[Voiceover] Welcome to The Pathologist Cut podcast. This RCPA podcast highlights the critical work of pathologists and the integral part pathology plays in medicine and health care.

[Dr Michael Dray] Welcome back. This is part two of our discussion on PCR and rapid antigen testing. For those of you just joining the podcast, we've been talking with Dr Michael Harrison, who's been giving us some insights into the role pathology testing and the COVID epidemic.

We've been discussing the role of PCR and we're about to discuss the role of rapid antigen testing. Now, you might have noticed that I'm sure you have over the last two or three weeks, there's been quite an increasing level of commentary promoting these rapid antigen tests, or was that the acronym R A T.

For the detection of COVID-19? As a college, we've been concerned about the level of evidence that's been used to back up some of the commentary. Can you tell us what you understand about rapid antigen tests? Are they a solution to a problem that we have, or are they a solution looking for a problem here in New Zealand and Australia?

{Dr Michael Harrison] The standard PCR test, which is we call it the gold standard, is the test that we've used throughout the pandemic. And we know that it's very sensitive and it's very, very specific, because it takes a segment of the RNA that specific for that virus.

And it may even be specific for that strain of the virus or variant. With the antigen tests, the detecting, actually the protein that that RNA codes for or some of that RNA code for. And as such, it's inherently less sensitive than a PCR test, which has got that enormous multiplication or amplification factor built into the actual chemical reaction.

And so the rapid antigen test, which does detect the viral protein, can actually take relatively small amounts of that protein. But the actual sensitivity is much less than a PCR assay. And we also do notice, we have noted that there are problems with specificity.

So we will occasionally get patient samples positive, even though they don't have the infection. And so those two issues associated with it, just the inherent chemistry of a rapid antigen test, will make them less useful in this circumstance.

The sensitivity is lower. It can be as low as 50 or 40 percent. And so that means that you'll miss half of the actual infections and the specificity will often be in the 90 percent. But when we're not, as you know, even in a time of a pandemic, 999 out of a thousand tests are going to be negative. You probably only need a very, very, very slightly less than 100 percent specificity for most of those positive tests in a RAT test to be false positives. And even though because the simplicity of it, the fact that you can do a test there with the person providing the sample at the time and give them the result right away, it seems very attractive.

But if you get the wrong information out of it, I don't think the attractiveness is so good. And in fact, I know that the public health people who are involved in contact tracing and identifying, once they've identified a positive case, identifying all the contacts for that case, I really don't know how they could actually manage a detection system that has those sort of attributes that where only half the positives are actually true positives. And may miss some of the positives as well. And I just don't think there's any appetite for degrading the quality of the testing that we're currently doing for COVID because of the problems of that would cause.

[Dr Michael Dray] That's very true Michael, and certainly our contact traces are busy enough tracing the real positive COVID diagnosis without having to chase false positives. And we then don't want the false reassurance of a false negative test, allowing people to continue on, reassured that they will, thinking that they are COVID free and continue to infect so it can affect our community in two ways. There seems to be quite significant differences between the performance as claimed by manufacturers and in the real world. How do we explain those differences?

[Dr Michael Harrison] Yeah, look, it is hard to do that. I think a lot of it relates to the fact that the trials are done in a different circumstance. For example, if you did a trial of a RAT test in an area where there was a lot of infection, you'd probably find that infected performs not that dissimilar to PCR test. But it's where if you're actually with telling everybody to come in, whether they've got a sniffle or even a really a very light exposure to come out to test, you're going to expect to find the vast majority of those tests negative.

And as we know, our current positivity rate is point 1 percent. So one in a thousand. And I don't think there's any rapid antigen test that will perform reasonably in that in that sort of prevalence.

[Dr Michael Dray] Michael, as you know, the college has recently updated its position on rapid antigen testing and issued a new position statement. I presume that you're up to speed with this. Wondering if you could talk about the circumstances where rapid antigen testing may be beneficial?

[Dr Michael Harrison] Yes. So, look, I am I think where you've got a closed community and you've identified that COVID is occurring there and you don't have an easy access to the PCR test then it's better than nothing. And it will allow you quickly to identify people who are positive and who can therefore be isolated.

And it can be useful to support an outbreak investigation. But as I say, it's not the sort of thing that you'd want to use more widely. So it's where you've got a confined outbreak. And I think an example of this could well be something like a mining camp or a prison or something like that, where there's a whole lot of people who are cohorted together and

you want to see it immediately, who's likely to be infectious and be able to take them out of contact with other people. We knew from very early on in the pandemic that the people who had symptoms are much more likely to be positive by the PCR test.

And in some of those patients, you didn't have symptoms would have very positive PCR assays. And therefore, we'd anticipate that most of those people would be rapid antigen negative, and they are, in fact. So the simple the asymptomatic patients are more challenging from a point of view of a diagnostic point of view.

And, of course, I've mentioned already that some of those people who've had COVID infection will maintain that PCR positivity for sometimes for months following the apparent resolution of their symptoms. And they're probably not infectious. In relation to what do you do with a positive result, every positive PCR result has subsequent testing done on it. We would always repeat the PCR assay, would do another PCR assay, looking at different targets. So we typically use a target screen with and that's the e gene and would use the n gene to confirm with.

We could also use an RDRP gene and some assays use that as well. But these certainly these days in Australia and New Zealand, every positive that we get like PCR then goes off for sequencing. So we can see which strain of COVID virus is there.

And so the same thing would have to happen with a positive rapid antigen test. The rapid antigen test would need to be confirmed. And probably the only way to confirm that is to collect another sample and submit that for PCR testing.

And then that really brings us on to quality assurance and quality control, PCR, because they're run in batches that have quality control, control samples with every batch will have negative and positive controls being tested the whole time. Every plate has got some of those on them.

And that's one of the things that you miss out on when you're doing a test by a rapid antigen test. You've got no way of controlling those sorts of things. But we also do run, and the QAP program was very quick in setting up a quality assurance program for COVID-19 testing.

They do send out lots of samples to people to test, to check that assays are performing well and to compare their assays with other assays. There is a little difference in sensitivity, but it's usually right at the high end of the amplification charts and also to make sure that there is adequate specificity.

It's usually not a problem with PCR saying that the results of the PCR, QAP have been really excellent. And across Australia.

[Dr Michael Dray] There's quality assurance, which sets a diagnostic pathology laboratory

apart from any other laboratory. That's that use of internal controls with known positives and known negatives to test your tests against. And it's also that participation in an external quality assurance programs. And a plug for the RCPAQAP, that were one of the first organisations in the world to develop a QA program for COVID-19 testing. And in fact, they were invited, or asked by the World Health Organisation to also participate in providing QA for other jurisdictions and other organisations. That's one of the weaknesses of the rapid antigen test that's missing out all that that QA framework to ensure that the test is giving the right answer for the right patient. Again and again and again.

[Dr Michael Harrison]That's correct.

[Dr Michael Dray] We talked earlier before we started recording, Mike, about the logistics of doing the rapid antigen test. Have you sort of experienced one being done and can you sort of explain what that would look like?

OK, so it's a manual process generally, although they do have some automated readers on these some of these tests. But still, it's the application of the material that you've obtained through a throat and nose swab onto a window or an application area of the test.

And then usually some other solution has to be placed on that, which will allow the antigen, if it's present, to actually be to go through to reaction through the reagent layers. And then you get a visible result coming out of that testing mechanism.

So it's a one time thing. It's done manually. Usually a lot of the manipulation is manual. And right up to the point of actually applying the material to the test strip or the test window. It's exactly the same as what you've been doing for the PCR test.

And then clearly there's a period of time that you have to wait for the test to generate a result. And therefore, it's not a scalable thing. If you had a small number of people that you wanted to do and you had an individual who was both collecting and doing the testing, then that person would be there for a long period of time, gradually working their way through that that number of people and samples. And compared to the sort of scalability that we have in central laboratory, some of the PCR test where we might be doing 10000 or 15000 tests in a day, not, 15 tests an hour.

So the scalability of the rapid antigen test is much less than that of things like the PCR assay.

[Dr Michael Dray] Well, that's really interesting. I'm coming to the end of my questions here, Michael. Is there anything that you think is important that you want to talk about regards antigen testing or PCR testing? Well, the role of laboratories in COVID-19,

[Dr Michael Harrison] I think we've actually identified that there are circumstances where we need a rapid result, but a lot of those circumstances are now actually being reasonably well catered for by point of care testing, PCR tests. So there are a variety of these, and they're being distributed throughout fairly wide geographical areas.

For example, in probably every regional centre in Queensland has got that capability now, both in the public and the private system. And a good example of where you want would want a rapid PCR test would be where somebody comes into an emergency centre with a clinical syndrome that's consistent with COVID-19.

And you want to know how to manage that person. And the result that you use to manage that person has to be highly sensitive and highly specific. Exactly the attributes of the PCR test. So in those people, we would do a rapid PCR test and then you can say, well, they do have COVID and will have to be managed, isolated, critique the risk of a hospital community or they don't have it and they don't have to be treated that way. And that's really important. And so I think we do have the we have the best of both worlds.

We've got a scalable, highly sensitive and specific test. It's done in a centralised facility with an appropriate turnaround time to follow up people. And then we've got this rapid PCR assay which enables you to deal with those exceptions.

Those rapid tests aren't able to be done at scale. You could do the most you could do would be four in an hour, for example. And that's not adequate in many circumstances for the sort of volume of testing that needs to be done.

[Dr Michael Dray] But as you say, they used in a quite a specific scenario where someone's got symptoms. They're in a they're in a hospital or medical care scenario, and a decision choice needs to be made, which is different from the sort of more screening in the community.

So it's a different, different role there, isn't it?

[Dr Michael Harrison] Yes, it is.

[Dr Michael Dray] So, Michael, it's been an interesting 18 months to be a pathologist. And have you enjoyed it?

Yeah, I have. It's been it's really I've described it as a as a sprint that turned into a marathon. And it's been a thing that's had all sorts of twists and turns to it. So there has been the science.

But this it's been also the management of risk, and it's the management of the public in relation to risks associated with infection and how you actually do that. It's how you communicate this information, which is often a highly technical and scientific matter to

people throughout pathology practice, let alone to the community itself.

And it's been a very interesting journey.

[Dr Michael Dray] And what's your crystal ball like for the next few years?

[Dr Michael Harrison] I think COVID's going to go the way of flu, albeit a very bad flu. So I think high levels of vaccination are the way out of these outbreaks that we're currently still seeing. And then once we've got high levels of vaccination, then it's very likely, I think, that the virus will keep mutating, as we've observed already.

And we will have to be likely to have an adaption of the of the vaccine on a regular basis. I think we'll be having at least annual, but maybe even twice yearly COVID booster shots with a new strain, with a new vaccine that actually covers most recent strains we are having.

And I think that's the way that we'll manage this process. People will still get COVID infection, but there'll be very little serious disease as a consequence of that. And so that's very analogous to the situation we were previously with flu.

And I think it's something we're going to find that we'll have to live with.

[Dr Michael Dray] That's right. It will become very much a vaccine controlled illness. And we forget how many thousand people a year die of influenza. And we've forgotten about that a little bit as well. And with the COVID epidemic.

[Dr Michael Harrison] That's right. It was several thousand a year in Australia would die every year from flu. And that's even with reasonable levels of infection, vaccination. And I think we can do better than that.

[Dr Michael Dray] And Michael, it's been lovely talking to you. Do you have any advice for the aspiring medical student or young person looking, looking for a career? What would you tell them now in 2021?

[Dr Michael Harrison] So I think I think this there's going to be a lot of consequences of this. And many of them really relate to, you know, how we best use our health care system to deal with these sorts of issues.

So there'll be a lot of organizational change that's going to occur and there'll be a lot of people involved in that. And but I think we'll get the outcome will be better for sure.

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