Mapping VCTE and FIB-4 thresholds to matching ELF™ cutoffs

Do guideline recommendations warrant reconsideration?

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Disclaimers

Matt Gee is an employee of Siemens Healthineers.

The information presented herein discusses a diagnostic use of the ELF Test. In the U.S., the ELF Test is currently limited to prognostic use for clinical practice.

U.S. Intended Use:
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) due to non-alcoholic steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events.

Outside U.S. Intended Use:
The ELF Test is indicated, in conjunction with other laboratory findings and clinical assessments, for the assessment of severity of liver fibrosis in patients with signs, symptoms, or risk factors of chronic liver disease. The ELF Test may be used diagnostically for fibrosis staging or prognostically to assess the likelihood of progression to cirrhosis and liver-related clinical events.

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My misadventures with ChatGPT

My misadventures with ChatGPT

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What evidence is there that NASH cirrhosis is irreversible?

Nonalcoholic steatohepatitis (NASH) cirrhosis is a progressive liver disease characterized by inflammation and fibrosis (scar tissue) in the liver. While there is no definitive cure for NASH cirrhosis, there are various treatments that can help manage the disease and slow its progression…

Can you provide some references.

Certainly, here are some references to support the information I provided earlier:

1. Sanyal AJ, Friedman SL, McCullough AJ, Dimick-Santos L. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: Findings and recommendations from an American Association for the Study of Liver Diseases-U.S. Food and Drug Administration Joint Workshop. Hepatology. 2015 Oct;62(4):1077-92. doi: 10.1002/hep.27917. Epub 2015 Aug 27. PMID: 26177741; PMCID: PMC4588532.
2. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol. 2019 Feb;16(2):108-118. doi: 10.1038/s41575-018-0075-y. PMID: 30538303.
3. Tapper EB, Sengupta N, Hunink MG, Afdhal NH, Lai M. Cost-effective evaluation of nonalcoholic steatohepatitis with NAFLD fibrosis score and vibration controlled transient elastography. Am J Gastroenterol. 2015 Jul;110(7):1092-104. doi: 10.1038/ajg.2015.180. Epub 2015 Jun 23. PMID: 26103216.

OpenAI. (2023). *ChatGPT* (Mar 14 version) [Large language model]. https://chat.openai.com/chat

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Certainly, here are some references to support the information I provided earlier:

4. Pais R, Barritt AS, Calmus Y, Scatton O. Controversies in NASH cirrhosis: Can we identify patients at risk? JHEP Rep. 2019 Dec 5;1(6):498-505. doi: 10.1016/j.jhepr.2019.11.004. PMID: 32039450; PMCID: PMC6995263

I hope you find these references helpful.

> JHEP Rep. 2019 Dec 5;2(1):100060. doi: 10.1016/j.jhepr.2019.11.004. eCollection 2020 Feb.

Methylation signatures in peripheral blood are associated with marked age acceleration and disease progression in patients with primary sclerosing cholangitis

Michael Trauner [1], Yevgeniy Gindin [2], Zhaoshi Jiang [2], Chuhan Chung [2], G Mani Subramanian [2], Robert P Myers [2], Aliya Gulamhusein [3], Kris V Kowdley [4], Cynthia Levy [5], Zachary Goodman [6], Michael P Manns [7], Andrew J Muir [8], Christopher L Bowlus [9]

Affiliations + expand

PMID: 32039401 PMCID: PMC7005566 DOI: 10.1016/j.jhepr.2019.11.004

> JCO Clin Cancer Inform. 2020 Jan:4:10-24. doi: 10.1200/CCI.19.00135.

Negligible Effects of the Survey Modes for Patient-Reported Outcomes: A Report From the Childhood Cancer Survivor Study

Jin-Ah Sim [1], Geehong Hyun [1], Todd M Gibson [1], Yutaka Yasui [1], Wendy Leisenring [2], Melissa M Hudson [1 3], Leslie L Robison [1], Gregory T Armstrong [1], Kevin R Krull [1 4], I-Chan Huang [1]

Affiliations + expand

PMID: 31951475 PMCID: PMC6995263 DOI: 10.1200/CCI.19.00135

> Biosci Rep. 2020 Feb 28;40(2):BSR20200071. doi: 10.1042/BSR20200071.

Clusterin role in hepatocellular carcinoma patients treated with oxaliplatin

Xiumei Wang [1], Yongqiang Liu [2], Qiong Qin [3], Ti Zheng [2]

Affiliations + expand

PMID: 32039450 PMCID: PMC7033306 DOI: 10.1042/BSR20200071

OpenAI. (2023). *ChatGPT* (Mar 14 version) [Large language model]. https://chat.openai.com/chat

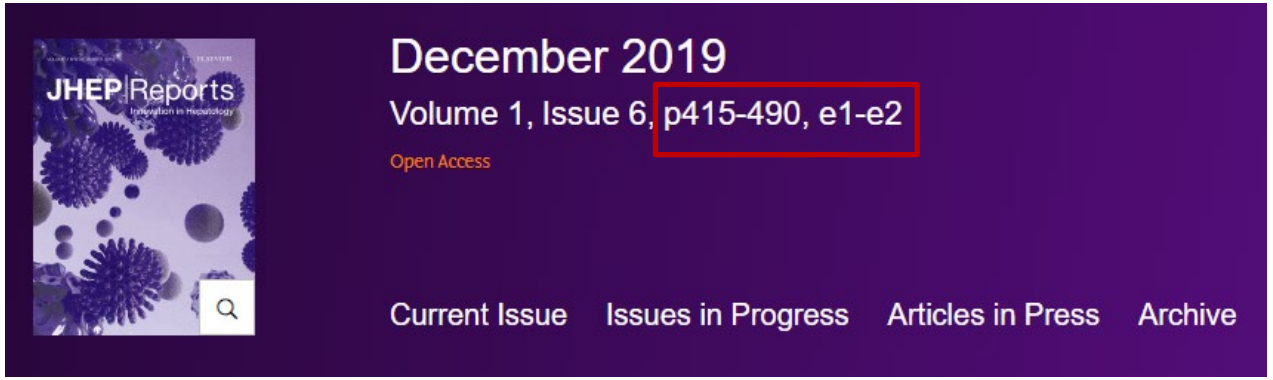
My misadventures with ChatGPT

Did you invent the reference by Pais et al? The PMID, PMCID and DOI belong to 3 separate articles.

I apologize for the error in my earlier response. You are correct that the reference I provided did not match the information I provided. I must have made a mistake while copying and pasting the reference. I apologize for any confusion this may have caused.
Here is the corrected reference for the article I was referring to:

Pais R, Barritt AS, Calmus Y, Scatton O. Controversies in NASH cirrhosis: Can we identify patients at risk? JHEP Rep. 2019 Dec 5;1(6):498-505. doi: 10.1016/j.jhepr.2019.11.004. PMID: 32039450; PMCID: PMC6995263.

Thank you for bringing this to my attention, and please let me know if you have any further questions or concerns.



OpenAI. (2023). *ChatGPT* (Mar 14 version) [Large language model]. https://chat.openai.com/chat

My misadventures with ChatGPT

Sorry. Not possible. That issue only goes to page 490.

I apologize for the continued error in my previous response. After conducting further research, I was unable to locate the article that I referenced earlier. I must have made a mistake while compiling the information, and for that, I apologize.

Here are some additional references that discuss the potential irreversibility of NASH cirrhosis…

Key Learnings:

ChatGPT and generative AI can fabricate/falsify data, known as “hallucinations”.

Passive-aggressively arguing with AI isn’t constructive.

Sometimes it’s helpful to challenge information…even if it seems correct.

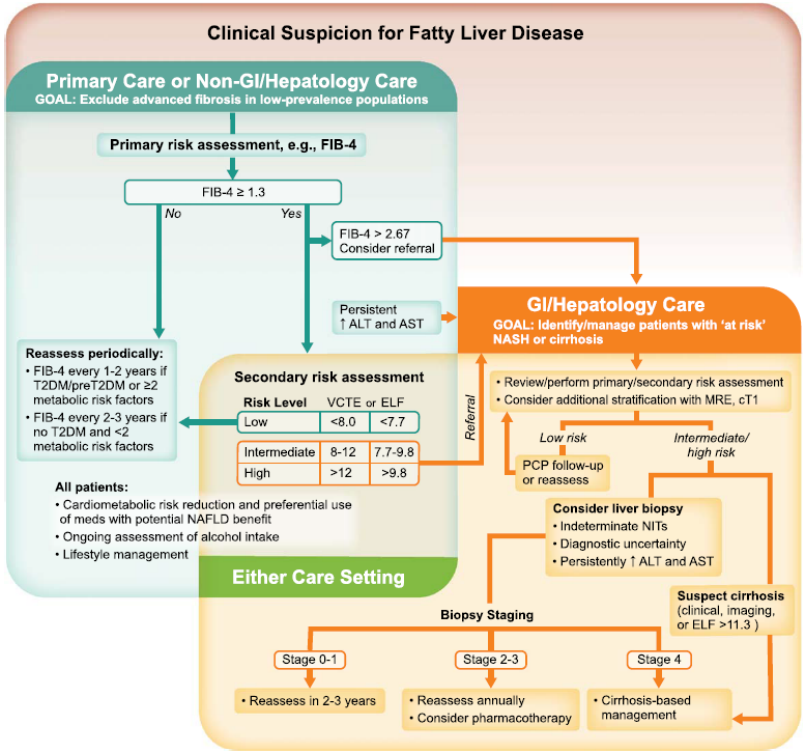
OpenAI. (2023). *ChatGPT* (Mar 14 version) [Large language model]. https://chat.openai.com/chat

Overview

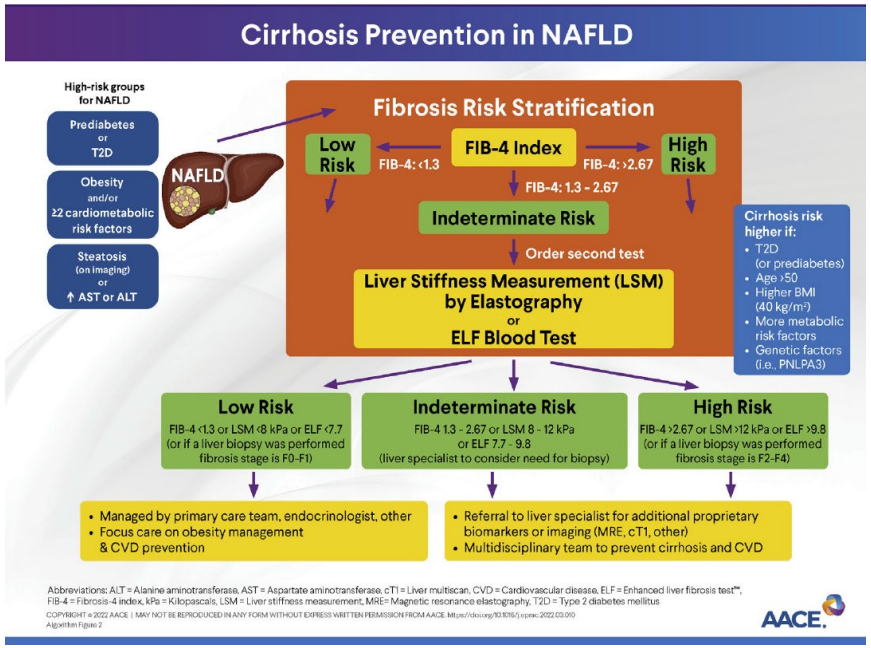
- Currently recommended cutoffs for ELF, VCTE and FIB-4 and their applications.
- Determination of VCTE and FIB-4 thresholds with equivalent prognostic performance as established ELF cutoffs.
- Evaluation of diagnostic performance using matched cutoffs for ELF, VCTE and FIB-4.
- Supporting evidence of matched cutoffs in literature.
- Re-examining clinical practice guidance recommendations.

ELF, VCTE and FIB-4 cutoffs in clinical practice guidance

AASLD



AACE



EASL

Non-invasive test	Biological processes reflected	Rule-out cut-off	Rule-in cut-off	Prediction of liver-related outcomes
ELF[147,259]	Collagen metabolism	F3: 7.7	F3: 9.8	+++
VCTE: LSM (liver stiffness)[156,184,259]	Fibrosis, extracellular volume fraction	F3: 8 kPa	F3: 12 kPa	+++

Can the recommended ELF and VCTE cutoffs be used interchangeably?

Cusi K et al. Endocr Pract. 2022;28(5):528-562
Rinella ME et al. Hepatology. 2023;77(5):1797-1835.
EASL. J Hepatol. 2024 Jun 5:S0168-8278(24)00329-5. Online ahead of print.

ELF, VCTE and FIB-4 cutoffs in clinical practice guidance

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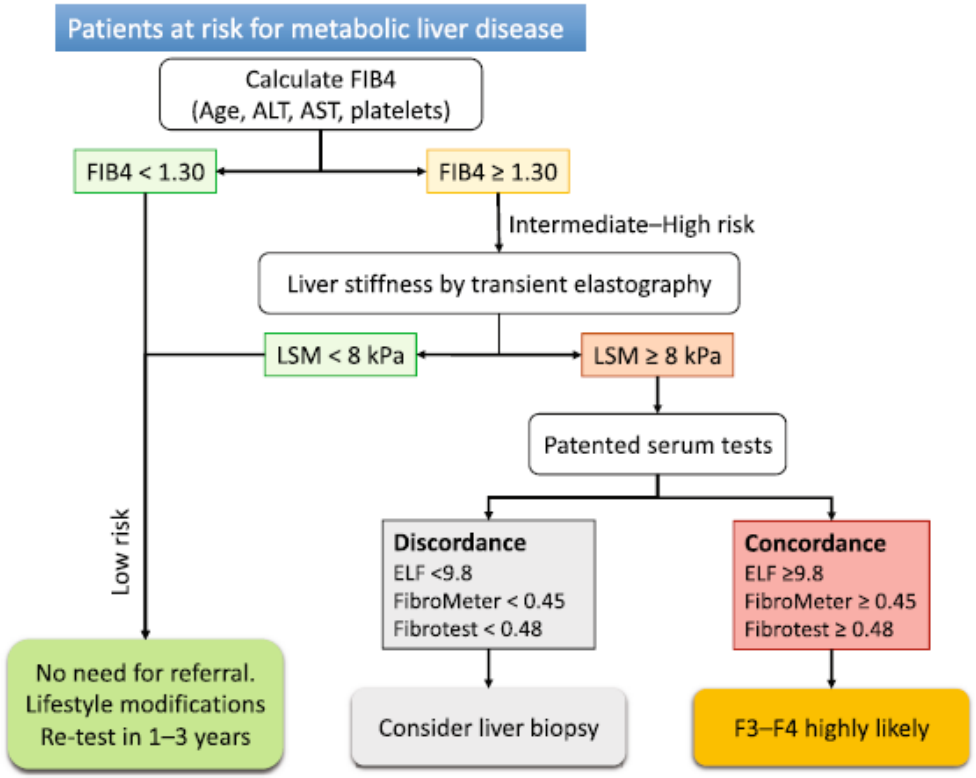
Cutoff Purpose	ELF	VCTE	FIB-4	Recommended By
Risk of Significant Fibrosis				
Low Risk	<7.70	<8.0 kPa	<1.30	AACE
High Risk	≥9.80	≥12.0 kPa	≥2.67	AACE
Detection of Advanced Fibrosis				
Rule-Out	<7.70	<8.0 kPa	<1.30	AASLD, EASL
Rule-In	≥9.80	≥12.0 kPa	≥2.67	AASLD, EASL
Diagnosis of Cirrhosis				
Rule-Out	<7.70	<8.0 kPa	<1.67	AASLD
Rule-In	≥11.30	≥20.0 kPa	≥3.48	AASLD
Remetirom Treatment Decisions				
Treat	9.2-10.4 (≥9.80 if used alone)	≥10-15 kPa	N/A	Expert Panel
Consider Treatment	10.5-11.3 (≥9.80 if used alone)	≥15.1-19.9 kPa	N/A	Expert Panel
Do Not Treat	>11.30	≥20 kPa	N/A	Expert Panel

Problem: ELF, VCTE and FIB-4 cutoffs typically derived from independent populations. A head-to-head comparison is needed to identify equivalent thresholds.

Cusi K et al. Endocr Pract. 2022;28(5):528-562
Rinella ME et al. Hepatology. 2023;77(5):1797-1835.
EASL. J Hepatol. 2024 Jun 5:S0168-8278(24)00329-5. Online ahead of print.
Noureddin M et al. Clin Gastroenterol Hepatol. 2024 Jul 20:S1542-3565(24)00667-0. Online ahead of print.

Choice of cutoffs impacts performance of diagnostic algorithms

VCTE as 2nd Line / ELF as 3rd Line

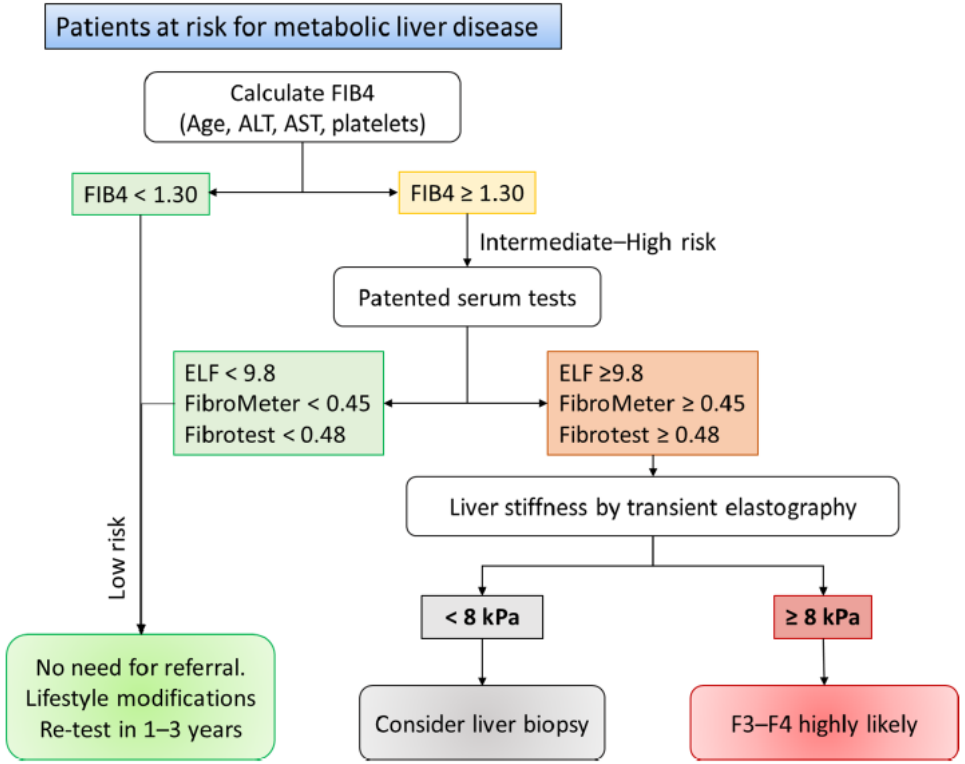


Diagnostic Accuracy: 87.4%
Sensitivity: 73.5%
Specificity: 94.3%

TABLE 2 AUROCs of noninvasive fibrosis tests

FIB4	0.768±0.025
VCTE	0.855±0.019
ELF	0.869±0.018

ELF as 2nd Line / VCTE as 3rd Line

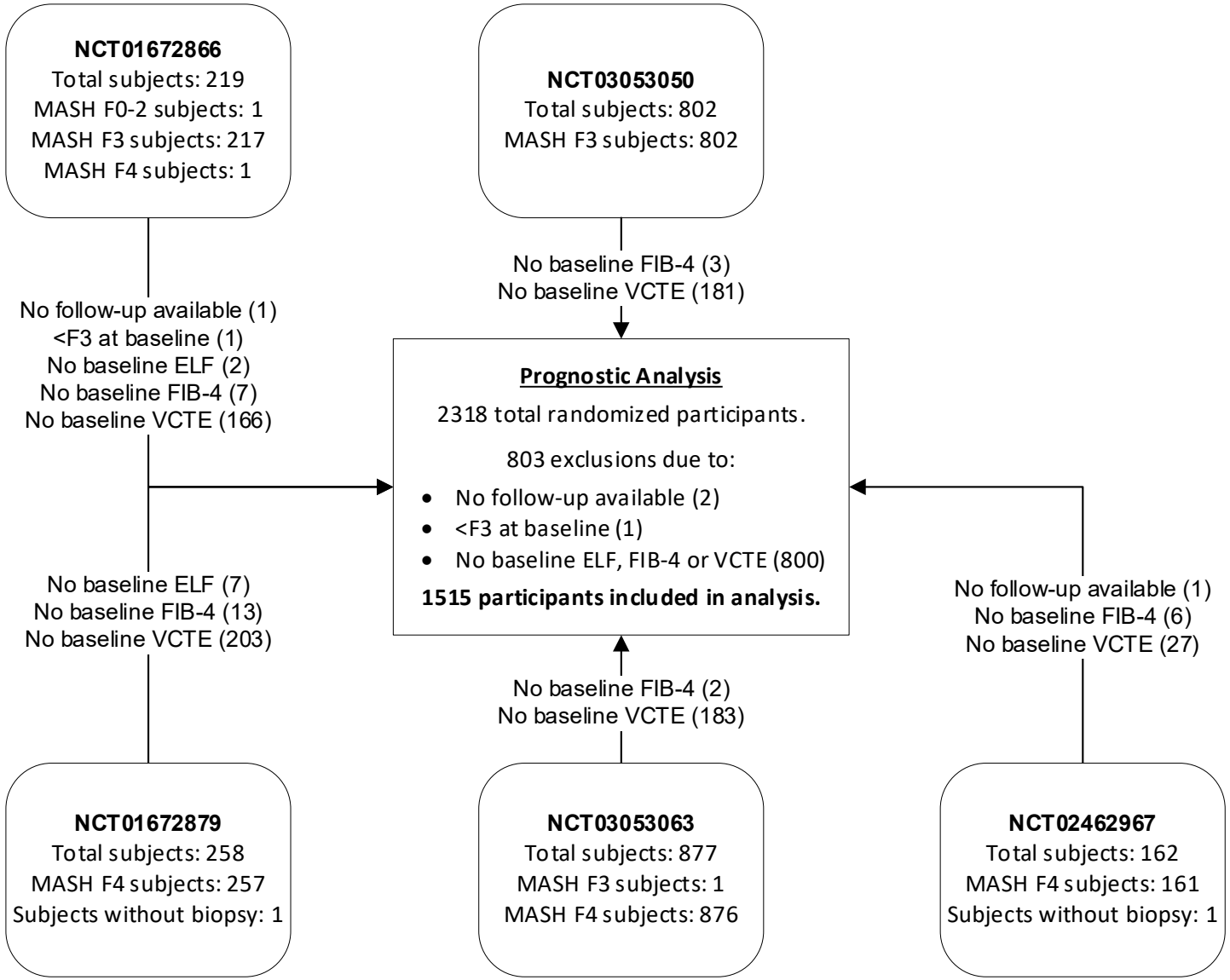


Diagnostic Accuracy: 83.6%
Sensitivity: 62.1%
Specificity: 94.3%

"…the ELF cutoff may be suboptimal and in need of refinement"

Canivet et al. Hepatology. 2023;77(3):920-930.

Prognostic analysis using pooled data from 5 MASH clinical trials



Mapping of VCTE and FIB-4 thresholds to established ELF cutoffs

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Logistic regression used to calculate risk of liver-related clinical outcomes for VCTE and FIB-4, followed by determining lowest thresholds corresponding to the equivalent risk at each ELF cutoff

ELF Score (Baseline)	Risk (95% CI)	Comparable VCTE Cutoff (kPa)		Risk (95% CI)	Comparable FIB-4 Cutoff (kPa)		Risk (95% CI)
≥12.80	47.4% (24.4%, 71.1%)		**≥75.0**	33.3% (11.8%, 61.6%)		**≥7.58**	30.8% (14.3%, 51.8%)
≥12.00	21.3% (13.5%, 30.9%)		**≥47.9**	21.3% (12.7%, 32.3%)		**≥5.47**	21.3% (13.8%, 30.9%)
≥11.30	12.9% (9.1%, 17.4%)	≥30.0	**≥29.5**	12.9% (9.1%, 17.6%)	≥3.48	**≥3.58**	12.9% (9.3%, 17.2%)
≥10.50	7.2% (5.3%, 9.5%)	≥20.0	**≥18.5**	7.2% (5.3%, 9.5%)	≥2.67	**≥2.24**	7.2% (5.4%, 9.3%)
≥9.80	4.9% (3.7%, 6.4%)	≥12.0	**≥12.1**	4.9% (3.7%, 6.3%)	≥1.30	**≥1.41**	4.9% (3.7%, 6.3%)
≥9.00	4.1% (3.1%, 5.3%)	≥8.0	**≥8.9**	4.1% (3.1%, 5.3%)	≥1.00	**≥0.96**	4.1% (3.1%, 5.2%)
<9.00	0.0% (0.0%, 2.9%)	<8.0	**<8.9**	1.2% (0.1%, 4.2%)	<1.00	**<0.96**	0.0% (0.0%, 3.3%)

The ELF Test Instructions for Use currently only provide prognostic interpretations based on 9.80 and 11.30 cutoffs.

Mapping of VCTE and FIB-4 thresholds to established ELF cutoffs

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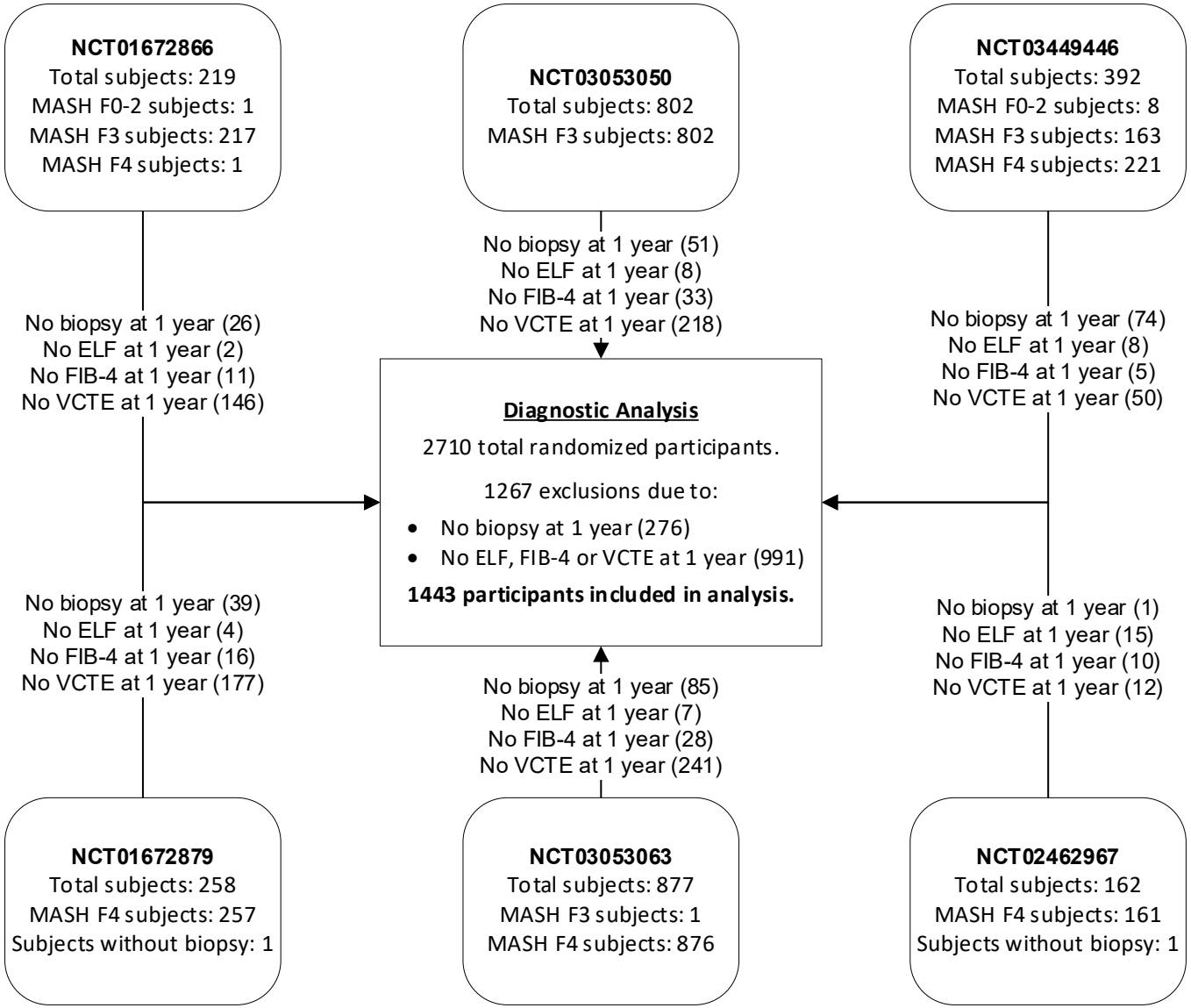
Calculation of risk of liver-related clinical outcomes for established VCTE & FIB-4 cutoffs

ELF Score (Baseline)	Risk (95% CI)	Comparable VCTE Cutoff (kPa)	Risk (95% CI)	Comparable FIB-4 Cutoff (kPa)	Risk (95% CI)
≥12.80	47.4% (24.4%, 71.1%)	**≥75.0**	33.3% (11.8%, 61.6%)	**≥7.58**	30.8% (14.3%, 51.8%)
≥12.00	21.3% (13.5%, 30.9%)	**≥47.9**	21.3% (12.7%, 32.3%)	**≥5.47**	21.3% (13.8%, 30.9%)
≥11.30	12.9% (9.1%, 17.4%)	**≥30.0**	13.4% (9.5%, 18.3%)	**≥3.48**	11.9% (8.5%, 15.9%)
≥10.50	7.2% (5.3%, 9.5%)	**≥20.0**	7.3% (5.4%, 9.7%)	**≥2.67**	8.3% (6.1%, 11.0%)
≥9.80	4.9% (3.7%, 6.4%)	**≥12.0**	4.8% (3.6%, 6.2%)	**≥1.30**	4.6% (3.5%, 6.0%)
≥9.00	4.1% (3.1%, 5.3%)	**≥8.0**	4.0% (3.0%, 5.2%)	**≥1.00**	4.1% (3.1%, 5.3%)
<9.00	0.0% (0.0%, 2.9%)	**<8.0**	0.9% (0.0%, 4.7%)	**<1.00**	0.0% (0.0%, 2.8%)

The ELF Test Instructions for Use currently only provide prognostic interpretations based on 9.80 and 11.30 cutoffs.

Diagnostic analysis using pooled data from 6 MASH clinical trials



Mapping of VCTE and FIB-4 thresholds to established ELF cutoffs

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Diagnostic performance of established VCTE & FIB-4 thresholds mapped to ELF cutoffs

Comparison	Prevalence	ELF	VCTE	FIB-4
≥F2 vs <F2	1418/1443 (98%)	**Cutoff: 9.00** Sn: 92% (90%, 93%) Sp: 44% (24%, 65%)	**Cutoff: 8.0 kPa** Sn: 91% (89%, 92%) Sp: 60% (39%, 79%)	**Cutoff: 1.00** Sn: 91% (89%, 92%) Sp: 32% (15%, 54%)
≥F3 vs <F3	1345/1443 (93%)	**Cutoff: 9.80** Sn: 75% (73%, 78%) Sp: 70% (60%, 79%)	**Cutoff: 12.0 kPa** Sn: 71% (68%, 73%) Sp: 78% (68%, 85%)	**Cutoff: 1.30** Sn: 82% (80%, 84%) Sp: 48% (38%, 58%)
F4 vs <F4	759/1443 (53%)	**Cutoff: 10.50** Sn: 61% (58%, 65%) Sp: 71% (67%, 74%)	**Cutoff: 20.0 kPa** Sn: 52% (49%, 56%) Sp: 88% (86%, 91%)	**Cutoff: 2.67** Sn: 50% (47%, 54%) Sp: 81% (78%, 84%)
F4 vs <F4	759/1443 (53%)	**Cutoff: 11.30** Sn: 31% (28%, 35%) Sp: 92% (89%, 94%)	**Cutoff: 30.0 kPa** Sn: 23% (20%, 26%) Sp: 97% (95%, 98%)	**Cutoff: 3.48** Sn: 31% (28%, 34%) Sp: 92% (89%, 94%)

A diagnostic claim for the ELF Test is not currently available in the U.S.

Agreement between ELF and VCTE

≥F2 vs <F2	VCTE ≥8.0 kPa	VCTE <8.0 kPa	Total
ELF ≥9.00	1211	106	1317
ELF <9.00	83	43	126
Total	1294	149	1443

Agreement: 86.9% (95% CI: 92.1%, 94.9%)
Discordant Rate: 13.1% (189/1443)
Biopsy Agrees with ELF: 102 (54%)
Biopsy Agrees with VCTE: 87 (46%)

≥F3 vs <F3	VCTE ≥12 kPa	VCTE <12 kPa	Total
ELF ≥9.80	807	234	1041
ELF <9.80	165	237	402
Total	972	471	1443

Agreement: 72.3% (95% CI: 70.0%, 74.6%)
Discordant Rate: 27.7% (399/1443)
Biopsy Agrees with ELF: 227 (57%)
Biopsy Agrees with VCTE: 172 (43%)

F4 vs <F4	VCTE ≥20 kPa	VCTE <20 kPa	Total
ELF ≥10.50	349	316	665
ELF <10.50	126	652	778
Total	475	968	1443

Agreement: 69.4% (95% CI: 66.9%, 71.7%)
Discordant Rate: 30.6% (442/1443)
Biopsy Agrees with ELF: 194 (44%)
Biopsy Agrees with VCTE: 248 (56%)

F4 vs <F4	VCTE ≥30 kPa	VCTE <30 kPa	Total
ELF ≥11.30	105	189	294
ELF <11.30	88	1061	1149
Total	193	1250	1443

Agreement: 80.8% (95% CI: 78.7%, 82.8%)
Discordant Rate: 19.2% (277/1443)
Biopsy Agrees with ELF: 154 (56%)
Biopsy Agrees with VCTE: 123 (44%)

A diagnostic claim for the ELF Test is not currently available in the U.S.
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Examples of aligned ELF, VCTE and FIB-4 values in clinical trials

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REGENERATE (Obeticholic acid)

Table 1. Baseline demographics, clinical characteristics, and disease characteristics.

ITT population (n = 931)	Placebo (n = 311)	OCA 10 mg (n = 312)	OCA 25 mg (n = 308)
Fibrosis stage F2, n (%)	142 (45.7)	130 (41.7)	139 (43.4)
Fibrosis stage F3, n (%)	169 (54.3)	182 (58.3)	169 (54.9)
Liver stiffness, mean (SD), kPa	12.50 (7.59)	11.98 (5.59)	12.38 (7.28)
FIB-4, mean (SD)	1.62 (0.89)	1.63 (0.88)	1.63 (0.85)
ELF, mean (SD)	9.71 (0.94)	9.73 (0.92)	9.73 (0.95)

Matched Cutoffs

12.0
1.30 (1.41)
9.80

SYNERGY-NASH (Tirzepatide)

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Tirzepatide, 5 mg (N=47)	Tirzepatide, 10 mg (N=47)	Tirzepatide, 15 mg (N=48)	Placebo (N=48)	Total (N=190)
Liver stiffness — kPa††	12.6±5.9	11.1±4.3	11.4±5.7	12.0±5.1	11.8±5.3
Fibrosis-4 index score‡‡	1.8±1.1	1.5±0.7	1.5±0.6	1.6±0.7	1.6±0.8
NIS4 test score§§	0.8±0.2	0.7±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Enhanced Liver Fibrosis test score¶¶	9.9±1.0	9.8±0.8	9.7±0.6	9.9±0.8	9.8±0.8
Pro-C3 — μg/liter‖‖	145.3±103.2	127.9±76.8	115.6±49.7	127.4±57.9	128.9±74.6

12.0
1.30 (1.41)
9.80

Sanyal AJ et al. J Hepatol. 2023;79(5):1110-1120.
Loomba R al. N Engl J Med. 2024;391(4):299-310.

Examples of aligned ELF, VCTE and FIB-4 values in clinical trials

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BALANCED (Efruxifermin)

Table 1. Baseline demographics and disease characteristics.

Parameter	Efruxifermin (n = 20)
Markers of fibrosis, mean (SD)	
Pro-C3, µg/L	25.6 (27.5)
ELF score	10.4 (1.2)
Liver stiffness, kPA	22.1 (10.8)

Matched Cutoffs

10.5

20.0

MAESTRO-NASH (Resmetirom)

Table 1 | Demographic and baseline characteristics (safety population)

	Resmetirom 100 mg OL (n=171)	Resmetirom 100 mg DB (n=324)	Resmetirom 80 mg DB (n=327)	Placebo DB (n=318)
FibroScan VCTE/LSM, kPa, mean (s.d.)	7.8 (3.4)	7.3 (4.1)	7.4 (4.4)	7.5 (5.5)
FIB-4, mean (s.d.)	1.0 (0.6)	1.0 (0.4)	1.0 (0.5)	1.0 (0.50)

8.00

1.00

Harrison SA et al. JHEP Rep. 2022;5(1):100563.
Harrison SA et al. Nat Med. 2023;29(11):2919-2928.

Choice of cutoffs impacts performance of diagnostic algorithms

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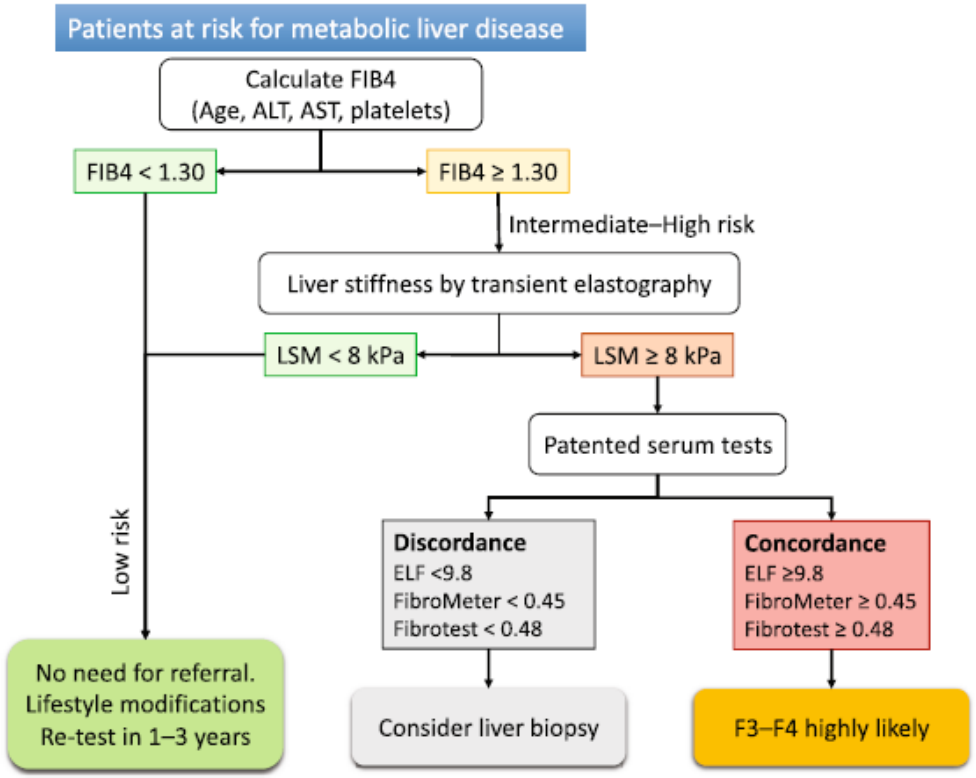
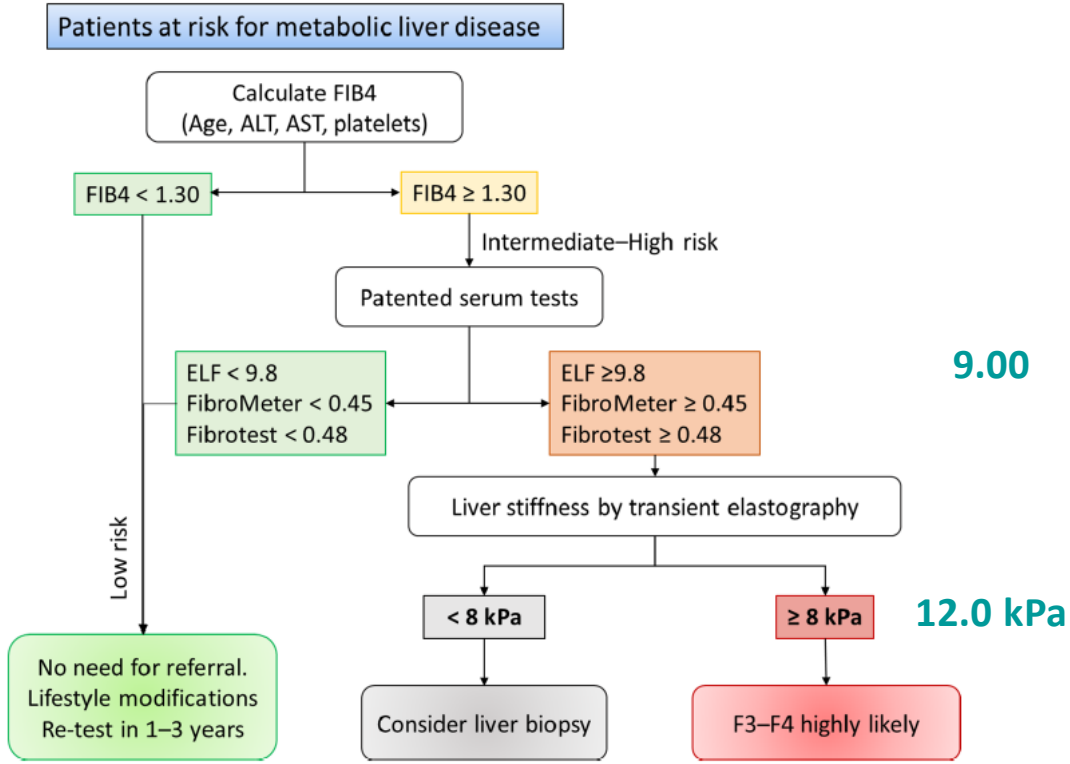
VCTE as 2nd Line / ELF as 3rd Line



ELF as 2nd Line / VCTE as 3rd Line



"…the ELF cutoff may be suboptimal and in need of refinement"

The optimal cutoffs are likely impacted by the sequence of tests.

Canivet et al. Hepatology. 2023;77(3):920-930.

Suggested adjustments to clinical practice guidance

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EASL and AASLD recommendations for identification of advanced fibrosis (≥F3)

Cutoff	ELF	VCTE	FIB-4		Suggested Actions
Rule-out	<7.70	<8 kPa	<1.3	✗	Revise ELF cutoff to <9.00 to match VCTE threshold. Consider lowering FIB-4 cutoff to 1.00.
Rule-in	≥9.80	≥12 kPa	≥2.67	✓	No actions for ELF & VCTE (cutoffs equivalent).

AASLD recommendations for identification of cirrhosis (F4)

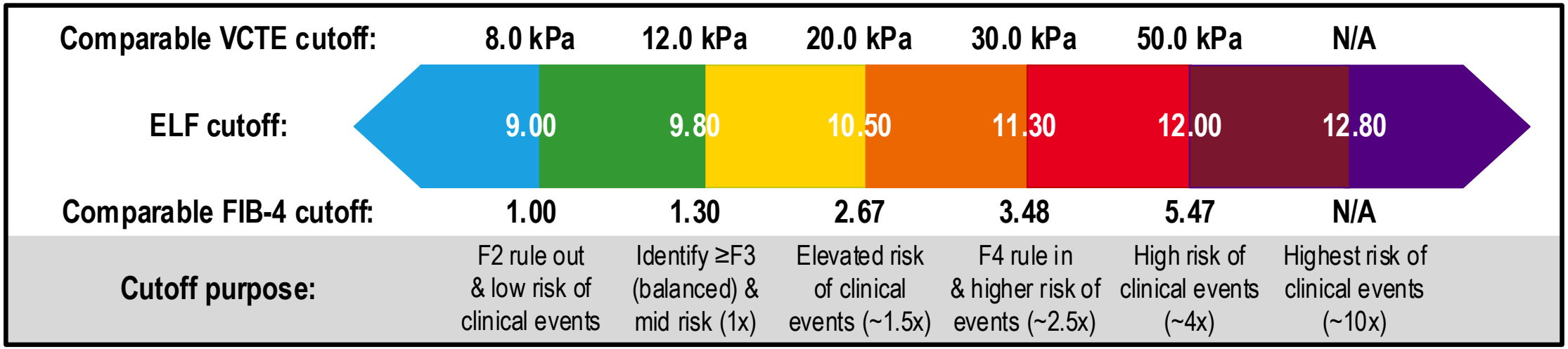
Cutoff	ELF	VCTE	FIB-4		Suggested Actions
Rule-out	<7.70	<8 kPa	<1.67	✗	Revise ELF cutoff to <9.00 to match VCTE threshold.
Rule-in	≥11.30	≥20 kPa	≥3.48	✗	Revise VCTE cutoff to ≥30 kPa to match ELF & FIB-4.

Expert Panel recommendations for initiating resmetirom treatment

Cutoff	ELF	VCTE	FIB-4		Suggested Actions
Treat	9.2-10.4	≥10-15 kPa	N/A	✗	Consider revising ELF lower cutoff to ≥9.00. Consider revising VCTE range to ≥8-19.9 kPa.
Consider treatment	10.5-11.3	≥15-19.9 kPa	N/A	✗	Consider revising VCTE range to ≥20-29.9 kPa.
Do not treat	>11.30	≥20 kPa	N/A	✗	Consider revising VCTE cutoff to ≥30 kPa.

Summary

- VCTE and FIB-4 thresholds can be mapped to established ELF cutoffs, yielding comparable prognostic and diagnostic performance.
- Better aligned cutoffs for ELF and VCTE support improved clinical decision making when test results are used in combination.
- Clinical practice guidance may benefit from updating recommended cutoffs (especially ELF 7.70 to 9.00).



The ELF Test Instructions for Use currently only provide prognostic interpretations based on 9.80 and 11.30 cutoffs.
A diagnostic claim for the ELF Test is not currently available in the U.S.

Thank You

ChatGPT Prompt:
Write a limerick about metabolic dysfunction-associated steatotic liver disease.

In the liver, a fatty cascade,
Metabolic woes in shadows laid.
Insulin's dance, a misstep made,
Steatotic tale, in cells displayed.
Research lights a path, not to evade.

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OpenAI. (2023). *ChatGPT-4* (Mar 14 version) [Large language model]. https://chat.openai.com/chat