Title: Qorvo Biotechnologies Omnia™ Platform- BAW-Based Biosensors For COVID-19 And Beyond

Bryan Bothwell[1], Deborah Whitehair[1]

[1]Qorvo Biotechnologies, 2300 NE Brookwood Pkwy, Hillsboro OR, 97133. bryan.bothwell@qorvo.com

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Abstract

This paper describes the Qorvo Biotechnologies Omnia testing system using bulk acoustic wave (BAW) sensor technology and performance data generated in a study conducted by the National Institutes of Health (NIH) as part of the RADx initiative for SARS-CoV-2 antigen testing. The Qorvo Omnia SARS-CoV-2 Antigen test was granted Emergency Use Authorization (EUA) for the qualitative detection of SARS-CoV-2 nucleocapsid viral antigens from direct anterior nasal swab specimens without transport media from symptomatic individuals who are suspected of COVID-19 by their healthcare provider within the first six days of symptom onset. The study illustrates the ease-of-use of the system and provides specific performance data: Limit of Detection (LoD) determination and a prospective study in two patient cohorts versus two high sensitivity real time polymerase chain reaction (RT-PCR) comparative methods, the Roche cobas® 6800 RT-PCR system (1800 NDU/mL) and the Hologic Panther® RT-PCR system (600 NDU/mL).

INTRODUCTION

The Qorvo Biotechnologies Omnia system, using BAW technology, enables low limit of detection similar to molecular testing capability while providing clinicians access to data that enables clinical decision making where time to result and performance are critical factors in the patient care workflow. In contrast to optical detection systems, the BAW detection system represents a new era in detection, supporting multiplexed capability in a variety of assay formats.

The Qorvo Biotechnologies Omnia system is designed as a benchtop instrument with a small footprint design to be used with disposable test cartridges packaged in single use pouches (Figure 1). The detection scheme utilizes a gravimetric sensor based on proprietary piezoelectric BAW technology, an immunosensor methodology that is well established in the literature [1-4]. The microfluidics technology integrates traditional biochemistry together with the BAW transducer enclosed entirely in the test cartridge,

allowing for customization of each assay. Using a positive displacement pump, fluid is aspirated from reagent wells on the cartridge and continually moved over the BAW sensor (Figure 2) where the assay reaction occurs.

Figure 1: Qorvo Biotechnologies Omnia instrument and test cartridge
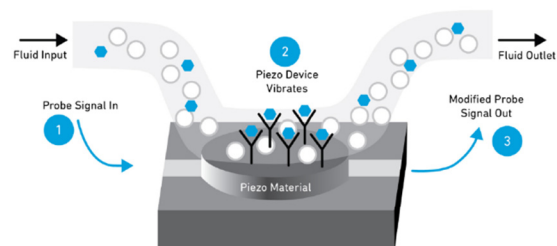

Figure 2: (1) RF signal is delivered to a BAW sensor as the fluid moves over the surface, (2) the sensor resonance frequency is modulated as mass is added to the surface and (3) the RF signal is output to the instrument.

As the analyte of interest binds to the device surface, the transducer's native resonance frequency is shifted and dampened due to mass loading (Figure 3). Because the sensitivity of the transducer increases with the square of the frequency, BAW provides extremely high sensitivity at its frequency of operation (~ 3 GHz). The sensor detection contrasts with previous immunosensors and conventional optical or fluorescence techniques in this regard. Additionally, by combining two or more sensors within the fluid path, it is possible to detect a multiplicity of proteins within the same test cartridge (Figure 4).
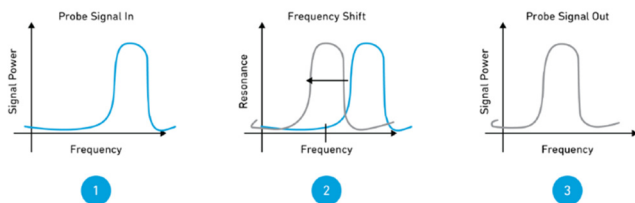
Figure 3: (1) Initial frequency reading under fluidic conditions. (2) Mass is added to the surface causing a frequency reduction due to the loading. (3) The final output signal can be used to calculate a total frequency shift proportional to the mass binding.
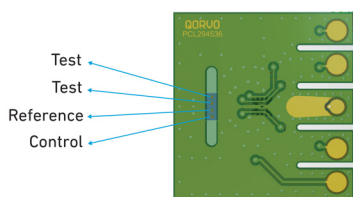

Figure 4: Radio frequency circuit board assembly and BAW die.

Qorvo Omnia SARS-CoV-2 Antigen Test

Qorvo Biotechnologies received EUA from the U.S. Food & Drug Administration (FDA) in April 2021 as a response to the SARS-CoV-2 pandemic. The Qorvo Omnia SARS-CoV-2 Antigen test utilizes a sandwich immunoassay format whereby two sensors are activated on the device surface; one with mouse monoclonal antibodies to the SARS-CoV-2 nucleocapsid protein; the second with a nonspecific reference antibody that allows for increased low-end sensitivity through common mode rejection.
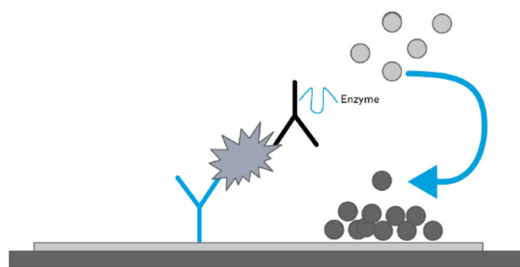

Figure 5: Sandwich immunoassay format with enhancing precipitate (spheres).

The SARS-CoV-2 assay additionally uses conventional enzymatic signal enhancement, during which insoluble precipitate amplifies the signal (Figure 5). All reagents are contained on the test cartridge and actuated by the Qorvo Omnia instrument.

Following a nasal swab collection, the swab is immersed into a lysis buffer to release any antigen present in the sample. The processed sample is simply deposited directly into the sample port on the test cartridge. The test cartridge is inserted into the Omnia instrument. Total time from inserting the test cartridge into the instrument to result generation is approximately 20 minutes (Figure 6).

Figure 6: SARS-CoV-2 Antigen workflow.

RESULTS

NIH Performance Data[5]

The Qorvo Biotechnologies Omnia instrument and Omnia SARS-CoV-2 Antigen test were selected by the RADx ACME-POCT team for an internal study in early March 2021. This study included an LoD study, a comparison study using fresh and frozen paired samples versus a RT-PCR method and a study using prospective patient samples collected from adult and pediatric collection sites.

***1.   Limit of Detection (LoD)***

The ACME-POCT LoD study utilized the same lot of BEI inactivated SARS-CoV-2 virus from the NIH National Institute of Allergy and Infectious Diseases that was used in Qorvo Biotechnologies EUA submission to the FDA. The LoD obtained by ACME-POCT study yielded 75 $TCID_{50}$/mL or approximately 50,000 copies/mL (Table 1 & Figure 7), significantly lower than the in-house LoD of 200 $TCID_{50}$/mL (125,000 copies/mL) in the EUA submission to the FDA.

Table 1: LoD (analytical sensitivity) from ACME-POCT study.

Gamma-Irradiated SARS-CoV-2, $TCID_{50}$/mL	Qorvo Omnia Antigen Test Result
149	3 of 3 Positive
100	3 of 3 Positive
75*	3 of 3 Positive
50	0 of 3 Positive
13	0 of 3 Positive
0	0 of 3 Positive

*Approximately 50,000 copies/mL

Figure 7: LoD (analytical sensitivity) from ACME-POCT study.

$y = 0.0184x - 0.0525$
$R^2 = 0.9889$

(y-axis: Omnia Dose (AU/mL); x-axis: SARS-CoV-2 (TCID$_{50}$/mL))
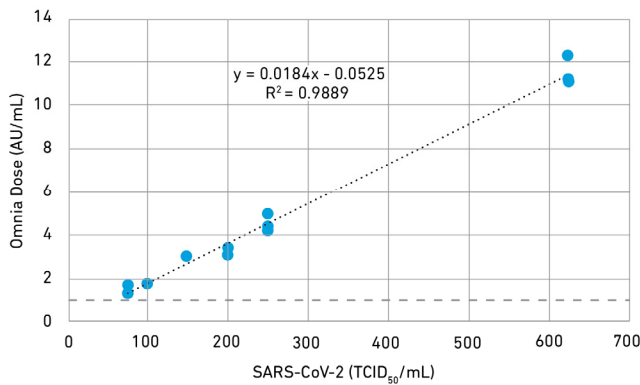
2. Prospective Comparison Study vs. RT-PCR Method

The ACME-POCT prospective comparison study was divided into two cohorts of patients: adult and pediatric.

Adult Cohort

50 fresh nasal swab samples were prospectively collected from adults presenting at a collection site and were tested on the Qorvo Omnia system and a companion nasopharyngeal swab was tested on the Roche cobas® 6800 system (Tables 2 & 3). The Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) results were 100%.

Table 2: Prospective adult samples Vs. Roche cobas® 6800 RT-PCR System.

| | Roche cobas® 6800 System | | |
Qorvo Omnia SARS-CoV-2 Antigen	Positive	Negative	Total
Positive	12	0	12
Negative	0	38	38
Total	12	38	50

Table 3: Qorvo SARS-CoV-2 antigen result summary.

Statistic	Estimate
Sensitivity (True Positive)	12/12 (100%)
Specificity (True Negative)	38/38 (100%)
Positive Predictive Value (PPV)	12/12 (100%)
Negative Predictive Value (NPV)	38/38 (100%)

Pediatric Cohort

77 fresh nasal swab samples were prospectively collected from a pediatric drive-thru collection site. The nasal swab samples were tested on the Qorvo Omnia system and a companion nasal pharyngeal swab was tested on the Hologic Panther® RT-PCR system (Tables 4 & 5). The Sensitivity, Specificity, PPV and NPV results were respectively 83%, 100%, 100% and 95%.

Table 4: Prospective pediatric samples vs. Hologic Panther® RT-PCR System.

| | Hologic Panther® System | | |
Qorvo Omnia SARS-CoV-2 Antigen	Positive	Negative	Total
Positive	15	0	15
Negative	3*	59	62
Total	18	59	77

*All three samples that tested negative on the Qorvo Omnia Antigen test had Ct values > 38 on the Hologic Panther® RT-PCR System which is indicative of very low viral loads found in the samples.

Table 5: Qorvo SARS-CoV-2 antigen result summary.

Statistic	Estimate
Sensitivity (True Positive)	15/18 (83%)
Specificity (True Negative)	59/59 (100%)
Positive Predictive Value (PPV)	15/15 (100%)
Negative Predictive Value (NPV)	59/62 (95%)

CONCLUSIONS

The ACME-POCT evaluation validates the utility and performance of the Qorvo Omnia instrument and the SARS-CoV-2 Antigen test. The LoD study validated Qorvo's internal data, and the sensitivity of the detection core. The paired fresh, frozen sample comparison showed no difference in result interpretation with 100% concordance. The prospective adult method comparison versus the highly sensitive molecular Roche cobas® 6800 RT-PCR system (1800 NDU/mL) produced 100% sensitivity and 100% specificity. The prospective pediatric method comparison versus the highly sensitive Hologic Panther® RT-PCR system (600 NDU/mL) results were 100% specificity and 83% sensitivity where the only samples (three) that were positive on the Hologic system and negative on the Qorvo Omnia system had Ct values > 38. Beyond that, the sensitivity and specificity for these combined prospective studies was 100% for each. The Qorvo Omnia SARS-CoV-2 Antigen test is an easy-to-use test system that produces results comparative to high sensitivity molecular testing systems used in this study.

ACKNOWLEDGEMENTS

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[5] The data was generated and analyzed by NIH-funded Atlanta Center for Microsystems Engineered Point-of-Care Technologies (ACME-POCT) as part of the RADx Initiative.

ACRONYMS

BAW: Bulk Acoustic Wave
NIH: National Institute of Health
RADx: Rapid Acceleration of Diagnostics initiative
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
EUA: Emergency Use Authorization
RF: Radio Frequency
ACME-POCT: Atlanta Center for Microsystems Engineered Point-of-Care Technologies
LoD: Limit of Detection
RT-PCR: Real-time Polymerase Chain Reaction
FDA: U.S. Food and Drug Administration
GHz: Gigahertz
Ct: Cycle Threshold
PPV: Positive Predictive Value
NPV: Negative Predictive Value