Author's response to reviews

Title: Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

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Version: 2
Date: 13 February 2015

Author's response to reviews: see over
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Title: Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

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Version: 1 Date: 13 February 2015

Authors’ response to reviews: see over
Reviewer's report

**Title:** Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

**Version:** 1  **Date:** 3 January 2015

**Reviewer:** Chester H Fox

**Reviewer's report:**
The article is well written and can be published as is. They clearly define an important problem and have a practical solution.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
They report the conflict of interest well
Reviewer's report

Title: Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

Version: 1 Date: 3 January 2015

Reviewer: Khaled Abdel-Kader

Reviewer's report:
This is a clustered prospective cohort study with patient matching examining a paper-based CDSS paired with lab results from Labcorp. This is a novel study, but there are several important limitations that require consideration and acknowledgement.

Major revisions:
1) Please include more information on the providers. What proportion were approached, agreed to receive the CDSS, refused, etc. Please provide comparisons re: provider characteristics (age/years since training, size of practice/pts seen per day, labcorp market share in the given practice locale). If these are not available, please acknowledge as a limitation).

We do not have further information about the providers. We have added a statement into the Discussion under limitations:
“Due to the way in which the program was proliferated, we were unable to determine what proportion of providers were approached, agreed to receive the CDSS, or refused the program. Likewise, we cannot provide information about provider characteristics such as age, years since training, size of practices, or LabCorp market share in the given practice locale.”

2) While the potential for chance associations is acknowledged, please more fully acknowledge additional key pt level confounders not assessed/adjusted for in the current study (comorbidities, SES, insurance status, etc).

This was added to the paper in the Discussion:
“We also lack data concerning comorbidities, socioeconomic status and insurance status for the patients. However provider zip code was used as a surrogate for socioeconomic status.”

3) Missing data is a significant limitation that should be acknowledged. This manifests in several ways. First, there is a disconnect between table 2 and 3. While there were 43K and 12K in usual care and CDSS arms, most of the analyses for frequency of monitoring only include 20K and 8K patients in the respective arms. It's not clear how similar those specific subgroups are based on table 2's baseline characteristics.
We have added to the Discussion under limitations:

‘The patients studied were in various stages of CKD and may or may not have been due for some of the testing we analyzed during the time period they were in the study. Each analyte analysis represents the subset of the population which was due for the testing.’

4) In addition, for table 4 and figure 4, missing data and ascertainment bias is likely to affect results. There are repeated measures of a subgroup of patients (while other patients have no values) when assessing achievement of the target range. Patients with elevated values are likely to have more frequent rechecks than those with goal values, thereby skewing the results. Patients without values are unknowns, but the missingness likely reflects their underlying clinical symptoms/state. Discussion of the achievement of goal values should be very cautious acknowledging these concerns.

We have added to the Discussion under limitations:

‘Finally, certain unavoidable biases are inevitable. Patients with elevated values are likely to have more frequent rechecks than those with goal values. Patients with multiple results may well have more complex and therapeutically recalcitrant disease.’

5) Please remove or provide further justification for the statement "The differential we found supports the validity of our study, as it would be difficult to imagine how an artifact of selection would create it." In a hypothetical exercise study, patients who choose to enroll (vs. controls who are not interested) are more likely to exercise (due in part to selection bias). The exercise intervention effect is blunted in the subgroup of patients who are professional athletes at baseline. I'm not clear why this differential effect in people with different characteristics alleviates concerns re: selection bias.

We have removed: ‘The differential we found supports the validity of our study, as it would be difficult to imagine how an artifact of selection would create it.’

6) The 3 mo 'add on' period (after the last accession date) represents a disproportionate period of time given the relatively short 8.4mo median f/u. Please consider a sensitivity analysis excluding this extra 3mo period (when providers may have used other labs or patients may have been lost to f/u for other reasons).

   The three month period reflects the guideline minimal interval and was not arbitrary. It biases away from the value of CDSS and therefore is already at one extreme of a sensitivity analysis - ie a most conservative approach. We beg the indulgence of the reviewer.

Minor essential revisions:

1) The potential use of outside commercial labs by a provider is not discussed.

   We have added: ‘The potential use of outside labs by a provider seems equally likely in either group.’
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests'
Reviewer's report

Title: Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

Version: 1 Date: 16 January 2015

Reviewer: Michael Choi

Reviewer's report:
Ennis et al. have submitted a well written interesting manuscript on the impact of a guideline based clinical decision support system (CDSS) on laboratory monitoring and achievement of laboratory target in 12,533 stage 3-4 CKD patients compared to 42,996 matched controls whose physicians did not receive the CDSS. Areas studied were kidney function, CKD mineral bone disorder, anemia and lipids. The authors concluded the automated laboratory based CDSS improved physician adherence to guidelines with respect to timely monitoring of CKD laboratory parameters although achievement of targets was variable. I have the following questions and comments

Major Compulsory Revisions:
1. If data was collected between 2009 and 2012, could the authors explain the short median follow up time? Was there a percentage of physicians who discontinued use of CDSS? I would think this would be uncommon.

We have added the following in METHODS:
‘The short median follow up interval reflects that the majority of providers were enrolled during 2011-2012.’

We do know that some physicians have discontinued use of CDSS, however tracking is incomplete and therefore we hesitate to speculate within the manuscript.

2. In the results section, would TSAT be expected to be checked in those who were not anemic?

We have added in METHODS: ‘in anemic patients’ after TSAT.

I am surprised by the magnitude of the p values for OR when absolute differences between CDSS and control in achievement of 25 D and LDL-C targets were small.

The size of the populations permitted such divergences; we hesitate to mention this in the manuscript.
Can the authors discuss why there would be a decrease in the % success for both CDSS and control groups in regards to testing for PTH and phosphorous for stage 4 vs. stage 3b (figure 2).

The guidelines for stage 4 recommend more frequent testing and perhaps physicians and patients demur; this is speculative and we prefer to omit from the manuscript.

Discretionary Revisions:
1. Although not controlled for in this study, it seems that there would be other data that would be interesting to the readers for those patients who had CDSS. Did the use of optional flow sheets seem to increase laboratory testing or achievement of laboratory targets? In those patients with longer follow up, was there increased adherence to testing or target achievement? In those patients who had physicians with a larger number of patients, was there increased adherence with testing or target achievement?

We agree with the reviewer but could not track effects of program components. Likewise, we think the questions about longer intervals are interesting but did not analyze this issue.

2. I would organize the data in the tables 1, 3 and 4. The data could be organized by the 4 areas tested. Kidney function (eGFR, CO2, urine albumin/creatinine, urine protein/creatinine), CKD-MBD (PTH, 25 –hydroxy vitamin d, calcium, phosphorous), anemia (hemoglobin, TSAT), then lipids. They would not have to be labelled by section.

We struggled to find a clear manner of presentation, and beg the indulgence of the reviewer in relation to these formats.

3. Do the authors think the Institute of Medicine’s target for 25 D of > 20 ng/ml could be contributing to the low achievement rates?

It is possible, but speculative and we would prefer not to comment on this.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests
Reviewer's report

Title: Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

Version: 1 Date: 21 January 2015

Reviewer: Ebony Boulware

Reviewer's report:
Summary: The authors present an analysis studying the effectiveness of CDSS to improve rates of guideline concordant laboratory testing and achievement of recommended clinical targets among patients with CKD. Physicians self-selected as utilizers of CDSS, and were more enriched by nephrologists. Patients of physicians were matched by demographic characteristics and clinical parameters. Overall, findings demonstrate that patients of CDSS physicians were more likely to have laboratory tests ordered in accordance with guidelines. However, for the most part, they were no more likely to achieve clinical targets (with the exception of LDL-c and 25-D). Generally, this study represents a very nice effort to obtain information on the value of this tool. More information on how the tool was used and the implications of findings would enhance the manuscript.

Major Compulsory Revisions Requested:
Methods:
1. A major weakness in the approach described in the manuscript is the potential self-selection of physicians using CDSS. Clearly, physicians that opted to use CDSS for CKD would be more likely to be interested in CKD or more likely to be nephrologists. The data actually bear that out, given more nephrologists in the CDSS group. Given this weakness, it would be very nice for the authors to revise the manuscript to discuss this.

We have added in the DISCUSSION: ‘The providers themselves are surely a source of selection bias. Those more interested may well have chosen to use CDSS. On the other hand, many of the physicians in the control group were not made aware of our CDSS program by the LabCorp sales force. This problem cannot be resolved within the present data set.’

Authors mention that physicians who would participate in an RCT would be different from those who did not. Indeed, that same logic applies to their own study. Those who opted in to CDSS are likely different from those who did not. It would be nice to see this issue further addressed in the discussion.
We believe the prior addition answered to this problem.

2. A second weakness is the use of CKD Epi non-African American as the default eGFR value. Why was this done? Please explain. Is it because race data are not considered reliable in the LabCorp data?

This is already in the MSS: ‘Race, used in computing eGFR, was not available for the overwhelming majority (approximately 96%) of patients. When race was unknown, the eGFR calculation for a non-African American patient was used by default.’ We added at the end after ‘default’: ‘because the majority of the US population is non-African American.’

We have already discussed the issue as follows: ‘Additionally, ethnicity was not known for most of our patients, so matching was imperfect in this respect. The default use of the non-African American eGFR calculation when race was unknown would tend to underestimate GFR and consequently over-diagnose CKD in African American patients.’

We hesitate to elongate the discussion further because we have no more concrete materials to add. Our use of zipcode would tend to ameliorate the problem of matching, and that is already in the manuscript.

3. On page 5, paragraph 3: Authors state: “CDSS physicians were those who chose to receive any of the program offerings.” Is there more detail on this? How many CDSS providers opted to receive all program offerings? To what extent do the authors know whether providers gave the information to all patients?

These are all excellent questions for which we have no data and cannot respond further. Anything we would add to the manuscript would be simple speculation.

Discussion:
4. On implications—Given lack of improvement in the majority of clinical parameters despite better testing, what are some potential solutions for improving actual clinical outcomes? If more tests are performed but no improvement in outcomes is achieved, the implication is that over testing is occurring or that needless testing is occurring.

Given the short follow-up interval, outcome data are still preliminary. The primary outcome of the study was improvement in guideline-recommended test ordering. Although these are excellent questions, we hesitate to express ourselves at this stage.

Authors mention prior clinical trials demonstrating a lack of CDSS effectiveness, particularly those that are used within EMRs. Given a move away from paper-based reporting systems and more EMR use, what do the authors recommend for future work to overcome barriers? How would CDSS fit into a larger model to improve patients’ clinical outcomes?
These are excellent questions which we hope to pursue, but the present study seems inadequate as a basis for further commentary.

5. Discussion of changes in iPTH guidelines brings up an important nuance. Prior studies have shown that when physicians do not trust guidelines, they are less likely to adhere to them. The extent to which the KDIGO guidelines are evidence based (and the level of evidence they rely on) and are trusted by health care providers could play a large role in whether providers actually adhere to recommendations. Can authors provide further insights?

We have added to the Discussion: ‘It may be that future CDSS studies using more widely accepted guidelines would demonstrate a higher rate of compliance.’

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests
Reviewer's report

Title: Clinical Decision Support Improves Physician Guideline Adherence for Laboratory Monitoring of Chronic Kidney Disease: A Matched Cohort Study

Version: 1 Date: 27 January 2015

Reviewer: Raquel Greer

Reviewer's report:
The authors conducted a matched cohort study to assess the effectiveness of an automated guideline-based clinical decision support system (CDSS) in improving provider’s delivery of CKD care (e.g., laboratory monitoring and achievement of laboratory targets) among patients with stage 3-4 CKD.

Major Compulsory Revisions:
1. The intervention targets providers, but the investigators chose to match based on patient characteristics, rather than provider and/or practice characteristics. The investigators need to provide a rationale for why they chose this strategy and include the potential limitations of this approach in the manuscript.

We matched on patients because the guidelines are patient-centered. We also could not match on providers because, as a company, LabCorp does not possess detailed information about providers other than their specialty.

We have added to METHODS: ‘We could not match on providers as well as patients because of limited information concerning provider details.’

2. Selection bias is a major concern with observational studies (versus an RCT) and the investigators fail to fully address this limitation in their manuscript. I believe this study has a very high potential for selection bias and the authors provide no information in their paper to demonstrate that the providers in the control group and the CDSS group are comparable (e.g., years in practice, practice type (academic, community based, etc), region, urban/rural, patient demographics, etc). The concern is that the providers who opt to participate in the CDSS are somehow different than the control providers? Perhaps the providers who opted to participate in the CDSS are more interested in care quality and/or perhaps already deliver higher quality care in general.

We have already added for other reviewers: ‘Because of the way in which the program was proliferated, we were unable to determine what proportion of providers were approached, agreed to receive the CDSS, or refused the program. Likewise, we cannot provide information about provider characteristics such as age, years since training, size of practices, or LabCorp market share in the given practice locale.’
And, as well, we have added: ‘The providers themselves are surely a source of selection bias. Those more interested may well have chosen to use CDSS. On the other hand, many of the physicians in the control group were not made aware of our CDSS program by the LabCorp sales force. This problem cannot be resolved within the present data set.’

It would be helpful if the investigators could assess providers’ pre-intervention performance and determine if providers’ performance in meeting these CKD metrics were equivalent between the two groups at baseline, as well as assess if their performance improved with the implementation of the intervention.

We agree with the reviewer but lacked the necessary information to assess this.

We have added to DISCUSSION: ‘We cannot assess provider performance in CKD care prior to our study because LabCorp did not keep a patient centered database at that time.’

3. It seems very problematic that race is missing for the majority of the study population. This is an intervention study to improve CKD care, but the investigators are unable to correctly identify their study population as truly having CKD. Additionally, they are not able to assess providers’ achievement of guideline-concordant care based on a patients’ actual estimated eGFR. This is a significant limitation/concern of the study and for future implementation if race data is routinely not provided when laboratory studies are performed. Did the investigators provide recommendations to physicians for both the African American and non-African American estimated eGFR? If not, the potential for this intervention to label a patient as having CKD when they don’t have it is very troubling.

LabCorp reports both eGFR values, so physicians would have made clinical decisions based on the proper eGFR calculation. We have added to METHODS: ‘Physicians received both eGFR calculations as part of their standard laboratory results report.’

We have already emended the MSS to make clear that our recommendations could not have used the correctly adjusted eGFR - being without racial information - but that this problem would selectively reduce the performance of CDSS vs. controls: Physicians would know the correct eGFR, the program would not. Since physicians take actions as they choose, and since they knew which estimate to use, our results are essentially filtered through their judgment and choices.

We have added to the MSS: ‘Because the CDSS did not ‘know’ the correct eGFR to use and physicians did know, the performance of CDSS in relation to guidelines would be reduced compared to control physicians whenever eGFR was critical in the decision making.’

4. The investigators need to provide more detail in their methods section regarding the following:
   o The study period is unclear. When was the study conducted (total period)? What was the period for identifying the study population?
We have added to METHODS: “All patients had a first laboratory order (accession) between April 2009 and June 2012. The date of the last accession was June 2013.”

- The investigators describe that their study strengths was the wide geographic distribution and range of practice sizes, but do not provide details of the reach of the intervention in their methods section.

We have added to METHODS: ‘The physicians who chose to use our CDSS practice in 32 US states. The practices range from solo physicians to very large multispecialty groups that use LabCorp as a laboratory provider.’

5. The reviewer offers in the 5th concern a wide range of individual issues for discussion. In response we have taken the liberty of separating each specific issue and answering, for the sake of clarity. We have used subscript letters to identify each.

5a. The investigator provided limited information in the background to support the significance of their research question;

Our purpose was to assess the ability of CDSS to guide physicians in achievement of CKD guidelines. The significance is that effective CDSS has value, ineffective CDSS does not. This is in the introduction, and we are not sure how make the point more strongly without burdening the MSS.

5b. Why is improving CKD care important?

This paper addresses CKD guidelines as a gold standard to be actuated via CDSS. We do not question the guidelines themselves. Likewise we do not attempt to delve into the extremely important issues of why CKD treatment has warranted large scale guideline efforts. However, as we agree about the importance for such care, we have emphasized the point by adding, in Background: ‘Because of manifest necessity for achieving proper care of patients with chronic kidney disease (CKD)’.

5c. What are barriers to providers following CKD guidelines?

We have emended the opening of Background to address this issue: (Changes are bold) ‘Many studies have shown that, as a rule, physicians do not follow clinical guidelines very well.[1-3] Common reasons include lack of awareness, familiarity, and agreement, inertia of previous practice, and external barriers such as the guidelines being inconvenient, confusing, and cumbersome. These facts have been important in driving the development of clinical decision support systems (CDSS) that convey guideline materials to physicians in ways that are convenient and therefore potentially effective in altering behavior.[4]’

5d. What are the evidence gaps regarding CDSS and CKD care.

We have reviewed all papers on CDSS in CKD in the discussion; if we have left out important papers, perhaps the reviewer could help us identify them.
5e. In addition, the investigators, included information in the background that seemed more appropriate for the discussion section (i.e., describing their findings in the context of other studies: “Despite the absence of any organized research…, we were able to show an improved alignment between guideline recommendations and both test ordering and, in two instances, test results.”).

We recognize that styles vary among writers, and beg the indulgence of the reviewer in relation to this matter of writing style.

6. Did the authors pilot the intervention prior to implementation? What was the perceived usefulness of the CDSS in informing practice?

We did not do a pilot study.

7a. It would be helpful if the investigators could provide more detail in their discussion of why they think their intervention was successful in improving provider performance while other CDSS focused on CKD care have not shown much benefit.

We have already commented in the DISCUSSION that ‘By contrast, our CDSS might have practical value. It is scalable, and imposes no extra effort on physicians or their support staff.’ We have added: ‘Our CDSS is specific to an individual patient and cognizant of changes over time.’

7b. In addition, the authors also need to expand their discussion on characteristics of effective CDSS and how their CDSS possesses some of these characteristics.

This section contains several subsections which we address with subscript letters and numbers for clarity.

7b1. What does “tested by CDSS creators” mean?

This phrase comes from reference 32 and is so referenced. It seems to denote CDSS which has been studied by its authors. The authors expand on their comment in the reference.

7b2. How did the investigators test their CDSS?

We believe this is in the MSS. We identify ourselves as the authors of the CDSS, and we performed this test of it. In METHODS we have stated: KDOQI™ and KDIGO® guidelines concerning kidney function, CKD mineral bone disorder, anemia, and lipids were translated into a comprehensive reporting program by some of the authors (FC, JA, EW, and JE). Guideline translation and adjudication of differences between guidelines were supervised by a panel of authorities, many of whom had participated in their development (Additional File 1).
The present MSS reports our test of the CDSS.

7b3. The authors also describe that systems that presented advice within EHR or order entry systems were less likely to be effective. The authors should explain why this is the case and why they think providing advice in the laboratory report outside of the EHR would be more effective in improving a provider’s performance?

This also came from the findings of the authors of reference 32. We have said in the MSS that our report imposes no extra effort and fits into workflow (response to 7a above). We believe this may be a fruitful area for future research.

8. The authors should include as a limitation that they are not be able to fully capture achievement of laboratory testing, since some patients may obtain their labs from other sites that are not affiliated LabCorp.

We have added to the DISCUSSION under limitations: “The potential use of outside labs by a provider may have occurred but seems equally likely in either group.”

Minor Comments:
9. What are the physician specialties that are included in the “other” category. Are they also primarily responsible for providing CKD care?

Because it includes essentially all other possible specialties of medicine, and is small, we prefer to avoid a breakdown. As a rule, primary responsibility for CKD is either nephrology or primary care which are identified.

10. Recommend adjusting analyses for risk factors for CKD progression (i.e. hypertension, diabetes, CVD)

We do not have the data for this analysis, unfortunately.

11. For the figures, I found the table portion useful, but not the figures on the right. They did not provide any additional information.

We like them, and prefer to use them unless there are scientific problems.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests