Article details: 2019-0231	
Title	Characteristics of high drug cost beneficiaries across Canada: a cross-sectional pan-Canadian analysis
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Reviewer 1	Frank Moriarty
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General comments (author response in bold)	Thank you for the opportunity to review this manuscript reporting a study on high drug cost beneficiaries across 9 Canadian provinces. The manuscript clearly describes the conduct of the study, and the results are presented in a simple and effective way which characterizes these beneficiaries. I have a small number of minor suggested revisions which I hope may strengthen this manuscript further. Comment 1: Although the typical structure of drug programs may be well known to Canadian readers, it may aid clarity to include a brief overview of drug programs in either the Background or Methods sections. This would give more context to the discussion of drug plans in the Interpretation section (e.g. reference to catastrophic drug programs). **We thank the reviewer for these suggestions. We have made changes to the manuscript to highlight some potential differences between plans. We have also added a citation to recent publication that fully describes these differences in details for readers. We have also added an example of a common high cost biologic that differs across provinces and how varying methods for payment of this agent likely varied costs.** **Changes:** **1. Added to background: "Additionally, how this varies by the differing provincial public drug program structures is unknown.** **2. Added to discussion: "Our results highlight the impact of differences between public drug program structures that should inform the development of any pharmacare strategy.5"** **3. Added to discussion: "Lessons should also be learned from the differing ways in which provinces cover specific medications to help in the development of a national formulary. For example, differing listing for the medication ranibizumab, a treatment for age-related macular degeneration, between British Columbia and Ontario led to Ontario having this agent as one of the top spends in both high-cost groups while it was not one of the top 10 most costly drugs in British Columbia."** **4. Added additional citations** Comment 2: - The term "clustering" is used in relation to proportion of total cost among the small number of high cost beneficiaries. While this is definitely accurate, on first reading in the Background, I expected this might relate to some form of clustering analysis in the statistical sense. I am not entirely sure if there is a more appropriate term that would reduce any potential confusion, perhaps "accumulation". **We thank the reviewer for this suggestion. Although we agree that this term may lead to confusion for readers ware of clustering analysis we think it is the most appropriate term to define what is actually happening with high drug-cost users. This terminology also aligns with the literature in this area**

	describing this issue. We have tried to make the definitions of the term clustering clearer and when not necessary changed the wording throughout. We aim to ensure it is known it is referring to the clustering of costs. **Changes:** **1. Changes throughout to make the term clustering clearer.** Comment 3: One characteristic examined is the median number of unique drugs dispensed per person. Is this the number dispensed over the one year study period? Also, on what basis were drugs identified as unique? (i.e. based on ATC code/drug ingredient, ATC code and route). **We have added language to the methods section to more clear define our definition of number of drugs dispensed and how this value was defined.** **Changes:** **1. Added to methods section: "4) median number of unique drugs dispensed in the last year per person" and "Medications were captured on the generic drug name level."** Comment 4: In Table 1, it may be helpful to either add Total program spending and Average Cost per beneficiary for "Other beneficiaries", for consistency with other tables, or substitute this for the "Overall" columns there currently. Also, are the total spending columns presented in units of million $ (i.e. overall being 8.185 billion)? There are no details of the total number of beneficiaries included, which could be added to Table 1 or the text. **We have added the information requested to the supplemental material. We worry that the tables are already too large and further information may make them challenging to navigate. We have also added units to the column ($ millions) to make it easier for readers to understand.** **Changes:** **1. Made changes to Table 1** Comment 5: Is average cost per beneficiary (mean) the most appropriate statistic to describe the distribution of costs overall and among the high and very high cost beneficiaries? Not knowing what the distribution looks, but I would assume that it may be potentially quite skewed, and that median and interquartile range may be informative to include, even as a supplementary table. **We thank the reviewer for this suggestion. We selected the mean to align with previous studies that have reported it in this manner. We have included a compairson of the median and mean in the appendix as requested.** **Changes:** **1. Added medians to supplemental table** Comment 6: The Interpretation states that "In fact, there appears to be evidence of two factors contributing to the clustering of high drug-cost beneficiaries", receipt of expensive medications and being on a high number of medications. I feel the paper would benefit from slightly more discussion on the evidence for this, pulling out the specific findings that support this. Further display of the results could help to support this and how these two factors relate to each other. For example, the authors might consider plotting the average cost per beneficiary by number of

	drugs among high-cost beneficiaries, or distribution of drugs among those with or without a high-cost claim. **We thank the reviewer for highlighting this issue. We have added to the discussion section to further support this finding. Although the suggested additional analysis sounds interesting we believe the current analysis already highlights the key characteristics we have explored in our analysis. The proposed analysis asks a very different question which is how does the number of drugs impact the cost, an interesting and potential future question we hope to study.**
Reviewer 2	Kristian Filion
Institution	Department of Medicine and Epidemiology, McGill University, Montréal, Que.
General comments (author response in bold)	In this cross-sectional study, Tadrous and colleagues use data from 9 Canadian provinces to describe the prescription drug use of high drug-cost beneficiaries across Canada relative to other drug-cost beneficiaries. This study has several strengths. With the ongoing discussions of a broader universal pharmacare strategy, it is very timely and is policy relevant. However, this study also has some limitations, and there remains a need to better contextualize some of the results; these issues are discussed in the Specific Comments below. Comment 1: Perhaps the most interesting findings are those related to inter-provincial differences, which were surprisingly large. Although the authors describe these differences, they do not attempt to explain the potential sources of this heterogeneity. While some differences in clinical practice may exist, some of the differences may also be due to differences in who is covered across provinces and what is covered. The inclusion of a table describing the provincial drug plans would be useful to help contextualize some of these findings. **We thank the reviewer for these suggestions. We have made changes to the manuscript to highlight some potential differences between plans. We have also added a recent publication that full describes these differences in details for readers. We have also added an example of a common high cost biologic that differs across provinces and how varying methods for payment of this agent likely varied costs.** **Changes:** **1. Added to background: "Additionally, how this varies by the differing provincial public drug program structures is unknown.** **2. Added to discussion: "Our results highlight the impact of difference between public drug program structures that should inform the development of any pharmacare strategy.5"** **3. Added to discussion: "Lessons should also be learned from the differing ways provinces cover specific medications to help in the development of a national formulary. For example, differing listing for the medication ranibizumab, a treatment for age-related macular degeneration, between British Columbia and Ontario led to Ontario having this agent as one of the top spends in both high-cost groups while it did not make the top 10 for British Columbia."** **4. Added additional citations** Comment 2: Along those lines, it may be useful to compare reimbursement policies across provinces. While it would not be feasible to do so for all drugs (or even many drugs), perhaps doing so for a couple of the drugs that account for

	large expenditures may be worthwhile (e.g., the biologics). **We thank the reviewer for these suggestions. We have added language to the discussion to highlight the difference in coverage of some of an example drug between Ontario and BC. As the reviewer highlighted it is challenging to cover all of these but have cited a specific example to demonstrate potential differences.** **1. Added to discussion: "Lessons should also be learned from the differing ways provinces cover specific medications to help in the development of a national formulary. For example, differing listing for the medication ranibizumab, a treatment for age-related macular degeneration, between British Columbia and Ontario led to Ontario having this agent as one of the top spends in both high-cost groups while it did not make the top 10 for British Columbia."** Comment 3: Patients were categorized as high-cost versus not high-cost, dichotomizing the distribution at the 95th percentile. While some categorization is likely needed to compare and contrast patients, this approach results in an important loss of information. The inclusion of some figures that allow for a more nuanced description of the distributions would be helpful. **We have conducted Lorenz curves nationally and by jurisdictions. These have been included in the appendix. The results of this analysis visually depict our discussion about the level of clustering and it also shows that the issue is more similar than different between provinces. We have added language to the paper to also mention these Lorenz curves and their usefulness.** **Changes:** **1. Added Lorenz curves to appendix** **2. Added language to methods and discussion to cite Lorenz curve results.** **a. "We also conducted Lorenz curves overall and my jurisdiction to visual depict the level of clustering in payments."** **b. "All provinces showed signs of clustering among high drug-cost beneficiaries (See Supplemental materials)."** Comment 4: Were data available to assess time trends in high drug beneficiary costs? **Although an interesting question, this was outside of the scope of the question asked in this study. We aimed to better understand characteristics of the high drug-cost users and differences across provinces rather than explore the changing time-trend. Additionally, the annual time-trend is reported by CIHI and would not add any novelty to the currently available information.** Comment 5: The stated objective was to describe the characteristics of high drug-cost beneficiaries but the characteristics presented appear to be mainly limited to dispensing and related cost data, with limited clinical data presented. This should be made clear throughout. In addition, it may be worth discussing the limited availability of clinical data as part of the Discussion. Along those lines, the authors describe high-drug beneficiaries as "complex patients with a high comorbidity burden"; this is inferred from their medication dispensing but comorbidity does not

	appear to have been assessed directly. **We agree that the lack of linkage used in the study limits our ability to better understand some characteristics of users we do gain a strong understanding from our analysis. However, drug data is a validated means to evaluate comorbidity and complexity, with a well-established link between complexity/comorbidity and number of drugs taken by a patient (Yurkovich et al). Additionally, we gain insights based on the types of drugs used as they highlight the general indications and population clusters that may exist. We have also added this as a limitation to our work.** **1. Added citation** **2. Added limitation** **a. Third, this analysis was informed by only drug claims data and we do not have information of comorbidities. We have inferred using types and number drugs the extent of comorbidities which is a validated method of assessing comorbidity when only drug claims data is available** Comment 6: The units are not always clear in the tables. For example, the total program spending for Prince Edward Island is listed as $26.0 in Table 1. Should this be $26.0 million? **We have added a note to make clearer the unit of reporting in table 1.**