

# Comparison of costs and referral rates of non-invasive testing strategies for metabolic dysfunction-associated steatohepatitis (MASH) in a Veteran population

Artem T. Boltyenkov, PhD<sup>1</sup>, Stephanie T. Chang, MD<sup>2,3</sup>, Donald Chalfin, MD, MS, MPH<sup>1,4</sup>, Kinpritma Sangha, PhD<sup>5</sup>, Ramsey Cheung, MD<sup>6,7</sup>

<sup>1</sup>Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA; <sup>2</sup>Department of Radiology, VA Palo Alto Healthcare System California, USA;

<sup>3</sup>Department of Radiology, Stanford University Medical Center, Stanford, CA, USA; <sup>4</sup>Jefferson College of Population Health of Thomas Jefferson University, Philadelphia, PA, USA; <sup>5</sup>Siemens Medical Solutions USA Inc., Malvern, PA, USA; <sup>6</sup>Department of Medicine, VA Palo Alto Healthcare System, CA, USA; <sup>7</sup>Division of Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA, USA

## Background/Aim

Non-invasive diagnostic tests (NITs) have emerged as promising tools for staging liver fibrosis, along with the determination of patient risk profile and the creation of evidence-based care pathways for individuals at risk of developing or having MASLD. Unlike liver biopsies, both in-vitro and in-vivo NITs can provide safer, more accessible, and potentially more cost-effective ways to assess liver fibrosis and track disease progression (Srivastava et al., 2019; Congly et al., 2021; Kjaergaard et al., 2023). Commonly used NITs in clinical practice for fibrosis staging and patient follow-up can be grouped into blood-based tests and imaging techniques.

The most frequently used blood-based NITs are the fibrosis index based on 4 factors (FIB-4) index and The Enhanced Liver Fibrosis (ELF™) tests. Most frequently used imaging NITs include vibration controlled transient elastography (TE), ultrasound-based elastography, and magnetic resonance elastography (MRE). The European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the American Gastroenterology Association (AGA) recommend the use of a combination of NITs as an alternative to liver biopsy for fibrosis staging and patient follow-up (Berzigotti et al., 2021; Rinella et al., 2023; Kanwal et al., 2021; Long et al., 2022). However, there is currently no accepted consensus on which, if any, NIT based strategies yield the best performance for the early detection of advanced liver fibrosis (F3/F4 stages) in MASLD.

As the prevalence of MASLD continues to rise and as NITs become increasingly incorporated into clinical practice, it is important to compare the diagnostic performance and economic impact of incorporating different NIT strategies into clinical practice in terms of their ability to triage referrals to hepatologists. The primary goal of this study is to evaluate the referral patterns of ten NIT-based strategies and compare referral rates and associated costs using data collected in a real-world study.

## Results

Patients (N=254) were enrolled with a mean age 65.3+/-9.3 years, and a mean BMI of 31.7+/-6. Of the 254 patients, 87.4% were male, 78.3% non-Hispanic/Latino, and 96.5% had T2DM. The mean +/- SD score of NITs were: FIB-4 1.2+/-0.7 (range, 0.26-4.6), ELF 9.9+/-0.8 (range, 7.7-12.2), TE 6.7+/-3.8 kPa (range, 2.6-39.3 kPa), and MRE 2.6+/-0.8 kPa (range, 1.6-7.0 kPa). Six out of ten strategies showed lower referral rate and lower costs compared to the FIB-4 only strategy. FIB-4/TE, FIB-4/ ELF/TE, FIB-4/MRE, FIB-4/ELF/MRE, TE only, and FIB-4/ELF strategies kept the highest proportion of patients within primary care at 91.9% (170/185), 90.9% (149/164), 87.9% (51/58), 86.2% (50/58), 81.1% (150/185), and 72.7% (165/227) respectively. These six strategies incurred the following costs per-patient: \$172.92, \$204.07, \$408.35, \$400.34, \$299.58, and \$411.70 respectively. FIB-4 alone strategy resulted in 63.1% (93/252) patients kept within primary care and \$445.4 per-patient costs.

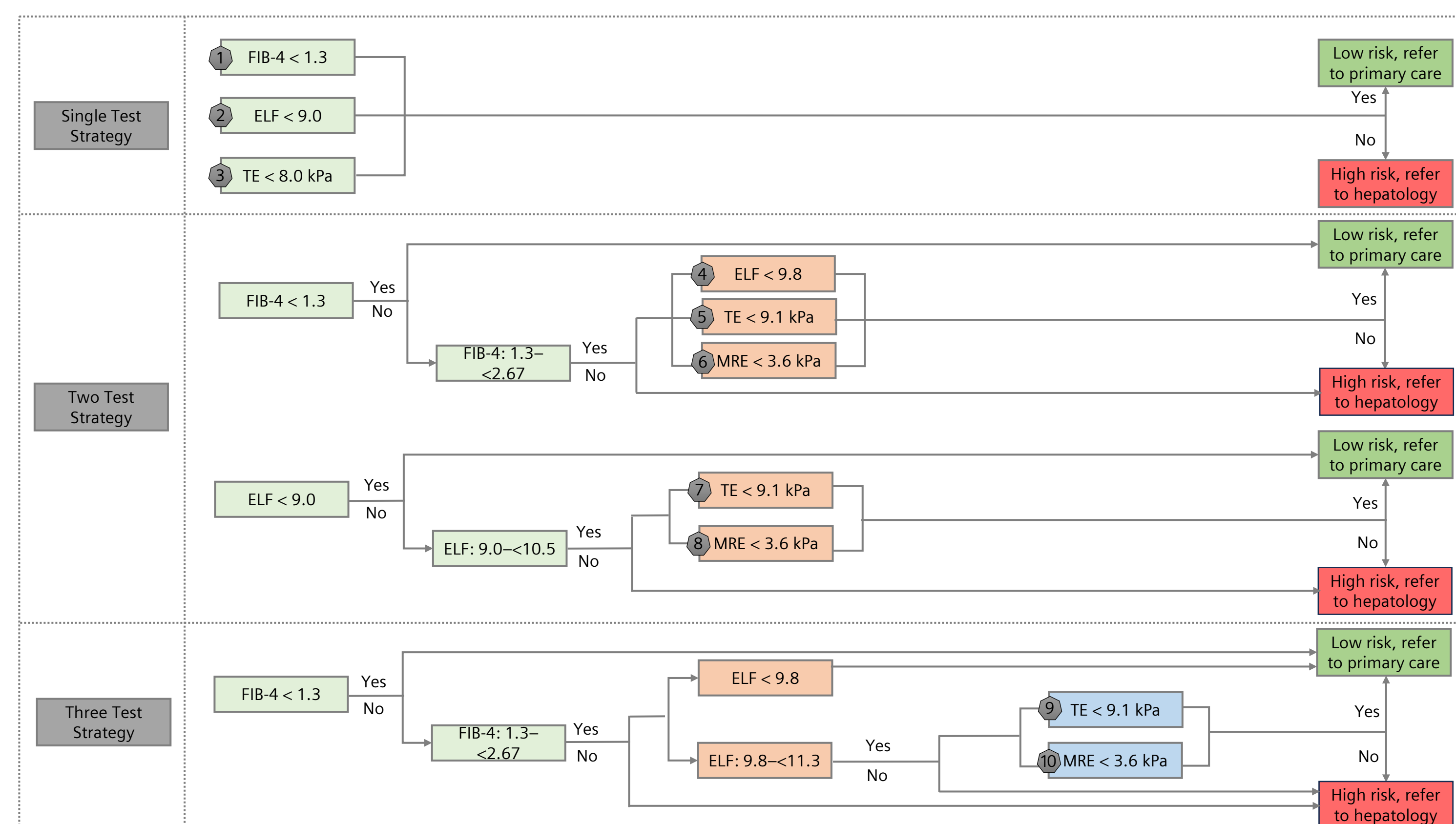
**Table 1.** Data on the distribution of patients remaining in primary care, referrals to hepatology, and the corresponding associated costs for each NIT strategy.

NIT Strategy	Patients Remaining in Primary Care	Cost of Non-referral	Number of Referrals to Hepatologist	Cost of Referral	Total Cost of Strategy	Cost of Strategy/Patient	Cost of Remaining in Primary Care/Patient
FIB-4 only	63.1%	\$13,192.07	36.9%	\$99,036.40	\$112,228.47	\$445.35	\$82.97
ELF only	15.4%	\$10,069.53	84.6%	\$264,534.19	\$274,603.72	\$1,089.70	\$259.16
TE only	81.1%	\$23,253.95	18.9%	\$52,240.50	\$75,494.45	\$299.58	\$113.81
FIB-4/ ELF	72.7%	\$20,087.44	27.3%	\$83,662.15	\$103,749.59	\$411.70	\$109.66
FIB-4/ TE	91.9%	\$21,523.43	8.1%	\$22,052.71	\$43,576.14	\$172.92	\$92.95
FIB-4/ MRE	87.9%	\$67,842.18	12.1%	\$35,061.25	\$102,903.42	\$408.35	\$306.17
ELF/TE	71.3%	\$50,809.29	28.7%	\$90,342.28	\$141,151.57	\$560.13	\$282.62
ELF/ MRE	67.2%	\$85,351.32	32.8%	\$103,791.42	\$189,142.74	\$750.57	\$503.70
FIB-4/ ELF/ TE	90.9%	\$25,832.12	9.1%	\$25,593.95	\$51,426.08	\$204.07	\$112.83
FIB-4/ ELF/ MRE	86.2%	\$61,004.46	13.8%	\$39,882.43	\$100,886.90	\$400.34	\$280.81

**Table 2.** Distribution of patients who either continue their care in the primary care or are referred to hepatology at the conclusion of the first, second-tier, and third-tier assessments for each NIT strategy..

NIT Strategy	n1_Test1	p1_PC	p1_Referred	n2_Test2	P2_PC	P2_Referred	n3_Test3	p3_PC	P3_Referred
FIB-4 only	252	63.1%	36.9%	-	-	-	-	-	-
ELF only	227	15.4%	84.6%	-	-	-	-	-	-
TE only	185	81.1%	18.9%	-	-	-	-	-	-
FIB-4/ ELF	227	61.7%	4.0%	78	32.1%	67.9%	-	-	-
FIB-4/ TE	185	62.2%	4.3%	62	88.7%	11.3%	-	-	-
FIB-4/ MRE	58	24.1%	8.6%	39	94.9%	5.1%	-	-	-
ELF/TE	164	17.1%	19.5%	104	85.6%	14.4%	-	-	-
ELF/ MRE	58	13.8%	31.0%	32	96.9%	3.1%	-	-	-
FIB-4/ ELF/ TE	164	60.4%	4.3%	58	34.5%	5.2%	35	85.7%	16.7%
FIB-4/ ELF/ MRE	58	24.1%	8.6%	39	23.1%	5.1%	28	96.4%	3.7%

n1=number of patients getting test1; n2=number of patients getting test2; n3=number of patients getting test3; p1\_PC=proportion of patients remaining in primary care after test 1; p2\_PC=proportion of patients remaining in primary care after test 2; p3\_PC=proportion of patients remaining in primary care after test 3; p1\_referred=proportion of patients referred to hepatologist after test 1; p2\_PC=proportion of patients referred to hepatologist after test 2; p3\_PC=proportion of patients referred to hepatologist after test 3



**Table 2.** Illustration of the referral pathways for the one, two, and three test scenarios.

## Methods

This is a retrospective analysis study utilizing patient-level information from a larger prospective cohort study currently underway at the Veteran Affairs Palo Alto Healthcare System (VAPAHCS) in Palo Alto, CA. Briefly, the prospective cohort study was designed to evaluate the performance of select NITs to improve the screening and monitoring of hepatic fibrosis among patients at risk of MASLD. The electronic medical records (EMR) of patients attending the VAPAHCS were examined to identify individuals with a BMI greater than 30 or those who were undergoing metformin therapy for T2DM.

Eligible participants (N=254) underwent serum biomarker screening by the Fibrosis-4 (FIB-4) index, the Enhanced Liver Fibrosis (ELF) test, and vibration-controlled transient elastography (VCTE). A subset of patients (N=59) selected on the basis of FIB-4 index scores underwent magnetic resonance elastography (MRE). A total of ten NIT strategies categorized into single-test, two-tests, and three-tests were evaluated for referrals rates to secondary care and cost savings.

For each of the 10 strategies, patients were categorized as low-risk or high-risk based on the score generated from the NITs. Patients with FIB-4 < 1.3 (FIB-4 only), ELF < 9.0 (ELF only), or TE < 8.0 (TE only) kPa were considered at low risk for advanced fibrosis (F3/F4) in the single-test strategies (strategies 1–3). In the two-test strategies (strategies 4-8), patients with FIB-4 < 1.3 or ELF < 9.8 in patients with indeterminate FIB-4 results (FIB-4/ ELF), FIB-4 < 1.3 or TE < 9.1 kPa in patients with indeterminate FIB-4 results (FIB-4/ TE), FIB-4 < 1.3 or MRE < 3.6 kPa in patients with indeterminate FIB-4 results (FIB-4/ MRE), ELF < 9.0 or TE < 9.1 kPa in patients with ELF > 9.0 but < 10.5 (ELF/ TE), ELF < 9.0 or MRE < 3.6 kPa in patients with ELF > 9.0 but < 10.5 (ELF/ MRE) were considered at low risk for advanced fibrosis. In the three-test strategies (strategies 9 and 10), patients with FIB-4 < 1.3 or ELF < 9.8 in patients with indeterminate FIB-4 results or TE < 9.1 kPa in patients with indeterminate FIB-4 and ELF > 9.0 but < 10.5 (FIB-4/ ELF/ TE), FIB-4 < 1.3 or ELF < 9.8 in patients with indeterminate FIB-4 results or MRE < 3.6 in patients with indeterminate FIB-4 and ELF > 9.0 but < 10.5 (FIB-4/ ELF/ MRE) were considered low-risk for advanced fibrosis.

## Conclusions

- Among ten strategies assessed, six strategies resulted in lower referral rates to hepatology clinics and lower costs compared to the FIB-4 only strategy. These six strategies in comparison to the FIB-4-only strategy realized substantial cost savings ranging from 7.6% to 61.1%.

- This study's primary strength lies in its utilization of real-world patient data and suggesting the value of NITs as screening approaches in patients at risk of MASLD in primary care and endocrinology settings.

- Future studies comparing different NIT strategies across diverse data resources from multiple centers is needed to enable more generalizable findings that will apply to a broader patient population likely to be afflicted by MASLD for both short-term and long-term assessments.

## References

