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Medical Newsletter

October 2019 – Newsletter 8

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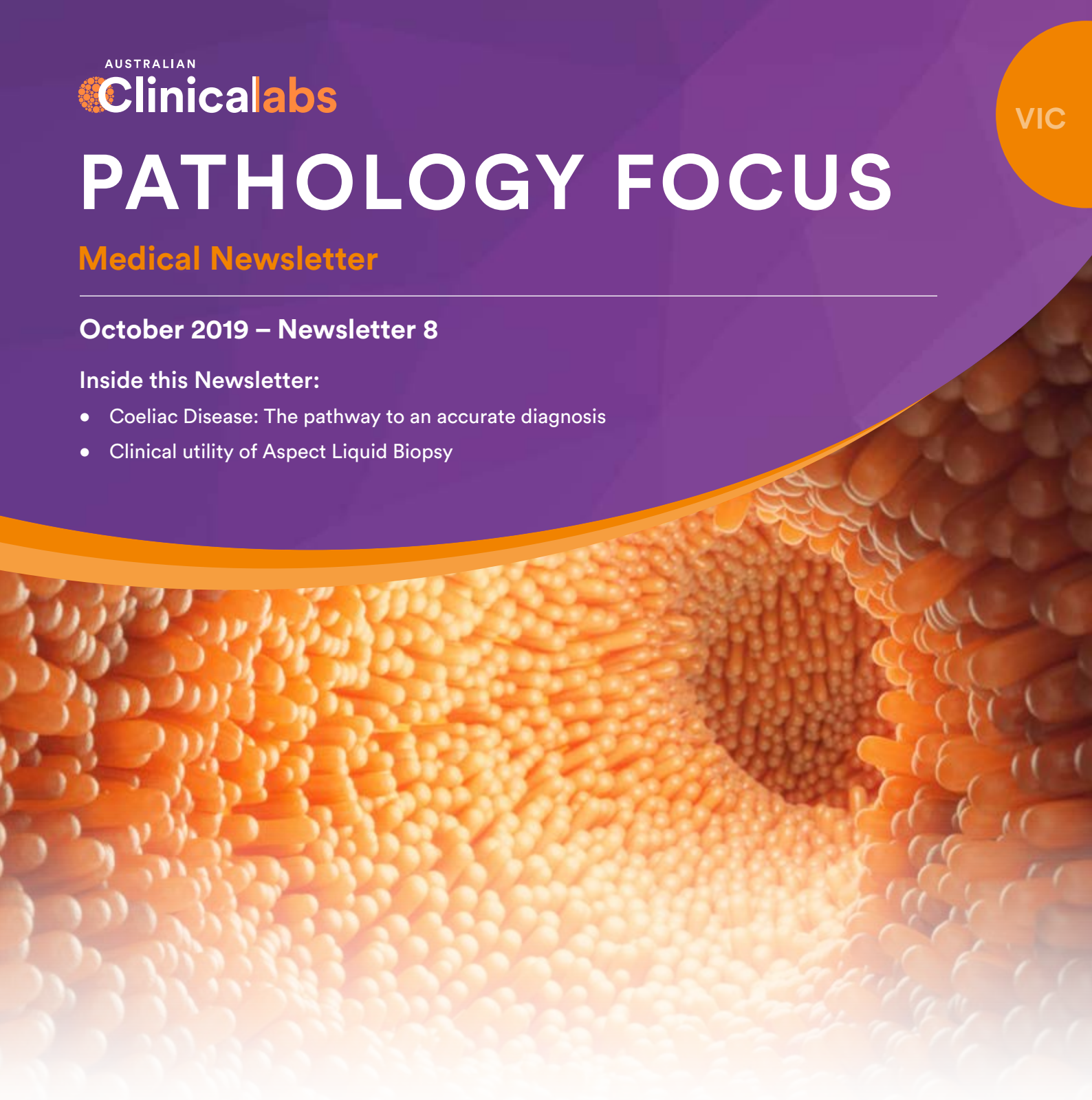


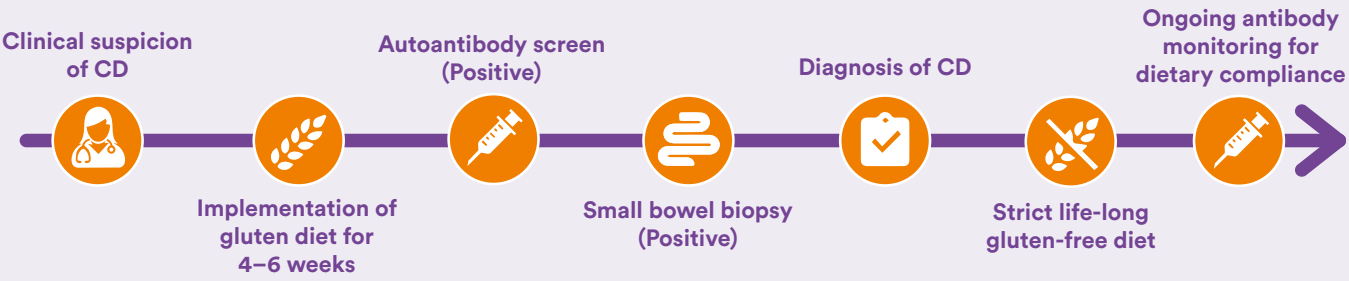
Coeliac Disease: The pathway to an accurate diagnosis

By Emeritus Prof. Ban-Hock Toh

If left untreated, coeliac disease can lead to major health complications for patients and severely affect their quality of life. To achieve an accurate diagnosis, a series of steps need to be carefully followed, to avoid patients being misdiagnosed and unnecessarily implementing restrictive life-long changes to their diet.

Coeliac disease (CD) is a chronic inflammatory CD4 T cell-mediated disease of the proximal small bowel induced by gluten present in wheat, barley and rye. It leads to atrophy of the proximal small intestinal villi resulting in nutrient malabsorption and is associated with diagnostic autoantibodies directed to endomysium tissue transglutaminase. In developed countries the incidence is increasing, but currently it affects approximately 1% of the Caucasian population. There is a strong genetic predisposing component with 10–15% of first-degree relatives of probands affected and 70% concordance between monozygotic twins. HLA-DQ2 and HLA-DQ8 genotypes are present in 99.6% of patients with CD, and the HLA type is requisite, but not sufficient for the development of disease. Clinical disease is initiated by consumption of gluten-containing wheat, barley and rye. Onset can occur in either childhood or adulthood, with a female to male ratio of 2:1. Once an accurate diagnosis has been reached, CD can be effectively managed through the implementation of a strict life-long gluten-free diet.

Coeliac Disease - Clinical Diagnosis Paradigm



Clinical indications for autoantibody tests

Along with a genetic predisposition (family history) of CD and gastrointestinal indicators such as chronic/recurrent diarrhoea, IBS, fatigue, weight loss, bloating and gas, abdominal pain, nausea and vomiting, and constipation, patients at high risk of CD may present with the following health issues:

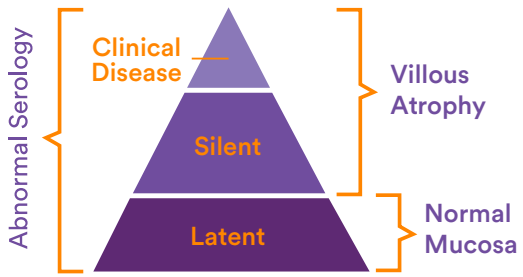
- Iron deficiency/anaemia
- Folate, vitamin E or K deficiency
- Osteoporosis
- Failure to thrive
- Pubertal delay
- Hypocalcaemia, vitamin D deficiency, secondary hyperparathyroidism

Patients may also present with diseases found to be associated with CD, including:

- Autoimmune liver disease, elevated transaminases
- Autoimmune endocrinopathy: type 1 diabetes, Hashimoto's thyroiditis, Addison's disease
- Sjogren's syndrome
- Inflammatory bowel disease
- Neurological disorders: peripheral neuropathy, epilepsy ataxia
- Arthritis of unknown aetiology
- Infertility
- Down and Turner syndromes

The onset of clinical symptoms can be represented by the tip of the 'Coeliac Pyramid' (see Fig. 1). Coeliac disease may present with classic malabsorption symptoms (as already listed), or more typically remains silent, latent, or becomes apparent through a wide range of non-classical symptoms arising from pathology in multiple organs (as previously listed). Therefore, a diagnosis of symptoms is likely to be missed unless CD is considered. If undiagnosed, CD can lead to nutrient deficiency and gastro-intestinal malignancy including enteropathy-associated T cell lymphoma (EATL) or intestinal malignancies such as adenocarcinoma of the small intestine, pharynx and oesophagus.

Fig. 1 Coeliac Pyramid

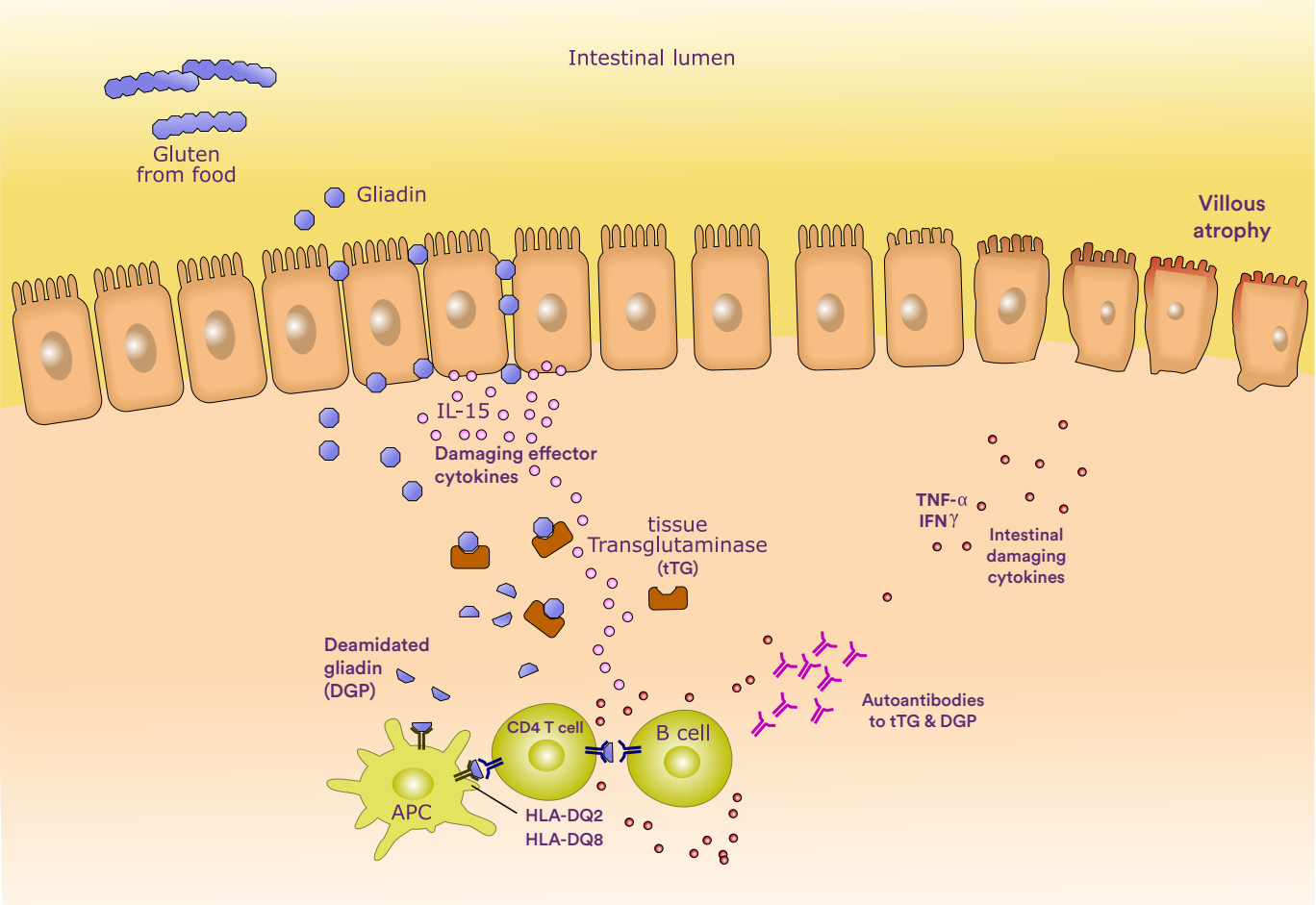


Genetic susceptibility:
HLA-DQ2 and/or HLA-DQ8

Autoantibody screen testing

HLA-DQ2 or HLA-DQ8 genotypes are present in >99% of people with CD, but are also present in up to 40% of Americans, Europeans and South East Asians, and similar proportions of Australians. The enzyme tTG deamidates dietary gluten in wheat, barley and rye. Deamidated gluten peptides form molecular complexes with DQ2 or DQ8 molecules that activate CD4 T cells to release damaging effector cytokines. Helper CD4 T cells then activate B cells to produce autoantibodies to tissue transglutaminase (tTG) and to deamidated gliadin peptide (DGP), diagnostic serological markers of CD.

Autoimmune response to gluten (gliadin) in a patient with coeliac disease.



Ordering an IgA antibody to tTG test is the first step in an accurate diagnosis for patients at high risk of CD, as this is a very sensitive and specific blood test for CD.

Ordering an IgG antibody to tTG or deamidated gliadin test for patients who test negative to IgA. This is a newer test, which is recommended in Australia alongside anti-tTG IgA. IgG antibody to deamidated gliadin may also identify patients who test negative to tTG antibody.

The patient is required to maintain a gluten-containing diet for 4–6 weeks before their blood test, as reducing or eliminating gluten from their diet can affect the results.

Genetic tests for HLA-DQ2 or HLA-DQ8 genotypes should be ordered for high-risk patients when:

- they refuse a gluten diet
- their tTG antibody test was negative
- their tTG antibody test was positive, but a biopsy of the small bowel shows healthy villi

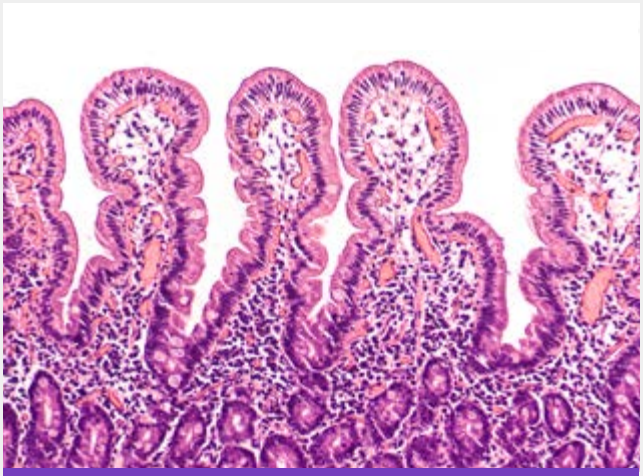
A negative result for the HLA-DQ2 or HLA-DQ8 genotypes virtually excludes CD. ***Note: 40% of Caucasians will test positive for HLA-DQ2 or HLA-DQ8 genotypes, but only 3% of these are at risk of CD.***

Other tests, such as a full blood exam, may be ordered to evaluate malnutrition, malabsorption and organ involvement.

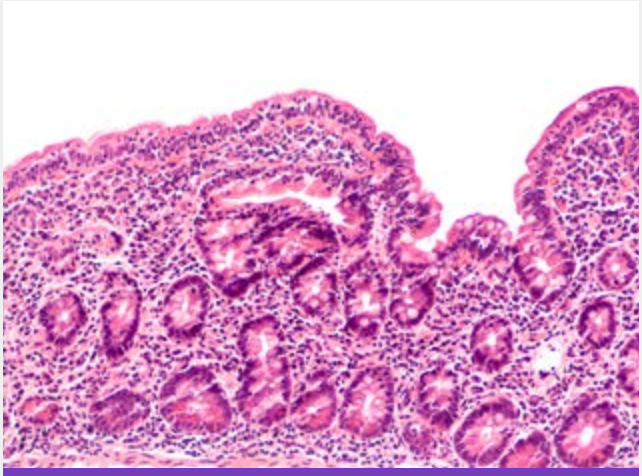
Small bowel biopsy

If the patient tests positive for serological and genetic markers, a small bowel biopsy via endoscopy is recommended to confirm CD before lifelong treatment is implemented.

In patients with CD, activation of CD4 T cells leads to production of inflammatory cytokines which causes villous atrophy, inflammation and flattening of the lining of the small intestine, reducing the surface area of the bowel available for nutrient absorption. There is an infiltration of intraepithelial lymphocytes of natural killer and CD8 phenotypes.



Healthy intestinal villi



Flattened and inflamed intestinal villi in a patient with coeliac disease

Diagnosis and treatment

Once CD has been formally diagnosed, via a combination of autoantibody blood tests, genetic blood tests and small bowel biopsy, treatment can commence. Although there is no cure for CD, the most effective treatment is a strict life-long gluten-free diet. Removing gluten from the diet allows the small bowel lining time to heal. If this diet is strictly adhered to, the patient's autoantibody levels should return to normal within 6–9 months and their symptoms and villous atrophy should resolve. Relapse will occur if gluten is reintroduced into the patient's diet.

While most of the intestinal damage caused by CD is reversible, some effects of prolonged malabsorption, such as short stature and weakened bones, may be permanent. It is therefore vital to detect and treat the disease as soon as possible.

Follow-up testing

For monitoring of dietary compliance, request a tTG antibody test.

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About the author

Emeritus Prof. Ban-Hock Toh

MBBS, PhD, DSc, FRACP, FRCPA

Areas Of Interest: Autoimmune Diseases
Speciality: Immunopathology

Expert pathologist

A/Prof. Louise Smyth

BA, MBBS, GCUT, DipHPE, FRCPA

Lab: Osborne Park
Areas Of Interest: Autoimmunity, Transplantation, Immune Deficiency, Allergy
Speciality: Allergy and Immunology
Phone: 1300 367 674
Email: louise.smyth@clinicallabs.com.au

A standard for the future

By Dr Prasad Cooray

Early detection has been called the 'Holy Grail' of cancer management, and thanks to a new widely accessible monitoring test, more clinicians are now able to detect cancer biomarkers in blood earlier than they could using conventional methods.

Dr Prasad Cooray is a specialist oncologist with consulting rooms at several locations in Melbourne's Eastern suburbs. Dr Cooray specialises in the treatment of oesophageal, gastric, colon, rectal, pancreatic, liver and biliary system cancers and is actively involved in cancer clinical trials, as a Principal and co-investigator at Eastern Health, Box Hill Campus. In addition, Dr Cooray is a participant in weekly multidisciplinary clinician meetings, where treatment decisions are made on the management of patients with complex gastrointestinal, pancreatic and hepato-biliary cancers.

In this article, he draws on his experience and elaborates on why he believes the Aspect Liquid Biopsy test will soon become a cornerstone in modern patient care.

Almost by default, as a medical oncologist, you are entrusted with the responsibility of completely coordinating your patient's journey of care. You oversee timing, you guide clinical approach, and you are responsible for all systematic treatments more generally, whether they are adjuvant or more advanced – for example, chemotherapy and biological treatments.

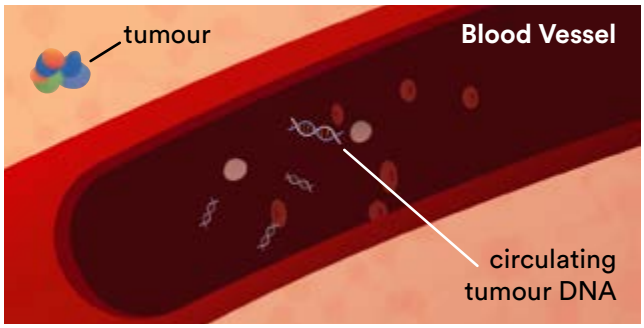
Recently, the Aspect Liquid Biopsy test became available, and now its benefits are accessible to oncologists throughout the community.

Particularly in the oncology field, we know that liquid biopsy tests have been around for quite a while – in fact, a number of Melbourne researchers have been at the forefront of their development. I specifically point to Dr Jeanne Tie, who led some pioneering studies three or four years ago demonstrating the tests could be a very useful indicator of early relapses in cancer patients.

However, despite the encouraging nature of these results, only recently have oncologists been given the opportunity to integrate this clinical tool in the care they offer patients.

It was one of those things that sounded good theoretically, and researchers were in the midst of realising its efficacy, but clinicians just didn't have access to it.

The awareness of the liquid biopsy test is growing within the industry, and more oncologists are not only learning about it but also relying on it in their day-to-day practice. We are very fortunate that the Aspect Liquid Biopsy test is now available to provide a non-invasive accurate and sensitive detection of the circulating tumour DNA (ctDNA) in patients' blood.



Clinical utility of Aspect Liquid Biopsy

How I use Liquid Biopsy with patients obviously changes on a case-by-case basis, but I have personally found that it lends itself to certain cancer types. For example, the test is a useful tool for patients with pancreatic cancer, as 90-95% of this patient population have the KRAS mutation.

Recently, I was part of a clinical trial where we looked at patients having liquid biopsies before their pancreatic cancer operations and then post-procedure, during their follow-up phase. It showed that people who still had circulating tumour DNA post-operation were at much higher risk of cancer relapse down the track. The liquid biopsy test results helped us to select a subgroup of patients who would then undertake chemotherapy.

That's one scenario that I think highlights the benefits of Liquid Biopsy. Ideally, you would want to conduct a preoperative biopsy and then a postoperative one, so a baseline is established. However, we sometimes don't get the benefit of doing a preop test because the patient may have already had the procedure by the time they come and see us clinically. However, I will always test them post-procedure. It helps me stratify their risk. And down the track, once all treatments are concluded, it acts as an extremely useful surveillance monitoring device as well.

Besides those with pancreatic cancer, I have also found Liquid Biopsy tests extremely useful for lung cancer and colorectal cancer patients, respectively.

The former, because the test picks up any resistant mutations emerging; and the latter (especially in stage 2 or 3), because this is usually the time that, as a clinician, you are deciding whether the patient needs adjuvant therapy or not.

In colorectal cancer, one of the limitations is having no KRAS mutation, meaning that the probability is not as high as in pancreatic cancer, for example. In those mutation negative cases, it's a wild type – meaning we have to rely on the circulating tumour DNA level and see how the levels correlate up or down with regards to treatment, rather than actually following a mutation.

Liquid Biopsy gives us another tool in our armament, which fuels our clinical decision-making. Additionally, for those cancer sufferers undergoing aggressive treatment with the aim of cure, these tests are a useful device to gauge how the cancer is responding to treatments, and to detect minimal residual disease and potential relapses.

"Without a doubt, I think Liquid Biopsy will become a standard part of oncology treatment in the future."

A patient-specific approach

When I have a patient whom I think could benefit from a Liquid Biopsy, I inform them of the tool, its efficacy and the associated costs. I also pick the time and point where we should do it and lay out a plan for them. For example, in pancreatic patients, I suggest they undertake the test postoperatively so we get a baseline result that I can then use for monitoring down the track. We know that DNA is cleared from the blood fairly quickly, so fortunately, we can pursue this as little as a week following procedure.

Most patients, following our discussion, see the utility of the test and are happy to self-fund. Generally, people see it as another test that is on their calendar, like a scan. Most are relieved it's just a simple blood test.

However, I contend that the utility of Aspect Liquid Biopsy becomes clearly evident when one undertakes a series of tests. There is just so much utility in continuing the testing and knowing what comes up in scans.

For example, let's say you treated someone with curative intent and you reached a very low level of circulating DNA. Further, it was an aggressive cancer to begin with, and the patient has a high risk of relapse. In this case, you may want to do a Liquid Biopsy every six weeks, or at least every two months. Of course, one must be mindful of the fact that each case is variable and multiple factors come into play.

The future of Liquid Biopsy

Without a doubt, I think Liquid Biopsy will become a standard part of oncology treatment in the future. I'm expecting the costs will go down in time as well, so I would expect it to become quite an important tool for oncologists in every stage. I think the real future lies in it being a screening test in the population – there is just a huge opportunity there, our "secret weapon" in the early detection of cancers.

Aspect Liquid Biopsy is only available at Australian Clinical Labs.

Expert pathologist

Assoc. Prof. Mirette Saad

MBBS (Hons), MD, MAACB, FRCPA, PhD

Lab: Clayton

Areas Of Interest: Molecular Genetics, Cancer Genetics, Antenatal Screening, NIPT, Endocrine, Fertility Testing and Research, Medical Teaching

Speciality: Chemical Pathology
Phone: 1300 134 111
Email: mirette.saad@clinicallabs.com.au

Associate Professor Mirette Saad is a Consultant Chemical Pathologist and the National Clinical Director of Molecular Genetic Pathology at Australian Clinical Labs. Upon receiving the National Health and Medical Research (NHMRC) Scholarship in 2006, Associate Professor Saad commenced her PhD studies at Melbourne University and Peter MacCallum Cancer Institute in Cancer Genetics. Associate Professor Saad undertook her specialty training at Healthscope Pathology (now Australian Clinical Labs) and Monash Health and obtained the Chemical Pathology Fellowship (FRCPA) and the Membership (MAACB) by examination from the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB), respectively.

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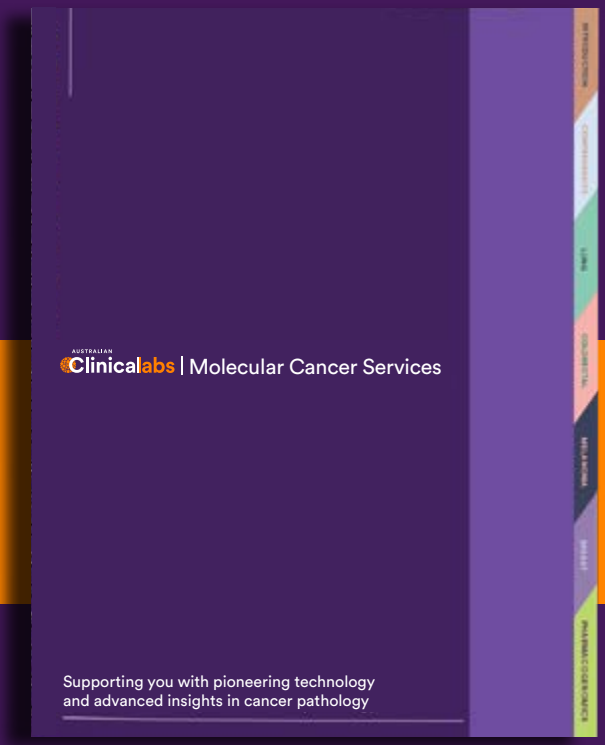

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Updates from the lab

Our Clayton laboratory has recently welcomed the expert experience of two consultant haematologists. Both have received multiple prizes commending them on their educational achievements and are actively involved in research projects in various haematology sub-specialities. Their in-depth knowledge in haematology is a great asset to the Clinical Labs pathology team.

Dr Michael Low

MBBS, BMedSci, FRACP, FRCPA, PhD

Lab: Clayton
Areas Of Interest: Haematological malignancies (i.e. lymphoma and myeloma) and iron deficiency
Speciality: Haematology
Phone: 1300 134 111
Email: michael.low @clinicallabs.com.au

Dr Michael Low is a Haematologist who has recently joined Clinical Labs. Dr Low undertook his undergraduate training at the University of Melbourne for which he was awarded an MBBS/BMedSci before completing his specialty training at the Royal Melbourne Hospital, Alfred Hospital and Monash Medical Centre. He is a fellow of both the Royal Australasian College of Physicians (RACP) and the Royal College of Pathologists Australasia (RCPA). Dr Low performed his PhD studies jointly at Monash University as well as the Walter and Eliza Hall Research Institute for which he was awarded the Gus Nossal Award by the National Health and Medical Research Council of Australia for his studies into survival pathways in myeloma.

Dr Low has been published in numerous international journals including *Journal of Nutrition, Canadian Medical Association Journal, British Journal of Haematology, Blood and Cochrane Library of Systematic Reviews.*

Dr Maciej Tatarczuch

MBBS, BBiomedSc, FRACP, FRCPA

Lab: Clayton
Areas Of Interest: Haematological malignancies (i.e. lymphoma and myeloid cancers)
Speciality: Haematology
Phone: 1300 134 111
Email: maciej.tatarczuch @clinicallabs.com.au

Dr Maciej Tatarczuch is a clinical and laboratory haematologist, holding fellowships with both RACP and RCPA. He graduated with a Bachelor of Biomedical Science and Bachelor of Medicine/Bachelor of Surgery from The University of Melbourne and was awarded the Sister Christina Welsford Haematology Prize. Dr Tatarczuch undertook specialist training at St Vincent's Hospital Melbourne, Peter MacCallum Cancer Centre and Melbourne Pathology. He completed a fellowship at Oxford University Hospital Trust, UK, where he gained experience in allogeneic bone marrow transplantation, haematological cancers and clotting/bleeding disorders. He has also completed a two-year clinical trials fellowship at Monash Health and is actively involved in translational research at the Monash Health Translational Precinct, where his PhD studies focus on improving outcomes for patients with non-Hodgkin Lymphoma.

Dr Tatarczuch currently holds positions at Monash Health, Australian Clinical Labs, Holmesglen Private Hospital and Jessie MacPherson Private Hospital. His private rooms are at Bayside Haematology, Mentone.

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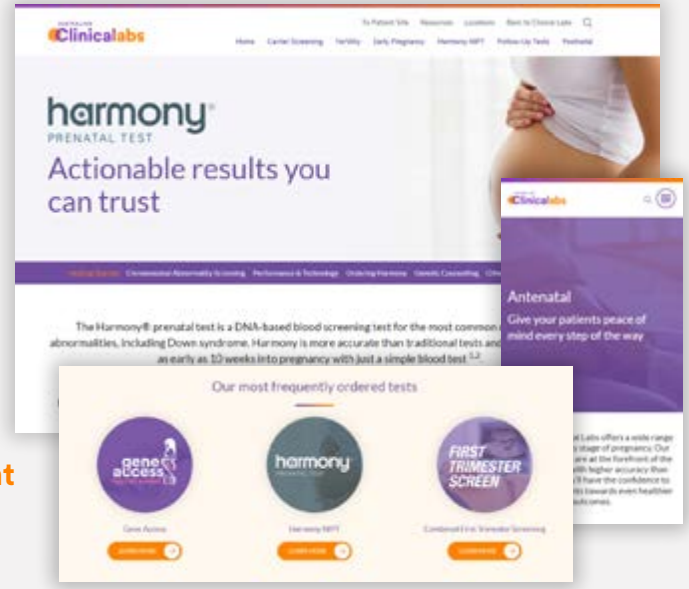

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