Learning

A part of your guide to
Neuroendocrine Tumours (NETs)

This book will help you better understand NETs. It is however a reference only; you should always go to your doctor or nurse if you have any questions about your condition, as well as ways of coping. The information shown here can in no way replace their professional advice.

Let's start with the basics of understanding the:

what, where, why, who and how.

Learning about NETs

What are NETs?

A NET, or neuroendocrine tumour, is a relatively rare, generally slow-growing tumour occurring in the neuroendocrine system. Usually, most NETs first occur in the digestive system (made up of your stomach and intestines), but can also sometimes occur on other parts of your body, like in the lungs or pancreas.

NETs were first identified as a specific type of disease in the mid-1800's.

The term "NETs" is an umbrella term, and can be used to refer to carcinoid tumours, gastrointestinal NETs, pancreatic NETs, and lung NETs.

These kinds of cancers are often referred to as the "quiet cancers," because they are relatively uncommon and difficult to diagnose. This is because NETs are very slow growing tumours, and the symptoms are not only hard to notice (until after they have already grown or spread), but can also be attributed to more common, and less serious conditions like irritable bowel syndrome (IBS), for example.

NETs – a brief history

NETs were first identified as a specific type of disease in the mid-1800's.

In 1907, they were given the term "carcinoid", meaning "cancer-like" – this is because NETs were so slow growing, it was thought they weren't life-threatening in the same way as other cancers.

By the 1950s it was well recognised that, although they were slow-growing, these tumours could still be aggressive and spread to other parts of the body, the same way other cancers can.

The term for NETs has changed since 1907, so while they are still sometimes referred to as carcinoid, the more accurate title of "NET", or "(GEP) NET", has been adopted. "GEP" stands for gastroenteropancreatic; which is used because the tumours often arise in the cells of the stomach (gastro), intestines (entero), and the pancreas.

NETs are still considered rare as compared to other cancers, with an average of around 113 cases diagnosed in Ireland each year.

This means that NETs can be more difficult to diagnose than other cancers because many doctors are unfamiliar with them and therefore less likely to suspect them when faced with the symptoms. On average, people see three different doctors, and sometimes wait 5 to 7 years before they receive a proper diagnosis. However now, with increased awareness, more people's NETs are being found – and earlier.

There are also a few different TYPES of NETs.

These can be classified by:

- Their location – the part of the body where NETs are found
- The types of hormones they produce
- Whether they are functioning or non-functioning tumours

Functioning vs non-functioning tumours

You may hear NETs referred to as being functioning or non-functioning. Some NETs produce too many hormones and, depending upon the tumour's location, the hormones that it releases can cause various symptoms and complications. These NETs are called functioning tumours.

NETs that don't produce hormones are called non-functioning tumours, but these can still cause complications.

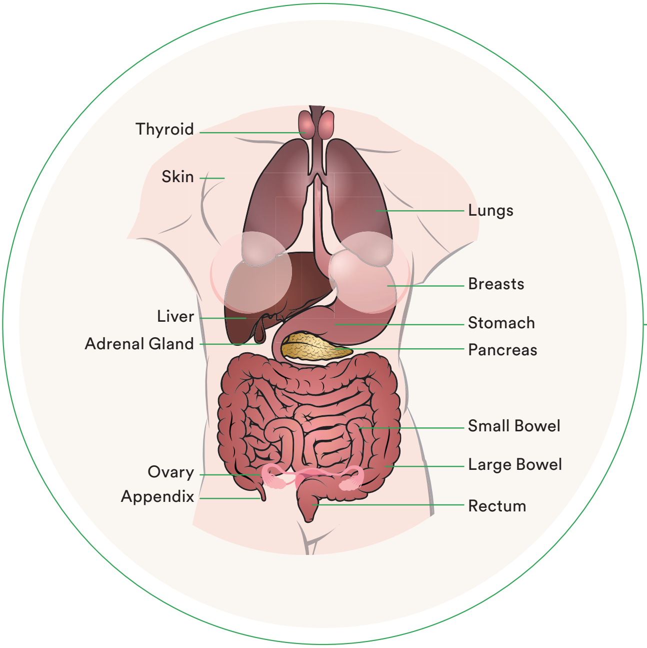
For example:

Pancreatic NETs (pNETs) may be classified as functioning or non-functioning:

Functioning pancreatic tumours make extra amounts of hormones, such as gastrin, insulin and glucagon, or other substances known as peptides, such as vasoactive intestinal peptide (VIP), that cause an associated syndrome – or collection of identifiable symptoms in the body. Most functioning tumours are initially benign.

Non-functioning pancreatic tumours may release certain hormones, but these do not cause an associated syndrome. Most non-functioning pancreatic tumours are malignant at diagnosis, but later on may cause abdominal symptoms, such as pain due to tumour growth.

Gastrointestinal NETs (GI-NETs) are the most common type of NETs (previously called carcinoid tumours). They are found in the gastrointestinal (GI) tract and include tumours that develop in the small intestine, the appendix, the stomach, the oesophagus, the colon and the rectum. NETs that occur in the GI tract or pancreas are sometimes grouped together and called gastroenteropancreatic neuroendocrine tumours (GEP-NETs).



Where NETs are found

In NETs, primary tumours can occur almost anywhere in the body, but are most commonly found in the gastrointestinal tract (digestive system), pancreas and lungs.

They can also start in other regions which contain neuroendocrine cells, like the ovaries or testes, and can spread to other areas, like the liver or bone.

Sometimes it's impossible to determine where the NET has originally started; in these cases, it is referred to as a carcinoma of unknown origin (CUP).

A cancer is usually named after the part of the body where it first started to grow. This is known as the primary site or the primary tumour. If the cancer cells spread from the primary site to another part of the body, it's called a secondary cancer or a metastasis.

The 3 main areas where NETs are found in the body are the gastrointestinal tract (digestive system), the pancreas and the lungs.

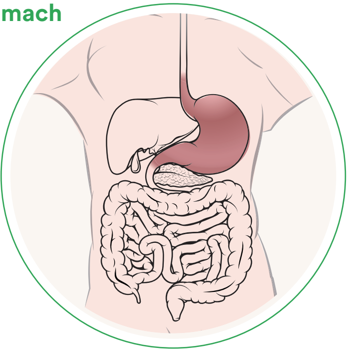
Gastrointestinal NETs (GI-NETs*): the most common type of NETs; these are found in the gastrointestinal (GI) tract (digestive system).

Pancreatic NETs (pNETs*): formed in the islet cells of the pancreas and include several uncommon types of NETs.

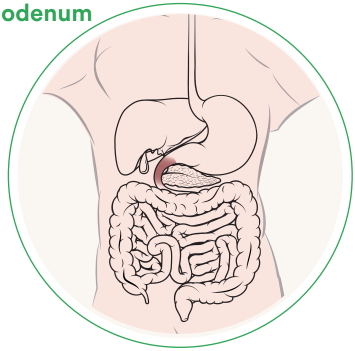
*When NETs are found in both the gastrointestinal system and the Pancreas, they are called gastroenteropancreatic NETs (GEP-NETs).

> In NETs, primary tumours can occur almost anywhere in the body, but are most commonly found in the gastrointestinal tract (digestive system), pancreas and lungs.

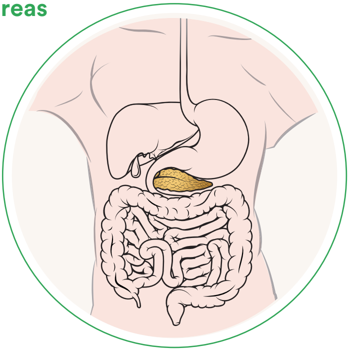
Stomach



Duodenum



Pancreas



For further information regarding different types of NETs, visit:
www.netpatientnetwork.ie

> Cancers, or tumours, arise when cells of a certain area multiply quickly and uncontrollably.

Causes of NETs

You may wonder why NETs have been caused. Like many other cancers, the exact causes of most types of NETs are unknown.

In general, cancers, or tumours, arise when cells of a certain area multiply quickly and uncontrollably. Whereas normally our cells would divide in a more controlled manner, in cancer, something happens to the cell's control signals which cause abnormal cells to form and then divide quickly causing a growth, which we call a tumour.

The neuroendocrine system, also known as the hormone system, is made up of nerve and gland cells called neuroendocrine cells; these cells release hormones into your body that regulate the function of different organs. So NETs can develop when neuroendocrine cells change and grow uncontrollably.

Who do NETs affect?

Understanding the demographics

Depending on the type of tumour, most NETs occur in people aged 50 to 60 years old, but they can affect anyone of any age.

Gender is not considered a factor when it comes to NETs; on average, there are similar numbers of diagnoses between men and women, and most NETs occur without any genetic link.

However, in rare cases they can be linked to a genetic syndrome.

For instance, people who have one of the following rare family syndromes, have a higher risk of developing NETs:

- Multiple endocrine neoplasia type 1 (MEN 1)
- Neurofibromatosis type 1
- Von Hippel-Lindau syndrome (VHL)

For further information regarding different types of NETs, visit:
netpatientnetwork.ie

Staging and grading of NETs

To help determine what treatment may be best for a particular situation, doctors will often stage and grade tumours.

Cancer staging gives a measure of how large a tumour is and how far it has spread from the original location in the body. Cancer stages range from 1 – 4; the higher the number, the bigger the size and spread of the tumour.

Stage 1	A solitary NET that's less than 1cm in diameter and hasn't spread to surrounding tissues or anywhere else.
Stage 2	A NET (usually more than 1cm in diameter) that has started to spread to nearby tissues or structures, but hasn't spread to other areas of the body or to any lymph nodes (the tiny glands that help to fight infection).
Stage 3	A NET of any size that's spread to nearby tissues and structures and to one lymph node.
Stage 4	A NET of any size that's spread to distant areas of the body, like the liver, and to one or more lymph nodes.

Cancer grading gives an indication of how quickly or aggressively tumours are growing. A specialist will look at a sample of tissue under the microscope and provide a measure of how severe the cancer is and how quickly the tumour(s) may develop.

The information provided by staging and grading gives clues to the likely long-term outcome for a patient, but it's important to note that having a high stage or grade does not necessarily mean the outcome is going to be any worse.

This table shows how the World Health Organisation grades NETs:

Grade 1	A NET with well differentiated cells, less than 3% of which are dividing.
Grade 2	A NET with well differentiated cells, between 3% and 20% of which are dividing.
Grade 3a*	A NET with well differentiated cells, more than 20% of which are dividing.
Grade 3b*	A tumour that's called a neuroendocrine carcinoma (NEC) rather than a NET, which has poorly-differentiated cells, more than 20% of which are dividing.

> A specialist will look at a sample of tissue under the microscope and provide a measure of how severe the cancer is and how quickly the tumour(s) may develop.

Recognising and diagnosing NETs

Symptoms of NETs

Symptoms will vary depending on where the NET(s) is located in the body, how fast it's growing and if and where it has spread around the body. Symptoms will also depend on the type of NETs – carcinoid tumours, gastrointestinal NETs, pancreatic NETs and lung NETs – can all produce very different symptoms.

NETs may not produce any symptoms at all, and if they do, symptoms can often be very vague and diverse, which is what can make them difficult to diagnose.

Carcinoid Syndrome is a common symptom of NETs and one of the more identifiable ones.

"Carcinoid Syndrome" is the term that is used to refer to a group of symptoms that can occur together when NETs release certain hormones, such as serotonin, histamine and bradykinin.

These symptoms vary from person to person, but may include diarrhoea, flushing of the skin (particularly the face), wheezing, stomach pain, heart problems — such as palpitations, and high blood pressure.

Always consult your doctor about which medications they recommend for your particular symptoms, their recommendations will be based on your specific NETs diagnosis and overall health.

Have a look through the “symptom management tips” section in the additional resources section of this book for some non-medical ways to help with symptoms; such as avoiding alcohol, eating certain foods to reduce diarrhoea or skin flushing, and for tips on reducing stress.

You can also keep track of your own symptoms in the symptoms tracker of your Journal.

Here you can note your various symptoms, when they occur, as well as how you address them; what works best for you, what doesn’t, as well as any other details, or questions about them you may have – which may be useful to have on hand at your next check-up.

> Always consult your doctor about which medications they recommend for your particular symptoms.

You can learn more about available treatment options in Ireland in the **treatments section.**

Symptoms and syndromes caused by functional NETs

Type of NET	Typical location	Characteristic symptoms
VIPoma (Vasoactive intestinal peptide tumour)	Pancreas	● Watery diarrhoea (also known as pancreatic cholera) which can cause hypokalemia or hypochlorhydria
Glucagonoma	Pancreas	● Rash ● Glucose intolerance (diabetes) ● Weight loss
Somatostatinoma	Pancreas, duodenum	● Hyperglycemia ● Diarrhoea (bulky, greasy, odorous) ● Hypochlorhydria

Type of NET	Typical location	Characteristic symptoms
Carcinoid	Stomach, bowel, small intestine, pancreas	• Diarrhoea (including night time) • Cramping • Flushing • Wheezing • Pellagra (cause abdominal pain, redness and swelling of the mouth and tongue, rash, memory loss) • May also cause lesions in the heart valves
Gastrinoma	Duodenum, pancreas	• Ulcers • Diarrhoea
Insulinoma	Pancreas	• Hypoglycemia • Weight gain • Poor or abnormal absorption of nutrients • Insulin resistance

Your healthcare team:

There will be a number of healthcare professionals you may encounter on this journey. Together they are referred to as your multidisciplinary care team (MDT).

NETs are very diverse in character. Because there are several kinds of tests involved, as well as a variety of treatments available, your care and treatment for NETs will usually involve a multidisciplinary care team.

The team will include healthcare professionals from various clinical areas who will help to advise you about the different aspects of your care.

General practitioner / practice nurse

A general practitioner (GP) or primary care physician is a medical doctor who diagnoses and treats all types of medical conditions. GPs are often the first healthcare professional a patient sees before they are referred to a specialist. A practice nurse works alongside the GP to assess, screen, treat and educate patients on health and can help monitor those with long term conditions.

Gastroenterologist

A doctor that specialises in diagnosing and treating disorders of the gastrointestinal tract (digestive system).

Endocrinologist

A doctor that specialises in diagnosing and treating conditions caused by hormonal or endocrine imbalances in the body.

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Radiologist

A medical doctor who specialises in diagnosing and treating disease and injury through the use of medical imaging techniques (X-rays, CT scans, MRIs, PET scans, ultrasound etc.).

Surgeon

A highly skilled doctor who performs operations; like the removal of neuroendocrine tumours for example.

Oncologist

A doctor that specialises in treating people with cancer. Cancer doctors who specialise in treating patients surgically, are known as surgical oncologists, those who treat patients with medications are called medical oncologists, and those who use radiation therapy are referred to as radiation oncologists.

Nurse Specialist

A nurse who has specifically trained to treat patients with a certain illness (like NETs), and can act as a consultant to help other medical professionals to treat patients.

Pathologist

These are the doctors who will examine the tissue taken for a biopsy.

Dietician

A healthcare professional who is an expert in diet and nutrition.

> NETs are very diverse in character, so your care and treatment will usually involve a multidisciplinary care team.

Tests and treatments

It is up to your doctor to decide which tests are best performed in your case, and they may choose several, or none of the following test methods; these are just some of the most common ones.

Biopsy

If your doctor suspects NETs, they might take a tissue sample from the suspected tumour in your body. This is usually carried out using a method called 'fine needle biopsy', in which a thin needle is inserted into the body to remove the tissue – similar to taking a blood sample.

Before this is done, you'll receive a local anaesthetic to numb the biopsy site. The sample will then be examined by a pathologist, who will analyse it under a microscope to confirm the presence of the tumour and describe its characteristics.

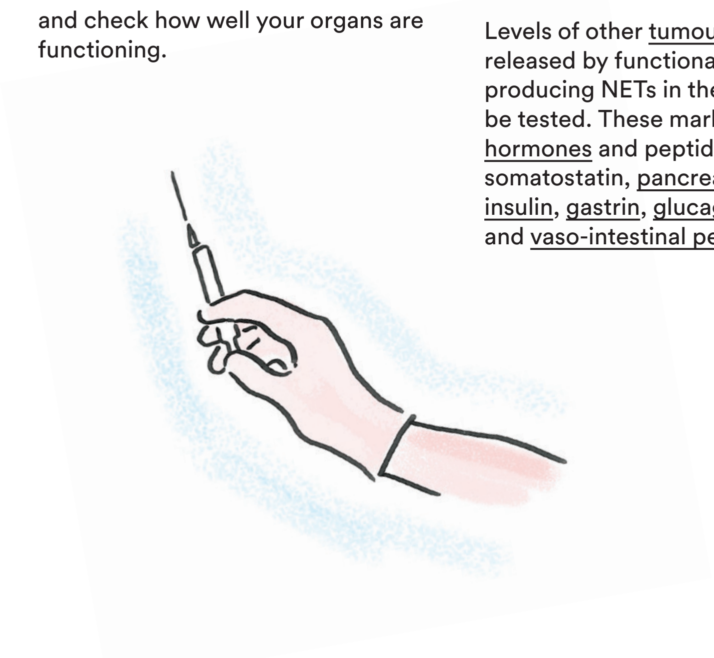
In some cases, the pathologist may give your tumour a proliferative index that you may see noted as 'Ki-67'. A proliferation index of less than 2% (Ki-67<2%) means that the tumour is growing very slowly, while an index higher than 10% (Ki-67>10%) suggests it has a faster growth rate.

The test will help your doctor to determine what treatment is necessary. Your doctor might repeat the test periodically to monitor the effects of certain treatments for NETs that you may receive.

Tumour marker tests

Tumour markers are chemicals – usually proteins – that are present in the blood or urine that can be measured to indicate the possible presence of NETs.

Your doctor will take samples of your blood and urine for diagnostic testing, and then a pathologist will examine them to look for certain NET markers and check how well your organs are functioning.



Blood tests

Blood samples will be collected for a range of tests. Markers for NETs that may be measured in the blood include:

- Chromogranin A (CgA)
  This is the most important circulating tumour marker for NETs.
  In blood tests, the levels of CgA are higher than normal in 60% to 80% of functional and non-functional gastrointestinal and pancreatic NETs.

Levels of other tumour markers that are released by functional and hormone-producing NETs in the blood will also be tested. These markers include hormones and peptides, such as somatostatin, pancreatic polypeptide, insulin, gastrin, glucagon, neurotensin and vaso-intestinal peptide (VIP).

> If the results of these tests suggest the presence of NETs, imaging tests will usually be carried out.

Other blood tests for NETs may include:

- Full blood count (FBC)
- Kidney function tests (urea and electrolytes)
- Liver function tests
- Thyroid function tests
- Pituitary hormone screen, measuring hormones such as adrenocorticotropic hormone (ACTH), prolactin, growth hormone (GH) and cortisol
- Serum calcium and parathyroid hormone level tests, for all patients with pancreatic NETs, as a screening test for MEN-1 syndrome
- NT proBNP is a blood test to check for carcinoid heart disease

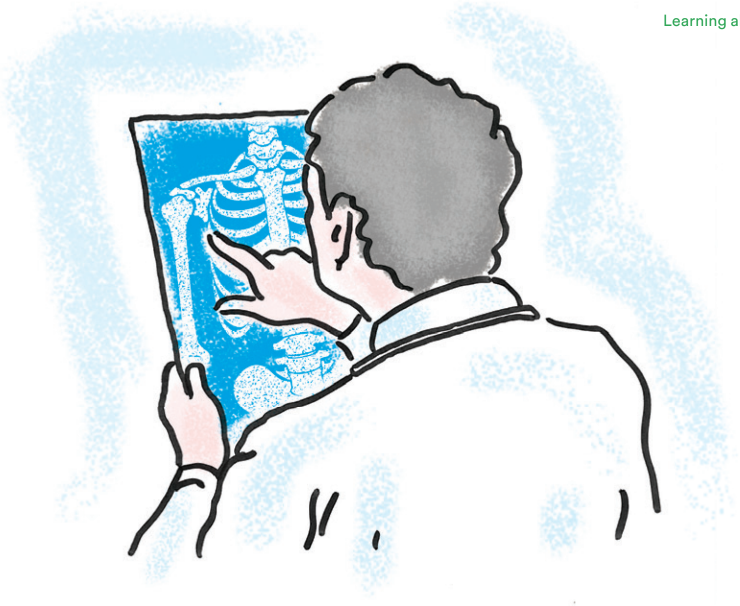
Urine tests

5-HIAA is a 24-hour urine test that measures the amount of 5-hydroxyindoleacetic acid (5-HIAA) in the body. 5-HIAA is a substance that is broken down (metabolised) in the body from serotonin by an amino acid called tryptophan.

A high level of 5-HIAA in a 24-hour urine test sample is likely to confirm whether a person's symptoms are due to carcinoid syndrome.

For the 5-HIAA test you will usually be asked to avoid certain foods beforehand and for 24 hours during the test as they contain substances that might artificially raise your 5-HIAA levels and so give a false positive result.

Visit the preparing for tests section at the end of this book for a list of these foods, as well as other some pre-test tips.



Imaging methods

Diagnostic imaging lets doctors look inside your body for clues about a medical condition. There are a variety of machines and techniques that can create pictures of the structures and activities inside your body.

The main imaging techniques used for diagnosing and monitoring NETs include:

- Ultrasound (sonography)
- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Positron Emission Tomography (PET)

More specialised imaging techniques include an octreotide scan, bone scintigraphy and an MIBG (metaiodobenzylguanidine) scan.

> During an ultrasound test, the sound waves are transmitted through body tissues using an instrument called a transducer.

Ultrasound

Ultrasound scans use high frequency sound waves to build up a picture of the inside of the body. These scans are completely painless. During an ultrasound test, the sound waves are transmitted through body tissues using an instrument called a transducer. The information is then displayed on a computer monitor.

Two types of ultrasound that may be used to help diagnose NETs include:

- Abdominal ultrasounds
  these can be used to examine organs inside the abdomen; they can easily detect NETs and secondary tumours (metastases) in the liver. However, abdominal ultrasounds are limited in detecting very small tumours.
- Endoscopic ultrasounds
  these can help pick up smaller tumours that might not be clearly visible on an abdominal ultrasound. They are usually carried out under sedation and involve looking at the digestive tract with an endoscope. The ultrasound endoscope is usually inserted into the digestive tract via the anus. A biopsy can also be performed during the endoscopic ultrasound.

Computed Tomography (CT)

A CT scanner is a special type of X-ray machine that uses radiation to provide a three-dimensional picture of the inside of the body. Regular CT scans are useful to find out more about the rate of tumour growth and how your NETs are responding to treatment.

Before the CT scan, you may be asked to have an injection, or drink a fluid containing a ‘contrast agent’, or dye, that shows up on the scan. The contrast agent can highlight specific areas inside the body which can show a clearer image of the results.

During the scan you will need to lie very still for 10 to 20 minutes as the CT scanner passes over you. Unlike an MRI machine, the CT scanner does not surround your whole body, so this type of scan might be more comfortable for people who don’t do well in small, or confined spaces.

Magnetic Resonance Imaging (MRI)

MRI is a type of scan that uses a powerful magnetic field and pulses of radio wave energy to make cross-sectional images of organs, tissues, bones and blood vessels. A computer then turns the images into three-dimensional pictures. An MRI may be used if an ultrasound or CT scan haven't provided doctors with enough information to make a diagnosis. The complete results will usually take a few days before they are ready for your doctor.

During an MRI, you will lie inside the machine while it scans your body. Similar to a CT scan, it will require you to lie very still and may take anywhere from 30 minutes to 1 hour. A radiologist will examine the images to determine the difference between normal and diseased tissue. If a tumour is identified, further tests may be needed to confirm the type of NET.

As MRI scans are based on magnetic fields and not X-rays, they are relatively harmless. There are, however, certain preparations and precautions that your doctor should tell you about before the test. For example, you'll need to remove any metal objects from your body, such as earrings or other jewellery.

> CT scans and MRIs are two of the most important imaging techniques for diagnosing NETs. These techniques can be used to determine the position and size of tumours.

Echocardiography

An echocardiogram is an imaging test that uses ultrasound to produce moving images of the heart and blood flow through the heart's valves and structures. Some types of NETs that are associated with carcinoid syndrome will release hormones called serotonin and tachykinins into the blood stream. These hormones can travel to the heart and affect the cardiac valves.

The echocardiography probe is placed on the thorax and images are taken through the chest wall (transthoracic echocardiography).

Depending on the results of the echocardiogram, you may need further investigations, such as transesophageal echocardiography or a cardiac MRI.

> An imaging test that uses ultrasound to produce moving images of the heart and blood flow through the heart's valves.

Positron Emission Tomography (PET)

A PET scan is a unique type of imaging test that allows doctors to see how the organs and tissues inside your body are actually functioning. This scan involves injecting a very small dose of a radioactive chemical, called a tracer, into the vein of your arm.

PET scans can detect and record the energy given off by the tracer in your cells and detailed, three-dimensional images from the PET scan are then produced through a computer. It is usually used in combination with a CT scan to build up a picture of the size, location and status of NETs.

Some useful tips on preparing for imaging tests can be found in the **preparing for tests** section at the end of this book.

Scintigraphy scans

Scintigraphy scans may be performed to determine where the neuroendocrine tumours started and if the tumours have spread in the body.

These scans are radioactive imaging techniques and are usually used after someone has already had another type of scan such as an Ultrasound scan, Magnetic Resonance Imaging (MRI) scan, Computed Tomography (CT) scan or PET scan.

Types of Scintigraphy Scans include:

- Octreotide scan
  An octreotide scan – also known as somatostatin receptor scintigraphy (SRS) – may be used to detect certain neuroendocrine cancer cells in the body. The test requires multiple scans, usually taken over two days.

  On the first day, you will receive an injection that contains a very small amount of a radioactive substance called an octreotide tracer.

  Octreotide is a drug very similar to somatostatin. Neuroendocrine cells with somatostatin receptors on their surface will attract and attach to the octreotide tracer.

  Later that day, the first set of scans will be taken to look for areas in the body that have picked up this trace, this may indicate where certain neuroendocrine cancer cells are located. Further octreotide scans will usually be taken over the next 24 to 48 hours to produce more detailed pictures.

- Bone scintigraphy scan
  A bone scintigraphy scan is an imaging test that uses a very small amount of a radioactive substance to determine if NET cancer has spread to the bones from another part of the body. Usually the entire body is scanned during a bone scan procedure and if the results show bone damage that may be caused by cancer, then more diagnostic NET tests, like a CT scan, MRI scan, biopsy may be necessary.
- MIBG scintigraphy scan
  A MIBG scan is another imaging test that can be carried out to find the location of NETs in the body, but it is used less often than an octreotide scan.

It works by injecting a substance called an isotope into your veins. The MIBG scan scan is named after the chemical 'iodine-131-metaiodobenzylguanidine' or MIBG for short, to which the isotope is attached.

After it's injected, the isotope travels around the body and sticks to any abnormal areas. Several hours or days later the body is scanned with a gamma camera to look for areas that have picked up the isotope, this allows doctors to identify and pinpoint any areas of abnormality, including certain types of NETs.

Other tests

You may undergo other tests as well in order to confirm and monitor the presence of neuroendocrine tumours, some of these may be:

- Digestive endoscopy
  A flexible camera, called an endoscope, will be used to examine your digestive tract. This flexible fibre-optic tube will be inserted down the back of the throat (gastroscopy) or through your rectum (colonoscopy).

  Your doctor may also order a small bowel capsule endoscopy. This involves swallowing a small capsule, about the size of a small pill, which contains a flexible camera, light source and transmitter. The camera takes six pictures every second for 8 hours, transmitting images to a small data recorder that you wear around your waist.

Endoscopy tests that may be used for diagnosing NETs include:

- Upper GI endoscopy
- Colonoscopy
- Small bowel capsule endoscopy
- Endoscopic ultrasound

If abnormal-looking tissues are found during an endoscopy test, a tissue sample can be collected during an endoscopy for a biopsy. The results can confirm whether the sample contains neuroendocrine cancer cells.

- Bronchoscopy
  A bronchoscopy test can be used to view the airways and diagnose lung diseases, such as lung NETs. A bronchoscope will be passed through your nose and down your throat to reach your lungs. This instrument is made of a flexible fibre-optic material and has a light source and a viewing device or camera on the end.

  Before the test, a local anaesthetic spray will be applied to your nose and throat. You will probably also be given a sedative to help you relax.
- Lung function tests
  Lung function tests, or spirometry, are a group of tests that measure how well your lungs work. These tests may involve you holding your breath before exhaling very hard into a measuring device to see how forcibly you can expel air over a short period of time.

  The results are used to diagnose certain types of lung disease, such as lung NETs.

Diagnosis

As NETs are an infrequent type of cancer, some people find that their own doctors do not know much about the condition.

After your diagnosis, ask your doctor to refer you to a specialist NET centre; details for these centres can be found on the NET Patient Network website: www.netpatientnetwork.ie. You may need to travel a lot further for these specialist appointments; however, it will give you the chance to receive more expert care.

All cases of neuroendocrine cancer are unique. They can vary a lot from person to person, even when they start in the same organ; only a specialist doctor who is familiar with the details of your medical history, the results of your NETs tests, and your response to treatments can offer you an individual prognosis.

What is meant by prognosis?

A prognosis is a doctor’s opinion about how well someone will recover from an illness. The prognosis and survival rates of people with NETs depend on several factors:

- Site – where the primary tumour started in your body
- Metastasis – whether it has spread to other organs
- Size – how large it is
- Symptoms – how it affects you physically and emotionally
- Functional or non-functional – whether it produces excess hormones
- Stage – how advanced the cancer is
- Grade – how fast or slow it is growing
- Complications – what other medical conditions it may have caused
- Overall, general health
- Previous/existing medical conditions

Remember, all cases of neuroendocrine cancer are unique, so your specialist will form a prognosis based on your individual case.

Treating NETs: current treatment options

Treatment for neuroendocrine cancer mainly depends upon the location of the tumour, whether the cancer has spread to other areas of the body and if the tumour is secreting hormones and is responsible for symptoms. In most cases surgery is performed.

> All cases of neuroendocrine cancer are unique. They can vary a lot from person to person, even when they start in the same organ.

Surgery

This is usually the first choice for treatment if imaging scans show that the primary tumour is contained in one area (localised) or there has been only limited spread within an organ of the body. If it is possible to remove the tumour completely with surgery, then no other treatment may be necessary.

Even if the primary tumour has spread (metastasised), surgery may still be possible to remove part of the tumour and any other secondary tumours. This is often referred to as tumour debulking.

If GEP-NETs or other NETs are blocking an organ, such as the bowel, then surgery may be helpful to relieve the blockage. If the tumour has spread to the liver, surgery can be used to remove the parts of the liver containing the tumour. Very occasionally, a liver transplant may be considered.

Medical treatments

Medical treatments are used to palliate the symptoms and/or to control the growth of the tumour. Radiotherapy might also be used, as well as chemotherapy. There are also cases where no treatment is given but the patient is monitored regularly – this is called watchful waiting.

If your specialist tells you that he or she will not be prescribing anything and that they are keeping you under observation it does not mean that you are not receiving any treatment. Most NETs are very slow growing.

While there are various treatments for neuroendocrine tumours, your doctor will discuss with you the most suitable option(s) for your own personal case based on which are available.

> Even if the primary tumour has spread (metastasised), surgery may still be possible to remove part of the tumour and any other secondary tumours.

As a general overview, here are some treatment options currently available in Ireland:

Somatostatin analogues

Somatostatin is a substance produced naturally in many parts of the body. It can stop the over-production of hormones that cause symptoms such as diarrhoea, flushing and wheezing. Lanreotide and octreotide are somatostatin analogues i.e. drugs that copy or mimic the action of somatostatin.

Some NETs produce hormones that can cause other symptoms, for example, patients with a carcinoid tumour may have diarrhoea, flushing and wheezing. You may have different symptoms depending on the type of tumour that you have. These symptoms can be distressing and often affect your quality of life.

The aim of this treatment is to block the release of the extra hormones your body is producing and therefore improve your symptoms.

Lanreotide LA can be given as an injection every 7-14 days, or lanreotide autogel every 28 days. The long-acting injection can be administered by a nurse, either in hospital or by a practice nurse. For some patients who are stabilised on their treatment with lanreotide, it may be possible for the patient, or a relative or friend, to be taught how to give the injection themselves. The injection is given in the upper, outer quadrant of the buttock or, if you are self-injecting, into the upper, outer thigh. If you are using lanreotide at home it should be kept in the refrigerator, in its original package, at a temperature between 2C and 8C — it should not be frozen.

> You may have different symptoms depending on the type of tumour that you have. These symptoms can be distressing and often affect your quality of life.

Octreotide can be given as a short-acting injection two to three times a day, or as a long-acting injection administered by a healthcare professional every 28 days. The short-acting form is injected into the tissue under the skin, either in the upper arm, thigh or stomach. The long-acting form is injected in the large muscle in the buttock. Octreotide should be stored between 2C and 8C; it should not be frozen.

If you have been diagnosed with carcinoid syndrome, you may need medical treatment for specific symptoms you might be experiencing. Some common treatments for NETs can also be used to treat the effect of carcinoid syndrome; a hormone therapy, like a somatostatin analogue for example, can be used to lessen diarrhoea and skin flushing. Interferon therapy can also be used to lessen skin flushing and diarrhoea if given as an injection under the skin.

Interferon

Interferon is a naturally occurring substance that is produced by the body's immune system during an illness such as a viral infection e.g. flu. It is sometimes referred to as biological therapy or immunotherapy and is used to treat some patients with NETs. Sometimes interferon is given on its own, but quite often it is given as a combination therapy with somatostatin analogues. It may not be a suitable therapy for all NET patients.

More details on treatments can be found on the NET Patient Network: **netpatientnetwork.ie**

Chemotherapy

Some people may be given chemotherapy to treat pancreatic and bronchial NETs, and also for some NET tumours which are growing a little quicker than they might normally do.

The exact type (sometimes called histology) of your tumour will help determine whether chemotherapy will be appropriate for you or not. If you have chemotherapy the oncology team, who are specialists in this field, will look after you.

Researchers are constantly looking at various chemotherapy regimens for NET patients and this may be discussed with you at your hospital appointment.

Chemotherapy drugs are normally administered through a cannula inserted in your arm but there are also tablet forms. You can normally receive your treatment as an outpatient, although if it is your first time, you may be asked to stay in overnight just to check that you tolerate the treatment.

The drugs used, and any possible side effects, will be discussed in-depth prior to commencing any treatments and written information will also be given. You will be given many opportunities to ask questions.

You may be given an information and record book from the chemotherapy team. It might be helpful to note down the specific contact numbers for them.

> The histology of your tumour will help determine whether chemotherapy will be appropriate for you or not.

Embolisation

If the tumour has spread to the liver, you may be offered hepatic artery embolisation (HAE). In this procedure, a catheter is placed in the groin, and then threaded up to the hepatic artery that supplies blood to the tumors in the liver. Tiny particles called embospheres (or microspheres) are injected through the catheter into the artery. These particles swell and block the blood supply to the tumour, which can cause the tumour to shrink or even die.

This treatment can also be combined with systemic treatments for people with liver metastases and metastases outside of the liver. It is a procedure that would be done by a specialist called an interventional radiologist. You will be sedated for the treatment.

Sometimes this embolisation process is combined with chemotherapy and called Hepatic Artery Chemoembolisation (HACE), or Transcatheter Arterial Chemoembolisation (TACE), or radiotherapy (Radioactive Microsphere Therapy [RMT] or Selective Internal Radiation Therapy [SIRT]).

Radiofrequency ablation

Radiofrequency Ablation (RFA) is used if there are relatively few secondary tumours. A needle is inserted into the centre of the tumour and a current is applied to generate heat, which kills the tumour cells.

Peptide receptor radionuclide therapy (PRRT)

Peptide receptor radionuclide therapy (PRRT) is also called Radionuclide therapy, or hormone-delivered radiotherapy. It is sometimes referred to as the ‘magic bullet’. This treatment involves a similar strategy as that applied in an octreoscan, but the dose of radiation is high enough to prevent further tumour growth or even kill the tumour.

Radioactive substances are chemically combined with hormones that are known to accumulate in a NET. This combination is injected, the hormones enter the tumour and the attached radiation will kill the tumour cells. There are a number of different radioactive agents available.

You will be admitted to hospital for these treatments, but usually you will only need to stay in overnight. You will remain in a lead-lined room for 12-24 hours afterwards and have a scan the following day so the doctor can see if the active agent has been taken up correctly.

The therapy is commonly delivered intravenously through a cannula in the arm. In certain centres it can also be delivered transarterially if the doctor wants to particularly target tumours in the liver.

This treatment is not available in Ireland but is offered by some very specialist centres around Europe. One such centre is the university hospital in Uppsalla, Sweden which has close links with several Irish hospitals. This treatment is accessible to Irish NET patients through the EU's E112 system as part of their overall healthcare strategy.

Learning about NETs can seem overwhelming at first.

With the right information you can feel confident about asking the right questions. This book is developed to help you learn about NETs in your own time, at your own pace. The next section covers some frequently asked questions and tips for preparing for tests, as well as additional information and resources.

FAQ

So you don't have to wait until your next appointment for all your questions, here are some frequently asked ones and their answers.

Always consult your doctor about specific questions for your individual health. These answers below are not intended to replace their medical advice.

Why did this take so long to diagnose?
NET cancers are difficult to diagnose because most neuroendocrine tumours develop slowly over a number of years and when symptoms present, they are often non-specific and vague. Most NETs are diagnosed at a later stage because of this, which unfortunately also means that they have likely spread to other parts of the body. This is often what triggers the symptoms.

Can my NETs be cured?

This can only be addressed on an individual basis and by your own professional team of doctors. However, once the cancer has spread to other parts of the body, it is rare that it can be cured entirely – but, with treatment, the symptoms can usually be successfully managed for a number of years, and the spread halted.

How common are NETs?

NETs make up about 2% of all cancers, but although they are rare and infrequent, increasing awareness of them and improves diagnostic testing has made them the fastest growing class of cancers worldwide. However, this means that they are now getting more attention and people are receiving the care they need sooner than ever before.

How fast will a NET grow and how far can it spread?

Compared with other cancers, NETs are small and usually grow slowly over a number of years, however some NETs can grow faster than others. NETs do not usually cause noticeable symptoms until they have already grown and spread. By the time they are found, most of NETs will have spread to other parts of the body.

Who will give me my treatment?

NETs are often diagnosed and treated by a number of different specialists, possibly even in different hospitals. This is to ensure you are seeing the right person for the right reason(s) – the same reason why you don’t go to a mechanic when you have a toothache. Together these specialists and nurses will make up your MDT (multidisciplinary team), who will work together to make sure you are getting the tests and treatment(s) you need.

> For urgent queries, such as those relating to a flare of symptoms, pain, or anything unusual you think might be related to you condition, you should call your doctor straight away and not wait until your next appointment.

Additional resources

Tips for learning more about NETs

- Find specialist NET consultants or cancer centres in your country by contacting patient support groups, or by searching online databases of medical experts
- Register to receive regular newsletters or email updates from these groups
- Read up on the various treatment options available in Ireland and ask your doctor about them
- Look out for annual patient conferences, meetings or events about NETs
- Keep the glossary book handy so that you can look up new or unfamiliar terms or phrases you hear or read while you are exploring the various NETs resources, or even during appointments.

Types of NET

- Carcinoids: Lung, Thymic, Gastric, Duodenal, Pancreatic, Small Intestine, Appendiceal, Colon, Rectal, Ovarian.
- Functioning/Non-Functioning Pancreatic Tumours
- Multiple Endocrine Neoplasias
- Gastrinomas
- Insulinomas
- Glucagonomas
- Phaeochromocytomas

Preparing for appointments

Do not be afraid to ask questions

Like other cancers, the right care for NETs starts with being seen by an experienced, specialist doctor, but it's also important to be a prepared patient, so you can have the right conversation with your doctor.

- Have a think and do some research before your appointments. Draw up a list of questions to ask your doctor about your NET diagnosis, your prognosis, your treatment and practical advice about dealing with any emotional or physical problems.
- There's a notes section included in the Journal book of this pack. You can use this space to note your questions, as well as the answers. In that section you'll also find trackers for appointments, symptoms, treatments and more.
- Ask your specialist to clearly explain any medical test results of yours that they may be looking at during your visit. Why not take some notes about their answers to remind you about what they have said? Ask them to explain something several times if you don't understand.
- Try taking a friend or relative with you to your medical appointments, you may feel more comfortable and relaxed if you have someone you know by your side.

> These tips and tools are meant as an additional aid, and do not replace medical treatment. Please talk to your doctor about treatment options, as well as additional ways of coping with your disease.

Questions you should ask your MDT

To get you started, here are some examples of important questions that you might want to ask your doctors:

- What type of tumour do I have?
- What grade of tumour is it?
- Where did it come from?
- Has it spread?
- Is it curable by surgery?
- Do I have options?
- What treatment options are available for me here?
- What treatment options are available elsewhere?
- Are you a NET specialist?
- Is this a specialist centre?
- What does this diagnosis mean for me?
- Have you treated people with this type of NET before?
- What treatments are there for my NETs?
- How will we know if my treatment is working?
- How will treatments make me feel?
- What changes should I expect in my daily life?
- What can I do to help manage my condition?
- Will my children get this type of NET too?

Preparing for tests:

5-HIAA 24-hr Blood Test

You will usually be asked to avoid certain foods beforehand and for 24 hours during the test as they contain substances that might artificially raise your 5-HIAA levels and so give a false positive result.

These foods include:

- Chocolate
- Olives
- Bananas
- Pineapple
- All tomato products
- Plums
- Aubergine
- Avocado
- Kiwi fruit
- Various nuts: walnuts, brazil nuts and cashew nuts
- Tea
- Coffee
- Alcohol

Your NETs specialist doctor should be able to advise you on this and provide you with a complete list.

Additional NET information and resources:

The NET Patient Network:
netpatientnetwork.ie
or
netpatientfoundation.org

> If you're feeling nervous about the scan, ask a friend or family member to go along with you.

Preparing for imaging scans

Wear comfortable clothes

A hospital gown may not be necessary during this scan, so wear loose-fitting, comfortable, cotton clothing and undergarments. There can be no metal present on the body during these scans, so make sure there are no zippers, snaps, button, hooks, etc. on your clothes. This also means you'll need to remove a belt if you're wearing one, as well as any eyeglasses and even dentures.

Don't wear jewellery

No metal also means no jewellery, so it might be a good idea to remove any piercings you may have and leave that jewellery – and the rest, at home to ensure you don't lose anything.

Ask about a pillow

Sometimes these scans can last up to an hour and you will need to remain very still throughout, so ask your doctor if there will be a pillow provided. If not, you may be able to bring a small pad or pillow of your own to help keep you more comfortable.

Bring snacks

Some scans might require you to fast from food and drink for a few hours beforehand, if this is the case, bring along a snack and drink for after – you'll be allowed to eat and drink as soon as the scan is finished – and you'll probably be hungry!

Bring a friend

If you're feeling nervous about the scan, ask a friend or family member to go along with you. Even if they can't be in the room, sometimes just knowing they're nearby is enough to calm the nerves and make us feel a little better.

Ask for the same radiologist

Seeing a familiar face might make you feel more comfortable when you're having the scans, so you can ask if the same radiologist you met previously can perform these for you. It might not always be possible, but it can't hurt to ask.

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