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Why testing is so critically important.

A great deal has been said about testing and test kits in recent days. But a great deal more needs to be said. Testing is critically important in preventing and treating infection with coronavirus SARS-CoV-2 - the cause of COVID-19 disease.

On March 2, 2020, FDA commissioner, Stephen Hahn, stated that "close to a million" tests would be available by the end of the week. Subsequently, Vice President Pence said that target would not be reached. A million tests may seem like a lot but number is woefully inadequate for the task at hand. What is actually needed are *hundreds of millions* of tests - enough kits to test a substantial percentage of the US population, to test animal reservoirs, to assess and monitor environment sources, to increase the global availability of testing, to deploy tests of multiple types from multiple manufacturers, and to repeat assessments in a rapidly iterative fashion. Along with treatment and education, the development, evaluation, industrial production, and deployment of diverse testing methodologies at an unprecedented scale should be an immediate national and international priority.

Testing and test kits are often discussed as if they represent a single entity. However, there are a multitude of ways to test for the virus. Diverse tests provide important tools in the battle against this deadly infection with the different types of tests contributing in unique ways to our understanding of this virus.

The type of test used in the first paper on the virus by Zhu and coworkers was called an RT-PCR test. This refers to reverse transcription- polymerase chain reaction. The importance of this type of test is underscored by the fact that several Nobel Prize discoveries went into the development of this test. RT-PCR assays test for specific genetic sequences that provide a genetic signature for the presence of the virus. RT-PCR is rapid, sensitive, and specific. But even RT-PCR tests can vary greatly in terms of which viral sequences are used.

In order to properly validate tests and ensure tests of the highest quality, it is necessary to simultaneous use multiple types of tests on the same individual. This also points to the importance of high capacity testing. These individuals should also be tested for the presence of other common respiratory infections such as influenza and even other coronaviruses that may lead to significant comorbidities and confound the interpretation of test results.

Outbreaks aboard ships such as the Diamond Princess and the Grand Princess provide an ideal natural experiment to acquire critical information about the virus. In the best-case scenario, every person on the ship should have had multiple types of tests on a daily basis. While this might seem like a bit inhumane to turn these

confined and imperiled individuals into guinea pigs, the fact is that such test would be far less onerous that what is endured by a typical hospital patient on a daily basis. In addition, these travelers may have greatly benefitted from such testing by knowing their status, for example, by the early diagnosis of infection or by earlier release from quarantine. In addition, the service they would be providing for humanity would be profound and certainly life-saving. It would not be unreasonable to offer these individuals financial and other incentives.

Serial testing allows us to determine the earliest point at which the virus is detectable and how long the virus is detectable before the occurrence of symptoms. Combined with epidemiological data of when people interacted and contracted the infection, serial testing would allow us to determine the period when individual first become contagious, when that contagion peaks, and when infected individuals are not longer contagious. If the presence of virus precedes the period of contagion, serial testing would allow us to do "molecular quarantine" whereby only individual who test positive would need to be isolated. Instead of confining individual we could simply test them and if the virus is present, quarantine them prior to the time when they can transmit the virus to others.

Polio provides an illustrative example where each symptomatic case that is detected may signal the presence of over a hundred asymptomatic cases. In order to prevent symptomatic cases, one needs to detect the asymptomatic cases to prevent the symptomatic ones. Of critical importance is determining the percentage of individuals with asymptomatic but transmissible infections.

One of the most frequent questions involves whether or not environmental sources such as doorknobs - so-called fomites -may transmit the virus, and also how long the virus can persist under various conditions. Again, like polio, environmental testing as well as human testing may be important. Therefore vast numbers of kits are needed for environmental testing.

RT-PCR has a great many uses, but it will not allow us to determine if someone was previously infected and their immune system successfully cleared the virus. The most useful test of this sort is a test that looks for the presence of antibodies to the virus. There are many antibody tests that are currently used for viral diagnosis. The most common type is called an ELISA antibody test and this type of test is used for a wide range of infectious agents including HIV and hepatitis C virus. ELISA stands for Enzyme Linked ImmunoSorbent Assay and refers to the method by which coronavirus antibodies are detected. A priority also needs to be placed on the immediate production and distribution of vast numbers of ELISA tests, again on the scale of hundreds of millions.

On the Diamond Princess, for example, some passengers may have had the virus and cleared it and were therefore being unnecessarily confined.

ELISA antibody tests may also be used to identify cured individuals with high levels of antibodies, individuals whose plasma may serve as life-saving therapy to the most seriously ill or as a preventive for the most vulnerable.

We can also identify individuals who have already had the virus but do not know it and therefore continue to live in fear. Testing will also allow us to determine if re-infection is possible, if bodily fluids other that respiratory secretions may pose significant risks, and if the virus may cause persistent infections of the sort that are seen in Ebola and Zika virus infections.

If we hope to have effective treatment in the future, assessment of candidate drugs needs to begin immediately and serial testing will be critical to determining whether or not such drugs are having the intended effect.

Another type of assay that is not being carried out at sufficient scale is determining the genetic sequence of the entire virus. This type of testing allows us to follow the evolution of the virus. It may be possible to determine whether specific genetic changes are associated with changes in the behavior of the virus such as super-spreading or susceptibility to drugs. As an RNA virus, coronaviruses mutate at a high rate and such changes are expected. This type of testing can also be used to do molecular epidemiology using changes in the sequence in order to follow the transmission of the virus from one individual to another and thereby provide a high-resolution picture of the patterns of viral spread.

Another use of testing is to confirm the source of the virus in various animal hosts. One issue that has not received sufficient attention is the possibility that humans may be transmitting the virus to new animal sources creating new reservoirs in new locations. Widespread testing will allow us to address this question.

It is important for the government of the United States and other economically developed countries to provide vast number of test kits to underserved regions of the world. As a global pandemic, every outbreak, especially if undetected, poses a risk of igniting new foci of infection domestically or abroad.

Other testing modalities may also provide important insights into the ways in which coronavirus spreads and causes disease. For example, viral culture can provide insights into disease pathology, and antigen capture may provide rapid point of care assessment of infection.

The development of megatesting may seem like an expensive proposition, but it will reap massive economic benefits in the long run. Anything that curtails the epidemic domestically and abroad is likely to slow down or reverse the economic tailspin. New technologies will be developed in conjunction with generating this expanded capacity. Most of the expanded capacities have a dual use in that they can be rapidly adapted for use with known infections and disease as well as emerging threats. Of

greatest importance, however, expanding our testing capacity will provide a bulwark against disease and save untold numbers of lives.

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For your reference, here is the article by Zhu et al.

Zhu, N. *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* NEJMoa2001017 (2020).

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