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Title	Health care costs associated with chronic hepatitis C virus infection in Ontario: a retrospective cohort study
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Reviewer 1	Chris Estes
Institution	CDA Foundation, Sacramento, Calif.
General comments (author response in bold)	This manuscript describes the economic burden of chronic HCV infection (including after cure), by disease stage and cost category, including a regression analysis of factors associated with costs. This research is an important contribution to understanding the national burden of HCV in Canada, and will be useful to decision makers in terms of understanding the economic trade-offs of screening, diagnosing and treating individuals with HCV **We thank the reviewer for these comments.** Abstract: Following was not clear on first read: "…and two death states (up to 6 months before liverrelated (LR) or non-liver-related (NLR) death)." Suggest removing 6-month qualifier from abstract and describing this in methods. **We have revised the abstract.** **Page 2: "Time from diagnosis until death or the end of follow-up was allocated to nine mutually exclusive health states using validated algorithms: no cirrhosis, cured HCV (ribonucleic-acid negative), compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), DC and HCC, liver transplantation (LT), and two pre-death states (liver-related (LR) and non-liver-related (NLR) death)."** Results & Discussion: Some results lack context that should be provided in discussion. The statements below seem to point to the co-morbid burden of injection drug use, mental health disorders, etc. that impact younger people and males at a higher rate (and may also correlate to higher ADGs, lower socioeconomic status, etc.). While the data from the current analysis may not be sufficient to quantify these factors, it should still be a point of discussion, as previous studies have described the burden of injecting drug use by age / gender in Canada. "…increasing age significantly decreased costs in the non-advanced liver disease states…"; "Male sex was associated with 7% higher costs than female sex in the nonadvanced liver disease states, but had no statistically significant effects in other states." **We agree with the reviewer that some of our results may indicate the co-morbid burden of injection drug use and/or mental health disorders. However, more data and analyses are needed to provide evidence for these assumptions and assessing them is outside of the scope of this paper.** A limitation of these data that should be discussed is the inability to distinguish between liver-related costs, and non-liver costs (including some costs associated with extrahepatic manifestations of HCV). Likewise, a strength of the data is the ability to identify venue / category where costs are incurred. This may ultimately be the more important measure for policy makers. **Thank you for these suggestions. We have revised the "Strengths and limitations" sub-section in the Interpretation section to include the following:.**

	Page 11: "… Further, our analysis was not able to distinguish between liver-related and non-liver-related costs. Thus, our results may over- or under-estimate the full economic burden of HCV…" **We also modified the second sentence in the "Strengths and limitations" sub-section in the Interpretation, to include our ability to identify venue/category where costs were incurred, for all patients diagnosed with HCV in Ontario from 2003 to 2014.** **Page 10: "Because Ontario has universal publicly-paid health insurance (over 97% of Ontarians have OHIP [15, 16]), we were able to capture utilization of almost all publicly-funded health care, by resource type. Although our cohort may not have included all asymptomatic CHC patients, it included all diagnosed cases of HCV infection in Ontario from 2003 to 2014."** Liver transplant cost appears to be more reflective of care subsequent to transplant. Can authors clarify if transplant costs are an average that includes months where the transplant actually occurred? **The liver transplant cost was calculated based on 372 cases who had a liver transplant during our observation period. However, the average duration of follow-up for these 372 patients was 1,480 days. Thus, it includes the months when the transplant actually occurs, but also includes care subsequent to transplant. Patients entered the liver transplant health state on the day of the transplant and remained in that health state until they met the criteria for another health state.** Supplement: Case definitions: References / crosslinks missing **We have inserted the references for the supporting information.**
Reviewer 2	Jee-Fu Huang
Institution	Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan
General comments (author response in bold)	The study period was quite long and ranged from IFN-based to DAA therapies. The treatment durations, regimens, and the efficacies were quite diverse across different time period. Focusing on DAA era with 8-12 weeks of treatment duration might be informative and more updated. **We have included a sensitivity analysis which used only the data since 2012, when the first generation DAAs were approved in Ontario. We have revised the Methods, Result, and Interpretation section to include information about the sensitivity analysis. Please see our replies to the Editor, comment #7, for details.** The molecular diagnosis has evolved rapidly and the costs of the diagnosis tools have also been changing rapidly. Therefore, the costs of the changes should be considered. **This comment is similar to comment 1, above, concerning therapies. Please see our replies to comment 1 and to the Editor, comment #7, for details.** In the DAA era, how're the difference of direct and out-of-pocket costs in different disease states, name from chronic hepatitis, cirrhosis, to HCC. The analysis may be stratified according to the achievement of SVR. **Our analysis took a public payer perspective and included only costs paid**

	by the Ontario Ministry of Health and Long-term Care. Thus, out-of-pocket costs were not included in our cost estimate. **However, please note over 97% of the residents of Ontario are covered by universal health care insurance (OHIP) which covers the costs of medically-necessary health care. Patients have out-of-pocket costs related to obtaining health care, and outpatient prescription drug coverage is limited to specific populations. We have highlighted this as potential limitation in the Strengths and limitations sub-section of the Interpretation:** **Page 11: "We could not include costs borne by private health insurers or, more importantly, out-of-pocket costs paid by patients, many of whom are unable to work because of HCV. Patients who are not covered by the ODB plan must pay for outpatient drugs, including antiviral therapy, out-of-pocket, or through private insurance."**
Reviewer 3	Darren Brenner
Institution	Oncology, University of Calgary, Calgary, Alta.
General comments (author response in bold)	The authors provide a thorough and detailed analysis of the health care costs associated HCV in Ontario. The paper is clearly written and the methods are well described. Only a few minor comments for improvement. **We thank the reviewer for these comments.** Consider including Ontario in the title. **Thank you for this suggestion. We have revised our title to: "Health care costs associated with chronic hepatitis C virus infection: A population-based analysis in Ontario"** Methods – the manuscript would benefit from some level of sensitivity analyses around the precision of state transitions or cost allocations. **We have revised our paragraph to include further information around the precision of the health states:** **Page 5: "We characterized the natural history of HCV using a set of relevant and commonly-used health states based on the literature [3, 4, 11] ….We defined health states from diagnostic, procedure and death codes in the administrative data, using validated algorithms whenever possible [12]. …. Health state definitions are described in Table 1, and Supplemental Tables S1-S4."** **Cost allocations were estimated using predefined standard methods for Ontario administrative data from reference 14. Sensitivity analyses on these are not feasible. We have included a sensitivity analysis using the data since the development of the first generation DAAs in 2012. We have revised both the Methods section and the Results section to include this information.** Discussion – In comparing the estimates here with previous estimates from Ontario, is possible to adjusted for the change in inflation or costs from 2005 to 2018 to give a clearer comparison to the estimates generated here. **We have revised the sentence to give a clearer comparison after adjusted for inflation:** **Page 10:"Krajden and colleagues, in 2005, estimated the total health care costs for early stage HCV to be $320 CAD per 30 days, and late stage HCV (including HCC, DC and/or CC) costs were $904 CAD per 30 days for the province of British Columbia, Canada [9]. After adjusting for inflation [22],**

	our cost estimate for no-cirrhosis is almost twice their estimate ($798 versus $386), and our estimates for late-stage disease are at least 36% higher ($1,487 for CC to $8,753 for DC and HCC versus $1,088)." Discussion – how do Ontario costs generally (likely to vary by province) translate across provinces. For other disease sites, are there trends that are generally observed outside of HCV? This may help the generalizability of the findings to include in the discussion section. **We have included two sentences to address the generalizability of the findings:** ***Page 12: "Although our results are most relevant to Ontario, Canada, the comprehensiveness of our study should allow analysts in other settings to understand relative costs across disease stages, the importance of end-of-life costs, and the implications of age, sex, and particularly comorbid illness as predictors of total costs. We believe that improving the quality of costing will strengthen the evidence basis of HCV elimination efforts in Canada and internationally."*** Other – consider a supplementary figure to show state transition order and any potential bias/limitation in the attribution of health states based admin data only. **Thank you for the suggestions. We have included a figure (Figure S1) in the supporting information to illustrate the conceptual transitions.**