

**Cost Effectiveness of Different Strategies for Detecting Cirrhosis in Patients
With Non-alcoholic Fatty Liver Disease Based on United States Health Care
System**

Short title: Non-invasive diagnosis of cirrhosis in NAFLD

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Funding: No external funding supported this study.

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This is the author's manuscript of the article published in final edited form as:

Vilar-Gomez, E., Lou, Z., Kong, N., Vuppalanchi, R., Imperiale, T. F., & Chalasani, N. (2020). Cost Effectiveness of Different Strategies for Detecting Cirrhosis in Patients With Non-alcoholic Fatty Liver Disease Based on United States Health Care System. *Clinical Gastroenterology and Hepatology*. <https://doi.org/10.1016/j.cgh.2020.04.017>

Abbreviations

NAFLD: Nonalcoholic fatty liver disease; **VCTE:** Vibration controlled transient elastography; **MRE:** Magnetic resonance elastography; **CLD:** Chronic liver disease; **NITs:** non-invasive tests; **LB:** Liver biopsy; **AST:** Aspartate aminotransferase; **ALT:** Alanine aminotransferase; **TP:** True positive; **FP:** False positive; **TN:** True negative; **FN:** False negative; **EV:** Esophageal varices; **HCC:** Hepatocellular carcinoma; **NASH:** Nonalcoholic steatohepatitis; **OLT:** Orthotopic liver transplantation; **AASLD:** American association for the study of the liver diseases; **CC:** Correctly classified; **AFP:** Alpha-fetoprotein; **NSBB:** Nonselective beta-blockers; **GI:** Gastrointestinal; **CPDP,** cost per death prevented.

Author Contributions

Eduardo Vilar-Gomez: Study design, data collection and analysis, manuscript preparation, final approval

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ACKNOWLEDGEMENTS

We thank Ms. Carolina Vivas-Valencia from Purdue Weldon School of Biomedical Engineering for her participation in initial meetings on decision tree construction and conceptualization of the microsimulation. Authors thank Mr. Robert W. Klein from Medical Decision Modeling Inc. for his thoughtful review and suggestions. Authors also thank Drs. Samer Gawrieh and Niharika Samala for their comments regarding study design and results. Authors thank Julianne Nanzer for her editorial assistance.

Conflicts of Interests:

There are none for this paper. For full disclosure, Dr. Chalasani has ongoing paid consulting activities (or had in preceding 12 months) with NuSirt, Abbvie, Afimmune (DS Biopharma), Allergan (Tobira), Madrigal, Coherus, Siemens, La Jolla, Foresite labs, and Genentech. These consulting activities are generally in the areas of nonalcoholic fatty liver disease and drug hepatotoxicity. Dr. Chalasani receives research grant support from Exact Sciences, Intercept, and Galectin Therapeutics where his institution receives the funding. Over the last decade, Dr. Chalasani has served as a paid consultant to more than 35 pharmaceutical companies and these outside activities have regularly been disclosed to his institutional authorities.

Abstract

Background & Aims: Several strategies are available for detecting cirrhosis in patients with non-alcoholic fatty liver disease (NAFLD), but their cost effectiveness is not clear. We developed a decision model to quantify the accuracy and costs of 9 single or combination strategies, including 3 noninvasive tests (fibrosis-4 [FIB-4], vibration controlled transient elastography [VCTE], and magnetic resonance elastography [MRE]) and liver biopsy, for detection of cirrhosis in patients with NAFLD.

Methods: Data on diagnostic accuracy, costs, adverse events, and cirrhosis outcomes over a 5-y period were obtained from publications. The diagnostic accuracy, per-patient cost per correct diagnosis of cirrhosis, and incremental cost-effectiveness ratios (ICER) were calculated for each strategy for base cirrhosis prevalence values of 0.27%, 2%, and 4%.

Results: The combination of the FIB-4 and VCTE identified patients with cirrhosis in NAFLD populations with a 0.27%, 2%, and 4% prevalence of cirrhosis with the lowest cost per person (\$401, \$690, and \$1024, respectively) and highest diagnostic accuracy (89.3%, 88.5%, and 87.5% respectively). The combination of FIB-4 and MRE ranked second in cost per person (\$491, \$781, and \$1114, respectively) and diagnostic accuracy (92.4%, 91.6%, 90.6%, respectively). Compared to the combination of FIB-4 and VCTE (least costly), the ICERs were lower for the combination of FIB-4 and MRE (\$2864, \$2918, and \$2921) than the combination of FIB-4 and liver biopsy (\$4454, \$5156, and \$5956) at the cirrhosis prevalence values tested. When goal was to avoid liver biopsy, FIB-4+VCTE and FIB-4+MRE had similar diagnostic accuracies, ranging from 87.5% to 89.3% and 90.6% to 92.4% for cirrhosis diagnosis, although FIB-4+MRE had a slightly higher cost.

Conclusions: In our cost effectiveness analysis based on United States health care system, we found that results from FIB-4, followed by either VCTE, MRE, or liver biopsy, detect cirrhosis in patients with NAFLD with a high level of accuracy and low cost. Compared to FIB-4 + VCTE which was the least costly strategy, FIB-4+MRE had lower ICER than FIB-4+LB.

KEY WORDS: comparison, expense, sensitivity, imaging, biomarker

What You Need to Know

Background: Several methods are available for detecting cirrhosis in patients with non-alcoholic fatty liver disease (NAFLD), but little is known about their cost effectiveness.

Findings: In an analysis of data from publications, we found that FIB-4, followed by either VCTE, MRE, or liver biopsy, detects cirrhosis in patients with NAFLD with a high level of accuracy and low cost. However, the combination of FIB-4 and liver biopsy has a higher ICER, compared to the combination of FIB-4 and VCTE or FIB-4 and MRE.

Implications for patient care: The FIB-4, in combination with VCTE, MRE or liver biopsy, identifies patients with NAFLD who have cirrhosis accurately and cost effectively.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease, hepatocellular carcinoma (HCC), and liver transplantation.¹ The extent of hepatic fibrosis is the strongest risk factor for long-term complications; patients with advanced fibrosis are at the highest risk of hepatic decompensation, HCC, and cardiovascular disease.² Thus, accurate staging of fibrosis is necessary for proper management of patients with NAFLD, both for estimating prognosis and guiding therapy. While liver biopsy (LB) is the gold standard for staging liver fibrosis and diagnosing cirrhosis, it is invasive, costly, and has technical limitations, including sampling error and variation in histological interpretation, making it impractical as a routine screening or diagnostic tool.

Several non-invasive tests (NITs) are available for staging liver fibrosis, including blood-based biomarkers (Fib-4)³, and modalities that assess liver stiffness such as vibration controlled transient elastography (VCTE)⁴ and magnetic resonance elastography (MRE).⁵ Most NITs are good at excluding advanced fibrosis (negative predictive value > 90%), but sensitivity is lower for detecting advanced fibrosis.⁶⁻⁸ Among the modalities assessing liver stiffness, VCTE is the most widely studied and validated method, yielding good intra- and inter-observer variability and low failure rates.⁴ Moreover, its wide availability and easy-to-operate feature make VCTE a potential point-of-care test. Most recently, 2D- and 3D-MRE have emerged as promising noninvasive tests for diagnosing advanced fibrosis in NAFLD patients. MRE and VCTE have high accuracy in identifying advanced fibrosis.⁸ The Fib-4 index is a simple and inexpensive blood-based panel that is useful for excluding advanced fibrosis.³ It has been extensively validated in patients with NAFLD. Fib-4 cutoffs ≥ 3.25 or ≤ 1.30 have 80% and 90% positive and negative predictive values,

respectively, for detecting or excluding advanced fibrosis among patients CLD, including NAFLD.⁷ Its major limitation is that a high proportion of values fall in the indeterminate range (1.30-3.25).⁷

In clinical practice, a sequential combination of two NITs may improve the detection of patients with advanced fibrosis and reduce the number of patients with indeterminate results;^{9, 10} however, its cost-effectiveness has not been fully explored. Herein, we developed a decision model to quantify the accuracy and costs of various non-invasive strategies for diagnosing cirrhosis in NAFLD patients to understand better which strategies might be considered preferable in clinical practice.

METHODS

Study population

Our study population consists of a hypothetical cohort of middle-aged patients with NAFLD seen in three different settings: (a) in a specialty clinic setting where the prevalence of cirrhosis in NAFLD is estimated to be 2%¹¹, (b) in a general population-based setting where the prevalence of cirrhosis is estimated to be 0.27%¹² and tertiary referral centers setting where cirrhosis prevalence is reported to be \approx 4%.^{5, 7, 8}

Model structures

We constructed a decision model to compare the accuracy and costs associated with liver biopsy and NITs alone and in a sequential combination for the diagnosis of cirrhosis. We considered Fib-4 and liver stiffness measured by VCTE or MRE, and assumed that liver biopsy, as the reference standard, would have the highest sensitivity and specificity for cirrhosis. Test

accuracy for each strategy was calculated as follows: $(\text{true positive (TP)} + \text{true negative (TN)})/(\text{total population})$. To evaluate the ensuing clinical events for future costs and outcomes; we attached a microsimulation to each leaf node of the decision tree to emulate subsequent clinical events over a 5-year time horizon. **Figures 1A-C** summarize the decision tree of the nine diagnostic strategies and the transitions in the microsimulation of patients after receiving a diagnosis of cirrhosis.

In the decision-tree portion of the model, we considered each test individually and in clinically appropriate combinations where either stiffness-based method was added sequentially to Fib-4 or where LB was added sequentially to either a stiffness-based method or Fib-4. For all test strategies, a positive test may suggest cirrhosis. Additionally, failure rates for VCTE (7.1%)^{4, 13} and MRE (4%)^{14, 15}, and indeterminate results for Fib-4 (32%)⁴ were included. For combination strategies, a second test was added if the initial test was either positive or indeterminate for Fib-4, or uninterpretable for VCTE/MRE. The result of the second test determined the final diagnosis of cirrhosis. Finally, a do-nothing approach was included along with all test strategies.

We assumed that all patients with cirrhosis diagnosis underwent periodic guideline-based screening for esophageal varices (EV) and HCC^{16, 17} over a 5-year period. The disease state and mortality status were updated during the 5-year period. As a result, costs of the periodic screening for EVs and HCC were accumulated over the 5-year period. For those who tested positive, the costs include: (1) periodic EV screening [every 2 years if EV is small and at 3-year intervals if EVs are absent],¹⁷ (2) HCC screening every 6 months using serum α -fetoprotein and ultrasound,¹⁶ (3) primary prophylaxis of EV bleeding with both endoscopic band ligation (EBL) and nonselective beta-blockers (NSBB),¹⁷ (4) outpatient clinic visit and (5) those derived from liver transplantation or HCC-related liver resection. For those who tested negative, the two screening costs as above were excluded.

Model Parameters

We performed a sensitivity analysis by varying the prevalence range from 0.27% to 4%. The prevalence of EV among cirrhotics was estimated to be 34.7%.¹⁸ We considered the annual incidence of EV and HCC to be 2.3% (unpublished data from Indiana University Medical Center) and 2.5%, respectively.² The pooled 3-year HCC mortality rate is 49.2% among patients undergoing HCC surveillance vs 72.1% among those without periodic surveillance.¹⁶ We assumed a 16.3% 6-month risk of mortality due to variceal bleeding.¹⁹ We considered a prevalence of 11.5% of large or high-risk varices among compensated NAFLD cirrhotics.²⁰ and assumed that 34% of small or no varices would progress to large varices at 3 years.²¹ The pooled 2-year risk of upper gastrointestinal bleeding is 17%²² and 31%²³ among patients with or without primary prophylaxis including both EBL and/or NSSB. **Table 1, Figure 1C and supplemental Tables 1-3** summarize some of the above-mentioned parameters used in the model.

An institutional cost perspective was adopted, expressed in 2017 U.S. dollars. Direct costs for LB, MRE and VCTE were obtained from Medicare reimbursement data (**supplemental Table 4**).

Analysis

We simulated the costs for a particular strategy, which included the costs of (1) each diagnostic strategy, (2) HCC and EV screenings, (3) periodic clinic visits, (4) management of LB-related complications (i.e., bleeding) and (5) liver transplantation or HCC-related liver resection. We also simulated the diagnostic accuracy for a particular strategy. Diagnostic accuracy was defined as the percentage of correct diagnosis, which equals the sum of numbers of people who were correctly identified with or without cirrhosis (excluding the numbers after the confirmation

test), divided by the total population. We next calculated the cost per correct diagnosis, which was used as a proxy in the ensuing cost-effectiveness analysis. We lastly calculated the incremental cost-effectiveness ratios (ICERs) and cost per death prevented (CPDP). ICERs were defined as the incremental cost for each additional correct diagnosis (see supplemental material): the strategies were sorted by ascending order of cost, and the current least costly strategy was compared with the previous least costly strategy. If the accuracy of the current least costly strategy was lower than the previous one, then the current strategy was considered dominated. CPDP was calculated using the same logic, and we used mortality instead of diagnostic accuracy.

We further plotted per-patient total cost and diagnostic accuracy, and per-patient total cost and mortality for each strategy. Any strategy, such that no other strategies would yield lower cost and higher accuracy (lower mortality) simultaneously, was considered to be a dominant strategy. In the presence of more than one dominant strategy, the dominant strategies formed an efficiency frontier; strategies below and to the right of the frontier were considered to be dominated.

To assess the robustness of model results, we performed sensitivity analyses on cirrhosis prevalence (0%-12%). In addition, we performed one-way sensitivity analyses on test characteristics and costs with cirrhosis prevalence being fixed at 0.27%.

RESULTS

Base case.

Low prevalence of cirrhosis (0.27%). Fib-4 alone correctly classifies the lowest percentage of persons (57%), while Fib-4+LB correctly classified 97.7%, the highest percentage (**Table 2**).

Figure 2A shows diagnostic accuracy by cost per person for each strategy. The solid line represents the efficiency frontier, which identifies strategies with the lowest cost and highest accuracy, and

includes: Fib-4+VCTE (89.3%, \$401), Fib-4+MRE (92.4%, \$491) and Fib-4+LB (97.7%, \$729). Relative to Fib-4+VCTE, which is the least costly strategy with 89.3% accuracy, ICERs for the frontier strategies range from \$2,864 per additional correct diagnosis for Fib-4+MRE to \$4,454 for Fib-4+LB (**Table 2**). **Figure 2B** and **supplemental Table 5** display mortality by cost per person for each strategy. Compared to do-nothing strategy, which yields highest mortality (46 deaths) and lowest cost (\$10), Fib-4+VCTE (41 deaths, \$401), VCTE+LB (39 deaths, \$613), VCTE (38 deaths, \$901) and LB (36 deaths, \$1663) show the best combination of cost versus mortality.

Supplemental Tables 6-14 depict detailed results on diagnostic accuracy for all strategies.

Intermediate prevalence of cirrhosis (2%). Both the cost per person for each strategy and the cost per correct diagnosis per person are higher for an intermediate prevalence of cirrhosis as compared with low cirrhosis prevalence. Fib-4 alone remains the least accurate strategy (56.5%). Base results for intermediate cirrhosis prevalence closely parallel results for low prevalence with the same three least costly strategies which are Fib-4+VCTE (88.5% accuracy, cost of \$690), Fib-4+MRE (91.6%, \$781), and Fib-4+LB (97%, \$1,060) (**Table 3**). VCTE+LB has the same cost than Fib-4+LB, but it yields lower diagnostic accuracy (**Table 3** and **Figure 2C**). **Figure 2C** shows 3 strategies on the efficiency frontier, including the three same frontier strategies for the low prevalence case, with ICERs ranging from \$2,918 (Fib-4+MRE) to \$5,156 (Fib-4+LB) per additional correct diagnosis (**Table 3**). Results based on cost versus mortality analysis (**Figure 2D** and **supplemental Table 15**), show the same four strategies on the frontier (Fib-4+VCTE [307, \$690], VCTE+LB [285, \$1,060], VCTE [279, \$1,347] and LB [270, \$2,183]) than those results based on low cirrhosis prevalence.

High prevalence of cirrhosis (4%). Baseline results for the high prevalence of cirrhosis closely parallel those from low and intermediate prevalence (**Table 4**, **Figure 2E**). The same three

strategies (Fib-4 followed by either VCTE, MRE or LB) comprise the 3 least costly strategies, with accuracies ranging from 87.5% for Fib-4+VCTE to 96.1% for Fib-4+LB. As expected due to a higher proportion of cirrhosis, both costs per person and cost per correct diagnosis are higher than in the two previous prevalence scenarios, ranging respectively from \$1,024 for Fib-4+VCTE to \$1,441 for Fib-4+LB and from \$1,170 for Fib-4+VCTE to \$1,500 for Fib-4+LB. Fib-4 alone remains the least accurate strategy (55.9%). Similar to findings under conditions of intermediate prevalence, the same three frontier strategies appear on the efficiency frontier, with ICERs ranging from \$2,921 to \$5,956 per additional correctly diagnosed case. Cost versus mortality analysis also show the same four diagnostic strategies on the frontier, with Fib-4+VCTE displaying highest mortality (613) followed by VCTE+LB (568), VCTE (559) and LB (540) (**Figure 2F** and **supplemental Table 16**).

Sensitivity analyses.

Prevalence of cirrhosis. When the prevalence of cirrhosis is extended to as high as 12%, cost per correct diagnosis increases for all strategies, as shown in **Supplemental Figure 2**. The largest cost increases are observed for Fib-4, VCTE, and MRE, with respective increases of \$4,276, \$4,030, and \$3,732 from the previously considered low prevalence. Cost increases are the lowest for the two NITs of FIB-4+VCTE and FIB-4+MRE, with respective increases of \$2,364 and \$2,298 from the previously considered low prevalence.

Test characteristics. Results of one-way sensitivity analyses on each test's sensitivity and specificity are shown in **Supplemental Figure 3A-D**. Within the ranges of test characteristics, the general pattern of cost per correct diagnosis are comparable: negligible effects of sensitivity on either individual or combination strategies, negligible effects of specificity for combination strategies, and a modest cost reduction for individual tests as specificity increases.

Test costs. Results of 8 one-way sensitivity analyses on the cost of each test are shown in **supplemental Table 17** and in **supplemental Figure 4**. Note that the baseline values were set at Medicare average price **supplemental Table 4**, i.e., \$0, \$1,411, \$150.34 and \$544.18 for Fib-4 LB, VCTE and MRE. For the one-way sensitivity analysis on each cost parameter, alternative cost values are based on the national average for facility fees among hospital-based clinics and the 90th percentile for charges submitted by hospital-based clinics; see **supplemental Table 17**.

Considering sensitivity in the tradeoff of cost vs accuracy with respect to the cost parameters, **supplemental Table 18** shows the percentage of times (9 in total) each strategy is on efficiency frontier. Fib-4+VCTE, Fib-4+MRE, and Fib-4+LB are on efficiency frontier in 89% of the scenarios, respectively. In contrast, MRE+LB and VCTE+LB are on the frontier only when the costs of MRE and LB are high, and in 11% of the scenarios, respectively. The Tornado plot of cost per correct diagnosis shows Fib-4+VCTE to be the least costly strategy with a range of \$397 to \$590, whereas LB and MRE, each alone, are the two most costly strategies (**supplemental Figure 4**).

DISCUSSION

Since cirrhosis is the major determinant of long-term morbidity and mortality in patients with NAFLD, there is a critical need to detect cirrhosis before complications occur, which are associated with a high mortality and increased healthcare utilization. The sequential combination of two NITs or a NIT test plus liver biopsy may detect cirrhosis more accurately,^{9, 10} however, whether these approaches are cost-effective is unknown. This study suggests that the use of Fib-4 followed by VCTE is likely the most cost-effective strategy for screening or detecting cirrhosis among

patients with NAFLD either in the setting of general population, or specialty clinics and tertiary referral centers. Other diagnostic strategies such as Fib-4 followed by either MRE or LB, and VCTE followed by LB are likely cost-effective approaches but might have higher costs than Fib-4 followed by VCTE across all cirrhosis prevalence scenarios.

There is a current knowledge gap regarding the cost-effectiveness of single versus sequential combined screening strategies for cirrhosis in NAFLD. Our findings support previous work suggesting that the use of sequential combination tests is more cost-effective than are single tests.^{9, 10, 24}

Among the 5 combination tests compared in the base case analysis, Fib-4+VCTE ranks first due to the best combination of cost per correct diagnosis and diagnostic accuracy. Fib-4+MRE ranks second, with higher percentage of people correctly classified (ranging from 90.6%-92.4% vs. 87.5%-89.3% with Fib-4+VCTE) but higher costs. The combinations of Fib-4+LB or VCTE+LB ranked third and fourth, respectively, across all cirrhosis prevalence settings. Although both combinations yield higher accuracy, they have higher costs per correct diagnosis as compared with either FIB-4+VCTE or Fib-4+MRE. Finally, the combination of MRE+LB ranked fifth among all combination tests.

Overall, using MRE together with either LB or Fib-4 moderately increases overall costs and therefore reduces cost-effectiveness as compared to combinations that include VCTE plus Fib-4 or LB. The results highlight the importance of diagnostic accuracy, with costs being more influential on strategies including MRE. This finding suggests that, due to its point-of-care availability and more affordable cost, a VCTE based strategy may be the most attractive approach when considering potential population-based screening program as well as in the setting of specialist clinics.

If the goal is to avoid liver biopsy, Fib-4+VCTE is a very cost-effective strategy among NITs. This strategy could be particularly important in the community setting or in resource-limited areas where Fib-4+VCTE can be used to screen for cirrhosis among patients with NAFLD. In the setting of higher prevalence of cirrhosis such as referral centers, either Fib-4 together with VCTE or MRE may be useful tools for detecting cirrhosis.

This analysis evaluated the cost-effectiveness of a comprehensive list of screening strategies for cirrhosis diagnosis in the context of NAFLD with varying prevalence of cirrhosis. Other strengths of this study include: (1) using liver biopsy as the reference standard for cirrhosis diagnosis and blood- and imaging-based tests, (2) simulated distribution of outcomes and its treatments considering real-world data, and (3) assessment of uncertainty including a wide range of cirrhosis prevalence, sensitivity and specificity values, as well as assuring the statistical confidence in comparative studies by running the microsimulation with a sufficiently large cohort multiple times for each strategy.

This analysis has limitations as well, including: (1) results are based on the U.S. costs and may not generalize to other healthcare systems; (2) MRI costs were used as a proxy for MRE; MRE is a relatively new diagnostic imaging technology without a CPT code for insurance reimbursement currently, although it is being used often in the United States for routine clinical care; (3) since the sensitivity and specificity of non-invasive tests in the context of a primary care setting are not available, this information was extrapolated from studies conducted at tertiary referral centers; (4) in order to minimize the complexity of our analysis, we simplified some aspects of our decision tree such as single time testing and binary cut-off values for VCTE and MRE and assuming that causes of death are limited to variceal bleeding and HCC during first five years of

follow-up; and (5) finally, our cost-effectiveness is not a traditional one, i.e., cost per life-year save or cost per quality adjusted life year. We used cost per correct diagnosis as a proxy for cost-effectiveness for several reasons. such that the risk of hard outcomes such as mortality due to hepatic and cardiovascular events is not common. Second, not well-described are the natural history of cirrhosis due to NAFLD and the effects of identifying and treating large esophageal varices and hepatocellular carcinoma in this setting.

In conclusion, this study suggests that Fib-4 followed by either VCTE, MRE or LB are cost-effective strategies for identifying cirrhosis in populations where the prevalence of cirrhosis varies between 0.27%-4%. Compared to the combination of FIB-4 and VCTE, the ICERs were higher for the combination of FIB-4 and MRE were lower than for the combination of FIB-4 and liver biopsy. If the goal is to avoid liver biopsy, the combination of Fib-4+VCTE with its lower costs and accessibility is likely the preferred strategy for the screening of cirrhosis in the setting of general or community-based populations.

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Table 1. Model parameters, base-case values and ranges.

Parameter	Value	Range (minimum-maximum)	Reference
Prevalence of biopsy-confirmed cirrhosis			
Population-based	0.27%	-	12
Community-based	2%		11
Prevalence of esophageal varices	34.7%	-	18
Prevalence of large or high-risk varices	11.5%	-	20
3-year rate of varices progression	34%	-	21
Annual incidence of esophageal varices	4.4%	-	-
2-year risk of bleeding with primary prophylaxis	17%	14%-20%	22
2-year risk of bleeding without primary prophylaxis	31%	18%-60%	23, 25
5-year mortality due to variceal bleeding	20%	20%-80%	17
Annual incidence of hepatocellular carcinoma	2.5%	-	2
3-year mortality due to hepatocellular carcinoma	49.2%	46.4%-77.2%	16
Liver biopsy *			
Sensitivity	93%	89%-100%	
Specificity	95%	92%-100%	
Fib-4 index			
<i>Optimal high cutoff (>3.25)</i>			
Sensitivity	38%	35%-41%	
Specificity	97%	95%-100%	
<i>Optimal low cutoff (<1.30)</i>			
Sensitivity	84%	74%-85%	
Specificity	69%	65%-71%	
<i>Indeterminate results</i>	32%	12%-46%	7
Magnetic resonance elastography			
<i>Optimal cutoff for cirrhosis (4.7)</i>			
Sensitivity	80%	60%-97%	
Specificity	86%	84%-93%	
<i>Failure rates</i>	4%	4%-6%	14, 15

<i>Vibration controlled transient elastography</i>			4, 13, 27, 28
<i>Optimal cutoff for cirrhosis (11.8)</i>			
Sensitivity	80%	78%-95%	
Specificity	81%	85%-89%	
<i>Failure rates</i>	7.1%	3.5%-50%	4, 13

* Considering optimal liver tissue specimens (≥ 2.5 cm in length and ≥ 10 portal tracts)

Specificity and sensitivity for cirrhosis were calculated using pooled data from published studies.

Table 2. Accuracy and cost-effectiveness of different diagnostic strategies. A microsimulation analysis based on 100,000 NAFLD patients considering a cirrhosis prevalence of 0.27%.

Strategy	Number of correctly identified out of 270 people with cirrhosis	Number of correctly excluded out of 99730 people without cirrhosis	Percentage of people correctly classified	Change in percentage of people correctly classified*	Cost per person (\$)	Cost per correct diagnosis (\$)	Mortality (bleeding)	Mortality (HCC)	Total mortality cases	ICER
No test	N/A	N/A	N/A	N/A	10	N/A	25	5	46	-
Fib-4+VCTE	116	89,145	89.3%	32.2%	401	450	21	5	42	Least costly
Fib-4+MRE	120	92,272	92.4%	35.4%	491	531	22	5	42	2,864
VCTE+LB	187	91,769	92.0%	34.9%	612	667	19	4	40	4,454
Fib-4+LB	145	97,592	97.7%	40.7%	729	747	21	5	42	Dominated
MRE+LB	193	95,071	95.3%	38.2%	888	932	19	4	40	Dominated
VCTE	201	75,046	75.2%	18.2%	900	1,197	18	4	39	Dominated
Fib-4	70	56,966	57.0%	Reference	908	1,592	21	5	41	Dominated
MRE	207	82,337	82.5%	25.5%	1,109	1,344	19	4	39	Dominated
LB	251	94,744	95.0%	38.0%	1,663	1,751	17	4	37	Dominated

Abbreviations: VCTE, vibration controlled transient elastography; LB, liver biopsy; MRE, Magnetic resonance elastography; HCC, hepatocellular carcinoma; ICER, incremental cost effectiveness ratio.

Total mortality includes mortality cases from variceal bleeding, HCC and other than bleeding or HCC.

Strategies are listed in order of increasing costs.

* It represents difference between tests and the reference strategy (Fib-4).

Table 3. Accuracy and cost-effectiveness of different diagnostic strategies. A microsimulation analysis based on 100,000 NAFLD patients considering a cirrhosis prevalence of 2%.

Strategy	Number of correctly identified out of 2000 people with cirrhosis	Number of correctly excluded out of 98000 people without cirrhosis	Percentage of people correctly classified	Change in percentage of people correctly classified*	Cost per person (\$)	Cost per correct diagnosis (\$)	Mortality (bleeding)	Mortality (HCC)	Total mortality cases	ICER
No test	N/A	N/A	N/A	N/A	77	N/A	187	41	344	-
Fib-4+VCTE	860	87,599	88.5%	32.0%	690	780	158	30	307	Least costly
Fib-4+MRE	888	90,671	91.6%	35.1%	781	853	159	30	307	2,918
Fib-4+LB	1,076	95,899	97.0%	40.5%	1,060	1,093	155	29	302	5,156
VCTE+LB	1,382	90,177	91.6%	35.1%	1,060	1,158	142	23	285	Dominated
Fib-4	517	55,978	56.5%	Reference	1,236	2,187	153	28	300	Dominated
MRE+LB	1,428	93,421	94.8%	38.4%	1,329	1,401	142	24	285	Dominated
VCTE	1,486	73,744	75.2%	18.7%	1,347	1,791	138	22	279	Dominated
MRE	1,536	80,909	82.4%	26.0%	1,557	1,889	139	22	280	Dominated
LB	1,860	93,100	95.0%	38.5%	2,183	2,299	131	19	270	Dominated

Abbreviations: VCTE, vibration controlled transient elastography; LB, liver biopsy; MRE, Magnetic resonance elastography; HCC, hepatocellular carcinoma; ICER, incremental cost effectiveness ratio.

Total mortality includes mortality cases from variceal bleeding, HCC and other than bleeding or HCC.

Strategies are listed in order of increasing costs.

* It represents difference between tests and the reference strategy (Fib-4).

Table 4. Accuracy and cost-effectiveness of different diagnostic strategies. A microsimulation analysis based on 100,000 NAFLD patients considering a cirrhosis prevalence of 4%.

Strategy	Number of correctly identified out of 4000 people with cirrhosis	Number of correctly excluded out of 96000 people without cirrhosis	Percentage of people correctly classified	Change in percentage of people correctly classified*	Cost per person (\$)	Cost per correct diagnosis (\$)	Mortality (bleeding)	Mortality (HCC)	Total mortality cases	ICER
No test	N/A	N/A	N/A	N/A	157	N/A	373	81	686	-
Fib-4+VCTE	1872	85659	87.5%	31.7%	1024	1170	316	60	613	Least costly
Fib-4+MRE	1863	88735	90.6%	34.7%	1114	1230	318	60	613	2,921
Fib-4+LB	2152	93942	96.1%	40.2%	1441	1500	310	57	603	5,956
VCTE+LB	3029	88073	91.1%	35.2%	1579	1733	283	47	568	Dominated
Fib-4	2224	53645	55.9%	Reference	1616	2892	306	56	599	Dominated
MRE+LB	3006	91366	94.4%	38.5%	1840	1950	284	47	569	Dominated
VCTE	3237	71975	75.2%	19.3%	1861	2474	276	44	559	Dominated
MRE	3221	79109	82.3%	26.5%	2077	2523	277	44	559	Dominated
LB	3720	91200	94.9%	39.1%	2777	2925	262	39	540	Dominated

Abbreviations: VCTE, vibration controlled transient elastography; LB, liver biopsy; MRE, Magnetic resonance elastography; HCC, hepatocellular carcinoma; ICER, incremental cost effectiveness ratio.

Total mortality includes mortality cases from variceal bleeding, HCC and other than bleeding or HCC.

Strategies are listed in order of increasing costs.

* It represents difference between tests and the reference strategy (Fib-4).

FIGURE LEGENDS

Fig. 1. Model structure.

(A) Decision analytic tree using single tests.

(B) Decision analytic tree using sequential tests.

(C) Microsimulation of patients' assessment after receiving a diagnosis of cirrhosis.

Abbreviations: **VCTE**, vibration controlled transient elastography; **MRE**, magnetic resonance elastography; **C**, cirrhosis; **NC**, no cirrhosis; **CD**, correctly diagnosed; **MD**, misdiagnosed; **CR**, correctly ruled out; **UD**, undiagnosed; **HCC**, hepatocellular carcinoma; **EV**, esophageal varices; **EVL**, endoscopic variceal ligation; **OLT**, orthotopic liver transplantation; **NSBB**, nonselective beta-blockers; **EGD**, esophagogastroduodenoscopy.

Fig. 2. Incremental cost-effectiveness or cost-mortality “Frontier” of 9 diagnostic strategies.

(A) Cost per person vs accuracy considering a cirrhosis prevalence of 0.27%.

(B) Cost per person vs mortality considering a cirrhosis prevalence of 0.27%.

(C) Cost per person vs accuracy considering a cirrhosis prevalence of 2%.

(D) Cost per person vs mortality considering a cirrhosis prevalence of 2%.

(E) Cost per person vs accuracy considering a cirrhosis prevalence of 4%.

(F) Cost per person vs mortality considering a cirrhosis prevalence of 4%.

The points on the line are the strategies on the frontier and considered dominating strategies, and points below the line are the less cost-effective strategies.

Abbreviations: **VCTE**, vibration controlled transient elastography; **LB**, liver biopsy; **MRE**, magnetic resonance elastography.

Figure 1A

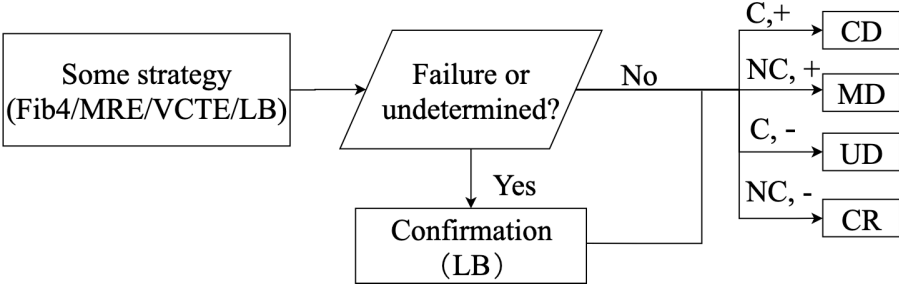


Figure 1B

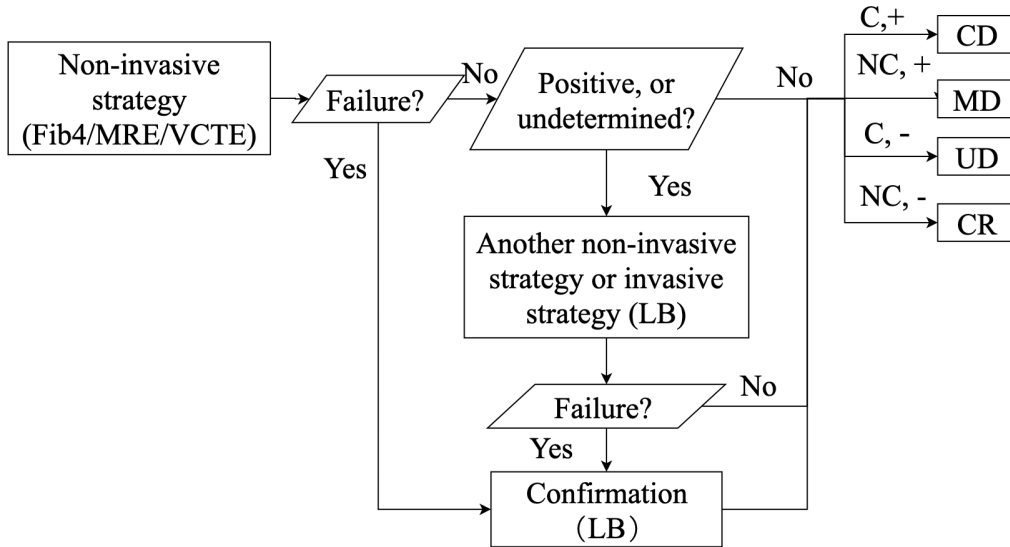


Figure 1C

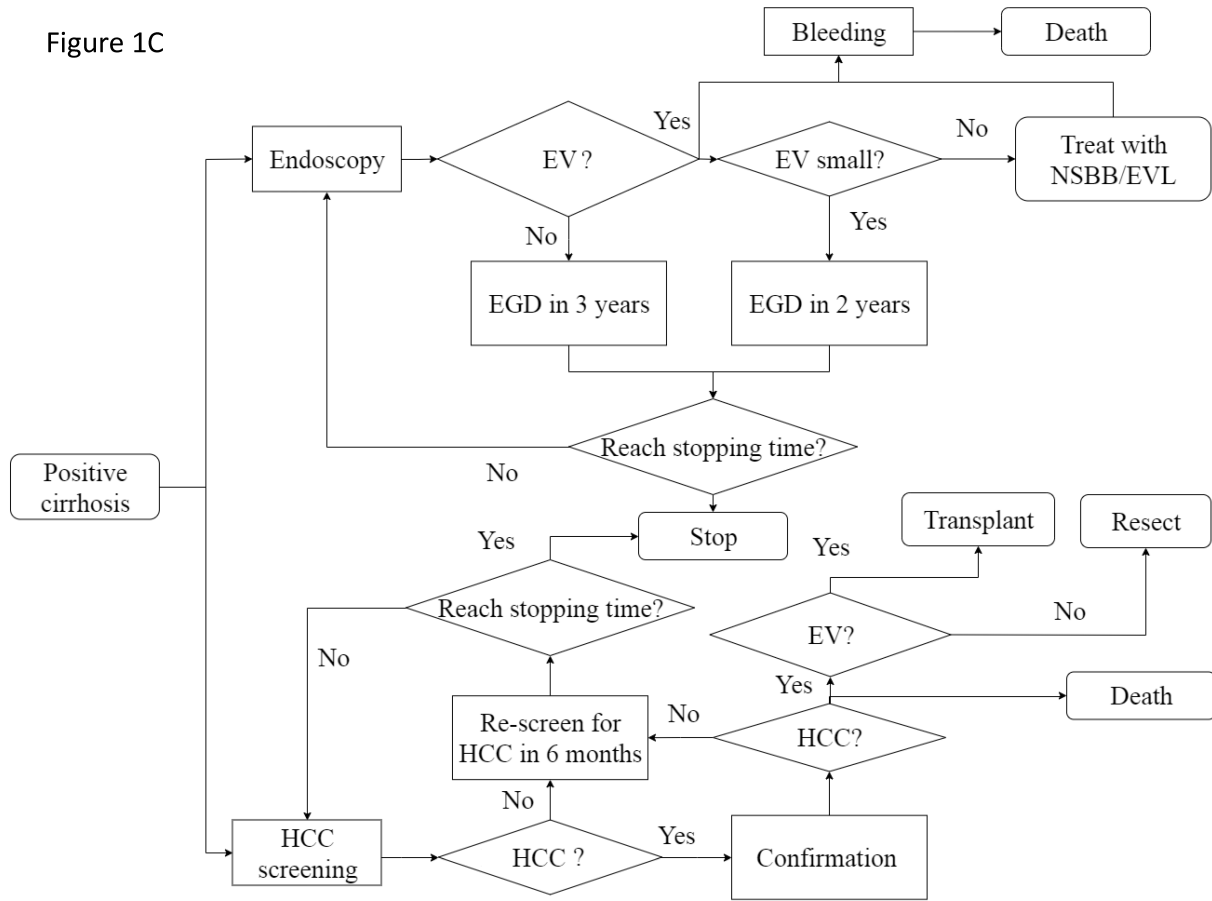


Figure 2A

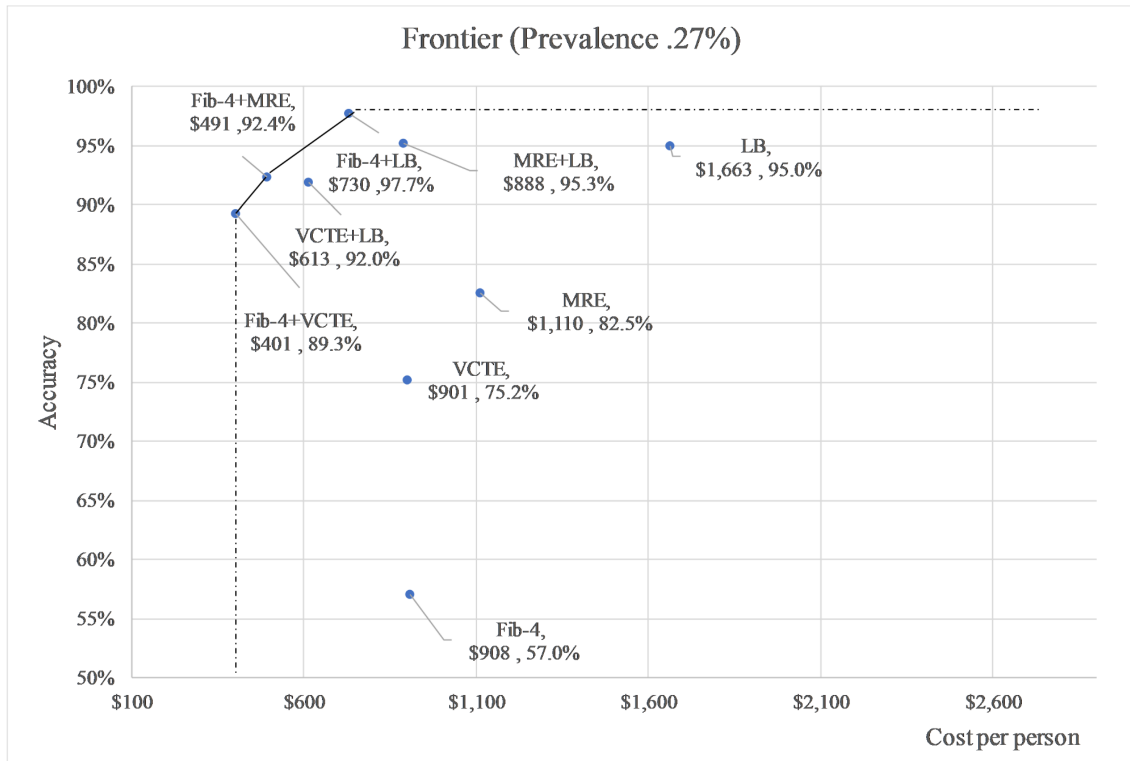


Figure 2B

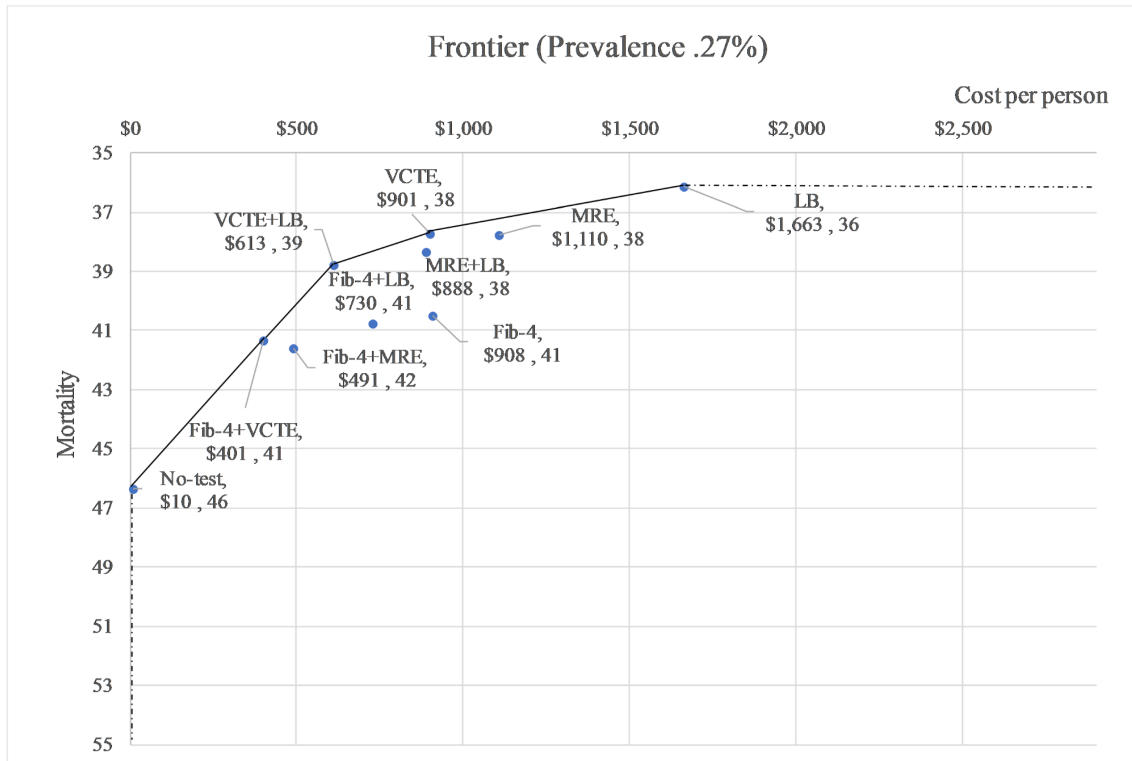


Figure 2C

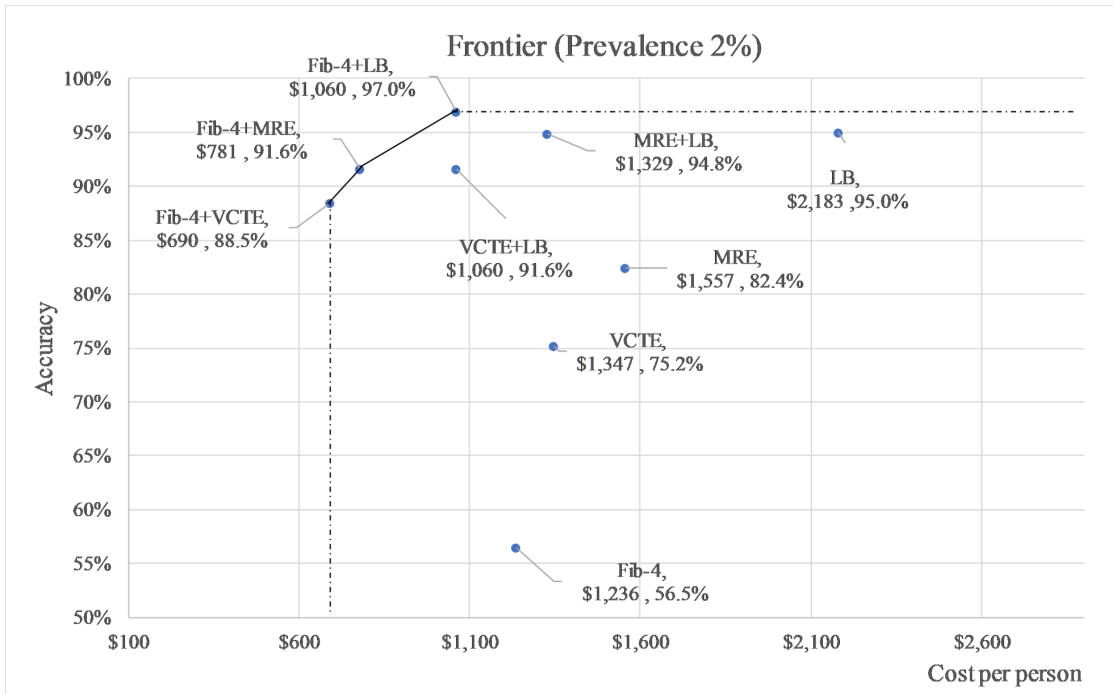


Figure 2D

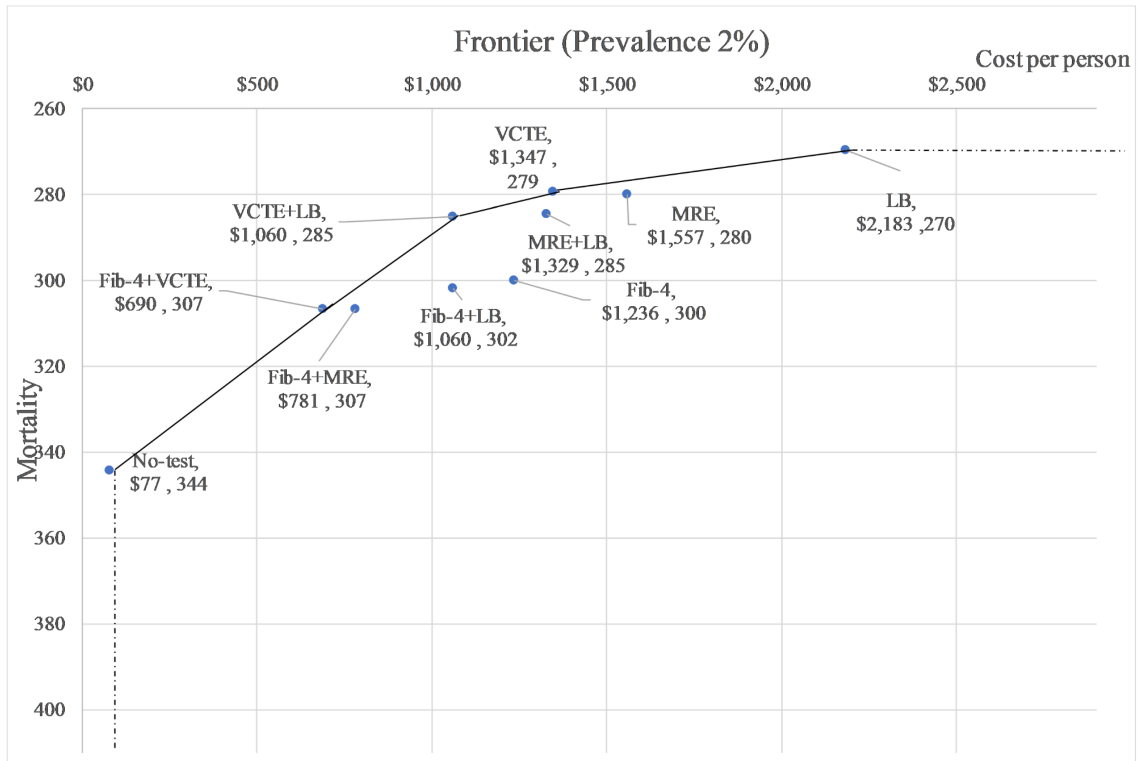


Figure 2E

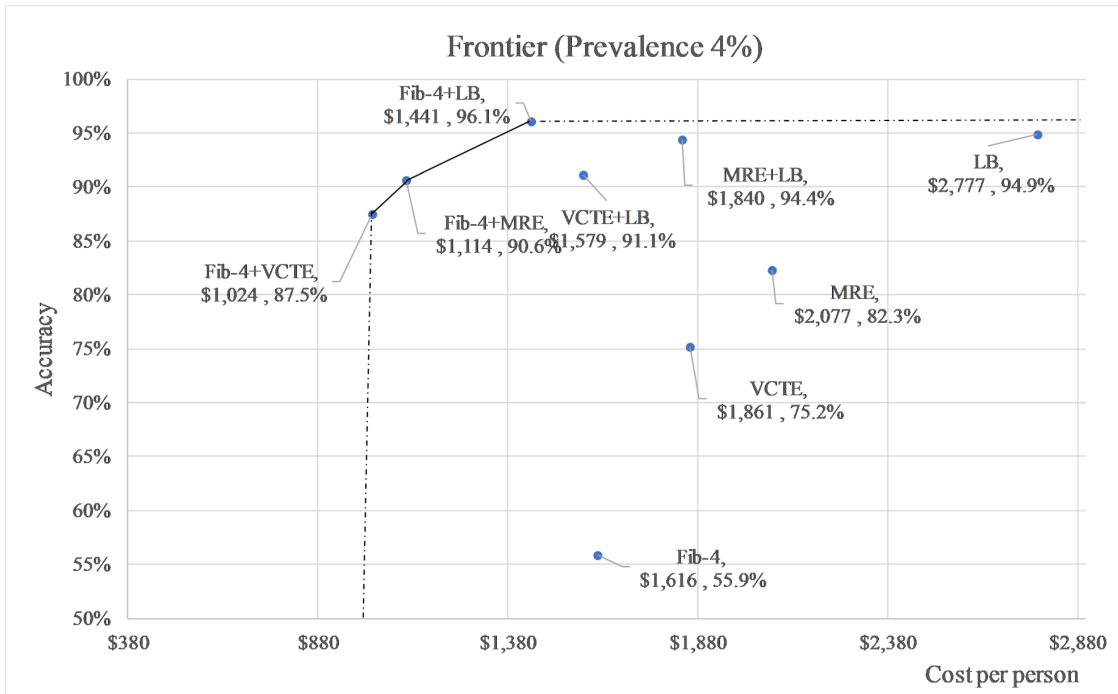


Figure 2F

