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To the Editors of Cell Systems:

Please find enclosed our revised manuscript, "The Landscape of Metabolic Changes Across Tumor Types," for consideration for publication in *Cell Systems*. The comments provided by the reviewers were, in our opinion, fair and relevant. In addressing them, we feel that our report has improved significantly. Below we highlight several key changes and additions, each of which is elaborated on in detail in the Response to Reviewers:

1) **A variety of new metabolic analyses**. These include a correlative study of metabolite levels in tumor and normal tissue to detect putative nutrient shuttling, examination of covariation in metabolites connected through common enzymes, an improved measure of metabolic variability, and an investigation of the contribution of infiltrating stromal/immune tissue to metabolite levels.

2) **Enhanced discussion and interpretation of findings.** In several parts of the text (*e.g.* pages 10-12, page 14), we discuss on our findings in the context of our contemporary understanding of cancer metabolism. Where appropriate, we interpret key data points and offer testable hypotheses to readers (*e.g.* the enantiomeric identity of 2-HG levels in kidney tumors vs. brain tumors).

3) **Improved data transparency and availability.** All data associated with the manuscript is now available on both the github repository (as before), but also in a large set of Supplementary Tables associated submitted with the manuscript. We also remind readers at several points in the manuscript of the web service we provide to interactively visualize our results, as well as the github code repository to replicate our analysis.

As before, we are excited for this report, the first description of the metabolomic landscape of many cancers, to reach the broad readership of *Cell Systems.* We look forward to hearing from you.

Sincerely,

Ed Reznik, Augustin Luna, and Chris Sander