



Editors

Nature Microbiology

Submission Date: November 6, 2020

Dear Editors:

Enclosed is our submission of a manuscript entitled, "Genome-scale network reconstruction and analysis of *Clostridioides difficile* identifies conserved patterns of virulence-related metabolic reprogramming" for consideration in Nature Microbiology. We report (1) novel metabolic network reconstructions for two strains of this important pathogen, (2) integrate transcriptomics data new to this manuscript with a method we developed to predict key metabolic factors in a virulence-related phenotype, and (3) experimentally validate these novel, conserved shifts in metabolism. We anticipate these validated, well-curated computational models will be of significant value to those studying *C. difficile* and that the pipeline we present here will serve as a model for other microorganisms. In addition, the model-driven discovery of metabolic regulation of this virulence-related phase variant phenotype could enable the development of therapeutic strategies.

We appreciate the attention to our submission.

With best regards,

Jason Papin, Ph.D.  
Professor, Biomedical Engineering  
Professor, Biochemistry & Molecular Genetics  
Professor, Medicine, Infectious Diseases & International Health  
University of Virginia