Recognizing and Treating Genetic Liver Diseases

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Today’s Focus

- Wilson Disease
- Hereditary Hemochromatosis

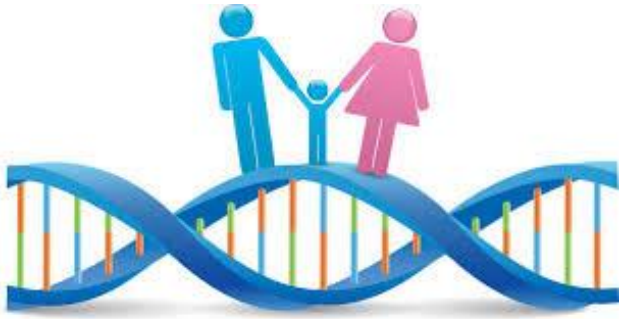
Wilson Disease

Rare autosomal recessive disorder of copper metabolism

- Caused by mutations in the ATP7B gene
- Reduced copper incorporation into ceruloplasmin
- Leads to impaired copper excretion into bile, free copper accumulates, oxidative damage in
  - Liver
  - Brain (basal ganglia)
  - Cornea
  - Kidneys

Epidemiology of Wilson Disease

- WD affects nearly 1 in every 30,000 people worldwide
- Typically presents between age 5-35, but can occur later
- Equal in males and females



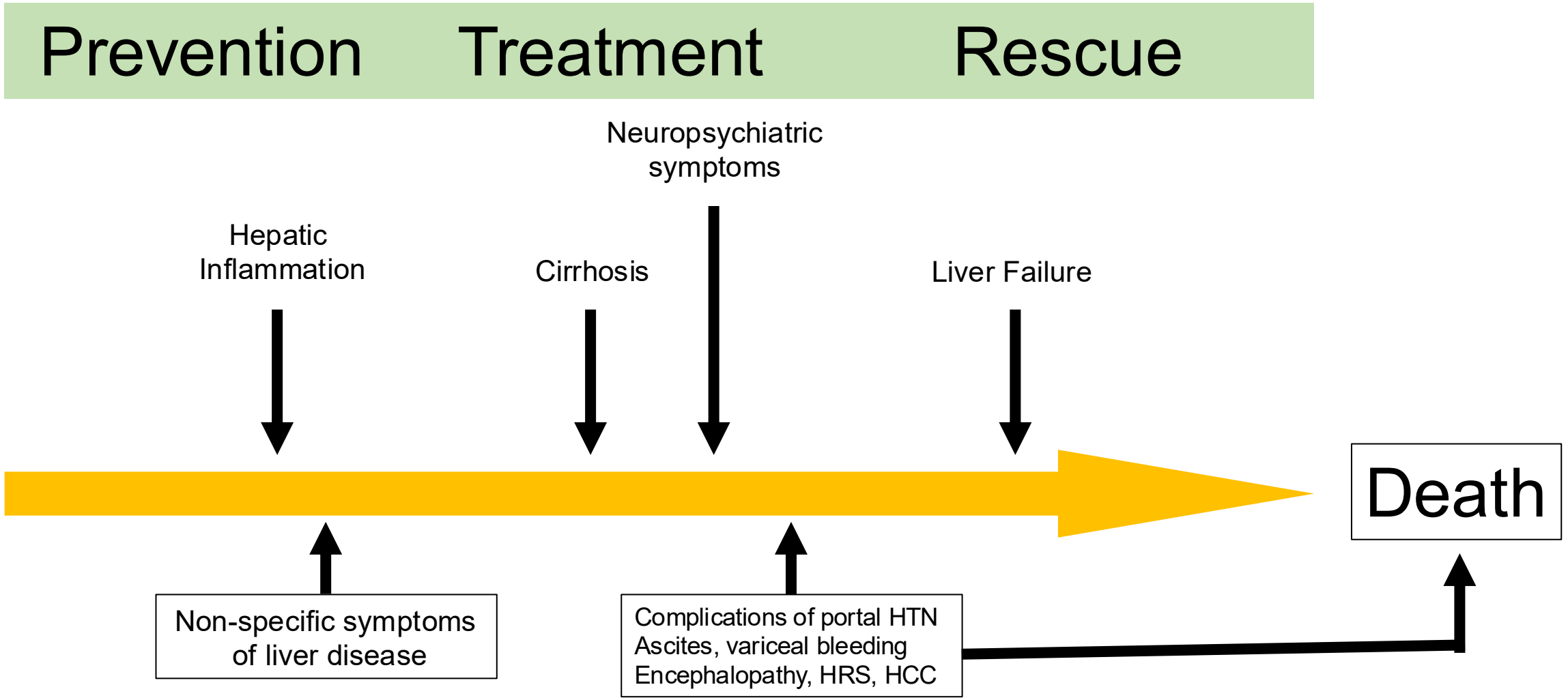
1. Immergluck J, Anilkumar AC. Wilson Disease. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441990/ Accessed January 29, 2025;

Wilson Disease: Case Study

- 18 yo female moved for college. No PMH.
- Became depressed and saw PCP during winter break.
- PCP attributed the depression to stress from school and prescribed an antidepressant.
- Depression improved but she developed a tremor.
- Blood tests revealed mild liver enzyme abnormalities which her PCP attributed to the antidepressant and made no changes.
- Nine months after her first complaint of depression, she started falling and ended up in the ER.
- Abnormal brain MRI and compromised liver function.
- Upon admission, common causes of liver disease were ruled out, and she was diagnosed with “viral syndrome”.
- She was discharged to a rehabilitation facility where a neurologist reviewed the MRI and considered the diagnosis of WD, which was quickly confirmed with blood and urine tests.
- After 6 months of chelation therapy and rehabilitation, she recovered almost completely and was able to return to college.

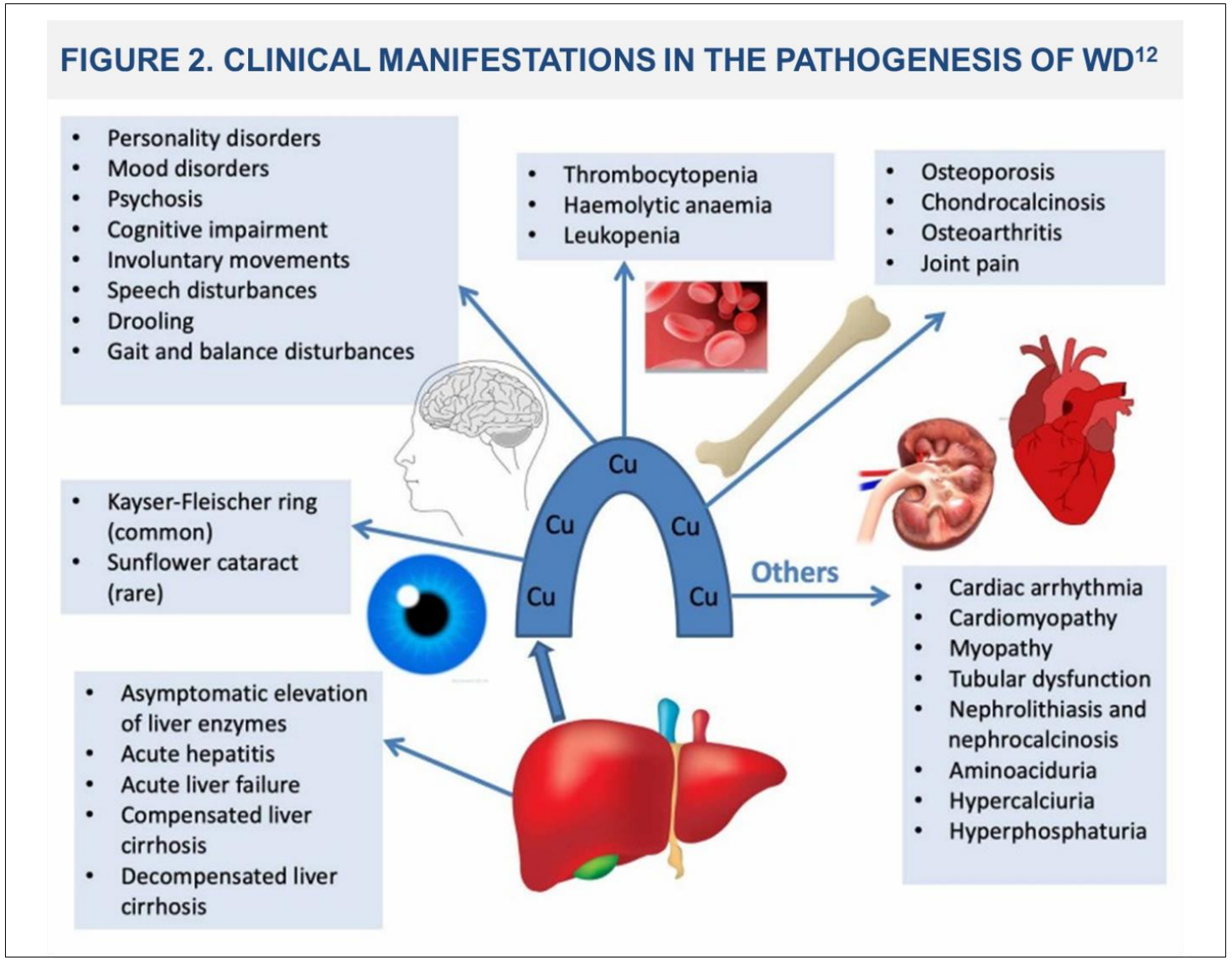
Saab S et al. https://wilsondisease.org/wp-content/uploads/2025/04/Chronic-Liver-Disease-Fdn_White-Paper.pdf

Natural History of Wilson Disease



Schilsky et al. *Hepatology*. 2022.

Clinical Manifestations of Wilson Disease



Mohr I et al. *The Clinical Biochemist*. *Reviews*. 2019; 40:59-77.

Kayser-Fleischer (KF) Rings

- Usually seen as a golden, brown ring in the peripheral cornea[1]
- Caused by deposition of excess copper on the inner surface of the cornea in the Descemet membrane[1]
- A slit lamp examination is mandatory to make a diagnosis, particularly in the early stages[1]
- Present in 90% of patients with neurologic WD[2-4]
- Absent in ~60% of patients with hepatic manifestations[2-4]

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1. Pandey N, John S. Kayser-Fleischer Ring. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2020; 2. Shribman S et al. *Ann Transl Med*. 2019; 7 (suppl 2):S60; 3. Litwin T et al. *Ther Adv Psychopharmacol*. 2018; 8:199-211; 4. Steindl P et al. *Gastroenterology*. 1997; 113:212-218; 5. Available at: https://www.wilsonsdisease.org/about-wilson-disease/kayser-fleischer-rings. Accessed September 14, 2021.

Diagnostic Testing for Wilson Disease

Diagnostic Test	Finding[1,2]
Clinical examination	Kayser-Fleischer rings (confirmed by slit-lamp examination)
Biochemical analysis	Low ceruloplasmin Increase liver and urinary copper
Blood testing	Coombs-negative hemolytic anemia (even without evidence of liver failure)
Imaging	Abnormal MRI or CT of the brain Neurologic and/or psychiatric symptoms
Genetic testing	Presence of *ATP7B* mutations

Use of the Leipzig scoring system can help to confirm a diagnosis of Wilson disease[3]

CT, computed tomography; MRI, magnetic resonance imaging.

1. EASL. *J Hepatol*. 2012; 56:671-685; 2. Schilsky ML et al. *Hepatology*. 2022; doi: 10.1002/hep.32801; 3. Ferenci P et al. *Liver Int*. 2003; 23:139-142.

Leipzig Scoring System

Typical Clinical Symptoms and Signs	
KF rings	
Present	2
Absent	0
Neurological symptoms	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>200 mg/dL)	0
100-200 mg/dL	1
<100 mg/dL	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

Other Tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>250 µg)	2
50-250 µg	1
Normal (<50 µg)	-1
Rhodanine-positive granules	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

≥ 4, diagnosis established; 3, diagnosis possible, more tests needed; ≤2, diagnosis very unlikely

EASL. *J Hepatol*. 2012; 56:671-685; Ference P et al. *Liver Int*. 2003; 23:139-42. doi: 10.1034/j.1600-0676.2003.00824.x.

Treatment of Wilson Disease

Primary (copper directed)[1,2]

- Avoid high copper foods (shellfish, liver, nuts, chocolate, mushrooms)
- Pharmacotherapy
  - Chelation of copper (trientine or penicillamine)
  - Blockade absorption (Zn)
- Liver transplant

Secondary[3,4]

- Treat neurologic symptoms
- Treat psychiatric symptoms

1. EASL. *J Hepatol*. 2012; 56:671-685; 2. Schilsky ML et al. *Hepatology*. 2022; doi: 10.1002/hep.32801;
3. Dusek P et al. *Ann Transl Med*. 2019; 7(suppl 2):964; 4. Cheung KS et al. *Word J Gastroentrol*. 2017; 23:7716-7726.

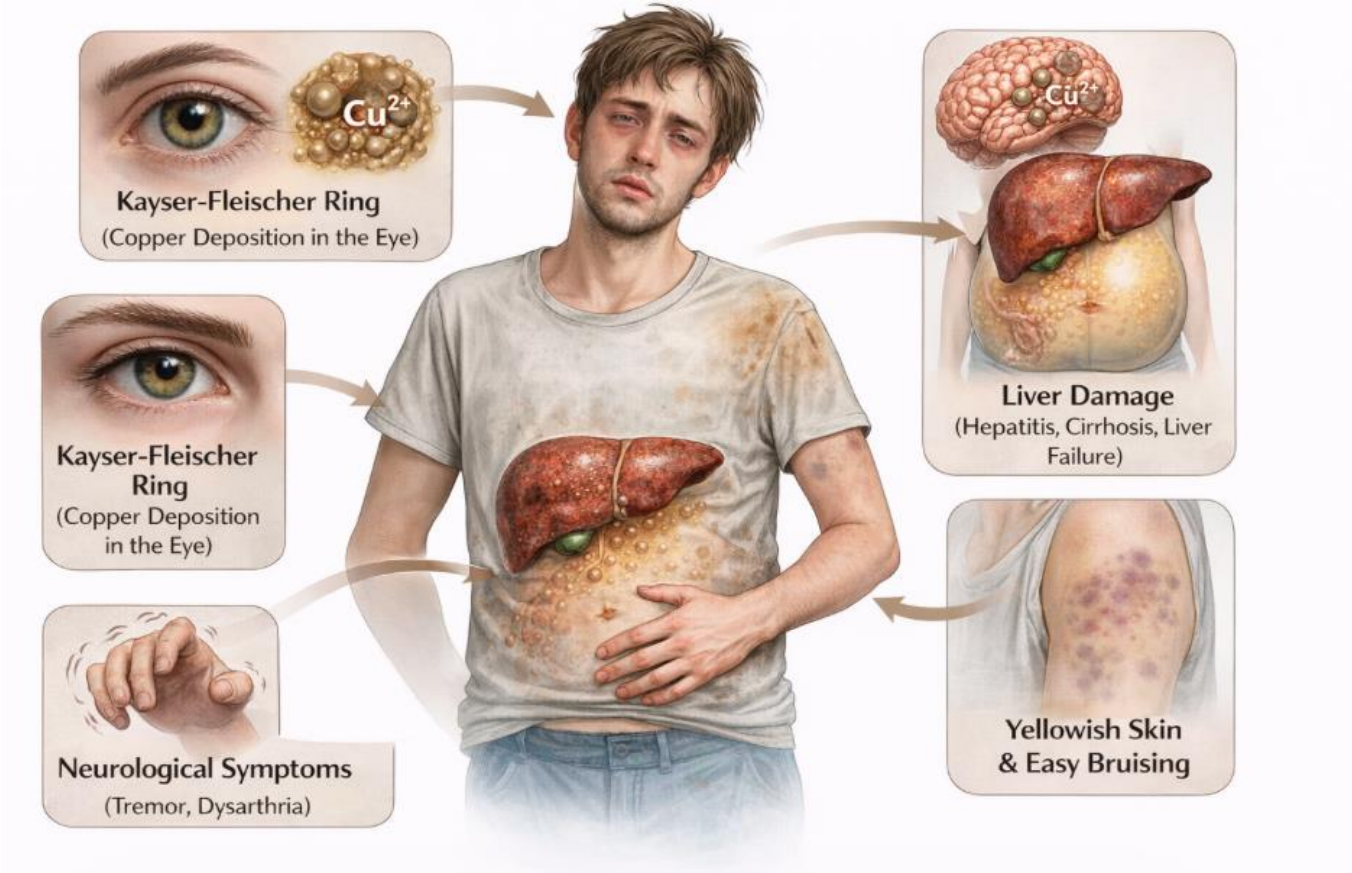
Currently Available Wilson Disease Treatments

Drug	Mode of action	Neurological worsening	Side effects	Comments
D-Penicillamine	General chelator induces renal excretion of copper	10%–20% during initial phase of treatment	• Fever, rash, proteinuria, lupus-like reaction • Aplastic anemia • Leukopenia • Thrombocytopenia • Nephrotic syndrome • Degenerative changes in skin • Elastosis perforans serpiginosa • Serous retinitis • Hepatotoxicity • Colitis	Reduce dose for surgery to promote wound-healing and during pregnancy
Trientine	General chelator induces renal excretion of copper	10%–15% during initial phase of treatment	• Gastritis • Aplastic anemia rare • Sideroblastic anemia • Colitis	Reduce dose for surgery to promote wound-healing and during pregnancy
Zinc	Metallothionein inducer, blocks intestinal copper absorption	Can occur during initial phase of treatment	• Gastritis • Biochemical pancreatitis • Zinc accumulation • Possible changes in immune function	No dosage reduction for surgery or pregnancy

Schilsky ML et al. *Hepatology*. 2022; doi: 10.1002/hep.32801.

Summary

- Wilson disease can lead to both hepatic and neurologic complications
- Diagnosis based on laboratory and histologic assessment
- Several treatment options exist
- Adherence to life-long therapy and management poses challenges



Hereditary Hemochromatosis (HH)

What is Hereditary Hemochromatosis (HH)?

- Inherited predisposition to absorb excess iron (Fe) from the diet
- Mutations in the *HFE* gene are the most common cause of adult-onset iron overload
- In some, excessive iron absorption and subsequent storage in various organs (i.e. liver, pancreas, heart, joints) eventually lead to cellular injury
- If untreated, over time this can cause irreversible tissue/organ damage and shorten life expectancy
- With early identification of at-risk individuals, surveillance of iron indices, and treatment, when necessary, complications can be avoided

Genetics of HH

- Standard testing by North American molecular genetics laboratories is targeted mutation analysis
  - Looks specifically for the two most common *HFE* mutations, C282Y and H63D
  - These account for over 90% of hereditary hemochromatosis
- About 1 in 3 individuals of Northern European ancestry are carriers (heterozygotes) of the C282Y or H63D *HFE* gene mutations
- About 1 in 260 individuals have two copies of (are homozygous for) the C282Y *HFE* gene mutation (genotype C282Y/C282Y)

What Does the Genetic Test Result Mean?

- Two mutations identified in an individual with biochemical evidence of iron overload confirm Hereditary Hemochromatosis diagnosis
- Two mutations identified in an asymptomatic individual suggest risk of developing iron overload and yearly monitoring of iron indices is recommended

***HFE* mutations identified**	**Risk of iron overload**
C282Y/C282Y	Highest risk of developing iron overload (38-50%) Many of these individuals never accumulate enough iron to cause disease (about 10-33% will develop symptoms)
C282Y/H63D	About 2% lifetime risk of developing iron overload
C282Y/S65C	Low lifetime risk of developing iron overload - similar to C282Y/H63D
H63D/H63D	About 1% lifetime risk of developing iron overload

HH: Presentation

- Typically, symptoms present in men aged 40-60 and in post-menopausal women; however, onset is variable and can occur much earlier or much later
- Symptoms are nonspecific and include:
  - Weakness, lethargy
  - Skin discoloration (bronze or grey)
  - Abdominal pain with or without hepatomegaly
  - Joint pain and/or stiffness, arthritis
  - Diabetes
  - Cardiomyopathy
  - Cirrhosis
  - Hepatocellular carcinoma
  - Testicular atrophy, erectile dysfunction
  - Menstrual irregularity

**While any of these health concerns can be caused by hereditary hemochromatosis, ≥2 greatly increases suspicion that the condition is present.

Biochemical Testing

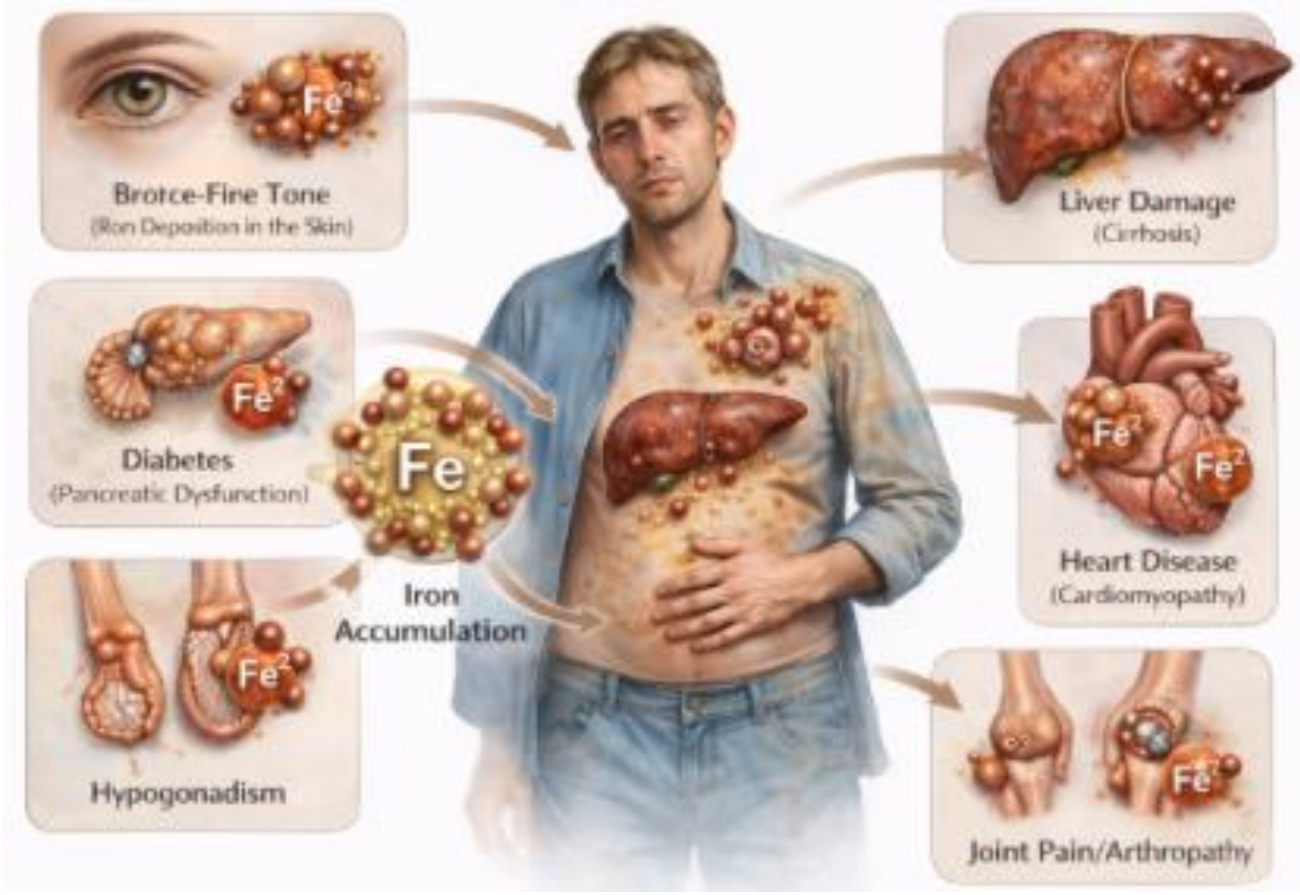
- If suggestive symptoms, physical findings or a family history, transferrin saturation and serum ferritin are ordered to determine the likelihood of iron overload
  - *Transferrin saturation (TS)*
    - TS is a reliable screen for iron overload
    - Fasting TS of >45% is considered a sensitive but not specific threshold for identifying individuals who may have iron overload
  - *Serum ferritin (SF)*
    - In combination with persistent elevation of fasting TS, elevated ferritin is suspicious for iron overload
    - SF is an acute phase reactant that can be elevated by other inflammatory processes. Therefore, an elevated SF does not necessarily imply iron overload and is not a reliable first or only screen

HH: Epidemiology & Clinical Importance

- Prevalence: ~1:200–300 (Northern Europeans)
- C282Y homozygosity most penetrant genotype
- Key drivers of progression: Alcohol, MASLD, male sex, age
- Major cause of preventable cirrhosis

Clinical Spectrum

- Early: Asymptomatic, mild ALT/AST elevation
- Intermediate: Fatigue, arthralgia (2nd/3rd MCP joints)
- Advanced: Cirrhosis, portal hypertension
- Extrahepatic: Diabetes, hypogonadism, cardiomyopathy
- Skin hyperpigmentation (late finding)



Diagnostic Steps

- Elevated ferritin or abnormal LFTs
- Check transferrin saturation (TSAT)
- TSAT ≥45% → high suspicion
- Order HFE genetic testing
- C282Y homozygous → confirm HH
- Assess fibrosis (FibroScan, MRI, biopsy if needed)
- If non-HFE or unclear → MRI iron quantification
- Evaluate secondary causes (transfusion, MASLD, alcohol)

HH: Medical Management Strategy

- Induction phlebotomy: Weekly (remove 500 mL blood)
- Target ferritin: 50–100 ng/mL
- Maintenance: Q2–4 months lifelong
- Monitor Hb, ferritin, TSAT regularly
- Avoid iron supplements, limit alcohol

HH: Advanced Disease & Surveillance

- Cirrhosis → HCC risk persists despite iron removal
- Ultrasound ± AFP every 6 months
- Manage portal hypertension per guidelines
- Cardiac iron: consider MRI + cardiology input
- Family screening (first-degree relatives) recommended