Liver disease includes Hepatitis B, Hepatitis C, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and alcoholic liver disease. As the obesity rate rises—about one-third of adults in the US were obese in 2008— the disease is tied to a greater prevalence of NAFLD. Globally, 350 million people are infected with Hepatitis B, causing 500,000 deaths yearly, and 170 million have Hepatitis C. According to Jayant A. Talwalker, MD, hepatologist at the Mayo Clinic (Rochester, MN), if no treatment is provided for the management of Hepatitis chronic C, then cirrhosis and hepatocellular carcinoma will almost double, decompensated cirrhosis will more than double, and liver-related deaths will triple.

To better understand the current state of non-invasive evaluation of liver diseases, GE Healthcare recently hosted a roundtable discussion of radiologists and hepatologists regarded as clinical experts on liver disease evaluation and management. The purpose was to explore non-invasive imaging techniques for diagnosing chronic liver disease, fibrosis, and cirrhosis—all leading causes of death worldwide.

Hepatic fibrosis, or a stiffening of the liver, occurs with liver disease and impacts the organ’s normal function. Hepatic fibrosis is potentially reversible with early intervention and adequate treatment. If left untreated, fibrosis often leads to cirrhosis which permanently scars the liver, cannot be treated, and is associated with high mortality. Also, fibrosis is a known pathogenic of portal hypertension and hepatocellular carcinoma (HCC)—the fourth-leading cause of cancer death worldwide—and can be a marker for the development of both diseases.
Economically, Hepatitis C is the underlying cause for one-third (approximately 1,000) of all liver transplants at a cost of $280,000 (USD) per procedure. The lifetime cost of Hepatitis C without transplant is estimated at $100,000 per individual.

**Assessing liver disease—background**

Alaninie transaminase (ALT) and aspartate transaminase (AST) are sensitive indicators of liver damage or injury from different types of disease, yet these enzyme levels are not a precise indicator of liver damage or prognosis. Both tests indicate only the presence of liver disease, not staging, and cannot be used to guide treatment. According to Dr. Talwalker, normal ALT values do not always indicate mild liver disease.

Three serum tests help evaluate overall liver function. Serum albumin measures how well the liver is producing the protein albumin; serum bilirubin determines how well the liver clears a blood waste product, bilirubin; and, prothrombin time (INR) measures the clotting time of plasma as an increase in prothrombin time may indicate liver damage. As with ALT/AST, these tests are also not conclusive for staging liver disease.

Currently, the gold standard for confirming a clinical diagnosis and assessing the severity of necroinflammation is liver biopsy. Biopsy is also used to evaluate possible concomitant disease processes and assess fibrosis and therapeutic intervention.

“The primary goal of biopsy is to differentiate state 1–2 from stage 2–3 and to diagnose cirrhosis," explains John R. Lake, MD, professor of Medicine and Surgery, University of Minnesota Medical School, “in order to determine whether there is an indication for treatment.” He adds that making a diagnosis of cirrhosis can also have important implications, such as screening for HCC and dosing antivirals.

Dr. Lake explains that although biopsy is the gold standard, it is costly (ranges from $1,500 to $2,000 USD) and poses risks to patients, namely moderate pain in 20% and hospitalization in 1 to 3%. It has a mortality rate of .01%, which increases to 0.4% in patients with cancer.

The procedure is also associated with potential sampling errors and subjective histology grading. Fewer than 11 portal tracts may be linked with sampling errors—one study found fibrosis stage discordance in 33% of cases. Pathology skill sets also vary widely. Another study found 20% of fibrosis and cirrhosis are understaged with the size of biopsy being a likely culprit. As a result, second opinions are often required.
“A real problem for liver biopsy is the ability to detect small changes in regression of fixed, fibrous lesions over the short time intervals associated with most controlled clinical trials,” adds Jeong Min Lee, MD, Department of Radiology, Seoul National University Hospital.

Higher incidences of chronic liver disease coupled with the complications and potentially unreliable biopsy results has led to increased interest in non-invasive methods for screening and diagnosis. Dr. Lake believes that non-invasive determination of fibrosis stage coupled with patient preference will further accelerate the decline in the need for liver biopsy.

**Non-invasive options for chronic liver disease management**

Hepatologists are interested in diagnosing chronic liver disease before its endpoint—cirrhosis—says Robert J. Fontana, MD, Medical Director of the Liver Transplant Program and Clinic, University of Michigan Medical Center. While diagnosis can be made for Hepatitis B, Hepatitis C, and alcoholic fatty liver, NAFLD—which affects 20% of the population—cannot be conclusively diagnosed via biopsy.

“Until we have effective treatments [for fatty liver disease], the value of the biopsy is limited,” he explains. In general, he says, clinicians tend to understage fibrosis and cirrhosis via biopsy. Knowing the extent of fibrosis is an important yet complicated clinical question.

While blood tests have been available for many years, they are not abnormal until the patient has cirrhosis, Dr. Fontana says. Specifically, AST/ALT provide a moderate correlation with staging, but are not specific.

The ideal non-invasive test for monitoring chronic liver disease would be simple, readily available, inexpensive, and reproducible, he adds. Additionally, it must provide accurate prediction of the full spectrum of disease severity, be sensitive to treatment effects, and be useful in tracking disease progression.

![Worldwide HCV prevalence](image-url)
Serum fibrosis markers

In chronic liver disease, the physiologic process includes inflammation, cell death, and the collagen deposits in the liver. Serum fibrosis markers (SFM) detect dynamic changes in the liver. Dr. Fontana cautions that SFM are dependent upon the rate of production and clearance, and currently are not liver specific. He cautioned that using a single analyzed serum marker is likely to be inconclusive. Studies have determined that combining serum markers with other tests—such as blood tests, transient ultrasound, or MRI—would provide a more conclusive result.

According to Dr. Fontana, serum marker tests available today have a very high negative predictive value but poor positive predictive value and require further refinement to increase their accuracy. Biochemical indices have limited sensitivity and specificity to replace biopsy in most patients. While proteomics and glycoproteomics may provide new markers, they require prospective, cross-sectional, and longitudinal studies for clinical use. However, Dr. Fontana believes that with additional study, SFM combined with other non-invasive testing may prove most useful in diagnostic and management algorithms.

“This area of research is not complete,” he explains, “and there is still discovery work and validation that needs to be done.” He is buoyed by the potential to utilize several different studies together—blood test, serum marker, and a radiology test—to conclusively diagnosis fibrosis and to reduce the number of patients who undergo biopsy.

“The question, ‘which one is best?’ is the wrong approach,” Dr. Fontana says. It will be through a combination of these tests that clinicians determine the course of clinical management.

### Ideal non-invasive test for monitoring chronic liver disease

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A large prospective study of 1,000 patients sponsored by NIH presented “a great opportunity to evaluate serum markers as a predictive of disease progression at the same time,” says Dr. Fontana. The study’s authors found the best model for predicting disease severity was the combination of albumen, bilirubin, INR, and YKL-40. However, Dr. Fontana and co-authors determined the results, while sufficient for research, were not yet ready for clinical practice.

### Transient and ultrasound elastography

Transient elastography and ultrasound elastography measure the speed of ultrasound propagation through the liver. The wave may be generated through mechanical vibration (transient elastography) or through an ultrasound source (ultrasound elastography).

By controlling vibration and energy and applying an algorithm, transient elastography calculates the stiffness of the region of interest (ROI). Typically, the ROI is 2.5 to 6.5 cm below the skin, 10 x 40 mm with limited visualization.

While similar to transient elastography, ultrasound elastography utilizes an acoustic shear wave. The region of interest can be anywhere—it is not limited to a finite depth—and provides direct visualization with an ROI of 5 x 10 mm. Results are directly measured (m/s).

Robert P. Myers, MD, MSc (Epid), Associate Professor, Liver Unit, Division of Gastroenterology, University of Calgary, notes that transient elastography may potentially also be used to detect complications of cirrhosis and steatosis, while ultrasound elastography can capture other data.
during the same session (e.g. masses, portal hypertension, fatty liver, etc.). Ultrasound elastography is readily available, relatively inexpensive, has no reported failures, and can provide rapid, “real time” assessment of fibrosis.

However, both techniques suffer from limited sensitivity for intermediate stages and end results are influenced by factors other than fibrosis, adds Dr. Myers. Transient elastography equipment is expensive—roughly five times the cost of ultrasound elastography—which could lead to limited availability. In approximately 5% of cases, the technique may fail, especially in patients who are obese, although Dr. Myers notes a new probe for obese patients has been trialed. With transient ultrasound, stiffness values are disease-dependent and exam success is influenced by a number of factors, making reproducibility fair at low-liver stiffness values, he adds. Ultrasound elastography also suffers from sensitivity to fibrosis changes over time and poses many unresolved issues that require additional validation for clinical efficacy.

Liver fibrosis

![Liver fibrosis images](Image)

Figure 3. MRE images concordant with stiffness and consistent to stages of fibrosis.

Performance of MR Elastography in difficult situations

![Performance images](Image)

Figure 4. MRE images in difficult to evaluate situations: obese patient with BMI = 40.7.

Figure 5. MRE images in difficult to evaluate situations: patient with ascites.

MR Elastography

Compared to transient and ultrasound elastography, MR Elastography (MRE) uses shear waves to assess the stiffness of the liver. According to Richard L. Ehman, MD, Professor of Radiology, Mayo Clinic, MRE adds approximately five minutes (with the scan taking 15 sec) to a conventional 30 minute MR abdomen exam.

A study that compared the diagnostic performance of MRE, transient ultrasound, and AST blood tests to biopsy samples found MRE to be 94% concordant, transient ultrasound 84% concordant, and AST blood test 70% concordant.

Additionally, MRE is not impacted by obesity (high BMI) or the presence of ascites as is the case with transient and ultrasound elastography. Also, the presence of steatosis does not affect liver stiffness with MRE. In several studies, explains Dr. Ehman, MRE demonstrated the ability to identify steatohepatitis before the onset of fibrosis—an important indicator for treatment.
When compared to DWI and morphologic MR, MRE is shown to have higher sensitivity and specificity than either conventional MR technique. According to Dr. Ehman, MRE is a reliable, non-invasive test for assessing hepatic fibrosis. It could be easily added to standard abdominal MRI protocols.

Conclusion

Based on the strengths and weakness of the different options for liver disease evaluation, the panel did not find one technology superior to another for all applications. However, the panel was confident that non-invasive staging of fibrosis would lead to the decline in the need for liver biopsy and that patient acceptance of these non-invasive techniques would accelerate the decline.

For use as a screening tool, a technique may be preferred due to its availability, cost, and examination time. Another technique may be used as a diagnostic tool based on its robustness, accuracy, and reproducibility. Further work is expected on defining the biologic and clinical implications of alterations in liver stiffness following therapy and how each technique fits within a clinical algorithm.

References: