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**Title:** Comparison of high drug-cost beneficiaries from Ontario, Canada and Australia: a cross-sectional analysis

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**Reviewer 1:** Kelly Zarnke

**Institution:** Medicine, Foothills Hospital, Calgary, Alta.

General comments (author response in bold)

Comment 1: This is an interesting comparison and set of analyses, given sizeable comprehensive population datasets over a ten-year period. There are interesting observations supportive of the pricing concentrations among beneficiaries, EG the the rising “minimum cost thresholds” and the decreasing number of medications per beneficiary in the higher drug costs groups. I would support that these analyses are worthy of publication to draw attention to these findings.

**Thank you for the thoughtful feedback to help us improve this work for readers.**

Comment 2: This reviewer is unsure of the utility of using the concept of the high-cost user or beneficiary as a denominator from a policy perspective. a. As perhaps preferable alternative considerations, the total aggregate cost burden to the public program, and disease or treatment-specific measures of health economic efficiency – IE cost-effectiveness using natural health units, QALYs – might be alternative outcomes that may more specifically help decision makers regarding program sustainability and/or choice of inclusion of specific products on a national formulary; whereas it seems to this reviewer that deliberations related to a small number of “high cost beneficiaries” may be more relevant to operational aspects of program delivery. Or if this is deemed relevant to how policy is crafted, this could be briefly outlined in the discussion?

**We appreciate the feedback. This is a very important point that this work does not address the cost-effectiveness of the programs or specific drugs but rather is a look at the program at a high level. Importantly- we think that future work could explore the impact of the entire program and their deliverables. We have added language to make clear that the decision to include and price drugs in both jurisdictions is based on a similar framework which utilizes HTA. We have also cited a paper that compares the two process. Importantly, from our perspective I think that policy makers benefit from a range of analyses – the purpose of the paper was to examine one of these – which does not imply the others are not valuable. In both countries, payers regularly monitor total aggregate costs and the value for money proposition comes into pay at the time of listing and there is regular monitoring to establish if the drug is being used withing the parameters in which it was determined to be cost-effective. Clearly these analyses are valuable. Again, payers have become very interested in understanding high-cost users, what characteristics they have and what drugs they are using. This helps support forecasting of likely costs in the future. Therefore, this work is meritorious in its own right and provides and alternative lens by which payers can evaluate their programs. We have made several changes to further highlight the importance of drug-specific evaluations.**

Changes:

1. Added to discussion mention of cost-effectiveness and control
2. Added citation

Comment 3: Does the focus on the "high-cost medicine user", as labelled in the discussion erroneously create the impression that the sustainability problem is driven by the "user" versus, say, the prices for niche products such as some biological therapies that manufacturers are permitted to charge?

**We appreciate this feedback – it is something we perhaps have not taken the time to think through. We agree that the wording may make it seem like a user vs a system problem. Any solutions would likely combine both lenses. We have used this terminology to align with currently available work that is often used by policymakers and people in the field. We have added some language to the discussion to highlight this thought and the importance of taking a system-level view rather than a user-level view. In reality this is driven by both. In our view we all too often we focus on single drugs rather than the people navigating through the system. I believe that both are important.**

Changes-
1. Added: Importantly, although both Canada and Australia have similar health-technology assessment to assess the price of new drugs they still may have divergent decisions and reimbursement structures.
2. Changed language to move away from person-specific language where possible
3. Added citations

Comment 4: It would be helpful for readers to be presented with some demographic features of the two broader populations whose data was compared and perhaps some demographics of the high-cost beneficiaries as well – both numbers of citizens included in the analyses, jurisdictional inclusion criteria for coverage, and, eg, average age or age distributions, population growth rates over the study periods, etc;

**We thank the review for raising this point. Unfortunately, due to the limitations of the data we are limited in the demographic factors we are able to report. We have highlighted the linking both data sources and having comparisons of subpopulations is important next steps. We have also added further information on the populations to help reader's contextualize the observed results we report.**

Comment 5: Could the authors provide a rationale for comparing a single province in the Canadian confederacy with the entire country of Australia? Was this simply a pragmatic decision? One can recognize the pragmatic feasibility of using one provincial data source and conversely, the difficulty of obtaining comparable data from multiple provinces. Would the authors speculate on the representativeness of the Ontario data as "typical" of the pan-Canadian experience?

**The decision to only use Ontario was based on both simplicity and feasibility. It was much easier to conduct the analysis in Ontario given that two of the authors currently have access to the Ontario data and the size Ontario made the comparison feasible since no issues with small anomalies would sway the trends. Also this work aligns with previous analysis that was requested by policymakers in Ontario. Additionally, we felt it would be easier to compare one payer to another. By including multiple provinces we would have to compare across various different payer structures, models and formularies. Our previous CMAJOpen paper (cited in the paper) used a similar methodology to compare across provinces and did highlight some important differences.**

**For these two reasons we felt it was best to compare two payers. Lastly, as previously stated we added language to highlight why Australia was of interest as a comparator.**

Comment 5: Could the authors clarify on why for Ontario all claims were included, while for Australia, a 10% random sample was used?

**Please see our previous response on this query.**

Comment 6: Could the authors offer some general commentary on the extend of drug coverage for their publicly funded formularies? Are there systematic differences that may explain why the total drug coverage cost are so much lower for a universal plan for ~25M Australians compared with the subset of ODB-eligible ~14M Ontario citizens? EG, is the extend of formulary coverage? Co-pays? Negotiated drug prices? Regarding the latter are there examples of similarities or differences between negotiated prices for high costs drugs?

Comment 7: Minor: Could the authors explain the rational for maintaining two different currencies in their analyses? Would there be any value in converting Australian to Canadian dollars (recognizing they are almost at par)?

**We thank the reviewer for these suggestions. We have made a number of changes based on previous suggestions that address these points. For example, we have added further comments on coverage basics for both jurisdictions and added citations. We have also discussed some differences of case-examples of differences in how some drugs were used. Lastly, we have now also included a supplemental table that converts the cost-thresholds from AUD to CAD.**

Comment 8: Minor: should lenalidomide (cited in E-figure 1) as an anti-neoplastic therapy be excluded from the analyses as this reviewer would suspect it's use is primarily for myeloma?

**Thank you for flagging this. Our drug class categorization was based on ATC codes. Given the coding of this drug it was captured in our analysis. We have highlighted this as a limitation. Note this also may vary by the formulation used.**

Change: Added to limitations" Additionally, drug indication was based on the ATC drug class system which uses the initial indication and formulation of the drug to classify drugs. Some drugs may be used across indications and thus the intended use for a specific patient may not be correctly captured."

Comment 9: Formatting query: Regarding Figure 4 and E-figure 1, the multiple coloring is a somewhat difficult to interpret (especially for someone who is color-blind, as is this reviewer!). Is there another way of presenting this data that enhances readability?

**We thank the reviewer for this honest feedback. We are happy to add the data in figure 4 to the appendix to allow further exploration by readers who may have difficulty reading the figure the way it is presented. We have also attempted to slightly change some of the colours selected but must admit it was challenging to find combinations that would solve for the problem.**

Comment 10: Minor: there are some awkwardly worded sentences and formatting of some of the references that may benefit from correction: presumably further editing to correct these will occur.

**We have made a number of changes throughout to improve the readability of our manuscript.**

**Reviewer 2:** Erica Lester

**Institution:** Surgery, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alta.
General comments (author response in bold)

Comment 1: I commend the authors on this international endeavour, and exploring this arena, which I believe is very important. I have a few concerns to address prior to publication that I hope will facilitate the clarity of the manuscript.

**Thank you! We are thankful for these thoughtful suggestions which believe have strongly improved our manuscript.**

Comment 2: I think a few of the statements are oversteps. For instance, saying this information is “essential to the sustainability of public medicine funding programs” is not quite true. This extends to the statement in the discussion about the importance of these high-resource patients to nationalizing a drug plan. These statements ignore the fundamental principles of the economics of health insurance, and the nationalization of insurance. This move would put the low resource use persons in the same “insurance pool” as the high-use persons. Resources are directed into large pool, with very few actually drawing from the pool. When private insurance companies are allowed to apply this principle, they have the ability to attract low-risk persons to the pool, collect their premiums, redistribute a portion and otherwise gain profit. They can cherry-pick. The “high-risk” persons are the high resource users, and are more likely to be state funded (which is what you describe here). The state pays for the most expensive health care users, and the private companies make a profit. Nationalizing drug insurance removes this issue, and moves closer to pareto optimum.These are basic principles of health insurance “markets”. I suggest the authors alter the wording of some of the statements to not over emphasize the importance of isolating these patients. The value in this study is quantifying some of these figures, identifying the high price tag items and demonstrating that these therapies are not as expensive in another place:  not in proving a point about insurance markets. The economics of drug national drug plans has been previously published, and the cost-effectiveness demonstrated.

**We thank the reviewer for these thoughts. We have made a number of changes throughout the manuscript that we feel address the reviewer’s suggestions. Specifically, we have toned down the language on the “essential” nature of our results. We have also added language related to the need to look at both the user and system level impacts of this work. Lastly, we have added important thoughts as the reviewer suggested of the benefits of risk-sharing.**

Comment 3: Along that same avenue, in highlighting the value of your work, I would elaborate on your points in the discussion about economies of scale and monopsony pricing power. A national plan in Canada would create a large market (albeit, smaller than if the US did this) that would have the capacity to negotiate lower prices. This is likely part of why the figures are lower in Australia.

**We thank the reviewer for this suggestion. We have added language to our interpretation to highlight this important point. This was also aligned with our previous changes as to why Australia was selected as an interesting comprator.**

Comment 5: There is a difference between the economics of creating a national drug plan, and the economic impact of how a national platform might facilitate targeted policies on cost reduction for specific groups (like starting patients on biosimilars). I’m certain the authors realize

this. However, these two concepts are too interwoven in this paper, and separating them would make it much easier to read (and would illuminate the papers relevance).

**We have made a number of changed in paragraphs 4 and 5 of the discussion to discuss the impacts of a universal model that allows the inclusion of healthier patients that do not require medications which in turn further clusters the proportion of total spending to a small number of beneficiaries - making these patients even more important to the sustainability to any program. Understanding which drugs and populations are more likely to be high drug-cost beneficiaries will be essential to the success of any expansion in Canada) and it would address their request.**

Comment 6: If I am understanding this correctly, you have very different samples. The Ontario sample is from the provincial government funded pool, which by nature is composed of more high-resource users. The Australian sample is a national random sample of the entire population. You must addresses the discrepancy in the interpretation. This is like saying the post-operative ward with all the young people post appendectomy on it costs less than the post-op ward with the transplant patients, so the transplant ward should look into what its neighbor is doing. Please elaborate on this in the discussion.

**Thank you for this suggestion. A number of changes will make this issue clearer for readers including language we added (see previous responses) related to populations and differences in data and access.**

Comment 7: Please clarify the statement "Addressing drug-and patient-specific issues will be important in the effort to develop robust and sustainable public drug programs". You are comparing a high risk portion of a population to a whole population that was public drug coverage for a while. There is clustering of resource use, which has previously been demonstrated, and also, simply makes sense. What issues are the authors referring to? How is this of value in a public program? Please clarify. Also, I would refrain from calling this patient specific issues. It implies individual issues. Disease process, or therapy specific issues would make sense.

**Thank you for this suggestion. We have changed this sentence now to read "Understanding drug- and disease-specific issues will be important in the effort to develop robust and sustainable public drug programs"**

Comment 8: Please clarify the statement about the "jump in the cost threshold to be included in the top 1%". The top 1% is the top 1%, there isn't a threshold.

**We have added the word "minimum" to show we are referring to the minimum cost threshold to be in the top 1%.**

Comment 9: There is no mention of adjusting for inflation (health or general) or converting the dollar values to a single currency for appropriate comparison (which, would be CAD in a Canadian journal). Please adjust to facilitate proper comparisons.

**Please see previous response on added information related to conversion from AUD to CAD.**

Comment 10: There is no mention of the cost effectiveness of national drug programs in the discussion. If you are going to discuss how this article lends itself to aiding in the development of a national program, you should reference the work that states that the drugs you are referring to are cost effective? Paying for the hepatitis C medications up front saves money in the long run with reduced sequela of hep c, for example. Saying these are high-cost drivers is superficial if the payer is to become the public payer (or, from the societal perspective). Perhaps to save money, drugs that are not cost effective should be targeted?

**We have added mention of the HTA process in Australia and Canada. We have also mentioned the importance of studying each drugs impact on the healthcare system from a CER lens and the opportunity to build on current process on a national level.**

Comment 11: Please alter the statements “our findings offer important insights for Canadian policymakers” and “our results emphasize the potential impact of an expanded coverage” to be more in keeping with the findings of the paper. This paper highlights drug costs and spending between two different samples and the types/numbers of drugs used. I think this is interesting: however I don’t think it is as relevant to the principles of national drug coverage as the authors implies. Rather, I would suggest focusing on the differences between the samples, and how this might highlight the benefits of the Australian approach.

**We have made a number of changes as suggested in the discussion (and in line with previous comments above) to make the purpose clearer as the reviewer has suggested.**

Comment 12: Line 42 on page 9 contains a grammatical error “total spending a small number”. As well, it is unclear to the reader how these clusters are threatening to national policy: see preamble regarding insurance “markets”.

**We have changed this sentence to read “ spending to a small number of beneficiaries” , We also made changes based on suggestions on inclusion of mention of insurance clusters. See previous response.**

Comment 13: Line 47 page 9: I think you mean recognizing the high-cost drivers will aid in development of policy that reduces cost. Not expansion. This would flow well into your next point, which is excellent: that having a national strategy would likely incur cost savings (economy of scale, larger market with “monopsony” pricing etc).

**We agree with the reviewer and a number of our changes in the discussion we believe better address this specific point.**

Comment 14: The finding that a small portion of users drive cost is not a new one. I would suggest referencing other works and developing on how this study is different/helpful.
**We have added a number of additional citations to show how our work build on previous foundational work and how this influenced our selected methadology. See previous response.**