“Test, Re-test, Re-test”: Using Inaccurate Tests to Greatly Increase the Accuracy of Covid-19 Testing

Professor Kamalini Ramdas1  Lord Ara Darzi2  Dr. Sanjay Jain3

Commenting recently on rapid point-of-care tests, US Covid-19 coordinator Dr Deborah Birx said, “We are very quality-oriented. We don’t want false positives.”

“If they are incredibly accurate, we will work out the quickest way to release them. If they are not accurate, we will not release any of them.” echoed UK chief medical officer Chris Whitty.

Given the need for testing, the end goal is a quick, accurate, and cheap test. With scientific innovation, we will, in time, attain this goal. But the best is becoming the enemy of the good. Meanwhile, avoidable infections are growing.

The “gold standard” RT-PCR test for Covid-19 is highly accurate and reproducible, but is costly ($125 per test kit, over $15,000 to set up a processing lab) and slow (4-6 hours processing time, turnaround of 2-4 days including shipping).

At the other extreme, a Bangladeshi lab has reportedly developed a $3 rapid test kit which gives a result in under 15 minutes. But the accuracy of such point-of-care tests is questionable.

Smart tactics can help break this tradeoff between cost and quality.

First, consider a quick and cheap test which is both inaccurate – with a false negative rate of 30% and, for simplicity, zero false positives – and unreproducible. If a patient is tested twice in succession using this test, the results could vary. Counterintuitively, this lack of reproducibility may be advantageous: if the results are independent, the chances of obtaining two false negatives drops to 9%. (And to less than 3%, on third repetition). Figure 1 illustrates this logic, which also applies to false positives. By comparison, since 2017, USFDA-cleared rapid influenza diagnostic tests have been required to achieve false negative and false positive rates of below 20% and 5%, respectively, compared to RT-PCR.

The implication is clear: even an inaccurate test tells us something. Or, to misquote the WHO: “test, re-test, re-test”.

Second, this recommendation to test and re-test can apply elsewhere too. Consider two cheap and quick tests that each display the same false negative and false positive rates as above, but this time combined with high reproducibility. What if both tests were administered to the same individual, each based on detecting a different antigen, or the same antigen, but via a different method? Again, if the results of the two tests are independent, the likelihood of two false negatives (or two false positives) drops to 9%.


2 Co-Director of the Institute of Global Health Innovation, Professor of Surgery, Faculty of Medicine, Department of Surgery & Cancer, Imperial College, London, UK.

3 Senior Fellow in Economics, Department of Economics, Oxford University, UK.
Use of this strategy would be made easier if there were a database – updated in real time – of point-of-care tests being generated by labs around the world. This database, which could be assembled by an international organization like the WHO, would list the target antigen (e.g., the spike (S) or the nucleocapsid (N) protein of Coronavirus) and antibody it detects, the detection method (e.g., ELISA or Western blot immunoassays), its accuracy, reproducibility, turnaround time, testing-kit cost and sample-processing cost. With this information in hand, governments and international organizations can advise scientists on what combination of cheap tests would be optimal for specific nations.

Third, consider a quick and cheap test with a 30% false positive rate, and for simplicity, zero false negatives. First, test many individuals with this test, and then test the subset who test positive with a highly accurate test. This economizes on the use of scarce but accurate test kits, while allowing for much wider testing than would have been possible with the few accurate test kits available. In short: “test, triage, re-test.”

Finally, smart tactics can enable cheaper testing with the expensive RT-PCR tests, if a sample taken can fuel multiple tests. Some German hospitals are doing ‘block tests’, using a pooled sample from 10 employees, and then testing individually only if there is a positive result.7

One can take this idea further, by applying principles from discrete optimization. If the test is positive, then test two blocks of 5 samples each, and then further test the arm that tests positive. This mimics “branch and bound” algorithms for solving discrete optimization problems like the famous “travelling salesperson” problem,7 which requires finding the cheapest route for delivering supplies to a fixed number of stores.

These simple examples are illustrative. Naturally, several factors would come into play in their implementation. For example, block testing would increase time to diagnosis and may be more useful for asymptomatic low risk cases.

Finally, all inaccuracies are not equal. Right now, tests with a high false positive rate are less problematic – since people are being advised to stay home anyway – than those with high false negative rates. Further, a false positive for SARS-Cov-2 is unlikely to initiate treatment with negative side effects, like chemotherapy for misdiagnosed cancer.

The key point here is that creative use of currently available cheap and quick tests – even if they are inaccurate and unreproducible – can go a long way to reaching adequate levels of accuracy and precision, at least until the gold standard tests can be developed.

References


   https://www.theguardian.com/world/2020/mar/25/uk-coronavirus-mass-home-testing-to-be-made-available-within-days

2
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30420-7/fulltext


5. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. “Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors.”
https://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm

http://www.centerforhealthsecurity.org/resources/COVID-19/200228-Serology-testing-COVID.pdf


---

**Why Re-testing Increases Testing Accuracy**

<table>
<thead>
<tr>
<th>Flipping a fair coin repeatedly</th>
<th>Probability of event</th>
<th>Testing the same patient repeatedly using an unreliable test with 50% false negatives</th>
<th>Probability of event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heads</td>
<td>False Negative</td>
<td>False Negative</td>
<td>False Negative</td>
</tr>
<tr>
<td>Heads, Heads</td>
<td>False Negative, False Negative</td>
<td>False Negative, False Negative</td>
<td>False Negative, False Negative</td>
</tr>
<tr>
<td>Heads, Heads, Heads</td>
<td>False Negative, False Negative, False Negative</td>
<td>False Negative, False Negative, False Negative</td>
<td>False Negative, False Negative, False Negative</td>
</tr>
</tbody>
</table>

1. In the UK, rapid tests are “more likely to detect 50%-60% of those with milder symptoms — the group for whom the tests were intended.” [i.e., false negative rates of 40%-50%]
https://www.theguardian.com/world/2020/apr/30/coronavirus-testing-labs-could-be-unreliable-says-scientist