# GENOAMP® REAL-TIME PCR TESTS FOR DETECTION OF COVID-19

## PURPOSE

To provide scientific evidence on the effectiveness, safety and cost-effectiveness of GenoAmp® Real-Time PCR Tests for the detection of COVID-19, following a request from the office of Secretary General, Ministry of Science, Technology and Innovation.

## BACKGROUND

The recent outbreak of Novel Coronavirus (COVID-19) has generated global concern given its rapid spread in multiple countries and possible fatal progression of the infection. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified as the causative virus, a virus belonging to the large coronavirus family of RNA viruses causing infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).[1]

It is associated with three major patterns of clinical course of infection; mild illness with upper respiratory tract presenting symptoms, non-life-threatening pneumonia and severe pneumonia with acute respiratory distress syndrome (ARDS).[1] Given that the manifestation of COVID-19 infection is highly non-specific, diagnostic tests specific to this infection are crucial and urgently needed to confirm suspected cases, screen patients, and conduct virus surveillance.

Nucleic acid detection methods based on polymerase chain reaction (PCR) is characterized by rapid detection, high sensitivity and specificity, and regarded as the "gold standard" for virus detection.[2] To date, Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) technology is the technology recognized by the World Health Organisation (WHO), US Center for Disease Control (CDC) and Ministry of Health Malaysia for the confirmation of COVID-19. [3,4,5]

Medical Innovation Ventures Sdn. Bhd. (Mediven®) is a fast-growing diagnostics company based in Malaysia which develops, manufactures and markets advanced high quality clinical diagnostic molecular and rapid tests. Mediven® provides solutions for screening of a variety of infectious diseases including COVID-19, dengue, chikungunya, zika, malaria, influenza and tuberculosis.[6] Two new laboratory test kits that have been developed for testing patient specimens for COVID-19, include GenoAmp® Real-Time RT PCR Flu A/Flu B/SARS-CoV-2/MERS-CoV and GenoAmp® Real-Time RT-PCR SARS-CoV-2. These tests were designed based on internationally recommended protocols for COVID-19 as stated in the WHO interim guidelines.[7,8]
There are two approaches for any RT-PCR applications, which are one-step RT-PCR and two-step RT-PCR (Figure 1).[9] The GenoAmp® tests are single-step RT-PCR that combines the synthesis of complementary DNA (cDNA) of the first strand (reverse transcript, RT) and subsequent amplification of specific gene fragments by PCR in a single reaction tube.

Fluorescence is emitted and measured using the real-time systems' optical unit during the amplification step.[7,8]

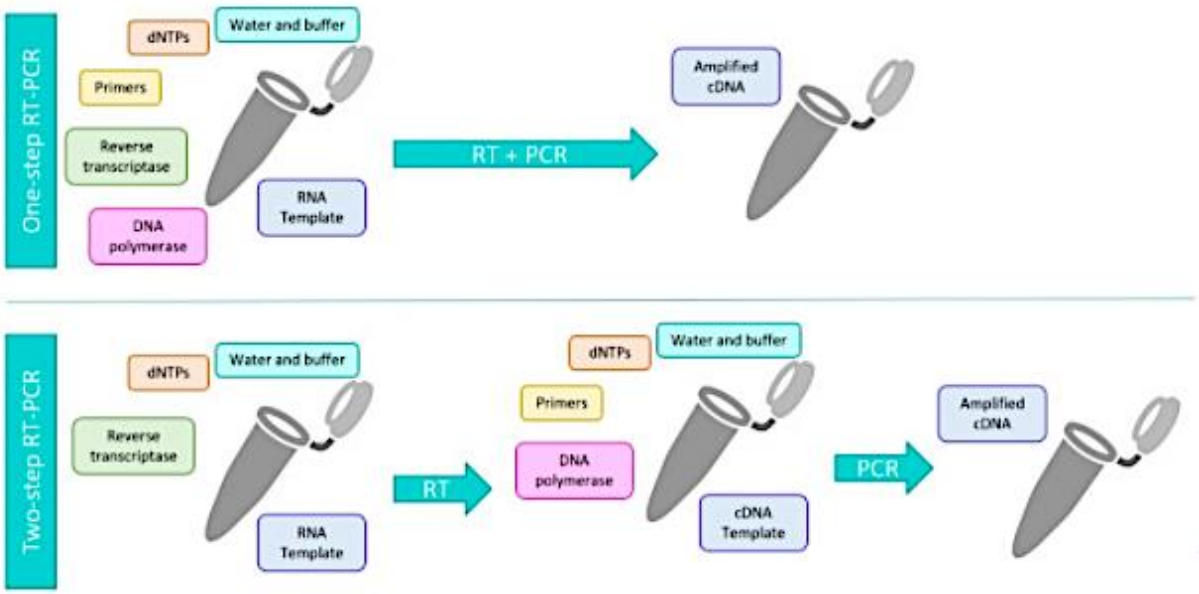


**Figure 1: Overview of One Step versus Two Steps Real Time RT-PCR**

### i. GenoAmp® Real-Time RT PCR Flu A/Flu B/SARS-CoV-2/MERS-CoV[7]

Using Multiplex Detection Technology, this test kit is designed for screening and differentiation influenza A (H1N1, H3N2), influenza B, SARS-CoV-2 (Nucleocapsid or N gene; RNA-dependent RNA polymerase, RdRP gene; and Spike, S gene) and MERS-CoV simultaneously from a single drop of patient's specimen (Figure 2).

### ii. GenoAmp® Real-Time RT-PCR SARS-CoV-2[8]

GenoAmp® Real-Time RT-PCR SARS-CoV-2 is designed for the confirmation of COVID-19 infection by screening the RdRp and S genes, and confirming by using N gene. It can test multiple gene targets from a single patient nasal swab simultaneously. Over 90 patient samples can be run on the real-time PCR machine at the same time and results can be obtained in about 2 to 3 hours, allowing for high throughput turnover (Figure 3).


**Figure 2: GenoAmp® Real-Time RT PCR Flu A/Flu B/SARS-CoV-2/MERS-CoV**

**Figure 3: GenoAmp® Real-Time RT-PCR SARS-CoV-2**

For both kits, virus specimen can be obtained using bronchoalveolar lavage, tracheal aspirate, sputum, nasopharyngeal swab, oropharyngeal aspirate or wash, nasopharyngeal aspirate or wash.

## EVIDENCE/INFORMATION SUMMARY

### *Efficacy/Effectiveness*

There was no retrievable evidence on GeneAmp® RT-PCR obtained from the scientific databases through Ovid interface, FDA website and non-scientific databases (Google Scholar search engine). Most of the information regarding the products was obtained from the documents provided by the company (via email communication) as well as from the company's website.[6,7,8]

The performance of the tests was reported in terms of analytical sensitivity which represents the smallest amount of substance in a sample that can accurately be measured by an assay, and analytical specificity that refers to the ability of an assay to measure one particular organism or substance, rather than others, in a sample.[10]

For GenoAmp® Flu A/Flu B/MERS-CoV/SARS-CoV-2 test, the analytical sensitivity (with a positivity rate of ≥ 95%) of Influenza A was 0.41copies/ul, Influenza B (5.90copies/ul), SARS-CoV-2 (13.5copies/ul) and MERS-CoV (29.9 copies/ul). Analytical specificity (Cross-reactivity of the test) was tested against 34 pathogens including HCoV-229E, HCoV-OC43, HCoV-NI63, SARS-CoV HKU39849 and Haemophilus Influenza. The empirical testing showed that all targets were negative for all tested microorganisms except for the SARS coronavirus which is expected to react with N3 target (target for the universal detection of SARS-like viruses).

The analytical sensitivity of GenoAmp® SARS-CoV-2 in terms of limit of detection of RdRp gene was 16.2copies/ul, S gene (14.2copies/ul) and N gene (13.5copies/ul). The analytical specificity (Cross Reactivity Test) was tested negative against HCoV-229E, HCoV-OC43, HCoV-NI63, SARS-CoV HKU39849 and MERS-CoV.

The diagnostic performance of these tests however, is not available. The GenoAmp® tests are currently being evaluated at Hospital Tuanku Ja'afar, Seremban and TIDREC, University Malaya

A recent study published in pre-print The Lancet in January 2020 reported that open reading frame 1b (Orf1ab) and S gene were very specific genes that can effectively distinguish COVID-19 from other coronaviruses (including SARS and SARS like viruses), which have been used to design specific PCR detection primers. N and E genes of the SARS-CoV-2 may form cross-reaction with other coronaviruses.[11]

A group of researchers at Hong Kong University have recently developed two one-step quantitative RT reverse transcription PCR tests targeting both the *ORF1b* and the *N* regions of the viral genome. The tests are explicitly designed to identify multiple viruses in the Sarbecovirus subgenus to which SARS-CoV-2 belongs, given a lack of data on the genetic diversity of SARS-CoV-2 in humans and animals. As no other Sarbecoviruses are known to be circulating in humans, a positive test can be considered as confirmation that a subject is infected

with SARS-CoV-2 or a related animal virus. The study concluded that the *N* gene assay is recommended as a screening test and the *ORF1b* test is recommended as a confirmatory test.[12]

The RT-PCR test is intended for use by trained clinical laboratory personnel specifically instructed and trained in the techniques of real-time PCR and in vitro diagnostic procedures. Suitable biosafety precautions should be taken for handling human clinical specimens suspected to be COVID-19 infections.

## SAFETY

The manufacturer met ISO 13485-certified Quality Management System, which means that each lot of GenoAmp® Real-Time RT-PCR tests is tested against predetermined specifications to ensure consistent in product quality.[7]

The SARS-CoV-2 RNA is generally detectable in respiratory specimens during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 RNA; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses. As the negative results do not preclude SARS-CoV-2 infection, it should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

## COST-EFFECTIVENESS

There was no retrievable evidence on cost-effectiveness of the technology in the scientific database. The price quoted was around RM 4000 per box, which contains 100 test kit.

## CONCLUSION

In conclusion, based on the above review, there was no evidence retrieved to suggest that GenoAmp® tests are effective, safe and cost-effective in detecting COVID 19. As the tests are still categorized as research-use-only (RUO), there was no clinical diagnostic accuracy data available. The analytical sensitivity and specificity of the tests however, were good which meant that the tests were able to screen and differentiate influenza A and B strains, COVID-19 and MERS-CoV simultaneously as well as confirming COVID 19.

The RT-PCR technology is considered the gold standard for diagnostic molecular testing for COVID 19, according to WHO and CDC guidelines. The timing of conducting the tests however is crucial to avoid false-negative results. Both positive and negative results must be utilised in conjunction with clinical observations, patient history, and epidemiological information.

The RT-PCR test is intended for use by trained clinical laboratory personnel only. Strict biosafety precautions should be adhered to when handling human clinical specimens suspected to be COVID-19 infections.

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**Disclaimer**: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.


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