

**Key Components of the Initial Evaluation and
Referral of NAFLD patients:**
*Role of Liver Biopsy, Non-invasive Testing and
Risk Prediction Algorithms*

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Sir Charles
Gairdner Hospital

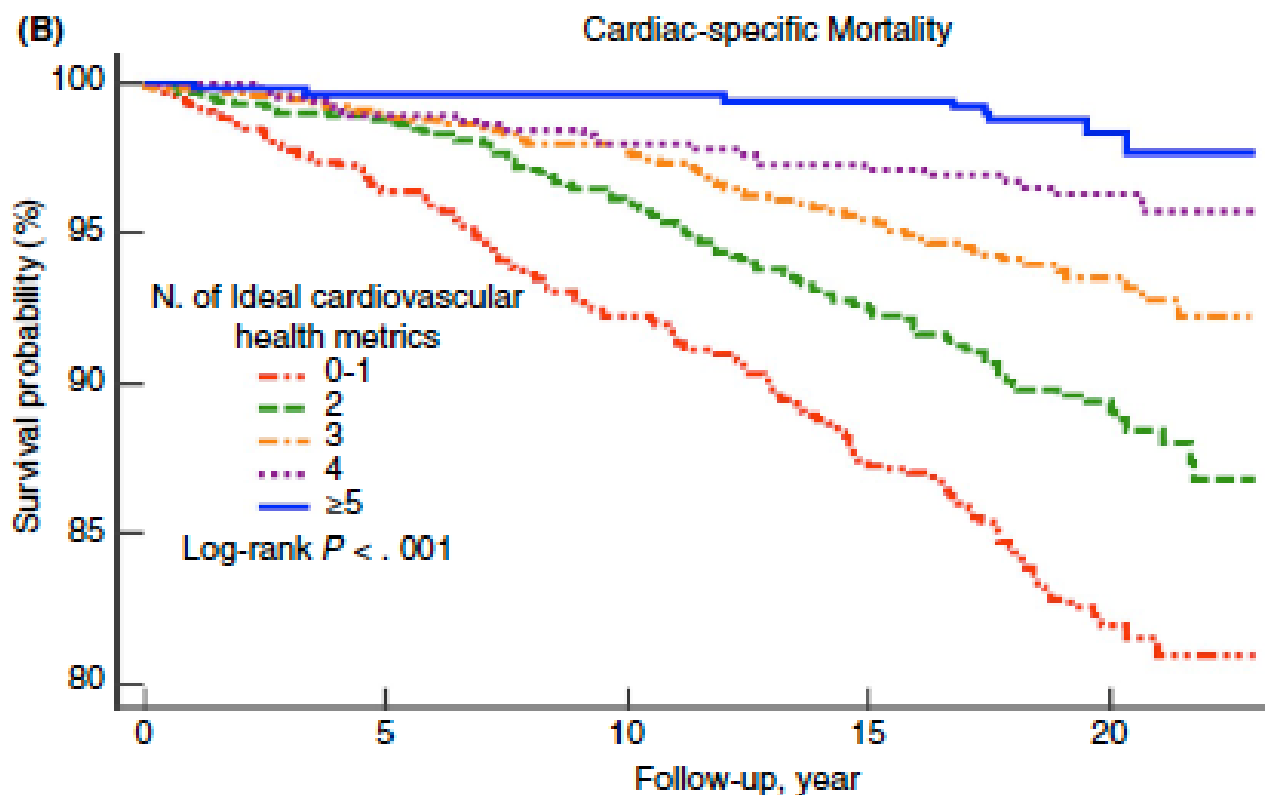
Disclosure

- Holder of US and Australian patents for Hepascore.
- Advisory boards: Metavention, Pfizer, Novartis.

Initial Evaluation: Questions

Perspective	Questions	Test Characteristics
Patient	<ul style="list-style-type: none">• Am I going to get sick or die?• Is the test convenient, acceptable?	<ul style="list-style-type: none">• Prognostic test• Non-invasive
Primary care physician	<ul style="list-style-type: none">• Do I need to refer this patient?• Is the test quick, easy and simple?	<ul style="list-style-type: none">• Screening test• High sensitivity• Good specificity• Bed-side
Specialist	<ul style="list-style-type: none">• Does this patient have cirrhosis?• Are they eligible for a clinical trial?• Should they receive pharmacotherapy?• Do they need to stay in my clinic?	<ul style="list-style-type: none">• Diagnostic test• High specificity• Prognostic
Payer	<ul style="list-style-type: none">• Is this test cheap and cost-effective?	<ul style="list-style-type: none">• Cost-effective test

Cardiovascular Risk Prediction in NAFLD



Among NAFLD patients;

- Atherosclerotic Cardiovascular (ASCVD) Risk Calculator predicts CVD mortality
- <20% take statins
- High dose statin or statin/ezetimibe may reduce CVD

Ideal CVD Health Metrics: Smoking, BMI, physical activity, Diet, blood pressure, blood glucose and cholesterol

Paik et al, APT 2019
Simon et al, Int J Cardiol. 2018
Tikkanen et al, Int J Cardiol. 2013
Gobali et al, Hepatol Comm. 2019
Shahab et al, Hepatol Comm. 2018

Prognostic Accuracy of NIT's in NAFLD

Follow-up

5 Years

6.4 Years

8.7 Years

10 Years

20 Years



	AUC (Liver Failure) n=284	AUC (Liver Death) n=360	AUC (Liver Failure) n=320	AUC (Liver Failure) n=34,541	AUC (Liver Failure) n=646
APRI	0.77	0.69	0.80	0.73	0.69
FIB4	0.85	0.78	0.81	0.76	0.72
NFS	0.82		0.86	0.71	0.72
Fibrometer ^{V2G}		0.84			
Hepascore	0.85	0.85			
Forns				0.76	
VCTE		0.88			

Angulo et al, Gastro 2013; Bouriser et al, J Hep 2016; Bertot et al, Liver Int. 2018; Hagstrom et al, Gastroenterol. 2019; Hagstrom et al, Hepatol. 2019

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Sensitivity: 0-46%

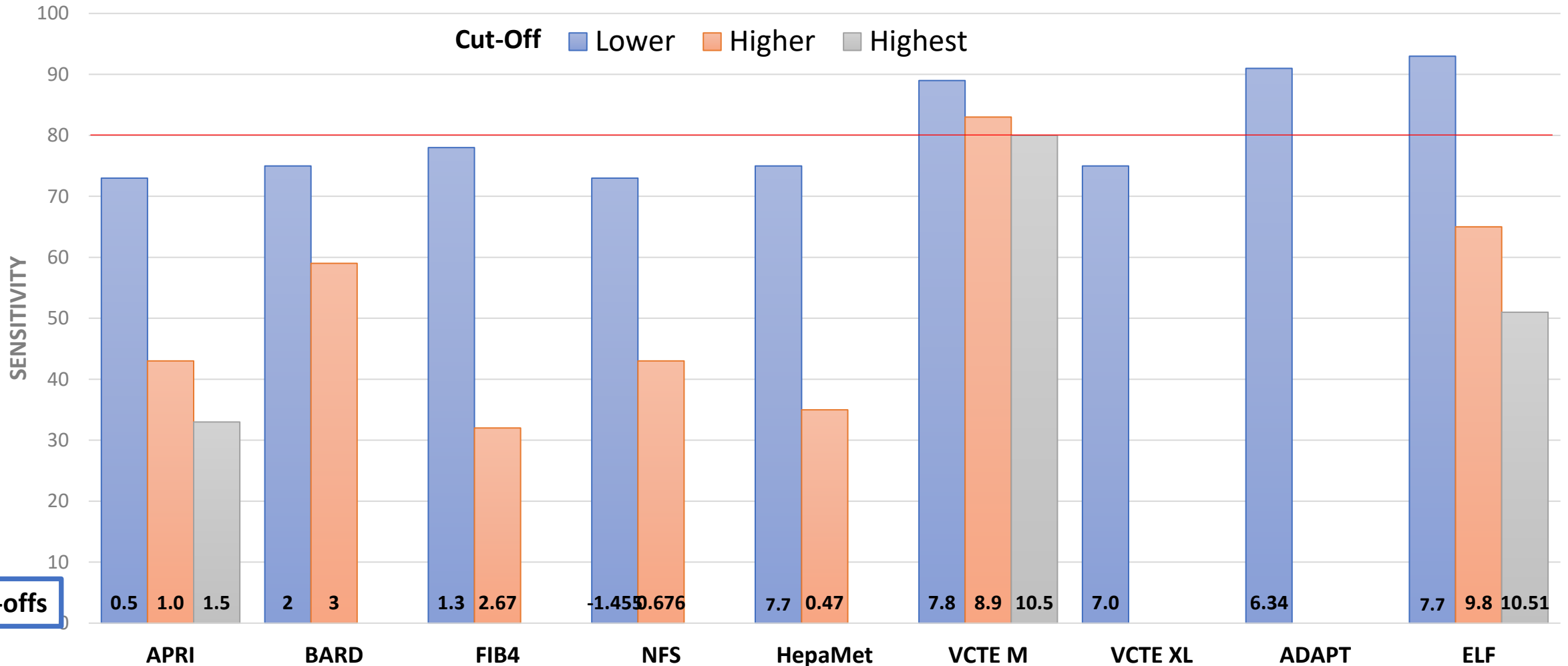
Specificity: 97-99%

PPV: 0-12%

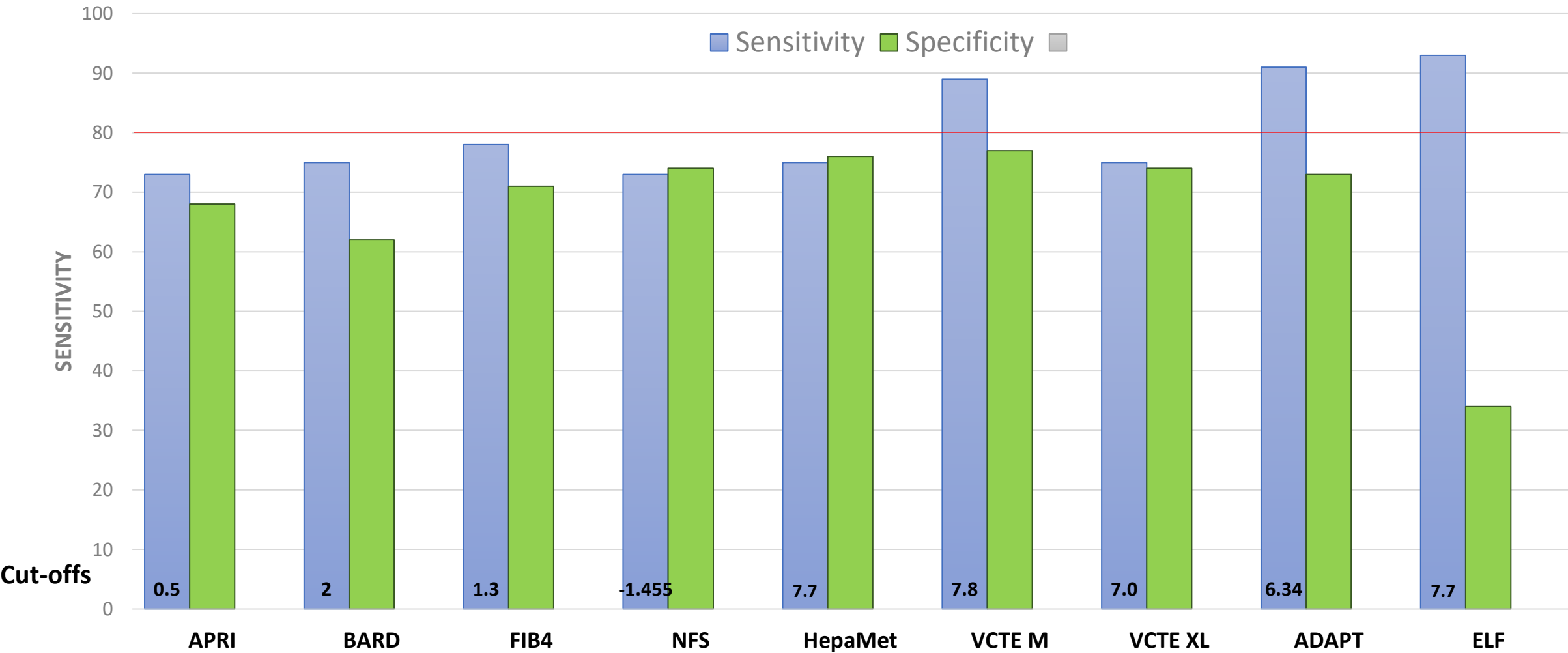
NPV: 99%

Angulo et al, Gastro 2013; Bouriser et al, J Hep 2016; Bertot et al, Liver Int. 2018; Hagstrom et al, Gastroenterol. 2019; Hagstrom et al, Hepatol. 2019

Sensitivity of NIT's for Advanced Fibrosis in NAFLD

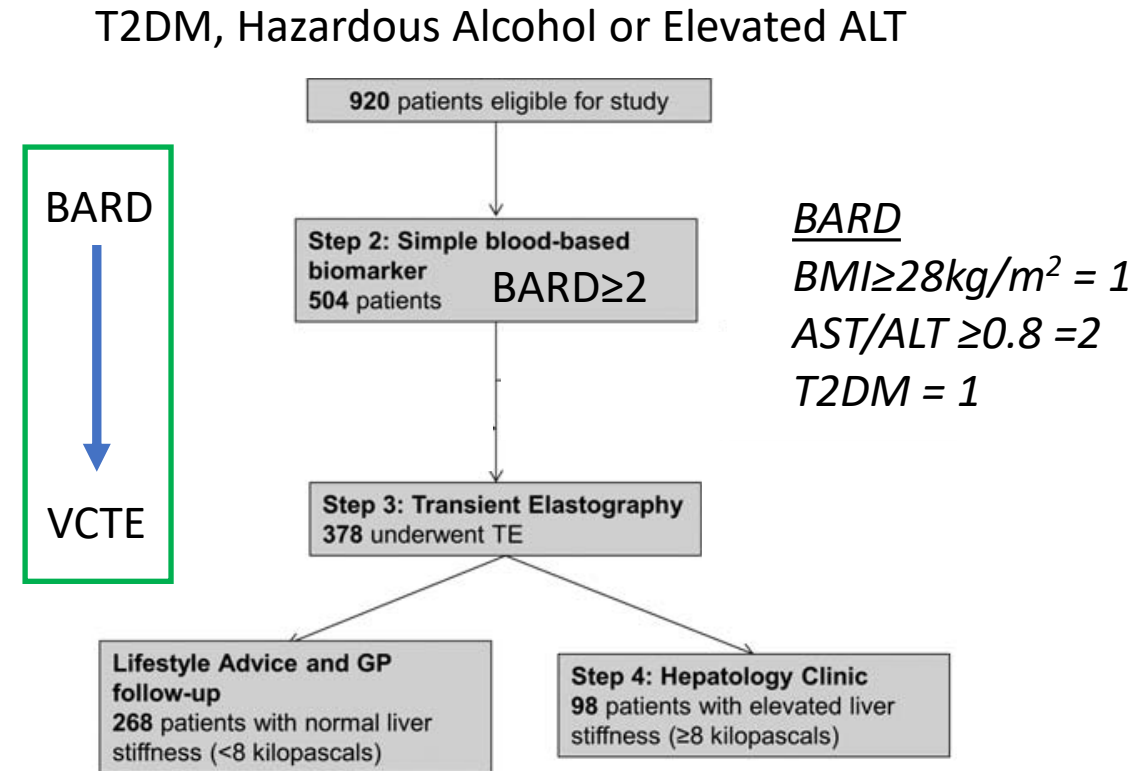
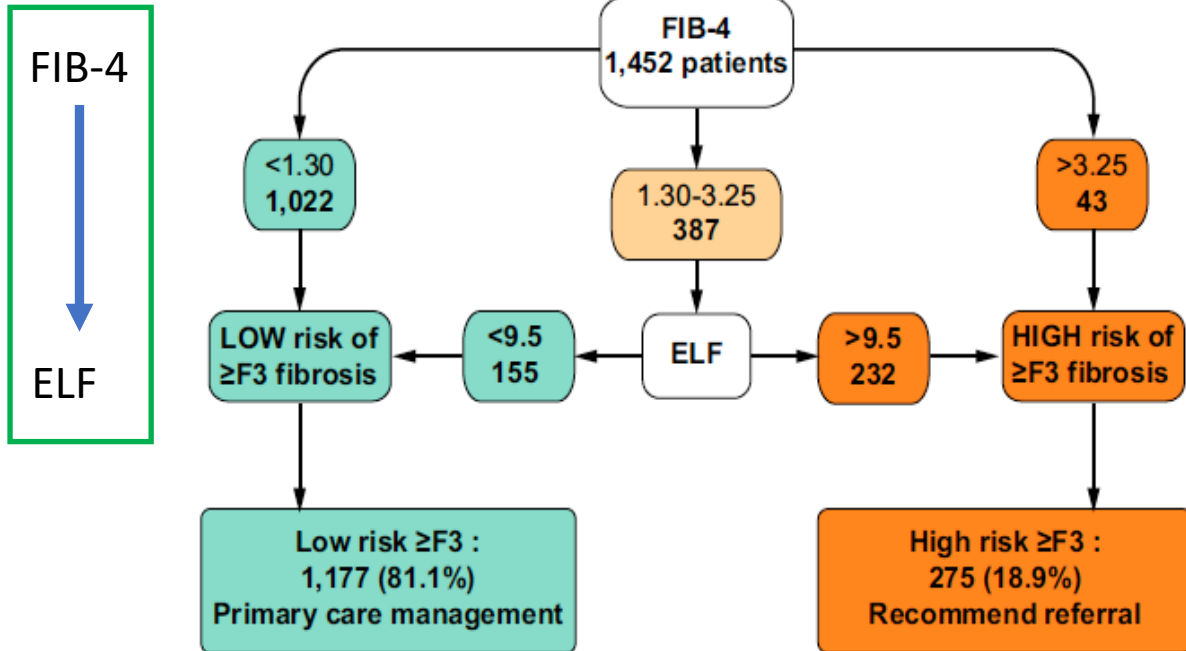


Sensitivity & Specificity of NIT's for F3/4 in NAFLD

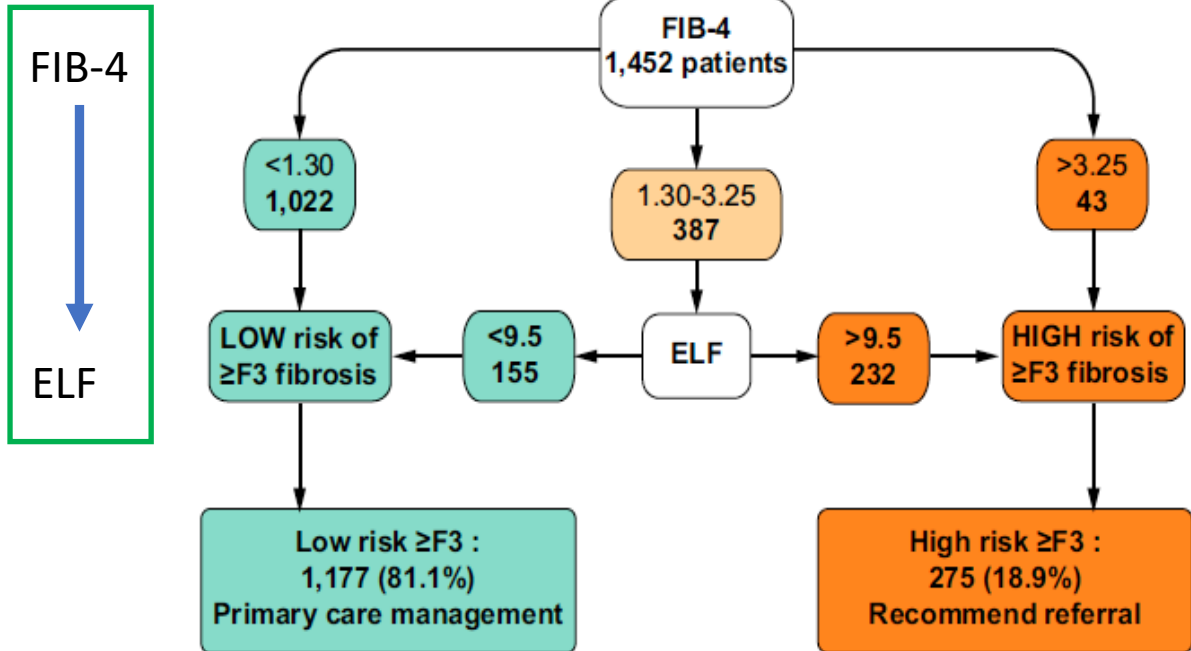


Xiao et al, Hepatology 2017; Ampuero et al, CGH 2019; Daniels et al, Hepatology 2019; Vali et al, J Hepatol. 2020

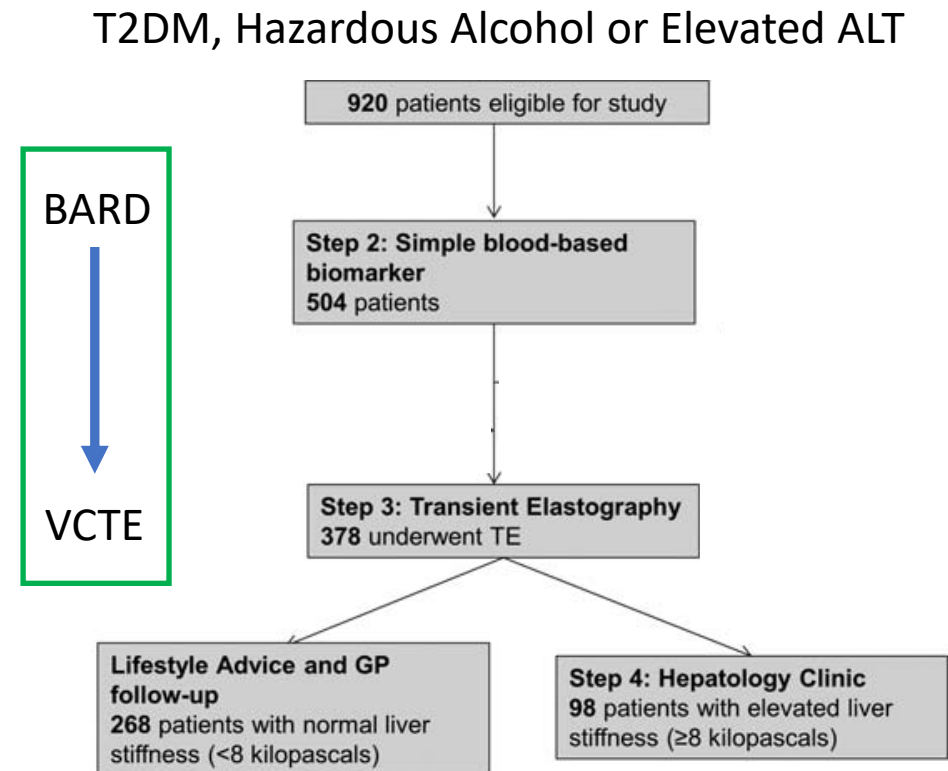
Screening Strategies in Primary Care for NAFLD



Screening in Primary Care Increases Cirrhosis Detection and Reduces Unnecessary Referrals

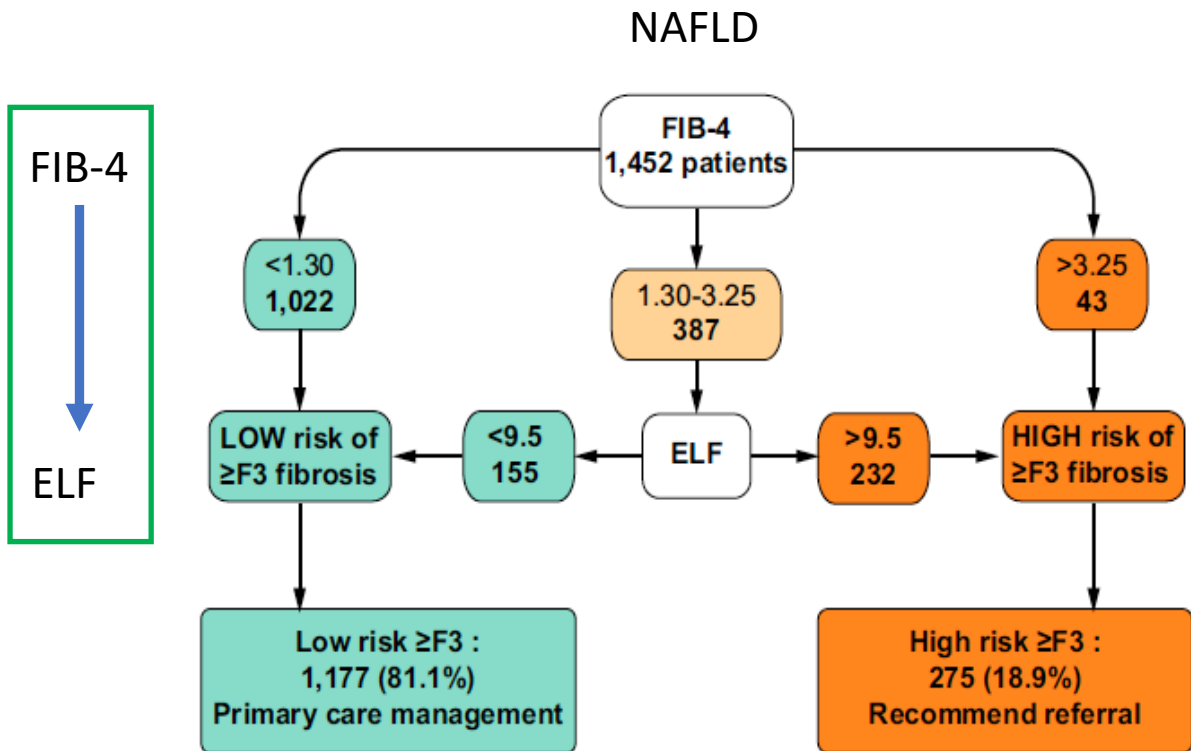


Increased Cirrhosis Detection
 (22 new cases, 8% increase in diagnosis rate)
Reduced 'unnecessary' referrals
 (22% reduction)

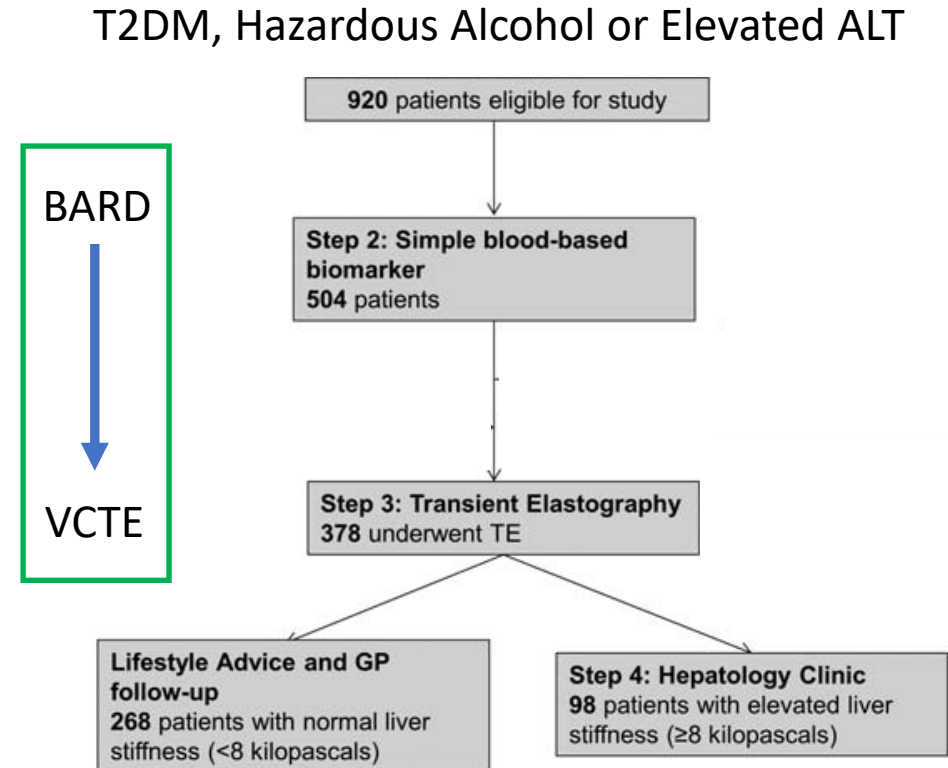


Increased Cirrhosis Detection
 (11 new cases, 140% increase in prevalence)

Screening in Primary Care Increases Cirrhosis Detection and Reduces Unnecessary Referrals



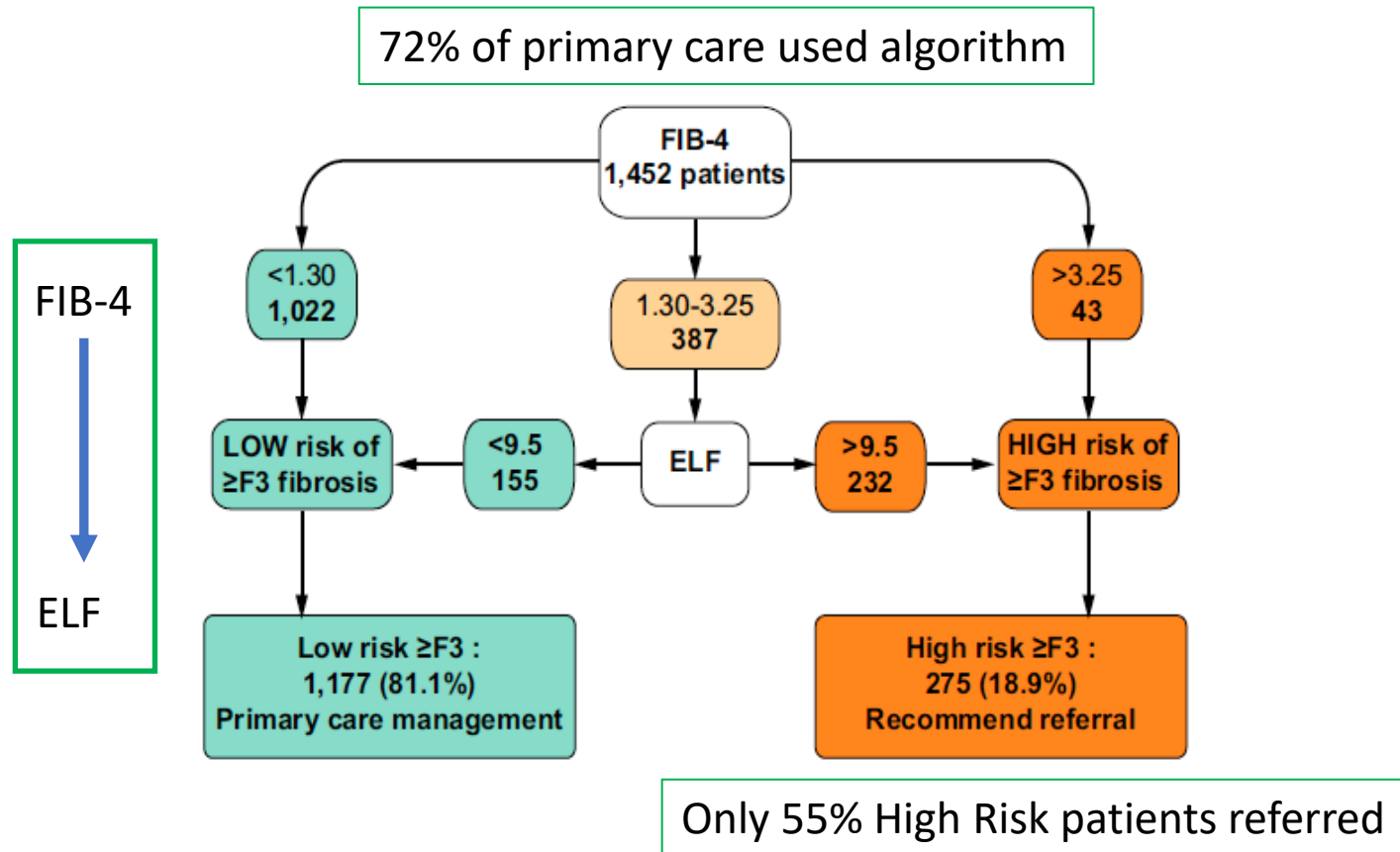
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Increased Cirrhosis Detection
 (11 new cases, 140% increase in prevalence)

82-100% of cirrhosis missed if FIB4 or APRI used
 Instead of VCTE

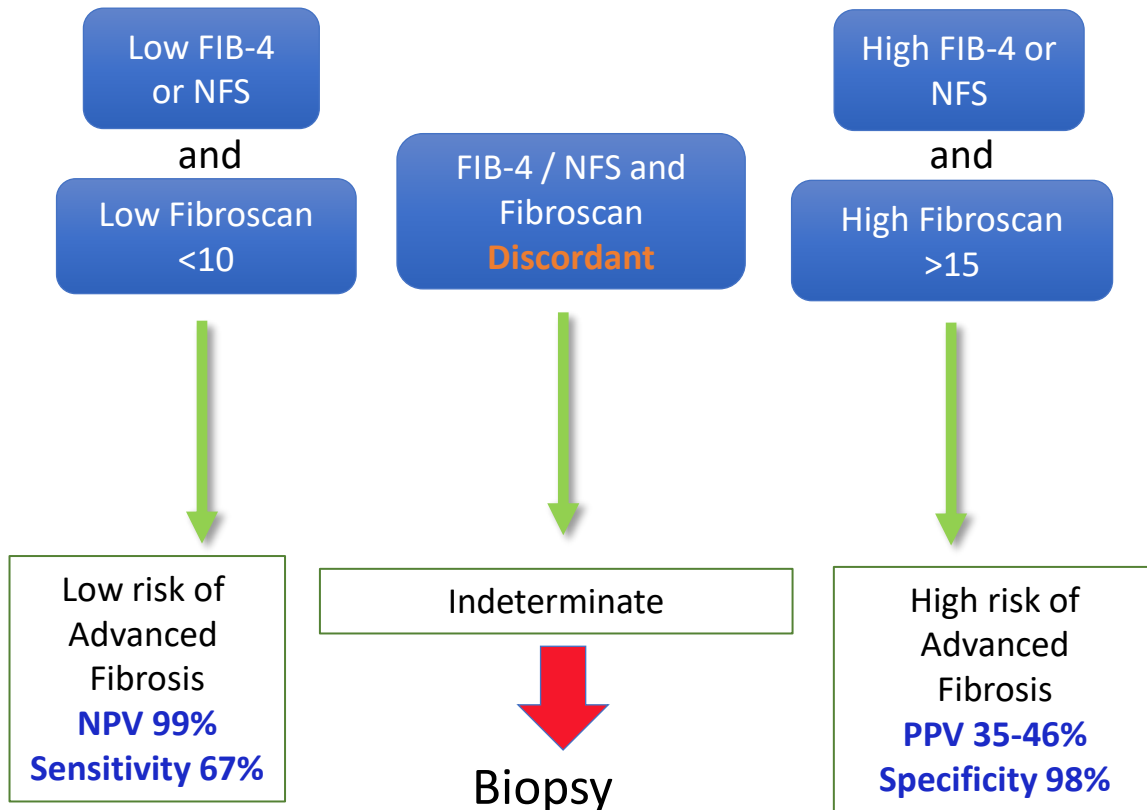
Screening Strategies in Primary Care: Importance of Implementation and Linkage to Care



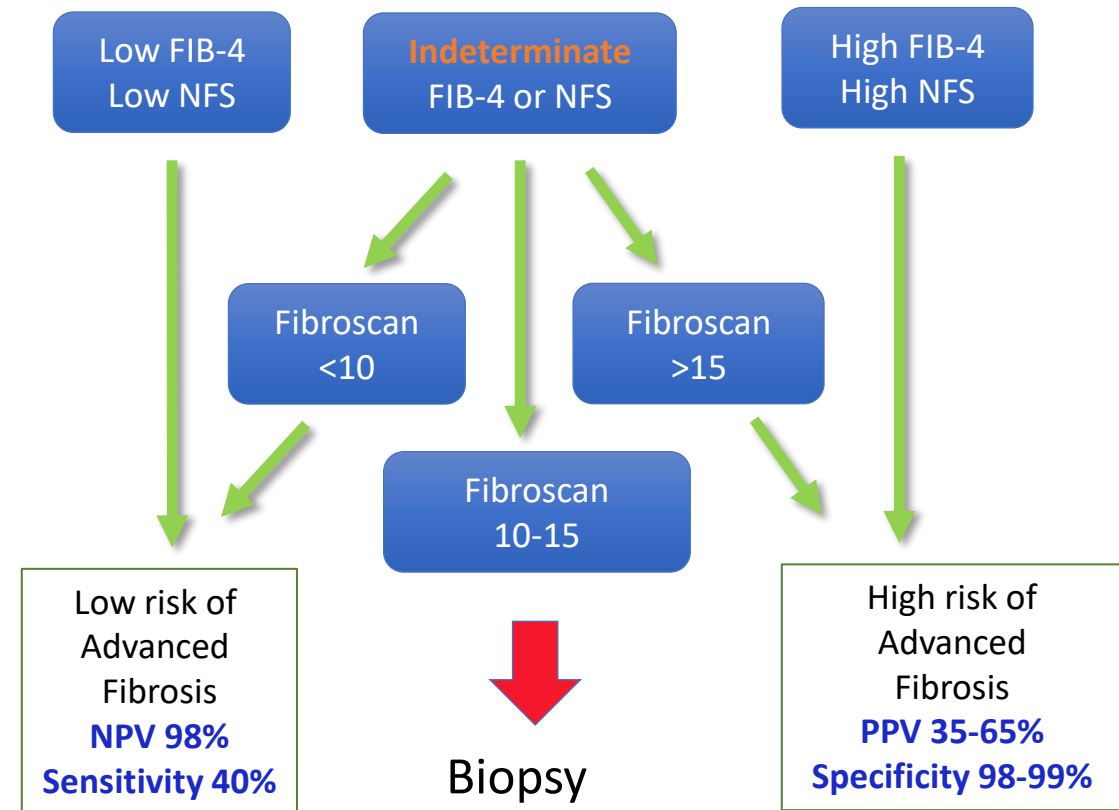
Combination Fibrosis Testing: Concurrent vs. Sequential

N=593 Biopsy Proven NAFLD, 3.7% F3/4

Concurrent Testing



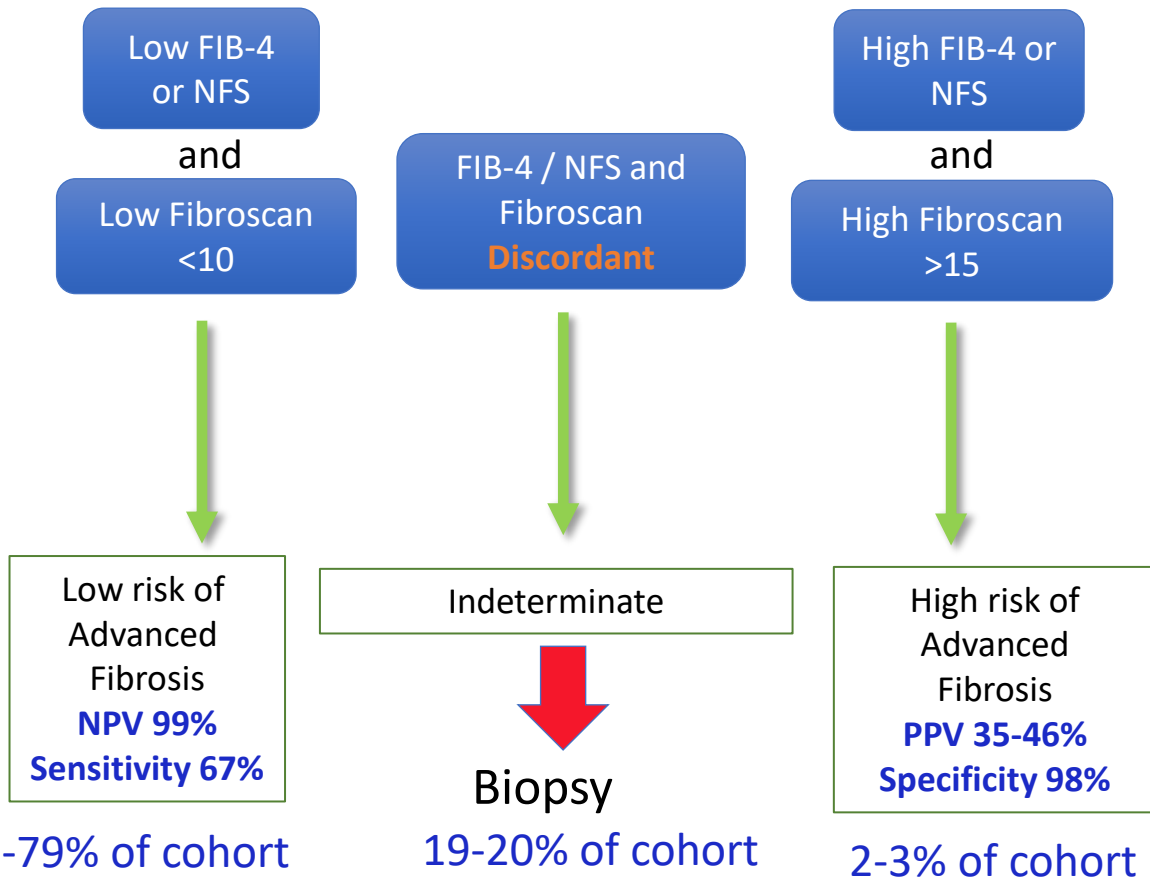
Sequential Testing



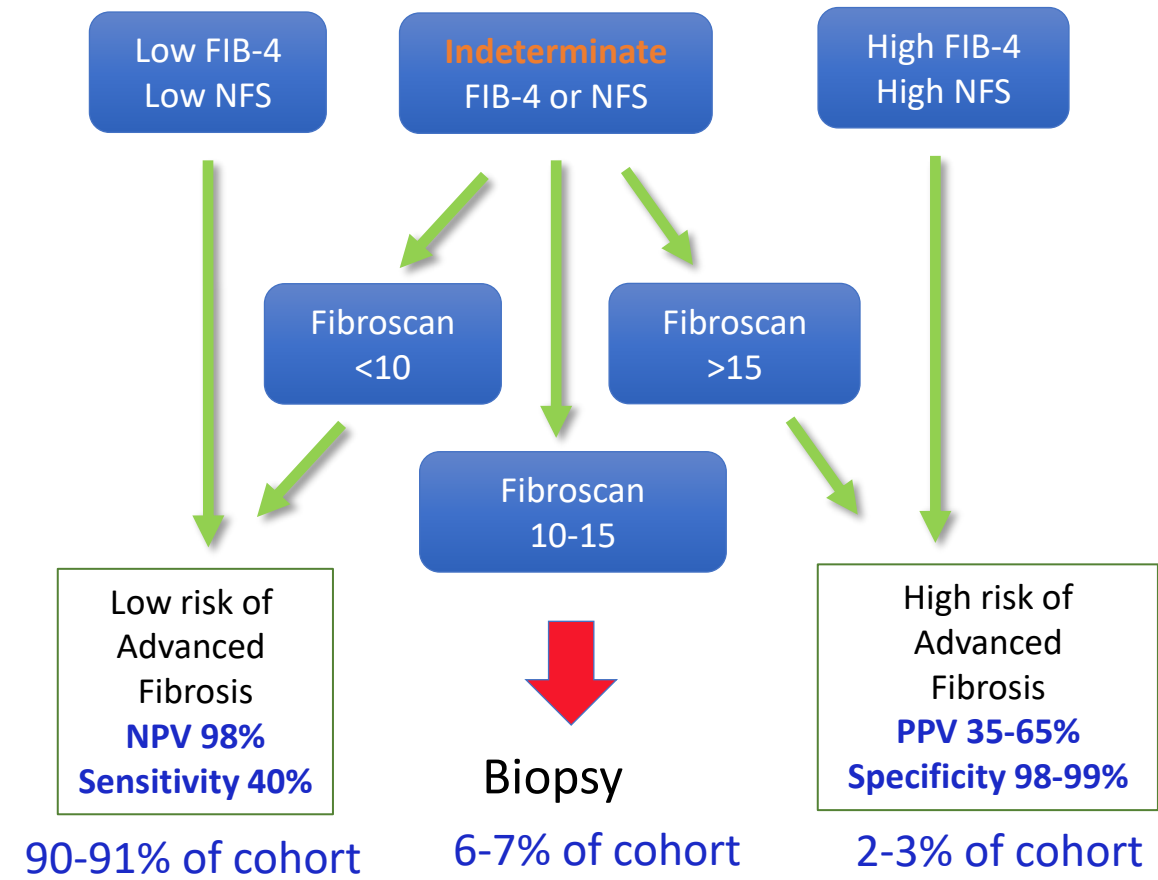
Combination Fibrosis Testing: Concurrent vs. Sequential

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Concurrent Testing

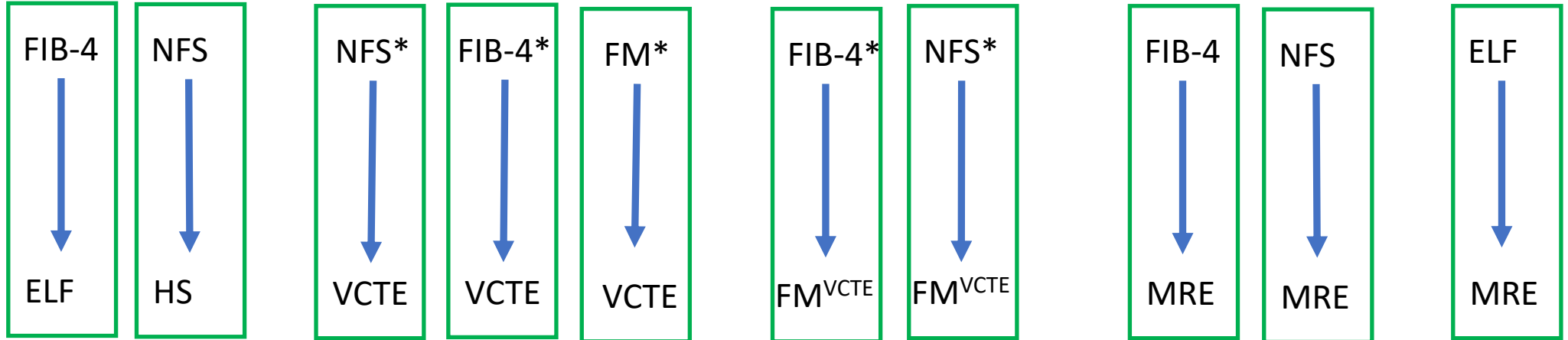


Sequential Testing



What is the Optimal Combination for Diagnosis of Advanced Fibrosis?

Validation set
N=313
Biopsy proven
NAFLD



Accuracy	?	83		88	91	88		89	86		?	?		?
Sensitivity	?	57		83	85	83		86	83		?	?		?
Specificity	?	100		92	95	92		91	87		?	?		?
Biopsy rate	?	35		33	30	27		21	20		?	?		?



*Optimized cut-offs
NFS: -1.669 / 0.927
FIB-4: 1.04 / 2.67

Cost of Non-invasive Strategies

- Cost Comparison: FIB4 + ELF, FIB4 + VCTE, ELF, FIB4
- Incremental Cost per Correct Dx: FIB4, NFS, NFS + VCTE, NFS + ELF
- Cost-Effectiveness: NFS, VCTE, NFS + VCTE, Liver biopsy
- Cost-Effectiveness: FIB4 + VCTE; FIB4 + MRE; FIB4 + Bx, VCTE + Bx, FIB4, MRE + Bx, VCTE, MRE, Bx.

Identifying F2/3 NASH Patients for Clinical Trials

FAST	
Fibroscan LSM + CAP + AST	
Validation n=1026	
AUROC	0.85
Sensitivity*	89%
Specificity^	92%
PPV^	69%
NPV*	94%
Grey Area	27%

MACK-3	
AST + HOMA + CK18	
Validation n=282	
AUROC	0.85
Sensitivity*	90%
Specificity^	94%
PPV^	82%
NPV*	97%
Grey Area	36%

MetS + AST ≥35	
NPV	98-99%

NIS4	
Mir-34a + α2M + YLK-40 + HbA1c	
Validation n=x	
AUROC	0.83
Sensitivity	74%
Specificity	75%
PPV	76%
NPV	73%
Grey Area	0

*Lower cut-off, ^ Higher cut-off

Role of Liver Biopsy



- **Diagnostic** doubt
 - ALT >180 IU/l
 - Auto-immune hepatitis, drug hepatotoxicity, viral hepatitis
- Determine **clinical trial** eligibility
- **Indeterminate or unreliable** non-invasive test
 - *Suspect advanced fibrosis/cirrhosis*
- **Conflicting** NIT/clinical assessment/imaging
 - *Suspect advanced fibrosis/cirrhosis*
- Should not be done in primary care

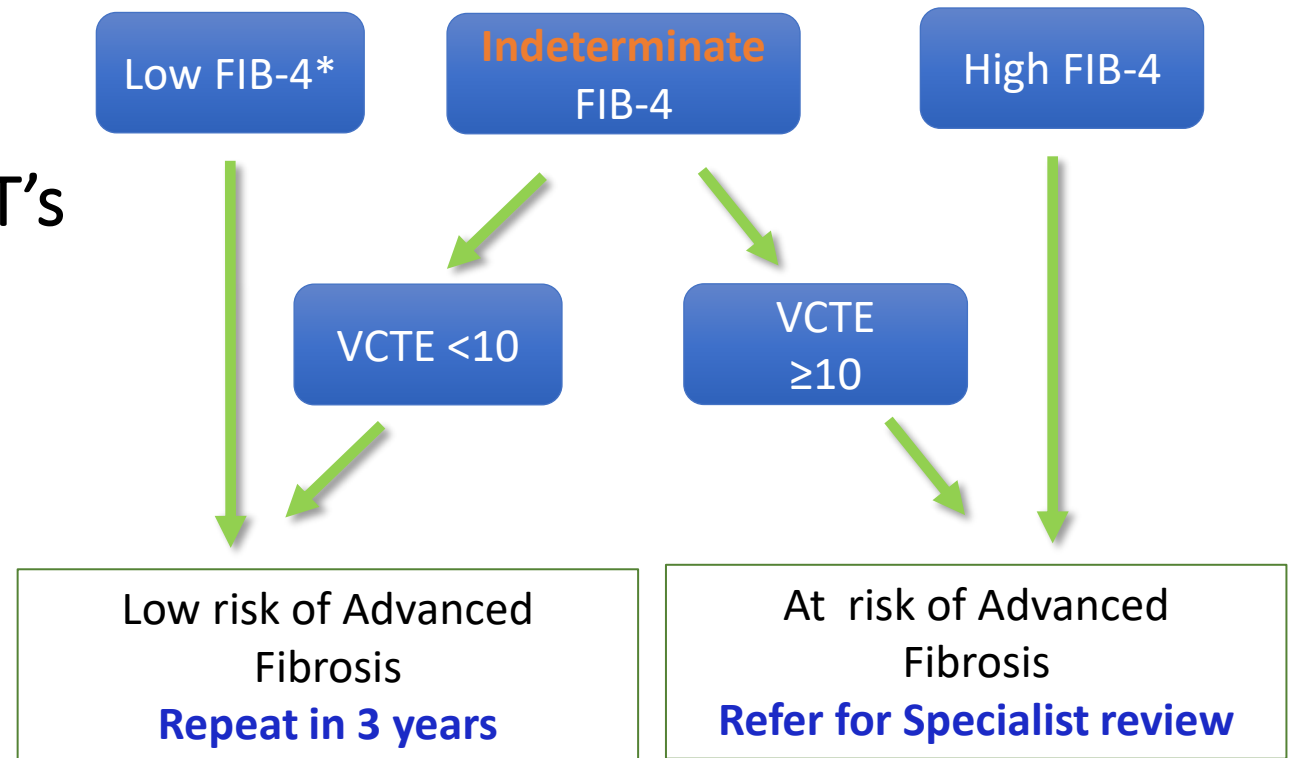
Initial Assessment of NAFLD

Cardiovascular Risk

- ASCVD Risk Calculator
- Simple 7 Modifiable Risk Factors

Fibrosis Assessment

- Clinical Risk Factors
- Potential confounders of NIT's
- Non-invasive Testing



* Modified low cut-off of 1.04

Summary

- **CVD Risk Prediction** essential for NAFLD patients
- Sequential NIT's in primary care **increases cirrhosis detection** and **reduces specialist referrals**
- Consider **revised cut-offs** for initial screening fibrosis test to increase sensitivity
- **Further data is required** to determine the optimal screening and confirmatory test
- **Screening intervals** for advanced fibrosis in primary care should be no greater than 5 yearly
- **Engagement, education and clinical support systems** with primary care critical for successful screening.