Reviewer's report

Title: Modelling the impact of improving screening and treatment of chronic hepatitis C virus infection on future hepatocellular carcinoma rates and liver-related mortality

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Reviewer: Ashish Aggarwal

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Reviewer Comments

This interesting study by Cramp et al aimed to estimate the future burden of Hepatitis C virus (HCV)-related disease in England if current management strategies remain the same and the likely impact as new therapies become available. Adapting a previously published model, authors compared the “Base-case scenario” model based upon current management strategies to the “increasing diagnosis and treatment or the best case” model that accounted for the new therapies as they become available. Authors estimated that compared to the “base case” projections, increasing treatment numbers by 115% by 2018 would significantly reduce HCV-related hepatic disease and mortality. While this is an interesting, with reassuring results, we would like the authors to consider following suggestions.

Major points

1. The introduction and results sections are well written, whereas Methodology section and Discussion sections need to be refined. In Methodology section, authors should consider adding more details about the model such as - how was the historical data extrapolated to make future assumptions, whether these involve patients listed for transplant/ transplanted, how were the costs calculated, if sensitivity analyses was done to identify uncertainties etc. Does this model assume that all the patients are treatment naïve?

2. In Methodology, please clarify if the dataset used to derive ‘base-case’ scenario reflects mostly patients treated with ribavirin and peg-IFN or do these also include patients treated with protease inhibitors like boceprevir/ telaprevir which have been approved for more than 2 years or even newer medications like sofosbuvir etc. If yes, then what modifications were made to adjust for the different treatment modalities and their potential impact on future predictions? If the ‘base case’ involves only the patients treated with ribavirin and peg-IFN, then do you think the ‘base case’ reflects an outdated treatment regimen as opposed to the ‘current treatment strategies’

3. Was the model tested to back calculate the expected prevalence of Hepatitis C, including the development of HCC or decompensated liver disease, mortality using the historical data and then compared with the actual data to see if the...
predictions are close to the actual data? Is it possible to do this testing?

4. In Methodology, under “Increasing diagnosis and treatment of HCV”, the model assumed that the number of patients treated increased from 5,430 in 2013 to 8,150 in 2014 and then to 11,710 in 2018. What was the basis of this assumption?

5. In Results Section, Please include the respective data for historical cohort for HCV related morbidity and mortality in Table 3 for easier readability and comparison

6. While it is certainly plausible and very likely that with Hepatitis C eradication, the rate of progression of liver disease will perhaps be slower. However, data is scant for patients who had already developed advanced fibrosis or cirrhosis and then undergo HCV treatment. In addition, it is not entirely known how HCV treatment changes the risk of HCC development in an already cirrhotic patient. This should perhaps be discussed in the Discussion/ Limitation section or an appropriate reference should be included that made the basis for calculation of reduction of HCV related morbidity/ mortality in ‘best case’ strategy

7. The authors very cursorily address the cost effectiveness with the new strategy. Further details should be given regarding the methodology behind cost estimations? If the primary aim is to see if the new treatments will be cost effective, then a detailed analysis should be included in the results including the current healthcare costs, main factors responsible for the cost including cost of treatment of HCV, cirrhosis related complications or HCV in addition to projected costs with base case strategy.

8. This section of Discussion on overcoming barriers to care can be curtailed as it does not add significantly to the strengths/ findings of the study. Neither is this the main focus or aim of the study. and goes beyond the scope of data presented. Authors should consider condensing the last 2 paragraphs in the Discussion section. In addition, since the analyses for cost effectiveness is incomplete without adjusting for the treatment costs, as the authors have correctly identified, discussion regarding cost effective strategies for reducing HCV-related morbidity and mortality should be curtailed.

Minor points

1. There is data that genotype 3 incidence is rising in UK and genotype 1 is declining. Do you anticipate any major changes to your analysis based upon that or do you anticipate that there won’t be any significant changes? (Ref: Costella, Annastella and Health Protection Agency United Kingdom. Hepatitis C in the UK 2008. The Health Protection Agency Annual Report. Health Protection Agency Centre for Infections, London, 2008)

2. “The model estimates that 5,430 HCV patients were treated in England during
2010, based on the number of standard units of peg-IFN sold (IMS Health Incorporated; Danbury, Connecticut). Does this reliably capture nationwide peg-IFN sale?

3. Page 13, Line 353, 2013 and 49,730 need to be separated

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests