PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing Trends and Variability in Outpatient Dual Testing for Chronic Kidney Disease with Urine Albumin and Serum Creatinine, 2009-2018: A Retrospective Cohort Study in the Veterans Health Administration System
AUTHORS	Bhave, Nicole M.; Han, Yun; Steffick, Diane; Bragg-Gresham, Jennifer; Zivin, Kara; Ríos Burrows, Nilka; Pavkov, Meda; Tuot, Delphine; Powe, Neil; Saran, Rajiv

VERSION 1 – REVIEW

REVIEWER	Fujimaru, Takuya Tokyo Medical and Dental University, Nephrology
REVIEW RETURNED	28-Jun-2023

GENERAL COMMENTS	In this study, the authors investigated time trends in serum creatinine (SCr) and urine albumin (UAlb) testing in the integrated Veterans Health Administration system. This study will identify the reality of chronic kidney disease (CKD) screening in actual clinical practice. However, there is room for improvement in the description of the methodology and the presentation of data. Several major and minor concerns are followings: Major: 1. Significance of evaluating UAlb. In this study, the authors evaluated the percentage of the patients undergoing UAlb testing. However, as the authors mentioned in this manuscript, CKD is defined by urine albumin-creatinine ratio, not by UAlb. Therefore, the reviewer could not understand why they evaluated only UAlb and what was different from the urine dipstick test. 2. Aim of this study. The reviewer considered that this study was intended for outpatients with chronic illnesses. Therefore, the reviewer could not understand why inpatients were included in this study. Furthermore, the reviewer thought that testing in the emergency department should be excluded because it deviates from chronic management. Additionally, the reviewer thought that dialysis patients should be excluded from this study because some patients are anuric. 3. Statistical methods. In the 3rd paragraph in the Results section, the authors compared testing rates in 2009 and 2018. Please specify the statistical analysis methods used for these comparisons. Additionally, in the same paragraph, the authors compared patients who saw a diabetologist or cardiologist with those who did not. Did the authors define it as a patient who saw a diabetologists or cardiologist in a given calendar

	year? Please specify the definition of a diabetologists or cardiologist visit. 4. Race and dual testing. From the mixed effect logistic model, Black patients were less likely to have dual testing (Table 2). However, in the Supplemental Figure 2B, dual testing rates for Black are higher than for white. The reviewer could not understand why the results were different. 6. Characteristics of the patients. Patient characteristics in Table 1 presented all observational data in this study. However, the reviewer thinks it would be better to use one data per patient. Additionally, the breakdown of renal function was provided in Table 1, however the reviewer could not understand how eGFR could be assessed without measuring SCr. Minor: 1. Dual testing rates by centers mentioned in the 4th paragraph in the Results section were not shown in Figure 2. 2. Table 2 shows what is described in the 5th and 6th paragraph in the Results section. Please cite Table 2 appropriately. 3. For the mixed effect logistic model, the authors randomly selected 10% sample of each annual cohort. However, the number of cases in each year is not shown in this manuscript. Please specify the number of patients in each year and the number of patients selected for the mixed effect logistic model. 4. Please describe the unit of the vertical axis in Figure 1 and 2. 5. Please specify the number of patients in each group in Figure 1. 6. The line graph in Supplemental Figure 1 B is difficult to distinguish. I hope my comment will be helpful.

REVIEWER	Mayne, Kaitlin J. University of Oxford
REVIEW RETURNED	09-Aug-2023

GENERAL COMMENTS	Although the study has a number of limitations which do require further discussion (as below), it does present a clear and important message on trends in albuminuria and serum creatinine testing which although not a novel finding is nevertheless important. Thank you for considering the following points to further improve the manuscript: Please use UK spellings and please quote equivalent UK units for uACR and HbA1c in addition to US Abstract The background section requires revision – this reads as if dual testing of urine albumin and serum creatinine is novel in kidney care when in fact this is routine practice Introduction P3 L7: it is incorrect to say that the presence of albuminuria alone

	indicates chronic kidney disease The final paragraph of the introduction very clearly sets out the aims and hypotheses of the study and nicely leads into the methods. Results P7 L13: suggest focusing reporting moreso on proportions of people with CKD, HTN, DM, CVD who had dual testing rather than first commenting on the prevalence of these conditions in those who had dual testing or not, it would be an important point to discuss and draw out from this study if veterans with these indications are attending healthcare for other reasons but NOT having urine albumin/serum creatinine checked when it is indicated for disease monitoring/screening as a missed opportunity and target for service improvement. P7 L19: spelling of increased Discussion Discussion of frequency of dual testing in people with indications (CKD, DM, HTN) is an important part of the discussion and much higher in this cohort than other reports, suggest also including the following reference DOI: 10.1161/HYPERTENSIONAHA.121.17323 P9 L43: suggest avoid referring to empagliflozin specifically since thought to be class effect of SGLT2i The limitations require further development. The fact that testing outside of the VHA is not available is a major limitation in accurately reporting rates of testing in patients with indications which the authors do briefly acknowledge. Limited generalisability of the VHA cohort should also be stated - 91% male population. Furthermore, the likely selection bias in that the study only assesses those seeking healthcare (inpatient/outpatient) is not discussed – these veterans are likely to be different from those not seeking healthcare and the reason for seeking healthcare may affect urine albumin/serum creatinine testing patterns and values. It should also be acknowledged that CKD defined by a single eGFR/uACR value using the most recent value likely overestimates CKD and will capture AKI and transient proteinuria of negligible clinical significance, this is suboptimal relative to sustained eGFR values. Similarly diabetes was defined based on a single blood glucose level – not fasted which again is likely to inaccurately capture diabetes in the scenario of transiently high blood glucose. Dual testing implies paired measurements but urine albumin and serum creatinine were not necessarily performed on the same day but any time within a calendar year, this might reflect various different factors/fluctuation across a year and is another limitation of the study. For these reasons, it is difficult to reliably establish true rates of albuminuria and serum creatinine in the study population and the proportions with true CKD and diabetes, limiting the overall value however the study does nicely demonstrate secular trends and highlights an important message that though testing is increasing over time, there is much room for improvement and for disparities to be addressed. Tables/figures Table 1: please report n(%), not just % - the percentages are misleading ie. 87% with hypertension and dual testing is 87% of those with dual

	testing had hypertension but it would be important to know how many people with hypertension had dual testing Table 2: It is surprising that participants with lower kidney function had much lower odds of dual testing than those with normal kidney function – it would be expected more frequent testing would occur in those with established/progressive CKD/transplants, is this likely to be done in other healthcare settings outside of the VHA? Context may be helpful for UK readers. However a recorded nephrology visit in the same year is associated with higher odds of dual testing which seems somewhat incongruous? The numbers in each CKD category are not presented (please add this) though the narrow confidence intervals go against unreliable estimates due to very small numbers in each category and the overall population is large, nevertheless it would be helpful to include an OR for eGFR as a continuous variable for example for each 10 unit increment Figure 2: suggest figure title “proportion of patients receiving dual testing 2009 vs 2018” rather than center-level variation which isn’t really what the figure is showing.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Takuya Fujimaru, Tokyo Medical and Dental University, St.Luke's International Hospital
Comments to the Author:
In this study, the authors investigated time trends in serum creatinine (SCr) and urine albumin (UAlb) testing in the integrated Veterans Health Administration system. This study will identify the reality of chronic kidney disease (CKD) screening in actual clinical practice. However, there is room for improvement in the description of the methodology and the presentation of data. Several major and minor concerns are followings:

Major:
1. Significance of evaluating UAlb.
In this study, the authors evaluated the percentage of the patients undergoing UAlb testing. However, as the authors mentioned in this manuscript, CKD is defined by urine albumin-creatinine ratio, not by UAlb. Therefore, the reviewer could not understand why they evaluated only UAlb and what was different from the urine dipstick test.
Response: we gave credit for any urine albumin testing here and we have acknowledged this as a limitation in the discussion “Data on UACR testing per se was not the focus, so analyses dealt with any urine albumin testing.”

2. Aim of this study.
The reviewer considered that this study was intended for outpatients with chronic illnesses. Therefore, the reviewer could not understand why inpatients were included in this study. Furthermore, the reviewer thought that testing in the emergency department should be excluded because it deviates from chronic management. Additionally, the reviewer thought that dialysis patients should be excluded from this study because some patients are anuric.

Response: We have chosen patients who have had at least one inpatient or outpatient visit to ensure that they have utilized the VA health system for their healthcare. The outcome we are assessing is outpatient dual testing, with tests from emergency visits being excluded. We add the word 'outpatient' as a descriptor wherever 'dual testing' is mentioned to ensure clarity and specificity in our paper.

We opted to include dialysis patients, particularly noting that a significant portion, especially those undergoing peritoneal dialysis, continue to produce urine. Consequently, the outcomes of urine protein testing may retain predictive value, albeit at a late stage for prognostication. Considering the relatively small proportion of dialysis patients in our cohort (0.6%), their inclusion is unlikely to substantially impact our results.

3. Statistical methods.
In the 3rd paragraph in the Results section, the authors compared testing rates in 2009 and 2018. Please specify the statistical analysis methods used for these comparisons. Additionally, in the same paragraph, the authors compared patients who saw a diabetologist or cardiologist with those who did not. Did the authors define it as a patient who saw a diabetologists or cardiologist in a given calendar year? Please specify the definition of a diabetologists or cardiologist visit.
Response: 1)Trend analysis using logistic regression, as described in the method section "A logistic regression model with adjustment of the year variable was used to analyze time trends of dual testing of SCr and UAlb in outpatient settings for the entire cohort...". 2) Yes, we added a description in the method section regarding the measurements of specialist visits: "Specialist visits to nephrologists, diabetologists and cardiologists were determined on an annual basis by categorizing each encounter according to the provider type specified in the VHA data."

4. Race and dual testing.
From the mixed effect logistic model, Black patients were less likely to have dual testing (Table 2). However, in the Supplemental Figure 2B, dual testing rates for Black are higher than for white. The reviewer could not understand why the results were different.
Response: The testing rate presented in Supplemental Figure 2B is a raw or unadjusted rate. In contrast, the mixed-effect logistic model accounts for demographic factors and comorbidities through adjustment.

6. Characteristics of the patients.
Patient characteristics in Table 1 presented all observational data in this study. However, the reviewer thinks it would be better to use one data per patient. Additionally, the breakdown of renal function was provided in Table 1, however the reviewer could not understand how eGFR could be assessed without measuring SCr.
Response: 1) We appreciate the reviewer's input on presenting patient characteristics in Table 1. Our approach to include multiple records per patient from 2009-2018, rather than a single entry, is deliberate. This method captures the variability in dual testing among veterans who may appear in the VHA data across multiple years from 2009-2018, influenced by changes in age, comorbidities, and kidney function. Considering each year's record independently provides a more accurate portrayal of dual testing practices. Summarizing one record per patient could introduce bias, omitting the variability and dynamics of healthcare utilization and disease management within the VHA system across different years. 2) The eGFR value may be obtained from other settings (e.g. inpatient, ER visits, etc.) other than outpatient visits.

Minor:
1. Dual testing rates by centers mentioned in the 4th paragraph in the Results section were not shown in Figure 2.
In the figure, proportion was presented, but we described as percentage. It may confuse the reviewer. Response: Updated the figures

2. Table 2 shows what is described in the 5th and 6th paragraph in the Results section. Please cite Table 2 appropriately.
Response: Added.

3. For the mixed effect logistic model, the authors randomly selected 10% sample of each annual cohort. However, the number of cases in each year is not shown in this manuscript. Please specify the number of patients in each year and the number of patients selected for the mixed effect logistic model.
Response: Number of patients in each year was added in the new supplement table 3. We added a statement "Patient characteristics on an annual basis are reported in Supplemental Table 3." The number of patients selected for the mixed effect logistic model were added in the table 2 (n=6910239).

4. Please describe the unit of the vertical axis in Figure 1 and 2.

Response: Updated the figures.

5. Please specify the number of patients in each group in Figure 1.
Response: Number of patients by year can be found in the new Supplemental Table 3, and total number of observations have been added to Table 1.

6. The line graph in Supplemental Figure 1 B is difficult to distinguish.
Response: Updated the figure, making one to the dash line and change the color to black.

Reviewer: 2
Dr. Kaitlin J. Mayne, University of Oxford
Comments to the Author:
Although the study has a number of limitations which do require further discussion (as below), it does present a clear and important message on trends in albuminuria and serum creatinine testing which although not a novel finding is nevertheless important. Thank you for considering the following points to further improve the manuscript:

Please use UK spellings and please quote equivalent UK units for uACR and HbA1c in addition to US

Response: Spellings have been updated as requested. We did not discuss UACR values in the document, but we have added UK equivalent units for serum glucose (mmol/L) and HbA1c (mmol/mol) to the text of the methods section and Supplemental Table 1.

Abstract
The background section requires revision – this reads as if dual testing of urine albumin and serum creatinine is novel in kidney care when in fact this is routine practice

Response: We appreciate the comment. We added a comment to the introduction to reflect that urine albumin testing may be overlooked in real-world settings, despite the fact that it is crucial for CKD diagnosis.

Introduction
P3 L7: it is incorrect to say that the presence of albuminuria alone indicates chronic kidney disease
The final paragraph of the introduction very clearly sets out the aims and hypotheses of the study and nicely leads into the methods.

Response: We have revised the sentence about the ADA guidelines to reflect the fact that both SCr and albuminuria testing are recommended annually.

Results
P7 L13: suggest focusing reporting moreso on proportions of people with CKD, HTN, DM, CVD who had dual testing rather than first commenting on the prevalence of these conditions in those who had dual testing or not, it would be an important point to discuss and draw out from this study if veterans with these indications are attending healthcare for other reasons but NOT having urine albumin/serum creatinine checked when it is indicated for disease monitoring/screening as a missed opportunity and target for service improvement.
Response: The third paragraph of the results section discusses trends in dual testing among patients with HTN, CKD, DM, and CVD, and these trends are also shown in Figure 1. As the reviewer has suggested, we feel that these data highlight potential opportunities for service improvement.

P7 L19: spelling of increased
Response: This spelling error on page 6 has been corrected.

Discussion
Discussion of frequency of dual testing in people with indications (CKD, DM, HTN) is an important part of the discussion and much higher in this cohort than other reports, suggest also including the following reference DOI: 10.1161/HYPERTENSIONAHA.121.17323

Response: Thank you for the suggestion. We have added this reference and a related comment to the discussion (page 9, line 15).

P9 L43: suggest avoid referring to empagliflozin specifically since thought to be class effect of SGLT2i
Response: We have edited this sentence to refer to SGLT2 inhibitors in general.

The limitations require further development. The fact that testing outside of the VHA is not available is a major limitation in accurately reporting rates of testing in patients with indications which the authors do briefly acknowledge.

Response: We appreciate the comment. We have expanded the sentence that addresses non-VA testing.

Limited generalisability of the VHA cohort should also be stated - 91% male population. Furthermore, the likely selection bias in that the study only assesses those seeking healthcare (inpatient/outpatient) is not discussed – these veterans are likely to be different from those not seeking healthcare and the reason for seeking healthcare may affect urine albumin/serum creatinine testing patterns and values. It should also be acknowledged that CKD defined by a single eGFR/uACR value using the most recent value likely overestimates CKD and will capture AKI and transient proteinuria of negligible clinical significance, this is suboptimal relative to sustained eGFR values. Similarly diabetes was defined based on a single blood glucose level – not fasted which again is likely to inaccurately capture diabetes in the scenario of transiently high blood glucose.

Response: We have added comments about the predominantly male population and the potential for selection bias to our discussion of limitations.

Dual testing implies paired measurements but urine albumin and serum creatinine were not necessarily performed on the same day but any time within a calendar year, this might reflect various different factors/fluctuation across a year and is another limitation of the study.
For these reasons, it is difficult to reliably establish true rates of albuminuria and serum creatinine in the study population and the proportions with true CKD and diabetes, limiting the overall value however the study does nicely demonstrate secular trends and highlights an important message that though testing is increasing over time, there is much room for improvement and for disparities to be addressed.

Response: We have added a comment that SCr and UAlb may not have been tested simultaneously.

Tables/figures
Table 1:
please report n(%), not just % - the percentages are misleading ie. 87% with hypertension and dual testing is 87% of those with dual testing had hypertension but it would be important to know how many people with hypertension had dual testing
Response: We added a new supplement table 2, which is same with Table 1 but adding frequencies. As mentioned in response to the reviewer's comments on the results section, dual testing in patients with specific comorbidities is also addressed in Figure 1.

Table 2:
It is surprising that participants with lower kidney function had much lower odds of dual testing than those with normal kidney function – it would be expected more frequent testing would occur in those with established/progressive CKD/transplants, is this likely to be done in other healthcare settings outside of the VYUHA? Context may be helpful for UK readers. However a recorded nephrology visit in the same year is associated with higher odds of dual testing which seems somewhat incongruous?

Response: As the reviewer suggested in the above reference to Shin et al., we suspect that dual testing is underperformed in many practice settings both in the US and globally. As mentioned above, we did note that generalizability of our findings may be limited. We were not surprised to find that patients seeing nephrologists were more likely to have dual testing.

The numbers in each CKD category are not presented (please add this) though the narrow confidence intervals go against unreliable estimates due to very small numbers in each category and the overall population is large, nevertheless it would be helpful to include an OR for eGFR as a continuous variable for example for each 10 unit increment

Response: Number in each CKD category are now presented in Supplement table 2

Figure 2: suggest figure title “proportion of patients receiving dual testing 2009 vs 2018” rather than center-level variation which isn’t really what the figure is showing
proportion of patients receiving dual testing among Veterans Health Administration (VHA) centers 2009 vs 2018 ?

Response: We revised the title to “Proportion of patients receiving dual testing among Veterans Health Administration centers 2009 vs 2018”

VERSION 2 – REVIEW

REVIEWER	Fujimaru, Takuya Tokyo Medical and Dental University, Nephrology
REVIEW RETURNED	05-Jan-2024

GENERAL COMMENTS	This second version of the paper is a great improvement. The authors have correctly revised the issues, which reviewers have mentioned.

REVIEWER	Mayne, Kaitlin J. University of Oxford
REVIEW RETURNED	04-Jan-2024

GENERAL COMMENTS	The authors appear to have satisfactorily addresses the major reviewer comments.