Methods for COVID-19 calculator

To estimate most accurate numbers to inform the COVID-19 testing and the Testing Wisely calculator, we assembled a group of experts to review the literature and make judgements where literature was limited. We will be updating this regularly. To provide a background and basis for many of the estimates shown in the calculator, we provide the follow summary of information.

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I. Estimating risk for COVID-19 infection

Geographical COVID-19 Risk

We identified geographical risk based upon publicly available data. We estimated the 7 day cumulative disease prevalence using reported numbers of positive tests for COVID-19 in the past week per county, divided by the total population for each county. This was performed for US states and counties. We used data compiled by usafacts.org,[1] using their "confirmed" field from the daily report file, aggregating new cases daily over the past 7 day period.

Given evidence of substantially higher true rates of COVID-19 beyond those identified by positive tests,[2–5] we created the ability to multiply geographical rates by 2, 5 or 10-times, consistent with data from the CDC.[5]

To allow use of geographical risk for areas outside the US, we created a box for which data could be entered directly.

Risk of COVID-19 from specific exposures

We sought to identify the quantifiable risk of COVID-19 associated with specific activities based upon the scientific literature. This literature consisted primarily of contact and outbreak investigations.

Estimates provided were approximate numbers that were judged to best represent data from the scientific literature. These are average risks for patients. When risk was different based on exposure to a symptomatic vs. asymptomatic person, this was represented.

Risk related to contact with a person known to have COVID-19 was represented as an absolute risk that could be additive with other exposures. This risk was not expected to change based upon rates of COVID-19 in a geographical area. Whereas, risk related to specific activities, such as indoor dining, are expressed in terms of Odds Ratio that amplifies underlying risk based upon rates of COVID-19 in a geographical region.

Exposure To A Known COVID-19 Patient:

Household Contacts[6–14]

Spouses: **40%** symptomatic / **8%** asymptomatic

Other family members: **18%** symptomatic / **4%** asymptomatic

Close non-household contact[6,7,10,13,15]

5% symptomatic / **1%** asymptomatic

Other Shared Spaces—no adjustment for symptomatic or not

1% office, healthcare, and other close contact settings[10,13,16–18]

0.1% public transit[10]

General Risky Activities (without known COVID-19 exposure):[17,19]

Indoor dining, bar, coffee shop. Increase in odds of exposure by an **OR=3**[8,13,20]

Evaluating Risk By Patient Factors Including Symptoms

There was limited information quantifying the impact of different symptoms on the chance of a person having COVID-19 or other patient level factors for increasing probability of disease. The most useful manuscript was by Menni et al.[21] Patient level factors were expressed in terms of odds ratios. These odds ratios multiplied the odds of COVID-19, which has variable impacts on risk expressed in terms of probability of disease.

Process and Equations for conversion between Risk and Odds Ratios[22,23]

For interpreting the meaning of symptoms, we incorporated data expressed as odds ratio (this was also the case for Risky Exposures, e.g. dining at a restaurant). The odds ratio is the factor by which the exposure increases the odds of disease, in this case, COVID-19. To determine the risk among those who experience an exposure, the process required starting with risk, which is commonly reported, and converting that number to odds. The odds ratio was then used to multiply the odds, and that odds was then converted back to risk at the end.

Step 1: Convert Pretest Probability Into Pretest Odds

To convert probability (P) to odds (O), the equation is: **O = (P) / (1 - P)**

Pretestodds = pretestprob / (1 - prepretestprob)

Step 2: Multiply Pretest Odds By Modifying Factors[21]

The pretest odds were multiplied by the following odds ratios due to different symptoms, and risk factors.

Loss of smell or taste OR 5.75

Cough OR 1.36

Fatigue OR 1.63

Loss of appetite/Skipped meals OR 1.48

Step 3: Convert Posttest Odds Back Into Probability

In order to have an easily interpreted output, we will convert the posttest odds back into posttest probability.

The equation we will use here is: **P = (O) / (1 + O)**

Posttestprob= posttestodds / (1 + postestodds)

II. Estimating the impact of vaccination

The estimated impact of vaccination was calculated for prevention of infection as well as preventing contagiousness.

Although individual variation has been reported for different vaccines using different methods, we estimated the consensus impact of vaccination was 95% reduction in infection.[24–26]
Vaccines were estimated to reduce contagiousness by 85%.[27–29]

III. Sensitivity and specificity of diagnostic tests for COVID-19 infection

We reviewed the literature to identify the clinical sensitivity and clinical specificity of COVID-19 tests. Clinical sensitivity is the proportion of patients *with* the disease in question who have a *positive* test.[30,31] Clinical specificity is the proportion of patients *without* disease who have a *negative* test. Patients who have recovered from COVID-19 yet have a positive test are considered clinical false-positives by this clinical definition. They do not have infection yet have a positive test. Clinical sensitivity and specificity are distinguished from analytic sensitivity and specificity or other measures. Analytic sensitivity is a laboratory metric comparing one test to another, using limit of detection. As described by Woloshin et al,[30] clinical sensitivity and specificity for COVID-19 diagnostic tests have not been rigorously studied. The evaluation of COVID-19 diagnostic tests is limited, in part, by absence of an independent gold standard. However, a number of studies exist estimating clinical sensitivity and specificity in relation to infection have informed clinical practice recommendations. We prioritized studies with clinical specimens over isolated laboratory experiments that determine analytic sensitivity often with artificially "spiked" samples. The numbers provided are primarily for nasopharyngeal or nasal samples. This review is consistent with IDSA guidelines **(Table 1)**.[32]

Standard laboratory-based PCR tests: we identified articles that best described the current tests performed in US laboratories including commercial platforms. We sought optimal sensitivity on the best day of sampling relative to onset of symptoms[33]. Across multiple studies, a best estimate clinical sensitivity provided that sampling is performed at the optimal time relative to symptom onset of 90% was identified.[9,34–39] The sensitivity of PCR and likely other tests is known to vary in relation to course of disease, as described below.

Reasons for negative tests when disease is present, or clinical false-negatives include poor specimen handling, inadequate sampling and lack of virus in sampling site (nasal, nasopharyngeal etc.). Earlier studies reporting lower clinical sensitivity had atypical gold standard for cases or did not report optimal sampling in relationship to symptom onset.[40–42]

Clinical specificity had not been studied for COVID-19 PCR but a number of authors suggested specificity between 95%-99.5%[33,43–47] Past evaluation of PCR vs. culture and serology for another respiratory virus, influenza identified specificity as low as 84% vs. culture or serology positive cases.[48]

Reasons for positive results without disease being present (clinical false-positives) include past infection with residual RNA, errors in instrument reading of Ct/Cq values, lack of laboratory optimization normally required by the FDA and contamination.[45–47] These numbers are dependent on recent COVID-19 activity in an area. For example, in the weeks after a surge in cases, the number of

positives that occur related to past infection will increase, and the clinical specificity may be lower than 95%. False-positives are clearly present but more difficult to identify on an individual patient level for PCR given PCR is often considered the Gold Standard. The best estimate of clinical specificity was 99% but could vary from 95% to 99.5% depending on factors that lead to false-positives including recent outbreaks and method of specimen handling, sampling and testing.

Identifying clinical sensitivity and clinical specificity for rapid NAAT COVID-19 tests was performed in a similar fashion. Given most studies were laboratory based, comparing these assays to PCR as a gold standard, we corrected sensitivity and specificity to be in relation to PCR performance characteristics.

Rapid NAAT tests: There was limited information published on these tests. Sensitivity of rapid NAAT tests were compared to standard laboratory-based PCR assays.[49–51] The Abbott ID Now was the only rapid test that differed from standard PCR as it uses different technology and appears to have lower sensitivity (50%-70%).[52,53] We estimated Abbott ID Now sensitivity at 60% compared to PCR, overall clinical sensitivity 54%. Rapid IDNow NAAT tests vs. PCR 98.5%.[50,51]

Antigen tests: There was limited information published on these tests.[49,54] Sensitivity of antigen tests were primarily compared to PCR. Antigen tests vs. PCR positive identified 50% of cases.[49,55,56] There were minimal reports on specificity.[49,55,56] Isolated reports of false positives have been reported.[57] False positive antigen tests have been reported to Public Health authorities.[58,59]
Bacterial antigen tests have been used in infectious disease diagnostics for decades with limited sensitivity and specificity. Reported bacterial antigen sensitivities and specificities range from 29%-70% and 87%-99.4%, respectively depending on specimen type and bacterial target.[60,61] Influenza and RSV antigen tests had similar performance numbers.

An initial large review indicated 50% sensitivity and 98% specificity of COVID-19 antigen tests vs. PCR.[44] The primary commercialy available antigen tests in the US (Binax Now and BD Veritor) appear to have better performance. The Abbott Binax Now Antigen test has been compared with PCR in multiple studies. The sensitivity appears to be approximately 70% and specificity approximately 99.8% compared to PCR.[62–64] After adjusting for clinical sensitivity and specificity of PCR we estimate the most commonly used antigen tests have a clinical sensitivity of 63% and a clinical specificity of 98% to detect COVID-19 infection.

Table 1. Diagnostic tests for **COVID-19 infection**

Test	Clinical sensitivity	Clinical specificity
Standard Laboratory based PCR	90%	99% (95-99.5%)
Rapid NAAT: Abbott ID Now	54%	98.5%
Antigen tests	63%	98%

Adjusting test sensitivity for day a sample was collected

The literature contains multiple reports that sensitivity of tests varies based on when a test is collected in relation to patient symptoms. The period when a test is most sensitive is in the days prior to and week following development of symptoms.

We used adjustments to test sensitivity from Kucirka et al. to allow for adjustment to test sensitivity **(Table 2)**. We assumed that sensitivity adjustments for rapid NAAT and antigen tests would be similar to PCR tests. Given updated literature suggests a higher sensitivity for PCR (90%) than that reported maximally by Kurcika et al (80%) we used their calculations for a relative adjustment.

We also note that the numbers below are in relation to day of onset of symptoms. Kurcika used date of exposure as their starting point given they summarized data from early in the pandemic. Although they reported day 5 as the average day for onset of symptoms, it should be noted that approximately half of patients were not symptomatic at this point. Those patients would be expected to have greater shedding after day 5. In effect, there is a rolling average of sensitivities that includes those with early symptoms and late symptoms. Given knowledge that patients appear to be most infectious, and correspondingly most likely to be PCR positive for COVID-19 in days immediately before and after onset of symptoms, we chose day 7 as the best estimate for adjusting sensitivity of a test. Adjustment for day of symptoms will be multiplied by maximum sensitivity of an assay. For example a PCR test done on day 2 would have a sensitivity of 90%, a PCR on day -2 of symptoms would be 69.75%.

Day 1—first day a patient experiences any symptoms

Day 2—day after symptoms

Day 3—3 days since symptom onset

Day -1—day before symptoms

Day -2—2 days before symptoms

Table 2. Method for adjusting test sensitivity by day[33]

Day of symptoms	Day after exposure (Kurcika)	Adjustment (to maximal sensitivity identified, e.g. 90% PCR)	Sensitivity (Kurcika)
-6	1	0	0
-5	2	0	0
-4	3	6.25%	5%
-3	4	41.25	33%
-2	5	77.5%	62%
-1	6	93.75%	75%
0	7	97.5%	78%
1	8	1	80%
2	9	98.75	79%
3	10	95%	76%
4	11	92.5%	74%
5	12	87.5%	70%
6	13	81.25	65%
7	14	77.5%	62%
8	15	71.25%	57%
9	16	65%	52%
10	17	60%	48%
11	18	57.5%	46%
12	19	52.5%	42%
13	20	47.5%	38%
14	21	42.5%	34%

IV. Identifying contagious COVID-19

We built a predictor of SARS-CoV2 contagiousness into our COVID-19 calculator. Contagious COVID-19 may be different from COVID-19 infection given that a person may be contagious prior to symptom onset but usually not longer than 10 days after first positive test. COVID-19 infection is defined solely by the presence of a COVID-like syndrome and/or a positive COVID-19 diagnostic test which may remain positive long after a patient is infectious.The goal of this project was to estimate the probability of an individual being contagious for SARS-CoV2. We defined contagious as the probability of a person being capable of infecting another person. COVID-19 contagious was determined starting with the COVID-19 infection calculation, modified by what is known from studies of live virus.

We reviewed studies that used viral culture to examine risk for being contagious.[65–77] We used data on live virus for risk of individuals using available data.[69,70] Live virus was chosen as the best single patient-level marker for being contagious. We recognize that culture is not a perfect surrogate for being contagious given that culture maybe positive even when inoculum is too small to cause infection, and, conversely, failure to culture may be due to insensitivity of culture for viable virus. Thus a patient with a low viral load but positive culture may not actually be infectious and conversely, a patient could be contagious even if virus wasn't cultivable. Furthermore, SARS-CoV-2 viral culture methods are not standardized, and there is likely to be substantial interlaboratory variability in results. Nonethless,

studies using viral culture are the best information available regarding contagious COVID-19 and have guided CDC and WHO policy regarding transmission based precautions and time periods for isolation.[73,78,79]

Using these studies, we estimated a timeline of contagiousness versus COVID-19 infection, using the probability of a positive cell culture by date of symptom onset to modify the likelihood of Covid-19 infection,. First, we identified the day at which a positive PCR test has the highest chance of also having a positive viral culture, This was day 3 of symptoms, when 80% of patients who have COVID-19 will have detectable live virus.[10,15,18,65–67,69,70,74,80] All initial assessments of COVID-19 infectiousness based on COVID-19 disease started with this adjustment. We expanded this timeline by proportion of cases with a positive viral culture by days from symptom onset (**Table 3**). Our analysis aligns with CDC and WHO guidance, with the daily proportion of infections defined by a curve with increasing proportions infectiousness until day 3, followed by declining proportion of infectious cases until day 10, at which point contagiousness becomes highly unlikely (for non-critically ill patients).[7,13,15,65,67,69–72,81]

We calculated chance of COVID-19 infection using geographical, exposure, and patient risk factors. We then added viral culture data to adjust prior estimates of disease to express the chance that a patient was contagious for COVID-19. The estimate was then multiplied by 0.8 to estimate maximal chance of contagiousness that was present on day 3 of symptoms as described above.

Then, we accounted for change in contagiousness over time by applying the impact of the number of days since onset of COVID-19 symptoms. Contagiousness increases to day 3 and decreases to day 10. Adjustments to chance of being infectious are described in this table. These numbers were identified from studies culturing live virus in relation to day of symptoms. The numbers are all adjusted for the 80% maximum infectiousness present on day 3.

Table 3. Estimate of being **COVID-19 contagious** by day

Days from onset of symptoms to current day	Adjustment in probability of being contagious
0	0.875
1	0.875
2	0.875
3	1
4	0.875
5	0.5
6	0.5
7	0.375
8	0.375
9	0.125
10	0.125
11 days or greater	0

Sensitivity and Specificity of diagnostic tests for contagious COVID-19

This probability of a patient with COVID-19 being contagious can be informed by testing. Beyond diagnosing COVID-19 disease, the sensitivity and specificity of SARS-CoV2 tests can be evaluated for their ability to identify people who are contagious. Using viable virus in a patient with a COVID-19 syndrome as a gold standard,[75,82] we evaluated available information for common tests in regards to contagiousness.

The most commonly compared tests were PCR vs. viral culture. Most studies included only patients who were PCR positive.[65,70,72,73,75] Only culturing PCR positive samples limited the ability to assess sensitivity of PCR for contagious COVID-19, given it was an inclusion criterion for most studies. However, alternate studies of laboratory analytic sensitivity support PCR being highly sensitive for contagious COVID-19.[69–71,81]

Summary statistics for ability of tests to identify contagious COVID-19 are presented in **Table 4** (identify live virus on culture).

Laboratory-based RT-PCR tests: We identified articles that best described the current tests performed in US laboratories including commercial platforms. Although most studies of viral culture were performed only on patients with a PCR+ diagnosis of COVID-19,[65,67,69,70,77] out of all of them, we are not aware of any reports of patients shedding live virus with a negative PCR. Therefore, we estimated a 99% sensitivity for infectious COVID-19 (unlike "COVID-19 infection", for which sensitivity decreases over time, sensitivity of tests for live virus doesn't change, although proportion of patients with live virus will decrease). Studies of live virus were more revealing for specificity.[65–67,69,76,83] We found that, overall, 25-75% of patients who were PCR+ had live virus isolated.[69,70,72,73,75,84] This estimate presents the positive predictive value of a PCR to identify live/infectious virus. To identify the specificity, we worked backwards working with assumptions of pretest probability. Assuming a 5% pretest probability, we calculated a clinical specificity of 90-98%, with 95% being the best estimate.

The PCR test was often positive in the absence of shedding of live virus.[66,83,85] These results likely represent patients who had past infection with COVID-19 but are no longer contagious.[85] The exact rate of positives when not infectious likely varies for different reasons, including rates of COVID-19 in the population over the past weeks and method of specimen handling, sampling and testing.

Rapid NAAT tests: We identified no studies examining the ability of rapid NAAT tests to identify culture positive specimens. Numbers provided are extrapolated from sensitivity and specificity from detection of COVID-19 infection and assumptions around specificity based on Ct values detected.

Antigen tests: There was limited information published on antigen tests identifying patients with live virus. An early study comparing antigen tests to live virus included only 38 patient samples that were PCR+ and tested with viral culture and antigen tests.[76] 28 samples were culture positive, of which 27 were antigen positive suggesting a sensitivity of 96%. Of 10 samples there were culture negative, 2 were antigen +, which would estimate a 80% specificity (8/10 samples). A further study of 32 COVID-19 PCR positive patients had 19 positive cell culture results, of which 16 (84% sensitivity) were detected by an antigen test.[86] Overall, these small studies suggest an average sensitivity of 91% and a specificity of 97% of antigen tests vs. culture.[49,76,86,87] Other studies making assumptions that low Ct values reflect infectiousness reported similar antigen sensitivities for identifying patients with live virus.[88–90] Newer,

larger studies of the Abbott Binax Now found the sensitivity appears to be approximately 92% and specificity approaching 100% although only a small number of samples were tested vs. culture.[62,63] We focused on symptomatic patients as "asymptomatic" patients are often defined by a positive PCR test as a Gold Standard that includes many patients who are not contagious but have residual RNA.

In summary, based on very limited data, antigen tests appear to identify culture positive samples with 92% sensitivity and 98% specificity.[62,63,76] Thus, though they have a lower analytic sensitivity and specificity when compared with PCR tests, antigen tests may serve a useful, rapid role in identifying infectious patients and guiding appropriate isolation and precautions based on assumption that replication-competent virus is contagious virus.

Table 4. Tests for **contagious COVID-19**

Test	Clinical sensitivity	Clinical specificity
Laboratory-based RT-PCR	99%	95%
Rapid NAAT: Abbott ID Now*	90%	98%
Antigen tests*	92%	98%

*very limited data

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