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To the editors of the Proceedings of the National Academy of the Sciences of the USA:

We submit for your review: "Viral and Bacterial Communities of Colorectal Cancer" by Geoffrey Hannigan and colleagues. We believe this work to be especially well suited for publication in PNAS and highly relevant to a broader scientific readership as well as the general public.

Both bacteria and viruses are capable of promoting cancer in humans, but cancer-associated microbiome studies to date have focused almost exclusively on bacteria. We understand very little about the cancer-associated virus communities, also termed the "cancer virome". To address this knowledge gap, we applied 16S rRNA gene sequencing, whole shotgun metagenomic, and purified virus metagenomic techniques to evaluate the cancer-associated changes in the virus and bacterial gut communities from our cohort of 90 human subjects. We found that the gut virome is significantly altered in colorectal cancer, can be used with machine learning algorithms to predict cancer with the same efficiency as bacterial community signatures, and is not a simple reflection of the bacterial community. Our findings inform our biological understanding of the disease by supporting a model in which the influential phages did not exclusively infect influential bacteria, but rather act through the community as a whole. Together, our findings provide a deeper understanding of colorectal cancer biology that will inform future studies and therapeutic endeavors.

Our lab strives to set high standards of reproducibility and transparency, while generating and publishing high quality data. As such, all analysis work-flows, scripts, and datasets have been made publicly available for other researchers to utilize.

The data presented in this manuscript are original and the manuscript is not under consideration elsewhere. A preprint version of this manuscript has been made available through BioRxiv (doi: PENDING). All authors have read and approve the manuscript for publication.

We suggest the following reviewers for this publication:

**Alejandro Reyes Muñoz, PhD**
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**Katrine Whiteson, PhD**
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Unfortunately, we must ask that Rob Knight and Matthew Sullivan not be used as an editor or reviewers since previous interactions with these individuals indicate that they are unable to provide an unbiased assessment of our work.

We thank you for your consideration and look forward to your response.

Sincerely,

Patrick D. Schloss
Professor