Reply to: Challenges in interpreting the diagnostic performance of symptoms to predict COVID-19 status: the case of anosmia

To the Editor:

We appreciate our colleagues Boscolo-Rizzo et al. for their work and letter that highlights limitations of research on olfactory dysfunction as a predictor for coronavirus disease 2019 (COVID-19). The authors pool data from several studies to evaluate the sensitivity and specificity of anosmia for COVID-19 positivity. They point out that negative and positive predictive values (NPV and PPV, respectively) are dependent on prevalence of disease, both temporally and geographically. Additionally, the authors refer to the variable and potentially low sensitivity of the current COVID-19 RNA polymerase chain reaction (PCR) test. Readers are asked to proceed with caution when considering their own patient populations and applicability of anosmia as a sole predictor of COVID-19.

The research done to date regarding olfactory dysfunction as a disease predictor was performed during the outbreak and ongoing evolution of the COVID-19 pandemic. Multiple studies suggest COVID-19 is associated with anosmia at higher rates than other viral upper respiratory tract illnesses.[1,2] Early work was valuable in drawing attention to the common symptoms of COVID-19 presentation in the setting of limited testing access and enhancing advocacy for adequate personal protective equipment. Unfortunately, even now, no steady state of COVID-19 disease prevalence is known. The emergence of "hot spots" and varying prevalence of disease based on geography and time are ongoing challenges.

In addition to the authors' points, we have a few comments regarding this review and analysis of the available literature:

1. Testing abilities are limited with many diseases. For example, the sensitivity of rapid antigen detection tests for respiratory syncytial virus is only 80%.[3] Limited testing sensitivity is not unique to COVID-19, but as testing capabilities evolve with the pandemic, attention is focused on improving the sensitivity of COVID-19 assessments.
2. The authors argue that testing sensitivity may also be limited when performed early or late in the infection when viral loads are low. This point is similarly valid and ever-present in other areas of medicine and research. For example, rapid antigen detection for influenza testing has also been shown to be limited by the timing of testing in relation to symptoms.[4]
3. Unfortunately, even at the present time, due to limited testing access and the possibility of asymptomatic carriers, the true prevalence of disease remains largely unknown. This represents an ongoing challenge of COVID-19 research.
4. Because of the heterogeneity of the studies included in this meta-analysis, the results may not be generalizable to all populations. The patient populations between studies were likely variable and the meta-analysis did not account for potential differences in comorbidities. Additionally, early on in the pandemic, anosmia alone would not have qualified a patient for testing. This issue of generalizability was not mentioned in the correspondence, but is another limitation.

We propose 3 ways to build upon the current work:

1. The letter included an estimated simulation of how NPV and PPV calculations would perform given a disease prevalence range. Specific prevalence rates can be used from selected studies based on location, to further strengthen the arguments made by the authors. For example, Yan et al.[5] included patients from a single institution over a finite time. We additionally acknowledge that studies with a wide geographic base[6] cannot be included in this type of analysis, because broad prevalence rates are not useful.
2. Although the authors focus on the single symptom of anosmia for predicting COVID-19, several of the included studies evaluated multiple symptoms as predictors.[6] Combinations of other symptoms, such as fever or fatigue, with or without anosmia, may enhance accuracy of COVID-19 predictions, as suggested by larger cohort studies.[7] Further work is required to understand how symptom profiles differentiate COVID-19 from other viral illnesses.
3. As we move into influenza season, more work can be done to improve our understanding of olfactory dysfunction in COVID-19 as compared to other viral infections. Objective olfactory assessments and improved accuracy of COVID-19 testing will make this research more robust. It will be vital to understand how details of olfactory impairment, severity, and timing can differentiate and predict COVID-19 disease presence, severity, and overall health recovery.

Again, we thank the authors for their comments and caution regarding interpretation of the COVID-19 literature on

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anosmia based on disease prevalence with respect to time and location. We continue to learn from the work that is being done in patient populations around the world as the pandemic evolves.

Sincerely,

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