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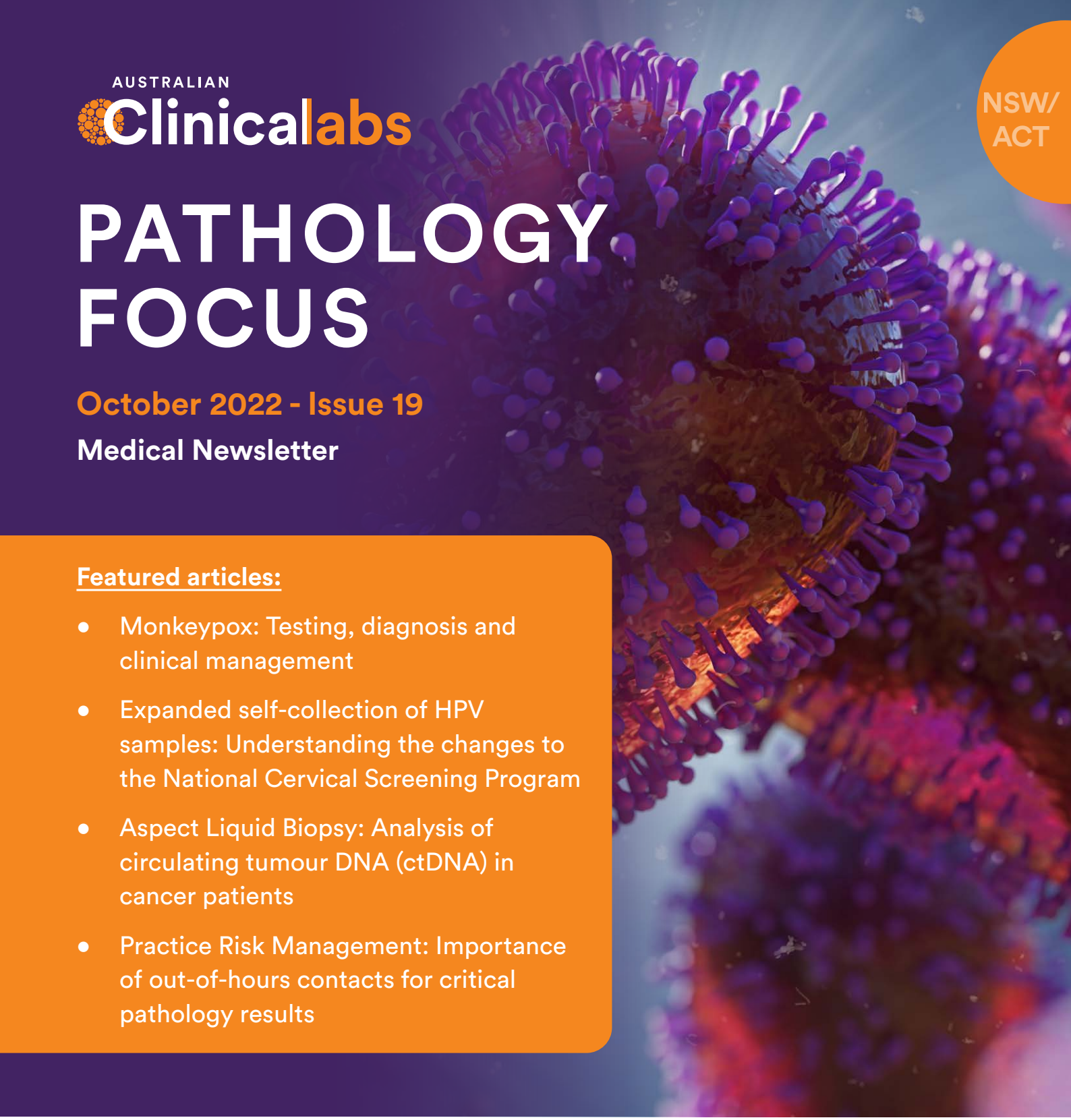

Featured articles:

Monkeypox: Testing, diagnosis and clinical management

By Dr Stella Pendle

In July 2022, the World Health Organisation declared monkeypox a public health emergency of international concern and called for a coordinated response to slow the spread of the disease. There have been over 54,000 cases of monkeypox in 92 countries where the disease is not endemic, predominantly among men who have sex with men (MSM). In Australia, 129 cases were reported as of 8th September. This included 67 in Vic, 50 in NSW, 3 in Qld, 5 in WA, 2 in the ACT and 2 in SA. Numbers are rapidly rising.

Article continues over page

Figure 1. Raised vesicles on the hands of a male with monkeypox.

Monkeypox virus was first discovered in 1958, causing a pox-like disease in laboratory monkeys, and the first case of human infection was reported in 1970 in a 9-month-old boy in the Congo. Monkeypox virus is an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family and is closely related to smallpox. The monkeypox virus has two distinct genetic clades: the Central African (Congo Basin) clade and the West African clade. The Congo Basin clade has historically caused more severe disease and was thought to be more transmissible.

How is monkeypox spread?

Monkeypox is transmitted by direct contact via respiratory droplets or exposure to infectious lesions on the skin or other bodily fluids. It may be acquired during close sexual contact. Contact with materials used by an infected person, including clothing or bedding, may also lead to transmission. It is unknown if the virus can be transmitted by individuals without skin lesions, and there is no evidence that it is spread by casual contact. Perinatal transmission can occur, leading to congenital monkeypox.

Clinical features

To date, most cases have occurred in MSM, but there have also been reports overseas of women and children acquiring the infection. The mean incubation period from the time of exposure to the first symptom appearing is 7 days, with 95% of individuals developing symptoms within 17 days.

Initial symptoms include a flu-like illness with fever, malaise, headache and fatigue. This is often accompanied by lymphadenopathy. Shortly after the prodrome, a rash appears with lesions starting as macules and progressing to raised papules and vesicles (see Figures 1 & 2). The vesicles may fill with pus, ulcerate, then scab and fall off. The rash is typically distributed on the face, extremities and genitals. MSM may experience symptoms that include anorectal pain, proctitis with bleeding, penal oedema with balanitis and phimosis. Sore throat, odynophagia, epiglottitis and tonsillitis may also occur. The most common location of lesions reported in MSM were the anogenital area (73%), trunk and extremities (55%), face (25%) and palms and soles (10%). Most cases had fewer than 10 lesions, and some had only a single genital lesion.

Complications can occur in immunosuppressed individuals, pregnant women and young children. These include pneumonia, encephalitis and eye infections. Hospitalisation is uncommon and mortality rare, but at least four people in nonendemic countries have died. People should remain in isolation for the duration of the illness, which usually lasts 2 to 4 weeks. The disease is notifiable in Australia.

Like many viruses, monkeypox cannot be diagnosed by symptoms alone. The symptoms closely resemble those of other rash-producing illnesses such as chickenpox, zoster, measles, syphilis, scabies, bacterial skin infections and allergic reactions. Laboratory testing is, therefore, essential for an accurate diagnosis.

"If clinically indicated, testing for other likely pathogens should also be performed, including herpes simplex, varicella zoster or bacterial infection."

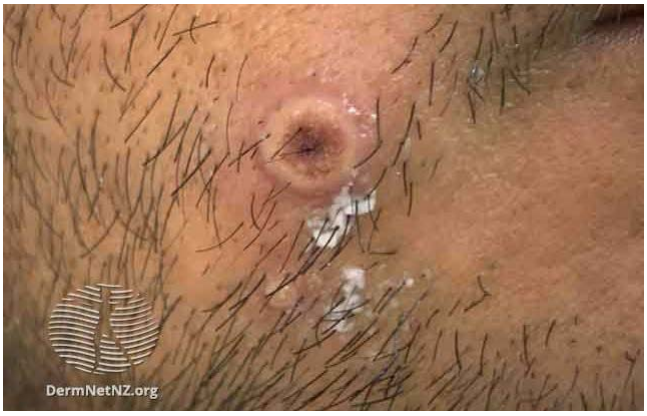

Figure 2. Umbilicated monkeypox vesicle on male's cheek at day 4 of infection.

Testing for Monkeypox

Who to Test: Patients at risk of acquiring monkeypox should be tested. Therefore, obtaining a detailed clinical history, including travel and lifestyle, is essential. Any unusual skin lesions should be investigated, particularly in the anogenital area. The rash may be limited to only a few lesions or even a single lesion.

Test Type: Nucleic acid amplification testing, also known as polymerase chain reaction (PCR), is the recommended test for diagnosis of monkeypox.

Request Form: Complete the Clinical Labs General Pathology Request Form, including monkeypox and other tests for investigation.

Specimen Collection: The WHO recommends the collection of fluid samples from pustules, dried crusts or scabbed lesions using a plain dry, sterile swab suitable for PCR testing. At least 2 swabs should be collected from 2 different sites, if possible, to improve uptake.

Other Pathogens for Investigation: If clinically indicated, testing for other likely pathogens should also be performed, including herpes simplex, varicella zoster or bacterial infection.

Handling of Monkeypox Swabs: The swabs for monkeypox should be packed separately to assist the laboratory in processing the specimens promptly. These are referred to the local public health laboratory for testing.

Antibody and antigen testing currently has limited utility due to cross-reactions with other Orthopoxviruses and is not recommended.

Treatment

For most patients, management is symptomatic, including pain relief. Treatment with antivirals is recommended for people with severe disease or who are at high risk of severe disease.

Vaccination

Vaccination is available in Australia for high-risk groups from the Department of Health. The JYNNEOS vaccine is FDA approved for smallpox and monkeypox. It uses live attenuated vaccinia virus that is incapable of replicating. It is administered as a two-dose series, with peak antibody response occurring 2 weeks after the second dose. It is thought to be 85% effective at preventing monkeypox. The vaccine can be administered as post-exposure prophylaxis. When administered up to 4 days after exposure, vaccination can prevent disease onset altogether, but even receipt of vaccine up to 2 weeks after exposure can reduce symptom severity.

Prevention of Infection

The risk of transmission of monkeypox in the healthcare setting is low if appropriate personal protective equipment is worn. Healthcare workers should wear a gown, gloves, eye protection and an N95 mask. A person with suspected or confirmed monkeypox infection should be masked immediately, have lesions covered and be placed in a single-person room.

A person with monkeypox infection should avoid close contact with others until the lesions are completely healed. This can take several weeks. It is unknown whether recovery from monkeypox protects against subsequent infection.

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- Australian Government monkeypox resources - https://www.health.gov.au/resources/collections/monkeypox-mpx-resources

Figure 2 reproduced with permission from ©DermNet www.dermnetnz.org 2022.

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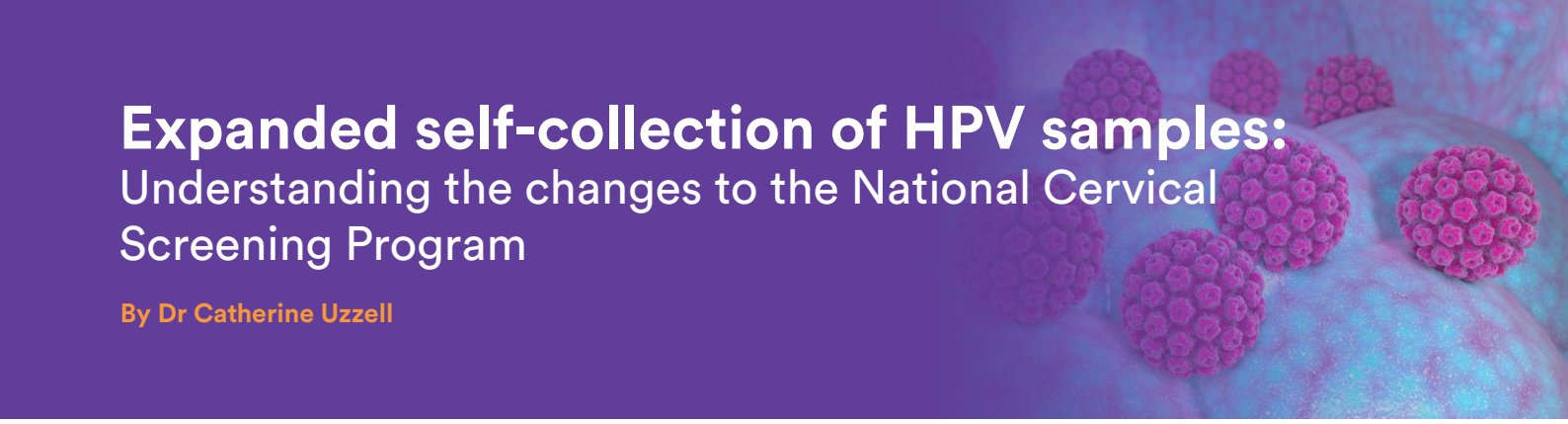
Dr Pendle has been working as a Clinical Microbiologist in Australia since 2005 when she obtained her fellowship of the Royal College of Pathologists of Australasia (FRCPA). She joined Australian Clinical Labs (formerly Healthscope Pathology) in 2012 as Supervising Pathologist in charge of the microbiology, infectious serology and molecular diagnostics departments. Dr Pendle has special interests in general bacteriology, infectious serology, syphilis and hepatitis. Dr Pendle has published several papers in her fields of interest, including VRE, chlamydial infections and HIV. She actively participates in hospital infection control and promotes rational antibiotic prescribing. She is a member of the Australasian Society for Infectious Diseases and the Antimicrobial Society of Australia.

Expanded self-collection of HPV samples:
Understanding the changes to the National Cervical Screening Program



By Dr Catherine Uzzell

Only about 50% of the population eligible to participate in the National Cervical Screening Program do so at the recommended interval. In some regions of Australia and among specific groups, the participation rate is far lower – this is despite the growing evidence that regular participation in the Program results in a significant decrease in the incidence and mortality of cervical cancer. Alarmingly, nearly three-quarters of the women diagnosed with invasive cervical carcinoma between 2012 and 2014 were either never screened or were under-screened at the time of diagnosis, according to data from the Victorian Cervical Cytology Registry[1].

Enhancing program accessibility

The National Cervical Screening Program aims to effectively eradicate cervical cancer in Australia via the dual strategy of HPV Vaccination availability and inclusion in the National Vaccination Schedule. A number of barriers to participation in the Screening Program have been identified, including regional or remote communities, specific cultural groups including Aboriginal and Torres Strait Islanders, linguistically diverse groups, those who are socioeconomically disadvantaged, and those with a disability. In addition, those who have experienced sexual assault, identify as lesbian or bisexual, trans men, and gender diverse individuals tend to be among the underrepresented groups in the Cervical Screening Program[1]. The expansion of the self-collection of HPV samples aims to break down some of these barriers and make the Screening Program more accessible to all.

"The self-collected sample can only be used for HPV testing and is not suitable for cytological examination."

Comparison: Diagnostic accuracy of self-collect vs clinician-collect

A Medical Services Advisory Committee (MSAC) review in 2021 noted extensive evidence showing no significant difference in the diagnostic accuracy of HPV testing between using self-collected and clinician-collected samples (relative sensitivity = 0.98; 95% CI: 0.96 to 1.01; relative specificity = 0.99; 95% CI: 0.98 to 1.01)[2], where PCR based assays are used. MSAC supported the expansion of Self-Collection availability to all participants on this basis and, being both safe and effective, would likely increase participation in cervical screening[3].

Expanded eligibility for self-collect testing

From 1st July 2022, HPV testing on self-collected samples was made available as a choice for all individuals eligible to participate in the National Cervical Screening Program. This included expanding the age limit to include participants between 25 to 74 years of age, removing the requirement that the individual is overdue for screening and allowing the collection of follow-up tests for managing intermediate type HPV types to be done by self-collection.

For self-collect testing, participants must:

- Be over 24 years and 9 months
- Be due for screening (first test or > 4 years and 9 months since a negative screening result)
- Not require a co-test
- Be collected under the supervision of a healthcare professional

"The true benefit of the expanded self-collect arm of the Cervical Screening Program will result from increased participation of women who would otherwise be unscreened or under-screened."

Clinical management of intermediate or high-risk HPV results from self-collection

Participants who choose to use self-collection will still need to access testing through their healthcare provider – this allows for appropriate counselling, education and follow-up to occur. It should be remembered that in the event of an intermediate-risk HPV (non 16/18 HPV) positive result on self-collect (approximately 6% of the screening population), the patient will still need to have a clinician-collected LBC sample taken for cytological examination and determination of further management, as the self-collected sample can only be used for HPV testing and is not suitable for cytological examination. In the event of a high-risk HPV (16 or 18) being identified on self-collect (approximately 2% of the screening population), the patient will be recommended to go directly to Colposcopy without an intervening clinician-collected sample being required (see Figure 1).

Patients ineligible for self-collect testing

Self-collection is a screening and intermediate-risk surveillance tool.

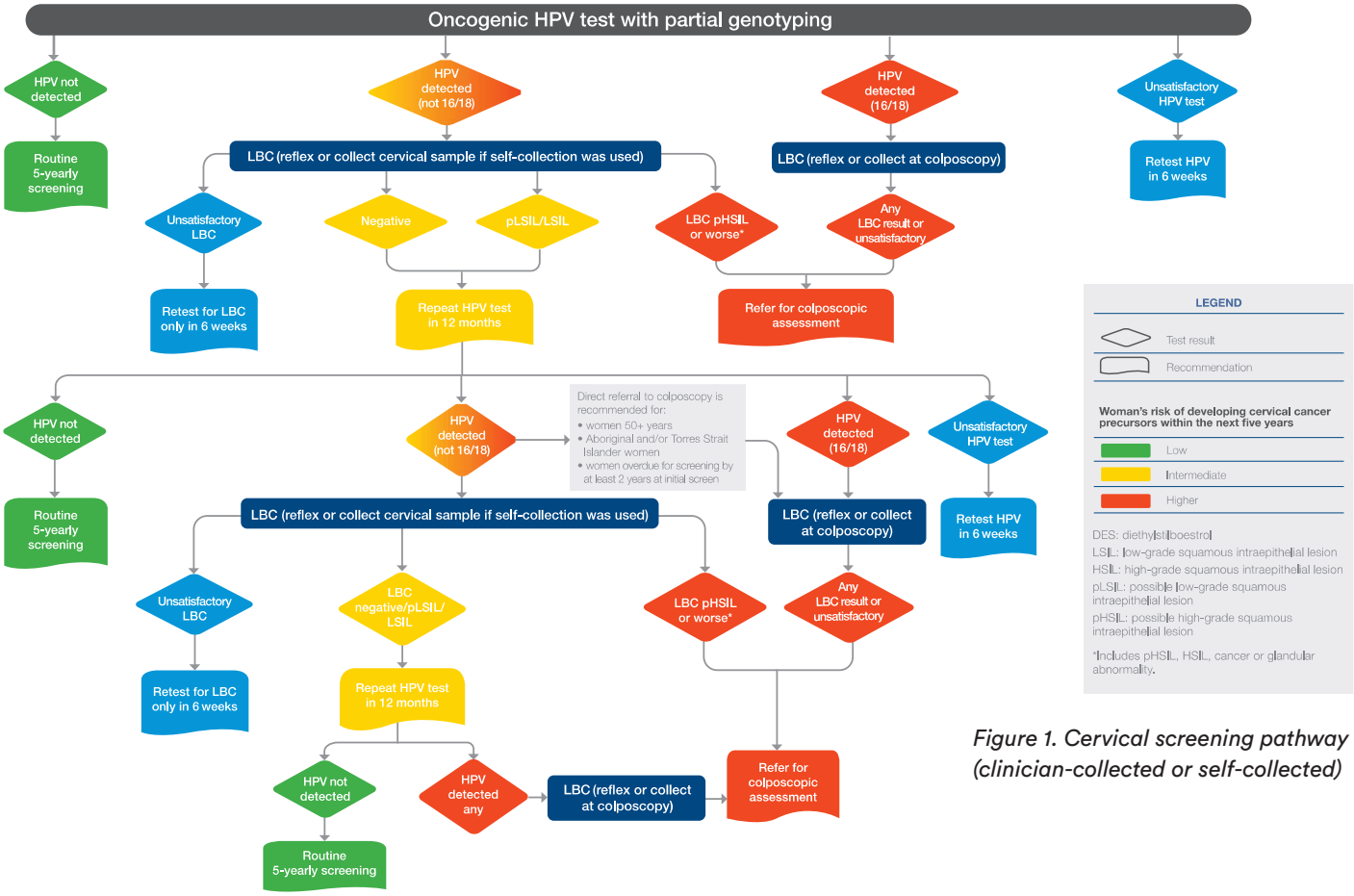


Figure 1. Cervical screening pathway (clinician-collected or self-collected)

Self-collect HPV sampling is not suitable for individuals in ongoing management for cervical abnormalities, such as:

- Symptomatic patients
- Ongoing High-Risk HPV surveillance
- Patients undergoing Test of Cure surveillance
- Previous total hysterectomy for high-grade squamous or glandular lesions
- Diethylstilbestrol (DES) exposure in utero
- Patients who have had adenocarcinoma in situ (AIS)
- Patients who require concurrent assessment of their cytology

The reason for the change

The true benefit of the expanded Self-Collect arm of the Cervical Screening Program will result from increased participation of women who would otherwise be unscreened or under-screened, particularly if disease is detected and treated. Decreasing the age of availability to 25 years will also likely result in earlier detection of disease in some cases. Women who have a negative Self-Collect HPV result can also be reassured with confidence that they are at low risk for cervical cancer.

How to Order:

For detailed information on how to order HPV self-collect testing, including the correct swabs and process required for self-collect testing 'at Medical Practice' and self-collect testing 'at Home', please see the Doctor Self-Collect Guide on our website clinicallabs.com.au/cervicalscreeningprogram

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Aspect Liquid Biopsy:
Analysis of circulating tumour DNA (ctDNA) in cancer patients

By Associate Professor Mirette Saad

Precision medicine in cancer

Cancer, a leading cause of mortality, is associated with aberrant genes. Today, molecular profiling is a recognised technique for classifying solid tumours. Analysis of tumour-associated genetic alterations is increasingly used for diagnostic, prognostic and treatment purposes.

Genetic biomarkers guide treatment decisions

Genetic variants identified in cancer are known to be associated with increased or decreased sensitivity to targeted therapy, such as tyrosine kinase inhibitors (TKIs). For example, while *PIK3CA* and *EGFR* mutations are sensitive to TKIs, *RAS* and *BRAF* are known to be resistant. Thus, elucidating the genetic profile of a given tumour is potentially useful in designing tailored treatment regimens that avoid unnecessary toxic therapy or overtreatment.

Circulating tumour DNA (ctDNA); Liquid Biopsy

Clinical application of liquid biopsies (Figure 1), to inform molecular-based risk stratification and guide therapeutic intervention strategies, may help to reduce morbidity, increased waiting times and overall costs.

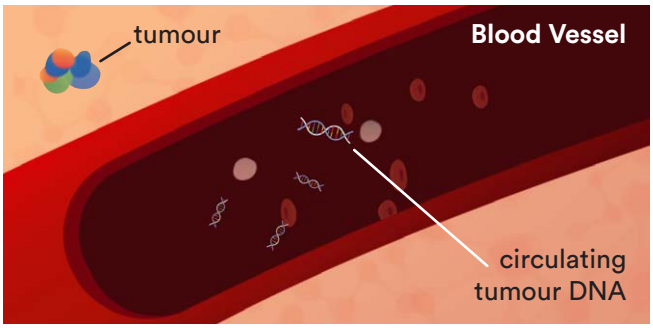

Figure 1. Circulating tumour DNA (ctDNA) in a patient with cancer.

ctDNA; A highly specific cancer biomarker

The analysis of ctDNA has already improved clinical outcomes across some cancer types, such as non-small cell lung cancer (NSCLC), colorectal and breast cancer.

The detection of circulating DNA has been observed by qualitative and quantitative changes. ctDNA has a short half-life allowing for evaluation of tumour changes in hours rather than weeks to months. Studies describe the relationship between ctDNA levels and prognosis and disease stage with a positive predictive value of approximately 94% in NSCLC.

Aspect Liquid Biopsy (LB) Testing at Clinical Labs

Recent technological advances have enhanced the performance of ctDNA analysis, with reported sensitivities and specificities ranging from 90%-100%. Clinical Labs has validated different comprehensive mutation profiling assays for clinical oncology patients using ctDNA extracted from patients' blood. Our technology, including Next Generation Sequencing (NGS), MassArray Agena Biosciences UltraSEEK and Droplet Digital PCR (ddPCR), can indentify clinically relevant variants, with high concordance to solid tissue, at a sensitivity down to 0.5% or less.

ctDNA is highly concordant with Solid Tissue Biopsy

ctDNA analyses demonstrated high concordance to solid tissue tumours (Bettegowda *et al.*, 2014). LB can reveal important information on genomic aberrations affecting the efficacy of targeted drugs, including mutations of the *EGFR, KRAS, BRAF, TP53* and *PIK3CA* genes in different cancers. The variability of ctDNA levels in cancer patients likely correlates with tumour burden, stage, vascularity, cellular turnover and response to therapy.

Liquid Biopsy, the quality approach in a less invasive test

Liquid biopsy offers a clear advantage for some cancer patients compared to conventional surgical methods, particularly for cancers where obtaining repeated tumour biopsies is challenging or unsafe. ctDNA testing has proven value and may replace traditional tissue biopsies in some cases. This non-invasive type of LB can be taken easily and repeatedly over the course of a patient's treatment.

> ***"Liquid biopsy offers a clear advantage... particularly for cancers where obtaining repeated tumour biopsies is challenging or unsafe."***

ctDNA provides broader information with less bias

Studies have revealed that ctDNA provides a more holistic view of tumour characteristics and progression emanating from primary and metastasised tumour foci. ctDNA LB is not biased by analysing only a small fraction of the

tumour, which may fail to detect certain clinically relevant alteration types (false negative), and is always accessible, in contrast to lung cancer tissue, for example.

ctDNA analysis is recommended by guidelines in NSCLC

Along with many international guidelines, Australian recommendations and NCCN guidelines were developed to test for resistance *T790M EGFR* mutations using plasma ctDNA testing in NSCLC if available, followed by a guided tissue biopsy (if feasible) if blood results are negative or indeterminate. Recently, a third-generation *EGFR* Tyrosine Kinase Inhibitor (TKI) was approved in Australia for patients with NSCLC harbouring the *EGFR* T790M mutation (~50-60% of lung cancer patients), following progression on an *EGFR* TKI.

The quality choice for monitoring tumour burden and therapeutic response

Serial analysis of ctDNA from the time of diagnosis throughout treatment can provide a dynamic picture of molecular disease change, including drug response and development of secondary resistance (see Figure 2).

Similar to lung cancer, plasma-Seq analysis of ctDNAs reveals a wide variety of mutations or aberrations that act as predictive resistance markers against therapies in various forms of cancer. For instance, *KRAS, NRAS* and *BRAF*-associated mutations in plasma ctDNA of metastatic colorectal cancer (CRC) patients drive primary resistance five to six months post-anti-*EGFR* regimens such as panitumumab and cetuximab. Liquid biopsy can be used to assess patient outcome with the addition of a specific *PI3K* inhibitor to standard treatment for *PIK3CA*-mutated breast cancer.

"Undetectable ctDNA levels at baseline or undetectable ctDNA during the first 6–9 weeks was correlated with prolonged PFS and OS."

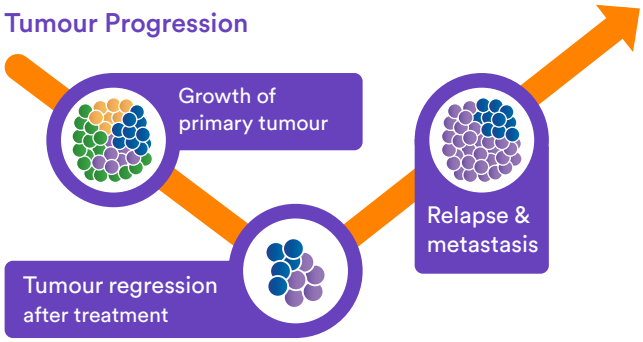

Figure 2. Tumour progression pathway

Liquid biopsy predicts the clinical outcome and minimal residual disease (MRD)

The clinical utility of ctDNA analysis is demonstrated through the detection or changing levels of ctDNA several weeks after curative surgery or chemotherapy. This could potentially identify patients with residual disease, which can be associated with shorter overall survival (OS) and predict future relapse. Undetectable ctDNA levels at baseline or undetectable ctDNA during the first 6–9 weeks was correlated with prolonged progression-free survival (PFS) and OS in melanoma patients treated with anti-PD1 therapy (Seremet *et al*., 2019).

ctDNA and real-time monitoring for early relapse

The biggest advantage of LB is the ability to detect cancer biomarkers in blood earlier than conventional methods. It has been demonstrated that monitoring for tumour-derived DNA in plasma can identify relapse well before clinical signs and symptoms appear (~6.5 months earlier than with CT imaging), enabling earlier intervention and better outcomes. Liquid biopsy analysis by NGS detected the presence of a ctDNA *PIK3CA* mutation five months earlier than the detection of a tumour relapse with multiple liver metastases by regular clinical follow-up in breast cancer (Cheng *et al*., 2019).

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"The biggest advantage of Liquid Biopsy is the ability to detect the cancer biomarkers in blood earlier than conventional methods... well before clinical signs and symptoms appear (~6.5 months earlier than with CT imaging)..."

In the future, instead of extensive imaging and invasive tissue biopsies, employing ctDNA as liquid biopsies could be used to guide cancer treatment decisions and perhaps even screen for the recurrence of tumours that are not yet visible on imaging.

Liquid biopsy and cancer screening

The non-invasive nature of LB represents an advantage over other approaches to define cancer biomarkers, particularly for the development of cancer screening tests. Despite the myriad of benefits, the potential of using liquid biopsy as a screening tool is still evolving.

Conclusion

The present literature supports the validity of LB as a minimally invasive diagnostic tool for monitoring therapeutic response and the detection of novel cancer driver mutations, this can enable earlier detection of tumour burden, long before conventionally-utilised tests.

Ordering Aspect Liquid Biopsy

When to Order: At diagnosis or on therapy for treatment selection.

How to Order: Using the Aspect Liquid Biopsy request form available on our website clinicallabs.com.au/molecularcancerservices

Turnaround Time: 5–7 business days from the sample receipt date.

Specimen Required: TWO 10ml blood samples (special tubes). These can be taken at any of our collection centres.

Test Cost: No Medicare rebate available. An out-of-pocket fee of $550 applies.

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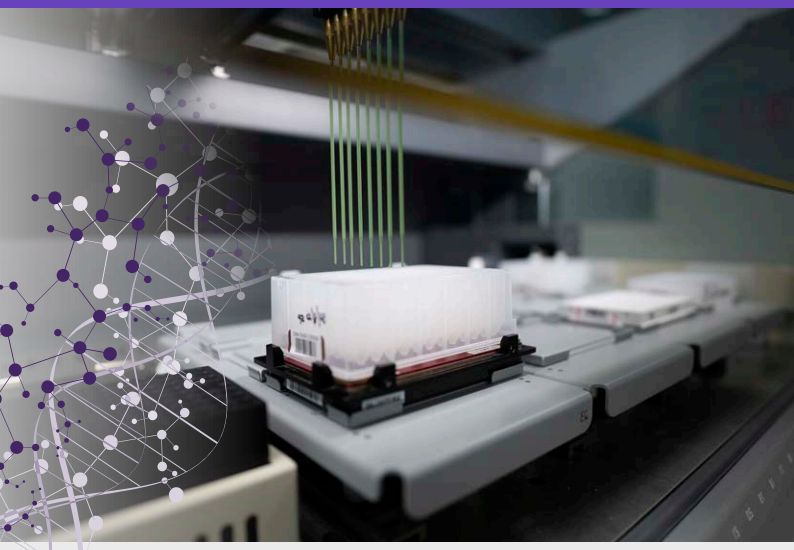
Molecular Genetics



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- Somatic Mutation in Solid Tumours
- Aspect Liquid Biopsy: ctDNA testing in plasma
- EndoPredict® for Breast Cancer
- Pharmacogenetic Testing

For further information on the Molecular Genetics Testing Services available at Clinical Labs, visit clinicallabs.com.au/moleculargenetics or scan the QR code.

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Practice Risk Management:
Importance of out-of-hours contacts for critical pathology results

By Associate Professor Chris Barnes

"Good afternoon. I have a very high troponin level on a patient, and I cannot contact the referring doctor. I have tried multiple times, but the practice is now closed, and the doctor is not picking up his mobile phone. Can I please get advice?"

Transcript from a conversation between a Clinical Labs scientist and our pathologist on-call.

The above call is not an uncommon scenario. Clinical Labs provides a roster of on-call specialist pathologists, who are available after hours for the management of urgent, high-risk results. It is clear, however, that the duty of care in following up on high-risk results is the responsibility of the referring doctor. When doctors order pathology or radiology tests, they must ensure that the results are conveyed to the patients in an appropriate manner, and follow-up care and treatment are provided if required. Two references which support this position are as follows.

The RACGP has developed its Standards for general practices, and 2.2E states:

- Your practice must manage seriously abnormal and life-threatening results identified outside of normal opening hours so you can provide prompt and adequate follow-up.
- Your practice must have a process so that pathology and diagnostic services can contact the practice in urgent circumstances so information about the patient can be accessed.
- You need to explain to deputising doctors what you expect them to do if they receive urgent and life-threatening results for one of your patients, as they have a responsibility to contact the general practice in such circumstances. This could be documented in a formal agreement between your practice and the service providing after-hours care.

The Royal College of Pathologists of Australasia (RCPA) guidelines state:

- 3.2 (1) (g) In the absence of the original Requester either during or outside normal business hours, a suitable delegate has been nominated to receive and act on the result.
- 7.1 (7) As Requesters may not always be available to receive pathology reports, they should have in place a mechanism by which Pathology Providers can communicate unexpected life-threatening test results to the Requester or their Nominated Delegate in a clinically appropriate timeframe.

When confronted with a high-risk result and with the referring doctor not contactable, our on-call pathologists will assess the clinical urgency and, if necessary, contact the patient directly and provide advice to attend the local emergency department for treatment. If patients are not contactable, a welfare check utilising emergency services (police) may be actioned. Both of these approaches to communicate the results directly to the patient without the full clinical context are problematic.

The Medical Board of Australia and Medical defence organisations are clear in their support that referring doctors are responsible for receiving high-risk pathology results. Practitioners may be placing the patients at risk of poor clinical outcomes and there may be subsequent legal action if they (or a delegate) are not available to receive high-risk pathology results.

If you would like to update your contact details, please email nsw.support@clinicallabs.com.au

Please note that patient results can be accessed 24/7 from any computer or device through eResults – Clinical Labs' online result-delivery platform. eResults allows you to customise your notifications, including URGENT results. To log in or register now, visit clinicallabs.com.au/eresults.

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