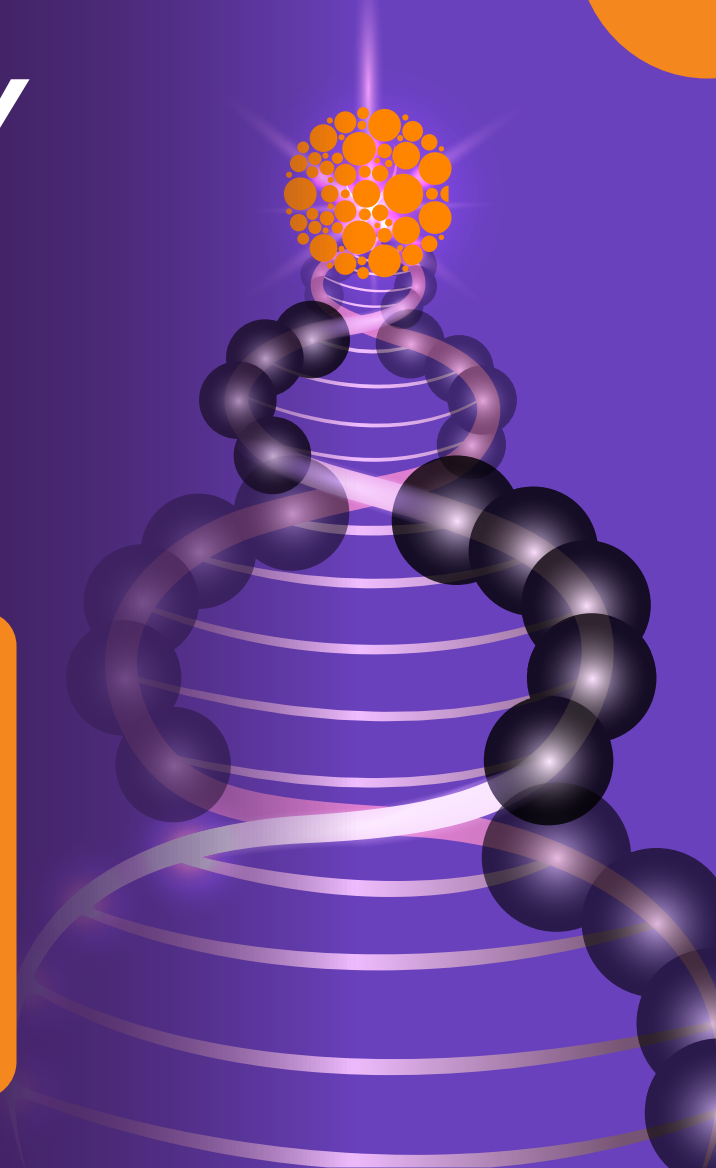# PATHOLOGY FOCUS

December 2021 - Issue 16
Medical Newsletter

Featured articles:

- Pharmacogenetic testing for optimised drug treatment outcomes

- Vitamin B12: Testing for the diagnosis of deficiency in general practice

- Understanding neutropenia in general practice

Thank you from the team at Clinical Labs

As we approach the end of our second year living and working during the SARS-CoV-2 pandemic, we reflect on the impact this virus has had on Australian healthcare. Providing healthcare services during outbreaks has continued to be challenging with snap lockdowns, telehealth consultations and strict health and safety measures.

In 2020, we saw COVID lead to a decrease in important medical screens and pathology tests due to widespread fear of catching this novel virus. This resulted in a concerning drop in the number of cancer and other serious health diagnoses last year (see our lead article in the March 2021 edition of Pathology Focus).

This year, we saw COVID's disruption of seasonal respiratory virus patterns, as international travel restrictions and non-pharmaceutical interventions remained in place. Data direct from our laboratories showed the virtual non-existence of flu type A&B cases and a dramatic increase in the number of rhinovirus and other respiratory virus cases (for the full article see our June 2021 edition of Pathology Focus).

As 2021 draws to an end, we thank you for continuing to partner with Clinical Labs, and allowing us to provide your patients with the pathology services required to complement your care. We wish you and your team a joyful festive season and a happy and safe New Year. We look forward to working together again in 2022, and sharing with you insights, innovations and topical content from the world of pathology.

Pharmacogenetic testing for optimised drug treatment outcomes

By Associate Professor Mirette Saad

Pharmacogenetics (PGx), an important part of precision medicine, is the study of how genetic variability influences drug treatment outcomes. Recommended by Guidelines, many medications currently prescribed have pharmacogenetic data to support appropriate dosing or selection. Like all diagnostic tests, pharmacotherapeutic genotyping is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient.

Clinical Labs offers a comprehensive range of pharmacogenetic testing in order to provide Clinicians and Healthcare providers with important information to help decide on the most appropriate treatment for each individual, particularly in areas such as mental health, pain management, cardiology and oncology.

> *"The field of pharmacogenetics involves using a patient's genetic makeup in combination with other clinical information to create a personalised medication regimen with greater efficacy and safety for the individual patient."*

PGx test utility

Implementation of clinical pharmacogenetics, allele function and inferred phenotypes is a crucial step toward optimum patients' health. Identifying responders and non-responders to medications can reduce morbidity, avoid adverse events and optimise drug dosing.

Literature has shown that a large number of people are injured or die each year in hospitals from adverse drug events (ADEs), costing millions of dollars in healthcare costs each year. The field of genomic medicine presents one potential solution to reduce healthcare costs associated with ADEs and poor response to pharmacotherapy.

PGx guidelines

Evidence-based guidelines with pharmacotherapeutic recommendations for combinations of specific drugs and genotypes or predicted phenotypes are essential for implementing acquired pharmacogenetics knowledge in daily clinical practice.

The Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have been developing guidelines for more than a decade (Swen *et al*. 2011a; Caudle *et al*. 2017).

Recommendations are preferably made available at the time of drug prescribing and dispensing for a patient with a genotype that requires an action, such as a dose reduction (Swen *et al*. 2011a; Deneer and van Schaik, 2013).

When to order the test?

Physicians may order the pharmacogenetic testing per drug at the point of care, or an alternative approach to ordering is the use of pre-emptive testing, perhaps as part of an annual exam in young adults or even children that require multiple treatments. As a result of the increasing number of drugs with pharmacogenetic data, the pre-emptive use of testing could significantly optimise drug outcomes (Schildcrout *et al*. 2012).

Regardless of when ordered (at time of treatment or prior), due to the continuing decline in the costs of genomic testing technologies, a broad-based pharmacogenetic screen may yield the greatest cost savings.

The *cytochrome P450 (CYP450)* and differences in drug metabolism

A family of enzymes (Figure 1), catalyses the metabolism of many drugs and xenobiotics. The genes that code for *cytochrome P450* enzymes are highly polymorphic, which can significantly affect drug metabolism in certain individuals. Differences in drug metabolism due to *CYP450* gene variants influence plasma levels of both the active drug and its metabolites.

For example, *CYP2D6, CYP2C19* and *CYP2C9* are responsible for the metabolism of a large number of commonly prescribed drugs, including warfarin, analgesics, clopidogrel, codeine, tamoxifen, some antidepressants, statins, proton pump inhibitors (PPIs) and anti-emetics (See Table 1). *CYP3A5* genotype results can be used to guide dosing of tacrolimus in organ transplant patients (Birdwell *et al*. 2015).
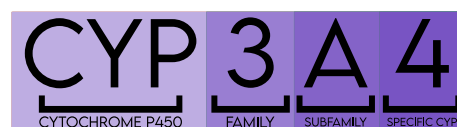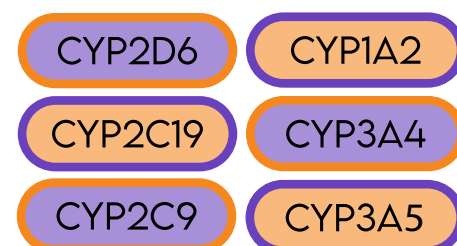

Figure 1. CYP Cytochrome P450 enzyme nomenclature and examples chart.

CYP2D6

CYP2D6 is the primary enzyme responsible for the metabolism of many commonly-used medications especially in mental health, oncology (tamoxifen and 5-HT3 receptor antagonists) (Goetz *et al*. 2018) and pain management (Crews *et al*. 2021) (Table 1 & Figure 2). *CYP2D6* is highly polymorphic with over 130 identified allelic variants and sub-variants identified (www.PharmVar. org; *CYP2D6* Allele Definition).

CYP2D6 alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups, and significant differences in allele frequencies have been observed. It is important to note that variation in *CYP2D6* may have implications for many therapies that may not be listed on this report (Gaedigk *et al*. 2017).
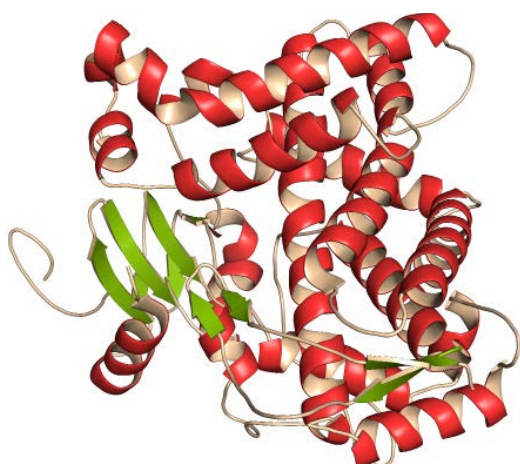

Figure 2. Cytochrome P450 (CYP2D6) liver enzyme in complex with a drug.

CYP2C19

The hepatic *CYP2C19* enzyme contributes to the metabolism of a large number of clinically relevant drugs such as antidepressants, benzodiazepines, mephenytoin, some proton pump inhibitors (Lima *et al*. 2021), and clopidogrel (Scott *et al*. 2013) and anti-fungal medication (voriconazole) (Moriyama *et al.* 2017) (Table 1). Like many other *CYP450* superfamily members, the *CYP2C19* gene is highly polymorphic, with >25 known variant alleles.

CYP2C9

Variants in the *CYP2C9* genes modify the rate at which some medications are metabolised. When considering antidepressant therapy such as tricyclic anti-depressants (TCAs), *CYP2C9* test is often combined with analysis of the *CYP2C19* and *CYP2D6* genes (Attia *et al*. 2014 and Hicks *et al.* 2017). When considering warfarin therapy, this test is often combined with analysis of *VKORC1*.

VKORC1 and CYP2C9 and warfarin

Warfarin is one of the most commonly prescribed medications worldwide, used for many indications including prophylaxis and treatment of thromboembolic disorders, atrial fibrillation, or cardiac valve replacement, and systemic embolism after myocardial infarction (MI). Approved in the US in 1954, the high efficacy of warfarin

is challenged by the high risk of ADEs due to its narrow therapeutic window, requiring careful monitoring and strict compliance.

While *CYP2C9* is predominantly involved in the metabolism of warfarin subtypes; *VKORC1* is the molecular target of the drug. In 2017, an international collaboration published an updated landmark paper defining appropriate warfarin doses based on a validated dosing algorithm of clinical biomarkers and *VKORC1/CYP2C9* genotypes (Johnson *et al*. 2017).

SLCO1B1 and statins

SLCO1B1 gene testing is clinically important in clearance of statins, especially simvastatin. Myopathy is reported in poor metabolisers of this gene. Alternative lipid lowering statins can be prescribed in lower doses such as atorvastatin, pravastatin and rosuvastatin (Ramsey *et al*. 2014).

Genetic variations can render some medications ineffective or toxic

Pharmacogenetic variants result in four distinct phenotypes: normal metabolisers (NMs), intermediate metabolisers (IMs), poor metabolisers (PMs), and ultrarapid metabolisers (UMs) which provides guidance to drug dosing and selection.

Overall, wild-type alleles are usually associated with functional enzyme-mediated metabolism. *Ultrarapid metabolisers* may not achieve therapeutic plasma levels due to decreased trough drug concentrations, whereas *poor metabolisers* treated with drugs that are metabolised by these enzymes are at increased risk for prolonged therapeutic effect or toxicity due to increased trough levels of therapeutic drugs.

Some anti-psychotic and SSRI medications can be contraindicated in intermediate *CYP2D6* metabolisers due to increased risk of adverse effects and so alternative agents must be prescribed.

CYP2D6 ultrarapid metabolisers treated with codeine exhibit symptoms of extreme sleepiness, confusion or shallow breathing; the lowest possible dose should be prescribed to these patients. Meanwhile, patients that are *CYP2D6 poor metabolisers* will not achieve sufficient pain control due to their inability to convert the drug to its active form of morphine (Crews *et al*. 2021).

CYP2C19 ultrarapid metabolisers should be prescribed alternative therapeutic agents other than benzodiazepines, such as citalopram (Celexa) and escitalopram (Lexapro) and TCAs such as impiramine (Tofranil) and clomipramine (Anafranil) due to possible decreases in the efficacy of these medications.

Pharmacogenetic markers in oncology

In addition to *RAS, BRAF, EGFR, ERBB2 (HER2), PK3CA* and *KIT* mutation and *PD-1, ROS, ALK* and *BCR-ABL* fusion genes, other genetic pharmacogenetic biomarkers play a role in patients' responses to oncology therapy.

UDP-glucuronosyltransferase gene (UGT1A1)

UGT1A1 is involved in the metabolism of **irinotecan** (Figure 3), a topoisomerase I inhibitor. *UGT1A1* gene polymorphism is associated with toxicity and clinical efficacy of irinotecan-based chemotherapy in patients with advanced solid tumours including colorectal, rectal and lung cancer (Fujii *et al*. 2019).
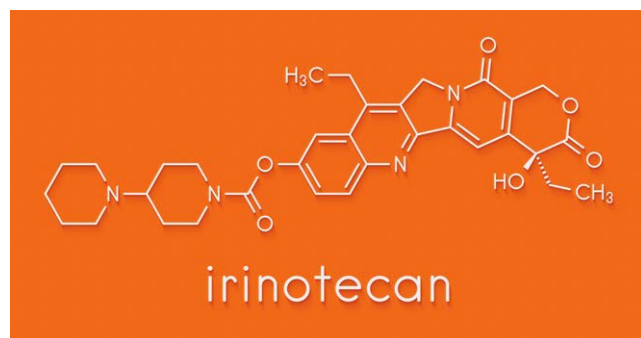

Figure 3. Irinotecan cancer chemotherapy drug molecule.

Thiopurine methyltransferase (TPMT)

TPMT is the primary enzyme responsible for thiopurine drugs (azathioprine, 6-mercaptopurine and 6-thioguanine) metabolism. These drugs are converted in the body to thioguanine nucleotides (TGNs).

Thiopurine therapy targets the replicating cells without overly harming normal cells. Several studies have established Single Nucleotide Polymorphisms (SNPs) in the *TPMT* gene that may lead to enzyme inactivity and therefore haematopoietic toxicity due to thiopurine drugs. It is recommended that physicians order *TPMT* genotyping before prescribing thiopurines to avoid bone marrow toxicity and consequent neutropenia (Relling *et al*. 2018).

Dihydropyrimidine dehydrogenase gene (DPYD)

DPD stands for dihydropyrimidine dehydrogenase, an enzyme made by the liver that breaks down uracil and thymine. The molecules created when pyrimidines are broken down (5,6-dihydrouracil and 5,6-dihydrothymine) are excreted by the body or used in other cellular processes. *DPYD* gene mutations result in excess quantities of the breakdown molecules in the blood, urine, and cerebrospinal fluid.

Mutations in the *DPYD* gene also interfere with the breakdown of drugs with structures similar to the pyrimidines, such as the cancer drugs 5-fluorouracil and capecitabine (two common chemotherapy drugs used as a treatment for a number of different cancers). As a result, these drugs accumulate in the body and cause the severe reactions and neurological manifestations as a result of DPD deficiency (Amstutz *et al*. 2017).

Conclusion

The incorporation of genetic information obtained from pharmacogenetic testing holds substantial promise to improve therapeutic decision making through improved efficacy and reduced adverse events. Considerations

for clinical implementation, such as optimal laboratory workflows, electronic health record integration, and stakeholder engagement, as well as provider education, are crucial for patients' health.

Pharmacogenetic (PGx) test list at Australian Clinical Labs

Our comprehensive pharmacogenetic tests can detect polymorphisms in genes coding for drug metabolising enzymes that predispose individuals to metabolising drugs inadequately.

Gene panels offered:

- ***Cytochrome P450 Comprehensive Gene Panel including****:

CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP1A2, SLCO1B1 and *VKORC1*

Single gene test:

- *TPMT (Medicare rebate)*
- *DPYD*
- *UGT1A1*

*Please note that the panel *Cytochrome P450* Genes can be ordered separately or together (*CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP1A2, SLCO1B1* and *VKORC1*)

> **When to order:** Before commencing therapy, with adverse reaction or resistance.
>
> **How to order:** Fill out our routine Clinical Labs testing request form, list the gene required or group of genes and prescribed medications if available.
>
> **Turnaround time:** Results will be available after 7-10 business days from the sample receipt date.
>
> **Specimen required:** 2x EDTA blood samples.
>
> **Report:** You will receive a comprehensive report that will indicate the genotype and the predicted phenotypes, such as the metaboliser status along with potential drug-gene interaction and guidelines' recommendations.
>
> **Test cost:** Apart from the *TPMT* gene, *CYP450* Variants are non-Medicare (an out-of-pocket fee applies).

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Scott *et al*. 2013. Clin Pharmacol Ther
Swen *et al*. 2011a. Clin Pharmacol Ther

Table 1: List of genes tested and examples of drugs metabolised

GENE	Type of Metabolised Medication	Medicare Rebate
CYP2D6	Anti-Psychotics SSRI TCAs Anxiolytics Oncology Cardiology Opioids and Pain Management Neurology - Anti-ADHD and Anti-Dementia Urology Medication Others	N/A
CYP2C9	Pain Management (NSAIDs) TCAs Neurology Anti-coagulant (Warfarin)	N/A
CYP2C19	PPIs Anti-Platelets (Clopidogrel) Anti-Depressants SSRIs Anti-Psychotics TCAs Neurology Benzodiazepines (Anxiolytics) MAOIs Anti-fungal medication (Voriconazole) Neurology	N/A
SLCO1B1	Lipid Lowering Medications (Statins)	N/A
CYP1A2	Anti-Psychotics (Olanzapine, Clozapine and Duloxetine) Anti-Depressants	N/A
CYP3A4	Psychiatric Medications Statins Organ Transplant (Tacrolimus) Pain Management Others	N/A
CYP3A5 (CYP3A4)	Organ Transplant (Tacrolimus)	N/A
VKORC1	Anti-Coagulant (Warfarin)	N/A
TPMT	Oncology (Thiopurines)	**YES**
DPYD	Oncology (5-fluoro-uracil (5FU), Capecitabine, Tegafur)	N/A
UGT1A1	Oncology (Belinostat, Binimetinib, Irinotecan, Nilotinib, Pazopanib)	N/A

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Vitamin B12: Testing for the diagnosis of deficiency in general practice

By Dr David Deam

Vitamin B12 is an important vitamin and deficiencies can be seen despite the availability of nutritious food.

Vitamin B12 is involved as a cofactor for two important enzymes, methionine synthetase and methylmalonyl CoA-mutase. (Fig 1)
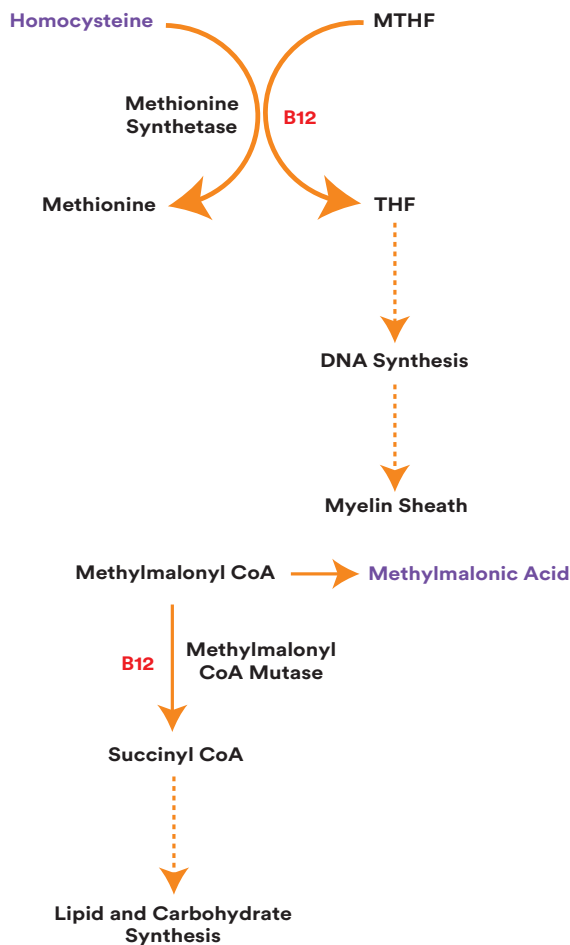

Figure 1. Enzyme reactions involving vitamin B12.

Deficiency of B12 can interrupt these key pathways, with consequent disruption of DNA synthesis resulting in megaloblastic anaemia and other adverse effects on the nervous system and other organs.

Vitamin B12 is not manufactured in humans but is absorbed from the diet. This is a complex process which requires gastric secretion of acid, pepsin, and intrinsic factor, normal pancreatic function, and an intact terminal ileum.

After absorption, vitamin B12 is bound to either haptocorrin (~80%) or transcobalamin (~20%). Only the transcobalamin-bound B12 vitamin (termed holotranscobalamin, or Active B12) can easily enter cells and is biologically active. (Fig 2)
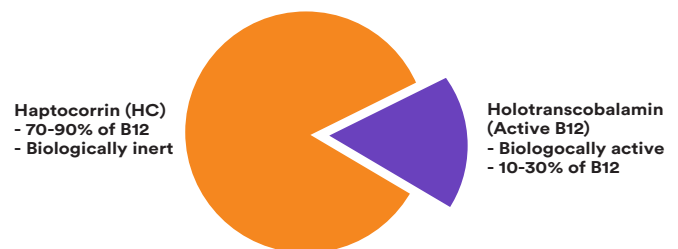

Figure 2. Serum B12 distribution amongst its binding proteins.

The role of the haptocorrin B12 component in the blood is still unknown. Haptocorrin levels may be affected by haemato-oncological disorders, solid tumours or liver disease which can increase levels or other conditions, such as pregnancy that can decrease levels.

Vitamin B12 testing

The most important component of B12 is its levels in tissues where it is utilised in the reactions described above. Although there is no gold standard test to define B12 deficiency, there are a number of tests to assess B12 activity. These include:

1. Tests of B12 levels

a. **Total vitamin B12**

This can be useful in more severe cases but overall it has poor discriminative ability for determining vitamin B12 deficiency. It can give misleading results due to the effect of the inactive haptocorrin-bound B12. This has resulted in our laboratory using an equivocal zone to help interpret B12 levels.

Normal levels	> 180 pmol/L
Borderline	150 – 180 pmol/L
Deficient	< 150 pmol/L

b. **Holotranscobalamin (Active B12)**

This measurement has a better correlation to tissue B12 levels and is an improved marker of B12 deficiency.

According to the MBS schedule, this test can be done where the initial serum vitamin B12 result is low or equivocal. Our laboratory will run this test automatically if these conditions are met and we have a sufficient, suitable sample.

Normal levels	> 35 pmol/L
Borderline	30 -35 pmol/L
Deficient	< 30 pmol/L

2. Tests of B12 metabolism

Reduced function of enzymes where B12 is a cofactor can cause accumulation of precursor compounds (Fig 1).

a. **Homocysteine**

Increased levels can be seen with B12 deficiency. Unfortunately, there are also other causes of raised homocysteine levels including folate and B6 deficiency as well as with some enzyme defects.

b. **Methyl Malonic Acid (MMA)**

Other factors such as renal impairment and enzyme defects can also influence the results.

Note: There is an out of pocket expense for this test.

3. Antibody tests

Anti-gastric parietal cell and Anti-intrinsic factor antibodies can be detected in autoimmune causes of B12 deficiency.

When to test B12 levels

Testing vitamin B12 levels is mainly done to diagnose or assess B12 deficiency. This can be useful if there are clinical features of possible B12 deficiency; these can include:

- Haematological abnormalities such as megaloblastic anaemia, pernicious anaemia and anaemia of uncertain origin
- Neurological abnormalities such as peripheral neuropathy, polyneuropathy, cognitive decline and dementia
- Possible malnutrition
  - Malabsorption (Coeliac disease, IBD)
  - Poor diet (including vegans and vegetarians)
  - Alcoholism
  - Post bariatric surgery
- Drug effects
  - Metformin
  - Proton-pump inhibitors
  - H2 blockers
  - Nitrous oxide abuse
- Non-specific symptoms
  - Fatigue, weakness
  - Depression
  - Difficulty walking
  - Glossitis
  - Various neurological changes

The incidence of low vitamin B12 levels appears to increase with age (> 65 years).

Interpreting B12 results

Our laboratory will automatically perform an active B12 test if the total B12 level is in a range where B12 deficiency is possible.

If the patient has both total B12 and active B12 levels within the reference range, then B12 deficiency is unlikely.

If the active B12 level is low, then it is likely that B12 deficiency is present, even if the total B12 level is within the reference range.

Note: B12 deficiency can sometimes be present even with normal levels of B12 and active B12. If there is a strong clinical suspicion, a trial of B12 treatment may be warranted.

Treatment

B12 treatment may be given to patients in a variety of formats. The best one will depend on the severity of symptoms, the degree of deficiency and the aetiology of the deficiency.

1. Dietary

If the diet is inadequate in B12 then dietary advice can be given. For vegans where this is not an option, there are some foods which are fortified with B12. These include some soy milks, yeast spread, and vegetarian meat substitutes.

2. Oral B12 supplements

Various supplements are available which contain a range of levels of B12 from 10 to 1,000 mcg. The type and dose to use will depend on the cause of the B12 deficiency and the frequency of use. The higher dose forms can also sometimes be useful in pernicious anaemia patients where enough B12 can be absorbed by non-intrinsic factor mediated means.

3. IM B12 injections

Various forms of parenteral B12 are available. The usual dose is in the order of 1,000 mcg with a dosage interval varying between every few days to every few months depending on the degree of deficiency, the urgency of treatment and whether the patient is undergoing initial treatment or maintenance therapy.

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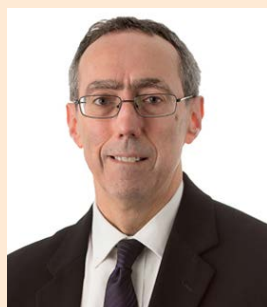
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Dr Deam graduated with Honours in Medicine from Monash University in 1978 and obtained his FRCPA in 1985, following postgraduate training in Biochemistry at the Royal Melbourne Hospital. After several posts in Chemical Pathology at the Royal Melbourne Hospital and the Royal Women's Hospital, he was appointed Head of Chemical Pathology at the Royal Melbourne in 1996. He joined Gribbles Pathology (now Australian Clinical Labs) in 1998. Dr Deam has played an active role in teaching scientific, nursing and medical staff at both undergraduate and postgraduate levels and has been an examiner for the Australasian Association of Clinical Biochemists as well as the Royal College of Pathologists of Australasia. Dr Deam's research interests and publications include work on thyroid function testing, various aspects of diagnostic protein measurement and the rational use of biochemical tests.

Understanding neutropenia in general practice

By Associate Professor Chris Barnes

Neutropenia is a common laboratory abnormality which may be detected incidentally during routine investigations. Reference ranges for neutrophil counts vary with age and ethnicity. A neutrophil count less than 1.5 X 10^9/l is considered low with severe neutropenia defined as a neutrophil count less than 0.5 X 10^9/l. Neutrophils are essential components of the immune system and neutropenia may be associated with a risk of life threatening infections, with this risk increasing with the degree of neutropenia.

Benign ethnic neutropenia

Benign ethnic neutropenia (BEN) is a condition observed in individuals of African descent and is characterised by a reduced absolute neutrophil count of less than 1.50 X 10^9/l in the absence of secondary causes. In contrast to other causes of neutropenia, BEN does not increase risk of oral or systemic infections.

Function of the neutrophil

Neutrophils are produced in the bone marrow in very large numbers (approximately 100 billion are produced each day). Neutrophils monitor for microbial infection and respond with phagocytosis, degranulation and the formation of neutrophil extracellular traps (NETS) responsible for containing microbial infection that is too large to be ingested. Neutrophils are also a critical part of the immune and inflammatory pathways responding by producing cytokines and other inflammatory factors (Rosales Front Physiol 2018).
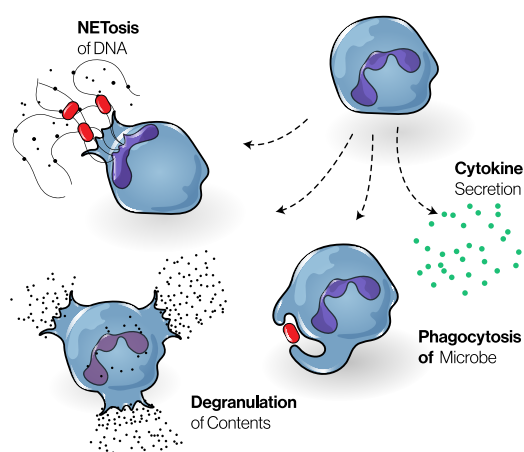

Figure 1. Function of neutrophil.

Causes of neutropenia

Mild neutropenia (a neutrophil count ranging from 1.0 – 1.5 X 10^9/l) is a common laboratory abnormality. Usually not associated with any impairment of host defence, the cause for the mild abnormality does warrant further investigation. Common causes for transient neutropenia include viral infections such as Epstein-Barr virus infection. In children, **chronic** (> 3 months) **mild neutropenia** may be secondary to chronic autoimmune neutropenia of childhood which resolves spontaneously by 3–5 years of age and may last for a median of 17 months. Chronic mild neutropenia in adults may also be secondary to mild autoimmune disorders. Patients with mild autoimmune neutropenia generally do not have an increased incidence of infection and may respond to infection with an increase in the neutrophil count. It is worth considering neutropenia as a sign of a broader autoimmune disorder in patients who present with symptoms of arthralgia, joint stiffness or rashes.
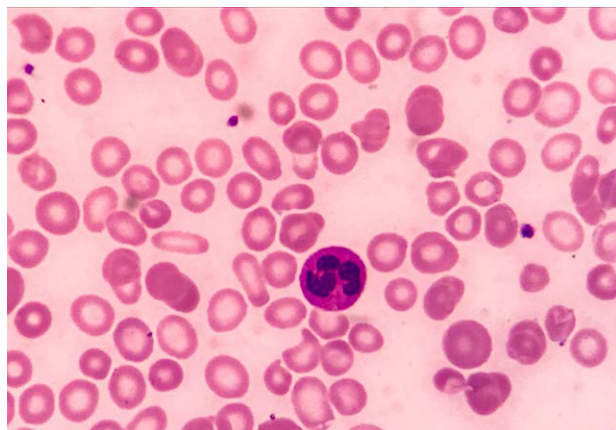

Figure 2. Low neutrophil count in peripheral blood smear of patient, indicating neutropenia.

Medications including anticonvulsants, antipsychotics and chemotherapy are all recognised to be associated with neutropenia.

Nutritional neutropenia may be secondary to deficiencies of vitamin B12 and folic acid or copper or may occur in the setting of severe malnutrition. Typically, nutritional causes are associated with additional cytopenias.

Persistent severe neutropenia (neutrophil count less than 0.5 X 10^9/l) may be associated with a significantly increased risk of overwhelming infection. Causes for severe neutropenia include severe congenital neutropenia. Whilst severe neutropenia in older patients may be secondary to medication effects or even occur as a result of autoimmune or post-viral conditions, bone marrow failure syndromes should be considered. In elderly patients, severe neutropenia may be a manifestation of a myelodysplastic syndrome or bone marrow infiltration disorder.

Work up of a patient with neutropenia

Careful history taking and examination is critical in the assessment of patients presenting with neutropenia. An understanding of the patient's ethnicity including any family history is also important. It is helpful to enquire regarding illnesses around the onset of neutropenia and the presence of any symptoms of mucosal inflammation. A history of infections requiring their treatment with antibiotics or surgical drainage is important to know in order to understand the clinical significance of the neutropenia. A thorough physical examination including assessment for stigmata of autoimmune disease and presence of organomegaly is important.

The **full blood count** is central in the evaluation of patients presenting with neutropenia. The presence of additional cytopenias raises the possibility of a bone marrow failure syndrome. It may be appropriate to assess the neutrophil count on a repeated basis over 3 months to determine if the neutropenia is persistent. Correlation with any past full blood count analysis can be very helpful. In the setting of clinical suspicion of autoimmune disease, assessment of **auto antibodies** including **ANA** may be helpful. If an immunodeficiency is being considered, assessment of **immunoglobulin levels** is recommended. Assessment of **haematinics** may be important in the setting of concern about nutritional deficiencies.

Anti-neutrophil antibody testing is generally not recommended, acknowledging that the findings may be affected by high false-positive and false-negative results. Anti-neutrophil antibody testing is generally only performed by specialist reference laboratories.

A bone marrow examination can be helpful in patients presenting with neutropenia associated with other full blood count abnormalities or in patients presenting with unexplained chronic marked neutropenia. Bone marrow examination can be helpful to exclude myelodysplastic syndromes in elderly patients. Next generation sequencing is emerging as a useful tool particularly in the assessment of young patients presenting with severe neutropenia.

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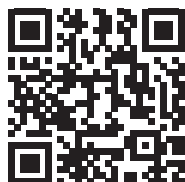**Phone:** (03) 9538 6777
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COVID-19 Travel Testing

At Clinical Labs we offer asymptomatic travellers fast and easy COVID-19 PCR and/or IgM Antibody Testing, with results available within 24 hours.

Travellers simply visit covidtraveltest.com.au, and complete these 4 easy steps:

1. Order their COVID-19 Travel Test.
2. Print their Travel Test Referral Form.
3. Visit a Clinical Labs Travel Collection Centre with a copy of their Travel Test Referral Form and passport.
4. Receive their Travel Test Result Certificate via email.

There are many benefits of Clinical Labs' COVID Travel Testing, including:

- Digitally verifiable QR Code
- Results available within 24 hrs of testing
- SMS notification when result is available
- Quick and easy payment via our secure web portal
- Specific collection centres for travel testing
- IATA compliant & internationally accredited

Visit covidtraveltest.com.au to order your test today!

We also offer travellers a dedicated phone line for any queries about COVID travel testing.

Travel Testing Support
Mon-Fri: 8am-8pm AEST
Sat, Sun & VIC Public Holidays: 9am-5pm AEST
1300 576 258

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1300 134 111

AUSTRALIAN
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