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Dear Editorial Board,

My coauthors and I are pleased to submit our manuscript entitled **“Multi-omic Signatures of Host Response Associated with Presence, Type, and Outcome of Enterococcal Bacteremia”** for consideration in *Msystems.* This research article includes a comprehensive multi-omic investigation into the systemic host responses underlying enterococcal bacteremia (EcB), which we believe aligns well with the journal’s scope and interests. Briefly, we combined human plasma samples including extensive clinical metadata with high-resolution tandem mass spectrometry-based proteomics and metabolomics to define and evaluate features (1) enriched in EcB relative to healthy controls, (2) capable of distinguishing *E. faecalis* vs *E. faecium* infection, and (3) associated with mortality or survival.

Our findings highlight several features that were capable of distinguishing EcB plasma from healthy with near perfect or perfect discriminatory accuracy. Comparisons of these features with those found in *Staphylococcus aureus* bacteremia we elucidate both conserved and diverging host responses from homeostasis. We also uncovered significant differences between *E. faecalis* and *E. faecium* bacteremiabut note that the degree of differentiation they provide is unlikely to be more effective than currently used clinical tests. Lastly, we uncover that HRG and FETUB abundances are effective at distinguishing patients that survived from those who succumbed to mortality, and thus may offer practical clinical utility.

Overall, our manuscript offers novel insights into the systemic host responses underlying EcB and potential clinical implications. We believe that our findings will be of great interest to the readership of *mSystems* and contribute to advancing our understanding of these clinically relevant enterococcal infections. Thank you for considering our manuscript for publication. We look forward to the opportunity to share our research with the scientific community through *mSystems*.

Sincerely,



David Gonzalez, Ph.D.