Dear PC chair,

Enclosed is a revision of our paper following the referee comments that we received. We have clarified the text, added implementation details and dataset versions, and added a conclusions section discussing the limitations of our work. Below we include a point-by-point response to additional major comments raised by the reviewers. [below I highlight the main comments to leave in; the rest should be handled by clarifying the text/adding to the conclusions and then removed from the cover letter]

**REVIEWER #1**

*I don’t totally understand figure 2A.  why is the p-values so much  
better for the “all cancer” cases?  how does it affect interpretation for  
AML vs other cancers?  is it a result of the number of genes tested in the  
different set?*

The number of genes in all cancer is 5-fold higher than AML  
only, this is a significance difference, but we're not sure it explains  
this p-value differences the reviewer rightfully mentioned. We're not sure  
about any other explanation for it.

Still not sure if and how to treat this. Truth is that the 5 fold variation can't explain this (as we've got a 7 fold variation between KEGG and COSMIC-AML, but the p-values are similar

**REVIEWER #2**

*The first part of the paper describes use of the network propagation  
method itself to predict the causal members of cancer pathways based on  
patient data. The authors successfully recapitulate pathway members with  
high significance. However, it's not really clear that this is an effective  
way to validate the network propagation score. It would be interesting to  
see the results with alpha=0 (i.e. no propagation). In other words, is all  
the signal contained in the set of patient mutants with the interaction  
network not playing any major role.*

Although we didn't display results with alpha=0, we did validated what the reviewer just mentioned in figure 3 using the red boxes - which signify common mutation in patient. This shows that our prior knowledge did not cover the all pathway and it was received by propagation.

**REVIEWER #3**

*The method/results section misses important details. For example it is  
not clear to me why the Vanunu method is applied here. It has been show  
that superior methods exist (see e.g. "The power of protein interaction  
networks for associating genes with diseases" by Saket Navlakha and Carl  
Kingsford).*

We have implemented our in-house method, which indeed was a top performer in the reference mentioned by the reviewer. We note that gene prioritization is a different task then the one sought here, where the main focus is to show that propagation-based methods can identify potential drug targets.

*Additionally, the authors fail to present the used data appropriately. It  
would be essential to know what the overlap is between the sets P and V,  
i.e. how many of the mutated genes are also in the set of known causal  
genes. Without this information is the remaining results are hard to  
assess. The same is true for the overlap between the mutated genes and drug targets.*

We purposely separated the different gene sets and drug targets,  
perhaps this should be more emphasized throughout the text. Perhaps we  
should also mention that our aim is to hunt down for the non-obvious drug  
targets, therefore we drop mutated genes from the process (and making the  
enrichment stronger)

*Why were the top 10% of the of ranked gene lists retained? Why not 5% ?  
Or 15%? Are the results not significant anymore if this values is varied?*

The results remain significant under varying top percentages:

%5: DrugBank –, COSMIC –

%15: DrugBank –, COSMIC -

This is also exemplified visually in figure 4, where it can be seen the drug targets get more dense in the right part of the rectangle.