Comparison of Immunologic and Serologic Tests for COVID-19

"Literature Review"

In response to the growing COVID-19 pandemic and shortages of laboratory-based molecular testing capacity and reagents, multiple diagnostic test manufacturers have developed and begun selling rapid and easy-to-use devices to facilitate testing outside of laboratory settings. These simple test kits are based either on detection of proteins from the COVID-19 virus in respiratory samples (e.g. sputum, throat swab)- or detection ***(Immunologic Tests)***, in blood or serum, of human antibodies generated in response to infection ***(Serologic Tests)***.

Immunologic Tests (PCR):

The first is a very sensitive test that looks for the RNA of the virus using a technique PCR. This can detect as little as one virus particle in swabs taken from inside the mouth or nose.

Although, PCR is a highly sensitive test for COVID-19 it has its limitations;

- PCR requires high-quality nasopharyngeal swabs containing sufficient amounts of viral RNA. This can be a challenge because the amount of viral RNA not only varies tremendously between patients, it can also vary within the same patient depending on the timing of the test and the start of the infection and/or the onset of symptoms.
- In addition, nasopharyngeal swabs are not only very unpleasant to the patient, the sampling techniques vary significantly from nurse to nurse. Without sufficient viral RNA PCR can return a false negative test result.
- PCR also requires highly trained personnel to perform complex RNA extraction steps and PCR. Normally, this would not be a problem when testing a few thousand samples. PCR becomes an issue when dealing with a global pandemic with potentially millions of people to test. This leads to delays in testing as medical facilities become overwhelmed with requests.

According to recent estimates, false negative results obtained with PCR are more common than initially thought. Some health care experts go as far as stating that, based on their own experience, one in three patients who has been infected with COVID-19 tests negative with the PCR method. False negative results can have devastating impacts on the current efforts to contain the COVID-19 outbreak as infected patients are mistakenly given the green light to return home, return to work and possibly infecting others. Relying solely on nucleic acid tests to diagnose COVID-19 is a risky strategy. As such, calls to add independent testing methodologies to complement PCR are becoming increasing louder.

PCR testing is important early in infection because it can help us isolate infected people and contain the outbreak. PCR testing is also important later in the outbreak because it shows us how the virus is transmitting through the population and we can then calculate the percentage of people that develop serious complications, which reveals how dangerous this virus is for different people (young and old, men and women, people with other health problems). If we don't test for the virus, we will be unable to decide if our measures to contain transmission are working.

Serologic Tests (Ig):

These tests detect immunoglobulins M and G (IgM and IgG). IgM is the largest immunoglobulin and is the first to appear after initial exposure to an antigen. IgG is the most common antibody found in the body, which will appear later but will be generated in abundance. These tests can determine whether a patient has previously been infected with coronavirus, as they will stay positive after active infection has gone.

Rapid tests – that work like pregnancy tests (but detect antiviral antibody instead of pregnancy hormones) – on the other hand are faster and potentially cheaper but have less accuracy than lab methods. Instead of a test tube, these tests use specially modified paper. The blood sample flows along the paper and gives that well-known "one line = negative, two lines = positive" stripes.

IgM/IgG serological tests also have some limitations;

- Mainly related to the slow pace of the human antibody response to COVID-19. Although, several studies are still on-going, COVID-19 antibodies may not be detectable before 3 days after onset of symptoms (or at least 7 to 10 days after infection)
- Because the antibody blood test is designed to check for an immune response that's most prominent after an infection has run its course, it could miss new infections. If a patient's blood is tested too soon, antibodies may not yet be present, even if the virus is already replicating in their bodies
- When tested alone in the first week of infection, the PCR test has a detection frequency 45-70%, while the Antibody test has a lower detection rate of 40% - 60%.
- When tested alone in the chronic phase of infection (a sick person who has had a disease, repeated illness), the PCR test has a lower detection rate of 35%-50%, while the Antibody test has a higher detection rate of 50%-70%

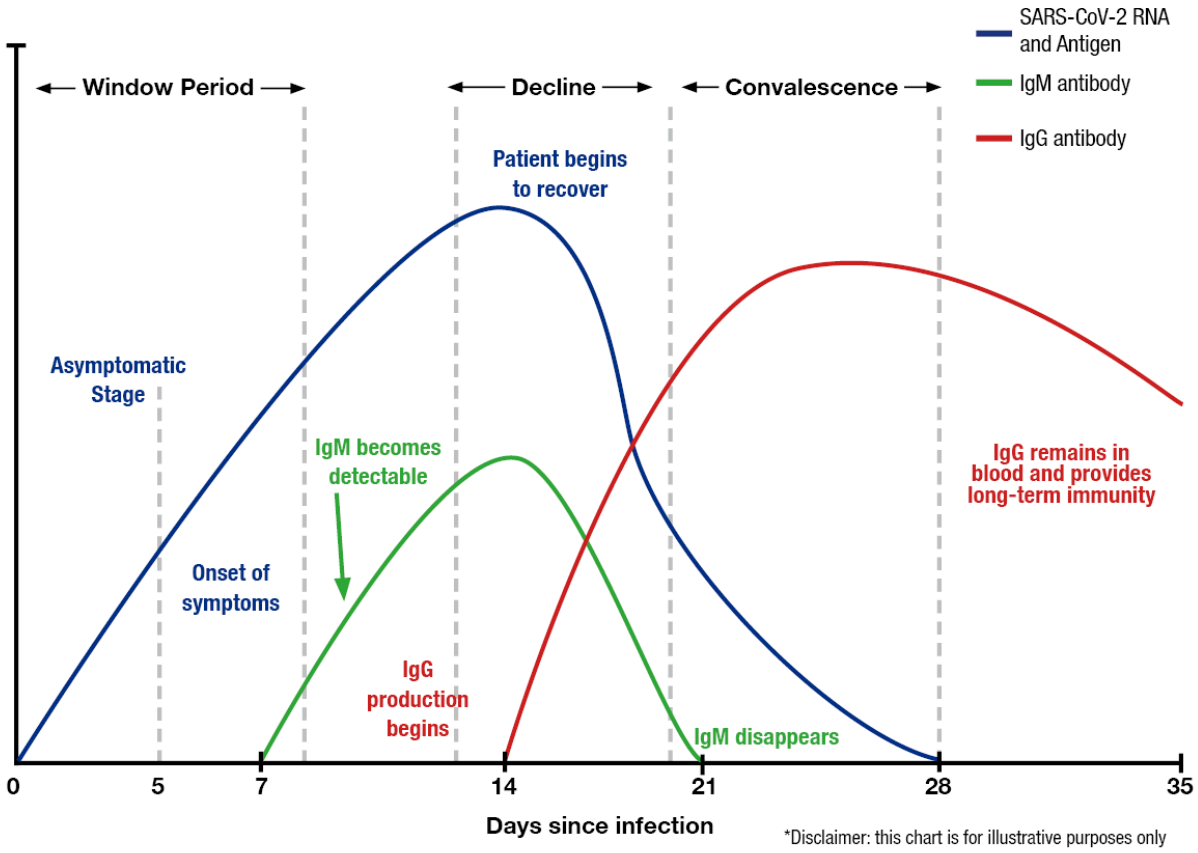
Widespread use of such a test would reveal what percentage of the population was infected with the virus, but these tests are less likely to detect cases in the early stages of the disease. In cases where the molecular test is negative but there is a strong clinical suspicion of COVID-19 disease, serological testing can support the diagnosis as soon as validated assays are available.

Although IgM/IgG serological tests alone may not be sufficient to diagnose COVID-19, they can be a valuable diagnostic tool in combination with PCR. Just as PCR tests alone are not enough, they should be used in combination with IgM/IgG Antibody tests. In addition, because of their scalability, serological analyses can be used in large-scale, whole-population testing to assess the overall immune response to the virus and identify asymptomatic carriers of the virus. Indeed, 20-80% of COVID-19 cases are assessed as asymptomatic.

Conclusion:

In General, while **PCR testing** may be appropriate for detecting COVID-19 virus in the **acute phase**, **IgM/IgG** is a suitable **test in the chronic phase**. Since the exact time of infection is often unknown, a combination of PCR and IgM/IgG testing can increase the accuracy of the COVID-19 diagnosis.

The more testing you do the clearer the picture is on who is infected and thus who needs to be isolated. Singapore, South Korea, Germany, they seem to have had a better course of the pandemic so far than other countries who don't have such a high testing capability. That can help alleviate some of the restrictions on movement sooner and give a better idea of what's going on. It's vital that testing, whether it's PCR or antibodies, is ramped up as much as possible to provide clear evidence on what is happening and where we should be going.



Variation of the Levels of SARS-CoV-2 RNA and Antigen, IgM and IgG after infection

Important Note:

Since the FDA issued the policy, over 70 test developers have notified the agency that they have serological tests available for use. However, some firms are falsely claiming that their serological tests are FDA approved or authorized, or falsely claiming that they can diagnose COVID-19. The FDA will take appropriate action against firms making false claims or marketing tests that are not accurate and reliable.

References:

1. WHO Policy Brief "Advice on the use of point-of-care immunodiagnostic tests for COVID-19"; April 2020
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3. COVID-19 tests: how they work and what's in development; March 2020
4. Why Do We Need Antibody Tests for COVID-19 and How to Interpret Test Results; April 2020.
5. FDA Statement – "Coronavirus (COVID-19) Update: Serological Tests"; April 2020
6. SMC – "Expert comments on different types of test for COVID-19"; April 2020
7. Verdict Medical Devices –"Different paths to the same destination: screening for Covid-19"; April 2020