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Reply to: "Is the pathway of energy metabolism modified in advanced cirrhosis?"

To the Editor:

We would like to thank Ganapathy-Kanniappan *et al.*, for relating to our work to suggest an interesting hypothesis for the origin of hepatocellular carcinoma (HCC). Based on the recent and historical findings that HCC is associated with elevated glycolysis [1,2], they propose an interesting hypothesis that metabolic adaptations in early stages of liver cirrhotic hepatocytes could be linked to the origin of tumorigenesis in liver and that end-stage failing cirrhotic hepatocytes undergoes metabolic adaptations leading to HCC. However, the mechanistic links between liver cirrhosis and HCC are unclear and identification of pathways connecting both remains elusive. The focus of our recent work was the study of adaptive energy metabolic changes during liver cirrhosis to understand hepatic failure in the terminal stages of chronic injury [3]. Even though the letter to the editor from Ganapathy-Kanniappan *et al.*, is not completely related to the study we designed, it is recognized that liver cirrhosis is considered as a precursor to HCC.

In addition to hepatocytes, it is important to consider the role of the tumor microenvironment in regulating the metabolism of cancer cells. Recent studies have shown that cells in the tumor microenvironment generate energy rich metabolites (e.g., lactate, beta-hydroxybutyrate) that are used by cancer cells for meeting their energetic demand through mitochondrial tricarboxylic acid cycle [4,5]. Based on the compelling recent results [6], one possibility is that microenvironment may induce metabolic transformations in early cirrhotic hepatocytes and when in contact with stromal cells to sustain their nutrient demand. Early cirrhotic hepatocytes may alter the surrounding cells metabolic phenotype to secrete high-energy metabolites for their energetic requirements. Metabolic alterations and adaptations are thus an exciting area of investigation.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Cost-effectiveness of upcoming treatments for hepatitis C: We need to get the models right

To the Editor:

We read with great interest the recent article on cost-effectiveness of current and future treatments of patients with HCV genotype 1 by Younossi and colleagues [1]. Although the authors explore a very pertinent issue regarding treatment decisions in such patients, there are certain aspects that somewhat decrease the validity of their findings.

Firstly, the authors assume that the health-related utility/quality of life is similar to all patients with HCV infection irrespective of fibrosis stage. The critical question is whether patients with F0/F1 could be left without treatment. There is a bias favoring a treat-all strategy if higher utilities are not ascribed to patients with F0/F1 [2].

Secondly, the SVR rates of the all-oral therapy combination are unclear and sourced from abstract publications in 2012. With huge steps in HCV treatment since then, we would expect more up to date source data. Moreover, we would favor a more

conservative disutility approach of new treatments or at least a sensitivity analysis.

Thirdly, although the authors used non-invasive assessment for the staging of fibrosis, they assumed a perfect sensitivity and specificity of this approach, which of course is not clinically plausible [3]. The authors should have incorporated evidence on the accuracy of the non-invasive test outcomes in their Markov model and the cost and health implications of each possible diagnosis: true positive, false positive, false negative, and true negative.

Fourthly, in terms of life expectancy, the actual difference between oral therapies for all *vs.* oral therapy after staging is 1.8 months over 30 years. This marginal difference is at the expense of treating 17% more patients and is not sufficiently discussed.

We recently completed a cost-effectiveness analysis of non-invasive tests in informing treatment decisions in patients with hepatitis C, taking into account the relative sensitivities and specificities of a wide range of non-invasive fibrosis tests [4]. We were able to identify a price threshold above which the treat-all strategy with new treatments is not cost-effective.

As more treatment options become available for HCV, cost-effectiveness models will become increasingly important in informing public policy. In order for such models to stand up to the occasion, we need to get the baseline data right.

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Conflict of interest

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Reply to: "Cost-effectiveness of upcoming treatments for hepatitis C: We need to get the models right"

Interferon free regimens for treatment of chronic hepatitis C genotype 1 patients lead to better clinical and cost outcomes

To the Editor:

We appreciate the input from Tshochatzis *et al.* in their letter to the editor about our recently published article [1]. One of the issues raised has to do with differences in health-related quality of life (HRQL) related to the stage of fibrosis. Although there is evidence to suggest that patients with advanced liver disease have more impairment of HRQL, there is absolutely no credible evidence to suggest that HRQL impairment is different between earlier histologic stages of fibrosis [2,3]. On the other hand, we do agree that when patients have cirrhosis, especially those with decompensated cirrhosis, their HRQL is significantly more impaired and this was considered in our analysis. As for the disutility of oral regimen, we used actual data obtained from patients who were treated in clinical trials [4] and did conduct sensitivity analysis (the online supplementary document provides additional details of sensitivity analyses). Therefore, we believe that our HRQL assumptions for our economic analysis were correct.

We also understand that our analysis was performed using efficacy data for all oral regimens from abstracts presented in international meetings. At the time, this was all the data that was available. Nevertheless, fully published data from all oral regimens suggest even higher SVR-12 rates than what we considered in our model [5,6]. In fact, we believe that our study may have actually underestimated the cost effectiveness of all oral regimens which should further strengthen our conclusions.

As far as the staging of liver disease by Fibroscan® is concerned, our initial analysis was performed using the "gold standard" for staging which is liver biopsy. In fact, this approach yielded very similar results to those of Fibroscan. It is also important to note that while Fibroscan® is widely used in Europe, despite FDA approval, Fibroscan® is still not widely used or available in the United States. Part of the problem is large scale vali-