APPENDIX A. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Comment	Response
The data is intriguing but in my view still somewhat preliminary. I would like to see this repeated in a year or two to see if the patterns observed hold up	We appreciate the assessment. We hope to repeat this analysis and plan to do so should funding permit.
Results of this report may influence decisions about future formulary status of boceprevir and telaprevir. Results have the potential to indirectly influence future decision making about formulary status of HCV medications as more DAA drugs are developed and come available. The VA also must review policy for future HCV antibody testing guidelines. These results are highly relevant to such guideline decisions.	Again, we appreciate this assessment and hope to be as relevant to VA decision makers.
No specific recommendations. It is appropriately structured as-is, given available data resources, to best inform decisions at hand.	Thank you.
p.18: This is a strong summary of the available data as they exist in the literature and in VA data resources. On p18, the authors discuss the sources used in concluding the estimates of number of veterans with HCV infection who are treatment eligible, and who take up treatment if eligible. As is pointed out, best estimates of these numbers vary quite a bit, and the conclusion arrived at here is that 45% of those in care are treatment eligible. I suspect that this figure may be a bit high, as it is derived quite substantially from samples selected for greater intensivity of treatment than is likely the national norm. However, pending better empiric data I suspect it is not too much of an overestimate and is reasonable.	We agree that this could be a possibility and that better data would help. We have noted this when we described this number stating “, though this may be somewhat lower in the VA population if the studies were conducted in populations who are more likely to be eligible for treatment.” (Page 18)
There are studies on the way genetic test can change behavior. In this case it is possible that knowledge of IL28B status might encourage compliance.	We have noted that this possibility exists but have not modeled this as there are no data on how IL28B changes behavior (and none specific to the VA) that we know of. We have noted this in the limitations: “Furthermore, there are other patient, provider, and facility characteristics that may play a role in determining use of these new technologies and additionally, depending on the results from IL-28B testing may also play a role in determining subsequent clinical actions and patient behaviors. Information in this area could help to further refine the analyses presented here.”

Comment	Response
It seems likely that use of DAAs and IL28B tests vary by more than just VISN (discussion). It is likely to vary among providers, and even vary within a single practitioner over time.	We have noted this in the discussion as an area of definite interest for future work. See our response to the comment above which includes how we have addressed this point in the revised text as well.
It is an early assessment of the testing for the new medications responsiveness. I would like to see a follow up in two years relative to the benefit of testing in the selection of patients for triple therapy.	We appreciate the assessment. We would love to repeat this analysis and plan to do so should funding permit.
Very good and I have no substantive recommendations. This is good work given the newness of the drugs and the brief period for which analysis can be provided. It would be good to repeat this in 2014.	Thank you.
P. 13, Sub-question 1.4 paragraph 3: Excluded cases: supply of drugs greater than 90 days. Unsure why this is excluded given that some of the patients are snow birds and may need more drugs for travel? Given this is only 3% I am ok with it. Just wanted to know the thought behind this exclusion.	The analysis of length of treatment excluded the 3% of individuals who had a dispensed prescription for a single day supply and those with prescriptions for more than 90 days' supply. This exclusion was applied only to the analysis of the length of treatment with DAA. All cases were used in estimating the number of individuals starting DAA. It was felt the including individuals who had records with extreme values of "days supply" in a single prescription record might bias the estimate of the duration of treatment, and these individuals were excluded. This exclusion is unlikely to have much effect, however, as only 3% of individuals were excluded, and the mean supply of medication dispensed to them (114 days) was similar to the mean of dispensed to individuals included in the analysis (102 days).
Page 14. The analysis uses ICD9 codes to assemble a cohort of HCV-positive patients. The report should indicate whether this approach using administrative data has been validated (either by the authors or others) or whether this is a pragmatic approach given the rapid nature of the report. It also seems that events such as decompensated cirrhosis were identified in administrative databases but the methods for identifying these are not outlined.	We identified prevalence of HCV by counting the number of persons with visits or stays assigned an ICD-9 diagnosis code for HCV during the year end 9/30/2010. This was a pragmatic (if inexact) means of identifying the relative prevalence in different regions to provide context for the utilization of the new treatments and the new genetic screening test. We did not have access to HCV test results, but will use those data to identify cases in our newly approved study.
Page 33, Paragraph 1: The report would benefit from a table outlining the breakdown of component costs.	This is a good suggestion but beyond the scope of the current study.

Comment	Response
The scope of the paper emerges upon reading but would benefit from being more clearly described near the beginning of the report.	We have made extensive edits for clarity and believe this helps the overall readability of the report per the reviewer's comments.
The report should clarify whether HIV-positive patients were excluded from the analyses (particularly the VA population with chronic HCV receiving VHA care) since the efficacy of DAAs in this population is only now emerging.	Patients with HIV were not excluded from the administrative data analyses, though due to the fact that efficacy in HIV co-infected individuals is highly uncertain we would expect utilization in this population to be relatively low. We have noted this in the appropriate section. For the simulation model, we have further highlighted the fact that HIV-infected individuals were excluded from the analyses for this same reason. The model focuses on treatment-naive, HCV monoinfected individuals only. We have added the following to the document: "The modeling analysis is confined to HCV monoinfected individuals as evidence of effectiveness for those co-infected with HIV is only beginning to emerge and utilization data needed to support VA-specific analyses stratified by co-infection status are also needed."
One of the main findings of the report is that the QALYs gained with IL-28B testing are lower than those obtained with treatment not guided by IL-28B testing. This is a counterintuitive finding to me, considering that IL-28B testing should have its maximal benefit in avoiding toxic therapy among those who would not benefit. This is worthy of discussion and clarification.	We believe the reviewer is asking about universal triple therapy versus IL-28B guided triple therapy. While the gain in efficacy in non-CC types is much higher for triple therapy compared to standard dual therapy, efficacy gains in studies for CC types is also somewhat higher. Hence, although side effects are more intense for triple therapy, its potentially shorter duration combined with increased efficacy appears to offset this though at increased overall costs.
Although it is only a one year time horizon, the report would benefit from some simple analyses to ascertain whether the use of DAAs in the VA has been stable or increasing over that time period. This is presented descriptively in the results but could also be addressed analytically.	According to the data source used, the DSS prescription dataset, the number of patients initiating DAA increased during the first 10 months of the analysis, and then decreased in the last 3 months in the dataset. It is uncertain whether the decrease represents an actual change in practice or is an artifact of the data processing. The decline in new starts at the end of the study may represent incomplete processing of VISTA pharmacy data for inclusion in the DSS extract.

Comment	Response
Several assumptions in Tables 3 and 5 are presented without justification or are presented only qualitatively without justification of the actual parameter used. For example, the report assumes a "higher rate" of liver transplants than observed but it is unclear how the value of 2500 per 100,000 person years was derived. Similar assumptions apply to some costs in Table 5, including the average adverse event costs and the annual post-successful treatment HCV care costs.	We have endeavored to clarify this point in the notes in the table, providing the numbers of the FY10 preliminary analysis to estimate liver transplantation rates. Adverse event costs were derived from studies conducted by others as cited in the notes in the relevant sections of Table 5. A number of the assumptions about costs were made based on non-VA-specific studies when no VA-specific data could be found. For example, the cost of post-successful treatment HCV care in non-VA-specific populations tends to be roughly half that of pre-treatment care costs (excluding the costs of medications and other clinical care and monitoring during treatment with two-drug or triple therapy). This is now noted more clearly in the table.
The report would benefit considerably from presenting sensitivity analyses.	Sensitivity analyses are planned for the approved HSR&D study, but are beyond the scope of this current preliminary effort.
Several abbreviations and acronyms are not fully defined (e.g. IPNUMBER). The report should be carefully edited to include these in the table of abbreviations.	We have clarified abbreviations in the appropriate places in the report.
The model considers age and race but does not present the results by these subgroups (i.e., it does not present variability in outcomes by subgroups but rather averages outcomes across the entire population). However, analyses by subgroups could be particularly beneficial for developing guidelines or targeting therapy within specific institutions.	We agree, though the main goal of the analysis was to highlight costs and resource use for the VA taking into account factors that might influence these things. The analysis also does not do a lifetime horizon cost-effectiveness analysis which would be important for considering guidelines for targeting therapy. We hope to do this contingent on appropriate funding.
Lai M, Afdhal NH. Clinical utility of Interlukin-28B testing in patients with genotype 1. Hepatology 2012; 56:367-372	We have incorporated this reference in our discussion of alternatives of how IL-28B may be used to guide treatment.
Thompson AJ, McHutchison JG. Will IL28B polymorphism remain relevant in the era of direct-acting anti-viral agents for hepatitis C virus. Hepatology 2012; 56:373-381	We have incorporated this reference in our discussion of alternatives of how IL-28B may be used to guide treatment.
Backus LL, Belperio PS, Thomas C, Cheung R, Mole LA. Week 24 and end of treatment response for direct acting antiviral (DAA)-based therapy in veterans with chronic hepatitis C. AASLD Late Breaker 30, 2012	This is an excellent and recent reference which is certain to be published in an appropriate journal. We look forward to incorporating it into future revisions of this and related work.

Comment	Response
Pearlman B, Ehleben C. Hepatitis C virus genotype 1 infection with low viral load and rapid virological response to peginterferon and ribavirin can be treated without a protease inhibitor, irrespective of IL-28B status or patient ethnicity. Hepatology 2012; 56 (4, suppl): 268A	We have incorporated this reference in our discussion of alternatives of how IL-28B may be used to guide treatment.
Thompson AJ, Shiffman ML et al. Six weeks of a NS5A inhibitor (GS-5885), protease inhibitor (GS-9451) plus peginterferon/ribavirin achieves high SVR4 rates in genotype 1 IL28B CC treatment naïve HCV patients: Interim results of a prospective, randomized trial. Hepatology 2012; 56 (4, suppl):556A	We thank the reviewer for the helpful reference on new treatments for HCV. We agree that it is an exciting time with more than 70 new treatments and combinations in various phases of clinical trials. Our recently funded HSR&D grant intends to examine these in the context of the VA.
It is unclear form this report that clinicians and patients are making treatment decision based on the IL28B result. This make extrapolation of current findings difficult.	We believe the reviewer is referring to the analysis of administrative data. Our current preliminary analysis does not directly address this question, which we agree is an important next step but which is beyond the scope of the report.
IL28B currently is a send out test. It was stated the cost was $300. However, I was told by our lab that it was only about $100. Not sure what is being used in the cost analysis.	We have clarified the text to note that we used total cost of care, including the direct cost of services and the associated indirect (overhead) cost.
p.11: 2.6% chronic hepatitis C prevalence appeared to be low for veterans. Many veterans were coded incorrectly as acute hepatitis C (070.51 instead of 070.54) if ICD-9 code is being used.	We used all ICD-9 codes for HCV infection, both acute and chronic, but only considered persons with care that was assigned this code in the study year. HCV laboratory test results were not available, but will be evaluated in the our newly approved study.
p.18: Preliminary triple therapy data of veterans was recently presented by Backus et al.	This is an excellent and recent reference which is certain to be published in an appropriate journal. We look forward to incorporating it into future revisions of this and related work.
p.21: 3-year survival rate for HCC of 70% was too high for all HCC patients- are these post-liver transplant?	The reviewer is correct. This was an error in data extraction from the VA review which cited an older article by Pawarode et al and also more updated SEER data. We have updated the note, the parameter, and the analyses. Notably this does not substantially change results over a 5 year horizon because relatively few HCCs are prevented in this period (< $1million dollar change in the estimates of total cost differences for total costs of $50-150 million).
p. 21: Did HCC treatment cost also include sorafinab which cost ~$3000/month. This is reserved for advanced HCC and might not be applicable in this analysis.	The cost of all medications and health services were included in the cost of care for persons with HCC.

Comment	Response
This report did not address the treatment experienced patients.	We have noted this in the limitations: "The modeling analysis is confined to treatment-naïve, HCV monoinfected individuals as evidence of effectiveness for those co-infected with HIV is only beginning to emerge and utilization data needed to support VA-specific analyses stratified by co-infection status are also needed. Analyses like those presented here for individuals with previous experience of HCV treatment would be important to conduct, though are complicated by a number of issues including fewer data on effectiveness, various types of treatment failures, and reasons for failure including lack of adherence to medication regimen versus non-response to appropriately taken medications."
Current model of IL28B guided therapy (figure 1) is an over simplification. See discussion by Lia and Afdhal (e.g. Fig 3 on p 371)	We appreciate the reviewer's comments. We agree that there are many ways that one could use IL-28B testing alone or with other predictive markers to optimize treatment response, side-effect profiles, and/or costs. We note that data are emerging on this important topic and have added the following sentence to the limitations: "IL-28B genotype along with other predictive markers for treatment response are an exciting new avenue. Our analysis considers one such approach, though others may also be possible. Ultimately, all such approaches attempt to optimize over treatment response, side-effects, and costs in achieving best outcomes for individual patients."
The other model would be to stratify patients based on the response during the lead-in phase. Even though majority of patients with IL28B CC had RVR, RVR is actually more important than IL28B as predictor of SVR. Patients with low viral load and achieve rapid virological response will not benefit from adding the protease inhibitor. However, this might be beyond the scope of this report.	This is an excellent point that we have noted in the report.
This report just presents the findings without any recommendations for the clinicians. The article by Lia and Afdhal actually discussed how IL-28B genotype could be used in patient management.	The goal of the report was to provide a preliminary view of current practices and a short-term (5 year) view on the impact of current practices and changes in these practices on health outcomes and costs. Informing VA clinical care guidelines with a life time cost-effectiveness analyses is a larger goal of work for which we have currently received funding from VA HSR&D.