Author's response to reviews

Title: Overview of the Alberta Kidney Disease Network

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Author's response to reviews: see over
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Dr Danielle Talbot
Senior Scientific Editor
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Dear Dr Talbot,

Thank you for allowing us the opportunity to resubmit our manuscript, based on the thorough review and thoughtful comments provided. We feel that we have been able to satisfactorily address all of the concerns raised, which has enhanced the quality of the manuscript. We have provided an itemized summary of the changes made to the paper below, with the reviewers comments provided in bold, followed by our responses. Corresponding changes are highlighted in the revised manuscript.

Reviewer #1:
1. I would remove the word “prospective” from the manuscript. In common parlance, prospective is typically reserved for protocolized data collection in the context of a known hypothesis so as to circumvent issues of surveillance bias. Although technically, these data are being collected going forward in time, they are nonetheless casual observations (i.e., resulting from clinicians’ decisions) and do not relate to a specific hypothesis. Although the authors are no doubt aware of potential limitations in this regard, it is best to be more conservative so as not to mislead the casual reader.

We appreciate the concern expressed by the reviewer, and have removed the term “prospective” from the manuscript as requested.

2. I would refrain from the term “population-based.” As the authors note in the discussion, observations do represent the whole of the population of Alberta (nor a random sample thereof), but instead the segment of the population that enters the database on the basis of having had certain biochemical measurements, who may or may not be representative of the broader population. Although, as the authors note, this should still provide for meaningful inference to many patient populations, it is not a true population-based study (a’la NHANES).

As requested, we have removed the term “population-based” as a reference to the AKDN dataset.

3. It was unclear to me, after reading the text on pp 5-6 and looking at figure 1 if ICD-9 codes and medications are available for the entire cohort, or only for the subgroup qualifying for Alberta Blue Cross. Please clarify.

AHW administrative data (and thus the ICD-9 codes) are available for all residents of the province of Alberta, while the Alberta Blue Cross drug program (and data) is available for residents aged 65 and older. We have clarified this in text on page 6.
AHW administrative data includes all residents of the province of Alberta, and contains data sources which permit determination of disease incidence and prevalence using validated algorithms for common medical conditions such as hypertension, diabetes, acute myocardial infarction, congestive heart failure and stroke.

Alberta Blue Cross administers extended health benefits paid by AHW on behalf of eligible individuals, including residents aged 65 and older, for services which include formulary drugs, permitting evaluation of drug use and its impact on outcomes.

4. The intriguing part of AKDN is the ability to integrate broad-based observations on laboratory measurements, demographics, and clinical parameters, and this is appropriately the focus of the manuscript. I think that the definition of baseline kidney function is (p. 6) is too specific, and any such definition might vary according to the aims of a particular study. I would remove this paragraph. (Also, would the authors define baseline kidney function based on a 6-month average of observed serum creatinine measurements if there was a clear trend to higher values over that interval?)

We appreciate the concern expressed, and acknowledge that the definition of baseline kidney function may vary depending on the study objective. The proposed definition is one example of how we are currently defining baseline function. We have revised this on page 6.

Other definitions of baseline kidney function however can be employed, depending on the objectives of the particular study.

Minor point:
1. In table 3, the authors may consider revising the classification categories. For example, terms including “albuminuria” are not correctly applied to urinary measurements of total protein; and terms including “proteinuria” are not correctly applied to measurements of urine albumin.

We have made these changes in Table 3 as requested.

Reviewer #2:

Major Compulsory Revisions
1. The authors do not address if other researchers (outside of the AKDN) can access this database. If not, then this article will not be nearly as interesting to other researchers in the nephrology community. If other researchers can access the data, what is the process to do so? Is there any documentation or a user guide that researchers can use? Is the database free to academic users? Are there any restrictions on use of this database?

Given the issues regarding patient confidentiality and privacy to date research using this data has primarily been undertaken by researchers within the AKDN. However we are currently exploring
options for external data requests. We are unable to expand on the details of that currently, as the process is still being developed. We have included this on page 10.

To date primary users of the database have included both clinician researchers and graduate students within the AKDN. We are currently exploring options for external data requests, which must take into account provincial privacy and security laws.

Minor Essential Revisions

1. Authors do a good job in text of explaining where pieces of data are coming from in text, however Figure 1 is not as clear as what is explained in the text. I would see the AKDN database as the central focus with arrows coming into that database from laboratory data, population registry, Alberta Blue Cross, etc… It would be useful to the reader to have each box labeled at top with the database name from which specific pieces of data are coming from, with the specific pieces of data listed below the database name.

With respect, we feel that the organization of the figure best depicts how this data is currently being used. That is the laboratory data is used to define a cohort, following which the cohort is linked to other data sources to obtain variables required for a specific study objective.

2. Authors need to explain more clearly the serum creatinine assays which are used across Alberta, prior to the creatinine standardization program. Authors note that a linear relationship between new and old methods for estimating GFR was established, however the underlying lab value in the GFR estimating equations is Scr. Before creatinine standardization was accomplished, Scr creatinine measurements were based on the results from assays that were not calibrated. Unless all the laboratories across Alberta used the same creatinine assay, then a simple regression between old and new methods of GFR estimation doesn’t seem to capture the inherent variability that may exist with GFR estimation before standardization.

We apologize for the confusion. We have in place a process to standardize creatinine measurements across provincial laboratories. We have included this on page 5.

To reduce inter-laboratory variation in eGFR creatinine measurements are standardized across provincial laboratories to an IDMS reference standard, and a laboratory-specific correction factor is applied where necessary.

3. Is the index calculated eGFR available along with each individual eGFR calculation within the index 6 month period. i.e. are the original values available to researchers who may not agree with the mean over 6 month methodology? For instance, the index eGFR calculation that is done would not allow assessment of a patient that had rapidly declining kidney function over a 6 month period.
See response #4 to reviewer #1 above. All creatinine measurements are available, thus different definitions of baseline function, and assessment of decline over time, can be employed.

4. In general, I found it difficult to determine if original data variables were contained in the AKDN database, i.e. all the ICD-9 codes for outpatient encounters for each patient vs only derived variables (e.g. comorbidities defined using algorithms). It also wasn’t clear if there were data quality control checks conducted before the data from the multiple sources were placed in the AKDN database. For example, quality control of the laboratory data was not addressed. Again, unless the same central laboratory was utilized, or all laboratories use the same assays for each of the laboratory measures, then there will be inherent interlaboratory variability that should be addressed in the text of the article as a data limitation.

See response #3 to Reviewer #1 above, clarifying data variables. Response #2 above addresses the issue of inter-laboratory variability in measurements.

5. Unclear how individual pieces of data are input or entered into the system or how data is retrieved from the system. Is some information entered manually, or is everything downloaded electronically? Also not stated is how researchers access or move around within system. Is there mapping between data coming from different datasets? And if similar pieces of data are coming from multiple sources, what constitutes the primary source?

All data is electronic, and there is no manual data entry. A unique patient identifier is used to link the different file sources. This has been clarified on pages 6 and 7.

The unique patient identifier is used to link the laboratory data to a number of such computerized data sources including Alberta Health and Wellness (AHW) administrative data, Alberta Bureau of Vital Statistics, the Northern and Southern Alberta Renal program databases [7], as well as other databases related to program delivery such as the Chronic Disease Management database. All data is available electronically, thus there is no requirement for manual data entry.

6. Page 1, 2nd para: following statement needs referencing; "As the initiative grows the AKDN research findings and activities are beginning to appear more frequently in peer-reviewed literature and health policy circles."

We have included references as requested (references 1-3)

7. Figure 1: would define abbreviations within Figure (e.g. SES)

Changes made as requested.

8. Font sizes need to be consistent throughout text
Changes made as requested.

**Discretionary Revisions**

1. A title that more accurately reflects main emphasis of the article might be “Overview of the Alberta Kidney Disease Network Database”

Title changed as requested.