Why FDA Recommendations for COVID-19 Tests Vary with Patient Population: *A Graphical Explanation*

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Background: FDA recommendations for molecular SARS-CoV-2 assays include sensitivity of 95%, and specificity that varies with patient population. Tests for asymptomatic individuals require specificity of 98%, while tests for symptomatic patients are acceptable with lower specificity of 95%. This may seem counterintuitive, especially since sicker patients with greater clinical risk are matched with less reliable tests. We present an intuitive visual explanation based on positive predictive values (PPV), and we share an interactive online interface that can be customized for any test.

Technology: Desmos is an online tool for interactive classroom activities, regression analyses and graphs. W built an interactive graph on Desmos to illustrate how post-test probability changes in different populations. PPV is calculated by from prevalence, sensitivity and specificity based on the following formulae: PPV=TP/(TP+FP), TP=prevalence*sensitivity, and FP=(1-prevalence)(1-specificity).

Method: Go to http://bit.ly/PPV-Graph-API-Summit-2021 on any computer or mobile device, and press “Play” to watch the simulation.

Results: Two unexpected observations become apparent as shown in **Figure 1**. When sensitivity is fixed at 95% and specificity changes at a constant fixed rate, the change in post-test probability is fast at high ranges of specificity and slow in low ranges. In addition, the change in PPV is always greatest where prevalence is lowest. In fact, when specificity moves from 100% down to 75%, a population with 50% prevalence would only see the PPV move down to 80%, while a population with 10% prevalence would see the PPV move to 30%. This illustrates that populations with low prevalence require higher specificity for an acceptable PPV. This is because low-prevalence populations have few true positives, and PPV is related to the balance of true positives to false positives. Asymptomatic individuals have low pre-test probability and are equivalent to low prevalence.

Conclusion: The simulation illustrates that different patient populations may need different diagnostics tests. Low-prevalence diseases, or common diseases in asymptomatic individuals, need very high specificity in order to have adequate PPV. This is why SARS-CoV-2 assays designed for asymptomatic individuals need specificity of 98%. These principles might not be apparent without mathematical reasoning, and interactive graphs are helpful.

FDA guidelines: Go to webpage below, scroll to bottom and download “Molecular Diagnostic Template for Manufacturers”. See pages 16 and 18. Accessed 2021-03-11. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-facilitating-diagnostic-test-availability-asymptomatic-testing-and