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COVID-19 testing – Impact of Prevalence, Sensitivity, and Specificity on Patient Risk and Cost.

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Brief Title: Covid19 - risk as false results and cost

Key points:

1. 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 PPA, PNA, PPV and NPV.

2. The number and cost of false positive and negative test results are driven by prevalence, percent positive agreement (PPA/sensitivity), and percent negative agreement (PNA/specificity.)

3. The clinical implications and cost of false positive and negative test results can guide test selection and decisions about repeating test results for confirmation.

Key words: Covid19, risk, clinical, metrics, cost, false-positive, false-negative, prevalence, sensitivity, , specificity

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Abstract: Since the beginning of the year 2020, the global healthcare system has been challenged by the threat of the SARS-COV 2 virus. Molecular, antigen, and antibody testing are the mainstay to identify infected patients and fight the virus. Molecular and antigen tests that detect the presence of the virus are relevant in the acute phase only. Serological assays detect antibodies to the Sars-CoV-2 virus in the recovering and recovered phase. Each testing methodology has its advantages and disadvantages. 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 (PPV and PNV), the probability that a positive or negative test result represents a true positive or negative patient. In this paper, we illustrate how patient risk and clinical costs are driven by false-positive and false-negative results. We demonstrate the value of reporting PFP (probability of false positives), PFN (probability of false negatives), and costs to patients and healthcare. 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 one positive SARS COV-2).

Introduction:

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 11th, 2020 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 World Health Organization (WHO), the disease COVID-19 has spread across continents, with 6,302,318 diagnosed cases and 376,210 deaths globally, and 1,811,277 cases 105,147 deaths in the USA until 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

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molecular, antigen and antibody tests that correctly classify patients as positive or negative for presence of the SARS-CoV-2 virus, 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 [A] prevalence of SARS-CoV-2 virus, or for antibodies in the test population, [B] Percent Positive Agreement (PPA/sensitivity), and [C] Percent Negative Agreement (PNA/specificity) of each test process. See glossary in appendix A.

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 (rRT-PCR) which is a nucleic acid amplification test (NAAT) that detects unique sequences of the virus that causes COVID-19 (SARS-CoV-2). (5) Antigen tests, that also detect the presence of the SARS-CoV-2 virus, 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 al (6) illustrates 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 serological 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) Serological assays detect IgG and IgM antibodies to the Sars-CoV-2 virus which could develop about 1-3 weeks after infection. Testing for IgG may be a

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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, CDC 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 as a possible treatment for those who are seriously ill from COVID-19." Contrary to early hopes to use serological testing to issue "immunity passports" to return to work and society, 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 three types of tests with advantages and disadvantages.

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.

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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 healthcare 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 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. FDA advises that, if prevalence is low, as it usually is, laboratories should confirm positive tests using "an orthogonal testing algorithm (i.e., employing two independent tests in sequence.") (10)
Risk of False Positive Test	The patient would falsely believe they are infected and self-isolate. There would be unnecessary contact tracing.	The patient would falsely believe they are infected and self-isolate. There would be unnecessary contact tracing.	The patient would falsely believe they have antibodies, not practice physical distancing, and be at risk of infection and infecting others. Contacts may be traced.

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Risk of False Negative Test	The patient would falsely believe they are virus-free, not self-isolate and infect Reff number of others.	The patient would falsely believe they are virus-free, not self-isolate and infect Reff number of others. FDA advises that negative antigen tests may need to by confirmed with PCR tests.	The patient would falsely believe they do not have antibodies, continue to practice physical distancing and fail to return to work and society.

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Risk is the combination of the probability and severity of harm.

ISO/IEC Guide 51defines risk as "the combination of the probability of occurrence of harm and the severity of that harm." To evaluate/select test methods, laboratory professionals usually compare sensitivity (percent positive agreement - PPA) and specificity (percent negative agreement – PNA), followed by positive and negative predictive value (PPV and NPV) - the probability that a positive or negative test result represents a true positive or negative patient 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, the authors calculated the probability of false positive (PFP) and probability of false negative (PFN) test results. Probability of false positive test results (PFP) is the number of false positive results as a percent of all positive results. PFP is the reciprocal of positive predictive value (PPV), the probability that a positive result is a true positive. Probability of false negative test results (PFN) is the number of false negative results as a percent of all negative results. PFP is the reciprocal of negative predictive value (NPV). The authors roughly estimated cost of false results and from those we projected severity of harm as the costs incurred by patients and healthcare institutions.

PPA (sensitivity) and PNA (specificity) 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

 doi:10.20944/preprints202006.0279.v1

52% will yield a positive predictive greater than 95%, meaning that less than one in 20 people testing positive will have a false positive test result." (10)

As of May 4, 2020, FDA requires that clinical agreement data should demonstrate a minimum overall 90.0% positive percent agreement (sensitivity) and 95.0% negative percent agreement (specificity.) (10) Most, but not all, values for sensitivity and specificity reported by FDA May 21, 2020 meet their goals. In the UK, recommended standards are set higher, at 98% PPA and 98% PNA (11). Recommendations are theoretical goals, and manufacturers' test results are created under controlled ideal conditions. The Foundation for Innovative New Diagnostics, FIND, working in partnership with 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 (12). We chose to model their meta-analysis results as the baseline in simulations as we felt 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 (ELISA), 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.

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Table 2. Baseline PPA and PNA (FIND) (20)	Molecular	Antigen	Antibody
PPA Percent Positive Agreement (sensitivity)	86.14%	61.70%	68.44%
PNA Percent Negative Agreement (specificity)	95.84%	98.26%	95.6%
Index Sample Type	10	4	6
Company Names	33	3	54
Test Names	35	4	74
Test Formats	3	2	6
Targets	4	4	5

The authors modeled the impact of +/-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 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 10%. The impact of the 'risk drivers' of prevalence, PPA (sensitivity) and PNA (specificity) on the 'risk metrics' of probability of false positive and false negative test results are shown in Tables 3, 4 and 5.

Table 3 shows that, as prevalence increases, the number of patients who are positive for the SARS-CoV-2 virus or antibody increases. Prevalence is governed by the

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spread of COVID-19 in 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 negative test results increase tenfold in proportion to prevalence because false negative tests are a portion of true positive samples. This dramatic increase may be masked by examining only negative predictive value (NPV) which decreases slightly from 99.7% to 96.5%.

False positive tests are a portion of true negative patients, so they also decrease. As prevalence increases from 2% to 20%, with PPA and PNA constant at baseline, the probability that a positive test result is a false positive (PFP) decreases significantly from 70.3% to 16.2% for molecular tests, 68.0% to 10.1% for antigen tests and 75.9% to 20.4% for antibody tests. These ranges differ due to the differences in the average PPA and PNA for each test type.

Table 4 shows the impact of modeled changes in percent positive agreement, PPA (sensitivity), on each test type with prevalence and PNA constant at baseline. True positive test results increase, but the number of false positives is not affected by PPA. False positives form a smaller portion of all positive results, decreasing PFP (probability of false positive) from 32.6% to 28.3% for molecular tests. Antigen tests have a lower range of PPA with a resultant smaller change in probability of false positives, PFP, from 22.0% to 18.7%. As PPA increases for antibody tests, the range of PFP decreasing from 39.1% to 34.4%.

Table 5 shows the impact of modeled changes in PNA (specificity) on each test type. When percent negative agreement (PNA) reaches 100%, all negative results are true negatives and probability of false positives decrease to zero. As PNA increases from 86.3% to 100%, PFP decreases from 58.9% to 0% for molecular tests. Antigen

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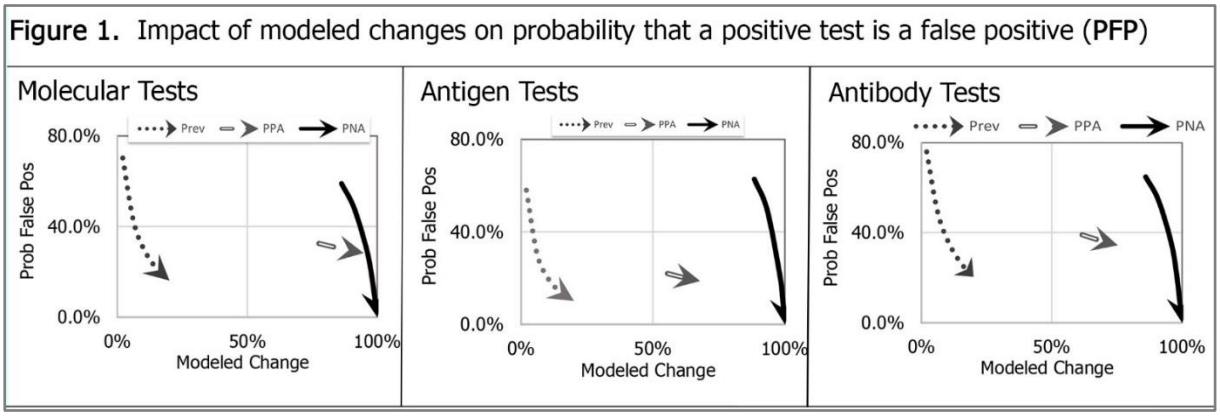
tests have a higher range of PNA with a resultant change in PFP from 62.8% to 0%. Antibody tests show a range of PFP decreasing from 64.7% to 0%. Notice that PPA (sensitivity) had less impact on PFP than prevalence or PNA (specificity.)

Probability of harm from false positive test results (PFP) decreases with prevalence, PPA and PNA

Figure 1 shows that probability of false positive test results (PFP) decreases as prevalence, PPA and PNA increase. The x-axis represents the modeled value of prevalence, PPA (sensitivity) and PNA (specificity); the y-axis shows the probability that a positive test result is a false positive (PFP.) The patterns for all tests are similar, but not identical because the baseline PPA and PNA values differ between test types, as shown in Table 2.



Probability of harm from false negative test results (PFP) varies with prevalence, PPA and PNA

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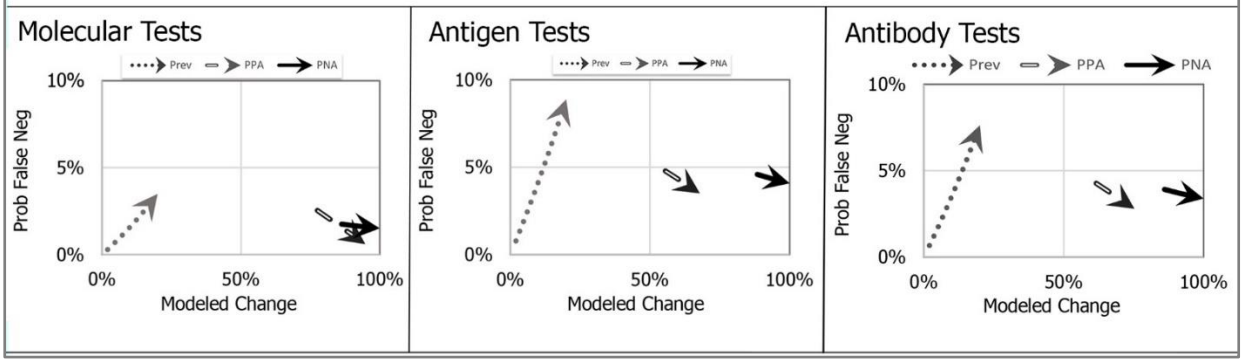
Figure 2 shows how the probability that a negative test result is a false negative (PFN) increases with prevalence but decreases with PPA and PNA for all test types. Again, the x-axis represents the modeled value of prevalence, PPA and PNA; here y-axis shows probability of false negatives (PFN.) Notice that the range of percent false negative results is much lower than the range of false positive results in Figure 1. Unlike false positives that decrease with prevalence, false negatives increase. Table 3 demonstrates how, when prevalence increases from 2% to 20%, the number of true positive samples and true positive test results increase. False negative results also increase as they are a portion of all positive test results. With PPA and PNA constant at baseline, PFN increases with prevalence from 0.3%, 0.8% and 0.7% for molecular, antigen and antibody tests to 3.9%, 8.9% and 7.6% respectively.

Figure 2. Impact of modeled changes on probability that a negative test is a false negative (**PFN**)



As sensitivity (PPA) increases, the number of true positive test results increases, and false negatives decrease. As specificity (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 probability of false negatives (PFN) down.

Implications 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. False positive and false negative results drive

 doi:10.20944/preprints202006.0279.v1

patient risk and clinical care costs. The potential harm of false positive and false negative results (13) as discussed in Table 1 is applied in Table 6 to create a rough estimate of patient and clinical care costs for the USA. These costs are used as a model to illustrate the process of converting risk drivers of the prevalence, PPA (sensitivity) and PNA (specificity) to risk metrics of the number and cost of erroneous results. The authors will provide an online calculator where users can modify costs and select where they are applied.

Table 6a shows the estimated costs and how they are applied to true and false positive patient samples. Remember that increased PPA (percent positive agreement) increases true positive tests (TP) and decreases false negatives (FN.) PNA (percent negative agreement) increases true negative tests (TN) and decreases false positives (FP.)

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Table 6a Costs associated with test type

		Molecular				Antigen				Antibody			
		True Pos		True Neg		True Pos		True Neg		True Pos		True Neg	
		TP	FN	**TN**	FP	**TP**	FN	**TN**	FP	**TP**	FN	**TN**	FP
A. Obtain, perform and report test	$200	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
B. Covid19 clinical treatment	$ 3,045	☑	☑			☑							
C. Contact tracing	$1,000	☑	☑		☑	☑			☑	☑			☑
D. Patient cost for self isolation	$1,400	☑	☑	☑	☑	☑	☑		☑				
E. Confirm with orthologous test	$50-$200						☑	☑		☑			☑
F. Cost is impacted by Reff (R_0)					☑								☑
G. Cost varies with prevalence													☑

With Reff, the number of people infected by one positive Covid19 case (19, 20) set at 1.0 and costs as above, total costs are calculated as:

A. Healthcare system costs to obtain, perform and report the test were roughly estimated by authors.

B. 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.” (16)

C. 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.” (17) The authors roughly projected cases at 3,600,000 based on the 2,157,768 cases as of June 16, 2020 (18) to estimate cost at $1,000 per patient.

D. Patient cost for self isolation was estimated by authors.

E. 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 treatment decisions or to prevent the possible spread of the virus due to a false negative." (19) The authors set cost to confirm positive antigen tests at $200, as that includes

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collecting a new sample and PCR testing.

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 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." The authors set cost to confirm positive antibody tests at $50, as a new sample is not required.

F. false positive antibody tests may mislead patients to move freely in society, become infected at the rate of prevalence and infect #Reff others. Costs for are multiplied by the individual plus Reff.

G. False negative molecular tests occur in true positive samples. These people are infected, incur the same costs as the true positive and will infect Reff others.

Table 6b. shows the total cost for each sample as calculated by adding all the checked costs and multiplying by Reff where indicated. An online calculator will be available for readers to modify costs and model various scenarios with changing risk drivers of prevalence, PPA and PNA.

Table 6b. Cost of true and false positive and negative test results	**Molecular**	**Antigen**	**Antibody**
H. Clinical & Patient cost per True Positive	$5,645	$5,645	$1,250
I. Clinical & Patient cost per True Negative	$200	$400	$1,600
J. Clinical cost per False Positive	$2,600	$2,600	$522 to $1618
K. Clinical cost per False Negative	$11,290	$400	$1,600

Figure 3 shows how patient and clinical costs incurred because of false-positive test results vary for the three test types, based on calculations in Table 7 Molecular, Table

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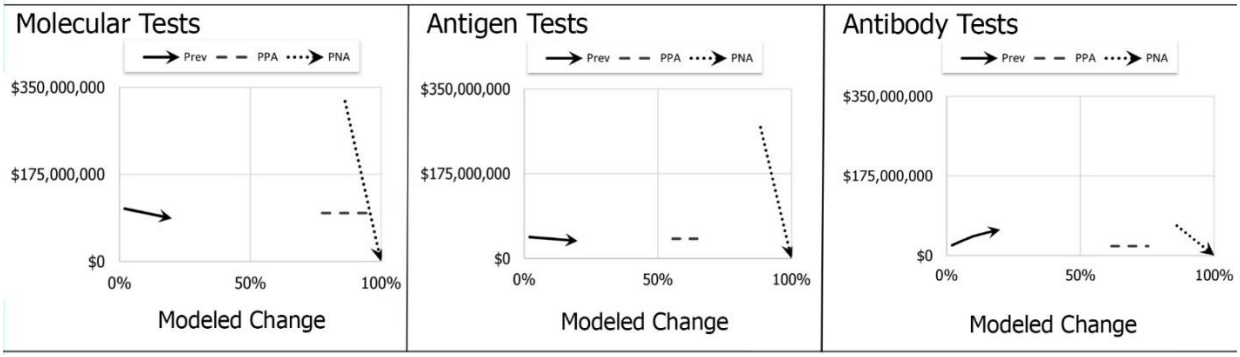
8 Antigen and Table 9 Antibody. The x-axis represents the modeled value of prevalence, PPA and PNA; the y-axis shows patient and clinical cost of error per one million samples tested. Cost of false-positive results decreases slightly as prevalence increases for molecular and antigen tests. The number of true positive samples increases with prevalence, driving true positive test results up and costly false negative test results down.

Figure 3. Impact of modeled changes on clinical and patient cost of **false positive results / 1,000,000 tests**



Costs are based on patient and clinical cost in Table 6b. For molecular tests, with the baseline prevalence of 10%, PPA (sensitivity) of 86.1% and PNA (specificity) of 95.8%, there are 37,440 false positive results creating costs for patients and healthcare systems of $97,344,000 per million tests performed. Although there are fewer false negative tests (13,800), these add $156,479,400 in costs because each false negative result would also incur the costs of people infected by the unknowingly positive initial patient. False results would add 39% to the patient and healthcare costs of true results. These costs and percentages vary with the risk-drivers of prevalence, PPA and PNA as shown in Tables 7, 8 and 9.

Costs increase with prevalence for antibody testing. Patients with false positive antibody results may assume they are immune and still become infected at the rate of

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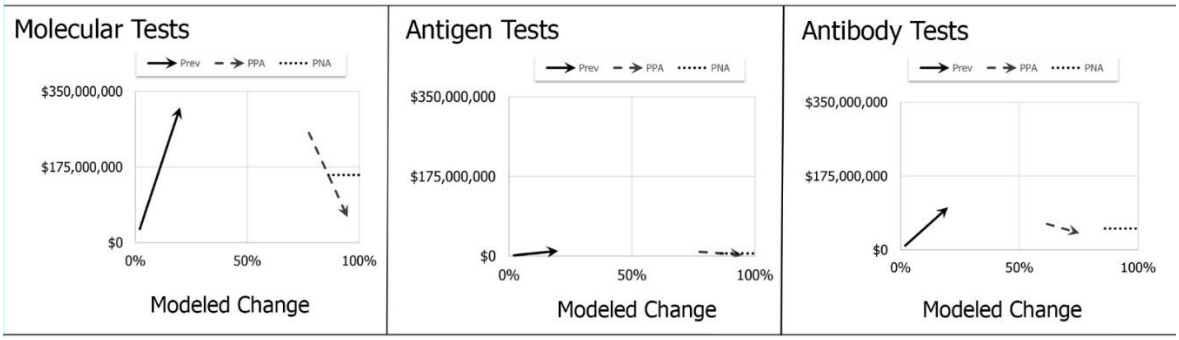
prevalence. Although the absolute number of false positives decreases with prevalence, the cost per person increases with the probability of infection of themselves and others.

PPA (sensitivity), percent positive agreement, drives the number/cost of false negative results down, but has no impact on false positives. Increased PNA (specificity), percent negative agreement, has the greatest impact on costs for all test types by decreasing the number of false positive test results because of the vastly higher portion of negative patient samples. It is worthwhile time to examine the numbers and patterns in Tables 7, 8 and 9 to understand the impact of risk drivers on risk metrics of the number and cost of false results.

Figure 4 shows cost for false negative test results per 1,000,000 samples tested. The range of costs is lower than for false positive test results for antigen and antibody tests. Costs of false negatives are higher for molecular tests than antigen or antibody tests (see Table 6.) Costs increase with prevalence as the number of true positive and costly false negative test results increase. As PPA (sensitivity) increases the number/cost of false negative test results decreases, driving their costs down. It is somewhat counterintuitive that PNA (sensitivity), percent negative agreement, has no impact on false negatives.

Figure 4. Impact of modeled changes on clinical and patient cost of **false negative results /1,000,000 tests**



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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 probability that a positive test result is false (PFP), and that a negative test result is false (PFN) add valuable information to method evaluation and review. Statistical indicators of PPA and PNA, 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 will post an online calculator to allow readers to simulate changes with their projected variables of prevalence, PPA, PNA, Reff number and cost.

ISO/IEC Guide 51defines risk as "the combination of the probability of occurrence of harm and the severity of that harm." (21) Examination of only PPA (sensitivity) and PNA (specificity) 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 (sensitivity) and PNA (specificity) plus estimates of prevalence, Reff number and cost for your healthcare setting. The authors estimated costs roughly for the USA and 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

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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 healthcare cost down. PNA (specificity), percent negative agreement, has no impact on false negatives.

The authors found it thought-provoking when examining Table 7 that for every one million molecular tests performed, you can prevent approximately 7,500 false positive test results and reduce costs to patient and healthcare by $19.5 million in patient and healthcare costs by selecting select a population with a pre-test prevalence of 20% instead of 2%. However, as the number of true positives increase with prevalence, false negatives increase proportionally adding risk of 25,000 false negative results and $282 million to costs. Selecting a molecular test with PPA (sensitivity) of 94.8% instead of 77.5% would reduce the number of false negative tests by approximately 17,000 and save patients and the healthcare system almost $200 million. A test with PNA (specificity) of 100.0% instead of 86.3% reduces false positives by approximately 124,000 and saves over $320 million. Similar obscure patterns were observed for antigen and antibody tests in Tables 8 and 9.

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

 doi:10.20944/preprints202006.0279.v1

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 (sensitivity) and PNA (specificity) fails to project risk as the probability and severity of harm. The probability and cost of false positive test results (PFP) decreases as prevalence and PNA increase. Probability of false negative test results (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 guides decisions of repeating test results for confirmation with an orthogonal method. The authors are providing an online calculator to encourage and enable future studies with localized statistical indicators and cost.

Glossary

WHO: World Health Organization
CDC: Centre for Disease Control
2019-nCoV : 2019-novel coronavirus
SARS-CoV-2- severe acute respiratory syndrome coronavirus-2
PPA: Percent Positive Agreement
PNA: Percent Negative Agreement

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rRT-PCR: Real-time reverse transcription-polymerase chain reaction

NAAT: nucleic acid amplification test

PPV: Positive predictive value

NPV: Negative predictive value

PFP: Probability that a positive result is false-positive

PFN: Probability that a negative result is false- negative

FIND: Foundation for Innovative New Diagnostics

PCR: Polymerase Chain Reaction

ELISA: Enzyme Linked Immunosorbant Assay

PPA: Percent positive agreement

PNA: Percent negative agreement

IgG: Immunoglubulin G

IgM: Immunoglobulin M

IgA: Immunoglobulin A

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Table 3. Impact of Prevalence on Probability of False-Positive and False-Negative Tests **(PFP & PNF)**

	All tests model changes in prevalence of patient samples with true positive tests	Prev = 2%	Prev = 6%	Baseline = 10%	Prev = 15%	Prev = 20%
A	Total number of samples Tested	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000
B	**Prevalence of Positives ↗**	**2%**	**6%**	**10%**	**15%**	**20%**
C (AxB)	Samples Truly Positive ↗	20,000	60,000	100,000	150,000	200,000
D (A-C)	Samples Truly Negative ↓	980,000	940,000	900,000	850,000	800,000
	Molecular Tests					
E	PPA Percent positive agreement ⇨	86.14%	86.14%	**86.14 %**	86.14%	86.14%
F	PNA Percent negative agreement ⇨	95.84%	95.84%	**95.84 %**	95.84%	95.84%
G (CxE)	Total Test Results Positive ↗	57,996	90,788	123,580	164,570	205,560
H (C-G)	Total Test Results Negative ↓	942,004	909,212	876,420	835,430	794,440
I (DxF)	Test Result Pos in True Pos Sample ↗	17,228	51,684	86,140	129,210	172,280
J (D-J)	**False Neg Test** in True Pos Sample ↗	**2,772**	8,316	13,860	20,790	**27,720**
K (G+J)	True Neg Test in Neg Sample ↓	939,232	900,896	862,560	814,640	766,720
L (H + I)	**False Pos Test** in True Neg Sample ↓	**40,768**	39,104	37,440	35,360	**33,280**
M (G/K)	PPV Positive Predictive Value ↗	29.7%	56.9%	69.7%	78.5%	83.8%
N (J/K)	**PFP Probability of False Positive ↓**	**70.3%**	43.1%	30.3%	21.5%	**16.2%**
O (I/L)	NPV Negative Predictive Value ↓	99.7%	99.1%	98.4%	97.5%	96.5%
P (H/L)	**PFN Probability of False Negative ↗**	**0.3%**	0.9%	1.6%	2.5%	**3.5%**
	Antigen Tests					
E	PPA Percent positive agreement ⇨	61.70%	61.70%	**61.70 %**	61.70%	61.70%
F	PNA Percent negative agreement ⇨	98.26%	98.26%	**98.26 %**	98.26%	98.26%
G (CxE)	Total Test Results Positive ↗	**29,392**	53,376	77,360	107,340	**137,320**
H (C-G)	Total Test Results Negative ↓	970,608	946,624	922,640	892,660	862,680
I (DxF)	Test Result Pos in True Pos Sample ↗	12,340	37,020	61,700	92,550	123,400
J (D-J)	**False Neg Test** in True Pos Sample ↗	**7,660**	22,980	38,300	57,450	**76,600**
K (G+J)	True Neg Test in Neg Sample ↓	962,948	923,644	884,340	835,210	786,080

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 June 2020 doi:10.20944/preprints202006.0279.v1

L (H + I)	**False Pos Test** in True Neg Sample ↓	**17,052**	16,356	15,660	14,790	**13,920**
M (G/K)	PPV Positive Predictive Value ↗	42.0%	69.4%	79.8%	86.2%	89.9%
N (J/K)	**PFP Probability of False Positive ↓**	**58.0%**	30.6%	20.2%	13.8%	**10.1%**
O (I/L)	NPV Negative Predictive Value ↓	99.2%	97.6%	95.8%	93.6%	91.1%
P (H/L)	**PFN Probability of False Negative ↗**	**0.8%**	2.4%	4.2%	6.4%	**8.9%**
Antibody Tests						
E	PPA Percent positive agreement ⇨	68.44%	68.44%	**68.44 %**	68.44%	68.44%
F	PNA Percent negative agreement ⇨	95.61%	95.61%	**95.6%**	95.61%	95.61%
G (CxE)	Total Test Results Positive ↗	56,710	82,330	107,950	139,975	172,000
H (C-G)	Total Test Results Negative ↓	943,290	917,670	892,050	860,025	828,000
I (DxF)	Test Result Pos in True Pos Sample ↗	13,688	41,064	68,440	102,660	136,880
J (D-J)	**False Neg Test** in True Pos Sample ↗	6,312	18,936	31,560	47,340	63,120
K (G+J)	True Neg Test in Neg Sample ↓	936,978	898,734	860,490	812,685	764,880
L (H + I)	**False Pos Test** in True Neg Sample ↓	43,022	41,266	39,510	37,315	35,120
M (G/K)	PPV Positive Predictive Value ↗	24.1%	49.9%	63.4%	73.3%	79.6%
N (J/K)	**PFP Probability of False Positive ↓**	**75.9%**	**50.1%**	**36.6%**	**26.7%**	**20.4%**
O (I/L)	NPV Negative Predictive Value ↓	99.3%	97.9%	96.5%	94.5%	92.4%
P (H/L)	**PFN Probability of False Negative ↗**	**0.7%**	**2.1%**	**3.5%**	**5.5%**	**7.6%**

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Table 4. Impact of PPA (sensitivity) on Probability of False Test Results (PFP)

All tests model changes in PPA from baseline		PPA -10%	PPA -5%	Baseline	PPA +5%	PPA +10%
A	Total number of samples Tested	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000
B	Prevalence of Positives ⇨	10%	10%	10%	10%	10%
C (AxB)	Samples Truly Pos ⇨	100,000	100,000	100,000	100,000	100,000
D (A-C)	Samples Truly Neg ⇨	900,000	900,000	900,000	900,000	900,000
Molecular Tests						
E	**PPA Percent positive agreement ↗**	**77.5%**	**81.8%**	**86.1%**	**90.4%**	**94.8%**
F	PNA Percent negative agreement ⇨	95.8%	95.8%	95.8%	95.8%	95.8%
G (CxE)	Total Test Results Positive ↗	114,966	119,273	123,580	127,887	132,194
H (C-G)	Total Test Results Negative ↓	885,034	880,727	876,420	872,113	867,806
I (DxF)	Test Result Pos in True Pos Sample ↗	77,526	81,833	86,140	90,447	94,754
J (D-J)	**False Neg Test** in True Pos Sample ↓	22,474	18,167	13,860	9,553	5,246
K (G+J)	True Neg Test in Neg Sample ⇨	862,560	862,560	862,560	862,560	862,560
L (H + I)	**False Pos Test** in True Neg Sample ⇨	37,440	37,440	37,440	37,440	37,440
M (G/K)	PPV Positive Predictive Value ↗	67.4%	68.6%	69.7%	70.7%	71.7%
N (J/K)	**PFP Probability of False Positive ↓**	**32.6%**	31.4%	30.3%	29.3%	**28.3%**
O (I/L)	NPV Negative Predictive Value ↗	97.5%	97.9%	98.4%	98.9%	99.4%
P (H/L)	**PFN Probability of False Negative ↓**	**2.5%**	2.1%	1.6%	1.1%	**0.6%**
Antigen Tests						
E	**PPA Percent positive agreement ↗**	**55.5%**	**58.6%**	**61.7%**	**64.8%**	**67.9%**
F	PNA Percent negative agreement ⇨	98.3%	98.3%	98.3%	98.3%	98.3%
G (CxE)	Total Test Results Positive ↗	71,190	74,275	77,360	80,445	83,530

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 June 2020 doi:10.20944/preprints202006.0279.v1

H (C-G)	Total Test Results Negative ↓	928,810	925,725	922,640	919,555	916,470
I (DxF)	Test Result Pos in True Pos Sample ↗	55,530	58,615	61,700	64,785	67,870
J (D-J)	**False Neg Test** in True Pos Sample ↓	44,470	41,385	38,300	35,215	32,130
K (G+J)	True Neg Test in Neg Sample ⇨	884,340	884,340	884,340	884,340	884,340
L (H + I)	**False Pos Test** in True Neg Sample ⇨	15,660	15,660	15,660	15,660	15,660
M (G/K)	PPV Positive Predictive Value ↗	78.0%	78.9%	79.8%	80.5%	81.3%
N (J/K)	**PFP Probability of False Positive ↓**	**22.0%**	21.1%	20.2%	19.5%	**18.7%**
O (I/L)	NPV Negative Predictive Value ↗	95.2%	95.5%	95.8%	96.2%	96.5%
P (H/L)	**PFN Probability of False Negative ↓**	**4.8%**	4.5%	4.2%	3.8%	**3.5%**

Antibody Tests

E	**PPA Percent positive agreement ↗**	**61.60%**	**65.02%**	**68.44%**	**71.86%**	**75.28%**
F	PNA Percent negative agreement ⇨	95.61%	95.61%	95.6%	95.61%	95.61%
G (CxE)	Total Test Results Positive ↗	101,106	104,528	107,950	111,372	114,794
H (C-G)	Total Test Results Negative ↓	898,894	895,472	892,050	888,628	885,206
I (DxF)	Test Result Pos in True Pos Sample ↗	61,596	65,018	68,440	71,862	75,284
J (D-J)	**False Neg Test** in True Pos Sample ↓	38,404	34,982	31,560	28,138	24,716
K (G+J)	True Neg Test in Neg Sample ⇨	860,490	860,490	860,490	860,490	860,490
L (H + I)	**False Pos Test** in True Neg Sample ⇨	39,510	39,510	39,510	39,510	39,510
M (G/K)	PPV Positive Predictive Value ↗	60.9%	62.2%	63.4%	64.5%	65.6%
N (J/K)	**PFP Probability of False Positive ↓**	**39.1%**	37.8%	36.6%	35.5%	**34.4%**
O (I/L)	NPV Negative Predictive Value ↗	95.7%	96.1%	96.5%	96.8%	97.2%
P (H/L)	**PFN Probability of False Negative ↓**	**4.3%**	3.9%	3.5%	3.2%	**2.8%**

Table 5. Impact of PNA (specificity) on Probability of False Test Results

All tests model changes in PNA from baseline	PNA -10%	PNA -5%	Baseline	PNA +5%	PNA +10% or max 100%

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A	Total number of samples Tested	1,000,000	1,000,000	1,000,000	1,000,000	1,000,000
B	Prevalence of Positives ⇨	10%	10%	10%	10%	10%
C (AxB)	Samples Truly Pos ⇨	100,000	100,000	100,000	100,000	100,000
D (A-C)	Samples Truly Neg ⇨	900,000	900,000	900,000	900,000	900,000
Molecular Tests						
E	PPA Percent positive agreement ⇨	86.1%	86.1%	86.1%	86.1%	86.1%
F	**PNA Percent negative agreement ↗**	**86.3%**	**91.0%**	**95.8%**	**97.9%**	**100.0%**
G (CxE)	Total Test Results Positive ↓	209,836	166,708	123,580	104,860	86,140
H (C-G)	Total Test Results Negative ↗	790,164	833,292	876,420	895,140	913,860
I (DxF)	Test Result Pos in True Pos Sample ⇨	86,140	86,140	86,140	86,140	86,140
J (D-J)	**False Neg Test** in True Pos Sample ⇨	13,860	13,860	13,860	13,860	13,860
K (G+J)	True Neg Test in Neg Sample ↗	776,304	819,432	862,560	881,280	900,000
L (H + I)	**False Pos Test** in True Neg Sample ↓	123,696	80,568	37,440	18,720	0
M (G/K)	PPV Positive Predictive Value ↗	41.1%	51.7%	69.7%	82.1%	100.0%
N (J/K)	**PFP Probability of False Positive ↓**	**58.9%**	48.3%	30.3%	17.9%	**0.0%**
O (I/L)	NPV Negative Predictive Value ↗	98.2%	98.3%	98.4%	98.5%	98.5%
P (H/L)	**PFN Probability of False Negative ↓**	**1.8%**	1.7%	1.6%	1.5%	**1.5%**
Antigen Tests						
E	PPA Percent positive agreement ⇨	61.7%	61.7%	61.7%	61.7%	61.7%
F	**PNA Percent negative agreement ↗**	**88.4%**	**93.3%**	**98.3%**	**99.1%**	**100.0%**
G (CxE)	Total Test Results Positive ↓	165,794	121,577	77,360	69,530	61,700
H (C-G)	Total Test Results Negative ↗	834,206	878,423	922,640	930,470	938,300
I (DxF)	Test Result Pos in True Pos Sample ⇨	61,700	61,700	61,700	61,700	61,700
J (D-J)	**False Neg Test** in True Pos Sample ⇨	38,300	38,300	38,300	38,300	38,300
K (G+J)	True Neg Test in Neg Sample ↗	795,906	840,123	884,340	892,170	900,000
L (H + I)	**False Pos Test** in True Neg Sample ↓	104,094	59,877	15,660	7,830	0

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M (G/K)	PPV Positive Predictive Value ↗	37.2%	50.7%	79.8%	88.7%	100.0%
N (J/K)	**PFP Probability of False Positive ↓**	**62.8%**	49.3%	20.2%	11.3%	**0.0%**
O (I/L)	NPV Negative Predictive Value ↗	95.4%	95.6%	95.8%	95.9%	95.9%
P (H/L)	**PFN Probability of False Negative ↓**	**4.6%**	4.4%	4.2%	4.1%	**4.1%**

Antibody Tests

E	PPA Percent positive agreement ⇨	68.4%	68.4%	68.4%	68.4%	68.4%
F	**PNA Percent negative agreement ↗**	**86.0%**	**90.8%**	**95.6%**	**97.8%**	**100.0%**
G (CxE)	Total Test Results Positive ↓	193,999	150,975	107,950	88,195	68,440
H (C-G)	Total Test Results Negative ↗	806,001	849,026	892,050	911,805	931,560
I (DxF)	Test Result Pos in True Pos Sample ⇨	68,440	68,440	68,440	68,440	68,440
J (D-J)	**False Neg Test** in True Pos Sample ⇨	31,560	31,560	31,560	31,560	31,560
K (G+J)	True Neg Test in Neg Sample ↗	774,441	817,466	860,490	880,245	900,000
L (H + I)	**False Pos Test** in True Neg Sample ↓	125,559	82,535	39,510	19,755	0
M (G/K)	PPV Positive Predictive Value ↗	35.3%	45.3%	63.4%	77.6%	100.0%
N (J/K)	**PFP Probability of False Positive ↓**	**64.7%**	54.7%	36.6%	22.4%	**0.0%**
O (I/L)	NPV Negative Predictive Value ↗	96.1%	96.3%	96.5%	96.5%	96.6%
P (H/L)	**PFN Probability of False Negative ↓**	**3.9%**	3.7%	3.5%	3.5%	**3.4%**

Table 7. Molecular tests - costs for patients and clinical care

7a. Impact of changes in prevalence with baseline PPA of 86.1% & PNA of 95.8%

Model Range of Prevalence	**2.0%**	**6.0%**	**10.0%**	**15.0%**	**20.0%**
Number of True Positive Samples	20,000	60,000	100,000	150,000	200,000
Number of True Negative Samples	980,000	940,000	900,000	850,000	800,000
Number of True Positive Tests	17,228	51,684	86,140	129,210	172,280
Number of True Negative Tests	939,232	900,896	862,560	814,640	766,720

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Number of False Positive Tests	40,768	39,104	37,440	35,360	33,280
Number of False Negative Tests	2,772	8,316	13,860	20,790	27,720
Cost of True Positive Tests	$97,252,060	$291,756,180	$486,260,300	$729,390,450	$972,520,600
Cost of True Negative Tests	$187,846,400	$180,179,200	$172,512,000	$162,928,000	$153,344,000
Cost of False Positive Tests	$105,996,800	$101,670,400	$97,344,000	$91,936,000	$86,528,000
Cost of False Negative Tests	$31,295,880	$93,887,640	$156,479,400	$234,719,100	**$312,958,800**
Total cost of false results	$137,292,680	$195,558,040	$253,823,400	$326,655,100	**$399,486,800**
Cost of false results as % true	**48%**	41%	39%	37%	35%

7b. Impact of changes in PPA (sensitivity) with baseline prevalence of 10% & PNA of 95.84%

Model change in PPA	**77.53%**	**81.83%**	**86.14%**	**90.45%**	**94.75%**
Number of True Positive Samples	100,000	100,000	100,000	100,000	100,000
Number of True Negative Samples	900,000	900,000	900,000	900,000	900,000
Number of True Positive Tests	77,526	81,833	86,140	90,447	94,754
Number of True Negative Tests	862,560	862,560	862,560	862,560	862,560
Number of False Positive Tests	37,440	37,440	37,440	37,440	37,440
Number of False Negative Tests	22,474	18,167	13,860	9,553	5,246
Cost of True Positive Tests	$437,634,270	$461,947,285	$486,260,300	$510,573,315	$534,886,330
Cost of True Negative Tests	$172,512,000	$172,512,000	$172,512,000	$172,512,000	$172,512,000
Cost of False Positive Tests	$97,344,000	$97,344,000	$97,344,000	$97,344,000	$97,344,000
Cost of False Negative Tests	**$253,731,460**	$205,105,430	$156,479,400	$107,853,370	$59,227,340
Total cost of false results	**$351,075,460**	$302,449,430	$253,823,400	$205,197,370	$156,571,340
Cost of false results as % true	**58%**	48%	39%	30%	22%

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7c. Impact of changes in PNA (specificity) with baseline prevalence of 10% & PPA of 86.14%

Model change in PNA	**86.26%**	**91.05%**	**95.84%**	**97.92%**	**100.00%**
Number of True Positive Samples	100,000	100,000	100,000	100,000	100,000
Number of True Negative Samples	900,000	900,000	900,000	900,000	900,000
Number of True Positive Tests	86,140	86,140	86,140	86,140	86,140
Number of True Negative Tests	776,304	819,432	862,560	881,280	900,000
Number of False Positive Tests	123,696	80,568	37,440	18,720	0
Number of False Negative Tests	13,860	13,860	13,860	13,860	13,860
Cost of True Positive Tests	$486,260,300	$486,260,300	$486,260,300	$486,260,300	$486,260,300
Cost of True Negative Tests	$155,260,800	$163,886,400	$172,512,000	$176,256,000	$180,000,000
Cost of False Positive Tests	**$321,609,600**	$209,476,800	$97,344,000	$48,672,000	$0
Cost of False Negative Tests	$156,479,400	$156,479,400	$156,479,400	$156,479,400	$156,479,400
Total cost of false results	**$478,089,000**	$365,956,200	$253,823,400	$205,151,400	$156,479,400
Cost of false results as % true	**75%**	56%	39%	31%	23%

Table 8. Antigen tests - costs for patients and clinical care

8a. Impact of changes in prevalence with baseline PPA of 61.70% & PNA of 99.26%

Model Range of Prevalence	**2.0%**	**6.0%**	**10.0%**	**15.0%**	**20.0%**
Number of True Positive Samples	20,000	60,000	100,000	150,000	200,000
Number of True Negative Samples	980,000	940,000	900,000	850,000	800,000
Number of True Positive Tests	12,340	37,020	61,700	92,550	123,400
Number of True Negative Tests	962,948	923,644	884,340	835,210	786,080
Number of False Positive Tests	17,052	16,356	15,660	14,790	13,920
Number of False Negative Tests	7,660	22,980	38,300	57,450	76,600
Cost of True Positive Tests	$69,659,300	$208,977,900	$348,296,500	$522,444,750	$696,593,000
Cost of True Negative Tests	$385,179,200	$369,457,600	$353,736,000	$334,084,000	$314,432,000
Cost of False Positive Tests	$44,335,200	$42,525,600	$40,716,000	$38,454,000	$36,192,000

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Cost of False Negative Tests	$3,064,000	$9,192,000	$15,320,000	$22,980,000	$30,640,000
Total cost of false results	$47,399,200	$51,717,600	$56,036,000	$61,434,000	$66,832,000
Cost of false results as % true	**10.4%**	**8.9%**	**8.0%**	**7.2%**	**6.6%**

8b. Impact of changes in PPA (sensitivity) with baseline prevalence of 10% & PNA of 98.26%

Model change in PPA	**55.53%**	**58.62%**	**61.70%**	**64.79%**	**67.87%**
Number of True Positive Samples	100,000	100,000	100,000	100,000	100,000
Number of True Negative Samples	900,000	900,000	900,000	900,000	900,000
Number of True Positive Tests	55,530	58,615	61,700	64,785	67,870
Number of True Negative Tests	884,340	884,340	884,340	884,340	884,340
Number of False Positive Tests	15,660	15,660	15,660	15,660	15,660
Number of False Negative Tests	44,470	41,385	38,300	35,215	32,130
Cost of True Positive Tests	$313,466,850	$330,881,675	$348,296,500	$365,711,325	$383,126,150
Cost of True Negative Tests	$353,736,000	$353,736,000	$353,736,000	$353,736,000	$353,736,000
Cost of False Positive Tests	$40,716,000	$40,716,000	$40,716,000	$40,716,000	$40,716,000
Cost of False Negative Tests	$17,788,000	$16,554,000	$15,320,000	$14,086,000	$12,852,000
Total cost of false results	$58,504,000	$57,270,000	$56,036,000	$54,802,000	$53,568,000
Cost of false results as % true	**8.8%**	**8.4%**	**8.0%**	**7.6%**	**7.3%**

8c. Impact of changes in PNA (specificity) with baseline prevalence of 10% & PPA of 61.70%

Model change in PNA	**88.43%**	**93.35%**	**98.26%**	**99.13%**	**100.00%**
Number of True Positive Samples	100,000	100,000	100,000	100,000	100,000
Number of True Negative Samples	900,000	900,000	900,000	900,000	900,000
Number of True Positive Tests	61,700	61,700	61,700	61,700	61,700
Number of True Negative Tests	795,906	840,123	884,340	892,170	900,000
Number of False Positive Tests	104,094	59,877	15,660	7,830	0

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Number of False Negative Tests	38,300	38,300	38,300	38,300	38,300
Cost of True Positive Tests	$348,296,500	$348,296,500	$348,296,500	$348,296,500	$348,296,500
Cost of True Negative Tests	$318,362,400	$336,049,200	$353,736,000	$356,868,000	$360,000,000
Cost of False Positive Tests	$270,644,400	$155,680,200	$40,716,000	$20,358,000	$0
Cost of False Negative Tests	$15,320,000	$15,320,000	$15,320,000	$15,320,000	$15,320,000
Total cost of false results	$285,964,400	$171,000,200	$56,036,000	$35,678,000	$15,320,000
Cost of false results as % true	**42.9%**	**25.0%**	**8.0%**	**5.1%**	**2.2%**

Table 9. Antibody tests - costs for patients and clinical care

9a. Impact of changes in prevalence with baseline PPA of 61.70% & PNA of 98.26%

Model Range of Prevalence	**2.00%**	**6.00%**	**10.00%**	**15.00%**	**20.00%**
True Positive Samples	20,000	60,000	100,000	150,000	200,000
True Negative Samples	980,000	940,000	900,000	850,000	800,000
True Positive Tests	13,688	41,064	68,440	102,660	136,880
True Negative Tests	936,880	898,640	860,400	812,600	764,800
False Positive Tests	43,120	41,360	39,600	37,400	35,200
False Negative Tests	6,312	18,936	31,560	47,340	63,120
Cost of True Positive Tests	$17,110,000	$51,330,000	$85,550,000	$128,325,000	$171,100,000
Cost of True Negative Tests	$1,499,008,000	$1,437,824,000	$1,376,640,000	$1,300,160,000	$1,223,680,000
Cost of False Positive Tests	$22,500,016	$32,916,356	$42,368,040	$50,263,730	$56,953,600
Cost of False Negative Tests	$10,099,200	$30,297,600	$50,496,000	$75,744,000	$100,992,000
Total cost of false results	$32,599,216	$51,879,248	$71,159,280	$95,259,320	$119,359,360
Cost of false results as % true	2.2%	3.5%	4.9%	6.7%	8.6%

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9b. Impact of changes in PPA (sensitivity) with baseline prevalence of 10% & PNA of 98.26%

Model change in PPA	**55.53%**	**58.62%**	**61.70%**	**64.79%**	**67.87%**
Number of True Positive Samples	100,000	100,000	100,000	100,000	100,000
Number of True Negative Samples	900,000	900,000	900,000	900,000	900,000
Number of True Positive Tests	61,596	65,018	68,440	71,862	75,284
Number of True Negative Tests	860,400	860,400	860,400	860,400	860,400
Number of False Positive Tests	39,600	39,600	39,600	39,600	39,600
Number of False Negative Tests	38,404	34,982	31,560	28,138	24,716
Cost of True Positive Tests	$76,995,000	$81,272,500	$85,550,000	$89,827,500	$94,105,000
Cost of True Negative Tests	$1,376,640,000	$1,376,640,000	$1,376,640,000	$1,376,640,000	$1,376,640,000
Cost of False Positive Tests	$20,663,280	$20,663,280	$20,663,280	$20,663,280	$20,663,280
Cost of False Negative Tests	$61,446,400	$55,971,200	$50,496,000	$45,020,800	$39,545,600
Total cost of false results	$82,109,680	$76,634,480	$71,159,280	$65,684,080	$60,208,880
Cost of false results as % true	5.6%	5.3%	4.9%	4.5%	4.1%

9c. Impact of changes in PNA (specificity) with baseline prevalence of 10% & PPA of 61.70%

Model change in PNA	**88.43%**	**93.35%**	**98.26%**	**99.13%**	**100.00%**
Number of True Positive Samples	100,000	100,000	100,000	100,000	100,000
Number of True Negative Samples	900,000	900,000	900,000	900,000	900,000
Number of True Positive Tests	68,440	68,440	68,440	68,440	68,440
Number of True Negative Tests	774,360	817,380	860,400	880,200	900,000
Number of False Positive Tests	125,640	82,620	39,600	19,800	0
Number of False Negative Tests	31,560	31,560	31,560	31,560	31,560
Cost of True Positive Tests	$85,550,000	$85,550,000	$85,550,000	$85,550,000	$85,550,000
Cost of True Negative Tests	$1,238,976,000	$1,307,808,000	$1,376,640,000	$1,408,320,000	$1,440,000,000
Cost of False Positive Tests	$65,558,952	$43,111,116	$20,663,280	$10,331,640	$0

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Cost of False Negative Tests	$50,496,000	$50,496,000	$50,496,000	$50,496,000	$50,496,000
Total cost of false results	$116,054,952	$93,607,116	$71,159,280	$60,827,640	$50,496,000
Cost of false results as % true	8.8%	6.7%	4.9%	4.1%	3.3%

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References

1) Pneumonia of unknown cause — China: disease outbreak news. Geneva: World Health Organization, January 5, 2020 (https://www.who.int/csr/don/05-january-2020-pneumonia-of -unknown-cause-china/en/).[Accessed: 5 Jun 2020]

2) WHO Director General's opening remarks at the media briefing on COVID-19-11 March 2020 https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [Accessed: 5 Jun 2020]

3) Guan WJ, Ni ZY, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med February 2020 DOI: 10.1056/NEJMoa2002032

4) World Health Organization. Novel Coronavirus (2019-nCoV) situation reports. https://www.who.int/emergencies/diseases/ novel-coronavirus-2019/situation reports. [Accessed: 5 Jun 2020].

5) Lippi G, Plebani M. The novel coronavirus (2019-nCoV) outbreak: think the unthinkable and be prepared to face the challenge. Diagnosis (Berl) 2020 Jan 28. doi: 10.1515/dx-2020-0015. [Epub ahead of print].

6) Yong SEF, Anderson DE, Wei WE, et al. Connecting clusters of COVID-19: an epidemiological and serological investigation. Lancet Infect Dis 2020;published online 21 Apr 2020 https://doi.org/10.1016/S1473-3099(20)30273-5

7) Lou B, Li T-D, Zheng S-F et al. Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset. medRxiv [preprint]. 2020 medRXiv 20041707 [Posted 2020 March 27]. https://doi.org/10.1101/2020.03.23.20041707.

8) Haveri A, Smura T, Kuivanen S, et al. Serological and molecular findings during SARS-CoV-2 infection: the first case study in Finland, January to February 2020. Euro Surveill. 2020;25(11):2000266. doi:10.2807/1560-7917.ES.2020.25.11.2000266

9) "Immunity passports" in the context of COVID-19. World Health Organization. 24 Apr 2020. https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19 [Accessed 5 Jun 2020]

10) FDA. EUA Authorized Serology Test Performance. https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance . Content current as of: 05/07/2020

11) UK Medicines & Healthcare products Regulatory Agency. Target Product Profile: antibody tests to help determine if people have recent infection to SARS-CoV-2: Version. Updated May 19, 2020.

https://www.gov.uk/government/publications/how-tests-and-testing-kits-for-coronavirus-covid-19-work/target-product-profile-antibody-tests-to-help-determine-if-people-have-recent-infection-to-sars-cov-2-version-2

12) FIND Foundation for Innovative New Diagnostic, Test performance Dashboard https://finddx.shinyapps.io/COVID19DxData/ [Accessed 5 Jun 2020]

13) Steven Woloshin, M.D., Neeraj Patel, B.A., and Aaron S. Kesselheim, M.D., J.D., M.P.H.. False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications. New England Journal of Medicine. June 5, 2020

14) Kevin Systrom and Thomas Vladeck. Rt Covid-19. https://rt.live/ [Accessed 5 June, 2020)

15) Binny RN, Hendy SC, James A, et al. Effect of Alert Level 4 on effective reproduction number: review of international COVID-19 cases. medRxiv [preprint]. 2020 medRxiv 20086934 [Posted . 2020 May 6] https://doi.org/10.1101/2020.04.30.20086934

16) Bartsch, SM, Ferguson MC, McKinnell JA, et al. The Potential Health Care Costs And Resource Use Associated With COVID-19 In The United States. Bloomberg School of Public Health https://jhu.pure.elsevier.com/en/publications/the-potential-health-care-costs-and-resource-use-associated-with-

17) Johns Hopkins University, A National Plan to Enable Comprehensive COVID-19 Case Finding and Contact Tracing in the US https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2020/200410-national-plan-to-contact-tracing.pdf

18) Johns Hopkins University of Medicine. Coronavirus Resource Center. https://coronavirus.jhu.edu/map.html [Accessed 5 Jun2020]

19) FDA. Coronavirus (COVID-19) Update. May 9, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapid-detection-virus-causes

20) CDC. Interim Guidelines for COVID-19 Antibody Testing. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html [Accessed 5 Jun2020]

21) ISO/IEC 51. Safety aspects – Guidelines for their inclusion in standards. ISO/IEC Geneva, Switzerland: International Organization for Standardization; 1999.

22) Laboratory Quality Control based on Risk Management, Approved Guideline. CLSI Document EP23-A. Wayne PA: Clinical and Laboratory Standards