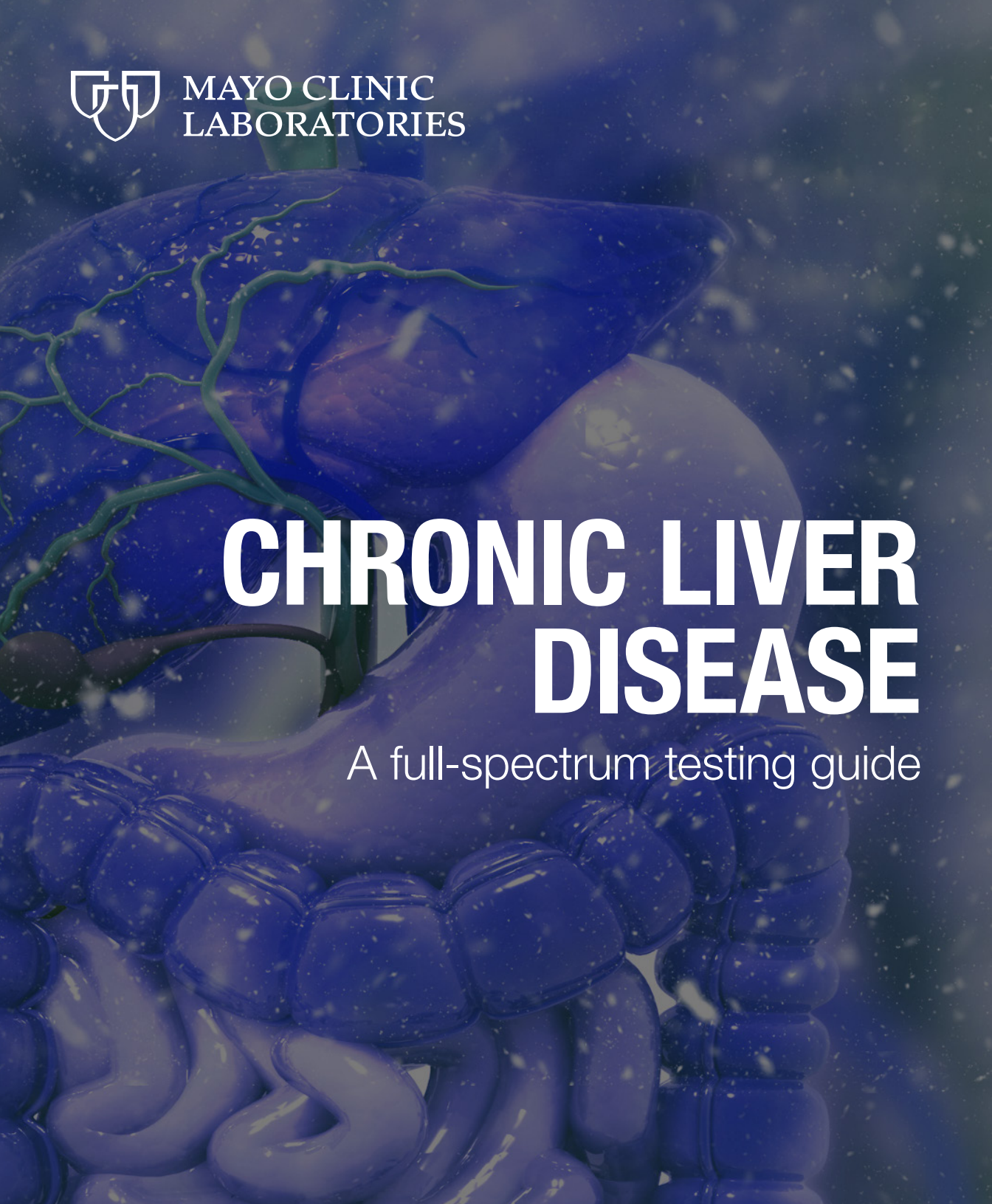
MAYO CLINIC LABORATORIES



CHRONIC LIVER DISEASE

A full-spectrum testing guide

TRUSTED ANSWERS, NOT JUST RESULTS.

Liver disease is a growing concern for health care providers, with approximately 844 million people suffering from chronic liver disease worldwide.[1] Mayo Clinic Laboratories offers the only comprehensive testing menu for liver disease developed by clinical experts that enables health care providers to determine the underlying cause and rule out other causes for the disease.

Access to clinical experts

When you partner with us, you extend your network to include some of the world's leading gastroenterology experts. Mayo Clinic physicians, scientists, laboratorians, and genetic counselors are available to discuss testing options, interpret results, or help with case review and coordination.

The full spectrum of testing to help identify the underlying cause and those at risk for progressing to cancer.

METABOLIC	VIRAL	GENETIC	AUTOIMMUNE	CANCER
Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)	Hepatitis B, Hepatitis C, and Hepatitis E	Wilson disease, alpha-1-antitrypsin (A1A) deficiency, Lysosomal acid lipase deficiency (LAL-D), and Hemochromatosis	Autoimmune Hepatitis and Primary Biliary Cirrhosis (PBC)	Hepatocellular carcinoma (HCC)

Stages of liver damage

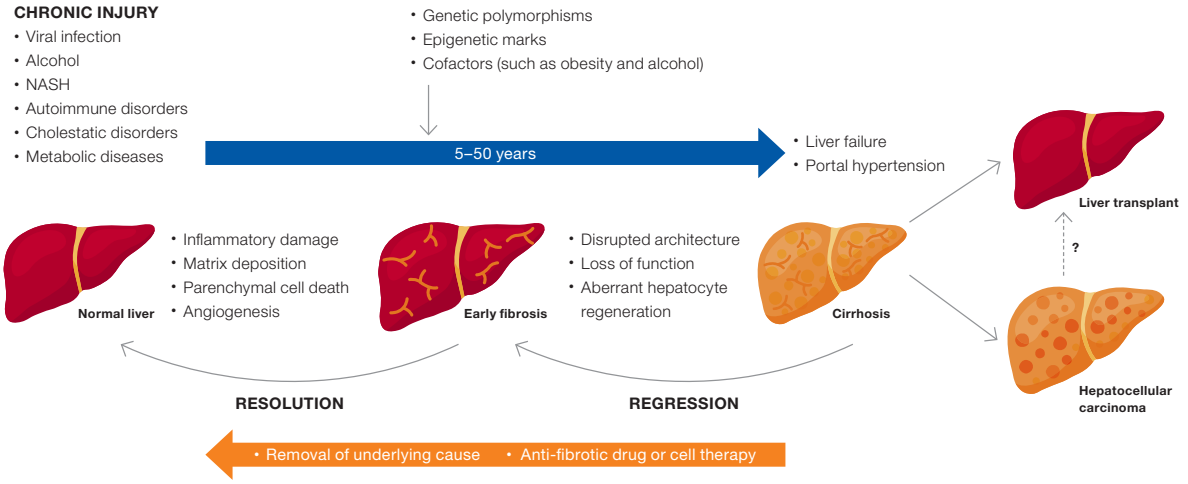


Figure. Adapted from Pellicoro A, Ramachandran P, Iredale JP, et al. *Nat Rev Immunol.* 2014;14(3):181-94.

DETERMINE LEVELS OF FIBROSIS AND NECROINFLAMMATORY ACTIVITY

FibroTest-ActiTest can be used as a first-line screen to assess the condition of the liver using two diagnostic scores—one for liver fibrosis and one for liver inflammation—based on component tests for six biomarkers.

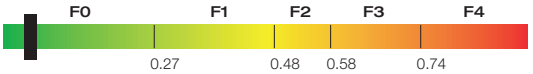
FIBRO | FibroTest-ActiTest, Serum

ADVANTAGES OF FIBROTEST-ACTITEST:

- Applicable to the largest number of patients (98%) as well as being the most reliable.[2]
- Offers the best performance of any test, at all stages of fibrosis, from a healthy liver to cirrhosis.[3]
- The noninvasive test that is least affected by known risk factors for false positives and false negatives.[4]
- Easy-to-read report shows both proprietary FibroTest and ActiTest scores and METAVIR fibrosis stage and activity grade.

FibroTest Score
0.05

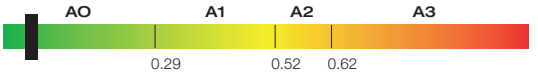
Fibrosis Stage
F0



FibroTest Score	Stage	Interpretation
0.00–0.21	F0	no fibrosis
0.21–0.27	F0–1	no fibrosis
0.27–0.31	F1	minimal fibrosis
0.31–0.48	F1–F2	minimal fibrosis
0.48–0.58	F2	moderate fibrosis
0.58–0.72	F3	advanced fibrosis
0.72–0.74	F3–F4	advanced fibrosis
0.74–1.00	F4	severe fibrosis (Cirrhosis)

ActiTest Score
0.07

Activity Grade
A0



ActiTest Score	Stage	Interpretation
0.00–0.17	A0	no activity
0.17–0.29	A0–A1	no activity
0.29–0.36	A1	minimal activity
0.36–0.52	A1–A2	minimal activity
0.52–0.60	A2	significant activity
0.60–0.62	A2–A3	significant activity
0.62–1.00	A3	severe activity

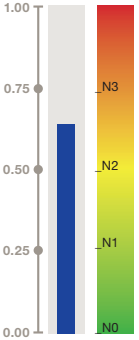
CONFIDENTLY EVALUATE FOR NASH, STEATOSIS AND FIBROSIS/CIRRHOSIS WITH ONE STANDARD BLOOD SAMPLE

In the United States, 80 to 100 million people are living with NAFLD.[5] More than 25% of these patients will go on to develop NASH[6]. Using a simple blood sample, this test combines 10 standard biomarkers into 5 scores to provide a complete assessment of the condition of the liver and the 5 main causes of liver disease including:

Hepatic steatosis • NASH • Alcoholic steatohepatitis • Fibrosis • Liver inflammation

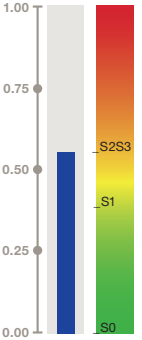
NSFIB | NASH-FibroTest, Serum

A COMPLETE NASH PANEL BASED ON A BLOOD SAMPLE (NO BMI)



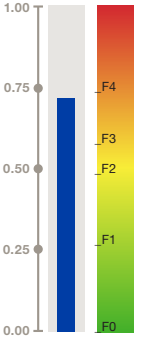
NashTest 2
Assesses NASH:

N0: no NASH
N1: mild NASH
N2: moderate NASH
N3: severe NASH



SteatoTest 2
Assesses liver steatosis:

S0: no steatosis (<5%)
S1: mild steatosis (but clinically significant) (5-33%)
S2S3: moderate to severe steatosis (clinically significant) (34-100%)



Fibro Test
Estimates liver fibrosis:

F0: no fibrosis
F1: minimal fibrosis
F2: moderate fibrosis
F3: advanced fibrosis
F4: severe fibrosis (cirrhosis)

HEPATITIS B, C, AND E

To expedite diagnosis and treatment of chronic viral hepatitis, our clinical experts have developed specific testing algorithms to guide the test-ordering process. This approach takes the guesswork out of ordering, and it focuses on test utilization, saving your institution time and money with better patient outcomes from faster turnaround times and treatment options.

DIAGNOSIS, DETECTION, AND CONFIRMATION

HEP B

HBAG | Hepatitis B Surface Antigen, Serum
Detects the persistence of HBsAg for >6 months in duration indicates chronic infection

HBAB | Hepatitis B Surface Antibody, Qualitative/Quantitative, Serum
A negative result (<5.0 mIU/mL) indicates a lack of recovery from chronic hepatitis B

HBC | Hepatitis B Core Total Antibodies, Serum
Detects the persistence of Anti-HBc indicates chronic infection

HEP C

HCVDX | Hepatitis C Antibody with Reflex to HCV RNA by PCR, Serum
Detects and confirms acute and chronic HCV for patients with symptoms.

HCSRN | Hepatitis C Antibody Screen with Reflex to HCV RNA by PCR, Serum
Detects and confirms acute and chronic HCV for patients who are asymptomatic.

HEP E

HEVG | Hepatitis E Virus IgG Antibody, Serum
Can be used to diagnose past exposure to hepatitis E virus.

HEVM | Hepatitis E Virus IgM Antibody Screen with Reflex to Confirmation, Serum
Detects and diagnoses an acute or recent (<6 months) hepatitis E infection.

HEVQU | Hepatitis E Virus RNA Detection and Quantification by Real-Time RT-PCR, Serum
Virologic detection and confirmation of hepatitis E virus (HEV) infection in immunocompromised individuals at risk for or suspected to have acute or chronic hepatitis E. Also useful for monitoring HEV RNA levels and determining eradication of chronic HEV infection in immunocompromised individuals.

QUANTIFICATION

HBVQN | Hepatitis B Virus (HBV) DNA Detection and Quantification by Real-Time PCR, Serum
Detects and quantifies hepatitis B virus (HBV) DNA in serum of patients with chronic HBV infection (e.g. hepatitis B surface antigen-positive). Monitors disease progression in chronic HBV infection and response to anti-HBV therapy.

HCVQN | Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum
Can be used to confirm chronic HCV infection and establish a baseline HCV viral load before initiating antiviral therapy and during treatment to measure response to the medications.

Cost-saving personalized treatment for managing HCV infection

GENOTYPING

HCVG | Hepatitis C Virus Genotype, Serum
Determines the HCV genotype to allow physicians to properly select antiviral therapy, including the use of direct-acting antiviral (DAA) drugs, to manage patients.

DRUG RESISTANCE ANALYSIS

Our genotypic antiviral drug-resistance testing is useful for:

- Guiding selection of a DAA drug combination for the most effective antiviral therapy
- Determining if a change in antiviral drug combinations is needed

HCVDR | Hepatitis C Virus Genotypic Drug Resistance, Serum
Detects and identifies codon substitutions in the HCV NS3, NS5A, and NS5B genomic sequences that confer resistance to current FDA-approved DAA drugs used for treating HCV.

DAA Target	HCV Genotype		
	1a	1b	3 (any subtype)
	Drugs		
HCV NS3 Inhibitors	Glecaprevir (Mavyret) Grazoprevir (Zepatier) Voxilaprevir (Vosevi)	Grazoprevir (Zepatier) Voxilaprevir (Vosevi)	Glecaprevir (Mavret) Voxilaprevir (Vosevi)
HCV NS5A Inhibitors	Declatasvir (Daklinza) Elbasvir (Zapatier) Ledipasvi (Harvoni) Pibentasvir (Mavyret) Velpatazvir (Epclusa, Vosevi)	Daclastasvir (Daklinza) Elbasvir (Zapatier) Ledipasvir (Harvoni) Velpatasvir (Epclusa, Vosevi)	Daclatasvir (Daklinza) Pibrentasvir (Mavyret) Velpatasvir (Epclusa, Vosevi)
HCV NS5B Inhibitors	Sofobuvir (Sovaldi)	Sofobuvir (Sovaldi)	Sofosbuvir (Sovaldi)

EARLY IDENTIFICATION OF UNDERLYING GENETIC CAUSES TO PREVENT ORGAN DAMAGE

Identifying underlying genetic disorders plays an important role in the treatment and care of patients with liver disease. Appropriate use of screening tests in routine clinical practice can:

- Rule out possible causes of liver disease.
- Assist in early identification and treatment of genetic liver diseases to prevent terminal organ damage.

Alpha-1-Antitrypsin (A1A) Deficiency

WHY PAY FOR THE "GOLD STANDARD" OF PHENOTYPING IF IT IS ONLY NECESSARY 3% OF THE TIME?

To aid in the diagnosis of A1A deficiency, we have developed a state-of-the-art proteotype assessment that detects disease-causing variants S and Z. When physicians begin by ordering our recommended proteotyping test, they will receive a definitive answer 97% of the time. In the other 3%, where the mass spectrometry proteotype and quantitative serum level are conflicting, phenotyping will automatically be ordered and performed.

A1ALC | Alpha-1-Antitrypsin Proteotype S/Z by LC-MS/MS, Serum
This profile also includes A1A serum-level testing.

Genetic testing to identify causative mutations may prove useful for patients suspected to have A1A deficiency, based on clinical findings or serum A1A levels, but that do not have evidence of the SZ or ZZ genotype by routine methods. Our testing performs full sequencing of the *SERPINA1* coding region for the detection of rare null and non-S or non-Z disease-associated mutations.

SERPZ | *SERIPINA1* Gene, Full Gene Analysis

Hemochromatosis

Once local lab testing has identified individuals with increased transerffin-iron saturation in serum and serum ferritin, molecular testing can be done to establish or confirm the diagnosis of hereditary hemochromatosis. Our *HFE* gene analysis test detects the 2 common disease-causing mutations: C282Y and H63D. The S65C mutation is reported only when it is observed as part of the C282Y/S65C genotype.

HFE | Hemochromatosis *HFE* Gene Analysis, Blood

Wilson Disease

Early diagnosis of Wilson disease (WD) allows for treatment and prevention of permanent organ damage. However, diagnosing WD can be challenging because its signs and symptoms are often hard to distinguish from those of other liver diseases, such as hepatitis. To aid clinicians, our algorithmic approach to testing ensures the right test is performed at the right time.

FIRST-TIER SCREENING

A variety of laboratory tests are recommended in the initial evaluation for WD, but in approximately 95% of cases, serum ceruloplasmin is below normal.

CERS | Ceruloplasmin, Serum

COPPER TISSUE TESTING AVAILABLE WHEN NECESSARY

Liver biopsy can be useful to help interpret discrepant biochemical or molecular results. Our Metals Laboratory has more than 30 years of clinical experience and a staff of 30 full-time employees.

CUT | Copper, Liver Tissue

GENETIC TESTING TO CONFIRM DIAGNOSIS AND IDENTIFY AT-RISK FAMILY MEMBERS

After initial testing, diagnosis can be confirmed through analysis of the *ATP7B* gene. Additionally, a confirmed genetic diagnosis enables the screening of siblings who may be able to start treatment before symptoms arise.

WDZ | Wilson Disease, Full Gene Analysis

LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D)

Late-onset LAL-D is likely underdiagnosed and frequently identified after liver pathology reveals findings similar to NAFLD or NASH. Early diagnosis of LAL-D is critical to stopping the progression of the disease, as studies have shown that nearly 50% of pediatric and adult LAL-D patients progress to fibrosis, cirrhosis, or liver transplantation within three years of first clinical manifestation.[7]

LALB | Lysosomal Acid Lipase, Blood

New Guidelines Recommend LAL-D be Ruled Out When Evaluating Children and Adults for NAFLD[8,9]

2017 NASPGHAN GUIDELINES: DIFFERENTIAL DIAGNOSIS FOR NAFLD IN CHILDREN[8]

Genetic/Metabolic Disorders	Medications	Dietary Causes	Infections
Fatty acid oxidation and mitochondrial disorders	Amiodarone	Protein-energy malnutrition (Kwashiorkor)	Hepatitis C (genotype 3)
Citrin deficiency	Corticosteroids	Alcohol abuse	
Wilson disease	Methotrexate	Rapid surgical weight loss	
Lysosomal acid lipase deficiency	Certain antipsychotics	Parenteral nutrition	
Uncontrolled diabetes	Valproic acid		
Lipodytrophies	Certain antidepressants		
Familial combined hyperlipidema	HAART		
Abeta-/ hypobetalipoproteinemia			

HAART=highly active antiretroviral therapy.
Adapted from Vos MB, et al. J Pediatr Gastroenterol Nutr. 2017;64(2):319-334.

2017 AASLD GUIDELINES: DIFFERENTIAL DIAGNOSIS FOR NAFLD IN ADULTS[9]

Excessive alcohol consumption	Reye syndrome
Hepatitis C (genotype 3)	Medications (valproate, anti-retroviral medicines)
Wilson disease	Acute fatty liver of pregnancy
Lipodystrophy	HELLP syndrome
Starvation	**Inborn errors of metabolism (e.g., LCAT deficiency, LAL-D)**
Parenteral nutrition	Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteriods)
Abetalipoproteinemia	

Adapted from Chalasani N, et al. Hepotology 2017,(Epub ahead of print).
Guideline tables originally printed in "Lysosomal Acid Lipase Deficiency" educational booklet. Used with permission from Alexion Pharmaceuticals, Inc., Boston, MA.

COMPREHENSIVE PANEL TO HELP DIAGNOSE THE TWO MOST COMMON FORMS OF AUTOIMMUNE LIVER DISEASE[10]

Autoimmune liver diseases result from inflammatory immune reactions that damage hepatocytes or cholangiocytes. Due to the variance in autoimmune disease forms (which include autoimmune hepatitis [AIH], primary biliary cirrhosis [PBC], and primary sclerosing cholangitis [PSC]), many patients can be misdiagnosed. Early and accurate diagnosis can lead to better treatment outcomes for patients, namely, the avoidance of liver transplants.

Our panel evaluates smooth muscle antibodies (SMA), antinuclear antibodies (ANA), and antimitochondrial antibodies (AMA) for patients with:

- Suspected autoimmune liver disease, specifically type 1 AIH or PBC.
- Liver disease of unknown etiology.

ALDP | Autoimmune Liver Disease Panel, Serum

Celiac disease may also be associated with severe forms of liver disease and/or coexist with other autoimmune liver diseases. Isolated hypertransaminasemia, with mild or nonspecific histologic changes in the liver biopsy (also known as “celiac hepatitis”) is the most frequent presentation of liver injury in celiac disease.[11] Histologic changes and liver enzymes reverse to their normal states after treatment with a gluten-free diet in most patients.

CDSP | Celiac Disease Serology Cascade

ASSESS CANCER RISK AND IDENTIFY OPPORTUNITIES FOR INCREASED SURVEILLANCE

Hepatocellular carcinoma (HCC) is the third leading cause of death from cancer in the world.[12] While HCC can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages when the disease is less responsive to therapies. Laboratory testing and imaging can identify at-risk patients needing increased surveillance to help aid in early diagnosis.

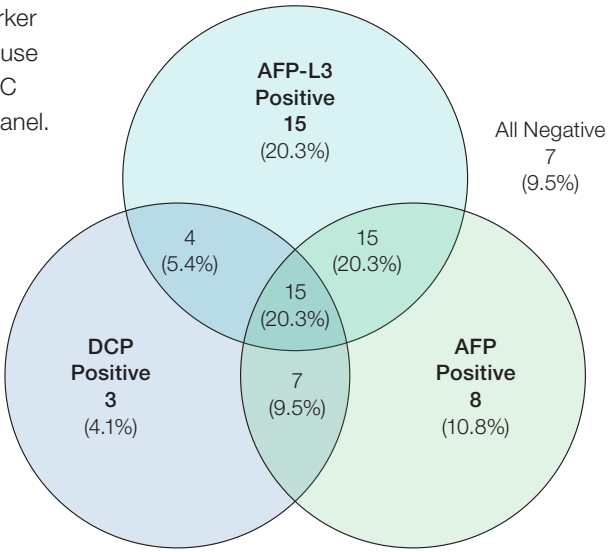
Increased Sensitivity through Panel Testing

Biomarkers included in the panel			
Alpha-Fetoprotein (AFP) Level	**Alpha-Fetoprotein L3% (AFP-L3%) Level**	**Des-Gamma-Carboxy Prothrombin (DCP) Level**	**86%** sensitivity is achieved when these three markers are combined, compared to 68%, 62%, and 73%, respectively, when used alone.[13]
Standard serum tumor marker utilized to evaluate suspected HCC.	An increase in the percentage of AFP-L3 relative to total AFP is associated with an increased risk of HCC development	DCP is considered a complementary to biomarker AFP and AFP-L3% for assessing the risk of developing HCC.	

HCCPR | Hepatocellular Carcinoma Risk Panel

IDENTIFY CASES THAT WOULD BE MISSED BY AFP ALONE[14]

In a study of 74 patients, the use of a 3-biomarker panel test detected 67 HCC cases (91%). The use of AFP alone would have detected only 45 HCC cases (60%), or 22 fewer cases than using a panel.



Designed with GALAD Calculation in Mind

The GALAD model (Gender, Age, AFP-L3, AFP, and DCP) is a statistical representation for estimating the likelihood of HCC in patients with chronic liver disease.

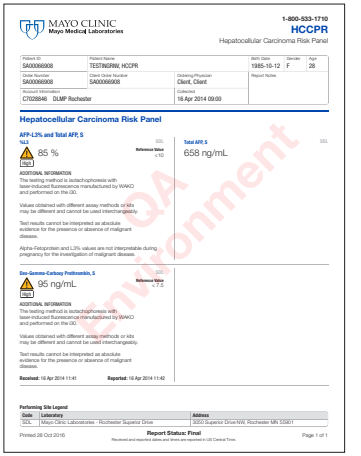
The GALAD model was developed using data from 670 patients (331 with HCC and 339 with chronic liver disease) from a single center in the United Kingdom and has been validated in independent cohorts of 6,834 patients (2,430 with HCC and 4,404 with chronic liver disease) recruited from Germany, Japan, and Hong Kong.[15,16]

Obtaining a GALAD Score for Your Patients

Mayo Clinic has an online, publicly available GALAD calculator that can generate a GALAD score using the results from our HCC risk panel.

mayoclinic.org/medical-professionals/model-end-stage-liver-disease/galad

1 ORDER TEST


MAYO CLINIC
Mayo Medical Laboratories

1-800-533-1710
HCCPR
Hepatocellular Carcinoma Risk Panel

Patient ID: SA00066908 | Patient Name: TESTINGWW, HCCPR | Birth Date: 1985-10-12 | Gender: F | Age: 28
Order Number: SA00066908 | Client Order Number: SA00066908 | Ordering Physician: Client, Client | Report Notes:
Account Information: C7028846 DLMP Rochester | Collected: 16 Apr 2014 09:00

Hepatocellular Carcinoma Risk Panel

AFP-L3% and Total AFP, S
L3 85 % (High)
Reference Value: < 10
ADDITIONAL INFORMATION
The testing method is isotachophoresis with laser-induced fluorescence manufactured by WAKO and performed on the i30.
Values obtained with different assay methods or kits may be different and cannot be used interchangeably.
Test results cannot be interpreted as absolute evidence for the presence or absence of malignant disease.
Alpha-Fetoprotein and L3% values are not interpretable during pregnancy for the investigation of malignant disease.

Total AFP, S
658 ng/mL

Des-Gamma-Carboxy Prothrombin, S
95 ng/mL (High)
Reference Value: < 7.5
ADDITIONAL INFORMATION
The testing method is isotachophoresis with laser-induced fluorescence manufactured by WAKO and performed on the i30.
Values obtained with different assay methods or kits may be different and cannot be used interchangeably.
Test results cannot be interpreted as absolute evidence for the presence or absence of malignant disease.

Received: 16 Apr 2014 11:41 **Reported:** 16 Apr 2014 11:42

Performing Site Legend

Code	Laboratory	Address
MAL	Mayo Clinic Laboratories - Rochester Superior Drive	3050 Superior Drive NW, Rochester MN 55901

Printed 28 Oct 2016 **Report Status: Final** Page 1 of 1
Received and reported dates and times are reported in US Central Time

2 INPUT REPORT VALUES INTO ONLINE CALCULATOR


Sex: ○ Female ○ Male

Age: 10-100 years

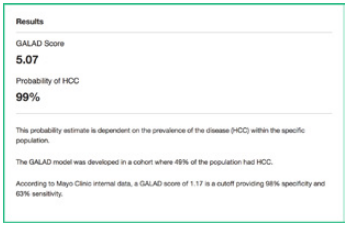
Alpha-fetoprotein (AFP): 0.1-10,000,000 ng/mL
More information (Mayo Medical Laboratories)

Alpha-fetoprotein-L3% (AFP-L3): 0-100 %
More information (Mayo Medical Laboratories)

Des-gamma-carboxy prothrombin (DCP): 0.1-75,000 ng/mL
More information (Mayo Medical Laboratories)

Submit | Reset

3 CALCULATE SCORE


Results

GALAD Score
5.07

Probability of HCC
99%

This probability estimate is dependent on the prevalence of the disease (HCC) within the specific population.

The GALAD model was developed in a cohort where 49% of the population had HCC.

According to Mayo Clinic internal data, a GALAD score of 1.17 is a cutoff providing 98% specificity and 63% sensitivity.

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