WHITE PAPER

Limiting Resurgence: How Omnia Battles Omicron and Other New SARS-CoV-2 Variants

Summary

COVID-19 is transitioning to an endemic state where testing for this disease must be simplified to catch outbreaks as soon as possible. Organizations can no longer wait for complicated molecular tests and the length of time it takes to get a result. The endemic state of the virus demands the speed and simplicity of antigen-based point-of-care tests that deliver quick results, but with the high accuracy typically associated with molecular tests.

The Qorvo Biotechnologies SARS-CoV-2 Antigen test has a demonstrated sensitivity of 88% measured directly against Omicron*. Reduction in overall sensitivity of other Antigen tests may be driven by the dominant prevalence of the Omicron variants. When comparing Omicron to Delta, infectious dose has been shown to decrease, resulting in higher Ct (cycle threshold) values in molecular tests. As variation continues to occur, it is critical to have effective, sensitive testing to support our public health initiatives and protect our community. For CLIA waived and POC settings, the Qorvo Biotechnologies Omnia SARS-CoV-2 Antigen test delivers a rapid, cost effective, and simple to use platform with minimal hands-on time and an automated data management capability.

Prevalence

Prevalence can be described in two ways; one is *which* Variant of Concern (VOC) is the leading cause of COVID infection, and the second is the number of new and emerging cases that exist at any given time. If a new strain will not become prevalent in infectious spread, there's limited utility or requirement for a diagnostic test to effectively measure a positive infection of that strain. Omicron, however, is a fast-spreading variant, and BA.5 was the most contagious subvariant in the fall of 2022, causing more than 50% of new cases, but a new Omicron variant (BQ.1) is rising in prevalence, accounting for 37% of new cases as of January 2023 [1]. This means it is more important than ever to effectively capture positive infection before people reach their peak viral load, and arguably their most infectious state. Data from nextstrain.org, shown in **Figure1** [2], clearly reveals that Omicron is dominating the COVID landscape, with cases of Delta or early variants becoming exceedingly rare or nonexistent.

* Based on external clinical study, data not yet reviewed by FDA.

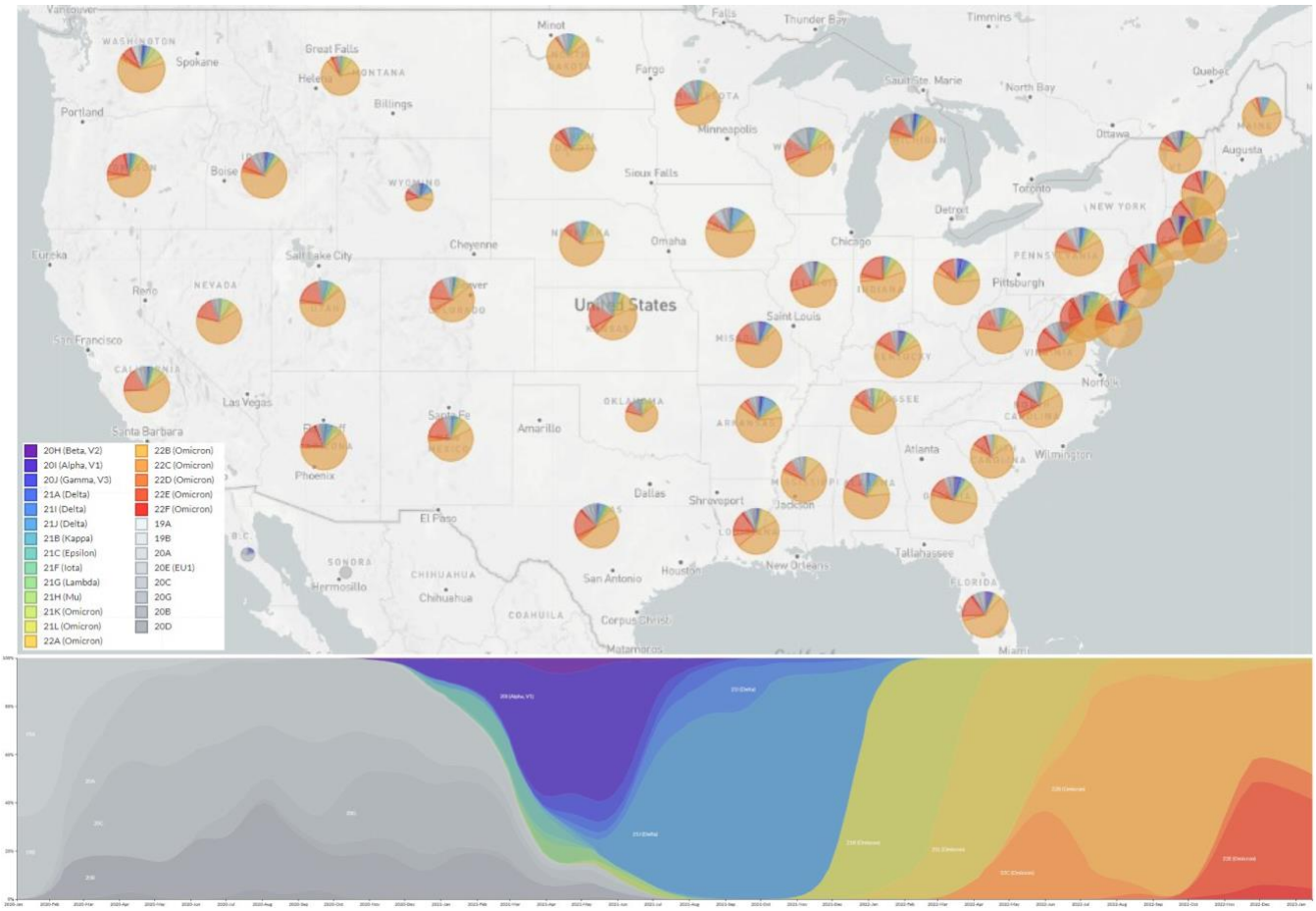

Figure 1: Data from nextstrain.org showing the prevalence of various strains over the past six months by region (top) and the overall prevalence of SARS-CoV-2 variants since the beginning of the pandemic (bottom). These data clearly show Omicron to be the dominant infective strain currently in the United States. Data accessed on 18-Jan-2023 (Source: nextstrain.org)

The second measure is the overall number of actual disease cases in a given population. While the death rate is now less than 1 in 100,000 [3], the number of cases of COVID in the United States remains concerning. On October 11, 2022, over 50,000 new cases were reported, which is the lowest case counts had been since April of this year. As shown in **Figure 2** in January of 2021, cases spiked to almost 250,000 daily new cases, suggesting opportunities for outbreak during typical illness seasons may still be on the horizon.

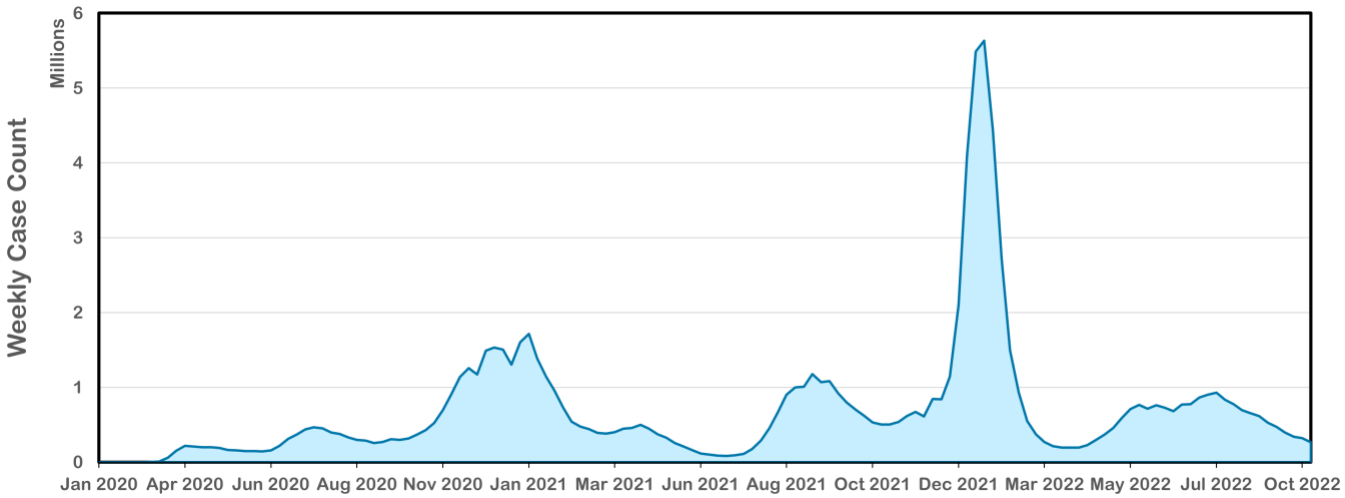

Figure 2: United States COVID weekly case count from January 2020 to October 2023, as reported by the U.S. Department of Health and Human Services via the CDC. (Source: created from data obtained from the CDC [4].)

Further, with the high increase in at-home testing, underreporting has become a critical challenge to estimating real case counts; in one case it is suggested that real cases outweigh reported cases by 7.7:1 [5].

Specificity – True Negative Rate

Due to Qorvo's thorough approach to assay design and development, our team has developed an Antigen assay that is robust against general mutagenicity of the SARS-CoV-2 virus. By carefully selecting our detection core materials, the test is specific to proteins coded by the more conserved region of the viral genome. Our assay specifically targets a region of the Nucleocapsid protein which is conserved in Omicron from original variants (data not shown). By partnering with the NIH and RADx Variant Task Force [6], Qorvo was able to quickly predict effectiveness against mutations present in emerging VOC.

A September 2022 [7] publication addressing the concern of SARS-CoV-2 mutations on detection performance of commercially available (EUA) rapid antigen tests, clearly showed that the Qorvo Omnia test performance was unaffected by mutations in the variants since the original Wuhan-Hu-1 strain (**Figure 3**). Frank, et al, further reassures us that their method, which uses escape mutations of the entire protein structure and thus considering both direct epitopic and indirect allosteric effects on binding, also predicts future Omnia performance against all possible mutations of SARS-CoV-2. These mutation escape data and locations support Omnia test robustness with the C524 and C706 antibodies used by Qorvo.

Data from the publication also shows that only 3 of the 11 tests, one of which was Omnia, successfully tested all variants since Wuhan to Omicron (**Figure 4**)**.** Although not the purpose of the experiment, an observation was that some lateral flow assay (LFA)-based tests were seen to exhibit Limits of Detection (LODs) at high viral loads and were unable to detect some of the pooled, inactivated non-clinical samples. The authors speculated that differences in LFAs could also be attributed to ancillary components such as release agents, swabs, etc. and not necessarily to the underlying core LFA technology. Although all tests will require ancillary components and should generally be evaluated as whole.

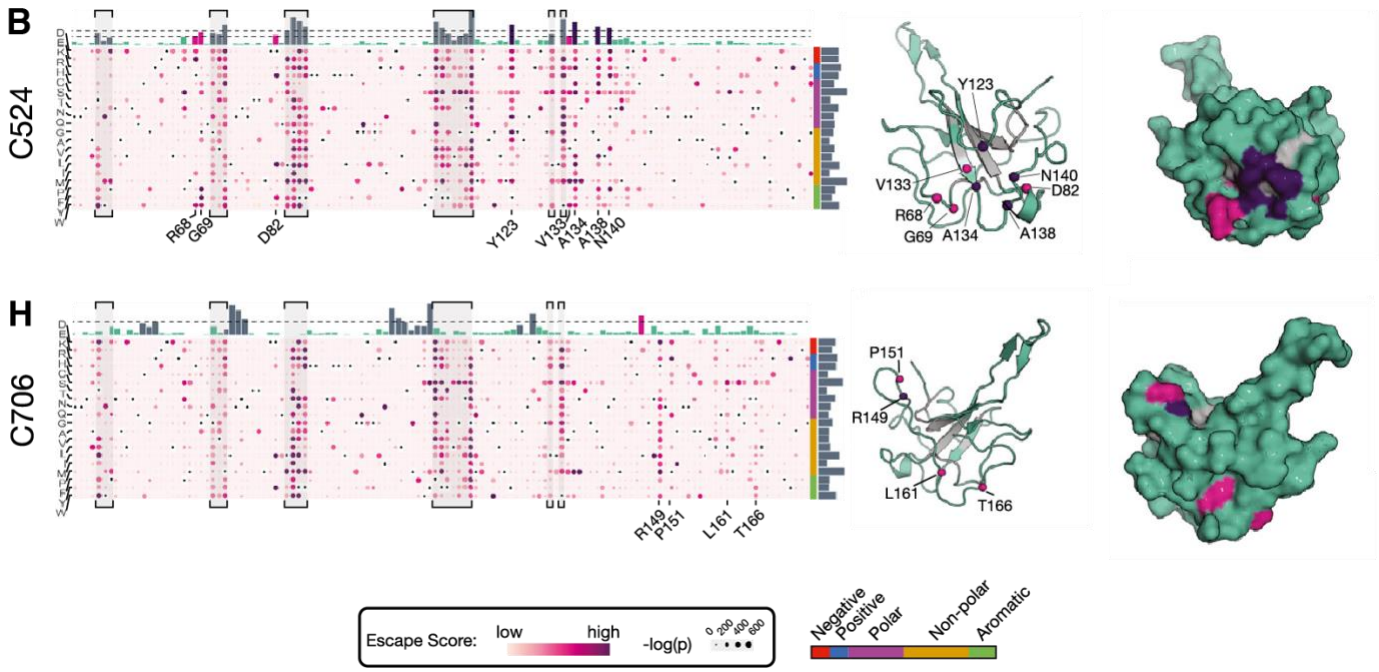

Figure 3: Escape mutations profiles for Qorvo Ab adapted subfigures B and H from figure in [7]. (Source: See reference [7], permission to reuse per CC BY 4.0 license.)

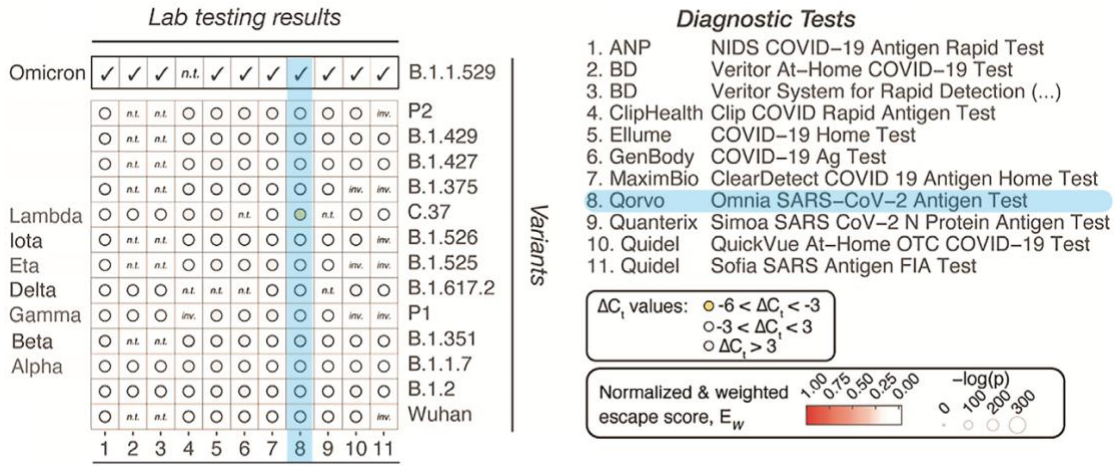

Figure 4: Qorvo detected all variants of SARS-CoV-2 since the Wuhan strain [7]. (Source: See reference [7], permission to reuse per CC BY 4.0 license.)

In a study performed by Qorvo Biotechnologies directly comparing the sensitivity of the Qorvo Biotechnologies Omnia SARS-CoV-2 Antigen test against the Delta and Omicron variants, it was found there was no loss in sensitivity between the variants when evaluating accuracy with the Roche Cobas RT-PCR test as the standard, in that case, both variants showed a Ct@50% detection cut-off of 34.5. This outcome verified the hypothesis that there should not be a significant change in sensitivity based on the escape score profile against the antibodies used in Qorvo's test (**Figure 5**).

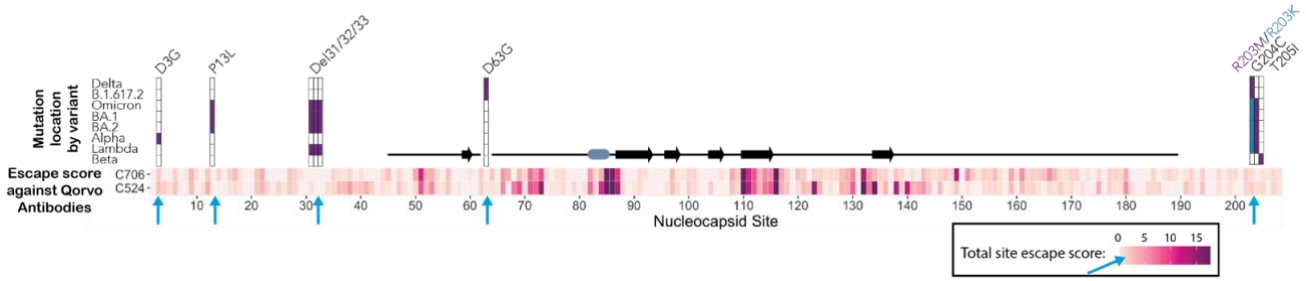

Figure 5: Evaluation of mutations in VOC against the antibodies used in the Qorvo Biotechnologies Omnia SARS-CoV-2 Antigen test [7]. The top portion of the image indicates the region where each VOC deviated from the Wuhan variant while the bottom portion of the image indicates the impact to capture efficiency that mutation had against the Qorvo antibodies. The arrows highlight the escape score at each mutated region, and in all cases the escape score is low, and unlikely to cause changes in sensitivity. NOTE: Graphic prepare for Qorvo by Emory University as part of the RADx task force. (Source: Graphic prepared for Qorvo by Emory University as part of the RADx task force.)

Sensitivity – True Positive Rate

A critical aspect for any test, but especially of the lateral flow type, is the accuracy at which it can detect the infecting virus at its minimum infectious dose. A test that cannot positively identify the virus when a person is infected has limited utility, leading to high false negative rates. Most at-home tests were reasonably effective at detecting the Delta variant and its predecessors, but the Omicron variant shows a marked decrease in the peak viral load, as shown in **Figure 6** [8],[9],[10].

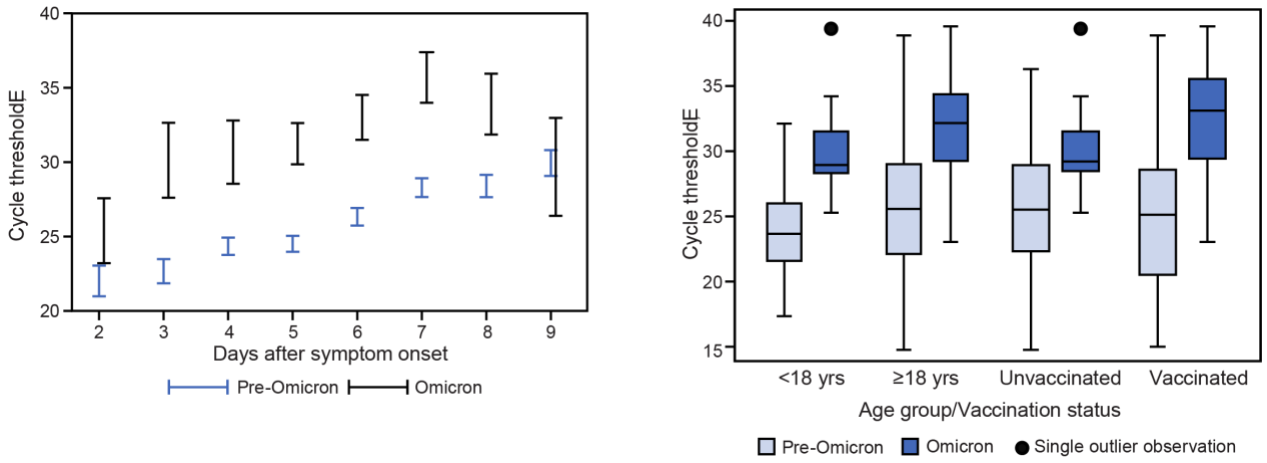

Figure 6: (left) Comparison of cycle threshold for Omicron vs Pre-Omicron Variants. Omicron shows a higher Ct (a lower viral load) throughout most of the days after symptom onset. (right) average Ct values for Omicron and Pre-Omicron variants across multiple populations. For all populations the average Ct is higher for Omicron, indicating a marked decrease in viral load [8]. (Source: CDC.)

As can be seen in **Figure 6**, the average Ct for Omicron variants is generally around 28, while Pre-Omicron variants averaged between 24 and 26. Commonly, publications reviewing the quality of LFA tests compared against a Ct cut off of 25 [11] or both 25 and 28 [12], but as can be seen, those cases would overpredict the effectiveness of those tests against the Omicron Variant(s). With Omicron, “the proportion of infectious people with SARS-CoV-2 missed by [LFAs] is substantial enough to be of clinical importance [13],” and we may need “tests able to detect viral loads 1000 to 10000 times lower than…current performance [13].”

In literature it's common to see sensitivity calculations below Ct thresholds as described, but another measure of sensitivity is to evaluate the 50% detection rate based on a logistic regression of the data compared to a gold standard test. For the Omnia results see **Figure 7** and **Figure 8**.

Detecting Omicron Using the Omnia Antigen Test

In January 2022, Qorvo completed supplemental clinical studies targeted directly at understanding the Omnia Antigen test performance for the Omicron variant (NOTE: this data has not been submitted or reviewed by the FDA). Given the criticality of understanding sensitivity and specificity with new VOC, it follows that it was also essential to understand diagnostic performance of these VOC. A study was designed to look specifically at positive samples confirmed to be the Omicron variant (confirmed by Emory University in partnership with RADx/NIH). For this study we tested against 108 positive PCR samples tested on the Rocha Cobas system (Target 2), 18.5% of which were considered "low-positive" as determined by having Ct values within 3 Ct of the comparator LOD (36.1). The Omnia platform demonstrated an 88% accuracy against the high-sensitivity predicate, and as can be seen in **Figure 7** the highest contributor comes from samples that measure above 33.1 Ct on the Cobas system.

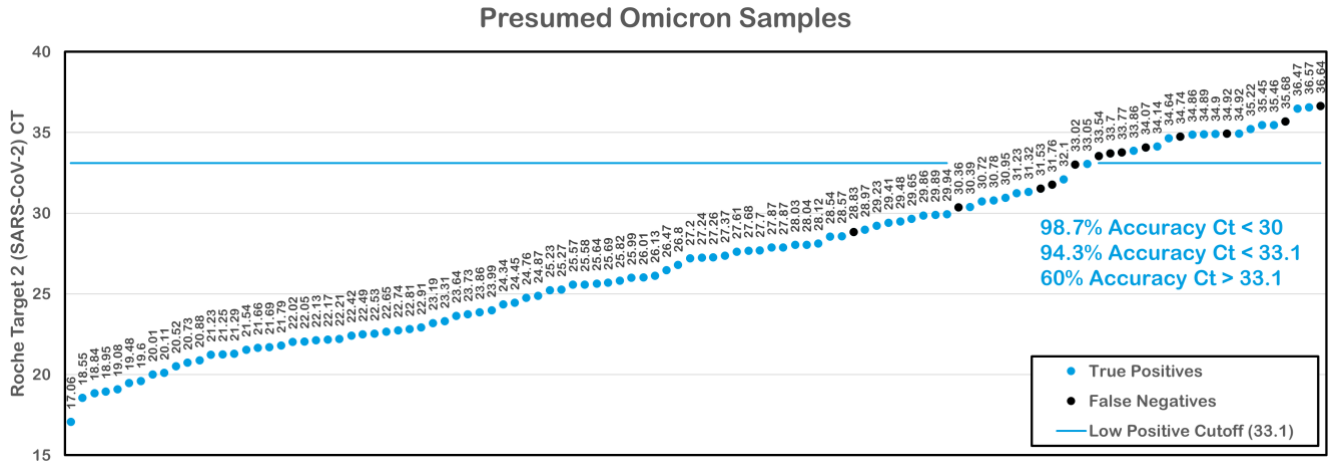

Figure 7: Comparison performance of 102 samples confirmed to be positive Omicron samples on the Roche Cobas system. Qorvo shows an overall accuracy of 88.0%, with 100% at Ct below 28, other accuracy evaluation indicated in the figure. NOTE: This data has not been submitted to, or evaluated by, the FDA. NOTE: One data point was excluded that was negative on Omnia, positive on Roche (Ct=22.51), but negative for pansarbecovirus. (Source: Qorvo US, Inc.)

Zero false positives results were observed in these research studies, consistent with clinical data provided in our POC EUA. Qorvo also evaluated the data based on the number of days post onset of symptoms seeTable 1, showing consistent performance even after 7 days post symptom onset, and specific capability (~96%) for within 2 days – critical window for symptomatic on-site testing.

Days Post Onset	(+) Tests	Total (+) Subjects	Sensitivity	Rolling Sensitivity
0	1	1	100%	100%
1	7	7	100%	100%
2	15	16	93.8%	95.8%
3	10	13	76.9%	89.2%
4	23	24	95.8%	91.8%
5	16	19	84.2%	90.0%
6	16	21	76.2%	87.1%
7	7	7	100.0%	88.0%

Table 1: Day by day and rolling sensitivity of the Omnia SARS-CoV-2 Antigen test. Performance is consistent across the data set, demonstrating the effectiveness of the Qorvo test for various settings. (Source: Qorvo US, Inc.)

Further, a logistics regression to evaluate the sensitivity of the Qorvo test compared with the Roche test (**Figure 8),** where the Ct@50% detection probability was found to be 35.7 (95% CI 33.7-39.8), further suggesting the Omnia SARS-CoV-2 Antigen test is highly effective at detecting the Omicron variant.

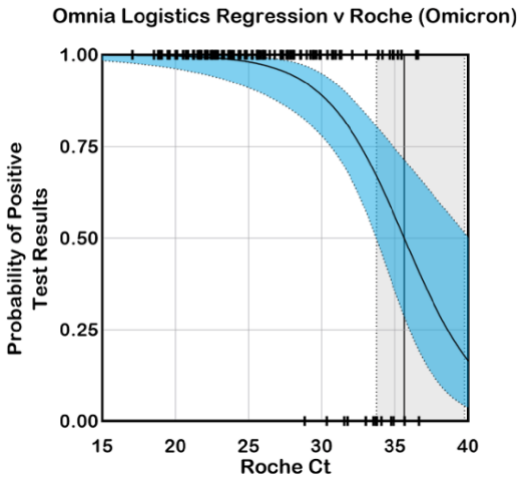

Figure 8: Logistics regression of presumed Omicron samples evaluated against the Roche Cobas RT-PCR test (Target 2). The evaluations shows a predicted 50% Ct cutoff of 35.7, near the LOD value for the predicate itself (36.15). Hash marks at the 100% and 0% probability axes indicate True Positives and False Negatives respectively on the Omnia test. NOTE: One data point was excluded that was negative on Omnia, positive on Roche (Ct=22.51), but negative for pansarbecovirus. (Source: Qorvo US, Inc.)

This effectively positions Qorvo and the Omnia test to be uniquely suited to testing for the Omicron variant, reducing false negatives, and supporting public health initiatives.

Market Effectiveness

With the reductions in sensitivity for At-Home COVID-19 Antigen tests, due to the Omicron variant, an added challenge arises for the effective reduction in spread of the SARS-CoV-2 virus. There are added costs, reduced confidence, and higher likelihood of poor compliance – either with At-Home testing or clinic-based PCR tests (e.g. a person, symptomatic or otherwise may choose not to get tested due to the greater barrier to effective test outcomes). The Qorvo Omnia SARS-CoV-2 tests addresses these concerns by having both a highly sensitive test (as shown throughout this paper) and an easy-to-use workflow (**Figure 9**). This allows for the effective testing in easier to access locations such as a pharmacy, minute-clinic, or other CLIA-waived facility with outcomes in a far reduced time to result (~20 min) compared to lab-based PCR.

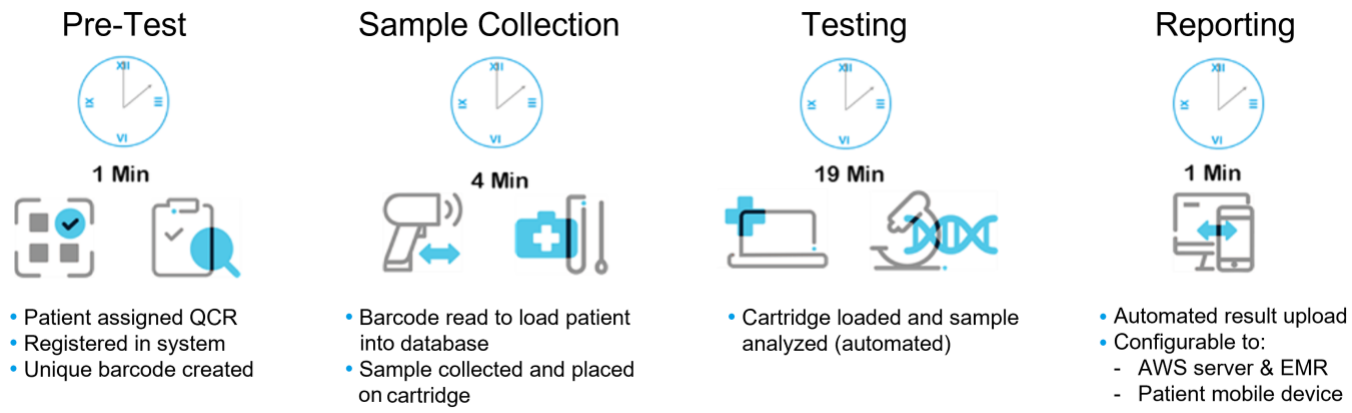

Figure 9: Graphical representation of the Omnia workflow. The device requires no operator interaction during the test, and results are automatically uploaded to relevant data storage locations. (Source: Qorvo US, Inc.)

Conclusion

The solution to challenges as we move into an endemic state for COVID and continue to effect improved health outcomes for current and future diseases lies at the nexus of highly sensitive, highly specific, and easy to use tests. Systems like the Rochas Cobas and other laboratory molecular tests are highly sensitive and specific, but they are neither fast nor accessible by untrained users. We also have easy to use tests in the at-home lateral flows, but as demonstrated, their sensitivity and false negative rate are impacted strongly by prevalence and the infectious dose of new variants. It has become essential to have PCR-likeperformance at the point-of-need without the high-technicality and high-cost associated with a PCR test. For CLIA waived and POC settings, the Qorvo Biotechnologies Omnia SARS-CoV-2 Antigen test demonstrates effective detection of the Omicron variant and delivers that strong performance at a rapid time to result in a cost-effective platform with limited hands-on time and automated data management capabilities.

Not all antigen tests are created equal. Omnia is the ‘go-to’ platform for Omicron testing.

References

[1] "Omicron and BA.5: A Guide to What We Know," Yale Medicine. https://www.yalemedicine.org/news/5-things-to-know-omicron (accessed Oct. 12, 2022).
[2] J. Hadfield et al., "Nextstrain: real-time tracking of pathogen evolution," Bioinformatics, vol. 34, no. 23, pp. 4121–4123, Dec. 2018, doi: 10.1093/bioinformatics/bty407.
[3] T. N. Y. Times, "Coronavirus in the U.S.: Latest Map and Case Count," The New York Times, Mar. 03, 2020. Accessed: Oct. 12, 2022. [Online]. Available: https://www.nytimes.com/interactive/2021/us/covid-cases.html
[4] CDC, "COVID Data Tracker," Centers for Disease Control and Prevention, Mar. 28, 2020. https://covid.cdc.gov/covid-data-tracker (accessed Mar. 08, 2023).
[5] H. Lau, T. Khosrawipour, P. Kocbach, H. Ichii, J. Bania, and V. Khosrawipour, "Evaluating the massive underreporting and undertesting of COVID-19 cases in multiple global epicenters," Pulmonology, vol. 27, no. 2, pp. 110–115, 2021, doi: 10.1016/j.pulmoe.2020.05.015.
[6] R. Creager et al., "RADx Variant Task Force Program for Assessing the Impact of Variants on SARS-CoV-2 Molecular and Antigen Tests.," IEEE Open J. Eng. Med. Biol., vol. 2, pp. 286–290, 2021, doi: 10.1109/OJEMB.2021.3116490.
[7] F. Frank et al., "Deep mutational scanning identifies SARS-CoV-2 Nucleocapsid escape mutations of currently available rapid antigen tests," Cell, vol. 185, no. 19, pp. 3603-3616.e13, Sep. 2022, doi: 10.1016/j.cell.2022.08.010.
[8] M. Tassetto et al., "Detection of Higher Cycle Threshold Values in Culturable SARS-CoV-2 Omicron BA.1 Sublineage Compared with Pre-Omicron Variant Specimens — San Francisco Bay Area, California, July 2021—March 2022," MMWR Morb. Mortal. Wkly. Rep., vol. 71, pp. 1151–1154, 2022, doi: 10.15585/mmwr.mm7136a3.
[9] J. A. Hay et al., "Quantifying the impact of immune history and variant on SARS-CoV-2 viral kinetics and infection rebound: a retrospective cohort study," medRxiv, p. 2022.01.13.22269257, Jan. 2022, doi: 10.1101/2022.01.13.22269257.
[10] A. Soni et al., "Performance of Screening for SARS-CoV-2 using Rapid Antigen Tests to Detect Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infection: findings from the Test Us at Home prospective cohort study," medRxiv, p. 2022.08.05.22278466, Jan. 2022, doi: 10.1101/2022.08.05.22278466.
[11] M. Kahn et al., "Performance of antigen testing for diagnosis of COVID-19: a direct comparison of a lateral flow device to nucleic acid amplification based tests," BMC Infect. Dis., vol. 21, no. 1, p. 798, Aug. 2021, doi: 10.1186/s12879-021-06524-7.
[12] S. Pickering et al., "Comparative performance of SARS-CoV-2 lateral flow antigen tests and association with detection of infectious virus in clinical specimens: a single-centre laboratory evaluation study," Lancet Microbe, vol. 2, no. 9, pp. e461–e471, Sep. 2021, doi: 10.1016/S2666-5247(21)00143-9.
[13] J. J. Deeks et al., "SARS-CoV-2 antigen lateral flow tests for detecting infectious people: linked data analysis," BMJ, vol. 376, p. e066871, Feb. 2022, doi: 10.1136/bmj-2021-066871.