Trivial Pursuit: Liver Conditions You Probably Never Heard Of

Fred Poordad, MD

Case 1

Case 1: Mr. Tanner Ferris

- A 47-year-old male with no significant past medical history came for evaluation of abnormal liver enzymes.
- BMI 25; recently diagnosed with diabetes.
- He is a moderate social drinker (2-3 glasses of wine, 3-4 nights per week).
- His AST was 68 IU/L, ALT 74 IU/L and ALP 115 IU/L.
- Hgb 16.9 g/dL, platelets 264,000/mm^3, Tbili 1.0 mg/dL and INR 1.0
- His work up showed fasting ferritin level of 800 mcg/L and fasting transferrin sat of 55%

Mr. Tanner Ferris

- What is the most likely diagnosis?
  - Nonalcoholic fatty liver disease
  - A1AT deficiency
  - Autoimmune hepatitis
  - Hereditary hemochromatosis
  - Wilson disease

Mr. Tanner Ferris

- Mr. Ferris' profile
  - Younger patient
  - New onset diabetes
  - Mildly elevated liver enzymes
  - Iron sat >50% and ferritin 800
  - Moderate alcohol consumption
- What further testing is necessary?

Molecular DNA Analysis Warranted

LabCorp Test:

Test Name	Test Number
Hereditary Hemochromatosis, DNA Analysis	511345

Table 1.—Relative Prevalence of HH Genotypes[2,3]

Genotype	Prevalence
C282Y homozygous	60%–>90%*
H63D homozygous	4.0%
C282Y/H63D compound heterozygous	6.7%
C282Y heterozygous	4.3%
H63D heterozygous	8.5%
S65C	4.0%

*Depending on ethnicity

- Homozygous for C282Y mutation in the HFE gene
  - Two copies of HFE gene with C282Y mutation confirms diagnosis

Mr. Tanner Ferris' Diagnosis

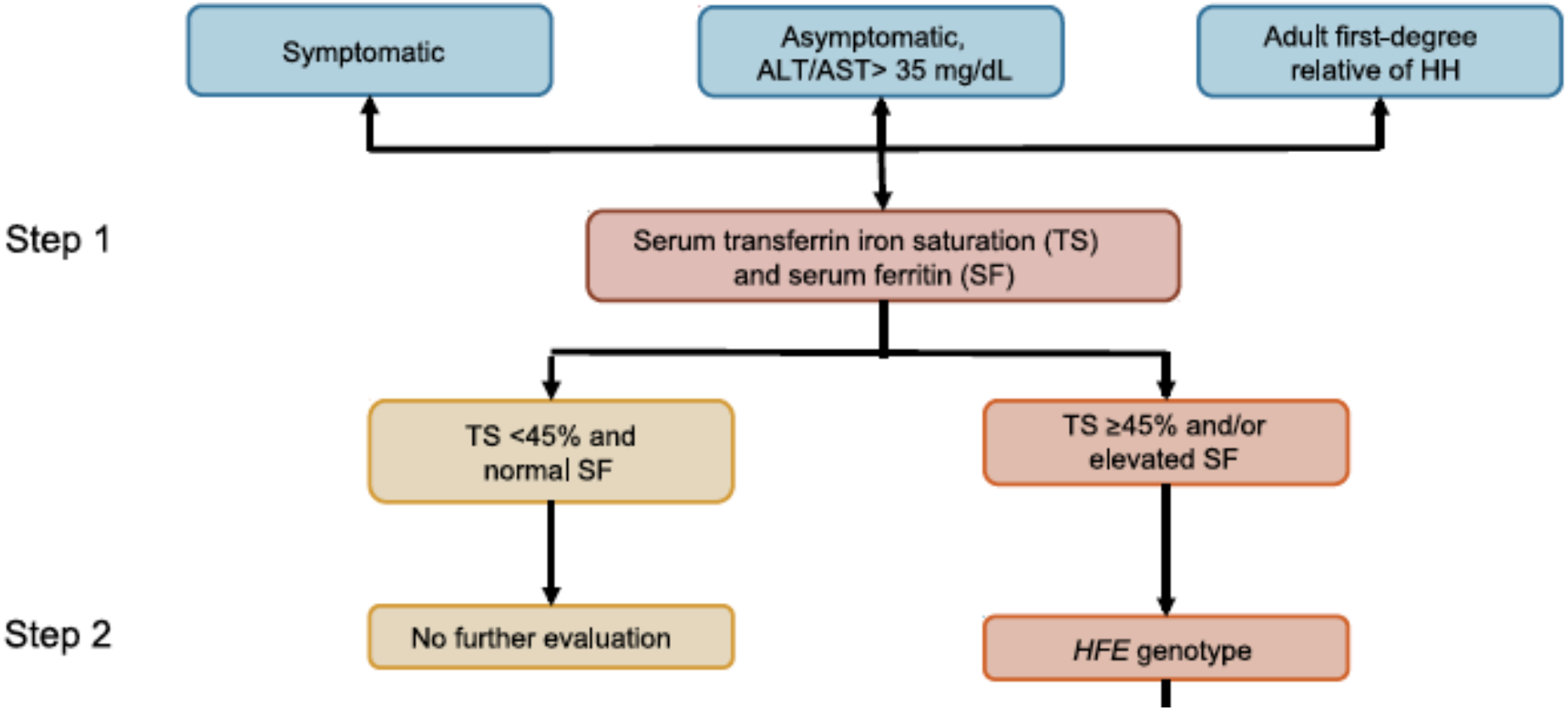
- Hereditary hemochromatosis
  - Disorder which causes excess iron deposition.
  - Iron buildup can damage the liver, heart, pancreas, endocrine glands and joints.
  - The most common autosomal recessive disorder in whites (prevalence of 1 in 300-500 individuals).
  - Men affected 2-3x as often as women.
  - Presentation: Typically, men in 5th decade & women in 6th decade
  - Common initial presentation is an asymptomatic patient with mildly elevated liver enzymes who is subsequently found to have elevated serum ferritin and transferrin saturation.

Lab Findings in Patients with HH

Measurements	Normal Subjects	Patients with HH	
		Asymptomatic	Symptomatic
Blood			
Serum iron level (μg/dL)	60-80	150-280	180-300
TS (%)	20-50	45-100	80-100
Serum ferritin level (μg/L)			
Men	20-200	150-1000	500-6000
Women	15-150	120-1000	500-6000

Bacon BR et al., *Hepatology* 2011; 54(1): 328-343.

Algorithm for Treatment of HH (ACG 2019 and AASLD 2011)



Kowdley K et al., *Am J Gastroenterol* 2019;114:1202–1218; Bacon BR et al., *Hepatology* 2011; 54(1): 328-343.

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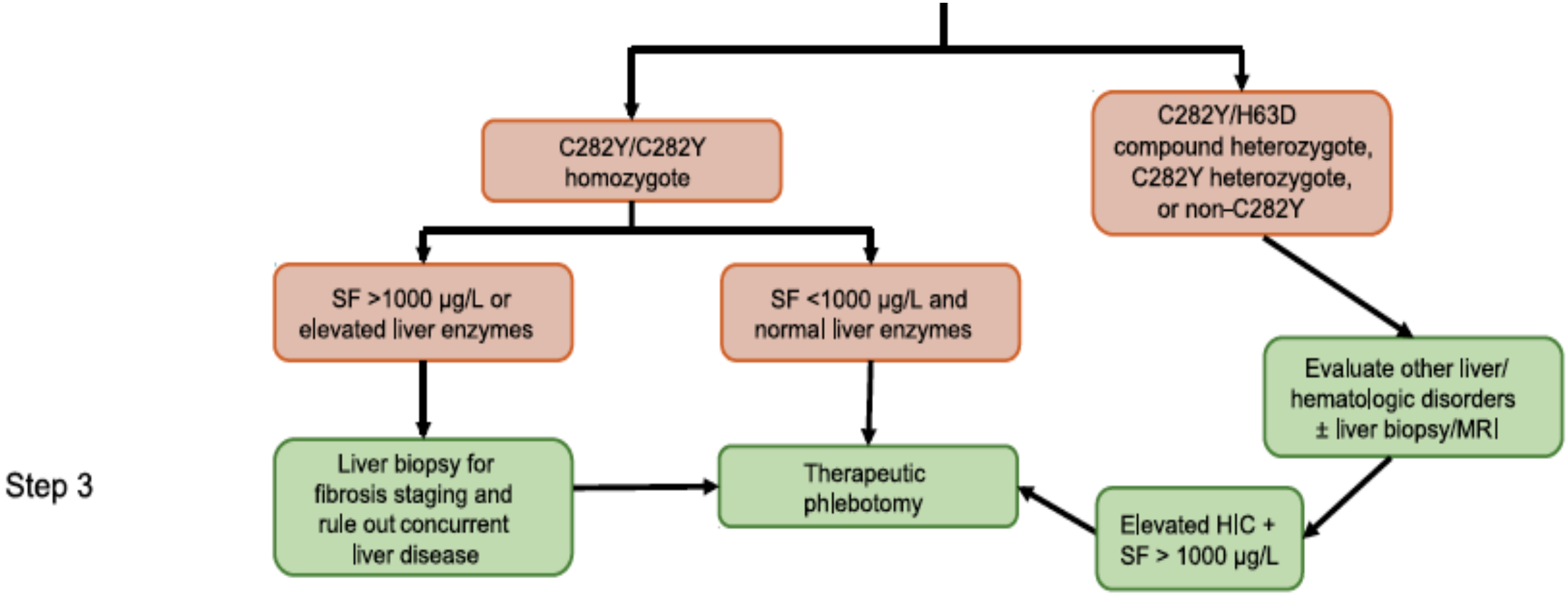


Kowdley K et al., *Am J Gastroenterol* 2019;114:1202–1218; Bacon BR et al., *Hepatology* 2011; 54(1): 328-343.

Mr. Tanner Ferris' Action Plan

- Next steps
  - First-degree relatives should undergo screening
  - Initiate phlebotomy on a regular schedule
    - Drawing off RBCs (major mobilizer of iron in the body) to minimize iron toxicity
    - Objective is to keep ferritin level <50 mcg/L
  - No signs of advanced liver disease so liver biopsy and transplant evaluation not warranted
  - Regular testing and follow up with liver specialist

Case 2

Case 2: Mr. Buddy Cleary

- A 61-year-old man is admitted to the ICU with hypotension, altered mental status, new onset jaundice and ascites.
- He is a heavy smoker.
- His lab evaluation reveals: Hgb 18 g/dL, Hct 53%, Platelets 340K, AST 1127 U/L, ALT 1546 U/L, ALP 674 U/L, Tbili 14.2 mg/dL, INR 3.2 and SCr 2.2 mg/dL.
- You order a hepatic ultrasound.

Mr. Buddy Cleary

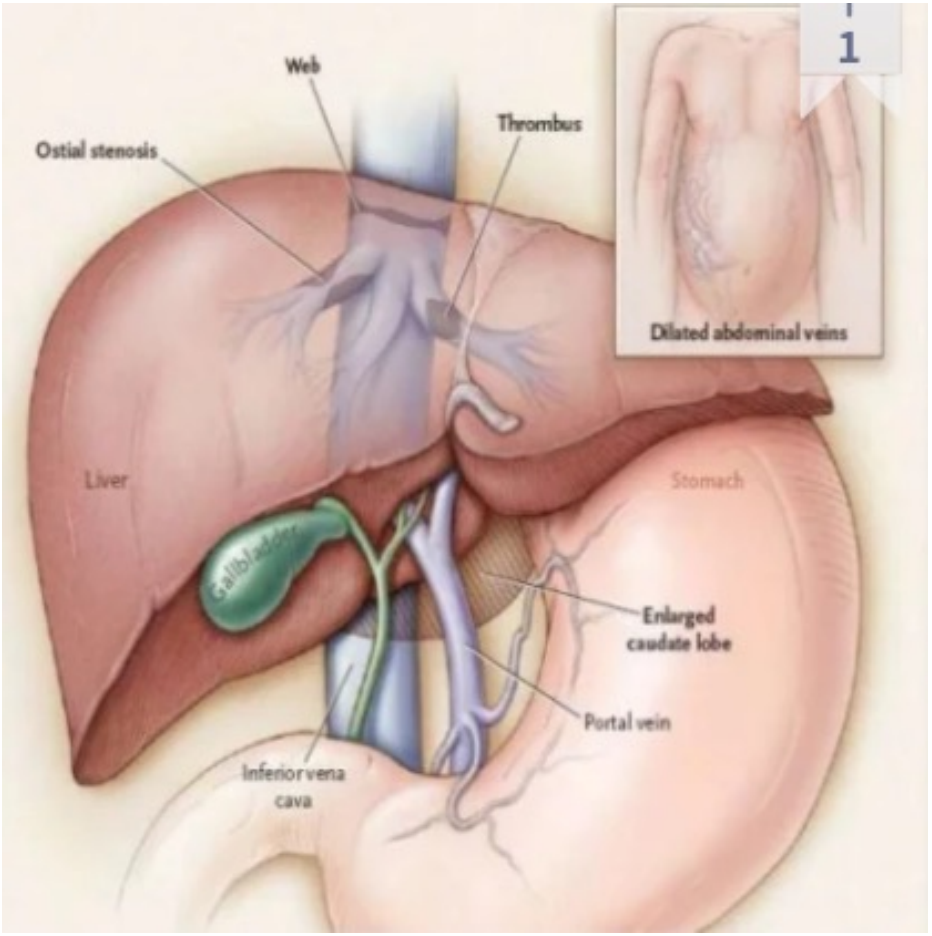
- Further blood work consistent with polycythemia vera (type of blood cancer known as myeloproliferative neoplasm)
  - Usually not fatal by itself
  - Risk is due to complications of blood clotting
- Hepatic ultrasound with Doppler reveals an enlarged, very heterogeneous liver, large volume ascites and a patent portal vein.
- No flow can be documented in his hepatic veins.

Mr. Buddy Cleary

- What is the most likely cause of the ascites?
  - Heart failure
  - Nephrotic syndrome
  - Peritoneal tuberculosis
  - Budd-Chiari syndrome

Budd-Chiari Syndrome

- Affects ~1 in 1,000,000 adults.
- Results from hepatic vein obstruction.
- Most commonly due to a thrombotic occlusion secondary to a chronic myeloproliferative neoplasm (e.g., polycythemia vera), but may be caused by other conditions associated with hypercoagulable states.



Diagnosis and Management

Step	A. Diagnostic Method	B. Therapy
1	Doppler-ultrasound	Anticoagulation
2	Magnetic resonance imaging	Angioplasty & Stenting*
3	Venography & transvenous biopsy	TIPS* or surgical shunt
4	Liver explant	Liver transplantation

* Concurrent thrombolysis to be considered

Janssen H et al., *Journal of Hepatology* 2003; 38(3): 364-371.

Mr. Buddy Cleary's Long-Term Prognosis

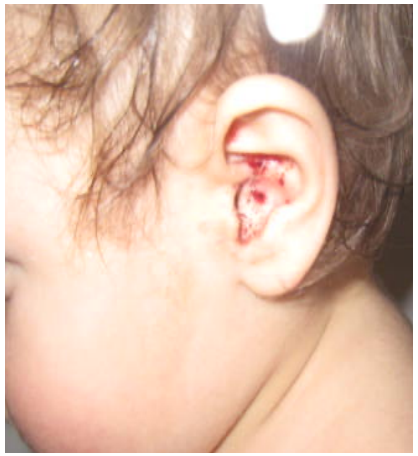
- Difficult to calculate due to small number of cases reported.
- Overall 5-year survival rates ~80% are reported.
- Serum albumin, bilirubin, prothrombin, ascites and encephalopathy or a combination of them have been found to be independent prognostic factors.

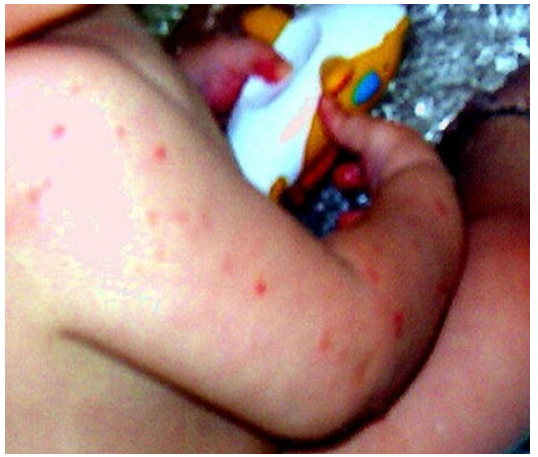
Deleve LD et al., AASLD Practice Guideline "Vascular Disorders of the Liver", *Hepatology*, May 2009

Case 3

Case 3: Albert A. Gill

- 13-month-old male
- Initial presentation
  - Neonatal jaundice (>3 weeks at initial presentation)
  - Pruritus from ~7 months of age
  - Failure to thrive, cholestasis
- Referred to liver specialist
- Medical history: No relevant medical conditions
- Physical exam
  - Cardiac murmur
  - Severe skin excoriations
  - Facial features distinct for a wide forehead and point chin
- You order additional labs





Images sourced from Mirum Pharmaceuticals.

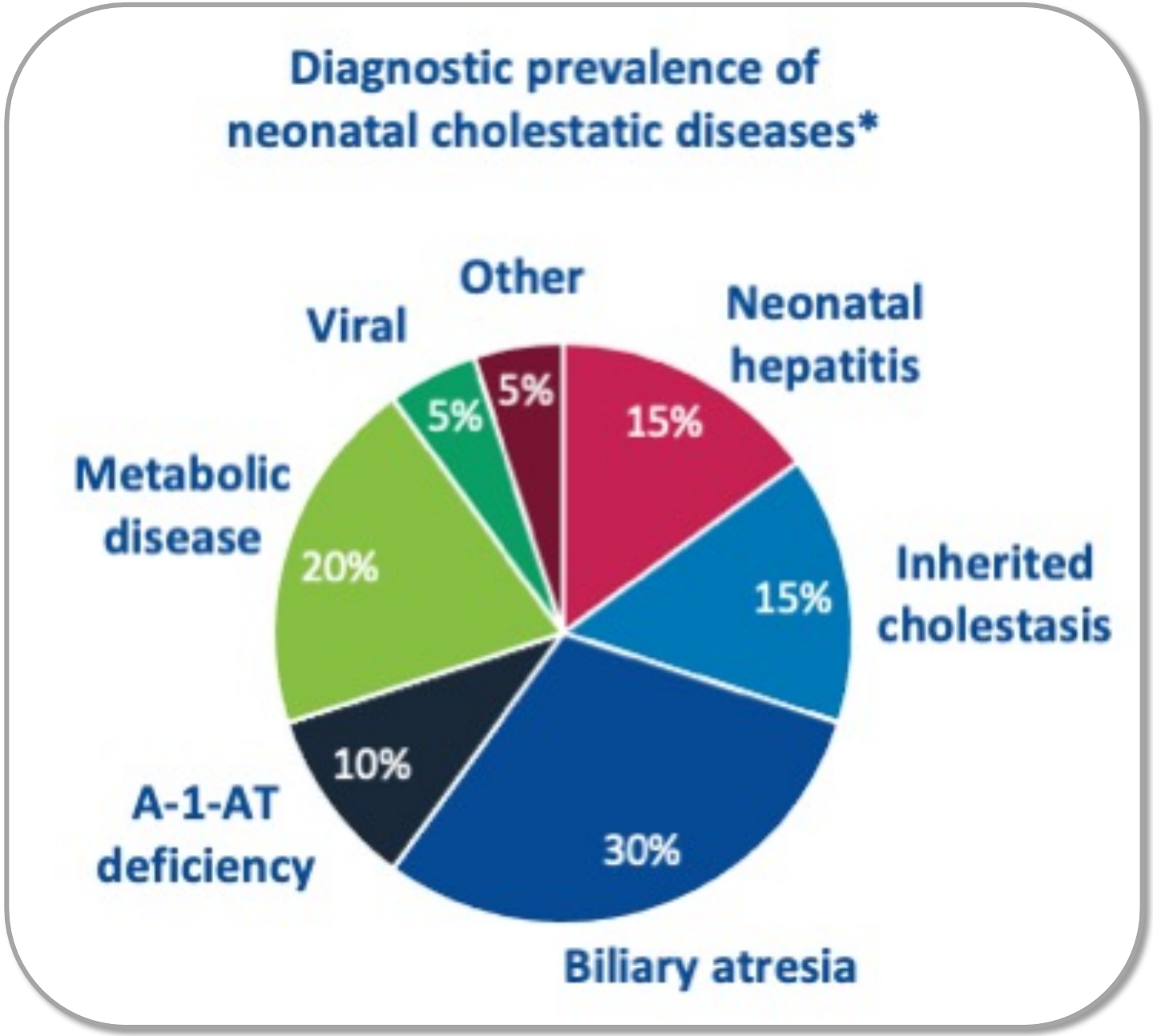


Figure adapted from Suchy FJ. *Pediatr Rev* 2004; **25**:388–396.

Albert A. Gill's Lab Results

- ALT: 225 U/L
- GGT: 100 U/L
- Tbili: 2.7 mg/dL
- Dbili: 1.9 mg/dL
- sBAs: 187 umol/L
- Vitamin D: <5 ng/mL
- Other labs WNL

- Cholestatic Pattern
- Diagnosis?
  - A1-AT deficiency
  - Alagille syndrome (ALGS)
  - Biliary atresia
  - Progressive familial intrahepatic cholestasis (PFIC)

ALGS, PFIC, and Biliary Atresia Present With Many of the Same Symptoms

Symptoms and signs	ALGS[1]	PFIC[2]	Biliary atresia[3,4]
Pruritus	✓	✓	
Jaundice	✓	✓	✓
Failure to thrive	✓	✓	✓
Pale stools, dark urine	✓	✓	✓
Hepatomegaly	✓	✓	✓
Vitamin A, D, E, K deficiency	✓	✓	✓
Primary bone abnormalities	✓		
Distinct facial features	✓		
Primary cardiac abnormalities	✓		✓

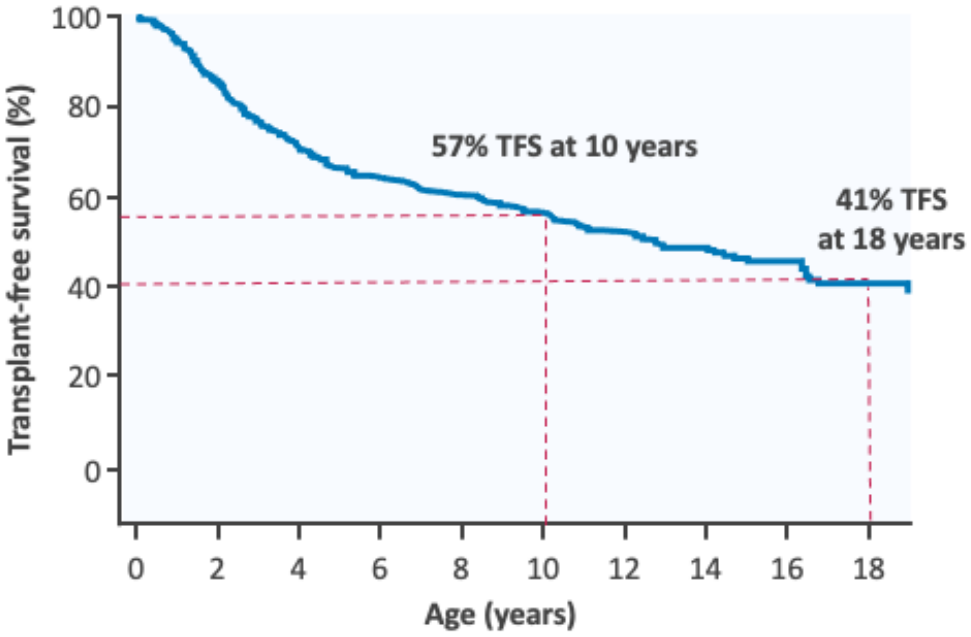
1. NORD. Alagille syndrome. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/ 2. Children's liver disease foundation. PFIC. Available at: https://childliverdisease.org/liver-information/childhood-liver-conditions/progressive-familial-intrahepatic-cholestasis. 3. NORD. Biliary atresia. Available at: https://rarediseases.org/rare-diseases/extrahepatic-biliary-atresia/. 4. Feldman AG & Mack CL. *J Pediatr Gastroenterol Nutr* 2015; **61**:167–175.

Alagille Syndrome

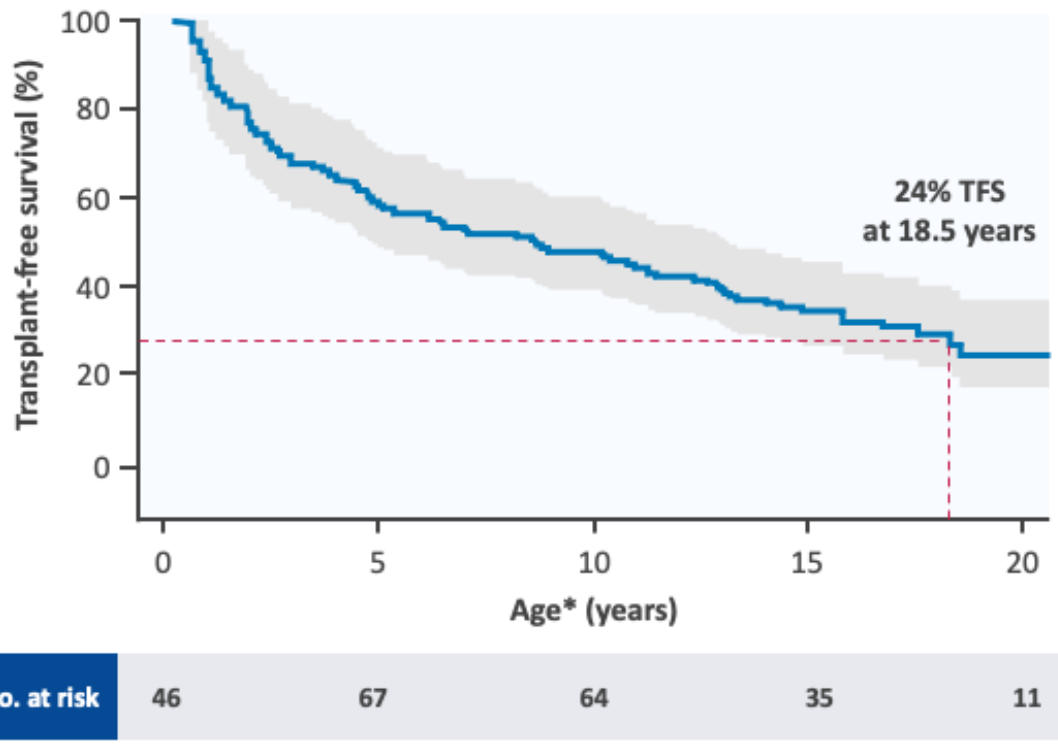
- Causes
  - Autosomal dominant (only 1 mutated copy necessary)
  - Caused by mutations in JAG1 gene (>88% of cases) or NOTCH2 gene
    - Can be inherited from either parent or new mutation
- Affects males and females equally
- Symptoms and severity can vary greatly
- Incidence ~1 in 30,000
- Can affect multiple organ systems including liver, heart, skeleton, eyes and kidneys
  - Affected person has fewer than the normal number of small bile ducts leading to cholestasis
  - Liver symptoms usually appear early and diagnosis typically before age 1
- Genetic testing available
- Treatment is directed towards symptoms and typically requires multiple specialists

Substantial Risk for Liver Transplant in Patients With ALGS

GALA[1] (Global)
Transplant-free survival in patients with ALGS presenting with neonatal cholestasis (N = 911)

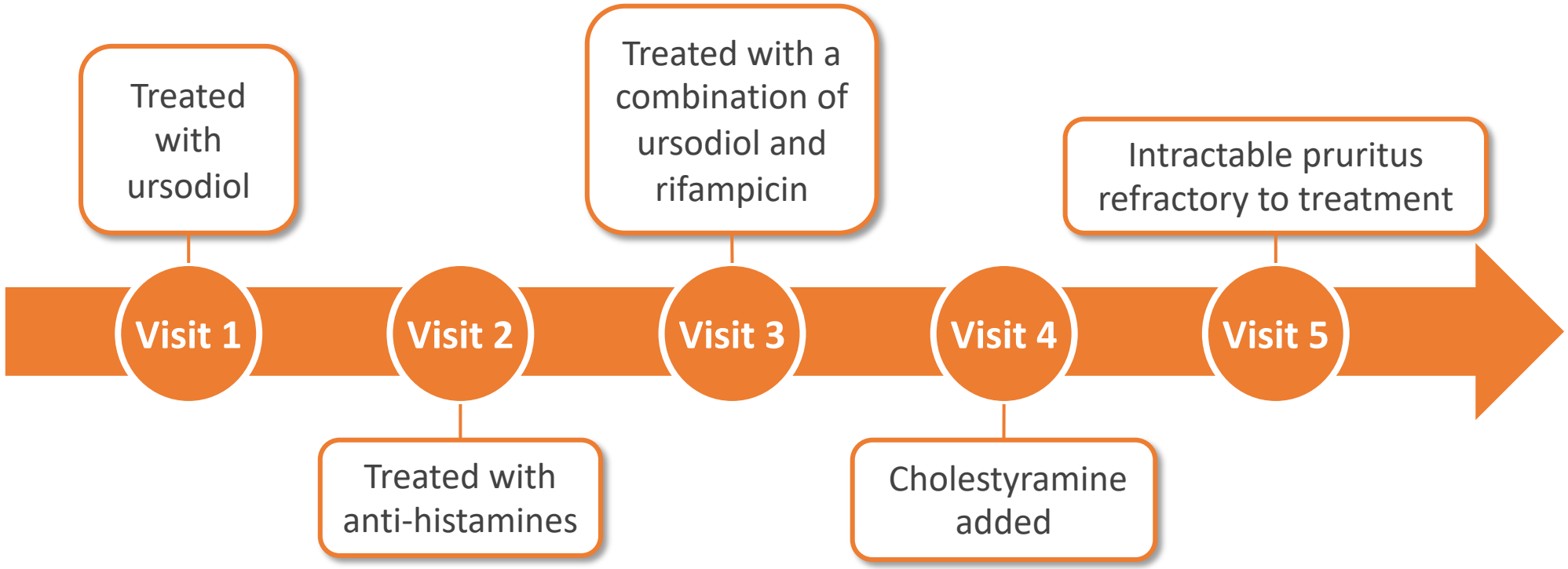


ChiLDReN (North America network)[2]
Transplant-free survival in patients with ALGS



* Left truncated at baseline age.
TFS, transplant-free survival.
1. Vandriel SM, *et al.* EASL 2020 (oral presentation); 2. Kamath BM, *et al. Hepatol Comms* 2020; **4**:387–398.

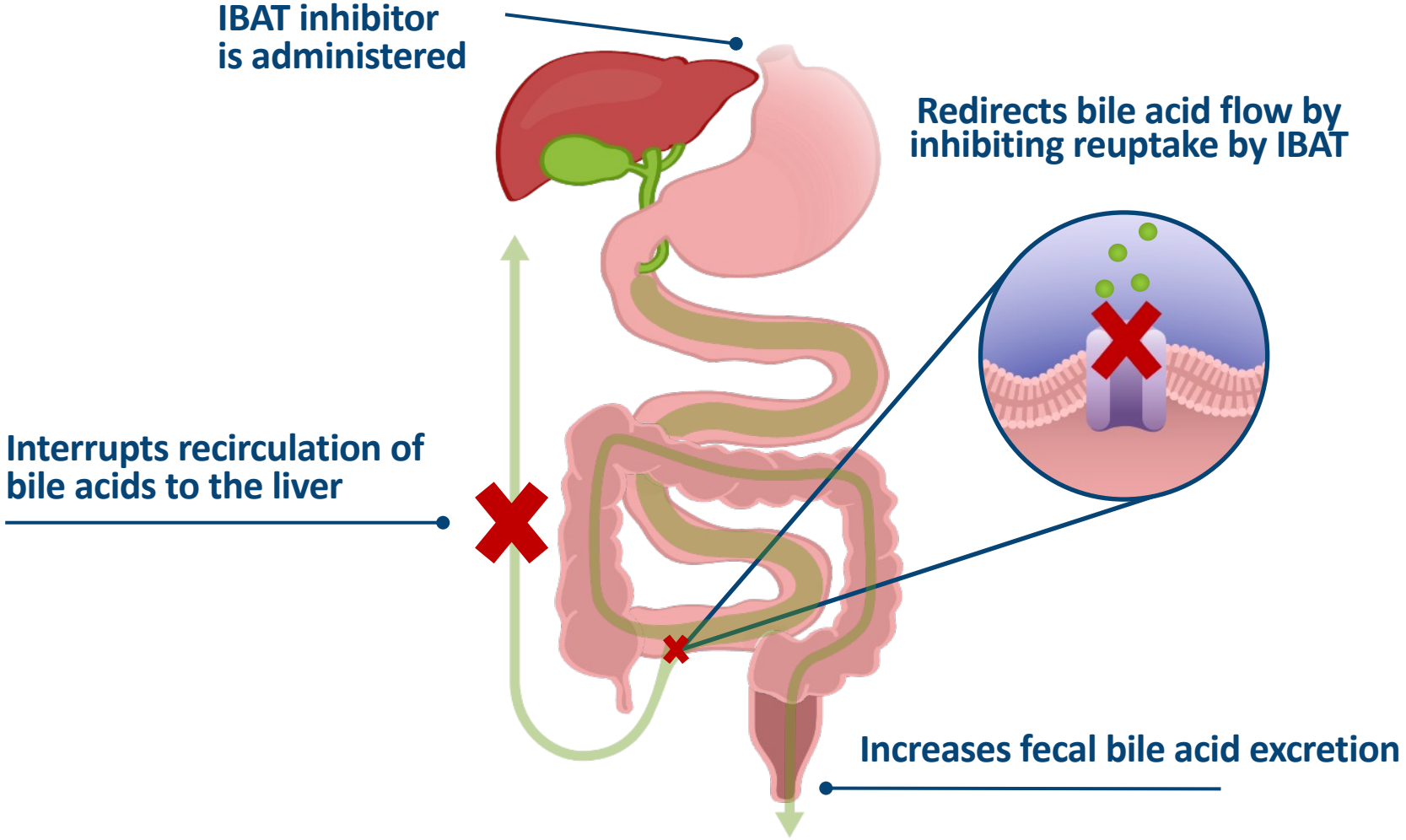
Albert A. Gill Continued



Treatment

- Repeat visits to control intractable pruritus
- Pruritus remains refractory; patient is put on the liver transplant waiting list and new agent, maralixibat (IBAT inhibitor), started

IBAT inhibitors: Pharmacologic Inhibition of Bile Acid Recirculation



Clinical effects of IBATi in cholestasis:

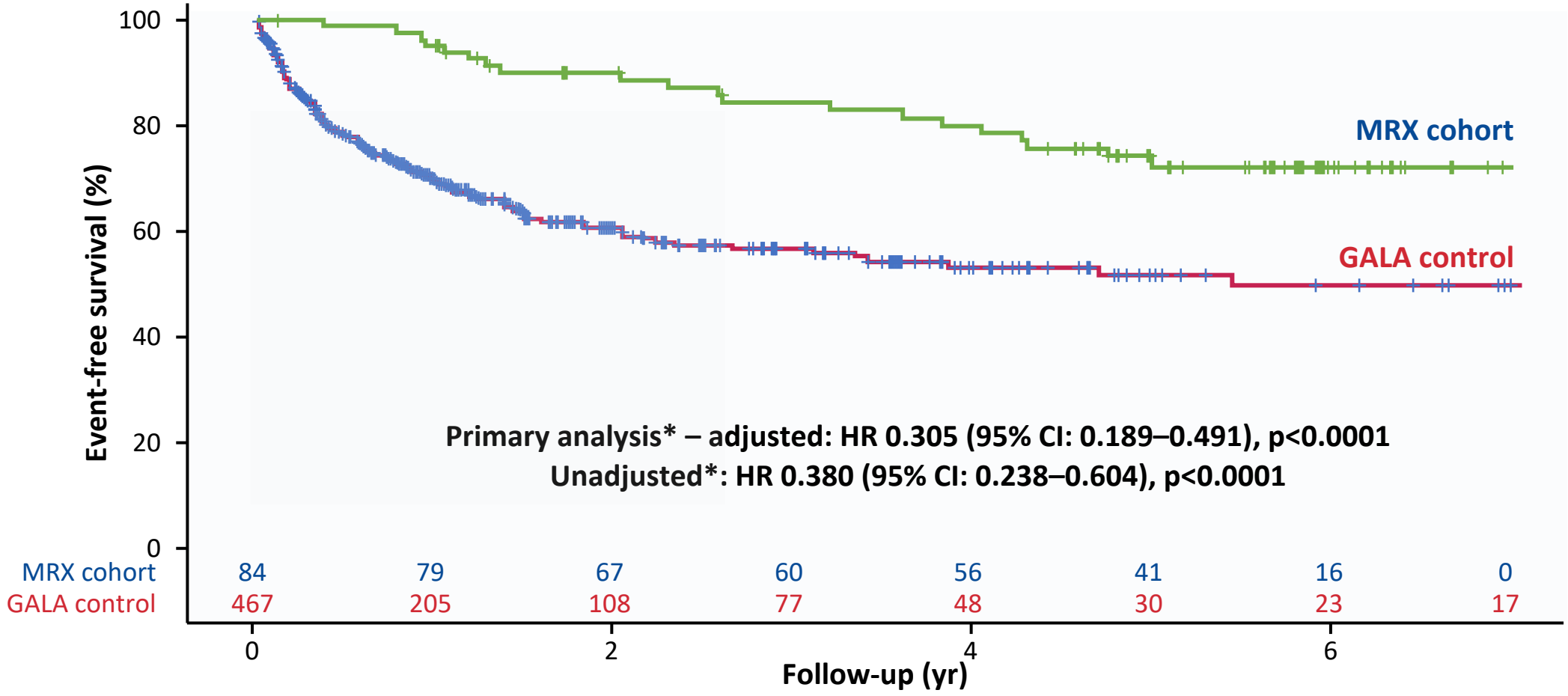
- ✓ Improvements in pruritus (itch)
- ✓ Reductions in sBA
- ✓ Improved transplant-free survival

IBAT(i), ileal bile acid transporter (inhibitor); sBA, serum bile acid.

Gonzales E, *et al. Lancet* 2021; **398**:1581–1592; Tiessen RG *et al. BMC Gastroenterology* 2018; **18**:3. Figure adapted from: Slijepcevic D & van de Graaf SFJ. *Dig Dis* 2017;35:251–258.

Maralixibat (MRX) Shows Significant Improvement in EFS

EFS: Biliary diversion surgery, decompensation event, liver transplantation, or death



* Cox regression models: Primary: Cox regression - effect of MRX vs GALA log likelihood test adjusted for age, sex, bilirubin, and ALT (according to the SAP).

ALT, alanine transaminase; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat; SAP, statistical analysis plan.

Hansen BE & Kamath BM. Oral presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.

Albert A. Gill Follow up

- Maralixibat (Livmarli) led to relief of pruritus
- Patient regularly followed by pediatric hepatologist & pediatric cardiologist