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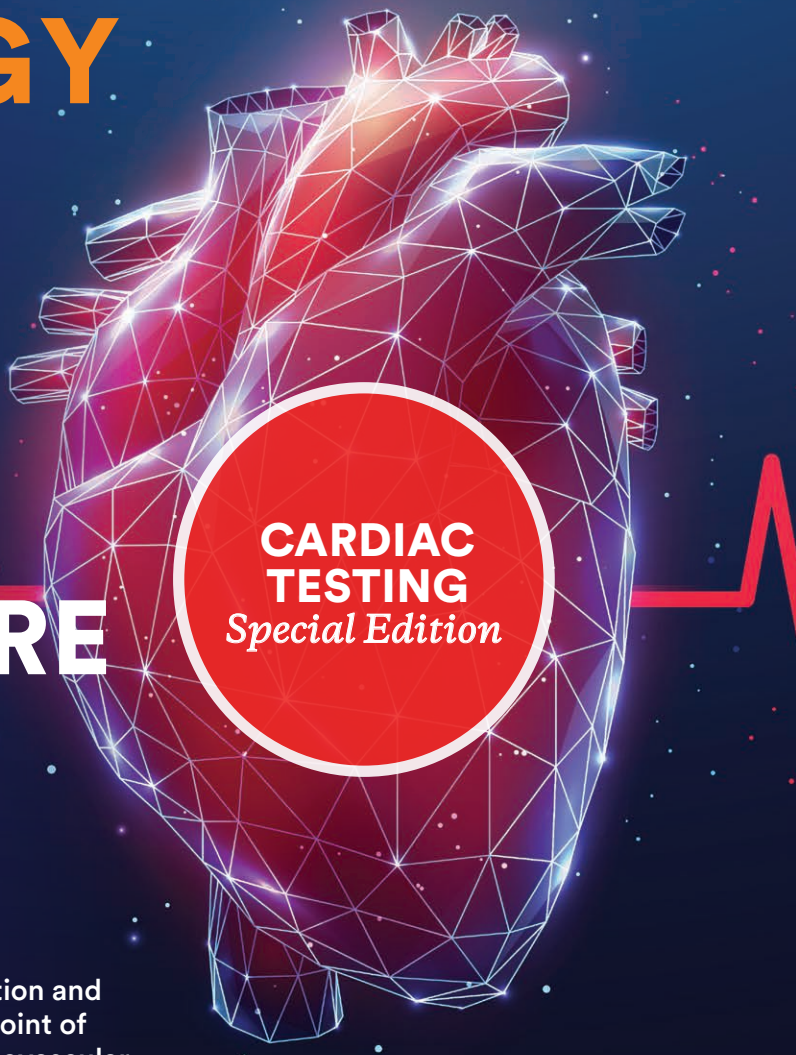

CARDIAC TESTING
Special Edition

OPTIMISING CARDIAC CARE

The role of investigative testing in general practice

By Associate Professor Harry G Mond and Dr David Deam

General practitioners are pivotal in the early detection and risk stratification of cardiac disease. As the initial point of contact for patients presenting with potential cardiovascular symptoms, including palpitations, dizziness or uncontrolled hypertension, GPs are uniquely positioned to initiate targeted investigations. This proactive approach facilitates timely risk assessment, expedites specialist referral pathways and optimises patient management while awaiting cardiology consultation.

In this article, Melbourne cardiologist and Founder and Medical Director of CardioScan, Associate Professor Harry G Mond, and Clinical Labs chemical pathologist Dr David Deam explore key investigative tests that GPs can order for patients presenting with cardiac symptoms in general practice.

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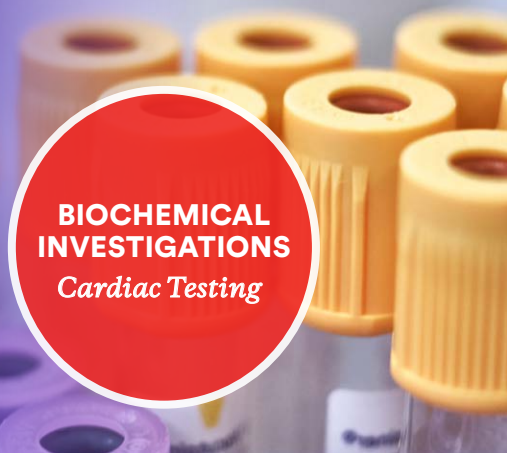
OPTIMISING CARDIAC CARE

Useful investigations for diagnosing and managing heart disease

By Dr David Deam



Assessing overall cardiovascular disease (CVD) risk

Assessing CVD risk using the Australian guideline and calculator (cvdcheck.org.au) is a useful first step when investigating or reviewing patients for possible increased risk of heart disease. This is appropriate for people without known CVD aged 45–79 years, diabetic patients 35-79 years and First Nations people aged 30–79 years. The tool provides an estimated 5-year CVD risk ranking of:

- High (≥10%)
- Intermediate (5% to <10%)
- Low (<5%)

Biochemical investigations

A wide range of biochemical tests can be useful in the assessment and treatment of heart disease. Some of these have been summarised in Figure 1.

The suggested investigations below are not exhaustive and should be considered within the clinical context.

Chest Pain

Investigating chest pain is best done in a setting where resuscitation facilities are available. Initial investigations include a troponin measurement and a 12-lead resting electrocardiograph (ECG). These tests are usually then repeated after a period of several hours, depending on local protocols.

Hypertension (BP)

Besides repeated blood pressure measurements or a 24-hour ambulatory recording, investigations for secondary causes of hypertension can also be appropriate. These are best done before the patient commences treatment. Typical tests include investigations for:

- Adrenal causes
  - Hyperaldosteronism (renin-aldosterone ratio)
  - Pheochromocytoma (urine catecholamine or metabolites)
  - Cushing's syndrome (cortisol)
- Liver disease (liver function tests)
- Renal disease (urea and electrolytes)
- Thyroid disorders (thyroid function tests)

Heart Failure

Patients with suspected or known heart failure can now be investigated with a B-type natriuretic peptide (BNP) measurement. A significant new MBS item for NT-proBNP or BNP testing, item 66829, was added to the Medicare Benefits Schedule on 1 November 2024. This new item broadens the range of clinical situations in which NT-proBNP or BNP testing can be ordered.

For more information about the clinical utility of BNP testing and MBS eligibly criteria, scan the QR code.

Cardiac Arrhythmias and Palpitations

The initial investigation for arrhythmias and palpitations is a resting 12-lead ECG, followed by 24-hour ambulatory ECG monitoring (Holter study). Biochemical testing for electrolyte imbalances (potassium, calcium, magnesium), digoxin levels and thyroid disorders can also be useful.

Atherosclerosis

Serum lipids (cholesterol, triglycerides, HDL cholesterol, LDL cholesterol and non-HDL cholesterol) have an important association with atherosclerosis and measuring levels is useful in diagnosing and managing lipid disorders. Some more specialised investigations, such as apolipoprotein (a) and high-sensitivity C-reactive protein (hs-CRP), can be helpful in selected patients.

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Figure 1. Useful investigations for diagnosing and managing heart disease

Assessing and Managing Cardiovascular Disease Risk

(Australian guideline and calculator) See cvdcheck.org.au

Factors in risk assessment:

- Age, sex
- Smoking status
- Systolic blood pressure (BP)
- Total cholesterol to high-density lipoprotein (HDL) cholesterol ratio (TC:HDL-C ratio)
- Diabetes status
- Cardiovascular disease (CVD) medicines
- History of atrial fibrillation (AF)

If diabetic, include:

- HbA1c
- Time since diagnosis of diabetes
- Urine albumin-creatinine ratio (uACR)
- Estimated glomerular filtration rate (eGFR)
- Body mass index (BMI)
- Insulin treatment

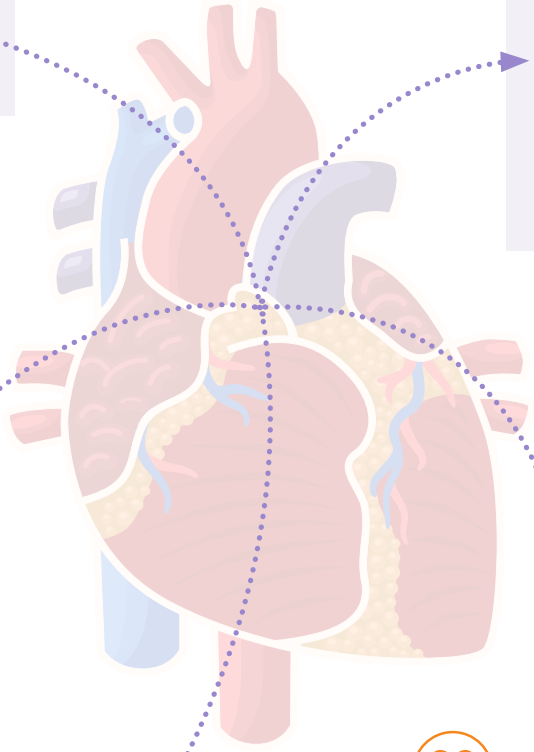
Chest Pain

- ECG
- Troponin

Preferable in an Emergency Department setting

Hypertension

- Ambulatory blood pressure (BP) monitoring
- Renin-aldosterone ratio (ARR)
- Urine catecholamines or metabolites
- Cortisol
- Urea and electrolytes (U&E)
- Liver function tests (LFT)
- Thyroid function tests (TFT)



Arrhythmias and Palpitations

- ECG
- Holter monitoring
- Urea and electrolytes (U&E), calcium, magnesium
- Thyroid function tests (TFT)
- Digoxin levels

Heart Failure

- B-type natriuretic peptides (BNP) or N-terminal pro B-type natriuretic peptide (NT-proBNP)
- ECG
- Imaging and echocardiogram

Atherosclerosis

- Serum lipids
  - Cholesterol
  - Triglycerides
  - HDL (high-density lipoprotein) cholesterol
  - LDL (low-density lipoprotein) cholesterol
  - Non-HDL cholesterol
- Apolipoprotein (a)
- High-sensitivity C-Reactive Protein (hs-CRP)

This figure was created by Dr David Deam, Clinical Labs Chemical Pathologist.

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OPTIMISING CARDIAC CARE

The value of the 12-Lead ECG, Holter monitoring and ambulatory blood pressure monitoring in general practice

By Associate Professor Harry G Mond

CARDIOVASCULAR INVESTIGATIONS
Cardiac Testing

In recent years, technological advances have enabled the widespread use of a number of cardiovascular investigations by general practitioners, specialist physicians and public and private hospitals to exclude or identify cardiac arrhythmias and occult hypertension. These include the resting 12-lead electrocardiograph (ECG), the 24-hour or multi-day Holter monitor (ambulatory ECG monitor) and the 24-hour ambulatory blood pressure monitor. For each investigation, the available recording equipment is reliable and robust, with results available to the referring doctor or hospital within a timely manner (ECG in 4 hours) of the procedure being completed. This has allowed general practitioners to immediately initiate appropriate and, in some instances, life-saving treatment, bypassing long waiting times for specialist or hospital investigations.

Resting 12-lead ECG

In 1905, Nobel laureate Willem Einthoven (Physiology/Medicine, 1924) first described both normal and abnormal ECGs in human subjects. The bulky, primitive equipment eventually became the primary investigative tool for any cardiology patient visiting a physician. Now, 120 years later, despite the vast improvements in cardiological investigations, the resting 12-lead ECG—greatly improved technologically—remains the first cardiology investigation performed during a consultation or hospital visit. Modern recording equipment is small, portable and battery-operated. Initially, tracings were recorded on heat-sensitive or photographic paper, but today, recordings can be sent electronically, allowing immediate reporting and transfer to the requesting physician.

In recent years, there have been expanding indications for the 12-lead ECG.

These include:

- Heart health
- Pre-operative evaluation
- Palpitations/skipped beats
- Bradycardia
- Chest pain
- Dizziness and syncope
- Familial sudden death syndromes, including athletes
- Hypertension
- Cardiomyopathy
- Dyspnoea
- Stroke
- Pacemaker evaluation

Holter (ambulatory ECG) monitoring

The resting 12-lead ECG provides only a 10-second "snapshot" of the heart's electrical activity. For a patient with intermittent palpitations and dizziness, longer recordings are essential. In the 1950s, Norman Holter, a Montana physicist, designed a 39 kg monitor and radio transmitter to record the ECG in real time. By the 1960s, magnetic tape recorders and later cassettes allowed for the development of smaller portable recorders. With further improvements in 24-hour and multi-day ambulatory ECG monitoring, our understanding of the natural history of arrhythmias has greatly improved, resulting in an expanding list of indications for both the standard 12-lead ECG and a broad range of ambulatory ECG monitoring devices.

These include:

- ***Cardiac palpitations.*** This is by far the most common indication for ambulatory ECG monitoring. Generally, a 24-hour monitor is performed even when symptoms are infrequent. Two and three channel, 24-hour and multi-day recordings can be diagnostic for supraventricular and ventricular arrhythmias.
- ***Unexplained syncope or dizziness.*** When these symptoms are frequent, such as daily dizziness, 24-hour monitoring is very useful and is generally the initial investigation, even with relatively infrequent episodes. When the symptoms are less frequent, multi-day monitoring is recommended.
- ***Suspected slow heart rhythms.*** 24-hour ambulatory monitoring remains the most important investigation in the evaluation of symptomatic patients who are being assessed for pacemaker implantation.
- ***Hereditary "electrical" abnormalities***. This diverse group involves a number of hereditary abnormalities associated with cardiac arrhythmias. The most common is Wolff-Parkinson-White syndrome, manifested by an accessory pathway, ventricular pre-excitation and atrioventricular re-entrant tachycardia. The value of ambulatory ECG monitoring is to record arrhythmias, particularly in symptomatic patients.
- ***Evaluating an abnormal ECG with ectopy and heart block.*** This is a particularly important indication for 24-hour ambulatory monitoring to determine the significance of an abnormal ECG finding.
- ***Cryptogenic stroke evaluation to document paroxysmal atrial fibrillation.*** The neurologic finding that atrial fibrillation can lead to cryptogenic stroke was the major stimulus for the development

of multi-day and long-term ambulatory monitoring technologies. Long-term monitoring includes implantable loop recorders.

- ***Evaluation of success of either antiarrhythmic or ablative therapy.*** 24-hour or multi-day ambulatory monitoring is valuable for recording breakthrough arrhythmias. On a long-term basis, non-prescription, single channel monitors such as smartwatches may also be used, although these items are of limited value in the initial diagnosis.
- ***Paediatric ambulatory monitoring.*** This is a special subgroup requiring paediatric equipment if available. Often, multi-day monitoring is necessary, particularly if the patient is unable to document symptoms.
- ***Following acute myocardial infarction.*** Patients who experienced atrial and ventricular arrhythmias or atrio-ventricular block during the acute phase of the infarction may require multi-day ambulatory monitoring following discharge.
- ***Potentially lethal arrhythmias with congestive and hypertrophic cardiomyopathy.*** Patients with cardiomyopathies require ambulatory monitoring to determine if antiarrhythmic or interventional therapy is necessary.
- ***Monitoring cardiac implantable electronic device therapy.*** Modern implanted cardiac pacemakers and cardioverter-defibrillators have inbuilt telemetric monitoring to determine usage and arrhythmia detection. Ambulatory monitoring is important in symptomatic patients where there is no documented telemetered abnormality.
- ***Chest pain or dyspnoea thought to be associated with arrhythmias or ST changes.*** These are unusual, but nevertheless valuable indications for ambulatory monitoring. Occasionally, cardiac arrhythmias, including both bradyarrhythmias and tachyarrhythmias, are the cause of dyspnoea. Patients with anginal-like chest pain may demonstrate marked ST elevation on the ECG due to coronary artery spasm, called Prinzmetal angina.

Monitoring hardware

The most frequently used hardware is the 5-lead, 3-channel, 24-hour Holter monitor. Current models are small, light, battery operated and feature a patient-actuated button for event recording. Multi-day recorders may be 1 to 3 channel, and because of artefacts seen with long-term monitoring, company-specific chest wall patches have been designed to which the monitor is attached. Two- and three-channel monitors are preferred over single-channel models.

Data analysis and report

Once the patient has completed monitoring, the equipment is returned to the Australian Clinical Labs laboratory, where the recorded data is retrieved from the memory card and sent to CardioScan, responsible for analysing the raw data. A report is provided and confirmed by an experienced CardioScan cardiologist, then sent to the referring doctor. The report includes a summary of the 24-hour or multi-day study, significant events and the conclusion. Although therapeutic options are not provided, a CardioScan cardiologist is available to explain the results if necessary. For the requesting physician, there is a minimal knowledge requirement for competency in interpreting ambulatory ECG monitoring reports.

Ambulatory blood pressure monitoring

Every doctor understands the importance of detecting and treating occult hypertension at all ages. In recent years, ambulatory blood pressure monitoring has become a recognised and reliable method for confirming hypertension. The National Heart Foundation of Australia, in its summary of recommendations, states that "ambulatory blood pressure monitoring be offered to patients with a blood pressure ≥ 140/90 in order to confirm the blood pressure level".[1] Indeed, guidelines from the United States, Britain and Europe recommend ambulatory blood pressure monitoring as a cost-effective diagnostic tool for all patients with suspected hypertension. Sophisticated, automated, 24-hour ambulatory blood pressure monitors are now available, and like all investigations, the results depend on the quality of the recordings and their interpretation in the clinical setting.

Ambulatory blood pressure monitoring should cover close to a 24-hour period, with >70% of recordings being valid. Recordings are usually performed every 30 minutes during the day and at least hourly overnight. It is recommended that at least 14 recordings be performed during the daytime period.[1] However, monitoring is not without its difficulties, as cuff inflation can sometimes be painful and uncomfortable, leading to the patient removing the monitor overnight because of difficulty sleeping. Invalid recordings may occur if the cuff is not appropriately attached, is removed and reattached by the patient or if there is a leak or obstruction in the tubing. Movement during the recording may also result in an invalid measurement. In these situations, measurements are often automatically repeated, and there may still be enough data (> 14 recordings) to establish a diagnosis, even if the percentage of valid measurements is < 70%. This is important, as the vast majority of patients who experience discomfort during the study will not be prepared to have the study repeated.

The interpretation of results requires a clinical assessment, taking into consideration well-established risk factors for cardiac disease. Consequently, the referring doctor can modify the report conclusions to suit the patient's individual circumstances, such as a young diabetic with renal disease who requires optimal control. The referring doctor, and not the reporting physician, should review the patient diary with the patient.

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On 1 November 2021, ambulatory blood pressure monitors were added to the Medicare Benefits Schedule under item number 11607. Certain patients may be eligible for a Medicare rebate. For further information and patient eligibility criteria, please visit clinicallabs.com.au/cardiactestingservices

Table 1: Accepted normal limits for ambulatory blood pressure recordings.

Ambulatory Blood Pressure	Systolic (mmHg)	Diastolic (mmHg)
Over 24 hours	≥ 130	≥ 80
Awake (daytime)	≥ 135	≥ 85
Asleep (night-time)	≥ 120	≥ 70
% allowed above limit	< 25%	< 25%

Table 2: Guidelines on severity of recorded pressures (Clinical and not 24-hour ambulatory recordings).[1]

Diagnostic Category	Systolic mmHg	Diastolic mmHg
Optimal	< 120	< 80
Normal	120-129	80-84
High normal	130-139	85-89
Isolated systolic	> 140	< 90
Grade 1: Mild	140-159	90-99
Grade 2: Moderate	160-179	100-109
Grade 3: Severe	≥ 180	≥ 110
Emergency	> 220	> 140

References

1. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults - 2016. Melbourne: National Heart Foundation of Australia 2016.

For more information on Ambulatory Electrocardiographic Monitoring, see Associate Professor Harry G Mond's article 'The Spectrum of Ambulatory Electrocardiographic Monitoring' published in Heart, Lung and Circulation (2017) 26, 1160–1174.

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Dr Harry Mond is an Associate Professor at both Melbourne and Monash Universities and has been practicing as a Cardiologist in Melbourne since 1975. He is a pioneer in cardiac pacing with extensive experience in pacemaker implantation and follow-up. Dr Mond is currently involved in ECG teaching and has completed a textbook on the subject.

How to Order Cardiac Testing with Clinical Labs

What to Write on the Request Form:
The Clinical Labs general pathology request form can be used to request Cardiac Testing Services (ECG, 24-hour Holter monitor and 24-hour ABPM) as well as biochemistry tests based on the patient's symptoms.

Please note: ECG service is not available in Qld. ECG, Holter and ABPM services are not available in the NT.

Testing Locations:
For Holter monitor and ABPM services in Vic and Qld, patients will need to call a Clinical Labs Collection Centre that offers these services to book a time for device collection and fitting. In SA, patients will need to call (08) 8205 5644.

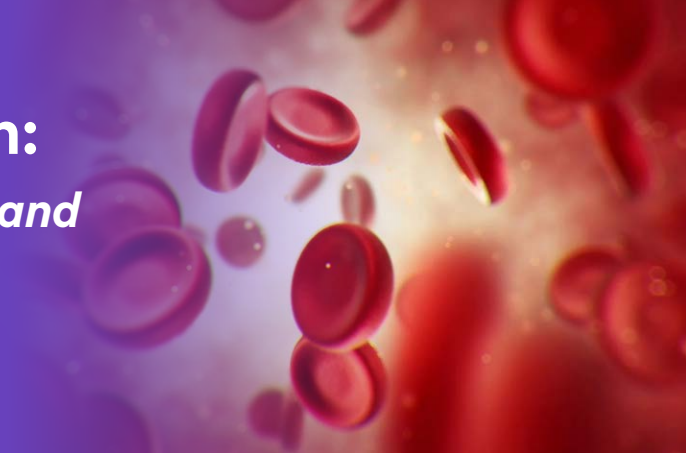
ECG is a walk-in service—no booking required.

Cardiac testing services are available at select Clinical Labs collection centres. To find the nearest location, visit clinicallabs.com.au/location and select the service from the 'All Facilities' drop-down menu. For blood tests, patients can visit any of our 1,300+ Clinical Labs collection centres.

Test Cost and Turnaround Times:
For current pricing and turnaround times for cardiac testing services, visit clinicallabs.com.au/cardiactestingservices. Most blood tests are bulk-billed, subject to Medicare eligibility criteria.

Annual Blood Tests for Men:

Overcoming barriers to healthcare and improving preventative health



By Associate Professor Chris Barnes

Men in Australia face higher rates of preventable diseases, lower engagement with healthcare services and shorter life expectancy than women.[1] Cardiovascular disease, type 2 diabetes and chronic kidney disease are among the leading causes of death in men, yet many of these conditions can be prevented or managed through routine health screening. Despite this, men are significantly less likely to visit their general practitioner (GP) for routine health checks, leading to late-stage diagnoses and poorer health outcomes.[2]

Blood tests present an underutilised opportunity for GPs to engage men in healthcare, promote preventative health strategies and improve health literacy. Annual blood tests provide objective, actionable data that can motivate men to take an active role in their health, facilitating early intervention and ongoing medical follow-up.[3]

Understanding the barriers to healthcare for men

Men are less likely than women to access primary healthcare, contributing to higher rates of undiagnosed and unmanaged chronic conditions. Several key factors contribute to this disparity:[4]

- **Time constraints and perceived inconvenience:** Many men cite work obligations, lack of time, and difficulty scheduling appointments as reasons for avoiding medical visits.
- **A culture of self-reliance and reluctance to seek help:** Societal expectations around masculinity often discourage men from acknowledging health concerns, leading to delayed medical consultations.
- **Lack of awareness about preventative health:** Many men associate healthcare with treatment rather than prevention, resulting in missed opportunities for early intervention.

GPs play a critical role in reducing these barriers by offering accessible, convenient and tailored approaches to men's health screening. Blood tests provide a clear and measurable entry point for engaging men, shifting the conversation from reactive treatment to proactive prevention.

Recommended blood tests for male patients

Blood tests are a key component of preventative healthcare for men, offering early detection of cardiovascular, metabolic, endocrine and renal conditions. Current Australian guidelines recommend routine screening for common risk factors, particularly for men over 40 or those with predisposing risk factors.

Cardiovascular and metabolic screening

- **Lipid Profile (Non-Fasting Preferred):** The Royal Australian College of General Practitioners (RACGP) and the National Heart Foundation recommend lipid screening for all men over 45 years (or over 35 years for Aboriginal and Torres Strait Islander men). Non-fasting lipid tests are now widely accepted, improving compliance by reducing the inconvenience of early-morning, fasting-required visits.[5]
- **HbA1c or Fasting Blood Glucose:** Type 2 diabetes remains underdiagnosed in men, with many cases detected at later stages. Annual screening is recommended for men with obesity, hypertension or a family history of diabetes.

Prostate and hormonal health

- **Prostate-Specific Antigen (PSA):** The RACGP advises shared decision-making regarding PSA testing for prostate cancer in men over 50 (or over 40 for those with a family history). While routine screening is not universally recommended, early detection in high-risk individuals can improve outcomes.[6]
- **Testosterone Levels:** Low testosterone can impact energy, libido, muscle mass and mental health. Testing is recommended in symptomatic men, with repeat morning testing before confirming a diagnosis. Routine testosterone screening is not recommended for asymptomatic men, as low levels are often related to underlying health conditions rather than true hypogonadism. Testing should be reserved for those with clear clinical symptoms[7]

Liver and kidney function

- **Liver Function Tests (LFTs):** Alcohol consumption and non-alcoholic fatty liver disease (NAFLD) are significant concerns among Australian men. Routine LFTs should be considered for men with metabolic syndrome, excessive alcohol intake or long-term medication use.
- **Renal Function Tests (eGFR, Creatinine, UACR):** Chronic kidney disease (CKD) is often asymptomatic in early stages. Routine screening is recommended for men with diabetes, hypertension or a history of cardiovascular disease.

Haematological and general health screening

- **Full Blood Count (FBC):** Anaemia and blood disorders often go undiagnosed until symptoms become severe.

- **Vitamin D and Iron Studies:** Low vitamin D and iron deficiency are associated with fatigue, muscle weakness and cardiovascular risk. Testing is particularly relevant for men with low sun exposure, dietary restrictions or symptoms of deficiency.

How laboratory testing can improve men's health engagement

Many men only visit a doctor when symptoms become severe, missing crucial opportunities for early intervention. Blood tests provide an objective, measurable starting point for discussions about long-term health risks, increasing the likelihood of continued engagement.[3]

Key benefits of laboratory testing for men's health engagement:

- **Providing clear, objective health data:** Many men respond well to quantifiable results. Discussing lipid levels, blood sugar trends or kidney function changes can motivate lifestyle modifications and adherence to medical advice.
- **Normalising preventative health screenings:** Integrating blood tests into routine health checks makes preventative care a habit rather than an exception.
- **Reinforcing the importance of follow-up care:** Tracking cholesterol levels, diabetes markers, or liver function over time allows GPs to guide incremental, achievable health improvements.
- **Overcoming access barriers:** Offering blood tests in workplace health programs, community centres or telehealth-supported models can improve uptake among men who struggle with time constraints and appointment scheduling.

Conclusion: A shift towards proactive men's healthcare

Routine blood tests should be positioned as an essential tool in preventative healthcare for men—not just for early disease detection but as an engagement strategy that fosters long-term health literacy and proactive care.

By incorporating accessible, targeted and structured screening programs, GPs can overcome traditional barriers to men's healthcare participation, ensuring more men take ownership of their health before conditions progress. Blood tests are a simple yet powerful intervention that can shift the focus from reactive treatment to long-term disease prevention, ultimately improving health outcomes and longevity for Australian men.

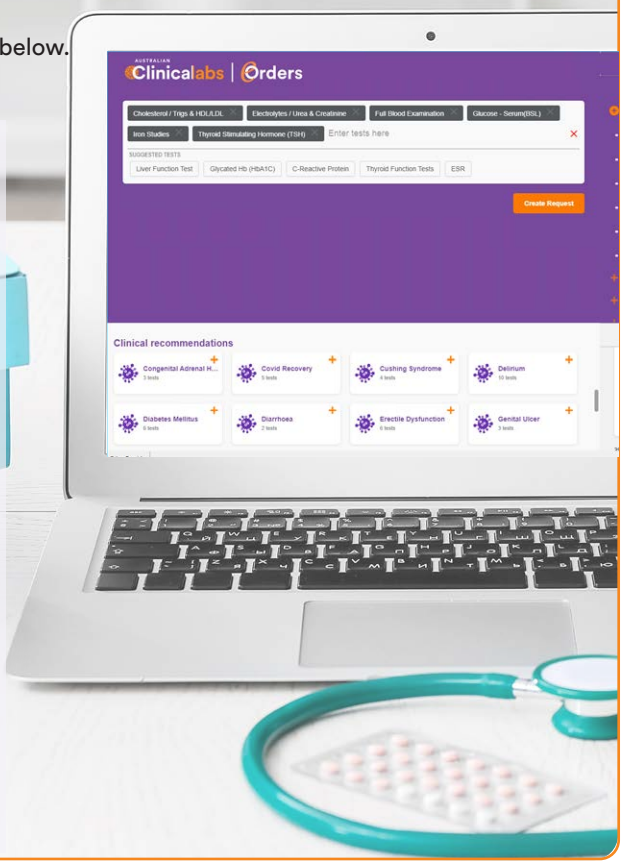
Order our 'Men's Annual Screen' profiles — only with Clinical Labs' eOrders

For clinicians using eOrders in Best Practice, MedicalDirector Clinical or Clinical Labs eResults, we have developed a series of 'Men's Annual Screen' profiles aligned with the clinical recommendations provided by A/Prof Barnes in this article.

How to order:

1. Ensure eOrders with Clinical Labs is activated in your practice management software.
2. Navigate to 'Clinical Recommendations' (MD) or 'Clinical Details' (BP).
3. Select the desired 'Men's Annual Screen' profile from the options outlined below.

Cost: Bulk-billed, subject to Medicare eligibility criteria.



eOrders Men's Annual Screen Profiles

Men's Annual Screen (General Health & Haem)
- Full Blood Count
- Vitamin D
- Iron Studies

Men's Annual Screen (Cardiovascular & Metabolic)
- Cholesterol, Trigs & HDL
- HbA1c
- Glucose

Men's Annual Screen (Prostate and Hormonal Health)
- Prostate-Specific Antigen (PSA)
- Testosterone

Men's Annual Screen (Liver and Kidney Function)
- Liver Function Tests
- Renal Function Tests
- Microalbumin

Men's Annual Screen (Full)
- Full Blood Count
- Vitamin D
- Iron Studies
- Cholesterol, Trigs & HDL
- HbA1c
- Glucose
- Prostate-Specific Antigen (PSA)
- Testosterone
- Liver Function Tests
- Renal Function Tests
- Microalbumin

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Associate Professor Chris Barnes joined Clinical Labs in 2016 and is the National Director of Clinical Pathology. Prior to this, he worked as a consultant haematopathologist with Healthscope Pathology from 2009. Chris is a dual-trained clinical and laboratory haematologist, having trained at the Royal Children's Hospital and the Royal Melbourne Hospital. He also undertook training at The Hospital for Sick Children in Toronto, Canada. He holds a part-time public hospital appointment at the Royal Children's Hospital, where he serves as the Director of the Henry Ekert Haemophilia Treatment Centre. Chris has extensive clinical research interests and is the principal investigator on eight separate clinical trials based at the Murdoch Children's Research Institute. He has held numerous leadership positions, including Chair of the Medical Staff Association at the Royal Children's Hospital and Chair of the Australian Haemophilia Directors Association. He is currently the Chair of the Australian Bleeding Disorders Registry with the National Blood Authority and a Director of Melbourne Haematology and Melbourne Paediatric Specialists. Chris' focus within Clinical Labs is the national supervision and management of clinical pathology disciplines, including haematology, biochemistry, microbiology and immunopathology.

Navigating the Diagnostic Complexities of Systemic Lupus Erythematosus:

Historical perspectives and modern advances

By Associate Professor Louise Smyth

Introduction

Systemic lupus erythematosus (SLE), as we know it today, is a Systemic Autoimmune Rheumatic Disorder (SARD) that can affect single or multiple organs and may also present as a disease limited to cutaneous manifestations (DLE). It is from the latter that the term 'lupus' has arisen, having been used for centuries to describe destructive or ulcerating skin lesions of varied aetiology.

Historical perspective

In 1851, Pierre Alphée Cazenave, a French dermatologist, described the facial (butterfly) rash that is archetypal of the disease, naming it *lupus érythémateux*:

"In some circumstances [lupus] manifests itself at first as a violet rubefaction on this or that part of the face, and mainly on the nose, which at the same time is rather swollen: over many months the colour rises little by little; the surface becomes animated; a small ulcer forms and on top of it, a scab, which then thickens and covers the ulcer, which becomes progressively deeper. Lastly, the skin may get thinner in imperceptible stages and adopt the appearance of a scar, without there being tubercles or ulcers, and without displaying worse injuries than a livid colour and, from time to time, a light and barely perceptible peeling."

Moritz Kaposi and Sir William Osler are generally credited with recognising lupus affecting internal organs, in particular, renal and CNS lupus. Descriptions of pulmonary, cardiac and haematological manifestations followed. Keil proposed a single disease that included Discoid Lupus Erythematosus and Systemic Lupus Erythematosus in 1937.

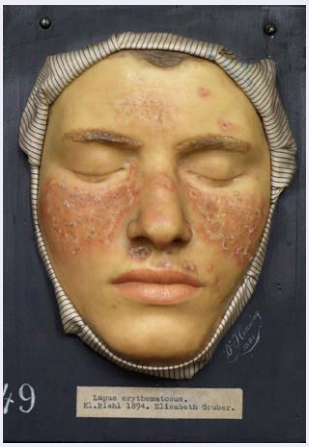

Figure 1.
Wax representation of lupus erythematosus (1894) housed in the Federal Pathologic-Anatomical Museum in Vienna.

Patzak B. Moulage: "Lupus erythematosus". Dermatol Pract Concept. 2011 Jan 31;1(1):1. doi: 10.5826/dpc. dp0101a01. PMID: 24396710; PMCID: PMC3881073.

Evolution of diagnosis

As clinical descriptions extended and recognition improved, the incidence of this disorder, recognised in at least one pre-Colombian mummy and possibly linked to Jane Austen, grew. LE cells were described in 1948, followed by an increasing array of autoantibodies, which were generally indicative and sometimes diagnostic. The advent of laboratory tests increased diagnostic capabilities, leading to increased recognition of less serious cases and a dramatic rise in both incidence and prevalence (Felten & al., 2022).

Diagnostic challenges

Lupus remains both a diagnostic and scientific challenge, which sometimes appears to deepen as knowledge expands. The disease we call lupus has multiple presentations within and between patients, may affect one or many organs or tissues, and has a variable course and prognosis. Given this heterogeneous clinical picture, diagnostic assessment will inevitably be equally complex. Since the 1982 American College of Rheumatology (ACR) Revised Criteria for the Classification of Systemic Lupus Erythematosus, circulating autoantibodies have risen in diagnostic importance. Antibodies to native DNA and Sm antigens were added to the criteria, along with the "false-positive serological test for syphilis," later shown to be anti-cardiolipin antibody.

This set of clinical and laboratory criteria improved diagnostic performance in both sensitivity (83% vs 78%) and specificity (89% vs 87% against a cohort of scleroderma and myositis patients) (Tan & al., 1982). Antinuclear antibody (ANA) by Indirect Immunofluorescence (IIF) was also introduced; however, even then, it was noted to have low specificity, despite being identified in 174 out of 175 SLE patients selected from specialist clinics, demonstrating high sensitivity. Thus, from its earliest inclusion, ANA was proposed as an *entry criterion* rather than a diagnostic test.

Advances in classification criteria

The ACR criteria were updated in 1997 and remained the reference criteria until the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria update. In 2019, the European Alliance of Associations for Rheumatology (EULAR)/ACR classification criteria for SLE were developed. As previously, the need to report homogeneously and consistently in clinical research settings drove the development of classification criteria that have become *de facto* diagnostic criteria. These latest collaborative criteria have been validated in both adult

and paediatric populations (sensitivity 92% and 89%, respectively) and have increased the sensitivity of the 2012 SLICC criteria while protecting the specificity achieved by the 1997 ACR criteria.

Using this standard, positive ANA (at a titre of 1:80) is still defined as an entry criterion, as at this titre, 98% of cases are captured, although its specificity is not sufficient for use as a diagnostic test. ANA at less than 1:80 is seen in other autoimmune disorders, notably in autoimmune hepatitis, where it contributes to the IAIHG simplified scoring system for the detection of autoimmune hepatitis (European Association for the Study of the Liver, 2015).

Delayed diagnosis and disease progression

The clinical diagnosis of lupus is, as stated, complex and is frequently delayed. Rees *et al*. showed that in the UK, between 1/1/1999 and 31/12/2012, patients who were eventually diagnosed with lupus presented to their general practitioners a median of 9.2 times per annum during the 5 years preceding diagnosis for symptoms associated with lupus, compared to 3.8 times per annum for case-based controls (Rees, 2017). Additionally, it has been known for several years that some autoantibodies, including anti-dsDNA, can be identified in the serum of individuals who are clinically well but who would later be diagnosed with lupus (Arbuckle, *et al.*, 2001).

As with anti-CCP antibody in rheumatoid arthritis, the concentration of antibody increases proximate to the development of clinical disease. Perhaps unsurprisingly, in a disorder that presents with a range of severity, milder and more frequent cases initially present to family practitioners, while cases that present directly to specialists with greater experience of this nebulous disease tend to be more severe. Nikopolous *et al.* demonstrated that, for Caucasian patients with a disease duration of at least a year, approximately 55% had a mild phenotype at diagnosis, but nearly half of those progressed to more severe disease. After three years, there was a more than 20-fold increased risk of accrued irreversible tissue damage (Nikolopoulos, *et al.*, 2020). In their study, high-risk patients were men, those with positive anti-dsDNA or those with neuropsychiatric disease.

Ethnic and age-related variation

Epidemiological differences in disease frequency and severity have been well documented. Pons-Estel *et al.* (2010) summarised that lupus is 2-4 times more frequent and severe in non-white populations. Although lupus most commonly affects women of childbearing age or later, it tends to be more severe in men, paediatric patients (<17 years at diagnosis) and late-onset patients (> 50 years at diagnosis).

EULAR/ACR classification criteria

The EULAR/ACR criteria were published in the Annals of the Rheumatic Diseases (Aringer, 2019) and a guide to the relevance of common ANA patterns was published by Lazar in 2023 (see below). All laboratory investigations listed in the EULAR/ACR criteria are available at Clinical Labs.

Table 1. Guide to the relevance of common ANA patterns

Antinuclear antibody pattern	Associated antigen targets	Clinical disease correlate
Homogeneous	dsDNA, histones, chromatin	SLE, drug-induced SLE, JIA, chronic autoimmune hepatitis
Dense fine speckled	DFS70	Healthy and other non-SARD conditions
Centromere	CENP-B (centromere)	Limited cutaneous SSc, PBC
Fine speckled	SS-A/Ro, SS-B/La, Mi-2, TIF1y, Ku	SjS, SLE, SCLE, neonatal lupus erythematosus, congenital heart block, DM, SSc, SSc-AIM overlap
Coarse speckled	Sm, RNP, U1RNP, RNA-polymerase III	SLE, SSc, MCTD, SSc-AIM overlap, UCTD
Nucleolar	Th/To, PM/Scl, U3RNP, RNA-polymerase I	SSc, SSc-AIM overlap, Raynaud's, SjS, cancer

Abbreviations: AIM, autoimmune myositis; DM, dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; PBC, primary biliary cirrhosis; SARD, systemic autoimmune rheumatic disease; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SjS, Sjogren's syndrome; SSc, scleroderma; UCTD, undifferentiated connective tissue disease.

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How to order laboratory investigations for Systematic Lupus Erythematosus at Clinical Labs

What to Write on the Request Form:
The Clinical Labs general pathology request form can be used to request the following laboratory investigations listed in the above EULAR/ACR criteria:

- **Antinuclear antibodies (ANA)** for initial assessment; followed by SLE-specific antibodies and serum complement when positive (anti-dsDNA antibody, ENA) or as directed in ANA report.
- **Antiphospholipid antibodies** (Anti-cardiolipin antibodies, Anti-ß2GP1 antibodies, Lupus anticoagulant), especially if thromboembolic disorder or pregnancy loss.

Clinical history is important for the laboratory interpretation of the results.

Test cost: Bulk-billed, subject to Medicare eligibility criteria.

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