Circulating Biomarkers and their Application for a Prognostic Context of Use

FDA biomarker qualification and marketing authorization

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Liver disease biomarkers

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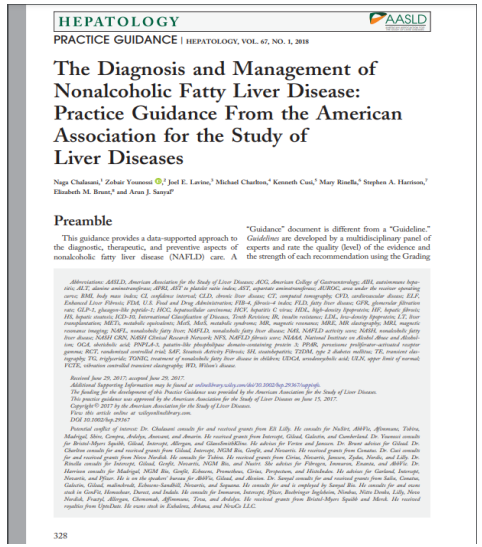
Simple Biomarker

Non-proprietary Algorithm & Established Clinical Practice



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The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

Preamble

This guidance provides a data-supported approach to the diagnostic, therapeutic, and preventive aspects of nonalcoholic fatty liver disease (NAFLD) care. A "Guidance" document is different from a "Guideline." *Guidelines* are developed by a multidisciplinary panel of experts and rate the quality (level) of the evidence and the strength of each recommendation using the Grading

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Examples:
ALT
NFS
FIB-4
APRI

Laboratory Developed Test (LDT)

Proprietary Test/Algorithm

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Examples:
NASH FibroSure
FibroMeter NAFLD
FIBROSpect NASH
LIVERFASt

Commercial Kit or Software

Proprietary Test/Algorithm

FDA

U.S. Marketing Authorization

Examples:
ELF
AFP-L3/DCP

Not Available in U.S.

Examples:
OWLiver
PRO-C3

Laboratory developed tests (LDTs)

NASH FibroSure LabCorp/BioPredictive	FibroMeter NAFLD ARUP/Echosens	FIBROSpect NASH Prometheus Laboratories	LIVERFASt Fibronostics
"surrogate marker of liver fibrosis"	"surrogate marker of liver fibrosis" "Fibrosis stage…strongest predictor of mortality associated with NAFLD"	"…aids in the detection, staging, and monitoring of liver fibrosis…risk stratify"	"…liver evaluation with the staging of fibrosis…"

- Indirect claims for prognosis are primarily based on correlation to histology.
- None of the above LDTs have been FDA cleared or approved.
- LDTs have no requirement for clinical validation (correlation to outcomes).

Other Challenges with LDTs:

Only single U.S. laboratory permitted to run the test
Issues with logistics and delays

VALID Act in 2022?
Could see FDA regulation of LDTs in near future

Liver disease tests with FDA marketing authorization

Biomarker	Manufacturer	Intended Use (Excerpt)	Comments
AFP-L3 (% Ratio to Total AFP) & **DCP** (PIVKA-II)	FUJIFILM	The device is intended for in vitro diagnostic use as an aid in the risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma (HCC) in conjunction with other laboratory findings, imaging studies and clinical assessment.	• For early detection of HCC (~60% of study subjects with HCC diagnosis had HCC at baseline) • Validated in viral hepatitis only: HBV+ (N=45), HCV+ (N= 330), HBV+/HCV+ (N= 119)
ELF	Siemens Healthineers	ADVIA Centaur ELF 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.	• Prognostic of histological progression • Prognostic of outcomes (decompensation, LTx, death)

Not every ELF is the same…

			
Proven Track Record	✓	✓	✓
Precise & Accurate	✓	✗	✓
High Throughput	✗	✓	✓
Quality Control	✗	✓	✓
Ships to CLIA Labs	✗ (restricted to Middle Earth)	✗ (restricted to North Pole)	✓
Indicated for NASH	✗	✗	✓

The real ELF™ uses ADVIA Centaur or Atellica IM reagents.

ELF Test: Prognostic clinical utility

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Healthy

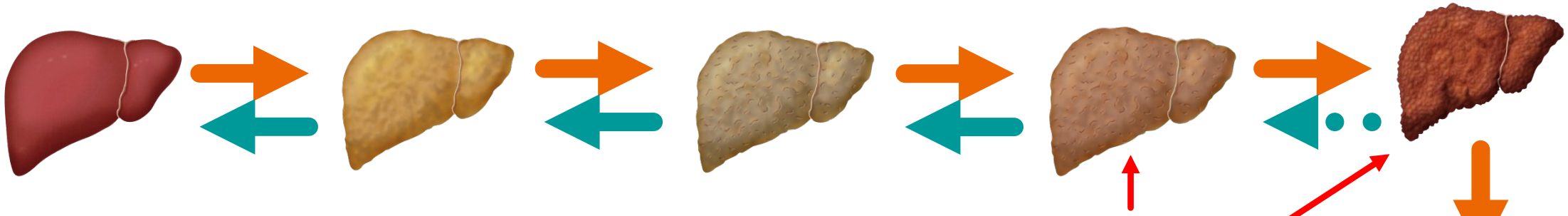
NAFLD
Fat accumulation

NASH
NAFLD + inflammation

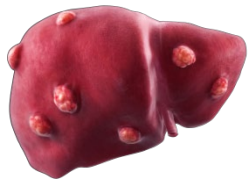
NASH + Bridging Fibrosis
Stage F3

NASH + Cirrhosis
Stage F4

Advanced Fibrosis



ELF Score	Risk of Disease Progression
< 9.8	Lower
≥9.8 – <11.3	Mid*
≥11.3	Higher



End-Stage Liver Disease
Decompensation
Liver Transplant
Hepatocellular Carcinoma#
Death

A claim specific to HCC progression risk is not available in the US.
None of the subjects in the US IFU performance claims had HCC as a first liver-related event.

* In the Mid group, the risk of disease progression is similar to the pre-test risk. Pre-test risk refers to the likelihood of disease progression in the overall intended use population without considering the ELF score.

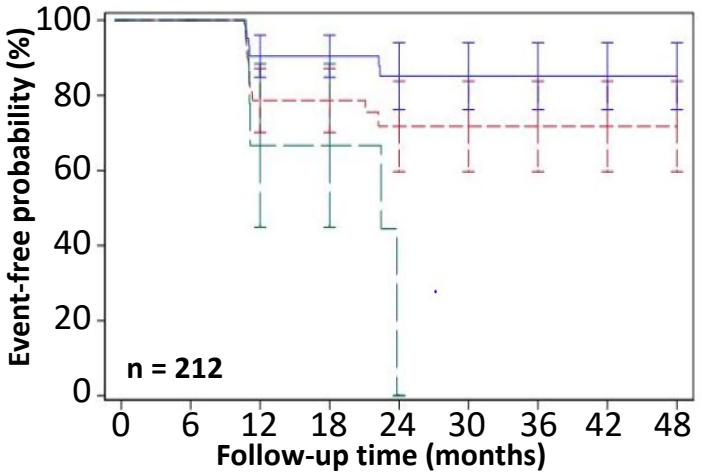
Wree A, et al. Nat Rev Gastroenterol Hepatol. 2013;10:627-36.
Vernon G, et al. Aliment Pharmacol Ther. 2011;34:274-85.
Schattenberg JM, et al. Curr Opin Lipidol. 2011;22:479-88.
Angulo P, et al. Hepatology. 1999;30:1356-62.

ELF Test: Clinical performance claims in label

F3 (Bridging Fibrosis)

Progression to Cirrhosis

Score	n	Events	Risk	Hazard Ratio
<9.80	105	12	11.4%	1.00
≥9.80 to <11.30	89	21	23.6%	2.30
≥11.30	18	8	44.4%	4.58

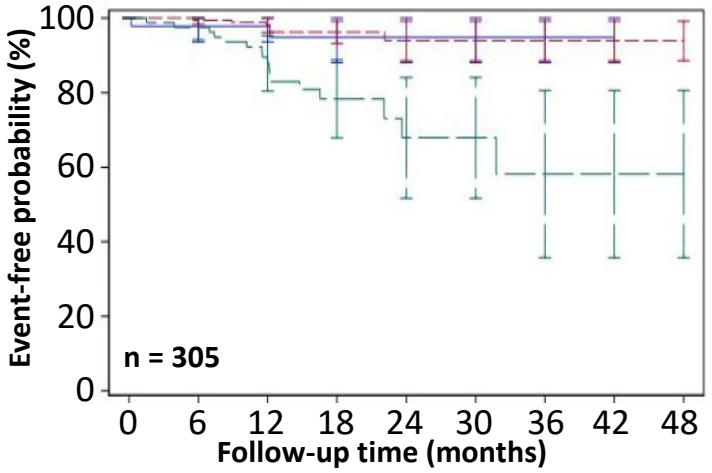


Data pooled from placebo arms of 2 clinical trials (SIM F3, STELLAR-3)

F4 (Compensated Cirrhosis)

Progression to Liver Related Events

Score	n	Events	Risk	Hazard Ratio
<9.80	47	2	4.3%	1.00
≥9.80 to <11.30	177	7	4.0%	0.93
≥11.30	81	17	21.0%	5.84



Data pooled from placebo arms of 3 clinical trials (SIM F4, STELLAR-4, NASH-CX)

ELF IFU 11205858_EN Rev. 01, 2021
See also: Sanyal AJ et al. Hepatology. 2019;70(6):1913–1927
Are VS et al. Clin Gastroenterol Hepatol. 2021;19(6):1292–1293.e3
Younossi ZM et al. Gastroenterology 2021;160:1608–1619.

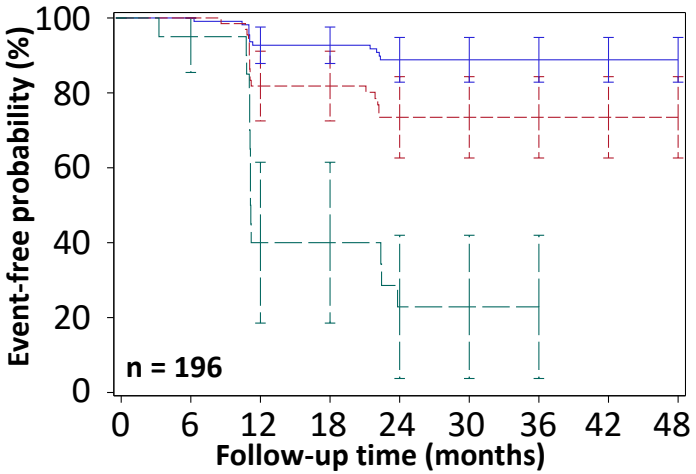
ELF Test: Clinical performance (using intra-study pooling)

F3 (Bridging Fibrosis)

Progression to Cirrhosis

Score	n	Events	Risk	Hazard Ratio
<9.80	110	12	10.9%	1.00
≥9.80 to <11.30	66	17	25.8%	2.61
≥11.30	20	15	75.0%	10.31

Data pooled from 3 treatment and placebo arms of SIM F3 Phase 2b study



Regression to F2*

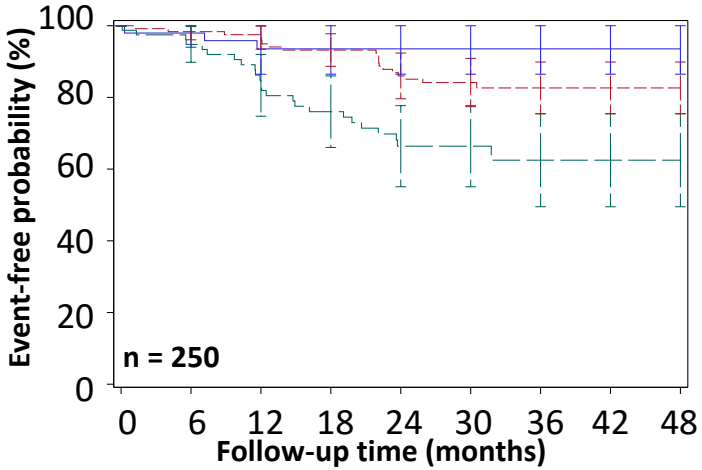
Score	n	Events	Likelihood
<9.80	110	45	40.9%
≥9.80 to <11.30	66	14	21.2%
≥11.30	20	0	0.0%

F4 (Compensated Cirrhosis)

Progression to Liver Related Events

Score	n	Events	Risk	Hazard Ratio
<9.80	49	3	6.1%	1.00
≥9.80 to <11.30	122	7	15.6%	2.42
≥11.30	79	24	30.4%	6.13

Data pooled from 3 treatment and placebo arms of SIM F4 Phase 2b study



Regression to F3*

Score	n	Events	Likelihood
<9.80	44	10	22.7%
≥9.80 to <11.30	116	14	12.1%
≥11.30	65	3	4.6%

* This claim has not been reviewed by the FDA and is not available in the U.S. for routine clinical use.

See also: Sanyal AJ et al. Hepatology. 2019;70(6):1913–1927

Data from placebo arms of these studies are included in the pooled study analyses in the U.S. Instructions for Use. Data on file at Siemens Healthineers.

ELF Test: Clinical trial prognostic enrichment strategies

GOAL: Enrichment of trial to increase the likelihood of disease progression events (i.e. more events, faster).

ELF Score	Risk of Disease Progression
< 9.8	Lower
≥9.8 – <11.3	Mid
≥11.3	Higher

ELF Score ≥ 9.8: Subjects most likely to show disease progression (histological or clinical)

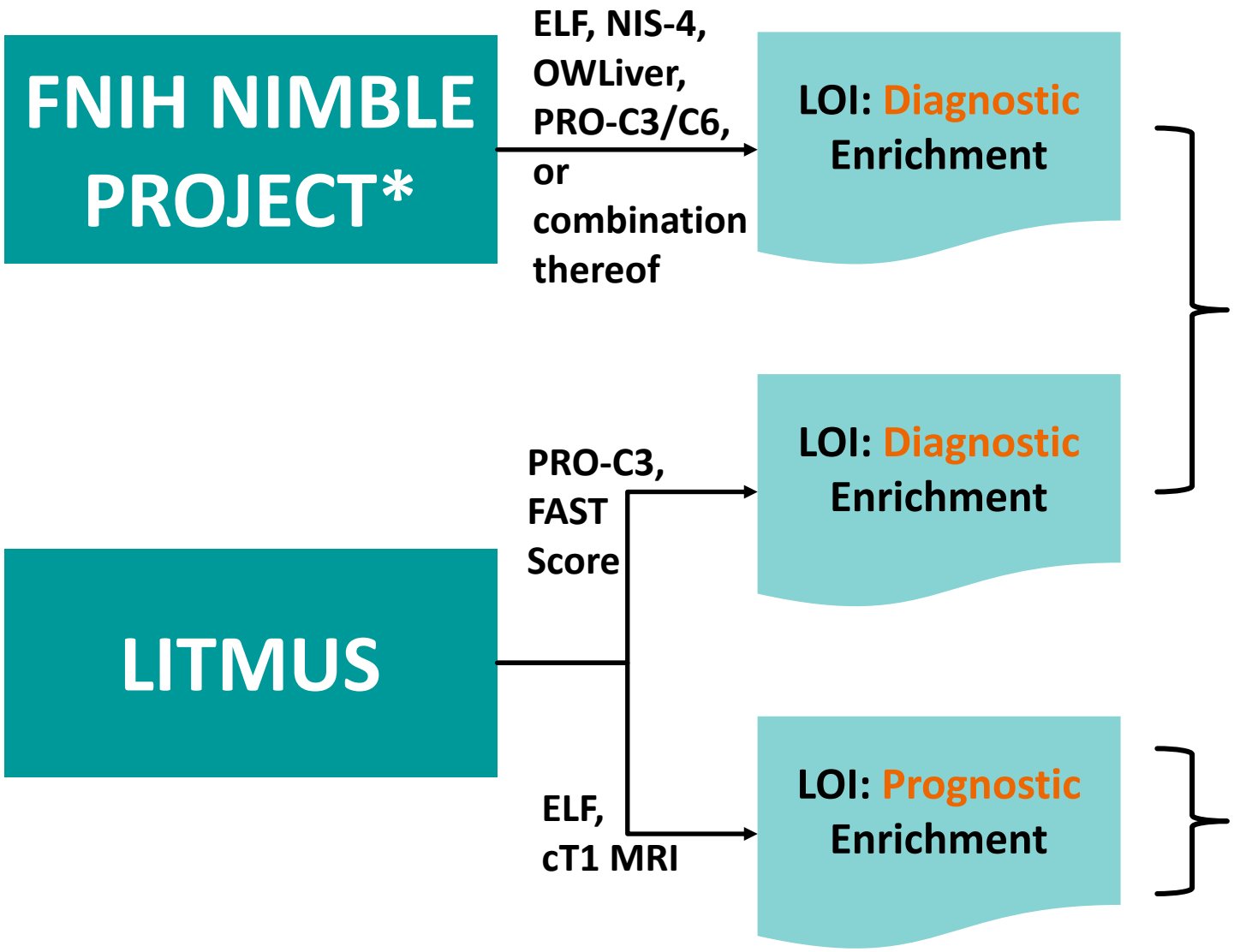
GOAL: Enrichment of trial to reduce the number of subjects unlikely to improve with treatment.

ELF Score	Likelihood of Regression*
< 9.8	Higher
≥9.8 – <11.3	Mid
≥11.3	Lower

ELF Score < 11.3: Subjects most likely to show histological regression

* This claim has not been reviewed by the FDA and is not available in the U.S. for routine clinical use.

Biomarker qualification submissions by major consortia



COU: …to identify patients likely to have liver biopsy histopathologic findings of nonalcoholic steatohepatitis (NASH) and with a nonalcoholic fatty liver disease activity score (NAS) ≥4 and liver fibrosis stages 2 or 3 (by Brunt/Kleiner scale)

COU: …to identify patients who are more likely to experience clinical endpoints such as progression to cirrhosis, hepatic decompensation events, death, or liver transplant (in patients with biopsy-proven NAS ≥4 & F2/F3)

* The Foundation for the National Institutes of Health Non-Invasive Biomarkers of Metabolic Liver Disease Project https://fnih.org/our-programs/biomarkers-consortium/programs/nimble

Moving biomarkers into clinical practice: Potential challenges

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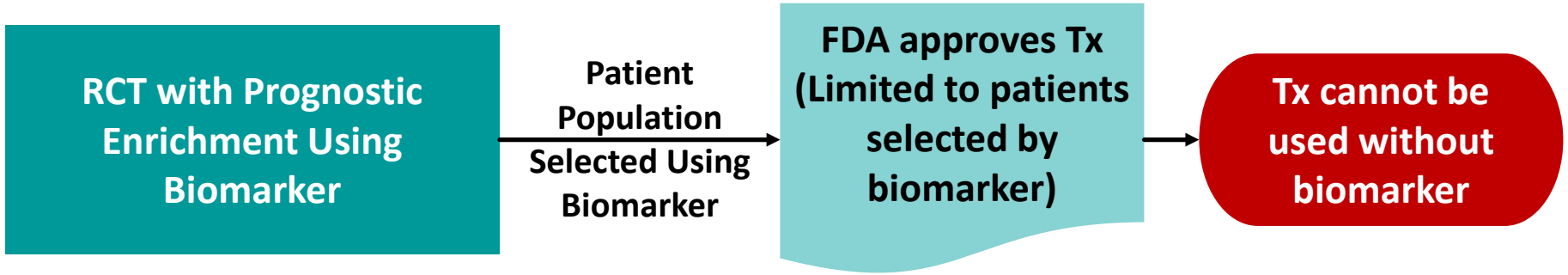
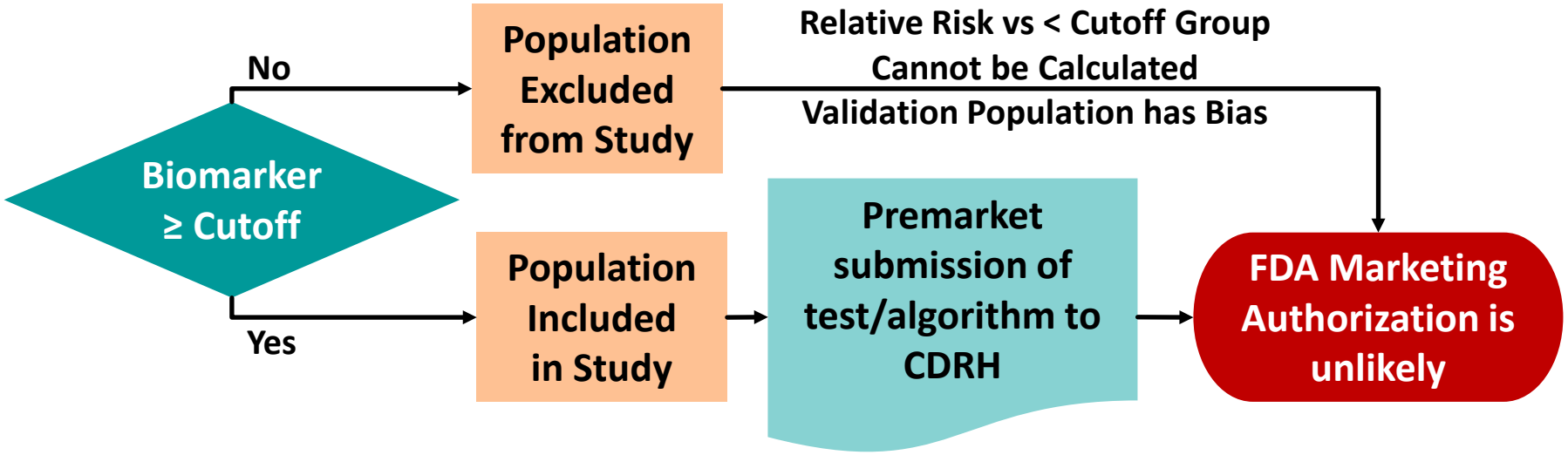
Pitfall: Biomarker is not commercially available for sale in the U.S. or not available for clinical use



Potential Solutions:

1. Use biomarker that has FDA marketing authorization
2. Validate biomarker in parallel to RCT

Pitfall: Prognostic enrichment could prevent validation of biomarker using the same dataset



Potential Solutions:

1. Validate biomarker using a separate RCT (placebo arm)
2. Validate using banked samples with known outcomes (CAUTION: Sample stability must be demonstrated)

Serum + imaging biomarker combinations: More challenges

CDRH expects clinical treatment algorithms to be cleared/approved if sold as software (stand-alone / with instrument)

- Applies even if all components individually have marketing authorization.
- For drug label: How can a population be described if the test is not cleared/approved?

What if components are sold by different manufacturers?

- Companies would need to cooperate with pre-market submission, manufacturing and distribution.
- Challenges with data sharing, coordination of product lot release, etc.

Summary

From a Regulatory Standpoint:

The best choice for a serum biomarker is one that already has FDA marketing authorization for that context of use.

Currently:

The ELF Test is the only prognostic tool for NASH patients with FDA marketing authorization.

Thank you for your attention

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Santa Needs his ELF Test