

## PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Identification of patients undergoing chronic kidney replacement therapy in primary and secondary care data - a validation study using OpenSAFELY and the UK Renal Registry
<b>AUTHORS</b>	Santhakumaran, Shalini; Fisher, Louis; Zheng, Bang; Mahalingasivam, Viyaasan; Plumb, Lucy; Parker, Edward; Steenkamp, Retha; Morton, Caroline; Mehrkar, Amir; Bacon, Sebastian; Lyon, Sue; Konstant-Hambling, Rob; Goldacre, Ben; MacKenna, Brian; Tomlinson, Laurie; Nitsch, Dorothea; Collaborative, The OpenSAFELY

### VERSION 1 - REVIEW

<b>REVIEWER 1</b>	Muller, Sara; Keele University. Competing Interest: None
<b>REVIEW RETURNED</b>	29-Nov-2023

<b>GENERAL COMMENTS</b>	<p>General comments</p> <p>I would like to thank my colleague Noor Daud for her contribution to this review.</p> <p>This was an interesting and well-written paper using UKRR data to validate primary and secondary care codes relating to KRT. However, I have some suggestions that I hope can help to improve it further.</p> <p>I understand that OpenSafely currently has a remit only for Covid-19 research but is it possible to widen the discussion slightly to the potential uses of this work in non-Covid research and also potentially in non-renal research. What implications might it have (or not) for defining other conditions where there is a registry, but it is not linked to primary/secondary care data. It feels to some extent that the need to produce Covid-19 research from this dataset has hampered the explanation of what is otherwise a neat methodological study that could have implications more for future research than clinical practice.</p> <p>I'm surprised by the lack of recording in primary care, which I always understood to be pretty good for major health problems. Do you think this lack of recording is specific to KRT? I can see why the recording would be better in secondary care where the KRT takes place, but then this makes me concerned about the lack of agreement between secondary care and the UKRR. How much is there a lack of agreement and how much is it a lag in recording? If it is a lag, then why should we assume that the UKRR is more accurate than the secondary care data? Perhaps this is an issue with the definition of "chronic" dialysis that puts someone on the register, but something just feels a bit wrong about it (please also see specific comment below).</p>
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	<p>It would be good to include some mention of the need to use different definitions of conditions in different scenarios and how the linkage to the UKRR, with the potential added time, governance requirements, etc, might be very necessary in some studies and less necessary in others, depending on how inclusive or specific a definition was required to answer a particular question.</p> <p>Are all of the abbreviations in the text needed? They are probably familiar to those from the renal field, but for those who might be interested in this from a methods point of view, there are quite a lot and to some extent they detract from the flow of the narrative.</p> <p>Specific minor comments</p> <p>At the end of the “Definition of kidney replacement therapy status” section, you say the UKRR prevalent cohort does not include those who previously received KRT, but the primary/secondary care data do include these people as prevalent, you conducted a sensitivity analysis excluding people from the primary and secondary care prevalent cohorts who had a CKD code after their last KRT code. It is not immediately obvious to me why this would be a sensible thing to do. I’m not questioning the decision, as I’m not a clinician and I don’t work in this field, but if I were to attempt to replicate this work in another field, I think a bit more explanation of why this decision was made (possibly in the supplement) would help to understand the wider applicability of this analysis choice.</p> <p>The Conclusion paragraph doesn’t really make sense to me. The first two sentences lay out how primary and secondary care recording would classify too many people as eligible for vaccination/antivirals in a future pandemic, but would miss very few people. This relates to prevalent cases. I can’t see how it then follows that these data would be poor at identifying people starting KRT in a timely manner. Although some of the data presented in the results show this could be the case, it also seems that secondary care data might be faster at identifying a high-risk group for vaccination/antiviral treatment, but that this group would be over-estimated. If so, would this over-estimation matter unless resources were very scarce?</p> <p>Figures – is it possible to use lower case lettering in the titles of each part of the figures to match the captions? (e.g. “A CKD” “B CKD” in Figure 2 looks like a type of CKD rather than the numbering for the panes).</p> <p>Figure 4 has 3 groups in the caption and only 2 in the figure itself. This makes it difficult to distinguish which Euler diagram relates to which group (KRT/transplant/dialysis).</p>
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<b>REVIEWER 2</b>	Fogarty, Damian; Belfast City Hospital Health and Social Services Trust, Nephrology. Competing Interest: Occasional educational lectures and consultancy (less than 3-5 episodes per annum over the last 5 years) for pharmaceutical companies that manufacture drugs that retard CKD progression such as RAAS drugs and newer SGLT2i drugs and have excellent evidence basis for their use.
<b>REVIEW RETURNED</b>	04-Dec-2023

<b>GENERAL COMMENTS</b>	This is an important topic that goes beyond kidney units and general practices as the planning and resourcing of services requires accurate and timely coding. The differences in the incident and prevalent RRT patients shows the timeliness aspect well but perhaps also the delays when there is no agreed data migration and
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	<p>sharing across the systems in the primary-secondary care interfaces. The wider applicability of this study needs more explicitly said arguably in the abstract and potentially the title to remind all readers that coding is everyone's responsibility and impacts staff and patients. It is also worth re-iterating that there are very few other secondary care areas that have the ability to validate KRT status with renal units in the way that the UKRR can. I think this is somewhat unique but possible in some of the cancer and vascular national audits.</p> <p>The findings that coding sensitivity was related to age and deprivation is a particularly important finding given the current challenges in the NHS and the levelling up agenda. The title/abstract could reflect these implications for policy and resource planning in complex medical care. Likewise the lower accuracy in children is a real concern for the those patients many of whom face a lifetime of RRT and very few children starting RRT have anything near a normal life expectancy. The authors need to reflect on the 'why' of these coding imbalances. In secondary care most of the discharge documentation is performed by the least experienced staff namely junior doctors in the foundation years and some administrative and coding staff. The involvement of consultants in these things is minimal and the appreciation of the link between coding and resource setting close to zero. As Electronic Health Records take on a more dominant role in hospitals and secondary care there is an opportunity to correct these deficiencies. Future studies should explore the status of the submitting hospital trusts with respect to their EHR maturity and use to help make the case, or not, that as well as safety EHRs contribute to improving resources and equity in the NHS.</p>
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<b>REVIEWER 3</b>	Riley, Richard; University of Birmingham, Institute of Applied Health Research. Completing Interest: None
<b>REVIEW RETURNED</b>	20-Dec-2023

<b>GENERAL COMMENTS</b>	<p>This is a well written and interesting paper examining the identification of patients receiving KRT, either existing users or new users. I only have minor comments</p> <ol style="list-style-type: none"> <li>1) Abstract: In the 'participants' section, it needs to use the words prevalent and incident to define the different groups of people. Then the results will be easier to understand when referring to these groups.</li> <li>2) 95% CIs are needed in the results text, not just the tables</li> <li>3) PPV needs to know the actual prevalence of KRT in the population. How is this estimated? In other words, is the prevalence in this database a good reflection of the actual prevalence? This needs to be justified – should a few different prevalences be used?</li> <li>4) In the databases, there is clustering by practice – is it worth examining how PPV and sensitivity vary by practice? Just to understand the heterogeneity in accuracy across practices?</li> <li>5) 'There were no codes whose exclusion would substantially improve the PPV without affecting sensitivity' – PPV and sensitivity are functionally related, so it is strange to suggest you would want to improve one but not the other.</li> </ol> <p>I hope these comments are helpful.</p>
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Reviewer: 1

## Comments to the Author

### General comments

I would like to thank my colleague Noor Daud for her contribution to this review.

This was an interesting and well-written paper using UKRR data to validate primary and secondary care codes relating to KRT. However, I have some suggestions that I hope can help to improve it further.

Thank you for your helpful and considered comments, and the resulting improvements to the paper. We hope we have addressed your comments in our responses below.

I understand that OpenSafely currently has a remit only for Covid-19 research but is it possible to widen the discussion slightly to the potential uses of this work in non-Covid research and also potentially in non-renal research. What implications might it have (or not) for defining other conditions where there is a registry, but it is not linked to primary/secondary care data. It feels to some extent that the need to produce Covid-19 research from this dataset has hampered the explanation of what is otherwise a neat methodological study that could have implications more for future research than clinical practice.

The OpenSAFELY platform was created for COVID-19 research but agree that having similar data outside of the COVID19 framework would be very useful. We agree that our work shows that standard renal registries which only collect data on people with chronic (>90 day) need for renal replacement therapies will struggle with capturing the much larger burden of kidney replacement that is being done in the acute setting. In the penultimate paragraph of the discussion, we mention implications beyond COVID-19/kidney settings, and have expanded this to place increased emphasis on other contexts. We have added some additional references to similar work outside renal research:

"Outside of the COVID-19 context, obtaining linked data can be challenging with additional resource and governance requirements. The current analyses can help to clarify for a particular project whether routine EHR suffice, thus saving resources if UKRR data are not required. However, when routine secondary and primary care data are used on their own as is standard for pharmaco-epidemiology studies, this study demonstrates that linkage to a kidney registry is required to accurately identify starting dates of those who require long-term dialysis or kidney transplantation. Conversely, our work shows the extent of acute kidney care that is performed (and uncaptured by chronic kidney failure registries), which is particularly relevant for settings where financing of kidney services is driven only by chronic need. More generally, this study highlights the value of linking registry data to routine EHR with implications beyond kidney medicine, as it adds to a growing body of work demonstrating similar benefits in a range of clinical areas such as cardiovascular events (5,6,29), cancer(30) and diabetes (31)."

I'm surprised by the lack of recording in primary care, which I always understood to be pretty good for major health problems. Do you think this lack of recording is specific to KRT?

This mismatch in information about a patient's health is not new, and most research using routinely collected data rests on validation studies for the conditions studied. In particular, most cancer researchers in the UK use the cancer registry and not hospital records on their own. Similarly we know for myocardial infarction that the respective audit does not capture all events in the UK. It is not

surprising that there is a mismatch with regards to dialysis when we consider that primary care doctors are not the people who deliver dialysis in the UK. In the penultimate paragraph of the discussion, we have mentioned other clinical areas where linkage of electronic health data and registry data has been used to show discrepancies:

"More generally, this study highlights the value of linking registry data to routine EHR with implications beyond kidney medicine, as it adds to a growing body of work demonstrating similar benefits in a range of clinical areas such as cardiovascular events (5,6,29), cancer(30) and diabetes (31)."

I can see why the recording would be better in secondary care where the KRT takes place, but then this makes me concerned about the lack of agreement between secondary care and the UKRR. How much is there a lack of agreement and how much is it a lag in recording? If it is a lag, then why should we assume that the UKRR is more accurate than the secondary care data? Perhaps this is an issue with the definition of "chronic" dialysis that puts someone on the register, but something just feels a bit wrong about it (please also see specific comment below).

The lack of agreement between secondary care and UKRR data is driven by the large number of people with a KRT code in secondary care. Given the extent of this discrepancy, we think it is unlikely to be due to a lag in the UKRR data as the start dates are submitted directly by the renal centre from their renal IT systems (as described in the 'Data sources' paragraph in the methods). We have discussed the possible reasons for the lack of agreement in the second paragraph of the discussion. We have made it clearer (at the end of the second paragraph of the discussion) that we believe the primary reason for the discrepancy is acute dialysis, which can also be delivered by intensive care without necessarily requiring input from renal care:

"Finally, the UKRR definition of incidence of KRT excludes those who recover kidney function before 90 days on dialysis, and those who die after starting acute dialysis. Previous UKRR analysis estimate that 20% of people who ever start dialysis are still alive but no longer receiving KRT at 90 days (19). Patients recovering within 90 days who are still alive will continue to be considered part of the KRT population in primary and secondary care, whilst they would not be captured as an 'incident patient' in the UKRR study population. Furthermore, acute dialysis can be delivered by intensive care without involvement from renal care. We believe acute dialysis to be the primary reason for the discrepancy between UKRR and secondary care data."

The implications of this for researchers are discussed in the final paragraph of the 'Strengths and weaknesses' section of the discussion.

It would be good to include some mention of the need to use different definitions of conditions in different scenarios and how the linkage to the UKRR, with the potential added time, governance requirements, etc, might be very necessary in some studies and less necessary in others, depending on how inclusive or specific a definition was required to answer a particular question.

We have amended the penultimate paragraph of the discussion to address this:

"Outside of the COVID-19 context, obtaining linked data can be challenging with additional resource and governance requirements. The current analyses can help to clarify for a particular project whether routine EHR suffice, thus saving resources if UKRR data are not required. However, when routine secondary and primary care data are used on their own as is standard for pharmaco-epidemiology studies, this study demonstrates that linkage to a kidney registry is required to accurately identify starting dates of those who require long-term dialysis or kidney transplantation. Conversely, our work shows the extent of acute kidney care that is performed (and uncaptured by chronic kidney failure registries), which is particularly relevant for settings where financing of kidney services is driven only

by chronic need. More generally, this study highlights the value of linking registry data to routine EHR with implications beyond kidney medicine, as it adds to a growing body of work demonstrating similar benefits in a range of clinical areas such as cardiovascular events (5,6,29), cancer(30) and diabetes (31)."

We have also amended the final paragraph of the 'Strengths and weaknesses' section of the discussion:

"Depending on the question, the distinction between acute and chronic dialysis is perhaps not important especially in terms of identifying risk factors for poor COVID-19 outcomes. For chronic KRT, particularly if correct start dates are needed, then registry data are required. If there is interest in 'ever having required any form of KRT' (eg as a baseline risk for other outcomes) then a dataset using primary and secondary care data on its own may be considered sufficient."

Are all of the abbreviations in the text needed? They are probably familiar to those from the renal field, but for those who might be interested in this from a methods point of view, there are quite a lot and to some extent they detract from the flow of the narrative.

We have removed the following abbreviations from the text: SUS (Secondary Use Services), APCS (Admitted Patient Care Statistics), OPA (Outpatient Attendances), IMD (Index of Multiple Deprivation). TPP is the company name of the primary care data provider so there is no full version. Due the frequency of use and limited word count we kept the remaining abbreviations (KRT, CKD, UKRR and EHR) in.

Specific minor comments

At the end of the "Definition of kidney replacement therapy status" section, you say the UKRR prevalent cohort does not include those who previously received KRT, but the primary/secondary care data do include these people are prevalent, you conducted a sensitivity analysis excluding people from the primary and secondary care prevalent cohorts who had a CKD code after their last KRT code. It is not immediately obvious to me why this would be a sensible thing to do. I'm not questioning the decision, as I'm not a clinician and I don't work in this field, but if I were to attempt to replicate this work in another field, I think a bit more explanation of why this decision was made (possibly in the supplement) would help to understand the wider applicability of this analysis choice.

We agree this is unclear and have amended the section you refer to.

"The UKRR prevalent cohort does not include people who received KRT in the past but have recovered or stopped treatment by 1st January 2020. This group would be included in the primary and secondary cohorts under the above definition. We considered that patients who experienced some recovery of renal function and no longer required KRT might have an earlier stage CKD code superseding their last KRT code. Therefore, as a sensitivity analysis we excluded people from the primary and secondary care prevalent cohorts who had a CKD code (SNOMED-CT for primary care and ICD-10 for secondary care; see supplementary S1 for details) which was more recent than their last KRT code."

The Conclusion paragraph doesn't really make sense to me. The first two sentences lay out how primary and secondary care recording would classify too many people as eligible for vaccination/antivirals in a future pandemic, but would miss very few people. This relates to prevalent cases. I can't see how it then follows that these data would be poor at identifying people starting KRT in a timely manner. Although some of the data presented in the results show this could be the case, it also seems that secondary care data might be faster at identifying a high-risk group for vaccination/antiviral treatment, but that this group would be over-estimated. If so, would this over-

estimation matter unless resources were very scarce?

We agree that this is confusing as they relate to different populations and have reworded to be more specific to the related analysis.

"Codes used in primary and secondary care data only miss a small proportion of prevalent KRT patients. However, they also capture many patients not receiving KRT in the UKRR data, particularly dialysis codes. This study also shows that new patients starting dialysis for the first time are not identified in a timely manner by primary care codes. This would lead to a delay in them receiving interventions to protect immunosuppressed people; indeed, poor coding has implications for any patient care that relies on KRT being recorded accurately in primary care records. "

Figures – is it possible to use lower case lettering in the titles of each part of the figures to match the captions? (e.g. "A CKD" "B CKD" in Figure 2 looks like a type of CKD rather than the numbering for the panes).

Thank you for the suggestion, we have changed to lower case

Figure 4 has 3 groups in the caption and only 2 in the figure itself. This makes it difficult to distinguish which Euler diagram relates to which group (KRT/transplant/dialysis).

Apologies, this was an error and fig 4c was omitted. We have added it back in. Thank you for bringing this to our attention.

Reviewer: 2

Comments to the Author

This is an important topic that goes beyond kidney units and general practices as the planning and resourcing of services requires accurate and timely coding. The differences in the incident and prevalent RRT patients shows the timeliness aspect well but perhaps also the delays when there is no agreed data migration and sharing across the systems in the primary-secondary care interfaces. The wider applicability of this study needs more explicitly said arguably in the abstract and potentially the title to remind all readers that coding is everyone's responsibility and impacts staff and patients.

Thank you, we agree that this is an important topic. We have expanded the penultimate paragraph of the discussion to include the wider implications:

"Outside of the COVID-19 context, obtaining linked data can be challenging with additional resource and governance requirements. The current analyses can help to clarify for a particular project whether routine EHR suffice, thus saving resources if UKRR data are not required. However, when routine secondary and primary care data are used on their own as is standard for pharmaco-epidemiology studies, this study demonstrates that linkage to a kidney registry is required to accurately identify starting dates of those who require long-term dialysis or kidney transplantation. Conversely, our work shows the extent of acute kidney care that is performed (and uncaptured by chronic kidney failure registries), which is particularly relevant for settings where financing of kidney services is driven only by chronic need. More generally, this study highlights the value of linking registry data to routine EHR with implications beyond kidney medicine, as it adds to a growing body of work demonstrating similar benefits in a range of clinical areas such as cardiovascular events (5,6,29), cancer(30) and diabetes (31)."

We have amended the discussion to include the importance of accurate coding more generally:

"We saw variation in coding accuracy across the age range, as well as by ethnicity and deprivation, limiting the ability to provide an equitable health service across the population. Coding is often carried

out by inexperienced staff, yet inaccuracies can have substantial local resourcing implications(29,30)."

We have highlighted this in the conclusion, and also in the conclusion of the abstract:

"This study also shows that new patients starting dialysis for the first time are not identified in a timely manner by primary care codes. This would lead to a delay in them receiving interventions to protect immunosuppressed people; indeed, poor coding has implications for any patient care, including resource planning, that relies on KRT being recorded accurately in primary and secondary data."

It is also worth re-iterating that there are very few other secondary care areas that have the ability to validate KRT status with renal units in the way that the UKRR can. I think this is somewhat unique but possible in some of the cancer and vascular national audits.

We agree that the UKRR places kidney research in a fortunate position and have expanded the comments on the UKRR in the 'Strengths and weaknesses' section of the discussion to reflect this.

"The UKRR has been established for over 25 years, providing in-depth data with complete UK coverage for all adults and children receiving chronic KRT, making it a unique resource for kidney medicine and facilitating analysis that is not feasible in other clinical areas. Data undergo extensive validation and cleaning and thus the UKRR can be considered a gold standard for defining incident and prevalent chronic KRT cohorts."

The findings that coding sensitivity was related to age and deprivation is a particularly important finding given the current challenges in the NHS and the levelling up agenda. The title/abstract could reflect these implications for policy and resource planning in complex medical care. Likewise the lower accuracy in children is a real concern for the those patients many of whom face a lifetime of RRT and very few children starting RRT have anything near a normal life expectancy.

We agree that these findings are important and have amended the first paragraph of the "Policy Implications and Interpretation" section:

"Evaluation of short-term COVID-19 outcomes is perhaps less pertinent in children due to comparably lower risk of adverse outcomes, but these findings suggest linkage of UKRR data is necessary to monitor vaccination trends and long-term outcomes post-infection for this cohort. More broadly, children living with kidney disease experience a substantial disease burden treatment throughout their lives with reduced life-years compared to their peers (29), and as such it is imperative that this cohort can be identified and the care they receive monitored. Poor coding in primary and secondary care data is therefore concerning. We saw variation in coding accuracy across the age range, as well as by ethnicity and deprivation, limiting the ability to provide an equitable health service across the population."

In the 'How this study might affect research, practice or policy' section we have added:

"Inaccuracies and variability in coding can affect subsequent resourcing levels of kidney care, and how equitable this is across the population."

The authors need to reflect on the 'why' of these coding imbalances. In secondary care most of the discharge documentation is performed by the least experienced staff namely junior doctors in the foundation years and some administrative and coding staff. The involvement of consultants in these things is minimal and the appreciation of the link between coding and resource setting close to zero. As Electronic Health Records take on a more dominant role in hospitals and secondary care there is



an opportunity to correct these deficiencies. Future studies should explore the status of the submitting hospital trusts with respect to their EHR maturity and use to help make the case, or not, that as well as safety EHRs contribute to improving resources and equity in the NHS.

Thank you, this is an important explanation of coding quality and we have added it to the discussion:

"We saw variation in coding accuracy across the age range, as well as by ethnicity and deprivation, limiting the ability to provide an equitable health service across the population. Coding is often carried out by inexperienced staff, yet inaccuracies can have substantial local resourcing implications (29,30)."

We have also highlighted this in the conclusion:

"This study also shows that new patients starting dialysis for the first time are not identified in a timely manner by primary care codes. This would lead to a delay in them receiving interventions to protect immunosuppressed people; indeed, poor coding has implications for any patient care, including resource planning, that relies on KRT being recorded accurately in primary and secondary data."

Reviewer: 3

#### Comments to the Author

This is a well written and interesting paper examining the identification of patients receiving KRT, either existing users or new users. I only have minor comments

Thank you for your very helpful comments, we hope the changes we have made in response make the paper clearer.

1) Abstract: In the 'participants' section, it needs to use the words prevalent and incident to define the different groups of people. Then the results will be easier to understand when referring to these groups.

We have added these words to the 'participants' section of the abstract:

"Of the 19 million people alive and registered with a practice on 1st January 2020 we included data on 38,745 prevalent patients (recorded as receiving KRT on 1st January 2020 in either UKRR, primary or secondary care data) and 10,730 incident patients (starting KRT during 2020)."

2) 95% CIs are needed in the results text, not just the tables

We have added these to the text.

3) PPV needs to know the actual prevalence of KRT in the population. How is this estimated? In other words, is the prevalence in this database a good reflection of the actual prevalence? This needs to be justified – should a few different prevalences be used?

The UKRR has complete coverage of all patients receiving kidney replacement therapy in the UK (as described in the 'Data sources' section of the methods), so we would expect UKRR prevalence estimates of chronic KRT to be accurate. In this study we link the UKRR to the subset of patients registered at a participating GP (around 19 million, covering 45% of English GP practices), and prevalence was similar in this subset. We have added the following sentence to the section 'Comparison of OpenSAFELY linked KRT data with England-wide UKRR KRT data':

"KRT population prevalence was similar in the whole of England (0.13%) and the OpenSAFELY subset (0.12%)."

4) In the databases, there is clustering by practice – is it worth examining how PPV and sensitivity vary by practice? Just to understand the heterogeneity in accuracy across practices?

As KRT is relatively rare the number of KRT patients at each practice is small, so looking at numbers by practice would not be permitted by the disclosure controls for OpenSAFELY, and estimates of heterogeneity would not be meaningful. We have commented on coding accuracy by demographic characteristics in the second paragraph of the ‘Sensitivity and positive predictive value’ section of the results.

5) ‘There were no codes whose exclusion would substantially improve the PPV without affecting sensitivity’ – PPV and sensitivity are functionally related, so it is strange to suggest you would want to improve one but not the other.

We had hoped that there would be some codes which primarily identified patients who were undergoing acute dialysis as opposed to chronic dialysis (or that gold-standard chronic dialysis patients with this code would also have other KRT codes present), and thus whose removal would increase the PPV with negligible decrease in sensitivity. Unfortunately this was not the case. We have amended this sentence to be clearer.

"There were no codes whose exclusion would substantially improve the PPV without a decrease in sensitivity."