Author’s response to reviews

Title: Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010-2013

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Version: 1 Date: 01 Oct 2017

Author’s response to reviews:

Sunday, October 01, 2017

Dafne Solera, PhD
BMC Cancer

Dear Dr. Solera,

We are pleased to attach our revised manuscript ID BCAN-D-17-01044, “Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010-
2013," for your consideration as a BMC Cancer original research article. We appreciate the effort that you, your staff, and the external reviewers have put into our analysis and presentation and we feel our manuscript has been greatly improved through the revision process.

On the following pages, we reproduce and address comments from the Editor and each of the reviewers. Along with this cover letter, we have uploaded a revised copy of our manuscript. We have tracked these changes for your review.

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. To the best of our knowledge, no conflict of interest, financial or other, exists. We have included acknowledgements, conflicts of interest, and funding sources after the discussion. We are also including our copyright disclosure form.

Please feel free to contact me should any questions arise during your review of our revised manuscript.

Sincerely,

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Please note that our responses to the editorial and reviewer comments are italicized below each comment, in order to more clearly demarcate our response.

Editor Comments:

1. Please state in your response whether the maps depicted in figure 1 are your own or taken from another source.

Response: The maps depicted in Figure 1 are original and were not obtained from any other source.

2. As indicated by our submission guidelines https://bmccancer.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article, please format your abstract to include the following subheadings: Background, Methods, Results, and Conclusions.

Response: We have made these changes to better comply with BMC Cancer’s formatting.

3. Please confirm whether the databases accessed and used in your study are public databases or whether permission was required for accessing them. If permission was obtained, please clearly state this in your manuscript, including the name of the entity by whom permission was granted.

Response: This research was funded by the Centers for Medicare and Medicaid Services (contract HHSM-500-2005-00029I). The funder only provided data for analysis and had no involvement in the research design, analysis, or development of conclusions. We have added this information in an acknowledgements section.

4. Please be sure to individually mention each author in the Authors' contributions section. Please note that all authors should be named by using their initials rather than full names.

Response: We have amended this on the title page.

5. Please provide a List of abbreviations after the Conclusions section. If abbreviations are used in the text, they should be defined in the text at first use and included in this list.
Reviewer reports:

Robert B. Hines, PhD (Reviewer 1): Comments to authors:

However, only specific patients will benefit from EGFR TKIs and even among patients who initially respond, "most patients inevitably progress despite initial dramatic and rapid response to EGFR TKIs" (Lee DH. Treatments for EGFR-mutant non-small cell lung cancer (NSCLC): The road to a success, paved with failures. Pharmacol Ther. 2017;174: 1-21.). The current recommendation from the National Comprehensive Cancer Network only recommends EGFR testing in metastatic lung cancer patients with specific recommendations based on histologic subtypes with further consideration based on a combination of histologic subtype and behavioral exposure factors (squamous cell carcinoma, in never smokers or small biopsy specimens or mixed histology). In a 2013 article, another guideline-issuing group was less restrictive regarding tumor stage (stating that testing was "encouraged" in patients with Stage I-III disease) but the recommendation was limited to tumors with an adenocarcinoma component or where an adenocarcinoma component could not be ruled out (Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013;8: 823-859).

Response: Yes, in 2013, guidelines were issued jointly by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP), then endorsed by ASCO the following year. While strongly recommending EGFR and ALK testing at diagnosis for all patients with late stage (IV) lung adenocarcinoma (or mixed lung cancers with adenocarcinoma component), regardless of characteristics such as gender, race and smoking status, they also encouraged testing patients who present presenting with earlier stage disease (I-III). The rationale for this suggestion was the availability of a fresh surgical specimen as compared to a later biopsy. Further, analysis at time of diagnosis would also allow clinicians to avoid delaying treatment for patients whose disease quickly progresses. The guideline recommended that this option of early testing be balance ed
against the cost of testing and that decisions be made by each laboratory in collaboration with its oncology team.

However, the authors had no ability to subset the data based on these recommendations given the limitations of the dataset.

Response: Yes, we agree that guidelines for testing evolved during the period studied. Supplement 2 summarizes these evolving guidelines. We also agree that claims data lack information about cancer stage and tumor histology, which impedes our ability to say conclusively whether any individual patient was eligible for EGFR testing. This limitation is cited on line 39, page 20 of the discussion section.

There were also other limitations that compromise the ability to make valid inferences from study results. Some study limitations could be overcome by using the SEER-Medicare dataset. The authors state that they did not use this dataset because it represents only 28% of the lung cancer population. However, internal validity is a prerequisite for establishing external validity. This study generates serious concerns regarding internal validity making external validity a moot point.

Response: We are happy to include text to clarify our findings. However, we do not fully understand the reviewer’s concern. Is he concerned that patients who have a claim billed with CPT code 83912, 81235, 81275 did not really undergo EGFR or KRAS testing, or that patients who were tested may have been ineligible for testing, or something else entirely? Any analysis of claims data has some uncertainty. Our objective was to conduct a population-level analysis of lung cancer molecular testing. We know from cancer registry data that approximately 35% of all new lung cancer cases are eligible for EGFR testing. The vast majority (86%) of newly diagnosed patients have metastatic disease and are either age 65 or older (68%) or become eligible for Medicare due to how disabling a lung cancer diagnosis is (94% of the 32%, who are under age 65, are eligible for Medicare due to disability). Therefore, 96% of lung cancer care in the U.S. is paid for by Medicare. In 2013, there were 215,036 newly identified lung cancer patients in Medicare claims. According to cancer registry data, in 2013 there were 228,190 newly diagnosed lung cancer patients in the U.S. Because we have captured the majority of lung
cancer patients, if there were individuals who are ineligible being tested, then this would even strengthen our finding that there is underutilization of testing among eligible patients.

Abstract:

Background: Even though the abbreviations is commonplace, I would define EGFR the first time they it used in the Abstract and manuscript. Less important to define KRAS as the name does not equate to what it actually is (i.e., a proto-oncogene).

Response: Abstract changed.

Background: Here, you state that EGFR testing is indicated for all newly-diagnosed, metastatic lung cancer patients who are candidates…”Grammatical error: "Patients who lived in the Boston", "the" should be deleted. MA can be used to abbreviate Massachusetts as state abbreviations are commonplace.

Response: Abstract changed.

I prefer the term association or increased/decreased odds vs. the term likelihood to describe odds ratios. It is true that odds ratios and probability (risk) ratios both describe the likelihood of an outcome. However, most people equate likelihood to probability (although there is debate concerning this point among the biostatisticians). Odds ratios, that is the ratios of odds (the probability of something occurring divided by the probability of something not occurring) are often interpreted the same as risk ratios (probability of occurrence in the exposed divided by probability of occurrence in the unexposed), but they are not the same (they will, however, approximate each other for rare outcomes). Therefore, if you are referring to a probability, should not equate an odds ratio with an increased/decreased probability. You can state an increased/decreased odds. Although odds ratios are commonplace and still considered appropriate for an analysis of dichotomous outcomes, if you are truly wanting probability (which I would argue would be a better choice here), you should perform binomial regression. Then you can provide estimates of effect that have more intuitive meaning for the reader. Using binomial regression, you can validly refer to the ratio measure x times more/less likely to occur in one group vs another. In summary, you can keep the odds ratios, but I would suggest you refer to increased odds or x times the odds rather than use the term likelihood which most readers will

Response: Due to restrictions on the data use agreement with CMS, are unable to perform additional analysis on these data. We changed use of the word “likelihood” to “odds.”

Background:

1st paragraph: "Lung cancer causes serious morbidity and mortality in 1.7% of Medicare beneficiaries." What does this sentence mean? There is no way to interpret this sentence because "serious morbidity" is not defined. Do you mean only 1.7% of patients diagnosed with lung cancer will die due to their disease?

Response: We mean that 1.7% of all Medicare patients will have serious medical problems or die from a diagnosis of lung cancer. Text changed to clarify.

1st paragraph: "Studying lung cancer molecular test utilization within Medicare claims provides a unique opportunity for a comprehensive, population-level analysis of precision medicine testing." OK, but there are limits to this recommendation. For example, "Use of the EGFR-TKIs gefitinib, erlotinib, and afatinib is limited to patients with adenocarcinomas who have known activating EGFR mutations" (http://emedicine.medscape.com/article/1689988-overview).

Response: The reviewer is citing who should be prescribed EGFR-TKIs. There is no way to tell whether a patient has an activating mutation unless they undergo EGFR testing. Our analysis of EGFR testing within the VA has illustrated that underutilization of EGFR testing results in overutilization of EGFR-TKIs because, in the absence of data illustrating the lack of a mutation, oncologists will prescribe EGFR-TKIs hoping that the patient responds to the drug.( Lynch JA, Berse B, Chun D, et al. Epidermal Growth Factor Receptor Mutational Testing and Erlotinib Treatment Among Veterans Diagnosed With Lung Cancer in the United States Department of Veterans Affairs. Clinical lung cancer. 2016.)
2nd paragraph: "Over the last decade, molecular testing of lung tumors has become an essential component of diagnosis and treatment of advanced non-small cell lung cancer (NSCLC)." A reference is needed to support this assertion. In addition, the nuances of testing associated with histologic subtype and disease stage is not cited.

Response: We do discuss this on page 2 of the background. “From 2011 through 2013, EGFR testing was indicated for all patients with newly diagnosed metastatic adenocarcinoma of the lung being considered for first-line therapy with an EGFR tyrosine kinase inhibitor. This indication corresponded to approximately 35% of all new lung cancer cases. EGFR testing was also recommended for patients with recurrent metastatic disease.”

4th paragraph: "From 2011 through 2013, EGFR testing was indicated for all patients with newly diagnosed metastatic adenocarcinoma of the lung being considered for first-line therapy with an EGFR tyrosine kinase inhibitor. This indication corresponded to approximately 35% of all new lung cancer cases." Ok, here you do get more specific regarding the guideline recommendation and the proportion of lung cancer cases this represents. However, a limitation of the dataset used for the study was the inability to subset tumors based on histologic subtype and disease stage.

Response: See above. This limitation is cited on line 39, page 20 of the discussion section.

5th paragraph: This paragraph is not clearly linked to the rest of the background section-I would delete it.

Response: Sentence added to provide context.

6th paragraph: "EGFR mutations are less frequent in squamous cell carcinomas therefore the guidelines suggest testing only those patients with squamous histology whose clinical or demographic characteristics (e.g., absence of smoking history, Asian descent) indicate an increased likelihood of mutations." Again, the ability to subset the data to directly test patients for whom the guideline is intended is not possible.

Response: See above. This limitation is cited on line 39, page 20 of the discussion section.
Last paragraph: You identify the objectives of the study in this paragraph. However, this does not include KRAS which was mentioned in the objectives of the abstract.

Response: Objective 3 changed to include EGFR and KRAS testing.

Last paragraph: The explicit evaluation of the second objective was not addressed.

Response: Two sentences added to the discussion to explicitly address this.

Even though 93% of lung cancer cases were incident cases in 2011-2013, I would exclude 2010 which includes both incident and prevalent cases to ensure an "apples to apples" comparison.

Response: Table 1 changed.

To ensure comparability with 2010-12, for 2013, I would use the same methodology used to identify combined EGFR/KRAS tests. That is, I would combine these two tests into one outcome as was done for the earlier time period.

Response: There are important reasons to keep these tests separated for 2013. It took many, many years to convince the AMA CPT board that molecular tests needed to be gene specific. This analysis is one of a few empirical studies to demonstrate the benefit of gene specific CPT codes. Further, EGFR testing is recommended, KRAS is not.

In Table 1a, I would label code "83912” as EGFR/KRAS because that is what it represents.

Response: Table 1 changed.

"There were 13,568 patients identified in 2011 and 14,302 patients identified in 2012 who underwent at least one molecular test." Ok, I now have finally figured out Table 1a and what the total column represents. I think you need to have clear, concise language explaining that the total column represents individual patients that received molecular testing (which corresponds to "83912” + EGFR + KRAS - Multiple).

Response: Table 1 changed.

2nd paragraph: Just to clarify, does the number given for "Claim for surgical pathology analysis" and "Claim for reporting a molecular test" correspond to incident cases of lung cancer diagnosed...
in that year or could those come from previously diagnosed cases? For example, for 2012, does the 13,818 claims for molecular testing out of the 155,408 claims for surgical pathology represents claims for those 227,929 diagnosed with lung cancer in that year? What about those patients who were diagnosed in late 2011 (for example) who could have had a claim in 2012?

Response: Yes, your understanding is correct and we specifically describe in the manuscript the fact that patients could have had a biopsy in 2013 and a claim for molecular testing in the following year.

2nd paragraph: "The absolute number of claims for molecular testing decreased slightly in 2013. This decrease may be explained by limitations in the data. Patients diagnosed in December of 2013 may have been tested in January 2014 or there may be an expansion of next generation sequencing, which would not be billed with the gene-specific billing codes." OK, does that limit our ability to compare this year to the previous years?

Response: Yes, as does the increased trend toward next generation sequencing. We stated that in the manuscript.

Patient characteristics by lung tissue analysis and molecular testing

1st paragraph: "Among the patients identified from 2011 through 2013, 642,570 (93%) had a prior year of claims data without any indication of a lung cancer diagnosis, which illustrates these patients represented mostly newly diagnosed cases." This has already been described in the METHODS.

Response: Sentence deleted.

2nd paragraph: National incidence data is reported for all cancers, therefore, I don't really see what this paragraph is adding.

Response: We were just establishing the slight differences in demographics that we found in our cohort compared to cancer registry reporting.

3rd paragraph: "Identifying patient-level differences in access to surgical pathology is important because these patients will not have access to lung tissue molecular testing." Avoid interpreting results in the RESULTS section, save for DISCUSSION if you think it is worth mentioning.
Response: Sentence deleted.

4th paragraph: "There were small but statistically significant differences by age, race, Medicaid status, and risk score and testing." Change "and testing" to "according to testing status" or something of the like to differentiate it from the list of variables.

Response: Sentence changed as requested.

4th paragraph: "Beneficiaries under age 55 were the least likely to be tested (5.9%), which may be explained by an earlier stage of diagnosis or by these patients being diagnosed and tested prior to enrolling in Medicare." Are younger lung cancer patients more likely to be diagnosed with earlier disease stage? Also, even I would save your interpretations for the DISCUSSION.

Response: Sentence changed as requested.

4th paragraph: You do not need to use the text to point out every difference and multivariable results are more important than bivariable.

Regional differences in lung cancer molecular testing

I think it is useful to have a map, but I would combine all years and use the same methodology used in years 2011-2012 to have one map. It is a bit busy to have four maps and unclear as to what the reader is supposed to "take home" from these four images. In my opinion, there is way too much text devoted to these results.

Response: We agreed that 2011 and 2012 could be combined. However, the graphic designers encouraged us to have 4 maps. Further, due to restrictions on the data use agreement with CMS, we are unable to perform additional analysis on these data, which creating new images would require.

Factors that predict utilization of lung cancer molecular testing

1st paragraph: Suggest that you change "likelihood" to "odds".

Response: Sentence changed as requested.
Table 4. What was the reference group in calculating the odds ratio? These numbers are meaningless without defining the reference group.

Response: Table 4 had information about the reference groups in the footer which was cut off. We fixed the table to make sure reference groups were illustrated.

2nd paragraph: "Clinical procedures had the next strongest correlation with testing." Given that these procedures are not mutually exclusive, there could be collinearity? Is it possible to collapse categories resulting in mutually exclusive patient groups?

Response: We tested the collinearity between the surgical procedures. While there clearly was collinearity with inpatient stay, there was not collinearity between the different procedures. Distinguishing between procedures is important because there is published literature that document racial disparities in biopsy procedures. Blacks have higher odds for transbronchial needle aspiration procedure, which does not generate enough tissue for molecular analysis. Due to restrictions on the data use agreement with CMS, we are unable to perform additional analysis on these data, which creating new variables would require.

2nd paragraph: "For a 0.10 increase in risk score, there was a 2.6% decrease in likelihood to be tested," (which corresponds to 23% decreased odd of testing for a 1-unit increase in risk score). Make sure your text is consistent with your table.

Response: Sentence changed as requested.

3rd paragraph: "Medicaid recipients, who disproportionately include Black patients, had an OR of 0.74 (CI 0.72-0.77)." Was there an interaction between Medicaid status and race?

Response: The interaction variable (Black Medicaid patient) was not statistically significant. We added a sentence to clarify that we only tested main effects.

DISCUSSION

5th paragraph: "Clinical reasons may explain variation in testing by age and level of comorbidities. Beneficiaries who were enrolled in Medicare prior to age 65 have disabilities,
including end stage renal disease, that may influence treatment decisions." Yes, but didn't you previously indicate (in the Results) that for many patients under 65, the disability associated with their lung cancer diagnosis is what made them eligible for Medicare?

Response: We indicated that lung cancer patients under age 65 “likely became eligible” due to their lung cancer diagnosis. For patients who are diagnosed with end stage renal disease (ESRD) before a lung cancer diagnosis, their ESRD status would make them eligible for Medicare first then this diagnosis may preclude treatment with cytotoxic chemotherapy. If the patient declines treatment or is unable to tolerate treatment, molecular testing is not necessary.

8th paragraph: "However, claims data do not contain clinical information that is relevant to eligibility for EGFR testing, such as the date of diagnosis, cancer stage, histological subtype of disease, and tissue availability." This was a significant study limitation which raises serious concerns regarding the ability to obtain valid inferences from the data.

Response: While we agree that there are limitations to the inferences we can make about any individual patient, we believe that it is possible to make population-level inferences from this analysis. As previously described, the vast majority of lung cancer patients are eligible for Medicare. Therefore, our analysis clearly illustrates that when analyzing the total Medicare lung cancer population from 2011 to 2013, there was significant underutilization of EGFR testing, as well as racial, income, and regional disparities in testing.

Kate Eddens (Reviewer 2): Manuscript number: BCAN-D-17-01044

However, the manuscript would be improved by clarity in writing and presentation. For example, some of the description of the inclusion process -- claims volume for testing and proportion of patients tested among newly diagnosed patients - is difficult to muddle through and may be better represented as a flow chart rather than a table.

Response: We agree that it can be complicated. We rewrote some of the methods section to try to clarify the text and to describe the clinical basis for using different denominators. We also eliminated the 2010 data from table 1b.
I don't have a specific recommendation, but the authors may try a few different ways of representing this information and running it past someone unfamiliar with the subject matter to make sure it's easy to understand at a glance.

Similarly, more succinct and well-organized results and discussion sections that follow directly the stated objectives would help readability.

Response: We made substantial changes to simply the results and discussion.

Finally, the paper would benefit from a compelling conclusion that drives the point home that there are disparities here that exist above and beyond what is expected due to racial differences in mutation prevalence.

Response: Added stronger conclusion.

Steven Patierno (Reviewer 3): Overall this is a well done study with appropriate analysis and conclusions.

In the discussion there is a very short paragraph on comorbidities, but it does not address this important factor in the context of race or disparities other than age. The well-known higher frequency of treatment-limited co-morbidities in blacks may play a role in the testing disparity found here. The paper would benefit from a more thorough analysis of this issue.

Response: We completely agree that a thorough analysis of the causes of racial disparities in needed. However, to really do such an analysis, we need more clinical data. We added text to better describe our elucidation of these factors.

The question of linkage to SEER data is raised in the Discussion as a limitation but then dismissed because it would limit analysis to 28% of the population. While the population-level analysis is useful, it would have been even more robust to conduct the mirror image analysis using SEER data with includes clinical annotation, and then compare those results to the population-level analysis

The Discussion paragraph on serum based tests seems a bit out of place with little relevance to this study.
Response: We added text to put in context the reasons for including the discussion of proteomic tests.