UT Southwestern Medical Center

Challenging Case Presentations

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Case 1: A 56-Year-Old Female with Elevated Transaminases

Presentation (2011)

- Patient referred to hepatology clinic from primary care physician for evaluation of elevated transaminases x 5 years
  - Patient described that her transaminases remained elevated despite losing weight
  - She also noted that her transaminases had risen further when she had taken a statin
    - Statin was discontinued by PCP
- Medications: Loratadine, Aspirin, Ergocalciferol, Fish Oil, Iron-vitamin C, Linagliptin/Metformin, Lisinopril, Omeprazole, Vitamin E

Exam
- BMI: 28

Past Medical History
- Diabetes
- Dyslipidemia
- GERD
- Vitamin D deficiency
- Goiter (non-toxic)
- Scalp psoriasis

Previous Study Results
- EUS-guided liver biopsy (fragmented): **stage 1 fibrosis (fragmented sample)**
- Abdominal ultrasound: **hepatomegaly**
- MRI: **splenorenal shunt**

Evaluation

Work-Up

Labs:		**Normal***
AST, IU/L	**99**	8-43
ALT, IU/L	**204**	<33
LDL-c, mg/dL	**196**	<100
HDL-c, mg/dL	**39**	≥50
TC, mg/dL	**277**	<200
TG, mg/dL	**208**	<150
Platelets, 10^9 /L	**137**	150-450

- Normal albumin, total bilirubin, and INR

Next Steps?

- Leading Diagnosis?
- Clinical Clues?
- Repeat Liver Biopsy?

Repeat liver biopsy performed (2016)

Stage 3-4 fibrosis (probably cirrhosis) with mixed steatosis

When is fatty liver more than NASH?

- Fatty liver, elevated ALT, and dyslipidemia that is out of proportion with the remainder of the metabolic risk profile.
  - Low HDL-C, **High LDL-C**, High TGs
  - *Failure to improve with lifestyle, statins, or fibrates*
- Splenomegaly in the absence of clinical evidence of advanced liver disease or portal hypertension (lipid storage).
- *Microvesicular steatosis*

Think of LAL-D

(Wolman disease; cholesteryl ester storage disease)

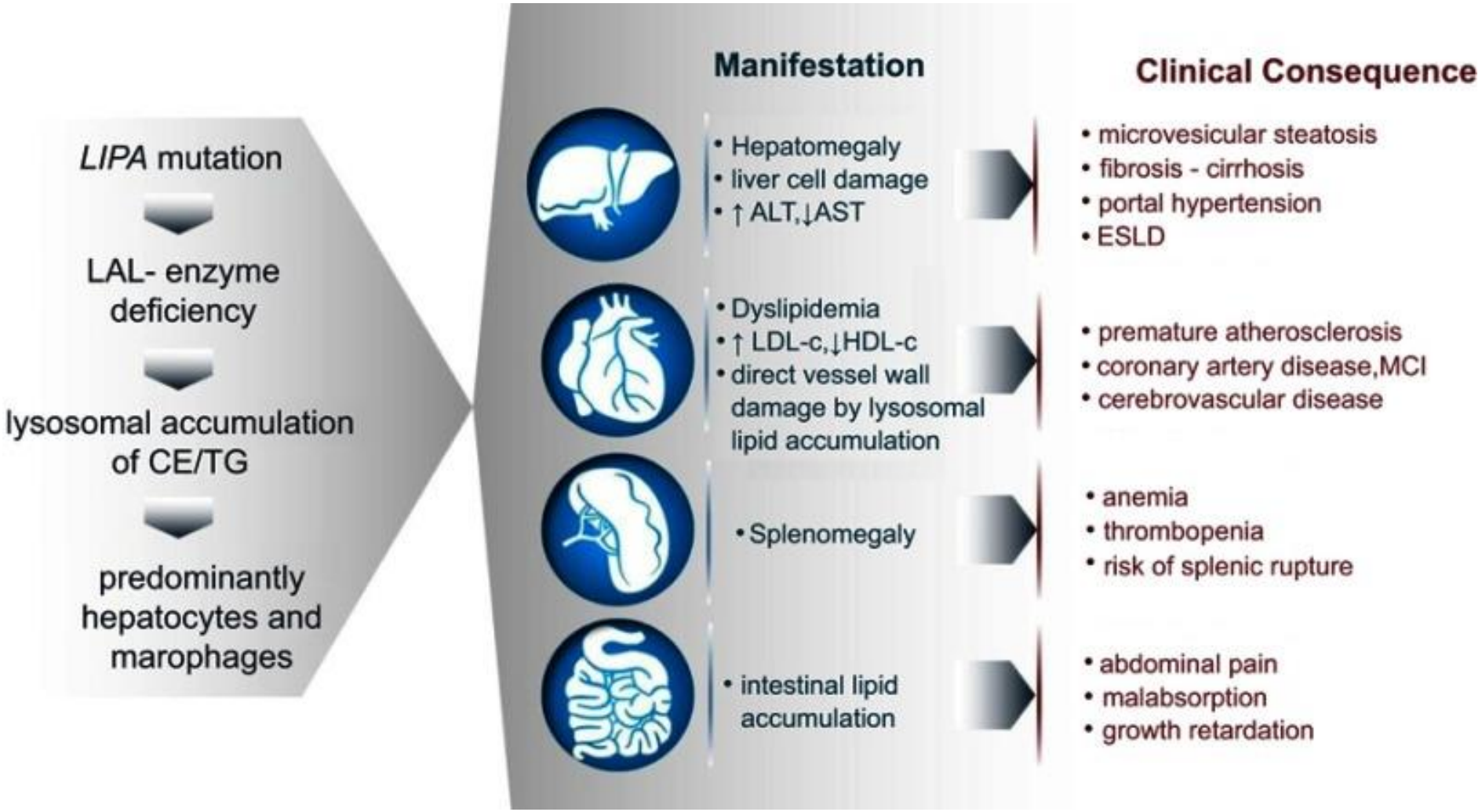
Lysosomal acid lipase deficiency (LAL-D) is an ultra-rare lysosomal storage disease that may present from infancy to late adulthood depending on residual enzyme activity.

Evaluation

- Based on the results of the liver biopsy, Dried Blood Spot (DBS) testing for LAL activity was performed
  - **AFFECTED** (Activity: 0.006 nmol/punch/hr)
- Genetic Testing (*LIPA* Sequencing) provided more clinical information
  - Homozygous c.920C>A (p.A307D) in Exon 9
    - Mutation previously seen in a patient with LAL-D

Diagnosed in 2016

Clinical Manifestations of LAL-D



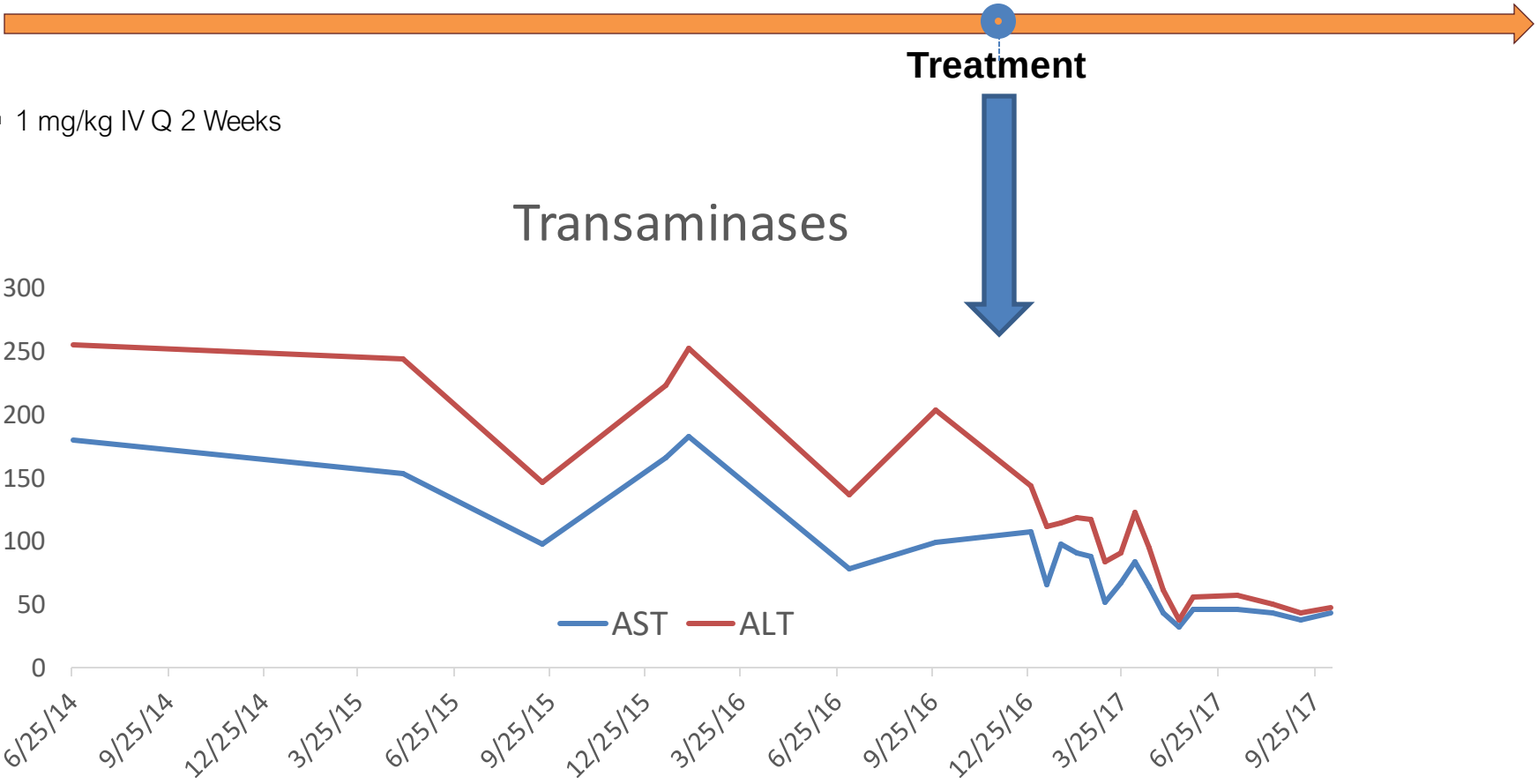
Strebinger et al Hepat Med 2019

Evaluation

Coronary CT Angiography:

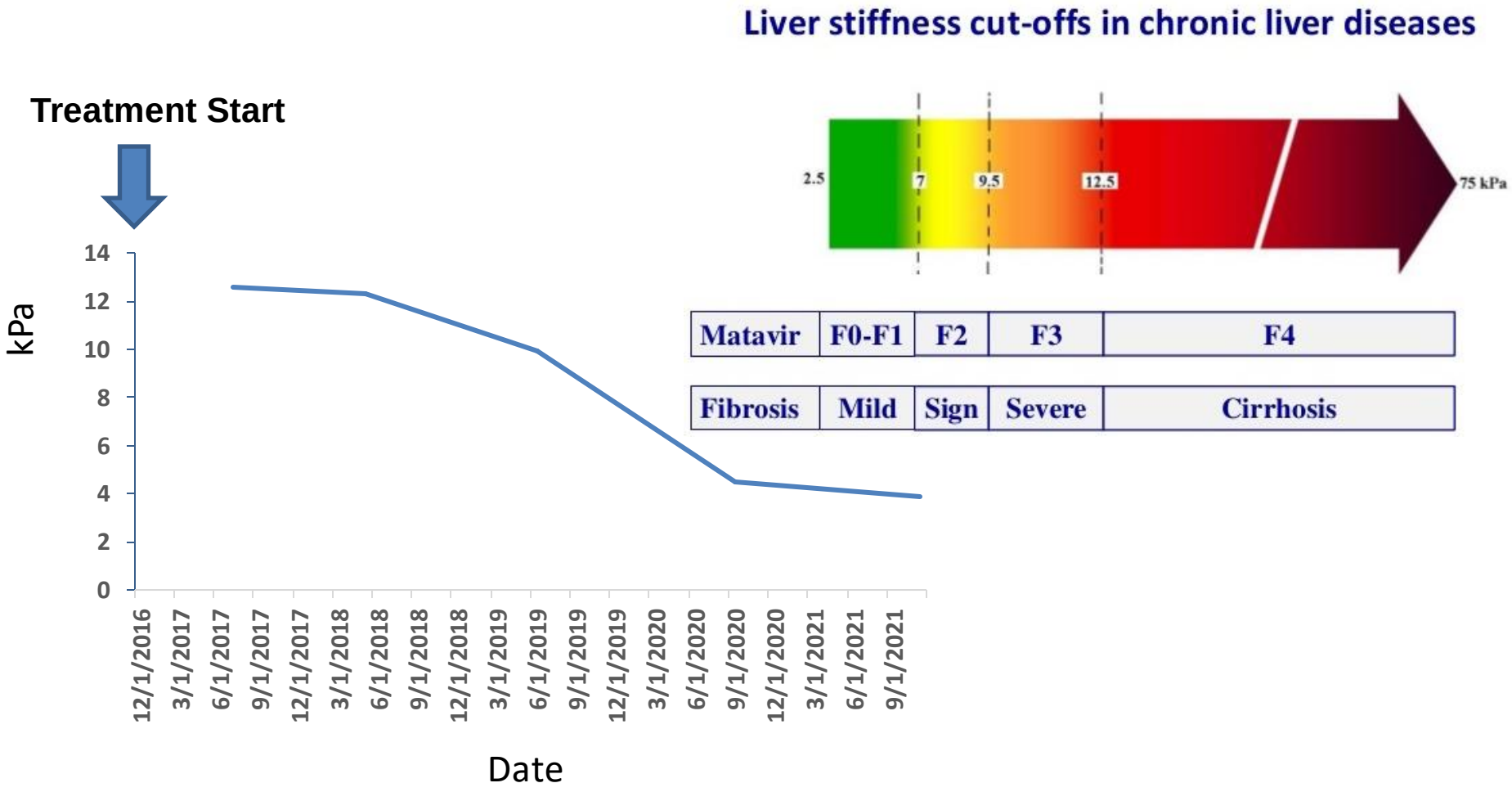
1. Coronary arteries: Nonobstructive calcified plaques in left main and proximal LAD, less than 25% luminal narrowing with remodelling.
2. Calcium score (Agatston): 99. The Agatston score is approximately 93rd percentile for age and gender. (MESA McClelland et al. Circulation. 2006)

Treatment: Sebelipase alfa enzyme replacement



- 1 mg/kg IV Q 2 Weeks

Treatment



- 1 mg/kg IV Q 2 Weeks

L. Castera, X. Forns, A. Alberti **Non-invasive evaluation of liver fibrosis using transient elastography** J Hepatol, 48 (2008), pp. 835-847

Case 2: 54 yo female with elevated ferritin

- Patient referred to hepatology clinic from primary care physician for evaluation of elevated ferritin
  - No symptoms
  - Denies history of blood transfusions
- Labs
  - Ferritin 3000, Fe 23
  - Hemoglobin 11, Hct 34, plts 250k
  - AST 45, ALT 32, AP 170, TB 0.5, alb 4.0, INR 0.8
  - Viral hepatitis panel negative, ANA 1:40

Exam
- Mild RUQ tenderness

Past Medical History
- Pregnancies x 2
- Menopause age 52

No Family History

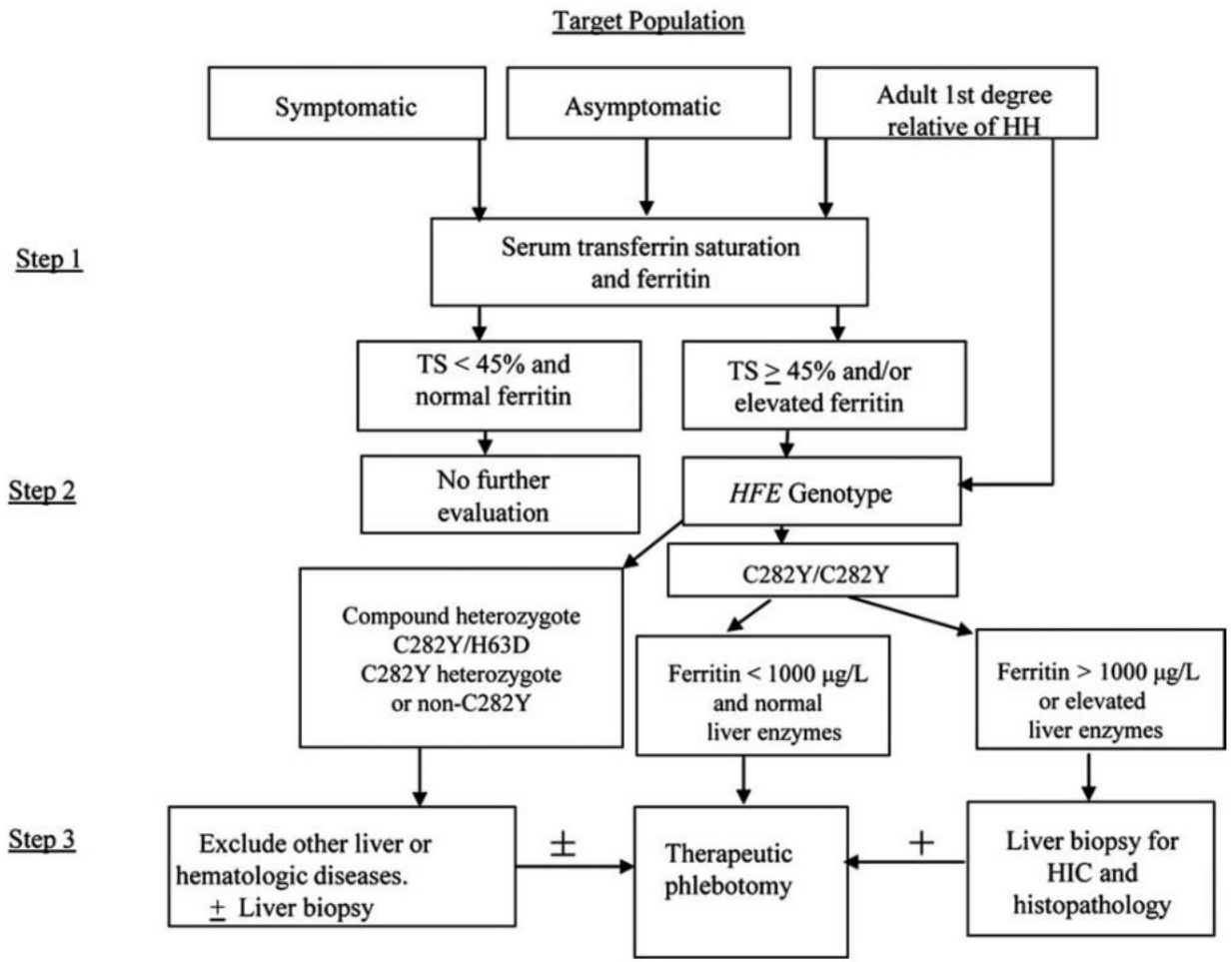
How do you approach this patient?

What additional information would you like to know?

Evaluation

- TSAT 54%
- HFE testing negative for C282Y, H63D, S65C
- What do you recommend?

AASLD Hemochromatosis Guidelines



Bacon et al Hepatology 2011

Is MRI becoming the new gold standard?

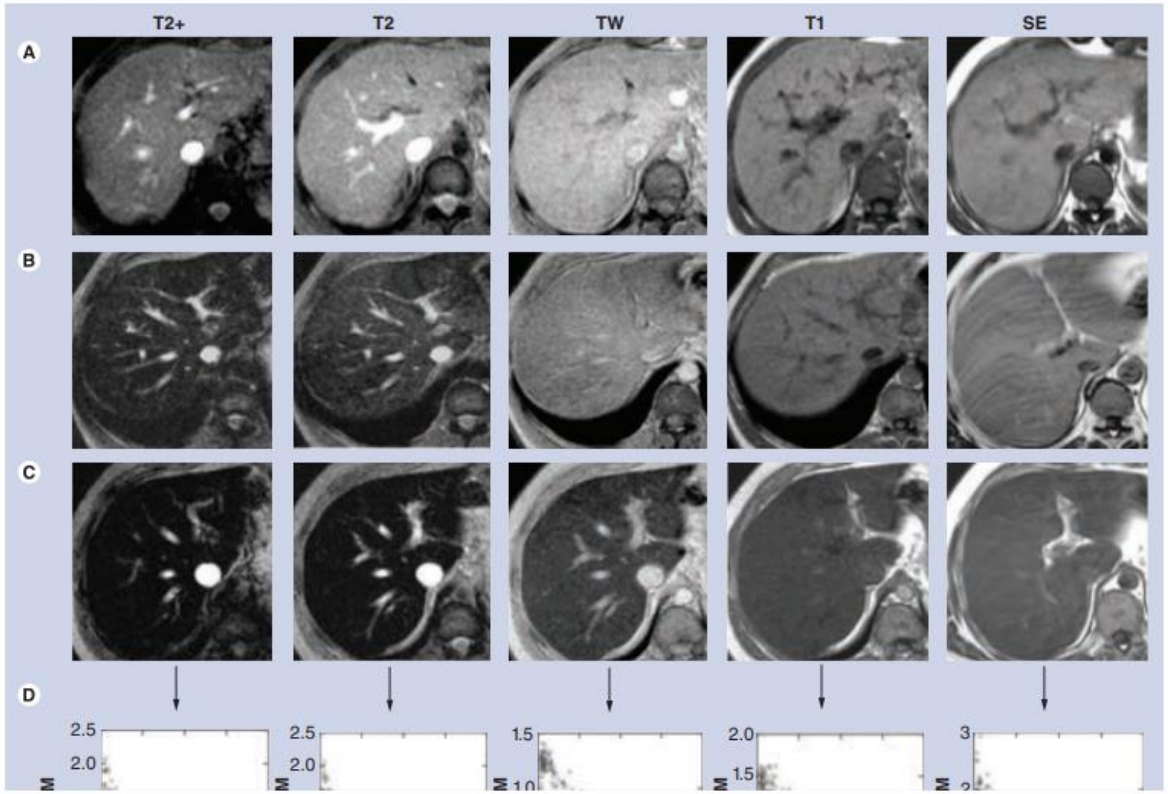
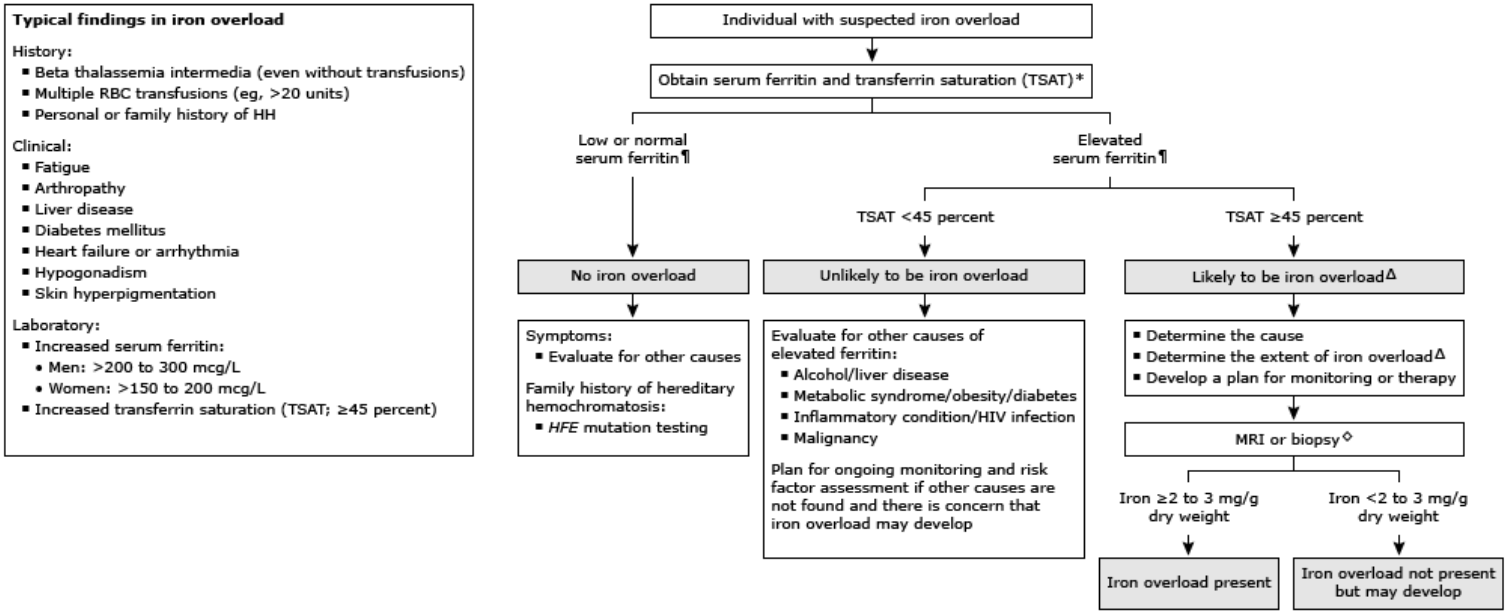


Figure 2. Calculation of R2* values by three different magnetic resonance methods for LIC determination. Correlation with liver biopsy values. LIC: Liver iron concentration.

- Excellent correlation to histology
- Can perform combined cardiac and liver MRI
- Provide liver iron content to guide treatment
- LIC > 3 mg Fe/g iron overload

Castiella et al Imaging Med 2013

Algorithm for evaluating suspected iron overload



This is a general approach and should not substitute for the judgment of the treating clinician. It presumes the patient has already had a history, examination, and complete blood count (CBC). Refer to UpToDate for details of the evaluation. Other diagnostic approaches such as determining the response to a course of therapeutic phlebotomy may be appropriate in some settings.

RBC: red blood cell; TSAT: transferrin saturation (serum iron ÷ TIBC × 100); HH: hereditary hemochromatosis; HIV: human immunodeficiency virus; MRI: magnetic resonance imaging; TIBC: total iron-binding capacity.

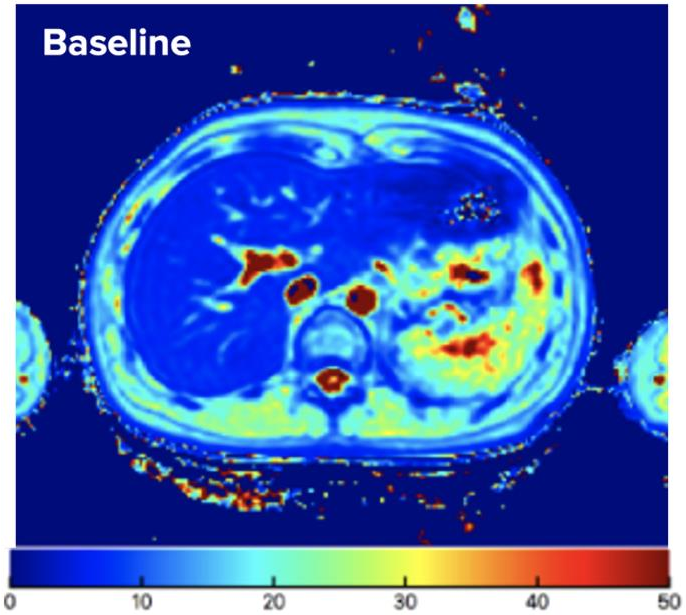
* Ideally two measurements are performed when the patient is not acutely ill, especially if results are borderline.

¶ The threshold for ferritin and TSAT above which to pursue additional testing depends on the patient's age, family history, medical history, and number of transfusions received.

Δ Findings of a very high ferritin and TSAT may be sufficient to diagnose iron overload in some individuals (eg, known *HFE* mutation, multiple transfusions). However, quantitation of iron stores remains useful for decisions about when to start and stop therapy and the urgency of intervening.

◇ MRI is increasingly accepted as the best test. However, liver biopsy may be preferable in some settings (eg, increased hepatic enzymes). Liver MRI may be done in combination with cardiac MRI in some institutions. Cardiac MRI is important in many cases, especially those associated with ineffective erythropoiesis and transfusional iron overload, because hepatic and cardiac iron deposition may not be uniform.

MRI LiverMultiScan



Pre Venesection
Iron: 4.17 mg Fe/g dw tissue
cT1: 843ms
PDFF :3%

LiverMultiScan:

cT1: 843 ms (indicative of fibrosis)
PDFF: 3% (within reference range)
Liver Iron Content: 4.17 mg/g (iron overload)

- Liver biopsy –Phagocytic Kupffer cell infiltration, expanded portal area, fibrous tissue proliferation, and a few of inflammatory cell infiltration. Iron staining was positive + 4 and copper staining was negative.
- Quantitative iron – 4.17 mg/g

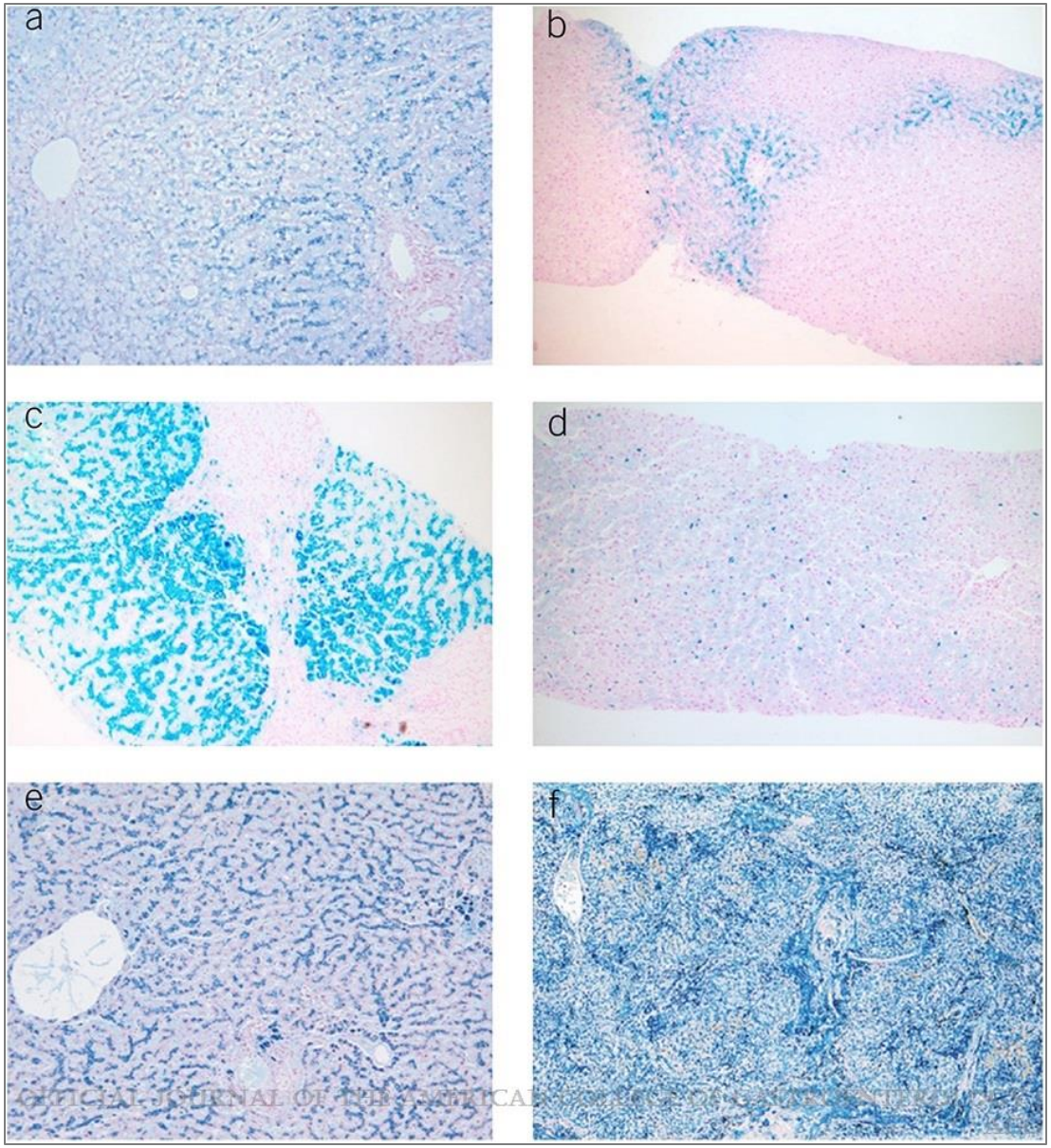
ACG suggests "a non–contrast-enhanced MRI in conjunction with software used for the estimation of HIC (i.e., MRI T2) be used to noninvasively measure liver iron concentration in the non-C282Y homozygote with suspected iron overload. If there is a concomitant need to stage hepatic fibrosis or evaluate for alternate liver diseases, then liver biopsy is the preferred method (conditional recommendation, low quality of evidence)."*

Kowdley et al ACG 2019

Kowdley, Kris V.; Brown, Kyle E.; Ahn, Joseph; Sundaram, Vinay

Official journal of the American College of Gastroenterology | ACG114(8):1202-1218, August 2019.

doi: 10.14309/ajg.0000000000000315



Pathologic findings in iron overload disorders. (a) HFE hemochromatosis (type 1): parenchymal iron overload with porto-central gradient; (b) Tfr2 hemochromatosis: parenchymal, periportal iron overload; (c) juvenile hemochromatosis: panlobular iron overload; (d) ferroportin disease: predominant Kupffer cell iron overload; (e) African siderosis: parenchymal cell iron overload; (f) thalassemia major: massive iron overload in the hepatocytes and Kupffer cells.

Types of Hereditary Hemochromatosis

Table 2. Categories of HH

Classification	Genes involved and location	Inheritance	Protein function	Clinical manifestations
Type 1A HH (homozygote)	*HFE* on 6p21.3 Mutations in *HFE*: 1. C282Y	AR	Involved in hepcidin synthesis via BMP6, interaction with TFR1.	Arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadism.
Type 1B HH (compound heterozygote)	*HFE* on 6p21.3 Mutations in *HFE*: 1. C282Y 2. H63D	AR	Involved in hepcidin synthesis via BMP6, interaction with TFR1.	Arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadism.
Type 1C HH				serum iron/ tissue iron
Type 2A juvenile H				rs old, rdiomyopathy
Type 2B juvenile H				rs old, rdiomyopathy
Type 3 HH	*TFR2* (transferrin receptor 2) on 7q22	AR	Involved in hepcidin synthesis, interaction with transferrin.	Arthropathy, skin pigmentation, liver damage, diabetes mellitus, endocrine dysfunction, cardiomyopathy, hypogonadism.
Type 4A HH (FPN disease)	*SLC40A1* (FPN) on 2q32 Loss of function for FPN excretion	AD	Duodenal iron export.	Iron deposition in the spleen is very common, lower tolerance to phlebotomies and may have anemia.
Type 4B HH (nonclassical FPN disease)	*SLC40A1* (FPN) on 2q32 Gain of function, FPN cannot be internalized after hepcidin binding	AD	Resistance to hepcidin.	Fatigue, joint pain.

AD, automosomal dominant; AR, autosomal recessive; FPN, ferroportin; *HAMP*, *hepatic antimicrobial protein*; HH, hereditary hemochromatosis.

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY | ACG

We suggest against further genetic testing among patients with iron overload testing negative for the C282Y and H63D alleles. (conditional recommendation, very low quality of evidence). ACG Clinical Practice Guidance 2019.

Kowdley et al ACG 2019

Secondary Iron Overload

Table 3. Causes of secondary iron overload

Iron-loading anemias
Thalassemia major
Hemoglobin H
Chronic hemolytic anemia
Sickle cell anemia
Aplastic anemia
Pyruvate kinase deficiency
Hereditary spherocytosis
Parenteral iron overload
RBC transfusions
Iron-dextran injections
Long-term hemodialysis
Chronic liver disease
Porphyria cutanea tarda
Hepatitis C
Hepatitis B
Alcoholic liver disease
NAFLD
Dysmetabolic iron overload syndrome
Miscellaneous
Malignancy (HCC, breast cancer, hematologic malignancies)
Chronic inflammatory states (systemic lupus erythematosus, rheumatoid arthritis)

HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; RBC, red blood cell.

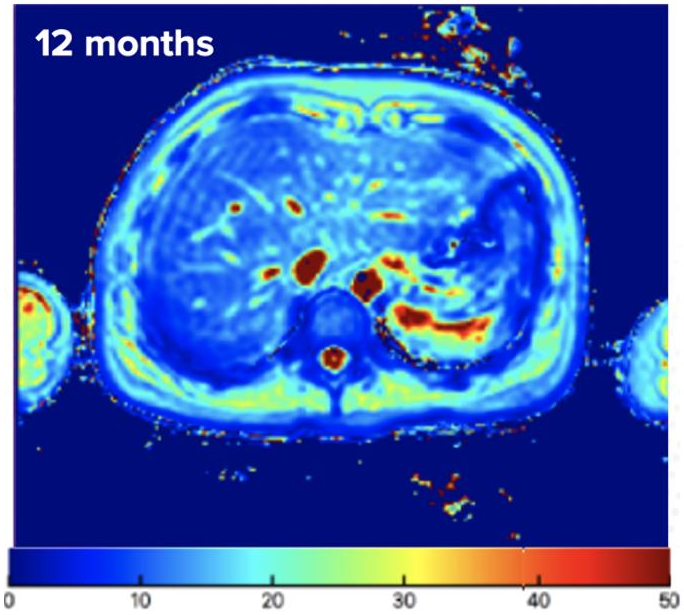
 Kowdley et al ACG 2019

Treatment?

- Indications:
  - –ferritin > 1000 ng/mL, end organ damage, elevated transaminases
  - –LIC> 5-7 mg Fe/g
- Phlebotomy
  - –500 mL weekly for goal ferritin 50-100 ng/mL keeping Hgb > 10
- Chelation
- Clinical Response?

- Patient begins phlebotomy sessions weekly
- 1 year later:
  - Ferritin 1800
  - TS- 32
  - MRI LiverMultiScan repeated in 1 year

cT1: 771 ms (within reference range)
PDFF: 3% (within reference range)
Liver Iron Content: 2.39 mg/g (mild iron overload)



Post Venesection
2.39 mg Fe/g dw tissue
cT1: 771ms
PDFF :3%

Case 3: 64 yo man with HCV cirrhosis

- Patient referred to hepatology clinic for newly diagnosed cirrhosis
  - Admitted with abdominal distension
  - Started on diuretics, spironolactone 100/furosemide 40 daily
- Labs
  - Hemoglobin 11.9, Hct 37, plts 74k
  - Na 134, K 4.1, BUN 15, Cr 0.67
  - AST 47, ALT 27, AP 78, TB 1.5, alb 2.6, INR 1.4
  - AFP 6.2
  - HCV G1a, VL 457,000

MELD Na 14, Child's B9

Exam
- Chronically ill appearing
- Temporal and proximal muscle wasting
- Right lung decreased breath sounds and dull ½ way
- Distended moderate ascites
- No jaundice

Past Medical/Social History
- IVDU in his 30's
- 20 pack year tobacco
- Rare alcohol
- Works as a roofer

No Family History

Recommendations

- Timing of Hepatitis C treatment?
  - –Which Regimen?
- How does transplant candidacy affect decision?
- Threshold MELD?

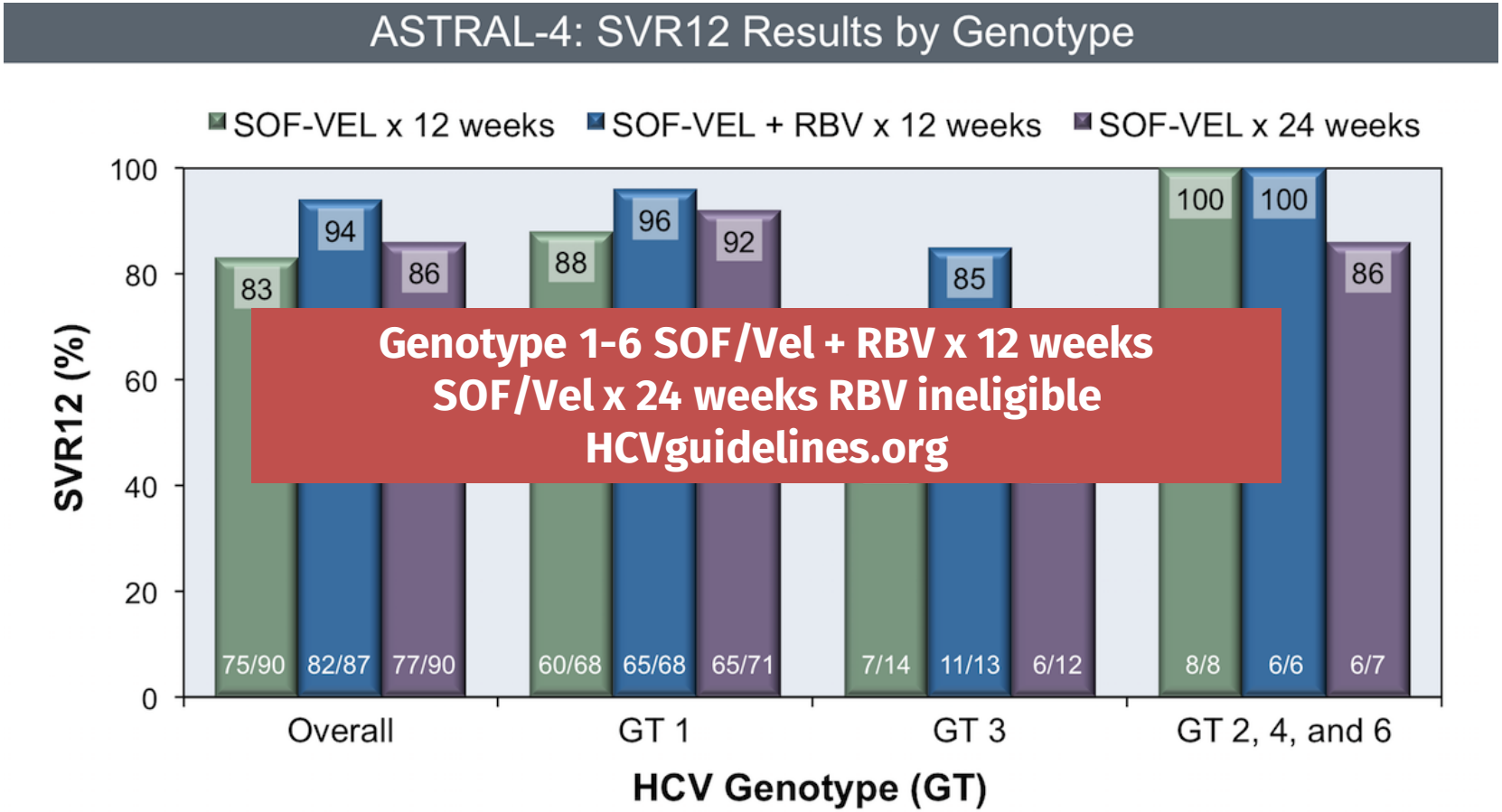
Treating HCV in Decompensated Cirrhosis

- For transplant candidates:
  - Increase donor pool to HCV positive organs
  - Potential improvement in liver disease
  - MELD purgatory
    - *Improvement does NOT necessarily translate into clinical improvement in Child's B/C patients with significant portal hypertension*

- For non-transplant candidates
  - Short-term goal achieve SVR with possible stabilization and improvement
  - DAA regimens containing protease inhibitor associated with worsening decompensation and are contraindicated in Child's B/C cirrhotics.

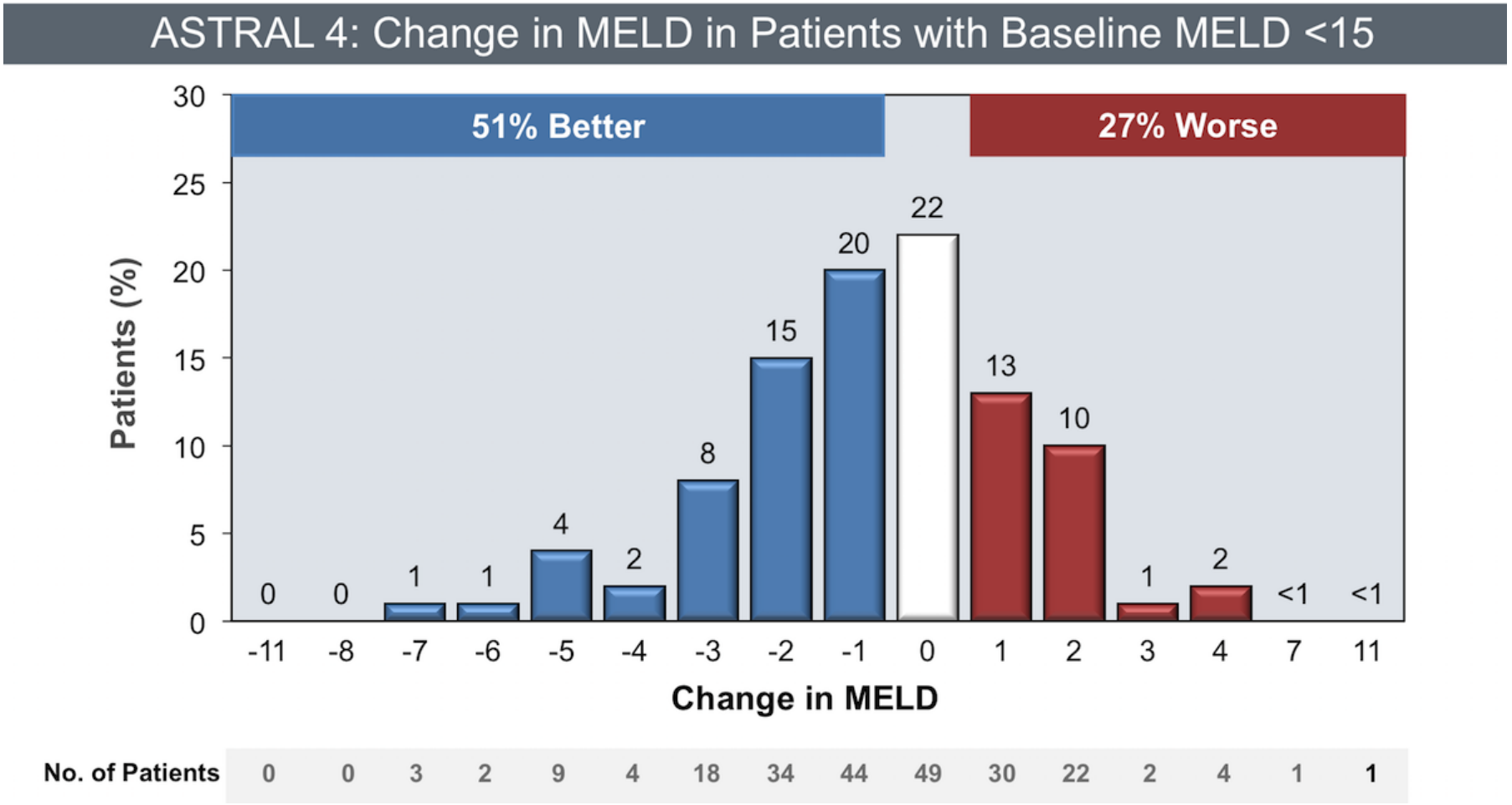
Verna et al J Hep 2020, Bitterman et al Clin Gastro Hep 2020
Krassenburg et al J Hep 2021

Sofosbuvir-Velpatasvir Treatment of HCV Genotypes 1-6 in Adults with Decompensated Cirrhosis



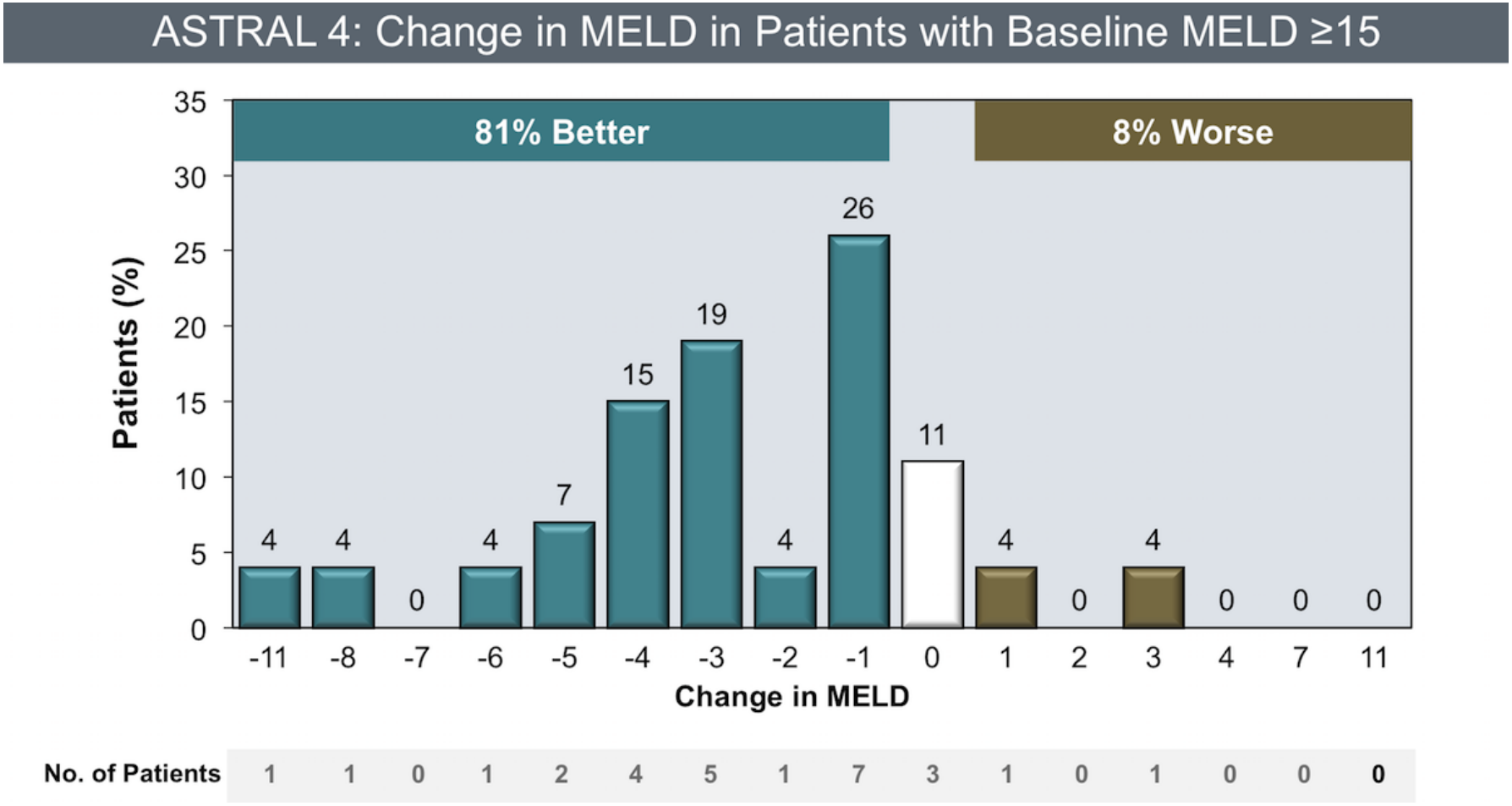
Curry et al NEJM 2015

Sofosbuvir-Velpatasvir Treatment in Decompensated Cirrhosis



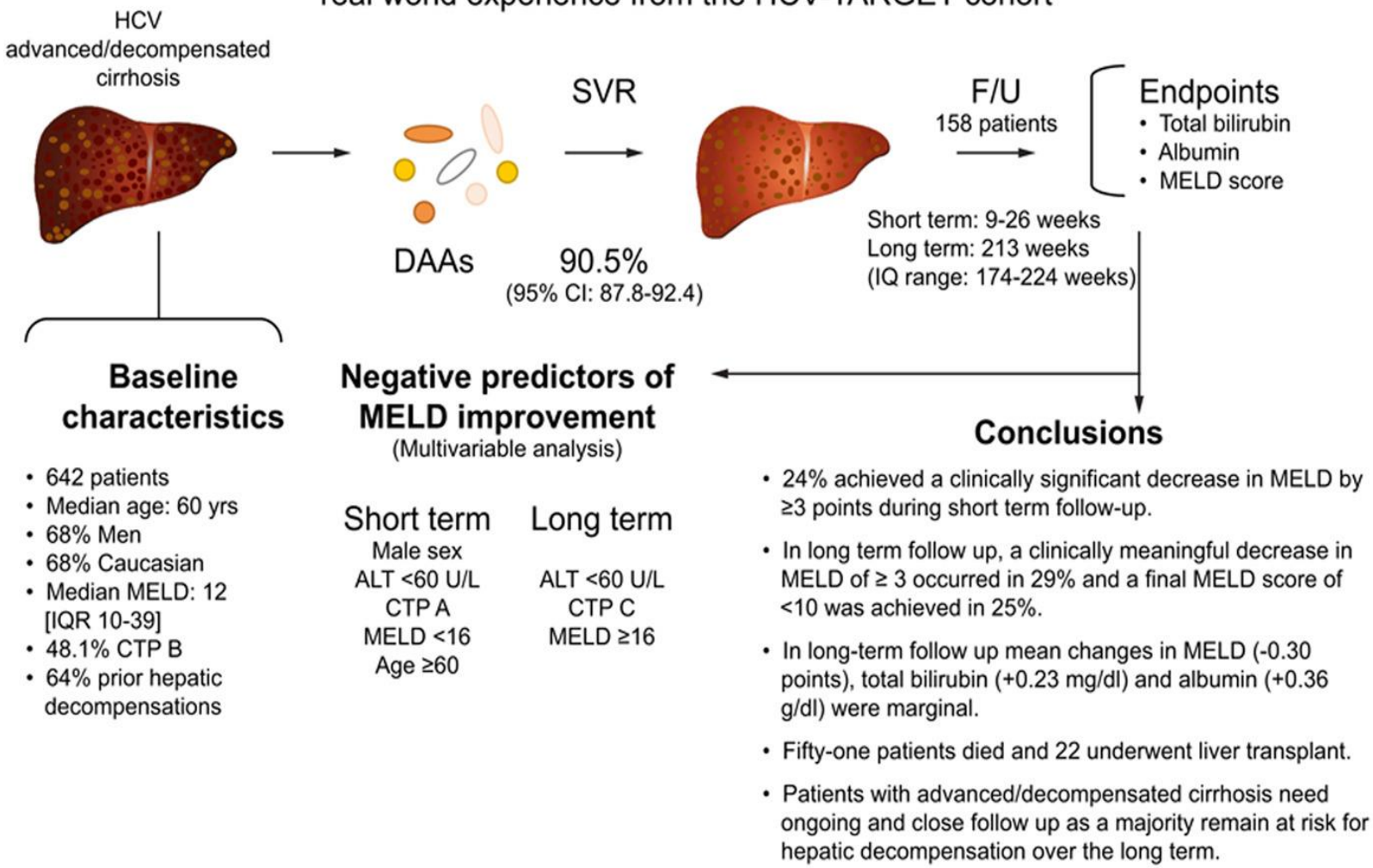
Curry et al NEJM 2015

Sofosbuvir-Velpatasvir Treatment in Decompensated Cirrhosis



Curry et al NEJM 2015

DAA HCV therapy and long-term hepatic function in advanced/decompensated cirrhosis: real world experience from the HCV-TARGET cohort



Journal of Hepatology 2020 : (10.1016/j.jhep.2020.03.031)

Case 3 continued

- HCV treatment deferred
- Evaluated and listed for liver transplant
- MELD continued to increase, managed with serial paracentesis and diuretics
- 1 year after presentation admitted with acute on chronic liver failure in setting of duodenal ulcer bleed
  - Received liver offer with MELD 37
  - Treated with SOF/VEL x 12 weeks post transplant with SVR
  - Doing well 1 ½ years post transplant