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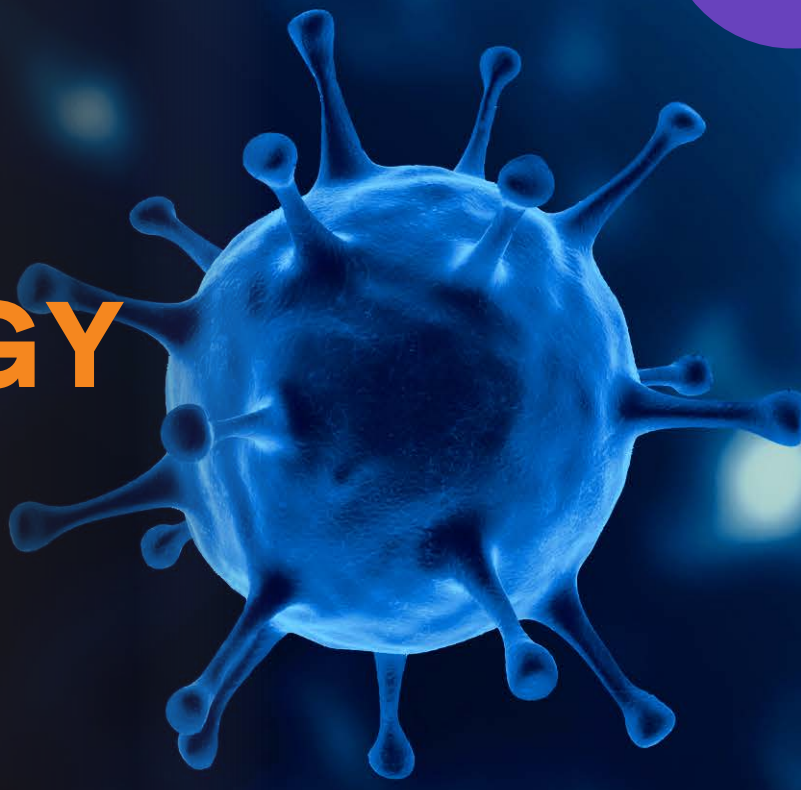
PATHOLOGY *focus*

Medical Newsletter



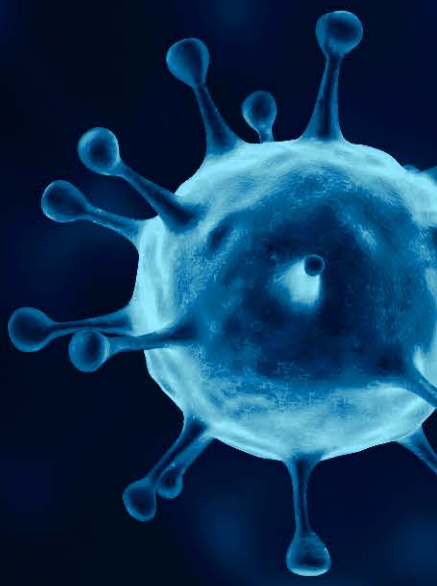
"Long COVID"

Laboratory investigations to support patient management

By Associate Professor Chris Barnes

Most people infected with COVID-19 will fully recover within a few weeks of infection. In a study of almost 3,000 patients with COVID-19 infection from NSW, 80% of patients had fully recovered by 30 days. However, up to 5% of patients will continue to have symptoms beyond 12 weeks following infection.[1]

There is no agreed definition of "Long COVID" syndrome. The WHO (World Health Organization) has provided a clinical case definition for "post COVID-19 condition". This definition includes patients with a range of potentially overlapping and intermittent symptoms including fatigue, shortness of breath, and cognitive dysfunction, that impact everyday functioning. The symptoms extend beyond 12 weeks from COVID-19 infection and are present for at least 2 months.[2] There is limited understanding of the pathogenesis and risk factors for patients developing Long COVID.



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There is an absence of well-established evidence-based guidelines for the investigation and management of patients presenting with potential Long COVID. Clinicians may be faced with the diagnostic and management dilemma of how best to approach patients suspected of having Long COVID syndrome. Tertiary referral centres are being inundated with patients suspected of having Long COVID syndrome, with some patients being forced to wait up to one year before being seen.[3]

Clinical assessment of patients presenting with symptoms suggestive of Long COVID syndrome can be difficult. Symptoms can be varied and overlapping, often without objective clinical signs. The **NICE** (The National Institute for Health and Care Excellence) guideline on Long COVID includes commonly reported symptoms, which can be classified as follows.[4]

Commonly reported "Long COVID" symptoms

Respiratory / ENT and Cardiovascular symptoms

- Breathlessness
- Cough
- Cardiovascular symptoms
- Chest tightness
- Chest pain
- Palpitations
- Tinnitus
- Earache
- Sore throat
- Dizziness
- Loss of taste and/or smell
- Nasal congestion

Gastrointestinal symptoms

- Abdominal pain
- Nausea
- Diarrhoea
- Weight loss and reduced appetite

Generalised and Neurological symptoms

- Fatigue
- Fever
- Pain
- Cognitive impairment ('brain fog', loss of concentration or memory issues)
- Headache
- Sleep disturbance
- Symptoms of anxiety
- Peripheral neuropathy symptoms (pins and needles and numbness)
- Delirium (in older populations)
- Mobility impairment
- Visual disturbance
- Symptoms of depression
- Symptoms of post-traumatic stress disorder

Musculoskeletal / skin symptoms

- Joint pain
- Muscle pain
- Skin rashes
- Hair loss

In the setting of high clinical demands, self-report questionnaires have been proposed as a potential guide to support clinical decision-making. The **Symptom Burden Questionnaire™ for Long COVID (SBQ™-LC)** is a comprehensive patient-reported outcome tool measuring the frequency and severity of symptoms in patients with Long COVID.[5] This questionnaire highlights the varied range of symptoms of patients presenting with Long COVID and includes 17 independent scales with a summed raw score, which can be transformed to a linear (0-100) score with higher scores associated with higher disease burden.

Recommended laboratory investigations

Targeted laboratory investigations are essential in supporting the assessment of patients presenting with symptoms suggestive of Long COVID. It is important to acknowledge that the variety of potential symptoms of patients presenting with Long COVID may make excluding underlying medical conditions difficult. Additionally, comorbidities that require targeted therapy may compound symptoms of Long COVID. The approach below is suggested to support the investigation of patients presenting with potential Long COVID with an initial baseline series of investigations followed by a more targeted methodology directed towards the patients' symptoms.

Baseline investigations

- Full blood count
- Kidney and liver function tests
- C-reactive protein
- Iron studies
- Vitamin B12
- EBV and CMV serology
- Beta HCG if appropriate
- ESR
- Thyroid function
- HbA1c
- Immunoglobulins

PATIENTS PRESENTING WITH:

Respiratory / ENT and Cardiovascular symptoms

- Troponin
- ECG / 24 Holter monitor
- B-type natriuretic peptide (BNP)
- Chest X-ray

Generalised and Neurological symptoms

- Blood culture (if fever present)
- Hormonal profile (e.g. early morning testosterone)
- Serum protein electrophoresis
- Calcium, magnesium and phosphate
- Cortisol and ACTH levels

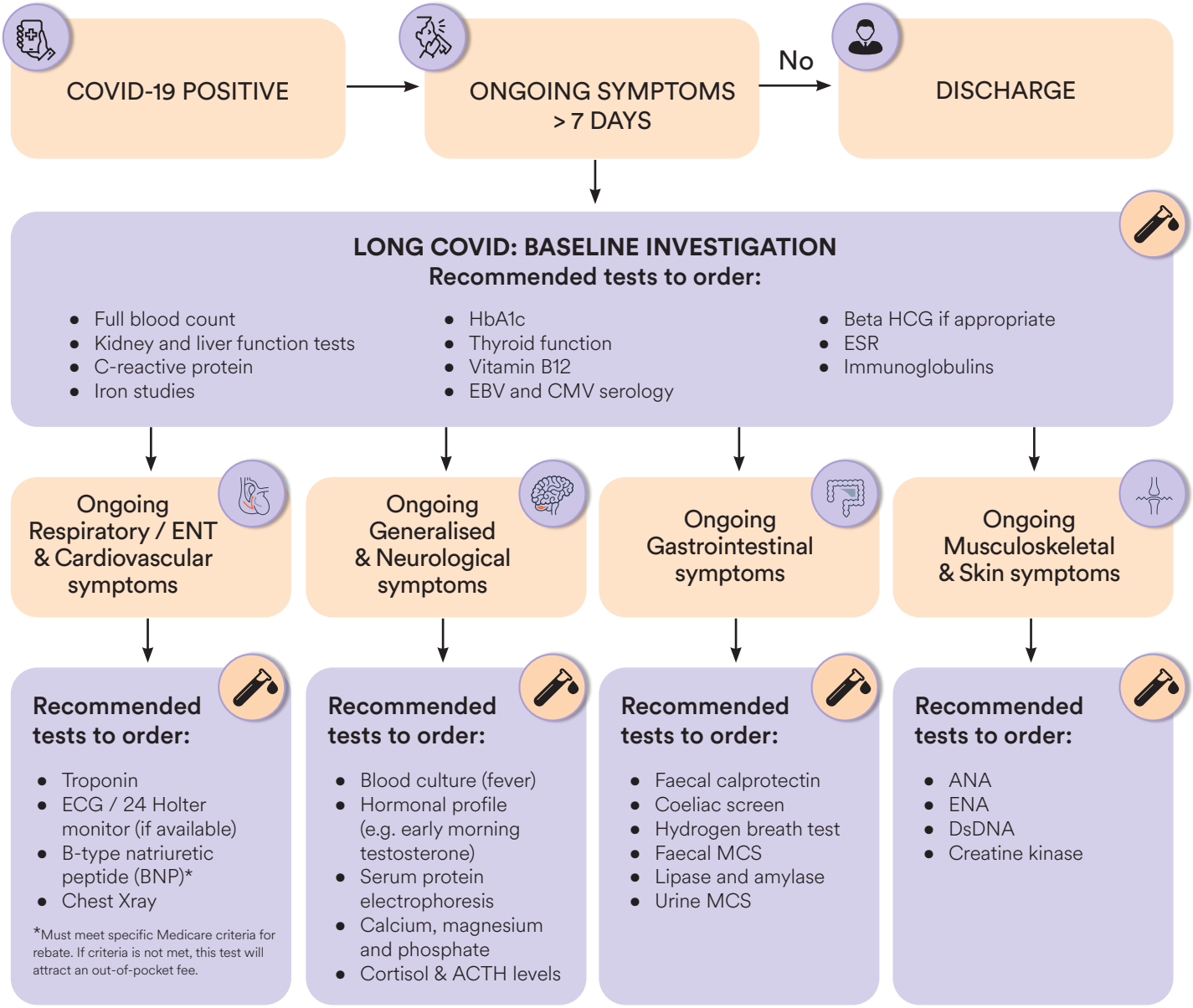
Gastrointestinal symptoms

- Faecal calprotectin
- Coeliac screen
- Hydrogen breath test
- Faecal MCS
- Lipase and amylase
- Urine MCS

Musculoskeletal / skin symptoms

- ANA / ENA / DsDNA
- Creatine kinase

Summary of Long COVID investigative recommendations



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COVID-19 AND URINARY SYMPTOMS

The COVID-19 pandemic has raised concerns about its potential impact on various body systems, including the urinary tract. Recent studies suggest that elderly patients with COVID-19 may experience urinary symptoms, such as urinary incontinence, urgency, frequency, and hematuria. This could be due to the direct or indirect effects of COVID-19 on the urinary tract or as a result of the systemic inflammatory response triggered by the virus.

It is important to note that urinary symptoms alone are not specific to COVID-19 and could be caused by other medical conditions, such as urinary tract infections, prostate enlargement, or bladder dysfunction. However, given the potential overlap of symptoms and the severity of the COVID-19 pandemic, it may be helpful to test for COVID-19 when elderly patients present with urinary symptoms.

Timely diagnosis of COVID-19 in these patients may facilitate appropriate management and prevent the spread of the virus to other vulnerable individuals. Healthcare providers should remain vigilant and consider COVID-19 testing in elderly patients with urinary symptoms, particularly if they have been exposed to the virus or have other risk factors for COVID-19. It is also essential to provide comprehensive care and support to older adults with COVID-19 and urinary symptoms to prevent further complications and improve their overall health outcomes.

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Associate Professor Chris Barnes is the National Director of Haematology and provides strategic direction for haematology at Clinical Labs on a national level. He is a clinical and laboratory-trained haematologist who has been part of Melbourne Haematology and has worked with Clinical Labs (and previously Healthscope) for several years. A/Prof Barnes is also the director of the Haemophilia Treatment Centre at the Royal Children's Hospital, and has experience in management and leadership positions. He has an active clinical research interest and serves as the director of both Melbourne Haematology (Clinical) and Melbourne Paediatric Specialists.

Faecal Multiplex PCR:
For accurate and timely diagnosis of gastroenteritis

By Dr Eric Chu

Gastroenteritis is a common presentation in both adults and children. Most acute cases are due to infection, with chronic cases more likely to be due to non-infectious causes such as inflammatory bowel disease or malabsorption syndrome. When infectious diarrhoea is suspected, two decisions need to be made: firstly, when to perform stool testing, and secondly, whether antibiotic therapy is required.

Most infectious diarrhoea is mild and self-limiting. In such instances, supportive therapy, such as rehydration, is sufficient, and microbiological testing is not required (1). However, in patients with severe illness and/or high-risk comorbidities, a diagnosis will help guide further management (see Table 1).

Cause of infection and testing

Infectious diarrhoea can broadly be categorised according to its aetiology: bacterial, viral or parasitic. Viral causes are the most common, while bacterial causes are more likely to cause severe illness (2). Identifying the underlying aetiology assists with ongoing management (see Table 2).

Table 1. Indications for stool collection

Severe illness
• Dehydration/hypovolaemia • Hospitalisation • Fever > 38°C • Bloody diarrhoea/dysentery
Co-morbidities
• Age > 70 • Malignancy • Immunosuppressed • Inflammatory bowel disease • Pregnancy
Prolonged symptoms > 1 week
Recent antibiotic exposures (*C.difficile* only)
If directed by public health/outbreak investigations

Table 2. Common causes of infectious gastroenteritis and respective testing

Cause	Testing available at Clinical Labs SA/NT	Comments
Organisms – Bacteria		
Campylobacter	Culture	Accounted for 94% of national notifiable enteric diseases in 2017 (3). PCR cannot differentiate between typhoid/non-typhoid strains.
Salmonella	Culture. Culture is required for serotyping of Typhi/non-Typhi strains. Blood cultures in returned travellers suspicious of typhoid fever.	
Shigella	Culture	Can cause dysentery.
C.difficile	PCR	May be bowel commensals (especially in children <2 years old). Test only in symptomatic patients with recent antibiotic exposure.
Organisms – Viruses		
Rotavirus	Faecal Multiplex PCR	Can be vaccinated. Common cause of childhood diarrhoea.
Norovirus	Faecal Multiplex PCR	Common cause of outbreaks in nursing homes/schools.
Adenovirus	Faecal Multiplex PCR	Most adenoviruses can cause gastroenteritis. Adenovirus F40/F41 common cause of gastroenteritis outbreaks in children.
Enterovirus, astrovirus, sapovirus, bocavirus	Faecal Multiplex PCR	
Organisms - Parasites		
Giardia spp.	OCP microscopy/Faecal Multiplex PCR	
Cryptosporidium spp.	OCP microscopy/Faecal Multiplex PCR	
Entamoeba histolytica	OCP microscopy/Faecal Multiplex PCR	Cause of dysentery and liver abscess in returned travellers.
Dientamoeba fragilis, Blastocystitis hominis	OCP microscopy/Faecal Multiplex PCR	Not pathogenic, treatment not required. May suggest exposure to contaminated food sources.
Helminths – e.g. *Enterobius, Strongyloides, Taenia, Schistosomiasis*	OCP microscopy only. Serology available for certain helminths.	Seen mainly in returned travellers. Travel history important. Collect 3 x specimens to improve sensitivity.

Diagnosis

Faecal microscopy, culture and faecal multiplex PCR are the main methods for diagnosing gastrointestinal infections. Faecal microscopy and culture have remained the gold standard for many years and are still commonly requested.

Faecal culture

Faecal culture continues to be routinely performed and will identify many bacterial pathogens. However, one of its weaknesses is the failure to identify viral pathogens, which account for a significant number of infectious diarrhoea, particularly in children.

Faecal microscopy

Faecal microscopy is another important diagnostic tool, particularly when a parasitic cause is suspected, such as in returned travellers or those with agricultural exposure. In these instances, patient history should be included on the request, and specific ova, cyst, parasite (OCP) microscopy should be requested as these samples require special processing in the laboratory. Sensitivity of microscopy is time-dependent and can vary significantly depending on the stage of illness and severity. Three specimens are recommended for increased sensitivity.

Faecal multiplex PCR

Multiplex PCR has become more readily available and commercially affordable, offering many advantages over traditional culture testing. PCR offers better sensitivity, allows for identification of viral aetiology, and provides faster turnaround times.

> ***"PCR offers better sensitivity, allows for identification of viral aetiology, and provides faster turnaround times."***

However, there are certain limitations. Firstly, PCR will only identify the specific pathogens on the testing panel, potentially missing other causes of infection. Secondly, identification of the pathogen genome does not necessarily indicate disease. This is most classically seen with *C.difficile*, which is a bowel commensal and may not cause disease in healthy individuals. Similarly, in immunosuppressed patients, persistent viral shedding can often be found and does not represent active infection. Thirdly, PCR does not allow for antimicrobial susceptibility testings for bacterial pathogens. Therefore, stool cultures remain an important part of microbiological workup.

Ordering Faecal Multiplex PCR Testing

When to Order:
Request 'Faecal Multiplex PCR' using the standard Clinical Labs request form. This will test for the viral and parasitic pathogens as listed in Table 2. Faecal M/C/S will also be completed by the lab.

Additional tests:

- In patients with gastrointestinal symptoms suggestive of inflammatory or functional bowel disease of more than 6 weeks' duration a Faecal Calprotectin test may be ordered.
- Faecal occult bloods can also be requested.
- If helminth parasites (worms) are suspected, then add OCP.
- *C. difficile* needs to be specified as an additional test on the request form.
- If Strongyloides is suspected, please also request Strongyloides serology (serum sample).

Specimens required:
A fresh faecal sample in brown top container. Frozen faecal samples are also accepted; however, culture cannot be performed on these.

Test cost:
Bulk-billing is available through Medicare.

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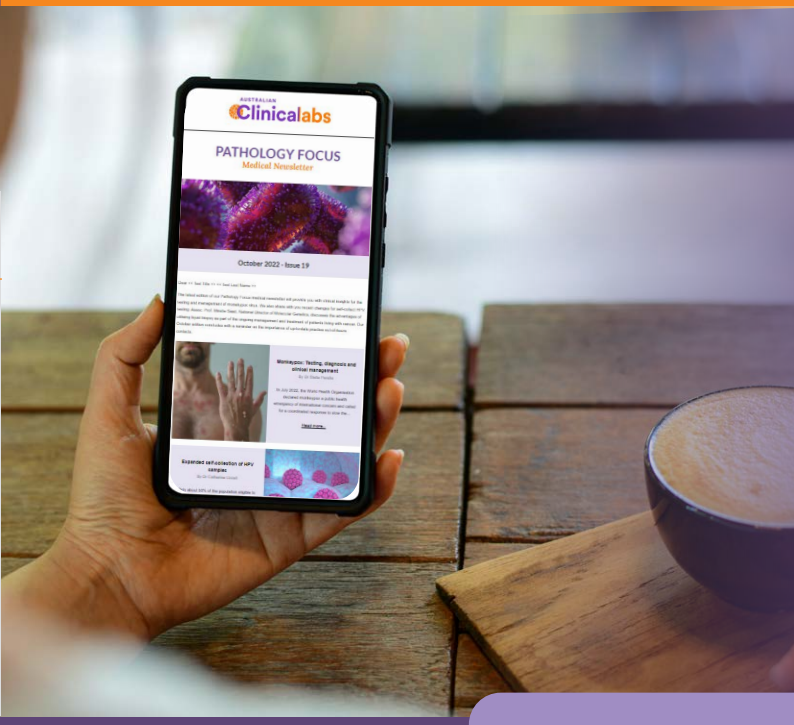

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Update from the lab:
Meet our new pathologists

Clinical Labs SA is thrilled to welcome two new pathologists to our talented team. Our highly skilled pathologists are focused on providing diagnostic excellence to help support the best patient outcomes. If you would like to discuss a patient's diagnosis or results, please feel free to contact Jane or Wayne via email or phone.

Dr Jane Thompson

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Dr Jane Thompson is a clinical and laboratory haematologist and an NHMRC PhD fellow. She completed her undergraduate studies at The University of Adelaide and is a fellow of both the Royal Australasian College of Physicians (FRACP) and the Royal College of Pathologists of Australasia (FRCPA). Dr Thompson underwent advanced training at The Royal Adelaide Hospital, Peter MacCallum Cancer Centre, and Royal Melbourne Hospital. She has research experience in iron deficiency and supplementation, as well as real-world costing of novel agents for the treatment of haematological malignancies. Currently, Dr Thompson is a PhD candidate at The South Australian Health and Medical Research Institute (SAHMRI), where she is exploring underlying genomics, novel fusions, rational treatment approaches, and drug resistance in Ph-like Acute Lymphoblastic Leukaemia.

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Dr Wayne Chou is a graduate of the University of Tasmania. Wayne began pathology training at the Royal Hobart Hospital in 2009, which included an 18-month rotation at Hobart Pathology. He gained fellowship of The Royal College of Pathologists of Australasia in 2013. He worked at Capital Pathology in Canberra for over 7 years, during which time he presented at a number of multidisciplinary meetings across various organ systems, including but not limited to lung, skin, endocrine, GIT/liver, lymphoma, head and neck, and soft tissue. Dr Chou is a broadly experienced pathologist who enjoys all aspects of histopathology and cytopathology. He is also a keen medical educator and a conjoint clinical lecturer at the Australian National University School of Medicine. He served as the supervisor of registrar training for over 5 years and has presented at a number of local meetings for the general practitioners within the ACT/NSW region. Dr Chou is a member of the Australian Society of Cytology and has served on the AMA advisory committee as a representative for private pathology for over 5 years.

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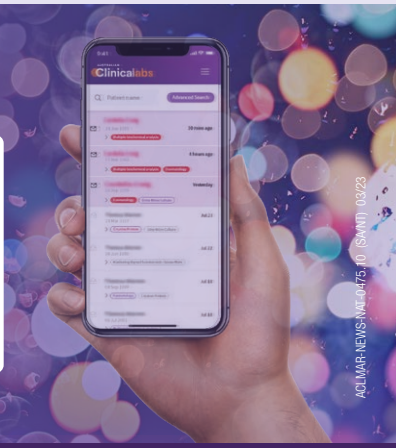

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