23

16 | 17
MAYO 2024

AULA MAGNA
Facultad de Medicina
MÁLAGA
Asistencia libre

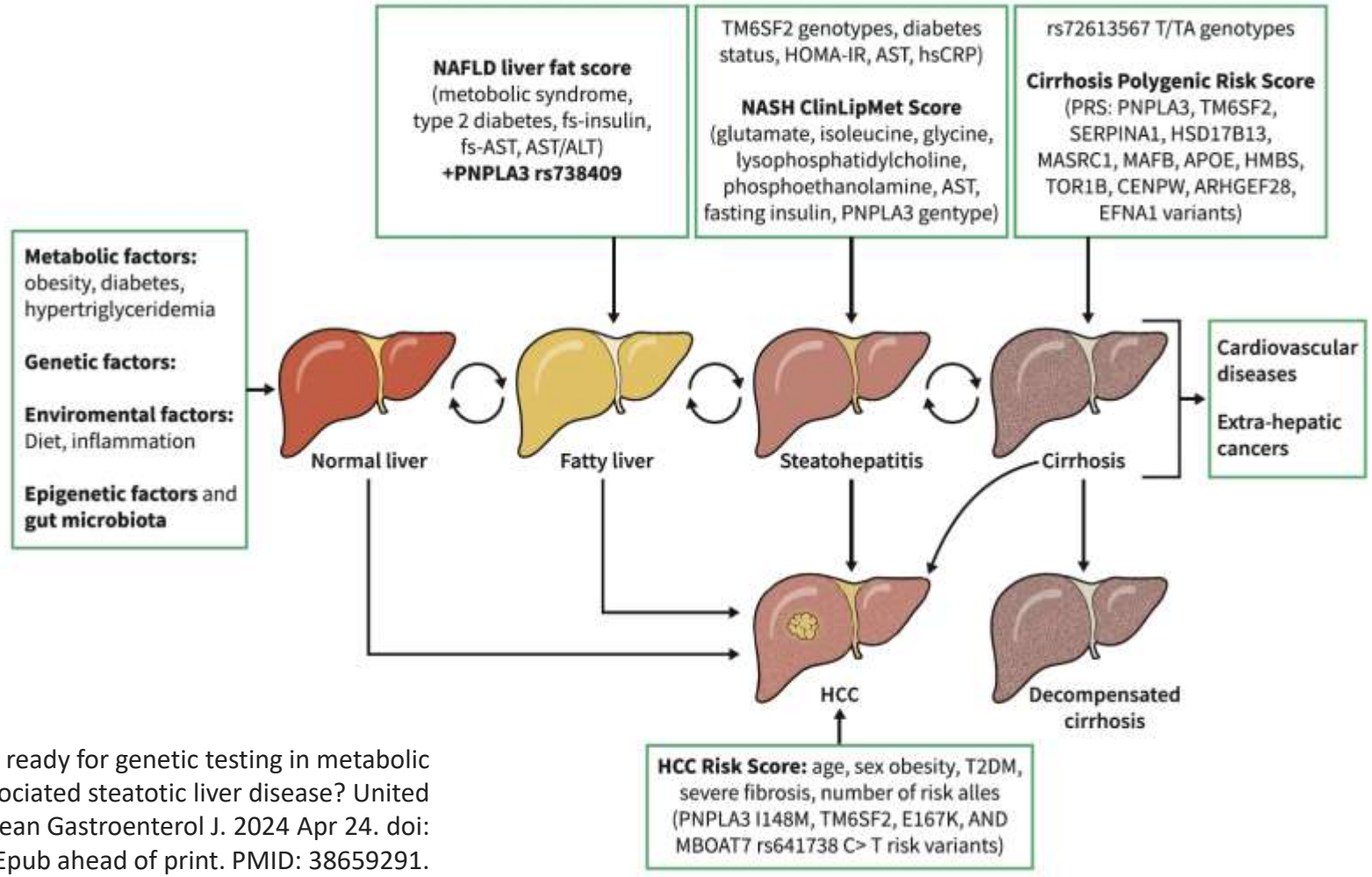
JORNADAS DE AVANCES EN HEPATOLOGÍA

PROGRAMA DE DOCTORADO
Biomedicina, Investigación Traslacional y Nuevas Tecnologías en Salud.

Actividad pendiente de ser acreditada por la Secretaría General de Investigación, Desarrollo e Innovación en Salud de la Consejería de Salud y Familias de la Junta de Andalucía. Con validez de 2 créditos (50 horas) para el Programa de Doctorado de Biomedicina, Investigación Traslacional y Nuevas Tecnologías en Salud. Reconocimiento de interés Científico-sanitario por la Junta de Andalucía.

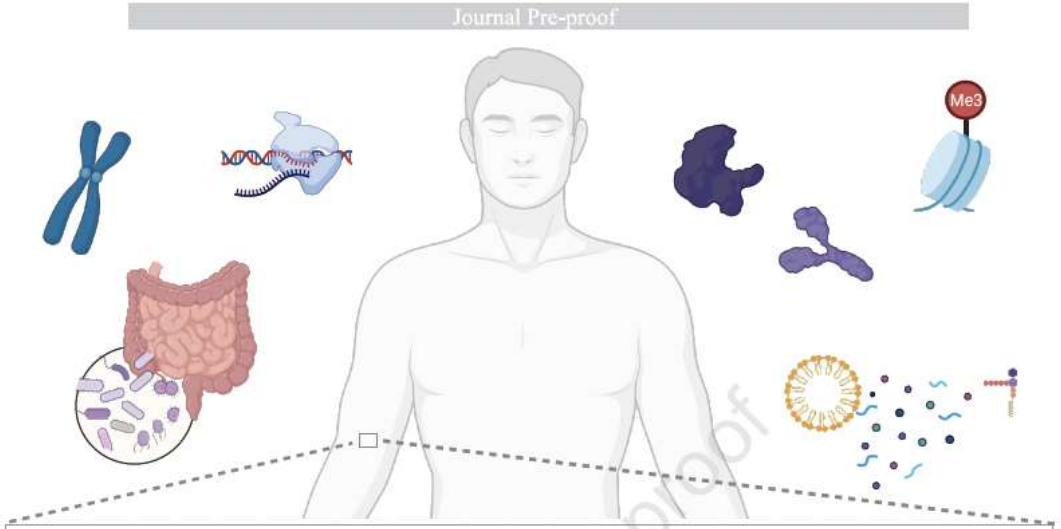
Biomarcadores;

¿Para qué?, ¿donde?, ¿para quién?, ¿cuando?, ¿Como?
¿Una vez, muchas veces?, ¿Un marcador, varios?, ¿Secuencial?, ¿Qué tipo?



Tulone A, et al. Are we ready for genetic testing in metabolic dysfunction-associated steatotic liver disease? United European Gastroenterol J. 2024 Apr 24. doi: 10.1002/ueg2.12556. Epub ahead of print. PMID: 38659291.

Biomarcadores en MASLD. ¿Para qué?



Population

Promise: Population health through the perspective of environmental exposure, nutrition and lifestyle. **Challenge**: Lacks specificity and a complete understanding of a healthy (liver) status from the omics perspective.

Example 1. miR-34a is part of the NIS2+ score, used to diagnose steatohepatitis in at-risk patients. **Example 2.** Glucose is commonly used to diagnose diabetes and determine treatment. **Example 3.** Plasma alanine aminotransferease and aspartate aminotransferase is used individually and as a ratio, in the general practice to indicate presence of liver damage.

Precision

Promise: Stratification of patients to improve outcome of treatment and reduce side effects. Monitoring of disease development. **Challenge:** Translational omics research in the clinics is still in its infancy; lack of bench-to-bedside investigations.

Example 1. Adding the genetic risk polymorphisms: PNPLA3, TM6SF6, GCKR, and MBOAT7 to known metabolic traits aids prediction of outcome. **Example 2.** Branched-Chain Amino Acids, diacylglycerol, triglyceride, phosphatidylcholines, phosphatidylethanolamine, sphingomyelin levels differentiates clinical clusters of people with type 2 diabetes **Example 3.** Distinct patterns of lipid depletion can be measured in circulation and are found to associate with progressive alcohol-related liver fibrosis.

Personalized

Promise: Response-guided therapy and medication on the individual basis. **Challenge:** Individual and daily variations may lead to significant noise level.

Example 1. Levels of ceramides are found to link genetic predisposition and dietary habits to cardiometabolic disease risk. **Example 2 (from oncology).** BRCA1 gene mutations are used in ovarian and breast cancers to determine treatment. **Example 3 (from oncology).** BCR-ABL fusion gene is used in leukemia to determine treatment and predict response to targeted therapy.

Thiele MA et al. MicrobLiver consortium; GALAXY consortium. Opportunities and barriers in omics-based biomarker discovery for steatotic liver diseases. J Hepatol. 2024 Mar 28:S0168-8278(24)00219-8. doi: 10.1016/j.jhep.2024.03.035. Epub ahead of print. PMID: 38552880.

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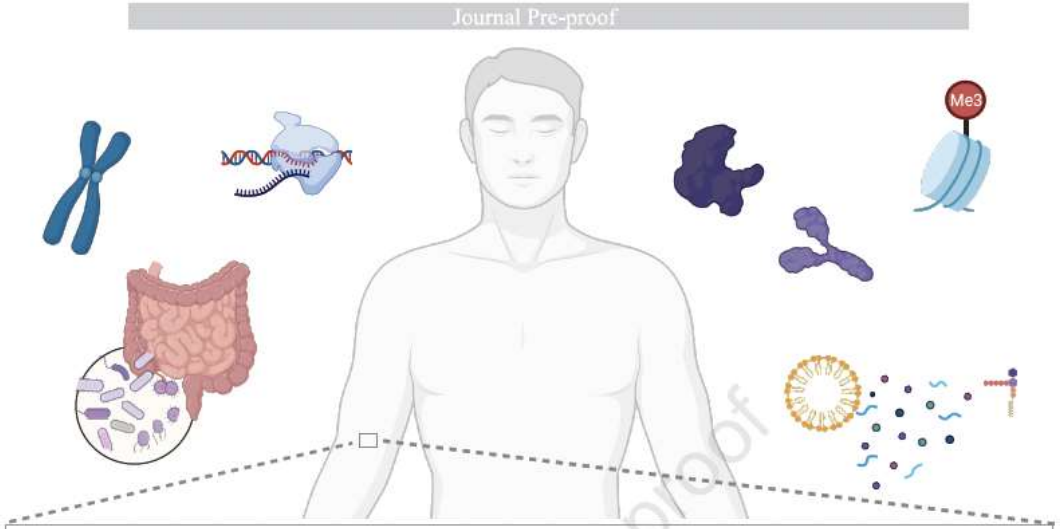

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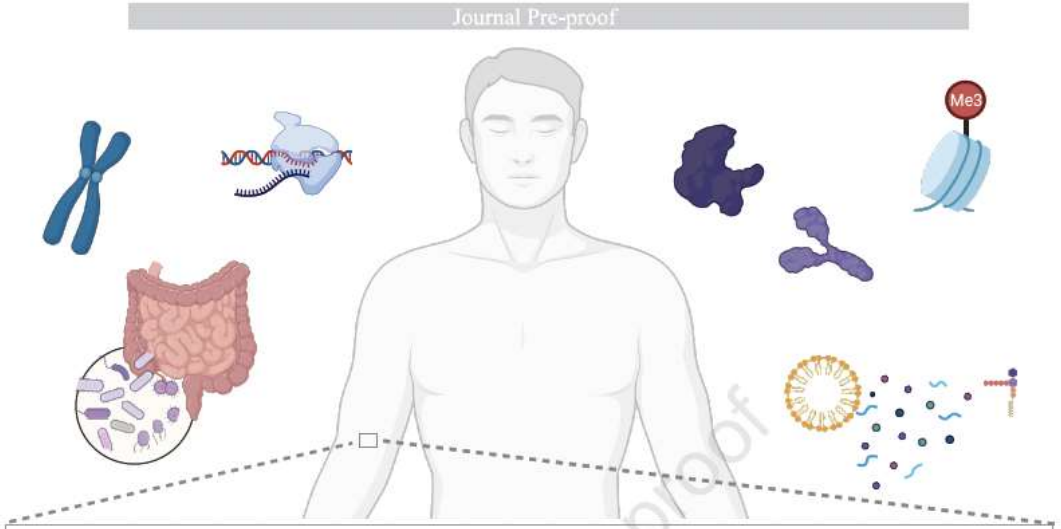

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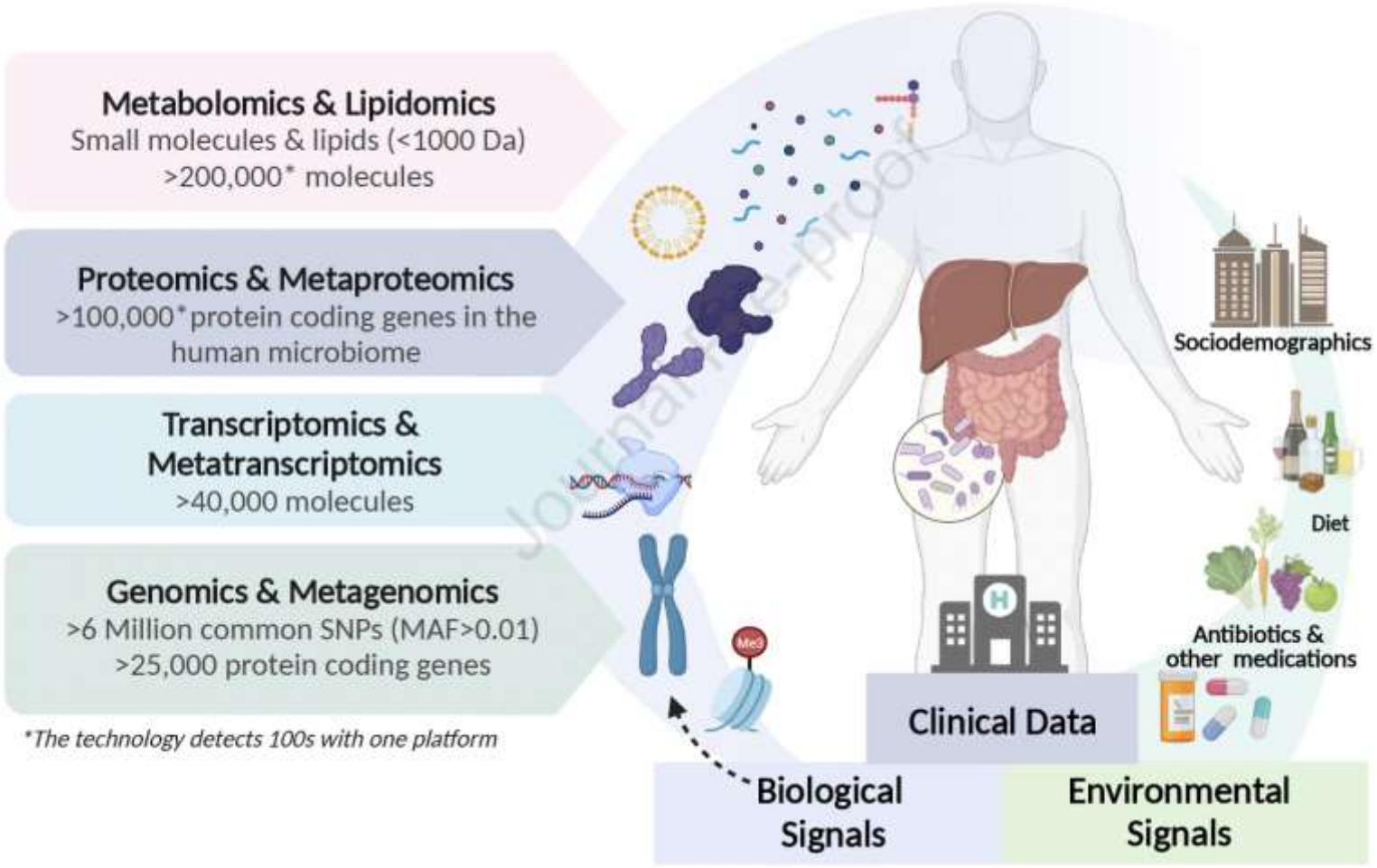
Biomarcadores en MASLD. ¿Para qué?

	Diagnostic	Prognostic	Monitoring	Prediction*	Surrogate endpoint
Outcome of interest	Disease present or not; disease staging	Development of clinical events, mortality	Change in disease severity	Effect of treatment	Substitute for one or more clinical outcomes
Subclasses of biomarkers	Screening	Susceptibility/ risk stratification	Efficacy of intervention; pharmacodynamic response	Safety (adverse events)	Reasonably likely surrogate endpoint
Measurement timing	Baseline	Baseline	Longitudinal	Baseline, before intervention	Start and end of intervention study
Clinical characteristic	Reflects true disease state	Reflects patient or disease characteristics	Biomarker changes correlate with changes in extent or status of disease	Reflects patient or disease characteristics	Effect on the surrogate endpoint predicts a clinical benefit
Statistics used	Discriminative accuracy, sensitivity, specificity, NPV, PPV, calibration curves, goodness of fit, information criterium, odds ratio	C-statistics, hazard ratio, time-dependent receiver operating characteristics curve, Aalen-Johansen or Kaplan-Meier estimator	Correlation coefficients: diagnostic and prognostic accuracy of Δbiomarker**	Treatment effect in biomarker positive vs. biomarker negative patients if patient groups have the same prognosis	Correlation coefficients: diagnostic accuracy of Δbiomarker to detect change; prognostic accuracy of Δbiomarker
Examples of omics-based biomarkers	Proteomics for diagnosis of ALD fibrosis, inflammation and steatosis(15)	Genetic risk polymorphisms for development of hepatocellular carcinoma in the population(47)	Changes in Lyso-phosphocholines by lipidomics in MASLD during dietary intervention(137)	A polygenic score to predict weight loss in response to physical activity(138)	No omics markers approved as surrogate endpoints, but single molecules may arise from omics discovery

Thiele MA et al. MicrobLiver consortium; GALAXY consortium. Opportunities and barriers in omics-based biomarker discovery for steatotic liver diseases. J Hepatol. 2024 Mar 28:S0168-8278(24)00219-8. doi: 10.1016/j.jhep.2024.03.035. Epub ahead of print. PMID: 38552880.

Biomarcadores en MASLD. ¿Qué tipo?



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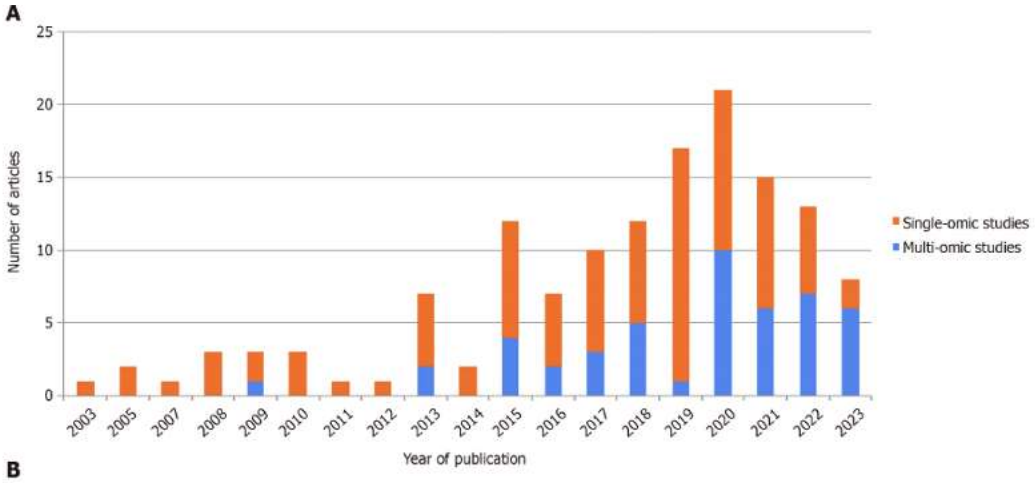
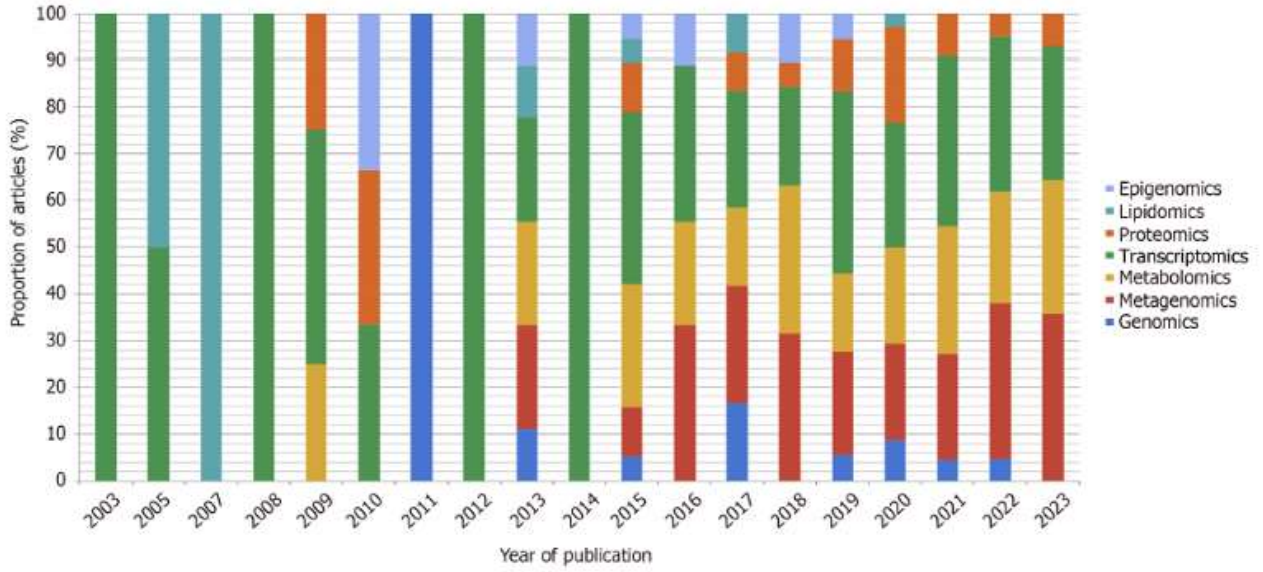
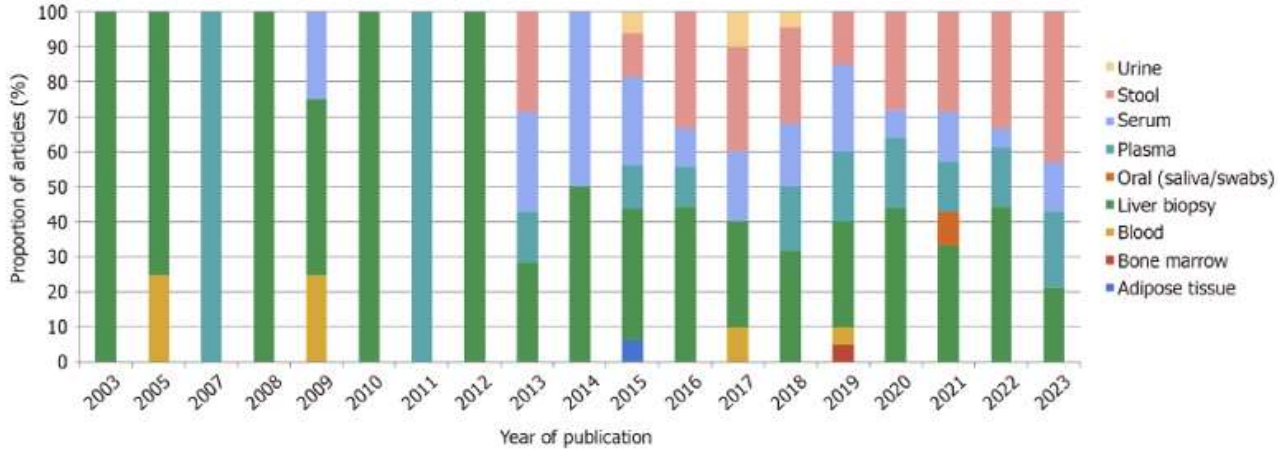
Biomarcadores en MASLD. Medicina de precisión.





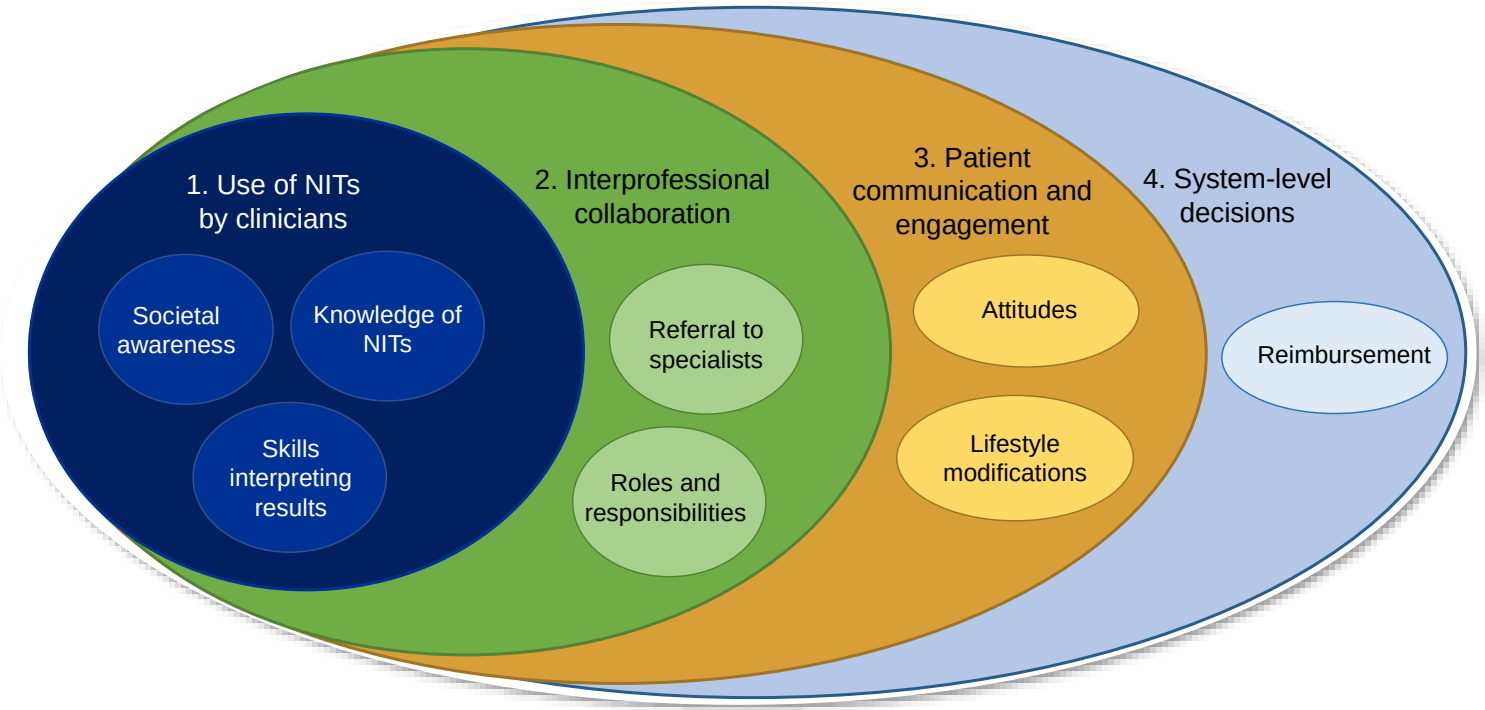
C



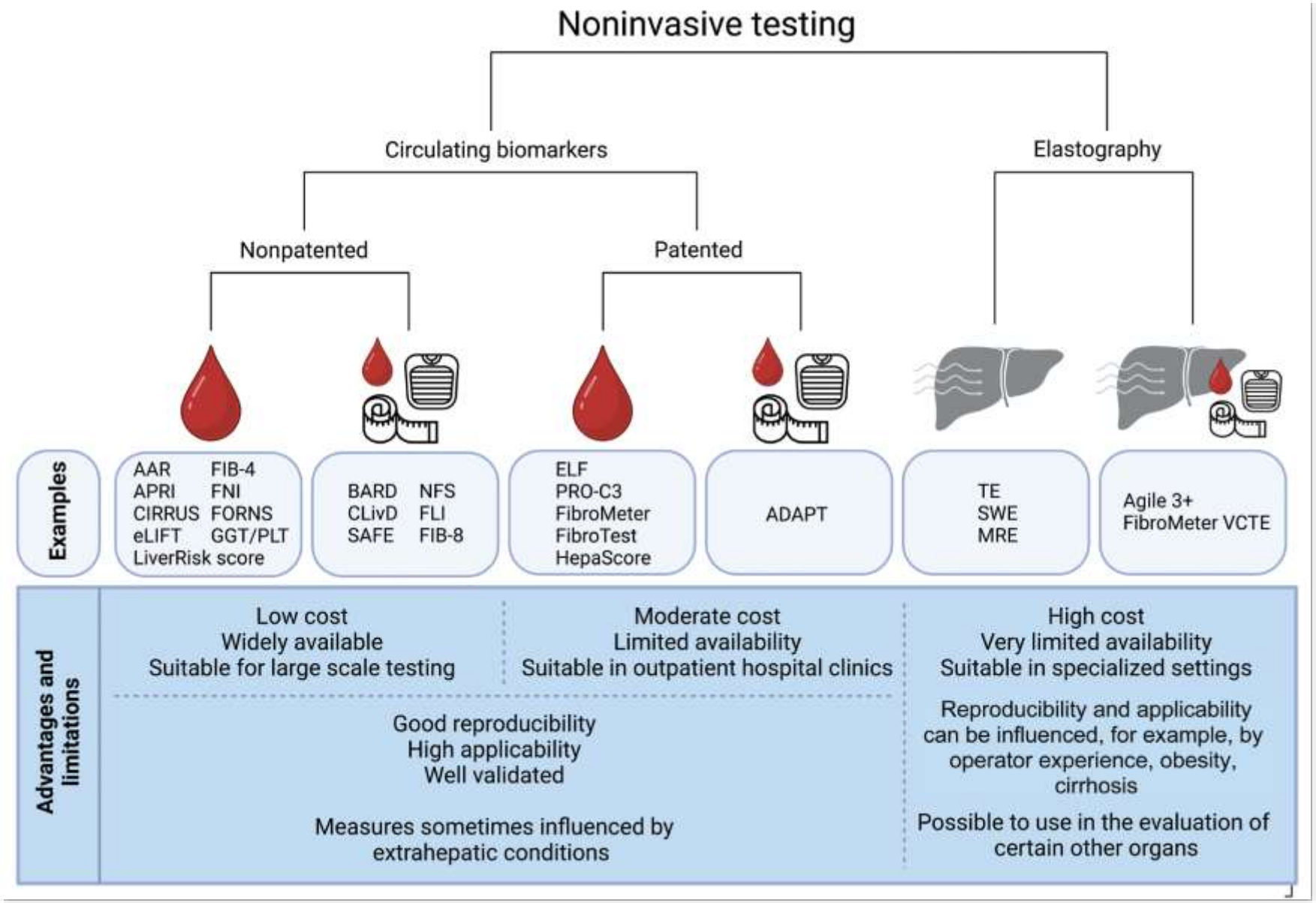
- Accesibilidad, usabilidad, implementación, costo, conocimiento y aceptabilidad, contexto de uso
- Biomarcadores directos e indirectos
- Biomarcadores de enfermedades asociadas / riesgos competitivos
- Precisión diagnóstica discriminativa
- Capacidad pronóstica
- Capacidad para indicar tratamientos y, en breve, marcadores de parada del tratamiento

- **Knowledge** and awareness gaps of liver disease
- Lack of clear **referral pathways** between primary and secondary care
- Challenge justifying system-level **reimbursement** of NITs
- **Low perceived value of NITs** in the monitoring and management of MASLD

Challenges, barriers, and gaps in four main spheres



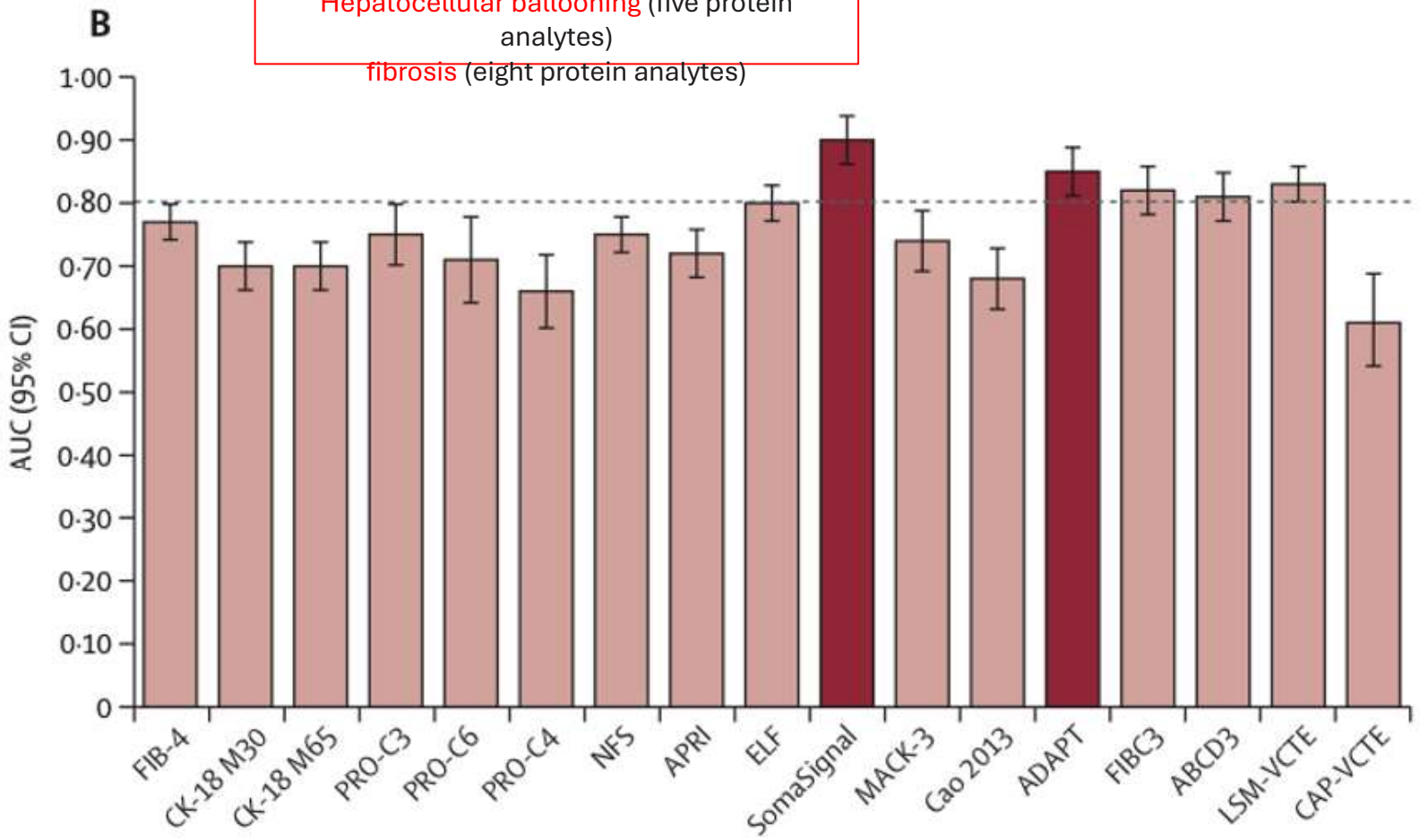
Tsochatzis, Valenti and Thiele, Liver Int 2024



Bech, Seminars in Liver Disease, 2024

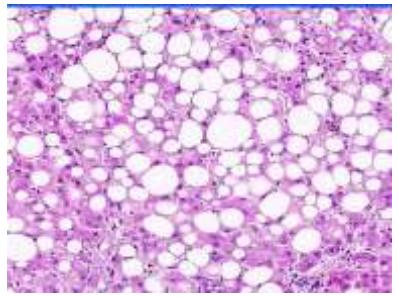
Biomarcadores para el diagnóstico. Fibrosis; Proyecto LITMUS.

Steatosis (12 protein analytes)
Lobular inflammation (14 protein analytes]
Hepatocellular ballooning (five protein analytes)
fibrosis (eight protein analytes)

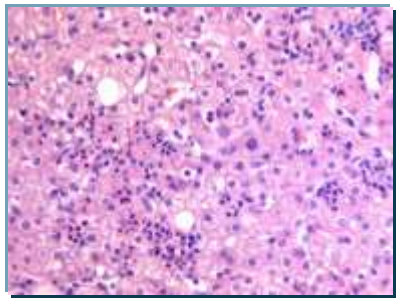


Vali Y, et al: Testing Marker Utility in Steatohepatitis (LITMUS) consortium investigators. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. Lancet Gastroenterol Hepatol. 2023 Aug;8(8):714-725. doi: 10.1016/S2468-1253(23)00017-1.

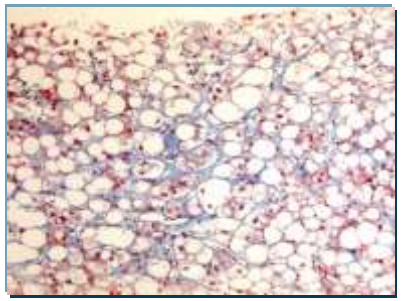
Biomarcadores. Estratificación de la enfermedad.



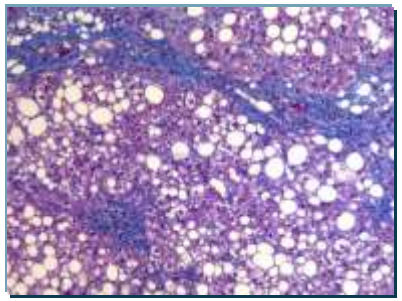
ESTEATOSIS



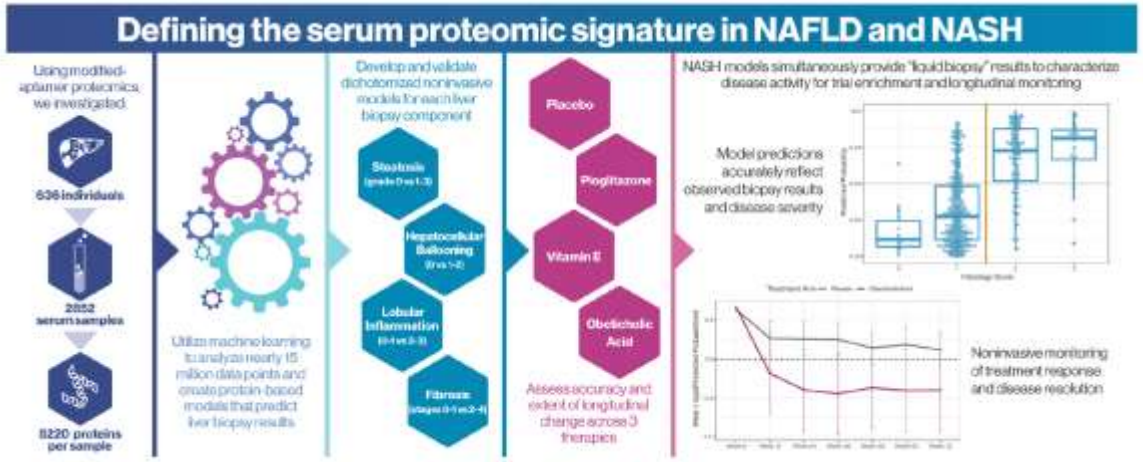
ESTEATOHEPATITIS



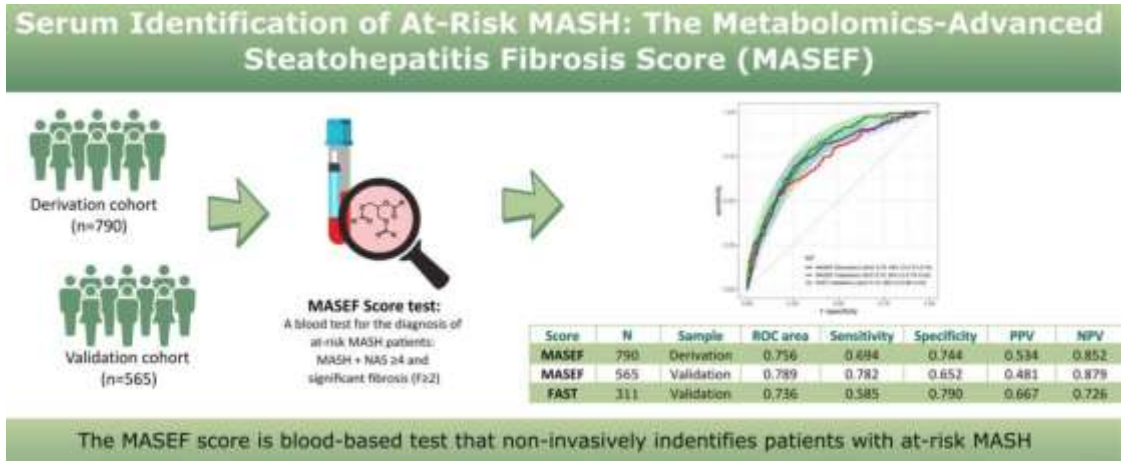
FIBROSIS



CIRRISOSIS

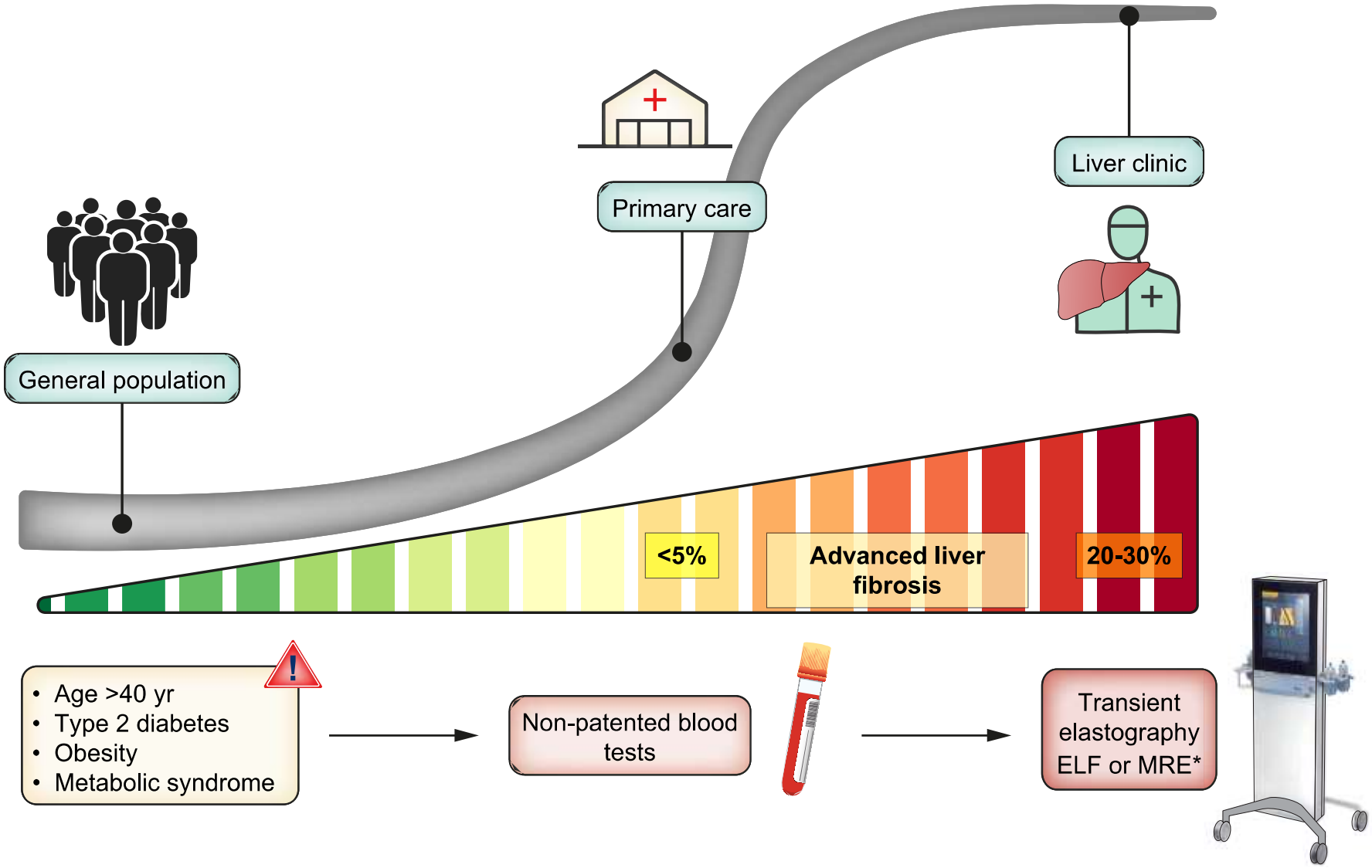


Sanyal AJ et al. J Hepatol 2023



Noureddin M et al. Hepatology 2024

Biomarcadores. Estratificación de la enfermedad.



* If VCTE not available

EASL. J Hepatol. 2021;75(3):659-689 / Anstee QM. *J Hepatol.* 2022;76(6):1362-1378 / Maya-Miles D, et al. Liver Int . 2021 Jun;41 Suppl 1:95-104

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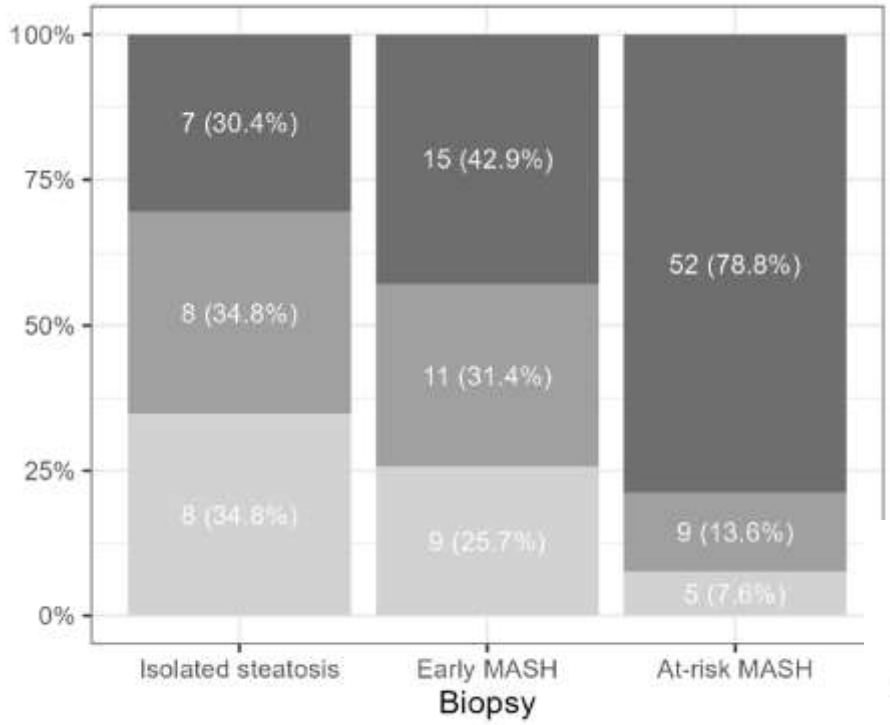
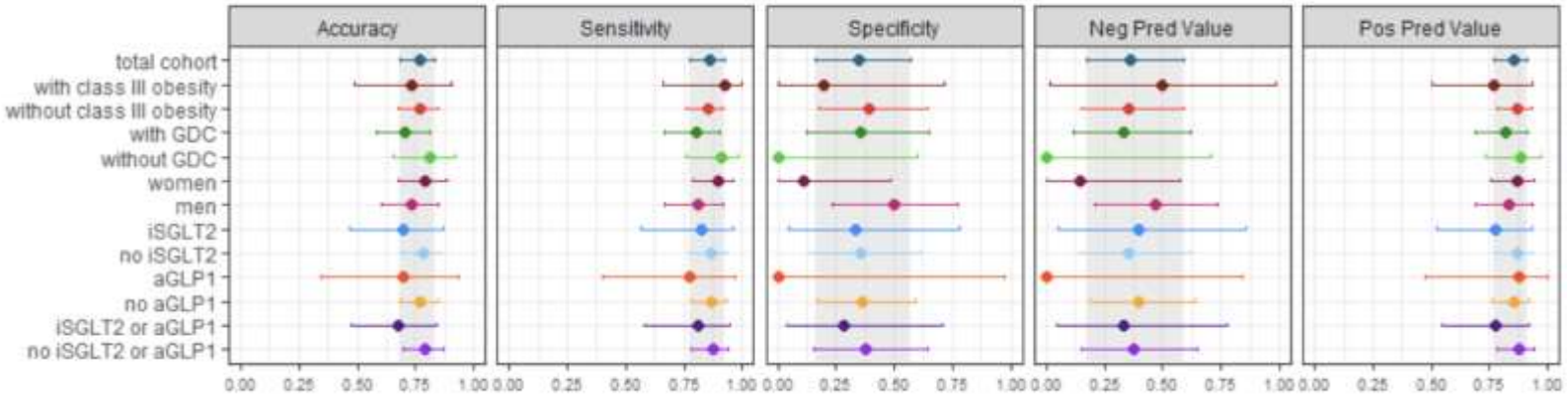




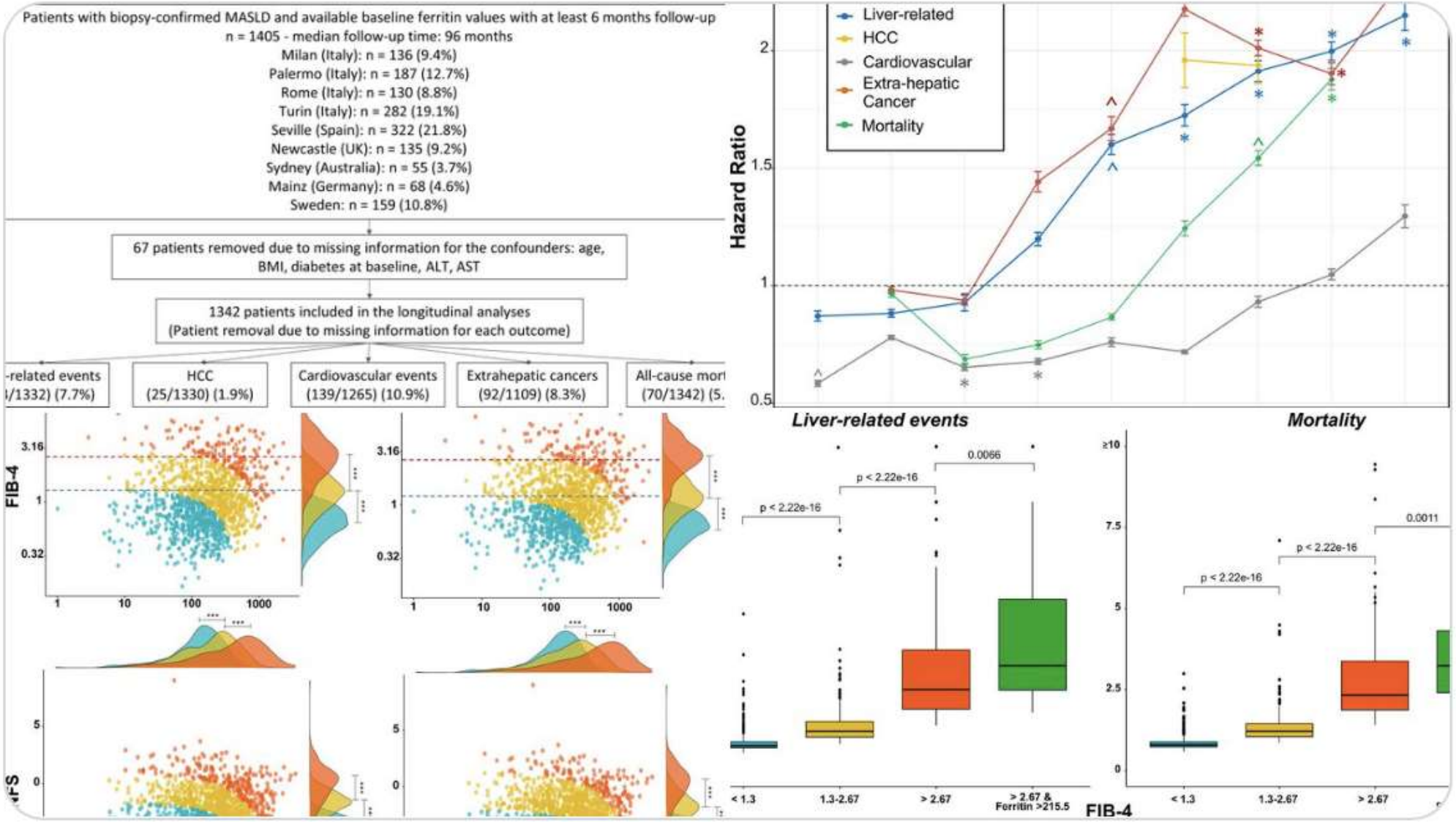
Iruzubieta P, et al. One-step non-invasive diagnosis of metabolic Dysfunction associated steatohepatitis and fibrosis in high-risk population. UEG 2024, in press.

METASight Liver Fibrosis Score

	Significant Fibrosis (F stage ≥ 2) Cases = 155 , Controls = 166	Advanced Fibrosis (F stage ≥ 3) Cases = 104 , Controls = 217	Cirrhosis (F stage 4) Cases = 40 , Controls = 281
MS-LFS	0.831	0.852	0.922
FIB4	0.745**	0.791*	0.861*
BARD	0.618**	0.65**	0.727**
NFS	0.708**	0.766*	0.804*
VCTE (Fibroscan)	0.736*	0.741**	0.873
FAST (Fibroscan & clinical parameters)	0.749*	0.722**	0.816*
Agile 3+ (Fibroscan & clinical parameters)	0.786	0.821	0.895
Agile 4 (Fibroscan & clinical parameters)	0.774*	0.808	0.912
	Comparison based on literature (NIMBLE)		
ELF	0.828	0.835	0.855
PRO-C3	0.809	0.764	0.728

*p < 0.05 for comparison with MS-LFS
**p < 0.001 for comparison with MS-LFS

Biomarcadores estratificación de la enfermedad. Ferritina.



Gut 2024

Biomarcadores para el diagnóstico. Uso secuencial.

Longitudinal non-interventional observational cohort study based in UK Primary Care setting

CPRD + Hospital Episode Statistics (HES) & Office for National Statistics (ONS)

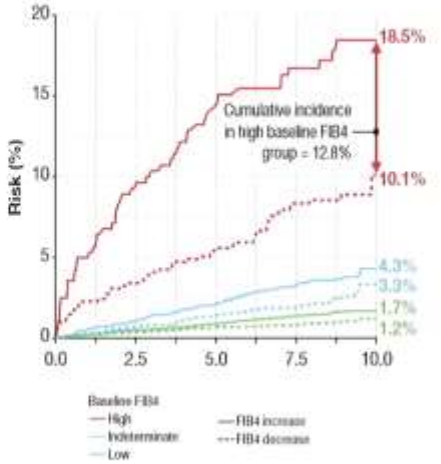
20,443 patients with two FIB4 measures at 12 ±3 months apart

Ten-Years Follow-up

Study period: 2001–2020

Endpoints

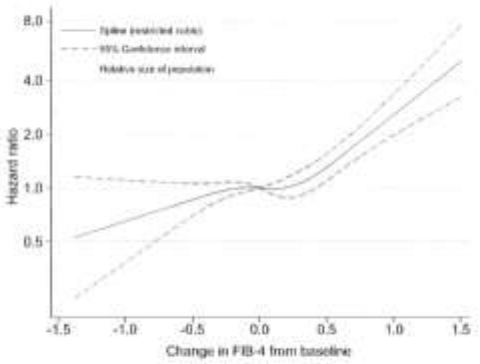
- Time to first **liver event** (liver-related hospitalisation or death)
- Time to first **CV event** (CV-related hospitalisation or death)
- Time to **death** of any cause



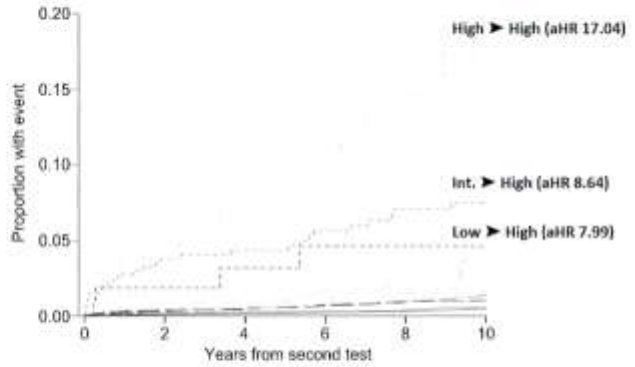
Cox proportional hazards models for liver events adjusted for age, sex, and baseline FIB4

Baseline FIB4	FIB4 Change	Adjusted HR (95%CI)
High	+1	24.27 (16.98, 34.68)
	−1	10.90 (7.90, 15.05)
Indeterminate	+1	4.44 (3.36, 5.98)
	−1	1.67 (1.22, 2.29)
Low	+1	2.48 (2.04, 3.02)
	−1	0.40 (0.33, 0.49)

40,279 people with two FIB4 measurements within 5 years (mean interval 2.4 years)

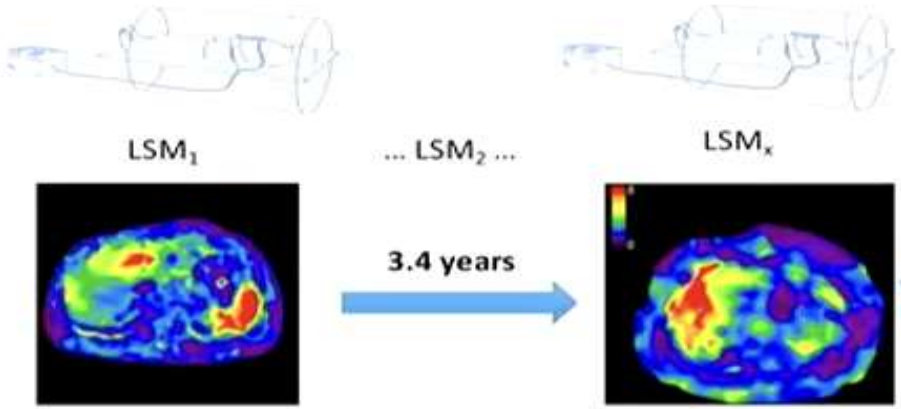


1 unit increase in FIB-4 associated with elevated risk of severe liver disease (aHR 1.81; 95% CI 1.67–1.96).



1. Hagstrom H et al. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. J Hepatol 2020;73:1023-1029.

CHANGE IN SERIAL LIVER STIFFNESS MEASUREMENT (LSM) BY MAGNETIC RESONANCE ELASTOGRAPHY (MRE) AND OUTCOMES IN NON-ALCOHOLIC FATTY LIVER DISEASE

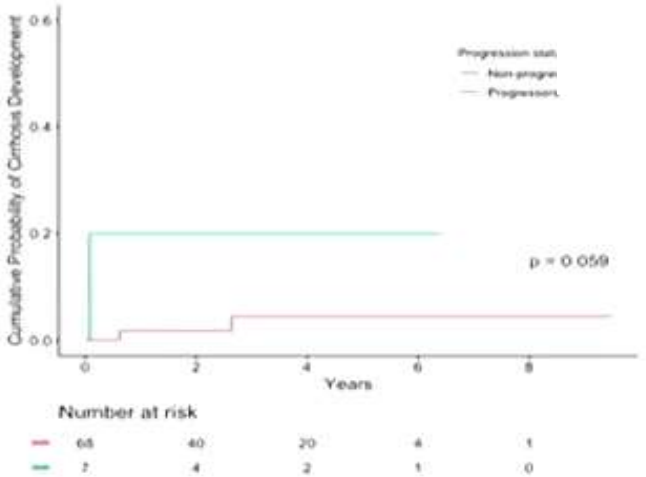


128 NAFLD adults

306 serial MREs

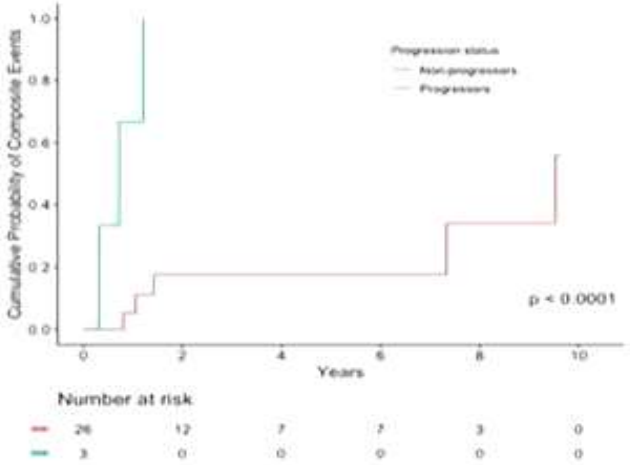
In NAFLD without cirrhosis, progressive LSM was borderline associated with 7-fold increase in risk of incident cirrhosis (p=0.059).

2.7 years



2.5 years

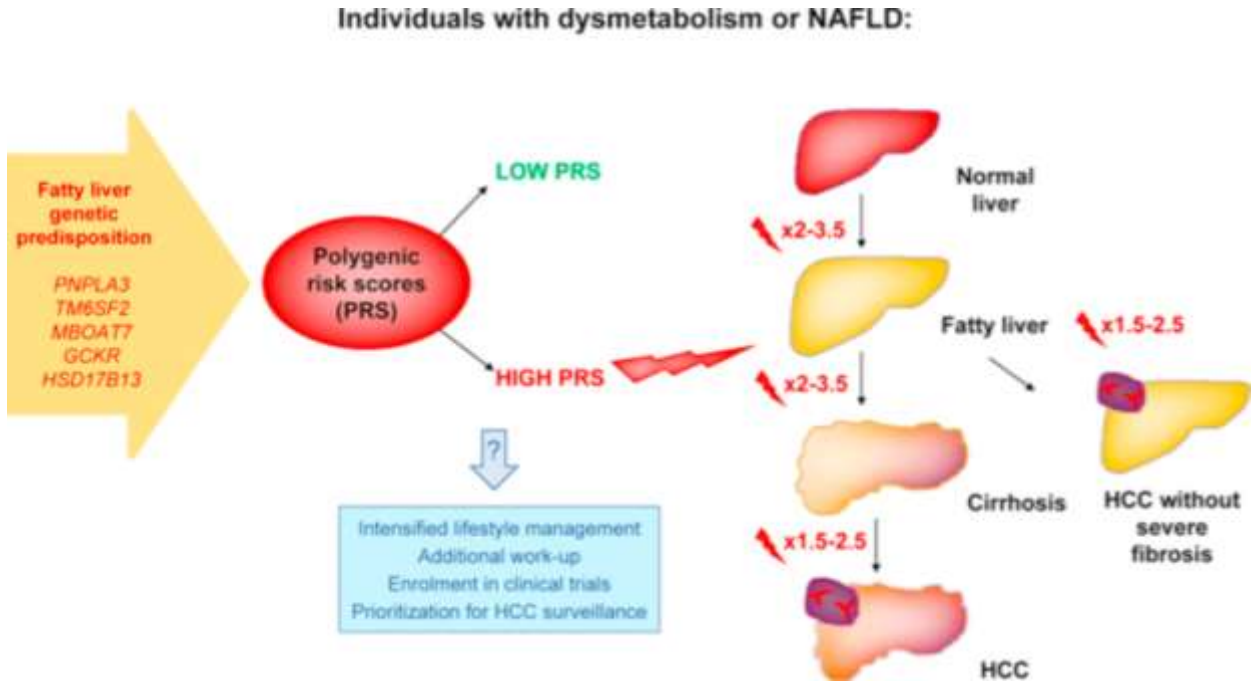
In NASH cirrhosis, those with progressive LSM were 19 times more likely to develop decompensation or die (p=0.001).

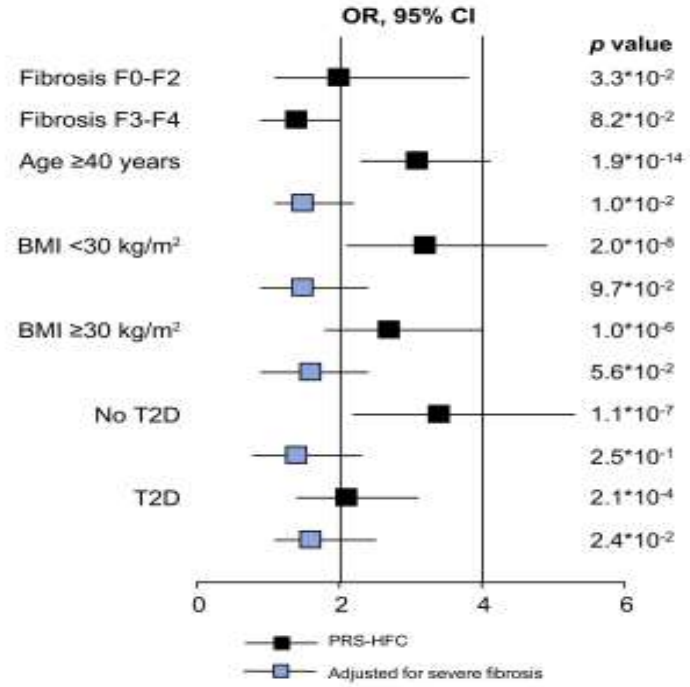


1. Gidener, T., *et al.* Change in serial liver stiffness measurement by magnetic resonance elastography and outcomes in NAFLD. *Hepatology* **77**, 268-274 (2023).

Genotipo MASLD

Estratificación del riesgo de HCC en NAFLD con un score de riesgo poligénico (PRS) (PNPLA3-TM6SF2-GCKR-MBOAT7).





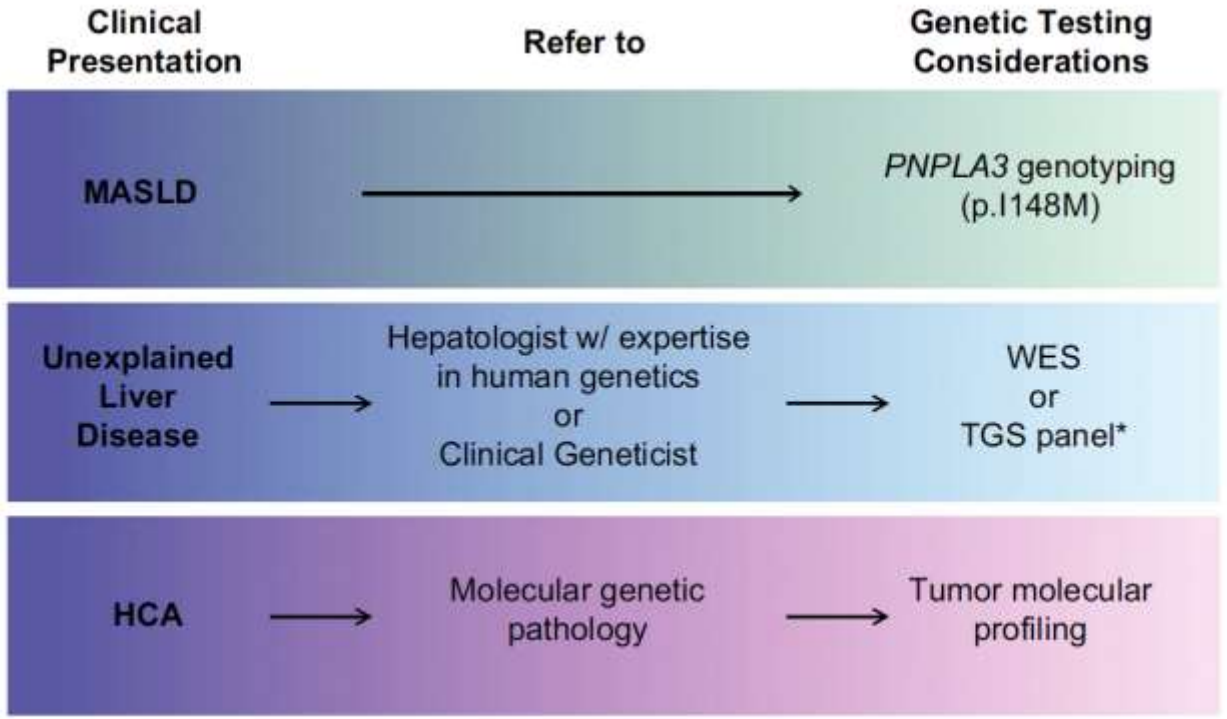
PRS predice HCC independientemente de los factores de riesgo clásicos y cirrosis.

¿Intensificación en el manejo/ seguimiento?

Bianco C et al. J Hepatol 2021

¿Aplicamos con precisión el conocimiento clínico adquirido?

Genotipo MASLD

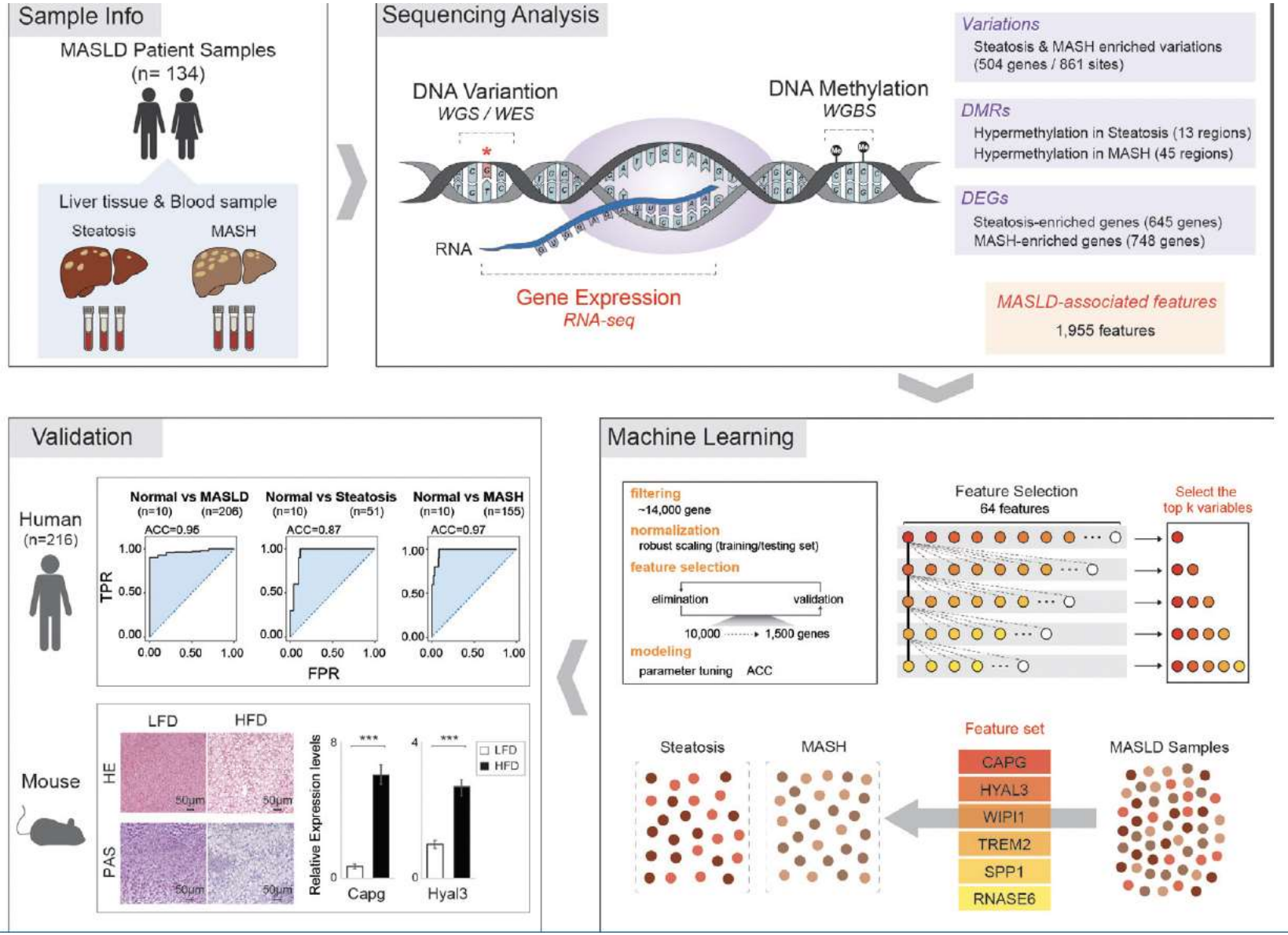


Genomic analysis should be considered in adults who are lean, with no visceral adiposity or alcohol overuse, and present with unexplained hepatic steatosis and transaminase elevation

While polygenic risk scores for the management of MASLD are still not prime time for routine clinical practice, individuals who are overweight (BMI > 25), obese (BMI > 30), or morbidly obese (BMI > 35) and carry homozygous risk allele p.I148M in PNPLA3 have a considerably higher risk to progress to cirrhosis and develop HCC. Thus, clinicians may consider determining their patients' PNPLA3 p.I148M genotype to inform personalized counseling on lifestyle modifications and weight loss more effectively, particularly in individuals at higher risk of CLD progression and complications

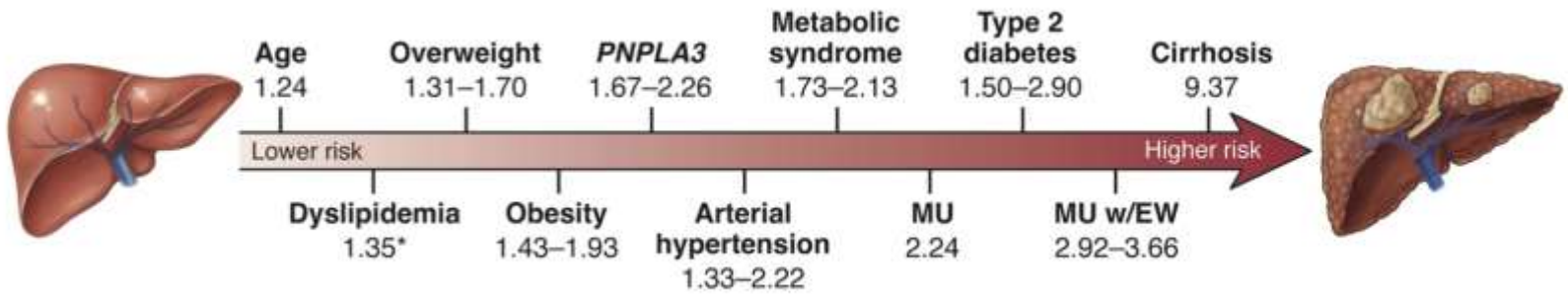
Konkwo C, Chowdhury S, Vilarinho S. Genetics of liver disease in adults. Hepatol Commun. 2024 Mar 29;8(4):e0408. doi: 10.1097/HC9.0000000000000408. PMID: 38551385; PMCID: PMC10984672.

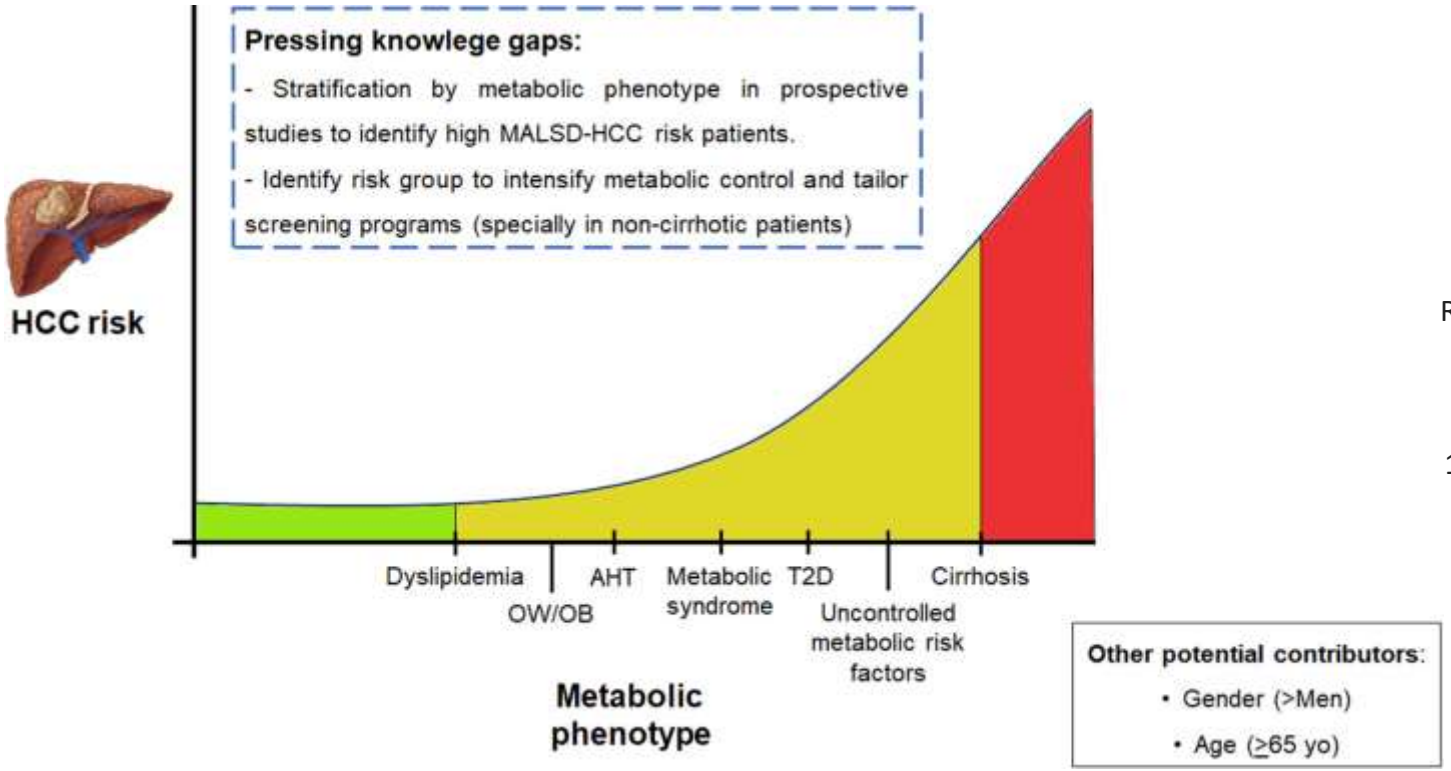
Biomarcadores. Progresión de la enfermedad.



Oh S, et al. Identification of signature gene set as highly accurate determination of metabolic dysfunction-associated steatotic liver disease progression. Clin Mol Hepatol. 2024 Apr;30(2):247-262. doi: 10.3350/cmh.2023.0449. Epub 2024 Jan 26. PMID: 38281815; PMCID: PMC11016492.

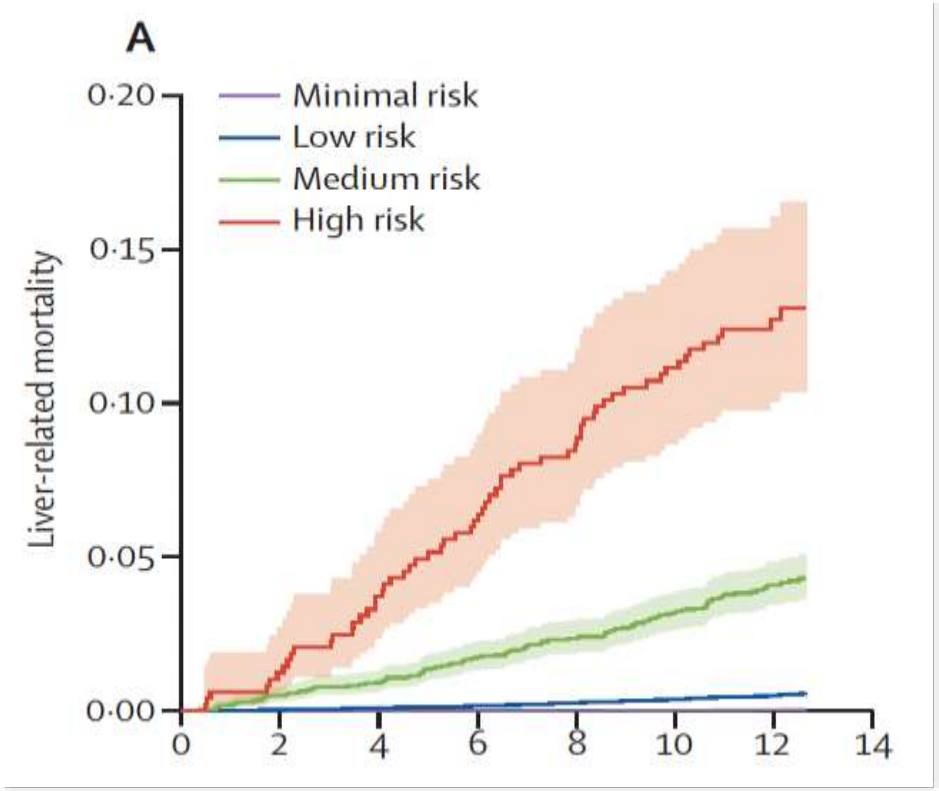
Biomarcadores. Riesgo de hepatocarcinoma

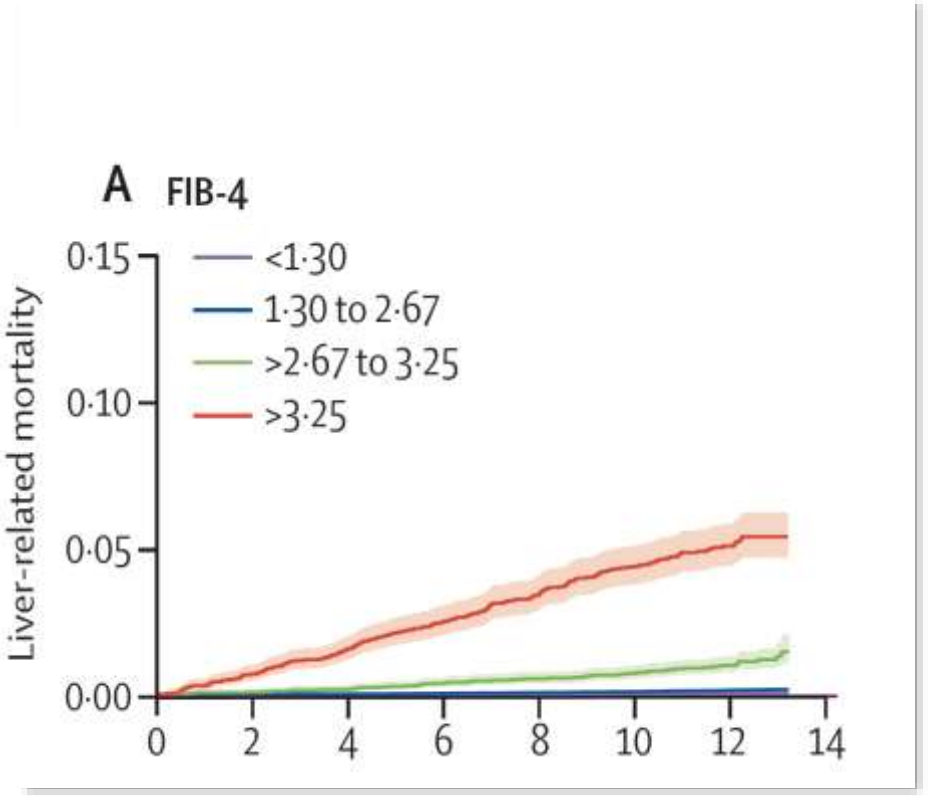




Rivera-Esteban J, et al. Phenotypes of MASLD-associated hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2024 Apr 9:S1542-3565(24)00310-0. doi: 10.1016/j.cgh.2024.03.028. PMID: 38604295.

Biomarcadores para el diagnóstico. Pronóstico vital = liver Risk score.





Serra-Buriel, Lancet 2023

Pronóstico vital = liver Risk score.

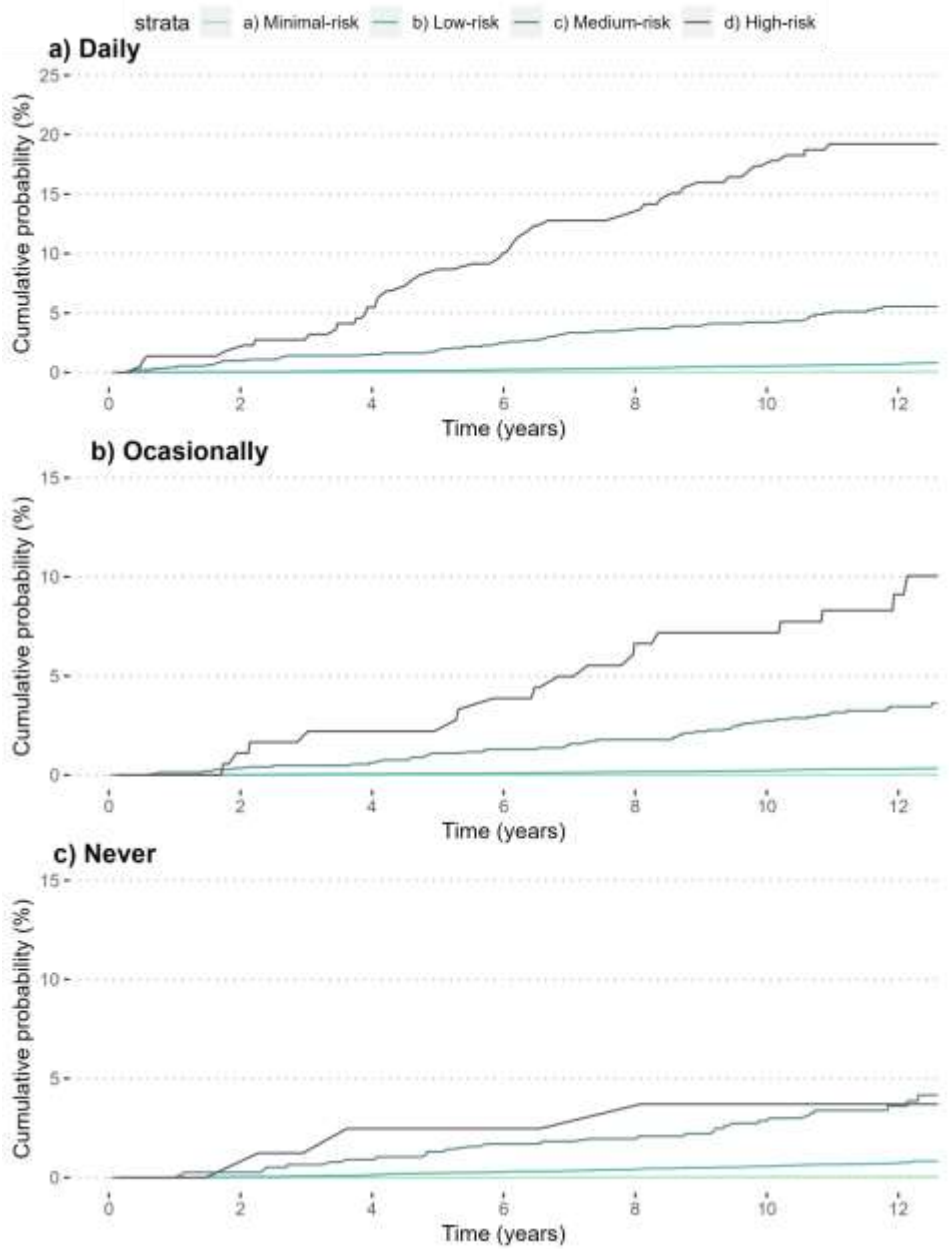


Figure S6. Cumulative incidence of liver-related mortality events by ©LiverRisk score groups and self-reported alcohol

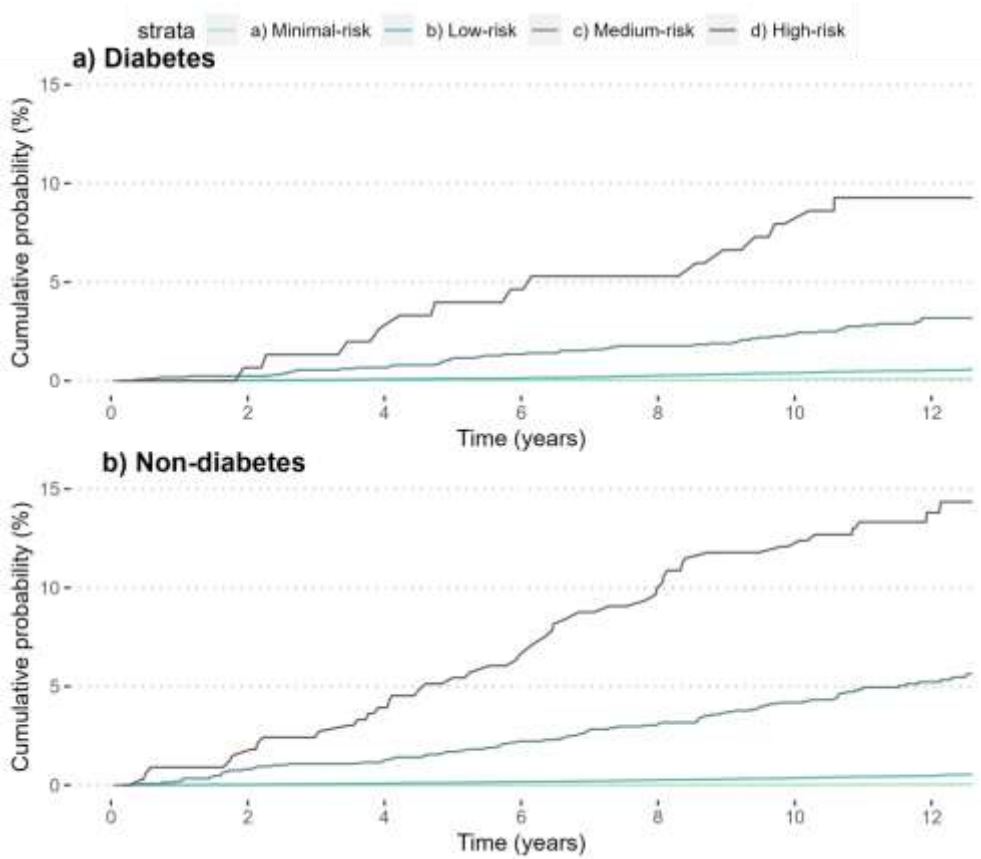
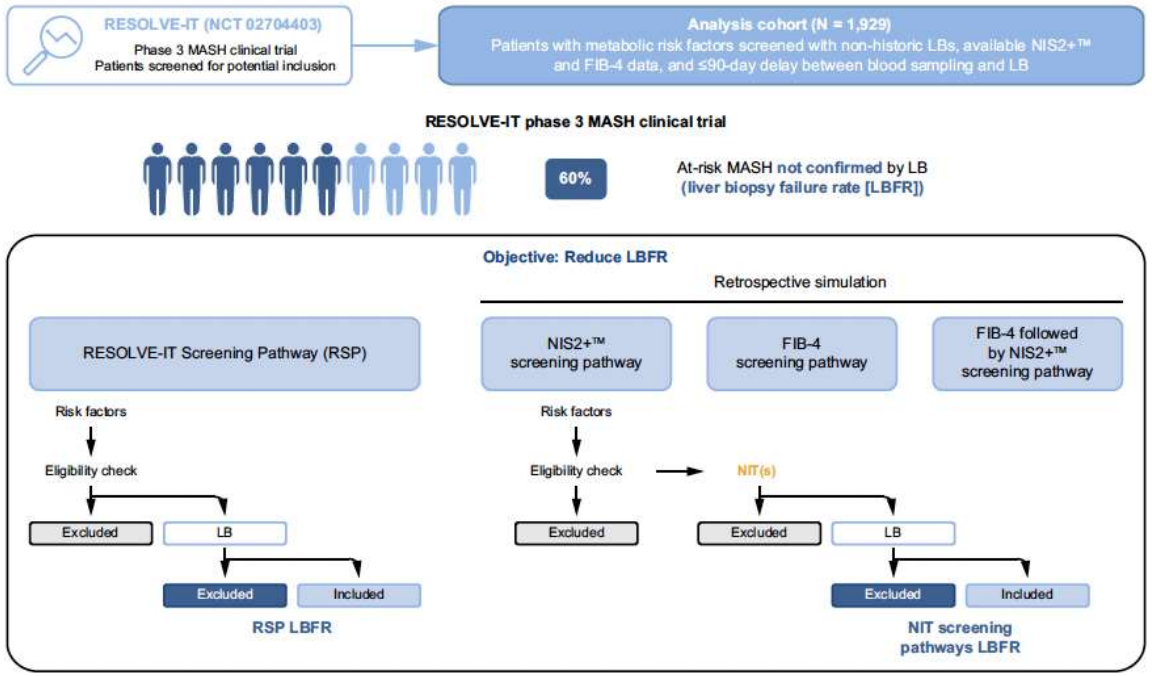
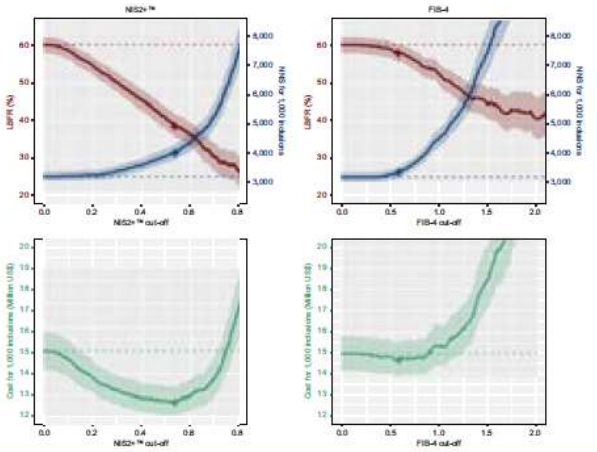


Figure S7. Cumulative incidence of liver-related mortality by ©LiverRisk score groups and presence or absence of diabetes.

Biomarcadores. Necesidad de tratamiento.



	RSP	FIB-4	NIS2+™	NIS2+™
Cut-off type	NA	Cost-optimized		High
Cut-off value	NA	0.58	0.53	0.68
Performance to achieve 1,000 inclusions				
Number needed to screen	3,220	3,379	4,033	5,099
LBFR (n)	60% (1,522)	58% (1,384)	39% (632)	31% (455)
LB failures avoided vs. RSP, % reduction (n)	NA	-9.0 (138)	-58.0 (890)	-70.0 (1,067)
Total cost of screening, US$ million	15.0	14.7	12.7	13.6



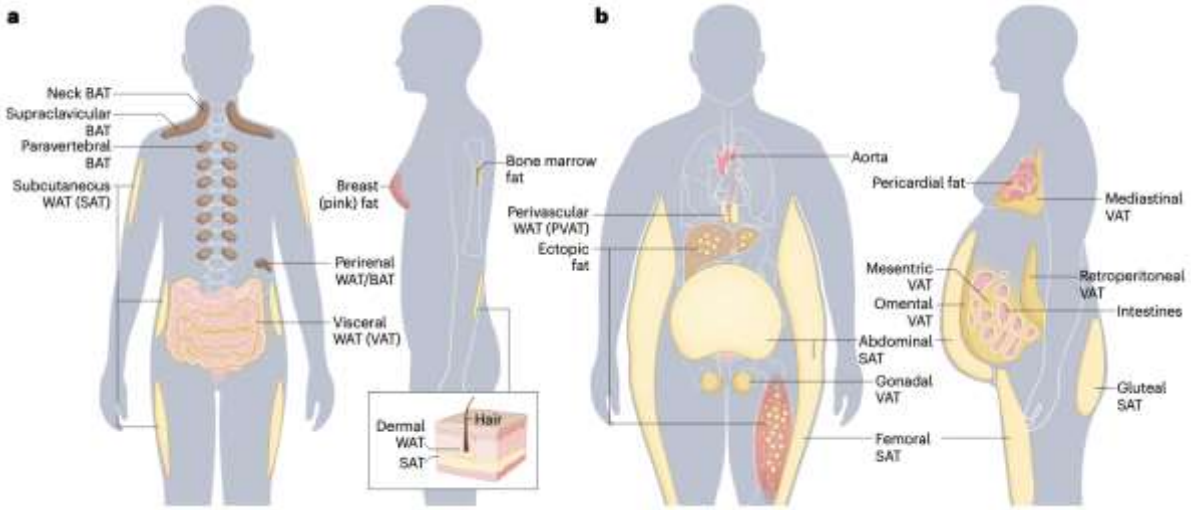
- Patient selection for LB through screening with NIS2+™ significantly reduced unnecessary biopsies and screening costs, which could greatly improve the screening process of future MASH clinical trials
- The NIS2+™ screening pathway did not introduce bias in the characteristics of the patients included

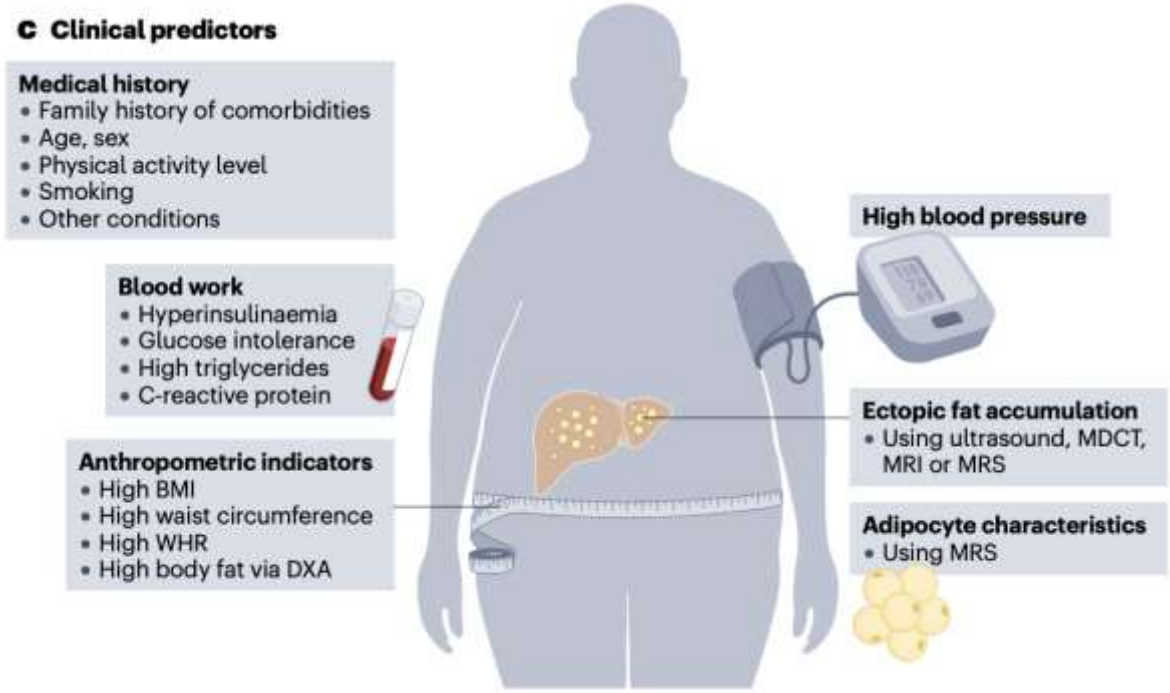
- The liver biopsy failure rate in MASH clinical trials is unacceptably high.
- We used NIS2+TM, a two-biomarker test, to refer patients
- with at-risk MASH for liver biopsy.
- NIS2+TM reduced liver biopsy failure rates and screening costs.
- NIS2+TM screening performance was superior to that of FIB-4.
- The profile of patients included with NIS2+TM screening pathway was not impacted.

Ratziu V et al. NIS2+™ as a screening tool to optimize patient selection in metabolic dysfunction-associated steatohepatitis clinical trials. J Hepatol. 2024 Feb;80(2):209-219. doi: 10.1016/j.jhep.2023.10.038. Epub 2023 Dec 5. PMID: 38061448.

Biomarcadores. Enfermedades asociadas.

Adiposidad visceral



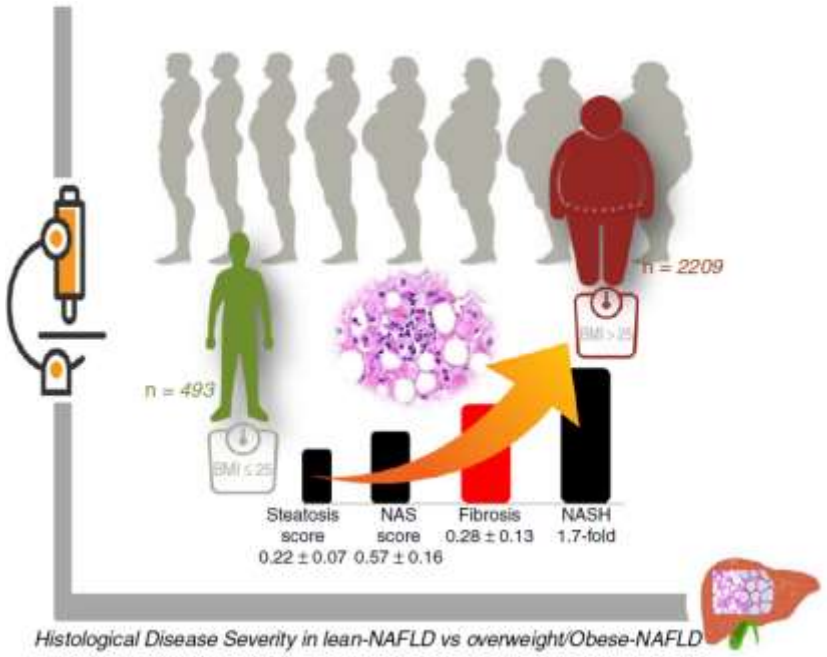


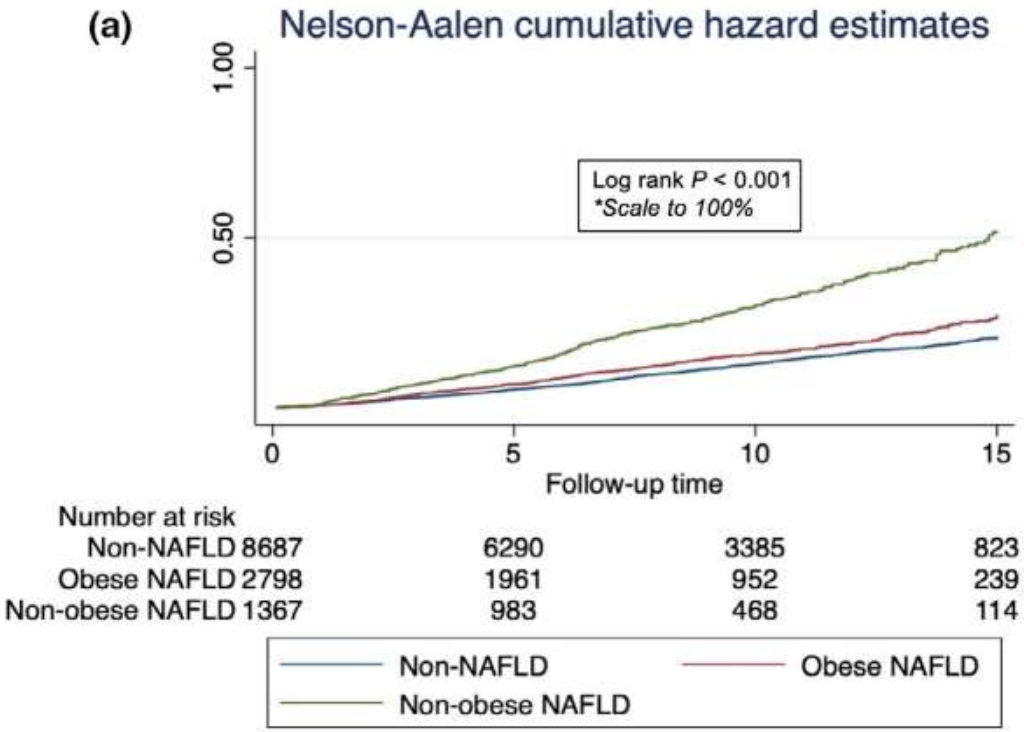
Hagberg & Spalding, Nat Rev Mol Cell Biol 2023

Biomarcadores. Enfermedades asociadas.

¿Lean MSLD?

Entre un 10-20 % de los pacientes MASLD son sujetos delgados o no obesos.





Puntuación NAS y de fibrosis más bajas entre los lean-NAFLD frente a los NAFLD obesos.

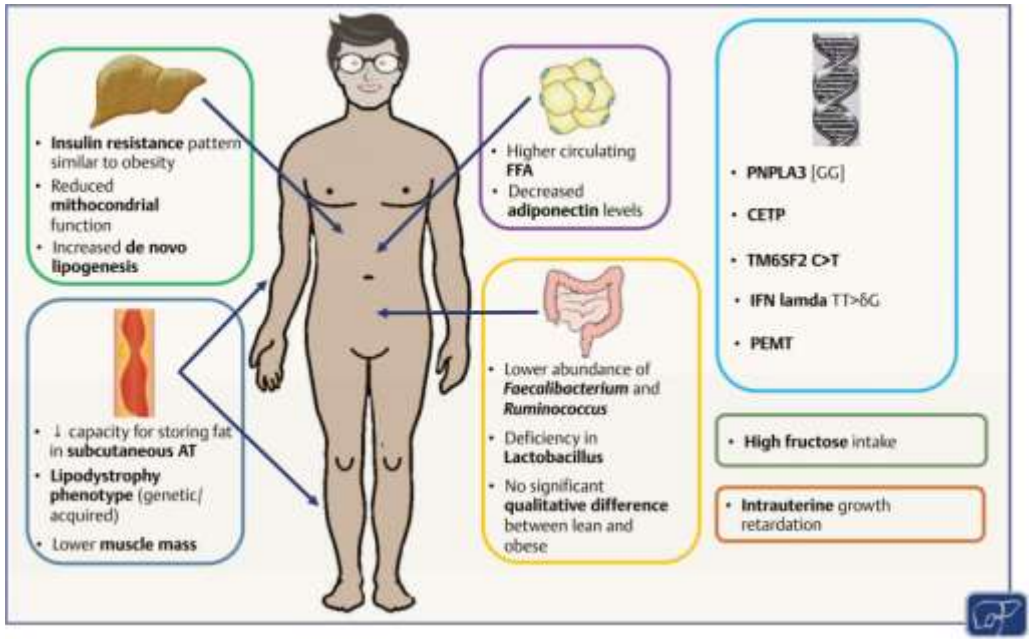
La mortalidad acumulada por todas las causas en 15 años fue mayor en NAFLD no obesos (51,7%), seguidos por los obesos NAFLD (27,2%), luego el grupo sin NAFLD (20,7%)

Sookoian S and Pirola CJ. AP&T 2017

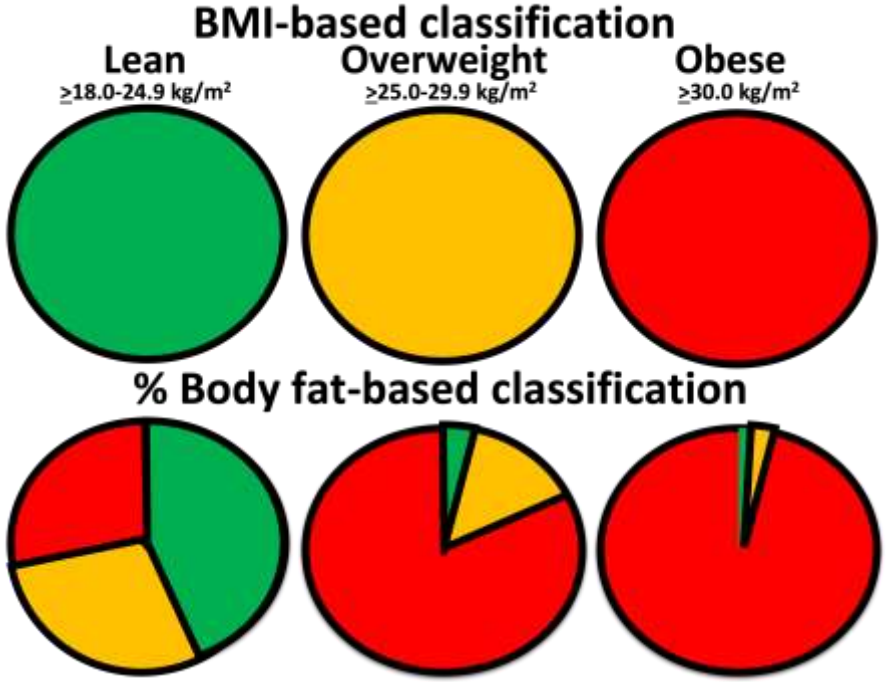
Zou B et al. J Intern Med 2020

Biomarcadores. Enfermedades asociadas.

¿Lean MSLD?



Determinantes fisiopatológicos de NAFLD en sujetos delgados



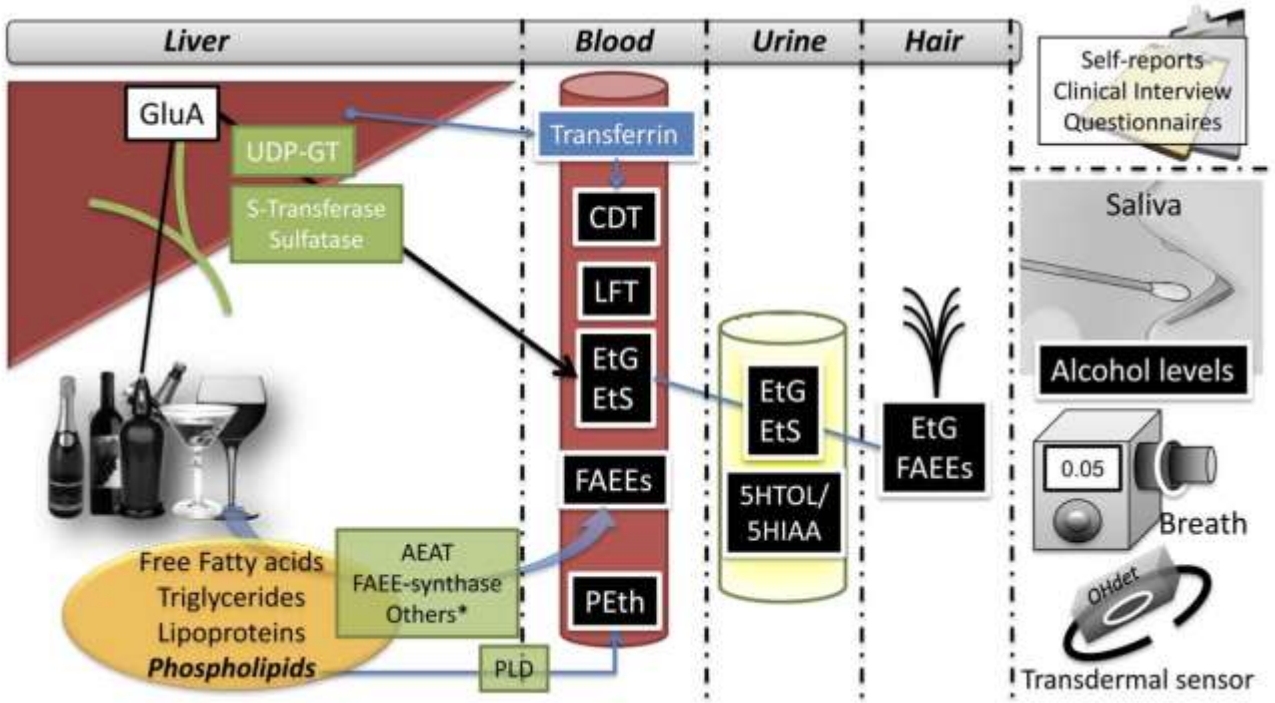
La clasificación del IMC omite a los sujetos con mayores factores de riesgo cardiometabólico relacionados con una adiposidad elevada.

El 29% de los sujetos clasificados como delgados y el 80% de los individuos clasificados con sobrepeso según el IMC tenían un % grasa corporal dentro del rango de obesidad.

Younes R and Bugianesi E. Semin Liver Dis 2019

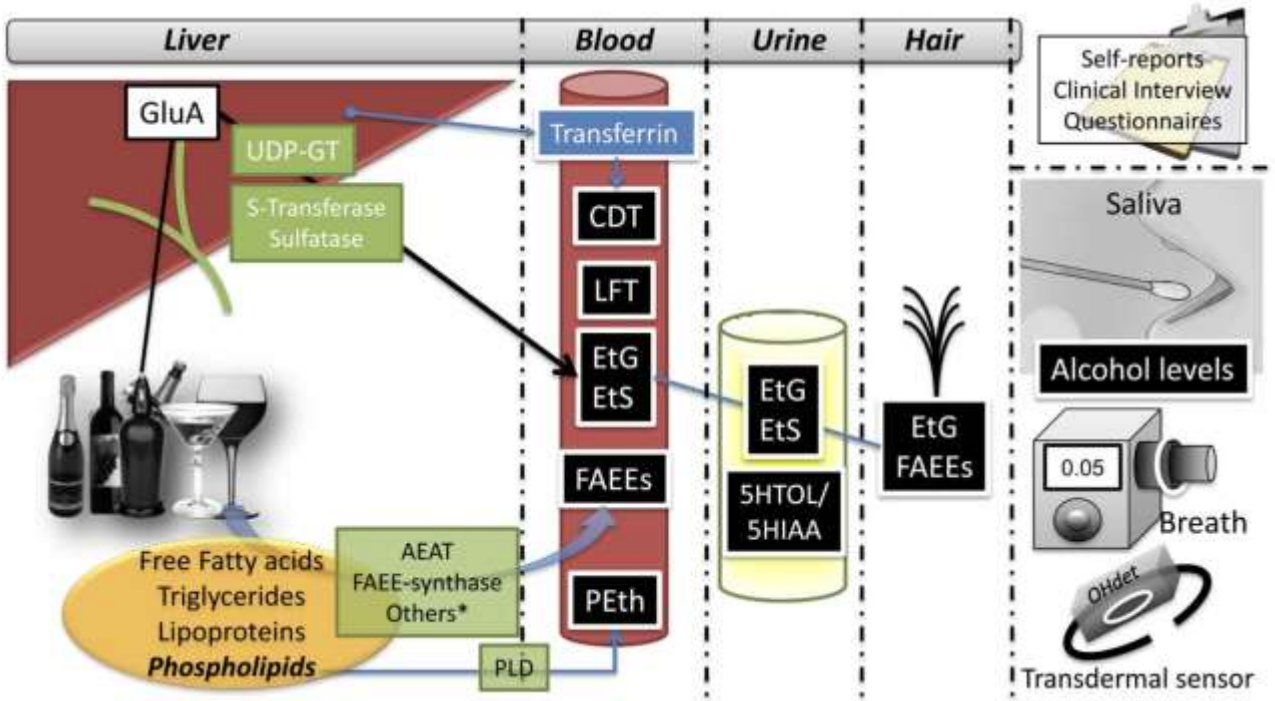
Gomez-Ambrosi J et al. Int J Obes (Lond) 2012

Biomarcadores. Consumo de alcohol

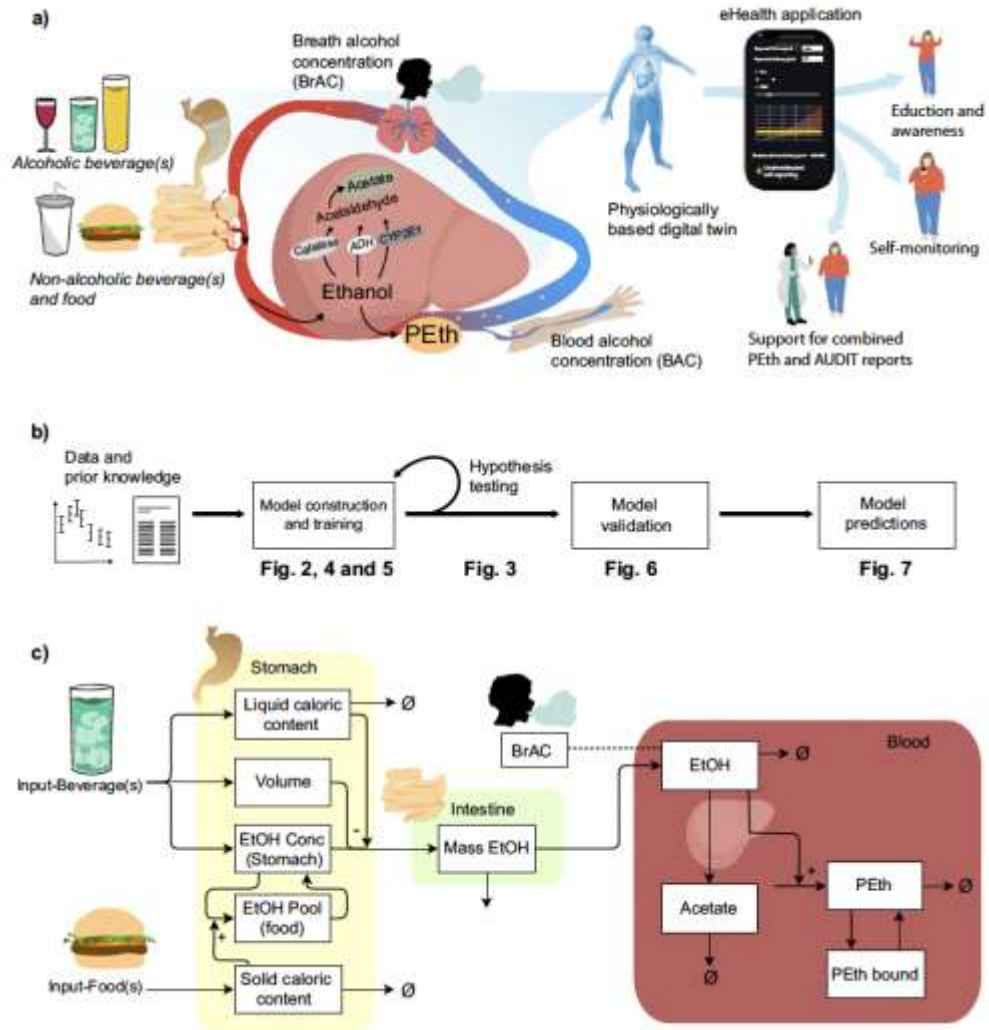


Cabezas J, Lucey MR, Bataller R. Biomarkers for monitoring alcohol use. Clin Liver Dis (Hoboken). 2016 Oct 2;8(3):59-63. doi: 10.1002/cld.571. PMID: 31041064; PMCID: PMC6490197.

Biomarcadores. Consumo de alcohol

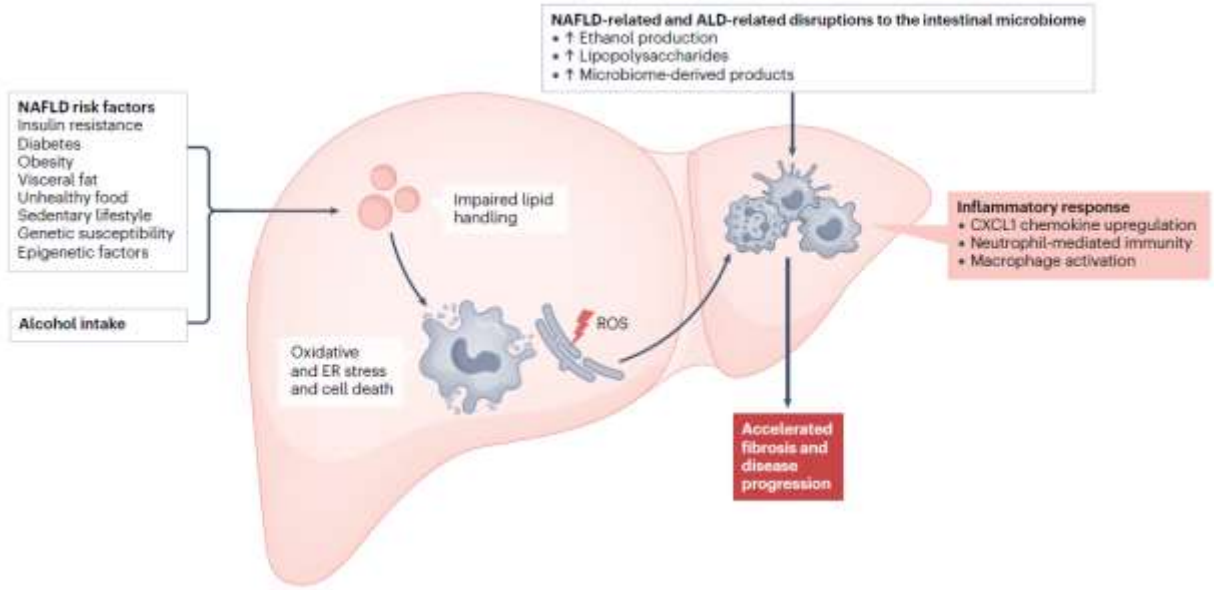


Cabezas J, Lucey MR, Bataller R. Biomarkers for monitoring alcohol use. Clin Liver Dis (Hoboken). 2016 Oct 2;8(3):59-63. doi: 10.1002/cld.571. PMID: 31041064; PMCID: PMC6490197.



Podéus H et al. NPJ Digit Med. 2024; 7: 112. doi: 10.1038/s41746-024-01089-6. PMID: 38702474; PMCID: PMC11068902.

Biomarcadores. Consumo de alcohol



El alcohol y la disfunción metabólica coexisten como factores etiológicos en muchos pacientes con esteatosis hepática.

El alcohol y los factores metabólicos interactúan para exacerbar la progresión de la enfermedad hepática.

Diaz LA et al. Nat Rev Gastroenterol Hepatol 2023

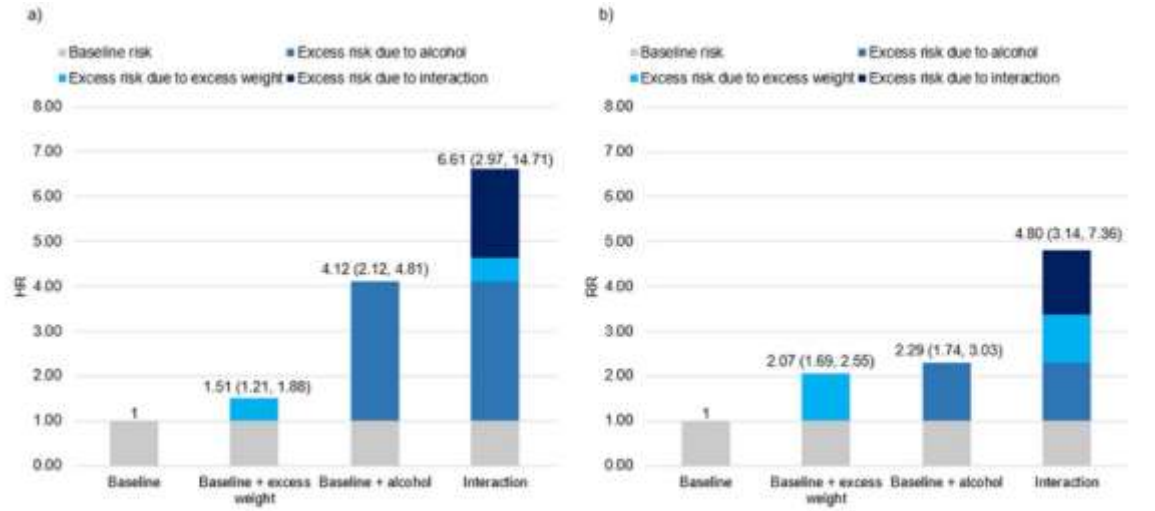


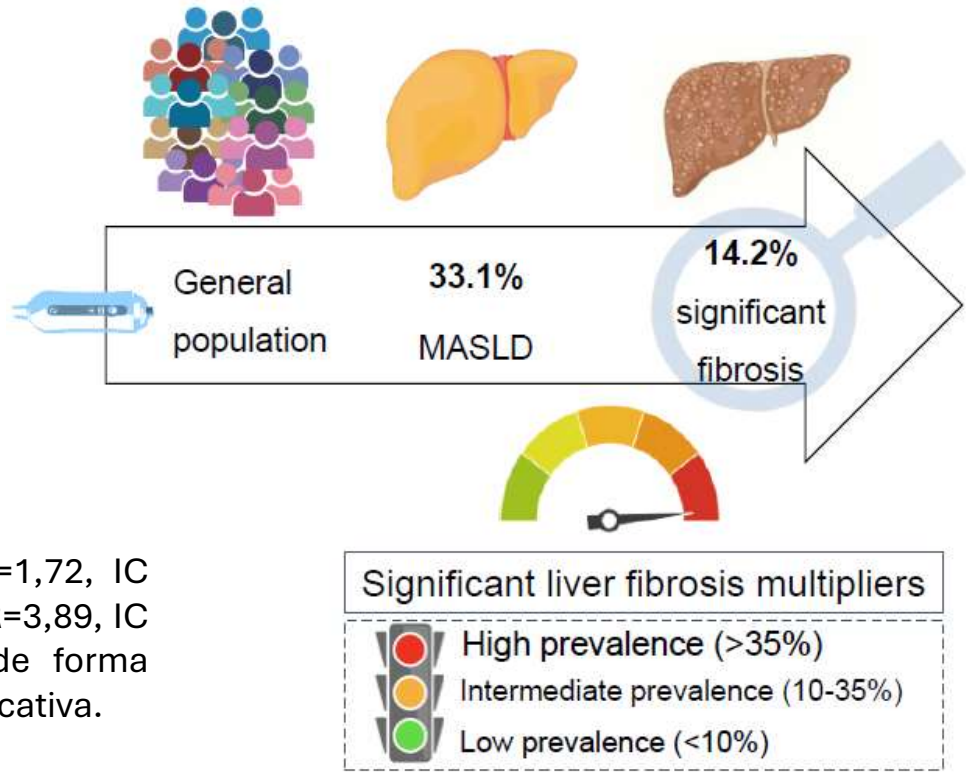
Fig. 4. a–b: Pooled HR (a) and RR (b) for the independent and joint association of drinking alcohol and excess weight and liver disease/death (n = 2,603,939).

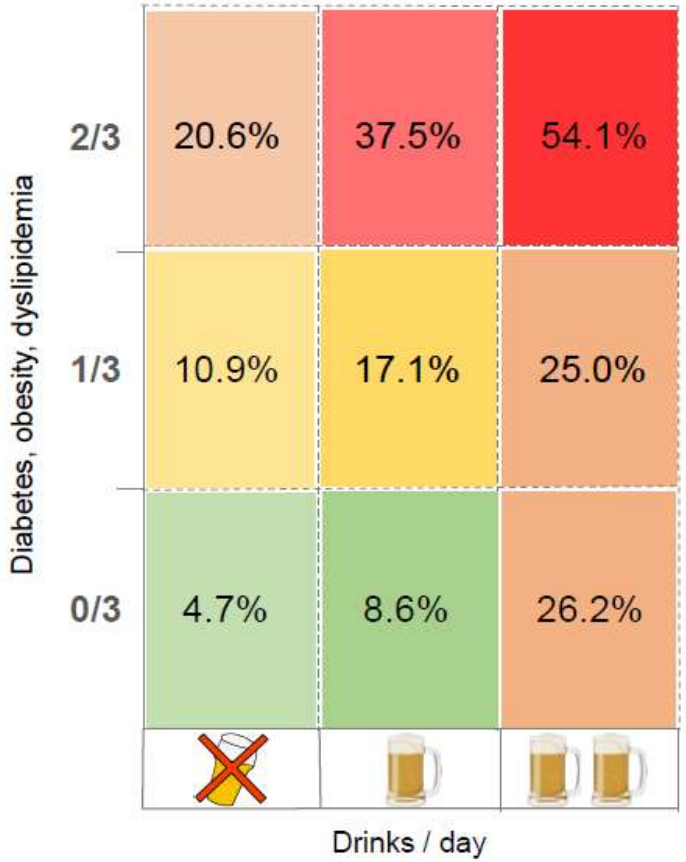
El consumo de alcohol aumentó significativamente el riesgo de enfermedad hepática o muerte, al igual que el exceso de peso. El efecto combinado del alcohol y el exceso de peso sobre la enfermedad hepática/muerte fue 1,61 veces mayor que el efecto aditivo de cada exposición (IC del 95 %: 1,34; 1,93).

El alcohol y la obesidad tienen un EFECTO SINÉRGICO

Burton R et al. Public Health 2023

Biomarcadores. Consumo de alcohol





Tanto el consumo mínimo (OR=1,72, IC 95% 1,10-2,69) como el bajo (OR=3,89, IC 95% 2,83-5,35) se asociaron de forma independiente con fibrosis significativa.

Se observó una interacción supra aditiva dosis dependiente entre el número de bebidas/semana y las principales comorbilidades metabólicas

Marti-Aguado D et al. J Hepatol. Submitted

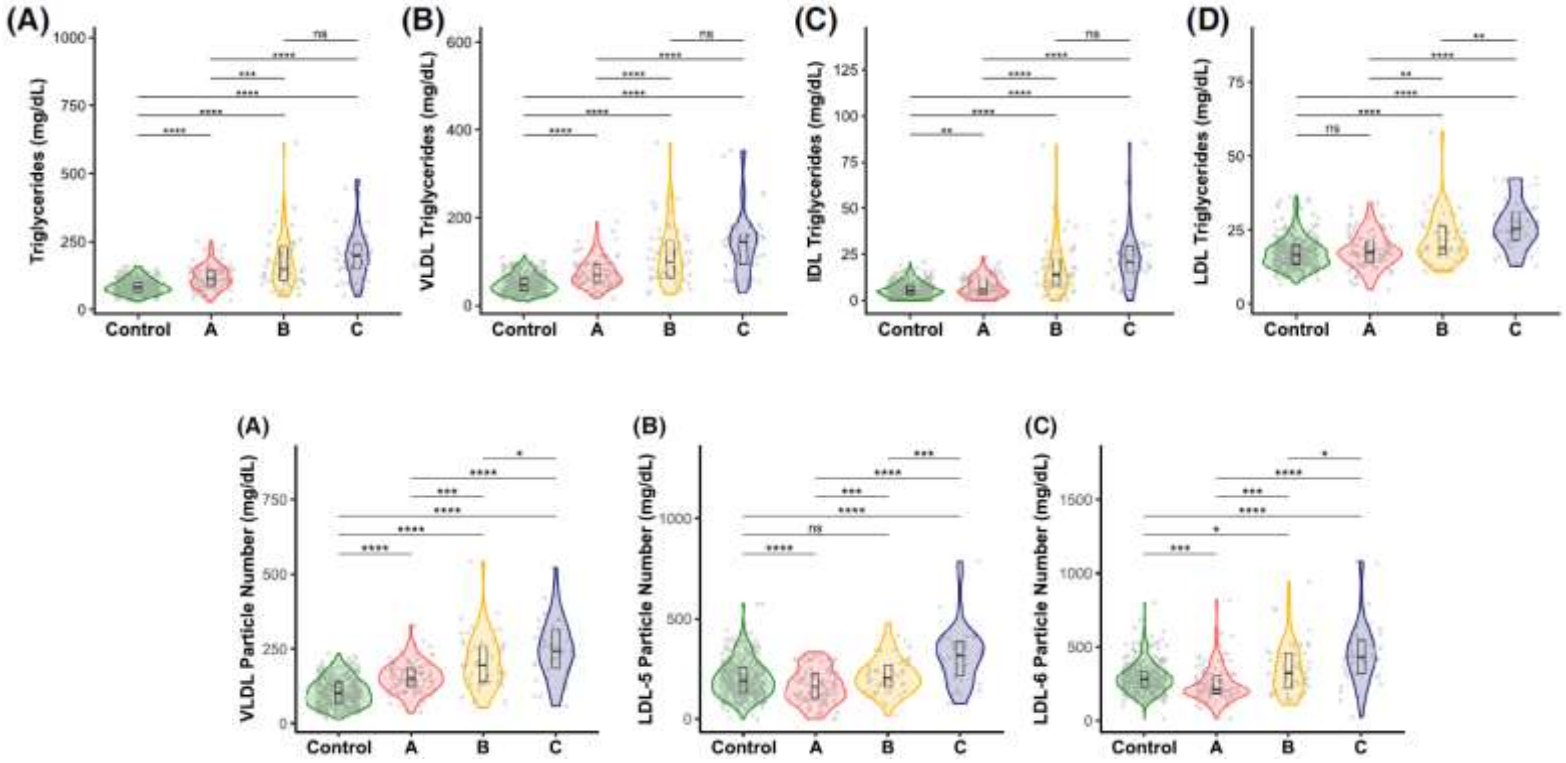
Biomarcadores. Riesgo vascular.

- Serum metabolome from 1154 NAFLD patients
- Serum metabolome from 5 mouse models of NAFLD
  - 4 with impaired VLDL-TG secretion (Mat1a-KO, 0.1MCD, Mttp-KO, and Tm6sf2-KO)
  - 1 with normal VLDL-TG secretion (Ldlr−/−.Leiden/HFD)

Subtype A: metabolome of mice with impaired VLDL-TG secretion

Subtype B: intermediate signature

Subtype C: metabolome of mice with normal VLDL-TG



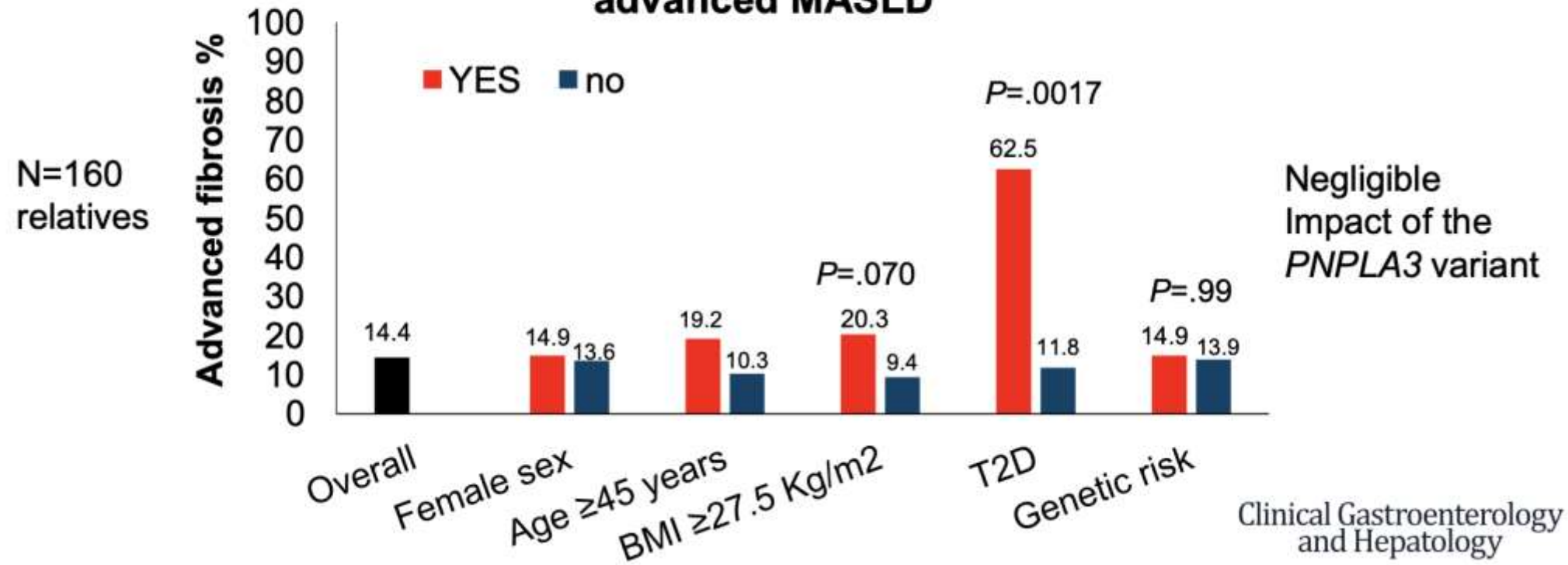
Serum VLDL-TG, TG, cholesterol, VLDL and small dense LDL were lower among subtype A

NAFLD patients with subtype A exhibit a favourable cardiovascular risk profile

Martinez-Arranz I et al. Hepatology 2022

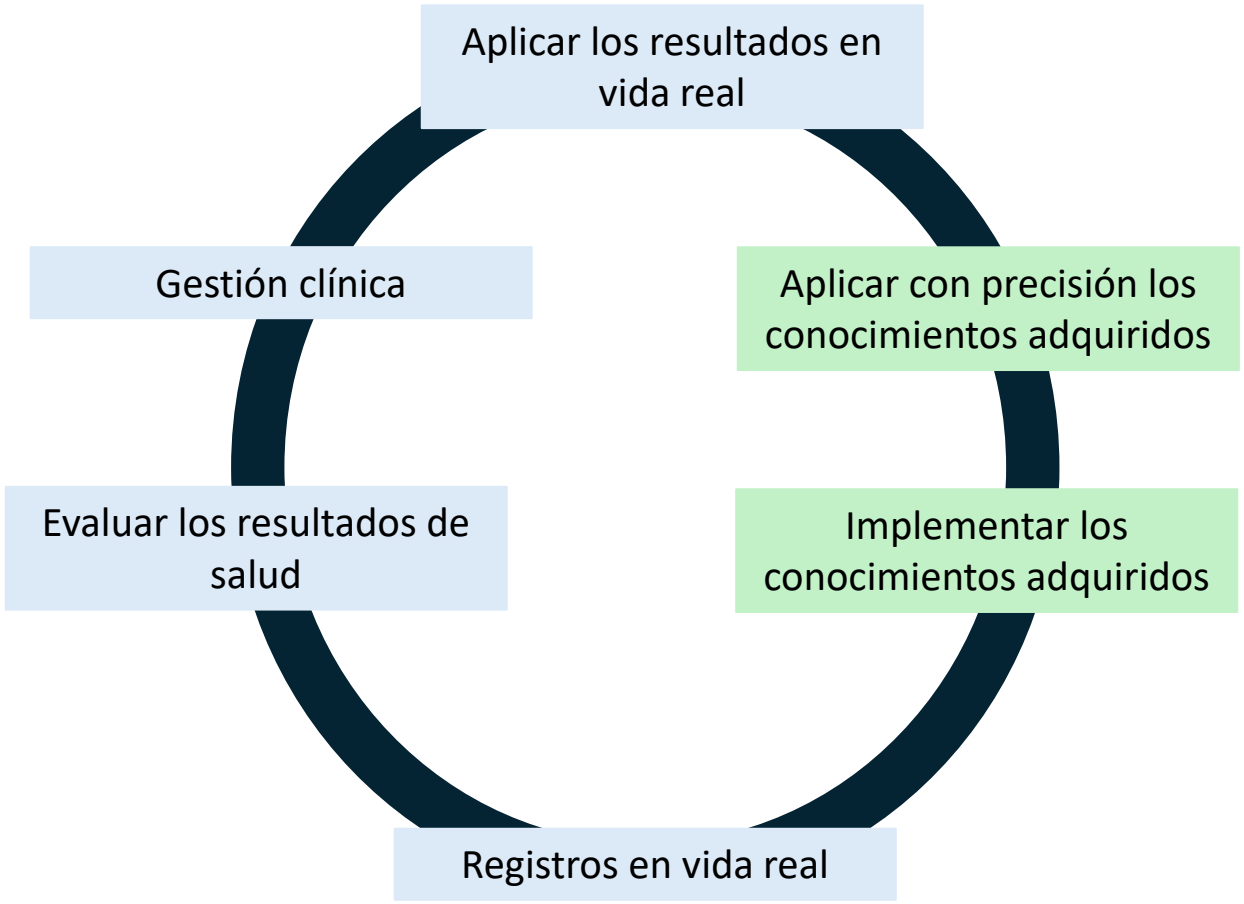
Biomarcadores. Riesgo enfermedad familiar.

Prevalence and determinants of liver disease in relatives of Italian patients with advanced MASLD



Pelusi S, et al. Prevalence and Determinants of Liver Disease in Relatives of Italian Patients With Advanced MASLD. Clin Gastroenterol Hepatol. 2024 Jan 11:S1542-3565(24)00046-6. doi: 10.1016/j.cgh.2023.12.033. Epub ahead of print. PMID: 38216023.

¿Aplicamos con precisión el conocimiento clínico adquirido?



¿Aplicamos con precisión el conocimiento clínico adquirido?