Post AASLD 2017 Update: Metabolic Diseases

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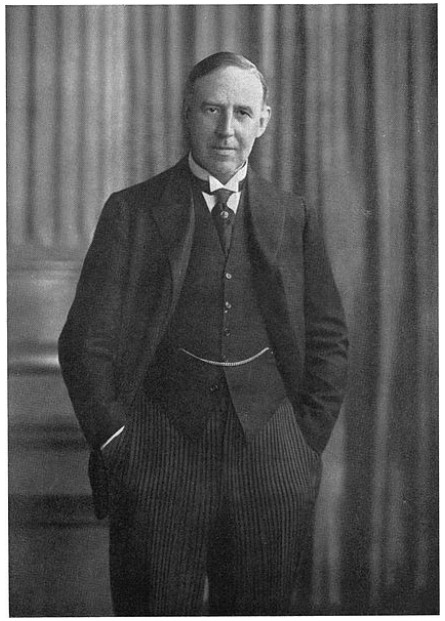
Outline: Review and Update

- Hereditary Hemochromatosis (HH)
- Alpha-1 Antitrypsin Disease (A1AT)
- Wilson Disease (WD)

Friedrich von Recklinghausen

Carl-Bertil Laurell



Samuel Kinnear Wilson

Hereditary Hemochromatosis

Iron Physiology

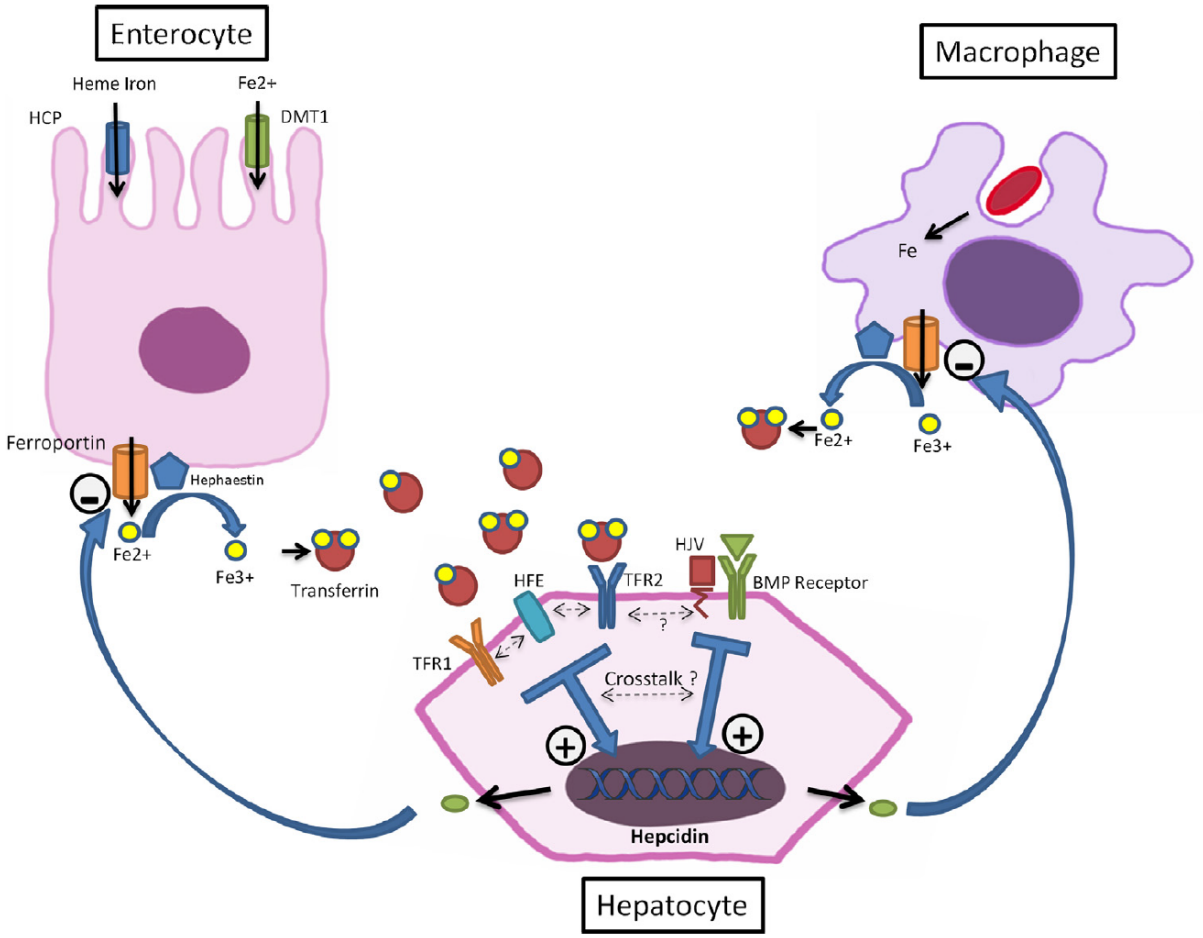


Figure 1 Iron metabolism regulation. HCP: heme carrier protein; DMT1: divalent metal transporter 1; HJV: hemojuvelin; TFR1: transferrin receptor 1; TFR2: transferrin receptor 2; BMP receptor: bone morphegenic protein receptor.

HFE senses Fe levels

Hepcidin turns off ferroportin

Ferroportin exports Fe out of cells

Bardou, Clin Res Hep Gastro 2015; 38: 143

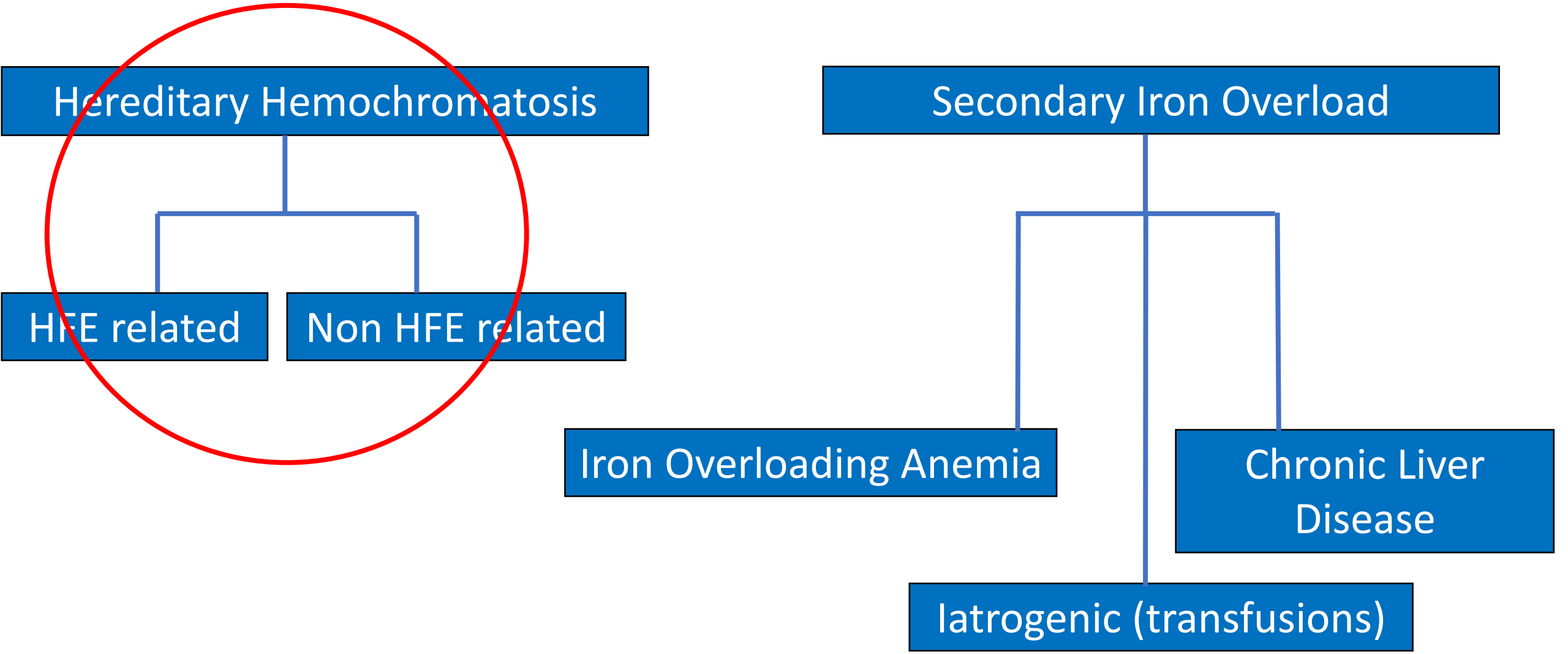
What is Hereditary Hemochromatosis?

- Iron deposition in multiple organs
  - Cirrhosis
  - Liver cancer (HCC)
  - Diabetes mellitus (iron deposition in pancreas)
  - Arthropathy
  - Congestive heart failure

- Genetic autosomal recessive disorder on the HFE gene

Friedrich von Recklinghausen

Etiologies of Hemochromatosis



Hereditary Hemochromatosis: HFE related, Type 1

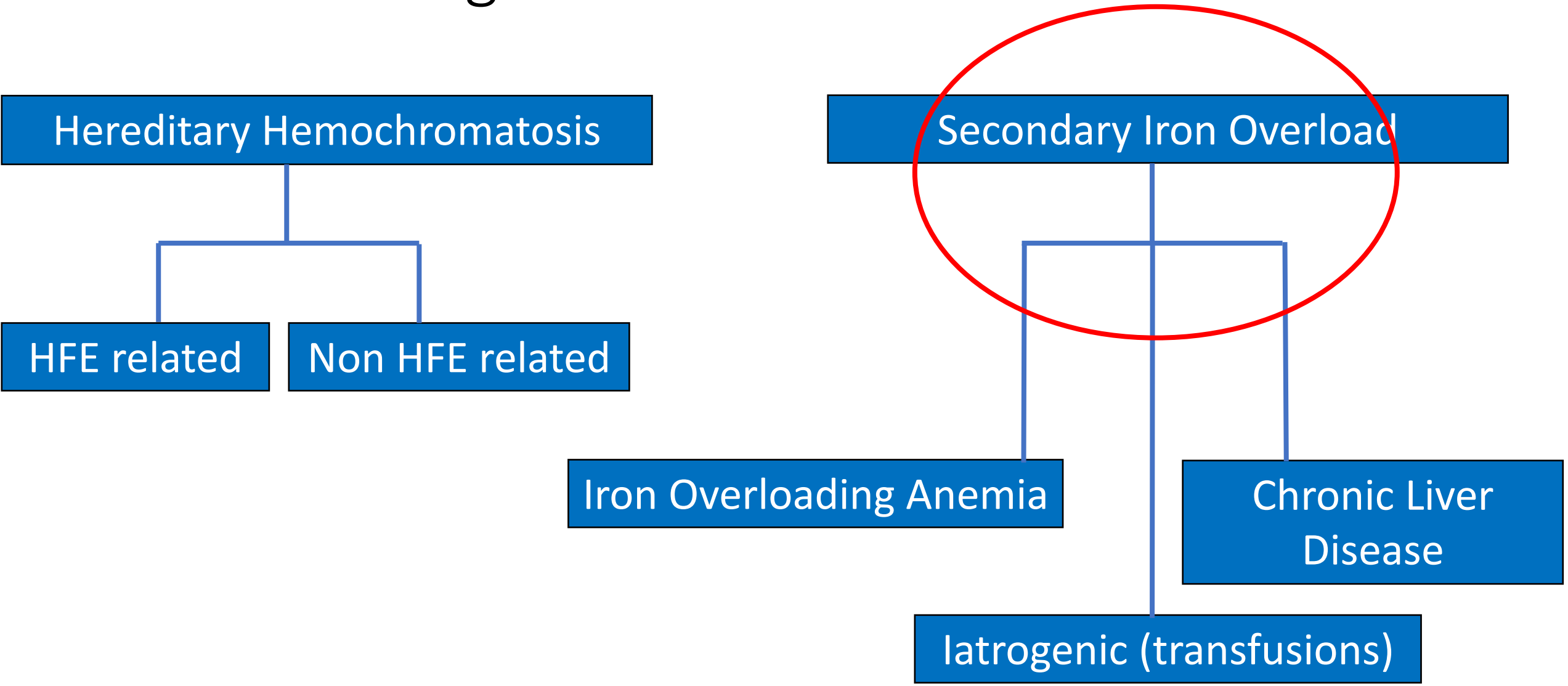
- C282Y/C282Y homozygotes
  - Most common HFE mutation
  - 85% of all cases
  - Highest level of hepatic iron deposition
- C282Y/H63D compound heterozygote
  - Only 1-5% with clinical phenotype of iron overload
  - If evidence of iron overload, look for another co-factor
- H63D, S65C mutation
  - ? important
  - Only lead to iron overload with another risk factor

AASLD Practice Guidelines 2011

Hereditary Hemochromatosis: Non-HFE Related

- 10-15% of cases
- Type 2 Juvenile Hemochromatosis (severe)
  - Type 2A: Hemojuvelin mutation: early symptoms with organ involvement
  - Type 2B: Hepcidin mutation: rare, also seen in children
- Type 3 Transferrin 2 receptor associated HH
  - Early onset disease with both heterozygotes/homozygotes
- Type 4 Ferroportin associated HH
  - Autosomal dominant
  - Loss-of function mutation leads to anemia, low transferrin saturation, high ferritin
  - Phlebotomy can often worsen anemia

Etiologies of Hemochromatosis



Causes of Secondary Iron Overload

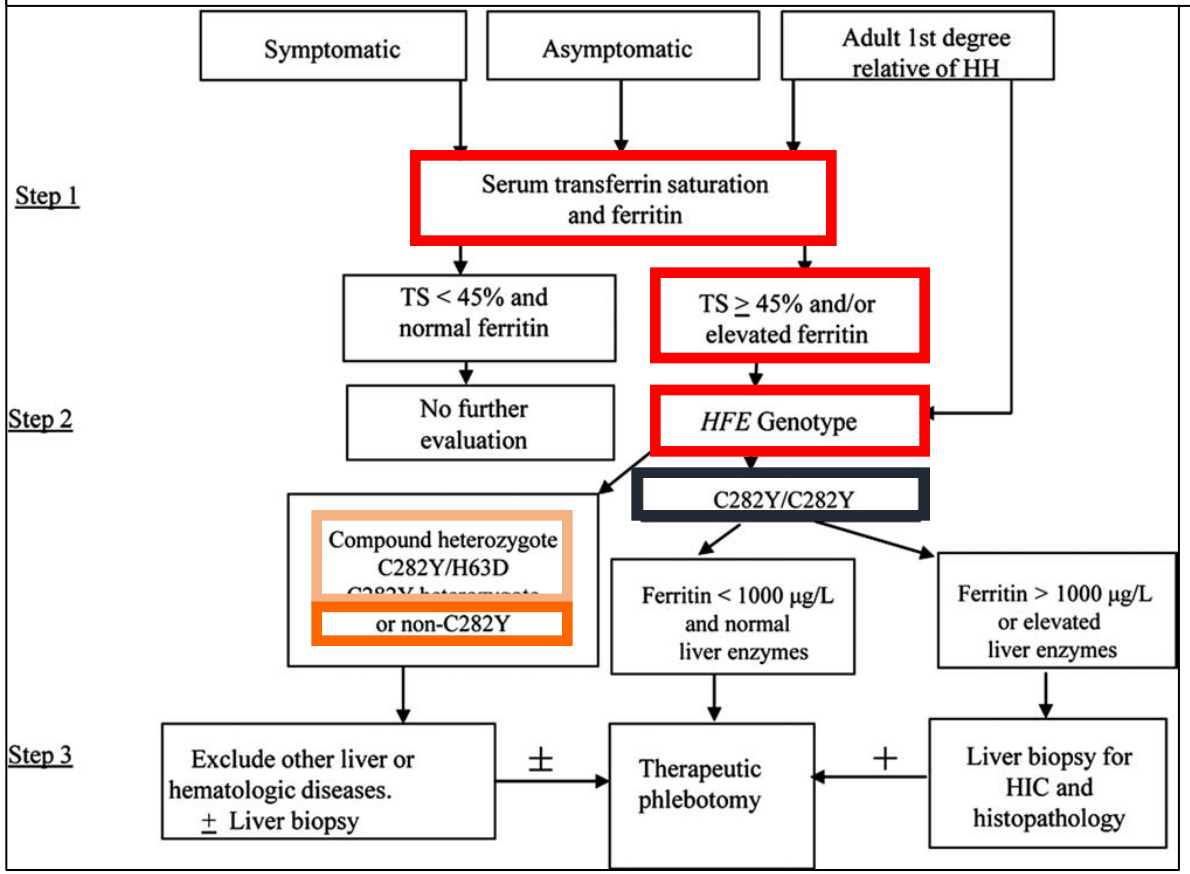
- Iron loading anemia (red cell disorders causing ineffective erythropoesis)
  - Thalassemia
  - Myelodysplastic anemia

- Chronic liver disease
  - Alcohol use
  - Non alcoholic fatty liver disease
  - Hepatitis C
  - Porphyria cutanea tarde

AASLD Practice Guidelines 2011

AASLD PRACTICE GUIDELINE

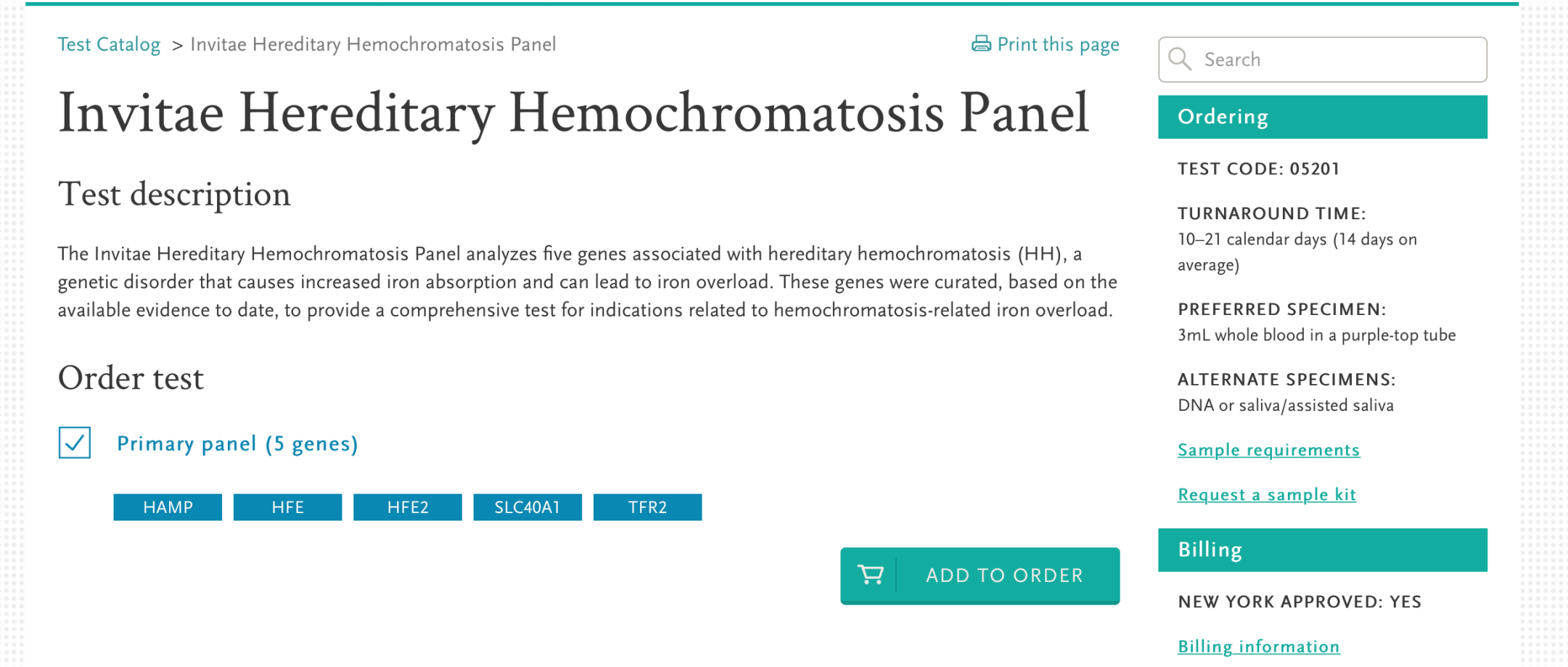
Diagnosis and Management of Hemochromatosis: 2011 Practice Guideline by the American Association for the Study of Liver Diseases



- Check ferritin and transferrin saturation
- 85% of HH are **C282Y/C282Y**
- Small minority are **C282Y/H63D**
- 10-15% are **non-HFE**

Slide courtesy of J. Ahn, MD

Non-HFE Genetic Testing



Test Catalog > Invitae Hereditary Hemochromatosis Panel

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Invitae Hereditary Hemochromatosis Panel

Test description

The Invitae Hereditary Hemochromatosis Panel analyzes five genes associated with hereditary hemochromatosis (HH), a genetic disorder that causes increased iron absorption and can lead to iron overload. These genes were curated, based on the available evidence to date, to provide a comprehensive test for indications related to hemochromatosis-related iron overload.

Order test

Primary panel (5 genes)

HAMP | HFE | HFE2 | SLC40A1 | TFR2

ADD TO ORDER

Ordering

TEST CODE: 05201

TURNAROUND TIME:
10–21 calendar days (14 days on average)

PREFERRED SPECIMEN:
3mL whole blood in a purple-top tube

ALTERNATE SPECIMENS:
DNA or saliva/assisted saliva

Sample requirements

Request a sample kit

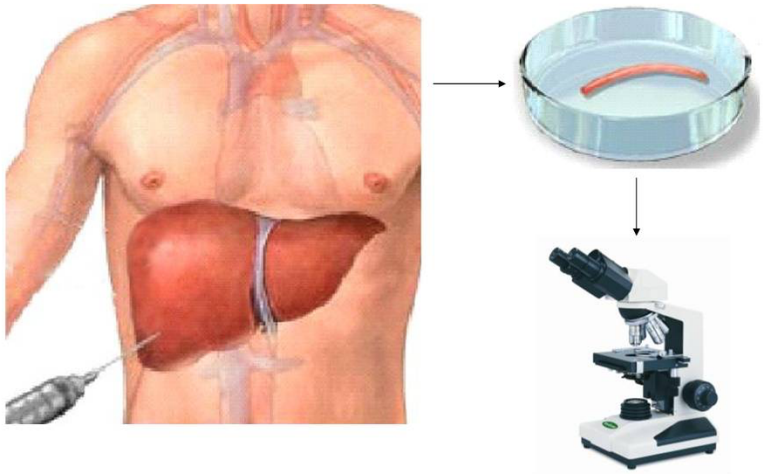
Billing

NEW YORK APPROVED: YES

Billing information

When Do You Perform a Liver Biopsy in HH?

- HFE C282Y/C282Y, ferritin > 1000, elevated ALT/AST
- Non-HFE, elevated liver test, abnormal Fe studies



AASLD Practice Guidelines 2011

Treatment: Phlebotomy

Rx: “Phlebotomize 500 cc weekly if Hg > 12.5”

Monitor:
- Hg @ each phlebotomy
- Ferritin after 10-20 x
- Decrease frequency once ferritin < 500

Maintenance phlebotomy
q 1-4 mo

Goal:
Ferritin 50-100

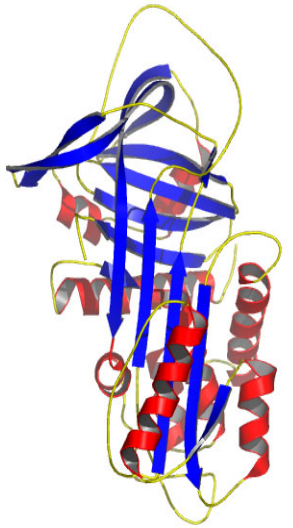
AASLD Practice Guidelines 2011
Slide courtesy of J. Ahn, MD

2017 AASLD Hemochromatosis

- Abstract #815: Risk and risk factors of HCC in patients with HFE-related hereditary hemochromatosis
- N = 196 at the VA with HH and cirrhosis
- HCC occurred in 25% of patients during median follow up of 5 years
- Older age at diagnosis associated with higher risk of HCC
- Degree of iron overload, receipt and adequacy of HH treatment not associated with higher risk of HCC

Alpha 1-Antitrypsin Deficiency

Introduction



- Inherited autosomal recessive condition affecting lungs and liver
- α-1 antitrypsin (A1AT) is a serine protease inhibitor made in the liver
- Inhibits destructive neutrophil elastase that circulates in the blood
  - No inhibition leads to lung disease

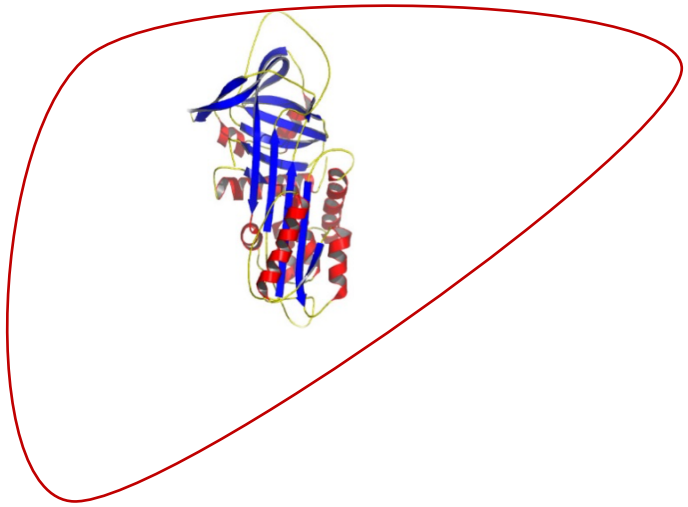
Carl-Bertil Laurell

Introduction

- Single amino acid substitution leads to an improperly folded A1AT protein

- Abnormal protein unable to leave the liver

- 2 problems:
  - Build up inside liver causes damage
  - *Deficiency* of the protein outside the liver



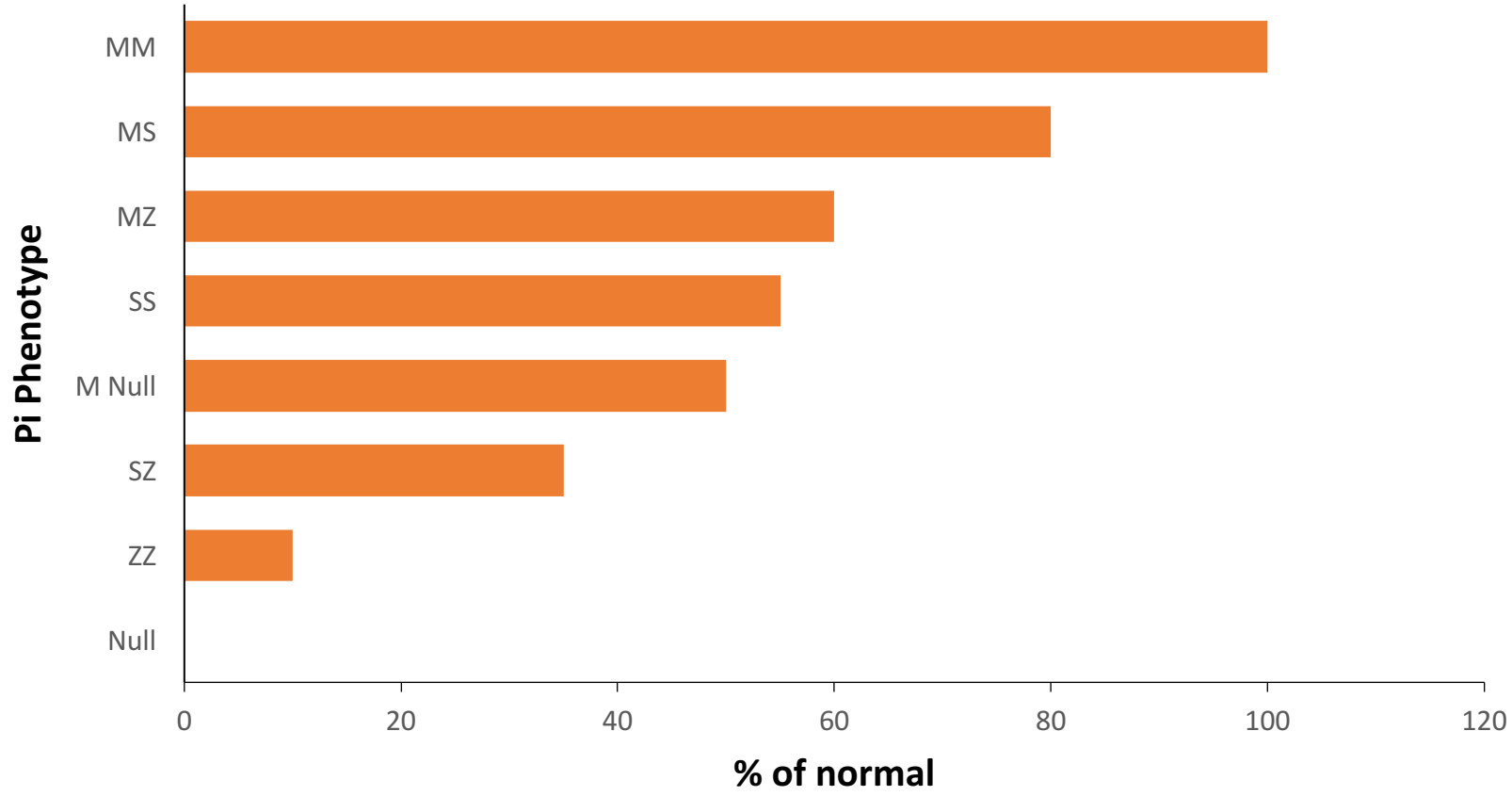
The Risk for Liver Disease in A1AT

Pi Phenotype	Risk for liver disease
MM	0
ZZ	10-20%
MZ	3-5% with another condition
Null	0

- M is normal version of protein
- Z is abnormal version of protein
- Variable presentation: not everyone with A1AT deficiency develops liver disease

Am J Respir Crit Care Med 2003 Oct 1;168(7):818-900

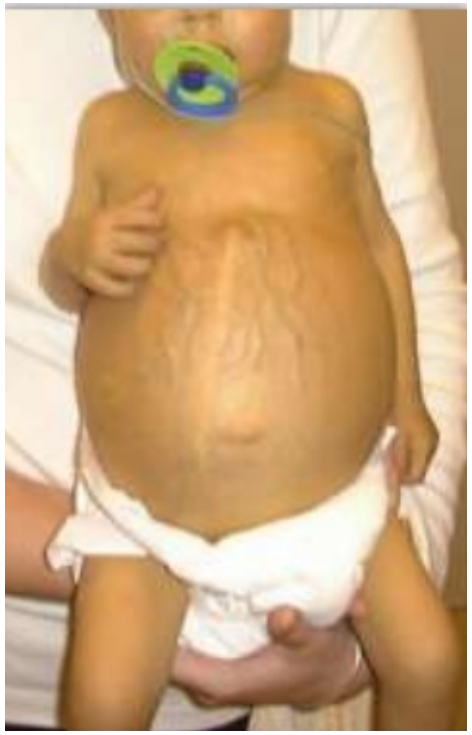
Blood levels of A1AT



Berg C. AASLD Sept 2010

Pediatric Presentation of A1AT in the Liver

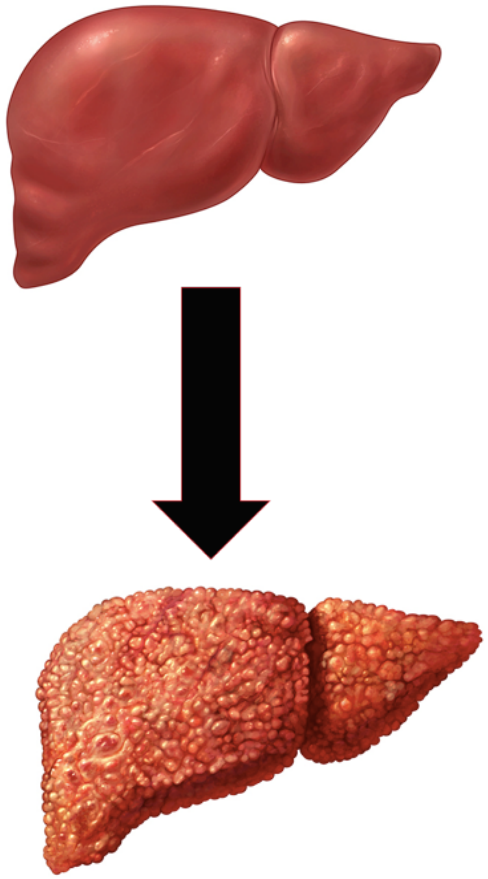
Neonatal hepatitis syndrome



- Infancy
  - Cholestasis
  - Jaundice
  - Elevated liver tests
- Childhood
  - Hepatomegaly
  - Elevated liver tests
  - Liver failure

Adult Presentation of A1AT in the Liver

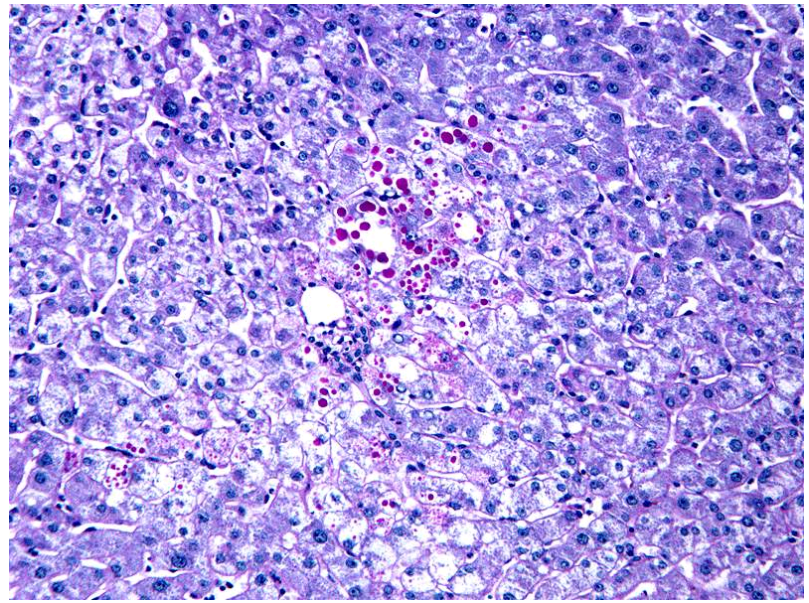
- Adults
  - Cryptogenic cirrhosis
  - Elevated liver tests
  - Unexplained chronic active hepatitis
    - Family history of liver disease
  - HCC
  - Emphysema



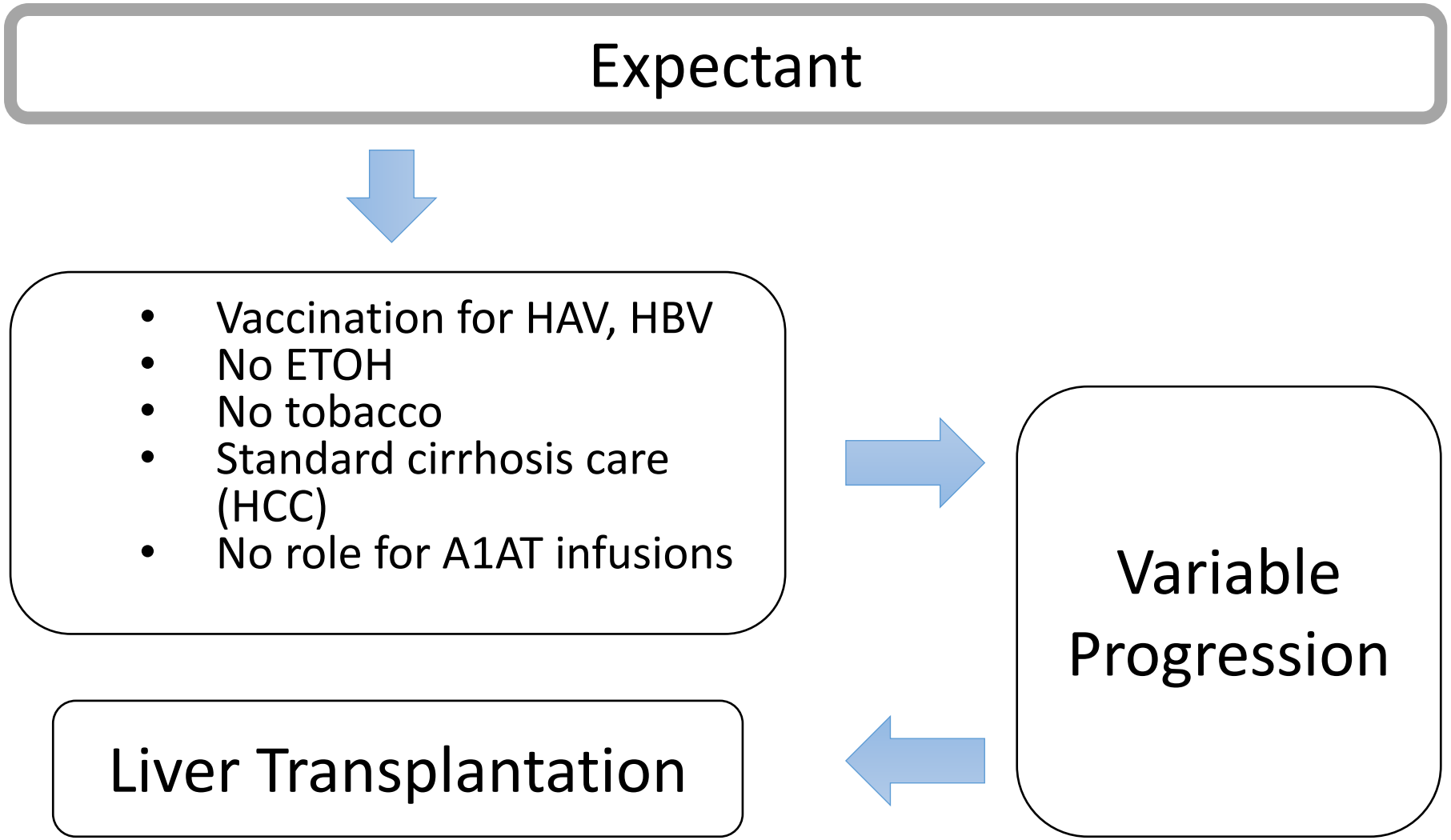
Cirrhosis

Diagnosis of A1AT

- A1AT blood levels
  - Acute phase reactant
- A1AT phenotype
  - Migration of alleles in an isoelectric gradient
- Liver biopsy
  - PAS = periodic acid-Schiff positive, diastase resistant globules in the ER of hepatocytes



Treatment of A1AT



Slide courtesy of J. Ahn, MD

How Do A1AT Patients Do After Liver Transplant?

Survival	ZZ patients	SZ patient
1 year	86%	91%
3 year	83%	86%
5 year	80%	79%
10 year	72%	79%

Liver Transpl. 2013 Dec;19(12):1370-6

2017 AASLD: A1AT

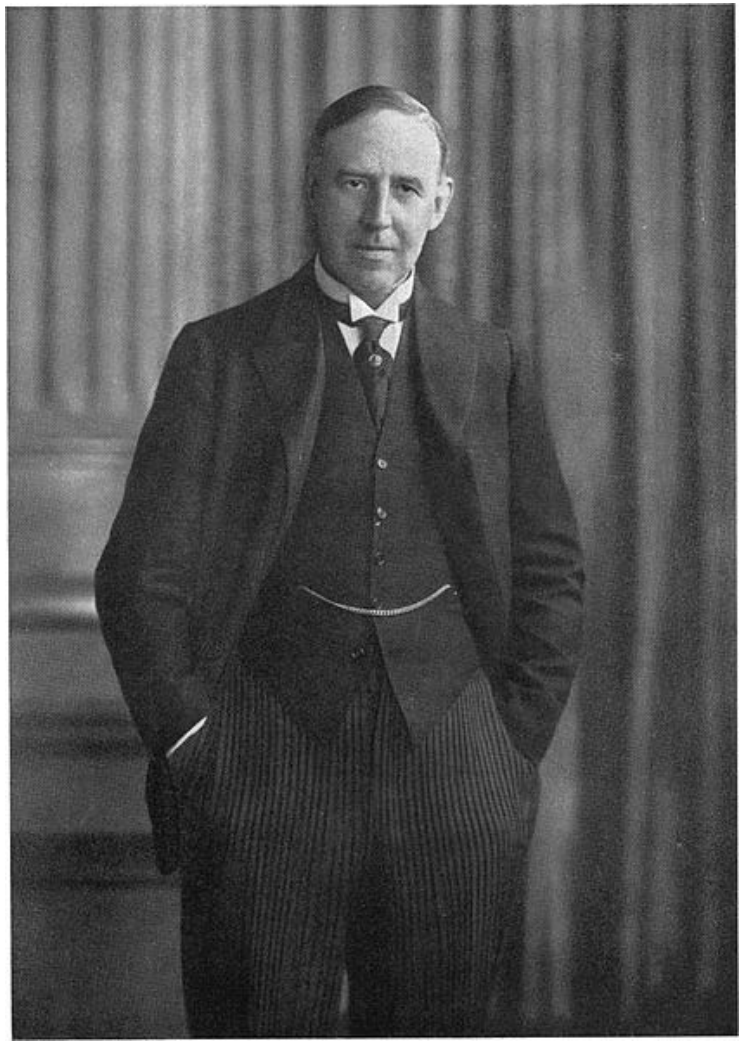
- Abstract #801: Z is the strongest polymorphism based risk factor for fibrosis

- Abstract #803: ZZ are at risk to develop both fibrosis and steatosis

- Abstract #823:
  - Patients with severe pulmonary manifestations of AAT rarely develop advanced liver fibrosis as adults
  - Steatosis may promote liver fibrosis (high BMI, GGT)
  - Z allele predisposes for development of significant portal hypertension

Wilson Disease

Wilson Disease



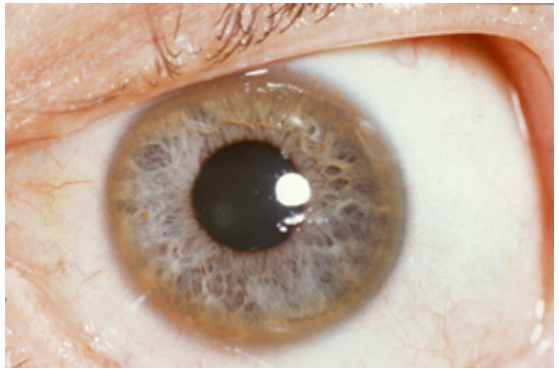
- First described in 1912 by Samuel Kinnear Wilson
- Defect of biliary copper (Cu) excretion
- Results in Cu accumulation

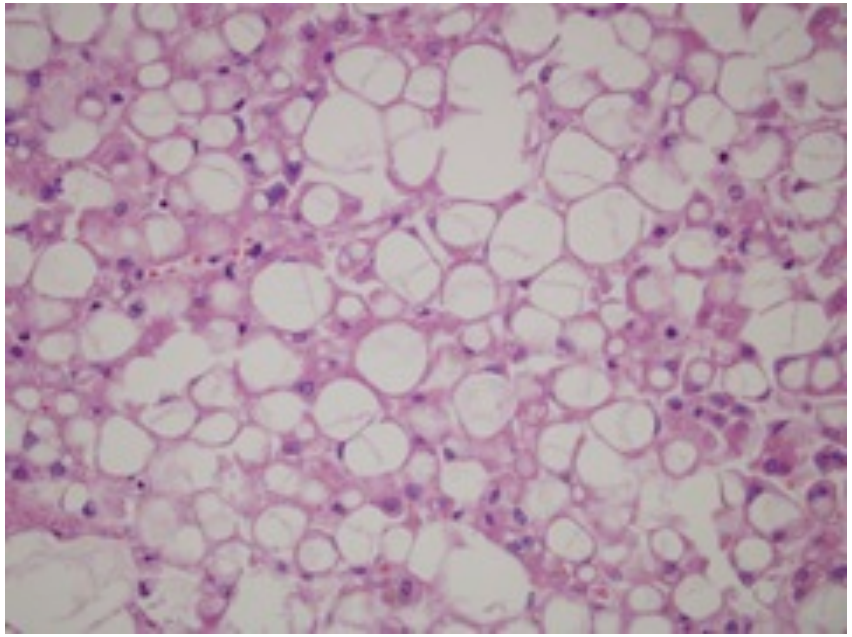
WD: When to suspect it

- Age 3-55, abnormal liver tests
- Abnormal liver tests and neurologic or psychiatric symptoms
  - Young adult with change in school work
- NASH without signs of metabolic syndrome or insulin resistance
- Autoimmune hepatitis unresponsive to therapy
- Kayser-Fleischer rings
- Acute liver failure with non-immune hemolytic anemia

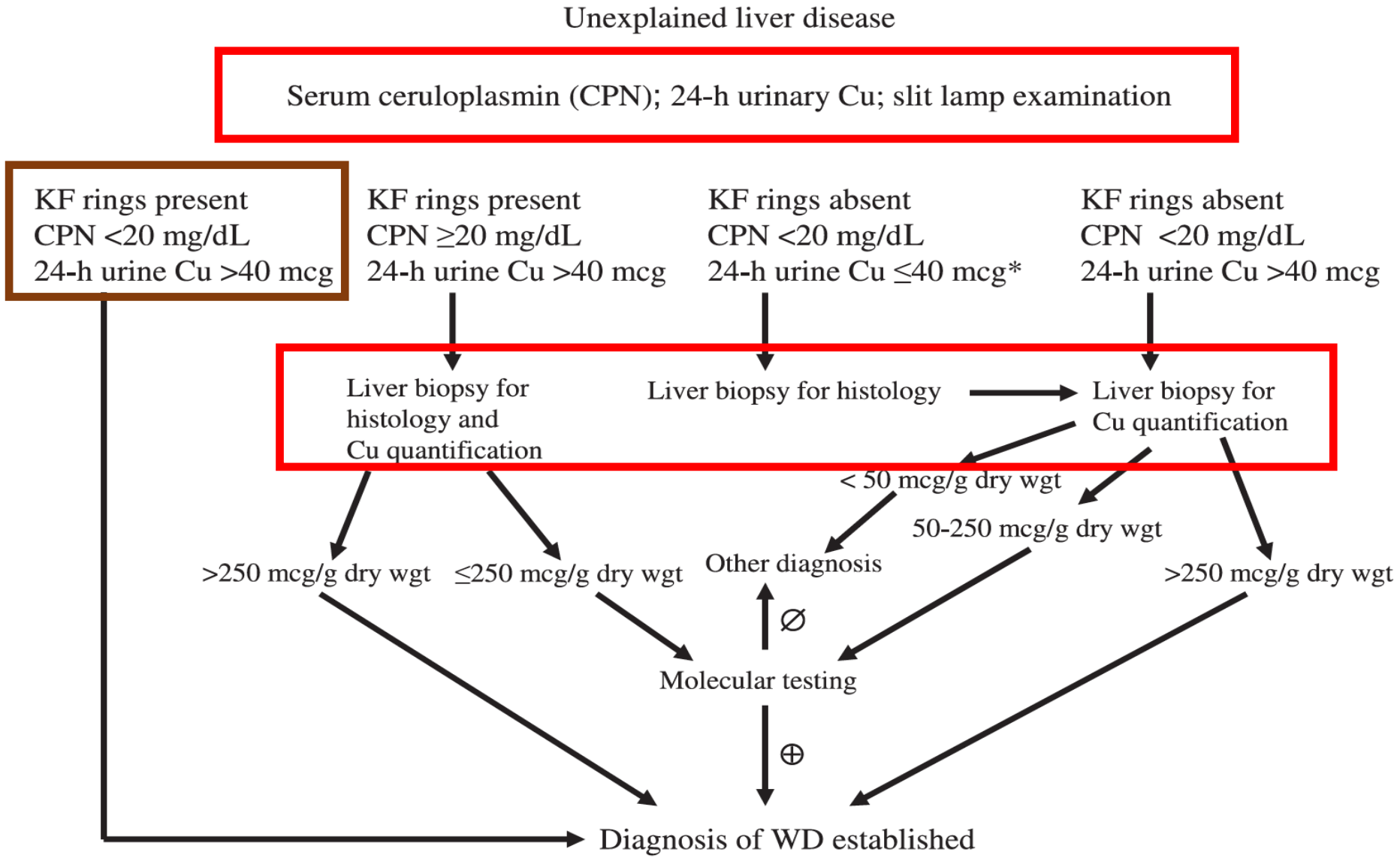
WD: Clinical Presentation

- Hepatic presentation
  - Increase liver enzymes
  - Hepatomegaly
  - Fatty liver
  - Acute hepatitis
  - Cirrhosis
  - Acute liver failure
- Neurologic presentation (up to 1/3)
  - Movement disorder
  - Rigidity
  - Micrographia
  - Kayser Fleischer rings
  - Depression, mania, psychosis





AASLD PRACTICE GUIDELINES



WD: Diagnosis

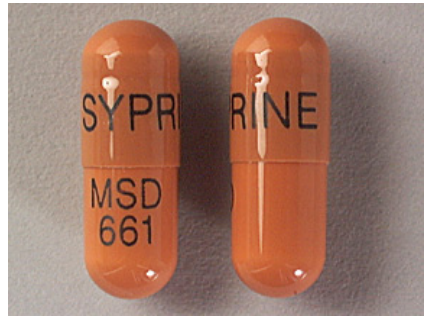
	Normal	Wilson Disease
Serum Cu (ug/dl)	80-140	< 80
Urine Cu (ug/24H)	< 40	>100
Serum ceruloplasmin (mg/dl)	20-40	<20
Hepatic Cu (ug/gm dry weight)	15-50	250-300

Kowdley K, AASLD Nov 2016

WD Treatment: Pharmacotherapy

- Chelation to increase urinary Cu excretion
  - D-pencillamine
  - Trietine

- Decrease intestinal Cu absorption
  - Zinc
  - Used as maintenance or first line in asymptomatic patients



Drug	Dose	Compliance Monitoring	Side Effect Monitoring
Trientine	Initial: 0.75-1.5 g/day divided in 2-3 doses Maintenance: Same	24-hour urinary Cu: 200-500 ug/d	CBC (Fe deficiency anemia), Gastritis
Penicillamine + pyridoxine B6	Initial: 1-1.5 g/day in 2-3 doses Maintenance: 0.75-1g/day	24-hour urinary Cu: 200-500 ug/d	CBC (anemia), UA (proteinuria), rashes, GI symptoms, worsens neurologic symptoms
Zinc	Initial: 50 mg elemental zinc three times daily Maintenance: titrate dose to 100-150mg/day	24-hour urinary copper: <75 mg/d	Gastric irritation

Modified from Sleisenger 8th ed. Table 72-2 and from J. Ahn, MD

Treatment: Zinc Formulations
Call the pharmacy

Formulation	Dose	Elemental Zn
Zinc acetate	25mg	7.5mg
Zinc gluconate	100mg	14mg
Zinc sulfate	220mg	50 mg
Zinc oxide	100mg	80mg

WD: Treatment

- Serum Free Cu concentration

  = Total Cu – (3.15 x ceruloplasmin)

  - > 25 ug/dl in most untreated patients
  - < 15 ug/dl normal range
  - < 5 ug/dl copper depletion

- On treatment
  - if 24H urine Cu is low and serum free Cu concentration is low, ? Cu deficiency
  - if 24H Cu is high and serum free Cu concentration is high, ? noncompliance

AASLD Practice Guidelines 2008

WD Treatment: Dietary Modifications

- Eliminate copper rich foods
  - Organ meats (liver)
  - Shellfish
  - Nuts (cashews, sesame, sunflower)
  - Chocolate
  - Mushrooms
  - Dried fruit

2017 AASLD: Wilson Disease

- Abstract #802
  - WTX101 (tetrathiomolybdate): Cu protein binding agent
  - Phase 2 study, PO, daily dose, 24 weeks
  - Lowered non-ceruloplasmin bound Cu, **improved** neurologic status, improved INR, ALT, albumin

- Abstract #830
  - Liver stiffness measurement in Wilson disease
  - Mean LSM 32.3 kPa for cirrhosis
  - Mean LSM 6.2 kPa in F0 – F2
  - Gradual decrease with chelator treatment

Summary

- Hereditary Hemochromatosis
  - Non-HFE up to 15%
  - Liver biopsy if HFE C282Y/C282Y, ferritin > 1000, elevated ALT
  - Risk for HCC
- A1AT
  - Variable progression of liver disease
  - Hepatic steatosis and Z risk factors for progression of liver disease
- Wilson Disease
  - New therapy: WTX101 (tetrathiomolybdate), a Cu protein binding agent

Thank you