[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 to our latest podcast. This episode is part one of a two part discussion surrounding PCR and rapid antigen testing. It's my pleasure to introduce and speak with Dr. Michael Harrison is the managing partner and chief executive officer Sullivan Nicolaides Pathology, which is one of Australia's largest diagnostic testing laboratories.

It was also my predecessor as an RCPA president from 2015 to 2017. Dr Harrison is an influential and respected national figure with a long history of service to pathology, holding numerous key professional and governmental positions. You've been in the media a lot, Michael, and you've done a lot of speaking and you've done a lot of thinking, obviously about the rolling out of COVID testing and what the pandemic means to the diagnostic laboratory setting. There's been a lot of talk in the media recently about Australia's COVID-19 testing strategy and which of the increasing variety of tests are appropriate in our current settings.

Now, Michael, as CEO of one of Australia's largest diagnostic testing laboratories. We thought it would be a good opportunity to get you on the podcast to discuss what testers recommended and what test isn't recommended.

[Dr Michael Harrison] So really COVID came along at the end of a development of different testing strategies for other respiratory viruses. And SARs clearly before that we were doing a lot of testing for things like influenza virus and respiratory virus, and we established a very proficient laboratory doing molecular pathology testing, looking for the RNA of those viruses. And so it was pretty easy for us to switch from influenza testing to COVID testing using the PCR technique. And the main challenges were finding how that assay worked and finding the attributes of the assay. What were the best specimens to use?

And it was going to be a respiratory specimen. And then some of the nuances in relation to, well, how do you actually scale something like this up to the levels that we've had to scale it up to. And everything is at least a level, greater than what we've previously been doing and more than that.

So now in our highest activity time during the last flu epidemic, which was 2019, we were doing up to 2000 tests a day here in my laboratory diagnosing flu A or flu B, this time with COVID with we've got to over 15000 COVID tests in a day.

So it's another scale altogether.

[Dr Michael Dray] And certainly those numbers are really tested, the whole the whole laboratory infrastructure to be able to do that, do that type of testing.

[Dr Michael Harrison] Yes, that's right. Because the laboratories have generally been involved in certainly in the community pathology area in actually collecting the sample and also then transporting the sample. Then it's received in the laboratory into a central

 

laboratory, because these are highly specialised tests that do need to be done in in a laboratory with specialised equipment, but also specialised expertise. And therefore, centralisation has been a feature of COVID-19 testing, as it was for influenza testing previously. And then the issue then was making sure that we could get that result down to where it needed to be used in a rapid time.

And there was some real changes occurring in that area, too. So the first thing that we did look at was the sort of specimen that we needed. And we'd traditionally been using nasal pharyngeal swabs for influenza testing and other respiratory viruses.

And quite early on in the COVID epidemic, we were aware that the Chinese were using mainly throat swabs. So we looked at a throat swabs and nasal pharyngeal swabs versus a combined swab. And very quickly, it was quite obvious that the most sensitive test was actually the one that used a combined specimen, so throat and nasal pharyngeal. So that's what we've actually landed on and that's where we stayed on to.

[Dr Michael Dray] So the testing we're talking about the platform is this PCR, that's a well known platform of testing that we've been using for a long time with influenza testing, et cetera. So it wasn't actually having to reinvent the wheel to get the PCR testing up and running, is that right?

[Dr Michael Harrison] No, that's right, Michael. Early on, most laboratories had started doing COVID testing, actually had to develop their own assays, and it's only further on into the pandemic. The commercial assays would become available. And we had to determine which were the best targets to look for.

And a lot of laboratories have chosen a target. Which we know is well conserved, and we use each target to take the COVID 19 virus. But then we use another target. When you do get a positive result to confirm and that we use an engine target for that, some assays have both targets in them.

And there are pros and cons in relation to that. But overall, if you looked across the breadth of COVID 19 PCR testing in Australia and New Zealand, the level of sensitivity and specificity of those assays has really been really excellent.

And we are so good now that we can pick up the remnants of an infection. That was several months ago in some people. And that in itself can create a problem because you'll find somebody who's persistently positive by the PCR test at very low levels.

But there's no doubt that that's a true positive. And yet we know that at that stage of their infection, they're non-infectious and therefore their not a risk to people.

[Dr Michael Dray] So the beauty of using the gene that you described and the engine you mentioned that conserved. So with these change in the nature of COVID 19 and the new variants of concern coming out, we haven't found that those genes have been altered dramatically.

[Dr Michael Harrison] That's correct, Michael. And every time a new variant is identified and the actual sequence of nucleic acid sequence of that, there is determined people will look at their assays and look at the actual probes that you're using for their assay and determine whether there are any issues.

And to date, that hasn't been an issue with the PCR assays that they've been very good at detecting the different variants.

[Dr Michael Dray] that you do have that capacity to fine tune as sort of on the on the fly as it's required?

[Dr Michael Harrison] Absolutely.

[Dr Michael Dray] Now, we've been talking about the volume and the log increase in numbers of tests. And of late, the New South Wales have been doing 100000 tests per day. So that's record numbers and it's all the gold standard PCR. What is it about the PCR testing platform that enables that scale of testing?

[Dr Michael Harrison] It's not as automated a process as, say, a chemistry test done in a big laboratory with track systems and that sort of level of automation. But there are components of automation within molecular pathology that allow people to do this sort of testing on scale.

And if we hadn't been able to adapt our systems to allow for that, then we would never have been able to test the number of samples that we've tested. And that would have had a very significant impact on our ability to control the pandemic.

So we do have automated tube sorters. We also have automated extraction robots. So the first part of the PCR test requires that the RNA of interest from a variety of sources, viruses, needs to be extracted out of the sample.

The sample itself being a respiratory sample, has a lot of extraneous material in it. It's got a lot of mucus and other things. And we know that that significantly impacts or interferes with the PCR reaction. Early on in the in the pandemic, we did try to see if we could actually do a PCR without doing an extraction by using and heat to release the virus and to try and neutralize some of these other competing substances. But it didn't work. So we had to continue with extraction. And this is the way that most PCR is performed.

It's performed on an extracted sample that where most of the interfering substances are removed. So once you've actually done the extraction process, and that takes several hours in an automated platform and in an extraction robot, you can load up a series of samples, maybe hundreds of samples, and the robot will actually process this through.

And most of those systems use magnetic beads to actually bind the RNA and then allow that to be taken out of the specimen. And all the other material is in discarded and only that are now that you're interested in is in submitted for the PCR testing.

And then it goes through the standard PCR process. And again, that's usually done as a

batch and batch size can be 100 hundred or could be 400 or 500, depending on the architecture of those PCR instruments. But certainly, once you get to the point where you've gone through extraction and you've gone into a PCR analyser amplification system, you do get significant economies of scale. And my goodness, we needed that because a lot of laboratories around Australia and New Zealand have been doing thousands of these tests a day. And the only way that we could actually maintain the throughput, so we didn't get a backlog, but also provide results in a clinically relevant timeframe was to work all day and all night, basically. And that's what laboratories have been doing.

[Dr Michael Dray] So you've been describing quite a small process of the actual PCR test, haven't you? You've been just describing the RNA retrieval process. But can you put that into the broader context from the person who comes to the drive through COVID swab testing to the clinician or the public health unit that gets the result?

[Dr Michael Harrison] The first thing that we need to know is exactly who the person is and document that. So identification of the individual is really critical. And then we need to get their consent and tell them what we're doing and then collect the specimen.

And you need a trained person to collect the specimen from a good respiratory specimen, a combined throat and nasal pharyngeal swab. So we don't go all the way back to the back of the nose now. We found that you can go to mid-nose, mid-nasal, and that's a good sample.

But you need somebody who's trained to do that. But more importantly, you need somebody who's trained to use PPE, personal protective equipment. So even if that person that they testing has COVID they are protected from becoming infected. And that's a really important issue.

So the collectors who do that need to be trained in not only collecting specimens and using PPE and in particular after they've used the PPE and taking it off in a way that they don't contaminate themselves. And in fact, the story in relation to PPE used by pathology collectors in our countries has been really good, that we've escaped infection of those people because people have been able to use that well. And if it's used properly, it's almost 100 percent effective. So once the specimens collected from the patient and it's properly labelled and the patient is identified and sent, transported to the laboratory, and then it gets sorted and then it goes through the RNA extraction process, the PCR process itself, the PCR traces, each PCR trace of each sample is read by a scientist. And the positive traces are identified. They usually quite obvious. But in some circumstances, you may have to do an additional tests looking for a different target, because the pattern is not unequivocally positive.

And then the result is transmitted. And these days has been a significant change to the way that patients are involved in this process, in that the majority of people will get their results next to them, which is really a that's a very big change in medicine and in pathology in our countries.

So we've used the SMS process to be able to send people a negative result. And that's really important if they're waiting a negative result, not only just because I want to know that

they're negative, but also they might be able to then come out of isolation.

But that's been a very significant change. And it also it has a significant impact on the turnaround time of the test result. So if you can communicate the test result very efficiently, and SMS seems to be the most efficient way to do that.

It's interesting. When we first implemented that process, we did it because we wanted to let people know what their result was, that it was negative. We didn't want people ringing up and blocking up our switchboard, which was happening all the time, and people getting anxious about how long it may be taking.

But we also could say that if we use that sort of mechanism, we could do it as soon as a test result was available. So we had a discussion here about whether we should actually send out SMS negative results in the middle of the night.

And there was a general feeling that we could and people would be OK with that. And in fact, we know now that they're more than okay with that. People are happy to get a negative COVID result at one o'clock in the morning, for example.

And even if it wakes them up.

[Dr Michael Dray] So that's been quite a change in the laboratory, having a direct relationship with patients, and it's been driven by COVID. Do you see that happening in other aspects as well?

[Dr Michael Harrison] Look, it probably will, because the test result was going to be negative and the vast majority of cases, in fact, the negative rate in Australia is about nine hundred ninety nine out of a thousand. And you don't really need too much interpretation of a negative result.

You might need some instructions from a GP or a public health physician who says, look, until you wait for the full incubation period of the infection, you may still be turned positive and therefore you'll have to have another test, for example.

But apart from that, there isn't a lot of complex interpretation of a negative result, which is very different to other pathology test results. And this is we're dealing here with really one test.

[Dr Michael Dray] So you've described a lot of activity going on behind the doors and in the laboratory. How have the staff, the large numbers of staff working large numbers of hours , how have they managed over the last 18 months?

[Dr Michael Harrison] They are very aware of the critical role that they're playing in controlling the pandemic, that they know that the testing that they're doing is the thing that's directing the whole of the public health response to COVID 19, whether it's isolating people or identifying contact points or even doing things like telling people that they have to go and be admitted to a hospital because they've been identified as being positive. So they are

aware of the significance of what they're doing. From their perspective, it's business as usual. They've done this sort of testing for years. It's just probably never done it at this scale.

And the other thing that's really quite different in this circumstance is the fact that the volumes changed so that we have these things we call surges now. So you could be going along at a certain amount of testing activity.

And then the next day, because something has turned up in the community and there's been publicity about it. You might have a tenfold increase in the amount of testing that's being done. And that's something we have never seen before.

This is a really unusual circumstance. So people have to be really nimble while we have to have the ability to cope with surges in the laboratory. It will often mean that people will say, well, because this is happening, I'll stop doing this other work and I'll transfer to this area.

So we've had a whole lot of people who've had the ability to work across different areas of the laboratory and accept that there will be times when other work has to be basically put aside while we're coping with our COVID surge.

And that's happening not just in the laboratory where we're doing the testing, but it's also happening in collections. So where, you know, you suddenly get these huge numbers of people turning up to be tested because they're being given information about a risk episode that's occurred.

[Dr Michael Dray] It's difficult to write a roster for that sort of eventuality, isn't it? And I suppose one person doing the tests can only test X number of people per hour. And if you've got 10 times as many people there, it's going to blow out queues and things. And that must be difficult to manage on the ground there.

[Dr Michael Harrison] Yeah, it is interesting. Probably the biggest rate limiting step is just those manual steps. So once you get beyond those and you get into, say, a semi-automated area of testing, like the RNA extraction or the PCR actual assays, it's not too bad, but it's the data entry of all the details of the individuals.

It's the actual physical process. So the collection of the sample and those sorts of things are the things we found ourselves most stressed about. And I'd have to say my observation, as we've been going on through this journey, is that we were really under the pump to start off with.

We really found the sort of volumes that we were doing early on in the pandemic, difficult to manage. And there were a few times when we got to get behind by a day or so. Now we're doing many times those sorts of volumes, and you wouldn't even notice it.

You describe it as no sweat.

[Dr Michael Dray] Well, and that's a credit to just the sort of the tweaking of the systems and things like this. But those initial steps are so important. You don't want to be texting the

wrong person the wrong result. You know, if you if you if you haven't got the right patient details right at the very beginning.

So crucial steps to get right at the beginning.

[Dr Michael Harrison] Yes, that's right.

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