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LIVER FUNCTION TESTS REIMAGINED: EMERGING BIOMARKERS, NON-INVASIVE DIAGNOSTIC ALGORITHMS, AND THE 2023–2025 GUIDELINE REVOLUTION

Naveen Prabakaran C

Associate Professor of Biochemistry,

Department of International Studies,

Asia International University, Bukhara, Uzbekistan

drcnpkaran.oxu@gmail.com

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Abstract: Liver function tests (LFTs) remain the most frequently ordered laboratory panel in clinical medicine, yet conventional aminotransferase-based testing has limited sensitivity for early fibrosis and often misclassifies clinically significant disease. Between 2023 and 2025, hepatology practice underwent substantial revision: fatty liver disease was renamed under the steatotic liver disease (SLD) framework, non-invasive fibrosis algorithms combining indirect indices with direct biomarkers were formally endorsed, imaging-based thresholds were codified, and transplant-allocation scoring was refined through MELD 3.0. This article reviews newer test protocols including the Enhanced Liver Fibrosis (ELF) test, vibration-controlled transient elastography with controlled attenuation parameter (CAP), the GALAD score, and algorithm-driven reflex pathways such as intelligent Liver Function Testing (iLFT) alongside the 2023–2025 AASLD and EASL–EASD–EASO guideline updates, to provide a concise, exam-oriented synthesis for clinicians and students.

Keywords: liver function tests; non-invasive fibrosis markers; MASLD; Enhanced Liver Fibrosis test; MELD 3.0; clinical guidelines

1. Introduction

Conventional LFTs such as Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin, albumin, and prothrombin time describe a pattern of hepatocellular or cholestatic injury but do not, in isolation, stage fibrosis or reliably identify individuals who will progress to cirrhosis.[1] Population data show that only a minority of patients with an abnormal LFT have clinically significant liver disease, while many with early fibrosis are missed on routine testing alone.[2] This gap has driven a decade of work on non invasive fibrosis biomarkers, and 2023–2025 marked a period of consolidation, in which several of these tools were formally incorporated into practice guidelines.[3,4]

2. The Conventional Liver Function Test Panel

Table 1 summarises the standard panel still used as the first step of any liver evaluation. Its principal limitation is that ALT and AST can remain within the reference interval despite advanced fibrosis, and isolated enzyme elevations rarely indicate a specific aetiology, necessitating reflex or second line testing.[2]

Table 1. Conventional liver function test panel and its clinical significance.

Test	Typical Adult Reference Range	Primary Clinical Significance
ALT	7–40 U/L (healthy range studies suggest lower cutoffs)	Marker of hepatocellular injury; most liver specific enzyme
AST	8–40 U/L	Hepatocellular injury; AST:ALT ratio aids alcohol related disease
ALP	40–129 U/L	Cholestatic/biliary injury; also elevated in bone disease
GGT	8–61 U/L (M); 5–36 U/L (F)	Confirms hepatobiliary origin of raised ALP; alcohol marker
Total bilirubin	0.3–1.2 mg/dL	Excretory function; conjugated fraction localises cause
Albumin	3.5–5.0 g/dL	Synthetic function; falls with chronic liver disease
PT/INR	INR 0.8–1.1	Synthetic/coagulation function; component of MELD scores

3. Beyond Aminotransferases: Emerging Biomarkers and Fibrosis Tests

Indirect indices such as the Fibrosis-4 (FIB-4) index and the NAFLD Fibrosis Score (NFS) use routinely available variables to triage risk but perform poorly when used alone for population screening, generating a large indeterminate zone.[10] Direct fibrogenesis markers, particularly the Enhanced Liver Fibrosis (ELF) test which combines hyaluronic acid, procollagen III N-terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase-1 (TIMP-1) offer materially better discrimination.[9] A 2023 population based comparison found ELF alone, or FIB-4 followed by ELF in indeterminate cases, substantially reduced unnecessary specialist referrals compared with FIB-4 or NFS alone (Figure 1).[10]

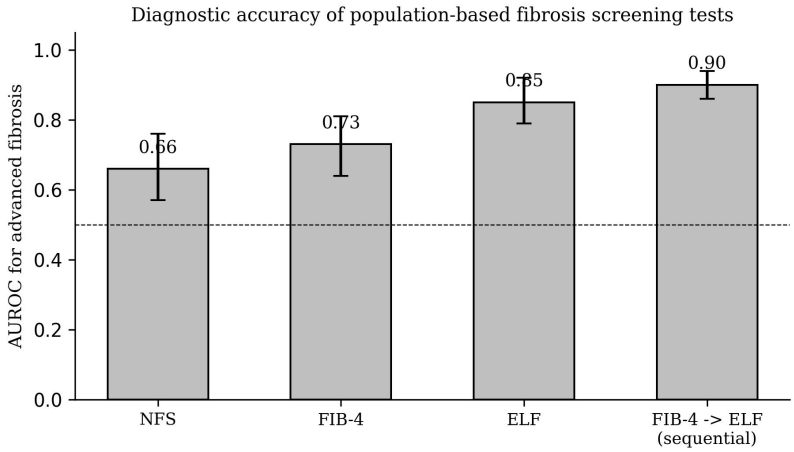


Figure 1. Diagnostic accuracy (AUROC with 95% CI) of NFS, FIB-4, ELF, and the sequential FIB-4→ELF strategy for advanced fibrosis, based on population screening data.

Imaging based non invasive tests have also matured. Vibration controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) now carries guideline defined thresholds, a CAP of 275 dB/m or higher indicates at least grade 1 hepatic steatosis under the 2024 AASLD imaging based practice guideline.[7] For hepatocellular carcinoma (HCC) surveillance in cirrhotic patients, the GALAD score (Gender, Age, AFP-L3, AFP, DCP) provides a validated serological alternative to ultrasound only surveillance.[12] Table 2 summarises these newer tools alongside their principal use and supporting evidence.

Table 2. Newer non-invasive biomarkers and composite scores used in liver disease assessment.

Test / Score	Components	Principal Use	Key Evidence
FIB-4	Age, AST, ALT, platelet count	First line fibrosis triage in primary care	AUROC ~0.73 for advanced fibrosis in population screening[10]
ELF test	Hyaluronic acid, PIIINP, TIMP-1	Second line/confirmatory direct fibrosis marker	AUROC ~0.85 for advanced fibrosis; ≥9.8 triggers referral[9,10]
VCTE + CAP (FibroScan)	Liver stiffness (kPa); controlled attenuation parameter	Bedside fibrosis staging and steatosis grading	CAP ≥275 dB/m detects ≥ grade 1 steatosis per 2024 AASLD guideline[7]
GALAD	Gender, Age, AFP-L3,	Hepatocellular carcinoma risk	Validated serological surveillance model in

Test / Score	Components	Principal Use	Key Evidence
score	AFP, DCP	stratification	cirrhosis[12]
MELD 3.0	Bilirubin, INR, creatinine, sodium, albumin, sex	Transplant listing priority and cirrhosis prognosis	Improves 90-day mortality prediction; reduces female disparity[14,15]
iLFT pathway	Reflex LFTs + FIB-4/NFS + ELF, algorithm driven	Automated primary care triage of abnormal LFTs	43% increase in chronic liver disease diagnosis rate[11]

4. Newer Test Protocols: Algorithmic and Reflex Testing

Rather than ordering fibrosis scores as discrete, clinician initiated tests, several health systems have moved to automated, algorithm driven reflex pathways.[11] The intelligent Liver Function Testing (iLFT) pathway, introduced across NHS Tayside, automatically cascades etiological and fibrosis testing from an initial abnormal LFT result using predefined minimum diagnostic criteria, and reflexes to ELF testing when FIB-4/NFS results are indeterminate.[11] In its first three years of use, iLFT increased the rate of chronic liver disease diagnosis by 43% while allowing roughly three quarters of patients to safely avoid hospital referral.[11]

5. The Guideline Revolution, 2023–2025

5.1 A new nomenclature for fatty liver disease

In 2023, a multisociety Delphi consensus replaced non alcoholic fatty liver disease (NAFLD) with metabolic dysfunction associated steatotic liver disease (MASLD), introducing steatotic liver disease (SLD) as an umbrella term that also encompasses MetALD (combined metabolic and alcohol related disease) and alcohol related liver disease (ALD), removing the previous artificial dichotomy between metabolic and alcohol related causes.[3]

5.2 AASLD practice guidance (2023–2025)

The AASLD's 2023 practice guidance formalised the clinical assessment and management of MASLD,[4] and was updated in October 2024 to incorporate resmetirom, the first FDA approved MASH targeted pharmacotherapy.[6] A dedicated 2025 AASLD practice guideline on imaging based non invasive assessment codified elastography and MRI based thresholds for fibrosis and steatosis, including the CAP ≥275 dB/m criterion referenced above.[7]

5.3 EASL–EASD–EASO joint guideline (2024)

The 2024 joint European guideline updated case finding strategy for individuals with cardiometabolic risk factors, recommending stepwise non-invasive testing (typically FIB-4 followed by a second line elastography or ELF based test) rather than universal biopsy or

elastography, mirroring the AASLD's risk stratified approach and reinforcing FIB-4 as the preferred first line triage tool in primary care.[5,8]

5.4 MELD 3.0 and transplant prioritisation

For patients with established cirrhosis, MELD 3.0 replaced MELD-Na as the primary US transplant allocation score in 2023, adding serum albumin and female sex to the original bilirubin, INR, creatinine and sodium variables, and lowering the creatinine ceiling.[14] This reduces waitlist mortality and specifically improves access for female candidates, who were previously disadvantaged by creatinine based renal function estimation.[14,15]

6. Conclusion

The 2023 to 2025 period reframed liver function testing from a single abnormal enzyme trigger into a structured, risk stratified pathway. FIB-4 remains the pragmatic first line triage tool, but direct fibrosis markers such as ELF, elastography based CAP thresholds, HCC specific scores such as GALAD, and refined prognostic tools such as MELD 3.0 now sit within formally endorsed, algorithm driven protocols.[4,5,14] For clinicians and students alike, familiarity with this stepwise, guideline anchored approach rather than isolated enzyme interpretation is now the standard of care.

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