Advances in Hepatology have come fast and furious over the last decade but perhaps none more so than improvements in diagnosing and staging liver fibrosis. These improvements have come with recognition that there are inherent limitations with liver biopsy and that the improvements in serological diagnostic testing have made diagnostic liver biopsy frequently unnecessary. The integration of new tests of liver fibrosis into clinical care has proven challenging and no definite consensus exists yet of how best to utilize these tests. In this supplement the role of liver biopsy, serological tests, elastography and combinations of these technologies has been discussed and in my conclusion I will attempt to place these advances into current clinical context.

Liver biopsy, since its initial introduction by Klatskin as a clinical tool, soon became the major diagnostic test for liver disease. Since that time improvements in our understanding of the pathophysiology of autoimmune and viral diseases have led to markedly improved biochemical and virological tests for the diagnosis of liver disease, which have led to a decreased need for the simple diagnostic use of liver biopsy. Diseases such as autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and viral hepatitis B and C can be well characterized and diagnosed with blood tests leaving little diagnostic role for biopsy except to stage the degree of liver fibrosis. Liver biopsy is still essential when the diagnosis of parenchymal or infiltrative liver disease is unknown. Clearly the ability to accurately stage liver disease with non-invasive tests would further reduce the need for liver biopsy, particularly for viral hepatitis B and C where the histological stage is often used for treatment decisions.

Thus, over the last 10 years there has emerged a plethora of non-invasive diagnostic tests for staging fibrosis. In this conclusion to this supplement I will address some of the issues and questions that remain in the diagnosis of liver fibrosis.

Is there still a role for liver biopsy

Clearly liver biopsy remains an invaluable test for the staging of liver fibrosis and has been used as the gold standard for many of the studies that have evaluated non-invasive markers of fibrosis. However, the diagnostic accuracy of biopsy has been questioned and liver biopsy may be a more of a bronze then a gold standard [1-6]. Recent modeling studies have suggested that if biopsy has a true diagnostic accuracy of 85 - 95% then utilizing it as a gold standard can only result in a limited diagnostic accuracy for biomarkers with a maximal AUC of 0.9 [7]. There has been a suggestion that liver biopsy only be utilized when biomarkers are non-diagnostic and within a “grey zone”. However, the reality is that there is also a significant grey zone for liver biopsy in differentiating between stage 1 and 2 fibrosis and that sampling error and inter-observer variability simply highlight this indeterminate area for staging. This area of limitation for both biopsy and biomarkers needs to be more broadly recognized by clinicians who need to realize that staging of liver fibrosis is an inexact art. This then leads to the more important question of why do we even need to stage fibrosis.
Why stage liver fibrosis

As clinicians we must have a valid reason to perform a diagnostic test and should utilize the results to assist in patient management. Does staging liver fibrosis meet those requirements? Knowing the stage of liver fibrosis for determining the prognosis of liver disease has been one justification for liver biopsy. However this requires some reexamination in light of both new treatments for liver disease and the potential reversibility of fibrosis [8, 9]. The histological stage of disease is not definitive in determining prognosis or rate of progression to cirrhosis. There is some retrospective data that the stage at index biopsy predicts the rate of progression but this has not been confirmed in large prospective cohorts [10]. Can we feel comfortable telling patients that they have little risk of progression on index biopsy or in fact that they will progress on to cirrhosis - in view of the recent suggestions that fibrosis progression is non linear these represent challenging clinical problems [11]. In fact perhaps the only really important stage to differentiate is cirrhosis or advanced fibrosis. The diagnosis of cirrhosis is associated with clinical outcomes and does necessitate screening for hepatocellular carcinoma and esophageal varices [12]. There is also significant emerging evidence that non-invasive markers can predict disease outcome and risk for clinical events by also differentiating cirrhosis from mild disease.

The 2nd argument for precisely staging disease is that treatment guidelines state that only patients with stage 2 or greater disease on biopsy should be treated with interferon and ribavirin for HCV. First let us examine these guidelines and their applicability in 2008. They certainly do not hold true when we have patients with genotype 2 and 3 where 24 weeks of treatment results in 70 - 80% SVR rate [13, 14]. However, the reality is that with new treatment we now have reported rates of 61 - 65% SVR for genotype 1 with 24 weeks of interferon therapy with ribavirin and a protease inhibitor such as telaprevir [15]. These SVR rates are only likely to improve over the next few years making the need for biopsy for treatment decisions even more obsolete.

Therefore I would suggest that the critical issue is not just the staging of disease, but rather the accurate detection of advanced fibrosis (bridging) or cirrhosis and the ability to predict risk of clinical outcomes.

How to best diagnose advanced fibrosis and cirrhosis

This issue of the journal comprehensively reviews the different tests for both invasive and non-invasive diagnosis of fibrosis. The one area in which almost all the tests excel is in the diagnosis of cirrhosis. The gold standard of liver biopsy is correct in 85 - 90% of patients and most serological tests have the same performance characteristics. Liver stiffness by both ultrasonography and MRI also has more than 90% accuracy in diagnosing cirrhosis. This leaves us with a clinical conundrum - what is really the best test to diagnose cirrhosis when we have so many choices? Assuming a similar accuracy of 90% between the 3 groups of tests, what is the optimal diagnostic sequence or combination for cost effectiveness, patient safety and acceptability, convenience and broad applicability? Liver biopsy is expensive, invasive, requires day care hospitalization and has a significant but small risk and clearly would not meet the requirements listed as a first line test. The multiple panels of serological tests have the safety and convenience issues but we need studies on cost effectiveness and also some degree of standardization since there are probably too many test choices with similar performance characteristics. Elastography with MRI has issues of significant cost and patient acceptability and is not particularly convenient. Elastography with ultrasound has high patient acceptability and no risk but cost effectiveness studies are also needed.

Therefore in 2008, a new algorithm exists for the staging of liver fibrosis and although not universally accepted nor endorsed by anyone except the Authors, we believe that this represents a cost effective, safe and patient friendly approach to the staging of liver fibrosis (Fig. 1).

However many challenges remain for the clinical and basic investigator. We clearly need studies to look at changes over time in non-invasive fibrosis markers so that we clearly know what indicates disease progression. Utilizing advanced
fibrosis and cirrhosis as our endpoints rather than single change in stage so make these studies somewhat simpler to design and perform but they will need funding and will take significant time to complete. We need to see if the non-invasive markers have the same ability to predict SVR as histology and they should be incorporated into all new clinical therapeutic trials being developed for HCV. Perhaps the most challenging need is the identification of new biomarkers that can rapidly and dynamically measure the changes between active fibrogenesis and fibrosis degradation so that we can better develop anti-fibrotic therapy. In conclusion, this is an exciting time to be in the field of liver fibrosis as diagnostics and therapeutics move inexorably forward to improve our ability to care for and treat patients with liver disease.

Conflict of interest:
Nezam Afshal participates to clinical trials and has occasional involvements for advisory services) on behalf of Echosens Quest. Darmund Manning has no conflict of interest.

References