Reviewer #1 (Comments on article's potential impact):  
  
The authors developed a novel analysis platform that can be used to predict drug synergistic effects using proteins downstream of drug targets. They shared their codes and some of the data on GitHub. I would like to suggest the below:  
  
- As to PRR, what were the criteria to determine whether the results are reliable and significant? For example, one of the criteria that were traditionally used was the number of case reports and the lower bound of the confidence interval of the PRR.  
*We didn’t calculate PRRs in our study, we used the reported PRRs from the TWOSIDES database. The TWOSIDES database corrected for “hidden, unmeasured covariates” in case reports when calculating PRRs. We further elaborated on this detail in the results section.*  
- I appreciate the authors' effort to export the supplementary materials. However, I would like to suggest a more organized and concise packet for readablity.  
*We removed the large and difficult-to-read tables into the supplemental Excel sheets to improve readability.*  
  
  
Reviewer #2 (Remarks to the Author):  
  
The manuscript examined an important and timely issue, the prediction of drug-drug interactions resulting in adverse reactions. Importantly, the authors suggest that a relevant fraction of DDIs does not happen on the level of target proteins but on the level of downstream pathways. Moreover, drug adverse reactions could be predicted using drug effect data of only proteins downstream from the target protein.  
  
I found the idea and the approach interesting and think that the methods are appropriate and the conclusions are well-supported by the results. The manuscript is written clearly and easy to understand. The figures and tables are clear and mirror the messages in the text.  
  
The only thing I missed is an attempt to compare the performance of the authors' approach with other algorithms as many of such are available (see <https://www.frontiersin.org/files/Articles/814858/fphar-12-814858-HTML/image_m/fphar-12-814858-t001.jpg>). I think that the inclusion of such comparison could improve the manuscript significantly.  
*This is a great comment and we’ve included mention of this review and compared our approach in the discussion section.*  
  
  
Editorial Office Comments:  
  
Please ensure the following items are addressed in your revision:  
  
1) The supplemental figure/table captions should be placed with the supplemental figure/table. Supplemental material does not receive copyediting or get reformatted and should be submitted exactly as you want it to appear online. Supplemental material can be submitted as one file or multiple files.

*We have confirmed that the supplemental figures and tables are as we would like them for final publication.*  
  
2) The Author Contributions should be formatted per our journal style. Note that the following four roles must be included: wrote the manuscript, designed the research, performed the research, analyzed the data. You may also include the role "contributed new reagents/analytical tools" where applicable. No other roles are allowed. Please see the below example:  
  
A.B.C., D.E., and X.Y.Z. wrote the manuscript; A.B.C. designed the research; A.B.C. and D.E. performed the research; A.B.C. analyzed the data; A.B.C. and X.Y.Z. contributed new reagents/analytical tools.

*We have updated the author contribution statement accordingly.*  
  
3) Please revise the Study Highlights section; copy each question into the text file and follow it with your response. Your responses should be under a maximum of 150 words total and answer each of the following questions:  
  
o What is the current knowledge on the topic?  
o What question did this study address?  
o What does this study add to our knowledge?  
o How might this change drug discovery, development, and/or therapeutics?

*We have updated the study highlights to answer these questions.*  
  
4) Article submissions are allowed 4,000 words with a 10% overage. Your paper is currently at 4463. Please keep this in mind when revising your paper and do not exceed further. If you do have remaining overage, you can provide a justification within your cover letter, which the editor will evaluate for approval.

*We have moved a result to the supplement to reduce the length of our article.*  
  
5) Please note in your Conflict of Interest statement the conflicts for all authors. If some of the authors do not have conflicts of interest, please use this statement: All other authors declared no competing interests for this work. If no authors have a conflict of interest, please use this statement: The authors declared no competing interests for this work. The conflict of interest statement should be included on the title page.

*We have made these changes.*  
  
6) All references should be accounted for and cited in the main text, and full publication details included in the reference list, including page numbers or DOIs as appropriate. References for figures and tables should appear at the end of the Reference list.  
*We have updated the references to include DOI numbers.*