

TESTS AND INVESTIGATIONS FOR MULTIPLE MYELOMA

A guide for patients and caregivers

Developed by the Myeloma Special Practice Network (M-SPN) of the Haematology Society of Australia and New Zealand (HSANZ) Nurses Group.

FOREWORD

Haematology Society of Australia and New Zealand Nurses' Group (HSANZ-NG) is a sub-group of the HSANZ professional organisation. Their mission is to enhance the care of patients undergoing treatment for haematological conditions, and support their relatives and caregivers, through the development and promotion of information and education aimed at improving standards of care. The Myeloma Special Practice Network (M-SPN) was specifically formed to focus on enhancing care of those affected by myeloma.

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Reasonable care is taken to provide accurate information at the time of creation. This information is not intended as a substitute for medical advice and should not be exclusively relied on to manage or diagnose a medical condition.

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INTRODUCTION TO TESTING

This booklet provides an overview of tests and investigations commonly used to diagnose, assess, and monitor people affected by **multiple myeloma (MM)**. This includes tests and investigations that are generally recommended, however each person's situation is different and will not require all the tests listed. Patients and those who support them – caregivers, family and friends – may find this booklet helpful in understanding what to expect during testing.

Doctors use tests to diagnose MM, they also perform tests to investigate how the disease is affecting other parts of the body, or to understand how well a treatment is working. There is no one single test that can diagnose MM. Typically, the disease is diagnosed using a combination of a person's clinical signs and symptoms, medical history, physical examination, laboratory tests, and/or imaging. Your doctor may consider the following factors when choosing which tests are appropriate in your case: disease signs and symptoms, age, other medical conditions, and the results of earlier tests.

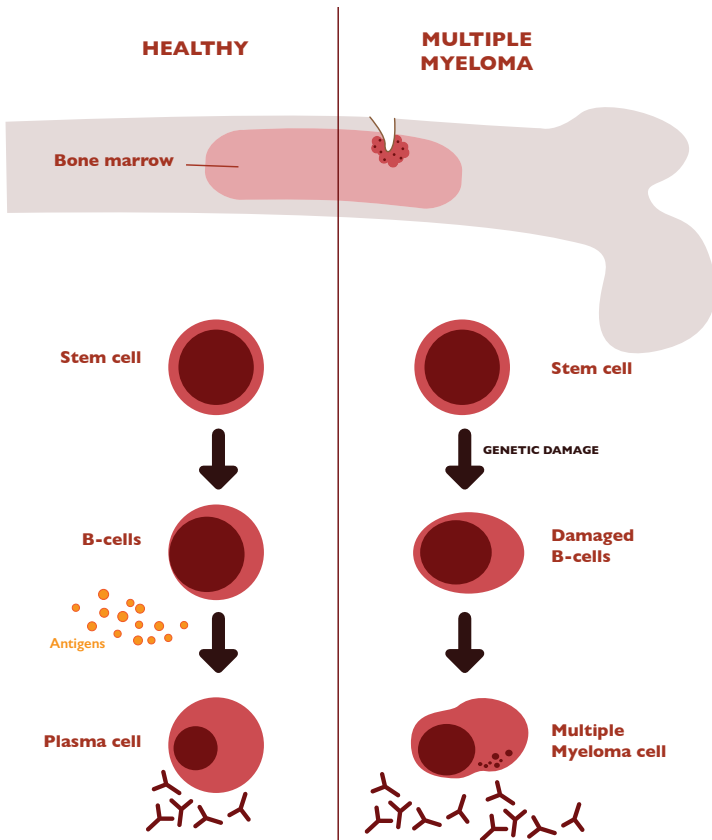
For some tests, there are several techniques available that require different samples (e.g., blood, urine, **bone marrow**) or use different methodologies (e.g., scans versus blood test). How often you will need to undergo testing will depend on your individual situation. Your doctor may order some tests to confirm your diagnosis, then order additional tests to assess your disease status. You may then need to undergo testing every few months during treatment to help monitor the disease and after completing treatment to assess your response.

You are unique and so is your disease. Your doctor will review the results of each test and use them to guide decisions about your treatment and management. Your results for the same test may differ at different time points; this may be due to the time-period in which they were completed, the testing centre completing the testing, and the method they used to perform the test. Therefore, you can't compare your test results with those of other people. However, your doctor will probably recommend that where possible, your tests are undertaken at the same testing centre to reduce differences in the results. You should discuss all test results with your doctor if you want to better understand what the results mean in your individual circumstances.

What is Multiple Myeloma (MM) and how will it affect my body?

MM is a type of cancer of the blood, specifically of **plasma cells**, and originates in the **bone marrow** found in the centre of large bones. Plasma cells live and grow in the bone marrow and are an important part of our immune system. As well as being the site of production of plasma cells, the bone marrow is responsible for all blood cell production (**red blood cells [RBC], white blood cells [WBC] and platelets**). The main function of plasma cells is to produce **antibodies (immunoglobulins)** that help the body fight infections (virus or bacteria). Different plasma cells produce different antibodies needed to attack specific infections (virus or bacteria).

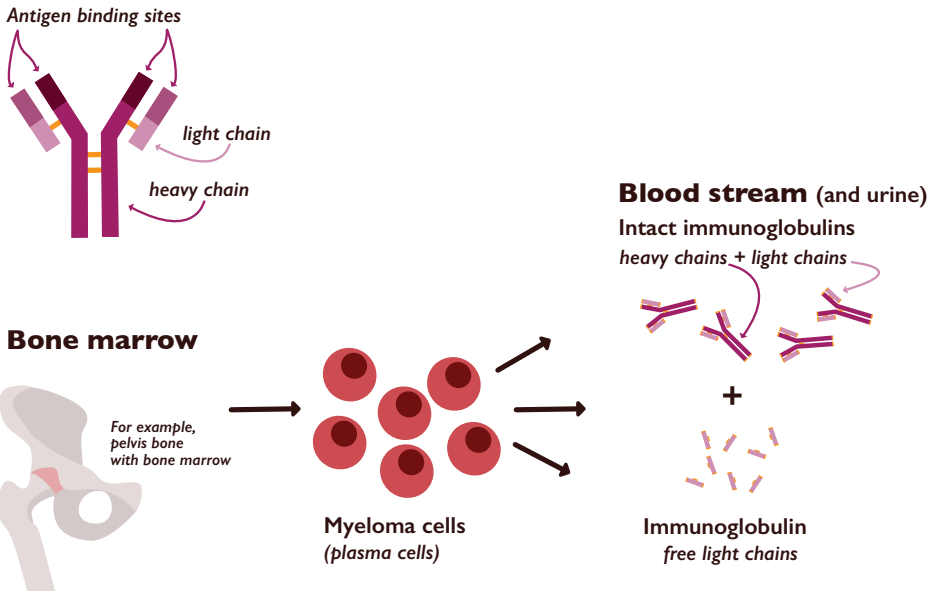
In MM, plasma cells become damaged causing them to divide uncontrollably – becoming **myeloma cells**. Myeloma (cancer) cells produce many copies of themselves, crowding out other cells in the bone marrow, stopping the production of normal blood cells and damaging the surrounding bone. A collection of these myeloma cells that form in the tissue leads to a tumour, called a **plasmacytoma**.



The production of plasma and myeloma cells in the bone marrow

Myeloma cells produce abnormal antibodies, called M-proteins, which are found in the blood and urine (where they may be called Bence-Jones proteins) of people with MM. Normally, the body makes five different types of antibodies, also called **immunoglobulins (Ig)**: IgG, IgM, IgA, IgE, and IgD. Each antibody has slightly different functions in the immune system. These proteins are all composed of four protein chains: two identical heavy (long) protein chains and two identical light (shorter) protein chains. The light chains consist of one of two different types, called kappa and lambda. M-proteins consist of two heavy and two light chains, however, some myeloma cells tend to make more light chains than needed to form an M-protein. This leads to an excess of light chains, called **free light chains (FLC)**. High levels of FLC can be found in the urine of people with MM.

The structure of an antibody (immunoglobulin)



The structure of normal antibodies and production of FLC in MM

Some people go on to develop MM after being diagnosed with a benign (non-malignant) condition called **Monoclonal gammopathy of undetermined significance (MGUS)**. This condition is characterised by raised levels of M-proteins, but no other symptoms of the disease. Some people are diagnosed with a pre-MM condition, called smouldering, or **asymptomatic MM**. This is similar to MGUS, with higher levels of M-proteins and no other symptoms of the disease. When a person develops signs and symptoms of the disease, this is called active (symptomatic) MM.

The main symptoms associated with MM result from the production of myeloma cells and M-proteins in the bone marrow. This reduces their ability to produce normal healthy blood cells, resulting in conditions such as **anaemia**, recurrent infections, and bruising. M-proteins collect in the kidney where they can cause damage. Myeloma cells can also cause bone damage, which leads to a build-up of calcium in the blood (**hypercalcaemia**).

Signs and symptoms of Multiple Myeloma

BRUISING OR BLEEDING

Myeloma cells in the bone marrow prevent platelet production. Platelets help the blood clot; a lack of these cells results in bruising and/or bleeding.

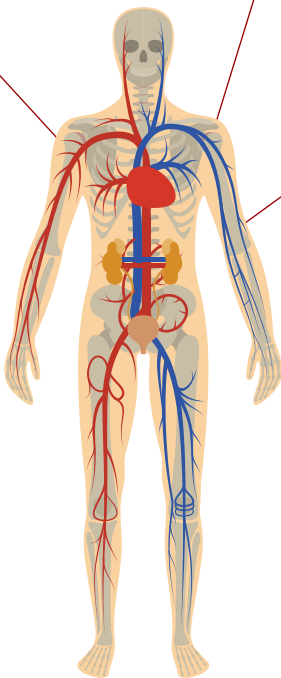
KIDNEY

High levels of M-proteins in the blood can cause damage to the kidney.

The breakdown of bones associated with MM also causes the release of calcium into the blood, which can damage the kidneys.

BONE DAMAGE AND PAIN

Myeloma cells release chemicals causing the bones to break down. Areas of bone damage, called lytic lesions, can be painful and weaken the bones, so they break (fracture) more easily. Myeloma cells also prevent new bone growth, making it slower for bones to repair themselves. Common areas of bone damage include the spine, ribs, hip bone, and skull.



FATIGUE

Myeloma cells in the bone marrow prevent the production of RBC; leading to anaemia, which is associated with fatigue (severe tiredness) and weakness. Myeloma cells growing in the bone marrow can also cause fatigue.

INFECTIONS AND FEVERS

Myeloma plasma cells don't make normal functioning immunoglobulins, which makes people with MM prone to infections. Myeloma cells in the bone marrow prevent WBC production; low levels of WBCs results in frequent fevers and infections.

WHEN WILL I NEED TO UNDERGO TESTING?

At diagnosis

A diagnosis of MM may be suspected during a routine health check-up. High levels of protein or calcium, or low **haemoglobin (Hb)** levels or WBC, may cause your doctor to want to order additional tests. These test results alone can't confirm a diagnosis of MM, as they may be associated with other conditions. After referral to a doctor specialising in blood conditions, the specialist (Haematologist) will order additional tests, which may include protein and **immunofixation electrophoresis**, urine and **serum FLC** count, and **bone marrow aspirate and trephine biopsy (BMAT)**.

The BMAT test will determine if there are abnormal plasma cells (myeloma) present in the bone marrow. Another key marker is the **M-protein**; high levels of M-protein in the blood or urine confirm a diagnosis of MM, and will help to identify whether the disease is **benign** (e.g., MGUS) and does not require treatment, or **malignant** requiring treatment. Further tests to assess how the MM may have affected the body include X-rays and scans, to assess for MM bone disease, and blood tests to assess kidney function.

Disease staging

Doctors use test results to provide an overall picture of your disease. This information will be used by your doctor to determine the stage of disease and inform how it should be managed. Your doctor may want to measure albumin, **β 2-microglobulin (β 2-M)**, and calcium levels in the blood, and use bone scans to assess your current level of bone damage. There are different staging systems used to assess MM. The most commonly used are the **Revised International Staging System (R-ISS)**, which is based on genetics and the results of two routine laboratory test results for specific blood proteins, and the **CRAB** system, which is based on an assessment of the common MM symptoms, raised calcium (C); renal (kidney) damage (R); anaemia - low RBC (A); bone (B).

Treatment assessment

After you have been diagnosed with MM, then your doctor may want you to start treatment. During treatment, your doctor will want to monitor your response. The main aims of treatment are to relieve any pain or other symptoms, reduce or slow the progress of the disease, and minimise any complications. To assess your response to treatment, your doctor will regularly measure your blood count and levels of specific chemicals in your blood, including **creatinine**, calcium, and M-proteins. Your doctor may also request imaging or scans to monitor your response to treatment. Although not required frequently, a BMAT may also be undertaken to assess treatment response.

Monitoring / surveillance

Once you finish treatment, your doctor will still want to monitor your symptoms and disease progression. In the months, even years after finishing treatment, your doctor will monitor your health for signs that the disease may have returned by ordering specific blood and urine tests.

SUMMARY OF MM TESTS

Tests required for most patients at diagnosis	Tests useful for disease staging in some patients
<p>Full blood count (FBC)</p> <p>Blood chemistry tests, including:</p> <ul style="list-style-type: none"> - creatinine, electrolytes, calcium, lactate dehydrogenase (LDH), β2-M, albumin <p>Serum protein electrophoresis (SEPG)</p> <p>Serum immunofixation electrophoresis (SIFE)</p> <p>Serum free light chains (SFLC)</p> <p>Serum quantitative immunoglobulins</p> <p>Total urinary protein (24-hour urine)</p> <p>Urine protein electrophoresis (UEPG)</p> <p>Urine immunofixation electrophoresis (UIFE)</p> <p>Skeletal survey (X-ray or low dose CT scan)</p> <p>BMAT</p> <ul style="list-style-type: none"> - Cytogenetic tests - FISH* - flow cytometry* 	<p>Tissue biopsy for solitary plasmacytoma</p> <p>Bone densitometry</p> <p>Whole body magnetic resonance imaging (MRI)</p> <p>Positron emission tomography (PET)</p> <p>Computed tomography (CT)</p> <p>Echocardiogram</p> <p>Gated heart pool scan (GHPS)</p>
Tests for treatment assessment	
<p>BMAT</p> <p>FBC</p> <p>Blood chemistry tests</p> <p>Serum quantitative immunoglobulins</p> <p>SEPG</p> <p>SIFE</p> <p>SFLC</p>	<p>24-hour urine for total protein</p> <p>UEPG</p> <p>UIFE</p> <p>Skeletal survey (X-ray or low dose CT scan)</p> <p>PET/CT scan</p> <p>MRI scan</p>

*Not Medicare funded at this time, and may not be offered by all testing centres or required for all patients.

ABOUT THE TESTS

It may help you to know what to expect when you are about to undergo a test and to understand why it is required. It is important to remember that your disease may change over time, so your test results will also vary over time. A test that provided reliable information about your disease at diagnosis may be less reliable as the disease progresses. In addition, a test that might not be useful at diagnosis may become more relevant later in the disease course to assess progression. Overall your test results show the most accurate picture of your disease when followed over time.

Test results can be affected by many variables, including:

- amount and type of fluids you have consumed,
- whether you have eaten prior to the test, and
- whether you have taken certain medications and supplements.

Some tests require you to take certain precautions before hand, for example, fasting before a blood test. It is important that you check with your doctor before undergoing any tests and follow any specific instructions. It is also important to tell your doctor about any medications or supplements you are taking, including herbal, or over-the-counter (non-prescription) medications.

Contact your doctor or nurse if you have any specific questions about a test and about any precautions you need to take prior to the test.

PATHOLOGY

Pathology is the study of disease, and pathologists are involved in the diagnosis and monitoring of disease. Pathology tests can be done by analysing tissue, cell, and body fluid samples, which are sent to a laboratory for testing. The pathologist will perform the test, then provide the results to your doctor in the form of a pathology report.

Test results reported from different laboratories may produce different results due to differences in the way the test is performed at these testing centres.

Pathology reports usually state the quantity of a specific substances and a 'reference range'. It is important to note that a 'normal' test result for one person might be an 'abnormal' result for another. Even though there is variation between individuals' results, these will fall within a normal range for a healthy person, this is the 'reference range'. Reference ranges may vary according to the technology used in the test, which may differ between laboratories, and the group of people tested. The reference ranges stated here are from the Royal College of Pathologists of Australasia (RCPA). The reference ranges used on your pathology reports may be different according to the laboratory that produced the report.

Your doctor is the best person to explain your pathology test results and interpret what they mean to your outcome.

1.0 BLOOD TESTS

What is the test?

Doctors test your blood to look for signs and symptoms of MM or examine how the disease may be affecting your general health. Different types of blood tests look for and measure different chemicals in the blood. Blood tests can be used to confirm a diagnosis of MM, or check the health of your bones, kidneys, and other organs.

How is the test conducted?

A blood sample will be collected by a nurse or blood sample collector. They will insert a needle into your vein to remove a small sample of blood, which is then sent to the pathology laboratory for testing. You may experience some discomfort when the blood sample is taken, with pain, throbbing or bruising at the injection site during or after the test.

How long will it take to get a result?

Blood test turnaround times depend on several factors, including the type of test requested and the pathology laboratory used. For example, an urgent blood test may only take a few minutes to complete, but for a non-urgent case it may be processed on the next day when a routine test is performed for several samples. Blood tests undertaken in a hospital with its own pathology laboratory often take less time to provide a result compared to a local high street pathology laboratory service. Blood tests are usually performed within 48 hours of the collection of the blood sample; however more specialised tests can take days to perform.

The turnaround time for a test will vary depending on the type of test and pathology laboratory where it is performed. It is best to ask your doctor at the time of sample collection to determine how long it will take for your results to be ready.

Common blood tests used in MM

1.1 Full Blood Count

Full blood count (FBC) is a test to measure the total number of blood cells, including WBC and platelets, as well as to determine Hb levels. This may include an assessment of the levels of different WBC types, including neutrophils. Hb is also often measured to determine if a person has anaemia, which is a common symptom of MM.

When is the test done?

At diagnosis, a low Hb level and WBC count may be a sign of MM. Ongoing monitoring of Hb is used to assess whether a person's anaemia is worsening due to treatment or disease progression. FBC is one of several tests that can help determine the disease stage, and how well your body is responding to treatment. You will need regular FBC tests after diagnosis to check how you are progressing on-treatment.

What is a normal result?

WBC	3.5–10.5 × 10⁹ /L
Neutrophils	2.0–7.5 × 10⁹ /L (Adult range)
Hb – Male	>130 g/L
Hb – Female	>120 g/L
Platelets	150–450 × 10⁹ /L

1.2 Blood Chemistry

These tests measure the levels of different chemicals in the blood. Results are used by your doctor to understand the impact of MM or treatment on different organs of the body (such as the kidney or liver). The chemicals that are measured are described below.

Urea

Urea is a waste product of the breakdown of proteins in the liver, which is filtered out of the blood into the urine by the kidneys. The urea test is performed to assess kidney function.

When is the test done?

High levels of urea in your blood are a sign of that your kidneys might not be working as well as usual, which is common in people with MM, especially during treatment. Your doctor will use this test at diagnosis and during treatment to monitor your kidney function.

What is a normal result?

Urea (adult range) 3.0–8.0 mmol/L

Creatinine

Creatinine is a waste product produced by the muscles, which is filtered out of the blood and into the urine by the kidneys. If your kidneys are damaged and unable to filter out creatinine from the blood it will build-up in the bloodstream, as shown by high creatinine levels on a blood test.

When is the test done?

Your doctor may request this test to assess your kidney function at diagnosis and regularly while on-treatment to monitor the effects.

What is a normal result?

Creatinine (adult male range)	60–110 µmol/L
Creatinine (adult female range)	45–90 µmol/L

Electrolytes

Electrolytes are minerals in your blood needed for your organs and tissues to work.

When is the test done?

High levels of electrolytes, such as sodium, potassium, and calcium, may be a sign that your kidneys are not working well. Your doctor may request this test at diagnosis and regularly while on-treatment to monitor your general health.

What is a normal result?

Bicarbonate (adult range)	22–32 mmol/L
Chloride (adult range)	95–110 mmol/L
Potassium (adult range)	3.5–5.2 mmol/L
Sodium (adult range)	135–145 mmol/L

Calcium

Calcium is a mineral found in many body tissues, especially the bones. Calcium is also required for the normal function of the muscle, nerves, and heart. Blood test results with high levels may mean kidney and/or bone damage.

When is the test done?

High levels of calcium can be a sign that you have active MM bone disease or your kidneys are not working well. Your doctor may request this test at diagnosis and regularly while on-treatment to monitor your general health.

What is a normal result?

Calcium (adult range) **2.10–2.60 mmol/L**

Lactate dehydrogenase (LDH)

LDH is a protein found in many cells throughout the body. When cells are damaged or destroyed, LDH is released into the bloodstream. LDH is also produced by myeloma cells.

When is the test done?

Your doctor may check LDH levels in your blood to assess the stage of your disease.

What is a normal result?

LDH (adult range) 120–250 U/L

β 2-Microglobulin (β 2-M)

β 2-M is a protein produced by many cells throughout the body, including myeloma cells. Although this protein itself doesn't cause problems, it can be an indicator of your disease stage, as high levels may be a sign of advanced disease.

When is the test done?

Your doctor may use this test to assess the stage of your disease and decide what is the best treatment plan. The β 2-M test is used as part of the International Staging System to grade MM.

What is a normal result?

β 2-M (adult <60 years range)	0.8–2.5 mg/L
β 2-M (adult >60 years range)	0.8–3.0 mg/L

Albumin

Albumin is a protein made by your liver and is a large component of the blood plasma (serum). Blood proteins help to maintain fluid balance and transport hormones, vitamins and ions throughout the body. Levels of albumin may be high if you have liver or kidney damage, or if you have an infection or are dehydrated or malnourished. Low levels of albumin can also be a sign of MM.

When is the test done?

Your doctor may use this test to determine the stage of your disease and to assess your overall health.

What is a normal result?

Albumin (adult range) 32–45 g/L

1.3 Myeloma Bloods

As discussed previously, test results can vary between different laboratories, so your doctor may suggest you have your tests performed by the same pathology laboratory each time. This is important with your myeloma bloods as your doctor may compare your results for the same test over time, to see if you are responding to treatment.

Serum Protein Electrophoresis (SEPG)

SEPG is a test used to assess levels of M-protein in the blood produced by myeloma cells. Electrophoresis of proteins in the urine may also be done if the results of the SEPG are abnormal.

When is the test done?

Your doctor may use this test and the presence of M-protein to diagnose MM and assess your disease stage, and it is also used to monitor your response to treatment.

What is a normal result?

M-protein in the blood is confirmation of a diagnosis of MM. Higher levels of M-protein generally mean that the disease is more active.

Serum Immunofixation Electrophoresis (SIFE)

SIFE is a test used to identify proteins in the blood or urine (UIFE). Your doctor can then identify the type of M-protein present by assessing the heavy-chain and light-chain make-up.

When is the test done?

Your doctor may use this test and the presence of M-protein to diagnose MM, and it can also be used to monitor your response to treatment.

What is a normal result?

If the SEPG test confirms M-protein is present in the blood; SIFE is then used by your doctor to determine which subtype is present.

Serum Quantitative Immunoglobulins

This test is used to measure levels of each type of immunoglobulin in the blood. There are 5 different types; IgA, IgM, IgG, IgD, and IgE. Immunoglobulins are also found in healthy individuals. In those with MM, one (or more) of the immunoglobulin levels would be raised, as it is producing more of the abnormal M-protein.

When is the test done?

Your doctor may use this test to help determine the specific type of MM you have at diagnosis.

What is a normal result?

IgG (adult range)	6.5–16.0 g/L
IgA (adult range)	0.6–4.0 g/L
IgM (adult range)	0.5–3.0 g/L
IgD (adult range)	<0.4 g/L
IgE (adult range)	150 and 300 UI/mL

Serum free light chain (SFLC) test

This test measures the amount of FLCs in your blood. FLCs are found in healthy individuals, where the amount and ratio would be stable. There are two types of free light chain; kappa and lambda. You will have either kappa or lambda light chains produced in excess amounts when you have MM. The ratio of these two levels is also an important measure. Similar to the M-protein level, the amount of free kappa or lambda in your blood is an important guide as to how active your disease is. Higher levels of kappa or lambda is generally related to having more myeloma cells active in the body.

When is the test done?

Your doctor may use this test at diagnosis to measure the amount of FLC in your blood to assess the disease severity. Your doctor may also regularly use this test when you are on-treatment to assess your response to treatment.

What is a normal result?

Your doctor will assess the FLC test results along with the results of a protein electrophoresis test.

Serum FLC - kappa	3.3–19.4 mg/L
Serum FLC - lambda	5.71–26.3 mg/L
Serum FLC - kappa / lambda ratio	0.26–1.65 (individuals with normal kidney function)

2.0 URINE TESTS

What is the test?

Urine tests can identify the presence of M-proteins and FLC and assess overall kidney function.

How is the test done?

Urine is collected for 24 hours and then sent to a pathology laboratory for testing.

Urinary protein electrophoresis (UEPG)

UEPG is a test that measures the presence and amounts of different proteins in the urine.

When is the test done?

Your doctor may use this test to confirm a diagnosis of MM, and it may be repeated regularly when on-treatment to assess your response; although the serum FLC test is more commonly done to assess M-protein levels.

What is a normal result?

The presence of M-protein in the urine is abnormal, and suggests a diagnosis of MM. M-protein is not present in the urine of healthy patients, but 75% of MM patients will have the M-protein in their urine.

Urinary Immunofixation (UIFE)

UIFE is a test that measures levels of specific types of proteins in the urine. The immunoglobulin light chains (which are produced in some cases of MM) are so small in size that they are filtered from the blood and can only be detected in the urine (heavy chains are too large in size to be found in the urine).

When is this test done?

Your doctor may use this test to confirm a diagnosis of MM, to assess the tumour burden, and it may be repeated when on-treatment to assess your response.

What is a normal result?

The presence of any M-protein in the urine is confirmation of a diagnosis of MM.

3.0 TISSUE TESTS

Tissue tests require a sample of tissue from the body for testing, called a biopsy. After the sample is collected, it is sent to a pathology laboratory for testing. A pathologist will view the sample under a microscope to look for myeloma cells and perform other tests.

Bone Marrow Aspiration and Trepine

This is an important test for MM patients and essential for a diagnosis, and throughout the disease to monitor disease progression.

How is the test done?

A needle is inserted into the bone to remove a liquid sample of the bone marrow (aspirate), as well as a small piece of solid bone (trepine); this is known as a BMAT biopsy. These two procedures are often done at the same time, which is referred to as a bone marrow examination. Your doctor will decide whether you need to have one or both. The samples are taken from the bone in the back of the pelvis; the breast bone (sternum) can also be used, but this is not commonly done. Patients often worry about having this test and sometimes find it uncomfortable when a sample is taken.

If you have any concerns about this test, you should discuss with your doctor or nurse to find the best way and time for you to have this important test.

Bone marrow aspiration and trephine is commonly undertaken as a day procedure at the hospital or clinic. When done together, the two procedures usually take about 30 minutes to complete. You may receive an anaesthetic to reduce the pain, this will be administered by intravenous injection or inhaler. The type of anaesthesia commonly used is made up of pain relievers and sedatives, so you stay awake, but do not feel any pain. This 'conscious sedation' usually allows you to speak and respond during the procedure, but most people have little or no memory of the procedure afterward. If you receive conscious sedation you may need to fast (no food or drink) for 6 hours before the procedure. You should tell your doctor if you have ever had an allergic reaction to an anaesthetic.

The test is undertaken by a doctor or specialist nurse. You will lie down on your side, on a bed, and then you will have the area of skin on the back of the pelvis cleaned and a local anaesthesia is administered to numb the area. You may feel the sting of a needle as the local anaesthetic is given. Once numb, a hollow needle is inserted into the bone, through the skin, and a sample of the liquid bone marrow (aspirate) and a further sample of solid bone (trepine) is removed. You may feel some pressure as this is happening and it may leave you with a small bruise afterwards. Following the procedure, you will be asked to remain in the bed lying on your back to reduce the risk of bleeding from the site. If you have received sedation, you will need to stay until you are fully recovered, this can take a couple of hours. You may have a small bruise where the sample was taken, which may be sore if you bump it. The area should be pain free otherwise.

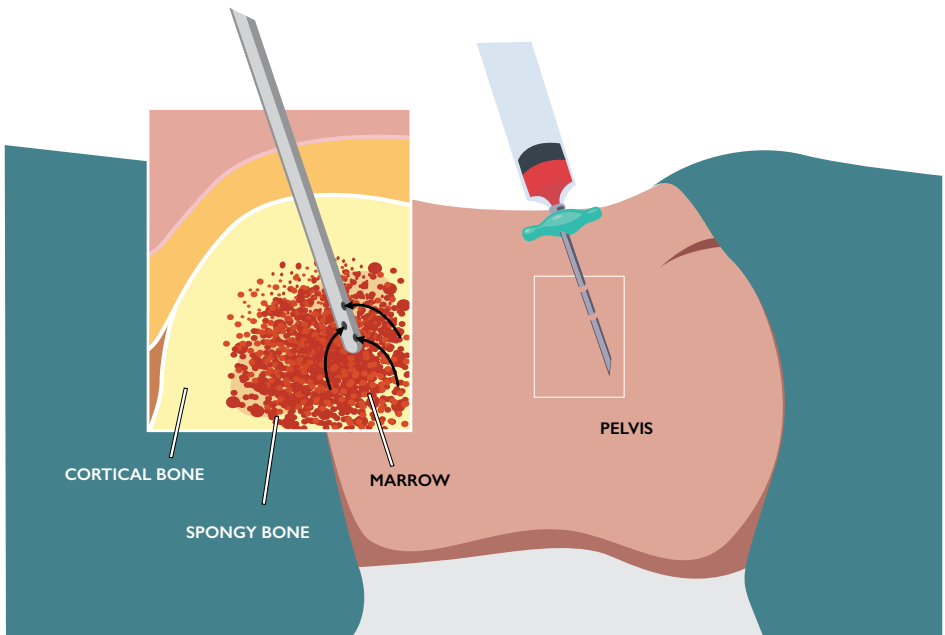
The way the procedure is performed may be different depending on the hospital or clinic, so you should ask your doctor for more information and how you should prepare for this procedure.

When is this test done?

Your doctor may request this test at diagnosis to assess how many myeloma cells are present in the bone marrow, and how they are affecting your normal blood cell production. Also the test can be used to assess your response to treatment and disease progression.

What is a normal result?

A specialist with expertise in the pathology of MM will perform the microscopic examination of the bone marrow samples. A normal healthy bone marrow sample would contain less than 10% healthy looking plasma cells. In someone with MM, these plasma cells would be increased in number and have an abnormal appearance (myeloma cells). By looking at the tissue under a microscope, the appearance, number, and size of the myeloma cells can be assessed. The aspirate may also be sent for other tests, including genetic or immunological tests.



Tissue biopsy

Sometimes myeloma cells can form a tumour outside of the bone marrow, which is called a plasmacytoma. A biopsy of this plasmacytoma can be sent for pathology testing.

How is the test done?

The sample is removed with a needle; the doctor will use X-ray imaging to correctly position the needle in the plasmacytoma. If it is a part of the body that is easy to access, this can be carried out under local anaesthetic. If the mass is in a hard to reach area, it may require sedation, and a short stay in hospital to extract a sample.

When is this test done?

If your doctor suspects you have a plasmacytoma, they will first perform a scan to confirm its location, then perform a biopsy.

What is a normal result?

A specialist with expertise in the diagnosis of MM will examine the sample under the microscope. By looking at the sample under a microscope they can assess the appearance, number, size, and shape of the myeloma cells. A healthy person would have no myeloma cells.

LABORATORY TESTS ON TISSUE SAMPLES

Once a tissue sample has been collected, several types of laboratory tests can be performed.

MM is a genetically complex disease and as we learn more about it, the range of available genetic tests and the techniques used may change. You should discuss your options with your doctor to determine which tests are right for you.

A. Genetic tests

Genetic testing identifies changes in chromosomes or genes. Genetic testing is performed to identify the presence of any abnormal chromosomes and/or genes in your cells.

Several genetic testing methods can be used:

- Molecular genetic tests look at single genes or short lengths of DNA to identify variations (**mutations**) that lead to a disease.
- Chromosomal genetic tests look at whole chromosomes or long lengths of DNA, to see if there are genetic changes, such as an extra copy of a chromosome. For example, half of all MM patients have a deletion of chromosome 13.

The availability of different genetic tests will vary depending on the hospital or clinic. Not all tests will be funded by Medicare, as they are not all required to be undertaken for every patient. Your doctor will discuss with you what tests they think are required and the costs that may be associated.

B. Cytogenetic Test

A sample of bone marrow from a biopsy is placed in a special dish and grown in the laboratory. As the cells grow and divide they are examined under a microscope to look at the size, shape, and number of chromosomes in the growing cells. The sample is then photographed to produce an image of the chromosomes, this technique is called karyotyping.

C. FISH test

Myeloma cells can also be examined by **fluorescence in situ hybridisation (FISH)**. This test uses a probe to attach to certain parts of the chromosome known to be affected by MM to look for abnormalities in the chromosome associated with low or high-risk disease.

The following FISH tests for high-risk disease are routinely available in Australia and are recommended:

- t(4;14)
- t(14;16)
- Del17p
- 1q21 amplification

Because genetic testing has benefits as well as limitations and risks, the decision to be tested is a personal one. A geneticist or genetic counsellor can help you decide by providing information about the test and discuss the emotional impact of the test and results.

D. Staining marrow and fat pad for amyloid

Amyloid is a protein found in some people with MM that produces too many light chains. Amyloid build-up in tissues and organs of the body, called amyloidosis, can cause damage to the organs, most commonly the heart and kidney. Tests for amyloid can be done on a bone marrow or fat pad sample (fat under the skin of the belly).

E. Immunohistochemistry

This is a test performed on bone marrow cells. Each cell has unique markers on their surface (called antigens). A special stain is used to identify these unique antigens and then count the number of cells expressing the M-proteins.

F. Plasma cell labelling index*

This is a test that is performed on bone marrow cells. The test measures the number of myeloma cells present that are dividing and how fast they are dividing. Cells that are dividing quickly are a sign that the cancer will grow fast.

*Available at Royal Prince Alfred Hospital NSW.

IMAGING / SCANS

Medical imaging (or scans) take pictures of the inside of your body. They can be used to help diagnose MM or identify damage done by the disease to other organs, such as the kidney or the bones. These scans are often easy to undergo, although a common complaint from patients is the noise of the imaging machines. You will often be lying down and at least part of your body will be in the machine. The types of scans commonly used for MM are described below, although not all of these are required for all patients, it will depend on your individual situation.

How long will it take to get a result?

With any of these imaging/scans you will usually receive a copy of the results immediately, but this will need to be interpreted by your doctor, based on your medical history, symptoms, and clinical examination. In hospital, scans are available immediately to your doctor, via the hospital computer system. If the imaging scan is done at an external imaging centre, they will provide you with a printed or electronic copy to provide to your doctor.

Some scans may require the use of a contrast dye to make the pictures clearer. Caution should be taken with contrast dyes as they may harm the kidneys. Check with your doctor each time you are due to undergo a scan, to see if it is safe for you to have contrast dye. If you are due to have a contrast dye, it is important to stay well hydrated (2.5 litres of fluid per day) prior to the scan. Some scans, such as X-rays and CT scans, expose you to radiation and the benefits of undertaking any scan should be considered alongside any potential risk.

While many scans are covered by Medicare, some will be associated with out of pocket expenses. Your doctor can discuss with you which scans you will require, any risks associated, and out of pocket expenses.

Most scans don't require you to take any special precautions but you should ask your doctor beforehand about any preparation that may be required for the test.

1.0 Whole body imaging

1.1 Skeletal (bone) survey

What is the test?

This test uses X-rays to take pictures of your entire skeleton, to look for broken or damaged bones. X-ray images show parts of your body in different shades of black and white, to highlight areas of bone damage. X-rays are only used to assess the bones.

When is the test done?

At diagnosis to assess the amount of bone damage caused by MM.

1.2 Low-dose computed tomography (CT) scan

What is the test?

CT scans take many pictures of the body at different angles using X-rays. The computer then combines these pictures to make one image of the whole body. CT scans are useful for looking at bones and organs. Low dose CT is increasingly being used, which reduces the amount of radiation exposure to the patient.

When is this test done?

Whole body low-dose CT scans are commonly undertaken at diagnosis, and ongoing to look for bone damage over the course of the disease. This test is increasingly used in place of the 'skeletal survey', which also uses X-rays.

1.3 Magnetic resonance imaging (MRI) scan

What is the test?

MRI scans use radio waves and powerful magnets to take pictures of the inside of the body. This produces a clearer picture of the bone, the bone marrow inside, and the organs, to show any damage caused by MM.

When is this test done?

Your doctor may order an MRI if you have been experiencing bone pain, but nothing can be seen on a CT scan or X-ray. A whole body MRI scan can be used to look for plasmacytomas, which do not show up on X-ray imaging. An MRI scan may take an hour or more, dependant on what length of the body needs to be scanned. You need to lie still for this period of time and the machine makes a loud 'banging' noise while it is actively scanning. Some people can find this scan claustrophobic. Talk to your doctor if you feel this will be a problem for you.

1.4 FDG-PET/CT scan

What is the test?

Fluoro-deoxyglucose (FDG)-positron emission tomography (PET) combined with a CT scan can be done at the same time using two different machines. The PET scan is done using a sugar marker dye that is injected into a vein; this allows the cells that are using

sugar to show up on the images. All cells use sugar, but cancer (myeloma) cells, and some other cells of the body, use sugar more quickly than normal cells, so show up brighter.

When is this test done?

Your doctor may order this scan if the CT scan alone, or the skeletal survey doesn't show any problems. Whole body PET/CT scans can also be used to look for plasmacytomas. PET scans are useful in seeing how the disease has spread through the body and for ongoing assessment of bone damage.

2.0 Imaging of the heart

2.1 Electrocardiography (ECG)

What is the test?

An ECG is a test that detects abnormalities in the heart by measuring the electrical activity generated as it contracts. ECGs from healthy hearts have a characteristic shape; if it shows a different shape, it may suggest a problem with your heart.

When is this test done?

Your doctor will request an ECG if they suspect you may have heart problems.

2.2 Echocardiogram (Echo)

What is the test?

This scan uses sound waves (ultrasound) to look at the heart muscle, and how well they are working. The scan can see if the heart size is normal and if it is pumping normally.

When is this test done?

Certain types of treatment, such as chemotherapy, can affect your heart. Your doctor will want to check the strength of your heart before prescribing certain types of high-dose chemotherapy, or before performing a stem cell transplant. Amyloidosis can often affect the heart, so if your doctor suspects you have this disorder, an echo may be ordered.

2.3 Gated Heart Pool Scan (GHPS)

What is the test?

GHPS is used to assess your heart function. The test requires the use of a special dye. First a small sample of your blood is taken, then a 'tracer' is added to the blood before it is re-injected into your vein. You will receive a small amount of radiation from the tracer that is well within safety limits. You then lie on the scanning bed and images are taken using a special (gamma) camera to see the RBCs and show how well the heart is pumping blood through the different chambers.

When is this test done?

This test is done to measure the size and function of the heart muscle and chambers. Your doctor will request this test before you start certain types of high-dose chemotherapy or a stem cell transplant.

QUALITY OF LIFE QUESTIONNAIRES

MM can affect people in different ways and the symptoms experienced from treatment can also differ between individuals. The best person to report these symptoms and experiences is the patient. Self-reported questionnaires help nurses and doctors better understand the experiences and quality of life of each patient, and allow them to deliver the best supportive care for maintaining or improving a patient's health-related quality of life (HRQoL).

To help nurses and doctors understand your individual symptoms and experiences with MM and its treatment, they may use specially designed HRQoL questionnaires. You will be asked to provide details about the symptoms you experience, the severity, and frequency with which they occur, and any problems you have with your overall health. Questionnaires may be specific to a certain side effect or symptom you have experienced, such as pain or peripheral neuropathy, or more general about the disease and its impact on your quality of life.

These questionnaires are sometime used in clinical trials, or for research purposes, but increasingly they may be used in your routine care during clinic visits with a nurse or doctor. Questionnaires may be completed in a paper-based form or using a mobile or tablet device.

GLOSSARY

Anaemia	Low levels of haemoglobin, due to a lack of red blood cells, results in a reduction in the oxygen levels in the body. Symptoms include fatigue, shortness of breath, light-headedness, dizziness
Antibodies (immunoglobulins)	Proteins produced by plasma cells, that help the immune system to fight infections (bacteria or viruses)
Asymptomatic	Person who shows no symptoms
β2-M	Beta-2-microglobulin
Benign	A tumour that is not cancerous
Bone marrow	Spongy tissue inside some bones of the body that is responsible for the production of blood cells
BMAT	Bone Marrow Aspirate and Trepine Biopsy
CRAB	C: Calcium (elevated), R: Renal failure, A: Anaemia, B: Bone lesions
Creatinine	A waste product of the normal wear and tear of muscles of the body that is excreted by the kidney
CT	Computed tomography
ECG	Electrocardiography
FBC	Full blood count
FISH	Fluorescence in-situ hybridisation
FLC	Free light chains, also called Bence-Jones proteins, are used as a marker of MM disease
GHPS	Gated heart pool scan
Hb	Haemoglobin - an iron-containing protein in red blood cells that carries oxygen around the body
Hypercalcaemia	Excess calcium in the body. This may cause increased thirst, urination, stomach pain, nausea, bone pain, muscle weakness, confusion, and fatigue
Ig	Immunoglobulin
LDH	Lactate dehydrogenase
Lytic lesions	Destruction of an area of bone due to MM
Malignant	A tumour that is cancerous and is growing or spreading
M-protein	Abnormal type of antibody that is produced in excess by myeloma cells
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma

MRI	Magnetic resonance imaging
Myeloma cell	Abnormal (cancerous) type of plasma cell
Mutation	A change in the DNA sequence due to a mistake when it is copied or a result of environmental factors
PET	Positron emission tomography
PET/CT	PET combined with a CT scan
Plasma cell	A type of white blood cell that develops from B cells, and produces antibodies, and in myeloma produces M-proteins
Plasmacytoma	A mass of plasma cells in the bone or soft tissue
Platelets	Blood cells that stop bleeding and help with clotting in the blood vessels
HRQoL	Health-related quality of life
RBC	Red blood cells, produced in the bone marrow. They are the most common type of blood cell, and carry oxygen around the body
RCPA	Royal College of Pathologists Australia
R-ISS	Revised International Staging System – a simple system to assess the stage of disease, based on genetics, and routine laboratory test results (β 2-M)
Serum	Protein-rich component of the blood that does not contain blood cells
SIFE	Serum immunofixation electrophoresis
SEPG	Serum protein electrophoresis
UIFE	Urinary immunofixation electrophoresis
UEPG	Urinary protein electrophoresis
WBC	White blood cells, produced in the bone marrow. They are an important part of the immune system, consisting mostly of B- and T-cells.

SUMMARY OF BLOOD TEST RANGES

These reference ranges are provided as a guide to what a normal result would be for a healthy person. Reference ranges may vary according to the methodology used by the laboratory and the group of people tested. The reference ranges stated in this booklet are provided by the Royal College of Pathologists of Australasia (RCPA). Note the ranges listed on your reports may be different.

TEST	REFERENCE RANGE
WBC	3.5–10.5 × 10 ⁹ /L
Neutrophils	2.0–7.5 × 10 ⁹ /L
RBC	Male 4.32–5.72 × 10 ¹² /L; Female 3.9–5.03 × 10 ¹² /L
Hb	Male >130 g/L; Female >120 g/L
Platelets	150–450 × 10 ⁹ /L
Urea	3.0–8.0 mmol/L
Creatinine	Male 60–110 µmol/L; Female 45–90 µmol/L
Sodium	135–145 mmol/L
Bicarbonate	22–32 mmol/L
Chloride	95–110 mmol/L
Potassium	3.5–5.2 mmol/L
Calcium	2.10–2.60 mmol/L
LDH	120–250 U/L
β2-M	Adult <60 years 0.8–2.5 mg/L; >60 years 0.8–3.0 mg/L
Albumin	32–45 g/L
IgG	6.5–16.0 g/L
IgA	0.6–4.0 g/L
IgM	0.5–3.0 g/L
IgD	<0.4 g/L
IgE	150 and 300 UI/mL
SIFE	N/A
Kappa light chains	3.3–19.4 mg/L
Lambda light chains	5.71–26.3 mg/L
Kappa/ lambda ratio	0.26–1.65 (individuals with normal kidney function)
UEPG	<102 mg/24 hours

MORE INFORMATION

For more information on MM testing, the following websites are useful resources. Although please consider the context of the information presented as it may not be updated regularly, and may reflect different practices according to the country and health care system it refers to.

Australian Multiple Myeloma information sources

Myeloma: A comprehensive guide (Myeloma Australia)

<http://myeloma.org.au/information/>

National Prescribing Service

<https://www.nps.org.au/australian-prescriber/articles/screening-for-multiple-myeloma>

Lab tests Online

<http://www.labtestsonline.org.au/>

Leukaemia Foundation

<http://www.leukaemia.org.au/blood-cancers/myeloma>

Cancer Council

<https://www.cancercouncil.com.au/myeloma/>

International MM information resources

American Cancer Society

<https://www.cancer.org/cancer/multiple-myeloma/detection-diagnosis-staging/testing.html>

Myeloma UK

<https://www.myeloma.org.uk/information/glossary/>

The International Myeloma Foundation (IMF)

<https://www.myeloma.org/sites/default/files/images/publications/tools/glossary.pdf>

The Multiple Myeloma Research Foundation (MMRF)

<https://www.themmr.org/multiple-myeloma/diagnosis/myeloma-diagnostic-testing/>

National Comprehensive Cancer Network (NCCN)

<https://www.nccn.org/patients/guidelines/myeloma/files/assets/basic-html/page-1.html>

