Dear editor,

I am writing to submit our manuscript, titled “An integrative ENCODE resource for cancer: interpreting non-coding mutations and gene regulation” for the exclusive consideration of publication in Nature.

This work is intended to serve as a resource for cancer research, in complement to the main ENCODE encyclopedia resource. The main contribution of this paper is deep annotation of cancer genomes using advanced and novel assays like STARR-seq, Hi-C, RAMPAGE, and eCLIP, together with a broad spectrum of traditional assays including hundreds of ChIP-seq experiments.

We were able to use these data to:

1. Build an accurate background mutation rate model through massive data integration
2. Develop extended gene definition with compact annotation for enhanced statistical power and improved biological interpretability in mutation burden analysis.
3. Construct transcription factor (TF) and RNA binding protein (RBP) regulatory networks from binding profiles of hundreds of ChIP-seq and eCLIP experiments.
4. Identify key regulators that drive differential tumor-normal gene expression
5. Measure direct regulation changes in the transition from normal to tumor cells
6. Prioritize key regulators, functional elements, and functional variants, and validate these prioritizations using small-scale functional assays.

This paper functions as a main resource for the ENCODE consortium and provides many annotation files that are useful for the cancer community. We make available all the results as flat text files on through URL describe the supplement.

We appreciate you taking the time to review and respond to our manuscript. Please address all correspondence concerning this manuscript to pi@gersteinlab.org. We also provide a list of suggested referees below.

We are also sending along a provisional list of referees for consideration:

* Matthieu Lupien (mlupien@uhnres.utoronto.ca, University of Toronto)
* Jan Kobel (korbel@embl.de, EBI)
* Lincoln Stein ([lincoln.stein@oicr.on.ca](mailto:lincoln.stein@oicr.on.ca), OICR)
* Daniel Geschwind ([dhg@mednet.ucla.edu](mailto:dhg@mednet.ucla.edu), UCLA)
* Aleksandar Milosavljevic ([amilosav@bcm.edu](mailto:amilosav@bcm.edu), Baylor College of Medicine)
* Gad Getz (gadgetz@broadinstitute.org , the Broad Institute)
* Han Liang (MD Anderson, hliang1@mdanderson.org)
* Kai Wang (Columbia University, kw2701@cumc.columbia.edu)

Many thanks,

Mark Gerstein