Covid-19 Diagnostic Testing: Test Accuracy and Plans to Reopen the Economy

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Abstract
As the US and other countries move toward formulating strategies for reopening their economies, the call for a substantial increase in Covid-19 diagnostic testing has intensified. However, Covid-19 test performance parameters, sensitivity and specificity are rarely quantified and even rarer are discussions about how test accuracy impacts reopening plans. It is well-known, but often not addressed in studies of diagnostic tests accuracy, that the relationship between the probability that a diagnostic test result gives the correct diagnosis depends not only on sensitivity and specificity, but also the prevalence of the disease in the target population. Where prevalence is low, as is expected of Covid-19, even a test with high sensitivity and specificity may be positive for many individuals who do not have the disease. Therefore, for Covid-19 diagnostic testing, many asymptomatic individuals who test positive may be mistakenly quarantined and unnecessary costly contact tracing would be initiated. I provide examples to show the relationship between test accuracy measured by sensitivity and specificity and the probability of a correct diagnostic conclusion for an asymptomatic individual, i.e., a test subject with no Covid-19 symptoms. I also comment on FDA's guidance for estimating sensitivity and specificity for Covid-19 diagnostic tests.

1.0 Introduction

Although there continues to be widespread agreement that significantly more diagnostic testing for Covid-19 is required to develop and assess strategies for reopening the US and other world economies, there has been virtually no published quantitative assessment of test accuracy. Where Covid-19 test accuracy is discussed, the data presented is on the probability that a test will be positive for an individual known to be infected (sensitivity) and the probability that a test will be negative for an individual who is known not to be infected (specificity). Estimates of sensitivity and specificity are essential for determining test performance; however, these parameters alone are not sufficient for analyzing strategies for reopening the economy. For the development and analysis of reopening plans, estimates are required for: (i) the probability of disease for an asymptomatic individual who tests positive; and (ii) the probability of no disease for an asymptomatic individual who tests negative. That these probabilities are not sensitivity and specificity is well-known by epidemiologists and statisticians (1, 2, 3); in litigation the misinterpretation is referred to as *The Prosecutor's Fallacy* (2). However, the misinterpretation is often overlooked in medical literature, at least in news and academic articles recently published on Covid-19. The two informative and necessary probabilities, (i) and (ii) above, may be calculated from sensitivity, specificity, and the prevalence of disease in the target population. Although prevalence is unknown at the time reopening strategies are being formulated and evaluated, reasonable estimates can be employed for planning purposes and for conducting sensitivity analyses for comparing alternative reopening plans.

For a low prevalence disease such as Covid-19, any test with reasonable accuracy, e.g., sensitivity and specificity at least 90%, will predict that almost all asymptomatic individuals who

test negative are unlikely to have the disease. However, many asymptomatic individuals who test positive also are unlikely to have the disease.

2.0 Covid-19 Diagnostic Test Characteristics for Asymptomatic Individuals

Given values for sensitivity, specificity, and prevalence, Bayes formula is used to calculate: (1) the probability of disease for an asymptomatic individual who tests positive; and (2) the probability of no disease for an asymptomatic individual who tests negative. The Bayes equations and an explanation concerning their use are available from many sources (1, 2, 3); therefore, the equations are not reproduced here. Instead, I provide examples in Tables 1-3 that show how the probabilities of presence or absence of Covid-19 based on a diagnostic test are related to sensitivity, specificity, and prevalence.

Table 1a. Steps for calculatiing probability of disease for asymptomatic individual who tests positive. Prevalence is 2%.

Test Reactive Specimens		Test Negative Specimens			
Sensitivity	1 - Sensitivity	Specificity	1 - Specificity	Prevalence of Disease	Probability of Disease for Asymptomatic Individual who Tests Positive
0.85	0.15	0.95	0.05	0.0200	0.2575758
0.85	0.15	0.99	0.01	0.0200	0.6343284
0.95	0.05	0.95	0.05	0.0200	0.2794118
0.95	0.05	0.99	0.01	0.0200	0.6597222
0.99	0.01	0.95	0.05	0.0200	0.2877907
0.99	0.01	0.99	0.01	0.0200	0.6689189

Table 1b. Steps for calculatiing probability of no disease for asymptomatic individual who tests negative. Prevalence is 2%.

Test Reactive Specimens		Test Negative Specimens			
Sensitivity	1 - Sensitivity	Specificity	1 - Specificity	(1 - Prevalence)	Probability of No Disease for an Asymptomatic Individual who Tests Negative
0.85	0.15	0.95	0.05	0.9800	0.996788
0.85	0.15	0.99	0.01	0.9800	0.996917
0.95	0.05	0.95	0.05	0.9800	0.998927
0.95	0.05	0.99	0.01	0.9800	0.998970
0.99	0.01	0.95	0.05	0.9800	0.999785
0.99	0.01	0.99	0.01	0.9800	0.999794

Note: The term *reactive specimens* is defined in FDA's guidance for validating Covid-19 tests. See Paragraph 3.1 below.

Table 2a. Steps for calculatiing probability of disease for asymptomatic individual who tests positive. Prevalence is 5%.

Test Reactive Specimens		Test Negative Specimens			
Sensitivity	1 - Sensitivity	Specificity	1 - Specificity	Prevalence of Disease	Probability of Disease for Asymptomatic Individual who Tests Positive
0.85	0.15	0.95	0.05	0.0500	0.4722222
0.85	0.15	0.99	0.01	0.0500	0.8173077
0.95	0.05	0.95	0.05	0.0500	0.5000000
0.95	0.05	0.99	0.01	0.0500	0.8333333
0.99	0.01	0.95	0.05	0.0500	0.5103093
0.99	0.01	0.99	0.01	0.0500	0.8389831

Table 2b. Steps for calculatiing probability of no disease for asymptomatic individual who tests negative. Prevalence is 5%.

Test Reactive Specimens		Test Negative Specimens			
Sensitivity	1 - Sensitivity	Specificity	1 - Specificity	(1 - Prevalence)	Probability of No Disease for an Asymptomatic Individual who Tests Negative
0.85	0.15	0.95	0.05	0.9500	0.991758
0.85	0.15	0.99	0.01	0.9500	0.992089
0.95	0.05	0.95	0.05	0.9500	0.997238
0.95	0.05	0.99	0.01	0.9500	0.997349
0.99	0.01	0.95	0.05	0.9500	0.999446
0.99	0.01	0.99	0.01	0.9500	0.999469

Table 3a. Steps for calculatiing probability of disease for asymptomatic individual who tests positive. Prevalence is 10%.

Test Reactive Specimens		Test Negative Specimens			
Sensitivity	1 - Sensitivity	Specificity	1 - Specificity	Prevalence of Disease	Probability of Disease for Asymptomatic Individual who Tests Positive
0.85	0.15	0.95	0.05	0.1000	0.6538462
0.85	0.15	0.99	0.01	0.1000	0.9042553
0.95	0.05	0.95	0.05	0.1000	0.6785714
0.95	0.05	0.99	0.01	0.1000	0.9134615
0.99	0.01	0.95	0.05	0.1000	0.6875000
0.99	0.01	0.99	0.01	0.1000	0.9166667

Table 3b. Steps for calculatiing probability of no disease for asymptomatic individual who tests negative. Prevalence is 10%.

Test Reactive Specimens		Test Negative Specimens			
Sensitivity	1 - Sensitivity	Specificity	1 - Specificity	(1 - Prevalence)	Probability of No Disease for an Asymptomatic Individual who Tests Negative
0.85	0.15	0.95	0.05	0.9000	0.982759
0.85	0.15	0.99	0.01	0.9000	0.983444
0.95	0.05	0.95	0.05	0.9000	0.994186
0.95	0.05	0.99	0.01	0.9000	0.994420
0.99	0.01	0.95	0.05	0.9000	0.998832
0.99	0.01	0.99	0.01	0.9000	0.998879

From Table 1 a and b where prevalence is 2%, if sensitivity and specificity are both 0.95 (95%), the probability of no disease for an asymptomatic individual who tests negative is 0.999 (99.9%). If 1,000 asymptomatic individuals test negative, only 1 would be expected to have the disease. However, for an asymptomatic individual who tests positive, the probability of disease is 0.279 (27.9%). Among 1,000 asymptomatic individuals who test positive, 279 would be expected to have the disease; however, it would be expected that 721 would not have the disease. From Table 3 a and b, where prevalence is 10%, if sensitivity and specificity are both 0.95 (95%), the probability of no disease for an asymptomatic individual who tests negative is 0.994 (99.4%). If 1,000 asymptomatic individuals test negative, approximately 4 would be expected to have the disease. For an asymptomatic individual who tests positive, the probability of disease is 0.679 (67.9%). Among 1,000 asymptomatic individuals who test positive, 679 would be expected to have the disease; it would be expected that 321 would not have the disease.

Generally, the data in the tables indicate that the probability of a correct test conclusion increases with increasing specificity. Further, for any test with reasonably high sensitivity and specificity, almost all asymptomatic individuals who test negative would be expected to be free of the

disease. The difficulty is the relatively large number of asymptomatic individuals who test positive but are unlikely to have the disease.

3.0 Estimating Test Performance

The accuracy of Covid-19 diagnostic tests, in fact the accuracy of any diagnostic test, is characterized by presenting values for sensitivity and specificity. Data used for estimating sensitivity and specificity should be collected in a defined study, preferably a designed experiment. The test, its application described in detail including equipment and reagents, would be applied to specimens known either to contain SARS-CoV-2 or be free of this coronavirus. The percent of detections of SARS-CoV-2 for those specimens containing it is an estimate of sensitivity, which also is referred to as the probability of a true positive. The complement, i.e., 1 – sensitivity, is the probability of a false negative. The percent of no detection for specimens that do not contain SARS-Cov-2 is an estimate of specificity, which also is referred to as the probability of a true negative. The complement, i.e., 1 – specificity, is the probability of a false positive. As discussed below, the reliability of these estimates depends in part on the number of specimens tested in the experiment.

3.1 FDA Guidance for Estimating Sensitivity and Specificity (4)[1]

For validating a diagnostic test method for Covid-19 FDA recommends analysis of 30 known positive samples and 30 nonreactive specimens. Recognizing that positive samples for testing may be difficult to obtain or ascertain, FDA recommends using "contrived reactive specimens" created by spiking RNA or inactivated virus into leftover clinical specimens. Twenty of the 30 reactive specimens should be spiked at a concentration equal to the limit of detection (LoD) or 2X the LoD.[2] The remaining 10 specimens should span the assay testing range. An acceptable test is one for which there is 95% agreement for the specimens with concentrations at LoD and 2X LoD, and 100% agreement at all other concentrations and for negative specimens. Therefore, a validated test has an estimate of sensitivity at least equal to 96.7% based on results for 30 positive specimens and specificity equal to 100% based on results for 30 negative specimens.

For FDA's rules for validating a Covid-19 diagnostic test, the 95% confidence intervals are: 82.8% to 99.9% for sensitivity; 88.4% to 100% for specificity. Uncertainty ranges may be wider due to statistical variation in the LoD estimate and the use of contrived reactive samples in place of known human positive samples.

[1] FDA statement: "The use of the word should in Agency guidance means that something is suggested or recommended, but not required."

[2] FDA describes a small study that should be conducted by a laboratory to estimate the limit of detection (LoD) for its Covid-19 test. The LoD is used in FDA's recommended procedure to validate the Covid-19 test. The method recommended for determining the LoD introduces statistical variation in the test validation results beyond the statistical variation directly associated with the validation procedure. To simplify, I have ignored variation in the estimate of LoD and treat it as if it were a known constant.

4.0 Conclusions

If a Covid-19 diagnostic test is to be used for analyzing proposed plans to reopen the economy, the sensitivity and specificity for the test should be reported including data that can be used to confirm the reported values. In addition, and of equal importance for assessing a plan to reopen the economy, estimates of (i) the probability of disease for an asymptomatic individual who tests positive; and (ii) the probability of no disease for an asymptomatic individual who tests negative should be presented. Ideally, both probabilities would be large. However, if the prevalence of Covid-19 in a population is low, only the probability of no disease for an asymptomatic individual who tests negative is large; the probability of disease for an asymptomatic individual who tests positive may be moderate at best. Therefore, it is likely that many asymptomatic individuals who test positive will not have the disease. These individuals would be unnecessarily quarantined and resources for contact tracing would be unproductively drained. Designers of plans to reopen the economy need to acknowledge the potential for errors associated with diagnostic Covid-19 tests and include strategies for addressing the consequences of these errors.

5.0 References

1. Rothman KJ, Greenland S, Lash TL (2008). Modern Epidemiology, Third Edition Wolters Kluwer, Lippincott, Williams and Wilkins 2008

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