Dear Reviewer,

Thanks very much for taking your time to review this manuscript. I really appreciate all your comments and suggestions! Please find my itemized responses in below and my revisions/corrections in the resubmitted files.

Thanks again!

You've come up with a novel approach to screening repurposed medications for cancer, one that takes into account both the drug's intrinsic properties and the link between the drug and cancer's pathogenesis. The DrugBank database was used to build a drug similarity network for cancer therapy, which took into account the medications' shared mechanisms of action and clinical efficacy. In the network, a drug-cancer correlation score was established and computed for each medication targeting that cancer. Those medications that made the top five percent of the list were subjected to a more thorough review of stability and druggable potential in order to test for possible repurposed pharmaceuticals to treat the malignancy. It would help cancer therapy by sparking fresh ideas for medication repositioning research.

Please rewrite the abstract in a more readable way. In my view, this section may be strengthened by providing a clearer and more direct statement of the study's purpose.

Response: we thank the Reviewer for this constructive comment. We have rewritten the abstract in a more readable way, beginning with a direct reference to the definition and benefits of drug repositioning and the importance of a network-based approach, leading to our work.

In the abstract, please describe the context and purpose of the investigation, then briefly discuss the methodology and findings, and conclude with your conclusion. However, take care not to confuse the reader.

Response: we thank the Reviewer for this constructive comment. In the abstract,

we begin by directly stating the background and purpose of the study, emphasizing the importance of the network-based approach and introducing our study in a smooth manner. Then the methodology and results are briefly described, and finally the conclusions are drawn. The abstract was revised as follows:

"Drug repositioning aims to discover novel clinical benefits of existing drugs, is an effective way to develop drugs for complex diseases such as cancer and may facilitate the process of traditional drug development. Meanwhile, network-based computational biology approaches, which allow the integration of information from different aspects to understand the relationships between biomolecules, has been successfully applied to drug repurposing. In this work, we developed a new strategy for network-based drug repositioning against cancer. Combining the mechanism of action and clinical efficacy of the drugs, a cancer-related drug similarity network was constructed and the correlation score of each drug with a specific cancer was quantified. The top 5% of scoring drugs were reviewed for stability and druggable potential to identify potential repositionable drugs. Of the 11 potential repurposable drugs for non-small cell lung cancer (NSCLC), 10 were confirmed by clinical trial articles and databases. The targets of these drugs were significantly enriched in cancer-related pathways and significantly associated with the prognosis of NSCLC. In light of the successful application of our approach to colorectal cancer as well, it provides an effective clue and valuable perspective for drug repurposing in cancer."

The section's introduction is significantly too short; the authors should include additional paragraphs and identify recent relevant papers. In addition, this section might utilize additional paragraphs to explain subjects such as the importance and utility of systems biology and cancer bioinformatics tools. I believe the reader will comprehend how to read the whole of your article.

Response: we thank the Reviewer for this comment. Therefore, the introduction section of our revised manuscript has an additional paragraph between the first two

paragraphs of the original introduction section. It pointed out the importance of systems biology based approaches to drug repurposing and the cancer bioinformatics tools that make drug repositioning against cancer more intentional. The importance of network-based approaches is elicited by pointing out that networks are a key feature of systems biology. Details are as follows:

"Systems biology enables the study of whole system components formed by the interactions between molecules, rather than just the characteristics of individual molecules [5, 6]. This allows systems biology based approaches to integrate and analyze different types of large-scale biological datasets [7, 8]. A series of systems biology based approaches to drug repositioning have been opened in the context of the ever-increasing volume of medical data [3, 9]. In recent years, the understanding of the molecular basis of cancer development, progression and metastasis, as well as the mechanisms of treatment, has grown exponentially [10-13]. At the same time, the increasing number of cancer bioinformatics tools, such as network propagation algorithms, similarity metrics, and more, have been widely used in systems biology based cancer drug repurposing studies [14-16]. Networks are a key feature in systems biology, providing tractability and interpretability of interactions between hundreds or even thousands of molecules, and network-based approaches to drug repositioning play an extraordinary role [17, 18]."

You may provide a brief description of the flowchart's activities in lieu of the highlighted statement "flow chart"

Response: We thank the Reviewer for this suggestion. We have therefore provided a brief description of each step in the flowchart in the Figure 1 section of the revised manuscript. We have also modified Figure 1 in a more readable manner. The details are as follows:

"

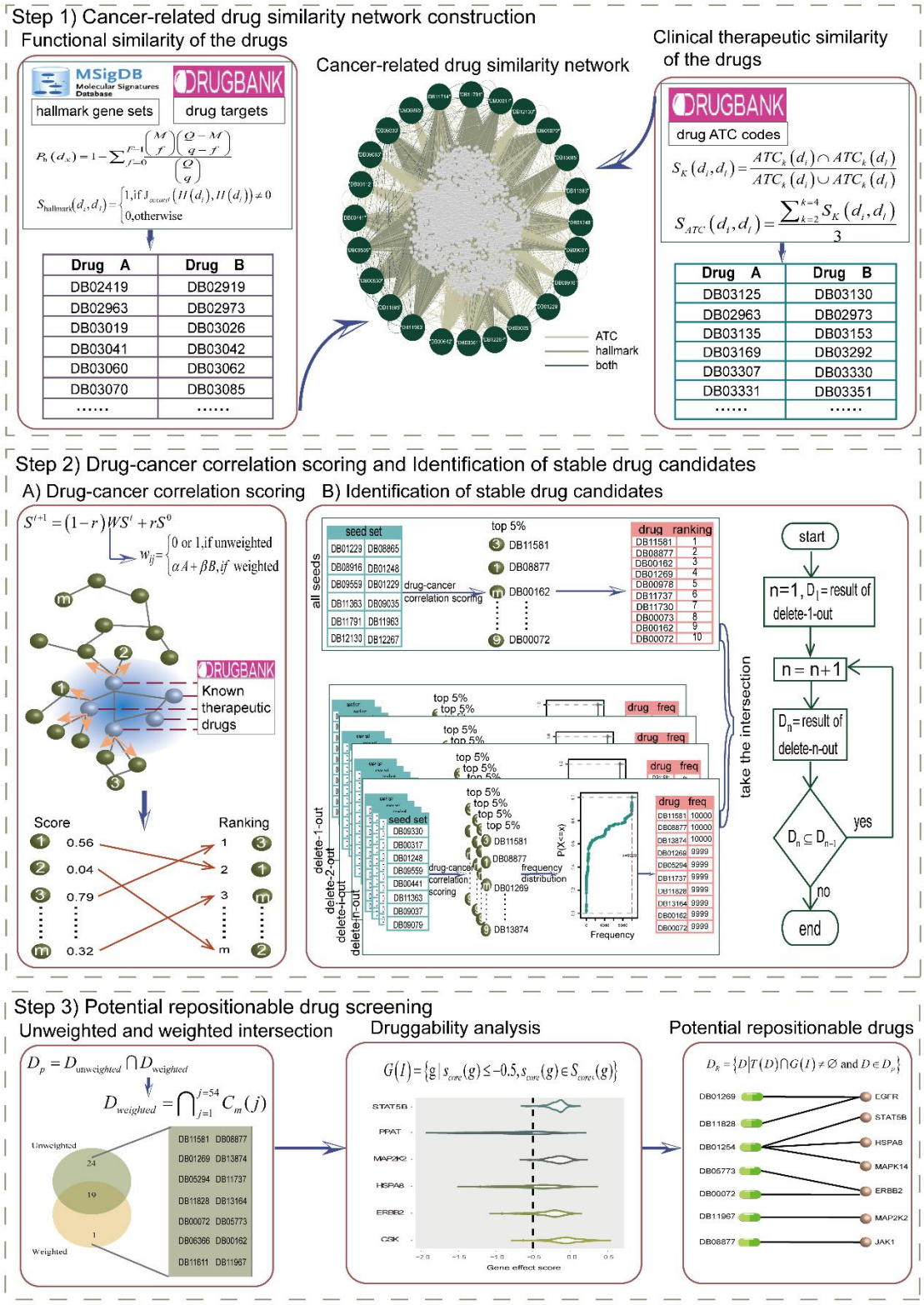


Figure 1

Flow chart of drug repurposing for specific cancer. Step 1, the functional similarity and clinical efficacy similarity between drugs are integrated to construct a

cancer-related drug similarity network. Step 2, the correlation score of each drug with a specific cancer is calculated by using the known therapeutic drugs for the cancer as a seed set. The stability of the top 5% of drugs is examined by removing seeds in a stepwise increasing number. Step 3, the druggable potential of the shared stable drug candidates recognized in different weighting patterns is reviewed to identify potentially repositionable drugs for the cancer."

Writers should generally check the English language and the overall structure of their work to avoid careless typos, missing commas, missing spaces between words, and cryptic sentences that should be changed to make them clearer.

Response: We thank the Reviewer for this careful check. The English language of the manuscript was checked in detail and corrections were made. For example, "clonidine" has been corrected to "niclosamide"; the word "essential gene" has been changed to "survival-essential gene" for easier understanding; missing periods have been added; the missing space between the inserted reference and the word has been added; released dates of data in DepMap and MSigDB have been added, etc. We have also corrected some obscure sentences in the paper and marked the whole paragraph in red.

6. I believe it is preferable to include the whole set of findings in a supplementary file.

Response: We thank the Reviewer for this comment and, as suggested by the Reviewer, we have included the whole set of findings on colorectal cancer in the form of a document in the Supplementary Document S1.

7. Please present the databases and software you utilized in a short essay, and be sure to cite them.

Response: we thank the Reviewer for this comment. As suggested by the Reviewer, the databases and software used were described in a document titled "Databases and

software used for this study" in the Supplementary Material.

8. I believe you will be able to tackle the problems mentioned.

Response: We thank the Reviewer for the careful review. We really appreciate the efforts of the Reviewer in reviewing our manuscript during this unprecedented and challenging time. Careful review by the Reviewer has helped to make our study clearer and more comprehensive.