



**NeuroEndocrine
Cancer** Australia

Diagnosis

“If you don’t suspect it, you can’t detect it.”

NETs are difficult to detect for a number of reasons:

- They are often very small.
- They can occur almost anywhere in the body.
- Symptoms can vary widely and some patients have no symptoms at all.
- There are many types of NETs and the diagnosis requires a series of tests, which may include blood tests, imaging (CT/MRI), endoscopy, nuclear medicine scans (PET scans) and biopsies to prove the diagnosis.

Patients who are diagnosed with a NET have often seen many different doctors (general practitioners and specialists) over many years and had many tests before the correct diagnosis is made.

On average it takes 4 to 7 years for this diagnosis. This is because NETs often present with similar symptoms to other common conditions. There is also a widespread lack of awareness of the disease among doctors.

You will be advised to have a number tests and scans that will tell your doctor about your disease, its spread and the rate of growth.

Tests

For your records it is useful to obtain copies of your tests to keep with your records. Some of the tests you might have are listed below.

Biopsy

This involves taking a piece of tissue from the suspected tumour and having it analysed in the a pathology laboratory.

Tissue biopsies are usually taken during medical tests (e.g. an endoscopy) or during operations. Doctors can sometimes tell from biopsies where in the body a cancer has started. Tissue can also be obtained using a fine needle biopsy, where a needle is inserted into a tumour (e.g. in the liver) to obtain a small sample of the cells. This is usually done under local anaesthetic, and an ultrasound is often used to help locate the correct area.

The pathology report is critical for oncologists to decide on the treatments that will best manage your NET.

Blood tests

Doctors will be looking for NET biomarkers for evidence of a rise in certain peptides and hormones in the blood. You may need special preparation, often including fasting, for some of these blood tests. Your pathology blood collection centre will tell you whether it will be advisable to make an appointment and any special preparation needed.

Common blood tests

These may include:

- kidney function test (urea and electrolytes)
- liver function tests
- thyroid function tests
- pituitary hormone screen (e.g. adrenocorticotrophic hormone (ACTH), prolactin, growth hormones and cortisol)
- serum calcium, parathyroid hormone levels (as a simple screening test for MEN-1 syndrome)
- hormone assays,

You may also be asked to give an extra blood sample for use in research studies. You should always be informed of this and asked to sign a consent form.

Chromogranin A (CgA)

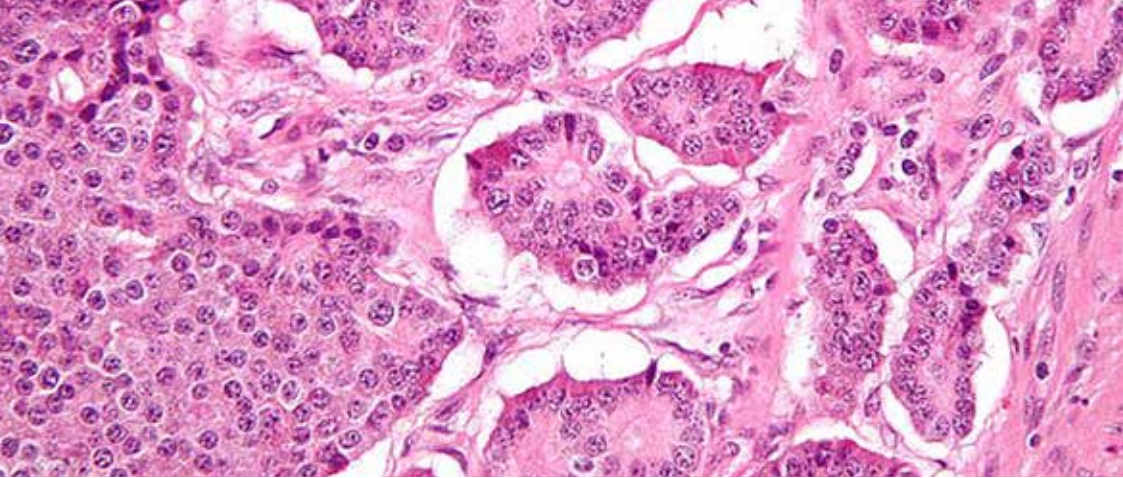
Chromogranin A is produced and released into the bloodstream by some neuroendocrine cells. It is a 'marker', or indicator that there is a NET in the body. Not all patients with NETs will have elevated CgA.

Chromogranin A blood levels can relate to the activity of the tumour in your body. They are often used for monitoring the disease or response to treatments.

Different laboratories use different methods (test kits or assays) to measure chromogranin A. It is important to go to the same laboratory company so that changes in the levels can be interpreted correctly.

Certain conditions can cause higher chromogranin A levels, especially:

- anti-acid medication especially the proton-pump inhibitors (omeprazole, esomeprazole, pantoprazole)
- kidney and liver diseases
- prostate cancer
- atrophic gastritis.



Plasma Metanephrines

Testing for plasma metanephrines is to diagnose or rule out a rare adrenal tumour called a pheochromocytoma or a rare similar tumour located elsewhere in the body called a paraganglioma; these tumors produce excess hormones called catecholamines, which are broken down to metanephrines. Refer to [Neuroendocrine Cancer Australia Fact Sheet](#) for the procedure for this test. Studies have shown that plasma testing is more sensitive than the more traditional 24-hour urine catecholamines testing. Refer to [FACT Sheet on NeCA Website](#) for procedure instruction.

Urine tests

When serotonin breaks down in the body it produces 5-HIAA (5-hydroxyindole-3-acetic acid), which is excreted into the urine.

To test for 5-HIAA in the urine, you will be asked to provide urine samples that have been collected over a 24-hour period. Keep the urine sample cold during the collection period.

Higher than normal levels of serotonin, produced by NET tumours, show up as raised levels of 5-HIAA in urine. Some foods are very high in serotonin/tryptophan and you will be asked to avoid them before and during the test: including chocolate, olives, bananas, pineapple, all tomato products, plums, eggplant, avocado, kiwi fruit, walnuts, brazil nuts, cashew nuts, tea, coffee and alcohol. You will also be asked to avoid certain cough, cold and flu remedies 3 to 7 days before the test.

Endoscopy

Gastroscopy and colonoscopy

This is a way of examining parts of the gut using a flexible fibre-optic tube called an endoscope. The tube can either be inserted down the back of the throat and into the stomach (gastroscopy) or into the colon via the rectum (colonoscopy). During the endoscopy, suspicious lesions in the large bowel and rectum, oesophagus and stomach can be biopsied.

You would usually have these procedures under sedation as a hospital outpatient.

Wireless capsule endoscopy (“Pill Cam”)

This involves swallowing a small capsule (the size of a large vitamin pill), which contains a colour camera, battery, light source and transmitter. The camera takes two pictures every second for eight hours, transmitting images to a data recorder about the size of a portable CD player that patients wear around the waist. This system allows your doctor to see the small bowel but is unable to take biopsies.

Endoscopic ultrasound

This is usually done under sedation and involves looking at the digestive tract with a flexible camera with ultrasound capabilities. This test is sensitive for detection of NETs in the stomach, duodenum, pancreas and rectum. Ultrasound guided biopsies can also be performed. The test can help pick up small tumours that might not be clearly visible on other scans.

Bronchoscopy

If you have a suspected lung NET, the doctor may suggest a bronchoscopy. This test looks at the inside of the airways. A doctor puts a narrow, flexible tube called a bronchoscope down your throat and into the airway to see the trachea and bronchus and also take biopsies.

You can usually have this procedure under sedation as a hospital outpatient.

Radiological imaging

CT scans

A multi-slice spiral (CT) scan can rapidly take fine slice (millimetres thick) images of the body with computer reconstruction providing a three-dimensional picture of the inside of the body.

The scan usually takes about 5 minutes. Depending on the scan, you need to arrive earlier in order to drink about a litre of oral contrast material (which outlines the bowel). Sometimes you will also have a drip inserted into your vein so you can have intravenous contrast. This helps to produce good images so a doctor can see the tumours or other abnormalities.

You may be advised to have a blood test prior to the scan to ensure normal kidney function.

If liver images are needed, it is important that a multi-phase liver scan is requested (non-contrast - arterial phase, portal venous and delayed). If this not requested often it is difficult to detect NETs in the liver.

MRI scans

The magnetic resonance imaging (MRI) scans use magnetic fields to create a signal that is processed into an image. MRI scans are safe; however, if you have any metal parts in your body (e.g. a pacemaker), you cannot have an MRI.

MRI scans take longer to perform than CT scans and are noisy (you can use ear plugs). Some people can feel claustrophobic when in the MRI tunnel and may require some sedation to tolerate the scan.

MRI can add further information to the results of CT scans.

Ultrasound scans

Ultrasound imaging (sonography) uses high-frequency sound waves to produce pictures of the inside of the body. Ultrasound scans are non-invasive and the images are captured in 'real time'. They can show the structure and movement of your body's internal organs, as well as blood flowing through blood vessels.

Nuclear imaging (functional imaging)

Nuclear imaging techniques use radiolabelled compounds (small radioactive particles connected to small proteins or peptides) that are injected into the blood stream. These compounds are then taken up by the tumour cells or bind to receptors (somatostatin receptors) on the surface of the tumour, which are then detected by monitors (cameras). Nuclear imaging techniques are very sensitive and specific in detecting NETs and their metastases.

It is important for these scans to be done during the initial assessment stage of any NET patient, and as a part of the ongoing follow-up and management.

PET (positron emission tomography) scan

A PET scan can show how body tissues are working, as well as what they look like. PET scanners are very expensive and only a few hospitals have one. This means that you may have to travel to another hospital for your scan. Increasingly, PET scans are being combined with CT scans to provide more detailed images. These types of scanners are known as PET/CT scanners.

With a PET scan, you first have an injection of a small amount of a low dose radioactive drug (radiotracer) which only stays in the body for a few hours.

PET scans usually take a few hours and are performed as an outpatient procedure.

Gallium-68 (Ga68) PET scan

This test can help reveal the site of NET tumours. This test is essential for any patient with a NET. As this may show tumours that don't appear on any other scans

18F-FDG PET ([18 fluorine] fluoro-D-glucose)

18F-FDG is a glucose analogue with the attached radiotracer 18fluorine. This compound is taken up by cells that rapidly metabolise glucose, which occurs in many different types of cancer including types of NETs.

This test can help to show whether there are cells, like cancer cells, that rapidly take up glucose in the body. Some NETs, particularly faster growing ones, may show up on this type of scan. If you have this test, you will need to fast beforehand and remain still before the test.

MIBG scan

This scan can help find NETs in the body.

Your doctor may ask you to stop taking certain medications a few days before this test. Your doctor may suggest taking iodine tablets to help protect the thyroid gland during the test. This investigation usually involves taking separate scans over two consecutive days and most patients are allowed home in between.

Bone scan

You may have a bone scan to see if cancer cells have spread to bone in your body. You will have a small injection of radioactive tracer into the vein and images taken by the camera 2 to 4 hours later. There are very few side effects or risks involved with nuclear medicine bone scans and you can usually have it as an outpatient or day-only procedure.





‘Grading’ the NET

NETs, like all cancer, are ‘graded’ into The European Neuroendocrine Tumour Society (ENETS) and World Health Organisation (WHO) system, low (G1), intermediate (G2) or high (G3). The grade represents the aggressiveness of the tumour—the higher the grade, the faster growing it is. Grading the tumour helps your doctors work out the best treatments for you.

Well Differentiated Neuroendocrine Neoplasms	Ki67	Mitotic
Neuroendocrine Tumours (NET) G1	<3%	< 2/10 HPF
Neuroendocrine Tumours (NET) G2	3-20%	2-20/10 HPF
Neuroendocrine Tumours (NET) G3	>20%	>20/10 HPF
Poorly Differentiated Neuroendocrine Neoplasms		
Neuroendocrine Carcinomas (NEC) G3 <ul style="list-style-type: none">• Small cell type• Large cell type	>20%	>20/10 HPF



Monitoring

There are no established protocols for monitoring NETs with CTs or PET scans.

For those who have no evidence of disease (e.g. after resection of NET), recent guidelines recommend relatively infrequent CT scans (e.g. every 2 years) for a longer time (10 years or even longer) compared to other tumours. There is no agreement amongst NET experts as to how often PET scans should be done (if at all) in this setting.

For patients who have known and present NET disease, imaging may consist of a mix of scans, pathology and other tests. PET scans are particularly helpful at particular times (for example, when a patient is being considered for PRRT, or when there is concern about more aggressive disease). Scans might be performed every 3-6 months, but this could be increased to every 12 months for patients with very stable/slow-growing disease.



NeuroEndocrine
Cancer Australia