Author's response to reviews

Title: The Chronic Kidney Disease Model: A General Purpose Model of Disease Progression and Treatment

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Author's response to reviews: see over
RE: The Chronic Kidney Disease Model: A General Purpose Model of Disease Progression and Treatment

To the Editors of BMC;

Thank you very much for the opportunity to respond to the reviewers of our paper The Chronic Kidney Disease Model: A General Purpose Model of Disease Progression and Treatment. As reviewer #1 had no comments for us to address we are focusing our response to those made by reviewer # 2. The comment is provided first and our response is below it in red.

Before addressing the individual reviewer comments we would like to take a moment to clarify the role of the initial starting parameters for the modifying variables used in the model. None are fixed for the model; but rather are up to the discretion of the user (including those mentioned by the reviewer in the comments). We provide default values that are set to the U.S. population; however we expect that most users will change these values to reflect a particular question. For example, if a state senator is interested in the impact of covering ACEI use for all state residents with CKD, he/she could enter the prevalence of CKD stages and distribution of diabetes, proteinuria, age, race, etc.. that reflects the population of that state. In another situation, the senator may want to focus upon the impact of ACEI coverage for only those with CKD and diabetes. In this case he/she would enter an initial distribution of 100% for diabetes at all stages. The importance of this point is to show that these initial modifying variable values are not fixed but rather flexible and not expected to be the same from user to user. The values that are fixed are the probability of moving from one state to another based upon the presence or absence of one or more of the modifying variables.

One final point is to note that since this paper focuses upon reporting the results of the validations (against existing cohorts), the starting parameters for these analyses did not use the default values for the US population (Table 1) but rather those that reflected the comparator study’s participants. Therefore, while we have made some changes to the default values based upon the reviewers thoughtful comments, the results reported in this paper are not affected by those changes.

Point #1. In Table 1, the prevalence of proteinuria is 100% for CKD stages 1 and 2, and close to 50% from stages 3-5. The 100% prevalence is based on NHANES data but in this survey CKD stages 1 and 2 were defined only on the basis of albuminuria. The KDOQI definition
includes other manifestations of kidney damage including hematuria and renal scarring. Thus the prevalence of proteinuria in CKD stage 1-2 is very unlikely to be 100%. Even the prevalence of proteinuria in CKD stages 3-5 is considerably higher that in the CRIC study (Lash JP et al. Clin J Am Soc Nephrol. 2009 Aug;4(8):1302-11).

In reviewing the referenced paper describing the CRIC study, I could only find the mean and range for the quantitative amount of protein excretion for the cohort. I could not find the prevalence of proteinuria. I do agree with the author’s comments that the KDOQI definition includes other forms of kidney injury besides proteinuria to define stage 1 and 2 CKD; however hematuria and other forms are considerably lower than proteinuria. I did however review the updated NHANES data from Coresh in Jama 2007 which separates micro and macroalbuminuria rates, therefore I was able to update the table to show only those with higher rates of albumin excretion- which is more reflective of the risk of disease progression. Note that for stages 1 and 2 I assumed everyone had some form of albuminuria, then calculated the percentage with macroalbuminuria to reflect proteinuria rates for these stages.

Point # 2. Similarly the prevalence of diabetes in each of the stages of CKD in Table 1 seems too high. The 2010 USRDS report shows a prevalence of diabetes of 49.4% for CKD stages 3-5. The value of 78% for prevalence of diabetes in CKD 5 seems much too high.

The USRDS 2010 data became available after our model was developed. We thank the reviewer for his comments and have updated the variable estimates to reflect those reported in this dataset.

Point #3 . The relative proportion of patients with each stage of CKD seems substantially different from that reported in reference 19 (NHANES): CKD 1 -30.3%; CKD 2 -27.2%; CKD 3 -39%; CKD 4 -2.6%; CKD 5 -1.5%

The values reported in Table 1 are an error. The values listed in the Table were the ones used when the model is run as an incidence model and not as a cohort model. Since this paper focuses upon the description and validation of the cohort component of our model we addressed this error by entering the correct values in the table (which are as the reviewer suggested they should be). Note that this was just an error in writing the paper – the model results reflect the correct stage distribution.

Point #4. The monthly changes in GFR shown in Table 2 seem extremely implausible. All of the values seem too high. The authors quote data from the AASK study that reported a mean rate of GFR decline of just 1.7ml/min/year. Thus the monthly values of -4.4 to –25 seems excessive.

In order for the model to be as accurate as possible across multiple strategies we needed to have values for GFR change that reflected the impact of each of the variables of interest (alone and in combination) as well as provide us with the distribution of values rather than just the mean and confidence intervals. There are no published studies that provide this level of detail. We therefore chose to analyze a primary dataset from the VA to obtain the information we needed; although we were concerned about the possibility that VA data may not be generalizeable. To address this question we performed extensive validations of the changes in the model’s simulated cohort’s GFR and compared those to AASK (as described in the paper). The results show that
the GFR change equation performs quite well and is within the CI of those reported by AASK. To clarify this point, I added text in the input section of the paper (under methods) and removed the mean and CI values from the table. The values shown in the table were unadjusted and thus confusing since each individual’s change values were dependent upon the presence/absence of specific variables (age, race, hypertension, diabetes, current CKD stage, etc…). In addition within each of these adjusted values, the actual value experienced by the simulated patient is pulled from a normal distribution around the adjusted values.

Please let me know if you or the reviewers have any additional questions and thank you again for this opportunity to respond.

Sincerely,

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