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DETECTING THE "SILENT EPIDEMIC" (MASLD AND MASH)

LiverSTAT and LiverFAST, Providing the Best Liver Assessment Tests in the Primary and Specialty Care Using Artificial Intelligence (AI) and Neural Network Technology

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Chronic liver diseases (CLDs), such as metabolic dysfunction - associated steatotic liver diseases (MASLD) and metabolic associated steatohepatitis (MASH) and chronic viral hepatitis, are leading causes of morbidity and mortality globally and usually develops over many years. The prevalence of MASLD has continued to increase in recent years and many remained undiagnosed or misdiagnosed.

The estimated global prevalence of MASLD among adults is 38.8% and is higher among males (40%) compared to females (26%). Patients often remain asymptomatic ("silent") despite having more severe liver disease and may present for the first time with complications of cirrhosis, including decompensation and hepatocellular carcinoma. Hence, strategies to triage MASLD patients are essential to ensure timely provision of appropriate care for patients with diseases of different severity. Patients with more severe diseases would require specialist care while those with milder diseases are best managed in a primary care setting.

A liver biopsy is required to diagnose steatohepatitis, which indicates a more severe form of the disease, and can be used to stage the degree of fibrosis. Histological changes constitute important endpoints in current therapeutic clinical trials for the disease. However, a liver biopsy requires technical expertise, is invasive and carries a small risk of serious complications. Moreover, it is limited by sampling and observer variability. These shortcomings have rendered it less practical to be used in routine clinical practice to assess severity of liver disease and to monitor response to intervention. Non-invasive tools are much desired to streamline the management of MASLD patients.

Diagnosis and Staging of Liver Disease
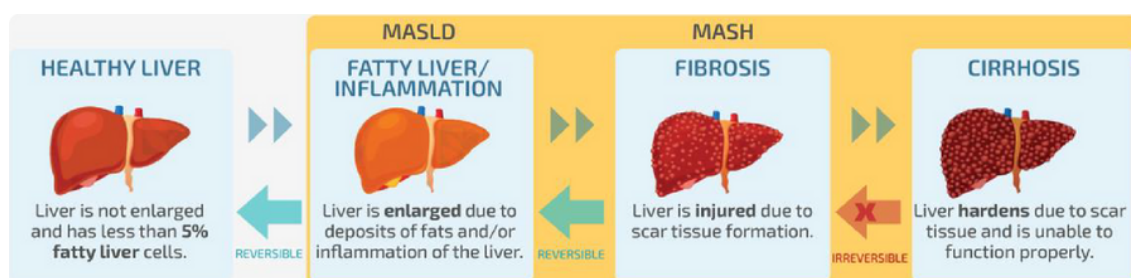
A challenging element of the diagnostic workup of patients with MASLD is the correct determination of disease severity. The goal here is to identify patients with more advanced diseases at increased risk for morbidity and mortality. The other goal is to identify the presence of steatosis and mild or moderate liver fibrosis conditions.

Percutaneous liver biopsy, despite its invasiveness, and inter/intra-observer variability issues, remains the gold standard for making a precise diagnosis of MASLD with specification categorisation and is necessary to assess the histopathologic criteria essential to making a diagnosis of MASH[8,9]. Biopsy allows for confirmation of steatosis as well as determining the degree of lobular inflammation, ballooning, and fibrosis.

Utilising AI with Neural Network Technology for Blood-based Test for Liver Disease

Artificial Intelligence using neural network and algorithm technology for LIVERSTAT and LIVERFASt tests are noninvasives that correctly classify or stage liver disease by utilising a combination of basic blood biomarkers to generate a report for physician's use and has been developed as an alternative to liver biopsy[8,11–13]. It is a reliable, and reproducible tool which provides classification of steatosis and fibrosis[11].

First Step in Performing the Evaluation

A simple blood draw will be performed, and the blood sample will then be centrifuged to collect the serum for analysis and to obtain the laboratory panel results, LIVERSTAT (7 biomarkers + age, gender and BMI) or LIVERFASt (10 biomarkers + age, gender and BMI) are required for entry into the platform. The final report will provide the patient's liver disease classification based on four categories: Class A, Class B, Class C and Class D for LIVERSTAT, and for LIVERFASt, it will generate fibrosis staging, activity grade and steatosis grade.

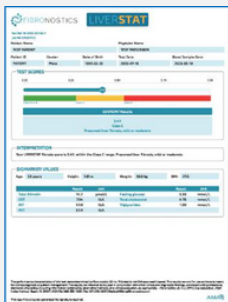## Required Biomarkers and Anthropometrics

To generate the steatosis and fibrosis classification for LIVERSTAT, the AI and Neural Network-based software analyses the results of 7 biomarkers and in combination with age, gender, height, and weight. To generate the fibrosis, activity and steatosis staging and grading for LIVERFASt, the AI and Neural Network-based software analyses the results of 10 biomarkers and in combination with age, gender, height, and weight.

These biomarkers are obtained and generated from CLIA and CAP certified laboratories, and the results are entered into the highly secured platform.

Those individual serum biomarkers have been identified as appropriate biomarkers for liver disease evaluation[14–19]. Each serum biomarker results from FDA cleared assays, in addition to patient characteristics including age, gender, height and weight, are used in the neural network algorithm for scoring the three liver histological features, as described below for LIVERFASt. A report of the test results is generated with all three non-invasive test scores, for the healthcare provider or the requesting physician to use.

The LIVERSTAT has four classification categories based on a proprietary algorithm utilising the required seven biomarkers and anthropometrics. According to a recent study wherein LIVERSTAT was validated against the gold standard liver biopsy, it was found that LIVERSTAT had a higher negative predictive value for advance liver fibrosis wherein patients who do not have liver disease condition was correctly classified.

LIVERSTAT also had had a lower misclassification rate compared to FIB-4 (a non-proprietary test for fibrosis) using the sequential approach in combination with liver stiffness measurement imaging. LIVERSTAT is a clinical aid that requires the most common blood biomarkers and anthropometrics thereby generating a test report that can provide enough information to the primary care clinician to determine the best management plan, risk stratify their patients and improve referral decisions.

Product	LIVERSTAT	LIVERFASt™
Description	**LIVERSTAT** is a blood-based test **utilising 7 biomarkers from patient's blood draw** and their anthropometrics to generate a quantitative fibrosis assesment and to determine the presence of steatosis only in those subjects without fibrosis. • Class A - No presumed liver fibrosis. No presumed steatosis • Class B - No presumed liver fibrosis. Presumed Steatosis • Class C - Presumed liver fibrosis, mild or moderate • Class D - Presumed liver fibrosis, advanced (severe)	**LIVERFASt™** is a blood-based liver evaluation test that **combines 10 biomarkers** and artifical intelligence technology to determine the fibrosis, activity, and steatosis stages of the liver. • Calculates three quantitative scores between 0.00 and 1.00 • Correlates to the hispopathology staging • Covers the entire spectrum of the disease, early to late stages • Differentiates the severity of cirrhosis
Clinical Purpose	Assessment on patient liver condition	Liver evaluation with Scoring & Staging
Evaluates	**Classifying the presence** of presumed steatosis and severity of presumed fibrosis	**Full and definitive Liver Injury Evaluation** (Fibrosis + Activity + Steatosis)
Intended Use	**A screening aid** for presumed clinical category of MAFLD and Liver Fibrosis in **patients having metabolic risk factors.**	Assessment (providing Score and Stage) for Fatty Liver Disease, Inflammatory Activity and Liver Fibrosis.
Requirements	7 Biomarkers + Age, Gender, BMI	10 Biomarkers + Age, Gender, BMI
Biomarkers	• Total Cholestrol • **Fasting Glucose** • Total Bilirubin • AST (P5P) • ALT (P5P) • GGT • Triglycerides • Age • Weight • Height • Gender	• Alpha2 Macroglubin • Haptoglobin • Apolipoprotein A1 • Total Cholestrol • Fasting Glucose • Total Bilirubin • AST (P5P) • ALT (P5P) • GGT • Triglycerides • Age • Weight • Height • Gender
Results Sheets		

Global Usefulness of AI and Neural Network-based Test in CLD

Artificial Intelligence and neural network-based tests has been successfully used worldwide as an advanced algorithm using the combination of serum biomarkers and patient demographics for staging of fibrosis, inflammatory activity, and steatosis of liver disease in adult MASLD patients from asymptomatic early stage through non-malignant late stage.

Early liver disease detection allows patients treatment options for a healthier and productive life. Once liver disease progresses to cirrhosis or cancer, treatment options are limited and expensive. To reduce the huge global economic burden impact of chronic liver disease, it requires breakthrough technology, which brings diagnosis to the patient.

Current liver disease diagnosis devices are dependent on fixed facilities, which utilise ultrasound, computerised tomography scan (CT), Magnetic resonance imaging (MRI) or biopsy sampling with pathology analysis. The dependency on fixed facility clinical procedures introduces barriers to patients receiving early detection. While it is known that early detection, wellness, and cost effectiveness mitigate these realities, and many trends today in clinicals are pushing greater early access to the patients, providers limit screening and detection to patients for which the procedure meets the cost-benefit in the ever-evolving value-based healthcare system. Additionally, requiring patients to travel to radiology or laboratory facilities introduces adherence issues.

From the patient and clinician perspective, current diagnostic techniques are mostly expensive, invasive and may display inter-observer variations[11,20]. Non-invasive diagnostic tools such as AI and neural network-based tests are easy to perform, less expensive, and readily available, and can aid in the early diagnosis and better prognosis in patients with NAFLD and NASH. After proper consultation and examination by your healthcare provider/attending physician, a prescription is required by your laboratory to obtain an AI-Based neural network test.

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