

gle test. In our opinion, the choice of a diagnostic strategy comprising sequential tests (conditionally independent) [2,3] with different operative characteristics may be more effective. For the diagnosis of fibrosis, a diagnostic flow chart can be designed using an initial highly sensitive test to rule out the diagnosis if negative and if positive followed by more specific tests to confirm it.

## References

- [1] Mehta SH, Lau B, Afdahl NH, Thomas DL. Exceeding the limits of liver histology markers. *J Hepatol* 2009;50:36–41.
- [2] Sebastiani G, Vario A, Guido M, Noventa F, Plebani M, Pistis R, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol* 2006;44:686–693.
- [3] Paggi S, Colli A, Fraquelli M, Viganò M, Del Poggio P, Facciotti C, et al. A non-invasive algorithm accurately predicts advanced

fibrosis in hepatitis C: a comparison using histology with internal-external validation. *J Hepatol* 2008;49:564–571.

Agostino Colli  
Department of Internal Medicine,  
Ospedale A Manzoni, Lecco, Italy

Mirella Fraquelli  
Second Division of Gastroenterology,  
Dept. of Internal Medicine,  
IRCCS Fondazione Policlinico,  
Via F. Sforza 35, 20122 Milano, Italy  
Tel.: +39 02 55033445; fax: +39 02 55033644.  
E-mail address: mfraquelli@yahoo.it

doi:10.1016/j.jhep.2008.12.012

## What is the actual role of diagnosis and how to assess it: Reply

*To the Editor:*

Drs. Colli and Fraquelli underscore several important implications of our analysis of non-invasive liver fibrosis test validity [1,2]. The central finding is that limitations in the validity of an imperfect gold standard obviate precise characterization of the validity of surrogates. When applied to the liver biopsy, our calculations demonstrate that a perfect marker of liver fibrosis could not be distinguished from what many consider to be a clinically unacceptable one, unless the biopsy sensitivity and specificity are above 90%. The degree to which error in the biopsy might affect the apparent validity of a surrogate should always be considered in non-invasive marker research.

Drs. Colli and Fraquelli make an excellent observation about the use of test results in medical management. Clinicians interpret a single test result in light of the outcome of other tests, their intrinsic validities, the pre-test probability of the condition, and many other considerations. Our study does not address the integration of these multiple factors but rather the simple interpretation of a substitute for a single test. A logical extension of our study would be to assess the performance of multiple diagnostic tests (e.g., serum marker panel and elastography). In addition, liver biopsy provides information on other factors like steatosis that cannot be ascertained from some non-invasive surrogates, and our computations do not account for these added diagnostic benefits. Likewise, Drs. Colli and Fraquelli correctly point out that our data showing the limitations

in the traditional way that surrogate markers are evaluated does not answer the pressing clinical question of what to do when there is a difference. Fortunately, non-invasive markers are increasingly being assessed in clinical trials of hepatitis C treatment. Results of these studies, and others employing alternative ‘gold standards’ like the natural history of disease, will be necessary to improve our use of pre-treatment testing to manage patients with chronic hepatitis C.

## References

- [1] Colli A, Fraquelli M. What is the actual role of diagnosis and how to assess it? *J Hepatol* 2009;50:828–829.
- [2] Mehta SH, Lau B, Afdahl NH, Thomas DL. Exceeding the limits of liver histology markers. *J Hepatol* 2009;50:36–41.

Shruti H. Mehta  
Department of Epidemiology, Johns Hopkins Bloomberg  
School of Public Health, Baltimore, MD, USA

Bryan Lau  
Department of Epidemiology, Johns Hopkins Bloomberg  
School of Public Health, Baltimore, MD, USA  
Department of Medicine,  
Johns Hopkins School of Medicine, Baltimore, MD, USA

Nezam H. Afdhal  
Liver Center, Beth Israel Deaconess Medical Center,

David L. Thomas  
*Department of Epidemiology, Johns Hopkins Bloomberg  
School of Public Health, 1830 E Monument St,  
Room 455-ID, Baltimore, MD 21287, USA*  
*Department of Medicine,  
Johns Hopkins School of Medicine, Baltimore, MD, USA*  
*Tel.: +1 410 955 0349; fax: +1 410 614 7564.*  
*E-mail address: dthomas@jhmi.edu*

doi:10.1016/j.jhep.2008.12.013