The pandemic - a driving force for innovation in diagnostics?

Ciaran Fulton, Head of Diagnostics, Centre for Diagnostics Development, LifeArc

To slow down the spread of SARS-CoV-2, many countries focussed on identifying and isolating infected individuals – and the rapid development of accurate and reliable diagnostic assays was instrumental to this strategy.

Driving innovation in clinical diagnostics can take time as, by necessity, it must be a controlled and regulated process. But the pandemic has created a melting pot for innovation at an incredible pace.

Ciaran Fulton, Head of Diagnostics, Centre for Diagnostics Development, LifeArc (Picture credit: Alex Orrow)

Mass screening strategies initially focused on the rollout of laboratory-based diagnostic assays. But as the virus gained momentum, we saw a greater push for more rapid tests that could be deployed in a wider range of settings - such as airports or schools.

The volume of new diagnostic tests hitting the market has been unprecedented - which is hardly surprising, given the scale of the problem. But with that came a fog of confusion around which tests are the best to use.

Picture credit: Alex Orrow

In this blog post, I reflect on the rapid evolution of diagnostics during the pandemic and the ongoing challenges. With the end somewhere on the horizon, I also look ahead to what it means for the future of our field.

Diagnostics thrust into the spotlight

Around one month after SARS-CoV-2 was first identified, its whole genome sequence was released - enabling researchers to design polymerase chain reaction (PCR) assays that remain the gold standard for diagnostics. PCR testing is reliable and accurate and lends itself to mass screening, but the downsides of the technology are that it requires specialised equipment and trained personnel.

The UK took the approach of setting up centralized laboratories to roll out large-scale PCR testing. But the combined logistics of getting samples to the laboratory and running the assay leads to a relatively slow turnaround time for delivering results - within a day or two of collecting a swab.

As the pandemic progressed and the role of asymptomatic transmission in the spread of the virus became more apparent, this highlighted the need for tests that could deliver results much quicker than PCR. Attention shifted towards lateral flow tests based on detecting the presence of viral antigens, which could be deployed as low-cost screening tools that can deliver on-the-spot results in a wide range of settings. But to date, no test on the market has yet matched the sensitivity or specificity of PCR - running the risk of false-negative results that could cause harm.

The other type of tests are immunoassays that are designed to detect specific SARS-CoV-2 neutralising antibodies in the bloodstream. However, as it takes a week or more for a patient to generate these at sufficient levels, their role lies more in monitoring how many people may have had the infection in a population - although we don't yet fully understand the immunology of the disease, such as the role that T cells play in long-term immunity.

LifeArc and COVID-19 diagnostics

As a charity, we are in the unusual and privileged position where we work to help research get to the patient, not to make money.

In the diagnostics arena, we partner with others to support diagnostic assay design, the development process and clinical validation. Our team has helped to develop diagnostic opportunities in advanced breast cancer and one of our current projects is a new test for tuberculosis (TB) in partnership with the University of St Andrews. The assay can be used as a diagnostic of active TB infection and as a tool to monitor a patient's response to treatment.

With so many others already developing COVID-19 diagnostic tests, we felt that we could make the most impact through driving innovation. We are funding two projects that are taking radically different approaches with huge potential to benefit patients.

A team at the University of Edinburgh is aiming to develop a new blood-based test that will detect a broader range of SARS-CoV-2 antibodies than those currently used. Such a test would enable researchers to better characterise the immune response, personalise treatment, predict re-infection rates, measure the length of the immune response, provide population-level data and monitor the effectiveness of vaccines.

The other project, which is led by researchers at Addenbrookes hospital in Cambridge, is developing a molecular profiling panel for critically ill COVID-19 patients. Targeting 96 genes including the host immune response, viral and microbial factors, the results will help inform the most effective treatment for each patient, giving them the best chance of a good outcome.

LifeArc, Edinburgh

A catalyst for change

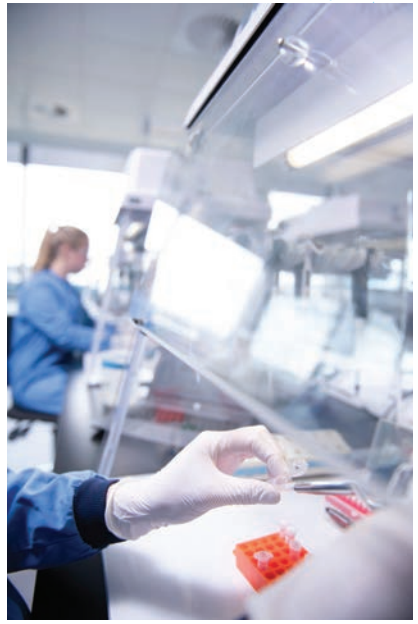
There can be little doubt about the central role of diagnostics in global efforts to control the pandemic - and we should now grab hold of the opportunities that have become available to continue that momentum.

In the UK, the establishment of centralized testing infrastructure has certainly been a monumental achievement. These laboratories now provide exciting new opportunities to roll out other PCR-based diagnostic tests, not just for infectious diseases, but also for non-communicable diseases such as cancer.

We've also collected a wealth of clinical data from this pandemic, from which I've no doubt we will tease out new angles for diagnostic testing other than detecting the virus - for example, looking at molecular signatures of the host immune response to predict disease severity.

But what stands out to me most is the gap we had in our diagnostics toolkit. We needed simple, accurate, reliable and low-cost tests that could deliver results in minutes. To reap the biggest benefits from diagnostics, we need to create tests that are easy to access and deliver more immediate results.

Over the coming years, I think we will see a shift in the diagnostics field - albeit at a less frenetic pace. We will move from centralised testing in hospital laboratories to a new generation of point-of-care diagnostic devices in community settings - such as in GP surgeries or pharmacies.



Picture credit: Alex Orrow

And it's not such a huge leap of imagination that the next step will be self-testing diagnostic kits that people can use at home. I imagine there will be a range of consumer devices that become available within the next five years or so, perhaps integrated into the Internet of Things, enabling people greater access to potentially life-changing information about their health on demand.

The ability to deliver results to patients faster will be a big step forward, improving accessibility to testing and enabling more timely interventions for a range of different diseases.

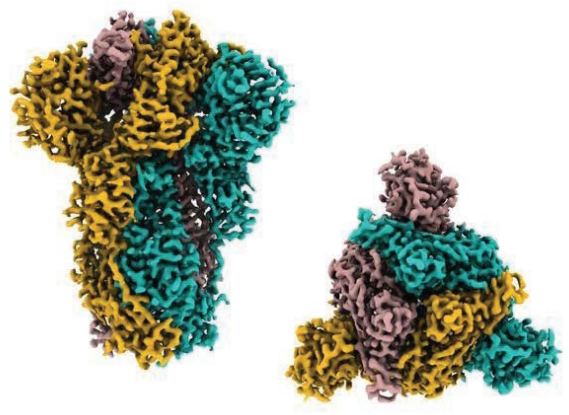
While the past year hasn't been a good one for humanity, we can only hope that we can learn from it to build a better future. The field of diagnostics has been thrust to centre stage, and I am certain that it will continue to play a transformative role in improving our lives beyond the pandemic.

Could Pangolins cause Coronavirus Infections in Humans?

Structural similarities between SARS-CoV-2 and a pangolin coronavirus found by scientists at the Francis Crick Institute, suggest that a pangolin coronavirus could affect humans although it doesn't rule out that another species may be a carrier of a coronavirus that will jump to humans. While SARS-CoV-2 is thought to have evolved from a bat coronavirus, its exact evolutionary path is still unclear as there are likely many undiscovered bat coronaviruses. Also due to differences between bat coronaviruses and SARS-CoV-2, it is thought that the virus may have passed to humans via at least one other species.

In the study, the scientists compared the structures of the spike proteins found on SARS-CoV-2, the most similar currently identified bat coronavirus RaTG13 and a coronavirus isolated from Malayan pangolins, seized by authorities after being smuggled to China. The pangolin virus was found to be able to bind to receptors from both pangolins and humans, while the bat coronavirus, could not effectively bind with human or pangolin receptors.

Antoni Wrobel, co-lead author and postdoctoral training fellow in the Structural Biology of Disease Processes Laboratory at the Crick, said: "By testing if the spike protein of a given virus can bind with cell receptors from different species, we're able to see if, in theory, the virus could infect this species.



Cryo-EM images of the spike of Pangolin-Cov, showing two different angles (credit: Francis Crick Institute)

"Importantly here, we've shown two key things. Firstly, that this bat virus would unlikely be able to infect pangolins. And secondly that a pangolin virus could potentially infect humans."

The team used cryo-electron microscopy to uncover in minute detail the structure of the pangolin coronavirus' spike protein, which is responsible for binding to and infecting cells. While some parts of the pangolin virus' spike were found to be incredibly similar to SARS-CoV-2, other areas differed.

The work does not confirm whether or not this pangolin virus is definitely part of the chain of evolution for SARS-CoV-2, but does support various possible scenarios for how the coronavirus jumped from bats to humans. One potential route is that SARS-CoV-2 originated from a different, currently unknown bat coronavirus which could infect pangolins and from this species it then moved to humans. Alternatively, RaTG13 or a similar bat coronavirus might have merged with another coronavirus in a different intermediate species, other than a pangolin.

Donald Benton, co-lead author and postdoctoral training fellow in the Structural Biology of Disease Processes Laboratory at the Crick, added: "We have shown that a pangolin virus could potentially jump to humans, so we urge caution in any contact with this species and the end of illegal smuggling and trade in pangolins to protect against this risk."

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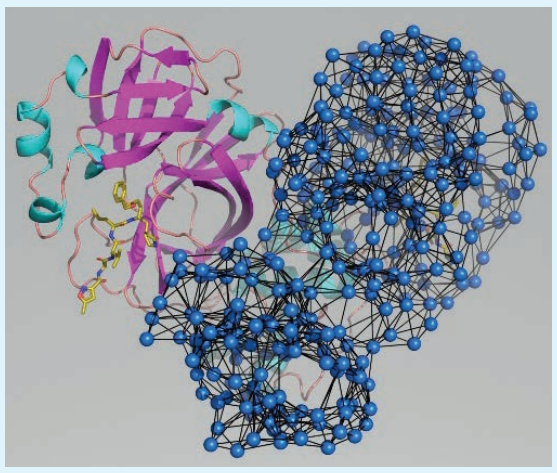
Modelling Highlights Vulnerable Sites on SARS-Cov-2 Protein



Picture credit: University of York

University of York scientists have been able to identify potentially vulnerable sites on a key protein found in coronavirus using computer modelling, paving the way for possible new drug treatments in the future.

The coronavirus responsible for the Covid-19 epidemic deploys dozens of viral biomolecules when it invades host cells with the disease. One of these is a compact protein, the main protease, whose function is critical to the virus. By analysing the structure of the protease using modelling techniques, the scientists have been able to simulate the protein's motions, suggesting sites that might be accessible to new drugs.

The study (1), by Tom McLeish, Professor of Natural Philosophy in the Department of Physics and Igors Dubanevics from the School of Natural Sciences, 'was not related to the current vaccines, which are based on the 'Spike' protein, but is a study of another key protein in the Covid process,' Prof McLeish said. He added: "It is more relevant to potential future drugs than to future vaccines, as the motions of the protein that it uncovers point to new 'sites' on the protein where binding small molecules might disrupt the protein function. The advantage of these sites, and our method in general, is that they are not the 'obvious' ones that compete with the normal binding of the protein, but other sites that can be accessed even when the usual binding sites are occupied."

Igors Dubanevics said: "We have identified promising druggable sites in the main protease via computer simulations and some of them have been supported by the newest studies by other groups. The next logical step would be to investigate the identified sites by conducting biological experiments in a lab.

(1) Published in the *Journal of the Royal Society Interface*.

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Consortium to provide Swifter Pandemic Predictions

UK Research and Innovation (UKRI) is providing funding of £3 million will bring together leading mathematical and statistical modellers from seven UK universities to produce rigorous predictions for the COVID-19 pandemic. The 'Joint UNIversities Pandemic and Epidemiological Research' (JUNIPER) consortium will develop and use bespoke models to provide predictions and estimates on key questions about the COVID-19 pandemic. These results feed regularly into SPI-M, the modelling group that provides evidence to the Scientific Advisory Group for Emergencies (SAGE) and the wider UK government.

The research groups include that of Professor Deirdre Hollingsworth of the Big Data Institute based on the Oxford University Campus. The other universities are the University of Cambridge University of Warwick, University of Exeter, University of Bristol, The University of Manchester and Lancaster University.

They will work closely with many other organisations and research teams active on COVID-19 research including the Alan Turing Institute, the Royal Statistical Society, Health Data Research UK, Public Health England, the Royal Society's 'RAMP' initiative and the Isaac Newton Institute for Mathematical Sciences.

More information online: ilmt.co/PL/lDlo

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Picture credit: Big Data Institute