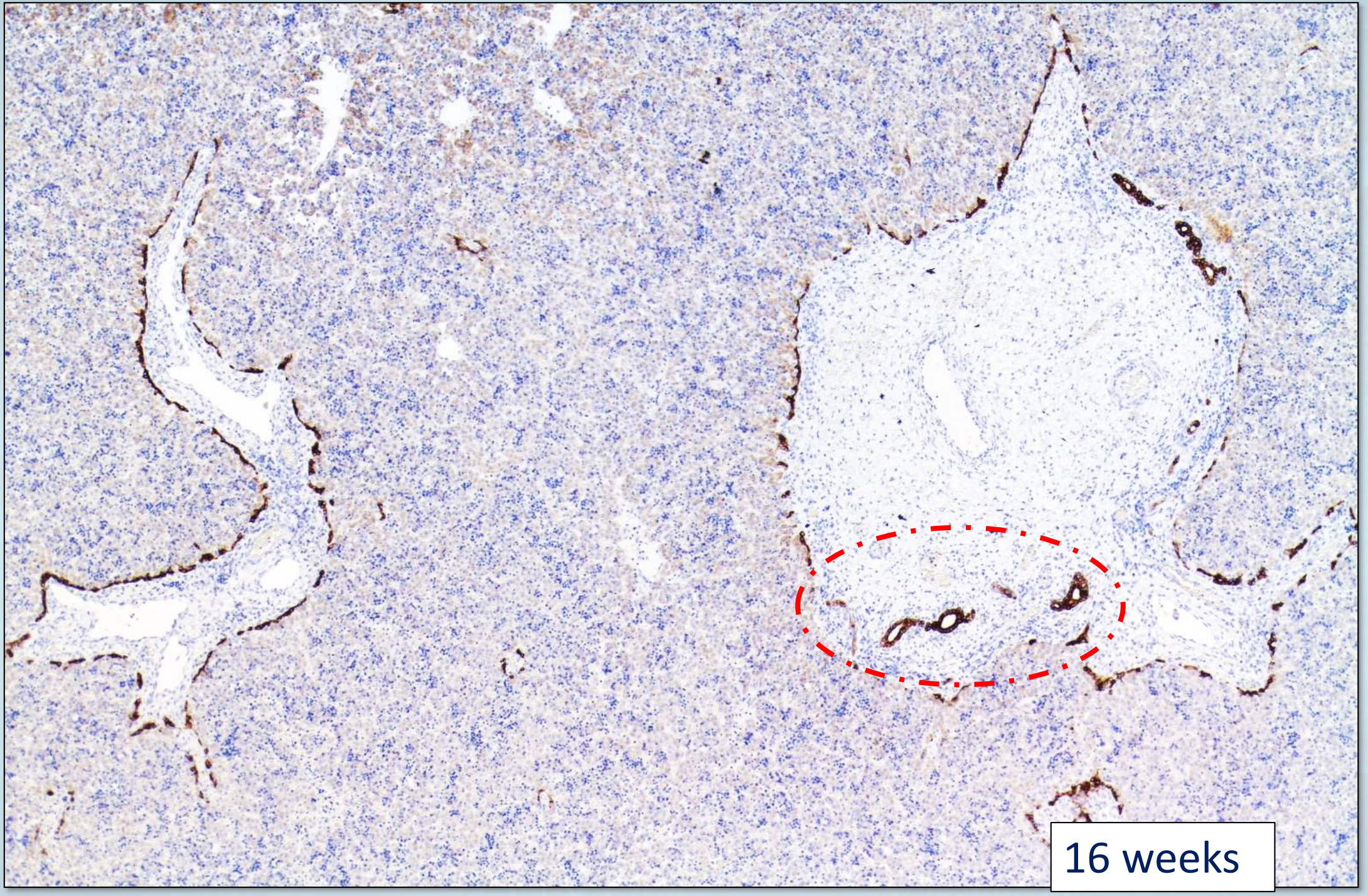
Hepatobiliary development

- 4 weeks – hepatic diverticulum develops from foregut endoderm
- 6-7 weeks – definitive vascular pattern established; hematopoiesis begins
- 8-12 weeks – hepatoblasts express CK-19; ductal plate develops
- 12 weeks – birth - remodeling of ductal plate with maturation of interlobular bile ducts
- 36 weeks - hematopoiesis ends



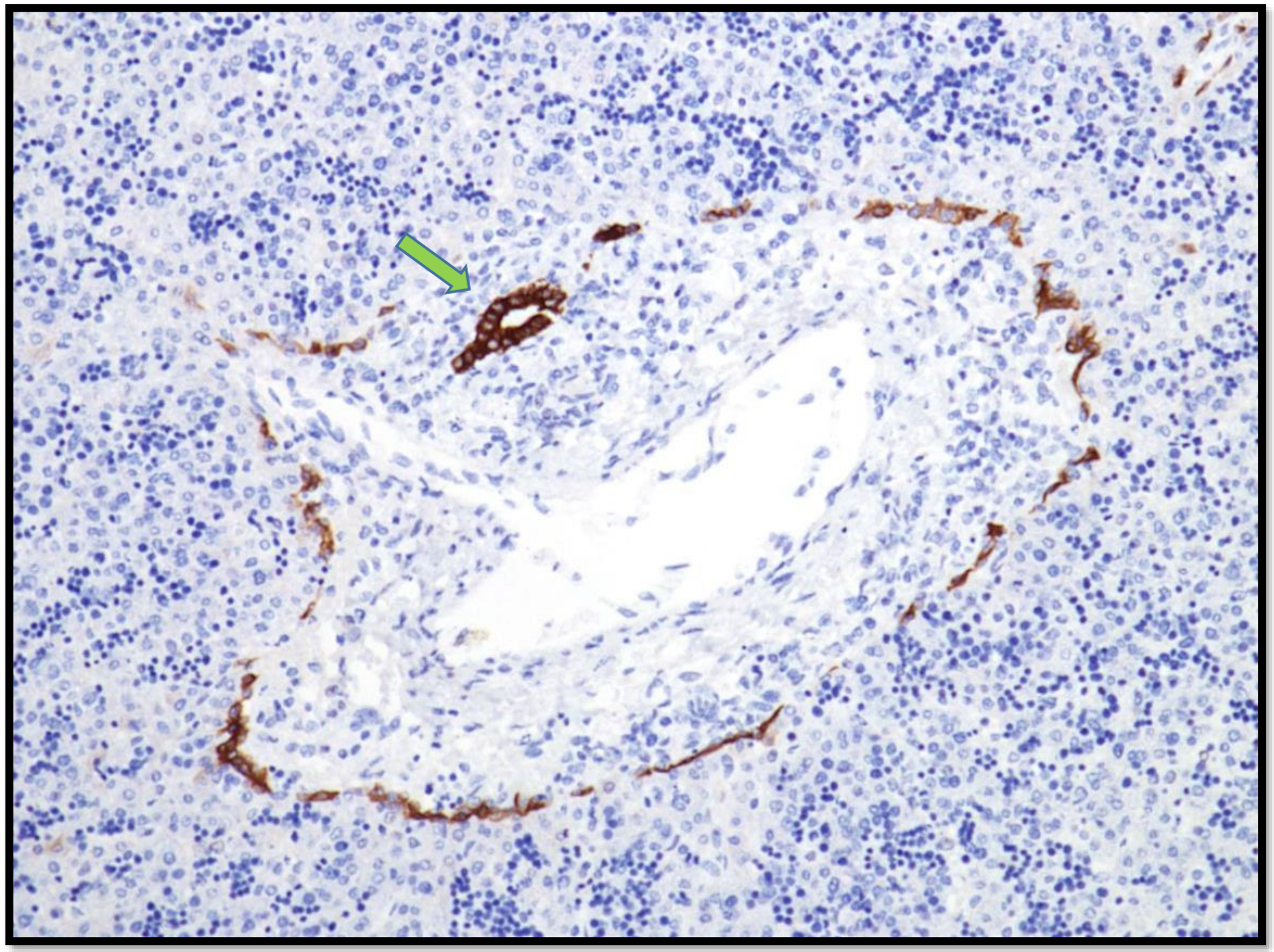



Circular
duct plate

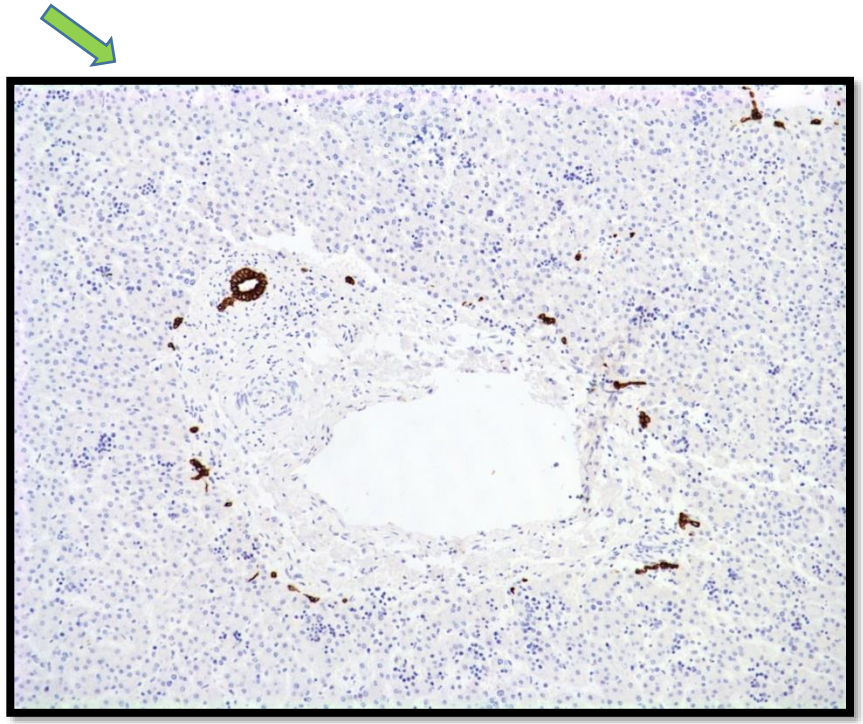

16 weeks

Centralized bile duct with diminishing duct plate

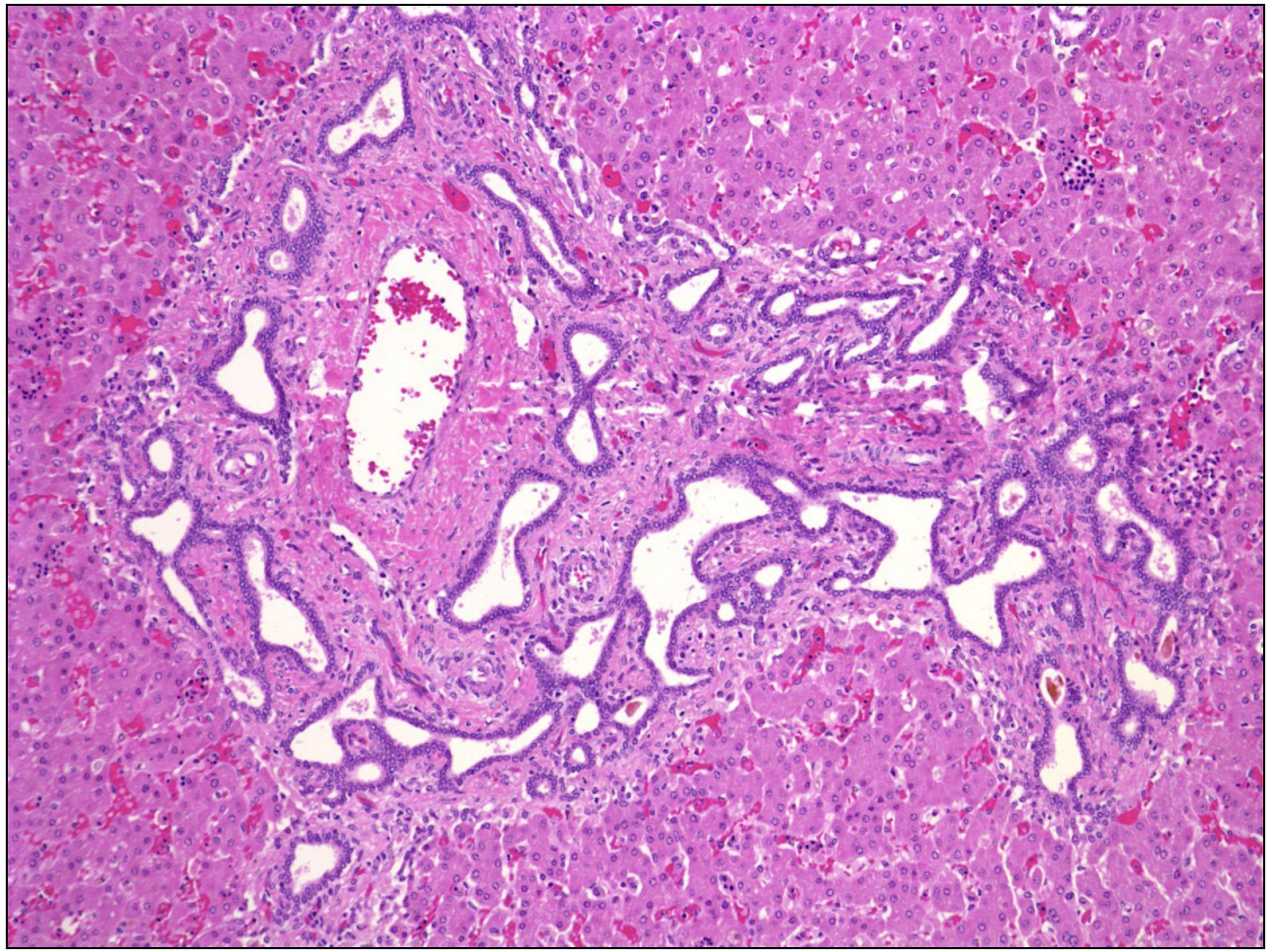
24 weeks



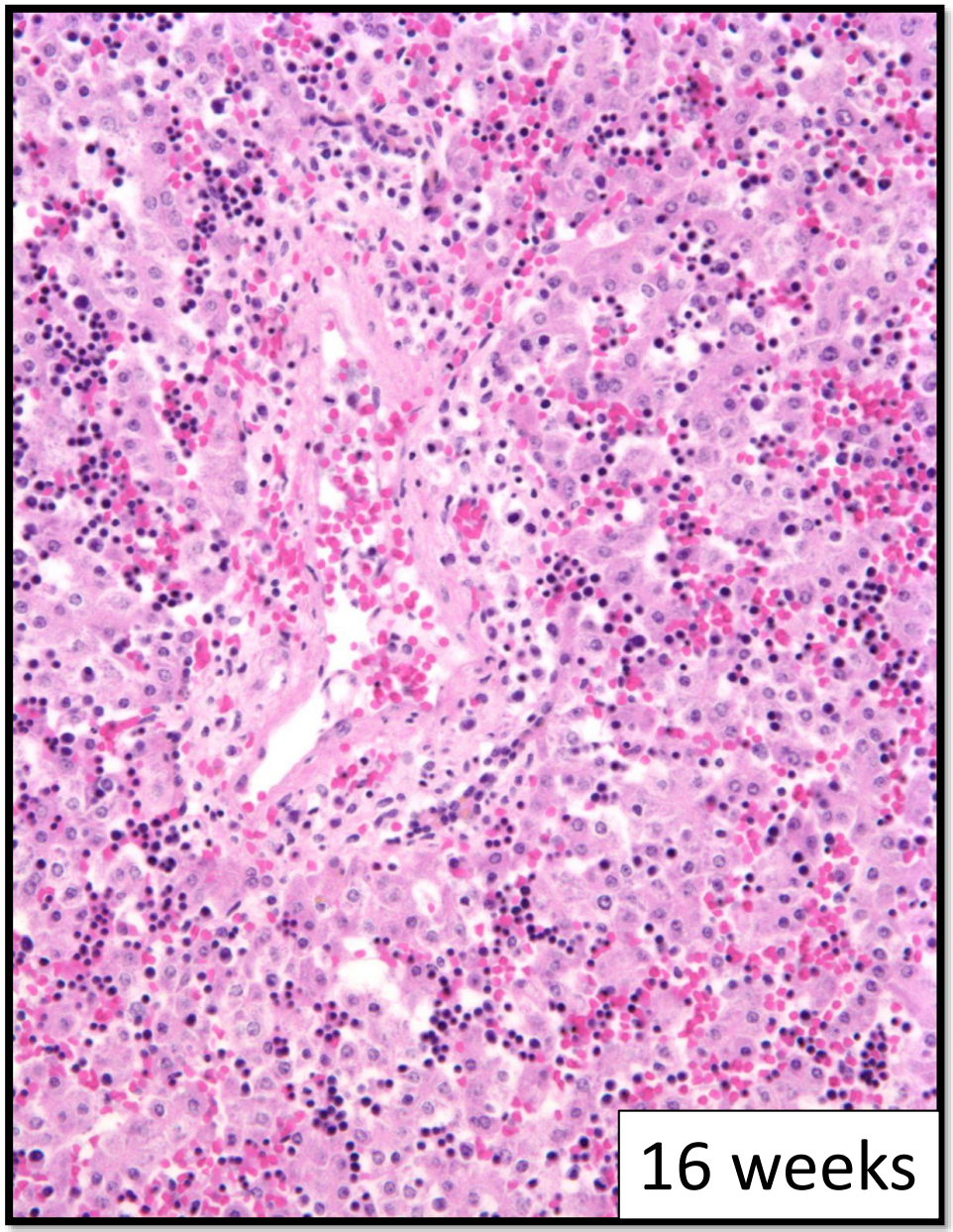
36 weeks

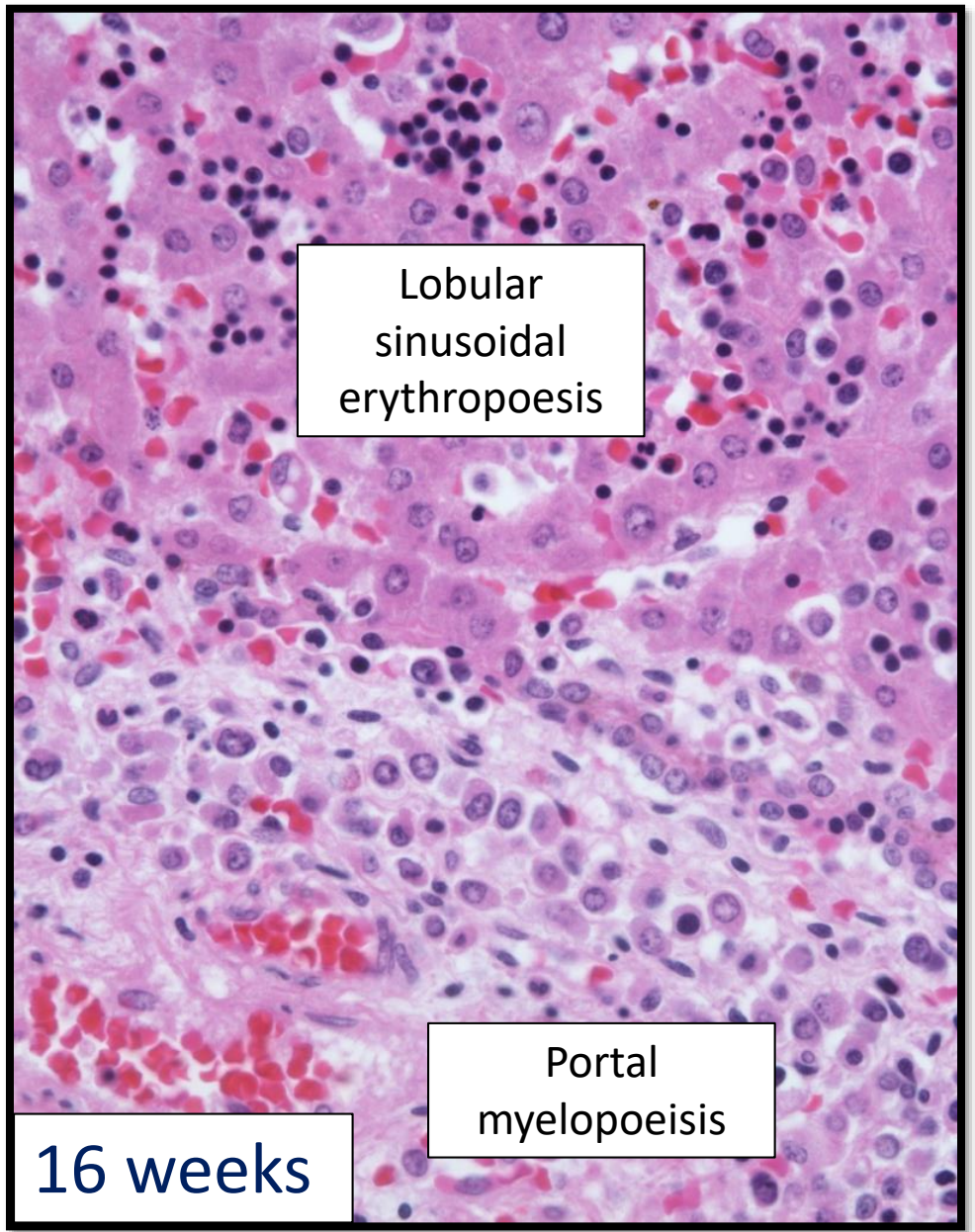


Persistence of the Ductal Plate (ductal plate malformation) – fibropolycystic diseases

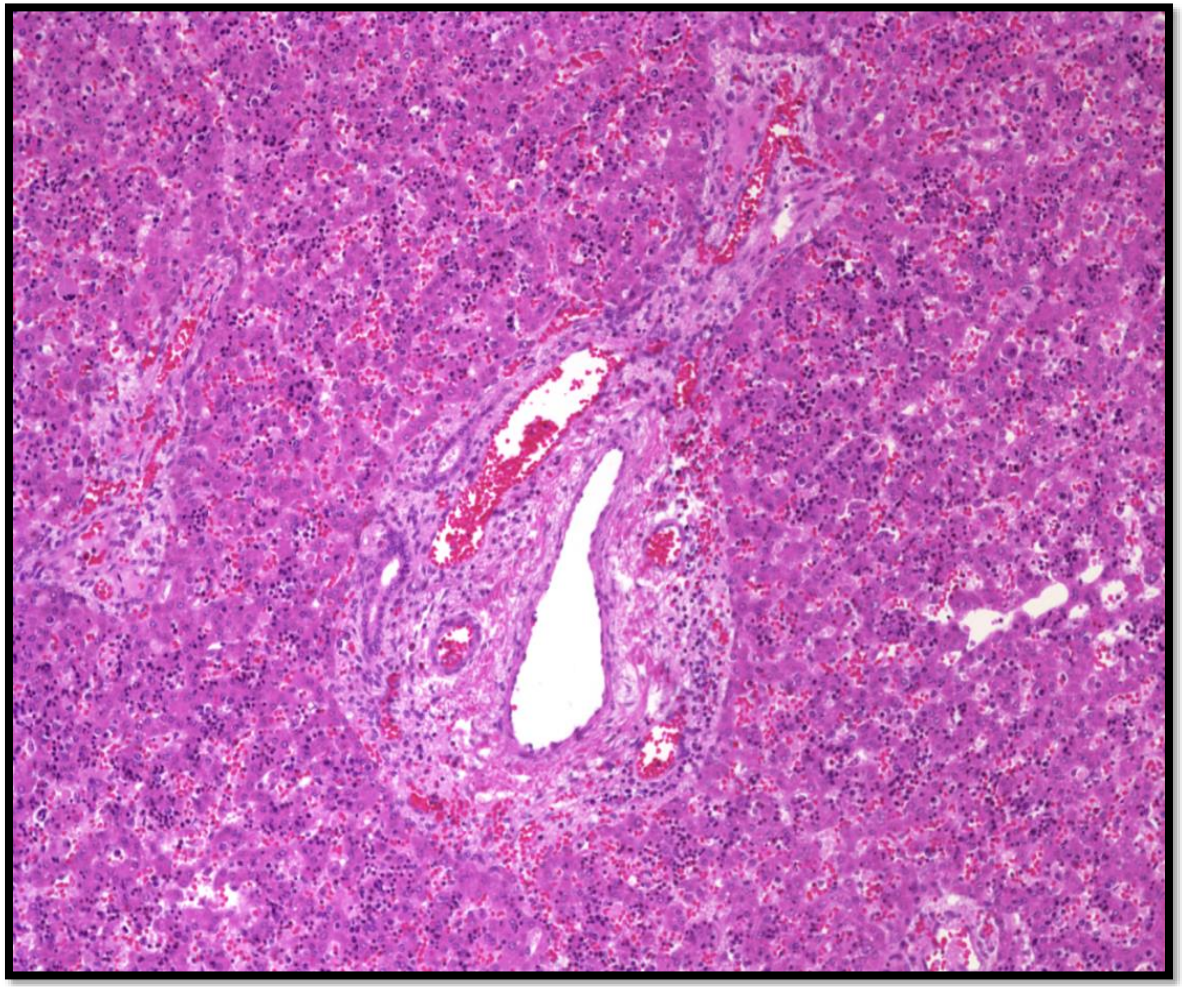


Extramedullary hematopoeisis

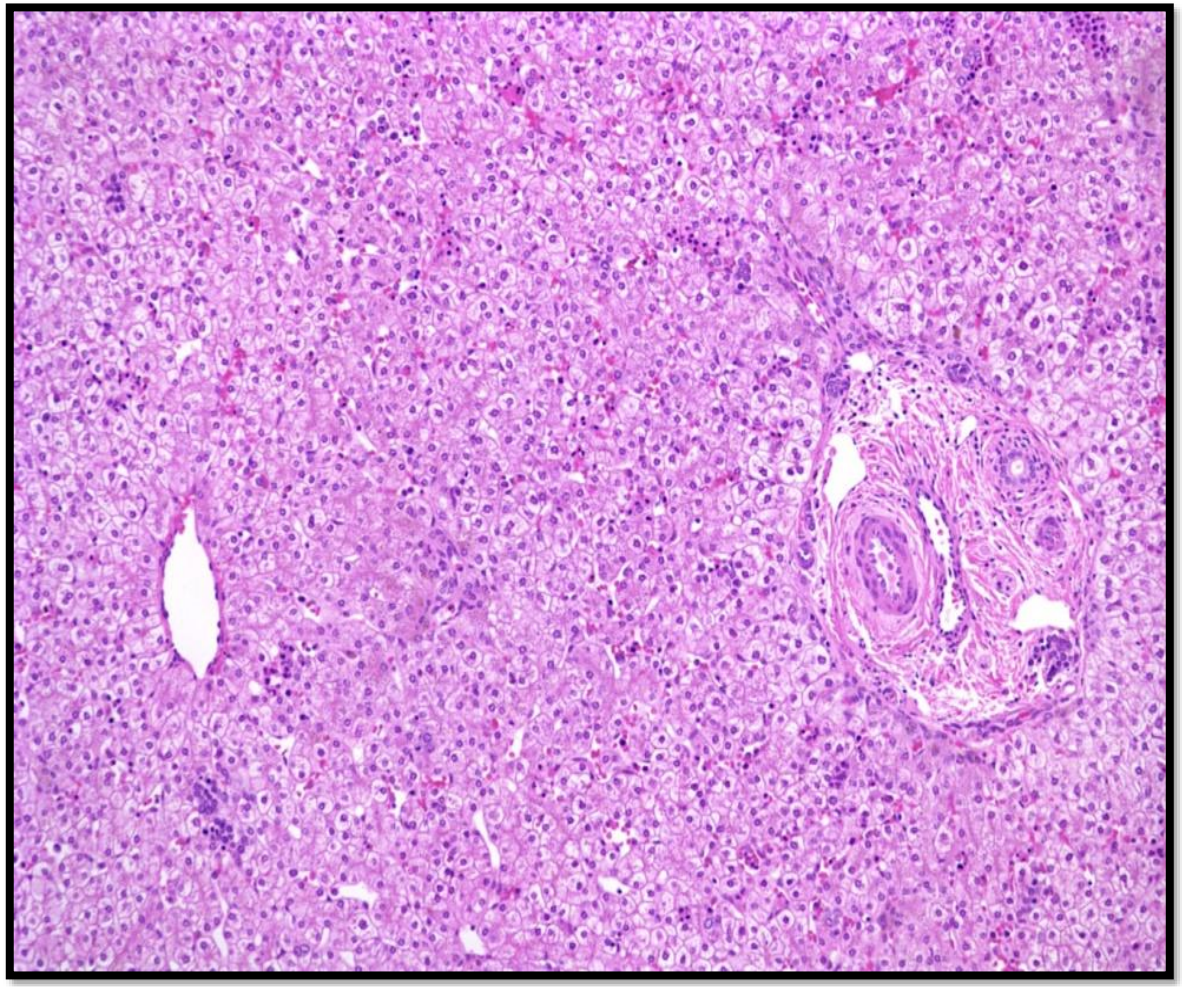


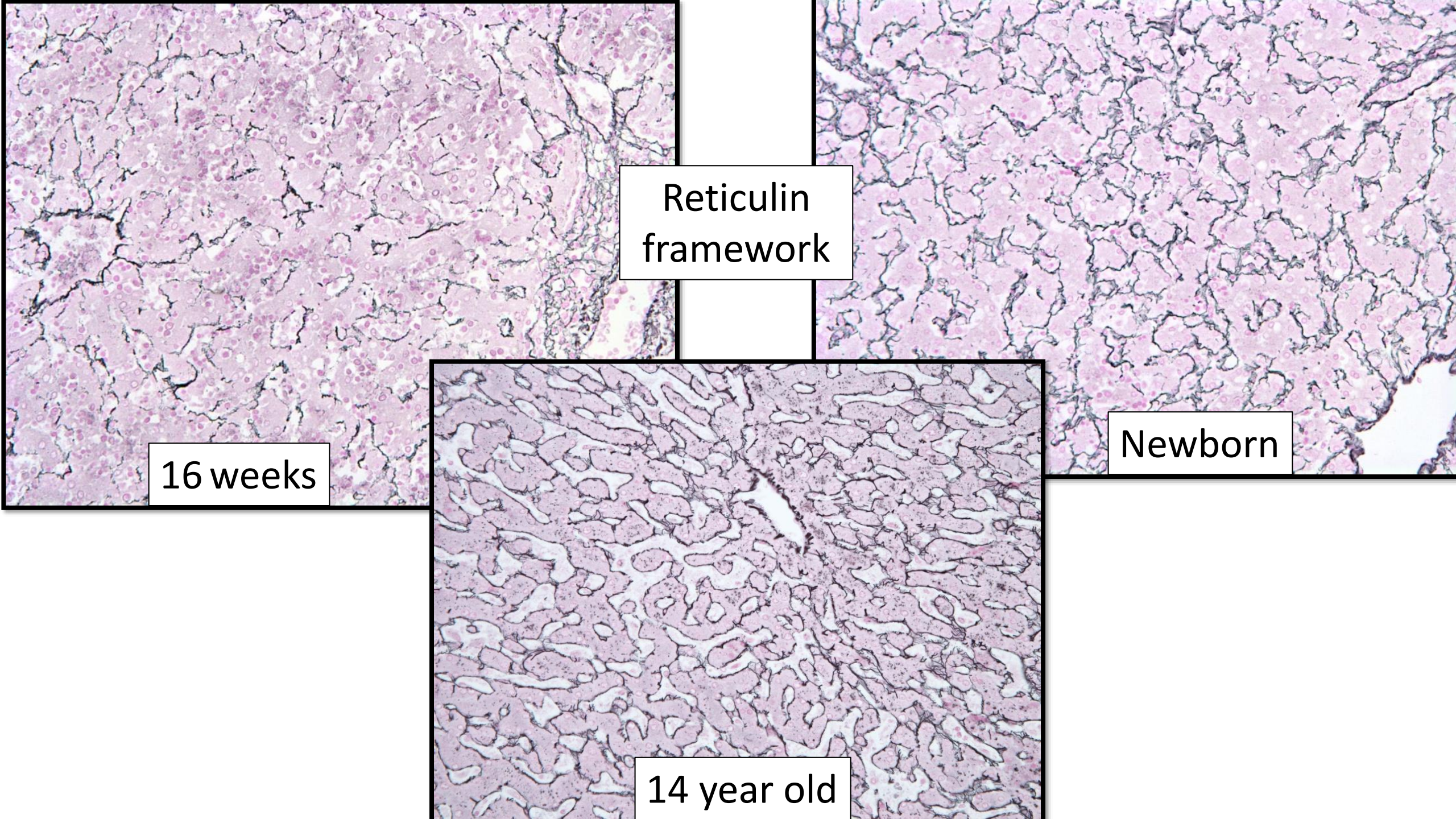


25 weeks



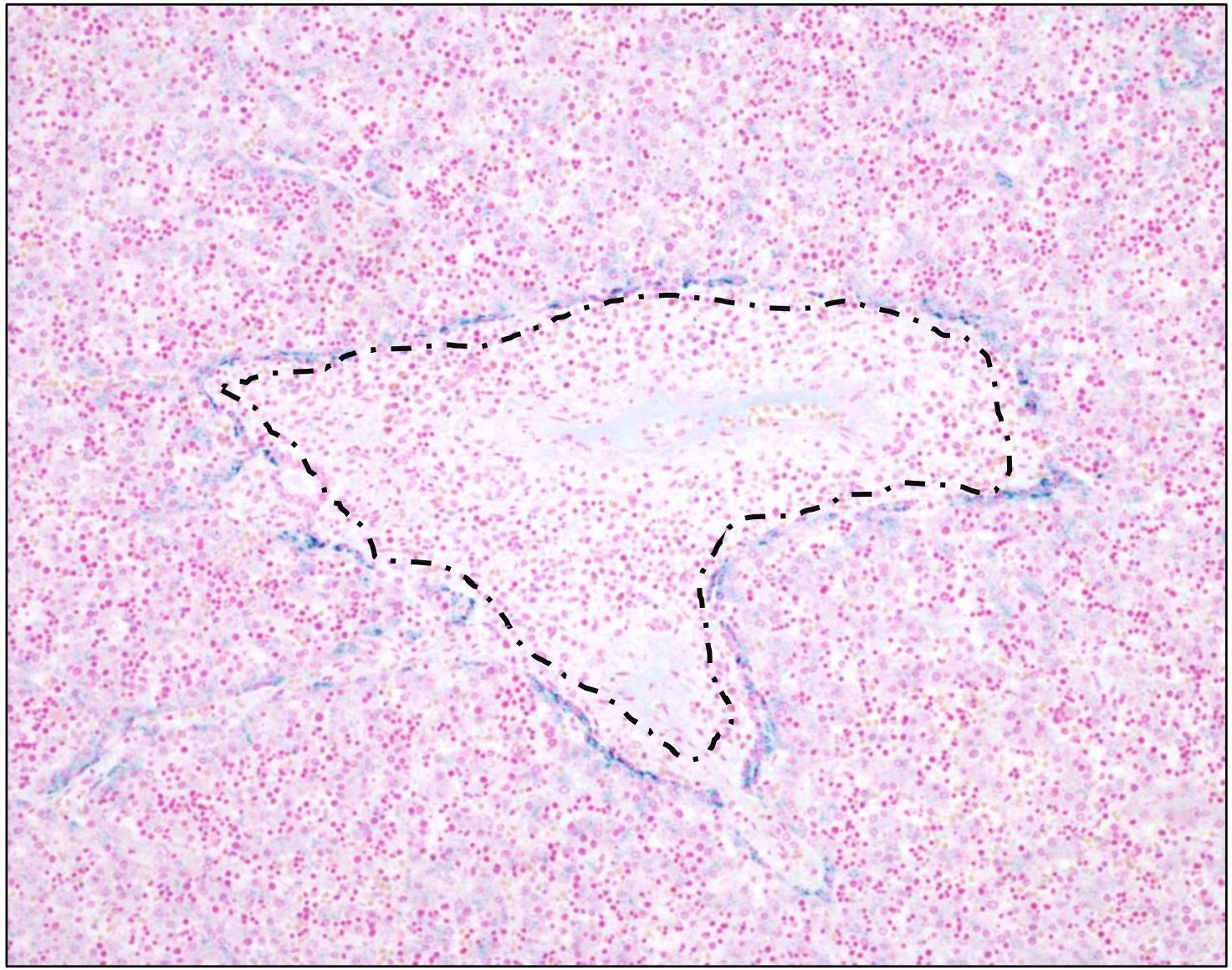
36 weeks



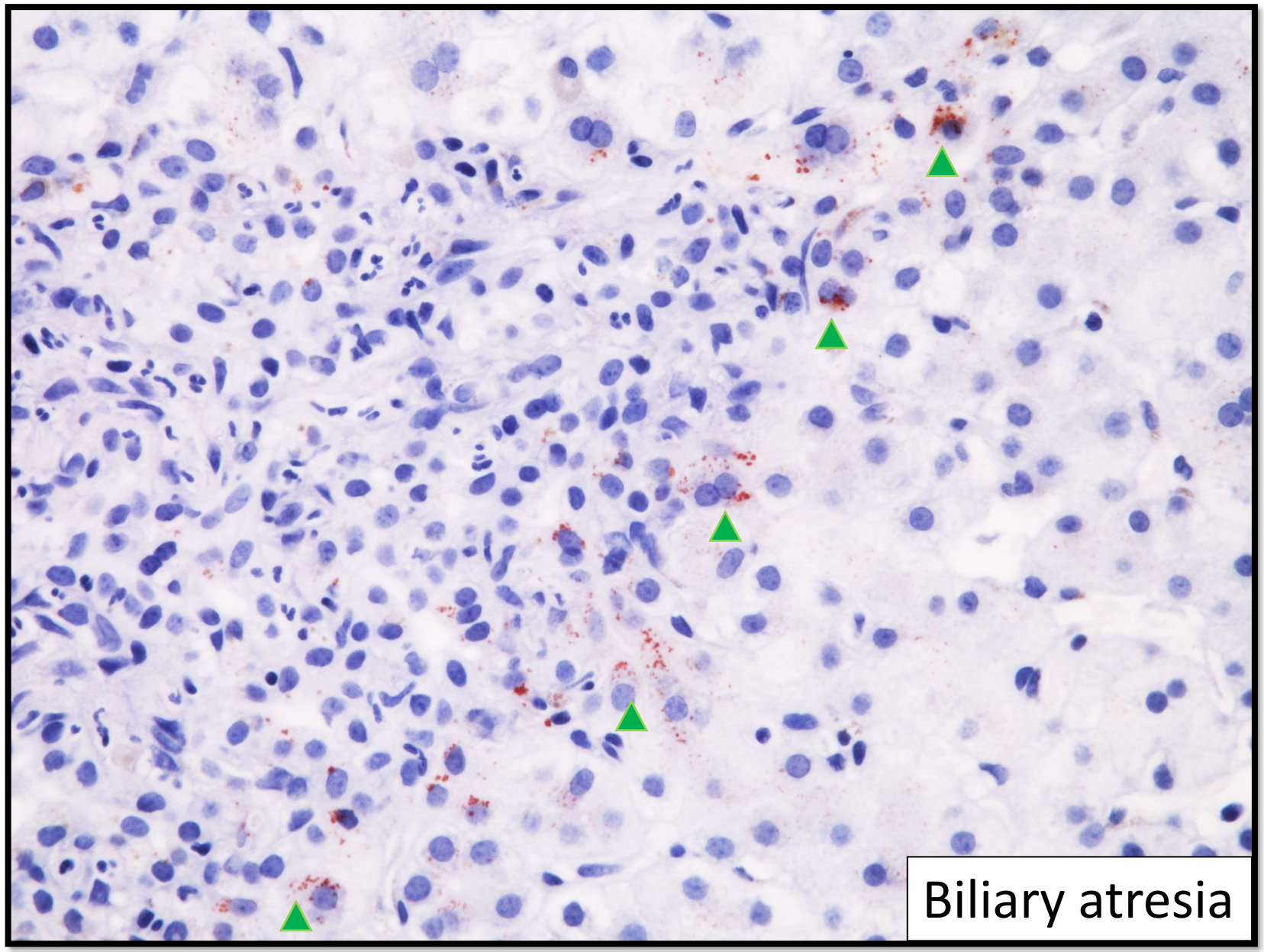

Reticulin framework
16 weeks
Newborn
14 year old

Prussian blue- Iron

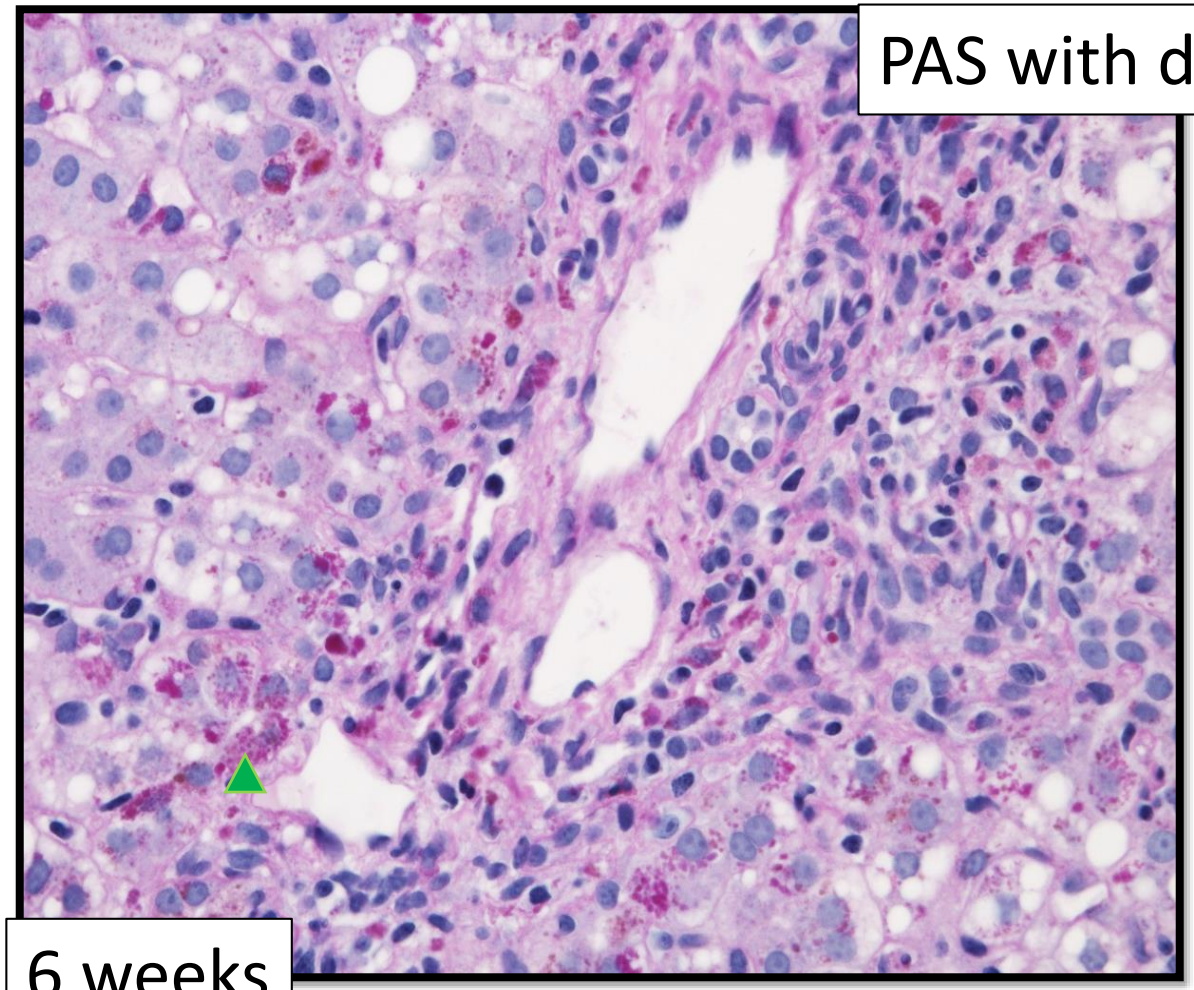
Iron in periportal hepatocytes is present throughout fetal life and up to several months postnatally



Rhodanine - Copper

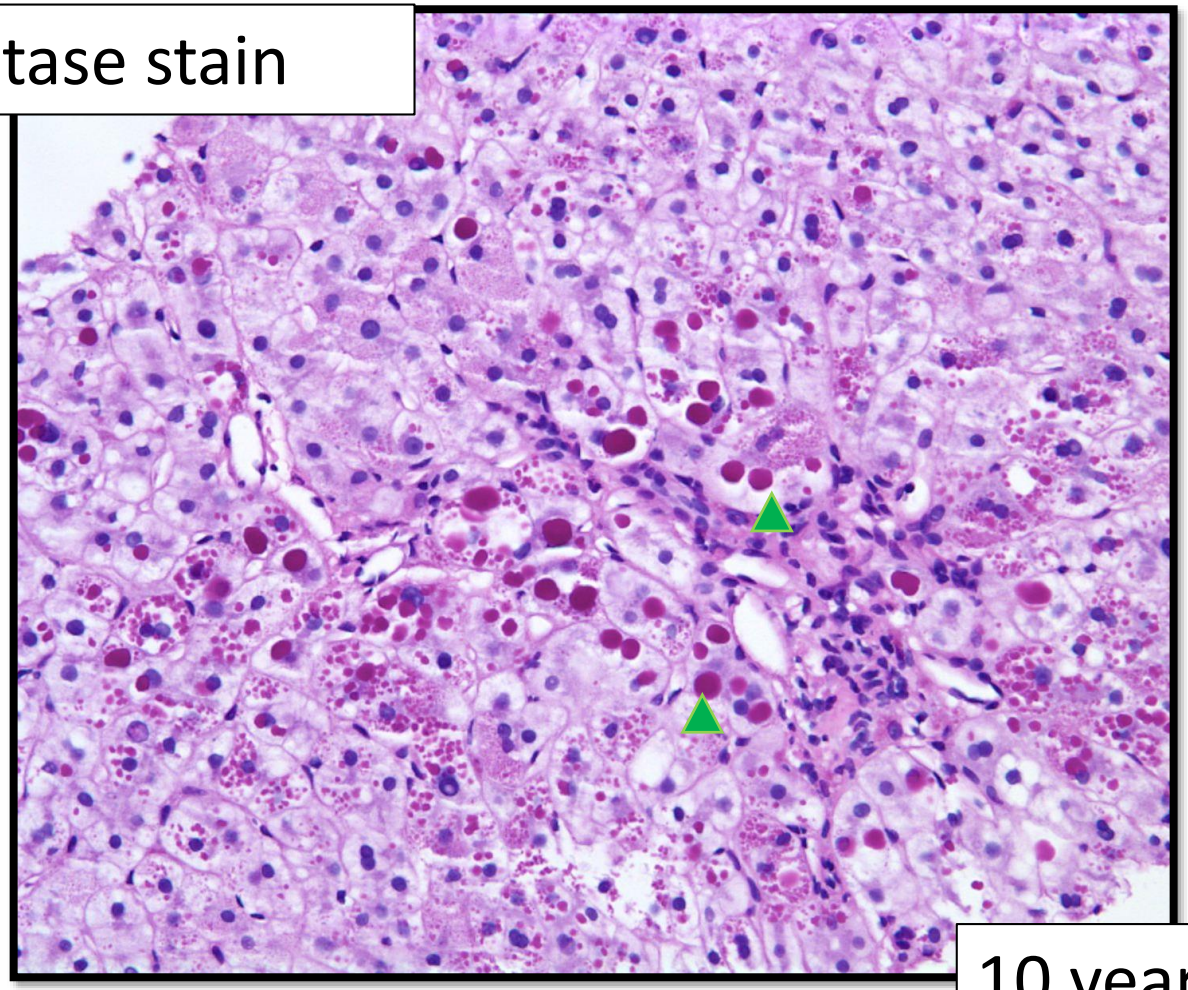


Histologic appearance of disease may vary with age: Alpha-1 Antitrypsin deficiency



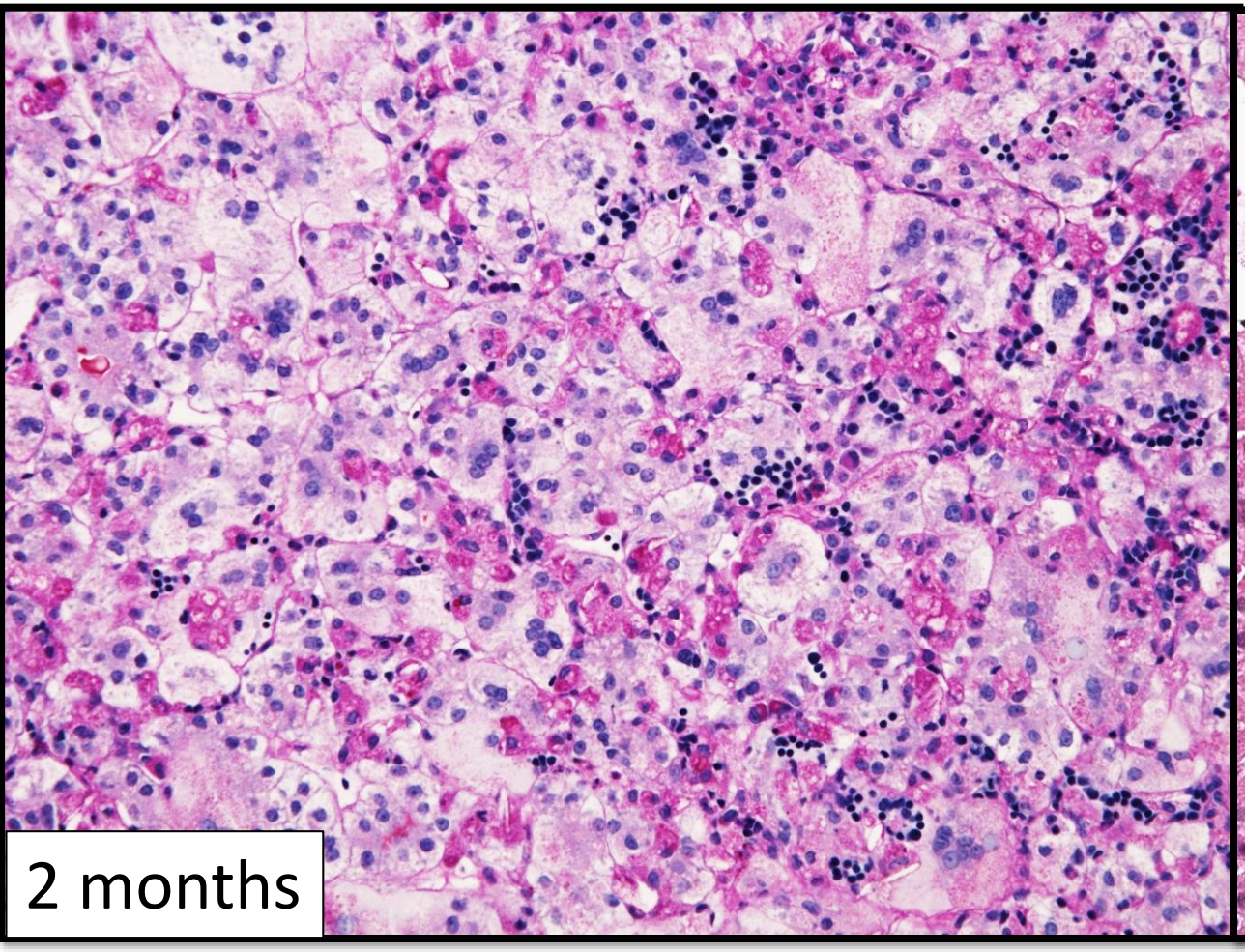
PAS with diastase stain

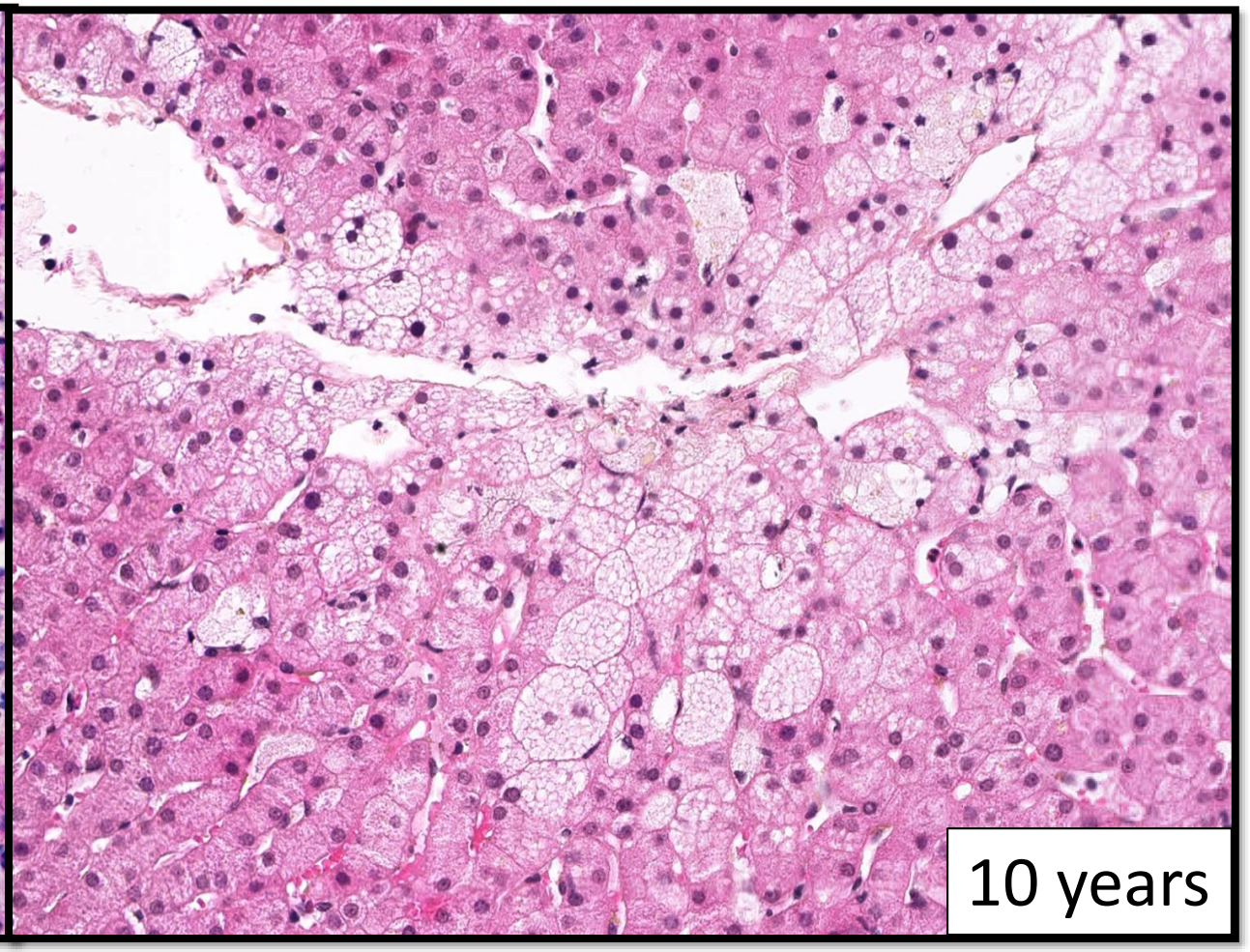
6 weeks



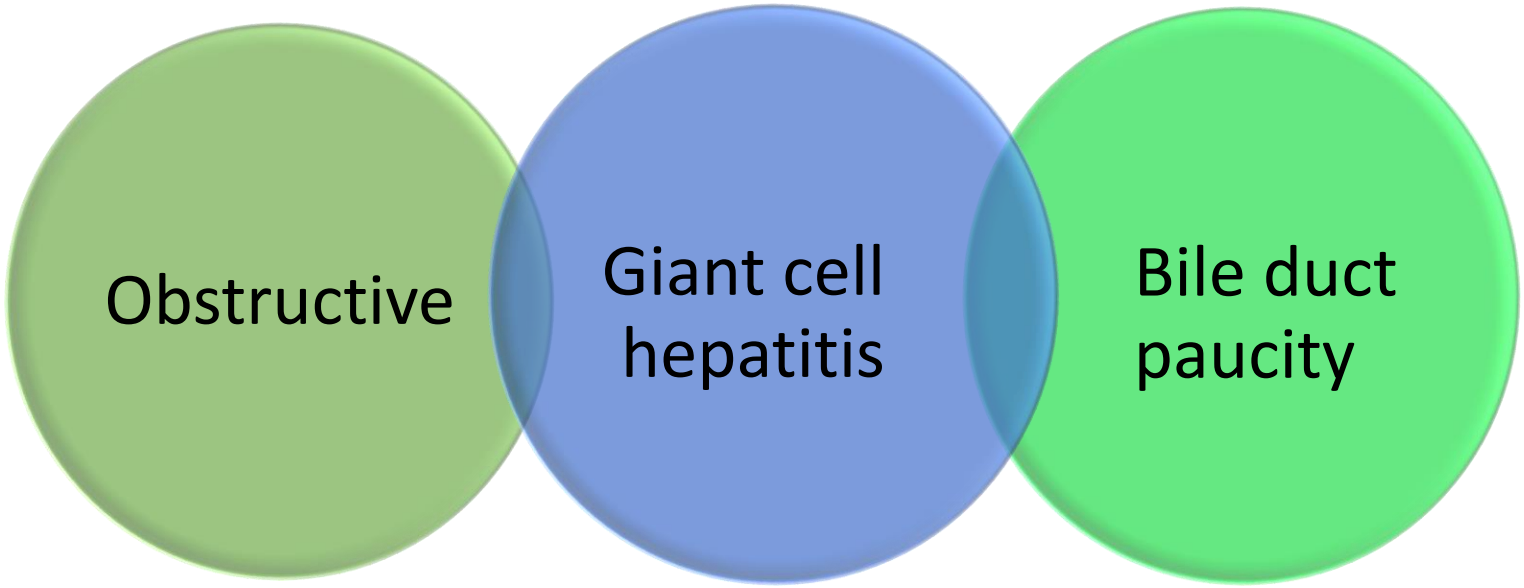
10 years

Histologic appearance of disease may vary with age: Niemann-Pick type C

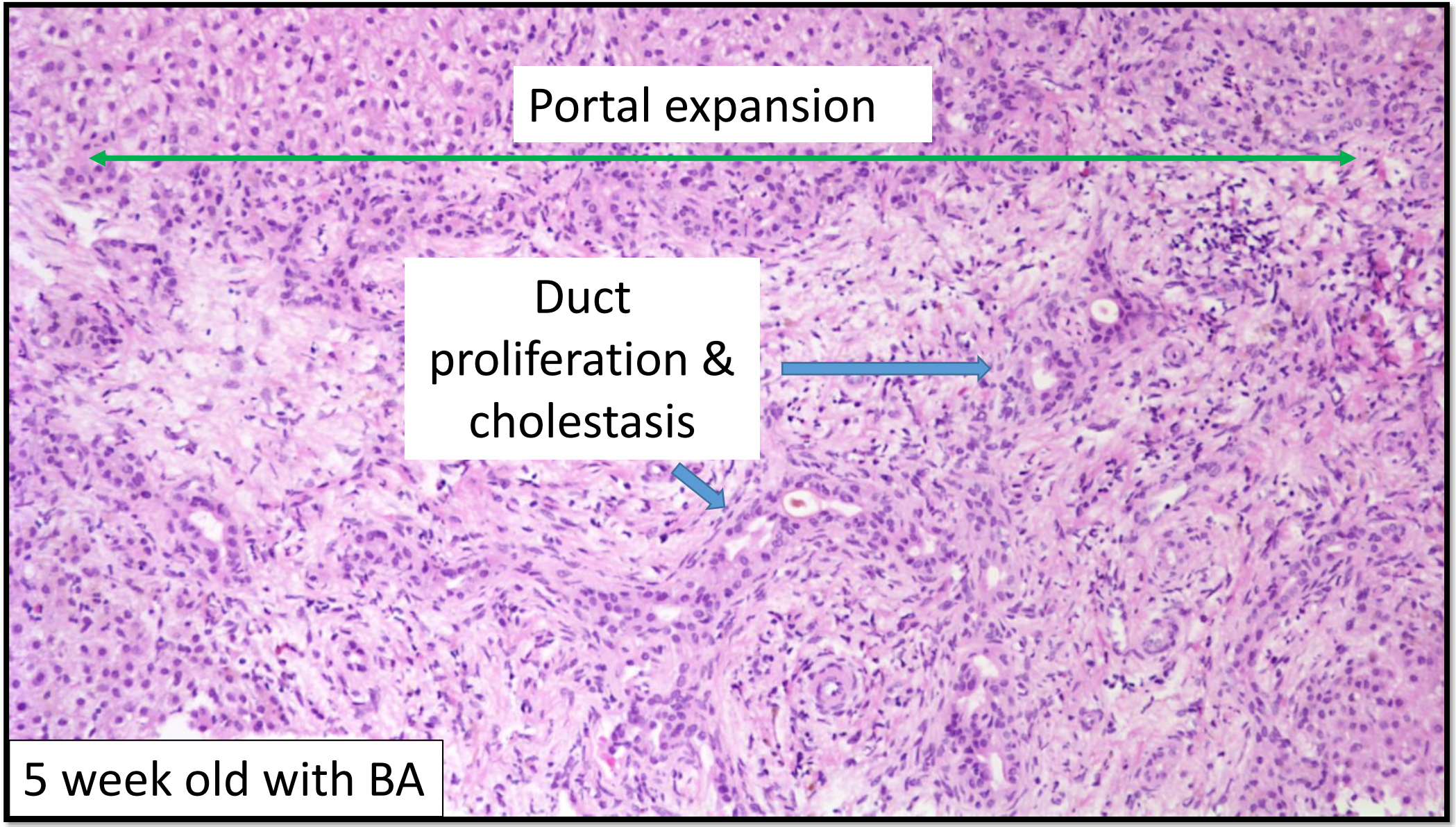




Major liver biopsy patterns in infantile cholestasis



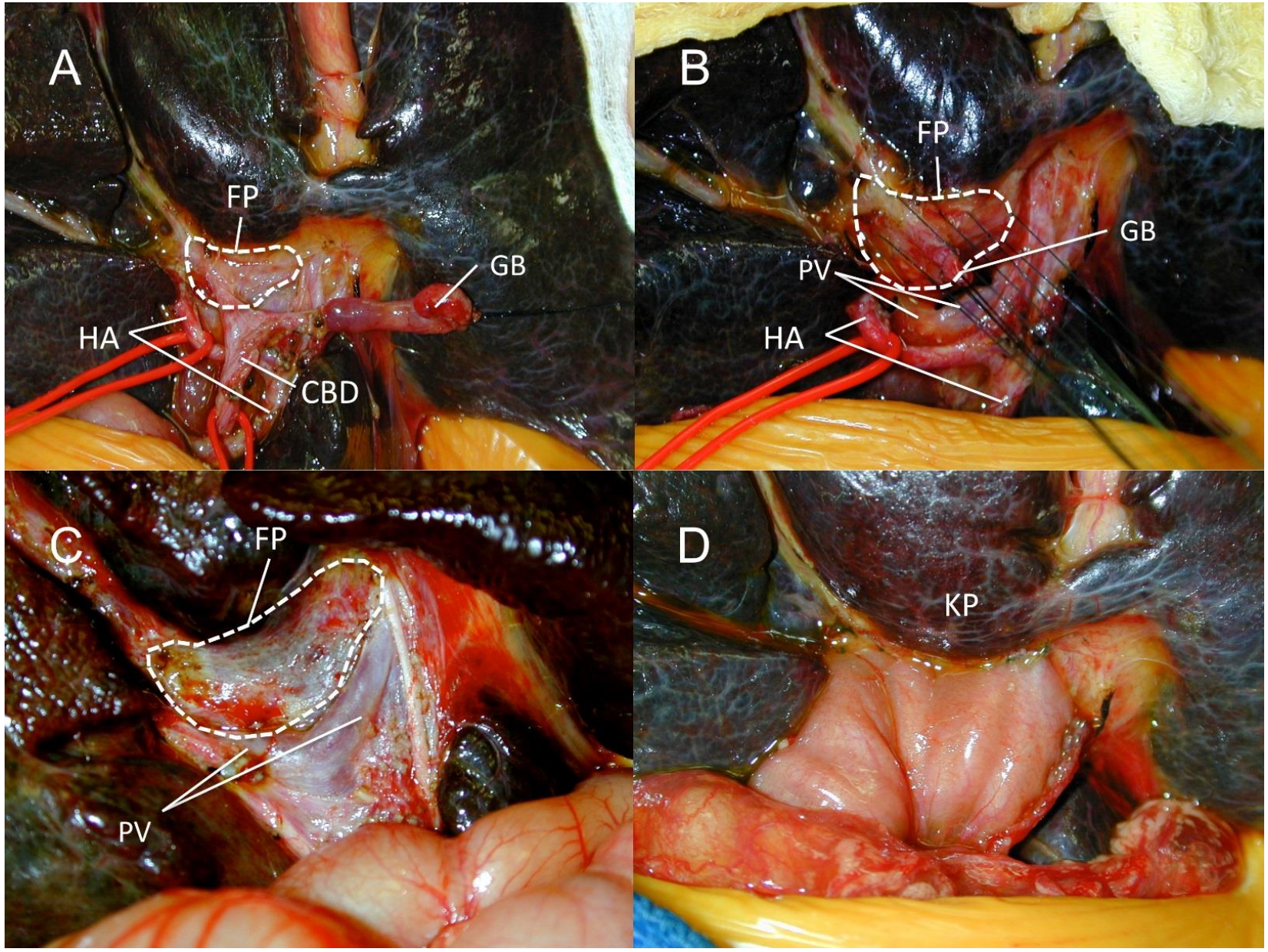
“Obstructive pattern” cholestasis



Biliary atresia

- 1/8000 live births; 400 cases/yr in US
- Most frequent indication for liver transplantation in children
- Clinical types of BA
  - Isolated – 80%
    - Jaundice-free interval after birth; no other anomalies
  - Syndromic form (BASM) – 10%
    - Laterality defects (a/polysplenia, situs inversus)
    - Frequently jaundiced from birth
  - BA with associated a major non-laterality malformation – 5%
  - Cystic form - 5%
- Etiology unknown; hypotheses include viral (reovirus), toxic, immune, malformative (*inversin*)
- Biliary drainage (Kasai portoenterostomy) crucial before 4 months of age; untreated, cirrhosis develops < 6 months

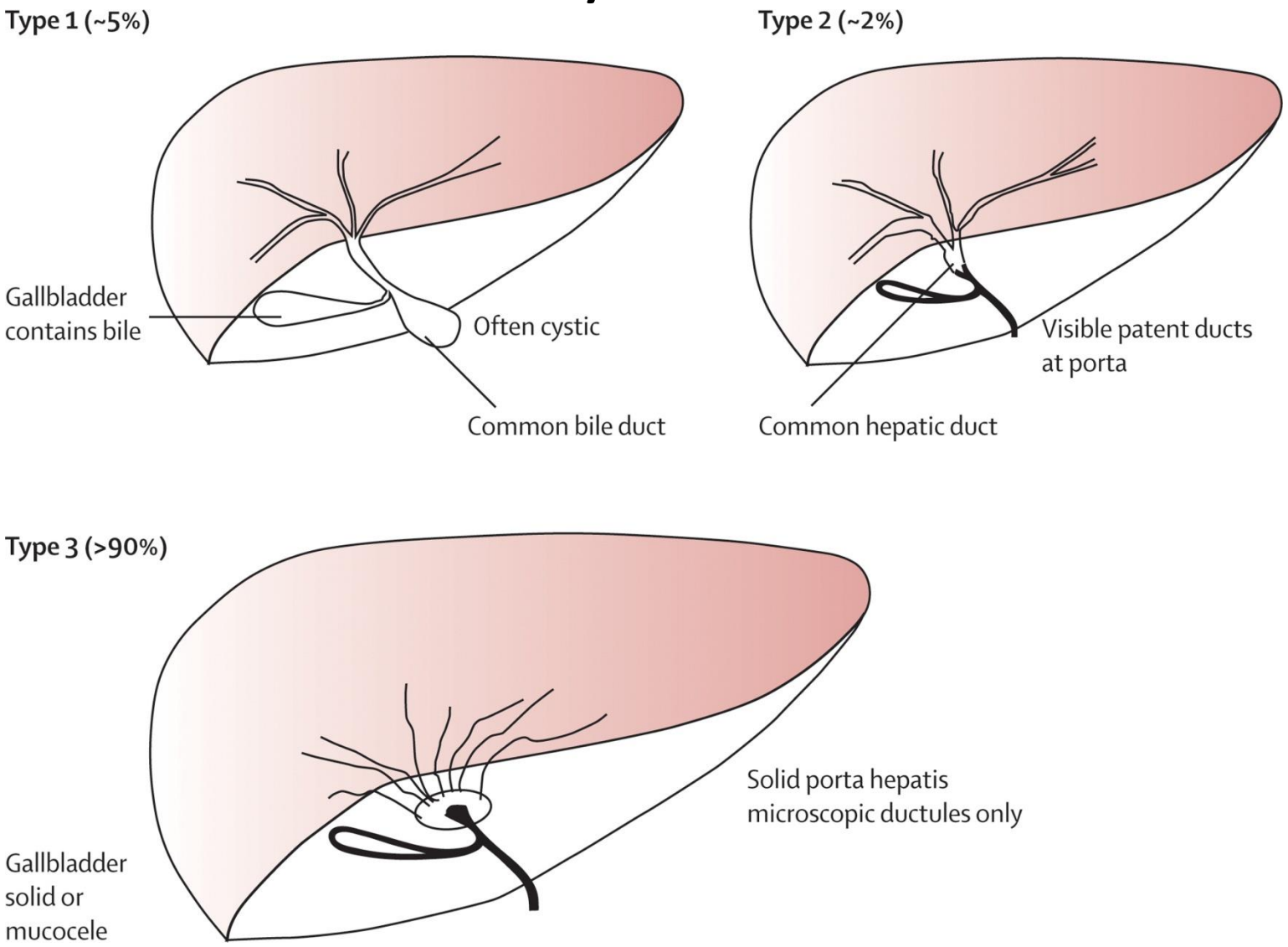
Kasai Hepatoportoenterostomy



Morio Kasai

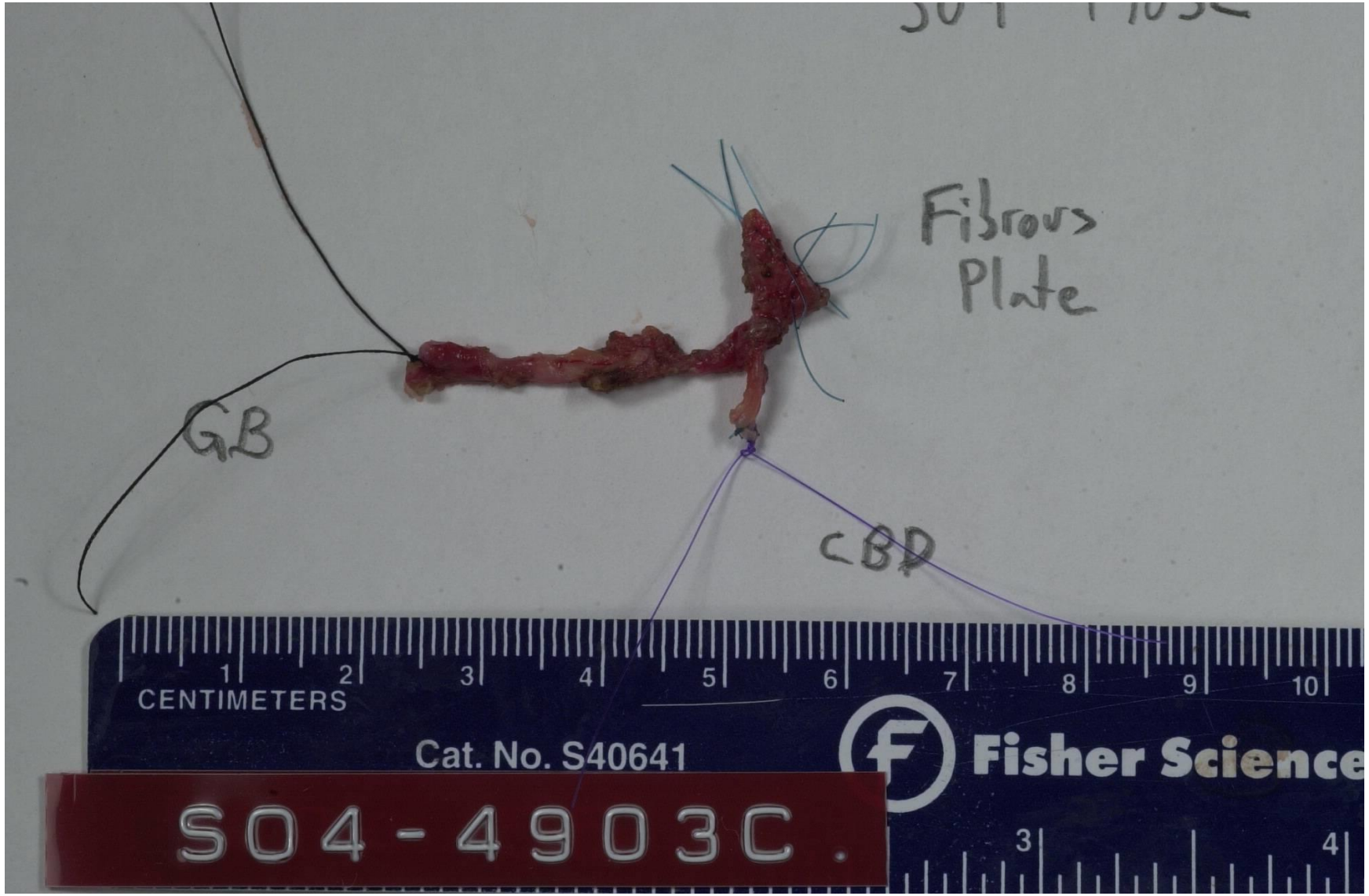
Alan Flake, CHOP

Biliary Atresia

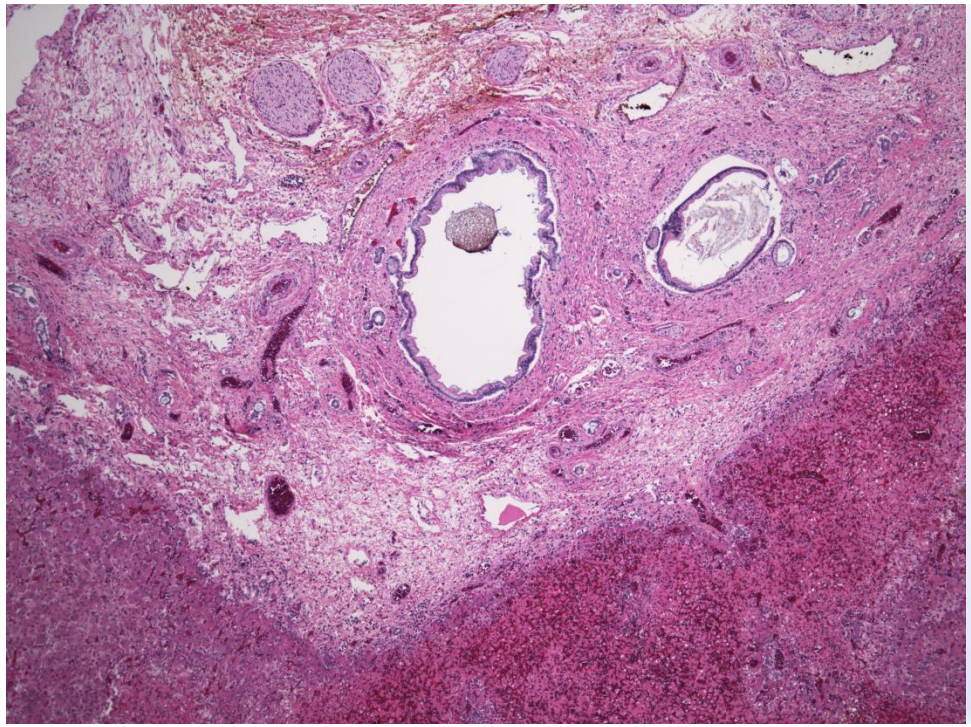


From *Davenport, The Lancet 2009*

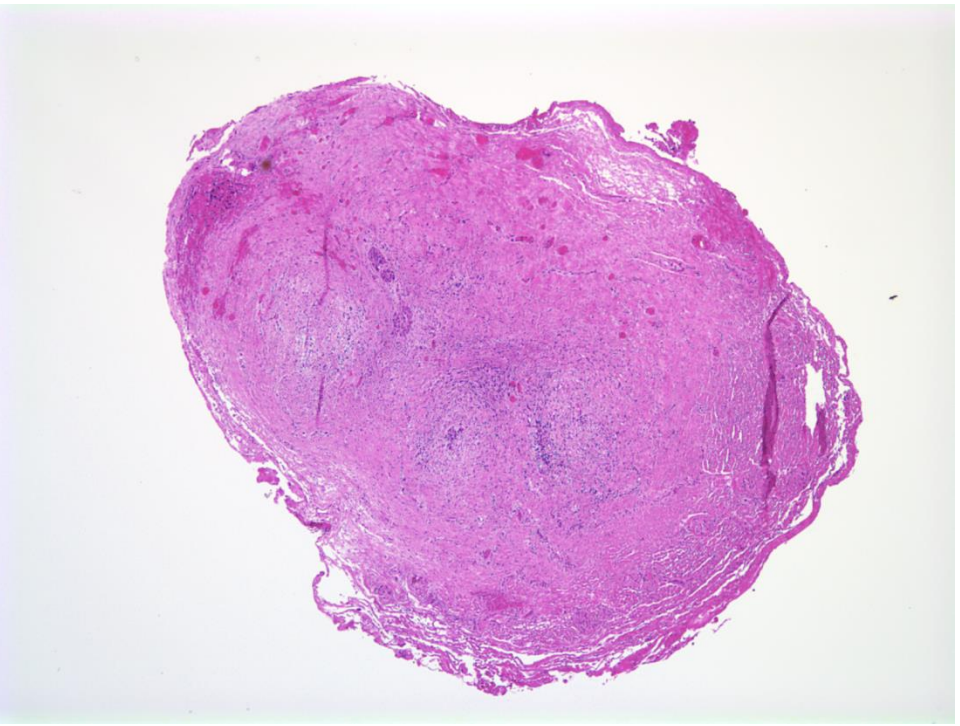
Biliary Atresia – the remnant



Hepatic ducts

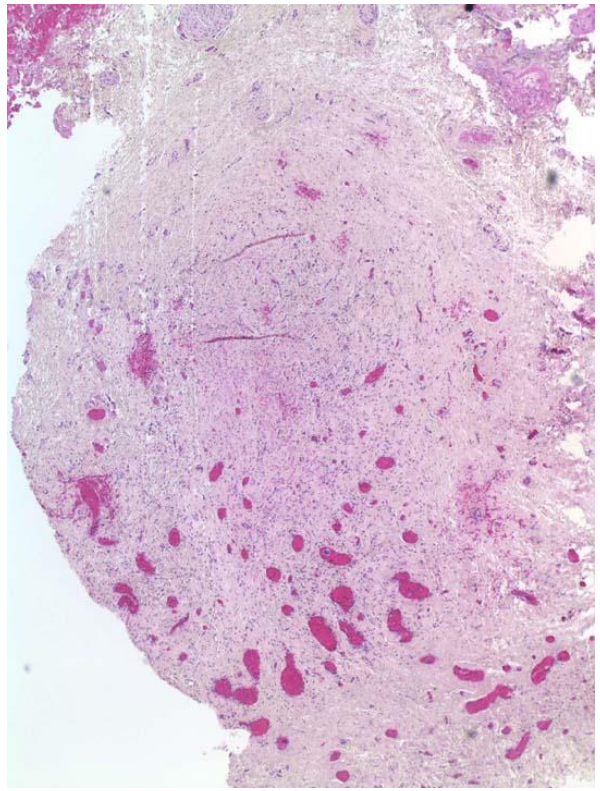
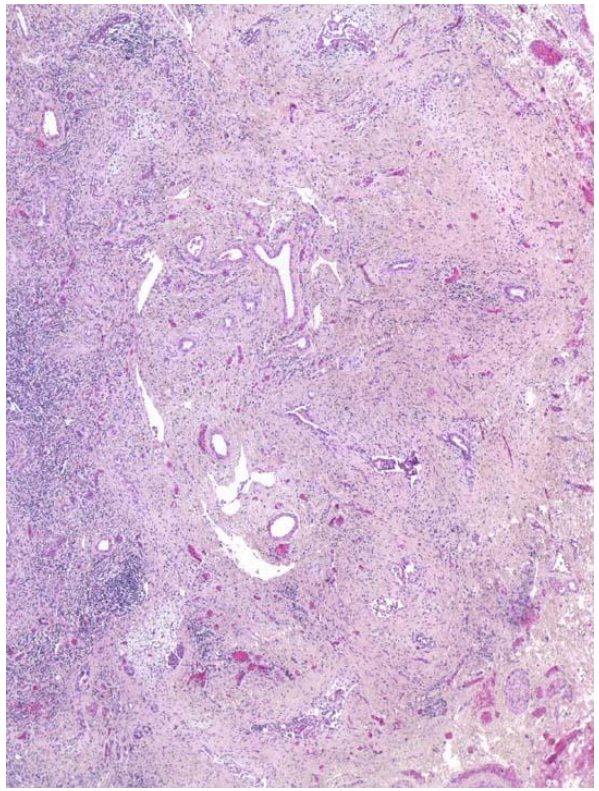
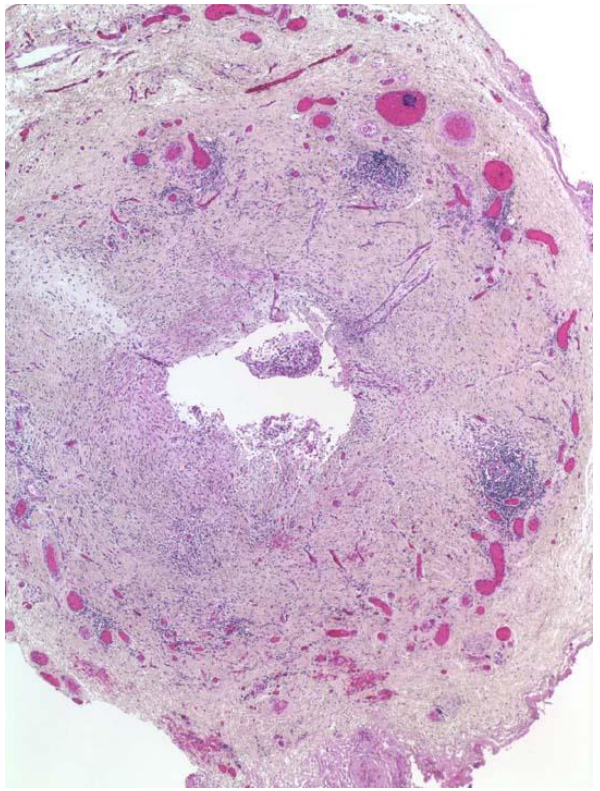


Normal, 40 weeks

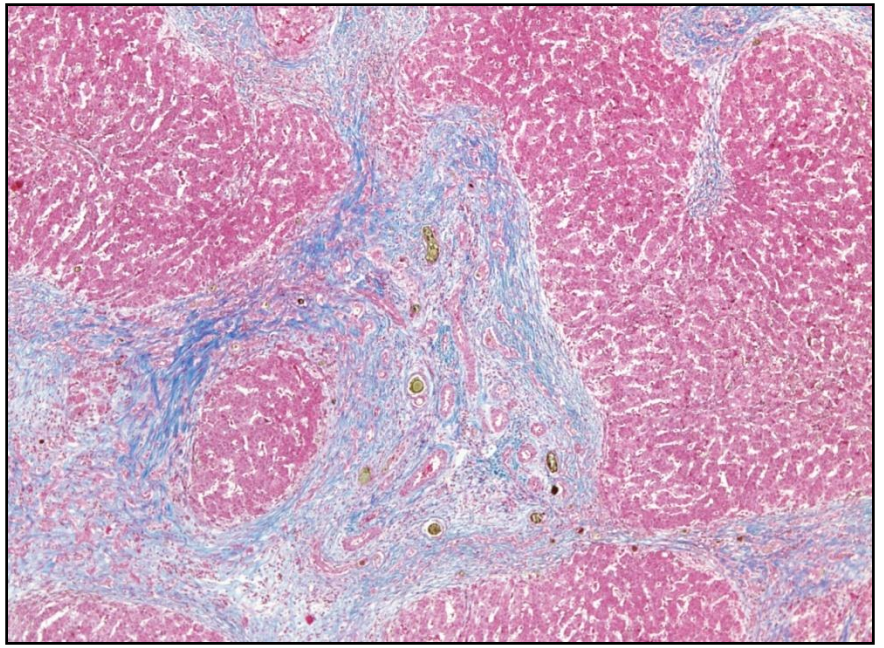


BA, 2 months

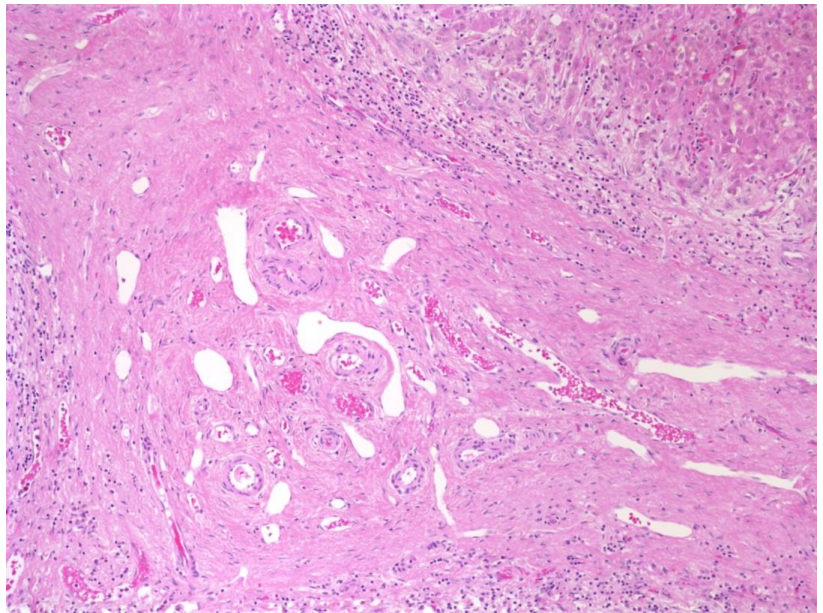
Biliary Atresia – remnant histology

Biliary Atresia – the explant



80% -85% of children will require liver transplantation
40% have failure of HPE without achieving good biliary drainage, leading to liver transplantation < 2 yrs of age
40% - 50% will develop cirrhosis and portal hypertension over a longer time span

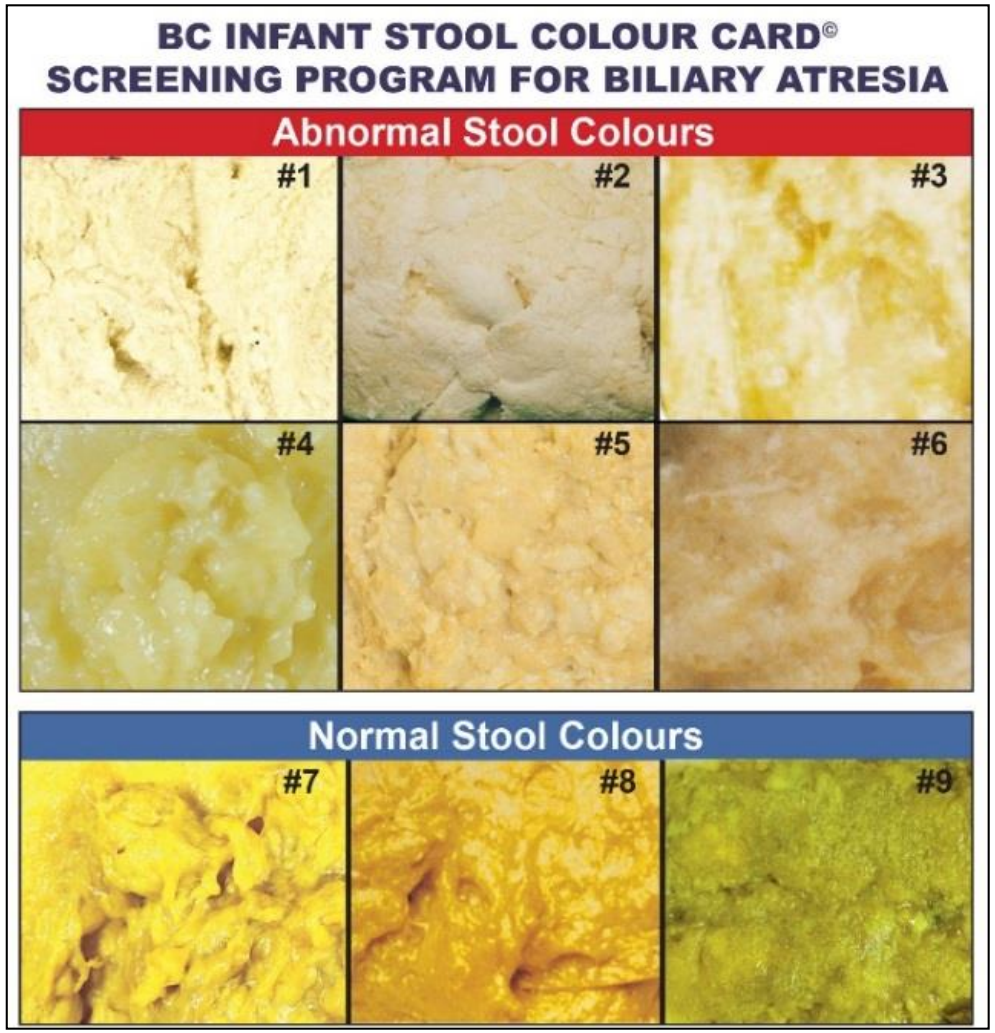


Bile duct loss

Improving the early diagnosis of biliary atresia (BA)

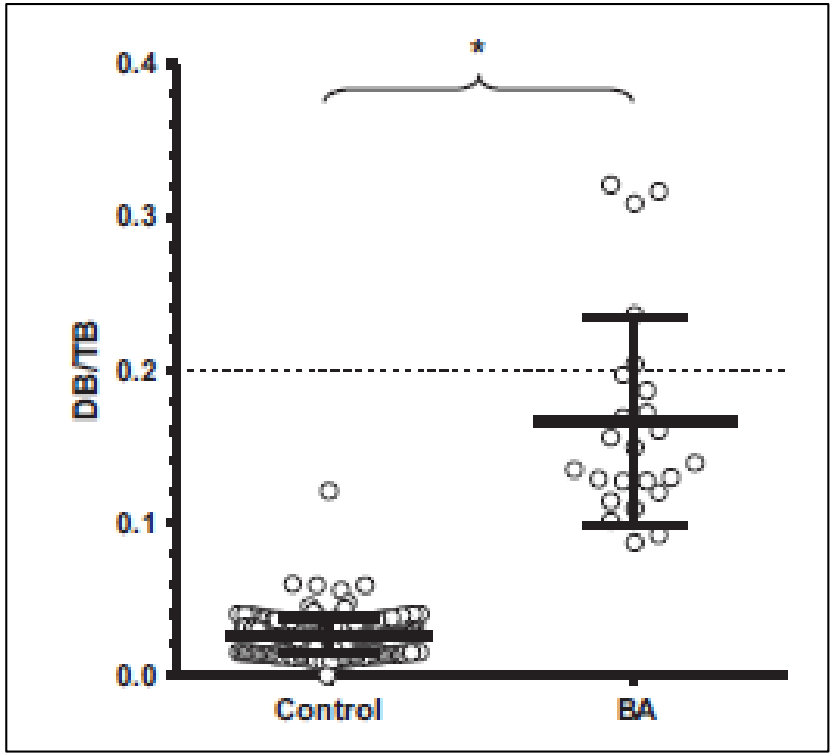
- Prognosis is related to earlier diagnosis and treatment
- Average age at diagnosis and treatment is ~ 60 days and has not changed in 20+ years
- Improving the *early* diagnosis of BA: Stool color cards (Taiwan, Japan)

  improved rate of Kasai < 60 days of life
  - Improved 5 year survival with native liver
  - Feasibility trials in Canada and other countries



Improving the early diagnosis of BA

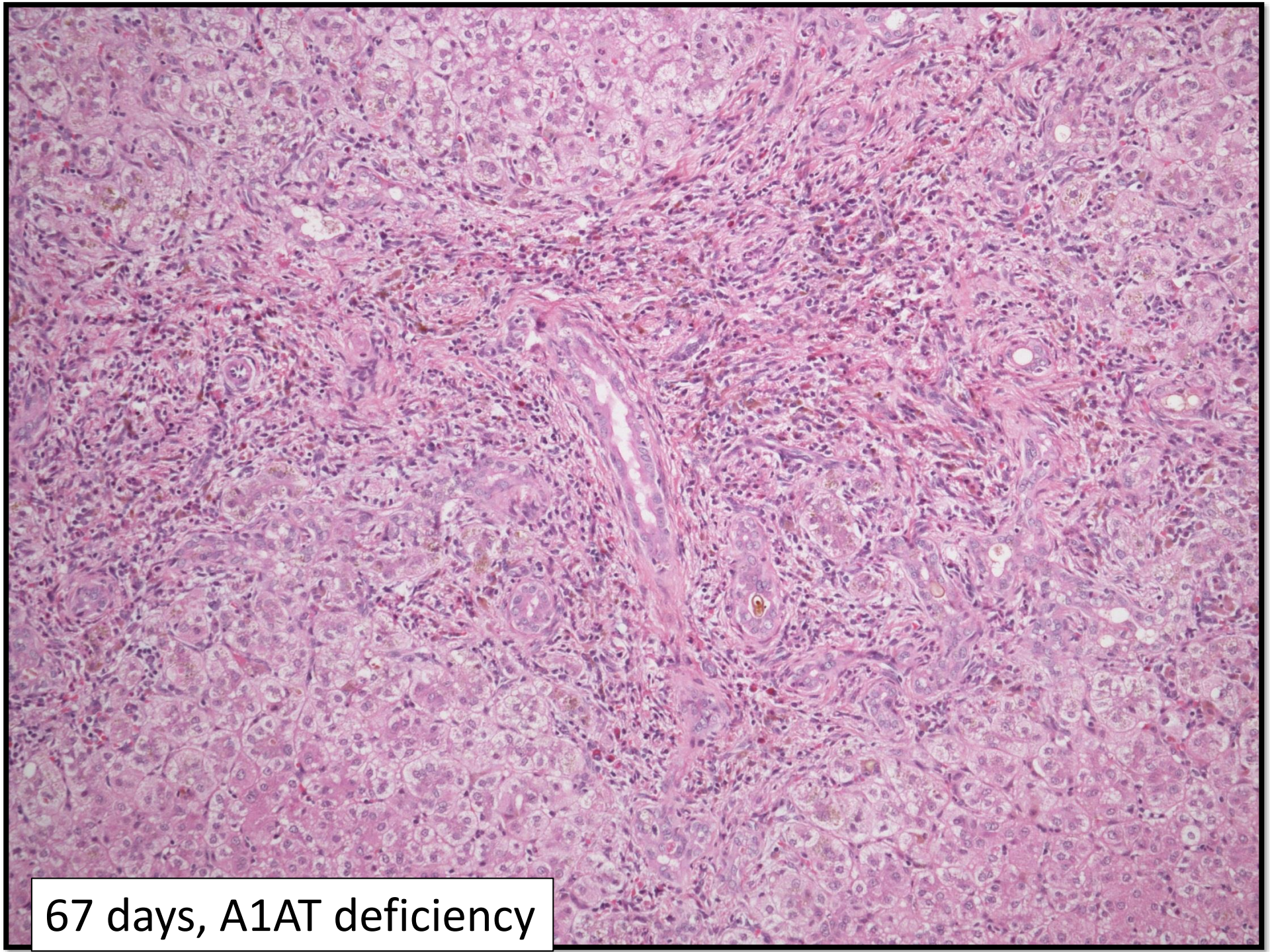
- Measuring direct/conjugated bilirubin in newborns (*Harpavat, J Peds 2011*)
  - Retrospective chart review of infants with BA showed elevated levels of conjugated bilirubin in first 24-72 hours of life (34/34 cases)
- Prospective evaluation of CB in >11,000 newborns found 2 BA's and 1 case of α1-anti trypsin deficiency (*Harvapat, NEJM 2016*)



Harpavat, J Peds 2011

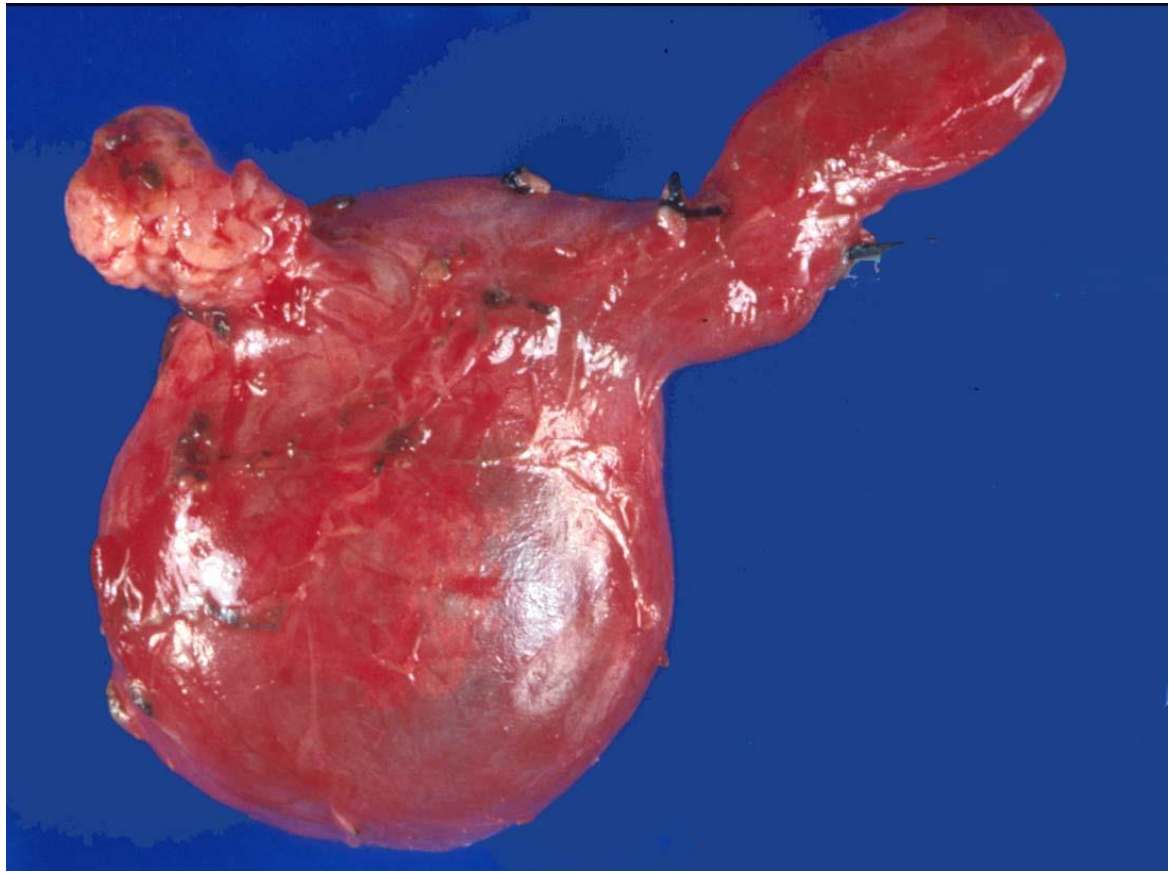
Differential Diagnosis of Obstructive Cholestasis other than BA on Liver Biopsy

Alpha-1 antitrypsin deficiency	**Low or absent serum alpha-1 antitrypsin level, PiZZ phenotype**
Choledochal cyst	Ultrasonographic and cholangiographic findings
Alagille syndrome (early)	Associated malformations, mutation in JAG1 or Notch2 gene
Cystic fibrosis	History of meconium ileus, failure to thrive, positive sweat test
Total parental nutrition (TPN) hepatopathy	History of prematurity and TPN use
Neonatal sclerosing cholangitis	Ichthyosis, scarring alopecia, dysmorphism, Claudin-1 mutations
Progressive familial cholestasis type 3, ABCB4 disease	Usually older infants at presentation; absence of immunohistochemical staining for MDR3 along canaliculi
North American Indian Cirrhosis	Incidence restricted to Native American groups in Canada
Tumor, stone or other mechanical obstruction	

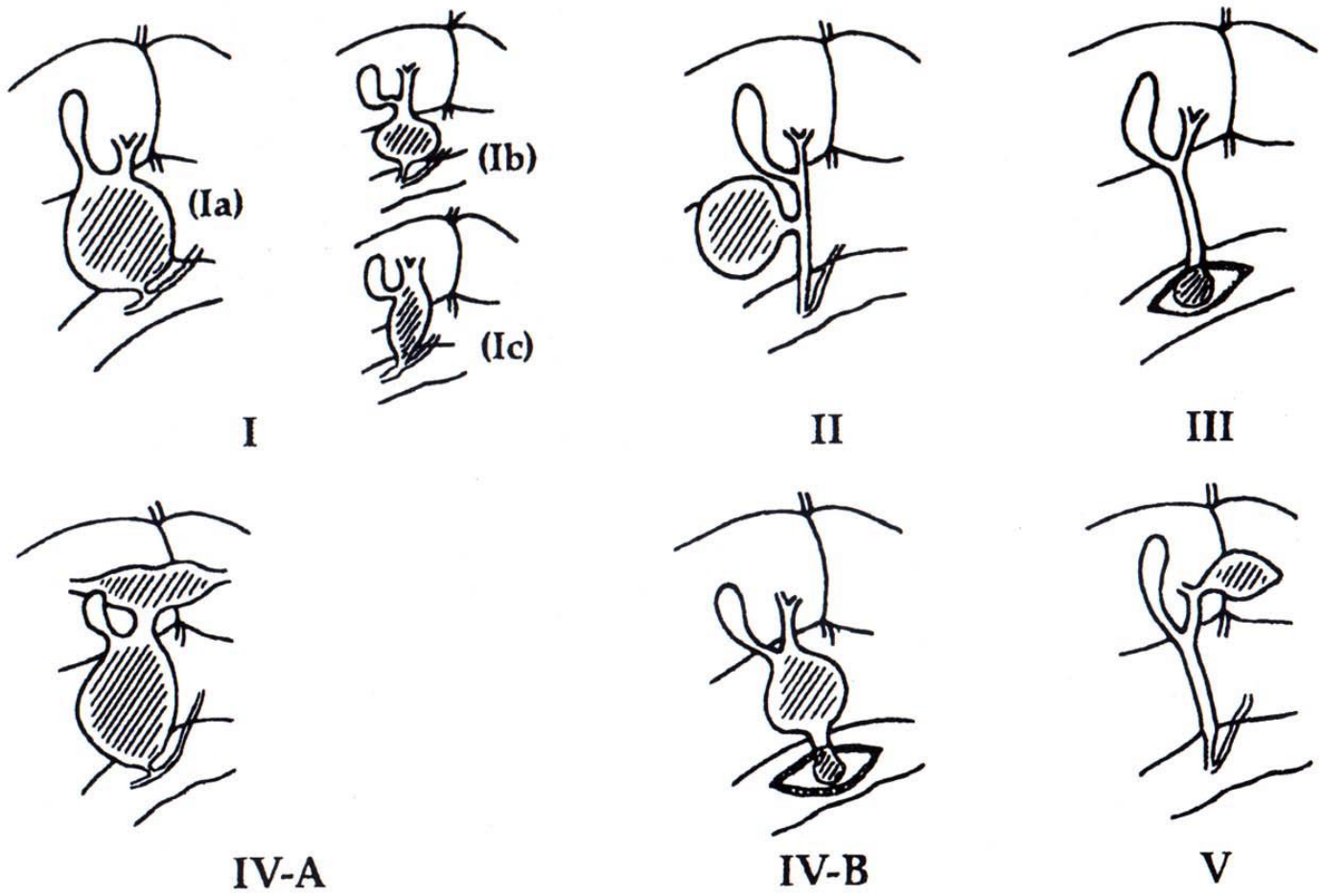

67 days, A1AT deficiency

Choledochal cysts

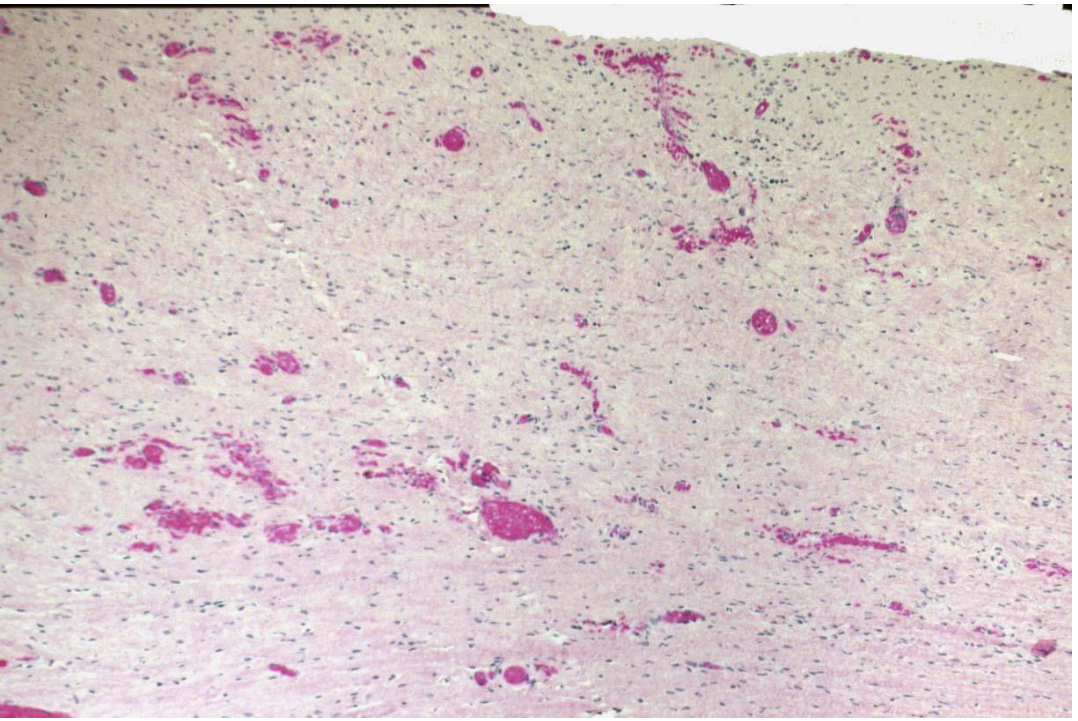
- 1/15,000 livebirths (1/1000 in Japan)
- 4:1 F:M
- 50% dx'd < 10yrs of age; 25% < 20 yrs of age
- Abnormal pancreatobiliary junction



Choledochal Cysts – Todaro classification



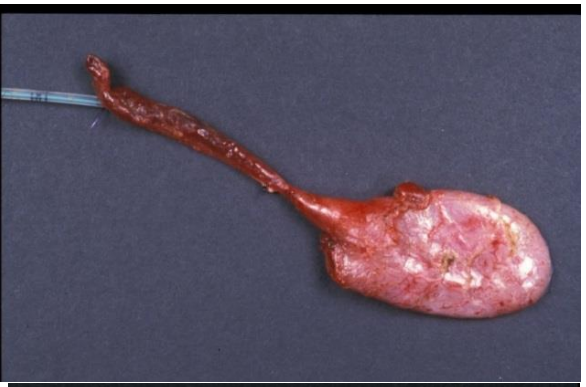
Choledochal cysts

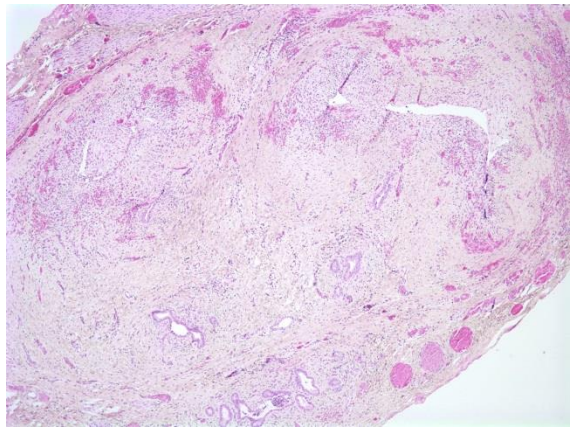


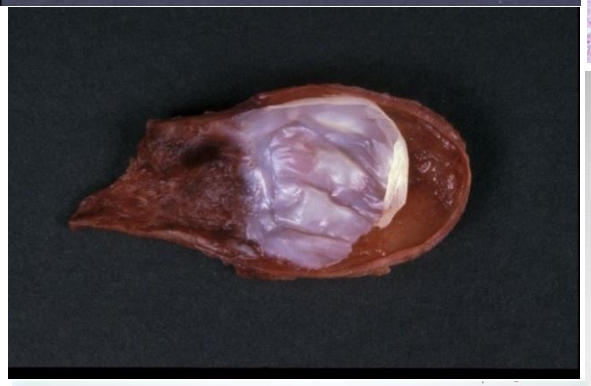
10% lifetime risk of carcinoma

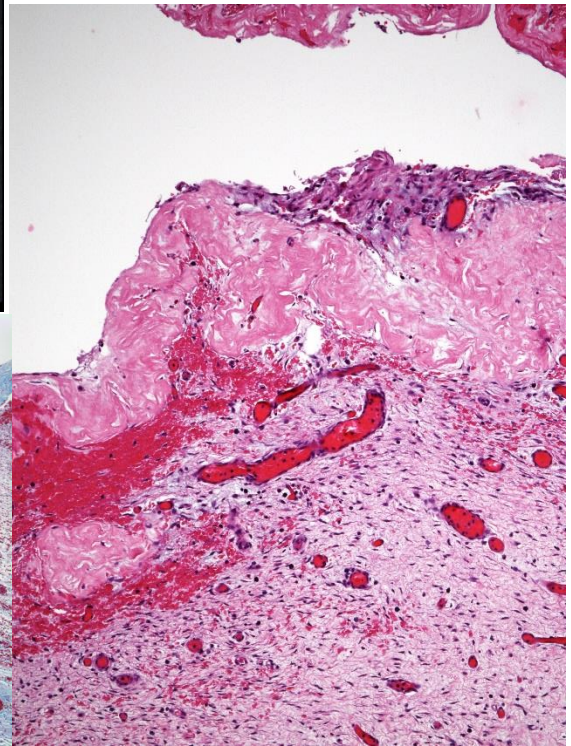
Cystic BA vs Choledochal cyst

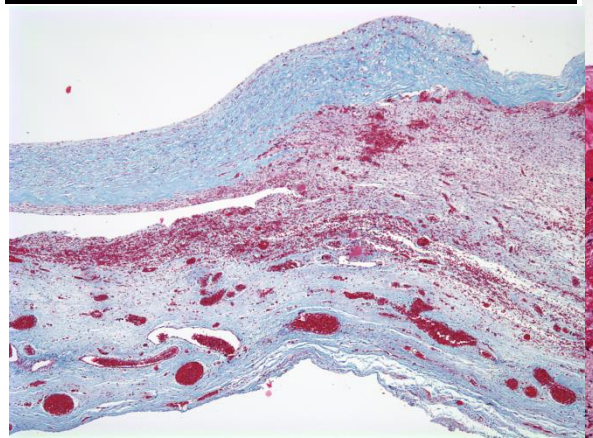
Cystic BA



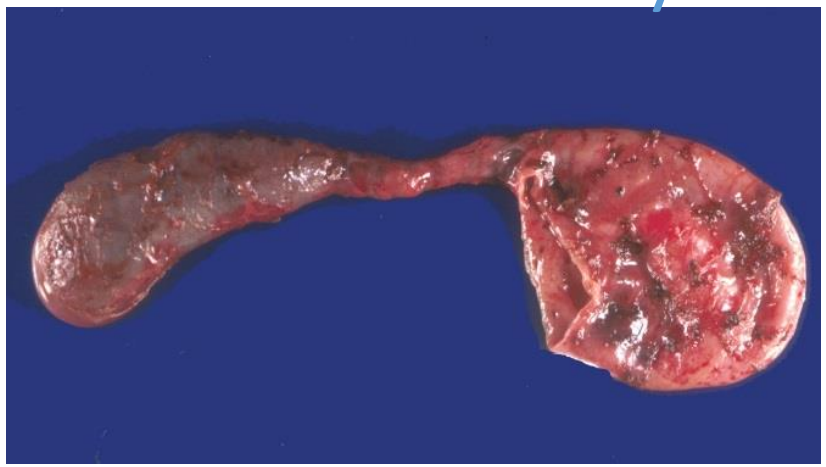


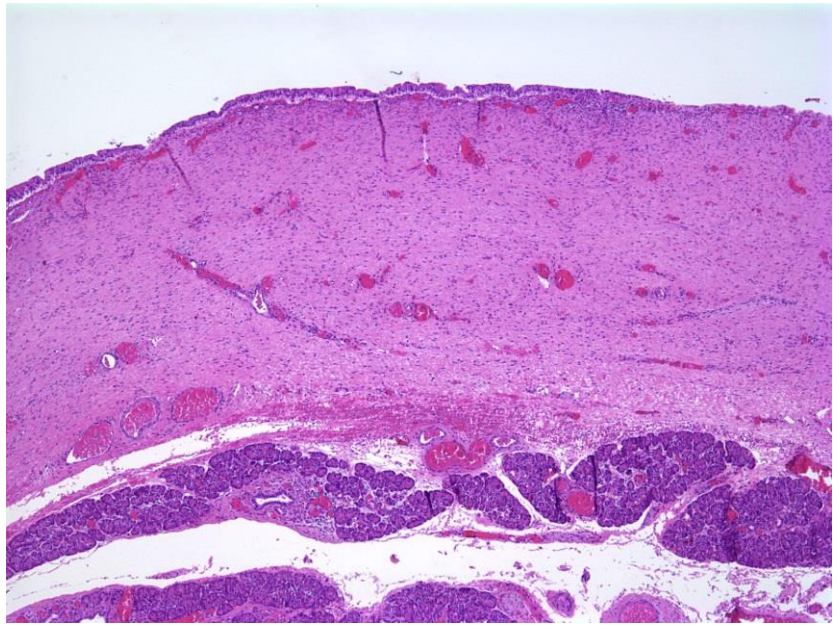






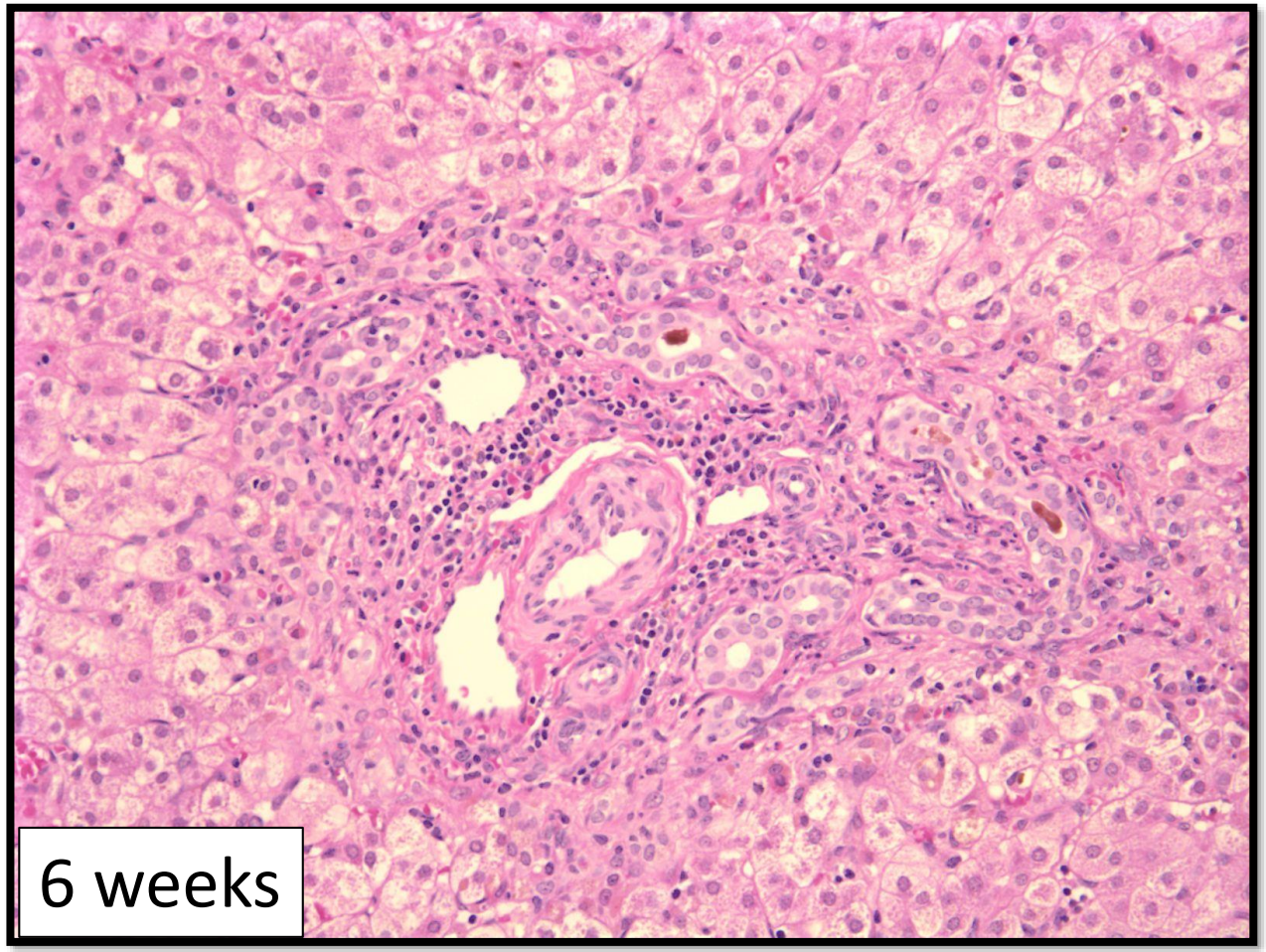
Choledochal cyst

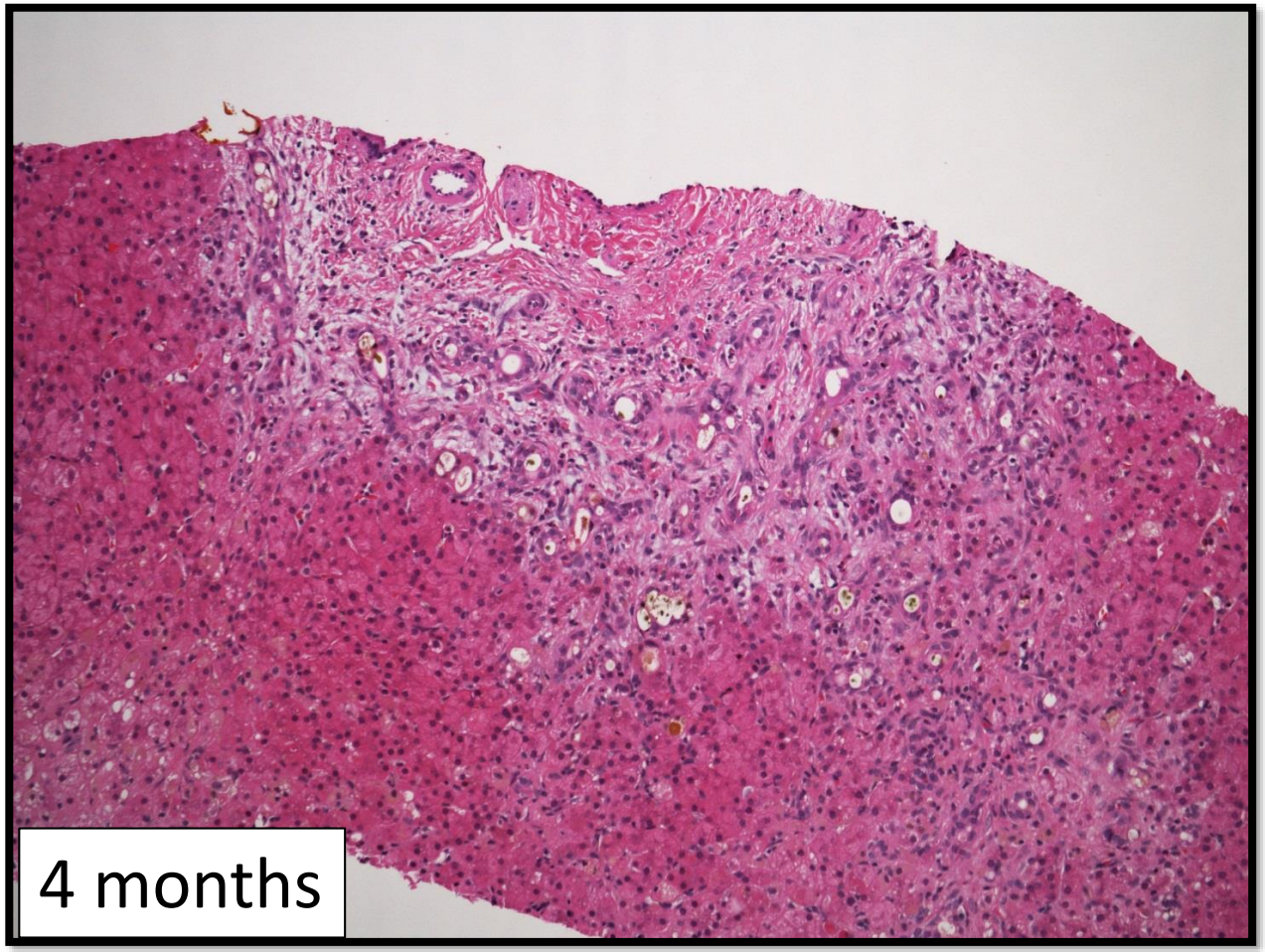




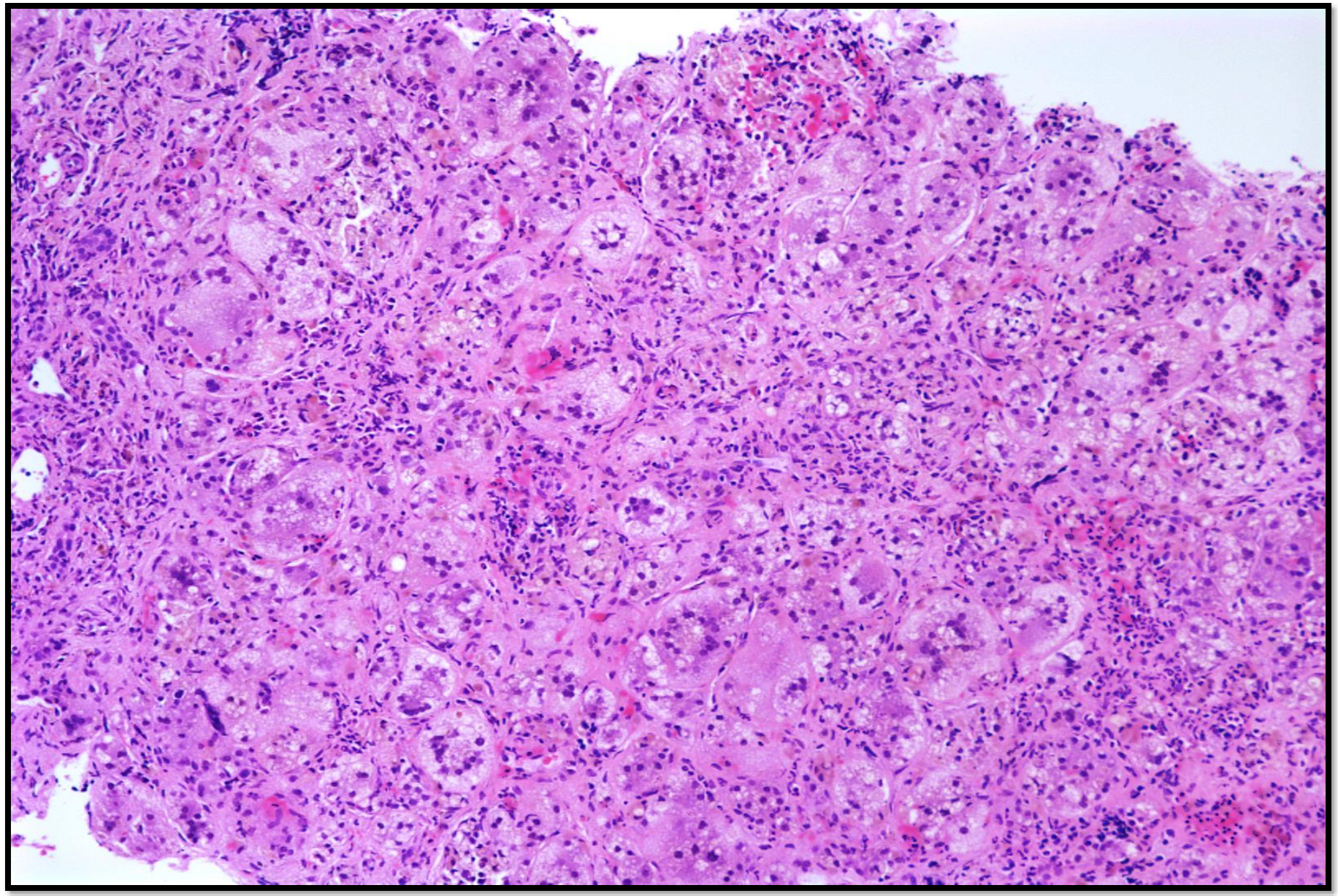
Normal gallbladder, no atresia, wall non-inflamed

Parenteral Nutrition-induced Cholestasis





“Neonatal” Giant Cell Hepatitis (NGCH)



Conditions associated with Giant Cell Hepatitis

- Idiopathic
- Infections
  - TORCH
  - Enterovirus
  - Parvovirus
  - Syphilis
  - Bacterial sepsis
- Biliary Atresia (occasionally)
- Metabolic
  - Alpha-1 antitrypsin deficiency
  - Niemann-Pick type C
  - Bile acid synthesis disorder
  - Progressive familial intrahepatic cholestasis
- Panhypopituitarism
- Chromosomal
  - Trisomy 18, trisomy 21. monosomy X
- Immune disorders
  - Severe combined immunodeficiency
  - Neonatal lupus

"Giant cell hepatitis" is a descriptive term, and not a diagnosis

Etiologic findings in NCGH: Two institution study (2010)

TABLE 1. Follow-up Etiological Findings in Cases of Neonatal Giant Cell Hepatitis

Follow-up Findings	Johns Hopkins, N = 32	University of Chicago, N = 30	Total, N = 63
Idiopathic	18	12	31 (49%)
Hypopituitarism	5	5	10 (16%)
Biliary atresia	2	3	5 (8%)
Alagille syndrome	2	1	4 (6%)
PFIC or other bile salt defects	1	3	4 (6%)
Neonatal hemochromatosis	0	3	3 (5%)
Autoimmune hepatitis	1	0	1 (2%)
SCID	1	0	1 (2%)
Cytomegalovirus	1	0	1 (2%)
Echovirus	1	0	1 (2%)
Alpha-1-antitrypsin deficiency	0	1	1 (2%)
Cystic fibrosis	0	1	1 (2%)

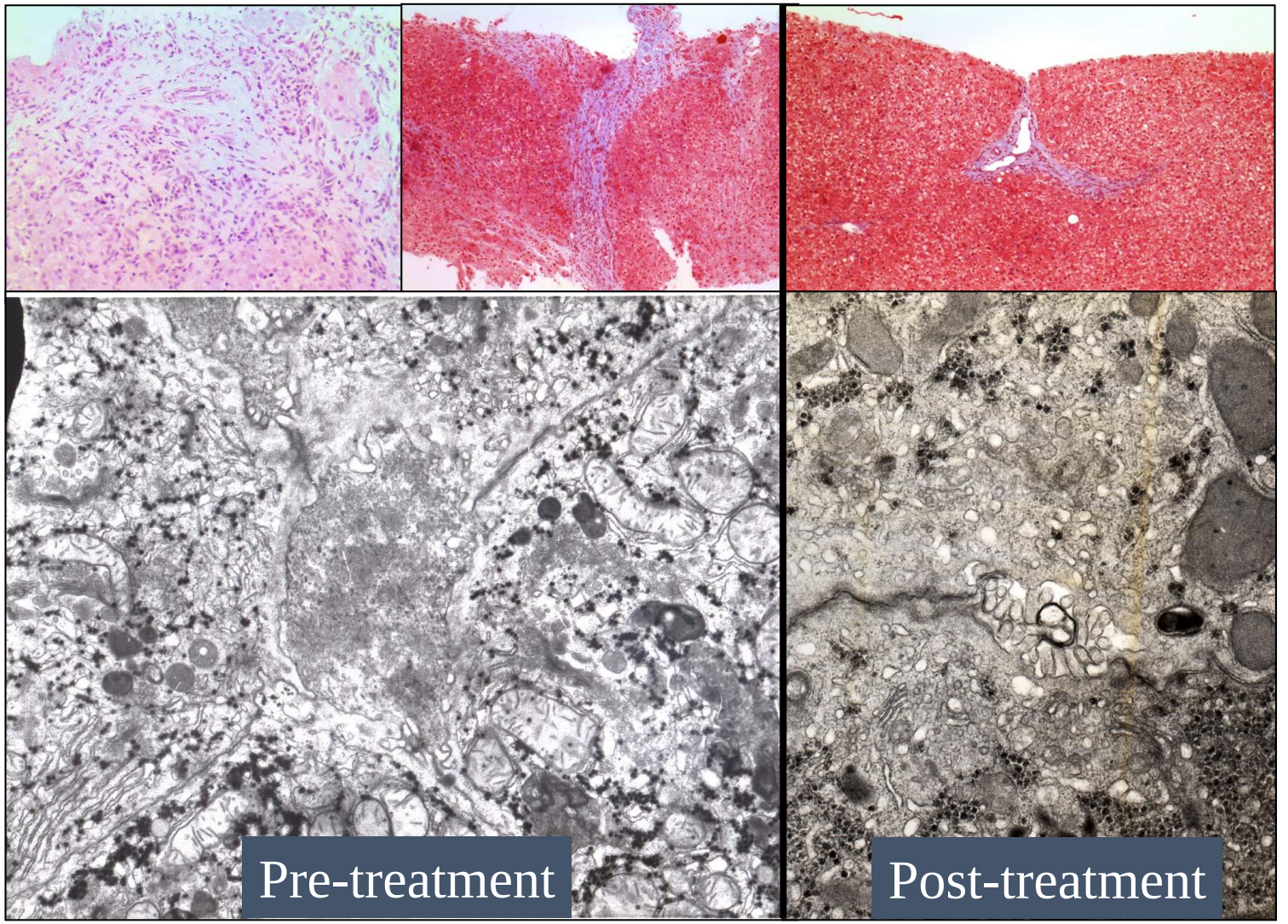
PFIC indicates progressive familial intrahepatic cholestasis; SCID, severe combined immunodeficiency.

- 49% Idiopathic
- 16% hypopituitarism
- 8% Biliary atresia
- 6 % Alagille syndrome
- 6% PFIC/ bile salt defects
- 5% neonatal hemochromatosis

Torbenson, AJSP 2010

Low GGT Cholestasis: Bile Acid Synthetic Defects

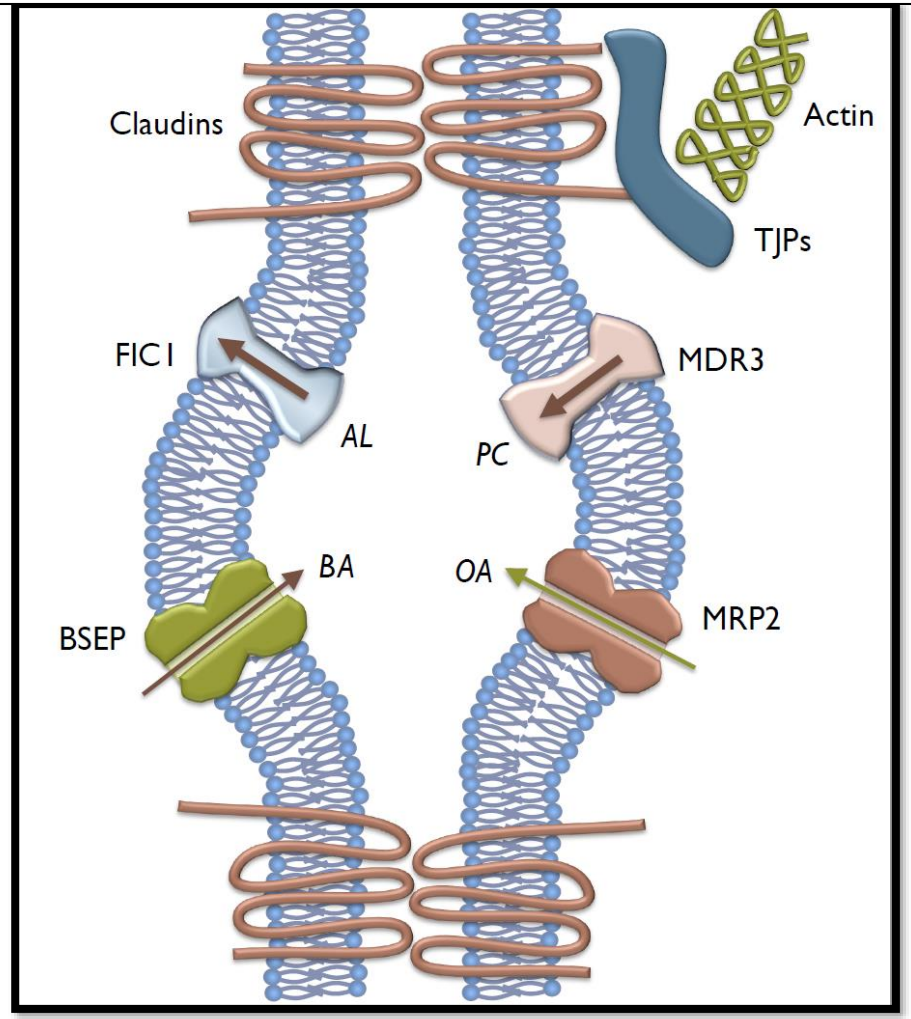
- Nine different defects described
- Two most common:
  - 5-Beta reductase deficiency
  - 3-Beta hydroxyl dehydrogenase deficiency
- Abnormal bile acids in urine
- Diagnosis by mass spectrometry of urine or bile
- Treatment with primary bile acids may be curative



3β-hydroxy δ5-C_{27} steroid dehydrogenase

“Progressive” Familial Intrahepatic Cholestasis

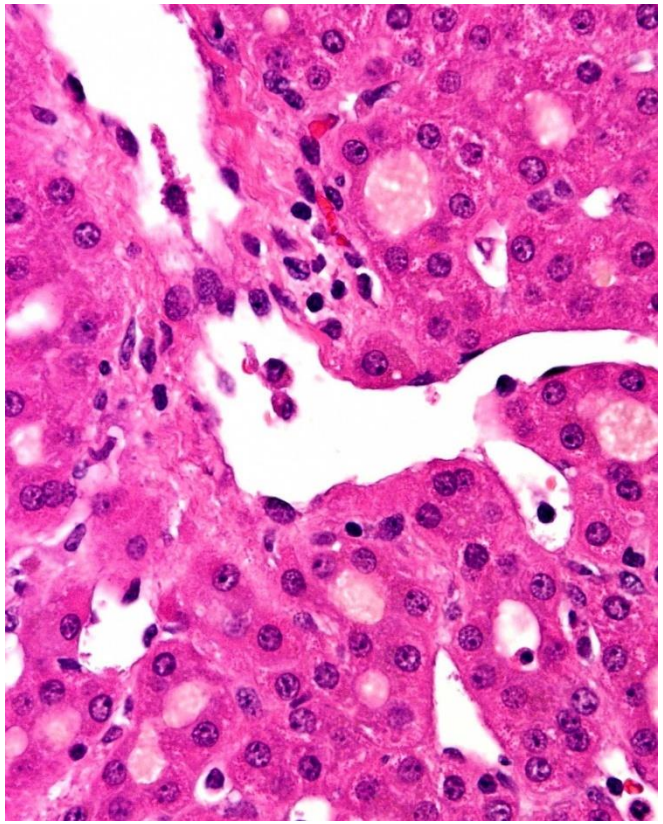
Hepatocyte canalicular membrane



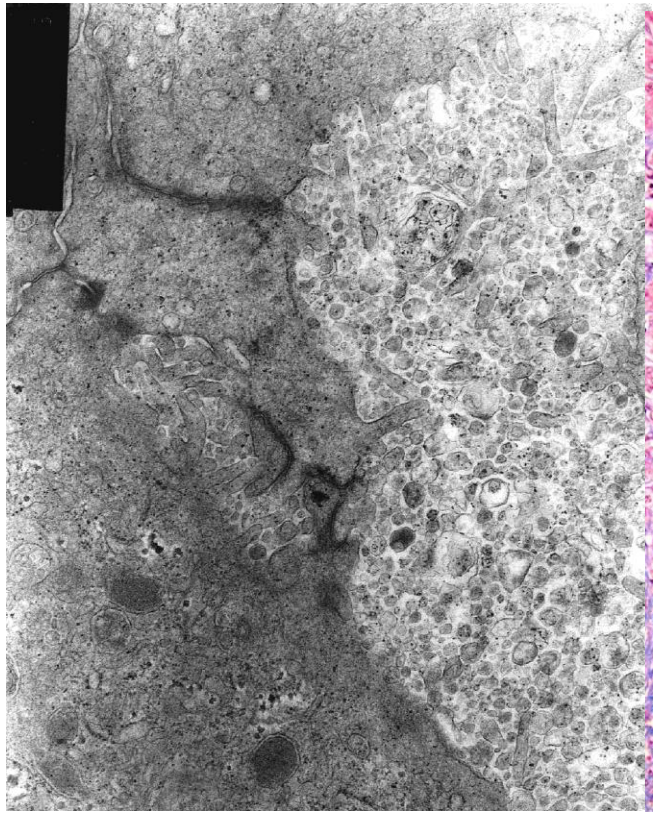
- Defects in bile acid handling
- Genetic disorders occur in clinical spectra, ranging from infrequent symptoms to severe early-onset disease
- Severe early-onset forms have autosomal recessive inheritance and are truly “progressive”

Courtesy: Richard Thompson, King’s College, London, UK

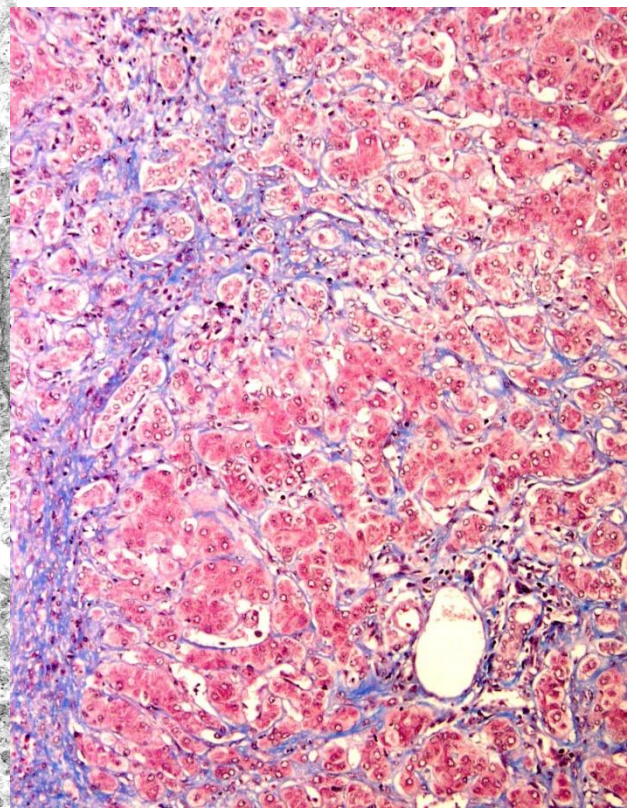
Progressive familial cholestasis – PFIC-1 (Byler's) (*ATP8B1*) and BRIC – low GGT



Early childhood

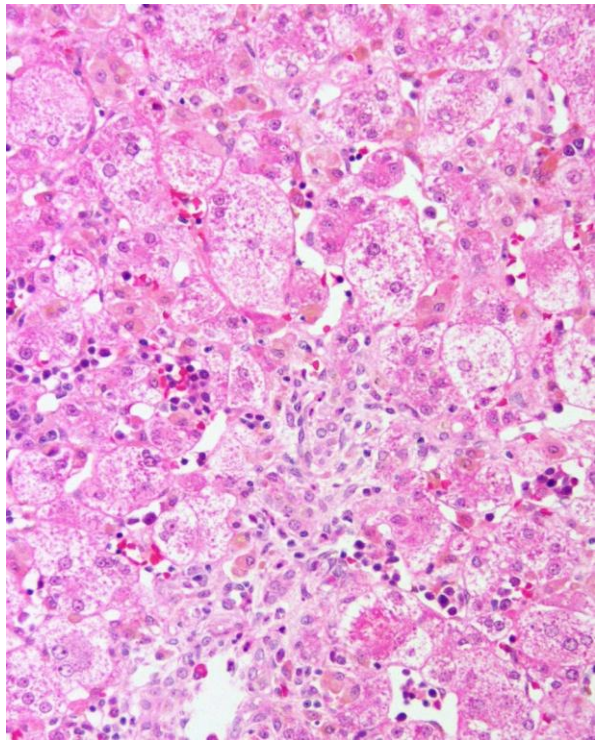


Granular bile

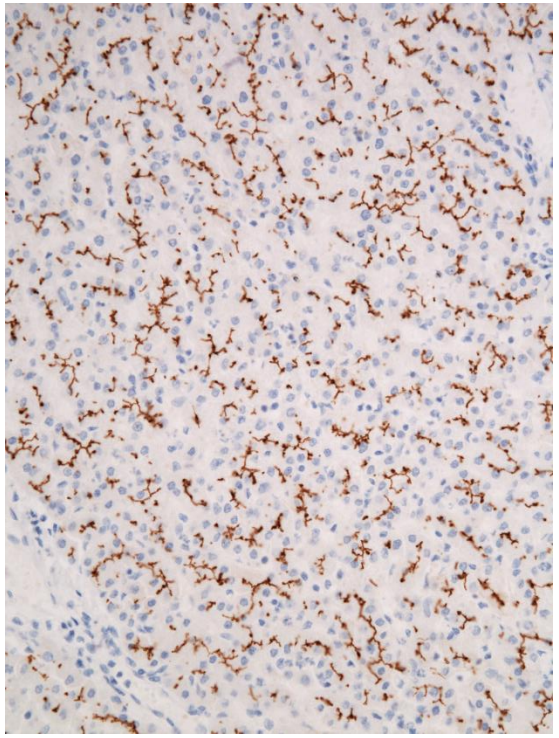


hepatectomy

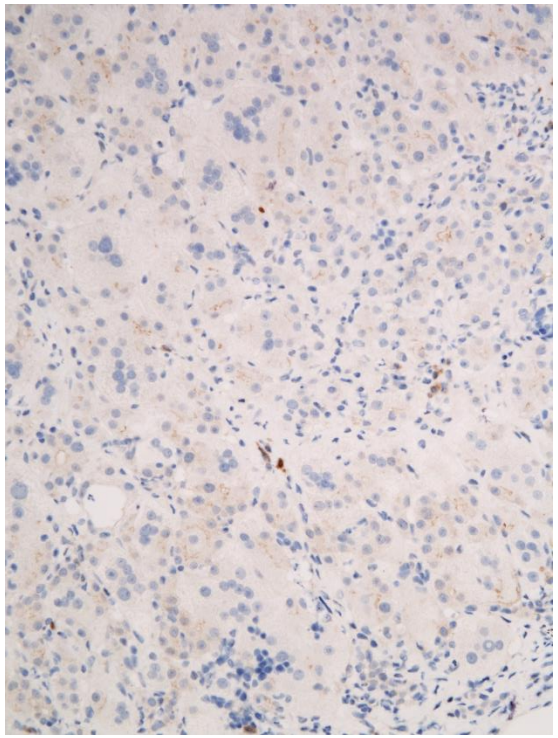
Low GGT - PFIC-2 (ABCB 11)



Neonatal hepatitis



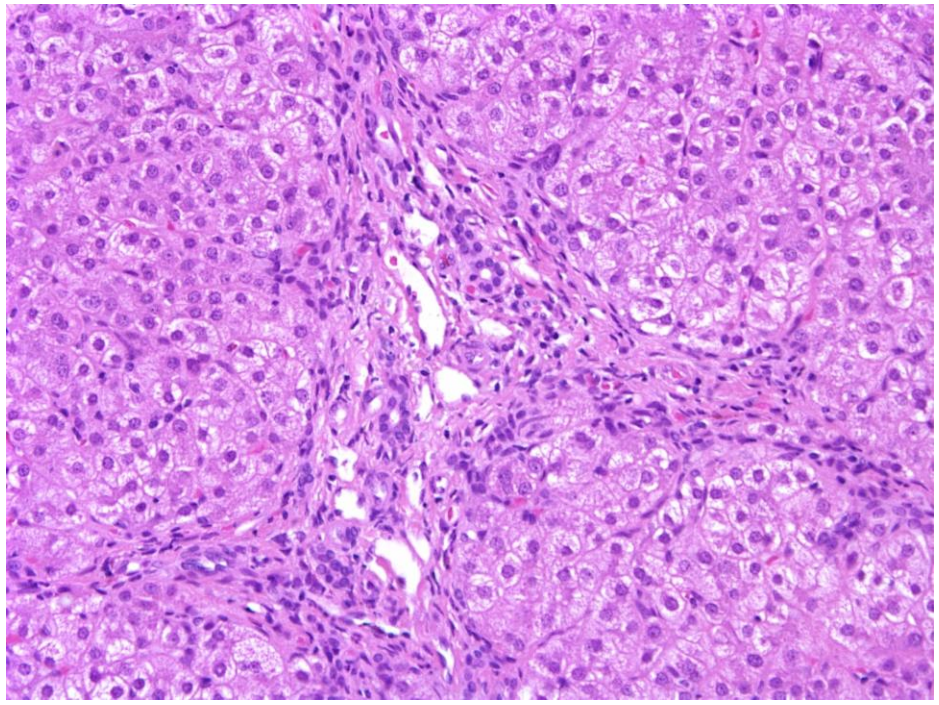
BSEP control



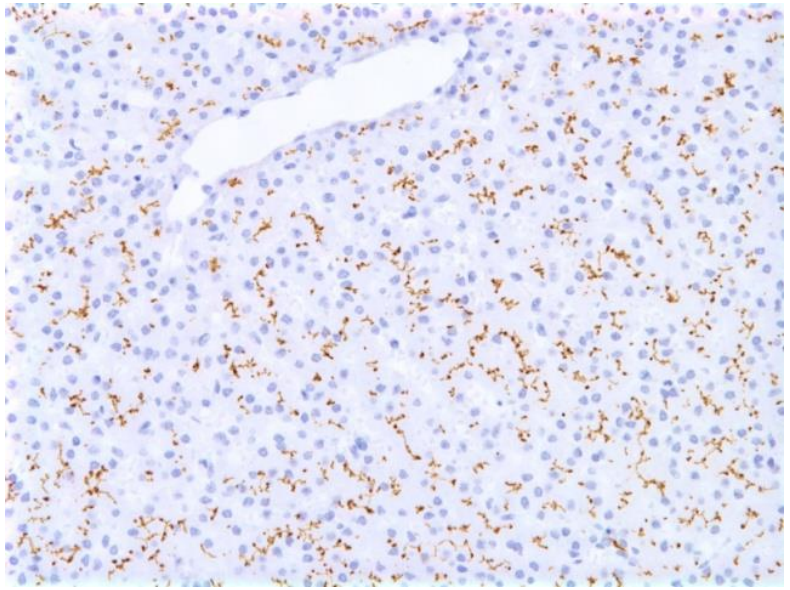
BSEP case

Increased incidence HCC

High GGT - PFIC III (ABCB4/MDR3)

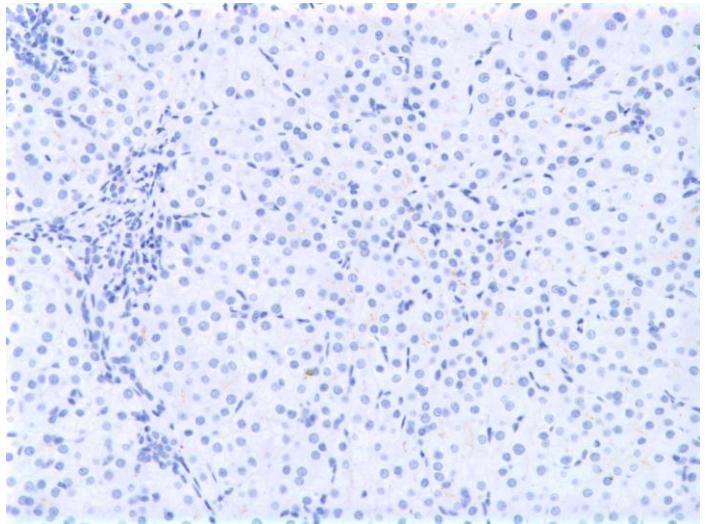


18 months,



+ CONTROL

MDR 3



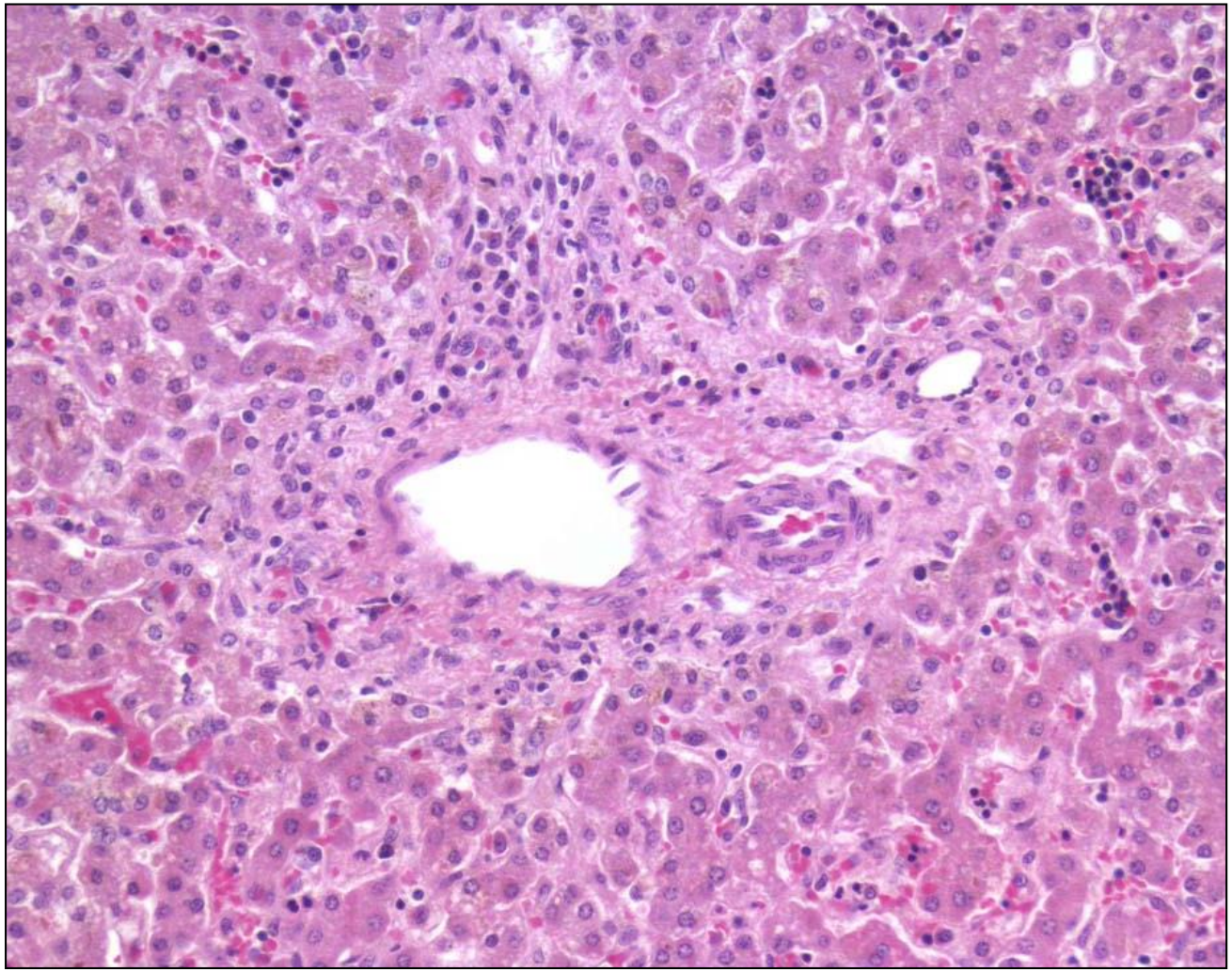
Summary of PFIC associated with different genetic etiologies

Adapted from Bull L Clin Liv Dis 2018

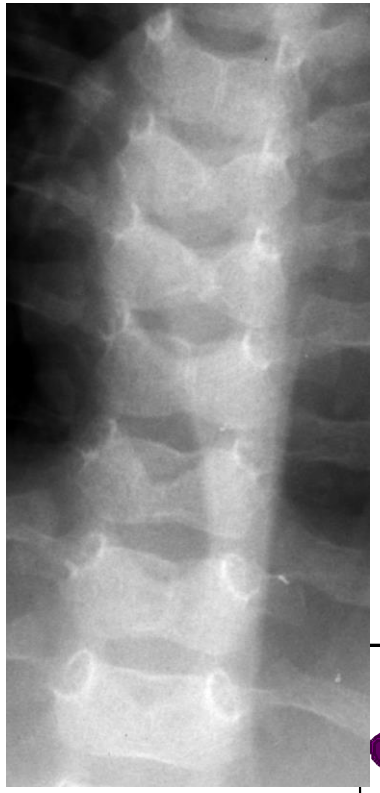
Deficiency	Gene	Clinical Features	Characteristic Histology	Typical Outcomes
FIC1	*ATP8B1*	Multisystem disease Normal GGT Mild transaminitis	Bland canalicular cholestasis "Granular" bile	Moderate rate of progression Post-TX steatosis and diarrhea
BSEP	*ABCB11*	Normal GGT High risk of HCC and CC Gallstones	Giant cell hepatitis	Moderate to rapid progression Post-TX alloantibodies
MDR3	*ABCB4*	Progressive cholangiopathy Elevated GGT	Cholangiopathy	Variable rate of progression
TJP2	*TJP2*	Normal GGT	Bland cholestasis	Rapid progression
FXR	*NR1H4*	Early-onset coagulopathy; normal GGT; elevated AFP	Giant cell hepatitis	Rapid progression
MYO5B	*MYO5B*	Normal GGT Variable intestinal involvement	Giant cell hepatitis cholangiopathy	Variable progression

Bile Duct Paucity

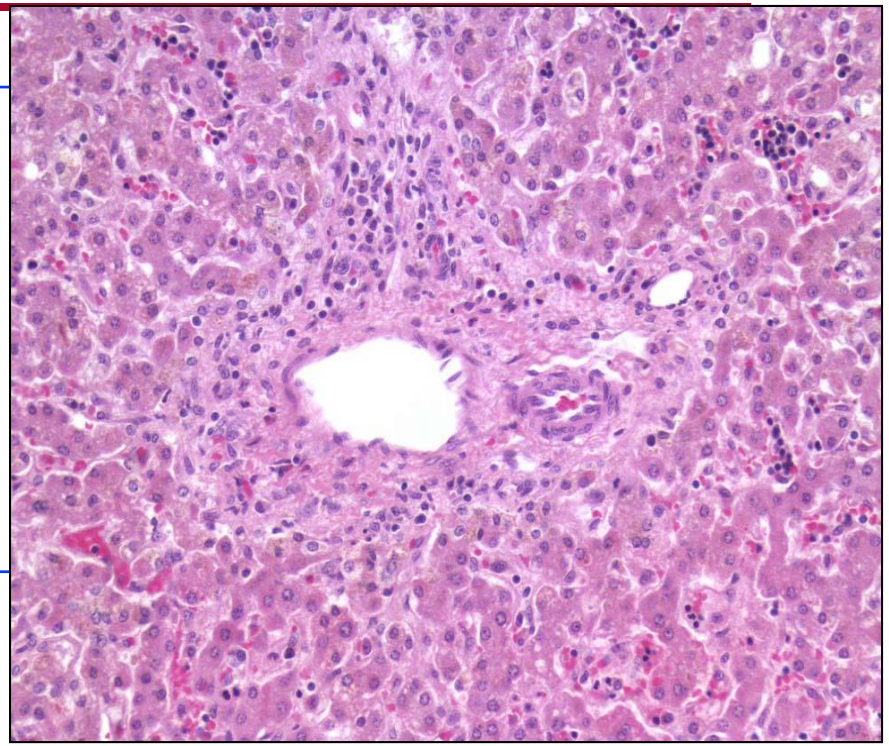
- Normal BD/PT ratio = 0.9 – 2.0
- In practice, diagnosis made when BD/PT ratio < 0.5
- Must have adequate # of portal tracts (~10)
- Syndromic - Alagille syndrome
- Non-syndromic
  - Metabolic and Genetic
    - Alpha-1-antitrypsin deficiency
    - Trisomy 21 (rare)
    - Peroxisomal disorders (rare)
  - Congenital Infections
    - » CMV
  - Inflammatory and Immune disorders
    - Biliary atresia, GVHD, rejection, PSC, sarcoidosis
  - Drug-induced
  - Idiopathic

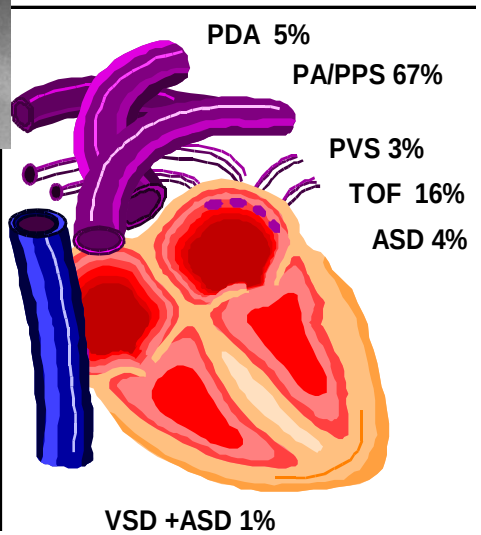


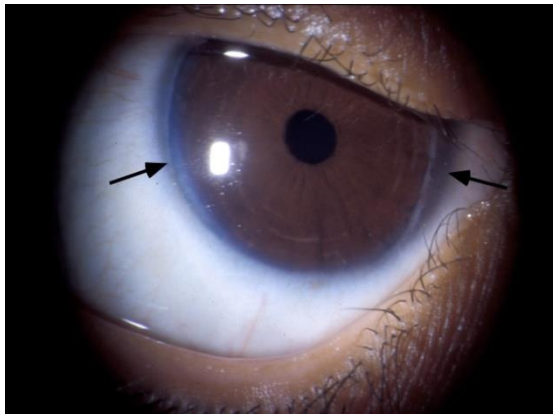
Alagille Syndrome (ALGS)



- Autosomal Dominant
- Multi-system
  - Liver, heart,
  - Skeleton, eye,
  - Face, kidney,
  - vasculature

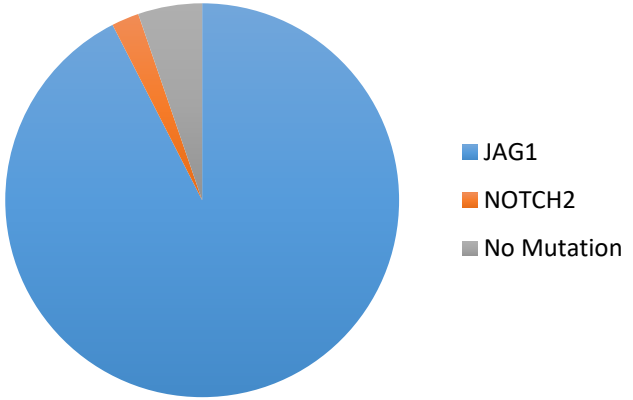


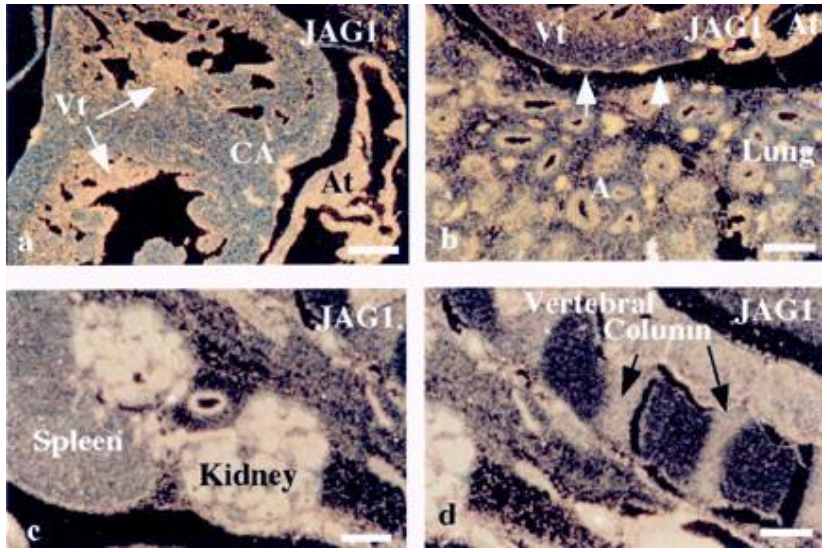




Genetics of ALGS

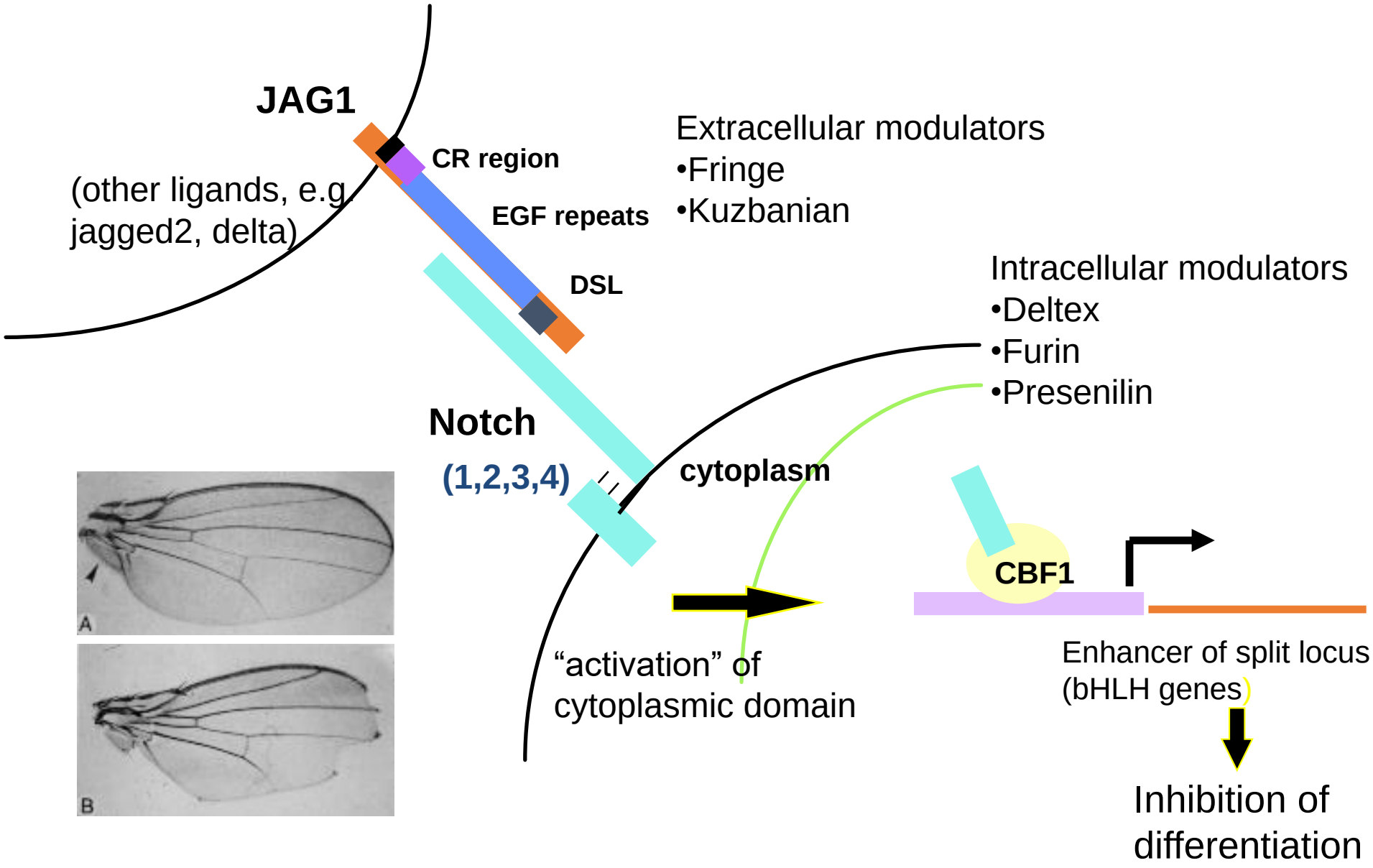
- Mutation in *JAG1* (20p12) in >90% of cases with “classic “ features
- 60% represent new mutations in the probands
- 1-2% of ALGS patients have mutations in *Notch2* (1p13) – more severe renal disease



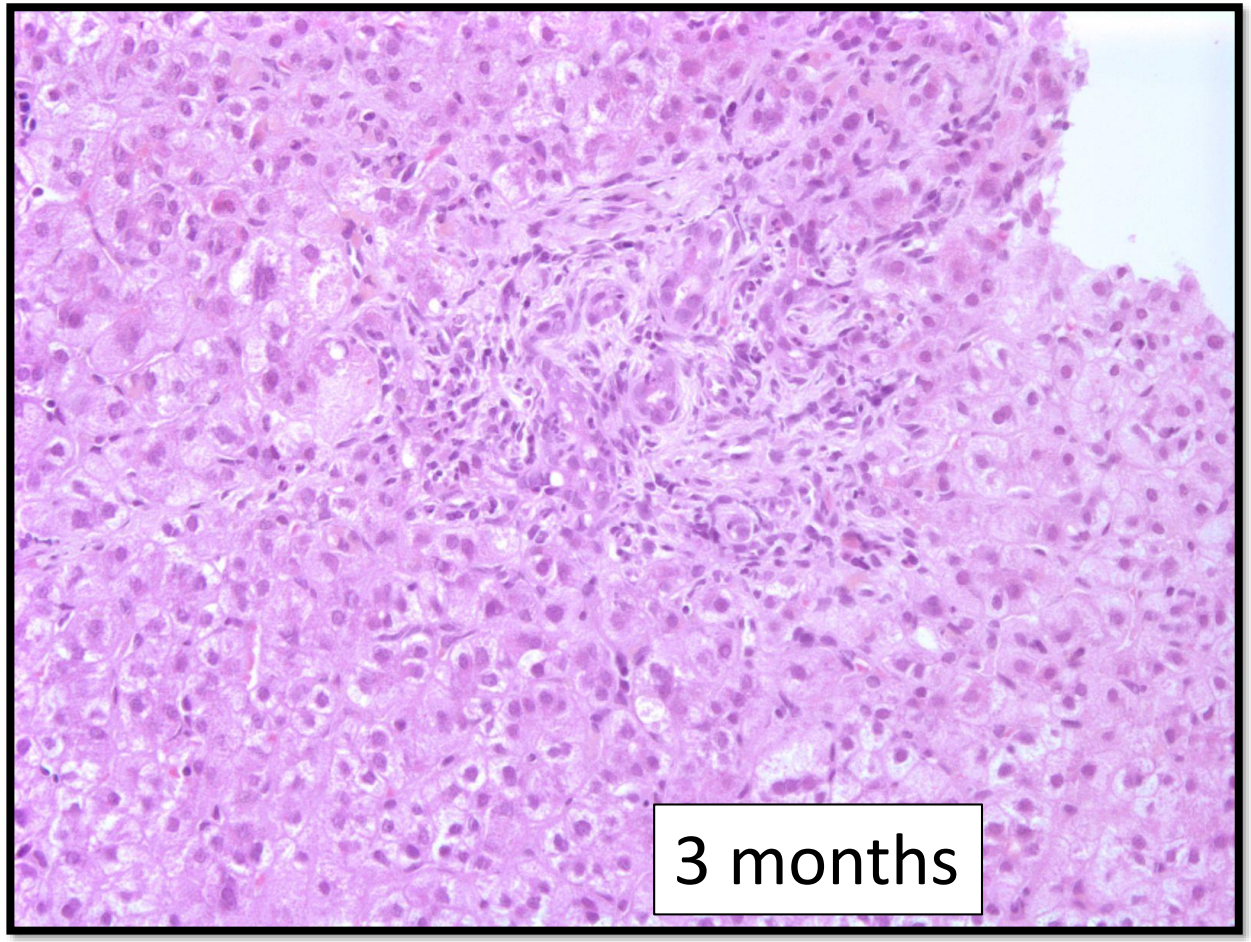


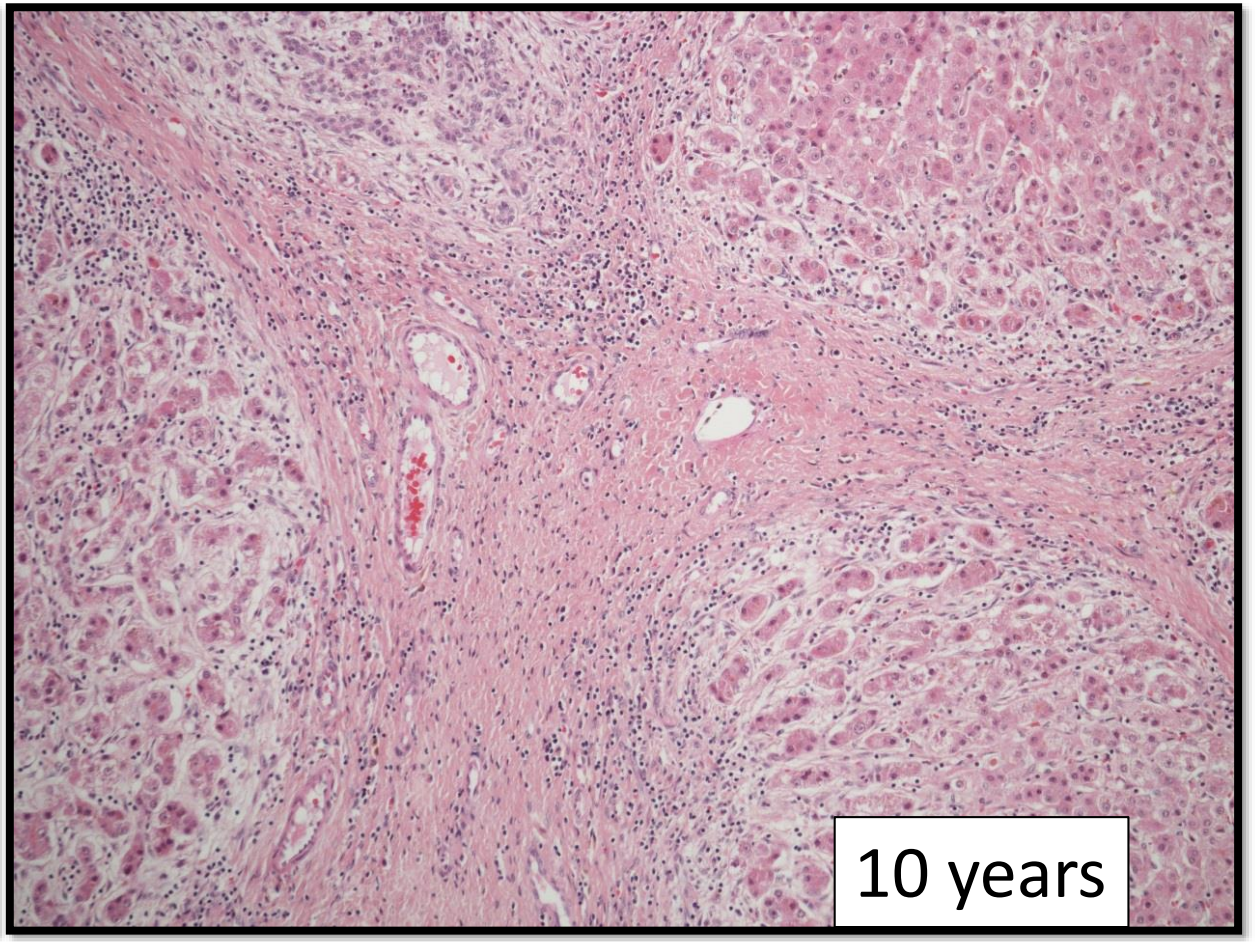
Jag1 is expressed in developing organs typically affected in ALGS
Loomes et al, Hum Mol Genetics, 1999

NOTCH SIGNALING



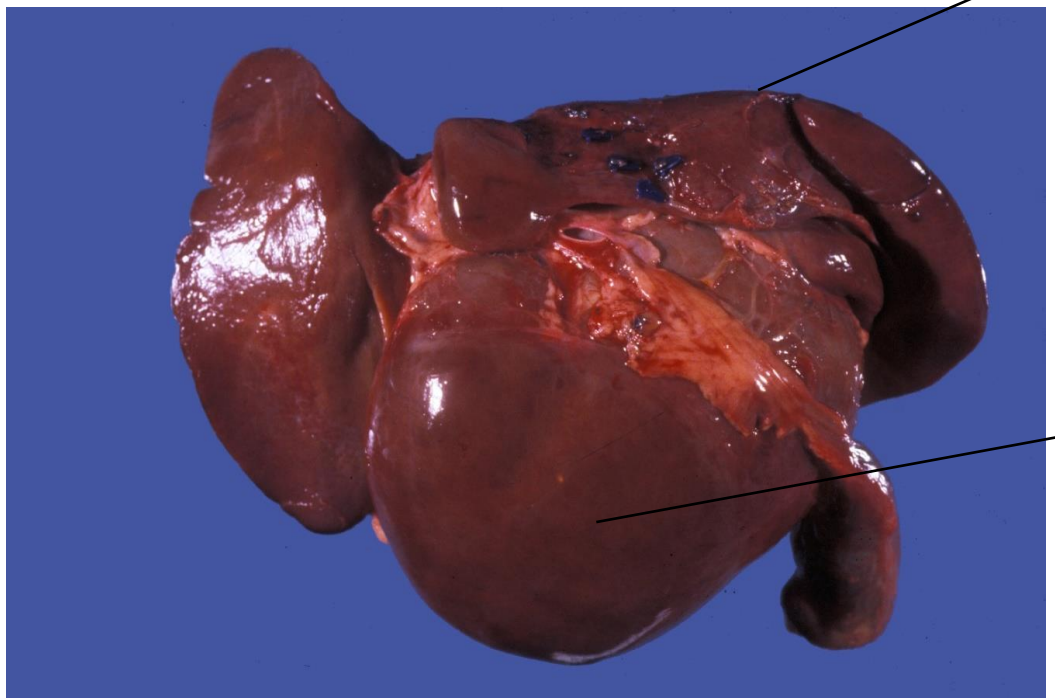
Bile duct paucity may evolve in Alagille syndrome

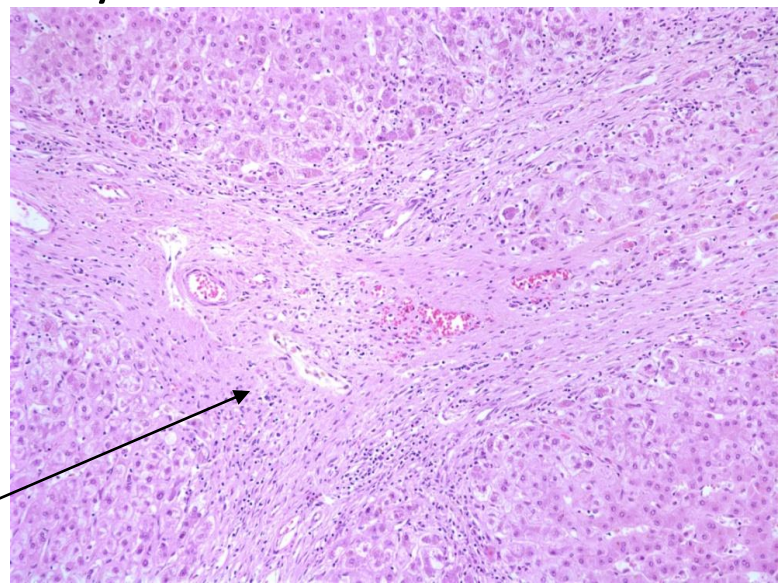


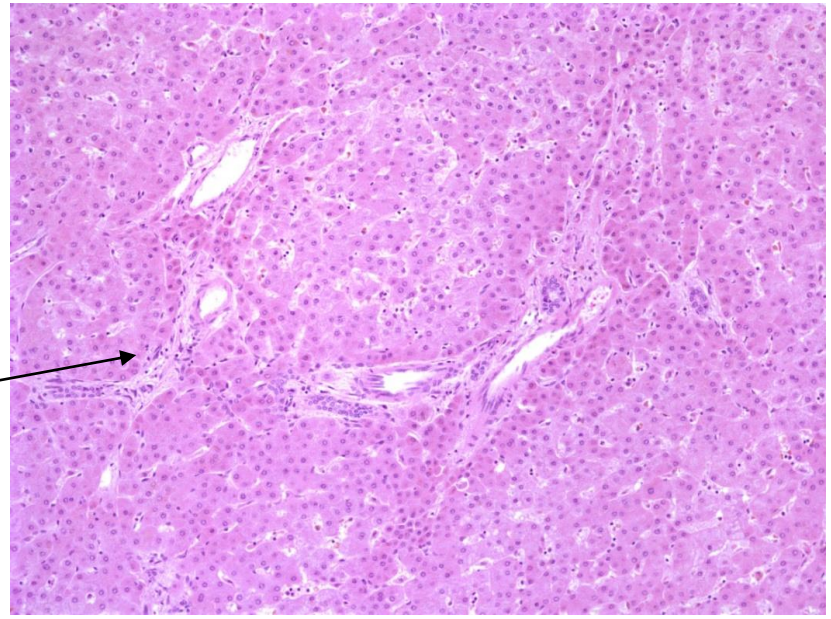


Alagille syndrome – heterogeneity in the progression of bile duct paucity

Liver transplantation in 13 year-old boy for posterior liver mass suspicious for tumor

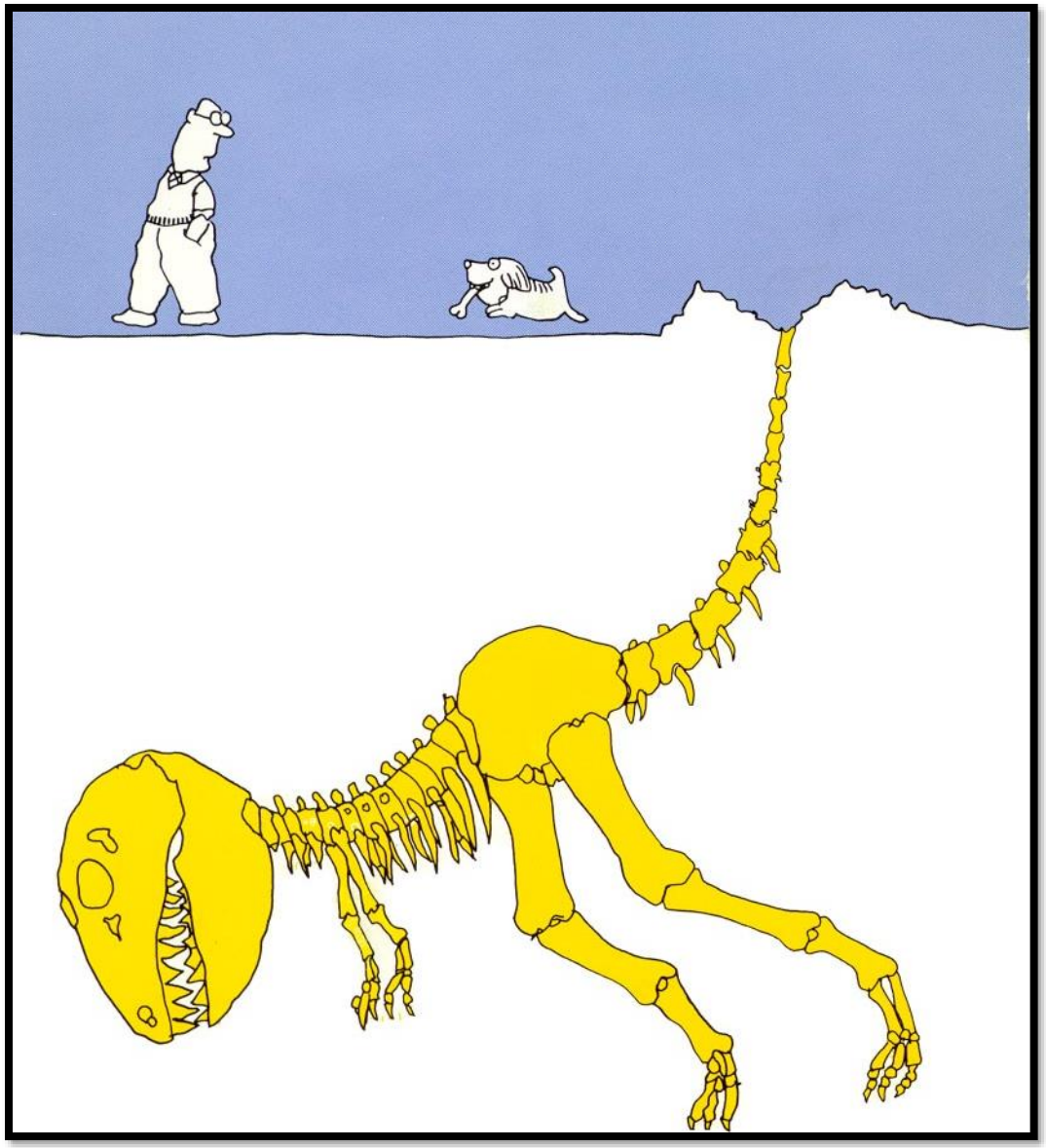






Conclusions

- Neonatal/infantile cholestasis has a broad differential diagnosis
- The aim of the diagnostic work-up is to identify as soon as possible a number of critical etiologies (ie, BA) where early treatment is key
- Liver biopsies play a critical role in the diagnosis of these disorders
- The pathologist must be familiar with the differential diagnosis of the various patterns observed on liver biopsies from cholestatic infants



You find only what you look for, you seek only what you know