Take Home Messages: Hemochromatosis EASL guidelines

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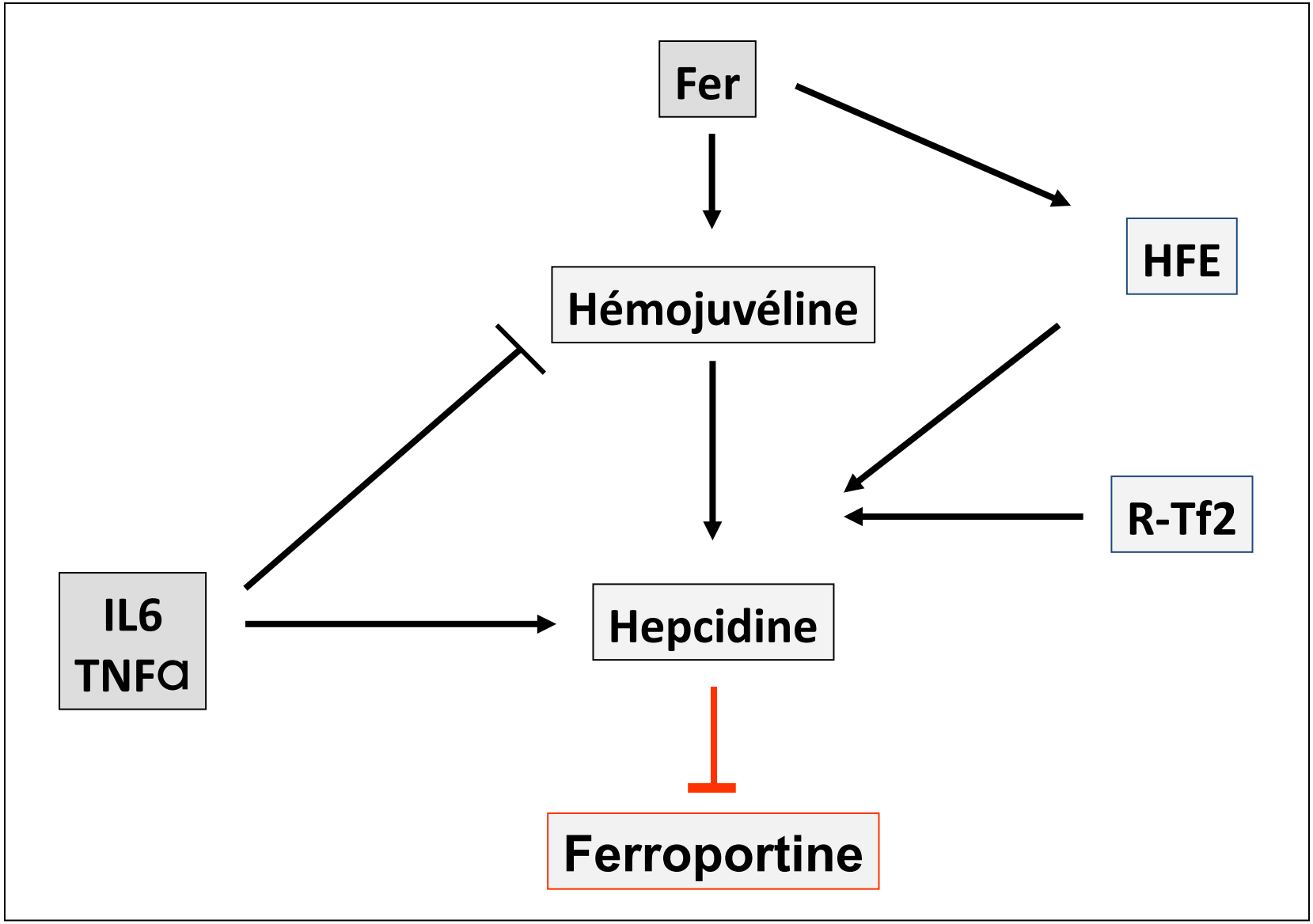
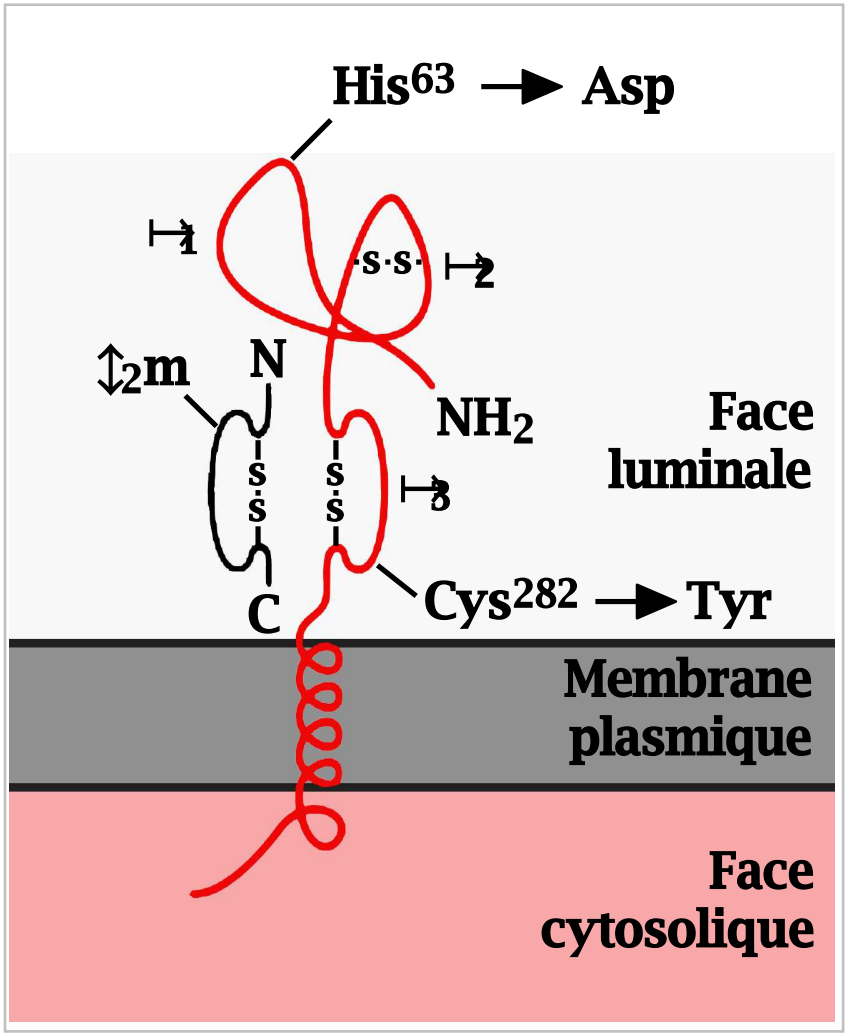


Niederkofler, J Clin Invest, 2005

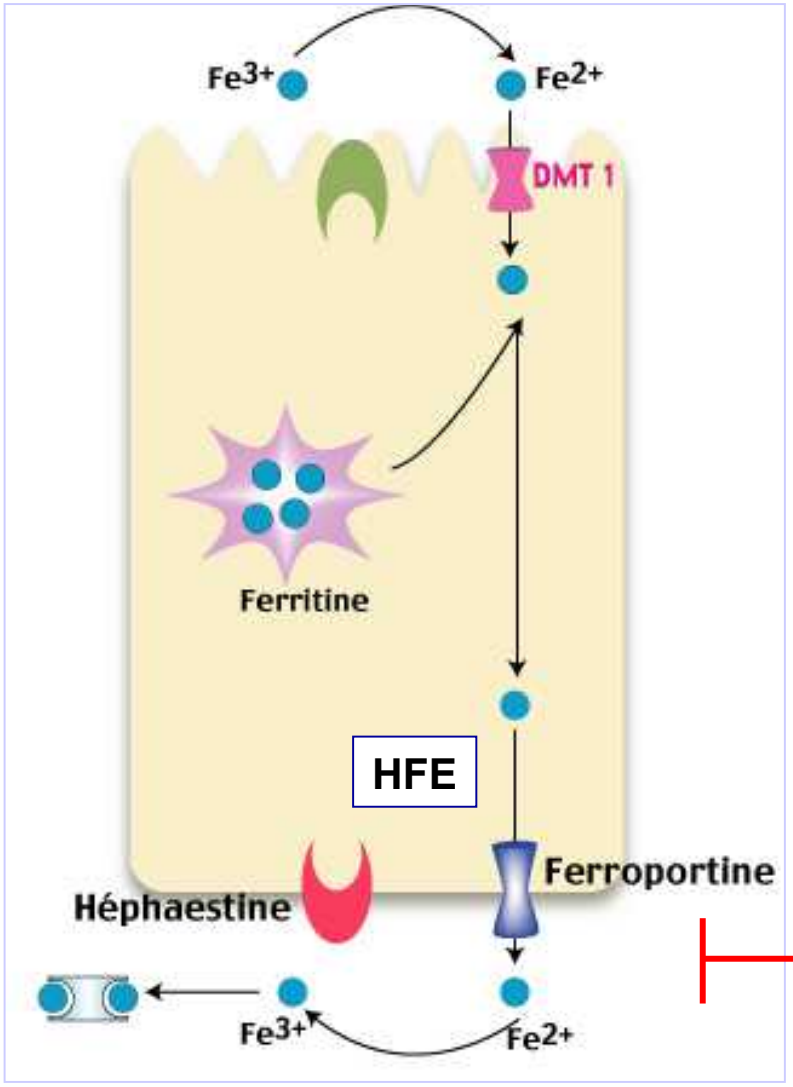
HFE	**6p21-R**	**↗ Influx**	**3e - 4e decade**
R-Transferrine 2	**7q22-R**	**↗ influx**	**3e - 4e decade**
Hamp/hepcidine	**19q13-R**	**↗ Influx**	**1e - 2e decade**
Hémojuvéline	**1p21-R**	**↗ Influx**	**1e - 2e decade**
Ferroportine	**2q32-D**	**↘ efflux**	**4e - 5e decade**

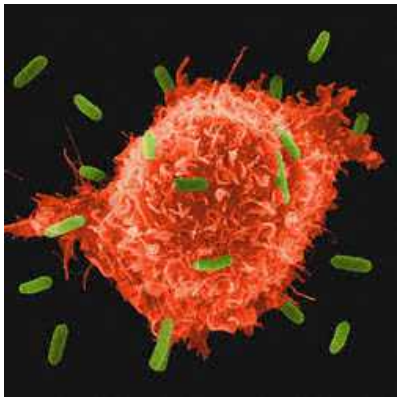
La protéine HFE inhibe l'absorption du fer via le récepteur à la transferrine



La mutation C282Y déstabilise la protéine HFE qui perd sa fonction régulatrice

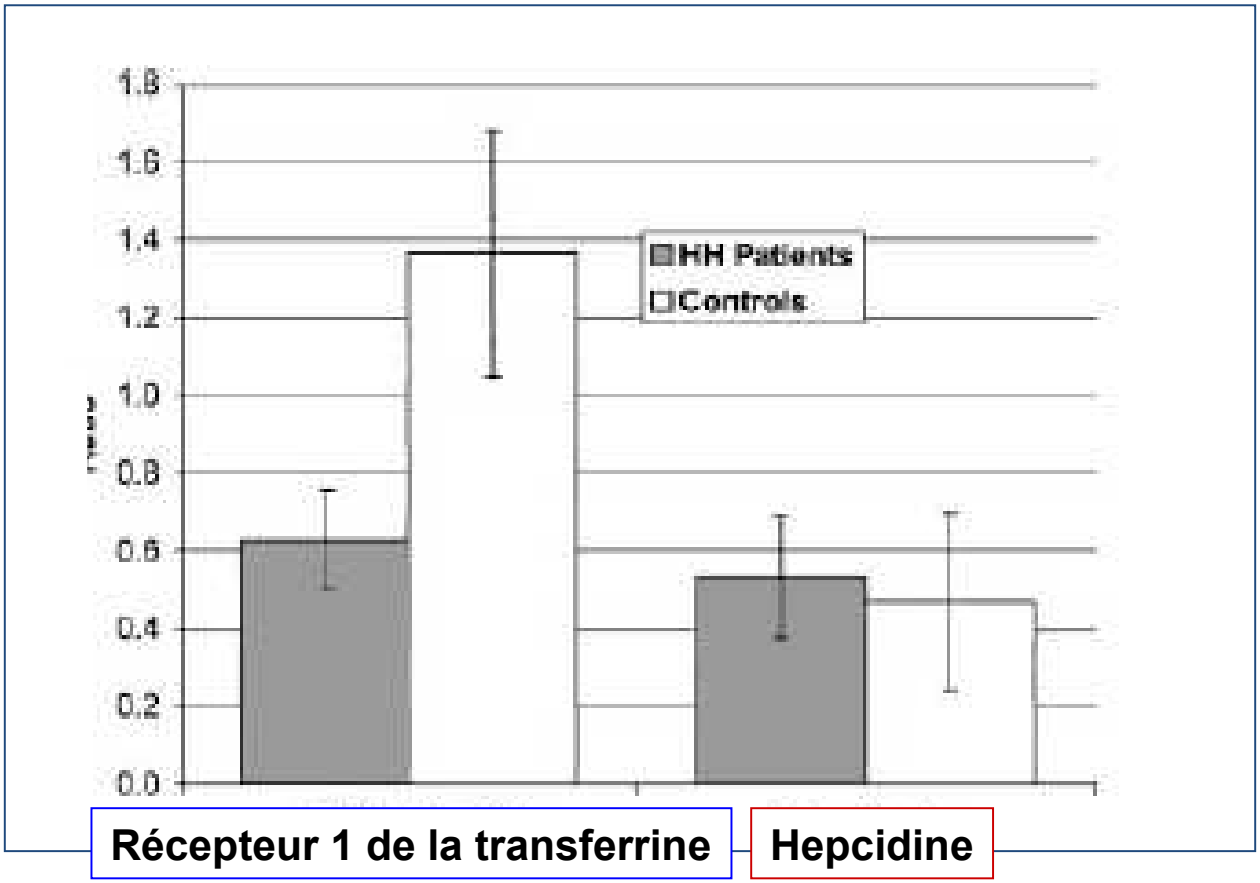
L'hepcidine bloque le relargage du fer au niveau de l'entérocyte et du macrophage





Hepcidine

L'hepcidine est paradoxalement basse chez les patients C282Y homozygotes

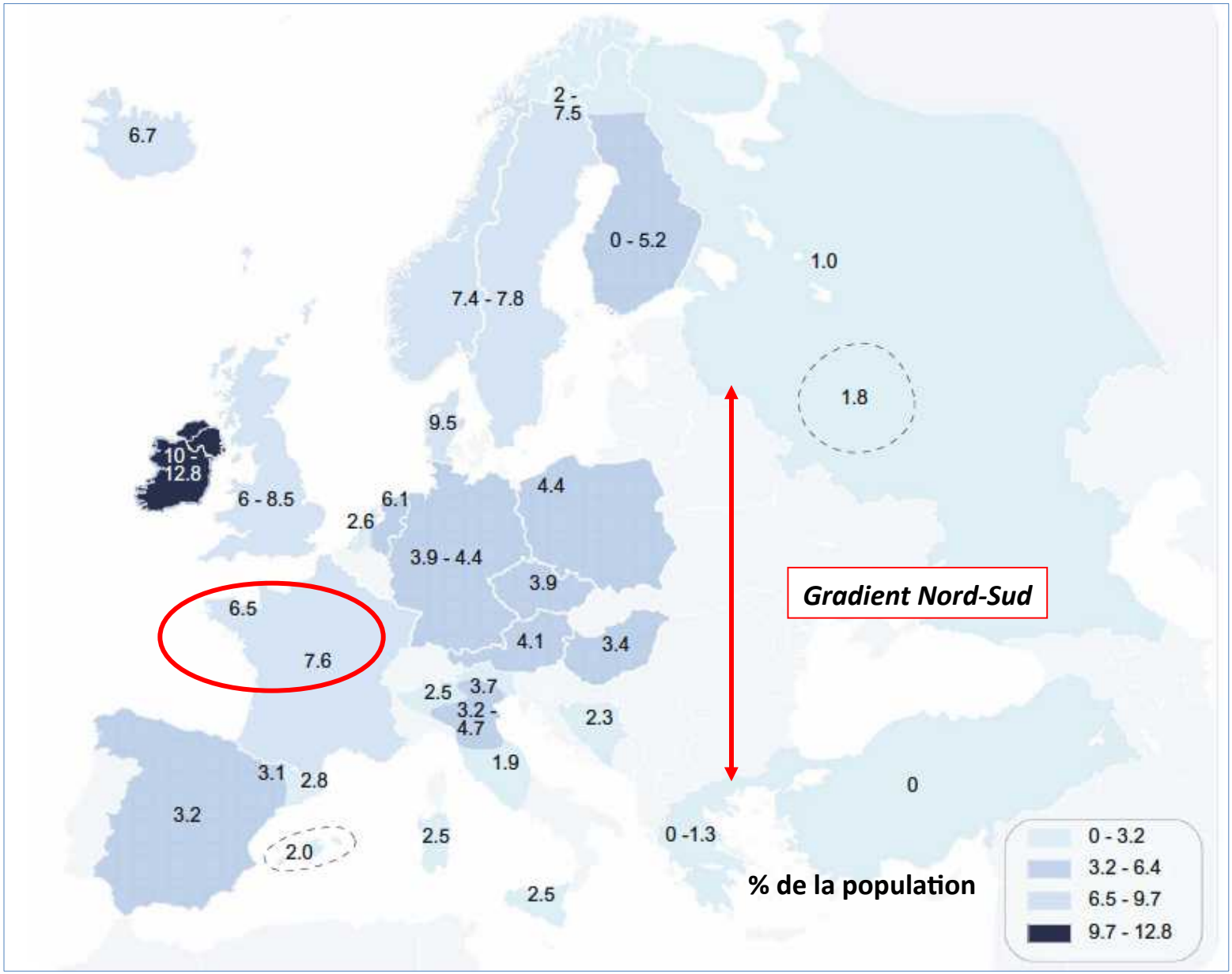


Gehrke, Blood 2003

Prevalence de la mutation C282Y homozygote chez les patients avec hémochromatose

Study population	Prevalence of HLA/HFE among clinical hemochromatosis cases			
	No. of cases	C282Y homozygote	C282Y/H63D compound heterozygote	Wild type both alleles
USA – Multicenter	187	148		21
Australia	112	112	0	
France	65	65	3	0
USA – European origin	147	121		
France – Toulouse	94	68	4	18
Italy – Northern	75	48	5	
Austria	40	31		
UK – Eastern England	18	18		
UK – Consortium	115	105		5
USA – Portland	37	12		
Sweden	87	80	3	1
Spain	31	27	2	1
Ireland	60	56	1	2
Germany – Northern	92	87	4	
Ireland	30	27		
France – Brittany	711	570	40	35
France – Northwest	217	209	4	2
USA	66	60	2	

Fréquence de l'allèle C282Y en Europe

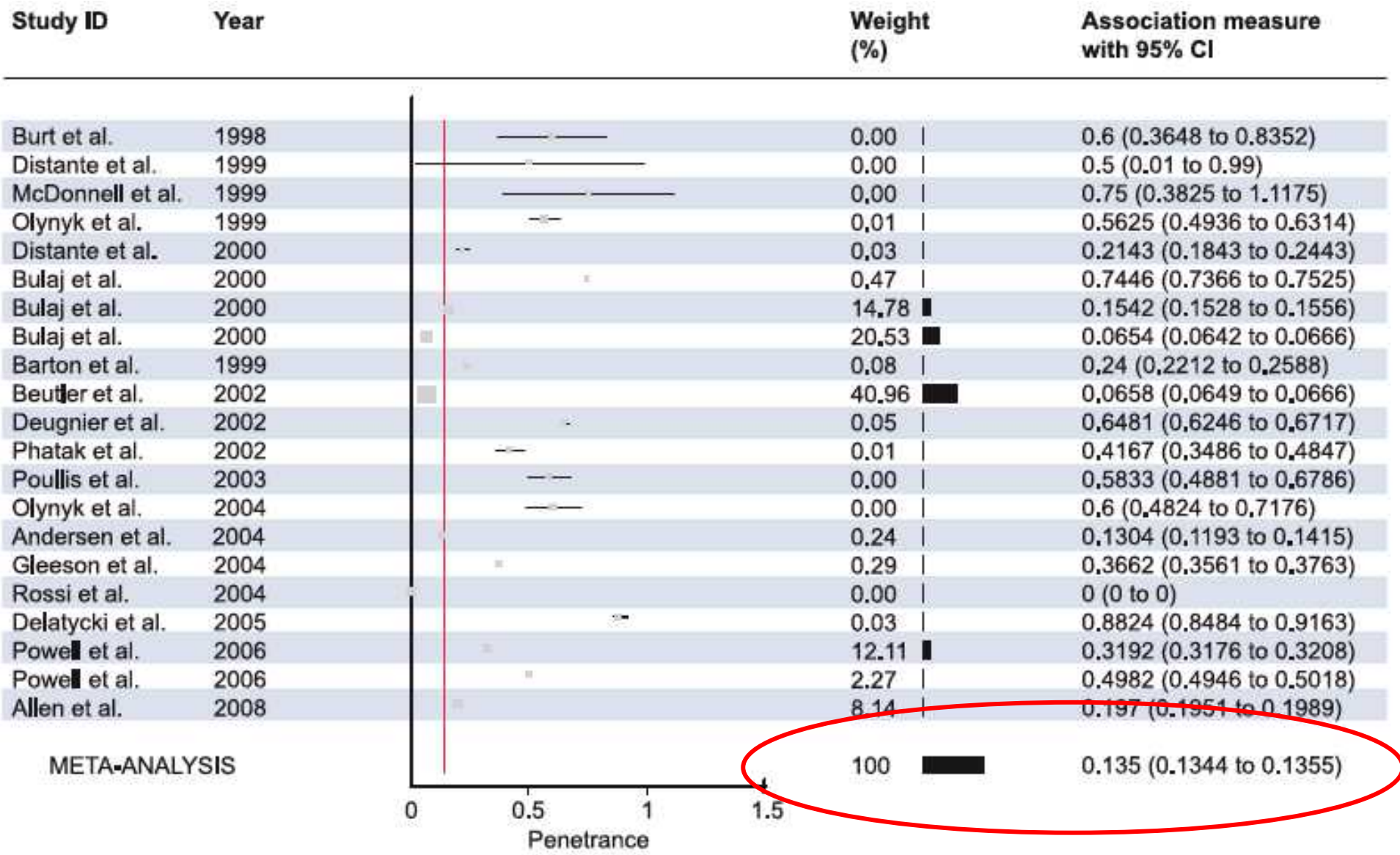


Prevalence de l'homozygotie C282Y dans la population générale

Population Sample	Country	*n*	Prevalence of Homozygotes	C282Y Homozygotes with Normal Ferritin Level (%)
Primary care ([12])	USA	41,038	1 in 270	35
General public ([11])	Norway	65,238	1 in 220	13
Primary care ([6])	North America	99,711	1 in 333	31
General public ([10])	Australia	29,676	1 in 146	32
Total		235,663	1 in 240	30

Bacon, Hepatology 2011

Pénétrance de l'homozygotie C282Y



Recommandations pour le dépistage

General population:

- Genetic screening for HFE-HC is not recommended, because disease penetrance is low and only in few C282Y homozygotes will iron overload progress (1B).

Patient populations:

- HFE testing should be considered in patients with unexplained chronic liver disease pre-selected for increased transferrin saturation (1C).
- HFE testing could be considered in patients with:
  - Porphyria cutanea tarda (1B).
  - Well-defined chondrocalcinosis (2C).
  - Hepatocellular carcinoma (2C).
  - Type 1 diabetes (2C).

- HFE testing is not recommended in patients with
  - Unexplained arthritis or arthralgia (1C).
  - Type 2 diabetes (1B).

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Recommandations pour le diagnostic (1)

- Patients with suspected iron overload should first receive measurement of fasting transferrin saturation and serum ferritin (1B), and HFE testing should be performed only in those with increased transferrin saturation (1A).
- Patients from liver clinics should be screened for fasting transferrin saturation and serum ferritin (1C) and offered genetic HFE testing if transferrin saturation is increased (1B).
- HFE testing for the C282Y and H63D polymorphism should be carried out in all patients with otherwise unexplained increased serum ferritin and increased transferrin saturation (1B).
- Diagnosis of HFE hemochromatosis should not be based on C282Y homozygosity alone, but requires evidence of increased iron stores (1B).
- C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin (>200 µg/L in females, >300 µg/L in males), increased transferrin saturation (>45% in females, >50% in males) or increased liver iron should first be investigated for other causes of hyperferritinemia (1C).

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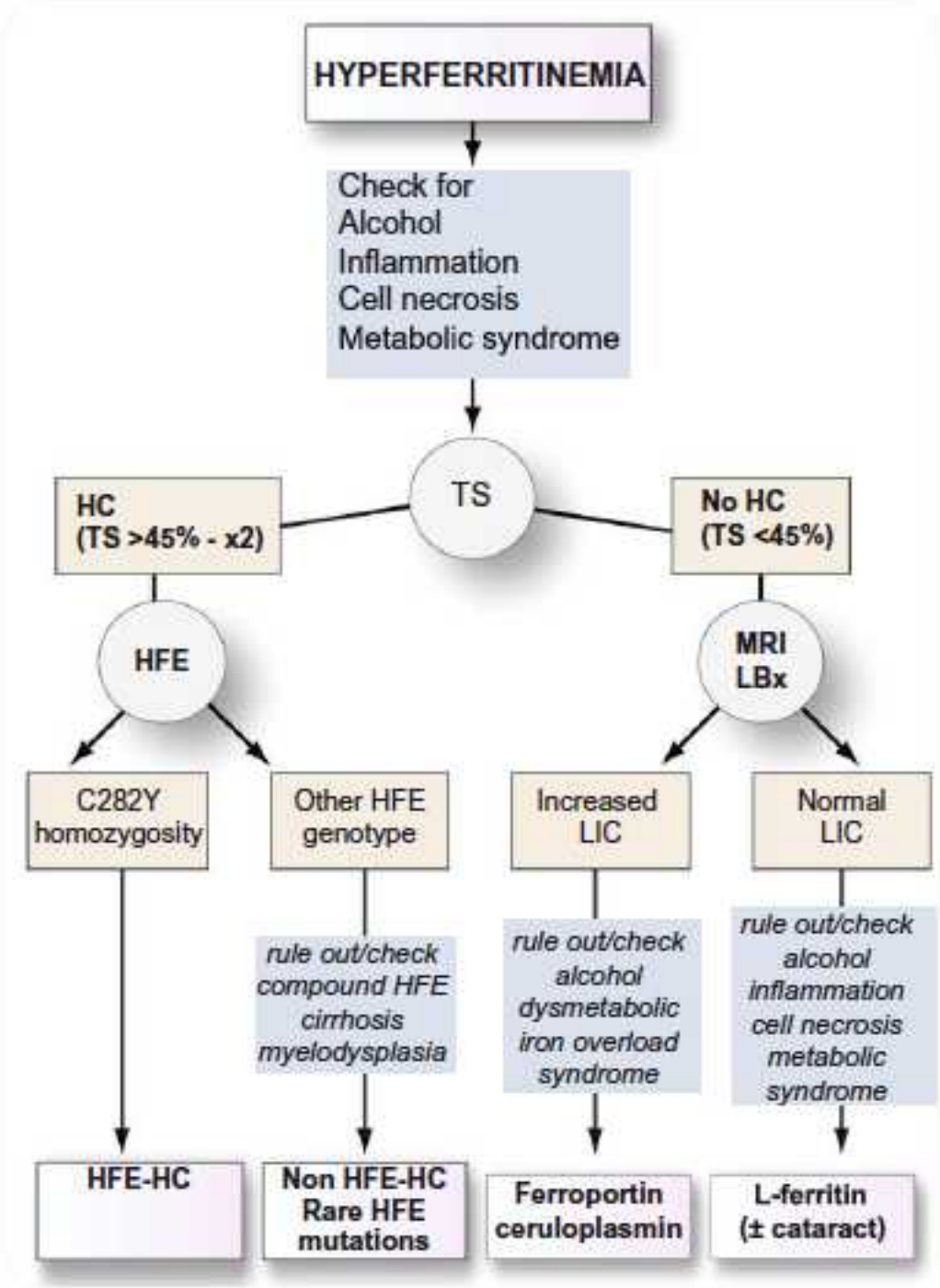
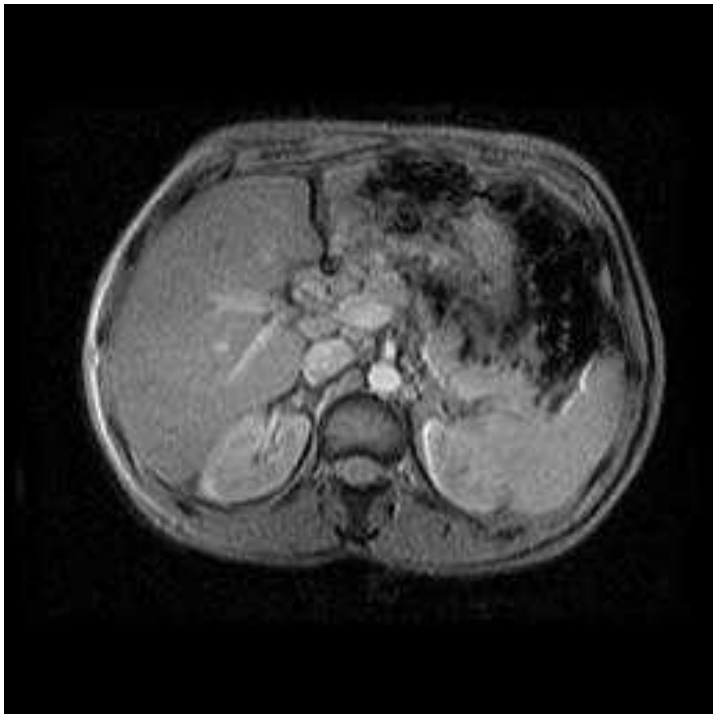
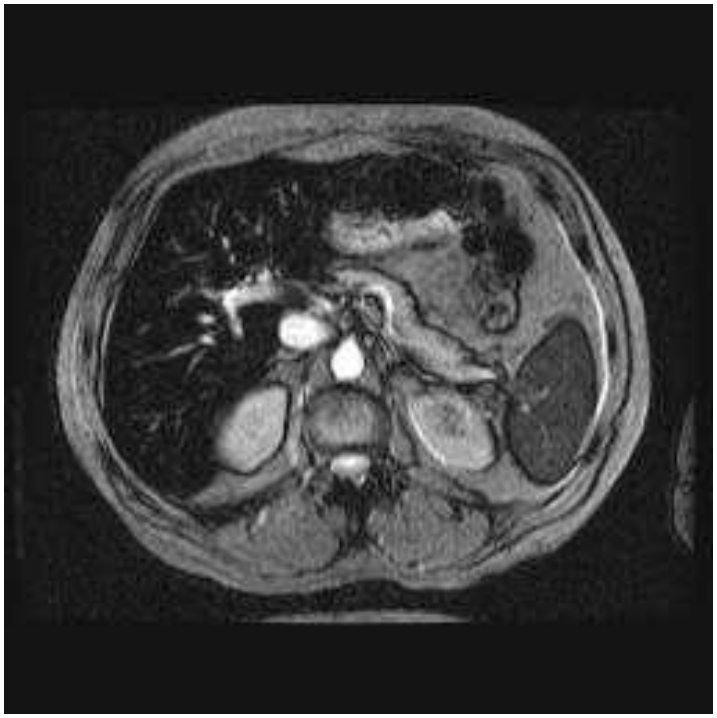

HYPERFERRITINEMIA
Check for
Alcohol
Inflammation
Cell necrosis
Metabolic syndrome
TS
HC
(TS >45% - x2)
No HC
(TS <45%)
HFE
MRI
LBx
C282Y
homozygosity
Other HFE
genotype
Increased
LIC
Normal
LIC
rule out/check
compound HFE
cirrhosis
myelodysplasia
rule out/check
alcohol
dysmetabolic
iron overload
syndrome
rule out/check
alcohol
inflammation
cell necrosis
metabolic
syndrome
HFE-HC
Non HFE-HC
Rare HFE
mutations
Ferroportin
ceruloplasmin
L-ferritin
(± cataract)

Quantification de la surcharge en fer par IRM



Foie normal



Surcharge majeure

Recommandations pour le diagnostic (2)

- In C282Y homozygote patients with increased iron stores, liver biopsy is no longer necessary to diagnose hemochromatosis. Liver biopsy could be offered to C282Y homozygous patients with serum ferritin above 1000 µg/L, elevated AST, hepatomegaly, or age over 40 years (1C).
- Genetic testing of 'other hemochromatosis genes' (TFR2, SLC40A1, HAMP, HJV) could be considered in patients with increased iron stores after exclusion of C282Y homozygosity if (i) iron excess has been proven by direct assessment, i.e. by MRI or liver biopsy, and (ii) other hepatic and haematological disorders have been ruled out (2C).
- According to the autosomal recessive transmission of HFE-HC, genetic testing of siblings of individuals with HFE-HC should be carried out. Genetic testing of other 1st degree relatives should be considered (1B). (Practical and cost effective strategies for family screening have been published [206].)

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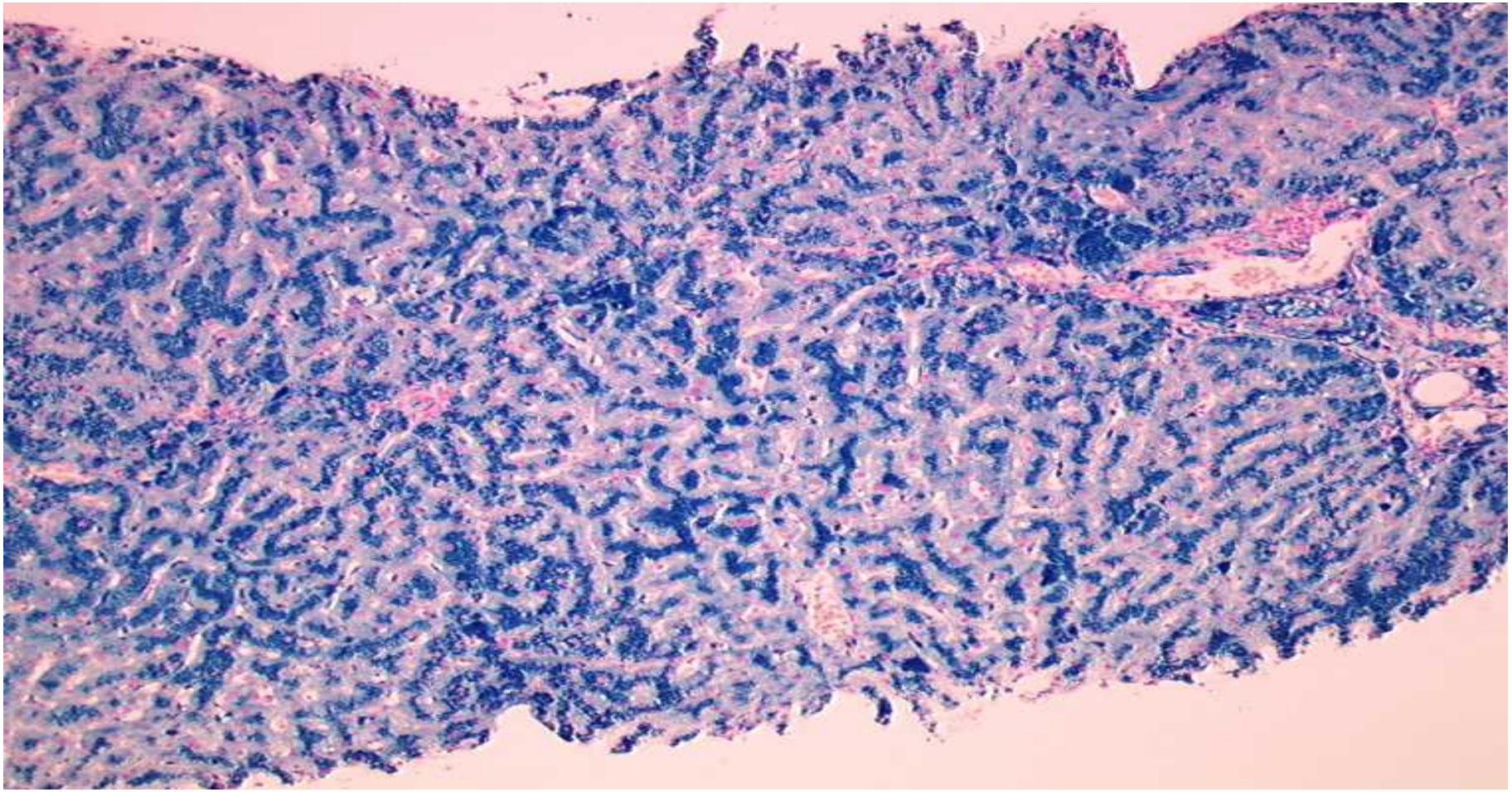
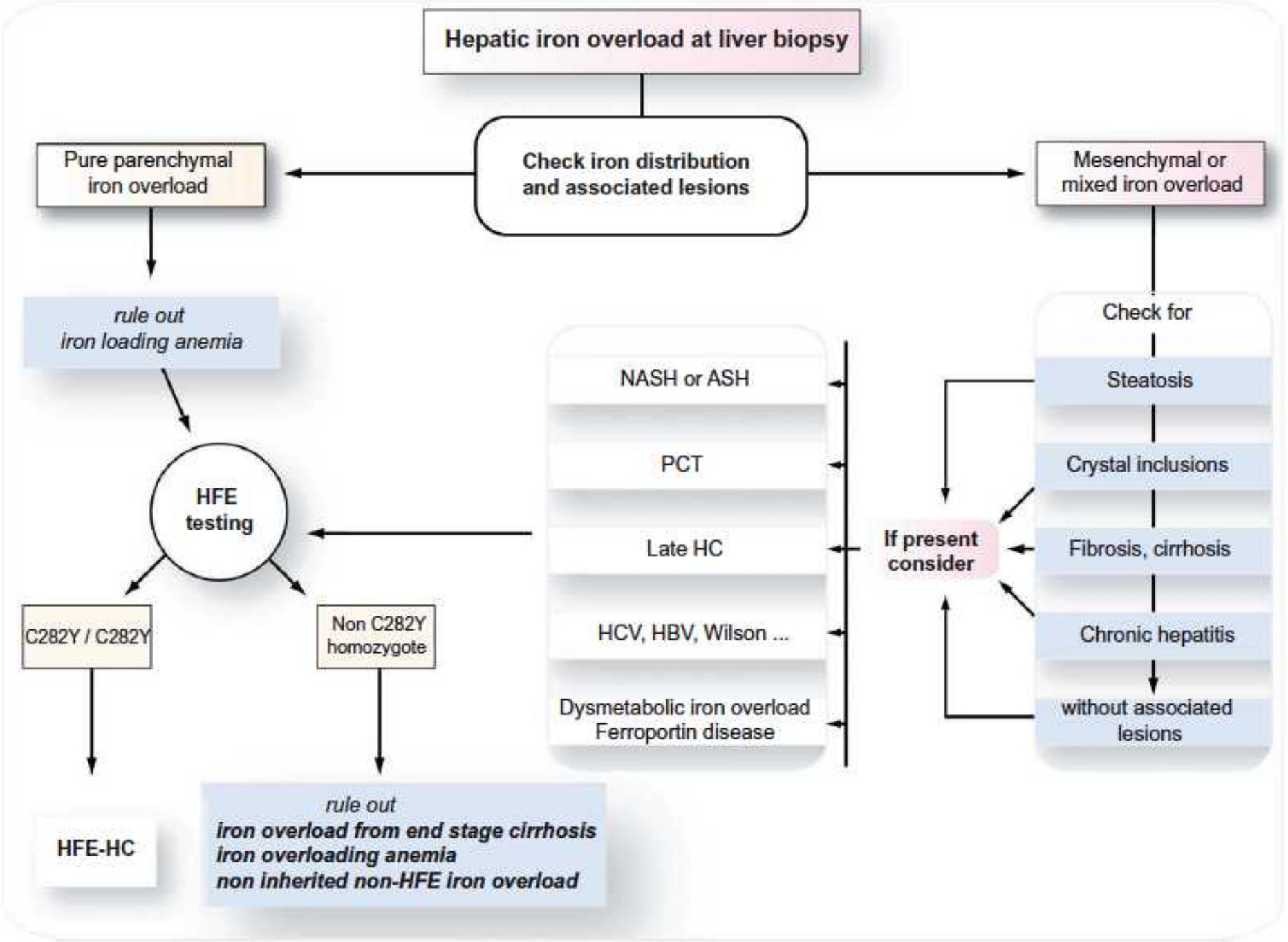
Surcharge en fer hépatique au cours de l'Hémochromatose




Hepatic iron overload at liver biopsy
Check iron distribution and associated lesions
Pure parenchymal iron overload
Mesenchymal or mixed iron overload
rule out iron loading anemia
HFE testing
C282Y / C282Y
Non C282Y homozygote
HFE-HC
rule out
iron overload from end stage cirrhosis
iron overloading anemia
non inherited non-HFE iron overload
NASH or ASH
PCT
Late HC
HCV, HBV, Wilson ...
Dysmetabolic iron overload
Ferroportin disease
If present consider
Check for
Steatosis
Crystal inclusions
Fibrosis, cirrhosis
Chronic hepatitis
without associated lesions

Recommandations pour le diagnostic (2)

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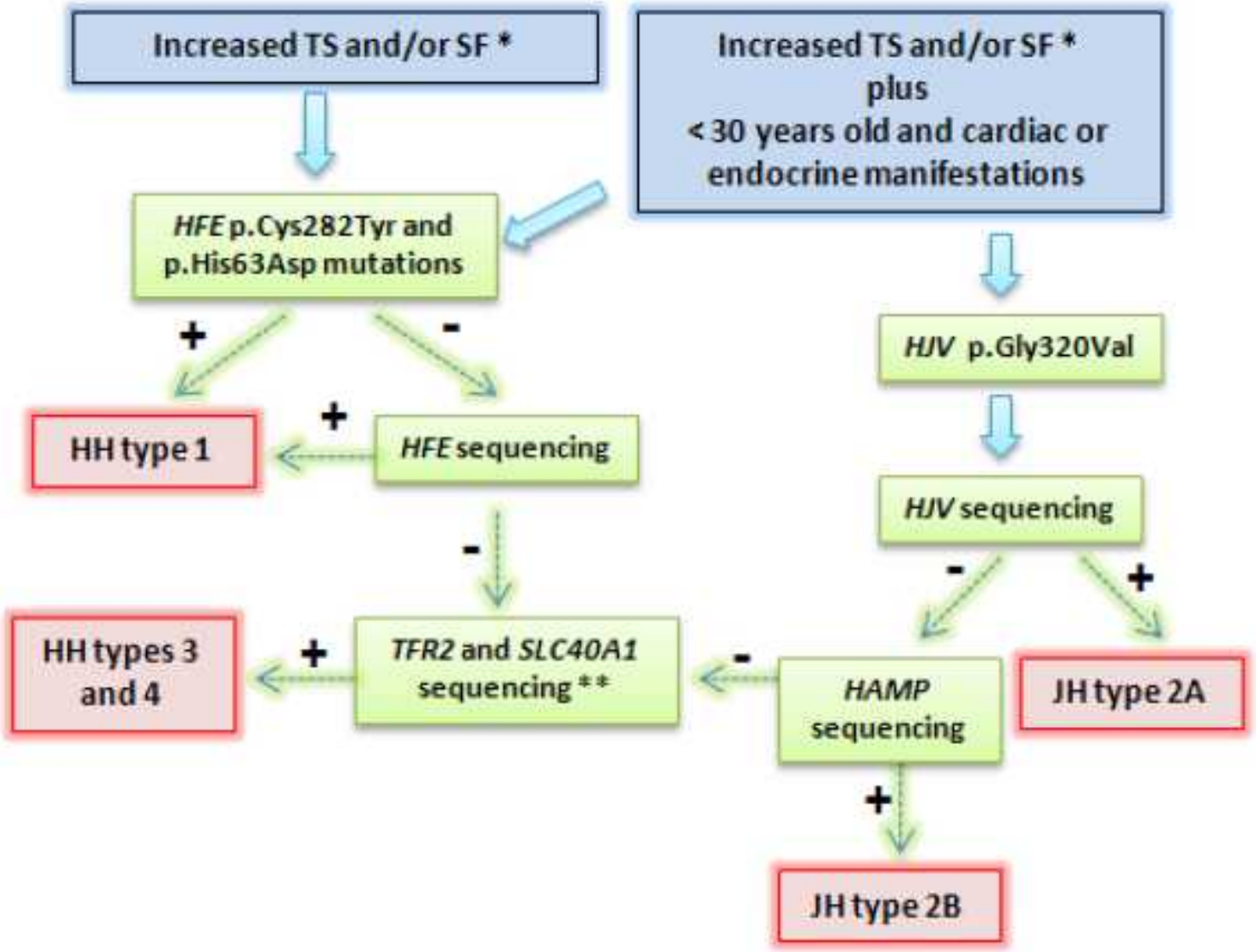
Algorithme diagnostique génétique



Recommandations pour la prise en charge

- Patients with HFE-HC and evidence of excess iron should be treated with phlebotomy (1C).
- C282Y homozygotes without evidence for iron overload could be monitored annually and treatment instituted when the ferritin rises above normal (2C).
- Phlebotomy should be carried out by removing 400–500 ml of blood (200–250 mg iron) weekly or every two weeks. Adequate hydration before and after treatment, and avoidance of vigorous physical activity for 24 h after phlebotomy is recommended (1C).
- Phlebotomy can be carried out also in patients with advanced fibrosis or cirrhosis (2C).
- Before the initiation of phlebotomy, patients with HFE-HC should be assessed for complications including diabetes mellitus, joint disease, endocrine deficiency (hypothyroidism), cardiac disease, porphyria cutanea tarda, and osteoporosis (1C).
- Complications of HFE-HC (liver cirrhosis, diabetes, arthropathy, hypogonadism, PCT) should be managed regardless of whether or not HC is the underlying cause and whether there is symptomatic relief or improvement during phlebotomy (1C).
- To minimize the risk of additional complications, patients with HFE-HC could be immunized against hepatitis A and B while iron overloaded (2C).

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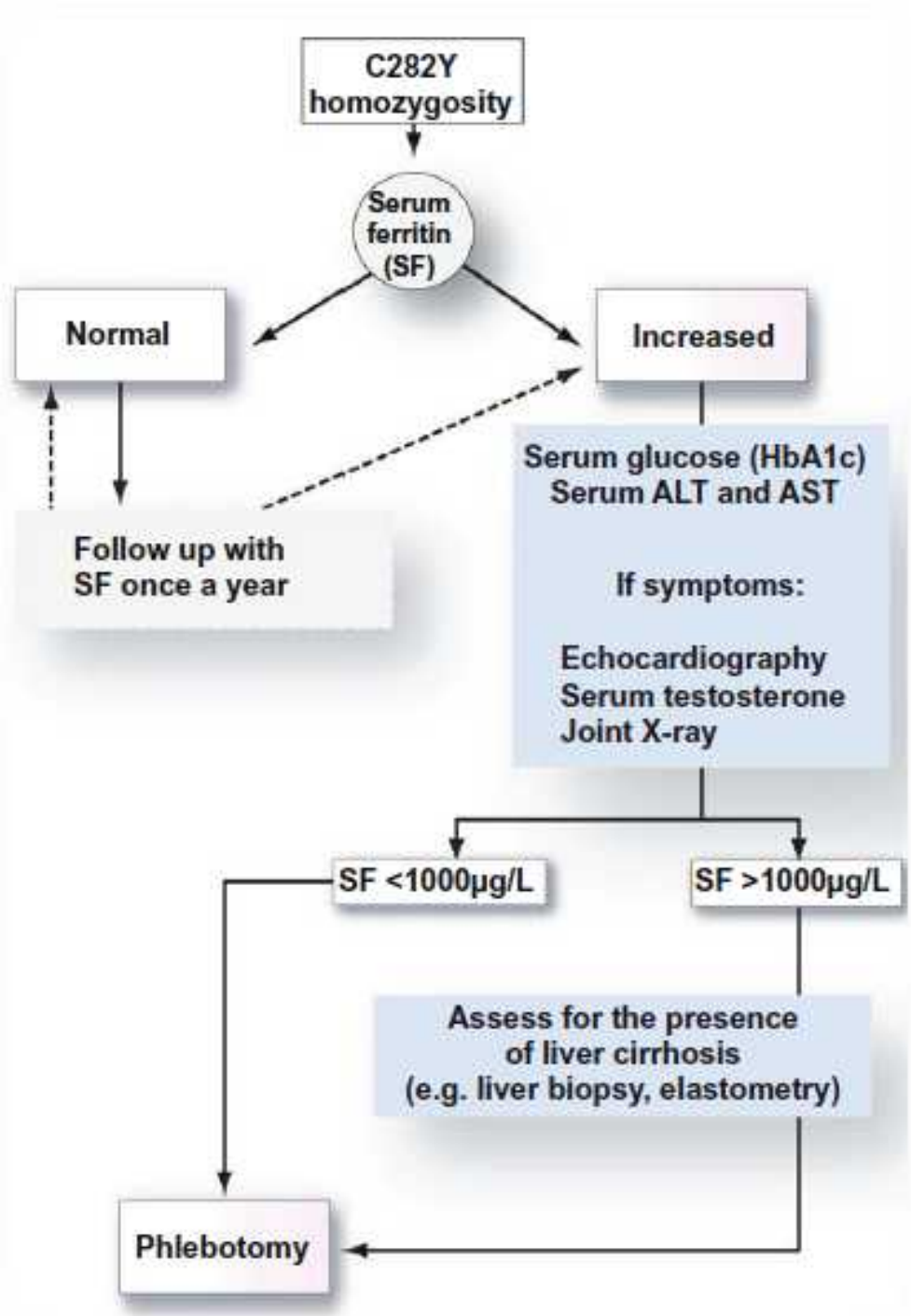
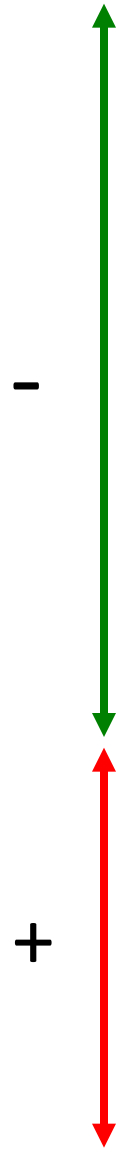

C282Y homozygosity
Serum ferritin (SF)
Normal
Increased
Follow up with SF once a year
Serum glucose (HbA1c)
Serum ALT and AST
If symptoms:
Echocardiography
Serum testosterone
Joint X-ray
SF <1000µg/L
SF >1000µg/L
Assess for the presence of liver cirrhosis (e.g. liver biopsy, elastometry)
Phlebotomy

Effets thérapeutiques des saignées



−	Reduction of tissue iron stores to normal
	Improved survival if diagnosis and treatment before development of cirrhosis and diabetes
	Improved sense of well-being, energy level
	Improved cardiac function
	Improved control of diabetes
	Reduction in abdominal pain
	Reduction in skin pigmentation
	Normalization of elevated liver enzymes
	Reversal of hepatic fibrosis (in approximately 30% of cases)
+	No reversal of established cirrhosis
	Elimination of risk of HH-related HCC if iron removal is achieved before development of cirrhosis
	Reduction in portal hypertension in patients with cirrhosis
	No (or minimal) improvement in arthropathy
	No reversal of testicular atrophy

Transplantation hépatique pour hémochromatose

Evaluation de la surcharge en fer (60 ± 35 mois)			
	Avant TH	Après TH	p
% saturation Tf	68 ± 30 %	28 ± 8,5 %	0,021
Hepcidine	1,61 ± 3,6 nmol/L	13,2 ± 8,1 nmol/L	0,006
	(N 4 -30)		
Concentration hépatique en fer (IRM)		Normale : 9/11 Modérément élevée : 1/11 Elevée 1/11 (sphérocytose)	

Bardou-Jacquet, Hepatology 2013

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