protective (proliferative) and destructive (apoptotic) mechanisms. Thus, natural occurring autoantibodies may stimulate or inhibit apoptosis by interfering with Bcl-2 proteins or with the large family of transmembrane receptors. This theoretical concept is convincingly backed up by recent findings that UDCA can prevent apoptosis by reducing the apoptotic threshold through modulation of the classical mitochondrial pathway [13].

References

[1] Selmi C, Zuin M, Gershwin ME. The unfinished business of primary biliary cirrhosis. J Hepatol 2008;49:451–460.
[2] Schwartz M, Ziv Y. Immunity to self and self-maintenance: a unified theory of brain pathology. Trends Immunol 2008;29:211–219.
[3] Matzinger P. The danger model: a renewed sense of self. Science 2002;296:301–305.
[4] Gershwin ME, Mackay IR. The causes of primary biliary cirrhosis: convenient and inconvenient truths. Hepatology 2008;47:737–745.
[5] Czömpöly T, Olasz K, Simon D, Nyárády Z, Pálinkás L, Czirják L, et al. A possible new bridge between innate and adaptive immunity: are the anti-mitochondrial citrate synthetase autoantibodies components of the natural antibody network? Mol Immunol 2006;43:1761–1768.
[6] Goldblatt F, Gordon TP, Waterman SA. Antibody-mediated gastrointestinal dysmotility in scleroderma. Gastroenterology 2002;123:1144–1150.
[7] Baroni SS, Santillo M, Bevilacqua F, Luchetti M, Spadoni T, Mancini M, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med 2006;354:2667–2676.
[8] Kovács L, Fehér E, Bodnár I, Marczinovits I, Nagy GM, Somos J, et al. Demonstration of autoantibody binding to muscarinic acetylcholine receptors in the salivary gland in primary Sjögren's syndrome. Clin Immunol 2008;128:269–279.
[9] Alvaro D, Mancino MG, Glaser S, Gaudio E, Marzioni M, Francis H, et al. Proliferating cholangiocytes: a neuroendocrine compartment in the diseased liver. Gastroenterology 2007;132:415–431.
[10] Kundu M, Thompson CB. Macrophagy versus mitochondrlal autophagy: a question of fate? Cell Death Diff 2005;12:1484–1489.
[11] Letai L. Pharmacological manipulation of Bcl-2 family members to control death. J Clin Invest 2005;115:2648–2655.
[12] Plotz PH. The autoantibody repertoire: searching for order. Nat Rev 2003;73:73–78.
[13] Amaral JD, Castro RE, Sola S, Steer C, Rodrigues CMP. p53 is a key molecular target of ursodeoxycholic acid in regulating apoptosis. J Biol Chem 2007;2282:34250–34259.

Peter A. Berg*
Department of Internal Medicine,
University of Tübingen,
72076 Tuebingen, Germany
Tel.: +49 07071 63075; fax: +49 07071 257854.
E-mail address: paberg@t-online.de

doi:10.1016/j.jhep.2008.12.001

What is the actual role of diagnosis and how to assess it?

To the Editor:

We read with interest the paper by Mehta et al. [1] that reported that due to imperfection of liver biopsy as a reference standard it is not possible to estimate the accuracy of a non-invasive test for the diagnosis of liver fibrosis. However, we would like to challenge some points raised.

Diagnosis cannot be regarded as a primary outcome but alternatively can be represented as a decisional node.

The identification and staging of a disease (diagnosis) should support the decision to treat a patient or not. The utility of diagnosis derives from the benefits of this decision. Thus, in the context of liver disease, patients with severe fibrosis have a worse prognosis and those with significant fibrosis fare better with treatment. The identification of these subgroups is useful and allows the definition of their prognosis and initiation of effective treatment, but these differences in prognosis and benefits of treatment have widely been evaluated using exclusively histological definition, even if imperfect. Actually, no diagnostic test can be regarded as perfect and thus there are no longer "gold" but only reference standards. The limitations of liver biopsy are well known; the most important being the high percentage of false-negative results yielded in the cases of significant or severe fibrosis.

In the study by Mehta et al. there is an implicit assumption that the prognosis and the response to treatment in patients with false-negative results at histology are actually the same as in those with true-positive results. This assumption has still to be unequivocally proved. So far, it has not been possible to assume that non-invasive fibromarkers are more useful only for the merit of reducing the false- negative rate of histology. In fact, only the assessment of the prognosis of patients with discrepant results (between histology and fibromarkers) could define their actual advantage.

An unequivocal demonstration would entail a randomized controlled trial comparing hard clinical outcomes in patients in which the diagnosis of significant or severe fibrosis was obtained either by histology or by non-invasive fibromarkers.

Furthermore, the analysis by Mehta et al. is limited to the overall accuracy and AUC assessment: these are two diagnostic measures of true results, but no information can be derived on false-positive or -negative results. However, the clinical utility of a diagnostic test depends on false-negative and positive rate (i.e. on sensitivity and specificity).

Finally, Mehta et al. [1] seem to conceive possible alternatives to liver biopsy only in the form of a sin-

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, Facciotto 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,