206P-An Innovative Evidence-Based Laboratory Medicine (EBLM) Test to Help Doctors in the Screening of Hepatocellular Carcinoma (HCC)

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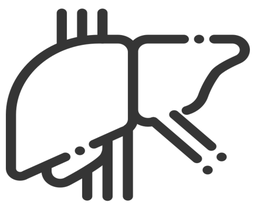
Background

- Hepatocellular carcinoma (HCC) is the major form of liver cancer. It is a heterogeneous tumor group with varied risk factors and genetic/epigenetic alterations.
- HCC accounts for **75-85% of liver malignancies** and ranks as the **3rd leading cause of cancer-related mortality globally**.
- Multiple factors including inborn and acquired metabolic diseases, viruses and chemicals are responsible for its development.
- The **main risk factors** are age, obesity, smoking, alcohol intake, metabolic syndrome, type 2 diabetes mellitus, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, liver fibrosis, liver cirrhosis, drug-induced liver injury, or certain rare diseases, among others (**Figure 1**).



- **Metabolic syndrome (MetS)**: 41%, 107 M people
- **Non-alcoholic fatty liver disease (NAFLD)**: 25%, 65 M people
- **Non-alcoholic steatohepatitis (NASH)**: 6.5%, 17 M people
- **Liver fibrosis, liver cirrhosis**: 10%, 21 M people

Figure 1. US incidence of major risk factors for liver cancer

- Early HCC detection is often difficult because **signs and symptoms**, such as weight and appetite loss, upper abdominal pain, and nausea, do not appear until **later HCC stages**.

- **Imaging and biopsies** are key for **HCC detection** but have **limitations**. Imaging is difficult due to the liver's position and liver biopsy, which is crucial for prognosis, is invasive and should be limited to high-risk patients with steatohepatitis, fibrosis, or cirrhosis.

Prognosis

- **Survival** in HCC **is strongly associated with tumor stage at diagnosis**:

5-YEAR SURVIVAL RATES ACCORDING TO STAGE AT DETECTION

Cancer is still confined to the liver	Cancer has grown into nearby organs or spread to nearby lymph nodes	Cancer has spread to distant organs or tissues
Stages I, II and some stage III **30.5%**	Stages IIIC and IVA **10%**	Stage IVB **3%**

➢ Unfortunately, **HCC often presents at advanced stages**, posing significant challenges for treatment and management. Therefore, **new methods/tools for the early detection of HCC are needed** to improve patient management and prognosis.

Objective

- To develop and evaluate the accuracy of a novel **non-invasive test for HCC detection**, even in early stages, before symptoms appear and when treatment is most likely to succeed.

  ✓ The test aimed to detect HCC in individual subjects with MetS, NAFLD, NASH, advanced fibrosis or cirrhosis.

Methods

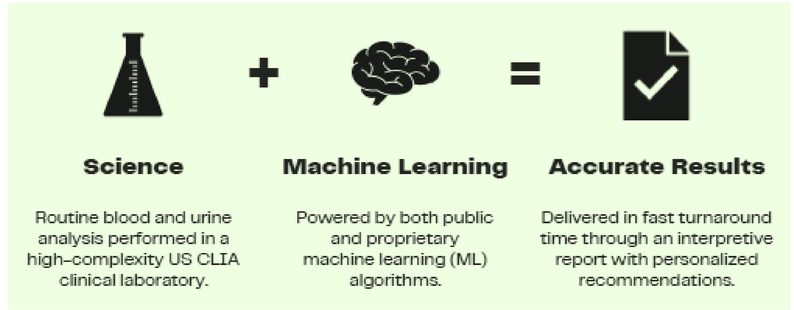
- This test is designed specifically around serum and urine biomarkers for HCC diagnosis.
- It is primary based on the GALAD, GALAD-C, GALADUS, GAAD and GAAP scores, a set of independent algorithms that estimate likelihood of HCC in patients with chronic liver disease.

Analyzed parameters

Serum Antibodies	Serum Hepatic Enzymes	Serum Tumor Markers
HbsAg Quantitative HCV Duo	ALP, AST, ALT, GGT, LDH	AFP, AFP-L3, PIVKA II

Other Serum Analytes	Other Urine Analytes	Other Clinical Data
Creatinine Total and direct bilirubin	Albumin Creatinine	Gender, ethnicity and age Blood pressure Anthropometric data Lifestyle habits

- Parallel approximations to optimize overall **sensitivity (Se)**, followed by serial approximations to enhance **specificity (Sp)**, a process performed by our own **machine learning (ML) algorithm** (**Figure 2**).
- To assess the estimated accuracy of our test, we conducted an **extensive literature review** of diagnostic accuracy studies about constituent algorithms, calculations, and combinations of analytes included within it.



US: United States; CLIA: Clinical Laboratory Improvement Amendments

Figure 2. How the test works

Results

STUDY POPULATION

4,581 subjects with MetS, NAFLD, NASH, advanced fibrosis or cirrhosis.

ACCURACY OF THE TEST (IC 95%):

- **Sensitivity, 0.94** and **Specificity, 0.96**.
- Approximation of the **Area under the receiver operating characteristic (AUROC)** curve, **0.95**.
- Estimation of the **Positive predictive value (PPV), 0.96**.
- Estimation of the **Negative predictive value (NPV), 0.94**.

Conclusions

- This data suggests that the innovative non-invasive blood and urine-based biomarker algorithm, **holds promise in providing timely HCC screening**, particularly among individuals aged 40 and above.
- We are conducting an extensive parallel clinical study involving 10,000 participants to validate and inform clinical practice.

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