PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patterns and trends of potentially inappropriate high-density lipoprotein-cholesterol testing in Australian adults at high risk of cardiovascular disease from 2008 through 2014: analysis of linked individual patient data from the Australian Medicare Benefit Schedule and Pharmaceutical Benefit Scheme
AUTHORS	Hajati, Farshid; Atlantis, Evan; Bell, Katy; Girosi, Federico

VERSION 1 – REVIEW

REVIEWER	Christopher Naugler University of Calgary, Canada
REVIEW RETURNED	31-Aug-2017

GENERAL COMMENTS	This paper presents an interesting analysis of administrative data combined with an economic analysis to show that there is both over and underuse of lipid testing. This is a useful contribution to the literature on lab test utilization.

REVIEWER	Renato Quispe Johns Hopkins School of Medicine
REVIEW RETURNED	25-Sep-2017

GENERAL COMMENTS	Thank you for inviting me to review this manuscript. I think the idea in general of this project is well explained throughout the manuscript, although I have a few comments for the authors: INTRODUCTION It is not fully clear what is the clinical utility of continuous blood lipid testing in clinical practice. In page 4, line 41-43, authors state that blood lipid testing is used for monitoring response to the therapy. Does that mean that in Australia lipid targets are used? I feel that paragraph 3 and 4 of introduction can be combined and summarized in order to shorten the Introduction. Page 4, line 41-42: could you please explain what you mean with pathology services? METHODS The selection criteria for the study population seems fair. Thanks for

	the detailed explanation. Page 5, line 39-42: I am not sure that this particular population can be considered as representative of the full Australian population. It seems to me, based on the description, that the study population (de-identified 10% sample of PBS and MBS) could be a quite particular population. Please provide more evidence that this population can be representative of the full population as you indicate. RESULTS Are the descriptive measures in Table 1 statistically significant different? Please provide the rate of correct utilization of HDL-C testing in the overall study population. Could you provide p-value for the trend in prevalence of underutilization and overutilization of HDL-C tests from 2008-2014. DISCUSSION Even though the guidelines remained the same since 2007, is there any other factor that could have changed the clinical practice that could affect the results?

REVIEWER	Verena Gounden Department of Chemical Pathology University of KwaZulu-Natal Durban, South Africa
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	professional statistical input is required as the validity of the the whole study is dependent on the statistical corrections done to overcome study weaknesses

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy
REVIEW RETURNED	10-Oct-2017

GENERAL COMMENTS	The authors report an interesting study on under and overprescribing of HDL testing in Australia. Despite the work strengths, I recommend adding a sensitivity analysis using missing data imputation, instead of complex but potentially biased formulas to impute over and underprescribing.

VERSION 1 – AUTHOR RESPONSE

Note: All page and paragraph numbers refer to the mark-up version of the manuscript.
Note: a Word version of this response has been attached for ease of reading.

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Editorial Requirements:

Comment 1:
Please revise your title to state the research question, study design, and setting (location). This is the preferred format for the journal.

Authors' Response:
The title has been revised according to the journal's format.

Changes to the manuscript:
The title has been revised as below:
"Patterns and trends of potentially inappropriate high-density lipoprotein-cholesterol testing in Australian adults at high risk of cardiovascular disease from 2008 through 2014: analysis of linked individual patient data from the Australian Medicare Benefit Schedule and Pharmaceutical Benefit Schemes."

Comment 2:
Please complete and include a STROBE check-list, ensuring that all points are included and state the page numbers where each item can be found: the check-list can be downloaded from here: http://www.strobe-statement.org/?id=available-checklists

Authors' Response:
The completed STROBE check-list has been attached.

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Reviewer: 1
Reviewer Name: Christopher Naugler
Institution and Country: University of Calgary, Canada

Comment:
This paper presents an interesting analysis of administrative data combined with an economic analysis to show that there is both over and underuse of lipid testing. This is a useful contribution to the literature on lab test utilization.

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Reviewer: 2
Reviewer Name: Renato Quispe
Institution and Country: Johns Hopkins School of Medicine

Comment 1:
It is not fully clear what is the clinical utility of continuous blood lipid testing in clinical practice. In page 4, line 41-43, authors state that blood lipid testing is used for monitoring response to the therapy. Does that mean that in Australia lipid targets are used?

Authors' Response:
We have added text to explain the different reasons for lipid testing in clinical practice, including monitoring response to therapy (short term and long term) to meet recommended lipid targets. The GP 'Redbook" recommends the following lipid targets after starting treatment:
"Lipid-lowering therapy for primary prevention should (while balancing risks and benefits) aim towards:
• total cholesterol <4.0 mmol/L

• HDL-C ≥1.0 mmol/L
• LDL-C <2.0 mmol/L
• non-HDL-C <2.5 mmol/L
• TG <2.0 mmol/L"

Changes to the manuscript:
Page 4, Paragraph 3: The following text has been added:
"Blood lipid testing is used by general practitioners and medical specialists for two main purposes:[21] (i) identifying patients at high CVD risk in order to offer lipid lowering treatment (who may or may not also have high blood cholesterol), and (ii) for monitoring response to the treatment after this has been prescribed,[22] aiming recommended lipid targets.[18]"

Comment 2:
I feel that paragraph 3 and 4 of introduction can be combined and summarized in order to shorten the Introduction.

Authors' Response:
We agree that these two paragraphs were unnecessarily long. Therefore, we have presented the same information in a more logical and concise way; the word count has been reduced from 302 to 220.

Changes to the manuscript:
Page 4, Paragraph 3: The changes have been done.

Comment 3:
Page 4, line 41-42: could you please explain what you mean with pathology services?

Authors' Response:
We have been using Australian terminology where "Pathology services" means "pathology tests".

Changes to the manuscript:
All "pathology services" in the paper have been replaced with "pathology tests" in order to make it clearer to international audiences.

Comment 4:
The selection criteria for the study population seems fair. Thanks for the detailed explanation.

Page 5, line 39-42: I am not sure that this particular population can be considered as representative of the full Australian population. It seems to me, based on the description, that the study population (de-identified 10% sample of PBS and MBS) could be a quite particular population. Please provide more evidence that this population can be representative of the full population as you indicate.

Authors' Response:
The Australian Department of Health has been very clear in the dataset's documentation that this sample is representative of the Australian population when the provided observation weights are used in the calculations. Unfortunately, the documentation of the dataset is not available online. However, we will be happy to share it with the reviewer if requested.

Changes to the manuscript:
Page 6, Paragraph 2: The following sentence has been added: "The dataset contains weights that allow accurate estimation of service use (not only at the national level, but also at the level of gender, age, and geography), making the dataset representative of the Australian population."

Comment 5:
Are the descriptive measures in Table 1 statistically significant different?

Authors' Response:
We agree with the reviewer that it is important to quantify the uncertainty in the observed patterns. Therefore, we decided to leave the raw, unadjusted estimates in Table 1 and add a new table (Table 2). Table 2 reports the results of a multivariate analysis for two dependent variables: the estimated number of HDL-C tests and the observed number of lipid-lowering medications. It shows how much variation can be attributed to individual characteristics such as age, gender, and location and whether there are significant differences among the groups defined by those variables.

Changes to the manuscript:
Page 15: Table 2 and related description have been added.

Comment 6:
Please provide the rate of correct utilization of HDL-C testing in the overall study population.

Authors' Response:
We have added the rate of the correct utilisation to the "Result" Section in Figure 2 accordingly.

Changes to the manuscript:
Page 17: The rate of the correct utilisation has been added to Figure 2. Also, the description text of the correct utilisation rate has been added.
Page 18: Figure 3 has been replotted to be consistent with Figure 2.

Comment 7:
Could you provide p-value for the trend in prevalence of underutilization and overutilization of HDL-C tests from 2008-2014.

Authors' Response:
We computed p-values for the linear trend in the prevalence of under- and overutilization as suggested. Their values are 0.228 and 0.21, respectively. However, these does not necessarily exclude the possibility that in recent years there is an upward and a downward trend in under- and overutilization, respectively. Just looking at the data, it seems that year 2008 or 2009 may be anomalous. If we only look at the most recent five years, we would conclude that those trends exist. However, those time series are too short, and no matter what p-value we found we do not feel confident in making quantitative statement. In the rest of the paper, we talk about trends, but we clarify that there is only suggestive evidence for them.

Changes to the manuscript:
Page 16, Paragraph 1: We added the following sentence: "A simple trend analysis shows no significant linear trend for any of the utilisation curves for the period between 2008 and 2014, with p-values for the trend over 0.2. However, an analysis of the most recent years suggests that there is an upward trend for underutilisation and downward trend for overutilization. Given the very limited lengths of the time series, it does not seem appropriate to draw any definite conclusion and take the presence of these trends as suggestive."

Comment 8:
Even though the guidelines remained the same since 2007, is there any other factor that could have changed the clinical practice that could affect the results?

Authors' Response:
Thank you for this helpful comment, we agree that there are other factors that have changed clinical practice and may have caused the observed results.
Firstly, although Australian guidelines continue to recommend treatment at risk threshold of >15% 5-year risk, the decrease in the risk thresholds internationally[14] is likely to have decreased implicit treatment thresholds locally. This is part of a global trend to increased lipid lowering treatment (in particular statins) in lower risk individuals. Although clinicians and patients may assess that treatment is worthwhile even in lower risk individuals, they may not judge that the same frequency of testing is indicated as for higher risk people who are started on treatment.
A second factor may be health policy measures that have made lipid testing more costly to the end user.

Changes to the manuscript:
Page 24, Paragraph 1:
"In particular, the clinical utility of annual testing in individuals who are not high risk according to previous explicit thresholds (>15% 5-year risk36 or >20% 10-year risk [13]), but who are treated as high risk with prescription of lipid lowering treatment, needs to be determined."

Page 25, Paragraph 2:
"Similarly, the benefit paid per pathology and diagnostic tests declined by 1.1% annually in real terms driven by funding agreements between the Australian Government and the relevant industries designed to cap growth in spending on these tests. [42] "

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Reviewer: 3
Reviewer Name: Verena Gounden
Institution and Country: Department of Chemical Pathology, University of KwaZulu-Natal, Durban, South Africa

Comment:
Professional statistical input is required as the validity of the the whole study is dependent on the statistical corrections done to overcome study weaknesses.

Authors' Response:
Our understanding is that this comment is meant for the editor.

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Reviewer: 4
Reviewer Name: Giuseppe Biondi-Zoccai
Institution and Country: Sapienza University of Rome, Latina, Italy
Please state any competing interests: None declared

Comment:
The authors report an interesting study on under and overprescribing of HDL testing in Australia. Despite the work strengths, I recommend adding a sensitivity analysis using missing data imputation, instead of complex but potentially biased formulas to impute over and underprescribing.

Authors' Response:
We apologies if the description of the coning mechanism was not clear. The implication of coning is that every time we observe a pathology record with 3 or more tests and each of the tests costs more than A$11 then an HDL test might have been performed but was not recorded. This implies that for these individuals HDL test is never directly observed, and therefore it is impossible to use missing

data methods. The reason we believe our calculations are not biased is that we have incorporated into the model the total number of HDL tests actually performed, which is provided by the Australian Department of Health. Our model is constructed in such a way that it correctly reproduces the total number of tests, and the probability modelling is only used to assign the distribution of those tests in the population.
The only sensitivity analysis one could perform is on the group of patients to which coning does not apply. These are the individuals who never had more than three pathology tests prescribed in an episode of care. Unfortunately, this is a very biased sample of healthier people who get few tests done in a year, and in fact it contains only 23% of the study target population. Therefore, we expect underutilization rates to be much higher in this group. We did perform this experiment (for year 2014) and found that the underutilization rate is 84% and the overutilization rate is 4% in this group. This is consistent with what we expected, and it does not seem to provide any particularly new insight into the problem, and therefore we did not report these figures.

VERSION 2 – REVIEW

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Italy
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	My comments have been reasonably addressed.

VERSION 2 – AUTHOR RESPONSE

Note: All page numbers refer to the mark-up version of the manuscript.

Editorial Requirements:

Comment 1:
Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study only. This section should not contain any results.

Authors' Response:
We have deleted an item that contained results and comparisons to a New Zealand study.

Comment 2:
Please include a paragraph describing the strengths, limitations and generalisability of the results in the discussion section, as per the requirements of the STROBE checklist.

Authors' Response:
We have added the requested paragraph toward the end of the discussion, on page 21-22. We have addressed strengths, limitations, and generalisability in that order. We have updated the STROBE checklist to reflect the correct page numbers where these issues are addressed.