Department of Health & Social Care

Technical Validation Report for be.well™ Covid-19 Test by VMD Health (UK) and Alveo Technologies Inc.

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Contents

Assay description and intended purpose

1. The be.well™ COVID-19 Test is a portable, cloud-enabled rapid molecular test utilizing a single-use multi-plex cartridge. It comes with a rechargeable multi-use analyzer, and a HIPAA-compliant mobile application for the qualitative or semi-quantitative detection of RNA from SARS-CoV-2 in direct nasal swab specimens from individuals suspected of COVID-19 by their healthcare provider. The be.well™ COVID-19 Test is intended for use by trained operators who are proficient in performing tests with the be.well™ system. The test detects N gene and includes a human gene control, returning results after 56 minute run time.

2. Results are for the detection of SARS-CoV-2 RNA (N-gene). SARS-CoV-2 RNA is generally detectable in upper respiratory samples during infection. Positive results are indicative of the presence of SARS-CoV-2 RNA; clinical correlation with patient history and other diagnostic information can support determination patient of infection status. Positive results do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease.

   Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results may be combined with clinical observations, patient history, and epidemiological information.

3. The sample swab is stirred within a vial of assay buffer and then discarded. The vial is flicked to mix further, then the sample mixture is transferred into a be.well™ COVID-19 disposable cartridge using a disposable fixed volume transfer pipette. Handling of the test specimen and loading the Alveo test cassette should therefore be performed in a biological safety cabinet (BSL II) as this requires pipetting. Once loaded the device can be used on the bench and cassettes are safe to handle once testing complete. Newer versions with dropper bottles instead of pipettes may be available in the near future; these will not need to be loaded within a safety cabinet but will require full PPE for the user of the device.

Type of sample to be used in validation

1. This test uses mid-turbinate Nasal Swabs: these are supplied as individually packaged, sterile mid-turbinate swabs within the kit.

2. The validation used data from three UK sites and three datasets from the US; one of which tested frozen samples (allowed within the IFU); all had comparator qRT-PCR results.

Equipment and reagents

1. List all the equipment required that is or is not supplied by the manufacturer.

   Product components supplied:

   - Mid-turbinate Nasal Swabs: individually packaged, sterile mid-turbinate swabs used for sample collection.
   - Vials of Assay Buffer: single-use vials, each containing 500 µL of assay buffer
   - Disposable Pipettes: single-use, fixed volume transfer pipettes used to transfer sample from vial to cartridge.
   - Disposable be.well™ COVID-19 Cartridges (25): single-use cartridge containing dried reagents.
   - be.well™ Analyzer
   - be.well™ Mobile App
   - Instructions for use

   Product components required but not supplied:

   - Mobile Device (1): Mobile device, currently recommended Apple® iPhone® 8, 8+, or SE with iOS 13 and an integrated camera, Bluetooth® capability, and internet connectivity to download the be.well™ mobile app.

Performance characteristics

Analytical Sensitivity and Linearity of SARS COV-2 targets

1. Dilution series: Ideally, this should be calculated using a validated standard dilution series. If not possible (as standard material not available), use 5 clinical positive replicates, with a 5 log dilution, plus 5 negatives. If feasible, repeat over several days, different users/machines (feasibility may be limited due to availability of positive material). Where dry swabs are to be used, known amounts of standard material should be added to the swab, and then tested as per IFU.

   Table 1. Results from dilution series WHO International Standard for SARS-CoV-2 RNA (nibsc.org).

Copies/ml	**Result on be.well™**
100,000	Positive
10,000	Positive
7,500	Positive
5,000	Positive
2,500	Positive
1,000	Positive
550	Positive
100	Positive

2. Linearity and Efficiency. The assay gives a qualitative result so this section is not applicable.

3. Lowest Limits of Detection (LLOD). There was sporadic detection <100 therefore LLOD is <100copies/ml.

   Company claims 4000copies/ml but used an additional heat step that isn't part of the normal test process and may degrade the sample being tested, thereby underestimating the true LLOD.

Precision and robustness

1. Intra-assay precision. The assay gives a qualitative result so this section is not applicable.

2. Repeatability: Spike 30 negative samples with known amount of agent/positive material (suggested 3x the LLOD), all should be positive. This information given within the manufacturer IFU

Analytical specificity (Interferences and cross-reactions)

1. Cross-reactivity to non-target samples/organisms. A range of samples either direct clinical samples or spiked samples that are known positives for other diseases, both closely related to be tested.

   Table 2. cross-reactivity check using the Zeptometrix panel

Zeptometrix panel	**Strain**	**be.well result**
Influenza A H1N1	A/New Calendonia/20/99	Negative
Influenza A H3	A/Brisbane/10/07	Negative
Influenza A 2009 H1N1pdm	A/NY/02/09**	Negative
Influenza B	B/Florida/02/06	Negative
Metapneumovirus B	Peru6-2003	Negative
Respiratory Syncytial virus A	N/A	Negative
Rhinovirus 1A	N/A	Negative
Parainfluenza virus Type 1	N/A	Negative
Parainfluenza virus Type 2	N/A	Negative
Parainfluenza virus Type 3	N/A	Negative
Parainfluenza virus Type 4	N/A	Negative
Adenovirus Type 3	N/A	Negative
Coronavirus NL63	N/A	*
Coronavirus 229E	N/A	Negative
Coronavirus OC43	N/A	Negative
Coronavirus HKU-1	N/A	Negative
M. pneumoniae	M129	Negative
C. pneumoniae	CWL-029	Negative

Zeptometrix panel	Strain	be.well result
B. pertussis	A639	Negative
Adenovirus Type 31	N/A	Negative
Adenovirus Type 1	N/A	Negative
B. parapertussis	A747	Negative

*First test was positive, following two were negative

Diagnostic sensitivity and specificity (clinical validation with confirmed positives and negatives)

1. Diagnostic sensitivity. Confirmed clinical samples from patients (positive PCR result) should be used. Preferably, depending on the availability of samples, ~150 samples should be included to align with MHRA TPP. Clinical sensitivity (95% CI) and positive predictive value (PPV) should be calculated in comparison with a CE reference method that itself has good sensitivity and specificity.

   Table 3. Comparison with reference method (note prevalence of 30.6%). Data have been included from Three UK sites and several datasets from the US.

		Comparator		
		Positive	Negative	Total
be.well	Positive	162	11	158
	Negative	8	356	361
Total		170	367	529

2. Sensitivity = 95.3% (95% CI 90.6-97.8) this meets the acceptable criteria for sensitivity of the POC TPP (desirable>97% = acceptable = >80%).

Table 4. Performance of be.well at different viral loads, as defined by CT value, for the two UK sites and US sites that could provide this data.

	Basingstoke			**Kings**			**USA**			**USA Frozen**		
CT	Viasure	Positive Match on Be. well	Sens %	Altona	Positive Match on Be. well	Sens %	Abbott/ Hologic Fusion PCR	Positive Match on Be. well	Sens %	Hologic Fusion/ Roche	Positive Match on Be. well	Sens %
<25	13	13	100.0	2	2	100.0	75	73	97.3	21	21	100
25-30	0	0	N/A	8	8	100.0	17	17	100.0	6	6	100
30-35	1	1	100.0	5	4	80.0	1	1	100.0	0	0	0
>35	1	1	100.0	1	0	0.0	1	0	0.0	0	0	0
undefined	0	0	N/A	0	0	0.0	0	0	0.0	0	0	0

Total		
Hologic Fusion/ Roche	Positive Match on Alveo	Sens %
111	109	98.2
31	31	100.0
7	6	85.7
3	1	33.3
0	0	0.0

3. Diagnostic specificity. Confirmed clinical samples from patients (negative PCR result) should be used. Preferably, depending on the availability of samples, ~250 samples should be included to align with MHRA TPP. Clinical specificity (95% CI) and negative predictive value (PPV) should be calculated in comparison with a CE reference method that itself has good sensitivity and specificity.

   Specificity = 97.0% (95% CI 94.5-98.4) this meets the acceptable criteria for specificity of the POC TPP (desirable>99% = acceptable = >95%).

Summary

1. TVG uses a wide range of sites in order to validate new technologies/tests. These independent sites use a range of RT-qPCR assays against different genomic regions and it is recognised that for some assay comparisons the sensitivity of RT-qPCR assay(s) may subtly differ from the true sensitivity of the test if compared to the same genomic region.

2. This assay meets the acceptable criteria for sensitivity and specificity of the MHRA TPP for POC assays, although data are weighted toward low CT range.

   To note: Of the 11 false positives

   - 3 were from Basingstoke who used the same lot as Leeds which was later confirmed to have a lot issue with late amplification: removing these 3 would increase specificity to 97.8% (95.5-99.0).

   - A further 3 from the US were compared to a comparator that did not detect N gene: removing these 3 would increase specificity to 97.8% (95.5-99.0).

   - Removing all 6 would increase specificity to 98.6% (96.6-99.5)-rounded to 95% CI entirely above 97% would move specificity to desirable, however sensitivity would still only be acceptable.

Extra data tables

Table 5. Failure rate of the be.well assay.

Total number of Samples Tested	Number of IC* failures	Percentage of IC failures (%)	Number of technical failures	Percentage of Technical failures (%)	Total number of failures	Percentage of total failures (%)
596	39	6	8	1	47	8

*internal process control

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