

July 17, 2020

Dear Editors, *PLOS ONE*

We appreciate the initial review of our article entitled, “Modeling *Plasmodium falciparum* Diagnostic Test Sensitivity using Machine Learning with Histidine-Rich Protein 2 Variants” for your consideration. This is a revision of our original submission from June 8, 2020 (PONE-D-20-17545) and we have addressed the mild reviewer comments in this revision.

Malaria is one of the largest and most durable health threats in the world. Over a decade ago, previous researchers modeled the sensitivity of rapid diagnostic tests using simple statistical techniques. Rapid diagnostic tests allow for quick testing of patients using only a small blood sample. However, as *Plasmodium falciparum* (the parasite that causes malaria) has mutated, rapid diagnostic test sensitivity has since diminished.

In this work, we use machine learning to model test sensitivity using specific types of genetic repeats found in the isolate sequences. We show that the previously identified types are no longer all that useful but have identified additional types that may be candidates for future iterations of rapid diagnostic tests. The utility of each type of genetic repeat was derived by measuring feature importances in the machine learning models, showcasing the innovation in using model explainability to direct real-world applications.

This article is the result of extensive work and partnership between Addis Ababa University in Ethiopia and the University of North Carolina at Charlotte in the United States, including population-level surveys of infection using rapid diagnostic tests, analysis of the pathogen through multiple observational modalities, and large-scale machine learning to help direct future testing. In the current pandemic situation, we expect that that these methodologies and analyses will be of broad interest.

On behalf of all authors, we thank you for considering our manuscript for publication.

Sincerely,



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