Reviewer’s report:

Title: Assessing the activity of nonsense-mediated mRNA decay in lung cancer

Version: 0 Date: 31 Jan 2017

Reviewer: Kim M Keeling

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NMD is a potential therapeutic target in tumors. NMD inhibition allows the expression of unique antigens in tumor cells that can be cleared by the immune system. However, NMD has also been found to be inhibited in certain cancers, making this approach moot for some tumors. This study investigates NMD efficiency in lung tumor cells versus adjacent, normal lung tissue by using RNA-seq to access the abundance of NMD substrates to determine what portion of the patient population might potentially benefit from NMD inhibition. For this study, NMD substrates were defined from previous studies and further categorized by the presence of alternative splicing constraints. This allowed 3 metrics to be developed to determine NMD efficiency, which included the mRNA expression of NMD target genes, the use of alternative splicing forms of NMD substrates versus non-NMD forms, and the ratio of NMD-inducing to NMD-free allele of the same gene for an individual.

This study is well-described and the methodology is laid out quite clearly. It is well written and the conclusions drawn from the data are logical and not overstated.

However, below I offer a few suggestions that I think might make your analysis clearer and more significant:

1) Only NMD substrates resulting from alternative splicing were examined. The authors did not explain why this was a criteria of NMD substrate compared to other NMD-inducing features such as uORFs or the length of the 3’ UTR. Please clarify this choice.

2) Although some patients were identified as having NMD efficiency that was significantly lower or higher than the norm, no mention of whether these differences in NMD efficiency among the tumors were associated with a more or less aggressive tumor growth.

3) How does the variability of NMD efficiency in normal tissues compare to NMD variability in tumor tissues? Are they significantly different among the patients you studied? In patients with significant NMD variability within normal tissues, is there also a similar corresponding significant NMD variability in tumors? Does the presence of significant NMD variability from the norm lead to a greater or less aggressive tumor formation?

Are the methods appropriate and well described? 
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

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