PATHOLOGY
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Position Statement

Subject: **COVID-19 Antigen and Point of Care Testing**
Approval Date: **13 October 2020**
Review By: **Board of Directors**

Rapid antigen tests of suitable sensitivity, greater than 80%, will have a role to play in the COVID-19 testing regimen deployed in Australia and New Zealand. These tests will best be deployed for serial testing (every 3 to 4 days) in screening high risk and essential workplaces to rapidly detect and isolate infected individuals. Thus, keeping workers safe and the economy running smoothly. PCR testing will remain the gold standard and will continue to complete high volume testing.

Background

Nucleic Acid Testing such as PCR and genome sequencing have been mainstays in diagnosing and monitoring COVID-19. These tests are performed on high volume testing platforms in our main pathology laboratories and at the point of care in regional and remote settings. The turnaround time for PCR tests ranges from less than 1 hour for point of care devices, up to about 48 hours in laboratories when testing numbers are high. These tests require technology of medium to high complexity and the operators needs to be well trained. COVID-19 antibody testing is also available for assessing the immune status of individuals post infection. Rapid antigen tests are now becoming available and are registered for use in Australia. These tests have relatively high sensitivity, between 80 and 97%, and very high specificity, >99%. The test is performed by lateral flow immunoassay – either colourimetric or fluorescent - and formats include human and machine readable. These tests can be performed on-site, within 15 to 30 minutes, require no complex equipment and are about 30% of the cost of PCR.

Specific comments on COVID-19 Rapid Antigen Testing

- COVID-19 antigen tests are generally performed on nasopharyngeal swabs although saliva-based tests are being developed. Testing can be performed in the laboratory, on automated immunoassay platforms, or at the point of care using a Rapid Antigen Tests.
- Rapid antigen tests whether read by eye or by machine, have approximately the same turnaround times. Reading the tests by machine can improve accuracy and consistency.
- Rapid antigen tests are based on technology that has been in professional use for decades. The technology is well understood, stable and reliable when sourced from high quality manufacturers.
- Rapid antigen tests are less sensitive than most PCR testing. Both the WHO and FDA have set a minimum acceptable clinical sensitivity limit at 84% and 80% (respectively). None of the tests registered so far in Australia have clinical sensitivity below 80%, the highest being 97%.
- While the clinical sensitivity of rapid antigen tests is slightly lower than that of PCR, several factors need to be recognised:

  - PCR is seen as the gold standard but does itself have a false negative and false positive rate. So, when comparing other tests there will be a bias favouring the gold standard. Meaning, that despite outstanding performance from a rapid antigen test, it is very difficult to reach the performance standards of PCR.
  - The serial interval— the time from illness onset in a primary case (infector) to illness onset in a secondary case (infected)— has been determined to be between 3 and 5 days[1]. Meaning that high frequency testing (every 3 or 4 days would be required to quickly detect and stop transmission in any specific cohort.
  - Larremore et al have published detailed analysis which clearly shows that frequency of testing and speed to act are only marginally improved by increased sensitivity[2]. Rapid antigen testing has the capability of delivering fast, actionable results. The data shows that improvements in sensitivity do not alter the outcome greatly.
  - The NEJM[3] has recently published a Perspective piece questioning, not how well we can detect COVID-19 in single samples, but how effectively infections can be detected in a population by the repeated use of a given test?
  - Prevalence is not a factor when considering clinical sensitivity. If a test has 95% sensitivity, it detects 95% of the positive cases regardless of the prevalence. In a very low prevalence setting, say 100 individuals in 1 million infected, 95 of those would be detected, leaving 5 individuals in 1 million not detected at the first testing encounter. In a high frequency testing environment, there is a high likelihood that positive cases will be detected in subsequent tests (depending on the test frequency).
- Rapid antigen tests are most likely to be used for high frequency testing (every 3 or 4 days) to screen workers in high risk and essential workplaces. The USA CDC recommends that high frequency testing “could quickly identify persons with a SARS-CoV-2 infection to inform infection prevention and control measures, thus preventing transmission”[3].
- All the rapid antigen tests registered so far with the TGA have extremely high specificity (extremely low false positive rates of less than 1 per 100). All so far are quoted in the high 99% region. It will be difficult for the clinical specificity of rapid antigen tests to reach 100% as the gold standard PCR test has a measurable false positive rate itself.
  - From a Public Health testing perspective, the positive cut-off of the test is optimised to minimise false negative results. This is done at the expense of false positives. False positives, in this sense, are of less consequence to the public health interest. However, false positives can have significant impact on an individual and their close contacts, on contact tracing resources and related workplaces. We have an outstanding PCR service that can confirm all positive results, typically in a 24 to 48 hour period.
  - In a high frequency testing workplace environment, false positives will have a much lower impact than in the general population. If staff at high risk and essential worksites are tested frequently and prior to commencing their work, the need to shut down a site is significantly reduced.
- There are now studies using rapid antigen tests which demonstrate excellent performance detecting infection up to about day 7 post symptoms (approximately 10 days post infection). The performance of this test declines between day 7 and 10, post

symptoms, when PCR can still detect small quantities of viral RNA. We know, from comparing the Ct scores from PCR tests, performed on samples collected at the same time (as the antigen test), that high Ct scores correlate with low viral load and low viral antigen levels. It is debatable whether the virus is still infectious at this late stage.

- As viral load declines so do the viral antigen levels. Evidence suggested that somewhere between day 7 and 10, post onset of symptoms antigens become undetectable (by some rapid antigen tests). It needs to be remembered that at this point, the individual is 10 to 13 days post actual infection day.
- These rapid antigen tests, when used for high frequency testing of workers in high risk and essential workplaces, will almost always be testing people in early phase infection where these tests perform extremely well.
- Evidence shows that rapid antigen tests detect both symptomatic and asymptomatic individuals up to 7 days post symptoms.
- Asymptomatic individuals have been shown to have similar viral loads to those with symptoms. There is evidence, however, to suggest that asymptomatic individuals transmit virus at a lower rate than symptomatic individuals. WHO data shows that between 14 and 20% of Australians with COVID-19 are asymptomatic and even at a lower rate of transmission, they could be a significant cause of community transmission of unknown origin.
- Lower limits of detection for these tests have been determined and are usually quoted in the product instructions for use; usually expressed as lowest $TCID_{50}$/mL detected.
- Rapid antigen tests are very specific for antigens of the SARS-CoV-2 virus and do not cross react with other human corona viruses or the common influenza and adenovirus strains.

Recommendations

Rapid antigen tests of suitable sensitivity, greater than 80%, will have a role to play in the COVID-19 testing regimen deployed in Australia. These tests will best be deployed for high frequency testing – every 3 or 4 days - in high risk and essential workplaces to rapidly detect and isolate infected individuals. Thus, keeping workers safe and the economy running smoothly.

The USA CDC[4] recommends high frequency rapid antigen testing in high risk cohorts. This parallels the role very much that these tests could play in Australia. Indeed, the CDC presents a useful table depicting the use of these tests in a low prevalence setting, stating that there is no need to confirm a negative antigen test in a low prevalence setting (if there are no contrary clinical indicators).

These tests are relatively inexpensive, deliver results in 15 to 30 mins and require no complex equipment to perform. People with nursing or other allied health training will readily be able to collect and test samples on-site (once trained in their use).

PCR testing will remain the gold standard and will continue to complete high volume testing.

Testing protocols for the various workplace settings are in development so that suitable safety and quality standards will be maintained. Training and certification programs will need to be established to maximise safety and quality. Some workplaces have already rolled out on-site testing and have adopted very good protocols. These can be modified to suit most settings. Some

of the training and standards already established for the current COVID-19 carpark collection sites can be rolled out at worksites, for those that don't already have them.

Data capture and reporting, not only of the rapid antigen test results but also of the relevant current clinical signs and recent contact history, will need to be established. These already exist in some parts of the building industry, for example. There are smart data capture and management systems being developed for release shortly.

Medical support and public health escalation points will need to be established, if not already done so for the workplace.

The limitations of rapid antigen testing will need to be well communicated. These should include the importance of fastidious cross infection prevention, competent use of PPE, adequate sample collection, correct testing procedures, the importance of frequent testing to the safety of individuals and the workplace and the importance of data management and reporting.

When used correctly, rapid antigen tests will have an important role in getting Australians safely back to work and the economy running smoothly again.

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