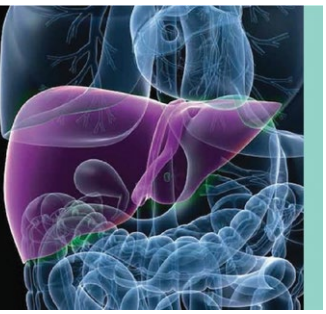

Con: Liver Biopsy Remains the Gold Standard to Evaluate Fibrosis in Patients With Nonalcoholic Fatty Liver Disease

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KEY POINTS

- Fibrosis is a histological criteria, and biopsy is the only modality that provides histology.
- All noninvasive modalities were validated using biopsy as the gold standard.
- All major liver and gastrointestinal society guidelines view biopsy as the gold standard for measuring liver fibrosis.
- Noninvasive modalities have significant confounders including obesity.

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in Western countries, affecting nearly 25% to 30% of the general population.[1] The natural history of NAFLD includes the potential for progression to nonalcoholic steatohepatitis (NASH), followed by fibrosis and ultimately cirrhosis. Knowledge of fibrosis stage in NAFLD is important in the management of this disease because prior studies have shown that for each increase in stage of fibrosis, there is a significant decrease in transplant-free survival.[2] Understanding an individual's stage of fibrosis allows clinicians to manage their patients with interventions tailored to their specific stage, from simple diet and exercise to more advanced therapies, such as surgical interventions or pharmaceutical treatments including referral for clinical trials. Because liver biopsy provides a direct visualization of fibrosis, we believe that this modality remains the gold standard test in assessing fibrosis in NAFLD.

A gold standard is defined in the Oxford Dictionary as *"a thing of superior quality which serves as a point of reference against which other things of its type may*

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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be compared." The four main qualities of a gold standard test are that: (1) it is of *superior quality*, (2) it has a *standardized interpretation*, (3) it serves as a *reference standard*, and (4) it is *widely accepted*. Compared with noninvasive modalities, liver biopsy is more adept at meeting all aspects of this definition. First, when considering the superior quality of a test measuring liver fibrosis, it is important to remember that fibrosis is by definition a histological measurement. Liver biopsy is the only modality able to provide a histological sample. In contrast, noninvasive approaches such as elastography make an assumption of fibrosis that is highly susceptible to several confounding patient factors including obesity, arguably the most common clinical characteristic in patients with NAFLD. Even using specialized equipment created for elastography in obese patients (such as the FibroScan XL probe), elastography was unreliable in 35% to 53% of patients with body mass index greater than 30.[3] Liver biopsy is also superior to alternative modalities in providing a standardized interpretation of results. Interpretation of fibrosis for liver biopsy is based on a standardized, universally accepted scoring system (METAVIR) that can be interpreted regardless of comorbid disease. In contrast, scoring for noninvasive modalities is highly variable depending on coexisting hepatic and nonhepatic diseases (a common problem in a high-prevalence disease such as NAFLD). In addition to being variable, elastography assumptions of fibrosis are occasionally uninterpretable, especially at low-to-moderate stages of fibrosis. One study demonstrated that transient elastography scores corresponding to stage 2 fibrosis overlapped with the standard error of elastography measurements corresponding to every other stage of fibrosis (1 through 4).[4] Liver biopsy is also considered the *reference standard* of liver fibrosis measurement, because almost every study performed to validate noninvasive liver fibrosis measurement modalities used liver biopsy as the reference gold standard. One study did, however, take an unbiased approach to directly assess which modality (biopsy versus elastography) was more prone to error. In this study that assessed discordance in fibrosis measurement between transient elastography and liver biopsy in patients who had received both tests, the percentage of error attributed to transient elastography was significantly higher than that attributed to liver biopsy.[5] Finally, liver biopsy is so widely accepted that it has been noted to be the gold standard for fibrosis measurement by both the American Gastroenterological Association and the American Association for the Study of Liver Diseases. The European Association for the Study of the Liver also notes that elastography "is less accurate and needs to be confirmed by liver biopsy." Liver biopsy provides several benefits over noninvasive modalities beyond its ability to better meet the definition of a gold standard. Unlike noninvasive methods, liver biopsy provides a dynamic view of liver fibrosis in NASH and can distinguish bland fibrosis from fibrosis associated with severe necroinflammatory activity that can greatly affect disease progression. In addition, in contrast with liver biopsy, which can be performed by hepatologists, gastroenterologists, and radiologists and is available in most medical centers, elastography often requires expensive equipment, software, and specialized training and has limited availability in only a select few centers.

Some arguments against liver biopsy for the evaluation of fibrosis in patients with NAFLD should be addressed. First, although we have demonstrated that liver biopsy is the gold standard, we are not advocating for its ubiquitous use in all patients with NAFLD. Rather it is a specialized test that is reserved for a select group of patients where the diagnosis/stage is in question or when the measurement must have the utmost accuracy, thus requiring the gold standard. A common criticism against liver biopsy is procedural complications. However, the complication rate is comparable with other (often diagnostic) procedures that are used far more frequently. For example, bleeding complications of biopsy occur in approximately 0.6% of cases.[5] This rate is comparable with colonoscopy, which also has a bleeding rate up to 0.6%.[6] Death from liver biopsy is reported to occur in 0.03% to 0.1% of cases. Cardiac catheterization mortality rate is 0.1% and is performed much more often than liver biopsy.[5,7] There exists a small amount of variability associated with liver biopsy. However, as discussed earlier, transient elastography is also highly variable, especially at low-to-moderate stages, including stage 2 fibrosis. The best noninvasive modality, magnetic resonance elastography, demonstrates a concordance with liver biopsy in up to 90% of cases, arguing that any variability in liver biopsy is shared with this noninvasive technology.

Noninvasive fibrosis technology has great promise and does have a role in disease staging in NAFLD. However, the question posited in this debate was not which method is most commonly used, but rather which method is the gold standard. Which test has superior quality, a standardized interpretation, serves as the reference standard, and

is widely accepted? Which method is to be used when you must have the most accurate result? The answer to all of these questions is the liver biopsy, the gold standard for liver fibrosis measurement in NAFLD.

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