**REVIEWER #1**

*Overall I really like this paper, and is relevant to the session topics.  
While not exactly a paper about precision medicine related to  
“diagnostics”, it is indeed very relevant the the broader topic of  
precision medicine in practice, which includes appropriate identification  
of drug targets for patients.*  
*The paper is 13 pages instead of 12, including the abstract.  This surely  
can be cut down following the concise form of citations with no title and  
no intermediate spacing as indicated in one of the templates here:*[*http://psb.stanford.edu/psb-online/psb-submit/*](http://psb.stanford.edu/psb-online/psb-submit/)

We think Dana contacted PSD regarding the citation template, but we can shorten the one extra sentence in many ways…  
  
*There is general revisions that need to be done to improve the paper for  
publication.  If the authors can address them, then I accept.*

*The authors have not listed where their code is for others to use and  
replicate.  Furthermore, no implementation details (language, platform,  
etc) were indicated.  Both would be a nice addition.*As far as we know, it wasn't required. However, if needed, we have all of  
our code in github and just need to work a bit to organize it for curious  
readers. The code is implemented in Python.  
  
*The work is on it’s way to being very important, but needs additional  
work to make it great.*  
  
*I very much like the author’s approach.  It just needs more experimental  
confirmation.  In particular, if there was additional work looking at  
variant-level differences (rather than just gene-level), that would be a  
very nice improvement.*  
  
*does the PPI take into account directionality of interaction?* No.  
 *or positive/negative regulation?* No.  
*a little more background would be really helpful here*. The PPI information was taken from HIPPIE - where the weight of the interaction is determined by the confidence in it.  
  
*It needs a conclusion at the end.  Additional reflection on the clinical  
relevance would be helpful.*  
  
*no date of access or version numbers for the data sets used in this  
study is listed.  please indicate in methods.* Will do.  
  
*would be nice if negative controls were tested and included in Figure 5.*It's very possible (we guess by using some random process and see if the 3  
targets align deferentially) - do we want it in your opinion?  
  
*page 7, “The results were insignificant (Figure 4B), underscoring the  
utility of a personalized approach.”  How was this significance measured?*

The (in)significance was measured in the same way, via enrichment testing, we can emphasize this and give the p-value.  
  
*The thing is, with personalized medicine, and in particular when  
discussing drug treatment, it may be highly variable the reaction to a drug  
even within one gene depending on what the variation is!  This needs to be  
discussed further as a limitation to the method.  You might consider  
obtaining pharmGKB data to evaluate this.*

We should discuss this limitation, however we're not sure introducing this new type of data at this stage is right.  
  
*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.  
  
*In 2B, you indicate that FLT3 is not in the top 10% of affected genes,  
even though you state in the intro that it is affected in 30% of patients.  
Why is that?  Please discuss.* The reason for this is as follows: for the  
FLT3 patients (30%~) we don't report FLT3 as a possible drug targets - as  
we try in our method to find the "non-obvious" drug targets. For non-FLT3  
patients, it seems FLT3 just didn't came up as a possible drug target many  
times, which fits with our personalized approach.  
  
 *which KEGG pathway do you refer (an id or URL, please) on page 4 used in  
your evaluation of genes , “…genes within the KEGG pathway…”* Will add  
  
 *is the source cancer data somatic or germline cancer variants?  i ask  
because if the TCGA data is somatic, but the gene-to-disease associations  
are germ line, you may end up with results that are hard to interpret.  
this would be another good discussion topic.* We didn't understand this  
comment, which gene-to-disease associations does s/he mean? We used TCGA data for our method.  
  
 *what were the top 10% scoring genes resulting with the shortest B2H  
distance that was part of the subgroup of patients with FLT3?*

**REVIEWER #2**

*The topic of predicting personalized drug targets is highly relevant*

*The algorithm is well described with the appropriate level of detail. The  
evaluation is mostly clear, but some details of the patient aggregation  
step were not completely clear. More discussion on limitations would be  
welcome.* Will discuss more limitations  
  
  
 *The method is implemented (rather than this being a theoretic paper). It  
is disappointing that the code is not available, but that does not appear  
to be a requirement of this meeting*. Indeed not required, but can share  
github link if needed.  
  
 *Network propagation falls in the general category of guilt-by-association  
techniques for ranking genes. These approaches are not in themselves  
particularly novel. However, the authors take this a step further and  
attempt to 'simulate' the effects of drugging targets on gene networks. I  
am not completely convinced that the approach was successful (the authors  
achieved significant p-values in their evaluation, but there may have been  
factors other than the network simulation - see comments below)*.  
  
*As mentioned above, the manuscript takes GBA approaches a step further in a way that is to my knowledge quite original.*

*The evaluation may be the weakest aspect.  
  
 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.  
  
 *The second part of the results involves the use of a Back2Healthy score,  
an interesting extension to the network propagation methods. Here the idea  
is to simulate a drug knocking out a gene in the pathway, with the aim to  
restore the network back to a healthy state. The evaluation is difficult  
here as personalized drug effectiveness data is not easy to obtain, so the  
authors aggregate the results over all patients. I have some reservations  
here about the evaluation. The signal could be coming entirely from the set  
of differentially expressed genes in the patients. According to my reading  
of the methods, the B2H score will only score a differentially expressed  
gene, and it may be the case that selecting for these alone would be  
sufficient to find a DrugBank target more than might be expected by chance*.

The reviewer missed a point here, we're not picking only differentially

expressed genes, but rather use them to calculate the B2H score for each  
gene.  
  
*The approach is interesting both biologically and computationally but  
a more detailed evaluation would be helpful*

**REVIEWER #3**

*The authors try to address the important question of using an  
individual's genome and gene expression information in order to predict  
personalized drug targets. This topic is highly relevant for PSB 2015. I am  
not sure about the length criteria, because I don't know what kind of  
submission this is and which length restriction is to apply*.  
  
 *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).* Honestly, don't know what to say about that.  
  
 *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)  
  
 *In general I think the first part of this paper is just application of an  
already known gene prioritzation algorithm to a specific gene set (AML genes in this case). The novelty here is the B2H score. But again it seems important to me to know more about the dataset used here. It is not clear how hard the prioritization task for B2H is. What is the overlap between mutated genes and drug target genes?*See above.

*The authors should try to compare their method to other network-based approaches, like shortest-path or  
betweeness centrality to make it possible  
 to put their results into some context.*   
Good point, not sure it is needed for a poster paper.  
  
  
 *The authors want to imply that their method works for every disease. They  
write "The framework we presented is general and can be applied to any  
personalized disease-related data,". I don't think this is appropriate,  
because just because the authors claim that their idea is technically  
applicable to other disease, it is not true that their method will provide  
reasonable results. The authors fail to describe the limitations of their  
idea. First of all, the algorithm work only if a given set of known disease  
genes is available. Second of all, if there is a set of known disease genes  
for a particular disease (other than AML), the author did not show that  
their method will work.*   
The method is general implementation-speaking, it can be applied on any  
disease with genomic data in few easy steps. We didn't mean to imply that  
it will definitely work for any disease.  
  
*Will the method work if non-coding mutations are involved?*

The problem is that non-coding genes don't correspond to nodes in the PPI network.. so no.  
 *Also does the set of mutated AML-genes contain all mutations of a patient  
or only the AML-related ones?*

The data is taken from TCGA, that as far as we know gathered mutation data over a big variety of genes (across many cancers)  
  
 *The plots in Figure 4 are hard to understand. What is on the x-axis?  
There seems to be some ordering, but I don't understand this.*

We did elaborate on the figure in the legend...  
  
 *The paper addresses an important questions, but is only showing results  
for one particular disease. I am not sure this is scaling up very well (at  
least it is not shown).*  
  
 *Using random walks on PPIs is not new at all. The method is not compared  
to any other method and only evaluated on one disease example (AML).*  
  
*No implementation details are given.*  
  
 *The authors do not motivate several decisions/choices very well. - Why  
was the Vanunu approach taken and not other random   walk based techniques?*Addressed above

*- The choice of alpha=0.9 is not motivated very well.*

This is true, but the point is that any choice of alpha is sufficient (as the p-value differences are minor) - this emphasized the original claim in the original  
paper. Perhaps we can drop the whole segment, if you think its unneeded.

*- The authors do not explain very well, what a mutation in a gene means  
in their case. Does that include non-coding mutations*? Addressed above

*If only coding only non-synonymous mutations?* Synonymous mutations are included.

*Details like that are essential for personalized NGS-based approaches.  
Again: Does the set of mutated genes of the AML patients contain all mutations of a patient or only the AML-related ones?* Addressed above.

*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?*

As can be seen in figure 4 visually, we're quite sure the significance would remain for various top percentages. We can calculate it easily, but we think the visual representation in fig. 4 is even better.