WILLKOMMEN!

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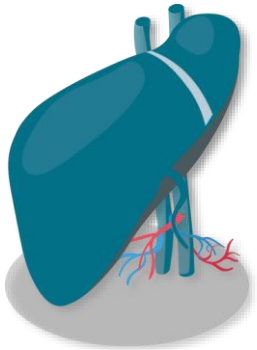
Autoimmune und metabolische Lebererkrankungen



Prof. Dr. med. Oliver Frey | Dr. rer. nat. Brit Kieselbach

Institut für Medizinische Diagnostik Berlin

18.06.2025

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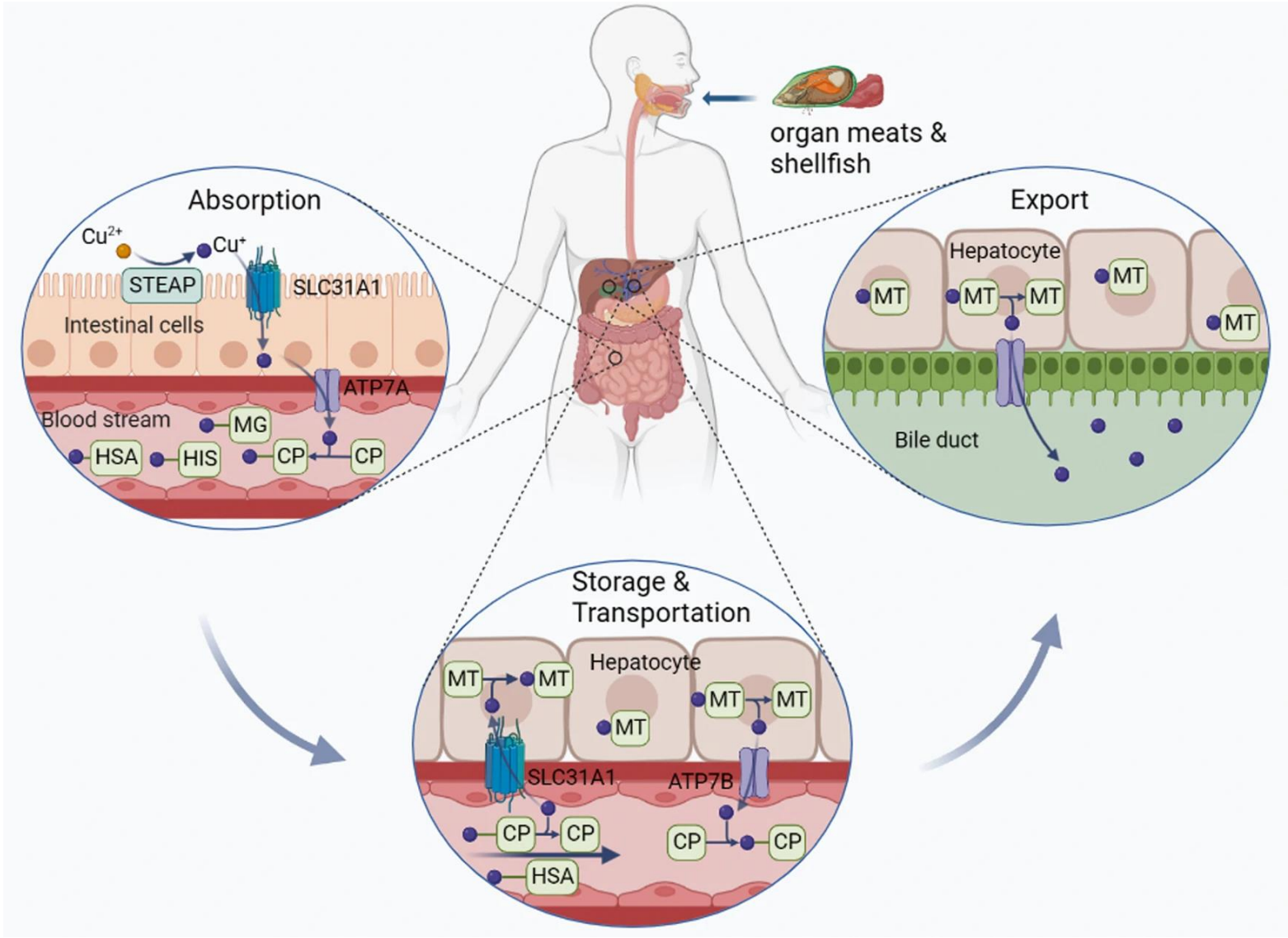
Was haben wir bereits besprochen?

- „Leberpanel“: welche Untersuchungen zum Screening?
- Weitere Abklärung in Abhängigkeit von der Höhe (nur Dynamik, nicht ob!)
- Ausschluss chronischer (und akuter) viraler Hepatitis
- Fibrosescores zur Risikoabschätzung

Übersicht

- Seltene (und nicht so seltene) Erkrankungen, die die Leber betreffen (können)
  - Morbus Wilson
  - Hereditäre Hämochromatose
  - Alpha-1-Antitrypsinmangel
  - Autoimmun-Hepatitis
  - Primär Biliäre Cholangitis
  - Primär Sklerosierende Cholangitis
- Wann welche Diagnostik durchführen?

Morbus Wilson



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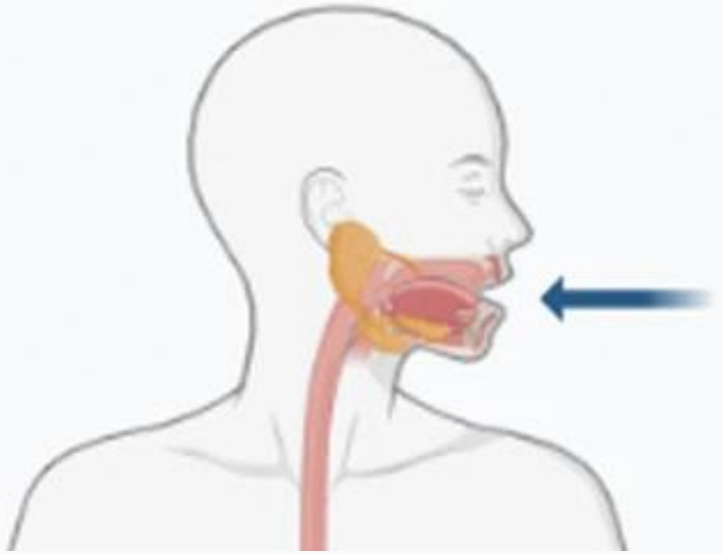
Morbus Wilson



Kupferhaltige Lebensmittel

- Kakaopulver: 4,2 mg/100 g
- Cashew: 2 mg/100 g
- Paranuss: 1,8 mg/100 g
- Schweineleber: 1,3 mg/100 g
- Garnele: 1,1 mg/100g
- Kichererbsen: 0,8 mg/100g
- Haferflocken: 0,4 mg/100 g

Angemessene Zufuhr

- 1-15 mg/d
- Mangel bei Malabsorbtion, Cave Zink!

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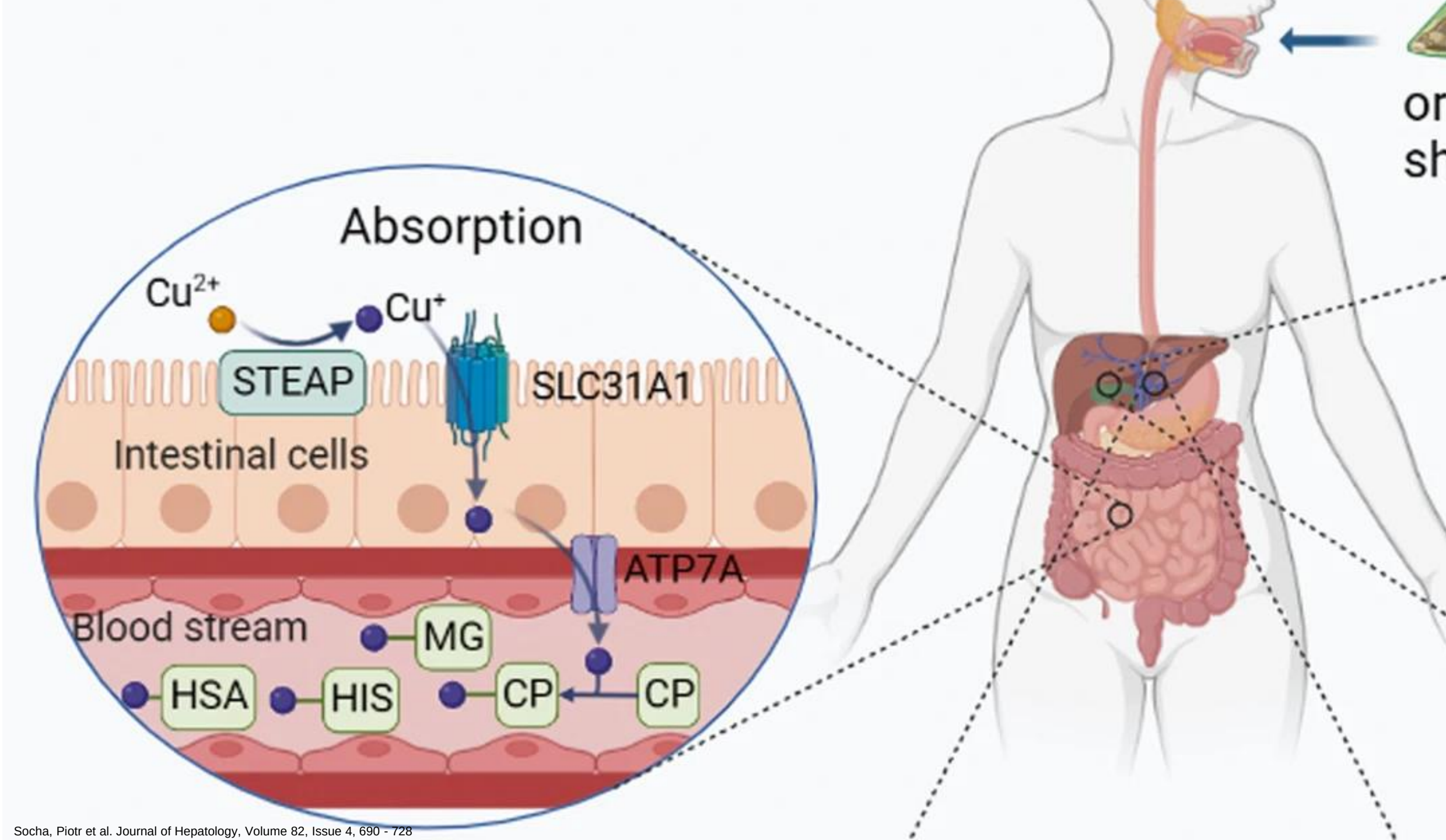

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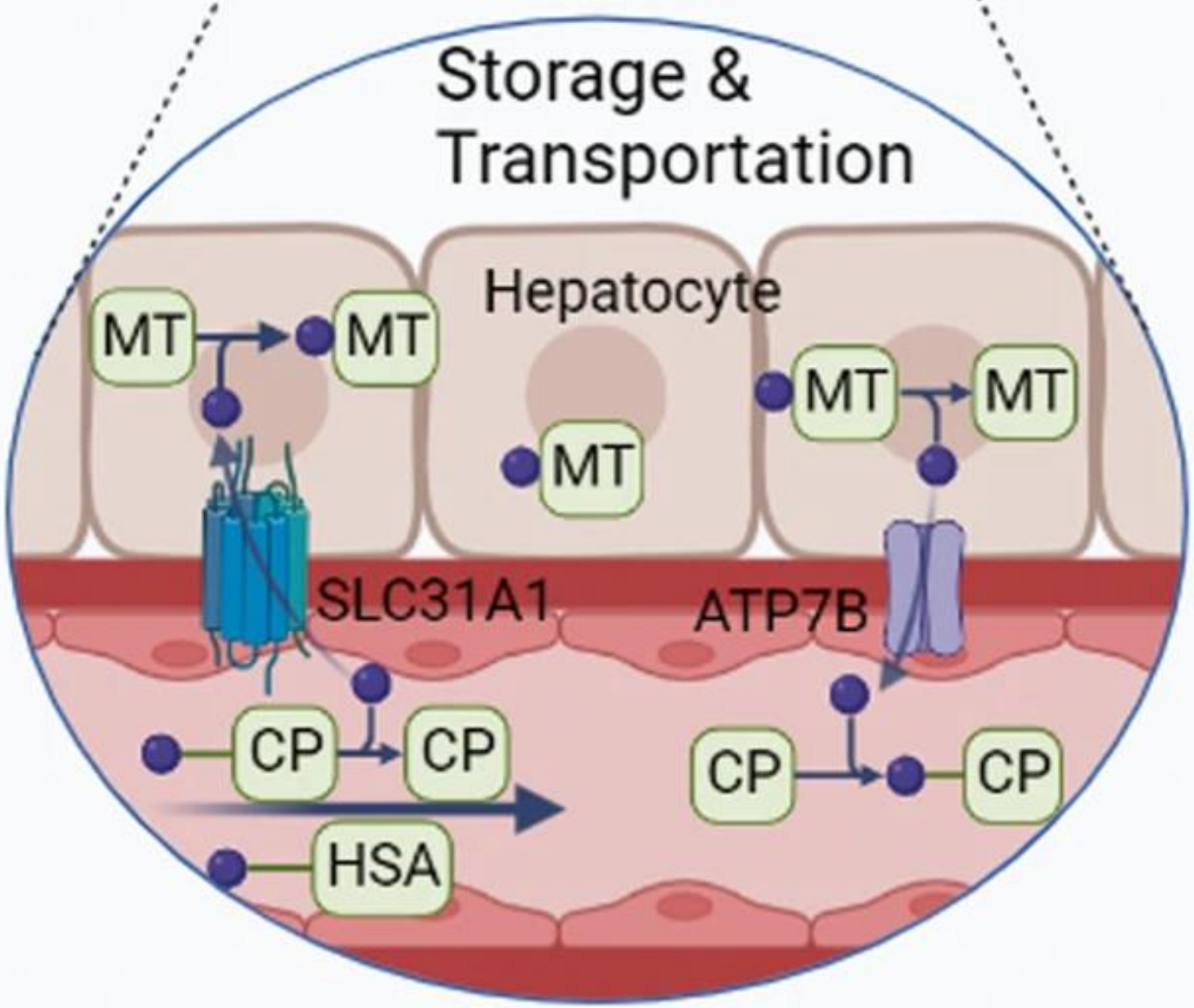

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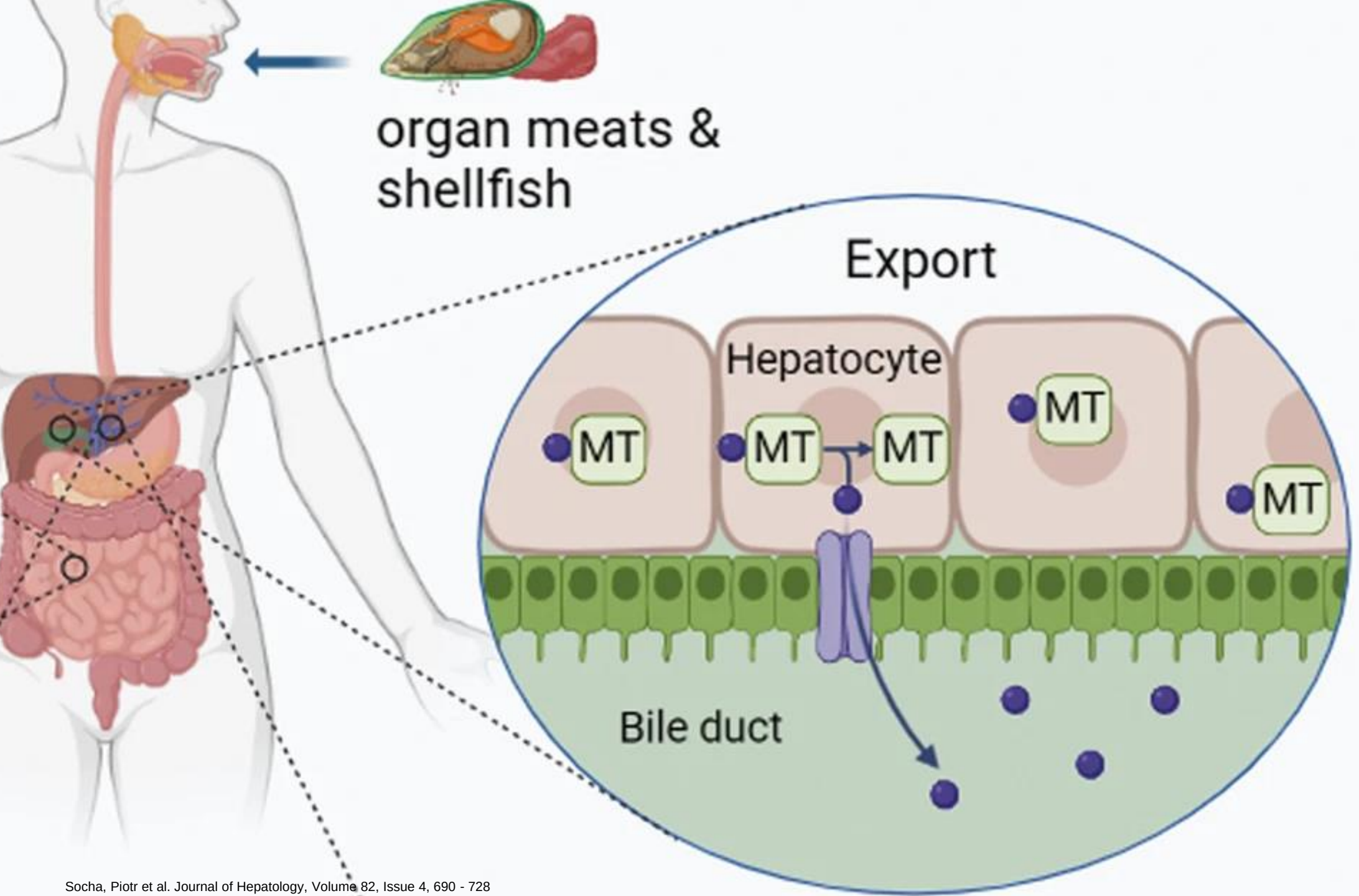

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Morbus Wilson

- Prävalenz 30 auf 1.000.000 Menschen
- Mutation im Gen *ATP7B*
- Insgesamt 2.700 Varianten, davon 800 sicher pathologisch
- toxische Akkumulation von Kupfer in Leber, Nervensystem und anderen Organen
- Variable Ausprägung der Symptome

Daran denken ist der wichtigste Schritt!

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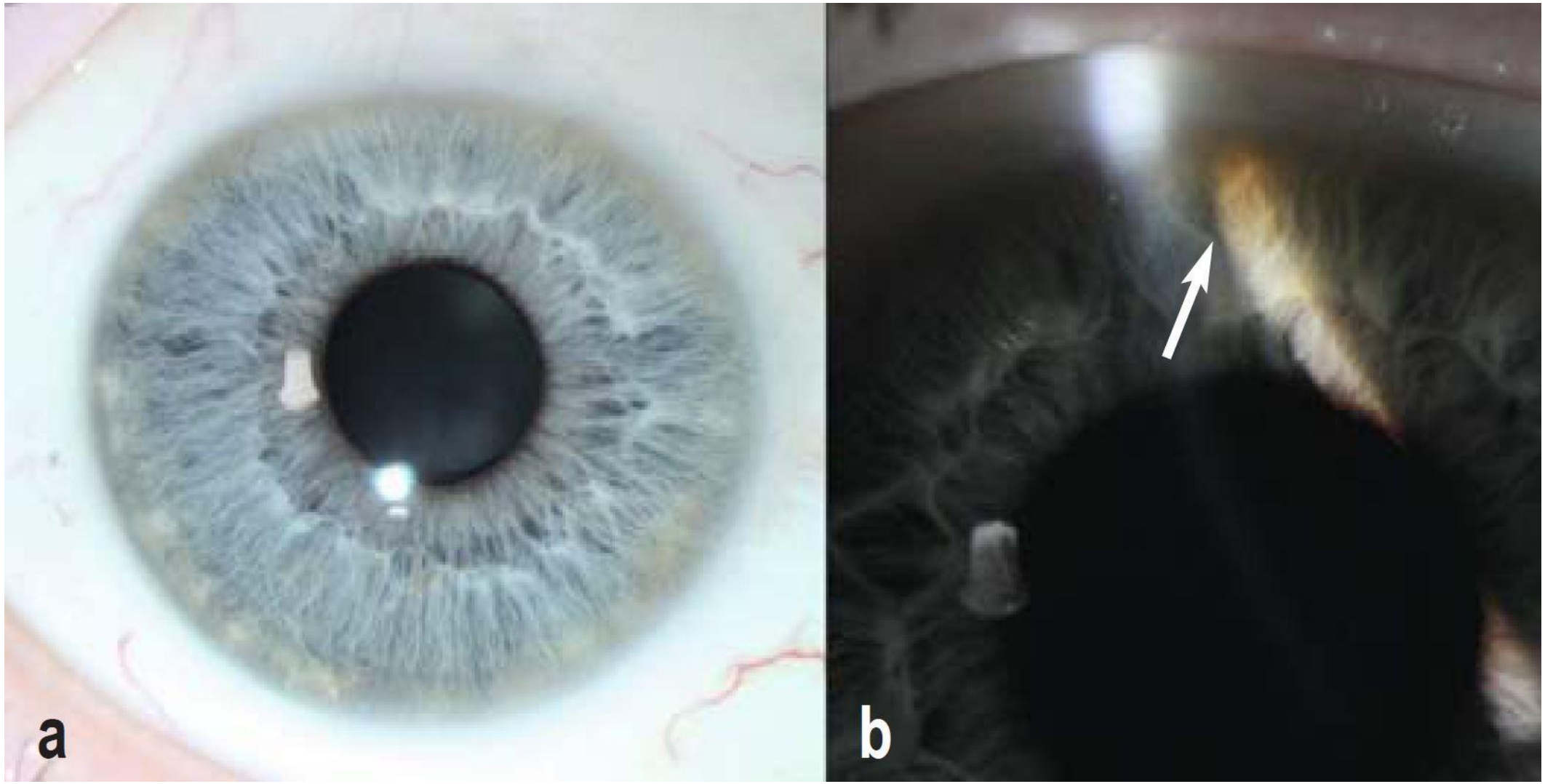
Morbus Wilson: Manifestationsalter

- kann in jedem Alter auftreten
- Hauptmanifestationsalter zwischen 5 und 35 Jahren
- Fallberichte von 3-jährigen
- 3-8% der Patienten nach dem 40ten Lebensjahr

Morbus Wilson: Klinische Features



Dtsch Arztebl Int 2024; 121: 544; DOI: 10.3238/arztebl.m2024.0048

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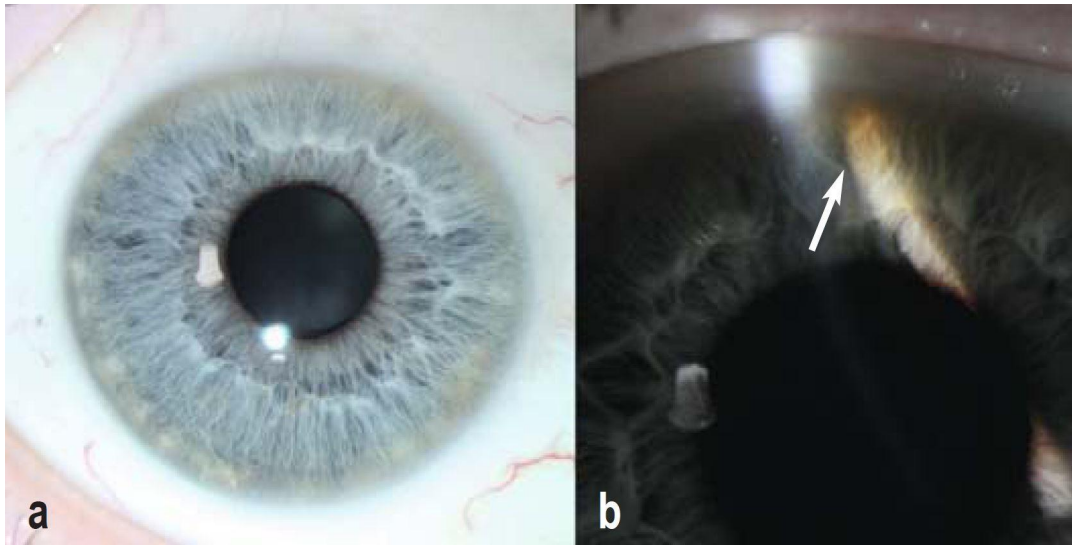
Morbus Wilson: Klinische Features

Kayser-Fleischer-Cornealring:

- >95 % der Patienten mit neurologischen Symptomen
- ~ 50 % der Patienten ohne neurologische Symptome
- kaum bei Kindern



Dtsch Arztebl Int 2024; 121: 544; DOI: 10.3238/arztebl.m2024.0048

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Morbus Wilson: Klinische Features

Leber:

- Labormedizinisch: Leberzellschaden
- Hepato-/Splenomegalie, Steatosis
- Portale Hypertension, Zirrhose
- Aszites, HE, Ikterus

Table 3. Frequency of clinical symptoms in patients with Wilson's disease presenting with liver disease.

Author (Country, Ref)	Walshe (UK)[67]	Stremmel/Merle (Ger)[23,68]	Taly (India)[69]	Scott (UK)[70]	Ferenci (Austria)[23,71]
No. with liver disease (out of)	87 (>250)	34/96 (51/163)	52 (282)	17* (45)	30 (64)
Presenting symptom [% of patients presenting with liver disease]					
Jaundice, anorexia, vomiting (%)	44	27/28	40	41	37
Ascites/oedema (%)	26	21/21	12.4	24	23
Variceal haemorrhage (%)	6		<1	6	3
Haemorrhagic diathesis (%)	8		3		3
Haemolysis (%)	20	15/12			10
Hepatomegaly/splenomegaly (%)	16	74/47	39	29	17
Fulminant hepatic failure (%)	NA	0/8	NA	NA	17
Asymptomatic[$] (%)	NA	18/7.4	5		23

*Only cases with chronic active hepatitis.
[$]Elevated alanine aminotransferase at routine testing, or incidental finding of cirrhosis or Kayser-Fleischer rings.

Socha, Piotr et al. Journal of Hepatology, Volume 82, Issue 4, 690 - 728

Morbus Wilson: Klinische Features

Neurologisch (40-60% Erstmanifestation!):

- Tremor, Dysarthrie, Ataxie, Dystonie…..

TABLE 2 Summary of neurological symptoms at presentation of Wilson disease based on four independent case series[31,37,280,419]

Neurological manifestations at onset	% of patients	Treatments
Dysarthria	46–97	Speech therapy
Gait abnormality/ ataxia/cerebellar	28–75	Physical therapy, assistive device
Dystonia	38–69	Trihexyphenidyl, botulinum toxin (for focal symptoms), clonazepam
Parkinsonism	12–58	Carbidopa/levodopa, dopamine agonist
Postural tremor	55	Primidone, propranolol, clonazepam
Dysphagia	50	Swallow therapy, thickeners
Chorea/athetosis	6–30	Neuroleptics, VMAT2 inhibitors
Seizures	6–28	Anticonvulsants
Rest tremor	4	Carbidopa/levodopa, dopamine agonist

Abbreviation: VMAT2, vesicular monoamine transporter-2.

Shilsky ML, et al. Hepatology. 2022 Dec 7 doi: 10.1002/hep.32801

Morbus Wilson: Klinische Features

Psychiatrisch:

- depressive Verstimmung, Antriebslosigkeit, schizophrene Psychose, Unruhe, Gedächtnisstörungen….

Hämatologisch:

- Coombs-negative hämolytische Anämie

Sonstige:

- Akromegalie, Nierenschädigung, Kardiomyopathie, Hypoparathyreoidismus, Osteopenie, Pankreatitis, Infertilität, Fehlgeburten….

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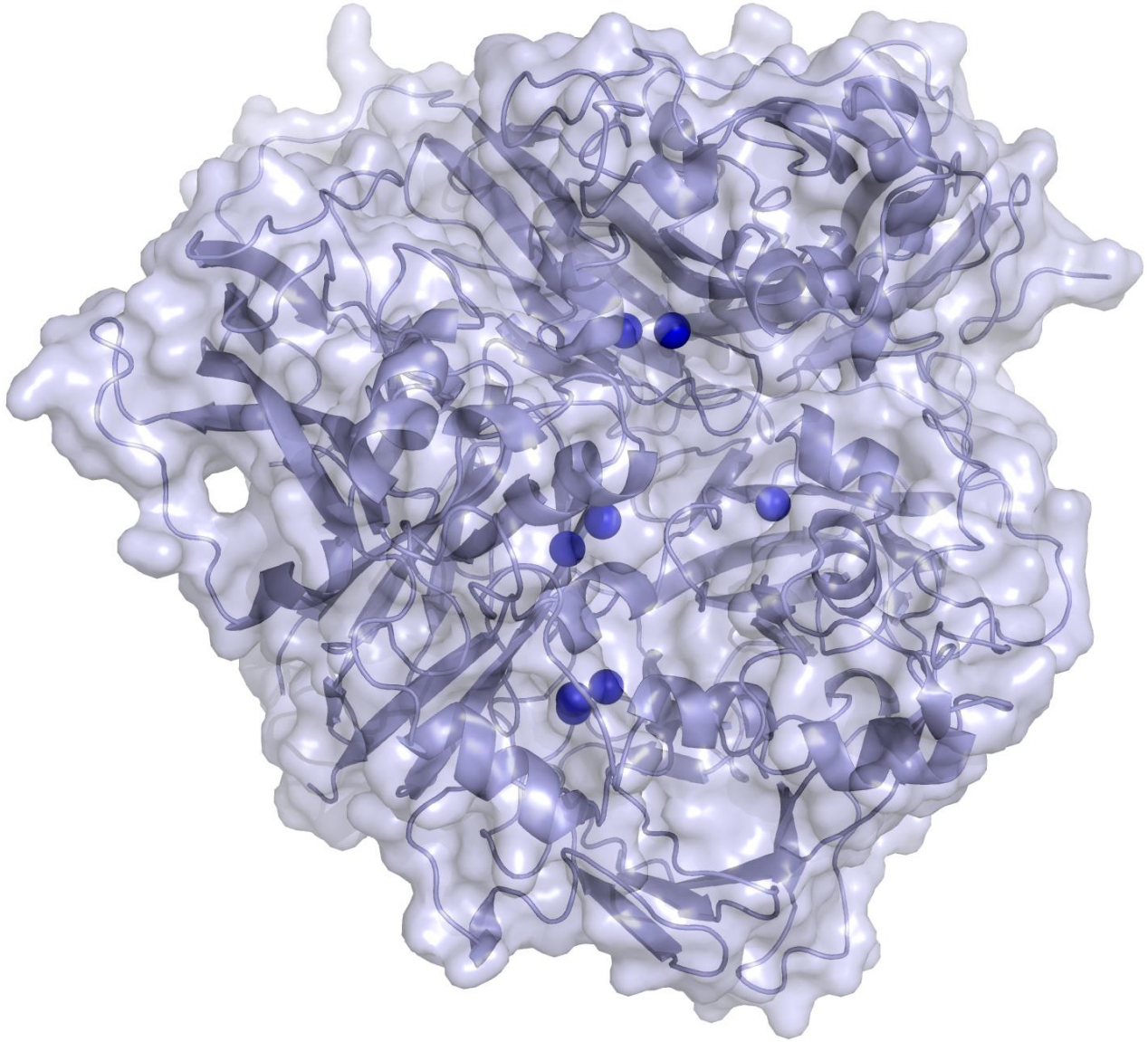
Morbus Wilson: Differentialdiagnose

- verstärkte Kupferakkumulation bei cholestatischen Erkrankungen (PSC, PBC, chron. Hep. C)
- Fettlebererkrankungen (MASLD, ARLD)
- AAk-Nachweis

Diagnostik: Coeruloplasmin



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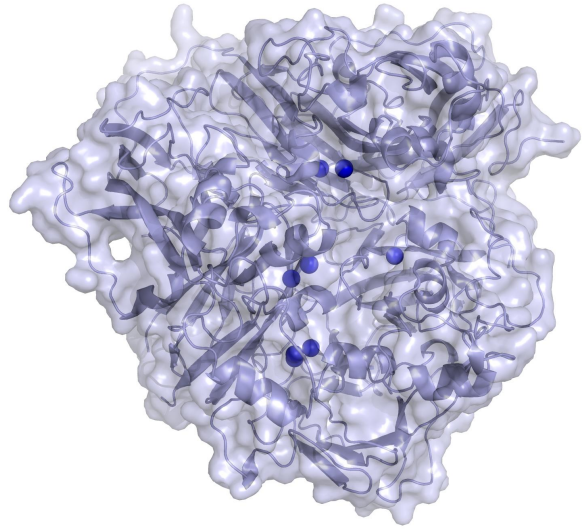
Diagnostik: Coeruloplasmin

- 132 kDa
- transportiert 90 % des Kupfers
- Akut-Phase-Protein
- Cave: Kinder!
- Sensitivität abhängig vom Cut-Off



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Diagnostik: Kupfer

- Gesamtkupfer im Serum (ca. 90 % an Coeruloplasmin gebunden)
- Freies Kupfer: Differenz aus Gesamtkupfer und CP-gebundenem Kupfer
- Kupfer im 24h-Sammelurin: Sensitivität abhängig vom Cut-Off
- Kupfer im 24h-Sammelurin nach d-Penicillamin-Gabe

Diagnostik: Kupfer

- REC (Relative Exchangable Copper): „locker“ an Albumin gebundenes Kupfer
- wird *in vitro* mit Chelator mobilisiert und gemessen
- Ratio aus „mobilisierbarem“ Kupfer und Gesamtkupfer
- >18,5 % spricht für Mb. Wilson

Diagnostik: Kupfer

- Kupfergehalt der Leber: invasiv

Table 5. Diagnostic value of copper metabolism parameters.

	Normal values	High suspicion of Wilson's disease
Serum ceruloplasmin	20–40 mg/dl	<10 mg/dl
24-h urinary copper excretion	<40 µg (<0.65 µmol) in children <50 µg (0.8 µmol) in adults	>100 µg (1.6 µmol)
Relative exchangeable copper (%)	3.4-8%	>15%
Liver copper content	<50 µg/g dry weight	>250 µg/g dry weight (>4 µmol/g dry weight)

Socha, Piotr et al. Journal of Hepatology, Volume 82, Issue 4, 690 - 728

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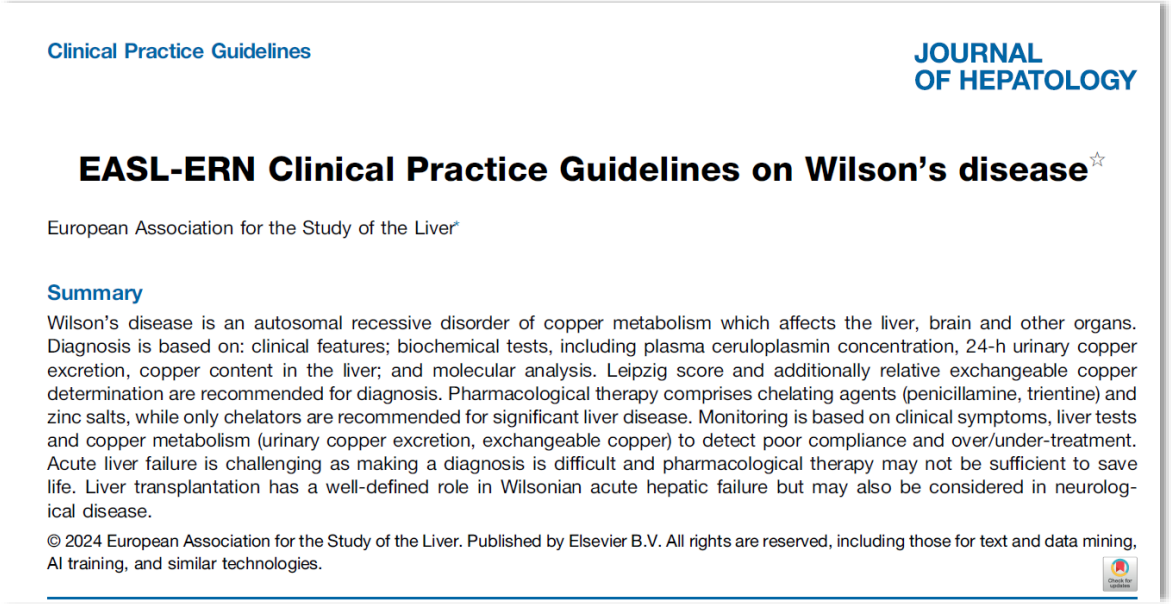
Empfehlung

- Coeruloplasmin und Kupferausscheidung im 24h Urin
- REC



Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL-ERN Clinical Practice Guidelines on Wilson's disease☆

European Association for the Study of the Liver*

Summary

Wilson's disease is an autosomal recessive disorder of copper metabolism which affects the liver, brain and other organs. Diagnosis is based on: clinical features; biochemical tests, including plasma ceruloplasmin concentration, 24-h urinary copper excretion, copper content in the liver; and molecular analysis. Leipzig score and additionally relative exchangeable copper determination are recommended for diagnosis. Pharmacological therapy comprises chelating agents (penicillamine, trientine) and zinc salts, while only chelators are recommended for significant liver disease. Monitoring is based on clinical symptoms, liver tests and copper metabolism (urinary copper excretion, exchangeable copper) to detect poor compliance and over/under-treatment. Acute liver failure is challenging as making a diagnosis is difficult and pharmacological therapy may not be sufficient to save life. Liver transplantation has a well-defined role in Wilsonian acute hepatic failure but may also be considered in neurological disease.

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PRACTICE GUIDANCE

AASLD

A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases

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Leipzig-Score

Table 6. Diagnostic Leipzig score in Wilson's disease.

Score	-1	0	1	2	4
Kayser-Fleischer rings		Absent		Present	
Neuropsychiatric symptoms suggestive of Wilson's disease (or typical brain MRI)		Absent		Present	
Coombs-negative haemolytic anaemia + high serum copper		Absent	Present		
24-h urinary copper excretion (in the absence of acute hepatitis)		Normal	1-2x ULN	>2x ULN, or normal but >5x ULN during challenge with 2 x 0.5 g D-penicillamine	
Liver copper quantitative	Normal		<5x ULN (<250 µg/g)	>5x ULN (>250 µg/g)	
Rhodanine positive hepatocytes (only if quantitative copper measurement is not available)		Absent	Present		
Serum ceruloplasmin (nephelometric assay)		>0.2 g/L	0.1-0.2 g/L	<0.1 g/L	
Disease-causing mutations detected		None	1		2
Assessment of the Wilson's disease diagnostic score					
0-1: unlikely	**2-3: probable**			**4 or more: highly likely**	

ULN, upper limit of normal.

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Diagnosealgorithmus

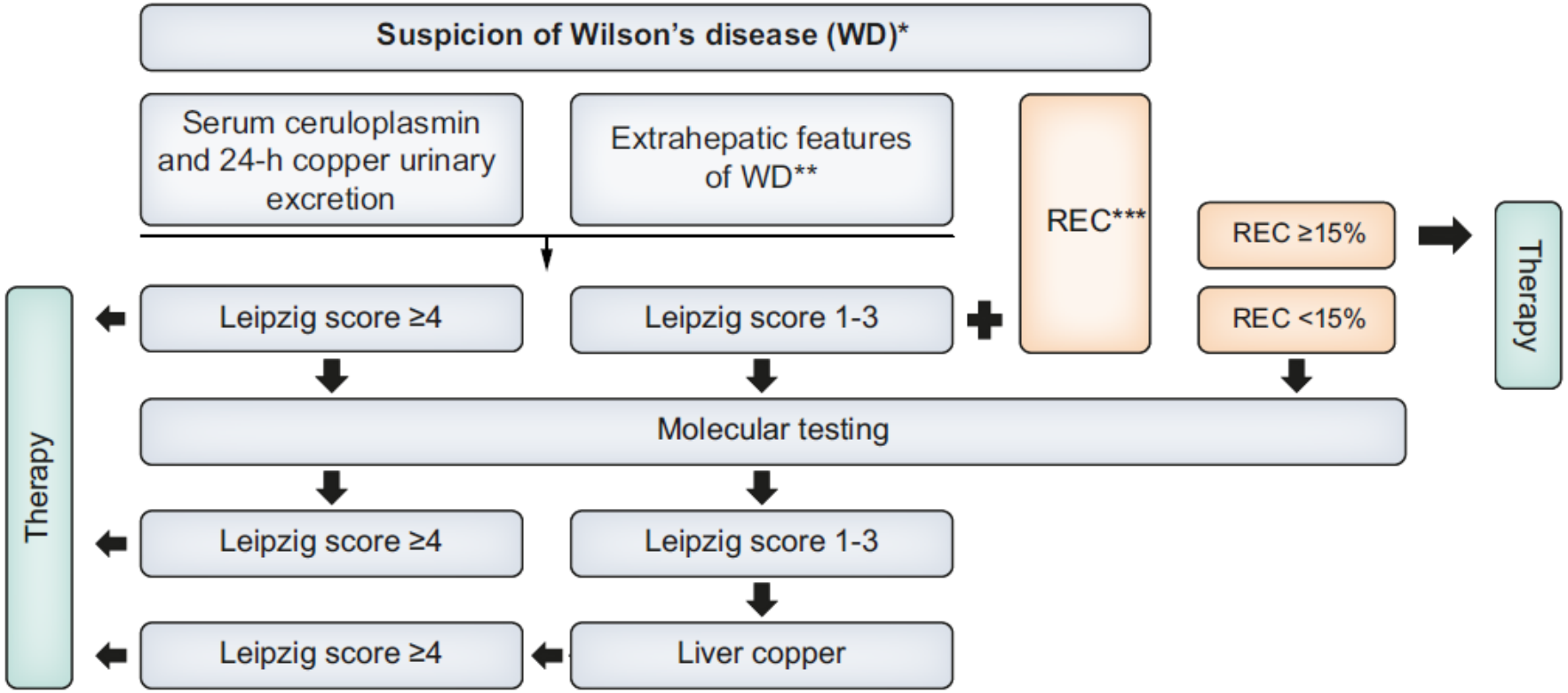

Fig. 2. Diagnostic algorithm. REC, relative exchangeable copper. *family screening may be performed by specific pathways including direct molecular testing **including neurological symptoms, Kayser-Fleischer Corneal-rings & Coombs-negative hemolytic anemia ***REC, relative exchangeable copper as percentage of exchangeable to total serum copper.

Socha, Piotr et al. Journal of Hepatology, Volume 82, Issue 4, 690 - 728

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Mb. Wilson: Take home

Wen testen?

- alle Patienten mit unklarer Leberwerterhöhung und/oder neurologischen/psychiatrischen Symptomen, unabhängig vom Alter

Wie testen?

- Coeruloplasmin und Kupferausscheidung im 24h Urin
- REC, wenn möglich
- Genetik zur Bestätigung

Hämochromatose

Eisenüberladung auf Grund eines genetisch verursachen Mangels an Hepcidin

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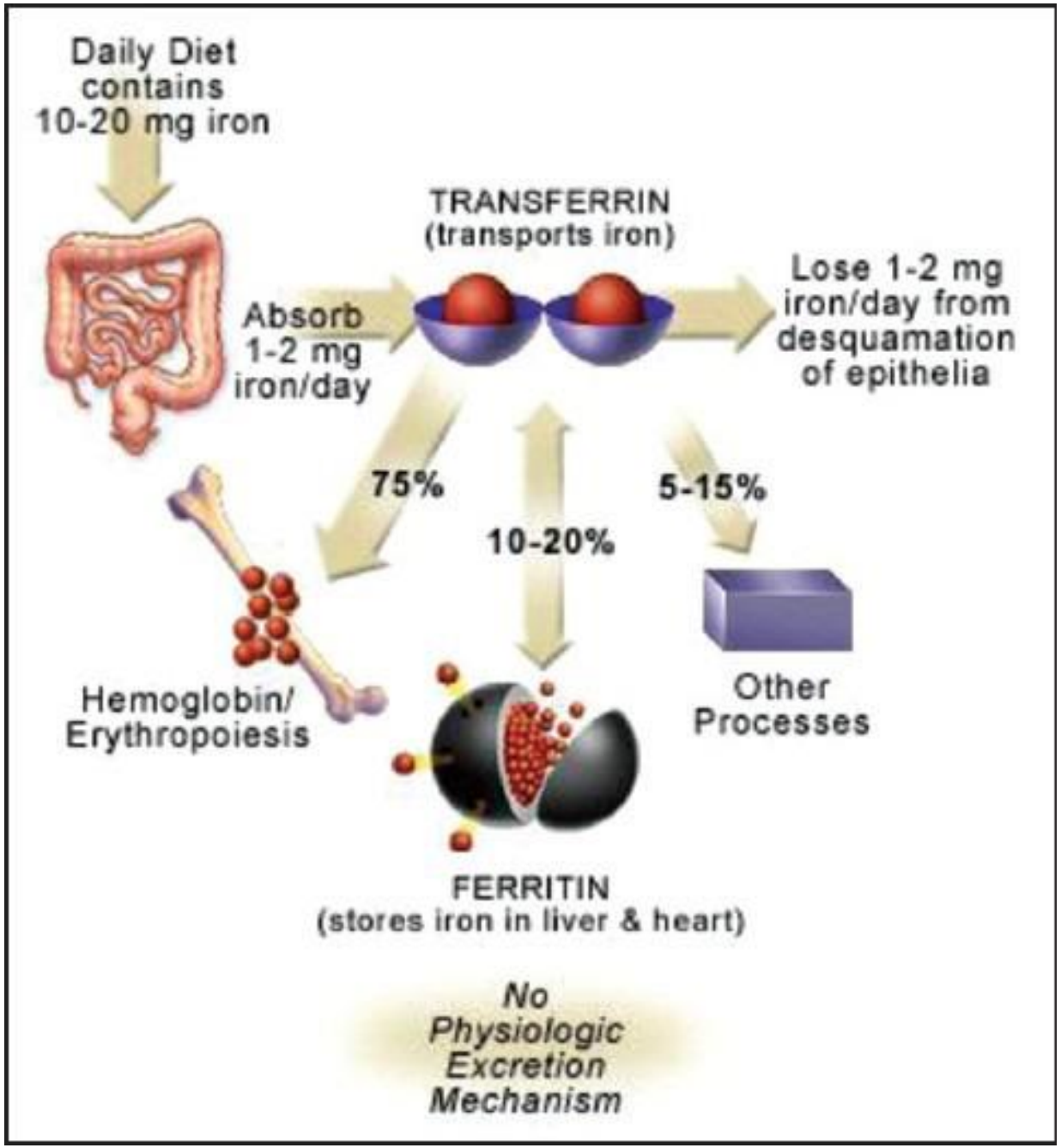

Abbaspour N. et al. J Res Med Sci. 2014 Feb;19(2):164-74.

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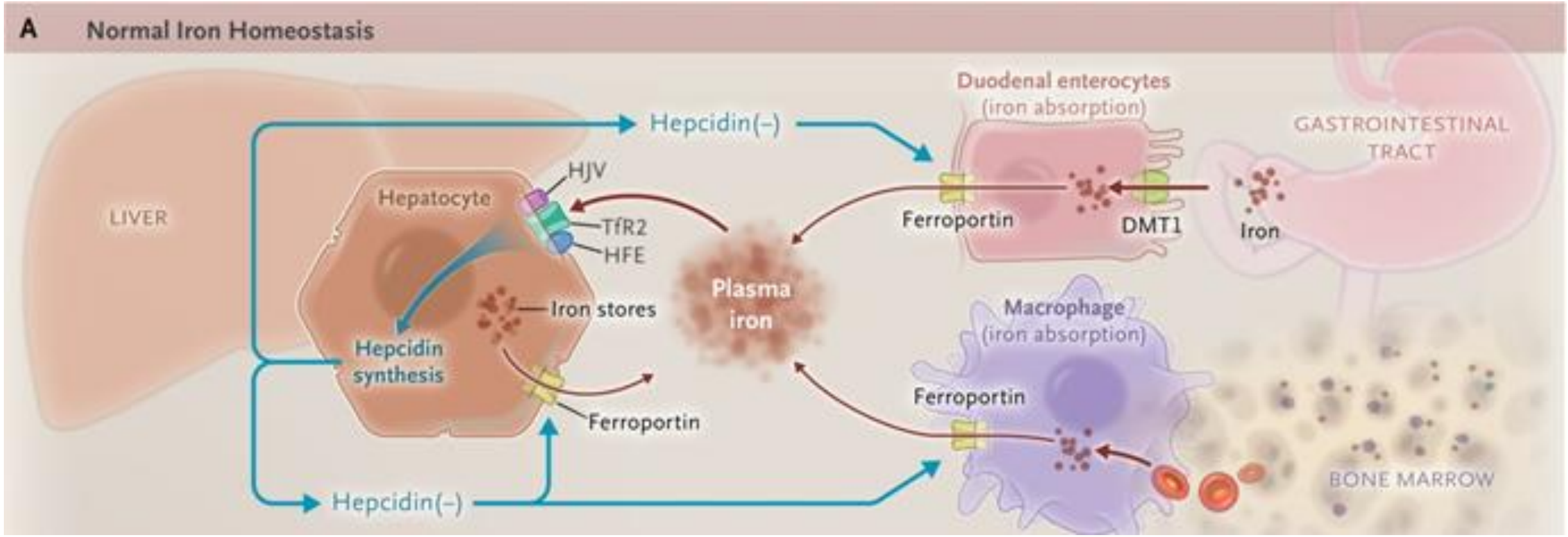
Normaler Eisenstoffwechsel



Olynyk JK, Ramm GA. N Engl J Med2022;387:2159-2170

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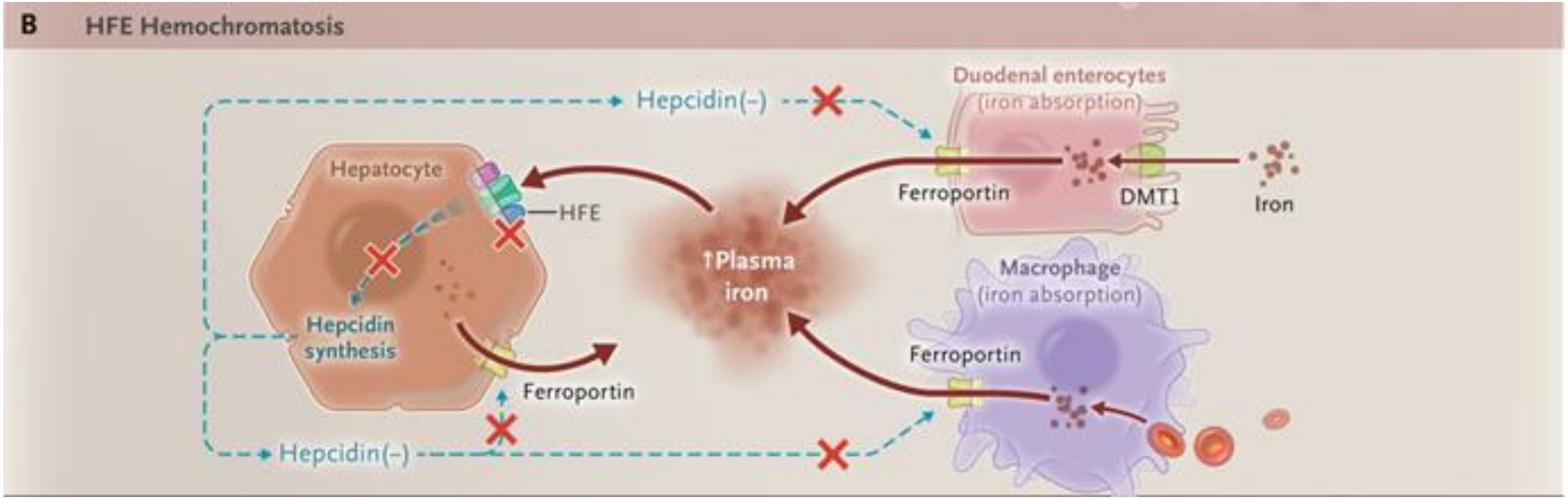
HFE-Hämochromatose



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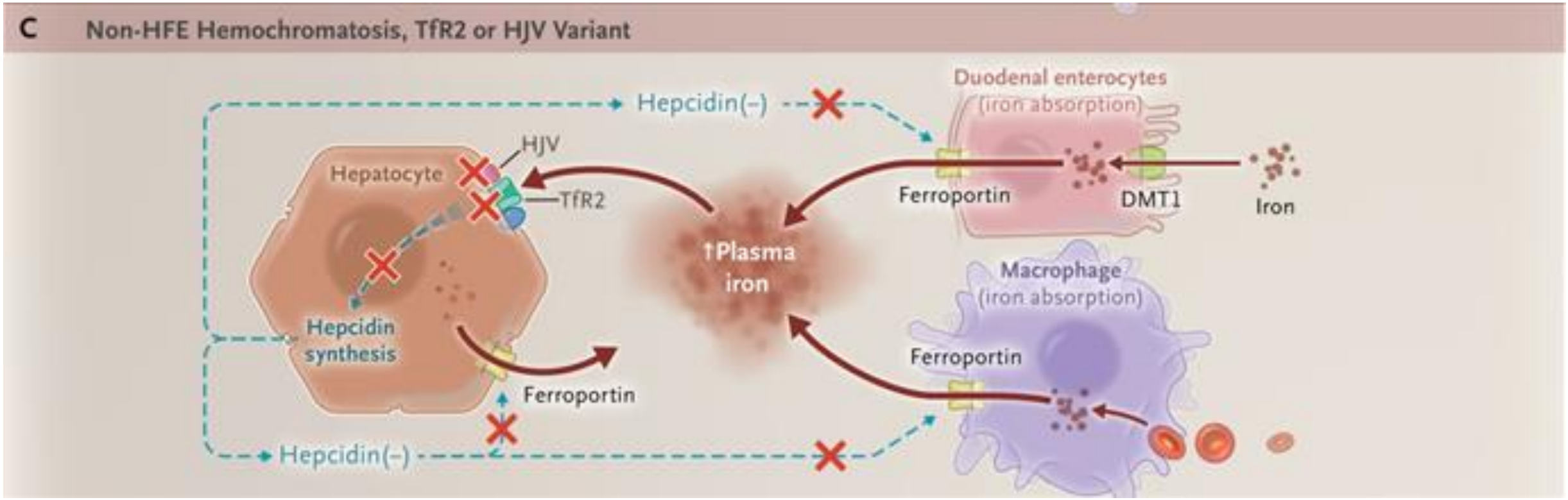
TfR2, HJV-Hämochromatose



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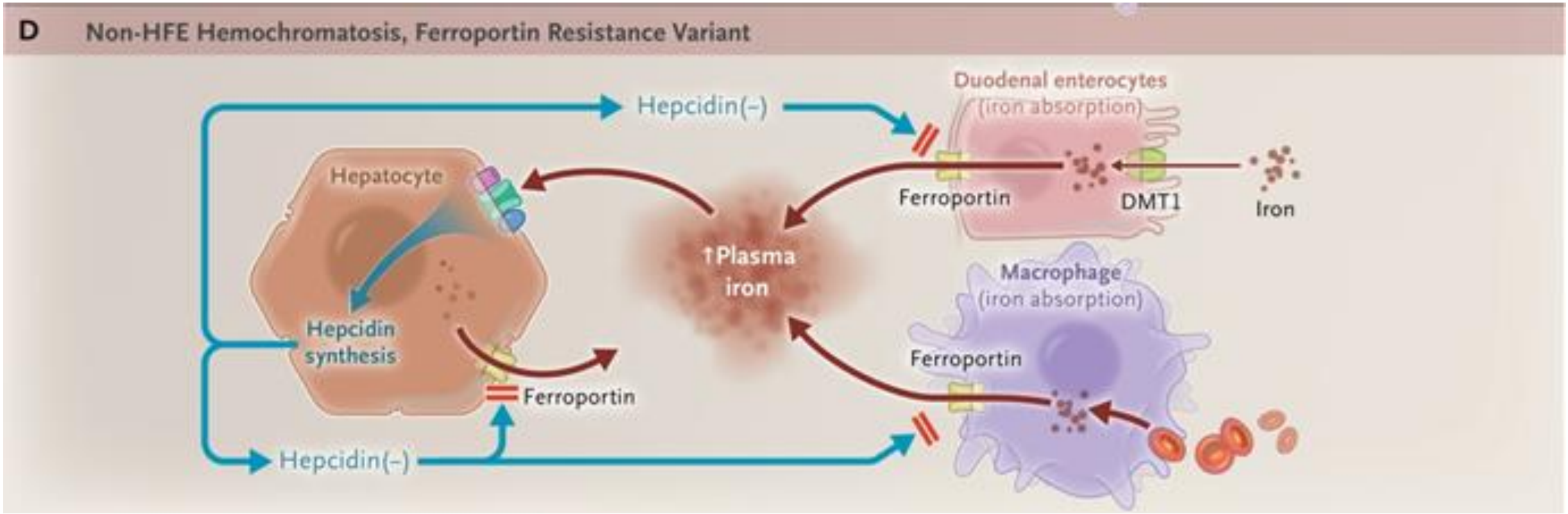
Ferroportin-Hämochromatose



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Hämochromatose: Genetik

Table 1. Classification of Hemochromatosis According to the Molecular Target.*

Variable	HFE Hemochromatosis	Non-HFE Hemochromatosis	
Molecular target	*HFE*	Genes encoding HJV, hepcidin, or TfR2	Gene encoding ferroportin
Frequency	Common; often due to p.C282Y homozygosity; in rare cases, due to compound heterozygosity	Very rare	Very rare
Population at risk	Northern European origin	Any population	Any population
Age group at clinical risk	Adults	Persons <30 yr of age (with HJV or hepcidin as target), or adults (with TfR2 as target)	Adults
Mechanism	Loss of function of target	Loss of function of target	Gain of function of target, resistance to hepcidin
Hepcidin production	Reduced	Reduced	Increased

* The classification is from Girelli et al.[1] HFE hemochromatosis is caused by mutation of *HFE* (most often the homozygous p.C282Y mutation), whereas non-HFE hemochromatosis is caused by mutation of the genes encoding hemojuvelin (HJV), hepcidin, transferrin receptor 2 (TfR2), or ferroportin.

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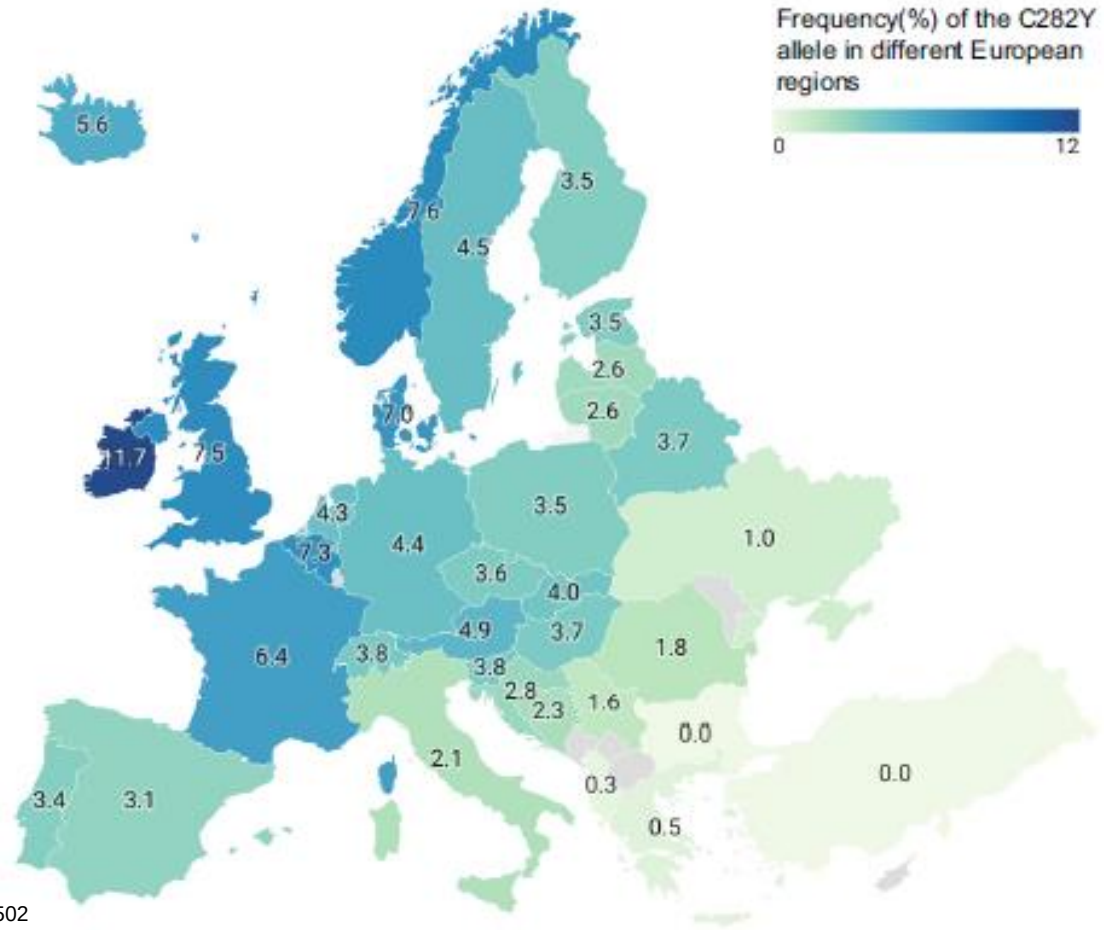
Hämochromatose: Genetik

- 95 % der Fälle beruhen auf einer homozygoten p.C282Y-Mutation



Zoller, Heinz et al. Journal of Hepatology, Volume 77, Issue 2, 479 - 502

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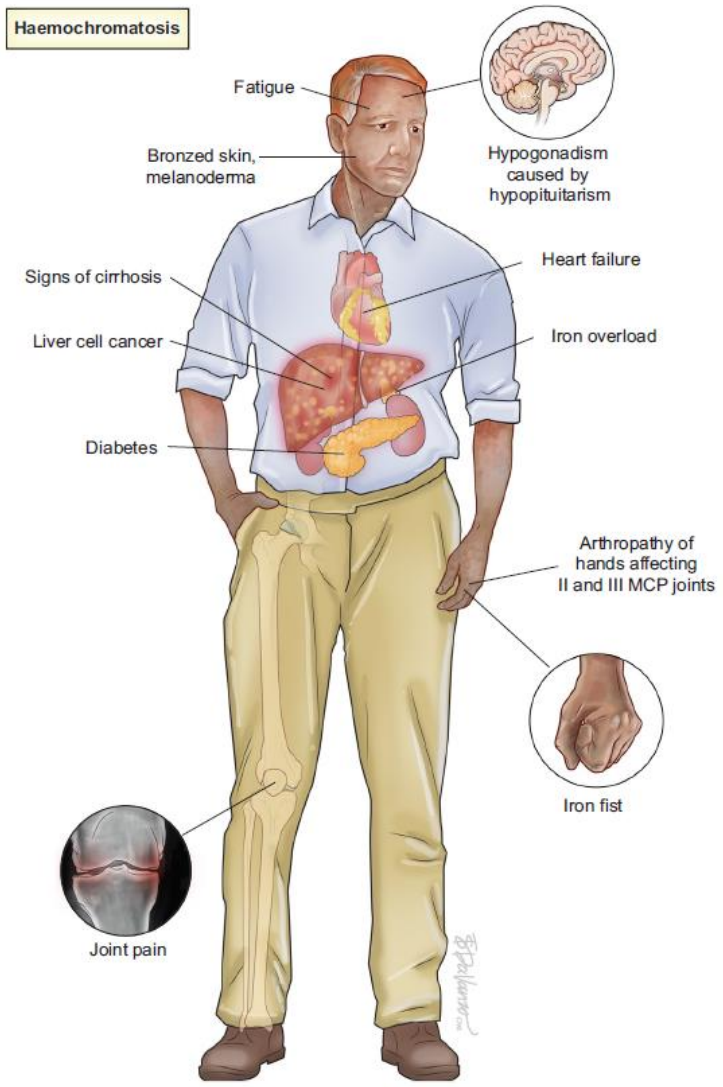
Hämochromatose: Genetik

- 95 % der Fälle beruhen auf einer homozygoten p.C282Y-Mutation
- Allelfrequenz von p.C282Y ist ca. 4,4 %
- Allelfrequenz von p.H63D ist ca. 15 %
- Unterschiedliche Penetranz:
  - 28 bzw. 1,2 % (Männer/Frauen; klinische Eisenüberladung)
  - 82 bzw. 55 % (Männer/Frauen, erhöhtes Ferritin)

Hämochromatose: Klinik



Beteiligung der Leber

- >45 Jahre, 8% der Frauen, 25 % der Männer
- Leber-Fibrose/-Zirrhose
- Hohes Risiko für HCC bei Männer mit p.C282Y ist 12x erhöht (7,2 vs. 0,6 %)

Beteiligung der Gelenke

- Arthritis (MCP, Hüfte, Sprunggelenk, Handgelenk, Ellenbogen, Schulter, Knie)
- Abgrenzung zur Arthrose kann schwierig sein

Andere

- Hyperpigmentation, Hypogonadotroper Hypogonadismus, Kardiomyopathie

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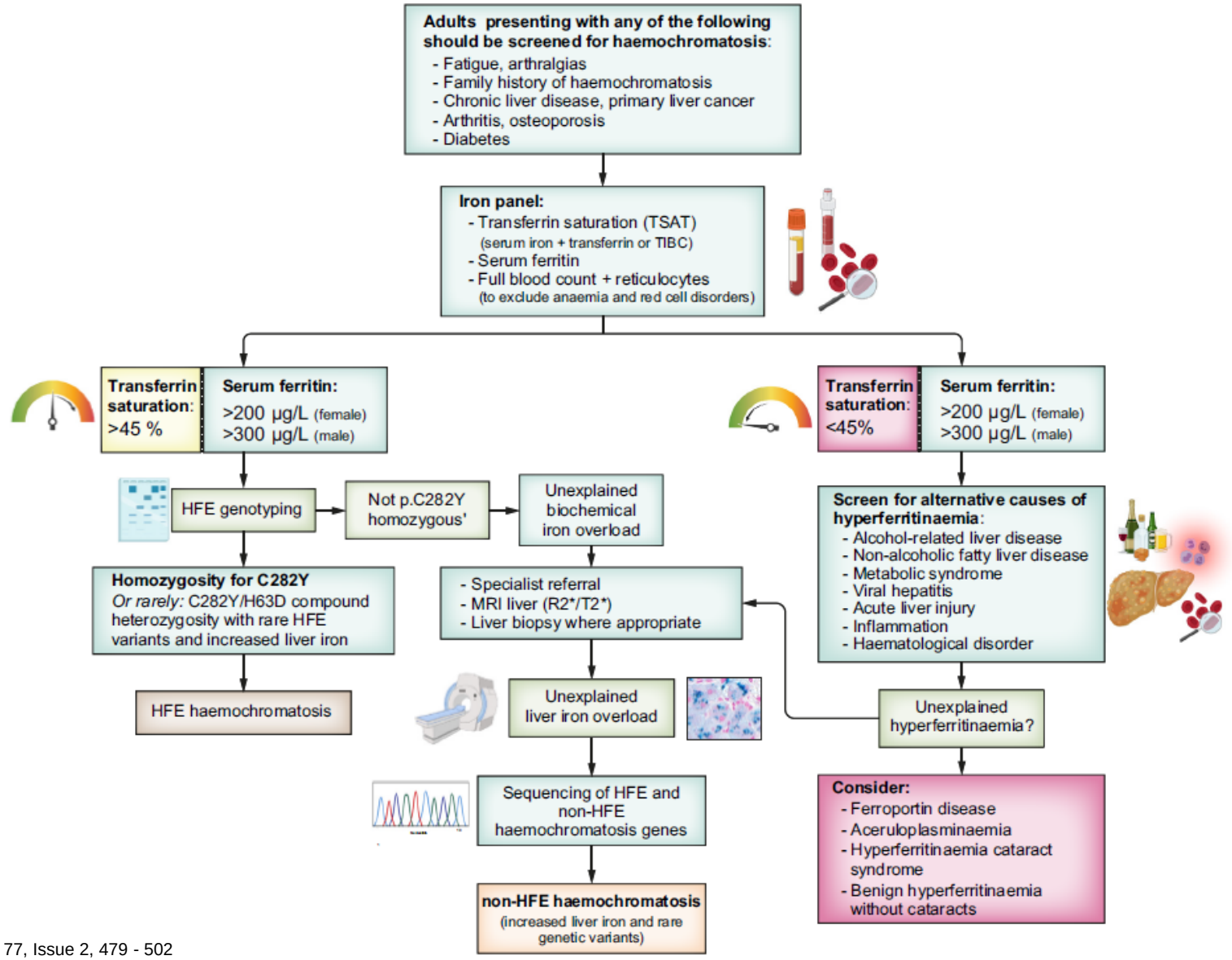
Hämochromatose: Diagnostik



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Hämochromatose: Diagnostik

Adults presenting with any of the following should be screened for haemochromatosis:

- Fatigue, arthralgias
- Family history of haemochromatosis
- Chronic liver disease, primary liver cancer
- Arthritis, osteoporosis
- Diabetes

↓

Iron panel:

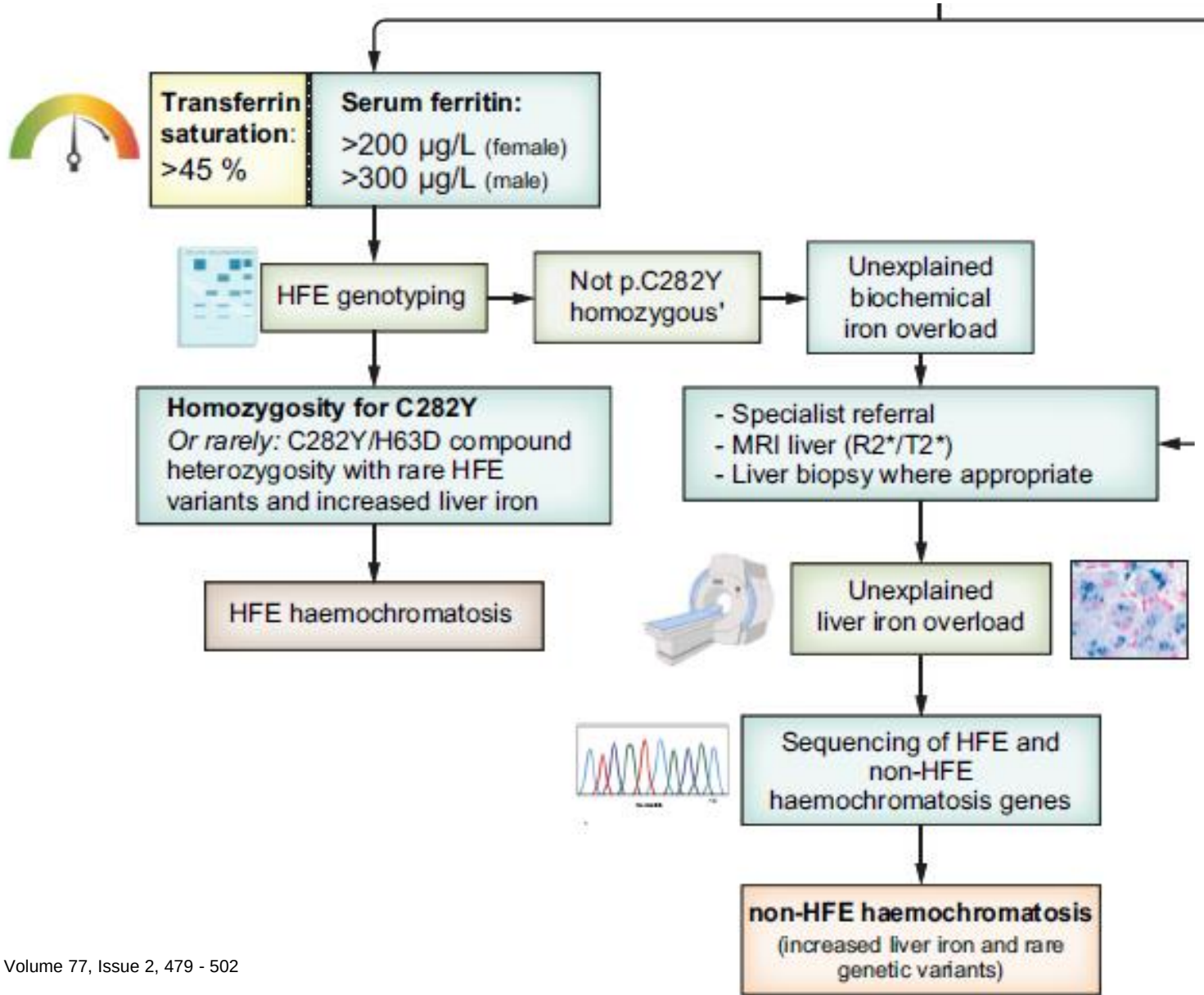
- Transferrin saturation (TSAT)
  (serum iron + transferrin or TIBC)
- Serum ferritin
- Full blood count + reticulocytes
  (to exclude anaemia and red cell disorders)

Zoller, Heinz et al. Journal of Hepatology, Volume 77, Issue 2, 479 - 502

Hämochromatose: Diagnostik

Zoller, Heinz et al. Journal of Hepatology, Volume 77, Issue 2, 479 - 502

Hämochromatose: Diagnostik



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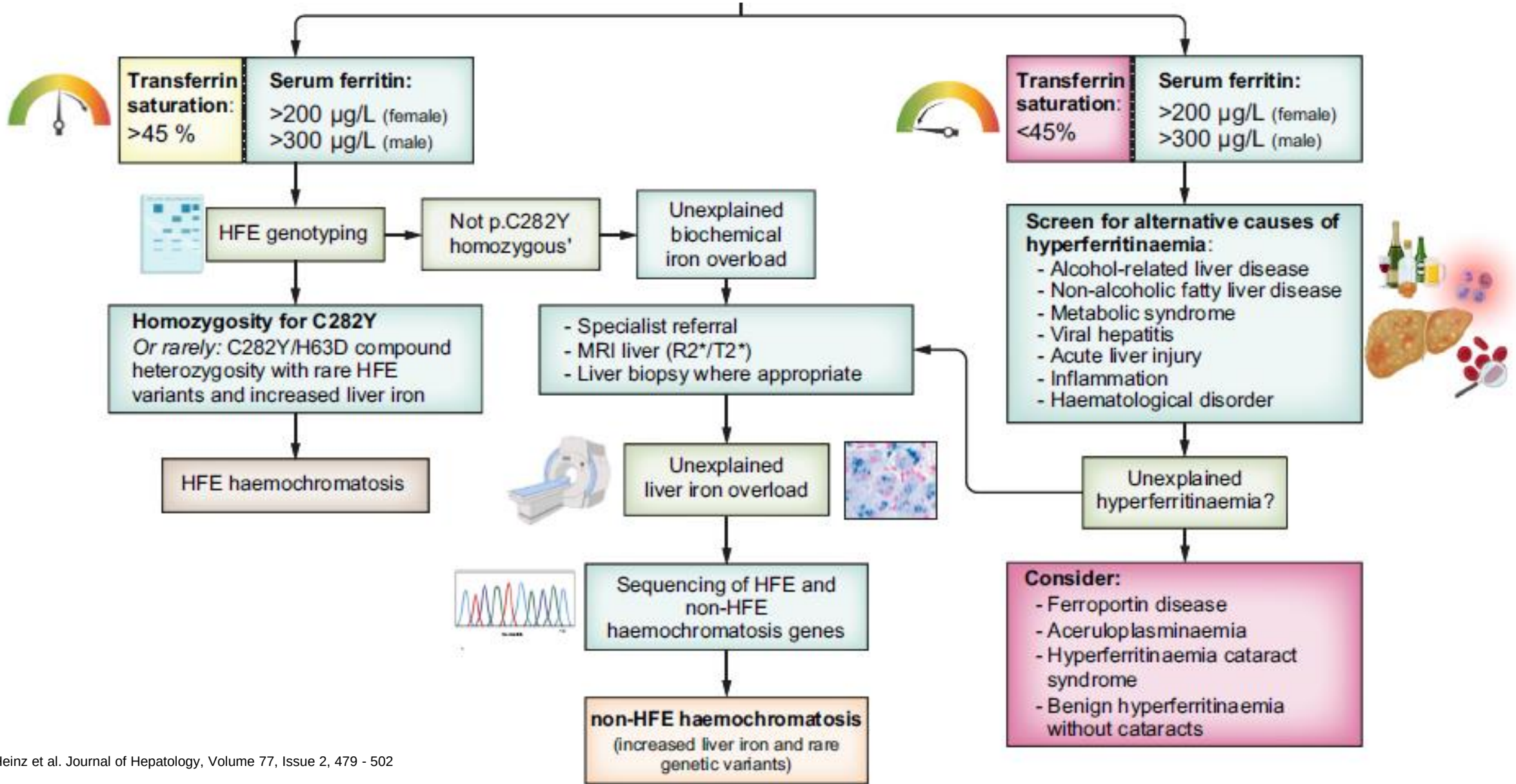
Hämochromatose: Diagnostik



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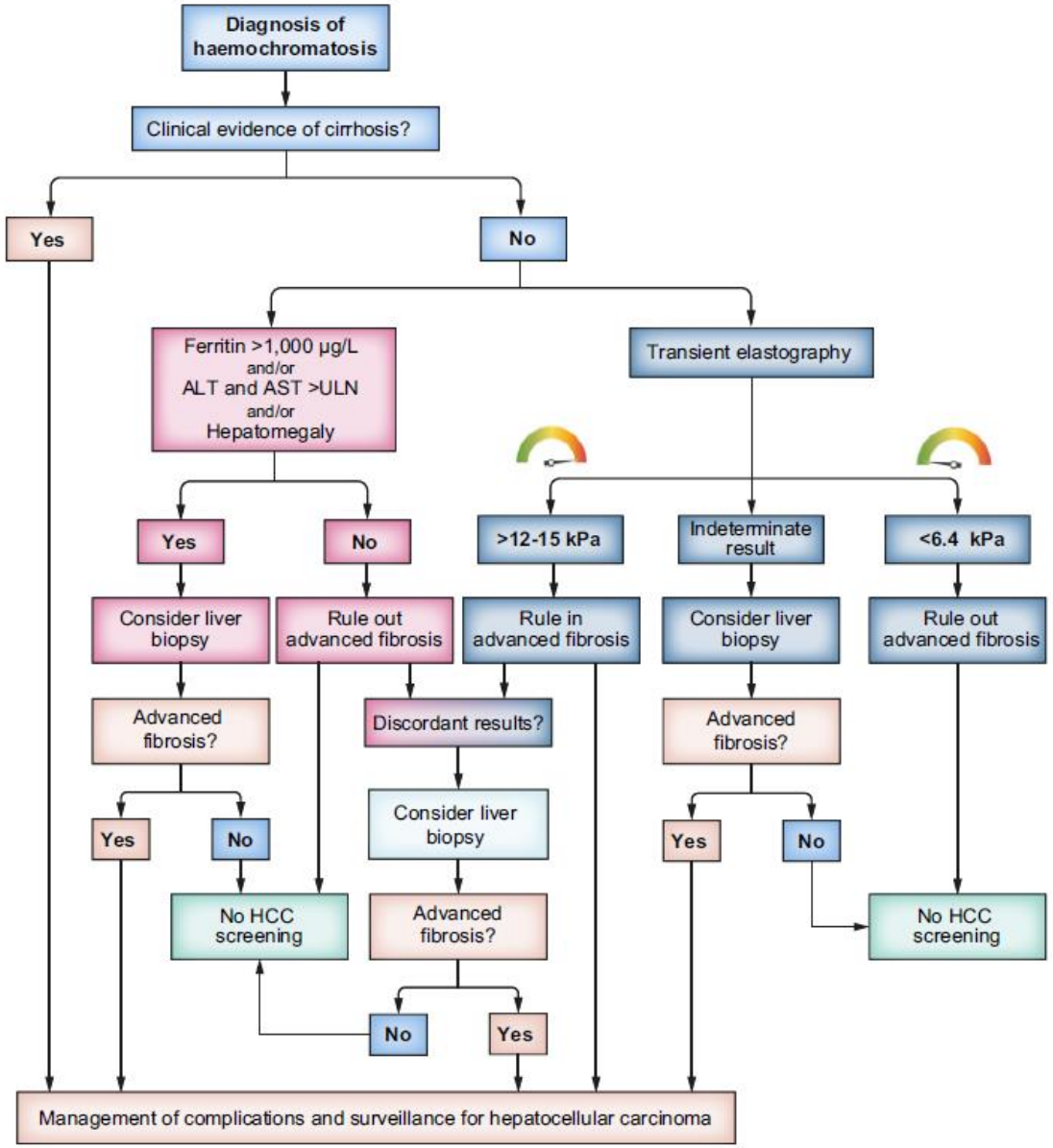
Hämochromatose: Erfassung Fibrose



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Hämochromatose: Take home

Wie testen?

- primär biochemische Testung (Ferritin, Transferrin-Sättigung)
- Cave: Akut-Phase-Reaktion
- Genetik nur zur Bestätigung, bei unklaren Fällen

Alpha-1-Antitrypsin-Mangel

- AAT ist ein Protease-Inhibitor
- Bildung in der Leber
- schützt den Körper vor proteolytischen Enzymen
- *SERPINA1*-Mutationen sind häufig, der AAT-Mangel ist daher eine der häufigsten potentiell lebensbedrohlichen Erkrankungen
- >100 Varianten des *SERPINA1*-Gen
- Zur Klassifikation wird das Pi-System verwendet

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Alpha-1-Antitrypsin-Mangel

M-Varianten

- normaler Genotyp

S-Varianten

- AAT leicht erniedrigt
- Pi*MS und Pi*SS: minimale Klinik

Z-Varianten

- abnorme Proteinfaltung→Polymerisation des AAT
- AAT stark erniedrigt
- Pi*ZZ und Pi*SZ: deutlich erhöhtes Risiko für Leber- oder Lungenerkrankung

0-Variante

- nicht messbare AAT-Spiegel

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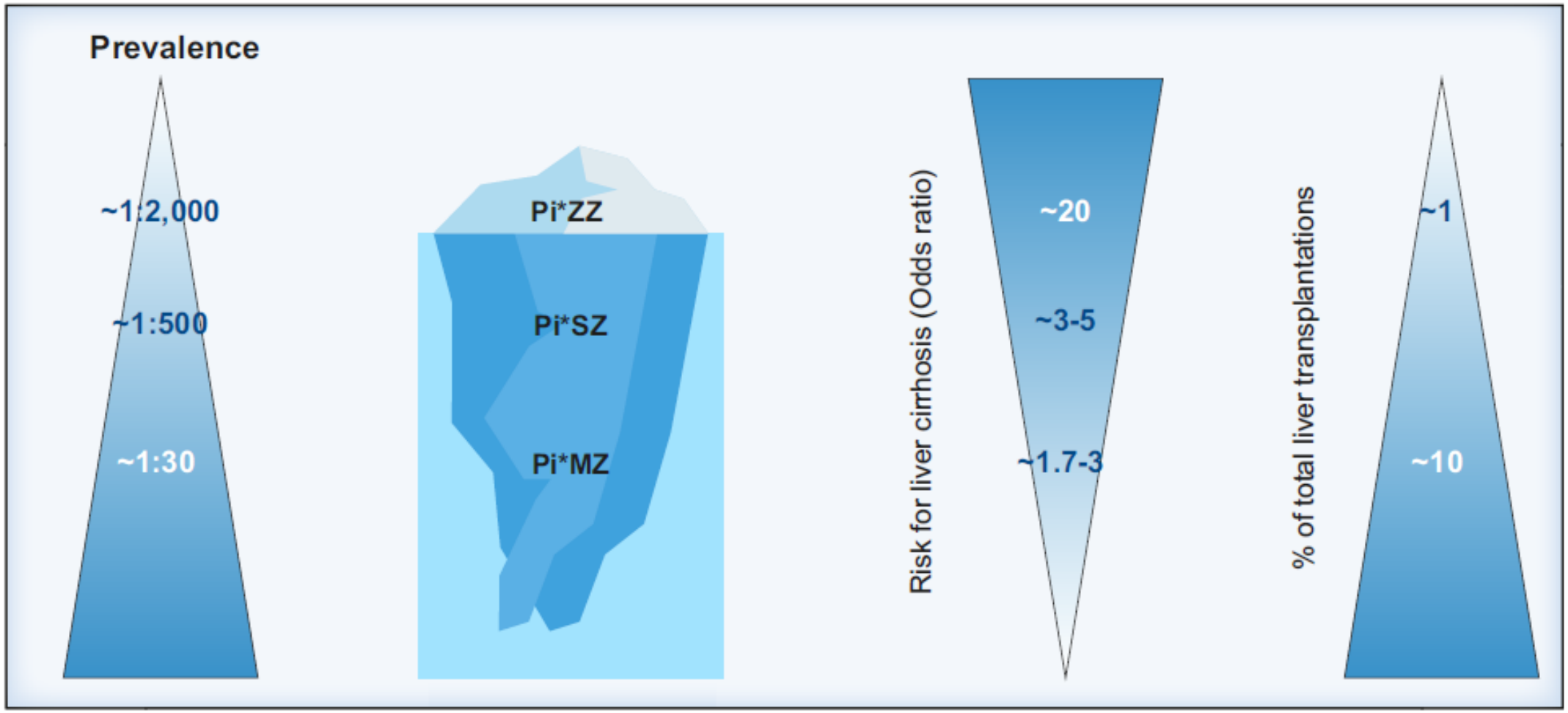
Alpha-1-Antitrypsin-Mangel



Fromme, Malin et al. Journal of Hepatology, Volume 76, Issue 4, 946 - 958

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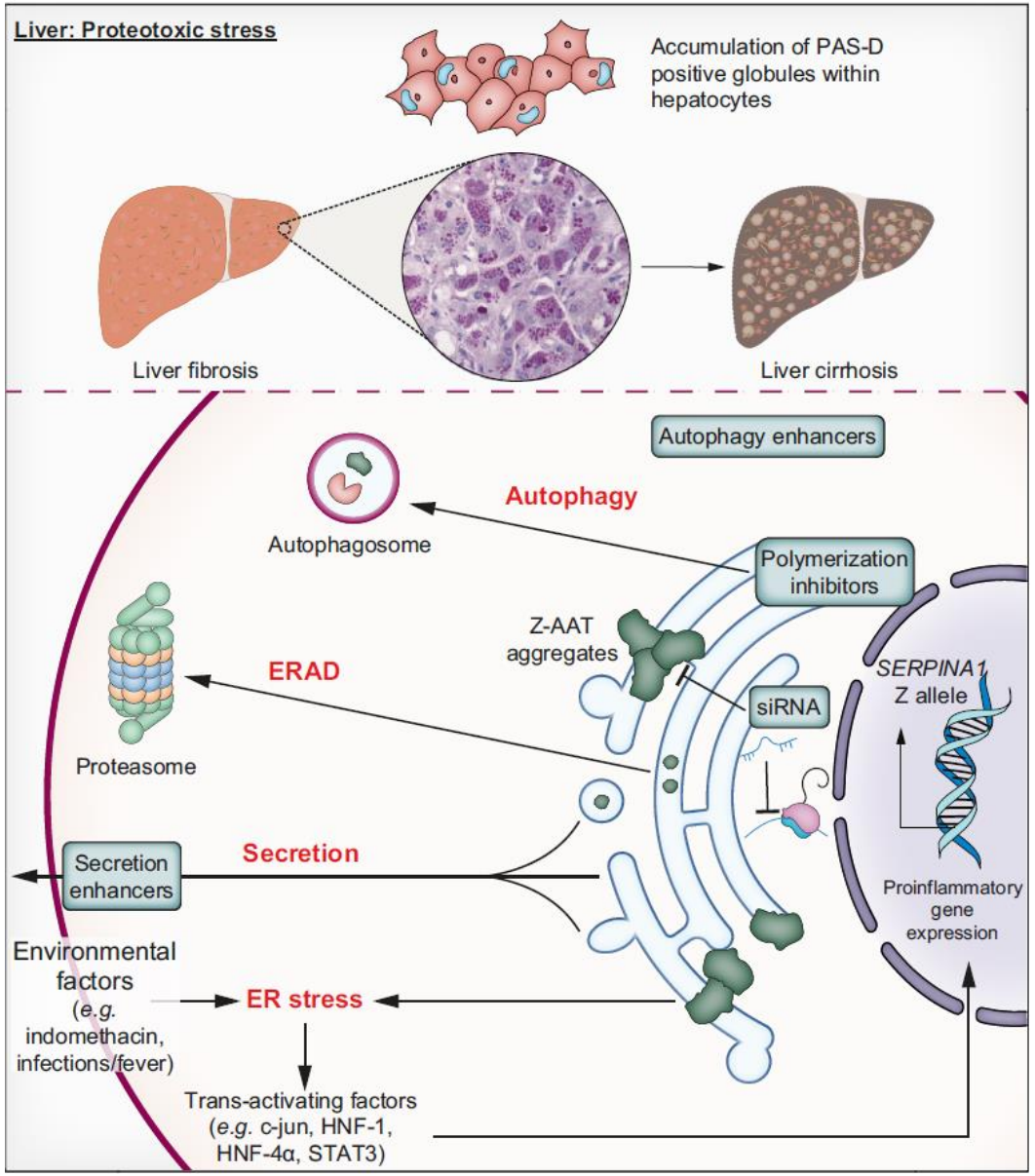
Alpha-1-Antitrypsin-Mangel und Leber



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Alpha-1-Antitrypsin-Mangel und Leber

Table 2. Range of alpha-1 antitrypsin serum levels and proportion of patients with Pi*ZZ, Pi*SZ, and Pi*MZ who have elevated liver enzymes.

SERPINA1 genotype	Range of serum AAT (mg/dl)	AST ≥ULN (%)	ALT ≥ULN (%)	GGT ≥ULN (%)
Pi*ZZ	20-45	15	11	22
Pi*SZ	75-120	5	9	18
Pi*MZ	90-210	5	7	17

AAT, alpha-1 antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; Pi*MZ, AAT genotype with heterozygosity for the Pi*Z variant; Pi*SS, AAT genotype with homozygosity for the Pi*S variant; Pi*SZ, AAT genotype with compound heterozygosity for the Pi*Z and Pi*S variants; Pi*ZZ, AAT genotype with homozygosity for the Pi*Z variant; ULN, upper limit of normal (sex-specific). Liver enzyme levels are based on data obtained from the UK Biobank in participants without an obvious liver comorbidity.[18] Range of AAT serum levels is in mg/dl.[94]

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Alpha-1-Antitrypsin-Mangel und Leber

- AAT-Mangel (Pi*ZZ) verursacht neonatale Cholestase
- AAT-Mangel (Pi*ZZ) verursacht eine Leberfibrose bei Erwachsenen
- Pi*Z-Varianten werden eher als Krankheitsmodifikatoren angesehen, „second Hit“ wird benötigt (z.B. MASLD, ALRD)

Alpha-1-Antitrypsin-Mangel und Leber

Table 3. Current evidence for the Pi*MZ genotype as a modifier of liver disease.

	Evidence	Odds ratio	References
Overall population	++	Increased liver-related mortality (HR ~1.7), higher odds for diabetic/obese individuals	Schneider *et al.*, 2020[55] Luukkonen *et al.*, 2021[95] Schneider *et al.*, 2021[58] Fromme *et al.*, 2021[18] Hakim *et al.*, 2021[96]
NAFLD-related cirrhosis	++	OR ~2-7	Regev *et al.*, 2006[97] Cacciottolo *et al.*, 2014[98] Abul-Husn *et al.*, 2018[65] Strnad *et al.*, 2019[54]
ALD-related cirrhosis	++	OR ~2-6	Goltz *et al.*, 2014[99] Cacciottolo *et al.*, 2014[98] Abul-Husn *et al.*, 2018[65] Strnad *et al.*, 2019[54]
Chronic hepatitis B-associated advanced liver fibrosis	+	Smaller studies, OR ~10 (1 study)	Propst *et al.*, 1992[100] Hashemi *et al.*, 2005[101] Kuscuoglu *et al.*, 2021[33]
Chronic hepatitis C-associated advanced liver fibrosis	+/-	Several studies, OR ~4 in one of them	Propst *et al.*, 1992[100] Eigenbrodt *et al.*, 1997[102] Serfaty *et al.*, 1997[103] Regev *et al.*, 2006[97]
Haemochromatosis-associated advanced liver fibrosis	+/-	Multiple studies, conflicting results	Rabinovitz *et al.*, 1992[104] Kaserbacher *et al.*, 1993[105] Elzouki *et al.*, 1995[106] Fargion *et al.*, 1996[107] Schaefer *et al.*, 2015[108] Guldiken *et al.*, 2019[34]
Cystic fibrosis-associated advanced liver disease	++	OR ~5	Bartlett *et al.*, 2009[64] Boëlle *et al.*, 2019[109]
Liver transplantation	+	Up to 10% of liver transplant recipients display Pi*MZ genotype	Carey *et al.*, 2013[74] Schaefer *et al.*, 2018[76]

AATD, alpha-1 antitrypsin deficiency; ALD, alcohol-related liver disease; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; Pi*MZ, AAT genotype with heterozygosity for the Pi*Z variant. +/-, conflicting data; +, weak positive evidence; ++, robust positive evidence.

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AAT-Mangel: Take Home

Wen testen?

- Patienten mit COPD (bes. <45 Jahre), therapierest. Asthma, Lungenemphysem
- Unklare Lebererkrankung

Wie testen?

- Bestimmung des Alpha-1-Antitrypsins im Serum
- Genotypisierung bei Auffälligkeiten