Sugentech

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# I. Characteristics of COVID-19 and its implication for its diagnosis

**COVID-19, the disease caused by virus named as 'SARS-COV-2', has been spread so easily and sustainably from patients with very mere or even without symptoms. From the asymptomatic patient the major upper respiratory tract sample for virus detection such as pharyngeal swap shows only 30% sensitivity. As COVID-19 clinical pathway is so aggressively processed up to lethality in many cases, the limitation of viral detection capability cannot be overlooked even the more in the phase of 'Pandemic Community Spread' of COVID -19.**

## 1.1 COVID-19, different clinical pathway from the existing any pneumonia.

A. **Mostly asymptomatic or with mild symptoms, but patients are all virus shedding**. For this period, patients cannot generate rhinorrhea or sputum, which could be a main source of diagnosis, in order to seek for and identify the virus itself.: "COVID-19 has different pathologic characteristics from the existing pneumonia, and even cases of spreading throughout the lungs without the recognition of the infected themselves, e.g. without or mere symptoms"

B. **Threatening pathway so different from other pneumonia causing virus or bacteria**:

   i. Prof. Kyung-Hyun Do, professor at Seoul Asan Hospital (the biggest general hospital in Korea), said, "To date, 20 to 30% of the entire clinical pathway of Corona 19 seems to require intensive care." Some asymptomatic patients are classified as mild, but among them, cases in which lung infiltration (invasion) has already progressed considerably.

   ii. Professor Oh Myung-don of Seoul National University Hospital (the top teaching hospital in Korea) said, "I have seen patients in this field for over 30

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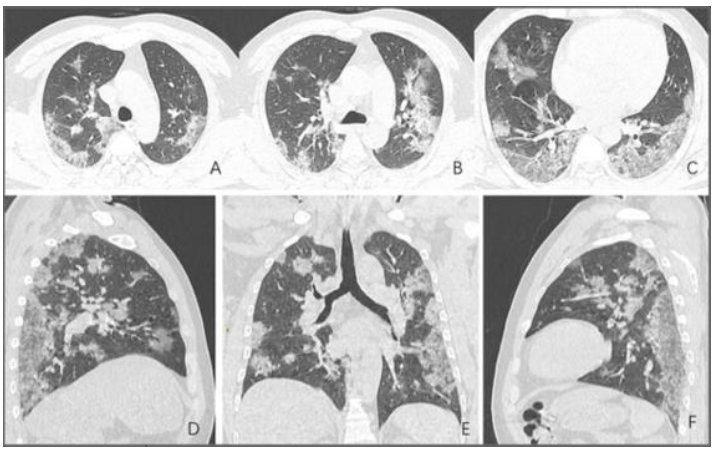
years, and this pneumonia has a very different and unique characteristic from the pneumonia I've seen." said.




Chest CT image of a 44-year-old patient infected with COVID-19

https://m.biz.chosun.com/svc/article.html?contid=2020031702320&utm_source=undefined&utm_medium=unknown&utm_campaign=biz

### 1.2 COVID-19, different clinical pathway from the existing any pneumonia.

A. **On 13 March, RT-PCR has negative result with even 2 samples from upper and lower respiratory but 17-year-old boy(A) died of COVID-19 at on the 18th of March, which was diagnosed after death.** The cause of death was identified as multiple organ failure caused by COVID-19. There were no underlying other diseases. Various parts of (A)'s lung turned white on X-rays. The first test on May 13th was negative with two replicate RT-PCR tests and even tests just before and after death, tests have different result, e.g. some of it positive while with some of it still negative"

https://news.naver.com/main/read.nhn?mode=LSD&mid=sec&sid1=102&oid=001&aid=0011481629

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**B. For the characteristic of COVID-19, special clinical pathway and asymptotic infectivity, it is hard to secure good sample of virus detection, so as to lead the incorrect diagnosis**

i. For COVID 19 there have been so many changes of test results, e.g. negative to positive, which is claimed to come from the sample problem. The issue, hard to get the good sample, stems from the COVID19 clinical pathway. Korea Lab doctor association asserted "Those changes of the test results of COVID-19, from negative to positive is not due to RT-PCR reagents, but due to sample collection or patient conditions"

Seongnam Bundang Pharmaceutical Hospital, Gyeonggi-do, is testing a new coronavirus infection (corona19). Photo Bundang Jesaeng Hospital

Peoople are being examined at a temporary inspection center in front of the Korea Building in Sindorim-dong, Guro-gu, Seoul, where a new epidemic of coronavirus infection has occurred. [yunhap news]

https://n.news.naver.com/article/025/0002985000

ii. Recent perspective on the RT PCR virus detection diagnosis shows the

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limitation of pharyngeal swap, only 32% (n = 126) positive rate. The best sample is broncho-aveolar lavage fluid specimens but this cannot be easily gotten from the potential patients.

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

| Specimens and values | Bronchoalveolar lavage fluid (n = 15) | Fibrobronchoscope brush biopsy (n = 13) | Sputum (n = 104) | Nasal swabs (n = 8) | Pharyngeal swabs (n = 398) | Feces (n = 153) |
|---|---|---|---|---|---|---|
| Positive test result, No. (%) | 14 (93) | 6 (46) | 75 (72) | 5 (63) | 126 (32) | 44 (29) |
| Cycle threshold, mean (SD) | 31.1 (3.0) | 33.8 (3.9) | 31.1 (5.2) | 24.3 (8.6) | 32.1 (4.2) | 31.4 (5.1) |
| Range | 26.4-36.2 | 26.9-36.8 | 18.4-38.8 | 16.9-38.4 | 20.8-38.6 | 22.3-38.4 |
| 95% CI | 28.9-33.2 | 29.8-37.9 | 29.3-33.0 | 13.7-35.0 | 31.2-33.1 | 29.4-33.5 |

Abbreviation: ND, no data.

Figure. Severe Acute Respiratory Syndrome Coronavirus 2 Distribution and Shedding Patterns Among 20 Hospitalized Patients

Source : [Detections of SARS-CoV-2 in Different Types of Clinical Specimens]

iii. Even the previous corona virus disease of SARS, many various kinds of symptoms including mere and asymptotic cases have been reported, where the lower capability of virus detection was reported and in result, the major specimen of upper respiratory sample has only 30% sensitivity.

**Various or minimal Symptoms of coronavirus infection (SARS)**

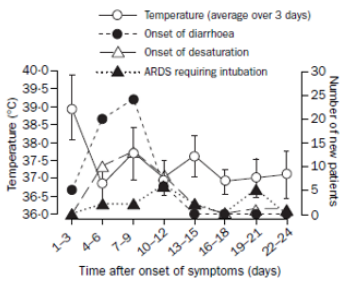


Figure 1: **Temporal clinical profiles in 75 patients with SARS**
Mean (SD) are presented.

**Virus detection capability of coronavirus infection (SARS)**

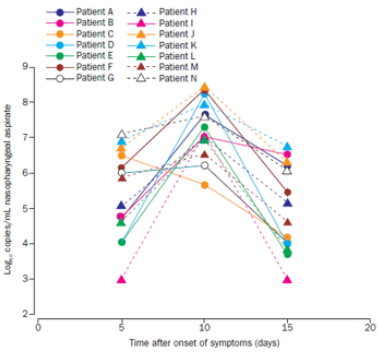


Figure 4: **Sequential quantitative RT-PCR for SARS-associated coronavirus in nasopharyngeal aspirates of 14 SARS patients**

**Corona disease confirmation test capability**

"…**SARSCoV RT-PCR has only a modest sensitivity of approximately 30% on a single respiratory sample collected early in the illness** (8), although its sensitivity improves if serial samples are collected in the first 2 weeks, since maximal viral shedding occurs 7 to 10 days after onset (4, 8). **The most reliable laboratory test for the confirmation of SARS is detection of SARS-CoV specific antibodies** (4, 8)…."

Source: Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia:

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a prospective study. THE LANCET • Vol 361 • May 24, 2003 /Kinetics of Severe Acute Respiratory Syndrome (SARS) Coronavirus-Specific Antibodies in 271 Laboratory-Confirmed Cases of SARS CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 2004,/ Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 362:263–270

iv. Ag test, seeking for virus with its protein, cannot exceed the sensitivity of RT PCR, for the fact the RT-PCR itself do amplify the specific target segment of virus gene in so many rounds. Additionally, Ag test has to be confronted with the exact same sample limitation of COVID-19. Please remember the COVID-19 is so complicate disease the more for its asymptomatic virus shedding and 'hard-to-secure good sample'.

## II. Advantage of Serology test

**Serology test is the only test both to diagnose the disease and to track the history of infection. Even though every methods of diagnosis have some limitation, especially if the patient has mild symptoms or is asymptomatic in the first several days, the overall diagnosis capability of serology test for the long and extended virus shedding COVID-19 is quite prominent in the recent studies.**

A. The researchers found that patients shed high levels of viral debris linked to Covid-19, which even appears to be true of patients who are asymptomatic. Carriers who evidence mild forms of Covid-19 may shed virus even more than 10 days after symptoms subside. The elongated virus shedding and high ratio of mere or no symptom patients emphasize repetitive test. Even for the potential contacts or carriers who have been asked to self-isolation to their own home, the removal of restriction has to be confirmed after serology test

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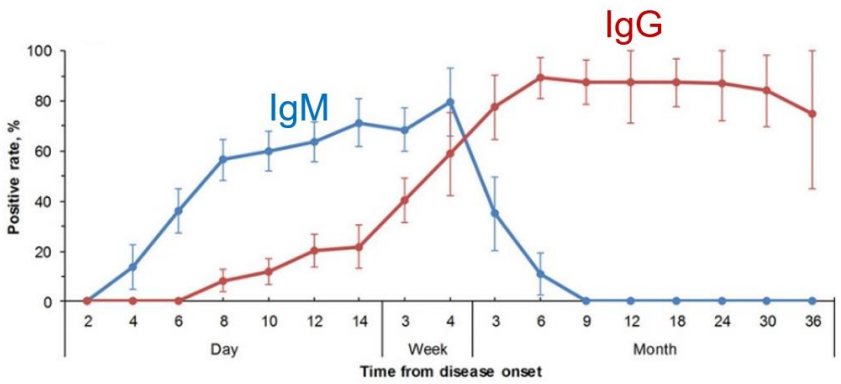
B. Normal Seroconversion kinetics tells that from the onset of disease, start of virus replication/shedding, within 1week, IgM appears in the blood and Ig G follows and sustains for long even up to 3 years to fight virus infection




<Kinetics of Seroconversion for IgM and IgG>

C. According to the 7th Ed. of Guideline of treatment of COVID-19, the specific IgM against COVID-19 virus appears 3-5 days from onset of disease. The serology test is assured as confirmation test and the only test to exclude from suspicious patients
http://www.nhc.gov.cn/yzygj/s7652m/202003/a31191442e29474b98bfed5579d5af95.shtml

D. The test capability of RT-PCR(RNA) and serology test for COVID-19 have been evaluated and reported in https://doi.org/10.1101/2020.03.02.20030189. Even though every methods of diagnosis have limitation, especially if the patient has mild symptoms or is asymptomatic in the first several days, the diagnosis capability of serology test of COVID-19 is quite prominent. Diagnosis with both RT-PCR and serology test can be the best and ideal for comprehensive test for COVID-19.

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## Serology Test Capability cannot be underestimated

Table 2. Performance of different detections in samples at different time since onset of patients.

| Days after onset | n | RNA n(+) | RNA Sensitivity (%, 95%CI) | Ab n(+) | Ab Sensitivity (%, 95%CI) | IgM n(+) | IgM Sensitivity (%, 95%CI) | IgG n(+) | IgG Sensitivity (%, 95%CI) | RNA+Ab n(+) | RNA+Ab Sensitivity (%, 95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total | 173 | 112$ | 67.1 (59.4, 74.1) | 161 | 93.1 (88.2, 96.4) | 143 | 82.7 (76.2, 88) | 112 | 64.7 (57.1, 71.8) | 172 | 99.4 (96.8, 100.0) |
| 1-7 | 94 | 58$ | 66.7 (55.7, 76.4) | 36 | 38.3 (28.5, 48.9) | 27 | 28.7 (19.9, 39.0) | 18 | 19.1 (11.8, 28.6) | 74 | 78.7 (69.1, 86.5) |
| 8-14 | 135 | 67$ | 54.0 (44.8, 63.0) | 121 | 89.6 (83.2, 94.2) | 99 | 73.3 (65.0, 80.6) | 73 | 54.1 (45.3, 62.7) | 131 | 97.0 (92.6, 99.2) |
| 15-39 | 90 | 25$ | 45.5 (32.0, 59.5) | 90 | 100.0 (96.0, 100.0) | 83* | 94.3 (87.2, 98.1) | 71# | 79.8 (69.9, 87.6) | 90 | 100.0 (96.0, 100.0) |

* Two patients missed IgM tests due to inadequate plasma samples. # One patient missed IgG tests due to inadequate plasma samples. $ There were 7, 11 and 35 patients had not been performed RNA testing during the 1-7 onset day, 8-14 onset day and 15-39 onset day, respectively.

Source: Antibody responses in COVID-19 patients

E. In the case of MERS corona virus infection, WHO guided that serology test is recommended for asymptomatic contact and for symptomatic patients with limited access to the RT-PCR diagnosis. The serology test could be more emphasized for much higher proportion of mere or little symptom patient in COVID-19 infection

# Laboratory Testing for Middle East Respiratory Syndrome Coronavirus

Interim guidance (revised)
January 2018
WHO/MERS/LAB/15.1/Rev1/2018

World Health Organization

Table 1. Specimens to be collected from symptomatic patients and asymptomatic contacts

| Patient | Test | Type of sample | Timing | Storage and transportation | Remarks |
|---|---|---|---|---|---|

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| | | | | | |
|---|---|---|---|---|---|
| **Symptomatic** | Serology | Serum for serological testing.<br><br>Only if NAAT is not available | Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 3-4 weeks later.<br><br>If only a single serum sample can be collected, this should occur at least 3-4 weeks after onset of symptoms for determination of a probable case. | As above, with storage and shipping at -20°C being sufficient. | As above. |
| **Asymptomatic Contact** (particularly in health-care centre associated outbreaks or other outbreak settings involving high-intensity contact. Testing asymptomatic individuals not associated with outbreaks is not recommended ) | NAAT | Nasopharyngeal and oropharyngeal swabs; lower respiratory tract specimens if possible. | Within 14 days of last documented contact. | As above for NAAT. | As above. |
| | Serology | Serum | Baseline serum taken as early as possible within 14 days of contact and convalescent serum taken 3-4 weeks after last contact.<br><br>If only a single sample is possible, collect at least 3-4 weeks after last documented contact | As above for serology. | As above. |

## III. Sugentech COVID-19 IgM/IgG test

**Sugentech is a certified in-vitro diagnostic(IVD) medical device manufacture, a KOSDAQ-listed company, and has been recognized for its technical advancement by various awards from Korean Government. SGTi-flex COVID-19 IgM / IgG is the serology test to seek for COVID-19 virus specific IgM and IgG in the patient blood. COVID-19 is CE-certified and its clinical capability has been proven in the 3rd party clinical evaluation.**

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* How to use video : https://youtu.be/1yET72A_e1M

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## 3.1 CE certificate of SGTi-flex COVID-19 IgM / IgG

www.mt-procons.com

promedt CONSULTING

**Certificate**
**of EU product notification**

Herewith we confirm that

**MT Promedt Consulting GmbH**
**Altenhofstraße 80**
**66386 St. Ingbert**
**Germany**

has taken over the function of an European Authorized Representative according to the requirements of Article 10 of the IVDD 98/79/EC for

**Sugentech Inc.**
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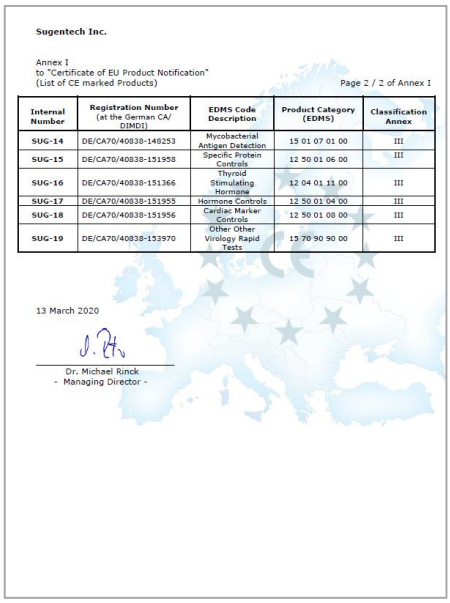
**Chungcheongbuk-do 28161**
**Republic of Korea**

MT Promedt Consulting GmbH has made the product notification at the relevant competent authority according to Article 10(3).
The in vitro diagnostic medical devices of the manufacturer, covered by the notification, are listed in Annex I of this certificate.

13 March 2020

Dr. Michael Rinck
- Managing Director -

**Enclosure**
Annex I



**Sugentech Inc.**

Annex I
to "Certificate of EU Product Notification"
(List of CE marked Products)

Page 2 / 2 of Annex I

| Internal Number | Registration Number (at the German CA/ DIMDI) | EDMS Code Description | Product Category (EDMS) | Classification Annex |
|---|---|---|---|---|
| SUG-14 | DE/CA70/40838-148253 | Mycobacterial Antigen Detection | 15 01 07 01 00 | III |
| SUG-15 | DE/CA70/40838-151958 | Specific Protein Controls | 12 50 01 06 00 | III |
| SUG-16 | DE/CA70/40838-151366 | Thyroid Stimulating Hormone | 12 04 01 11 00 | III |
| SUG-17 | DE/CA70/40838-151955 | Hormone Controls | 12 50 01 04 00 | III |
| SUG-18 | DE/CA70/40838-151956 | Cardiac Marker Controls | 12 50 01 08 00 | III |
| SUG-19 | DE/CA70/40838-153970 | Other Other Virology Rapid Tests | 15 70 90 90 00 | III |

13 March 2020

Dr. Michael Rinck
- Managing Director -

## 3.2 Clinical Study Results

**Sugentech Clinical Study Clinical Institution**

Clinical study was done in one of major clinical institution in Daegu city and Eulgi University Hospital







계명대학교 동산병원
KEIMYUNG UNIVERSITY DONGSAN HOSPITAL

Base Camp Hospital for outbreaks of COVID-19 in Daegu-city of Korea



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## Sugentech Clinical Study Results (1/3)

### Test Samples (Specimens)

**Positive samples**

- A total of 150 specimens were collected from patients who were positively confirmed by the real time RT-PCR with nasopharyngeal swab, oropharyngeal swab or sputum specimens at Keimyung University's Daegu Dongsan Hospital, Keimyung University Dongsan Hospital and Daejeon Eulji Medical Center, Eulji University.
- The specimens (plasma or serum) were paired samples obtained from the same subjects at the same time point who provided nasopharyngeal swab, oropharyngeal swab or sputum samples which were used in the real time RT-PCR as confirmative diagnosis for COVID-19.

**Negative samples**

- A total of 200 specimens were collected from 100 clinically non-infected healthy individuals and 100 patients with respiratory symptoms.
- The specimens of respiratory symptom patients were paired samples obtained from who were negatively confirmed by the COVID-19 real-time RT-PCR test conducted by Keimyung University Dongsan Hospital during the same period.

### Conclusion

- Comparison studies between the test device (SGT i-flex COVID19 IgM/IgG) and the predicate device (Reference method, real time RT-PCR) were conducted by lab professionals, using total 350 specimens.
- Through three different tests, the results showed the accuracy (overall percent agreement) was 94.00~97.00%. The sensitivity and specificity (positive and negative agreements) were 90.00~96.00% and 96.00~98.00%, respectively.

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## Sugentech Clinical Study Results (2/3)

### Clinical Evaluation 1

| | | RT-PCR | | |
|---|---|---|---|---|
| | | Positive | Negative | Total |
| SGT i-flex COVID-19 IgM IgG | Positive | 48 | 1 | 49 |
| | Negative | 2 | 49 | 51 |
| | Total | 50 | 50 | 100 |

- **Accuracy** (Overall agreement) = 100 x (48+49) / 100 = 97.00%
- **Sensitivity** (Positive agreement) = 100 x 48 / 50= 96.00%
- **Specificity** (Negative agreement) = 100 x 49 / 50 = 98.00%

### Clinical Evaluation 2

| | | RT-PCR | | |
|---|---|---|---|---|
| | | Positive | Negative | Total |
| SGT i-flex COVID-19 IgM IgG | Positive | 45 | 1 | 46 |
| | Negative | 5 | 49 | 54 |
| | Total | 50 | 50 | 100 |

- **Accuracy** (Overall agreement) = 100 x (45+49) / 100 = 94.00%
- **Sensitivity** (Positive agreement) = 100 x 45 / 50= 90.00%
- **Specificity** (Negative agreement) = 100 x 49 / 50 = 98.00%

### Clinical Evaluation 3

| | | RT-PCR | | |
|---|---|---|---|---|
| | | Positive | Negative | Total |
| SGT i-flex COVID-19 IgM IgG | Positive | 46 | 4 | 50 |
| | Negative | 4 | 96 | 100 |
| | Total | 50 | 100 | 150 |

- **Accuracy** (Overall agreement) = 100 x (46+96) / 150 = 94.67%
- **Sensitivity** (Positive agreement) = 100 x 46 / 50= 92.00%
- **Specificity** (Negative agreement) =100 x 96 / 100 = 96.00%

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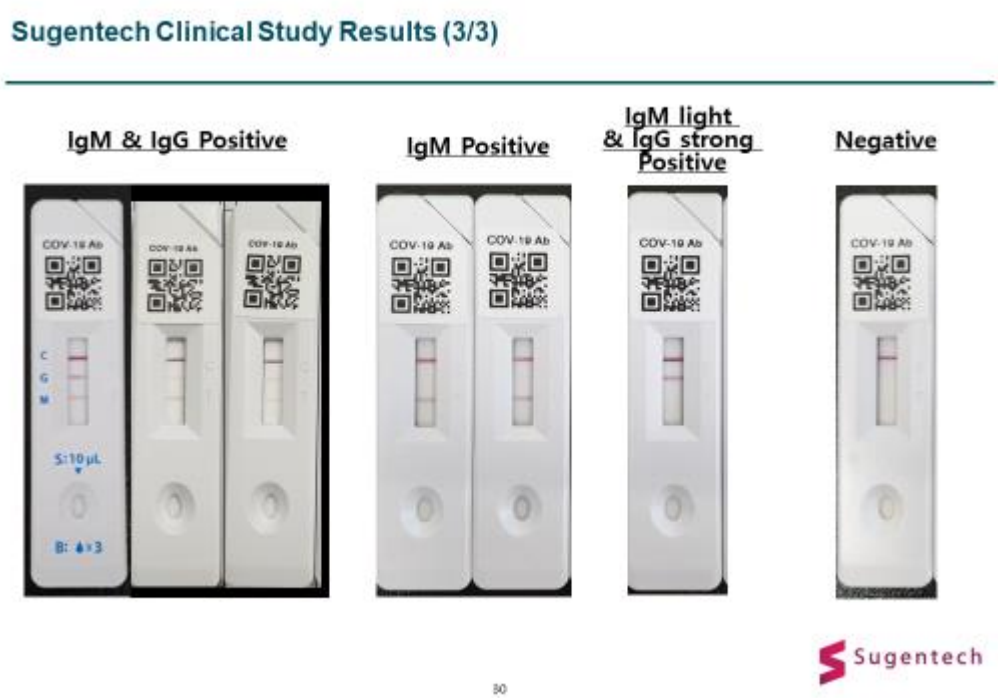
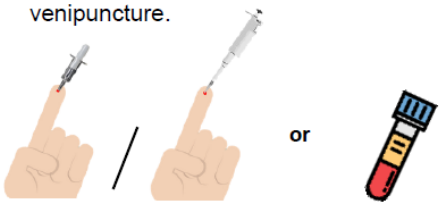



## 3.3 Usability

### 1 Collecting of Sample

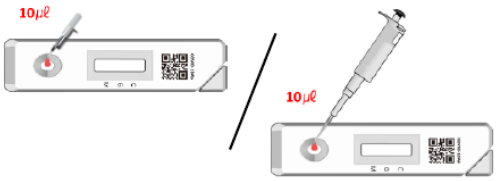
For the test, 10 µl of whole blood, plasma or serum is used.

- Collect fingertip blood using a pipette or blood transfer pipette.
- Or use a blood sample obtained by venipuncture.



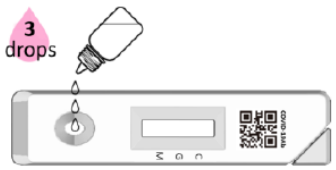

### 2 Adding of Sample

Add the collected sample(whole blood/ serum/plasma) to the sample well of the test cassette.




### 3 Dropping of Sample buffer

Add 3 drops (90µl) of sample into the sample well of the test cassette.




### 4 Reading Test result

Read test result at 10~15 minutes.


**Read after 10 mins.**

**Do not read after 30 mins.**

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## 3.4 Package


1 KIT(25tests/1box), 215 x 115 x 70(mm) -260g, is composed of 25 cassettes, independently sealed and a buffer bottle, can be stored in RT without refrigerator

pettyPip is design- patented small device, intended conveniently to pick up 10 ul blood to load on the well of cassette. It is sold separately