MÁSTER EN HEPATOLOGÍA

ORGANIZA:

Hospital Universitario Virgen del Rocío Aparato Digestivo

UAM UNIVERSIDAD AUTONOMA DE MADRID

Universidad de Alcalá

IBIS INSTITUTODEBIOMEDICINADESEVILLA

Asignatura: Oportunidades en hepatología

"Medicina de Precisión en Enfermedades hepáticas"

ciberehd

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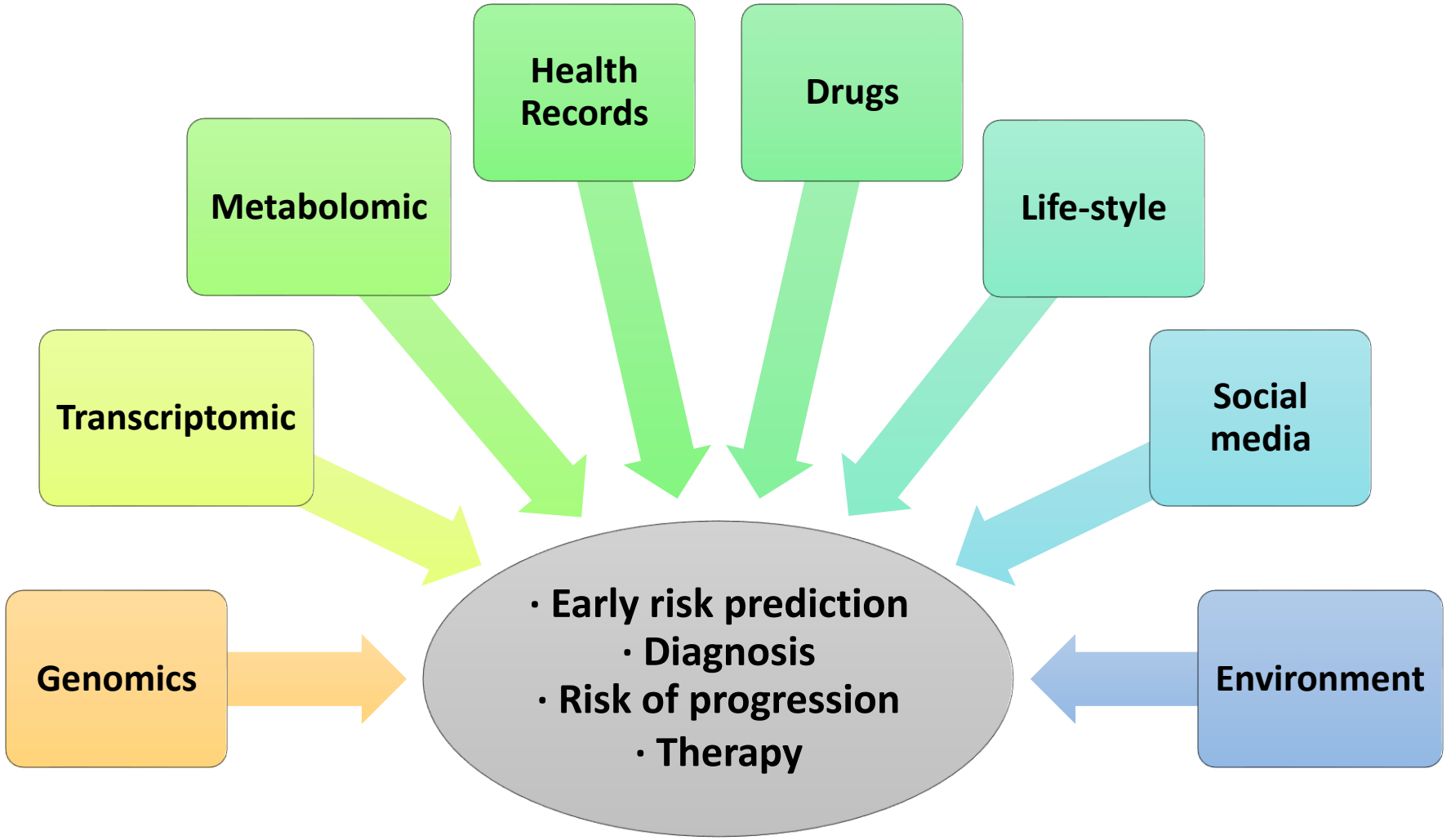
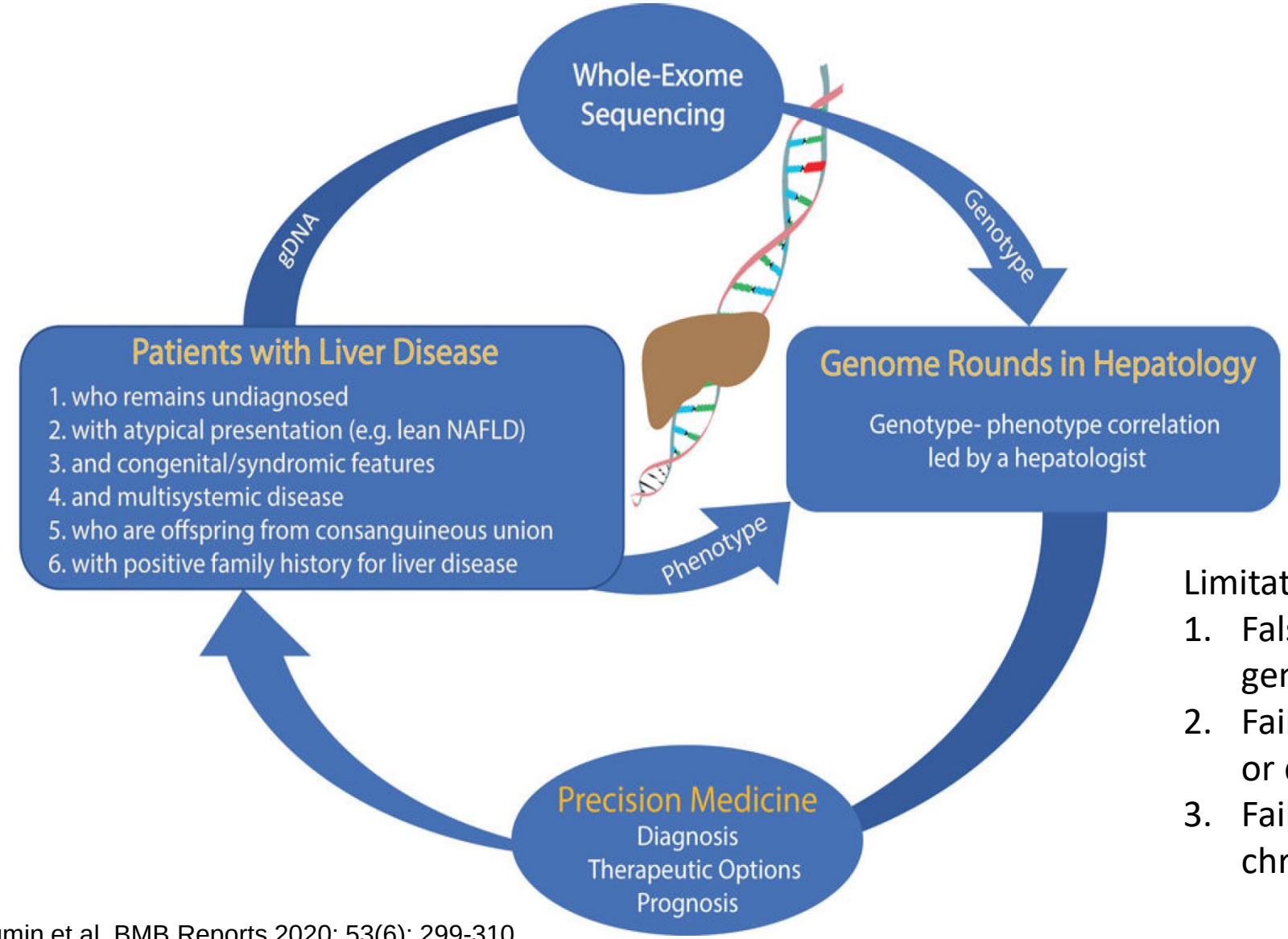
Madrid, 5 de Mayo de 2023

Precision and personalised medicine in chronic liver diseases



Prosperi M. BMC Med Informat Dec Med 2018

Clinical utility of genomic analysis in adults with idiopathic liver disease

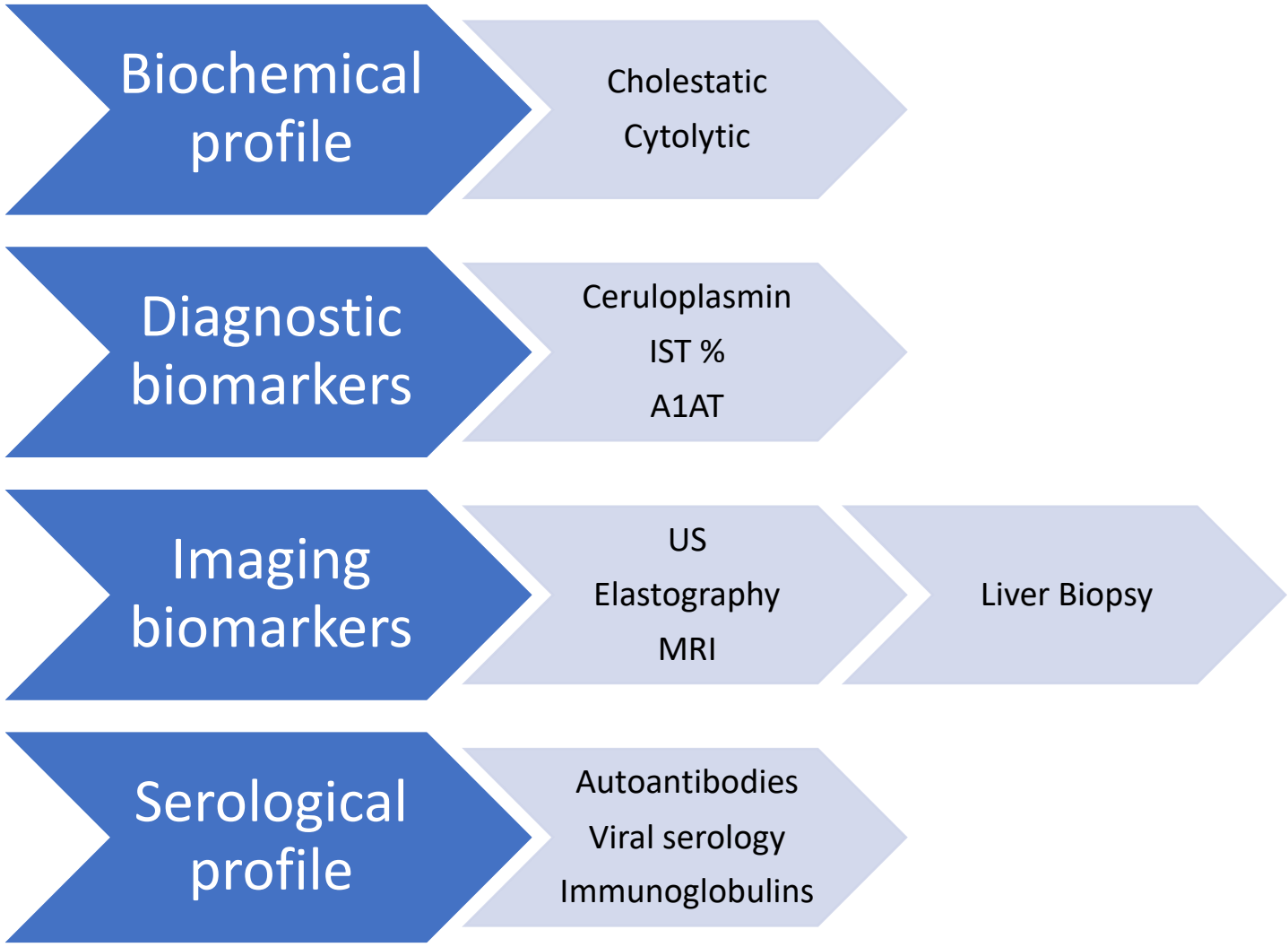


Limitations:

1. False negative (some segments of the genome are not amenable for sequencing)
2. Failure to detect large genomic insertions or deletions
3. Failure to detect structural or chromosomal abnormalities

Sumin et al. BMB Reports 2020; 53(6): 299-310
Hakim et al. J Hepatol 2019;70:1214-1221

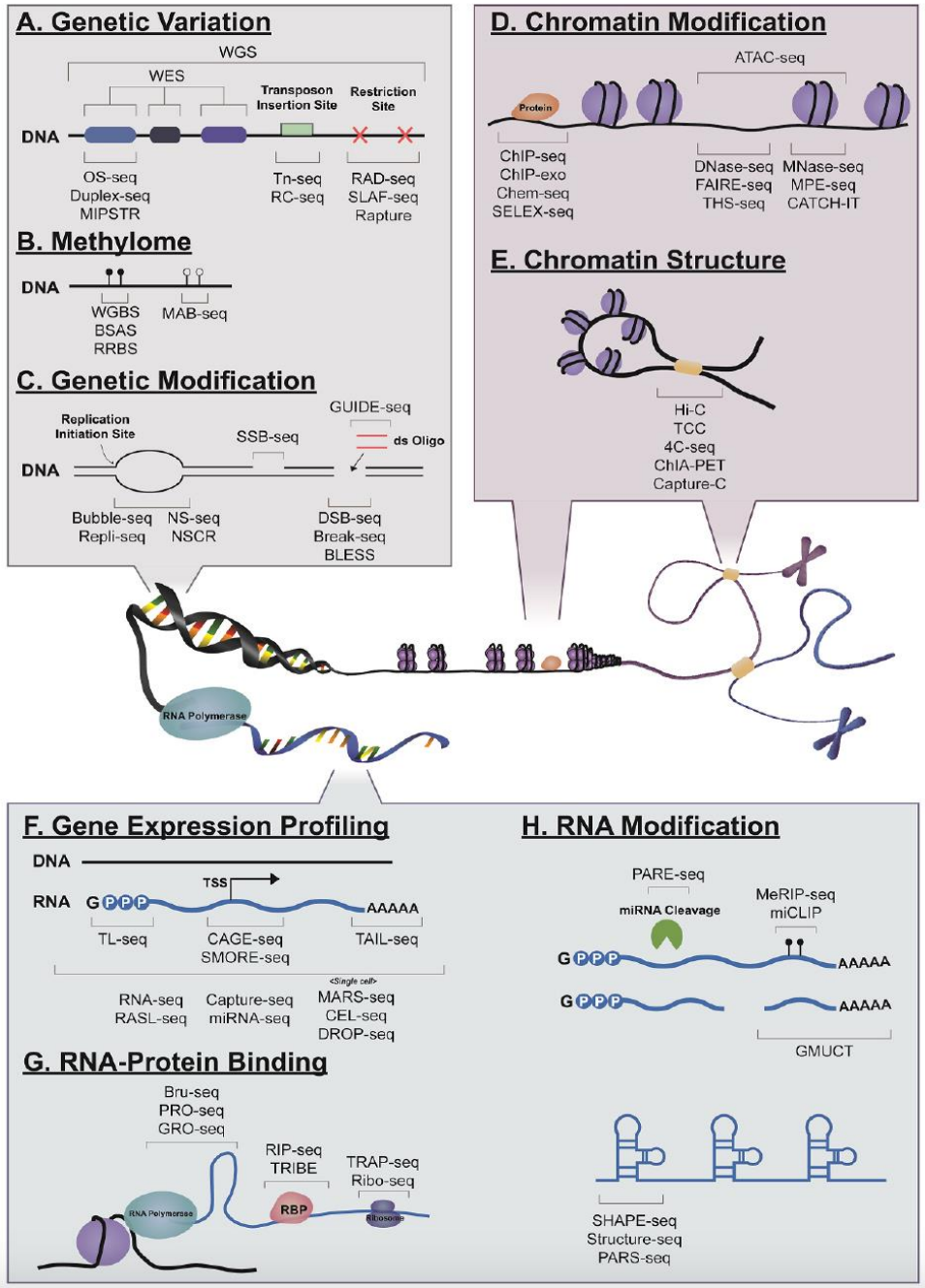
How could Precision and Personalised Medicine help us in the diagnosis of Liver diseases?
DNA seq



1. To address Monogenic Genetic Liver disease by Whole Genome Seq

2. To diagnose idiopathic chronic liver diseases

3. To address etiology of acute liver failure



ADN: Variantes genéticas

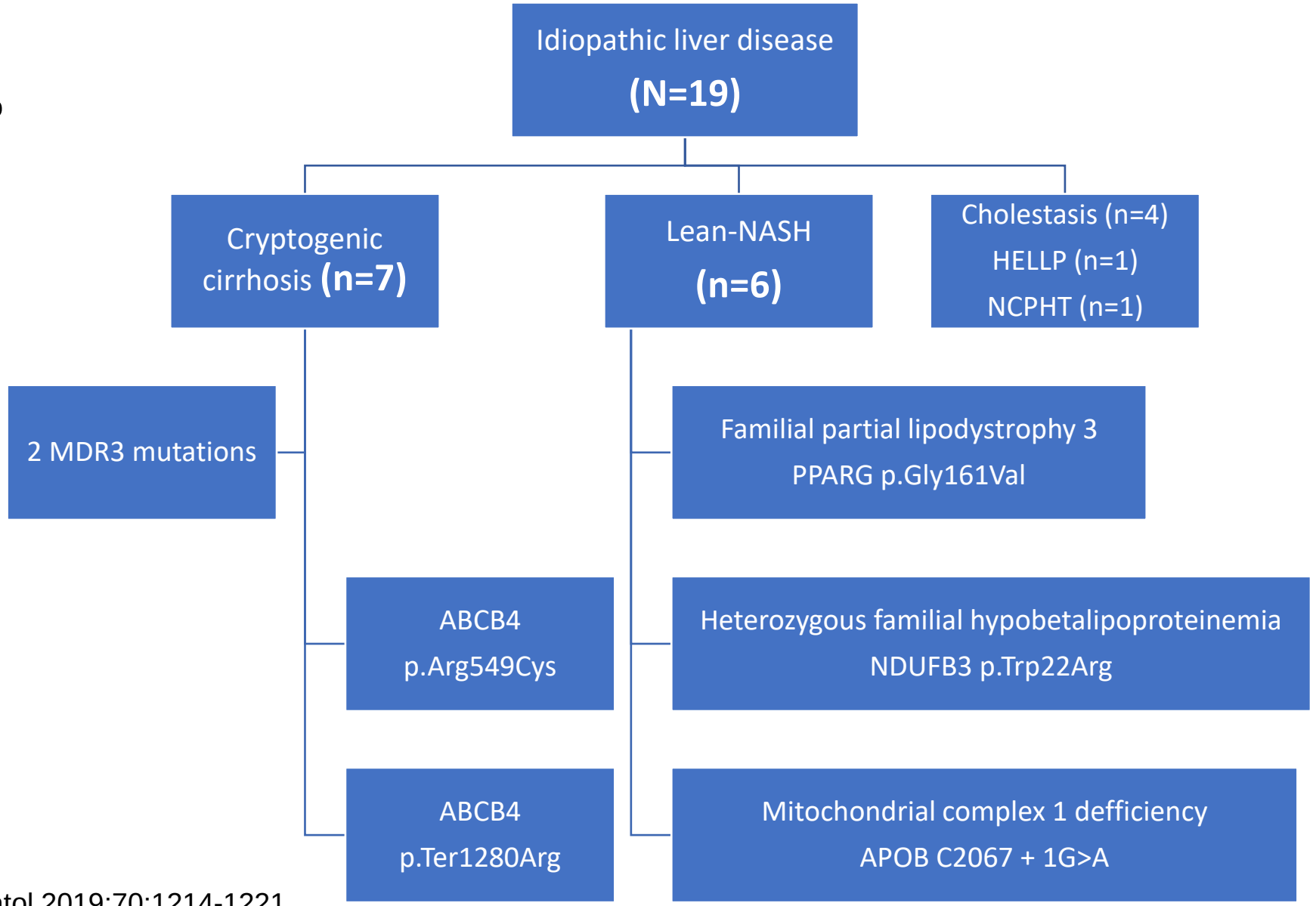
Fig. 1. Overview of next-generation sequencing techniques. (A) Detection methods for genetic variations, including in whole genome and whole exome. (B) Applications for methylation patterns. (C) Methods of genetic modifications, such as strand breaks enzyme digestion. (D) Various sequencing techniques for observing chromatin modifications. (E) Chromatin structures could be explained with sequencing applications. (F) Gene expression profiling with the form of RNAs. (G) Identification methods for RNA binding proteins and enrichment levels. (H) The formation of RNAs also detectable through sequencing applications.

ARN: Transcriptómica

Sumin et al. BMB Reports 2020; 53(6): 299-310
Hakim et al. J Hepatol 2019;70:1214-1221

Clinical utility of Whole Exome Sequencing in adults with idiopathic liver disease

5/19: 26%



Hakim et al. J Hepatol 2019;70:1214-1221

Clinical utility of Whole Exome Sequencing in patients with Acute Liver Failure

Idiopathic ALF 150/2718 (5.5%)

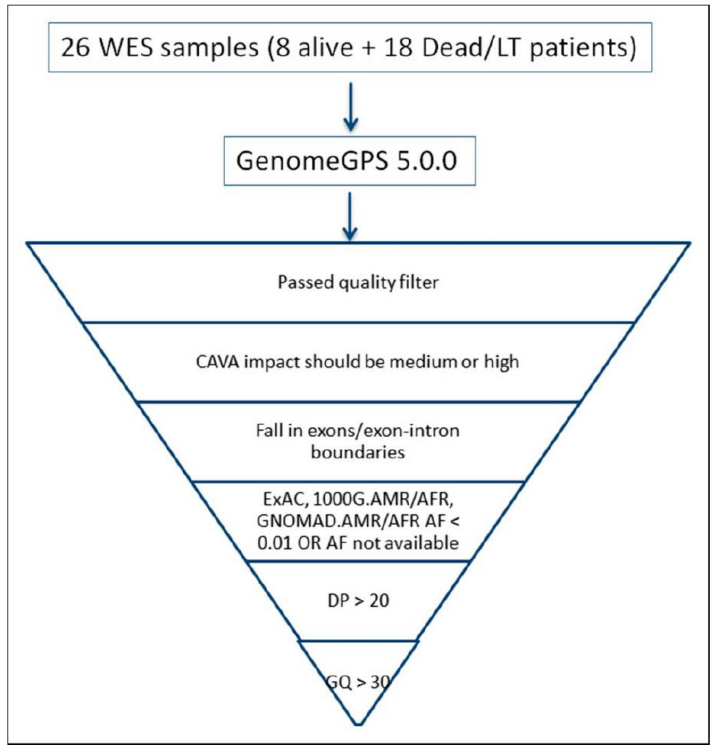
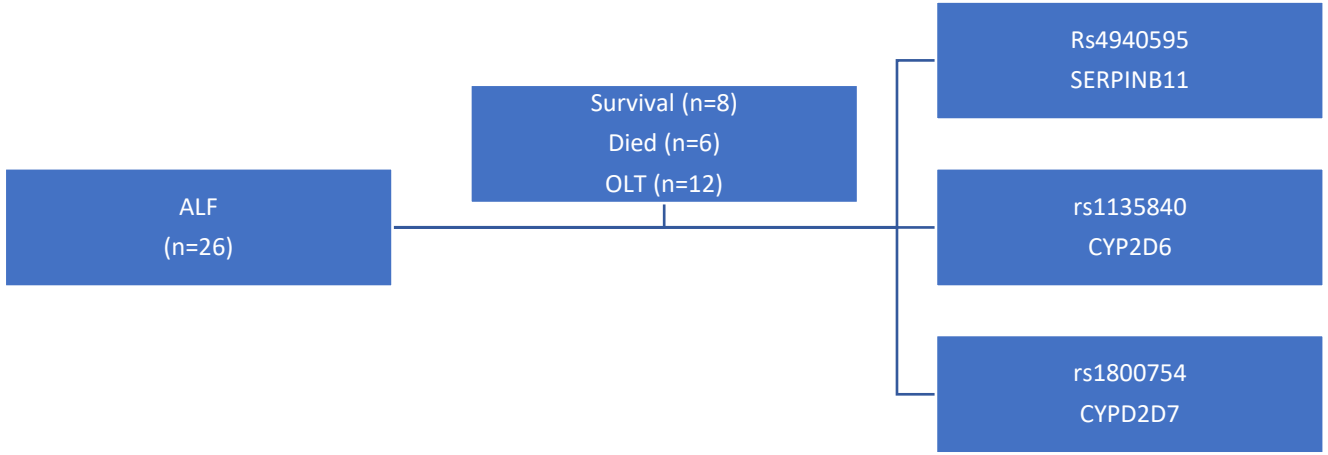


Figure 1. Functional filters applied in 26 DNA samples from 26 patients with *indeterminate* ALF. AF, allele frequency; ALF, acute liver failure; CAVA, clinical annotation of variants; DP, filtered depth of coverage for each sample; GQ, quality of the assigned genotype; LT, liver transplantation; WES, whole exome sequencing.



DILI
Xenobiotics

Table 1. Twelve variants from 11 genes significantly associated with *indeterminate* ALF among 26 patients with ALF

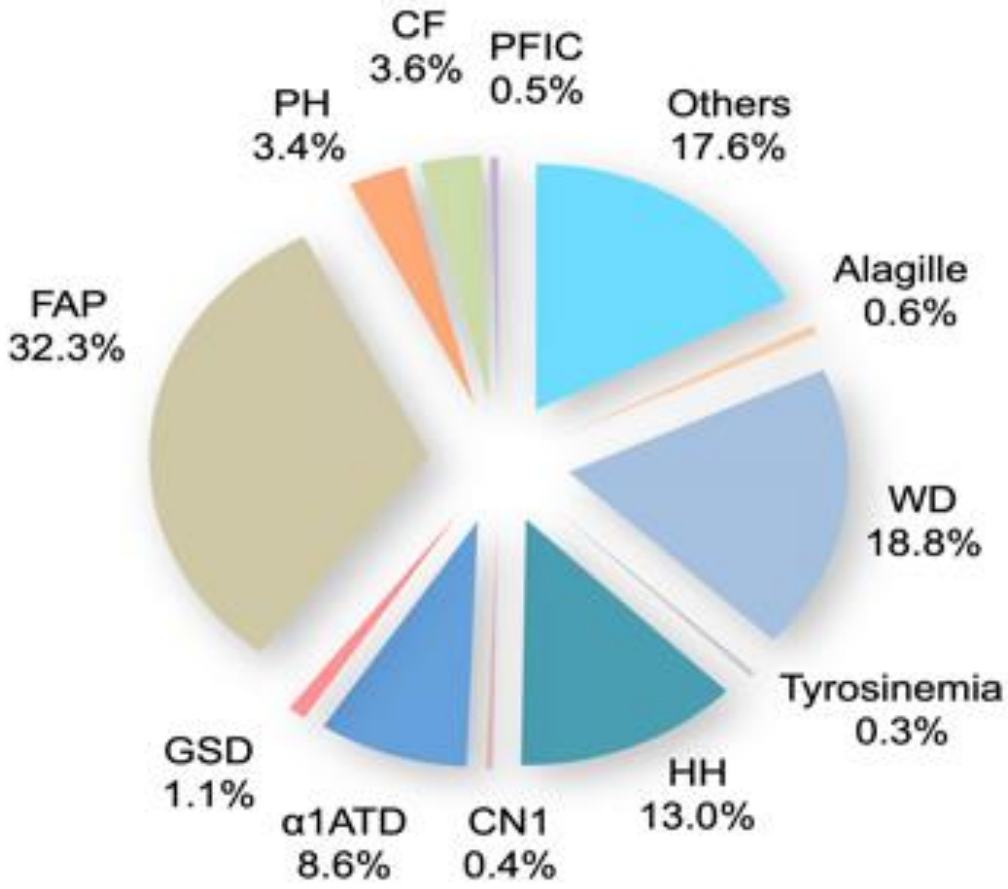
Gene	No. of chromosomes	Variants in dsSNP	No. of patients
ANTXRL	10	rs7091749	8
MUC6	11	rs776572312	9
OR6J1	14	rs1753430	14
GNAL	18	rs201898548	3
SERPINB11	18	rs4940595	23
AADACL3	1	rs3010877	7
MCL1	1	rs11580946	3
CYP2D6	22	rs1135840	16
CYP2D7	22	rs56404506	11
CYP2D7	22	rs1800754	15
RRP36	6	rs200886831	9
KIAA1161	9	rs4879782	6

ALF, acute liver failure.

Rakela J et al. CTH 2019;10:e00087

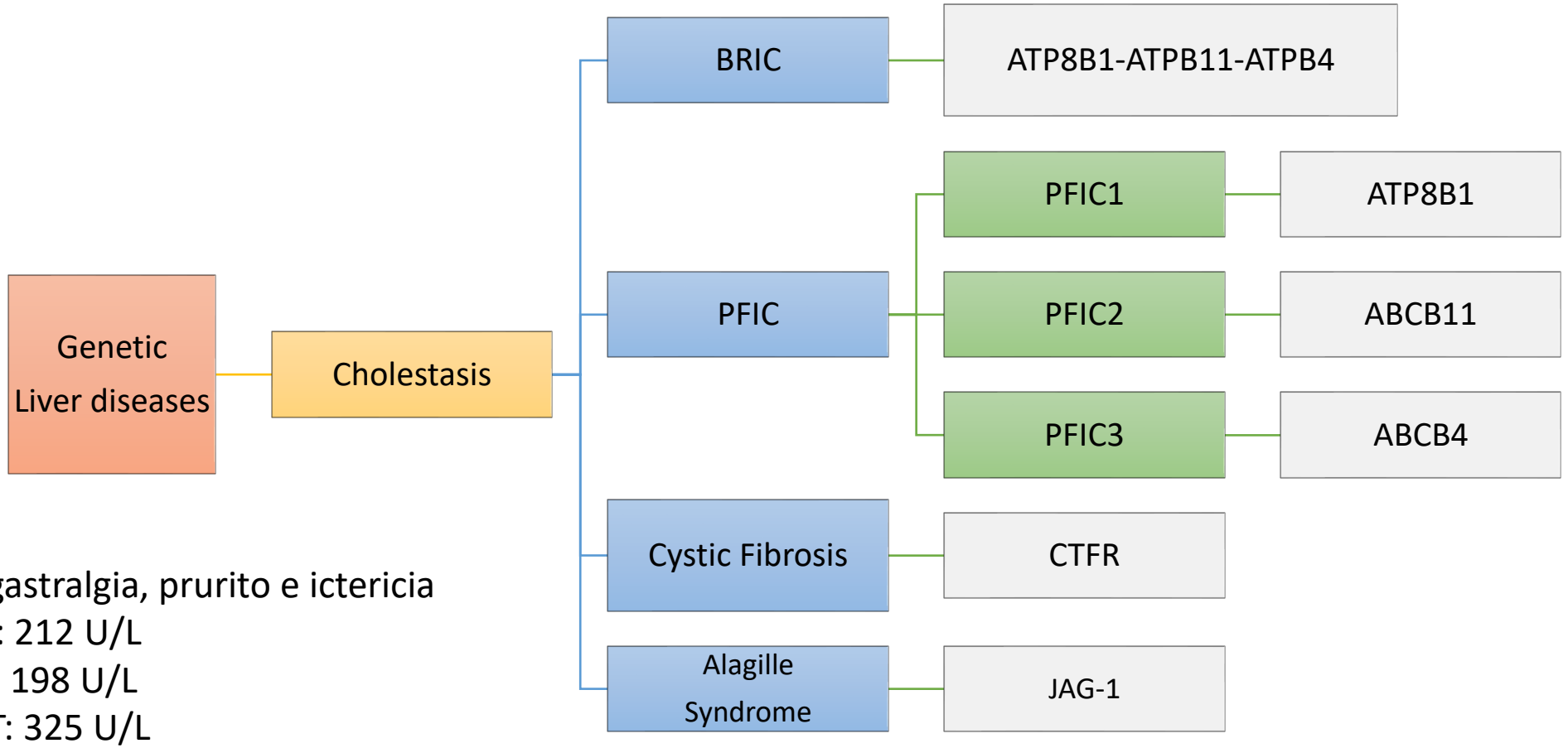
Monogenic liver diseases
Testing genetics: A diagnostic tool

- Genetic Liver diseases
  - Cholestasis
  - Fibrocystic diseases
  - LFT altered
  - Storage Liver Diseases
  - Genetic diseases with Extrahepatic manifestations



ELTR-Adult series
4082 out of 73,615 OLT (5.4%)

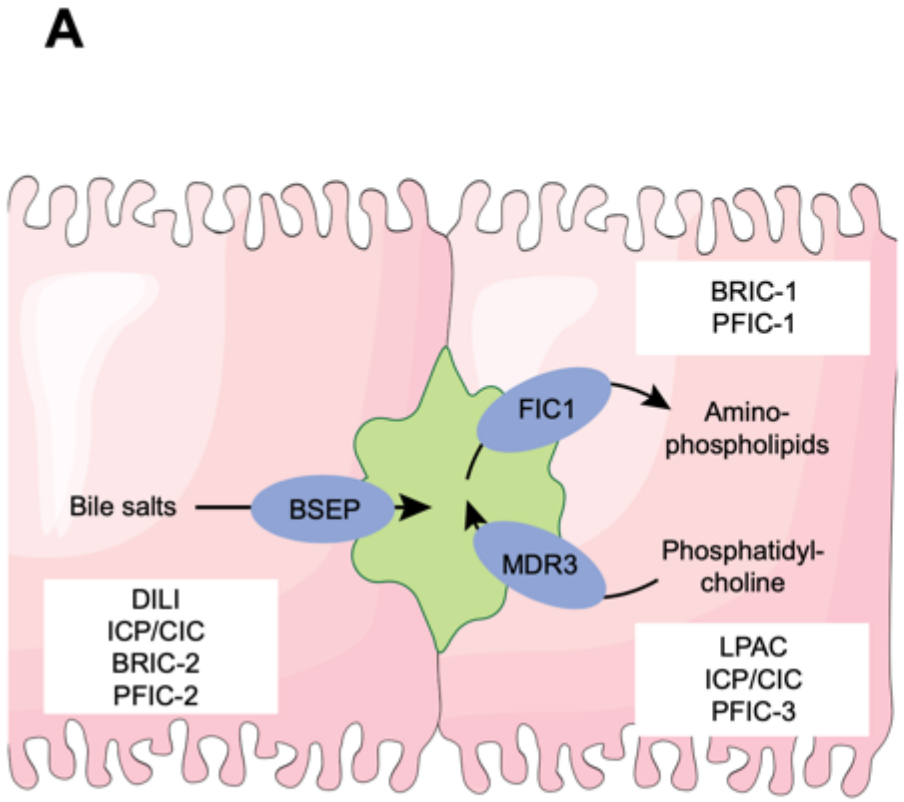
Monogenic liver diseases - Testing genetics: A diagnostic tool in patients with cholestasis



Epigastralgia, prurito e ictericia
AST: 212 U/L
ALT: 198 U/L
GGT: 325 U/L
FA: 190 U/L
Bilirrubina total: 14,3 mg/dl

Genes
ATP8B1
ABCB11
ABCB4
PKD1
PKHD1
ATP7B
SERPINA1
CFTR
HFE
JH
HAMP
TFR2
SLC40A1
FAH

Addressing Genetic cholestasis: a large number of variants



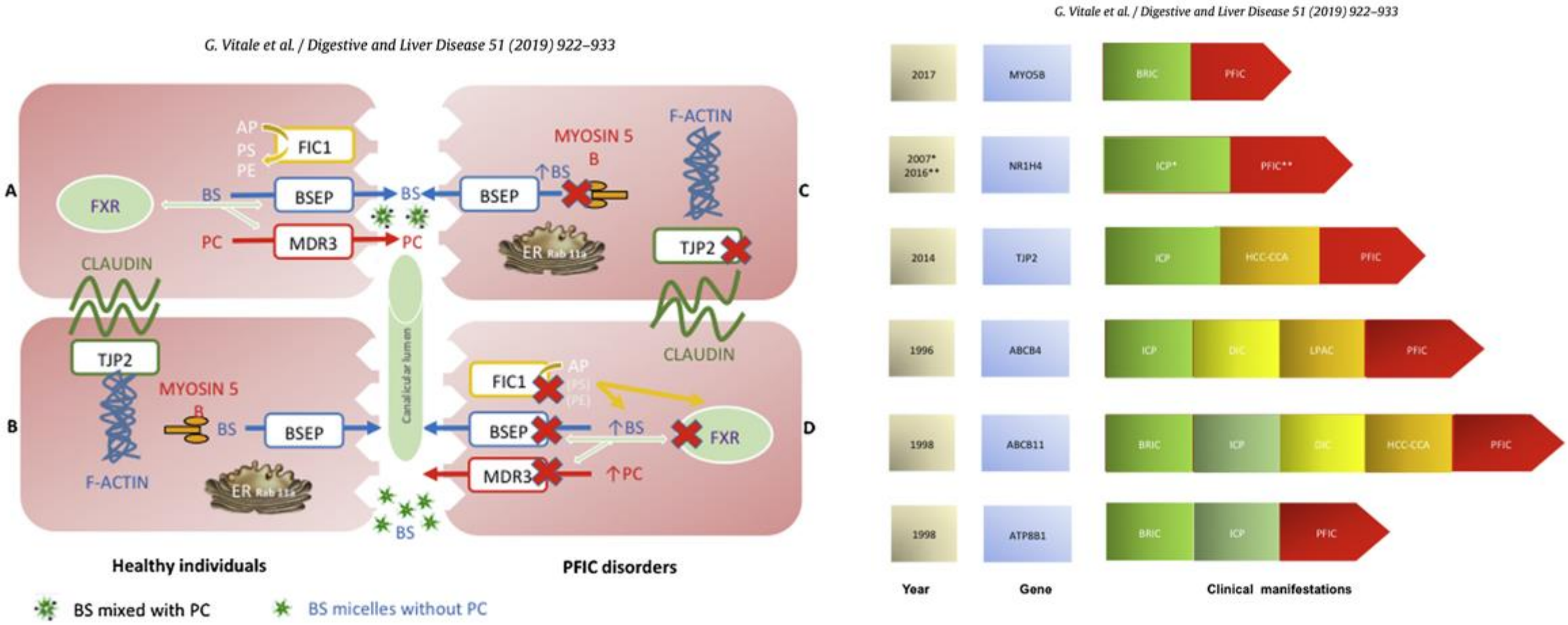
B

427 patients with a suspected genetically based cholestasis		
248/427 (58%) low γGT cholestasis	**179/427 (42%)** high γGT cholestasis/ICP/GSD	
185/427 (43%) sequenced for ≥2 genes		
651 sequencing analyses of patients		
184 patients analysed for FIC1	**252** patients analysed for BSEP	**215** patients analysed for MDR3
18/184 (9.8%) with at least one disease-causing FIC1 mutation	**88/252 (34.9%)** with at least one disease-causing BSEP mutation	**43/215 (20.0%)** with at least one disease-causing MDR3 mutation
4/18 (22.2%) with LT	**21/88 (23.9%)** with LT (+3 planned for LT) and **7/21 (33.3%)** with AIBD	**10/43 (23.3%)** with LT
65/184 (35.3%) with no disease-causing mutation but at least one FIC1 SNP	**162/252 (64.3%)** with no disease-causing mutation but at least one BSEP SNP	**156/215 (72.6%)** with no disease-causing mutation but at least one MDR3 SNP

Fig. 1. Cholestasis-related canalicular transport proteins and cohort characteristics. (A) Genetic variants in the genes encoding the hepatobiliary transport proteins familial intrahepatic cholestasis 1 (FIC1), bile salt export pump (BSEP), and multidrug resistance protein 3 (MDR3) are related to a variety of cholestatic liver diseases. (B) 427 patients with a suspected genetically-based cholestasis were sequenced for FIC1, BSEP or MDR3. 248 patients presented with a low γGT and 179 patients with high γGT cholestasis, ICP or gallstone disease (GSD). 185 patients were sequenced for 2 or 3 genes. In total, 651 sequencing analyses of these three genes were performed. FIC1: 184 patients, BSEP: 252 patients, MDR3: 215 patients. In 18, 88, and 43 patients, respectively, at least one disease-causing mutation was detected. From these patients with mutations, 4, 21, and 10 underwent liver transplantation (LT). For transplanted patients with BSEP mutations, 7 experienced disease recurrence in the form of antibody-induced BSEP deficiency (AIBD). In 65, 162, and 156 patients, respectively, no disease-causing mutation but common SNPs were detectable in the analysed gene. BRIC, benign recurrent intrahepatic cholestasis; CIC, contraceptive-induced cholestasis; DILI, drug-induced liver injury, ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholelithiasis; PFIC, progressive familial intrahepatic cholestasis. (This figure appears in colour on the web.)

Dröge et al. J Hep 2017;67:1253-1264

Genetic cholestasis



Next generation sequencing of selected genes.

Addressing Genetic cholestasis: a large number of variants

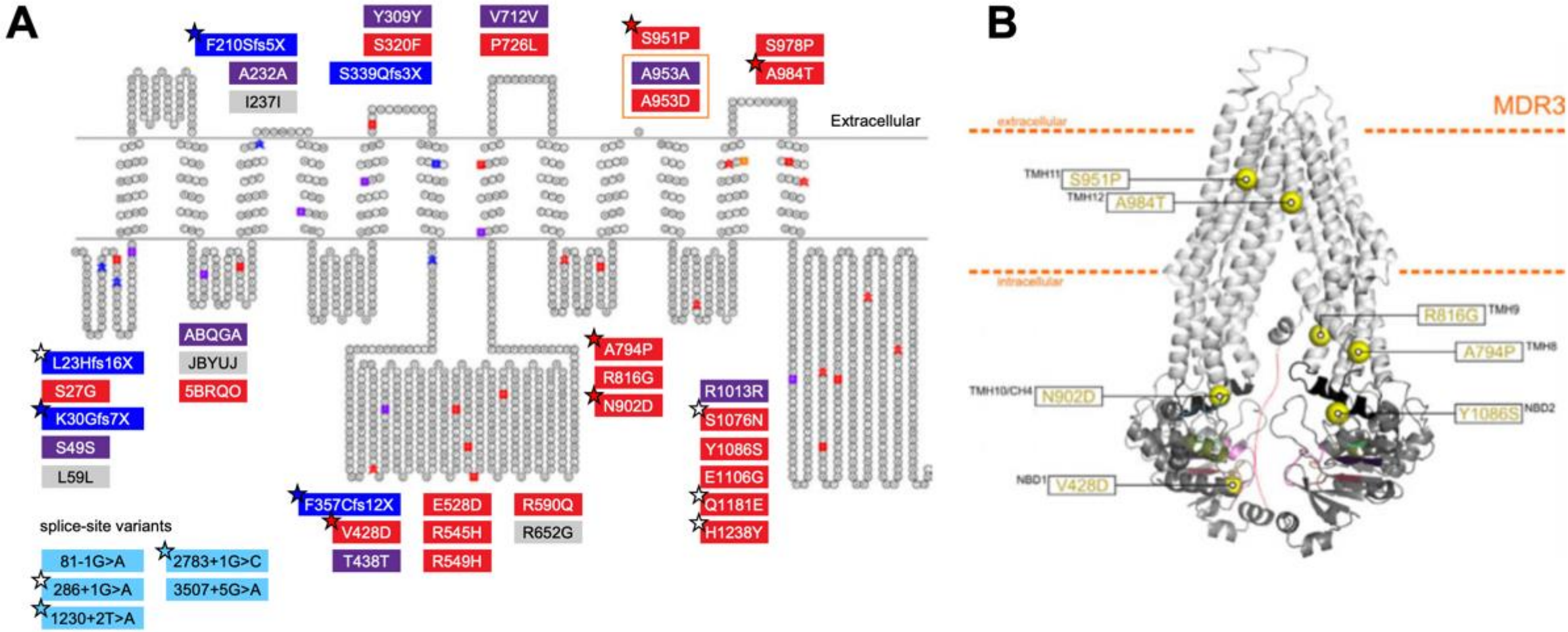
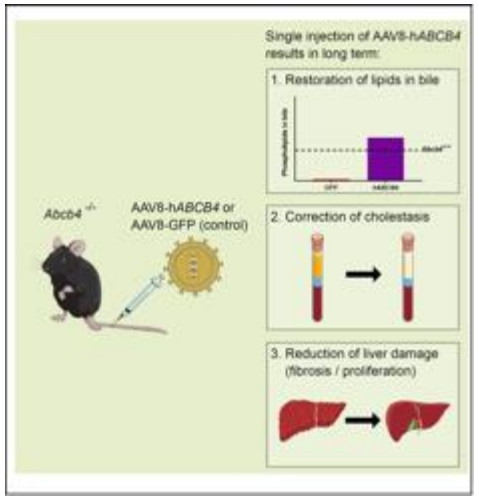
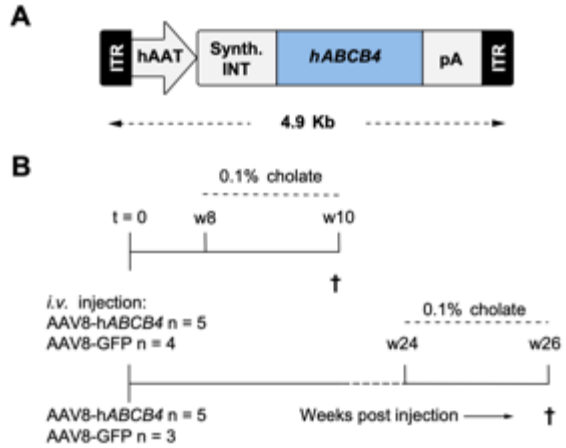


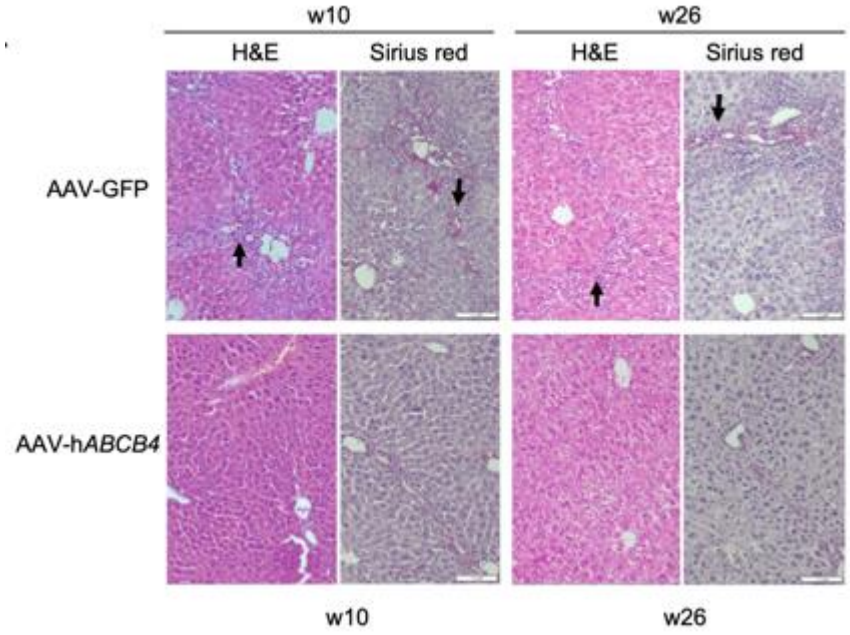
Fig. 4. 2D and 3D representation of detected MDR3 variants. (A) MDR3 TOPO2 model with coloured squares or stars indicating mutated AA. For frameshift mutations, the first affected position is marked. Red: missense, blue: frameshift, cyan: splice-site, purple: synonymous, grey: polymorphism, orange: position of two different variants, stars highlight new variants. (B) Specific missense mutations in a 3D MDR3 model based on P-gp structure (PDB-Code 4M1M). TMH, transmembrane helix.

Liver-directed gene therapy results in long-term correction of progressive familial intrahepatic cholestasis type 3 in mice

- Adeno-associated virus (AAV)-mediated gene therapy can correct Abcb4 deficiency (PFIC3) in mice.
- By restoring phospholipid transport to bile:
  - Cholestasis and liver damage were strongly reduced.
  - Stable transgene expression resulted in long-term correction of the phenotype (26 weeks).



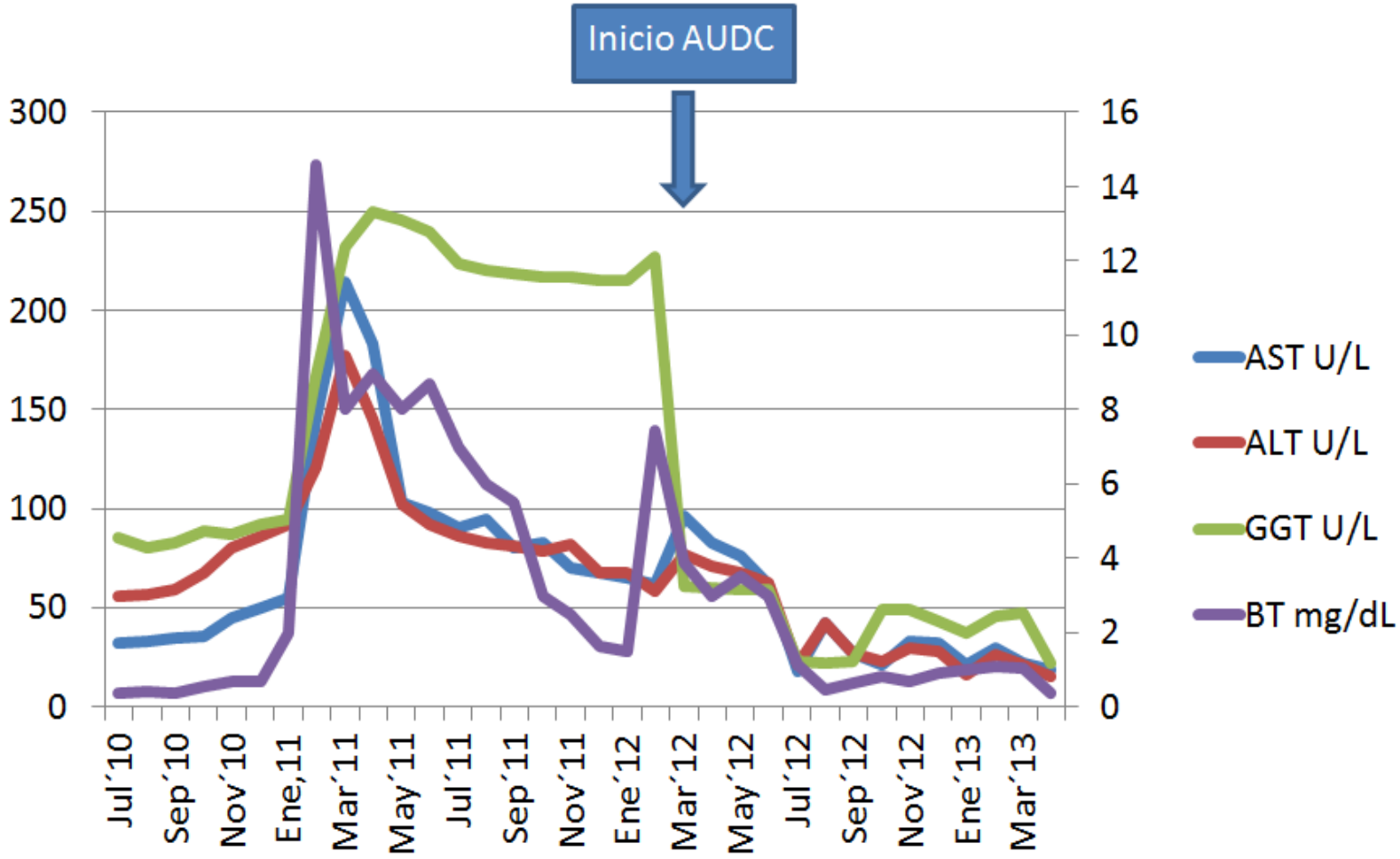




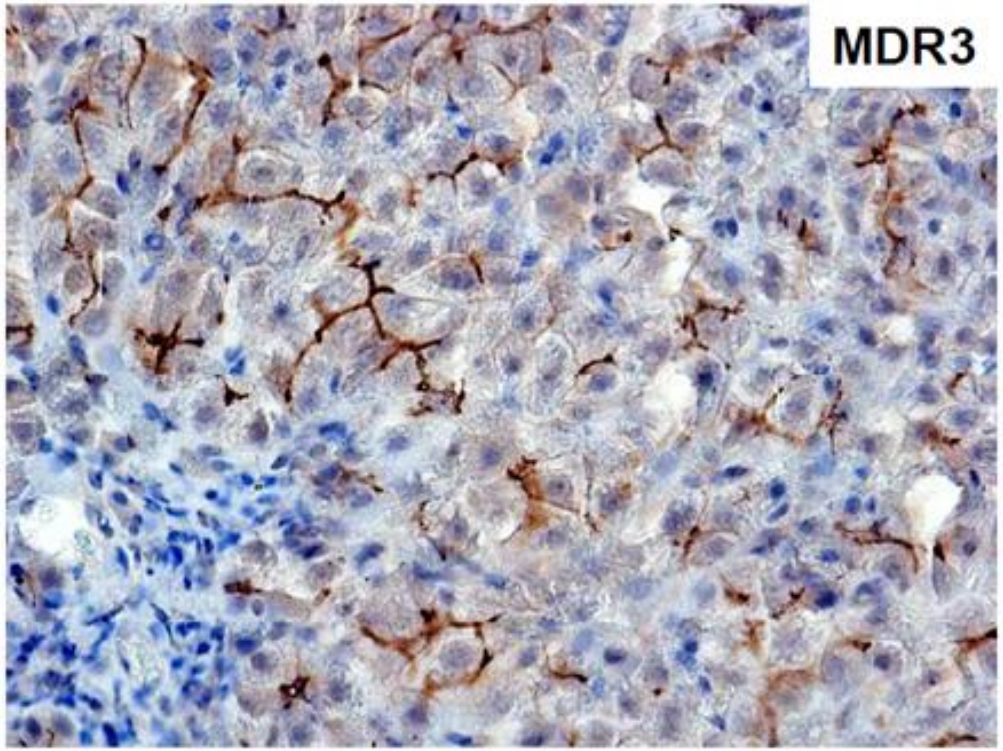
Aronson et al. J Hepatol 2019;71:153–162

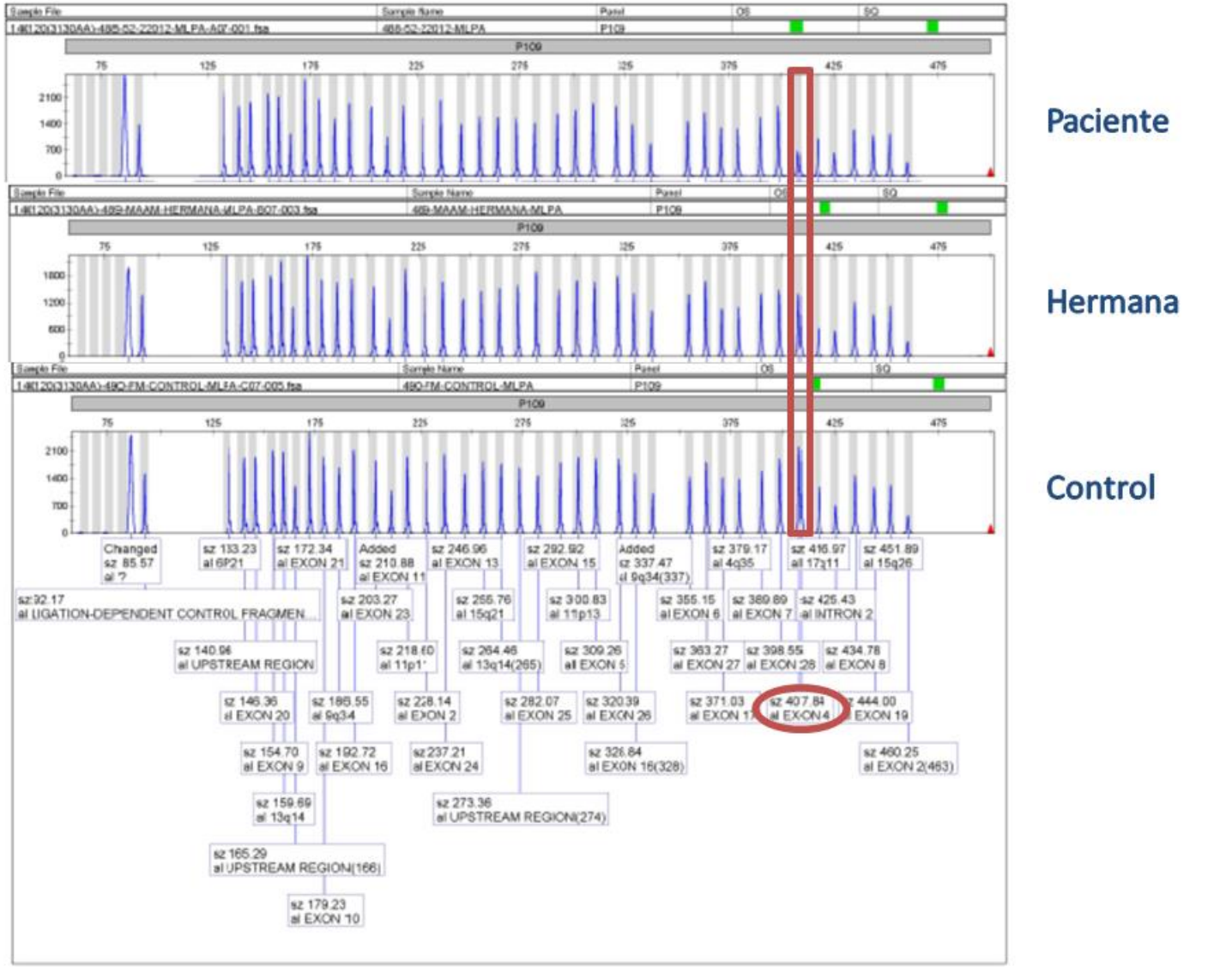
LPAC:
Low Phospholipids Associated Cholestasis

En Febrero de 2011 presentó un episodio de **ictericia intensa, con prurito y epigastralgia**.
Los valores analíticos más destacables fueron: AST 145 U/L (0-37 U/L), ALT 121 U/L (0-37 U/L), fosfatasa alcalina 116 U/L (50-190 U/L), GGT 167 U/L (6-50 U/L), bilirrubina total 14.6 mg/dL (0-1.8 mg/dL), y alfa-feto proteína 19.14 ng/mL (0-5 ng/mL), así como carga viral VHC de 14.600.000 UI/mL. Se realizaron las siguientes pruebas diagnósticas:
Ecografía digestiva en la que no se apreciaban lesiones ocupantes del espacio, ni dilatación de las vías biliares, mostrando una bilis espesa sin datos concluyentes de colelitiasis;
Colangio-RM donde se descartó coledocolitiasis y litiasis intrahepática; endoscopia oral normal;
Angio-TAC que mostró hepatomegalia homogénea y Ecoendoscopia que descartó lesiones en páncreas o la vía biliar.
Biopsia hepática: Hepatitis crónica C en estadio F3.



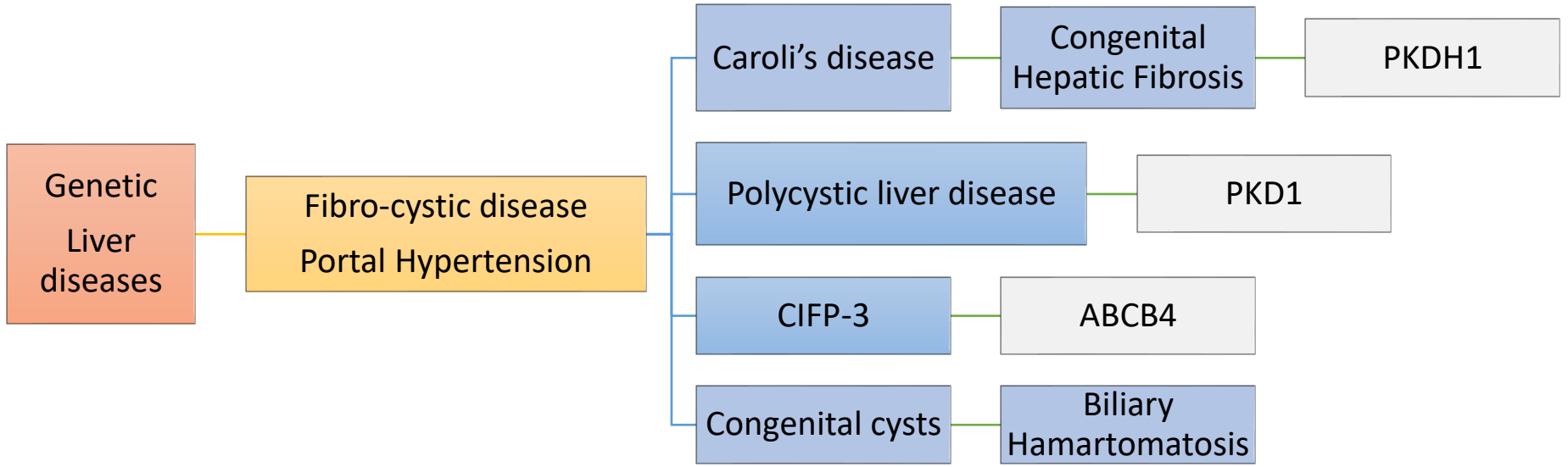
LPAC:
Low Phospholipids Associated Cholestasis

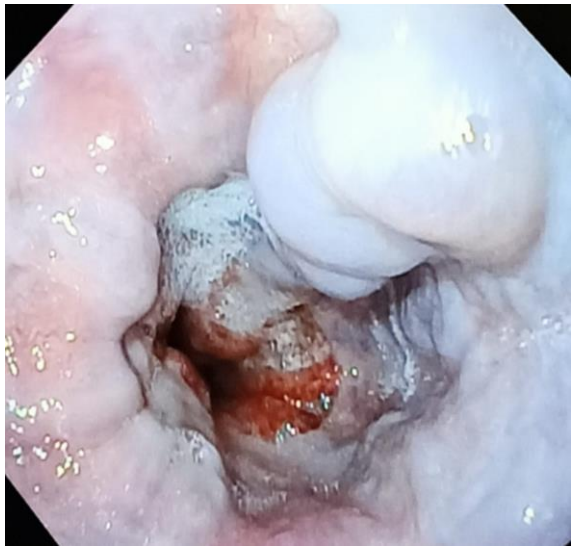




Mutación en heterozigosis por la deleción de un fragmento de gen que contiene el exón 4 completo (**Figura**), compatible con una deficiencia parcial de MDR3[11], confirmándose el diagnóstico de LPAC por MLPA (Multiplex Ligation-dependent Probe Amplification)

Monogenic liver diseases
Testing genetics: A diagnostic tool in patients with portal hypertension





Non-cirrhotic PTH

HVPG
Cholangio-RM
Liver Bx

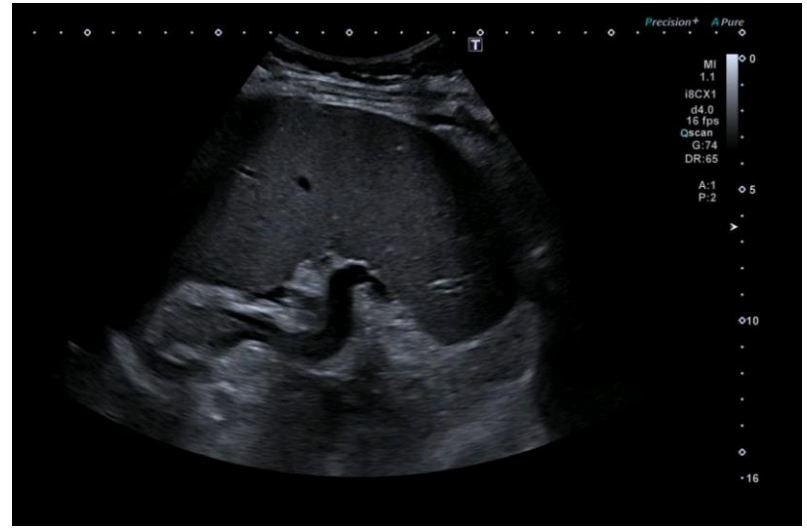
Genetic studies

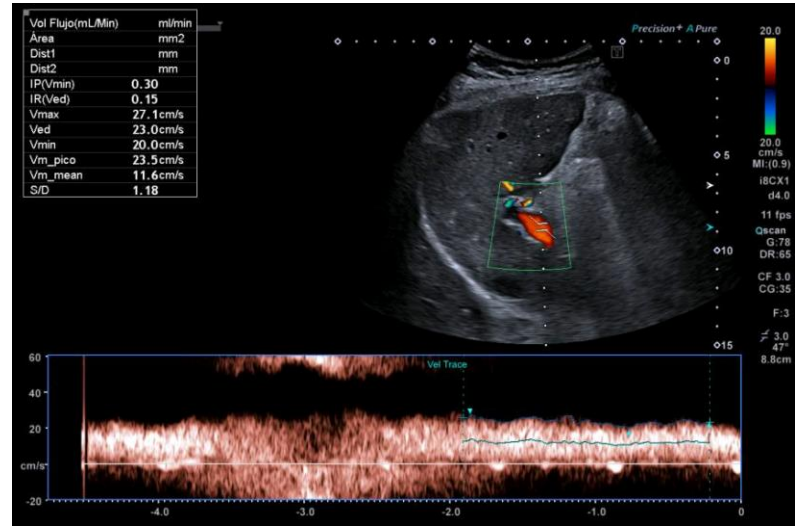
Caso Clínico

- Mujer de 32 años
- AF: Sin interés
- AP: No alergias. Síndrome de ovario poliquístico. Hipercolesterolemia.

- Estudiada desde los 18 años por cuadros recurrentes de hipertransaminasemia, dolor en hipocondrio derecho e ictericia.

Analítica: AST: 220 U/L; ALT: 398 U/L; Bt: 1,68 mg/dl; FA: 768 U/L; GGT: 1369 U/L. Plaquetas: 63.000 céls/mcL.
ANOEs, virus, tóxicos, A1AT, metabolismo del hierro y cobre: normales o negativos.
Colangio-RM: Sin alteraciones valorables.
Biopsia hepática: Piecemeal necrosis modrada, necrosis lobular leve (Actividad inflamatoria A2). Expansión fibrosa periportal (F2).
Endoscopia oral: Varices esofágicas incipientes.
Inicia tratamiento con ácido ursodeoxicólico + Prednisona sin respuesta bioquímica.
Se indicó colecistectomía en 2015: Hepatomegalia, esplenomegalia, circulación colateral, repermeabilización del conducto de Arancio.

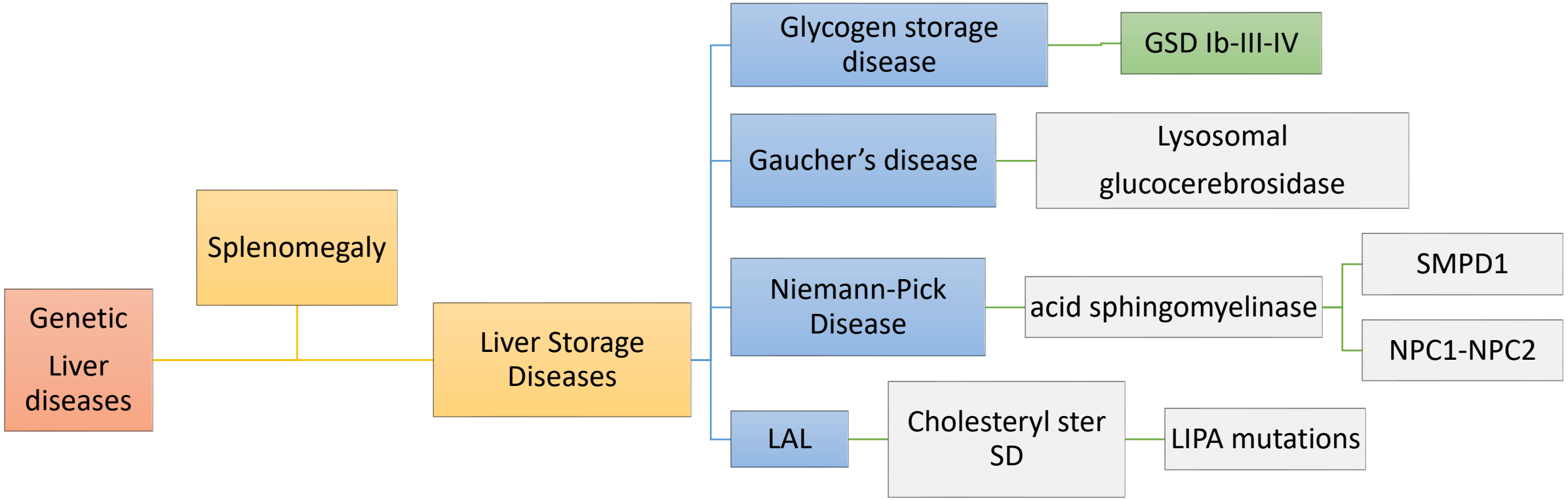




Gen MIM*171060	Cambio detectado*			Referencia
	Condición	RefSeq NM_018849.2	Proteína NP_061337.1	
ABCB4	Homocigosis	c.959C>T	p.Ser320Phe	Rosmorduc O. et el. Gastroenterology. 2001;120(6):1459-67.

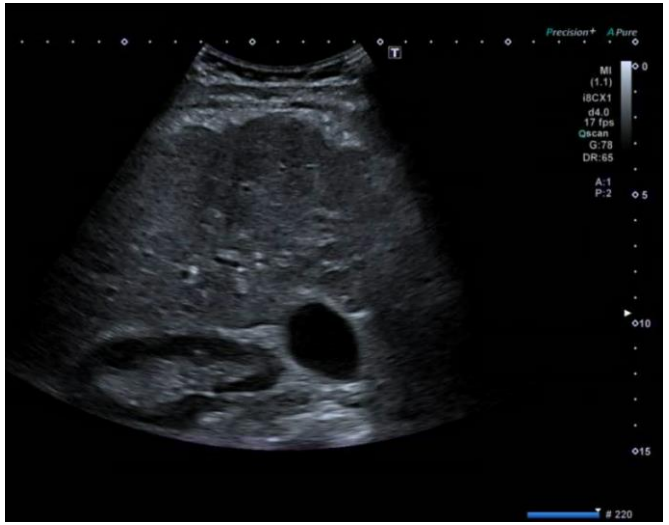
* Se ha empleado la nomenclatura recomendada por la Human Genome Variation Society (HGVS).

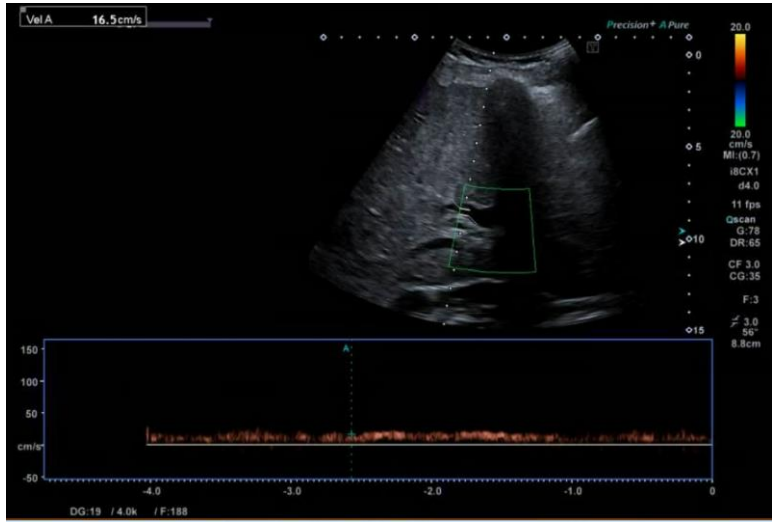
Monogenic liver diseases
Testing genetics: A diagnostic tool in metabolic and storage liver diseases

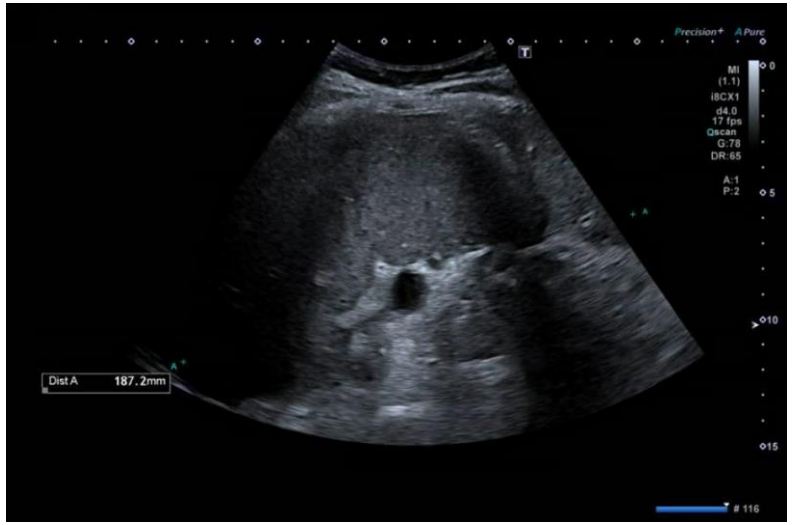


Caso Clínico: Hombre de 33 años

- Hemograma: leucocitos: 5500, Hb: 15.1 g/dl, plaquetas: 133.000 céls/mcL; INR 1.07.
- Bioquímica: Creatinina: 0.67mg/dl, AST 151 U/L, ALT 140 U/L, GGT 148 U/L, FA 81 U/L, Bt 0.47 mg/dl. Colesterol 177 mg/dl, Tg 87 mg/dl. Albúmina 4.8 g/dl; AFP 3 ng/ml Hb1Ac 5%.
- Metabolismo férrico: Ferritina 190 ng/ml, IST 18%.

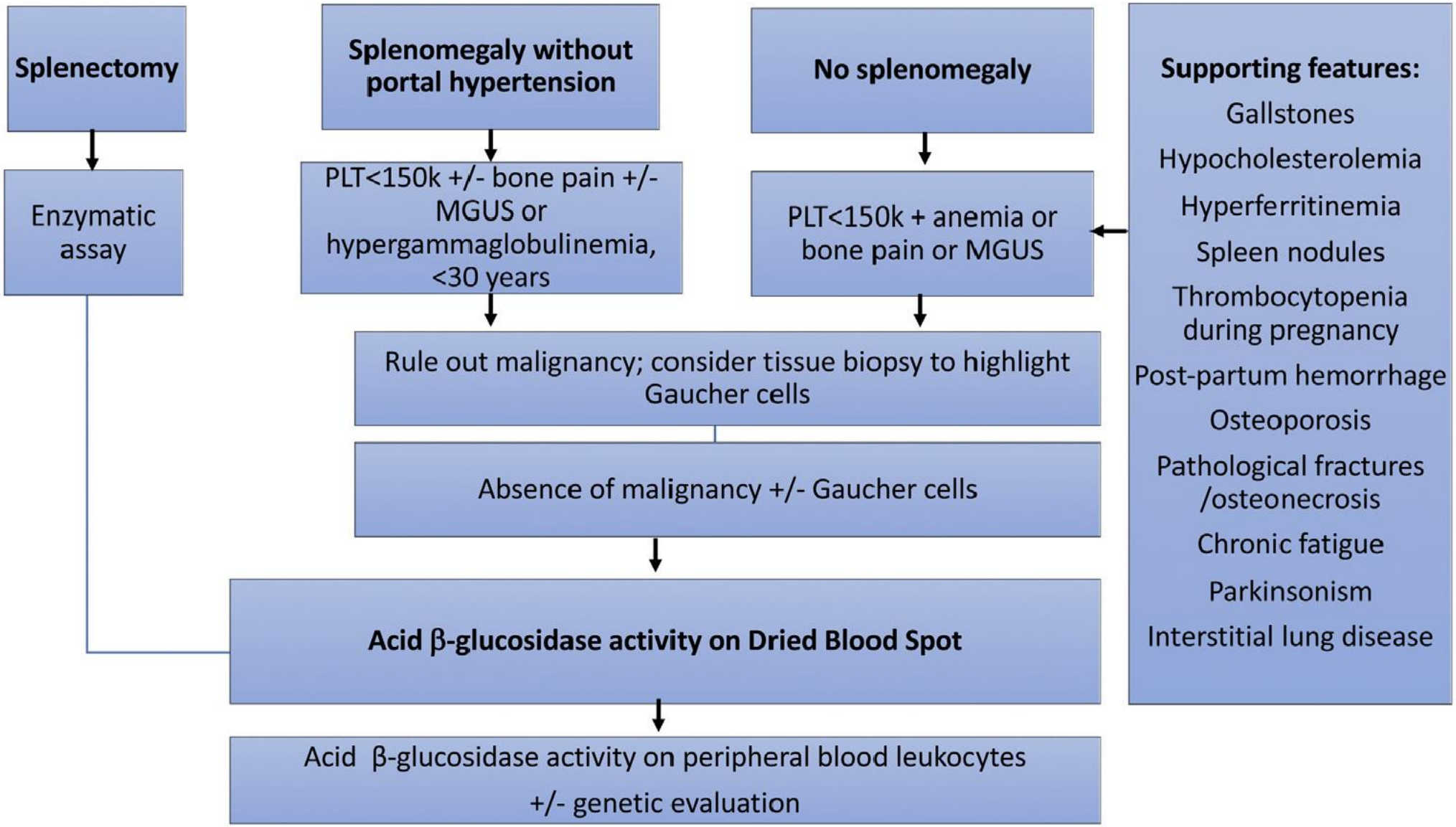






Estudio genético >> Glucogenosis tipo III (Enfermedad de Cori) gen AGL

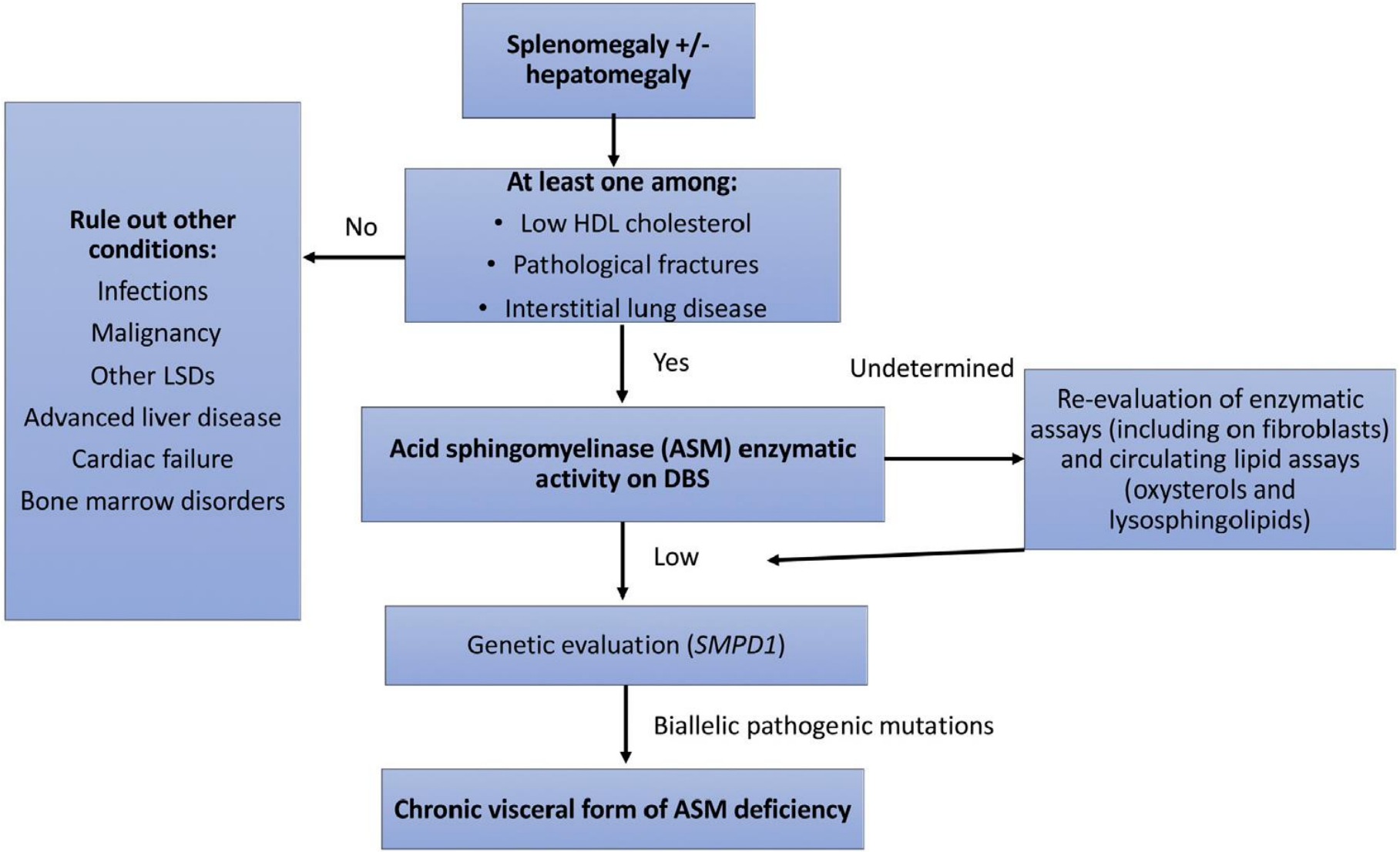
Gaucher Disease management



Nascimbeni et al. Dig Liv Dis 2020;52:359-367

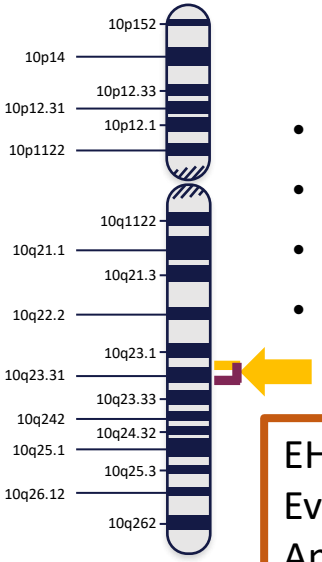
* MGUS: monoclonal gammopathy of undetermined significance

Niemann Pick Disease



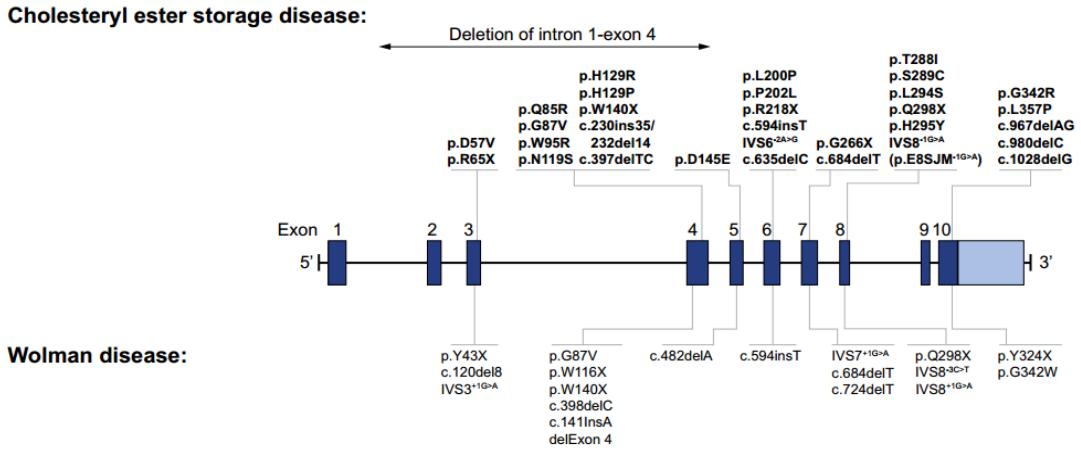
Nascimbeni et al. Dig Liv Dis 2020;52:359-367

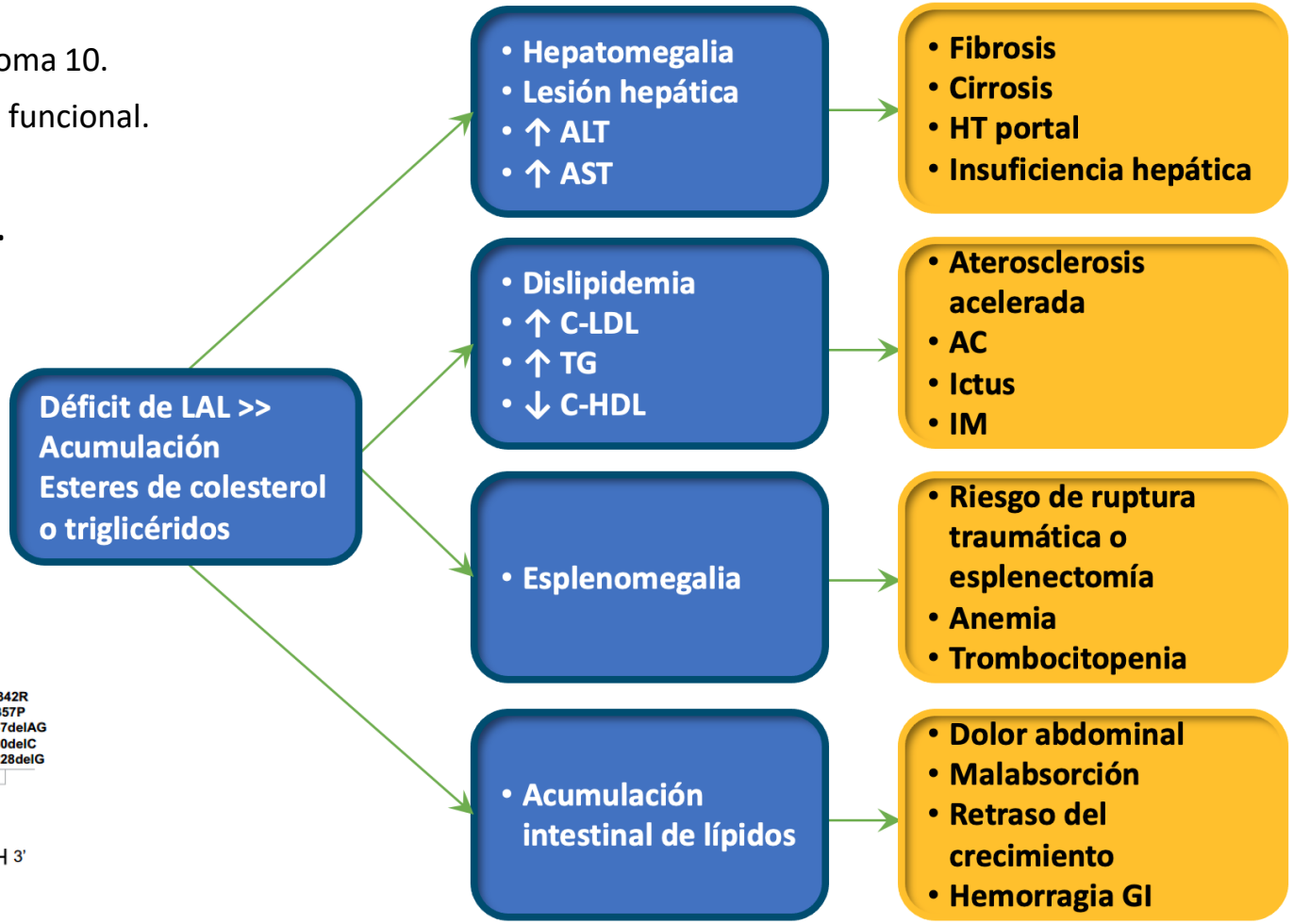
LAL-Defficiency



- El gen LIPA se localiza en el brazo largo del cromosoma 10.
- Más **de 40 mutaciones** que ocasionan una pérdida funcional.
- Entre 50 %- 60 % presenta la mutación c.894G>A.
- **NO CLARA CORRELACION ACTIVIDAD / FENOTIPO.**

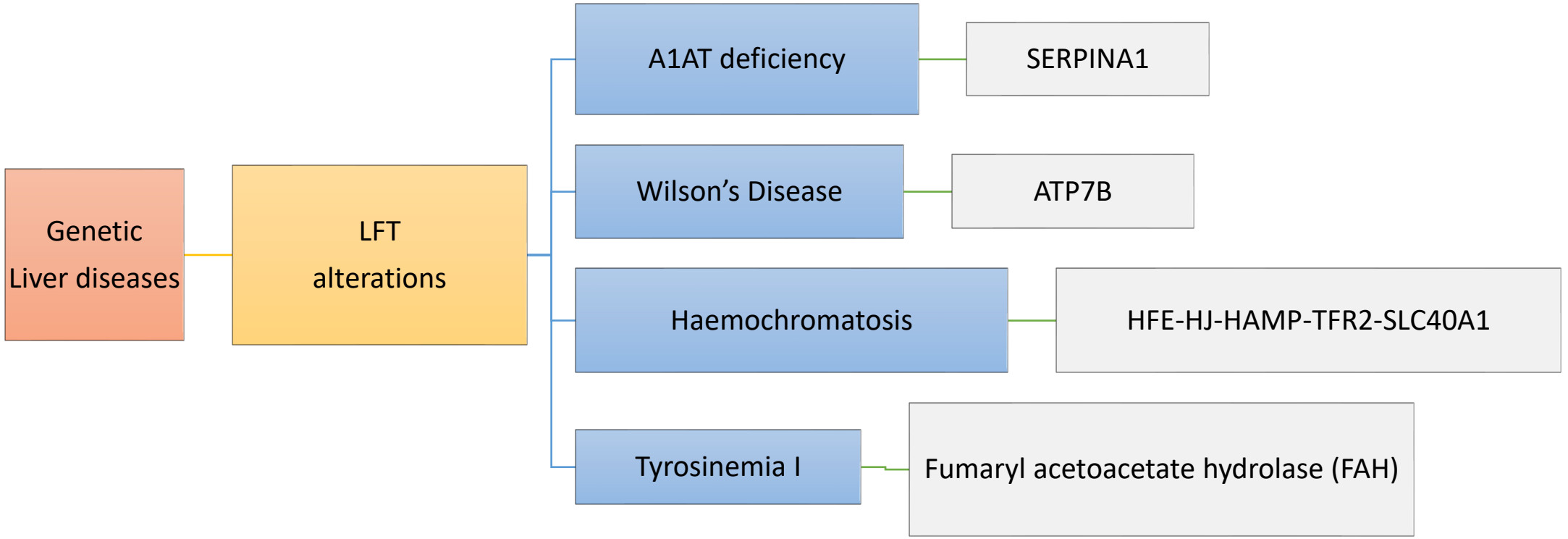
EHmet + LDL>160mg/dl + HDL<40-50mg/d
Evaluar actividad LAL en DBS
Análisis gen LIPA





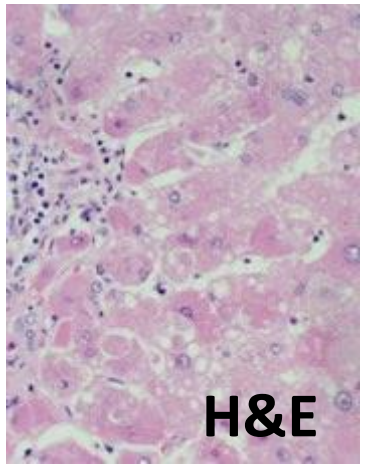
1. Bernstein DL, et al. *J Hepatol*. 2013;58(6):1230-1243. 2. Reiner Ž, et al. *Atherosclerosis*. 2014;235(1):21-30. 3. Nascimbeni et al. Dig Liv Dis 2020;52:359-367

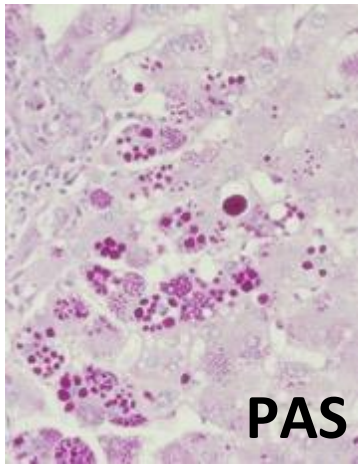
Monogenic liver diseases
Testing genetics: A diagnostic tool in metabolic liver diseases

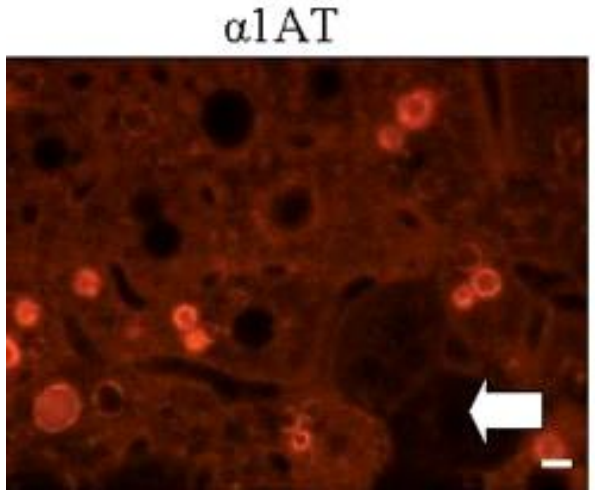


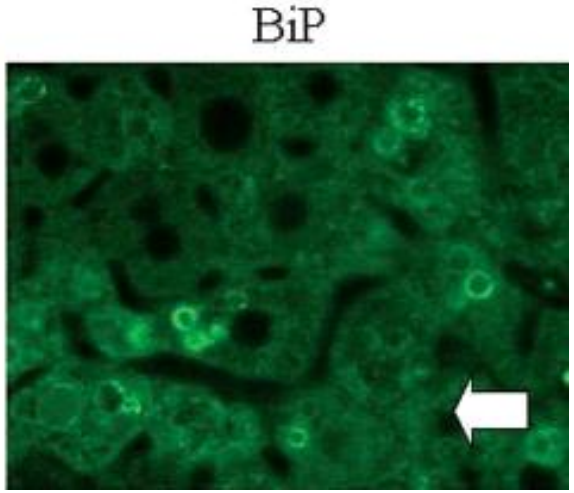
A1AT: Human ZZ Liver

Liver: Accumulation of mutant Z protein in hepatocytes causes liver injury.
Lung: “Deficient” serum level leaves host tissues susceptible to damage by neutrophil proteases.
Highly variable disease course suggests important modifiers.









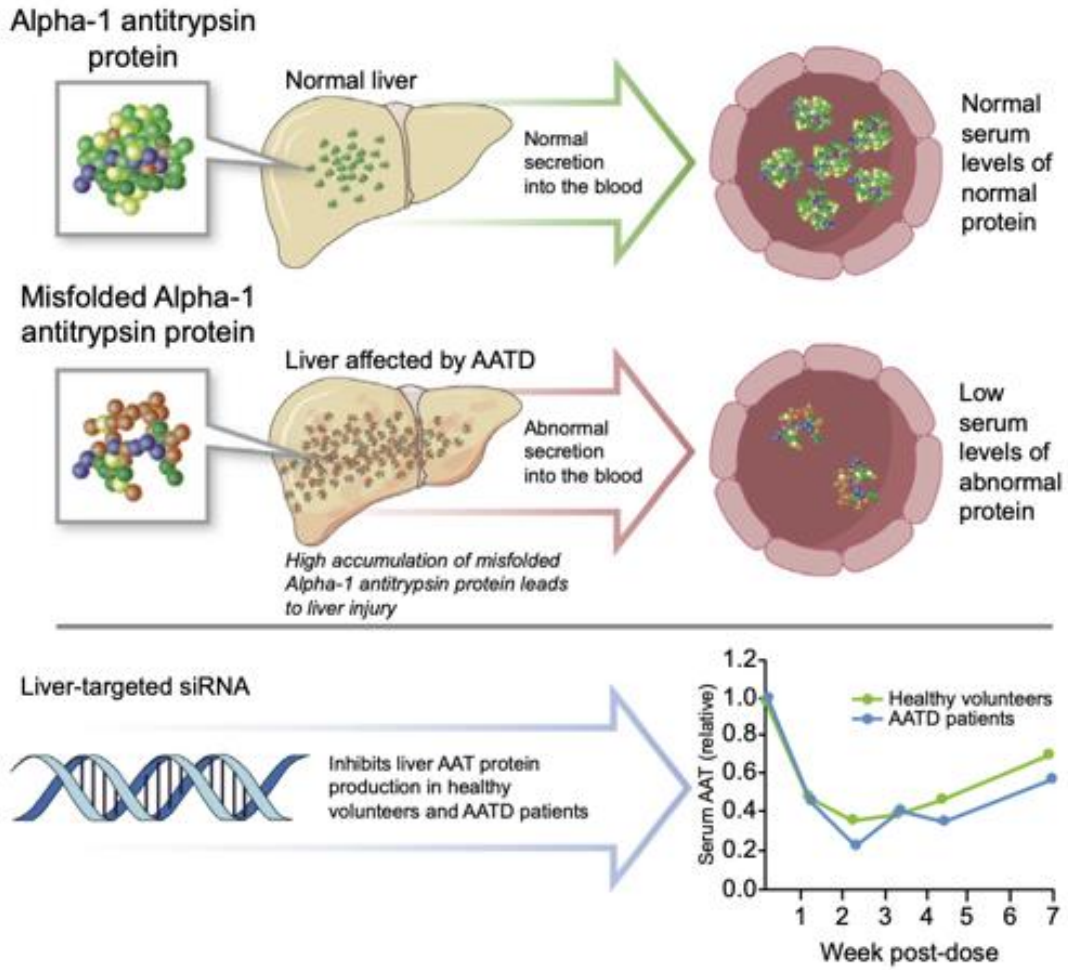
Disease	Common Laboratory Abnormalities	Presentation of Disease
Alpha-1 antitrypsin deficiency	+ AST/ALT + Alkaline phosphatase Phenotype analysis, most commonly ZZ	Early emphysema, especially in smokers Cirrhosis HCC

What test to order?
Alpha-1 antitrypsin level; if low, then
Alpha-1 antitrypsin isoelectric focusing; if normal, then
SERPINA1 genetic testing

Tratamiento DA1AT en pacientes ZZ:

Enfermedad pulmonar: Terapia sustitutiva con A1AT recombinante.

Enfermedad hepática: RNAi para evitar la acumulación de A1AT.



Alpha-1 antitrypsin deficiency is associated with liver fibrosis and cirrhosis due to hepatocyte accumulation.

RNAi drugs (ARC-AAT) directed to the liver (ARC-EX1) reduced alpha-1 antitrypsin protein accumulation in the hepatocytes

Turner et al. J Hep 2018;68: 378-384

RESEARCH SUMMARY

Fazirsiran for Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency

Strnad P et al. DOI: 10.1056/NEJMoa2205416

CLINICAL PROBLEM

The gene *SERPINA1* encodes alpha$_1$-antitrypsin (AAT). Patients with a homozygous "Z" mutation in *SERPINA1* (i.e., the proteinase inhibitor [PI] ZZ genotype) have AAT deficiency owing to production of a mutant protein called Z-AAT. Accumulation of Z-AAT in hepatocytes can lead to progressive liver disease and fibrosis, and targeted treatments are needed.

CLINICAL TRIAL

Design: A phase 2, multinational, open-label trial examined the safety, pharmacodynamics, and efficacy of fazirsiran, an RNA interference therapeutic, in patients with liver disease associated with AAT deficiency.

Intervention: 16 patients with the PI ZZ genotype and fibrosis received subcutaneous fazirsiran (100 mg or 200 mg) on day 1, at week 4, and every 12 weeks thereafter. The primary end point was the change from baseline over time in liver Z-AAT concentrations, assessed by means of liquid chromatography–tandem mass spectrometry of liver-biopsy samples.

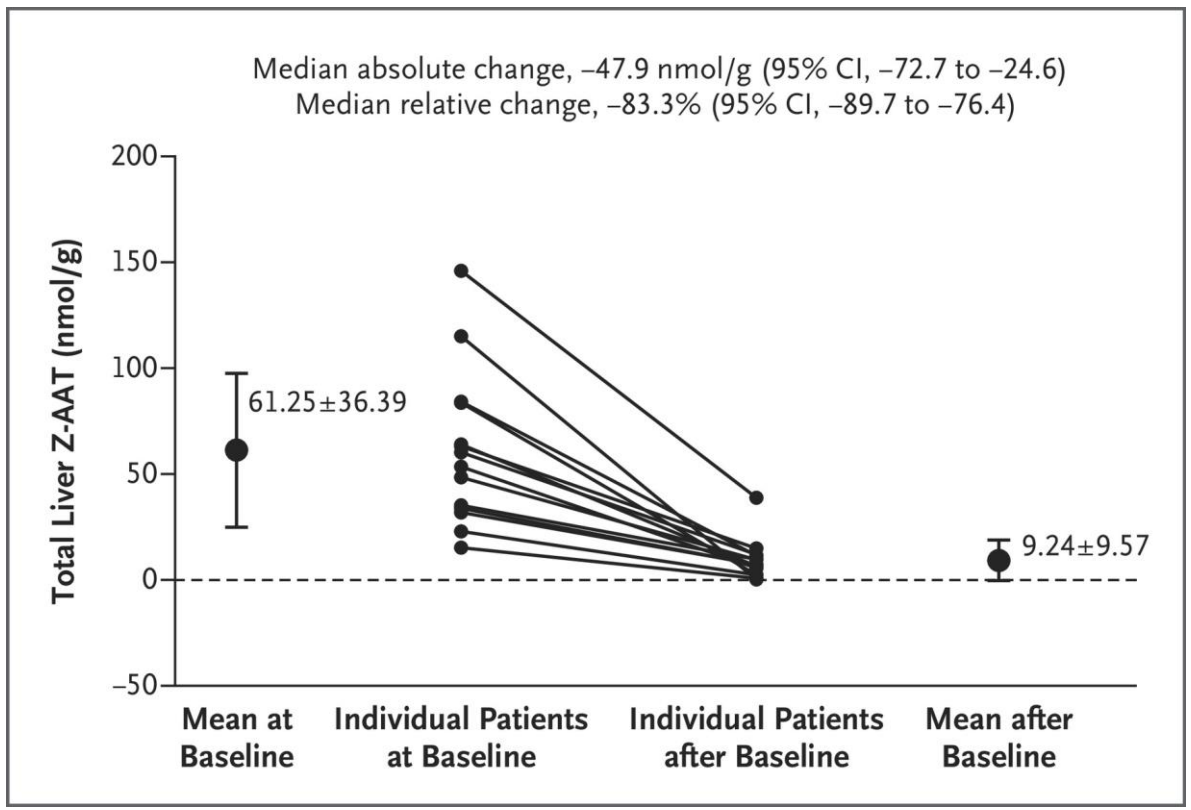
RESULTS

Efficacy: All 14 evaluable patients had reductions in total liver Z-AAT concentrations at week 24 or 48 of follow-up.

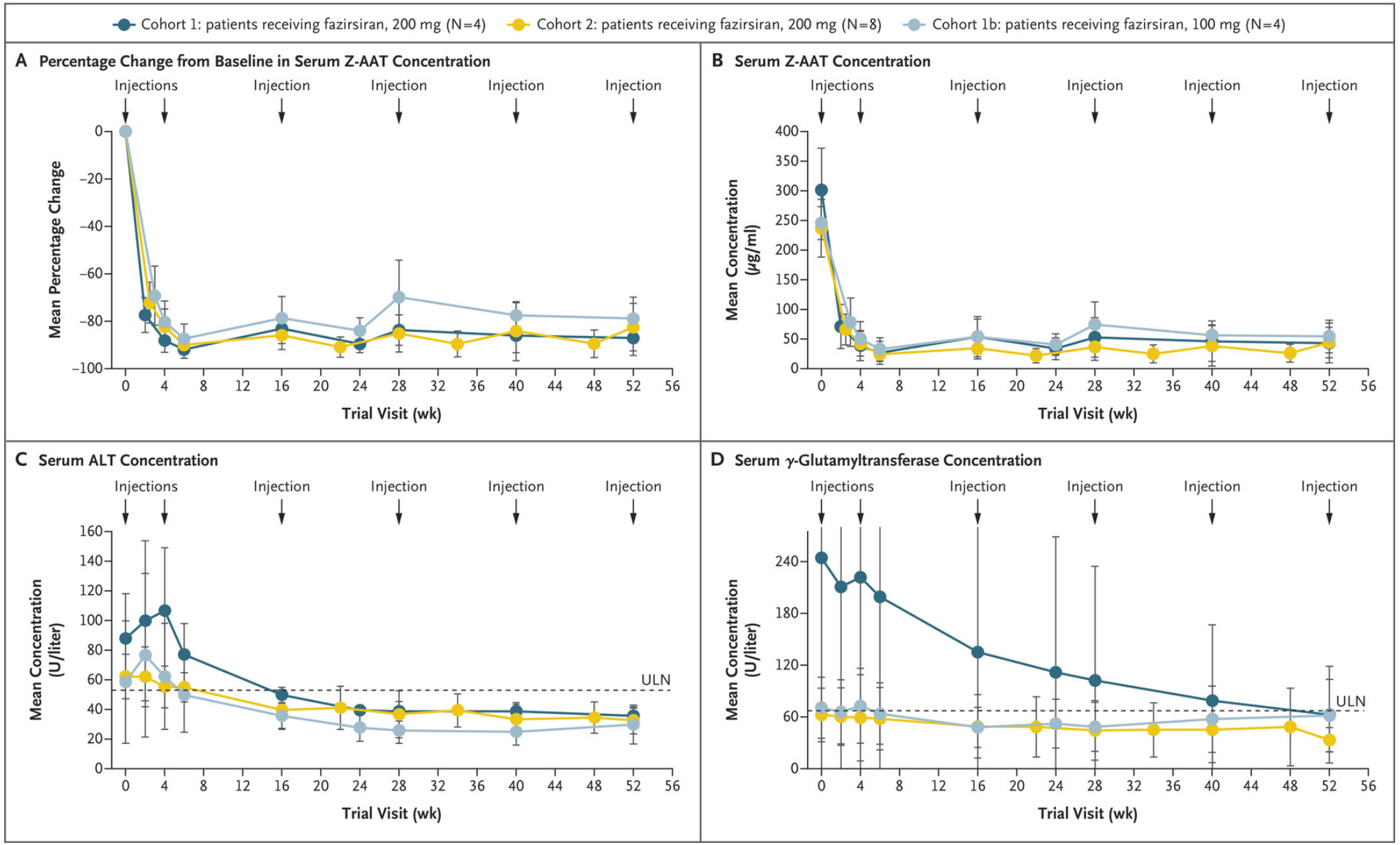
Pharmacodynamics and Safety: Serum Z-AAT concentrations decreased in all patients. The nadir was reached at week 6. Over a period of 1.5 years, no deaths, treatment discontinuations, or dose interruptions occurred. Four serious adverse events — viral myocarditis, diverticulitis, dyspnea, and vestibular neuronitis — were reported, and all resolved.

LIMITATIONS

- The trial was small and lacked a control group.



Fazirsiran for Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency



Monogenic liver diseases

Patients with iron overload

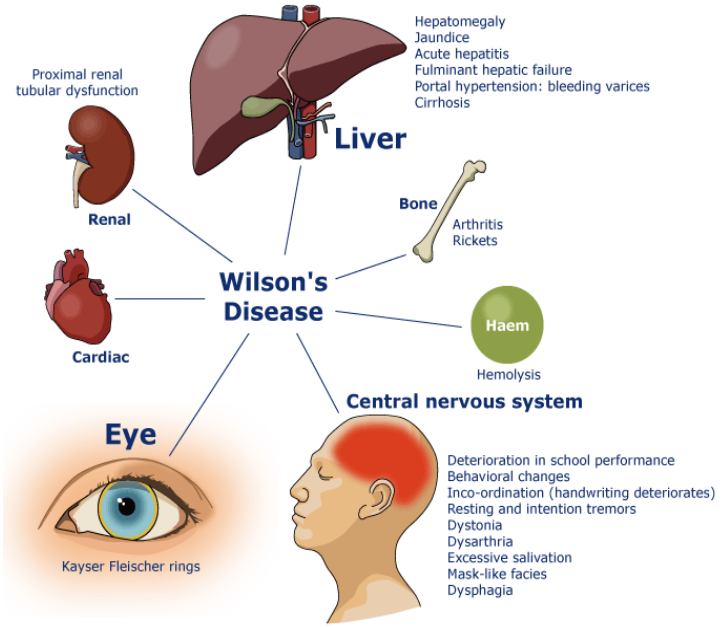
Monogenic liver diseases	Gene	Protein
HH Type 1	HFE	HFE
HH Type 2A	JH	Hemojuvelin
HH Type 2B	HAMP	Hepcidin
HH Type 3	TFR2	Transferrin receptor 2
HH Type 4	SLC40A1	Ferroprotin

HEREDITARY HAEMOCHROMATOSIS

Wilson disease

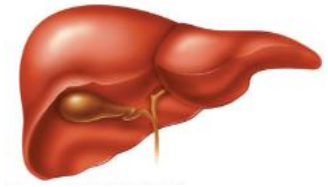
- Autosomal recessive defect in cellular copper transport.
- Prevalence: 1 case in 30.000

✓ Liver is progressively damaged and eventually becomes cirrhotic and fails.
✓ Patients may develop neurological manifestations.



DIAGNOSIS

- *Liver biochemical tests*
- *Serum ceruloplasmin and copper levels*
- *Ocular examination*
- *Urinary copper excretion*
- ***ATP7B Gen mutations (300 mutations)***



ATP7B ⇨ **Ceruloplasmin + copper**

Bile excretion

Ferenci score			
Liver copper (in absence of cholestasis)		**Serum ceruloplasmine**	
<50 µg/g (normal)	-1	>0.2 g/L (normal)	0
<5 x ULN (50-250 µg/g)	1	0.1-0.2 g/L	1
>5 x ULN (250 µg/g)	2	<0.1 g/L	2
Rhodanine stain (in absence of quantitative liver copper determination)		**Coomb's negative haemolytic anaemia**	
absent	0	Present	1
present	1	Absent	0
Mutation analysis		**KF rings**	
2 chromosomes mutations	4	Present	2
1 chromosome mutation	1	Absent	0
no mutation detected	0		
Urinary copper (in absence of acute hepatitis)		**Neurologic symptoms**	
normal (<0.9 µmol/d or <100 µg/d)	0	Severe	2
1-2 x ULN	1	Mild	1
>2 x ULN	2	Absent	0
normal but >5 x ULN after penicillamine	2		

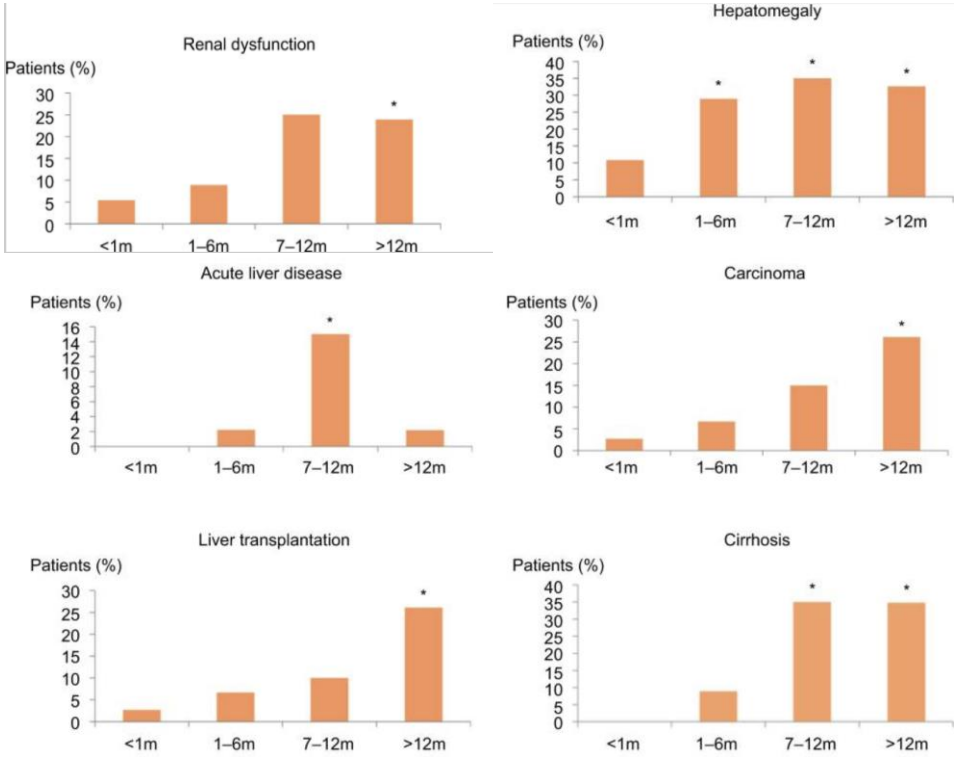
Disease	Common Laboratory Abnormalities	Presentation of Disease
Wilson disease	+ AST/ALT	Hepatomegaly
	Low or normal alkaline phosphatase level	Cirrhosis
	Low ceruloplasmin level	Neurologic symptoms
	+24-h urine copper	Acute liver failure
	+ Serum-free copper	Kayser-Fleischer rings
	+ Hemolysis workup	
	Genetic analysis with *ATP7B* mutation	

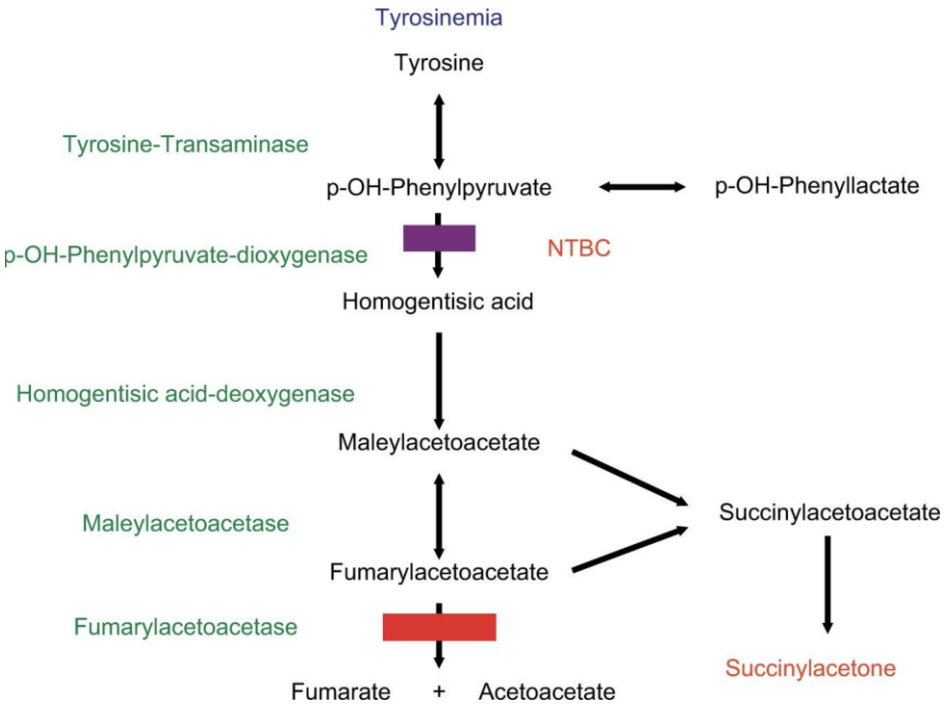
What test to order?
- Ceruloplasmin; if low, then
- 24-h urine copper; if high, then
- Evaluation for Kayser-Fleischer rings and/or
- Consider a biopsy with hepatic copper quantification
- If workup positive or concerning for Wilson disease, can then send *ATP7B* genotype

Usefulness of genetic testing in Wilson Diseases

Type 1 Tyrosinemia

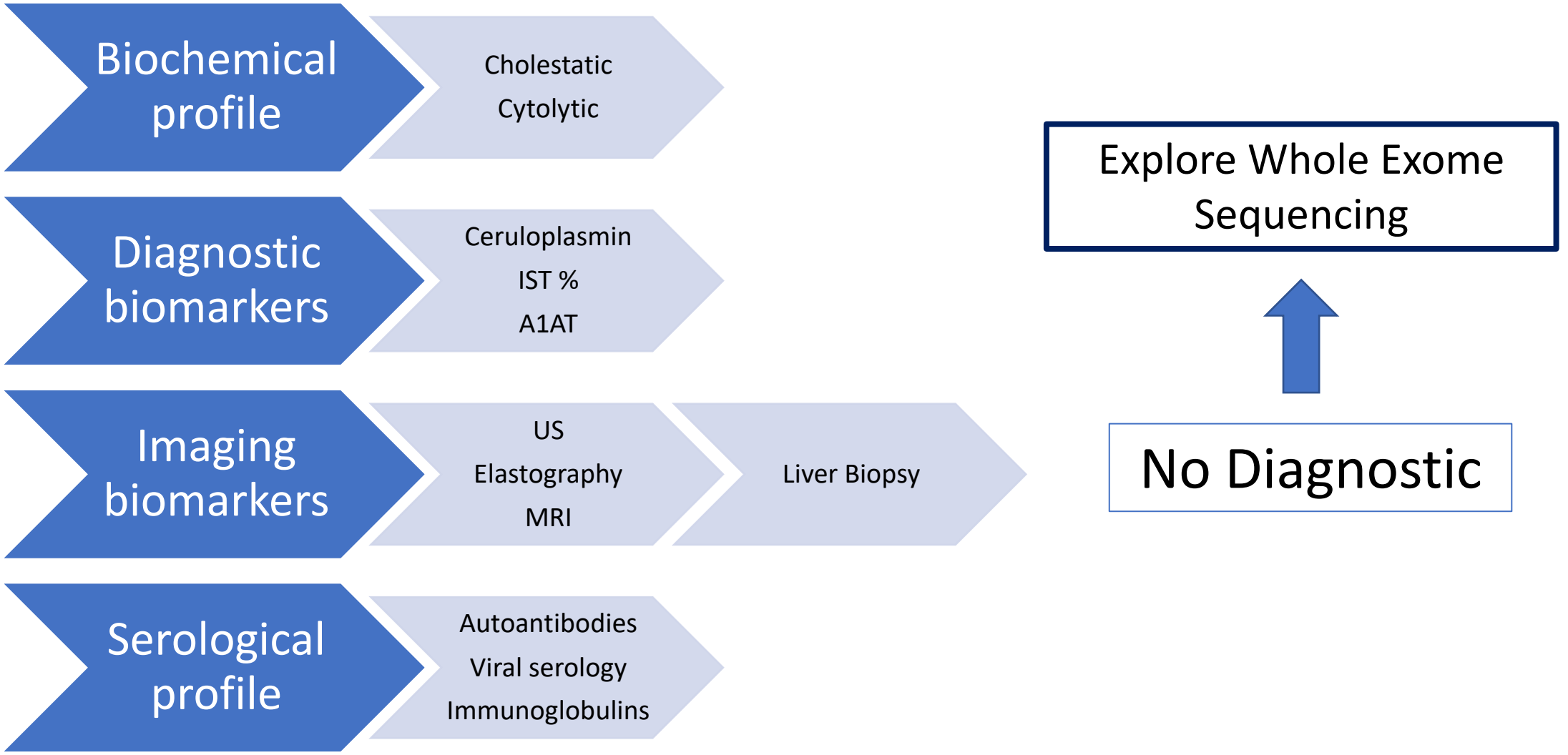
- Autosomic recessive Hereditary HT-1 affects liver and kidney. Promoting fibrosis, cirrhosis and HCC.
- Fumarylacetoacetase *FAH* (15q23-q25) deficiency leads to tyrosine, maleylacetoacetate, fumarylacetoacetate and succinylacetone (SA) (biomarker in blood and urine). Moreover, patients showed raised levels of phenylalanine, methionine, and urine δ-ALA
- Nitisinone (NTBC) based therapy orally 1-2 mg/kg/d + Low protein diet.





Das AM. Appl Clin Genet. 2017; 10: 43–48

How could Precision and Personalised Medicine help us in the diagnosis of Liver diseases?
DNA seq



DATA FROM SC-RNA SEQ ANALYSIS DIAMOND MICE
19-04-2023

		Pnpla3				Serpina1				Tm6sf2			
Cell type	Diet intervention	Log2FC	lfcSE	p-value	FDR	Log2FC	lfcSE	p-value	FDR	Log2FC	lfcSE	p-value	FDR
HEPATOCYTES	20w												
	33w												
CHOLANGIOCYTES	20w												
	33w												
ENDOTHELIAL CELLS	20w												
	33w												
HEPATIC STELLATE CELLS	20w												
	33w												
MACROPHAGES	20w												
	33w												
KUPPFER CELLS	20w												
	33w												
B-CELLS	20w												
	33w												
T-CELLS	20w												
	33w												
NK CELLS	20w												
	33w												
MONOCYTES	20w												
	33w												
GRANULOCITES	20w												
	33w												

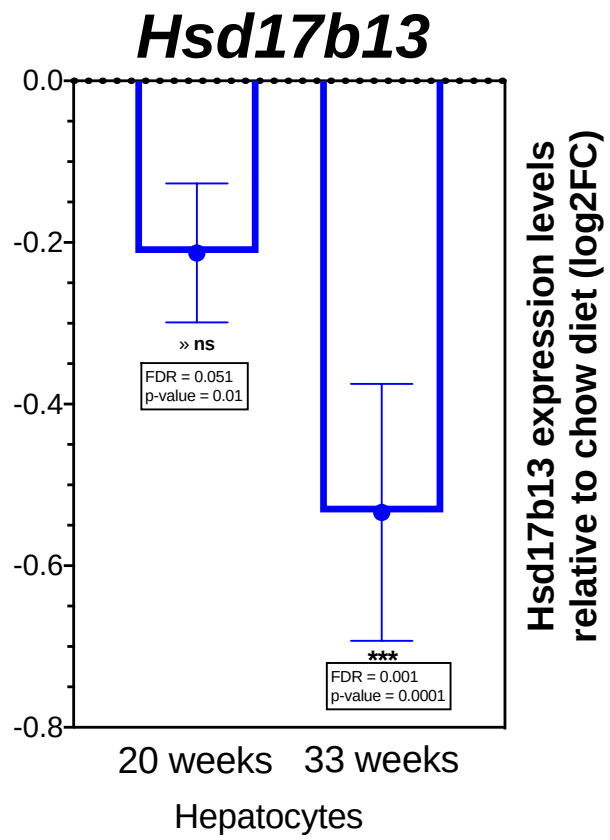
No signal | Signal and significant difference | signal but no significant difference

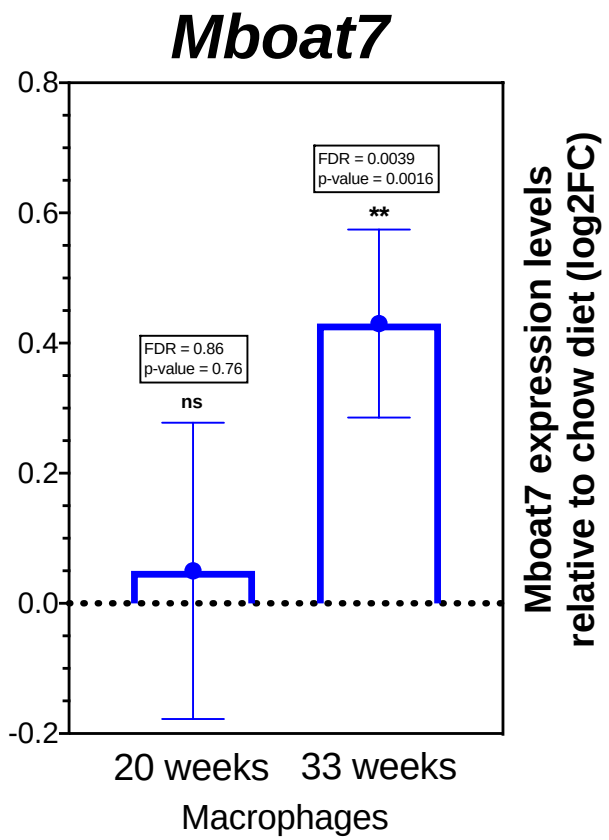
DATA FROM SC-RNA SEQ ANALYSIS DIAMOND MICE
19-04-2023

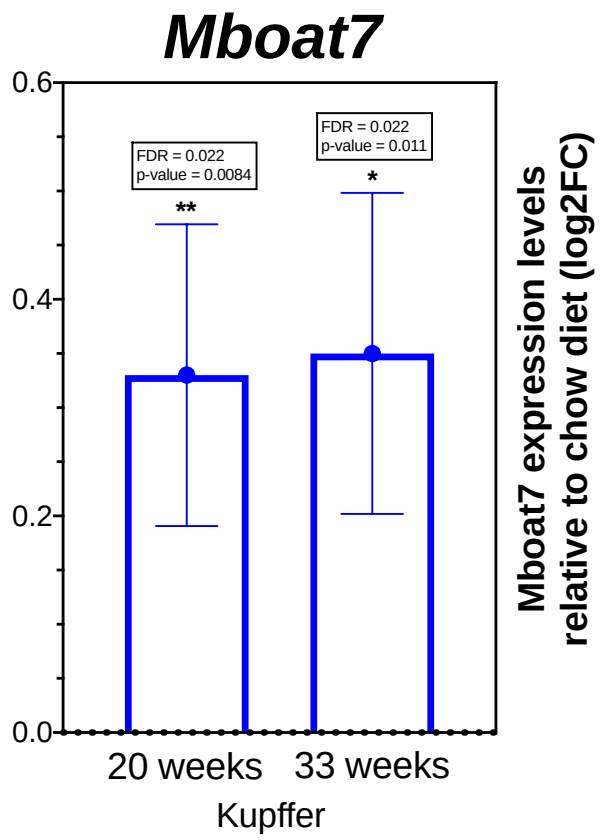
		Gckr				Hsd17b13				Mboat7			
Cell type	Diet intervention	Log2FC	lfcSE	p-value	FDR	Log2FC	lfcSE	p-value	FDR	Log2FC	lfcSE	p-value	FDR
HEPATOCYTES	20w	-0,07	0,18	6,72E-01	8,29E-01	-0,21	0,09	1,11E-02	5,05E-02				
	33w	0,00	0,12	9,60E-01	9,81E-01	-0,53	0,16	1,17E-04	1,03E-03				
CHOLANGIOCYTES	20w									0,06	0,16	3,76E-01	8,52E-01
	33w									0,31	0,28	3,80E-02	2,69E-01
ENDOTHELIAL CELLS	20w												
	33w												
HEPATIC STELLATE CELLS	20w												
	33w												
MACROPHAGES	20w									0,05	0,23	7,59E-01	8,66E-01
	33w									0,43	0,14	1,63E-03	3,95E-03
KUPPFER CELLS	20w									0,33	0,14	8,43E-03	2,19E-02
	33w									0,35	0,15	1,08E-02	2,20E-02
B-CELLS	20w									-0,07		4,69E-01	6,80E-01
	33w									-0,20		5,24E-02	1,73E-01
T-CELLS	20w									0,02		9,34E-01	9,57E-01
	33w									0,03		8,64E-01	9,00E-01
NK CELLS	20w												
	33w												
MONOCYTES	20w												
	33w												
GRANULOCITES	20w												
	33w												

No signal | Signal and significant difference | signal but no significant difference

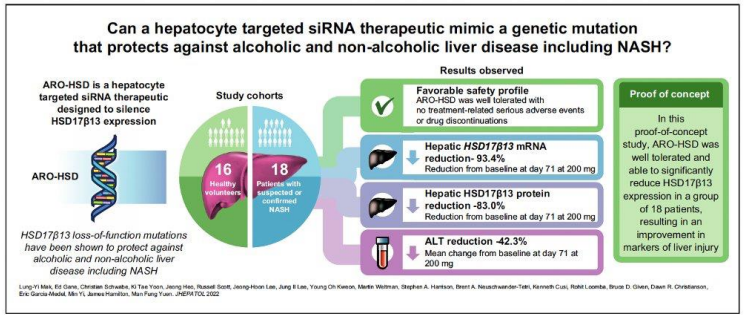
DATA FROM SC-RNA SEQ ANALYSIS DIAMOND MICE
19-04-2023







siRNA technology to improve chronic liver disease (CLD) by *HSD17B13* gene silencing



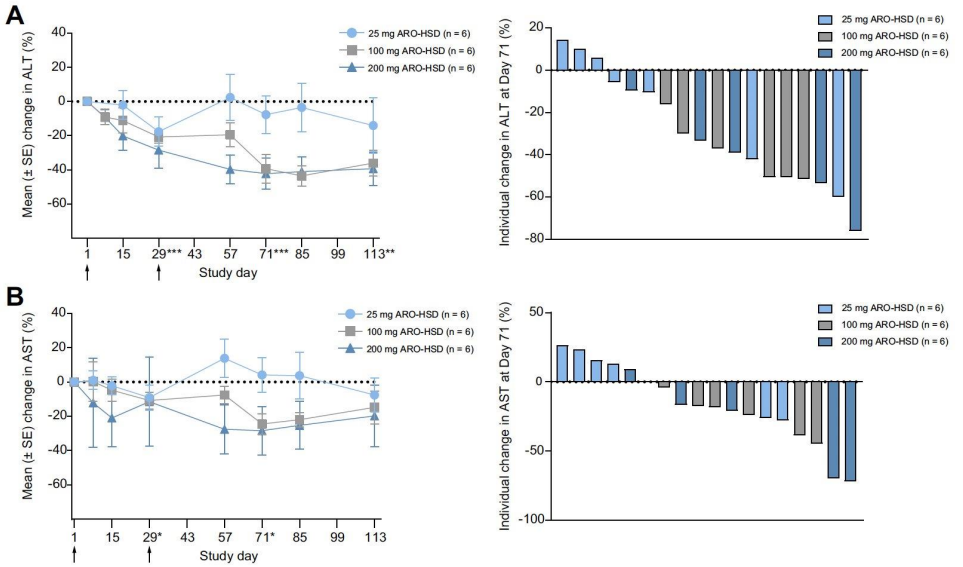
- Individulas with *HSD17b13* loss-of-function mutartions → ↓ risk CLD

Phase II study

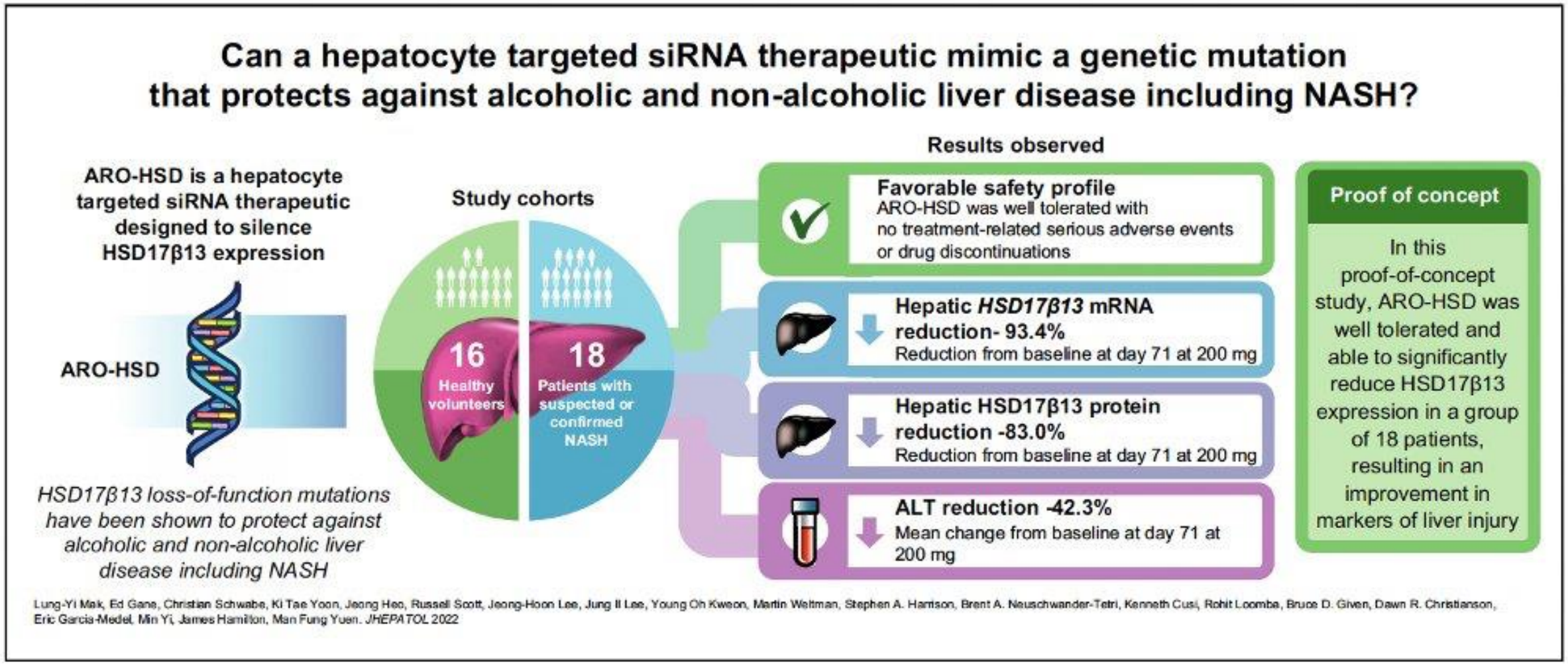
Aim: to test the potential terapeutic value of inhibiting HSD17B13 in hepatocytes by using RNAi (ARO-HDS) in normal healthy volunteers (NHVs) & individuals with confirmed or suspected NASH

Short-term treatment with ARO-HSD:

- ➢ Safe
- ➢ ↓ hepatic HSD17B13 mRNA & protein leves
- ➢ ↓ ALT



Mak LY et al. J Hepatol 2023;78:684-692



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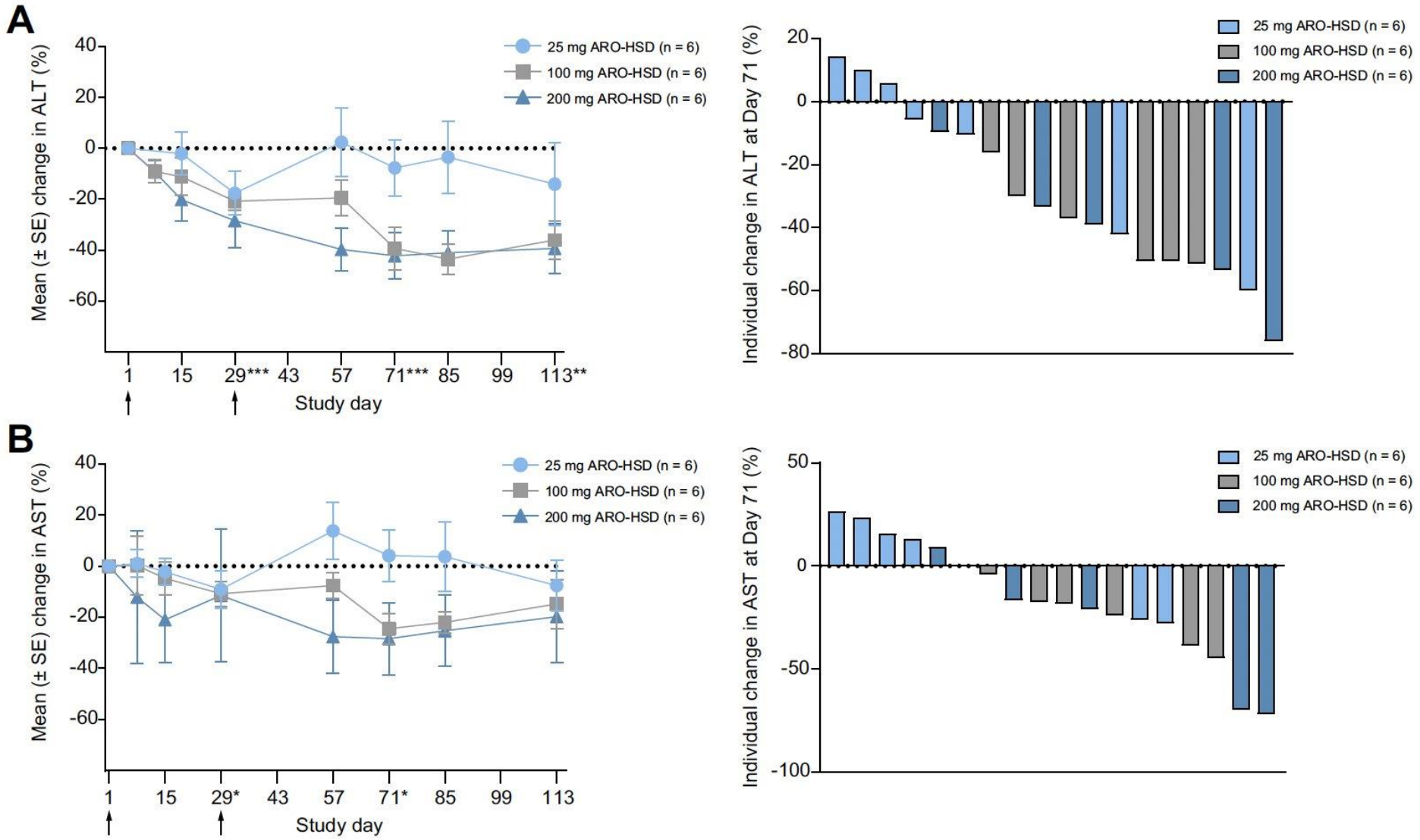

Mak LY et al. J Hepatol 2023;78:684-692

Conclusiones

- La secuenciación genética completa complementa el estudio etiológico y el proceso diagnóstico, al tiempo que define dianas terapéuticas para futuros tratamientos basados en la Medicina de Precisión.
- La colestasis intrahepática familiar progresiva tipo 3 (gen ABCB4) puede tratarse mediante terapia génica corrigiendo el gen defectuso.
- La terapia de sustitución ha cambiado el pronóstico de enfermedades como déficit de LAL y tirosinemia.
- La hemocromatosis hereditaria puede estar relacionada con mutaciones en diferentes genes que han de ser explorados en pacientes con sobrecarga férrica.
- El déficit de alfa-1-antitripsina puede manejarse desde dos frentes: a) la inhibición de la síntesis de la proteína mediante RNAi y b) la terapia sustitutiva con A1AT exógena recombinante.
- La Enfermedad de Wilson podría abordarse mediante terapia celular mediante iPSC - hepatocitos puede ser una fuente de células funcionantes con gen ATP7B restituido.

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