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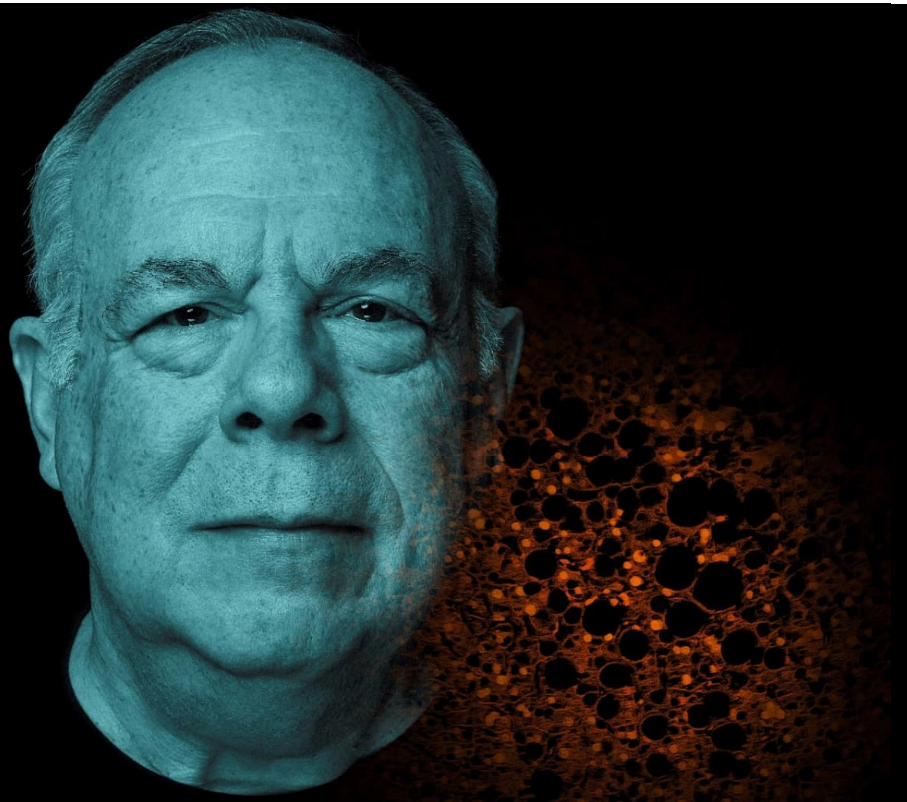
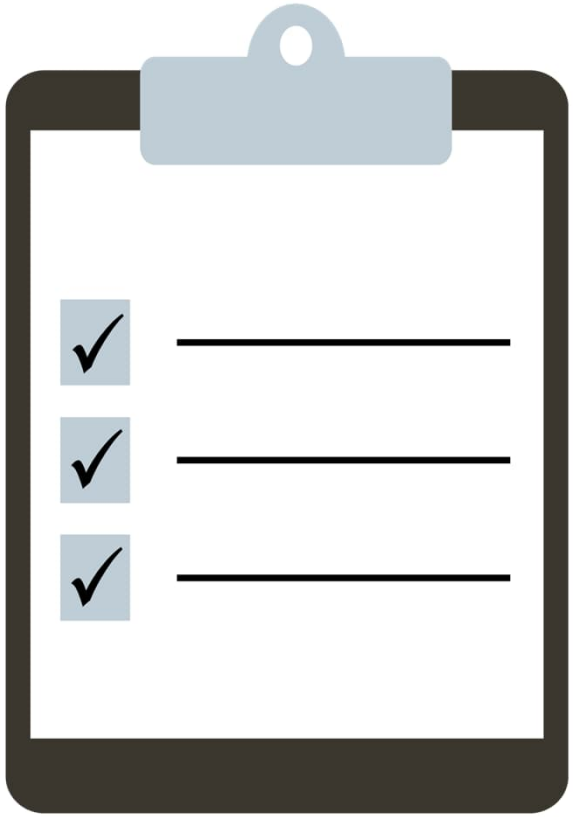
The Enhanced Liver Fibrosis (ELF™) Test: A blood test to identify at-risk patients with chronic liver disease

Katherine Soreng, PhD

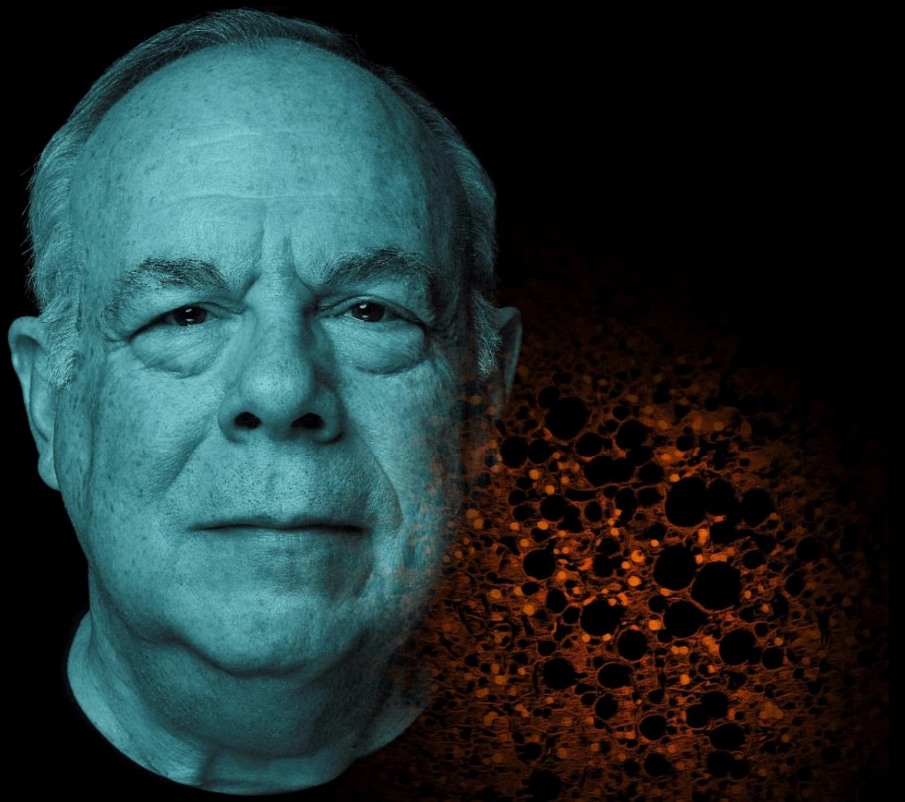


Agenda

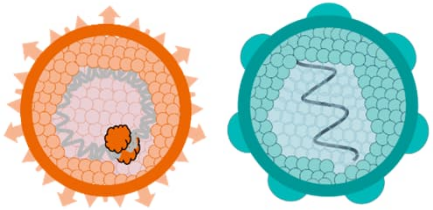


- Chronic Liver Disease: Global and in Estonia
- Benefits of early identification and intervention
- Non-invasive tests (NIT's) as an improvement over biopsy
- Enhanced Liver Fibrosis (ELF™) NIT
- Testing algorithms using NIT's to identify those at higher risk

Chronic liver disease: An epidemic



Chronic liver disease (CLD) has many etiologies



HBV HCV

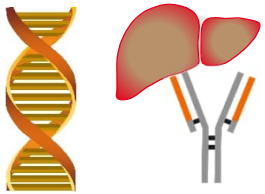
Viral hepatitis (including HIV/HCV coinfections)

Alcoholic liver disease

Global population ~8 billion

Global NAFLD ~25%

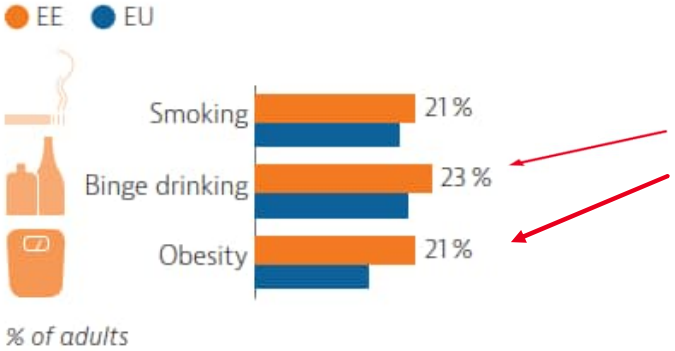
Obesity and associated metabolic diseases: NAFLD/NASH (~59% of current CLD's)



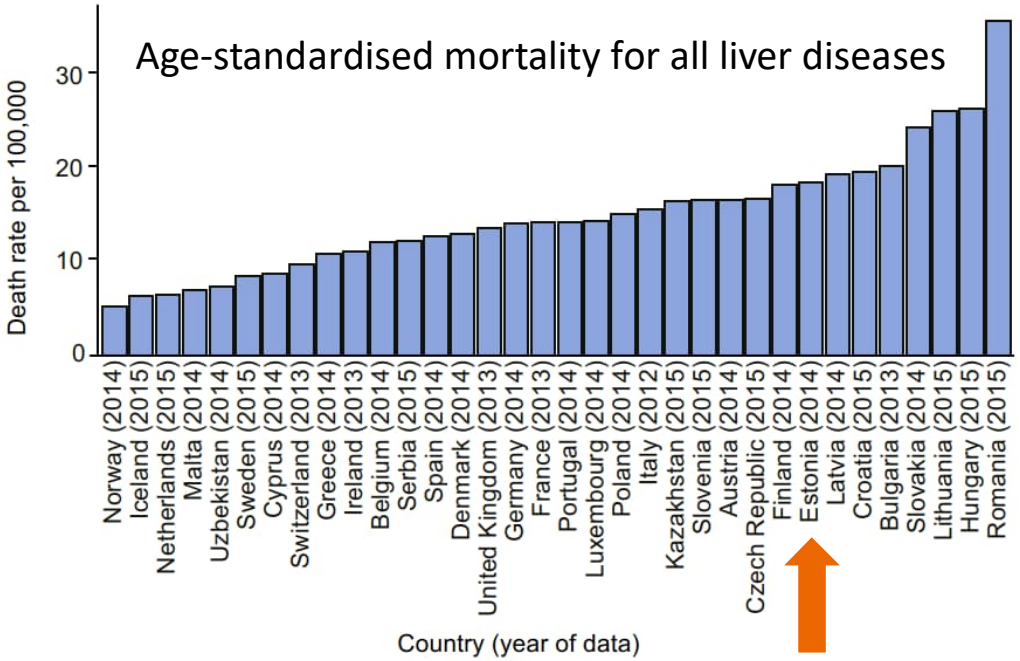
Primary biliary cholangitis PBC), autoimmune hepatitis, hemochromatosis, Wilson's disease, other

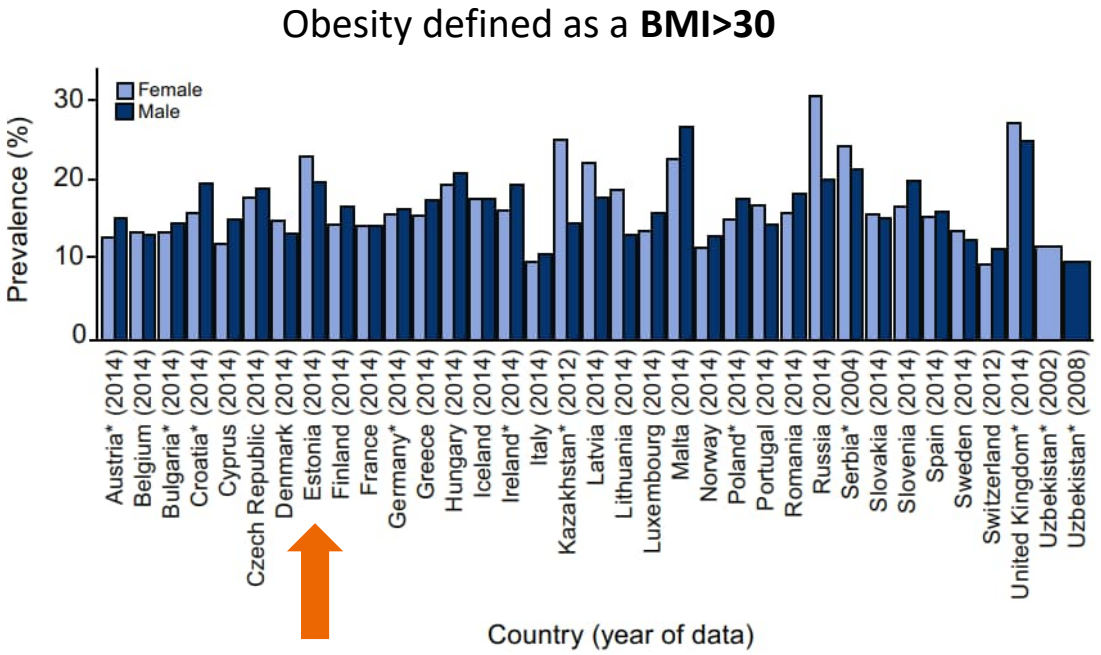
Moon, AM., et al. Clin Gastroenterol Hepatol 2020;18(12): 2650-66.

Deaths from liver disease are increasing in Estonia



Deaths from liver disease and BMI>30: European data





Obesity is a key contributor to increasing rates chronic liver disease

Nonalcoholic fatty liver disease describes a continuum

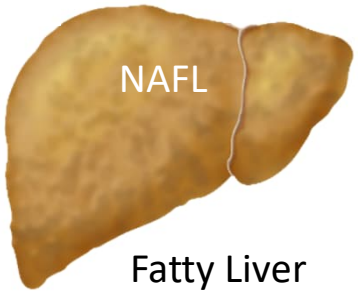
BMI ≥30

Obesity and associated metabolic diseases: NAFLD/NASH

NAFLD: Non-Alcoholic Fatty Liver Disease

- **NAFL**: Non-Alcoholic Fatty Liver
- **NASH**: Non-Alcoholic Steatohepatitis

~20% progress

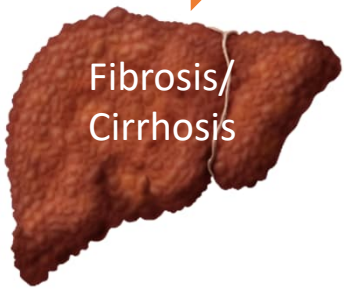


Fatty Liver
"Steatosis"

>5% fat

Ultrasound-based testing detects **~>30% fat**

Fatty Liver
+ Inflammation



Progressive liver damage driven by fibrosis

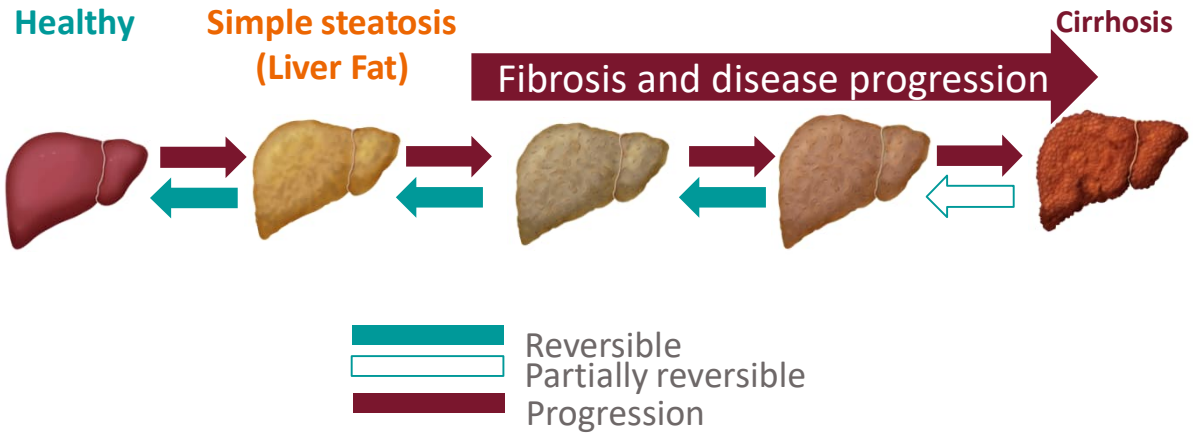
Liver-Related Events (LRE) include:

- Varices
- Bleeding
- Clotting issues
- Portal hypertension
- Liver failure
- Liver transplant
- Liver Cancer
- Death

Symptoms often <u>after</u> decompensation has occurred
Patients often diagnosed too late!

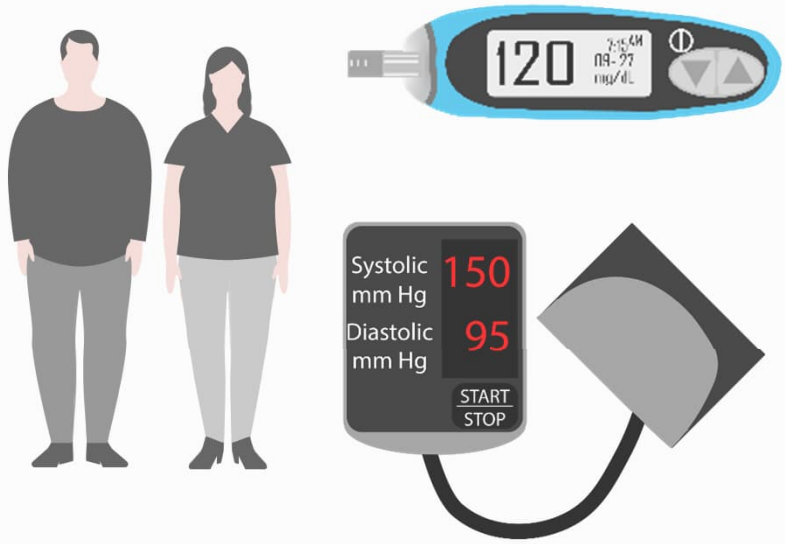
Stal, P. World J Gastroenterol. 2015;21(39):11077–87. https://gi.org/topics/fatty-liver-disease-nafld/

Obesity and Diabetes significantly increases NAFLD risk



How to identify the subset at risk of liver disease progression?

A high % of the population have risk factors



- **Obesity** impacts ~25% of the global population
- **Metabolic syndrome** is associated with high prevalence of fatty liver
- ~55~70% of people with **diabetes** ALSO have fatty liver

Obesity, Diabetes, Metabolic Syndrome

Sanyal AJ, et al. Hepatology. 2019;70(6):1913-1927.
Tsochatzis EA, et al. The Lancet 2014;383:1749-61.
Alkouri N, et al. AASLD Digital Liver Meeting Nov. 13-16, 2020.

2022: Liver Disease is the 2nd leading cause of working life lost in Europe

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The EASL–*Lancet* Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality

Tom H Karlsen, Nick Sheron†, Shira Zelber-Sagi, Patrizia Carrieri, Geoffrey Dusheiko, Elisabetta Bugianesi†, Rachel Pryke†, Sharon J Hutchinson, Bruno Sangro†, Natasha K Martin, Michele Cecchini, Mae Ashworth Dirac, Annalisa Belloni, Miquel Serra-Burriel, Cyriel Y Ponsioen, Brittney Sheena, Alienor Lerouge, Marion Devaux, Nick Scott, Margaret Hellard, Henkjan J Verkade, Ekkehard Sturm, Giulio Marchesini, Hannele Yki-Jarvinen, Chris D Byrne, Giovanni Targher, Aviad Tur-Sinai, Damon Barrett, Michael Ninburg, Tatjana Reic, Alison Taylor, Tim Rhodes, Carla Treloar, Claus Petersen, Christoph Schramm, Robert Flisiak, Marieta Y Simonova, Albert Pares, Philip Johnson, Alessandro Cucchetti, Isabel Graupera, Christos Lionis, Elisa Pose, Núria Fabrellas, Ann T Ma, Juan M Mendive, Vincenzo Mazzaferro, Harry Rutter, Helena Cortez-Pinto, Deirdre Kelly†, Robyn Burton, Jeffrey V Lazarus†, Pere Ginès†, Maria Buti†, Philip N Newsome†‡, Patrizia Burra*‡, Michael P Manns*‡*

Executive summary

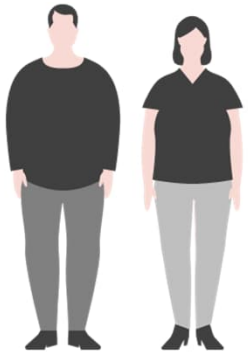
Liver diseases have become a major health threat across Europe, and the face of European hepatology is changing due to the cure of viral hepatitis C and the control of chronic viral hepatitis B, the increasingly widespread unhealthy use of alcohol, the epidemic of obesity, and care using multilevel interventions acting on current barriers.

Underlying this transformative shift is the need to enhance awareness of the preventable and treatable nature of many liver diseases. Therapeutic nihilism, which is prevalent in current clinical practice across a

Lancet 2022; 399: 61–116
Published Online
December 2, 2021
https://doi.org/10.1016/S0140-6736(21)01701-3

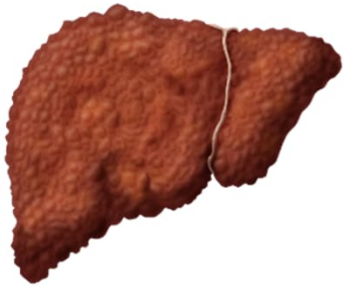
See **Comment** pages 7 and 9

Alcoholic liver disease



Obesity and associated metabolic diseases: NAFLD/NASH

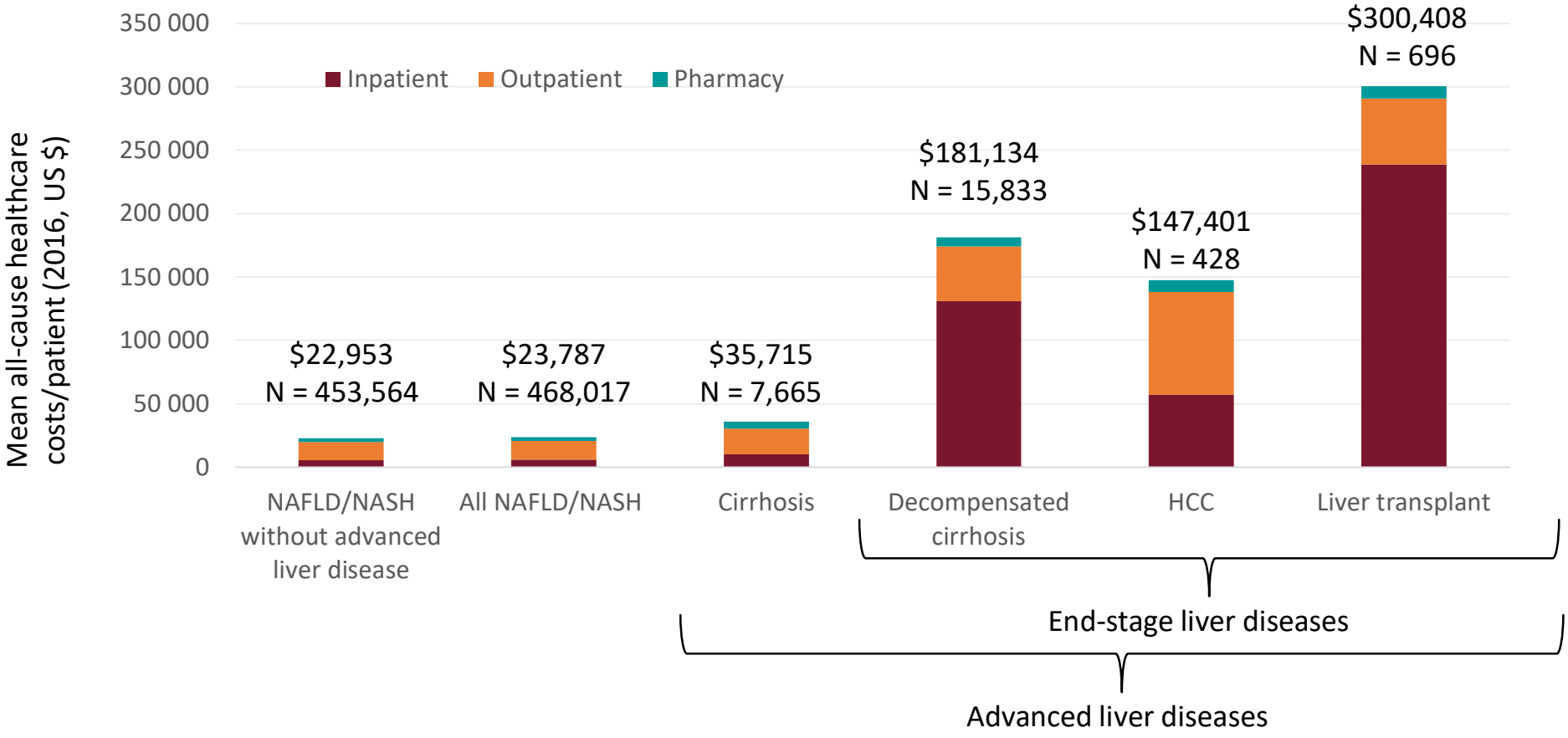
"The clinical focus in patients with liver disease is oriented towards cirrhosis and its complications, **whereas early and reversible disease stages are frequently disregarded and overlooked."**



Lancet Liver Commission:
~75% of patients with fatal cirrhosis were unaware of their disease until diagnosed in a hospital

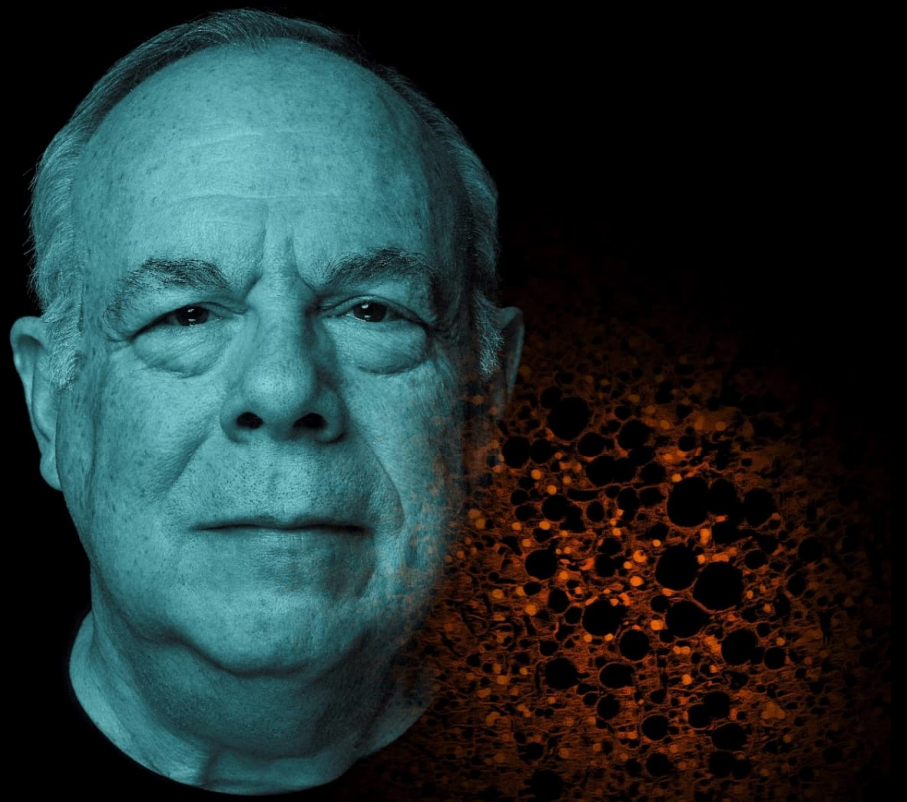
Karlsen, TH. Lancet 2022; 399: 61–116
Pimpin, L. Journal of Hepatology 2018 vol. 69 j 718–735

Mean healthcare costs for decompensated cirrhosis and HCC are substantially higher than for either NASH or cirrhosis

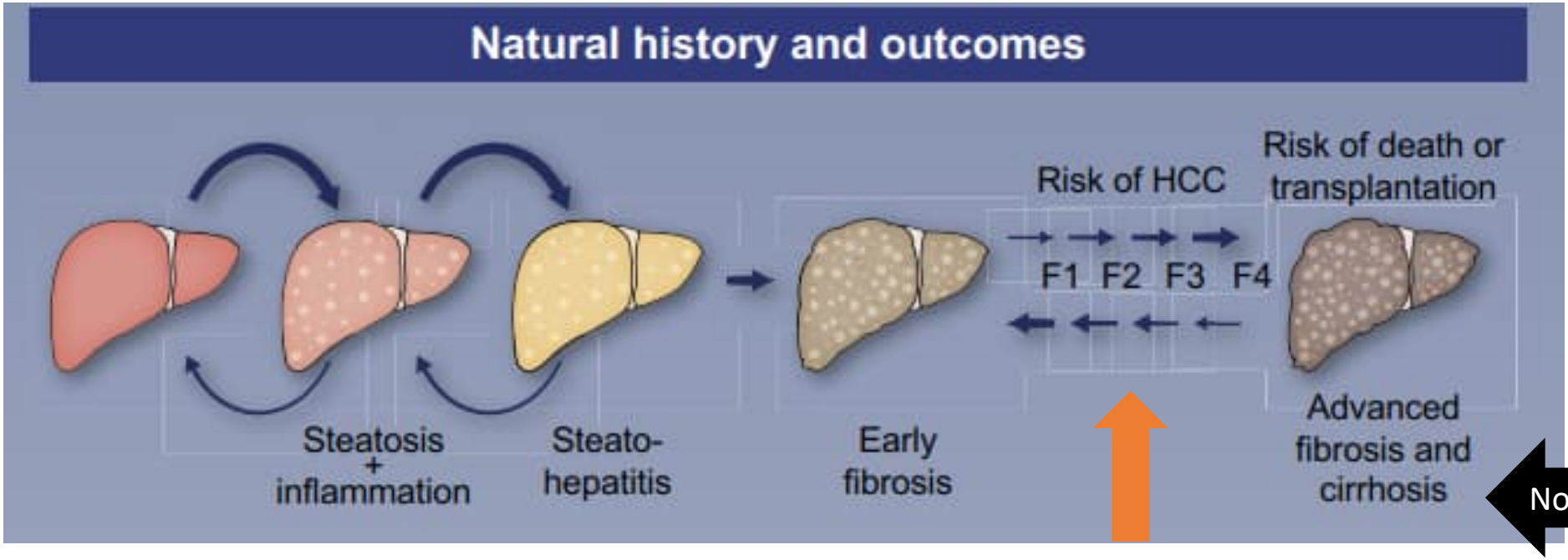


Wong RJ, et al. J Clin Gastroenterol. 2020 DOI: 10.1097/MCG.0000000000001409

Identifying high-risk patients



Fibrosis and disease progression/regression



Identify earlier

Elisabetta Bugianesi1, Salvatore Petta2*: Poster

Contributors to progression and therapies in development

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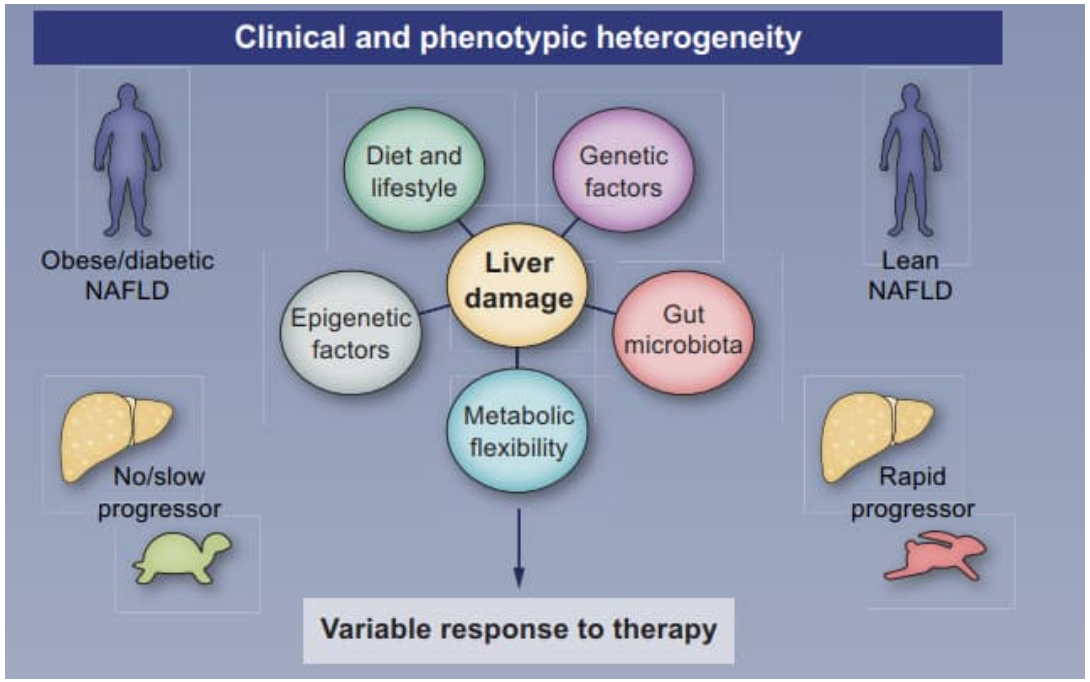
Factors influencing progression and treatment response



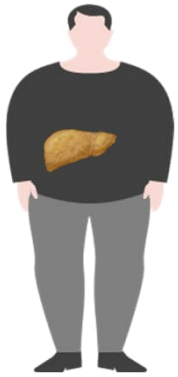
Therapies in late-stage development

Classes of drugs under development in Phase 2/3 trials and targeting metabolic and/or inflammatory and/or fibrogenic pathways

- Acetyl-CoA carboxylase (ACC) inhibitor
- Stearoyl-CoA desaturase (SCD) inhibitor
- Farnesoid X receptor (FXR) agonist
- Fibroblast growth factor (FGF) 19 and 21 analogs
- Peroxisome proliferator-activated receptor (PPAR) alpha and/or delta and/or gamma agonists
- Thyroid hormone receptor (THR) beta-selective agonist
- Mitochondrial pyruvate carrier (MPC) inhibitor
- Glucagon-like peptide 1 (GLP-1) agonist
- Galectin-3 inhibitor

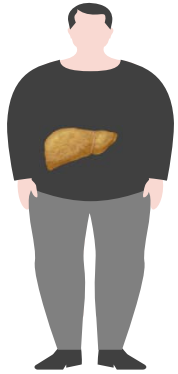
Identifying patients at risk:

"Based on a meta-analysis of studies of paired liver biopsy studies, liver fibrosis progresses in patients with NAFL and NASH."



Fatty Liver

Fibrosis no NASH



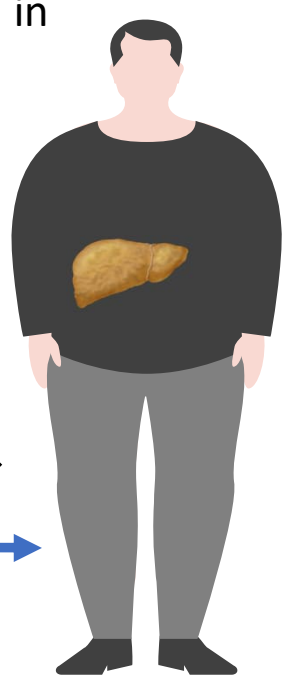
NASH

Slow progressors

Repair

Fibrosis

Fast progressors



Advanced fibrosis
Cirrhosis???

https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts Accessed Nov. 2019
Singh S et al. Clinical Gastroenterology and Hepatology 2015;13:643–654

Staging Indicates Degree of Fibrosis

1/50,000

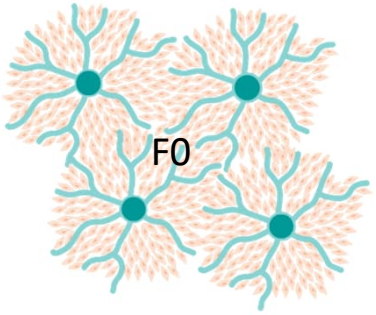
Biopsy is imperfect (~70% accuracy), carries risk, and has limited utility in large populations

Non-invasive tests or NIT's (imaging, blood biomarkers) are increasingly preferred

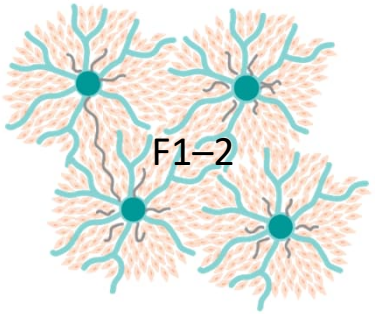
NIT's now dominate new guidelines

Staging system	Stages
Ishak	F0, F1, F2, F3, F4, F5, F6
METAVIR	F0, F1, F2, F3, F4
Batts-Ludwig	F0, F1, F2, F3, F4
Scheuer	F0, F1, F2, F3, F4
Brunt	F0 , F1, F2, F3, F4
Kleiner, Brunt, et al.	F0, F1a-c, F2, F3, F4

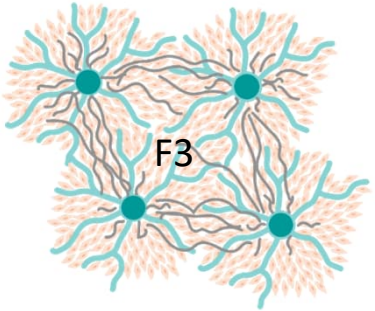
None



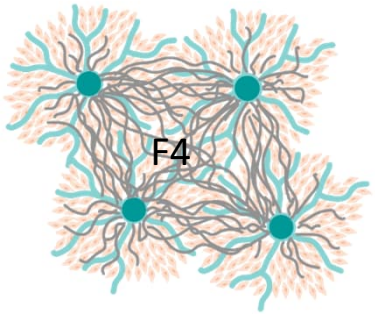
Mild to moderate



F1: Zone 3 perisinusoidal fibrosis
F2: Stage 1 + portal fibrosis



F3: Stage 2 + bridging fibrosis (severe)



Cirrhosis

Advanced fibrosis

https://img.freepik.com/free-photo/woman-doctor-medical-gown-gloves-looking-through-microscope-table-indoors_163305-72200.jpg?w=900

Theise ND. Mod Pathol 2007;20 Suppl 1:S3-14.
Ferrell, L.. http://labmed.ucsf.edu/uploads/472/227_Ferrell,%20LiverUpdateOnStagingOfFibrosisAndCirrhosis.pdf

NAFLD progression and regression: A complex biochemistry

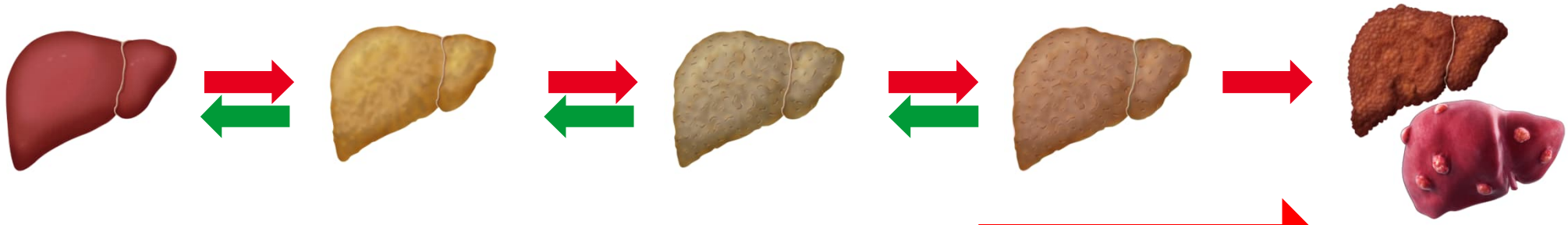
Healthy

NAFLD
Fat accumulation

Nonalcoholic steatohepatitis (NASH)

Advancing Fibrosis (F1,F2, F3)

Cirrhosis (F4) (Compensated, Decompensated)



Progressive Fibrosis

Fibrinolysis/Repair

Liver–Related Events

- Damage and repair driven by biochemical activity
- Involves many different proteins

http://www.sydneynwgastro.com.au/services/liver-disease/fatty-liver
Wree A, et al. Nat Rev Gastroenterol Hepatol. 2013;10:627-36.
Vernon G, et al. Aliment Pharmacol Ther. 2011;34:274-85.
Schattenberg JM,, et al. Curr Opin Lipidol. 2011;22:479-88.
Angulo P, et al. Hepatology. 1999;30:1356-62.
Naim, A. et al. J CLIN EXP HEPATOL 2017;7:367–372

Non-Invasive tests (NIT's) to assess liver fibrosis include:

Invasive, Risk,
Limited number of patients

Non-Invasive

Liver biopsy (histopathology) "Damage done"

Percutaneous tissue sample

Imaging (Elasticity) "Damage done"

FibroScan, ARFI, MRE

Indirect or "surrogate" markers

e.g. inflammation, dysfunction

Examples:

FibroTest
FibroMeter*
FIB-4

ELF (Direct Markers*) "Active fibrosis"

Atellica and ADVIA Centaur

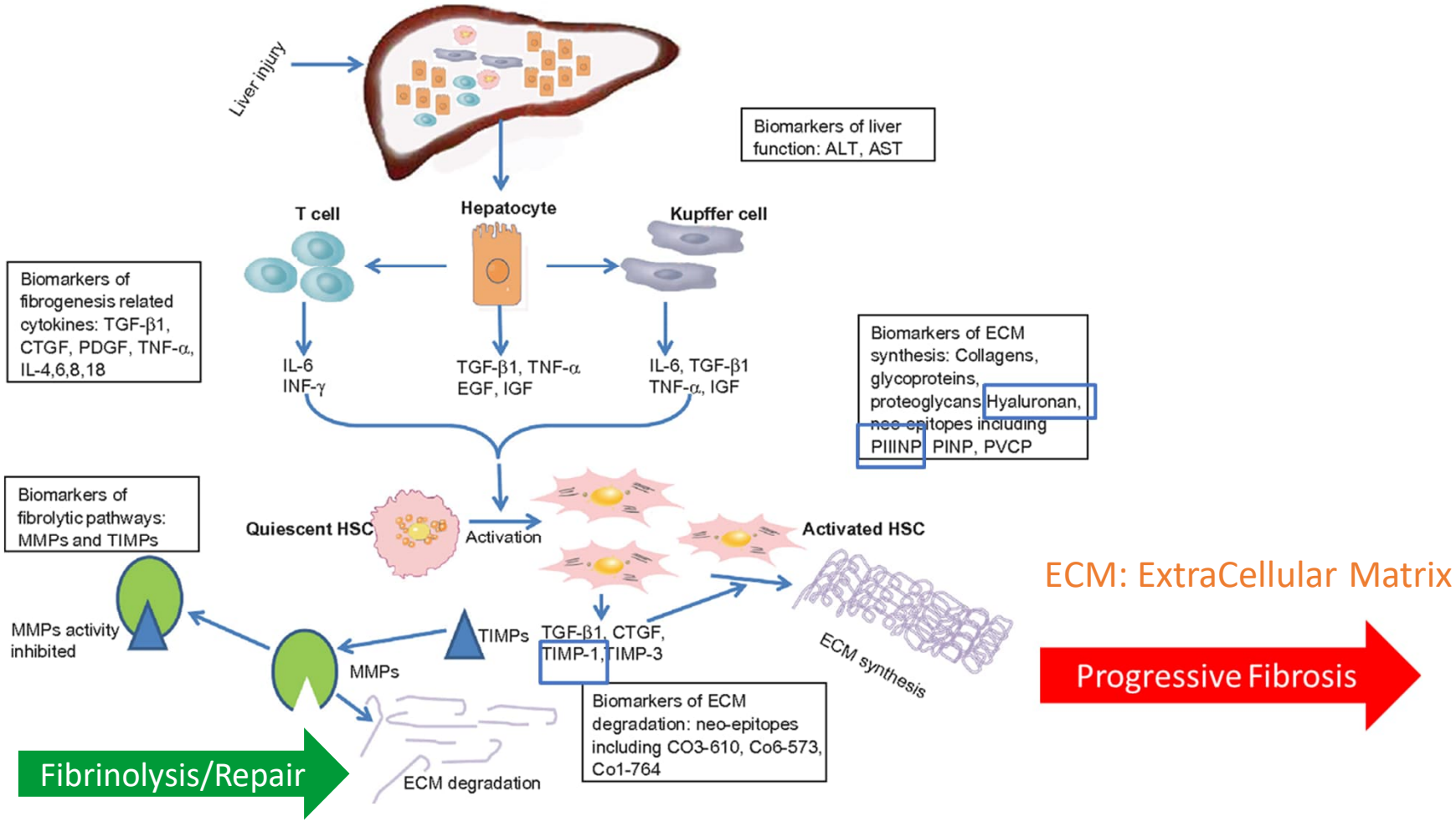
Direct score reported off analyzer

*Direct markers reflect the biochemical pathogenesis and turnover of ECM

*FMV2G includes HA

Chin JL et al. Front Pharmacol. 2016; 7: 159.

Progressive fibrosis is driven by ECM deposition



ECM: ExtraCellular Matrix

Progressive Fibrosis

Younossi, ZM. Am J Gastroenterol 2021;116:254–262. https://doi.org/10.14309/ajg.0000000000001054
https://d3i71xaburhd42.cloudfront.net/55b1663767d8f1f73ab07d0ac6fccf28feb8d104/3-Figure1-1.png

Development of the scar matrix in fibrosis: An active process

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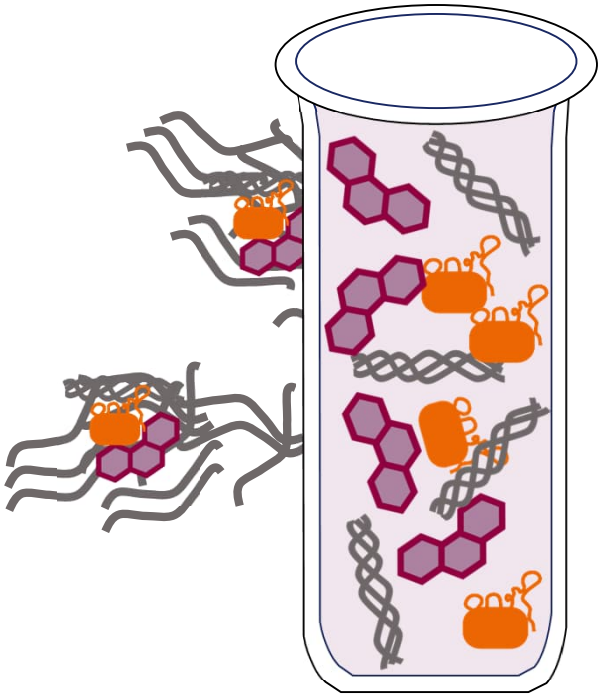
ELF: A marker of "active fibrosis"

ECM: Extra-Cellular Matrix proteins



Blood sample

ECMs

HA

PIINP

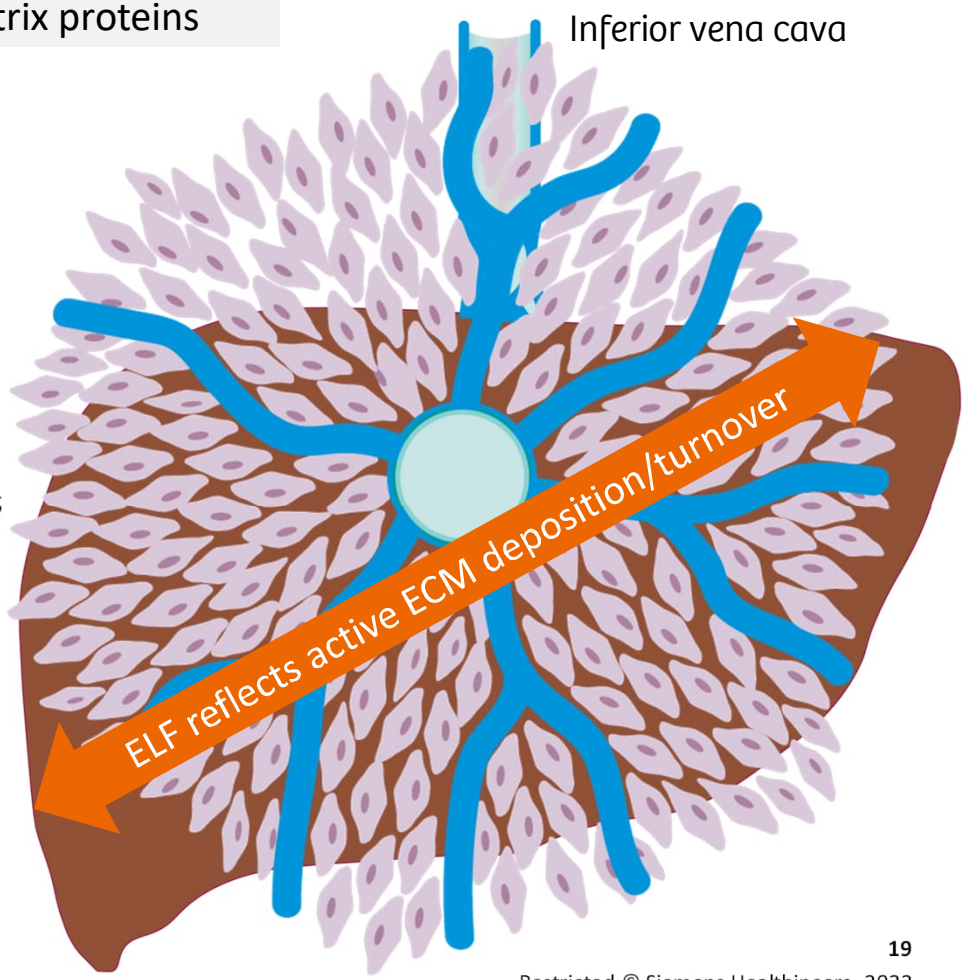
TIMP-1

Collagens

Laminin

Fibronectin

Proteoglycans



Selection of the ELF markers (first publication was in 2004)

GASTROENTEROLOGY 2004;127:1704–1713

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

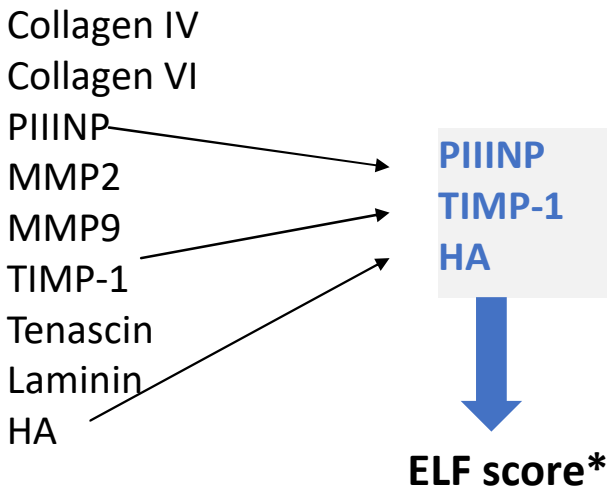
Serum Markers Detect the Presence of Liver Fibrosis: A Cohort Study

WILLIAM M. C. ROSENBERG,* MICHAEL VOELKER,† ROBERT THIEL,§ MICHAEL BECKA,† ALASTAIR BURT,‖ DETLEF SCHUPPAN,¶ STEFAN HUBSCHER,# TANIA ROSKAMS,** MASSIMO PINZANI,†† and MICHAEL J. P. ARTHUR* on behalf of the European Liver Fibrosis Group

*Liver Group, Division of Infection, Inflammation and Repair, University of Southampton, Southampton, England; †Bayer HealthCare AG, Leverkusen, Germany; §Thiel Statistical Consultants, Oxford, Connecticut; ‖School of Clinical and Laboratory Sciences, University of Newcastle Upon Tyne, Newcastle Upon Tyne, England; ¶Department of Medicine, University of Erlangen, Erlangen, Germany; #Department of Pathology, University of Birmingham, Birmingham, England; **Department of Pathology, University of Leuven, Leuven, Belgium; and ††Department of Medicine, University of Florence, Florence, Italy

- Examined multiple (9) biomarkers run as immunoassays as potential markers (singly and in an algorithm) in to assess severity of liver fibrosis
- Compared biomarkers to histology specimens (biopsy) across a range of CLD
- Three markers ultimately selected for inclusion in a defined algorithm

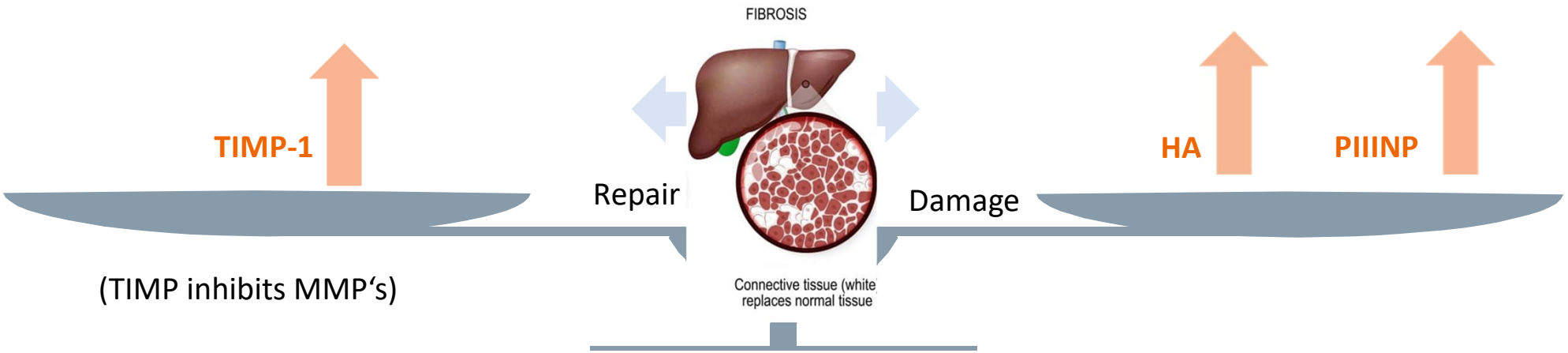
9 Markers Assessed
(singly and in various combinations/algorithms):

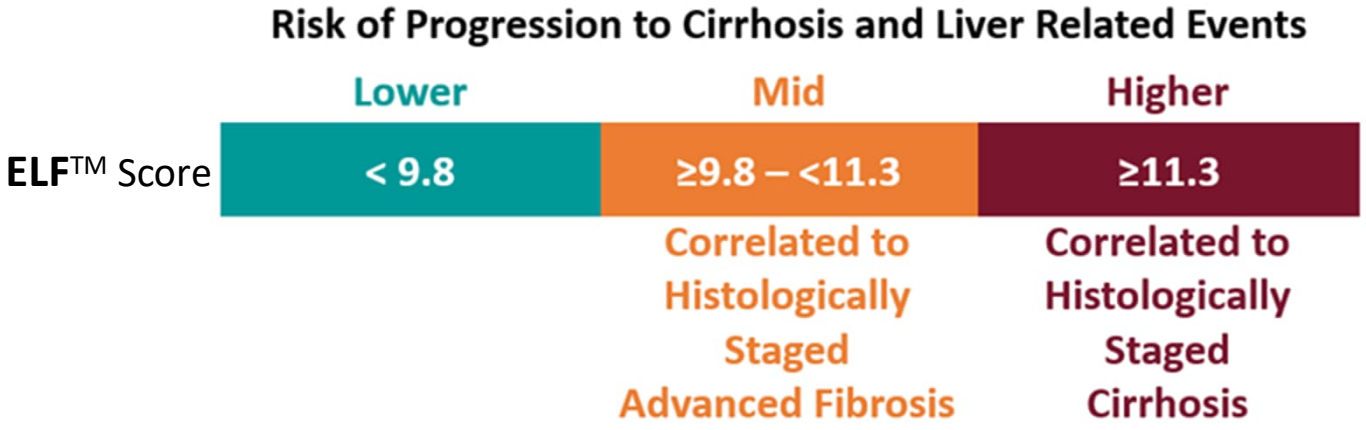


*The ELF score was originally developed on the Bayer IMMUNO-1 platform. When the ELF test was transferred to the new Centaur® platform, the algorithm was adjusted by a factor of 10 to reflect whole, positive, numbers and is the ELF™ score currently in use on both Centaur and Atellica platforms. Older literature on ELF reflects the values found using the IMMUNO-1 Note the relative values do not change.

Rosenberg, W et al; Gastroenterology, 2004; 127:17041713

ELF™: A dynamic evaluation of ECM activity

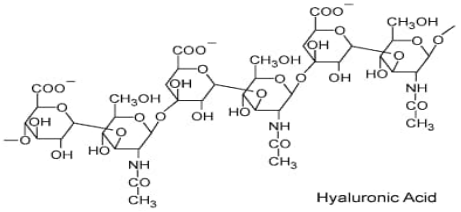




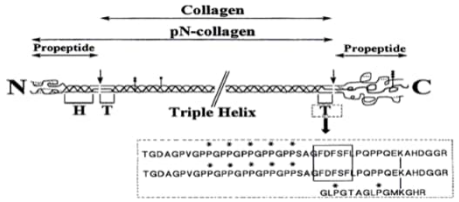
.
Score shown is for the test run on the ADVIA Centaur XP system.

Arpino V, Brock M, Gill SE. The role of TIMPs in regulation of extracellular matrix proteolysis. Matrix Biol 2015;44-46:247-54.
Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704-13.

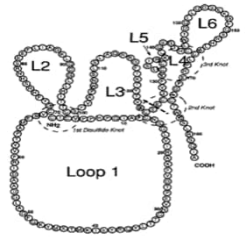
ELF Test: Three biomarkers of fibrogenesis and measurable by immunoassay



Hyaluronic acid (HA)



Procollagen III amino terminal peptide (PIIINP)



Tissue inhibitor of metalloproteinase 1 (TIMP-1)

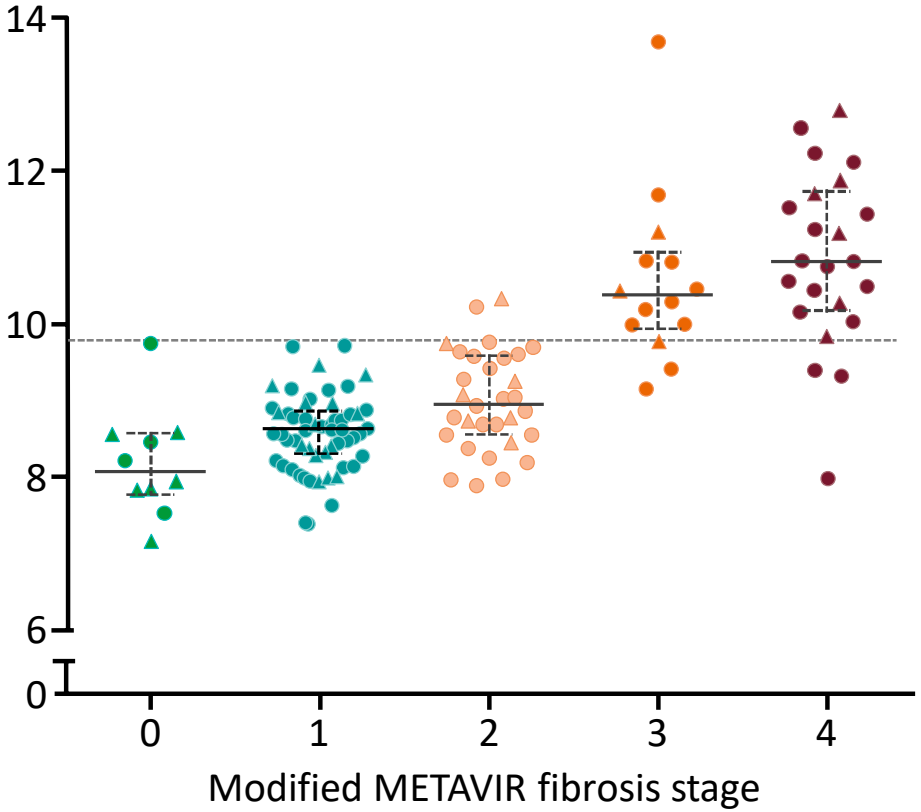
≥9.8

≥11.3

Fully Automated: ELF Score Calculated and Reported < 60 minutes

In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events. In the U.S., the ELF Test is not for use in the diagnosis of NASH or for the staging of fibrosis.

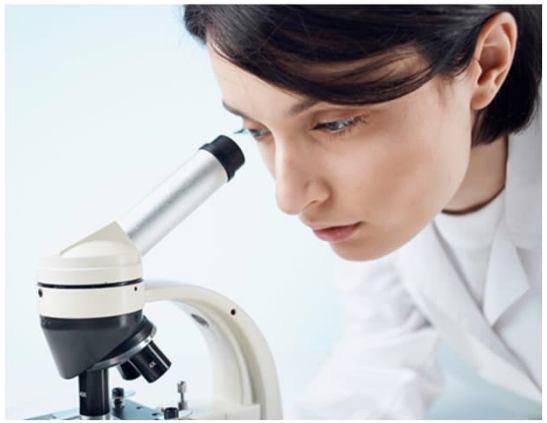
ELF values reflect stage using biopsy scoring systems



● Patients with all other etiologies of liver disease

▲ Patients with fatty liver disease

ELF score ≥9.8



Fagan KJ, et al. Liver Int. 2015;35:1673-81.

In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events. In the U.S., the ELF Test is not for use in the diagnosis of NASH or for the staging of fibrosis.

ELF performs well in a diabetic and older populations

JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Performance of the Enhanced Liver Fibrosis Test to Estimate Advanced Fibrosis Among Patients With Nonalcoholic Fatty Liver Disease

Zobair M. Younossi, MD, MPH; Sean Felix, BS; Thomas Jeffers, BS; Elena Younossi, BS; Fatema Nader, MS; Huong Pham, BS; Arian Afendy, BS; Rebecca Cable, BS; Andrei Racila, BS; Zahra Younoszai, MPH; Brian P. Lam, PA; Pegah Golabi, MD; Linda Henry, PhD; Maria Stepanova, PhD

Abstract

IMPORTANCE The most important surrogate for increased risk of adverse clinical outcomes among patients with nonalcoholic fatty liver disease (NAFLD) is the patient's stage of liver fibrosis. There is a significant barrier to risk-stratifying patients in clinical practice owing to the need for liver biopsy.

OBJECTIVE To determine the performance of the enhanced liver fibrosis (ELF) test as a noninvasive test for assessment of liver fibrosis among patients with NAFLD.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cross-sectional study was conducted among patients recruited from a large, community-based hospital system's outpatient liver clinic from 2001 to 2020. Patients with NAFLD defined as steatosis greater than 5% without evidence of other liver disease or excessive alcohol use were included. Data were analyzed from August 2020 through February 2021.

INTERVENTION Enhanced liver fibrosis score was calculated.

MAIN OUTCOMES AND MEASURES Advanced fibrosis was identified by liver biopsy or transient elastography.

RESULTS Among 829 patients with NAFLD, the mean (SD) age was 53.1 (14.0) years, there were 363 (43.8%) men, 294 patients (35.5%) had type 2 diabetes, and the mean (SD) fibrosis-4 (fib-4) score was 1.34 (0.97). There were 463 patients with liver biopsy, among whom 113 individuals (24.4%) had bridging fibrosis or cirrhosis; among 462 patients with transient elastography data, 79 individuals (17.1%) had liver stiffness results of 9.6 kPa or more (ie, advanced fibrosis). Patients with advanced fibrosis had statistically significantly increased mean (SD) ELF scores compared with patients without advanced fibrosis as determined by biopsy (10.1 [1.3] vs 8.6 [1.0]; $P < .001$) or transient elastography (10.0 [1.1] vs 9.0 [0.8]; $P < .001$). Among all patients with NAFLD, the area under the receiver operating characteristic curve (AUROC) for ELF in identifying patients with advanced fibrosis was 0.81 (95% CI, 0.77-0.85) for patients diagnosed by biopsy and 0.79 (95% CI, 0.75-0.82) for those diagnosed by transient elastography. Performance of the ELF score was similar among patients with NAFLD who were aged 65 years or older (AUROC, 0.74; 95% CI, 0.58-0.87) or had type 2 diabetes (AUROC, 0.78; 95% CI, 0.71-0.84). The combination of an ELF score of 7.2 or greater with a fib-4 score of 0.74 or greater was associated with a negative predictive value of 95.1% (95% CI, 91.8%-98.4%) and a sensitivity of 92.5% (95% CI, 87.4%-97.5%), which can reliably rule out advanced fibrosis. An ELF score of 9.8 or greater with a fib-4 score of 2.9 or greater was associated with a positive predictive value of 95.0% (95% CI, 85.5%-100%) and a specificity of 99.7% (95% CI, 99.1%-100%), which can be used to rule in advanced fibrosis.

Key Points

Question Can noninvasive tests be used to accurately rule in and rule out advanced fibrosis among patients with nonalcoholic fatty liver disease (NAFLD)?

Findings This cross-sectional study of 829 patients with NAFLD found that the noninvasive enhanced liver fibrosis (ELF) test can be used to estimate advanced fibrosis among patients with NAFLD with an area under the receiver operator characteristic curve of 0.81, with a similar performance observed among patients with NAFLD who had diabetes or were age 65 years or older and in an independent validation set. Different combinations of cutoff values to rule in advanced fibrosis were associated with a specificity of 99.7% and positive predictive value of 95.0% or a sensitivity of 92.5% and negative predictive value of 95.0%.

Meaning These findings suggest that the ELF test can be used in gastroenterology, endocrinology, and primary care practices to identify patients with increased risk of nonalcoholic steatohepatitis who would require aggressive treatment.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

- NAFLD patients enrolled in a real-world hepatology practice
- ELF performed well in NAFLD patients including those with diabetes and >65 years

Table 2. Accuracy of Estimating Advanced Fibrosis With ELF Score

	Performance in predicting advanced fibrosis, % (95% CI)[a]			
	Among patients with liver biopsy		Among patients with TE	
Score cutoff value	All patients (n = 463)	Patients with type 2 diabetes (n = 161)	All patients (n = 462)	Patients with type 2 diabetes (n = 177)
Patients with advanced fibrosis, No. (%)	113 (24.4)	73 (45.3)	79 (17.1)	55 (31.1)
AUROC curve (95% CI)	0.81 (0.77-0.85)	0.78 (0.71-0.84)	0.79 (0.75-0.82)	0.80 (0.73-0.86)

Diabetic

Diabetic

Biopsy vs. ELF All patients

Imaging vs. ELF All patients

JAMA Network Open. 2021;4(9):e2123923.doi:10.1001/jamanetworkopen.2021.23923

In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events. In the U.S., the ELF Test is not for use in the diagnosis of NASH or for the staging of fibrosis.

ELF performs well in multiple CLD etiologies (2021 meta-analysis)

Journal of Gastroenterology and Hepatology JGHF

doi:10.1111/jgh.15482

META ANALYSIS AND SYSTEMATIC REVIEW

Systematic review: Accuracy of the enhanced liver fibrosis test for diagnosing advanced liver fibrosis and cirrhosis

Chetanya Sharma,* Sara Cococcia,*,† Nicola Ellis,* Julie Parkes‡ and William Rosenberg*

*Institute for Liver and Digestive Health, University College London, Division of Medicine and Royal Free London NHS Foundation Trust, London, ‡Department of Public Health and Medical Statistics, Faculty of Medicine, University of Southampton, Southampton, UK; †First Department of Internal Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy

Key words
Diagnostic accuracy, enhanced liver fibrosis test, liver biopsy, liver fibrosis.

Accepted for publication 22 February 2021.

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Email: w.rosenberg@ucl.ac.uk

Declaration of conflict of interest: WMR has received sponsorship from Gilead Sciences to attend meetings and has served on advisory boards for Gilead Sciences. WMR is an inventor of the ELF test and has received speaker's fees from Siemens Healthineers.
Author contribution: C. S. performed the research. C. S., S. C., and N. E. collected and analyzed the data. C. S., S. C., and N. E. designed the research study and wrote the paper. W. M. R. and J. P. supervised C. S., S. C., and N. E., reviewed the paper, and made final critical revision for important intellectual contents. All authors have approved the final version of this manuscript.
Financial support: W. M. R. is supported by the UCLH NIHR BRC and is a NIHR senior investigator.
Guarantor of the article: W. M. R. is the guarantor for this article.

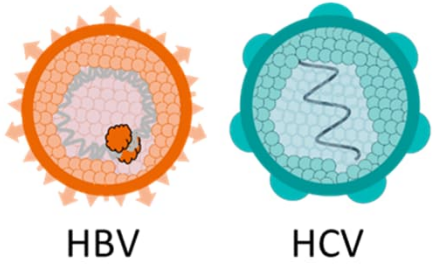
Abstract

Background and Aims: The rising incidence of chronic liver disease (CLD) has increased the need for early recognition. This systematic review assesses the diagnostic accuracy of the enhanced liver fibrosis (ELF) test in cases of advanced fibrosis and cirrhosis due to multiple etiologies in at-risk populations.
Methods: Studies evaluating the ELF accuracy in identifying advanced fibrosis or cirrhosis, defined as METAVIR stage $F \geq 3$ and $F = 4$ or equivalent, in patients with non-alcoholic fatty liver disease (NAFLD), alcohol liver disease (ALD), or viral hepatitis were included. Liver biopsy was used as the reference standard. Medline and Embase databases were searched. The QUADAS-2 tool was used as a framework to assess risk of bias and applicability. The area under the receiver operator curve (AUROC) was extracted as a summary measure of diagnostic accuracy.
Results: Thirty-six studies were included: 11 hepatitis C, 4 hepatitis B, 9 NAFLD, 2 ALD, and 10 mixed. The ELF test showed good diagnostic performance in detecting advanced fibrosis in patients with viral hepatitis (AUROC 0.69 to 0.98) and excellent performance in NAFLD (AUROC 0.78 to 0.97) and ALD (AUROC from 0.92 to 0.94). There is also evidence of good diagnostic performance for detecting cirrhosis in patients with viral hepatitis (AUROC 0.63 to 0.99), good performance in NAFLD (AUROC 0.85 to 0.92), and excellent performance in patients with ALD (AUROC 0.93 to 0.94).
Conclusion: This systematic review supports the use of the ELF test across a range of CLD as a possible alternative to liver biopsy in selected cases.

Background

Target condition. Chronic liver disease (CLD) is a leading cause of death globally, with liver-related deaths increasing in England compared with other major killers.[1] The commonest causes of CLD are alcohol, obesity, and viral hepatitis. CLD can lead to liver fibrosis characterized by increased synthesis and altered deposition of extracellular matrix. Fibrosis is usually silent until cirrhosis leads to complications of portal hypertension including variceal bleeding, ascites, and hepatocellular carcinoma. Many patients with CLD present when it is too late to prevent these complications, and they can only be ameliorated. There is a need for tests to detect the presence of fibrosis before it causes irreversible damage, to stratify which patients might benefit from specialist care, and to target surveillance for complications.[2]

Liver biopsy is the reference test for assessing liver fibrosis, but its accuracy is limited by sampling error and inter-observer and intra-observer variation.[3,4] Additionally, it is invasive and can



AUROC 0.69 to 0.98

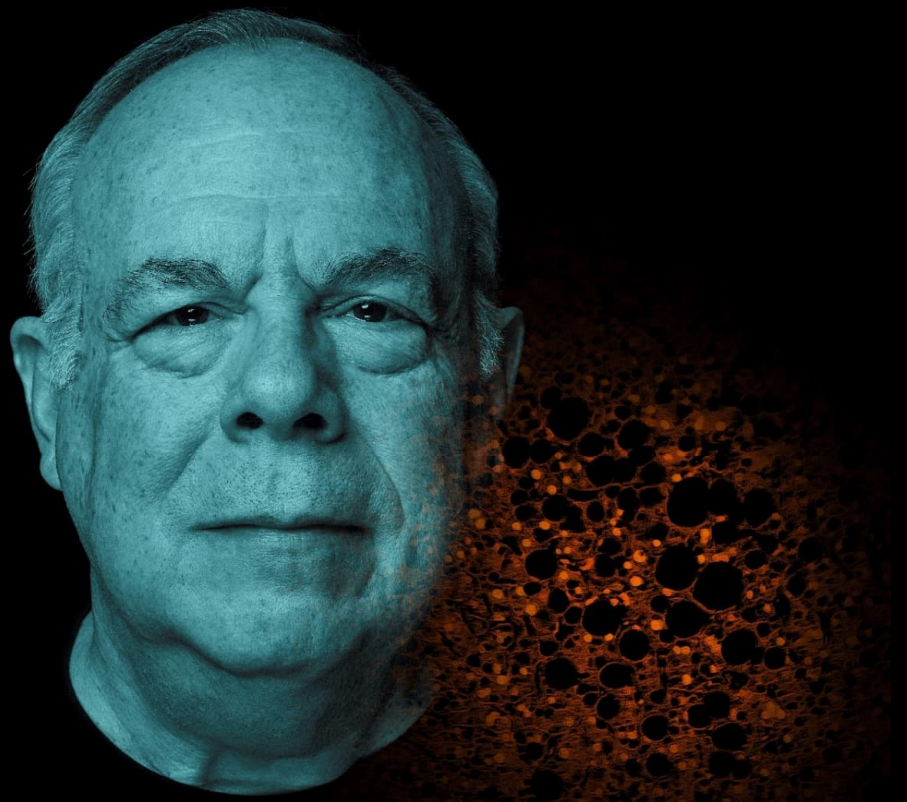
AUROC 0.78 to 0.97

AUROC from 0.92 to 0.94

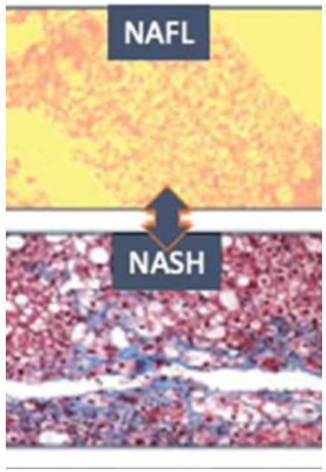
Sharma et al. Journal of Gastroenterology and Hepatology 36 (2021) 1788–1802

In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events. In the U.S., the ELF Test is not for use in the diagnosis of NASH or for the staging of fibrosis.

Fibrosis drives disease progression

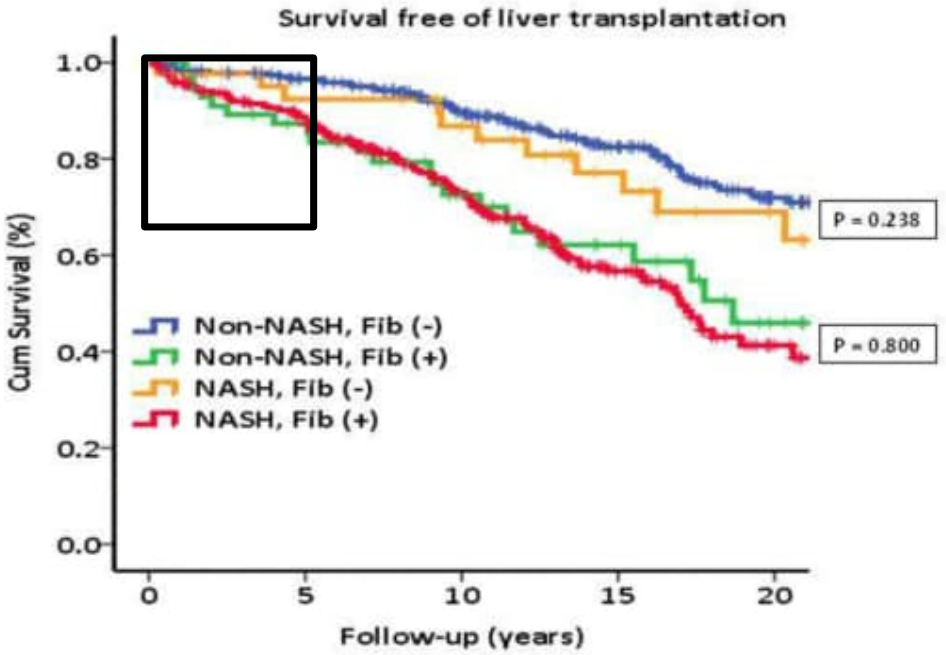


Fibrosis not NASH linked to poor outcomes (biopsy data)



Fibrosis +/- NASH

"In a longitudinal study of patients with NAFLD, **fibrosis stage, but no other histologic features** of steatohepatitis, were independently associated with long-term overall mortality, liver transplantation, and liver-related events."

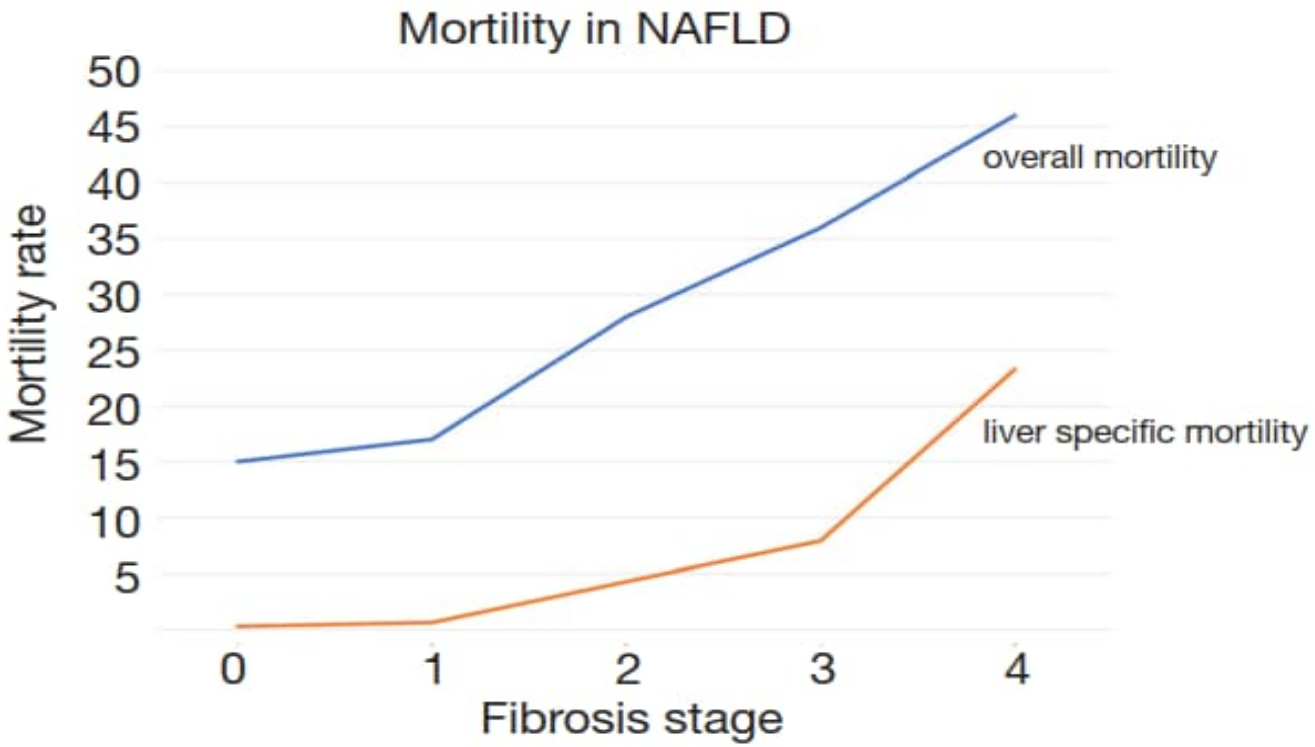


Fibrosis No NASH

Fibrosis with NASH

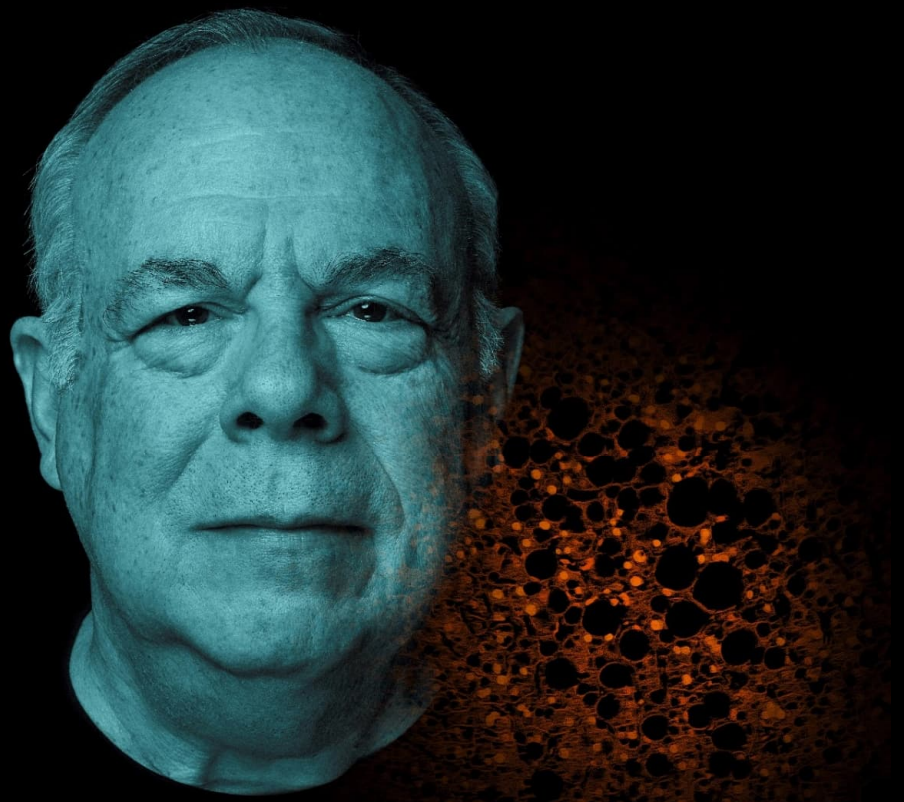
Angulo P et al. Gastroenterology. 2015 August ; 149(2): 389–397.e10. doi:10.1053/j.gastro.2015.04.043.

Liver fibrosis and mortality

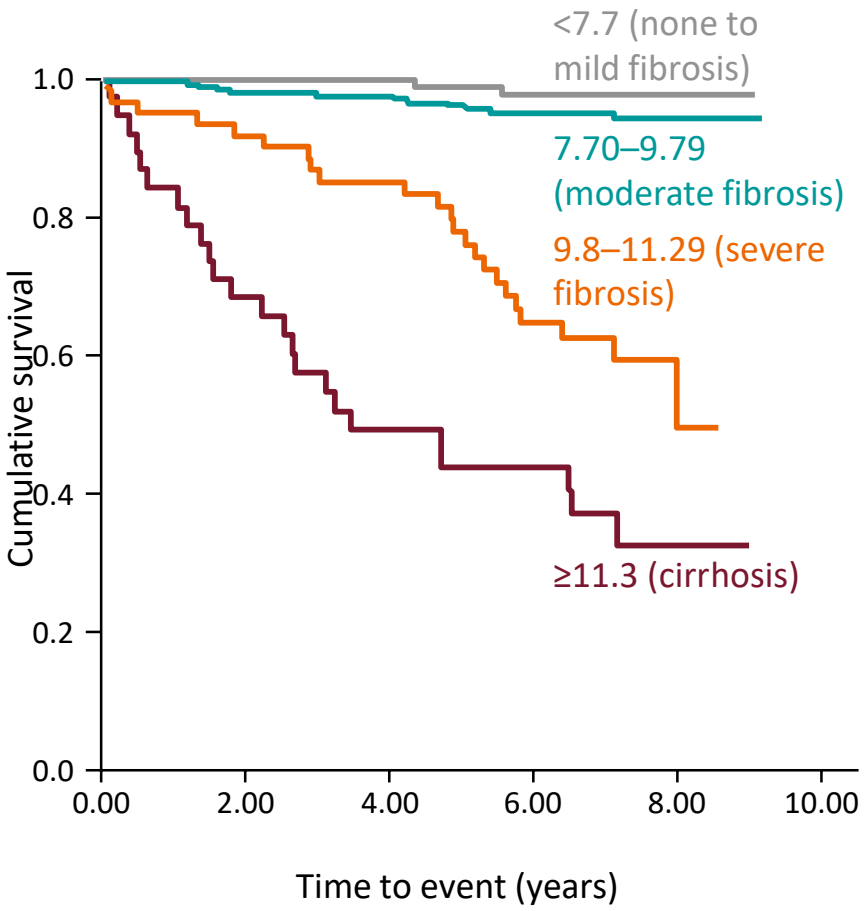


Roeb, E. Ann Transl Med 2021;9(8):726 | http://dx.doi.org/10.21037/atm-20-3760

ELF™ as a prognostic marker of disease progression



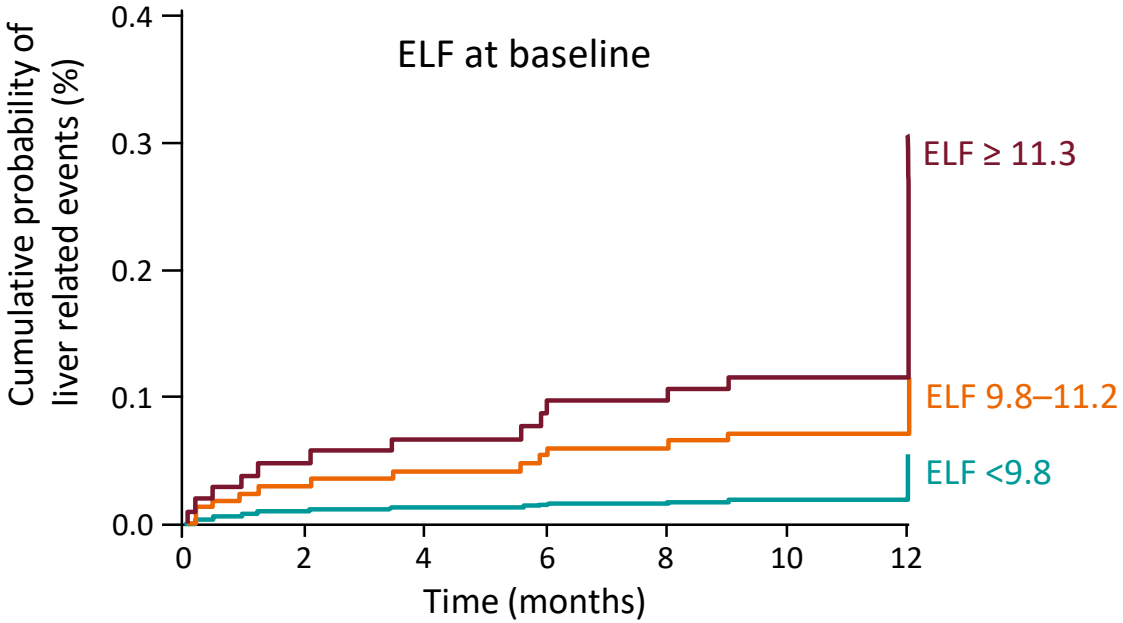
ELF is prognostic: Supporting risk assessment



		Risk %	Cox proportaional hazard ratio adjusted for age and sex
Liver-related outcomes, 5 years	<7.7	1.1	1.0
	7.70–9.79	4.1	3.5
	9.8–11.29	23.6	21.0
	≥11.3	56.8	71.0

Day J, et al. JALM, 2019;3(5):815-26
In the U.S., the cutoffs for prognostic use are 9.8 and 11.3

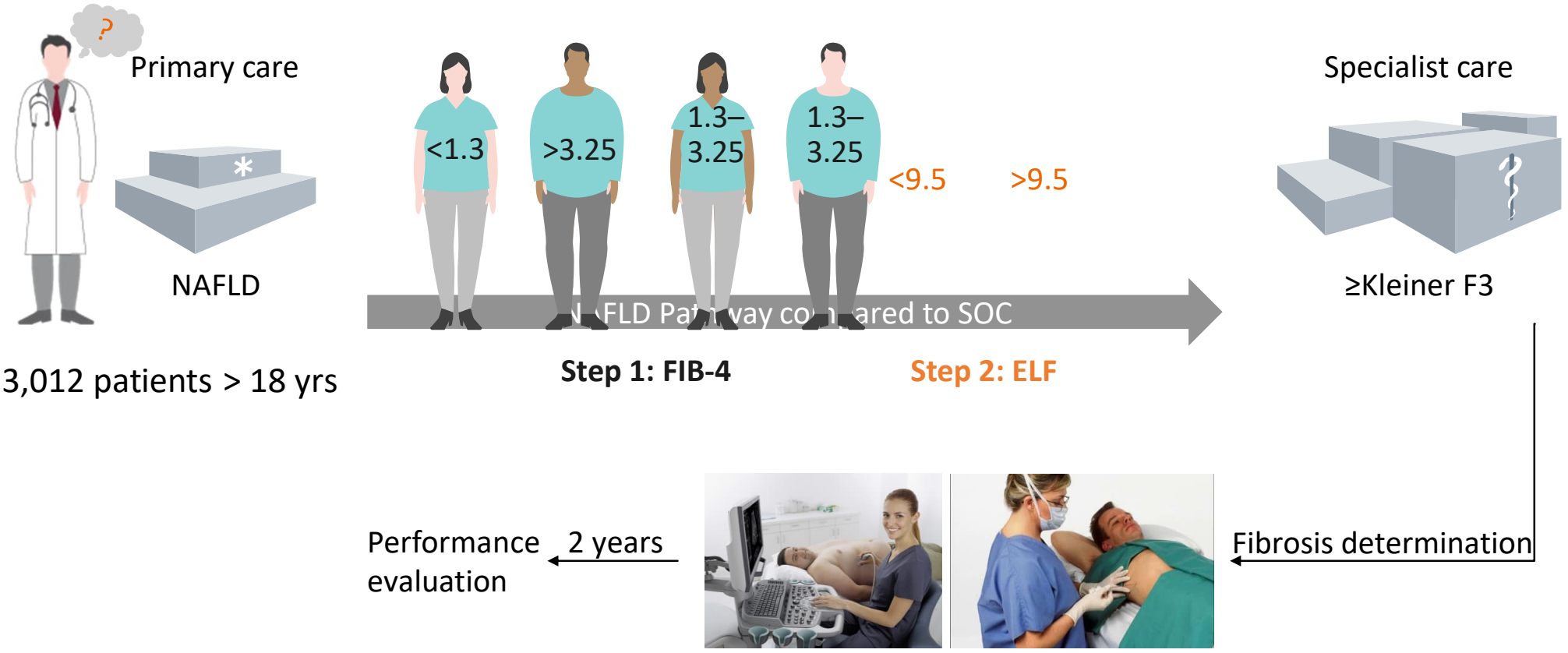
ELF can help determine risk of liver-related events in patients with NASH and compensated cirrhosis



ELF score	Absolute risk	Likelihood ratio	Hazard ratio
≥11.3	32.7	1.88	4.81
9.8–11.2	16.9	0.79	1.46
<9.8	10.5	0.46	1.00

Are VS, et al. Clin Gastro Hepatol. 2021;19:1292-3 e3.

ELF in a primary care setting: Risk-stratification supports appropriate referral to a hepatology specialist

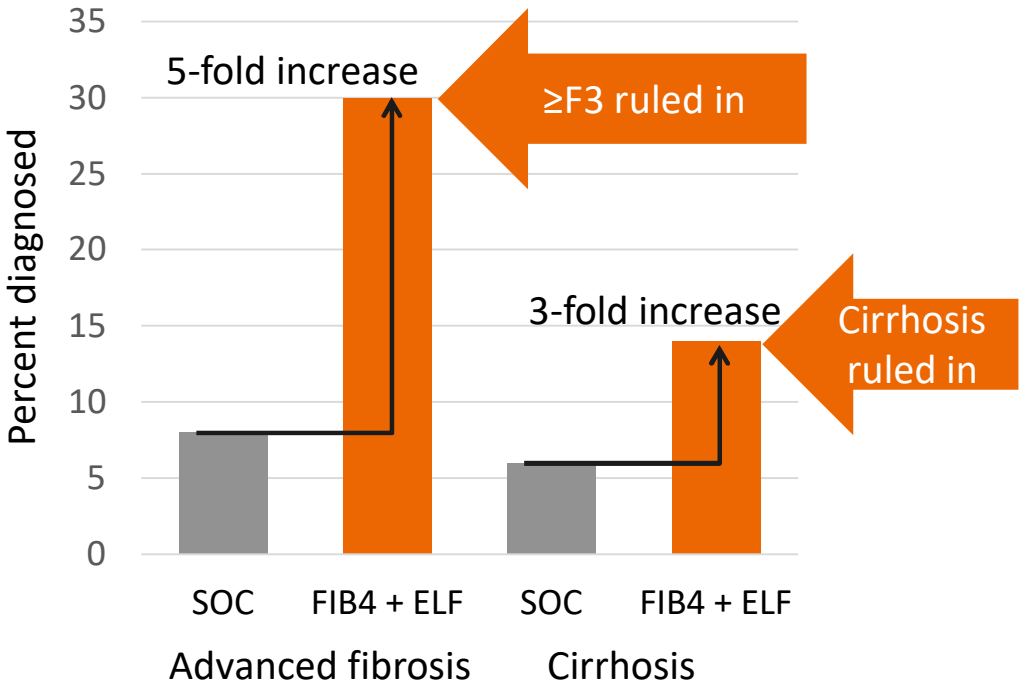


Srivastava A, et al. J Hepatol. 2019;Apr 6:S0168-8278(19)30227-2. doi: 10.1016/j.jhep.2019.03.033

Outcomes summary

FIB4+ELF stratified most patients to low risk

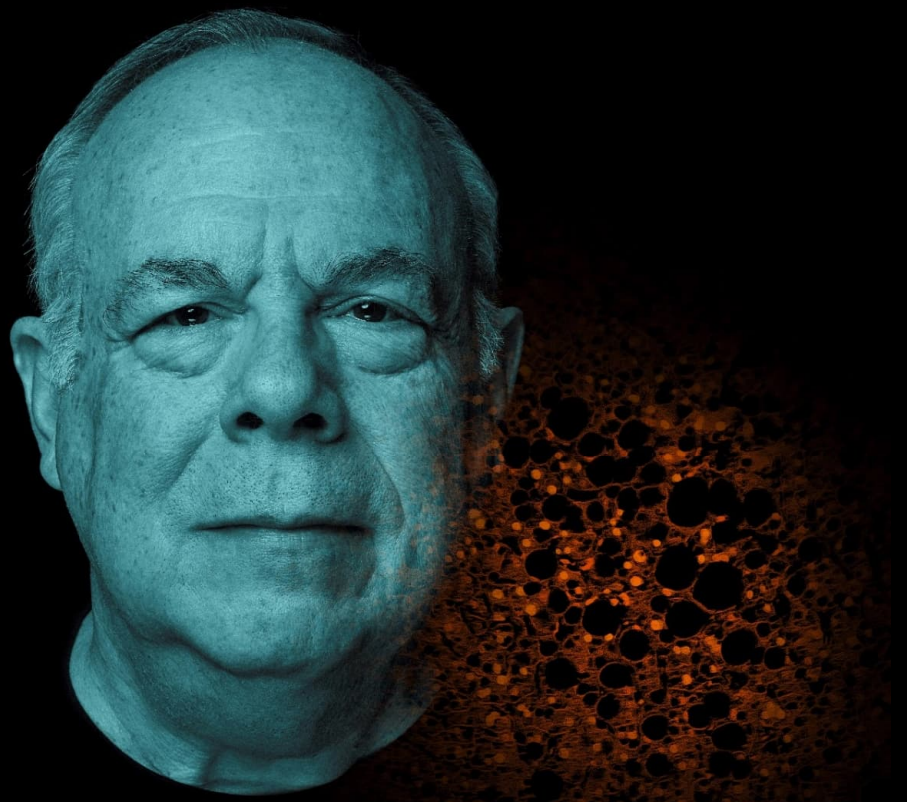
FIB4+ELF identified a higher rates of fibrosis and cirrhosis



81% reduction in unnecessary referrals

Srivastava A, et al. J Hepatol. 2019;Apr 6:S0168-8278(19)30227-2. doi: 10.1016/j.jhep.2019.03.033

NIT’s in Testing Guidance



Non-Invasive Testing (NIT's) as an alternative to liver biopsy (published 2021)

REVIEW ARTICLE

Open

Role of Noninvasive Tests in Clinical Gastroenterology Practices to Identify Patients With Nonalcoholic Steatohepatitis at High Risk of Adverse Outcomes: Expert Panel Recommendations

Zobair M. Younossi, MD, MPH[1], Mazen Noureddin, MD[2], David Bernstein, MD[3], Paul Kwo, MD[4], Mark Russo, MD[5], Mitchell L. Shiffman, MD[6], Ziad Younes, MD[7] and Manal Abdelmalek, MD, MPH[8]

Nonalcoholic fatty liver disease (NAFLD) is generally considered a silent and potentially reversible condition. The subtype of NAFLD that can be classified as nonalcoholic steatohepatitis (NASH) can progress to advanced fibrosis and cirrhosis. Because of the metabolic nature of the pathogenic mechanism underlying NAFLD and NASH, it is often accompanied by common comorbidities such as obesity, insulin resistance, and type 2 diabetes mellitus. The increase in the prevalence of these comorbidities has resulted in a parallel increase in the prevalence of NAFLD and NASH, globally, nationally, and even in children. In recent years, it has been identified that the stage of fibrosis is the most important predictor of liver outcomes; therefore, identifying patients with NAFLD and NASH with more advanced stages of fibrosis can be essential for optimal management. Several noninvasive tools for diagnosing and staging NAFLD and NASH are

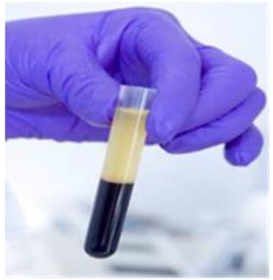
"As an invasive tool for staging the severity of underlying liver disease, liver biopsy has no effective role in population-based screening."

"NITs for liver fibrosis are attractive alternatives for disease risk stratification in NASH"

"**The most important step at this time is for clinicians to use NITs through an algorithm to risk stratify** and identify patients with NASH who are at highest risk of adverse clinical outcomes."

Younossi, ZM. Am J Gastroenterol 2021;116:254–262.
https://doi.org/10.14309/ajg.0000000000001054

Accessible testing is essential



Blood testing offers high volume testing

Imaging has more limited access

Increasingly available

How to interpret?

Front-line testing for fibrosis or a 2-step approach?

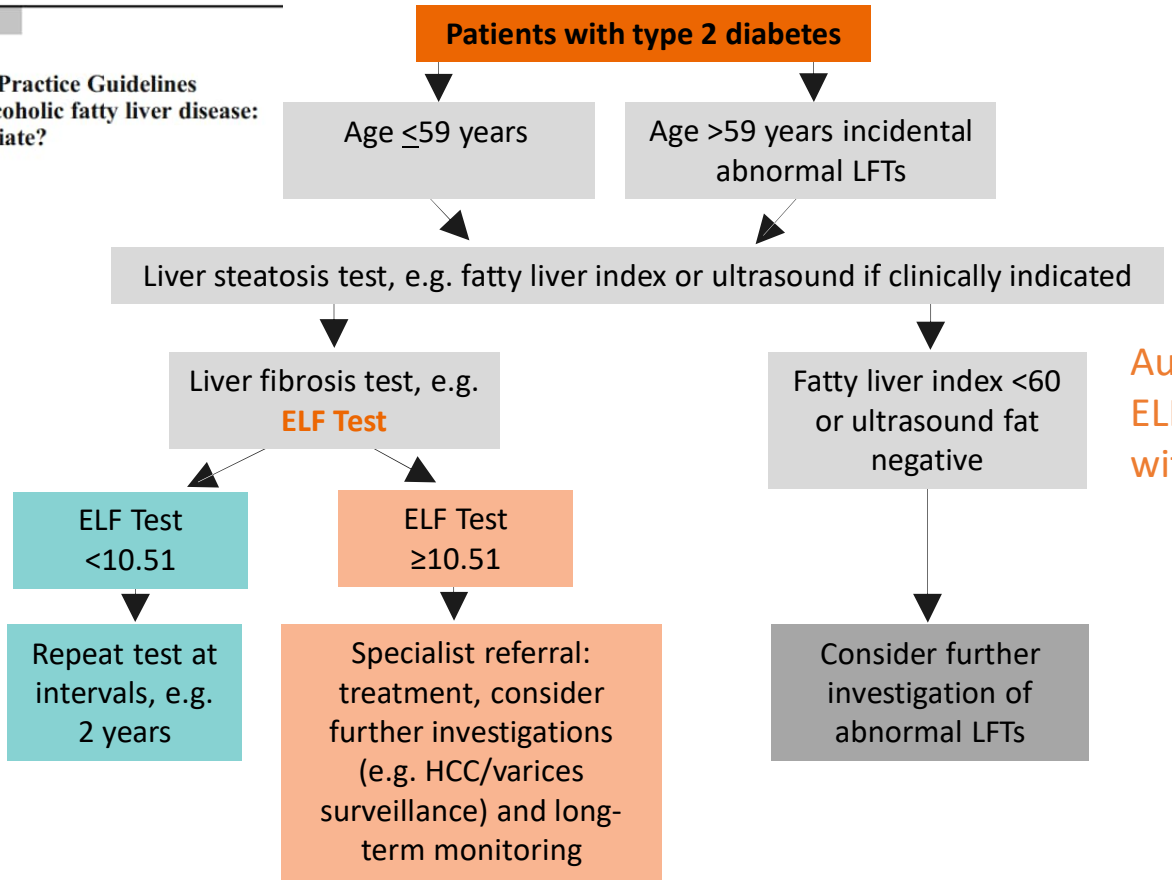
EASL-EASD EASO Clinical Practice Guidelines: Screening for ELF in Type 2 Diabetes mellitus

Diabetologia (2016) 59:1141–1144
DOI 10.1007/s00125-016-3910-y

COMMENTARY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: is universal screening appropriate?

Christopher D. Byrne[1,2] · Giovanni Targher[3]



Authors recommend that clinicians use ELF as a front-line test help identify those with clinically significant liver fibrosis

Byrne CD, et al. Diabetologia 2016;59:1141-4.

NICE algorithm: diagnosis of fibrosis in adults, children, and young people

Non-alcoholic fatty liver disease

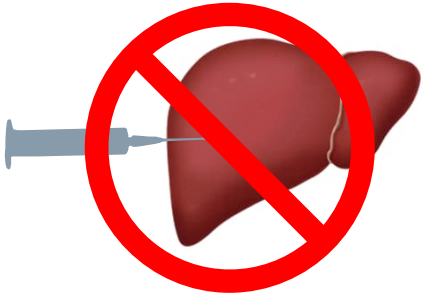
Assessment and management

NICE guideline NG49

Methods, evidence and recommendations

July 2016

Diagnosed with NAFLD (Fatty Liver)



Use ELF Test to test for advanced fibrosis (F ≥ 3)

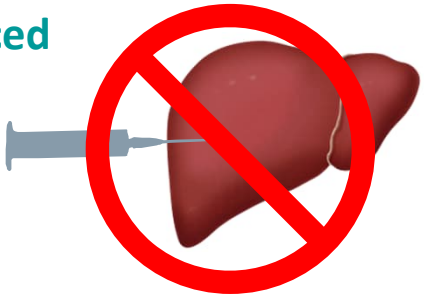
<10.51

Do not diagnose with advanced fibrosis (F≤2)

Retest

Adults: every 3 years

Children and young people: every 2 years



≥10.51

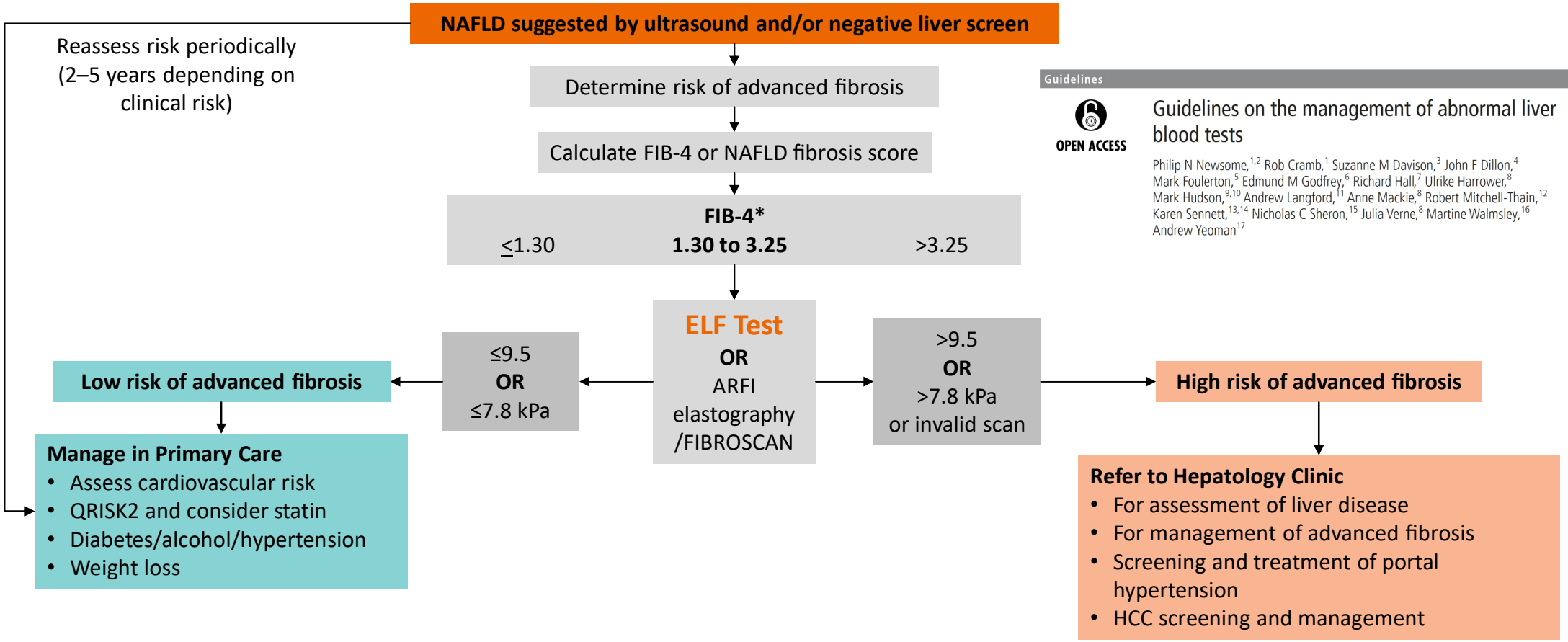
Diagnose with advanced fibrosis (≥F3)

Refer to a relevant specialist in hepatology

NICE guideline NG49. National Institute of Health and Care Excellence; 2016.
Nobili V, et al. Gastroenterology 2009;136(1):160-167.

British Society of Gastroenterology Guidelines: NAFLD Fibrosis Algorithm

SIEMENS Healthineers



Guidelines

OPEN ACCESS

Guidelines on the management of abnormal liver blood tests

Philip N Newsome,[1,2] Rob Cramb,[1] Suzanne M Davison,[3] John F Dillon,[4] Mark Foulerton,[5] Edmund M Godfrey,[6] Richard Hall,[7] Ulrike Harrower,[8] Mark Hudson,[9,10] Andrew Langford,[11] Anne Mackie,[8] Robert Mitchell-Thain,[12] Karen Sennett,[13,14] Nicholas C Sheron,[15] Julia Verne,[8] Martine Walmsley,[16] Andrew Yeoman[17]

*A higher low-end FIB-4 cut-off of <2.0 should be used for patients aged over 65 years.
Newsome PN, et al. Gut 2018;67:6-19.

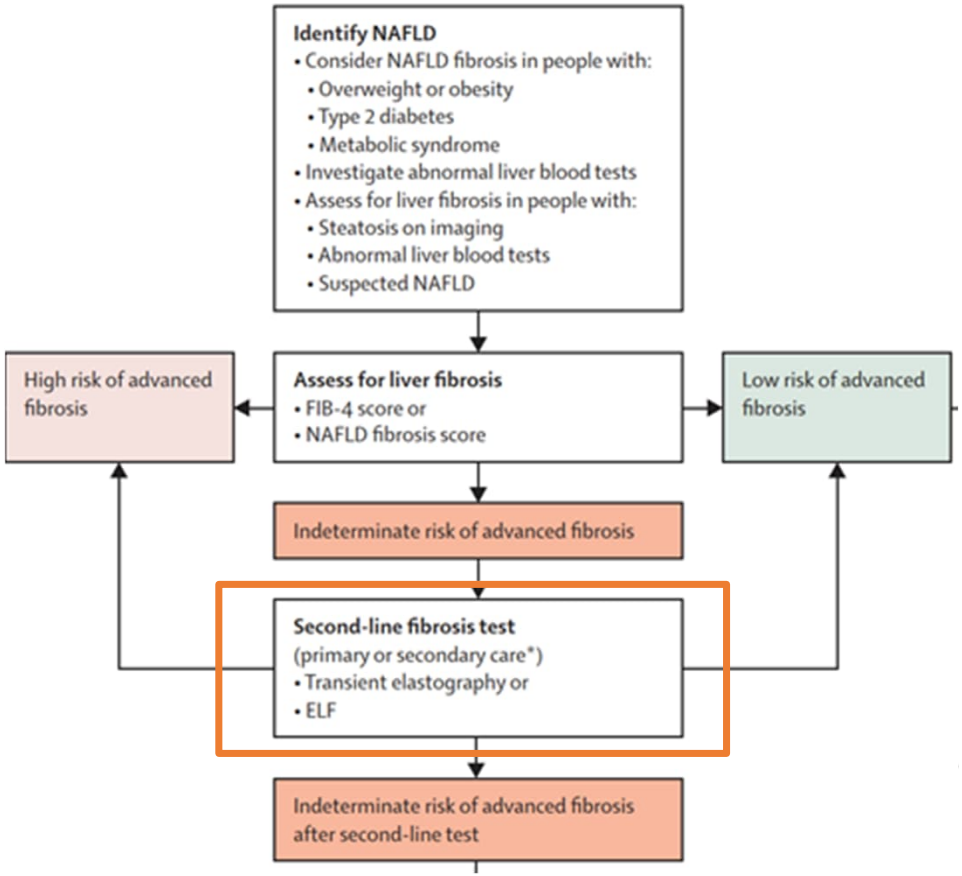
Just Published….

Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group

Stuart McPherson, Matthew J Armstrong, Jeremy F Cobbold, Lynsey Corless, Quentin M Anstee, Richard J Aspinall, Stephen T Barclay, Paul N Brennan, Tessa M Cacciottolo, Robert D Goldin, Kate Hallsworth, Vanessa Hebditch, Kathryn Jack, Helen Jarvis, Jill Johnson, Wenhao Li, Dina Mansour, Mary McCallum, Ashis Mukhopadhya, Richard Parker, Valerie Ross, Ian A Rowe, Ankur Srivastava, Prarthana Thiagarajan, Alexandra I Thompson, Jeremy Tomlinson, Emmanuel A Tsochatzis, Andrew Yeoman, William Alazawi

Non-alcoholic fatty liver disease (NAFLD) is common, affecting approximately 25% of the general population. The evidence base for the investigation and management of NAFLD is large and growing, but there is currently little practical guidance to support development of services and delivery of care. To address this, we produced a series of evidence-based quality standard recommendations for the management of NAFLD, with the aim of improving patient care. A multidisciplinary group of experts from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group produced the recommendations, which cover:

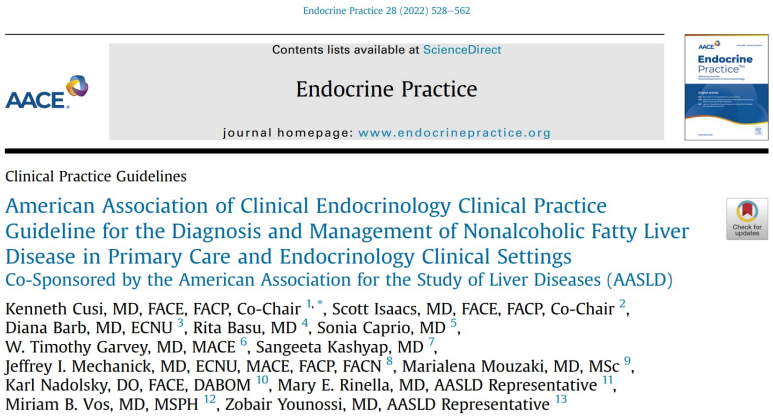
"**Proactive** assessment for the presence of **liver fibrosis** in patients at risk can permit earlier identification of significant liver disease…"



An **ELF value of 9.5** for Specialist referral is suggested but authors note the "optimum care pathway" is still in development

McPherson, S. Lancet Gastroenterol Hepatol 2022 https://doi.org/10.1016/S2468-1253(22)00061-9

Just published: Guidance for the U.S.



Endocrine Practice 28 (2022) 528–562

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Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

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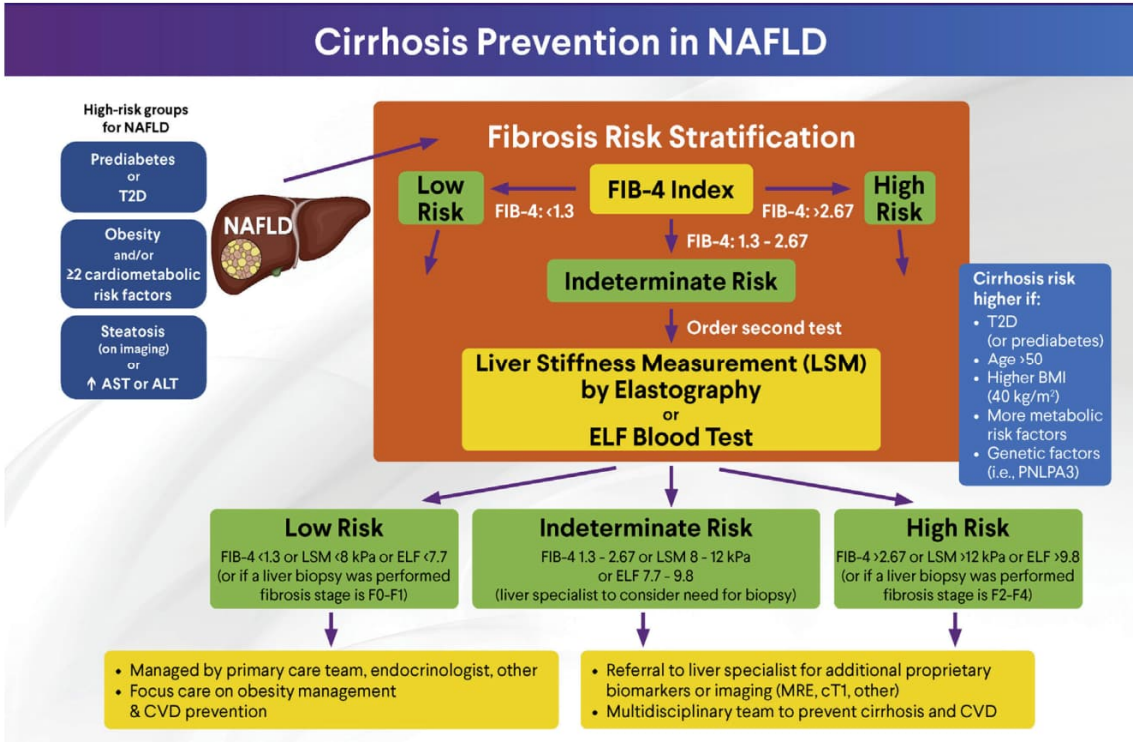
Focus is on testing in Primary Care or Endocrinology for Specialist referral



The preferred noninvasive initial test is the FIB-4

Indeterminate FIB-4 (between 1.3 and 2.67) test with:

ELF™ blood test or imaging for liver stiffness

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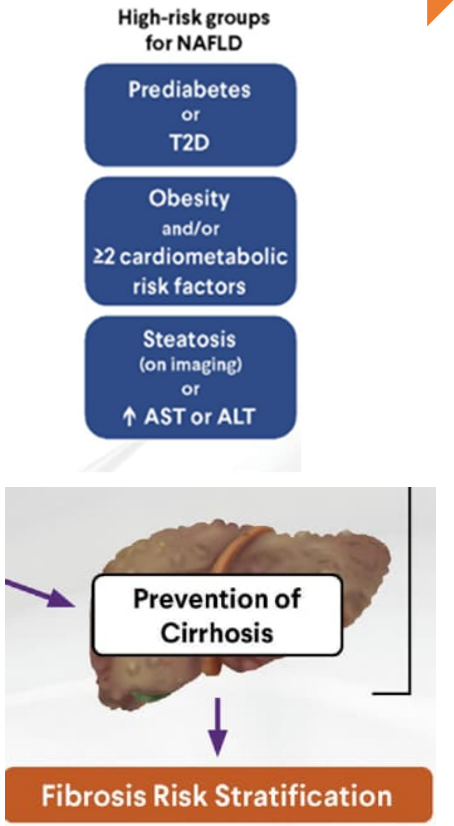
Education of both Labs and Clinicians is essential

Education on fibrosis testing

Lab professionals



Clinical Doctors

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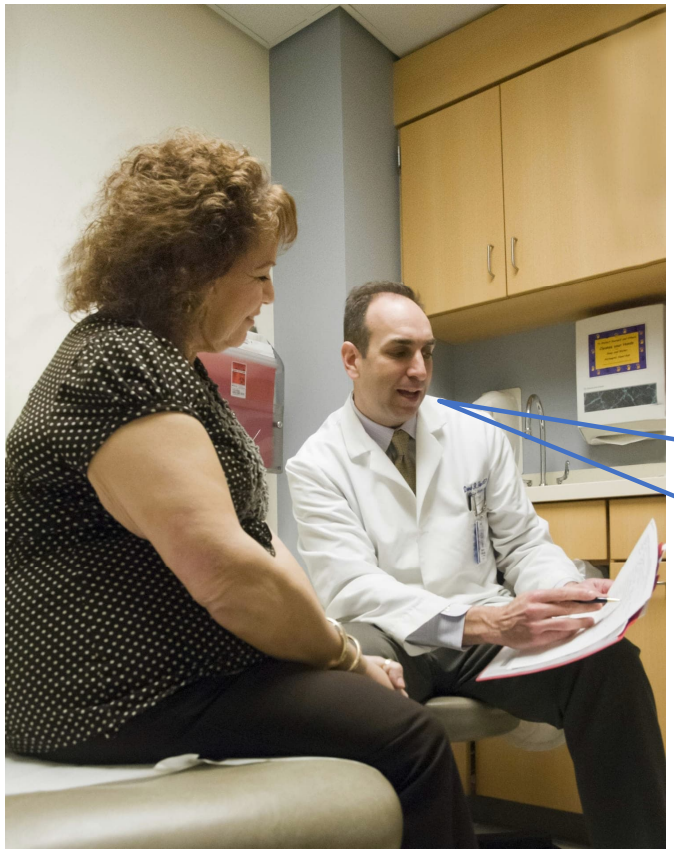
The ELF™ Test: A paradigm shift in at-risk patient management



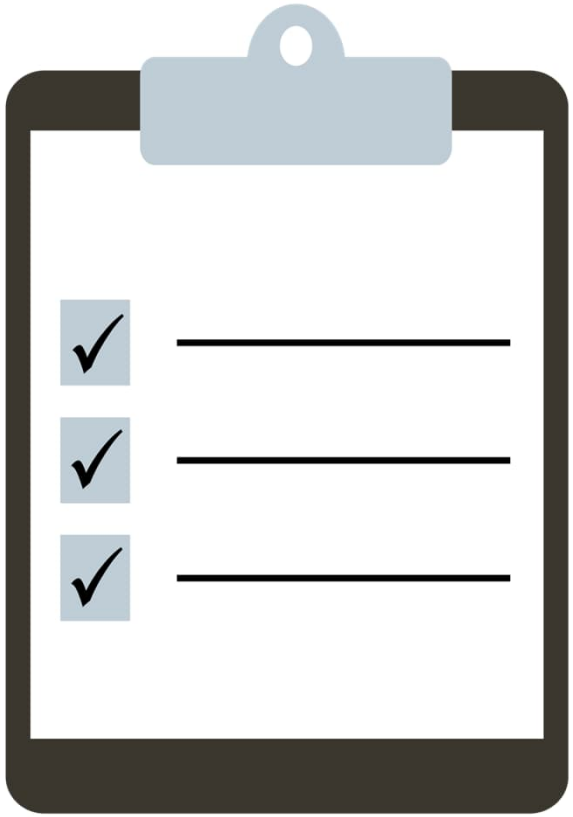
- Biopsy staging indicates only “damage done”
- ELF reflects <u>active</u> fibrosis

I’m concerned about this liver fibrosis test result. We need to address this urgently as few treatment options if you progress.

>9.8 A call to action

≥11.3 Urgency!!

Summary



- NAFLD and other CLD is a silent epidemic with diagnosis occurring too late in many patients
- Using the ELF™ Test to assess prognostic risk in those with advanced fibrosis (F3 or F4) can act as an early alert system for intervention
- ELF™ indicates “active fibrosis” and risk of progression to cirrhosis and liver-related events
- ELF™ is found in multiple Guidelines including NAFLD and Diabetes

Siemens Healthineers welcomes your questions

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