

COVID-19 Testing

Impact of Prevalence, Sensitivity, and Specificity on Patient Risk and Cost

Zoe C. Brooks, ART^{1,✉} and Saswati Das, MD^{2,✉}

From ¹AWEsome Numbers, Worthington, Canada; and ²Dr Ram Manohar Lohia Hospital, Central Government Health Services, New Delhi, India.

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ABSTRACT

Objectives: To illustrate how patient risk and clinical costs are driven by false-positive and false-negative results.

Methods: Molecular, antigen, and antibody testing are the mainstay to identify infected patients and fight the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To evaluate the test methods, sensitivity (percent positive agreement [PPA]) and specificity (percent negative agreement [PNA]) are the most common metrics utilized, followed by the positive and negative predictive value—the probability that a positive or negative test result represents a true positive or negative patient. The number, probability, and cost of false results are driven by combinations of prevalence, PPA, and PNA of the individual test selected by the laboratory.

Results: Molecular and antigen tests that detect the presence of the virus are relevant in the acute phase only. Serologic assays detect antibodies to SARS-CoV-2 in the recovering and recovered phase. Each testing methodology has its advantages and disadvantages.

Conclusions: We demonstrate the value of reporting probability of false-positive results, probability of false-negative results, and costs to patients and health care. These risk metrics can be calculated from the risk drivers of PPA and PNA combined with estimates of prevalence, cost, and Reff number (people infected by 1 positive SARS-CoV-2 carrier).

Key Points

- Measuring risk metrics as the number and cost of false-positive and -negative results adds a great deal of knowledge that is masked by the usual statistical metrics of percent positive agreement (PPA), percent negative agreement (PNA), positive predictive value, and negative predictive value.
- The number and cost of false-positive and -negative test results are driven by prevalence, PPA (sensitivity), and PNA (specificity).
- The clinical implications and cost of false-positive and -negative test results can guide test selection and decisions about repeating test results for confirmation.

In early December 2019, a pneumonia of unknown cause was detected in Wuhan, China, and was reported to the World Health Organization (WHO).¹ On March 11, 2020, the WHO declared the virus a pandemic.² The novel virus, previously named the 2019-novel coronavirus (2019-nCoV), is currently designated as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).³ According to the recent statistics of the WHO, the coronavirus disease 2019 (COVID-19) has spread across continents, with 6,302,318 diagnosed cases and 376,210 deaths globally, and 1,811,277 cases and 105,147 deaths in the United States as of June 2, 2020.⁴ Laboratory diagnosis and management of COVID-19 has been instrumental in combating the spread of SARS-CoV-2. Clinical decisions rely on accurate molecular, antigen, and antibody tests that correctly classify patients as positive or negative for presence of SARS-CoV-2, or for antibodies to that specific virus. The risk metrics of number and cost of false-positive

and -negative test results are driven by risk drivers of prevalence of SARS-CoV-2, or for antibodies in the test population, percent positive agreement (PPA; sensitivity) and percent negative agreement (PNA; specificity) of each test process.

Three Test Types

The gold standard at present for diagnosing suspected cases of COVID-19 is molecular testing, such as real-time reverse transcription polymerase chain reaction (RT-PCR), which is a nucleic acid amplification test that detects unique sequences of SARS-CoV-2.⁵ Antigen tests that also detect the presence of SARS-CoV-2 do not amplify viral components and are less sensitive (more likely to produce a false-negative result) than molecular tests. Negative antigen tests should be confirmed with a molecular test before considering a person negative for COVID-19. Molecular and antigen tests detect patients in the acute phase only.

A study by Yong et al⁶ illustrated the shortcomings of RT-PCR as the only diagnostic method in surveillance, because of its inability to detect past infection, and the added value of serologic testing. Serology tests can detect both active and past infections if the antibodies are captured within the relevant timeframe after the onset of the disease.⁷ Serologic assays detect IgG and IgM antibodies to SARS-CoV-2, which develop 1 to 3 weeks after infection. Testing for IgG may be a superior marker of sustained immunity to SARS-CoV-2.⁸ More scientific data on the immune response to SARS-CoV-2 is required to design evidence-based recommendations for all testing scenarios and interpretation guidelines.⁹

On May 27, 2020, the Centers for Disease Control and Prevention issued interim guidelines for COVID-19 antibody testing, stating “Although serologic tests should not be used at this time to determine if an individual is immune, these tests can help determine the proportion of a population previously infected with SARS-CoV-2 and provide information about populations that may be immune and potentially protected. Serologic test results may assist with identifying persons who may qualify to donate blood that can be used to manufacture convalescent plasma as a possible treatment for those who are seriously ill from COVID-19.” Contrary to early hopes to use serologic testing to issue “immunity passports” to return to work and society, the CDC now states clearly that “Serologic test results should not be used to make decisions about returning persons to the workplace.”⁹

Table 1 describes the purpose of the 3 types of tests, with advantages, disadvantages, and risks.

Risk Is the Combination of the Probability and Severity of Harm

The International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) guide 51 defines risk as “the combination of the probability of occurrence of harm and the severity of that harm.”¹⁰ To evaluate/select test methods, laboratory professionals usually compare sensitivity (PPA) and specificity (PNA), followed by positive predictive value (PPV) and negative predictive value (NPV), the probability that a positive or negative test result represents a true-positive or -negative patient, respectively, in the population tested. These metrics alone do not adequately or easily project the levels of patient risk or clinical costs associated with each test method. To estimate the probability of harm, we calculated the probability that a positive result is a false positive (PFP) and probability that a negative result is a false negative (PFN). PFP is the number of false-positive results as a percent of all positive results. PFP is the remainder of PPV; $PFP = 1 - PPV$. PFN is the number of false-negative results as a percent of all negative results. PFP is the remainder of NPV; $PFN = 1 - NPV$. We roughly estimated the cost of false results, and from those we projected the severity of harm as the costs incurred by patients and health care institutions.

PPA and PNA are inherent to the test method. Probabilities of true and false results in clinical settings change with prevalence of the virus or antibody in the population tested. “In a population where the prevalence is 5%, a test with 90% sensitivity and 95% specificity will yield a positive predictive value of 49%. In other words, less than half of those testing positive will truly have antibodies. Alternatively, the same test in a population with an antibody prevalence exceeding 52% will yield a positive predictive value greater than 95%, meaning that less than one in 20 people testing positive will have a false-positive test result.”¹¹

As of May 4, 2020, the Food and Drug Administration (FDA) required that clinical agreement data should demonstrate a minimum overall 90.0% PPA (sensitivity) and 95.0% PNA (specificity).¹¹ Most, but not all, values for sensitivity and specificity reported by the FDA on May 21, 2020, meet their goals. In the United Kingdom, recommended standards are set higher, at 98% PPA and 98% PNA.¹² Recommendations are theoretical goals, and manufacturers’ test results are created under controlled ideal conditions. The Foundation for Innovative New Diagnostics (FIND), working in partnership

Table 1
Overview of Three Test Types

	Molecular Test	Antigen Test	Antibody Test
What does it detect?	This test detects the viral genome using a lab technique called polymerase chain reaction (PCR).	This test detects certain proteins from the surface of the virus.	Antibody testing detects IgG and IgM antibodies produced by the immune system in response to infection by the virus.
Sample type	A health care worker collects fluid from a nasal or throat swab or from saliva.	A nasal or throat swab is collected by the health care worker to get a fluid sample. Antigen tests can produce results in minutes.	A health care professional takes a blood sample, usually by a finger prick or by drawing blood from a vein in the arm.
Advantages	Molecular tests are considered very accurate. Molecular tests are useful to track the spread of disease, identifying strains and mutations.	These tests are faster and less expensive than molecular tests. Antigen tests may be more practical to use for a large population.	Accurate antibody testing can identify convalescent plasma donors and identify people who may have immunity.
Disadvantages	Molecular tests do not quantify viral load, which becomes undetectable at the end of the disease course. A molecular test will not detect a prior infection, even one that has recently resolved.	Antigen tests are less sensitive than molecular tests. A molecular test may be recommended to confirm a negative antigen test result.	Positive antibody tests indicate that you were likely infected with SARS-CoV-2 at some time in the past and may have some immunity. The timing and type of antibody test affects accuracy. The Food and Drug Administration (FDA) advises that if prevalence is low, as it usually is, laboratories should confirm positive tests using "an orthogonal testing algorithm (ie, employing two independent tests in sequence.") ¹⁰
Risk of false-positive test	Patients would falsely believe they are infected and self-isolate. There would be unnecessary contact tracing.	Patients would falsely believe they are infected and self-isolate. There would be unnecessary contact tracing.	Patients would falsely believe they have antibodies, not practice physical distancing, and be at risk of infection and infecting others. Contacts may be traced.
Risk of false-negative test	Patients would falsely believe they are virus-free, not self-isolate, and infect Reff number of others.	Patients would falsely believe they are virus-free, not self-isolate, and infect Reff number of others. The FDA advises that negative antigen tests may need to be confirmed with PCR tests.	Patients would falsely believe they do not have antibodies, continue to practice physical distancing, and fail to return to work and society.

with the WHO, maintains a diagnostics resource center that includes an interactive dashboard showing SARS-CoV-2 sensitivity and specificity, as assessed in laboratory on-site evaluation studies.¹³ We chose to model their meta-analysis results as the baseline in simulations, as we believe these are more representative of current test performance in use in testing laboratories. **Table 2** shows baseline FIND PPA and PNA values for each test type, plus the number of different sample types, companies, individual test names, test formats, or targets detected. Index sample types include nasopharyngeal swab, lower respiratory system, sputum, tracheal aspirate, capillary blood, serum, and plasma. Test formats include integrated systems, manual isothermal amplification, manual PCR, rapid diagnostic tests (with and without reader), chemiluminescence immunoassay, enzyme-linked immunosorbent assay, and more. Notice the large number of companies and test names. Targets include RNA with and without extraction, nucleocapsid protein, nucleoprotein antigens, IgG, IgM, and IgA.

We modeled the impact of $\pm 10\%$ in PPA (sensitivity) from baseline. We modeled up to 100% PNA (specificity), with a lower limit of -10% from baseline. Prevalence of the SARS-CoV-2 virus and antibody is unknown and

Table 2
Baseline PPA and PNA (FIND)¹³

	Molecular	Antigen	Antibody
PPA (sensitivity), %	86.14	61.70	68.44
PNA (specificity), %	95.84	98.26	95.6
Index sample type, No.	10	4	6
Company names, No.	33	3	54
Test names, No.	35	4	74
Test formats, No.	3	2	6
Targets, No.	4	4	5

PNA, percent negative agreement; PPA, percent positive agreement.

may vary widely between locations. Estimating prevalence is complicated by the existence of false-positive and false-negative tests. We modeled changes in prevalence for all tests from 2% to 20%, with an estimated baseline of 11%. The impact of the risk drivers of prevalence, PPA and PNA, on the risk metrics of PFP and PFN are shown in **Figure 1**, **Figure 2**, and **Figure 3**.

Figure 1 illustrates how increasing prevalence of true-positive samples impacts the PFP and the PFN. The number of patients who are positive for the SARS-CoV-2 virus or antibody increases with prevalence. Prevalence is governed

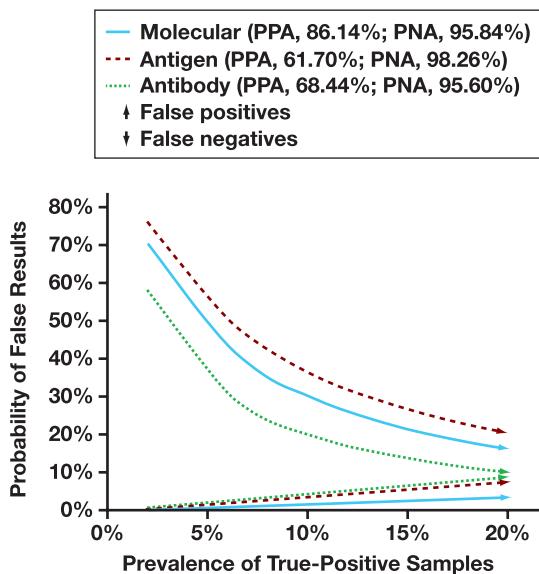


Figure 1 Impact of prevalence on false results, with baseline percent positive agreement (PPA) and percent negative agreement (PNA).

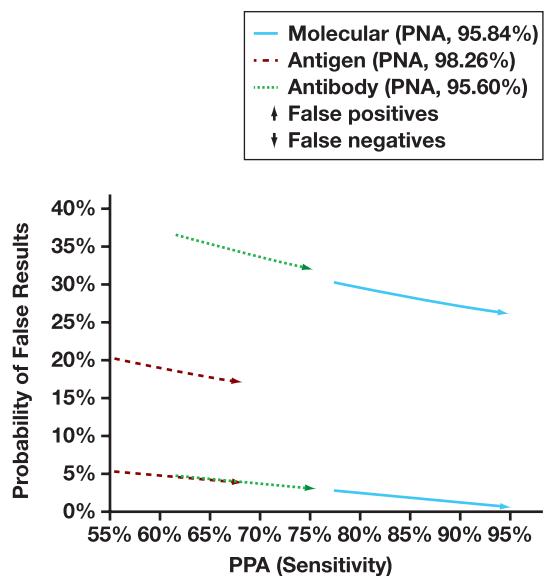


Figure 2 Impact of increased percent positive agreement (PPA) (sensitivity) on false results with baseline prevalence and percent negative agreement (PNA).

by the spread of COVID-19 in the population tested and is beyond control of test selection and quality. The number of true-positive samples increases with prevalence and true-negative samples decrease. False-positive tests are a portion of true-negative samples, so they also decrease. The patterns for all tests are similar, but not identical because the baseline PPA and PNA values differ between test types. As prevalence increases from 2% to 20%, with PPA and PNA constant at

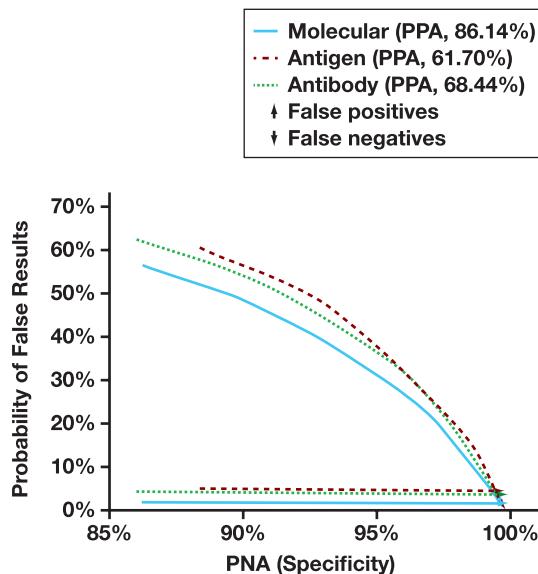


Figure 3 Impact of changes in percent negative agreement (PNA) (specificity) on false results with baseline prevalence and percent positive agreement (PPA).

baseline, the PFP decreases significantly from 70.3% to 16.2% for molecular tests, 58.0% to 10.1% for antigen tests, and 75.9% to 20.5% for antibody tests. Unlike false positives that decrease with prevalence, false negatives increase. False-negative test results are a portion of true positive samples, so they increase over tenfold in proportion to prevalence: from 0.3% to 3.5% for molecular tests, 0.8% to 8.9% for antigen tests, and 0.7% to 7.6% for antibody tests. This dramatic increase may be masked by examining only NPV, which decreases slightly from 99.7% to 96.5% overall.

Figure 2 shows the impact of modeled changes of $\pm 10\%$ from baseline PPA for each test type, with prevalence and PNA constant at baseline. Higher PPA indicates a larger percent of positive test results in true-positive samples. True-positive test results increase, but the number of false positives is not affected by PPA. As true-positive tests increase with PPA, the constant number of false-positive tests (that are driven by PNA) forms a smaller portion of all positive results, decreasing PFP from 30.3% to 26.2% for molecular tests. Antigen tests have a lower range of PPA and a higher PNA, causing a smaller change in PFP from 20.2% to 17.2%. As PPA increases for antibody tests, PFP decreases from 36.6% to 32.1%. As PPA increases, the number of true-positive test results increases and false negatives decrease.

Figure 3 shows the impact of modeled changes in PNA on false test results for each test type. When PNA reaches 100%, all negative results are true negatives and the probability of false positives decreases to zero. As PNA increases from 86.3% to 100%, PFP decreases from 56.3% to 0% for molecular tests. Antigen tests have a higher range of PNA (88.4%-100%) with

a resultant change in PFP from 60.3% to 0%. Antibody tests, with a range of PNA from 86.0% to 100%, show a range of PFP decreasing from 62.3% to 0%. Notice that PPA had less impact than prevalence or PNA on probability of false-positive tests.

As PNA increases, the number of true-negative results increases; false negatives are unchanged in number but form a smaller portion of all negatives, driving the PFN down. PFN decreases from 2.0% to 1.7% for molecular, 5.1% to 4.5% for antigen, and 4.3% to 3.8% for antibody tests.

Implications of False Results for Patient and Clinical Cost

Laboratories invest a great deal of effort in test selection to minimize patient risk and clinical cost caused by false results. Table 1 presented the different clinical interpretation of each type of test. False-positive and false-negative results drive patient risk and clinical care costs. The authors estimated costs for the United States in May 2020 as shown in Table 3, with the understanding that these are rough estimates.

The potential harm of false-positive and false-negative results,¹⁴ as discussed in Table 1, is applied in Figure 4, Figure 5, Figure 6, and Figure 7 to create a rough estimate of patient and clinical care costs for the United States. These costs are used as a model to illustrate the process of converting risk drivers of prevalence plus method PPA (sensitivity) and PNA

(specificity) to risk metrics of the number and cost of erroneous results.

Figure 4 shows how costs are applied to true- and false-positive patient samples. Individual costs were roughly estimated based on research and opinion. The total cost for each sample is calculated by adding all the checked costs and multiplying by the Reff where indicated. An online calculator is available at <https://awesome-numbers.com/risk-calculator/> for readers to modify costs and model various scenarios with user-input variables of prevalence, PPA, PNA, and Reff.

- Health care system costs to obtain, perform and report the test were roughly estimated to be \$200.
- Although costs are much higher for hospitalized patients, “A single symptomatic COVID-19 case could incur a median direct medical cost of \$3,045 during the course of the infection alone.”¹⁵
- A report from Johns Hopkins University put the cost of hiring 100,000 new community health workers for contact tracing at an estimated \$3.6 billion, and the Association of State and Territorial Health Officials has echoed that estimate as the minimum requirement in a memo to Congress.¹⁶ We projected cases at 3,600,000 based on the 2,157,768 cases as of June 16, 2020¹⁷ to estimate cost at \$1,000 per patient.
- Patient cost for self-isolation was estimated to be \$100 per day.
- The FDA advises that “antigen tests may not detect all active infections, as they do not work the same way as a PCR test. ...negative results from an antigen test may need to be confirmed with a PCR test prior to making

Table 3
Total Cost of False Results per 1,000 Samples With Variations in Risk Drivers

Impact of prevalence of cost of false results on patient and health care costs/1,000 samples tested					
Prevalence	2.0%	6.5%	11%	15.5%	20%
Molecular	\$137,293	\$202,841	\$268,390	\$333,938	\$399,487
Antigen	\$47,399	\$52,257	\$57,116	\$61,974	\$66,832
Antibody	\$32,599	\$54,289	\$75,979	\$97,669	\$119,359
Impact of PPA (sensitivity) of cost of false results on patient and health care costs 1,000 samples tested					
Modeled range of PPA	-10%	-5%	Baseline	+5%	+10%
Molecular PPA	77.53%	81.83%	86.14%	90.45%	94.75%
Antigen PPA	55.53%	58.62%	61.70%	64.79%	67.87%
Antibody PPA	61.60%	65.02%	68.44%	71.86%	75.28%
Molecular	\$375,367	\$321,878	\$268,390	\$214,901	\$161,412
Antigen	\$59,830	\$58,473	\$57,116	\$55,758	\$54,401
Antibody	\$88,025	\$82,002	\$75,979	\$69,957	\$63,934
Impact of PNA (specificity) of cost of false results on patient and health care costs/1,000 samples tested					
Modeled range of PNA	-10%	-5%	Baseline	Midpoint	100%
Molecular PNA	86.26%	91.05%	95.84%	97.92%	100.00%
Antigen PNA	88.43%	93.35%	98.26%	99.13%	100.00%
Antibody PNA	86.04%	90.82%	95.60%	97.80%	100.00%
Molecular	\$490,164	\$379,277	\$268,390	\$220,259	\$172,127
Antigen	\$284,489	\$170,802	\$57,116	\$36,984	\$16,852
Antibody	\$120,376	\$98,178	\$75,979	\$65,762	\$55,546

PNA, percent negative agreement; PPA, percent positive agreement.

	Molecular		Antigen		Antibody			
	Pos	Neg	Pos	Neg	Pos	Neg		
	TP	FN	TN	FP	TP	FN	TN	FP
Obtain, perform, and report test (\$200)	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
COVID-19 treatment (\$3,045)	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Contact tracing (\$1,000)	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Patient cost for self-isolation (\$1,400)	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Confirm with orthologous test (\$50-\$200)	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Cost is impacted (multiplied) by Reff R_0			<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Probability of cost varies with prevalence							<input checked="" type="checkbox"/>	
Estimated total cost of each true and false test result reported								
Clinical and patient cost per true-positive test	\$5,645		\$5,645		\$1,250			
Clinical and patient cost per true-negative test	\$200		\$400		\$1,600			
Clinical cost per false-positive test	\$2,600		\$2,600		\$522-\$1,618			
Clinical cost per false-negative test	\$11,290		\$400		\$1,600			

Figure 4 Clinical and patient costs per COVID-19 sample by test type. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

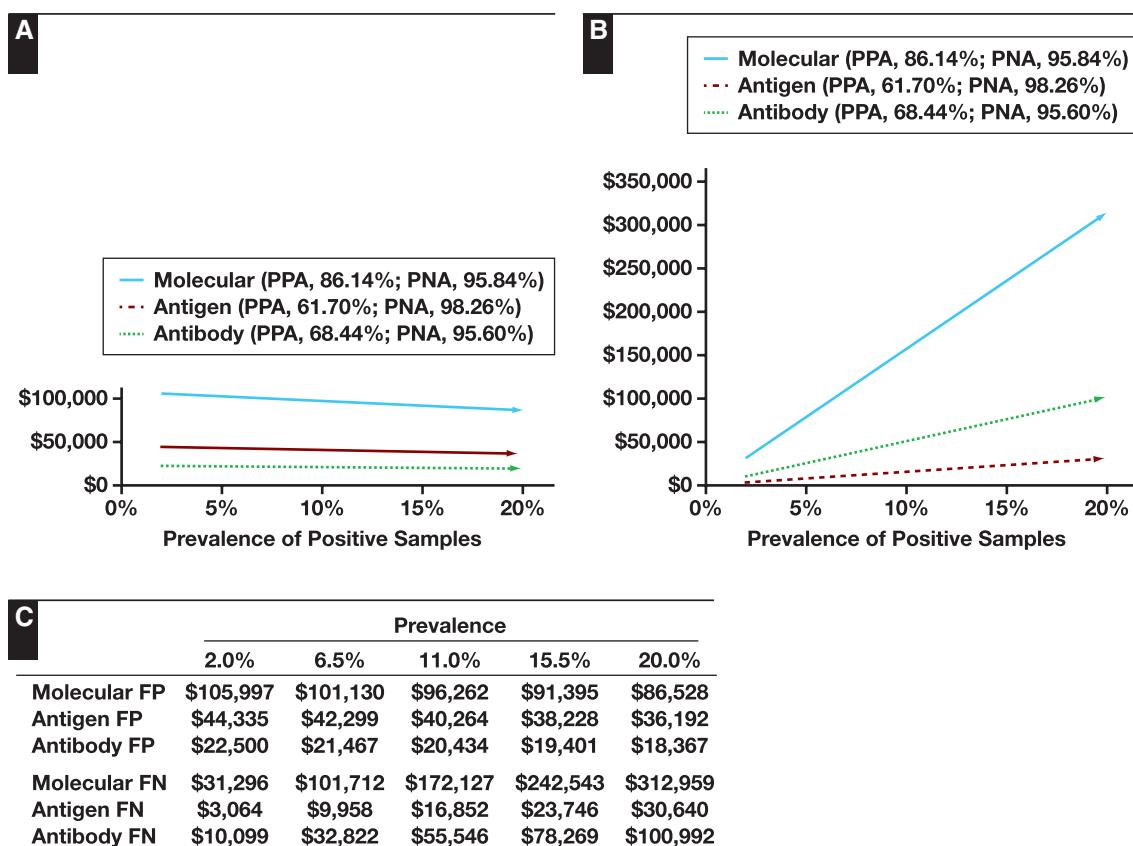


Figure 5 Impact of prevalence on cost of false results, with percent positive agreement (PPA) and percent negative agreement (PNA) at baseline. **A**, False-positive (FP) results. **B**, False-negative (FN) results. **C**, Impact of prevalence on cost of false results per 1,000 samples.

treatment decisions or to prevent the possible spread of the virus due to a false negative.”¹⁸ We set cost to confirm positive antigen tests at \$200, as that includes collecting a new sample and PCR testing. The CDC

advises that “Three strategies can be used to improve positive predictive value: 1. Choose a test with a very high specificity, perhaps 99.5% or greater. 2. Focus testing on persons with a high pre-test probability of

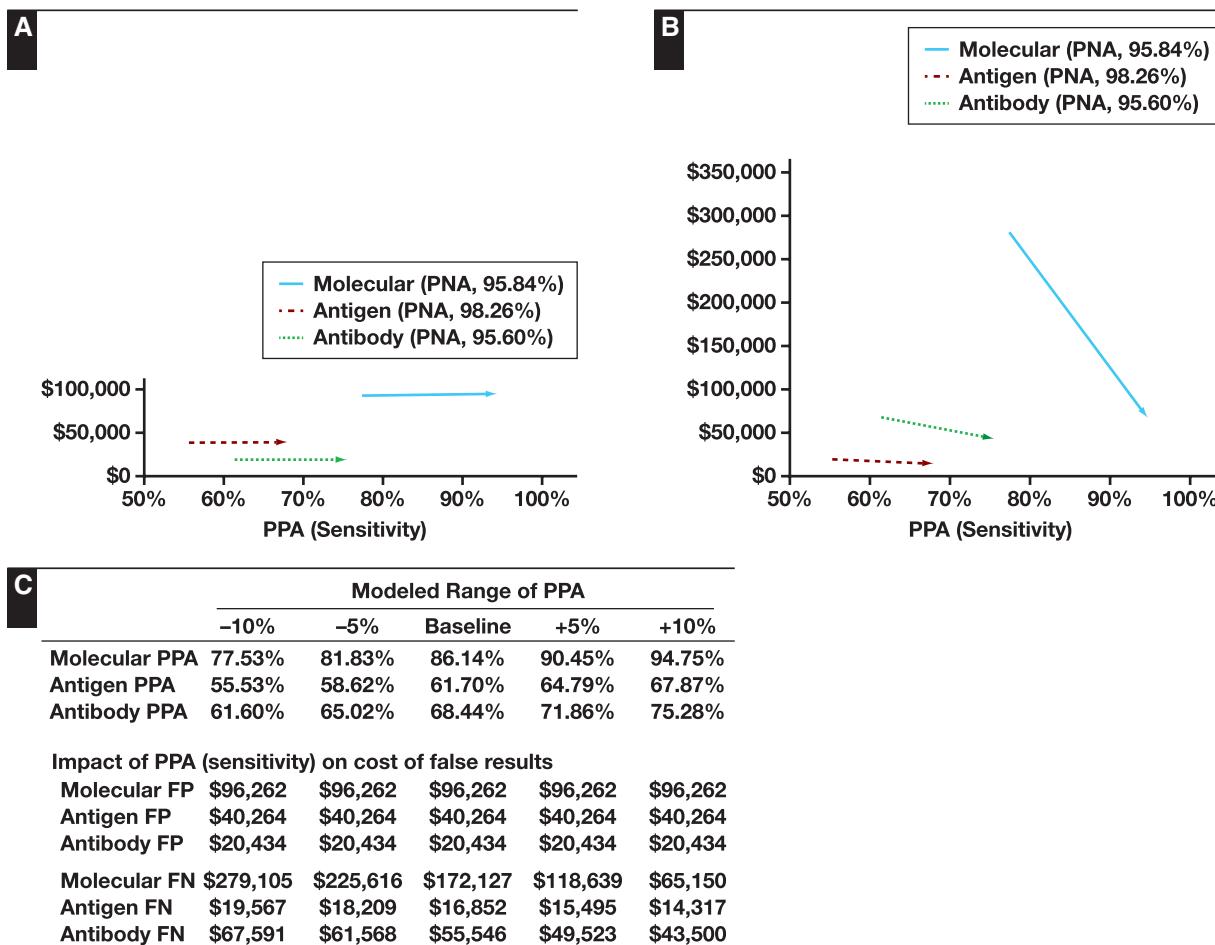


Figure 6 Impact of percent positive agreement (PPA) on cost of false results, with prevalence and percent negative agreement (PNA) at baseline. **A**, False-positive (FP) results. **B**, False-negative results (FN). **C**, Modeled range of PPA and impact on cost.

having SARS-CoV-2 antibodies, such as persons with a history of COVID-19-like illness. or 3. Employ an orthogonal testing algorithm in which persons who initially test positive are tested with a second test.”¹⁹ We set the cost to confirm positive antibody tests at \$50, as a new sample is not required.

- Reff or R_0 is the effective number of people infected by one positive COVID-19 case.^{20,21} False-negative molecular tests in true-positive samples and false-positive antibody tests in true-negative samples may mislead patients to move freely in society, and infect Reff others. These people are or may become infected, incur the same costs as the true positive patients, and will infect Reff others. Other checked costs are multiplied by $(1 + \text{Reff})$ where indicated. False-positive antibody tests may mislead patients to move freely in society and become infected at the rate of prevalence. Other costs are multiplied by prevalence.

- True-positive tests (disease [D]+/test [T]+) include costs of all checked items. Molecular and antigen positives indicate current infection with associated clinical costs (\$5,645.) True-positive antibody tests were assumed to protect patients from infection; costs include sample testing, contact tracing, and confirmation with an orthogonal test (\$1,200.)
- True-negative tests (D-/T-) include only testing for molecular tests (\$200); testing and confirmation for antigen tests (\$400); and testing plus self-isolation for antibody tests (\$1,600.)
- False-positive tests (D-/T+) incur costs of testing plus self-isolation and contact tracing for molecular and antigen tests. Costs of false-positive antibody tests include the risk that the patients receiving these results may become infected and infect others and are calculated as $[(\text{Cost of treatment} \times \text{prevalence}) \times (1 + \text{Reff})] \times [(1 + \text{Reff}) \times \text{Testing}]$.
- False-negative molecular tests (D+/T-) occur in people who are actually infected, will incur costs of the

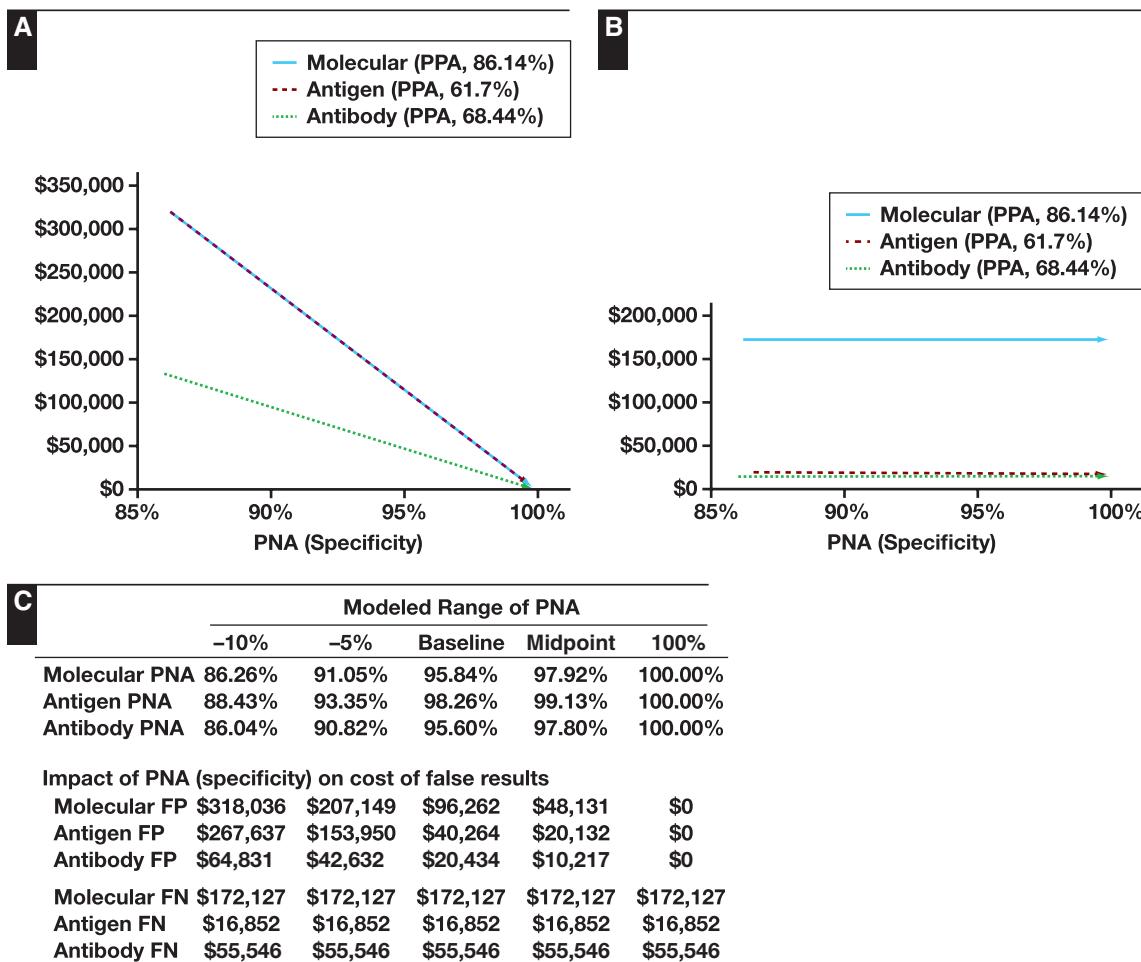


Figure 7 Impact of percent negative agreement (PNA) on cost of false results, with prevalence and percent positive agreement (PPA) at baseline. **A**, False-positive (FP) results. **B**, False-negative results (FN). **C**, Modeled range of PNA and impact on cost.

true-positive result, multiplied by $(1 + \text{Reff})$ to account for other people infected. With Reff set at 1.0, false-negative molecular tests cost \$11,290. False-negative antigen tests are confirmed with an orthogonal test to incur total costs of \$400. False-negative antibody tests incur the same costs as true negatives for testing plus self-isolation for antibody tests (\$1,600.)

Figure 5 presents the impact of increased prevalence on cost of false results. The x-axis represents the modeled value of prevalence; the y-axis shows patient and clinical cost of error per 1,000 samples tested. Cost of false-positive results decreases slightly as prevalence increases because the number of true-negative samples decrease from 980 to 800 per 1,000 samples. False-positive tests are a fraction of true-negative samples, which is driven by PNA. The number of true-positive samples increases from 20 to 200 per 1,000 samples as prevalence increases from 2% to 20%, driving up true-positive

and false-negative test results and costs. False-negative tests are a fraction of true-positive samples, which is driven by PPA.

Costs vary between test types due to variation in baseline PPA and PNA. Costs are based on patient and clinical cost in Figure 4. Costs of each false-negative molecular test result are much higher than other tests.

Figure 6 shows the impact of PPA on cost of false results, with prevalence and PNA at baseline. The x-axis shows the baseline PPA for each test type $\pm 10\%$; the y-axis shows patient and clinical costs as shown in Figure 4. With baseline prevalence of 11%, the number of total positive samples is constant at 110 per 1,000. It is somewhat counterintuitive that PPA has no impact on false positives. False-positive tests are a fraction of true-negative samples (890 per 1,000 samples); that fraction is driven by PNA.

Increasing PPA drives the number/cost of true-positive results up and number/cost of false-negative

results down. Again, because false-negative molecular tests cost more than false-negative antigen or antibody tests, their costs show the greatest impact. If one looks only at the statistical indicator of probability of false results, the impact on cost is not apparent.

Figure 7 shows the impact of PNA on cost of false results, with prevalence and PPA at baseline. The x-axis shows the baseline PNA for each test type $\pm 10\%$ (to a maximum of 100%); the y-axis shows patient and clinical costs as shown in **Figure 4**. With baseline prevalence of 11%, the number of total positive and negative samples are constant at 110 and 890 per 1,000, respectively. Increasing PNA drives the number/cost of true-negative results up and number/cost of false-positive results down. False-positive tests are a fraction of true-negative samples (890 per 1,000 samples); false positives decrease as PNA increases. Increased PNA has the greatest impact on costs of false-positive test results because of the vastly higher portion of negative patient samples.

PNA has no impact on false-negative test results. Again, because false-negative molecular tests cost more than false-negative antigen or antibody tests, their costs show the greatest impact.

Table 3 presents the total cost per 1,000 samples tested of false results for each test type, with modeled variations in risk drivers of prevalence, PPA and PNA. In each case, molecular tests carry the greatest risk of cost of false results due to the high cost of false-negative results. The specific numbers vary with baseline prevalence, PPA, PNA, and costs of each test type.

Discussion

The authors combined PPA and PNA values from user evaluation studies with estimates of prevalence, cost, and Reff number to illustrate a model showing how patient risk and clinical cost are driven by test selection. Knowledge of the PFP and the PFN add valuable information to method evaluation and review. Statistical indicators of PPA, PNA, PPV, NPV, PFP, PFN, or even the number of false results alone cannot evaluate risk as the patient risk and clinical cost of the analytical method selected. It would be worthwhile repeating this exercise with locally verified costs, prevalence, and Reff number. The authors have posted an online calculator at <https://awesome-numbers.com/risk-calculator/> to allow readers to simulate changes with their projected variables and estimates of cost in local currency.

ISO/IEC guide 51 defines risk as “the combination of the probability of occurrence of harm and the severity of that harm.”¹⁰ Examination of only PPA and PNA does

not give an indication of patient risk as the number and clinical cost of false results. Risk as the probability and severity of false-positive and false-negative results can be extrapolated from manufacturers’ claims and/or user data for PPA and PNA plus estimates of prevalence, Reff number, and cost for your health care setting. Reff values for each US state can be found at <https://rt.live/>.²⁰ We estimated costs roughly for the United States but did not enter a value for loss of life in our equations, as human life is invaluable. It may be wise, if difficult, to factor that in when evaluating cost in your location and currency.

The relationships between the various acronyms are confusing. Increased PPA (sensitivity), percent *positive* agreement, drives the number and cost of false-*negative* results down, but has no impact on false positives. Increased percent *negative* agreement, PNA (specificity), drives the probability of false *positives* (PFP) and the resultant patient risk and health care cost down. PNA (specificity), percent negative agreement, has no impact on false negatives.

We found it thought-provoking that, as prevalence increases from 2% to 20%, cost of false molecular test results increase by over \$250,000 for every 1,000 molecular tests performed. This happens because the number of true-positive and very costly false-negative tests increase in proportion to prevalence. With the baseline PNA of 95.8%, there are few false-positive results (41 at prevalence of 2% and 33 at prevalence of 20%), and the decrease in their cost make little difference to the total costs.

For each 1,000 samples tested, selecting a molecular test with PPA of 94.8% instead of 77.5% would save patients and the health care system over \$200,000. A test with PNA of 100.0% instead of 86.3% reduces patient and clinical cost by over \$300,000. Similar patterns were observed for antigen and antibody tests.

Acceptable risk is “a state achieved in a measuring system where all known potential events have a degree of likelihood for or a level of severity of an adverse outcome small enough such that, when balanced against all known benefits—perceived or real—patients, physicians, institutions, and society are willing to risk the consequences.”²² The COVID-19 pandemic has brought “patients, physicians, institutions, and society” together as never before; ask them if they are willing to risk the consequences of your chosen method. What is their maximum acceptable risk level as the number and cost of false results? Although methods report a qualitative result, these are typically based on quantitative measurements and cutoff levels. The same concept can be applied to risk-based standards through on-site method validation experiments and daily quality control to maintain risk within acceptable risk limits.

Conclusion

Three types of laboratory tests play critical roles in the diagnosis and management of COVID-19. The existing practice of examining PPA and PNA fails to project risk as the probability and severity of harm. The PFP decreases as prevalence and PNA increase. The PFN increases with prevalence and decreases with PNA. Measuring risk metrics as the number and cost of false results adds a great deal of insight that is masked by the usual statistical metrics. Patient risk and clinical cost are governed by the number, clinical implications, and cost of false-positive and false-negative patient results for each test type. Small changes in statistical metrics can produce large changes in risk metrics. Knowledge of the clinical implications and cost of false-positive and -negative test results can add valuable insight to test selection and guide decisions of repeating test results for confirmation with an orthogonal method. We provided an online calculator to encourage and enable future studies with localized statistical indicators and cost.

Corresponding author: Zoe C. Brooks, ART; zoe@awesome-numbers.org

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