

# A COVID-19 Pretest Probability Calculator

Frederick Hayden Jr. (✉ [frhayden@outlook.com](mailto:frhayden@outlook.com))

DuPage Medical Group

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## Article

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**Frederick Hayden Jr., MMSc, PA-C**

**DuPage Medical Group**

**Frederick Hayden Contact Information:**

**FH.PUBLISH@OUTLOOK.COM**

**ABSTRACT****BACKGROUND:**

COVID-19 presents with a wide variety of symptoms which also vary in severity. Clinical gestalt is required to help distinguish between COVID-19 and other viral illness. As the pandemic heads into the second year, patient compliance with isolation and quarantine precautions is starting to diminish. The COVID-19 Pretest Probability Calculator is proposed to help offer pre-test probability of COVID-19 to assist in medical decision making.

**METHODS:**

Patient's presenting with COVID-19 like illness were grouped to high, intermediate, or low pretest probability risk based on total scores from reported criteria, which was correlated with the resulting SARS-CoV-2 PCR nasal swab. The calculator was applied in both a prospective and retrospective fashion.

**RESULTS:**

A total of 412 patients were recorded, with a total of 132 positive results. Of low-risk patients, only one patient resulted as positive, while 85% or 111 of total positive results being categorized as high-risk. Overall demonstrated sensitivity was 99% with 50% specificity. Individual criteria were analyzed with anosmia and dysgeusia being the most significant. These symptoms demonstrated 92% specificity, and no low-risk patients reported these symptoms.

**CONCLUSION:**

The COVID calculator demonstrates strong rule-out capability for patients who are low risk. Furthermore, 85% of positive patients were high risk which suggests the need for longer isolation or

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retesting especially when an alternative diagnosis cannot be established. If a patient reports anosmia or dysgeusia a higher index of suspicion for COVID-19 should be considered.

## INTRODUCTION

COVID-19 presents with a wide variety of symptoms and severity. In the acute outpatient care setting patients may present with significant life-threatening events, or with mild and inconspicuous symptoms. Common presentation may include constitutional symptoms such as fevers, fatigue, myalgias. There are frequent acute lower and upper respiratory changes which may include cough, shortness of breath, rhinorrhea, nasal congestion, sinus pressure, sore throat. Gastrointestinal involvement may present as appetite loss, nausea, vomiting, abdominal pain, diarrhea. Many other symptoms have been reported including anosmia and dysgeusia. Further complicating the clinical presentation, many of the common symptoms overlap with other common viral illnesses.<sup>1</sup>

Given the complexity of presentation, significant clinician gestalt is needed to distinguish potential COVID-19 cases from other viral illness in the outpatient setting. A crucial factor in bringing the pandemic to an end is successful case identification and isolation. However, as the pandemic draws into the second year, patient compliance with pandemic precautions— such as mask wearing, post-exposure quarantine, and isolation when symptomatic—has started to diminish.<sup>2,3</sup> This makes for accurate diagnosis of potential COVID cases more important, as it is unrealistic to expect isolation compliance with all patients presenting with viral respiratory infections. Access to COVID testing and expanded vaccination has helped alleviate some unwarranted isolation however, there are still clinical cases where COVID-19 tests cannot be reliable in ruling out Sars-Cov-2.<sup>4</sup> The availability of a simplified calculator can help support the provider in times when they may need to isolate a patient based on symptoms; or can confidently allow a patient to continue daily activities. There is much evolving research with clinical COVID calculators, but few of them address pre-test probability. Ones that do, tend to require more complex data input and may not offer much utility for routine use.<sup>5</sup>

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### *The Calculator*

The COVID-19 Pretest Probability Calculator was designed to offer predictive value if presenting COVID-like illness would test positive. The calculator has been designed for acute visits such as emergency room, urgent care, or outpatient sick visits. A similar example to this calculator is the Centor Criteria for potential streptococcal pharyngitis patients.<sup>6</sup>

Criteria for the calculator were devised by the author based on symptoms and exposure history. Criteria were categorized by similar symptoms or anatomical changes. For example: rhinorrhea, sore throat, nasal congestion are all considered upper respiratory changes; while cough, shortness of breath, and chest discomfort are considered lower respiratory changes. A weighted point value was assigned to each criterion based on CDC reported symptom frequency.<sup>1</sup> Additionally if reported exposure was a household contact, additional weight was given. Based on the cumulative number of points, a patient was categorized to a pre-test probability risk: low, intermediate, or high.

**Figure 1. COVID-19 Pretest Probability Calculator**

Criteria	Point Value	Pretest Risk
Close Exposure	2	<b>High</b> 5 or more points
• Household Exposure? Add:	1	
Acute fevers, fatigue, myalgias	2	<b>Intermediate</b> 3-4 Points
Acute lower respiratory symptoms	2	
Acute loss of taste or smell	2	<b>Low</b> 1-2 Points
Acute upper respiratory symptoms	1	
Acute gastrointestinal symptoms	1	

## METHODS

The primary outcome was to identify if pre-test risk correlated well enough with positivity rates to meaningfully apply clinical decision making. For example, deciding if a presenting patient may return to activities, or should they have further isolation. A secondary outcome was to evaluate if specific symptoms or exposures held high enough sensitivity or specificity for clinical decision making as well.

Data was gathered from patient encounters in an urgent-care type setting. Patients that presented with possible COVID-like symptoms were included in the study. Patients that presented for asymptomatic post-exposure testing were excluded due to variability in sensitivity depending on time from exposure, and lack of application to the primary outcome.<sup>7</sup> Patients that were unable to verbalize their subjective answers were excluded whether due to age, language barrier, or cognitive baseline were excluded. Criteria were included if the relevant symptoms were reported regardless of severity, timing, or duration. Exposures were included if they were within 14 days. Household exposures included anyone actively living in same residence.

Data was gathered in both prospective and retrospective application in the following manner:

- Prospective application was performed on all patients which met inclusion criteria from 11/2020 to 01/2021. Criteria were recorded during history taking, and if required, specific criteria were elicited. The patients' age and sex were recorded for demographic purposes. Individual criterion values, total score, and risk category were assigned at the end of the visit. A temporary encrypted identifying marker was placed until the COVID-19 PCR result was recorded. After all the necessary data was recorded, the identifying marker was removed from the data.

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- Retrospective application was also used by reviewing departmental PCR results between 06/20 and 12/20. Two random days per week were selected, then an equal amount of positive and negative results was initially selected from each day in non-specific fashion. Retrospective analysis was performed until a minimum of 100 samples of each risk category were gathered, thus a higher number of high-risk sample size.
  - Individual charts were then reviewed; and if the required criteria were documented in the visit note, and no barriers to subjective data were documented; the demographic data, criteria values, total score and risk category were recorded along with the correlating PCR result.
  - If the chart review did not provide the associated data for all criteria, or a barrier to subjective data was documented; the specific PCR result was disregarded, and a further equivalent result was reviewed for eligibility from the same day.

### *PCR Testing*

The majority of COVID-19 testing was performed using Quidel Lyra Direct SARS-CoV-2 Assays. Dry nasal swabbing was obtained by trained urgent care technicians or trained swab-clinic staff. The assay was approved by the FDA under emergency use authorization (EAU). No peer-reviewed, published data on specificity / sensitivity was available for this specific assay. FDA provided data demonstrates 100% positive and negative percent agreement with controlled spike samples at 5x level of detection (LoD), and 1 false negative at 1x LoD. A comparison study to similar EAU assays was conducted resulting in 96% positive percent agreement (PPA) and 100% negative percent agreement (NPA).<sup>8</sup>

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In the later period of sampled data, the Cepheid Xpert Xpress SARS-CoV-2 assay used in limited case by case basis for rapid results—mostly for patients requiring stat admission testing for other non-COVID-19 problems. It is undetermined if any of this study’s samples include results from this assay. These swabs were obtained via nasopharyngeal samples by the same trained staff. Similarly, there is no peer-reviewed published data; however, FDA EUA documentation reveals the Cepheid assay has 97% PPA and 95% NPA to other EUA samples.<sup>9</sup>

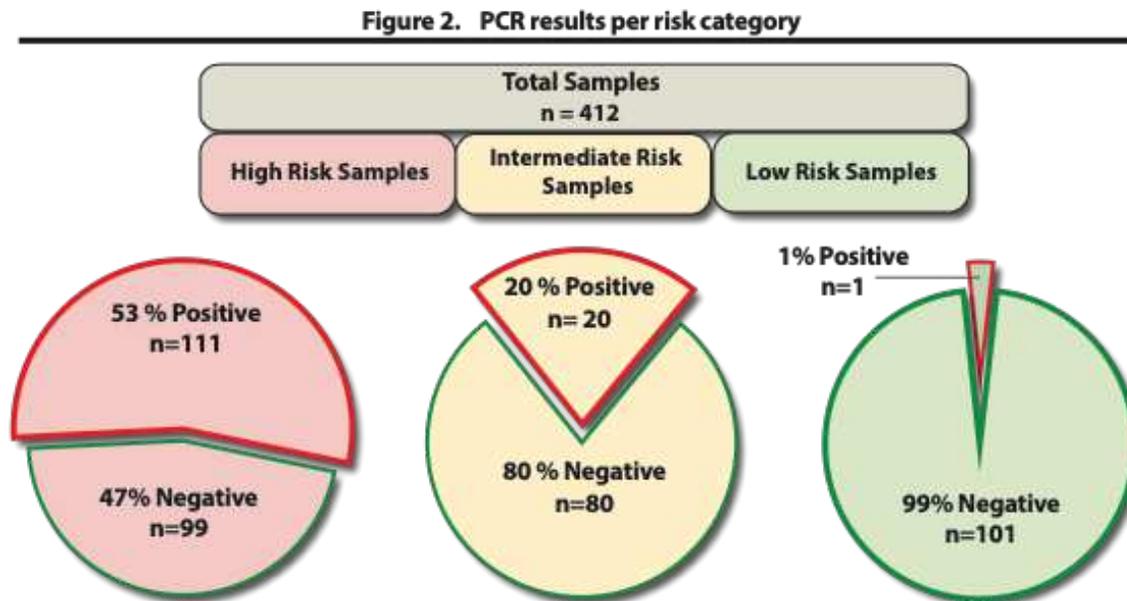
### *Statistical Analysis*

High-risk and low-risk categories were utilized for end-point calculations. The intermediate category was treated as equivocal and not included in end-point statistical analysis. Chi-square testing was used to calculate statistical significance of positive and negative results of each risk category. P value was set to <0.01 for Chi-square testing. The Kolmogorov-Smirnov test of normalcy was applied to the distribution of positive results per point values. Pearson’s Coefficient Correlation testing was applied to the linear correlation of total point values and positivity rate.

Sensitivity and specificity were applied to the overall calculator performance comparing the high-risk category as the true positive (TP) and false positive (FP) values; and the low-risk category for the true negative (TN) and false negative (FN) values. Sensitivity and specificity were also applied to each reported criterion using the high-risk category data.

## **RESULTS**

A total of 412 test results were included and analyzed. There were total of 132 positive results, with an average positivity rate of thirty-three percent overall. The overall calculator sensitivity is 99.1% (95% CI: 95.1%, 99.9%) and overall specificity is 50% (95% CI: 43.4%, 57.6%). Looking at the breakdown of positive results, 84 % were high risk.



*Chi Square  $X^2$  value 93.64, Degrees of Freedom 2,  $p < .00001$*

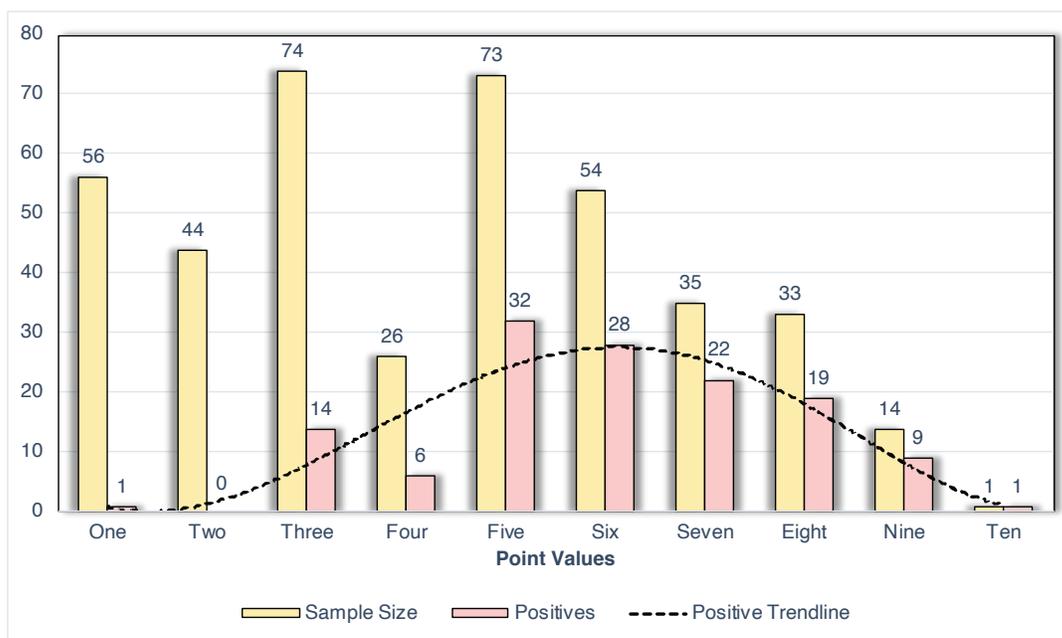
Sensitivities and specificities of reported criteria above were calculated. See *Table 1* at the end of the manuscript for full reported criteria results. For high-risk patients: Acute constitutional symptoms including fevers, body aches, fatigue held a 91% sensitivity, however, were only 8% specific. Acute lower respiratory changes were 88% sensitive, 10 % specific. Acute upper respiratory symptoms were 72% sensitive, 33% specific. Exposures demonstrate 65% sensitivity, 42% specificity, and household exposures were 25% sensitive, 83% specific. Acute anosmia and dysgeusia held lower sensitivity of 28% but was highly specific at 92%.

The number of positive patients per point value began to develop a normal distribution with a mean of 6, standard deviation of 1.75, however was not statistically significant when Kolmogorov-

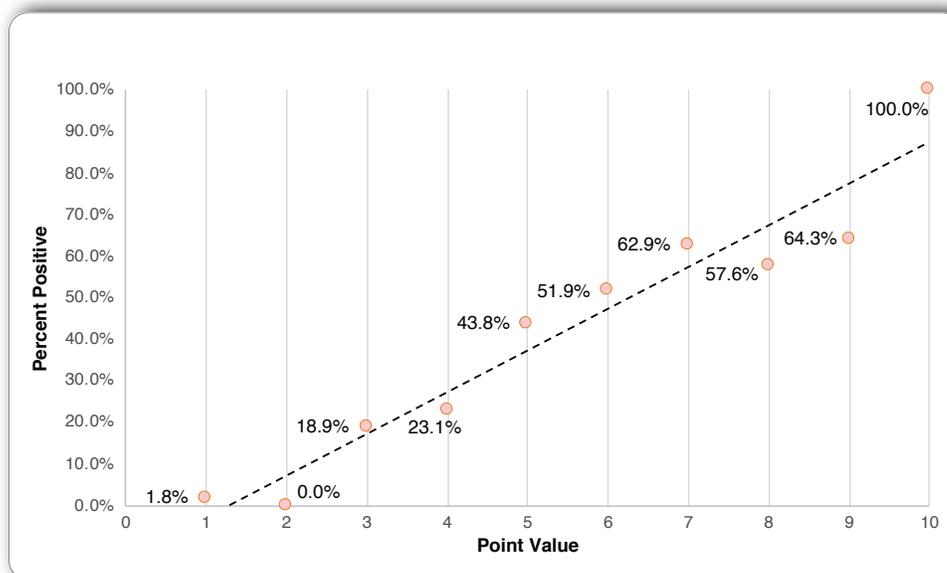
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Smirnov Test of Normality was applied. However, when looking at the positivity rate per point values, a strong positive correlation is demonstrated.

**Figure 3. Number of positives per point values**



**Figure 4. Percent of positive results per point value**



*Pearson's Coefficient Correlation 0.965, p<.0001*

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Demographics of the 412 included patients could be broken down into: Female: 244, Male 168, Age range 5-89 years old, Median age 45.

### **DISCUSSION**

There is a clear pattern demonstrated between risk categories and test results. The calculator shows an overall high sensitivity, 99%. Specificity was lower at 50% overall. However, when looking at specific positive patients, there was a predominant high-risk distribution. These results lead to a number of clinical implications.

Low-risk patients—those with isolated systemic symptoms and without known exposures are unlikely to test positive. In clinical practice, a patient presenting as low-risk is unlikely to be presenting with COVID-19; and could more confidently have shorter isolation pending results. If a low-risk patient tests negative, and their symptoms do not progress they may confidently return to activities without further isolation.

High-risk patients have a significant higher probability of testing positive for COVID-19. If an alternative diagnosis cannot be established such as influenza, bacterial pneumonia, or other detectable viral infections; then a patient should consider full recommended isolation. Or alternatively, longer isolation until a second test can be performed. This should be especially true with household contacts or anosmia and dysgeusia given higher specificities of these criteria.

Further analysis was performed on anosmia and dysgeusia because of their higher specificity. Alternative point value scenarios were applied to anosmia/dysgeusia criteria, to evaluate if pre-test risk would change at higher point values. No low-risk patients reported this criterion, so there were no false negative patients that were identified. However, it was decided to assign this criterion an ultimate point

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value of 2 points (initially 1 point). This would ensure no false low-risk, patients would result in the setting of anosmia / dysgeusia with exposures or other COVID-like illness.

### **LIMITATIONS**

There were a number of limitations recognized with this study. First a relatively small sample size was considered, however, statistical analysis suggests results would be reproducible with larger samples. Selection bias needs to be considered given patients were pre-screened and presented to the urgent-care because of potential COVID-19 concerns. A further limiting factor is the study had a single observer. This may have allowed for observer bias; however retrospective data review was set with empiric design to avoid bias. A final limitation recognized is the variability of PCR sensitivity and lack of “gold-standard” comparison for PCR testing during the period of this study.

### **CONCLUSION**

This COVID-19 Pretest Probability Calculator demonstrates a high sensitivity and may be used to help prevent unwarranted isolation for low-risk patients. Furthermore, given 84% of positive results were ‘high-risk’ it would be recommended to consider longer isolation of high-risk patients or retesting. If a patient reports acute anosmia or dysgeusia, a higher index of suspicion should be appreciated, especially when presenting with other COVID symptoms or known exposure.

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**ACKNOWLEDGEMENTS**

- There are no conflicts of interests or funding to report.
- Data was gathered in compliance to HHS Part 46 – Protection of Human Subjects S46.104 Exempt research: 4- Secondary Research, ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.

**ADDITIONAL TABLES****Table 1. Reported criterion by category and test result**

<b>Risk</b>	<b>Exposure</b>	<b>Household</b>	<b>Const.</b>	<b>LRTI</b>	<b>Smell</b>	<b>GI</b>	<b>URI</b>
<b>Totals</b>	159	50	263	238	44	128	260
<b>High</b>	129	45	192	187	39	88	146
(+)	72	28	101	98	31	44	80
(-)	57	17	91	89	8	44	66
<b>Intermediate</b>	16	5	57	40	5	21	69
(+)	3	1	13	8	3	1	13
(-)	13	4	44	32	2	20	56
<b>Low</b>	14	0	14	11	0	19	45
(+)	0	0	0	0	0	0	1
(-)	14	0	14	11	0	19	44

Const. = Acute Fevers, Fatigue, or Myalgias  
 Smell= Acute loss of taste/smell  
 URI- Acute upper respiratory changes

LRTI= Acute lower respiratory tract symptoms  
 GI= Acute gastrointestinal changes

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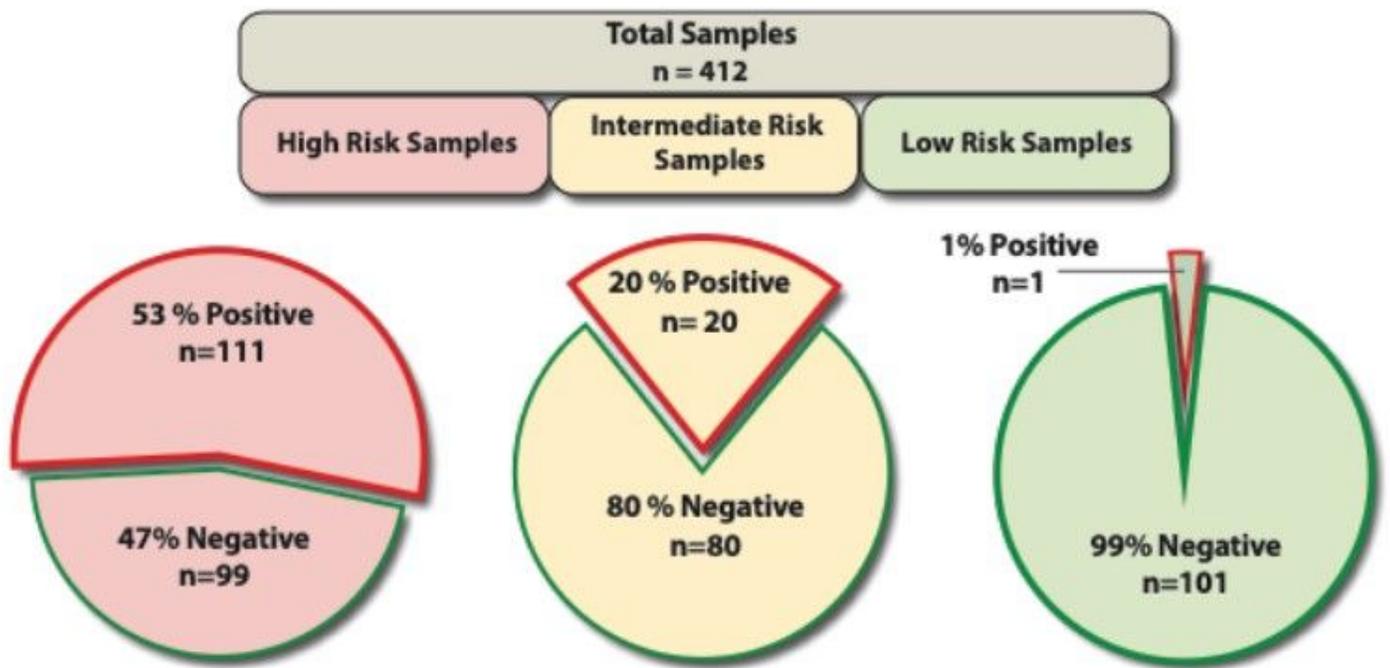
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# Figures

Criteria	Point Value	Pretest Risk
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Figure 1

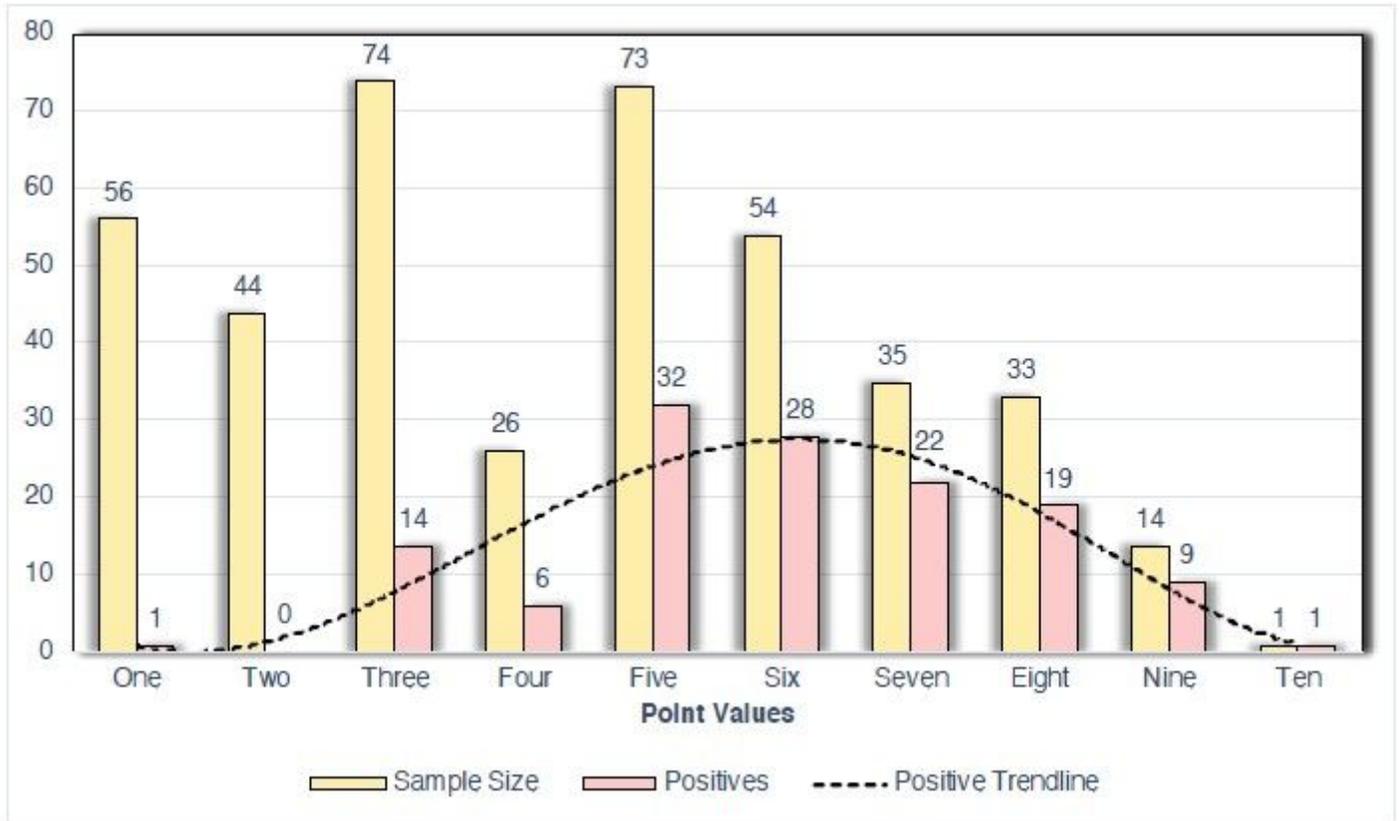
COVID-19 Pretest Probability Calculator



Chi Square  $X^2$  value 93.64, Degrees of Freedom 2,  $p < .00001$

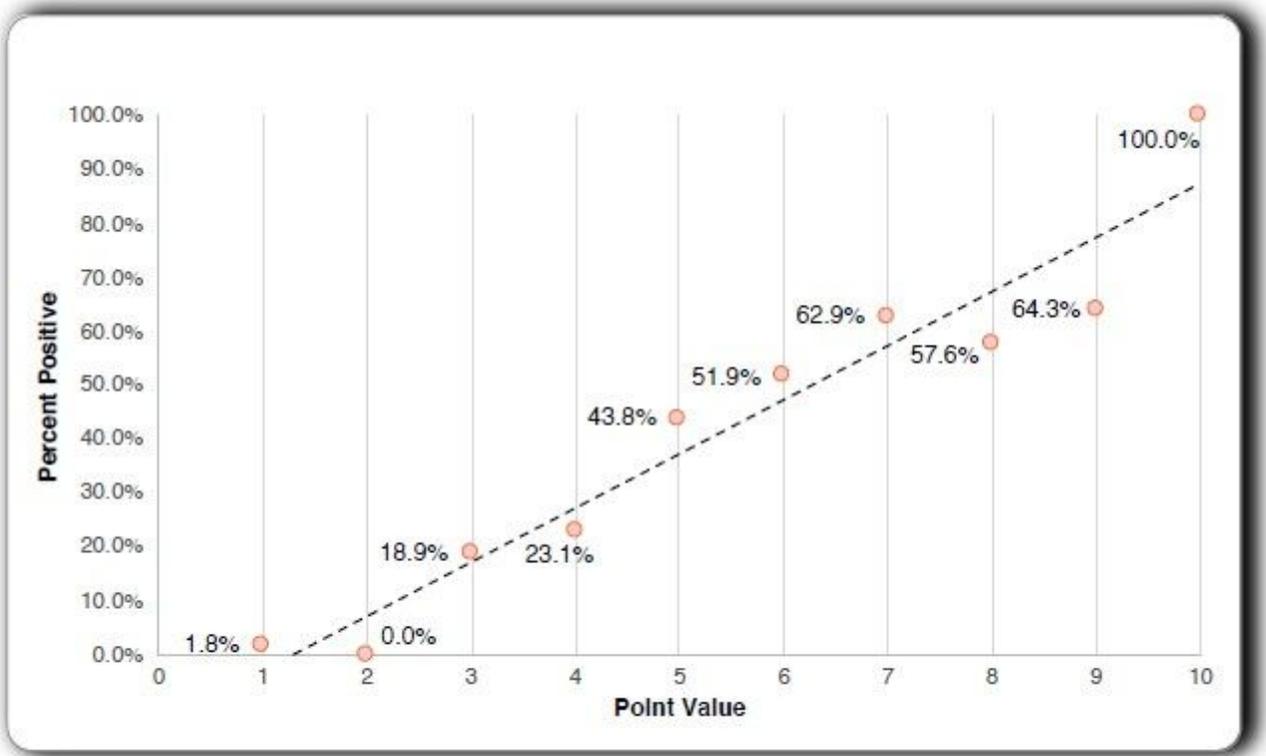
Figure 2

### PCR results per risk category



**Figure 3**

Number of positives per point values



*Pearson's Coefficient Correlation 0.965, p<.0001*

**Figure 4**

Percent of positive results per point value