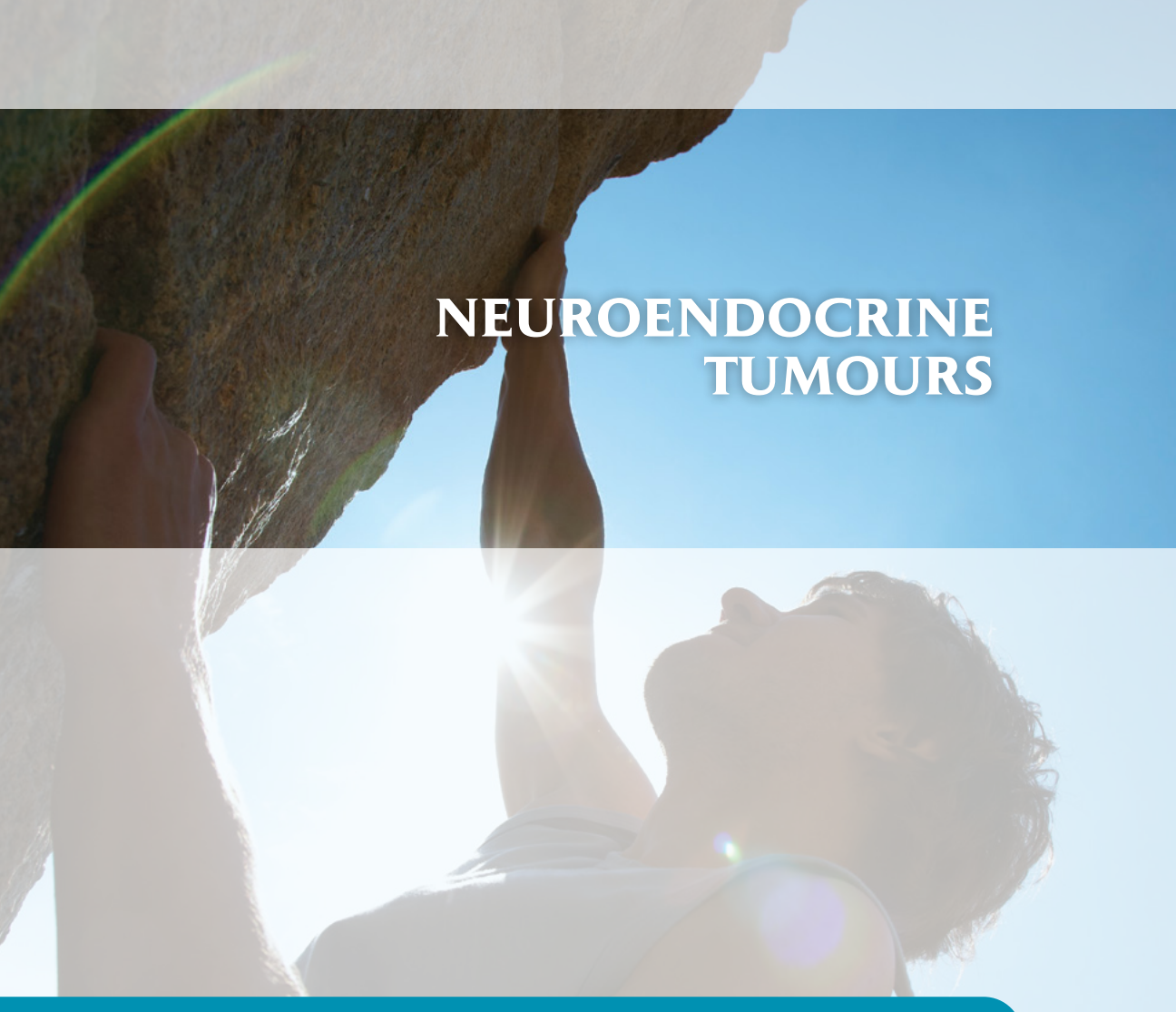


NEUROENDOCRINE TUMOURS

Reference Guide for Patients and Families

CANADIAN NEUROENDOCRINE TUMOUR SOCIETY

CNETS

Version 3.0

CANADIAN NEUROENDOCRINE TUMOUR SOCIETY

About Us

Why a zebra? In medical school, doctors are taught "*when hearing hoofbeats, think horses, not zebras*." Carcinoid cancer and neuroendocrine tumours have been thought of as "rare" and therefore may be considered a zebra. With greater awareness and quicker diagnosis, it is being shown that carcinoid cancer and neuroendocrine tumours are not as rare as was thought a few years ago!

The information provided in the *Neuroendocrine Tumour Reference Guide for Patients and Families* is for general use only and **is not a substitute for professional medical advice** regarding your health or the medication(s) and treatments you have been prescribed. If you have questions, please contact your doctor.

Introduction

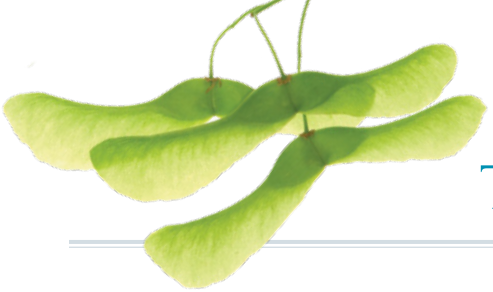
Welcome to the *Neuroendocrine Tumours Reference Guide for Patients and Families*. This handbook was developed to provide you with information and support as you confront and adapt to a neuroendocrine tumour (NET) diagnosis.

Our goals are to help you navigate through the process of diagnosis and treatment and work with your healthcare team, while maintaining a balanced lifestyle.

Although the cause of NETs is currently unknown, it is clear that NETs are now being diagnosed more frequently, and are not as uncommon as previously believed. Nevertheless, credible resources for patients and care providers may be difficult to find. It's important for you and your loved ones to know that you are not alone. With this in mind, a wide range of experts – medical professionals *and* patients – have contributed to helping make this a practical, comprehensive resource that you can refer to time and time again.

In the *Neuroendocrine Tumour Reference Guide for Patients and Families* you will find general information of interest to all NET patients displayed near the front of the handbook. More detailed information on specific tumour types can be found in subsequent sections.

For many patients, NETs are now being treated as a chronic, manageable disease. We hope that this guide will serve as a helpful and informative resource throughout the coming weeks, months and years.



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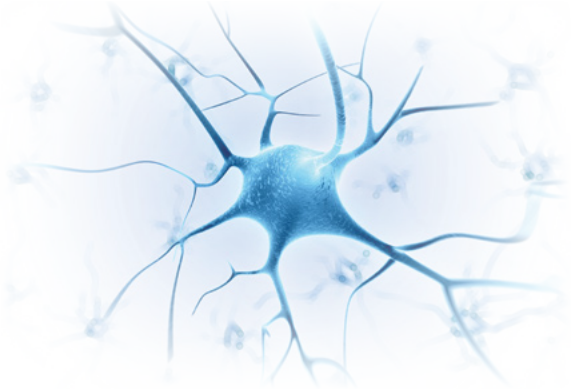
The Neuroendocrine System

The neuroendocrine system is a network of highly specialized cells that are distributed throughout the body. Together, the *diffuse neuroendocrine system* and the *endocrine system* form the neuroendocrine system.

Diffuse Neuroendocrine System + **Endocrine System** = **Neuroendocrine System**

Neuroendocrine cells are similar to nerve cells (neurons) but they are also able to produce hormones as endocrine cells do. In fact, when stimulated by signals from the nervous system or other cells, neuroendocrine cells release hormones into the bloodstream.



NETs are believed to arise from cells throughout the diffuse endocrine system and can be found anywhere within the diffuse endocrine system.

The Diffuse Neuroendocrine System

As the name suggests, cells in the diffuse neuroendocrine system are dispersed among several different regions of the body. Neuroendocrine cells in the gastrointestinal tract control the release of digestive enzymes and regulate intestinal function. Likewise, neuroendocrine cells in the lungs help maintain certain respiratory organ functions. Clusters of neuroendocrine cells known as paraganglia also occur along the spinal column and in and around the adrenal glands. These cells produce the hormones epinephrine (adrenaline) and norepinephrine (noradrenaline), which play a role in controlling blood pressure, heart rate, muscle relaxation and other body functions.

The Endocrine System

The endocrine system comprises the pituitary, adrenal, pineal, thyroid and parathyroid glands, as well as islet cells in the pancreas, and the ovaries of women and the testes of men. Although the thyroid, pancreas, ovaries and testes are not considered *endocrine glands*, they contain scattered neuroendocrine cells that perform specialized functions.

Overview of Neuroendocrine Tumours

Neuroendocrine Tumours

Neuroendocrine tumours (NETs) are a broad group of complex tumours that arise from neuroendocrine cells. The most common types are **carcinoid*** NETs which occur in the lungs, bronchi, thymus, small intestine, appendix or rectum, and **pancreatic neuroendocrine** (PNET† or PET) tumours, which arise in the endocrine tissues of the pancreas. NETs may also arise in the parathyroid, adrenal and pituitary glands, as well as in specific cells of the thyroid.

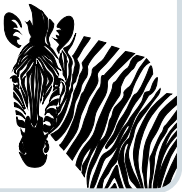
Less frequently, NETs may also occur in the ovaries, cervix, testicles, spleen and breast but these are considered very rare.

NETs are classified as being ***functional*** or ***non-functional***.

Functional tumours produce hormones and/or peptides that cause symptoms.

Non-functional tumours generally do not produce hormones – but even if they do – the patient will not experience symptoms as a result.

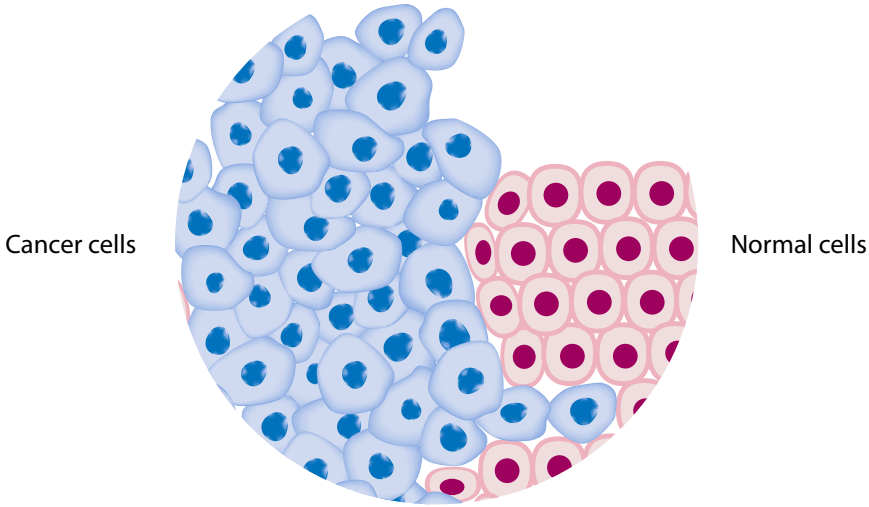
Many neuroendocrine tumours are non-functional and do not cause any symptoms.



* Today, there is a shift away from describing these tumours as "carcinoid," meaning slow-growing and "cancer-like," to using the term neuroendocrine tumours or neoplasms. It is now recognized that "carcinoid" inadequately describes the characteristics of many NETs.

† The abbreviation PNET is also used to describe a *completely different* group of cancers – primitive neuroectodermal tumours: cancers that arise from early cells and develop in the brain, central nervous system or other sites including the limbs, pelvis or chest wall. As you research your illness, do not become confused by this overlap in terminology.

Like other types of cancer, NETs occur when particular cells in the body become damaged and begin to grow out of control. These masses of abnormal, malignant cells develop into tumours. In time, malignant cells can travel to other parts of the body, via the blood and lymph systems, where they invade other organs – a process known as metastasis.



Obtaining A Diagnosis

Despite vast improvements in diagnostic techniques, neuroendocrine tumours remain difficult to diagnose. The reasons are twofold: NETs are often slow-growing tumours and many of the symptoms associated with NETs are also typical for hundreds of other diseases and conditions. Regardless, it's worrisome, frustrating and unsettling to feel that you are the only person who is facing this uncertainty.

It is important to work with your physician and other members of your healthcare team, track your symptoms, undergo tests and ask questions.

Early, accurate diagnosis is the first step towards successful treatment and better outcomes.

Tests That Your Doctor May Perform

Your doctors will choose which tests and investigations are appropriate, depending on the type of tumour that exists or is suspected.

Blood Tests	Description
ACTH*	Helps determine the cause of high and low cortisol levels
Calcitonin	Diagnosis and follow-up of medullary thyroid carcinoma
Chromogranin A	Because of its wide distribution in neuroendocrine tissues, this test can be a useful diagnostic marker for NETs. Note that chromogranin A levels may be falsely elevated if PPI* medications are being used, if there is kidney dysfunction, or if the patient had pernicious anemia and other metabolic conditions.
Complete blood count	A basic screening tool for many blood disorders and assesses bone marrow function
Cortisol	Evaluates adrenal dysfunction, particularly in the diagnosis of Cushing syndrome (excess cortisol) or in states of deficiency
Electrolytes (serum)	Tests levels of sodium, potassium, chloride, bicarbonate (and other substances), to identify a range of clinical disorders
FSH*	Useful for diagnosing pituitary disorders and evaluating levels of sex hormones and menopausal status
Gastrin	Used to investigate levels of the stomach acid–producing hormone (gastrin), including suspected cases of Zollinger-Ellison syndrome/gastrinoma. Note that gastrin levels may be falsely elevated if PPI medications are being used, if the sample is not fasting, and in other metabolic conditions.
GH-RH*	Used to evaluate the ability of NET to produce a hormone driving the pituitary gland to release more growth hormone

Glucagon	Evaluates levels of glucagon, produced by pancreatic cells, which help to maintain blood glucose levels, typically in the setting of a glucagonoma pancreatic NET
IGF-1*	Increased levels of IGF-1 are frequently found in conditions associated with growth hormone excess, including pituitary tumours and rarely NETs
Insulin	Used to help diagnose insulinoma when used in conjunction with glucose, proinsulin, and C-peptide measurements
Insulin C-peptide (serum)	Part of a diagnostic evaluation of blood glucose and insulin in search of an insulinoma
Insulin/glucose ratio	Used as a screening test for inappropriate insulin production including insulinomas
LH*	Used to help diagnose damage to the testes or ovaries
Neurokinin A (substance K)	A test that evaluates circulating levels of neurokinin A, high levels of which may indicate a poor prognosis in certain types of NETs *Not yet available in Canada. Available in the U.S.†*
Pancreastatin	A test that uses measurements of pancreastatin to potentially identify NETs at an earlier stage with greater sensitivity *Not yet available in Canada. Available in the U.S.†*
Pancreatic polypeptide	Used for detection of some types of pancreatic NETs
Plasma catecholamine	Used to help diagnose pheochromocytoma and paraganglioma. Also used for the diagnosis and follow-up of neuroblastoma and related tumours.
Plasma fractionated metanephrines	The gold standard test used in the diagnosis of pheochromocytoma
Proinsulin	Used as part of the diagnostic work-up of suspected insulinoma
Prolactin	Used in the evaluation of pituitary tumours, menstrual disorders, abnormal milk production, infertility, and low sex hormones
PTH*-related peptide	Used as part of a diagnostic work-up in patients who may have high calcium levels resulting from non-parathyroid cancer
Somatostatin	Used to evaluate the amount of somatostatin in the blood in suspected pancreatic NETs

Blood Tests (con't)	Description
TSH*	Used to evaluate thyroid function and/or symptoms of hyperthyroidism or hypothyroidism, or to evaluate the function of the pituitary gland
Vitamin B_{12}	Helps identify certain types of anemia
VIP*	Used to evaluate vasoactive intestinal polypeptide-producing tumours in patients who are experiencing severe watery diarrhea from a suspected pancreatic NET

Scans	Description
Bone scan	An imaging test that shows areas of increased or decreased bone turnover, often used to determine if a cancer that began elsewhere has spread to the bones
CT* scan	Uses specialized x-ray equipment to obtain cross-sectional images. The CT computer is able to display detailed images of organs, bones and other tissues.
Contrast-enhanced CT scan	A contrast agent, or "dye," is given by mouth, injected or given by enema before a CT scan is performed. The contrast agent can highlight specific areas inside the body, resulting in a clearer image.
CT-Enterography	A special type of CT scan that uses higher doses of radiation to display detailed images of the small intestine. A contrast agent is used to further enhance the images obtained during the CT scan.
Doppler ultrasound	A non-invasive test used to measure blood flow and blood pressure by bouncing high-frequency ultrasound waves off circulating blood cells
Echocardiogram	An imaging test that uses ultrasound to produce moving images of the heart and blood flow through the heart's valves and structures
Enteroclysis	An imaging technique that combines MRI and CT to display images of the small intestine. In this test, a small tube is passed from the nose or mouth, through the stomach and into the small intestine. A contrast agent is used to further enhance the images obtained during the MRI or CT scan.

MIBG*	An imaging test that uses a radioactive substance (radioisotope) injected into a vein to help diagnose a variety of tumours. A specialized scanner is then used to look for evidence of disease, including the possible diagnosis of pheochromocytoma, paraganglioma, or neuroblastoma. *See page 20 for more information*
MRI*	A type of scanner that uses a powerful magnet and radio waves to create detailed images of organs and structures inside the body. In many cases, a contrast agent will be used to further enhance the images obtained during an MRI scan.
MR*-Enterography	A special type of MRI (Please see MRI* above) that is directed specifically at the small intestine. A contrast agent is used to further enhance the images obtained during the MR scan.
Octreotide (also called an OctreoScan or an SRS* scan)	Radiolabelled octreotide (a hormone that attaches to tumours) is injected into a vein. Its ability to attach to tumours enables a specialized camera to detect the location of tumours throughout the body. *See page 19 for more information*
PET* scan with radiolabelled glucose (FDG*)	A nuclear imaging test that uses radiolabelled glucose (FDG) as a tracer. When injected into a vein, this tracer binds to NET lesions that have increased metabolism, which can then be detected and precisely located by imaging with a PET camera about an hour later. This procedure can help to better characterize NETs in select patients.
PET scan with gallium 68 (Ga68) octreotide	Ga68 is a radioactive diagnostic agent for positron emission tomography (PET) imaging is now approved for use in Canada. Ga68 is a nuclear imaging test that uses radiolabelled octreotide (a hormone) as the tracer. When injected into a vein, the Ga68 tracer binds to NET lesions, which can then be detected and precisely located by imaging with a PET camera. The Ga68 tracer is sometimes called Ga68-DOTATATE or DOTATOC.
Ultrasound	Ultrasound imaging uses high-frequency sound waves to create images of organs and structures inside the body

Scopes	Description
Bronchoscopy	A test to view the airways and diagnose, or sometimes treat, lung disease. Tissue samples for biopsy may be obtained during bronchoscopy. A flexible device (a bronchoscope) is inserted through the nose or mouth, through the trachea (windpipe) and into the lungs.
Colonoscopy	A flexible tube (a colonoscope) is inserted into the rectum and a small camera at the end of the scope allows a view of the entire colon. Tissue samples for biopsy can be taken during a colonoscopy.
Endoscopic ultrasound (also called EUS*)	A narrow, flexible, lighted tube with a small ultrasound probe attached to the end is passed through the patient's mouth into the stomach and duodenum. The ultrasound component of the endoscope uses sound waves to create visual images of the pancreas and/or other organs. Usually performed under sedation.
Upper GI Endoscopy (also called EGD*)	*Please see Endoscopic ultrasound, above.*

Urine Tests	Description
5-HIAA* (24-hour urine)	In patients with small-intestine or other serotonin-producing NETS. Decreasing levels may indicate a response to treatment. Diet and medications significantly affect 5-HIAA levels. *Please see precautions listed in the footnote on page 17.‡*
Urinary fractionated metanephrines	Used to investigate a diagnosis of pheochromocytoma or paraganglioma
Urine catecholamine	Used to evaluate levels of norepinephrine, epinephrine, dopamine, and other substances that can indicate the presence of pheochromocytoma

Other Tests	Description
Biopsy	All or part of a tumour is removed during a surgical procedure and then a sample of the tumour (biopsy specimen) is examined by a pathologist. Biopsy procedures are used to determine if a tumour is benign or malignant and to further analyze the characteristics of the tumour. Fine needle aspiration and core samples are two types of biopsies. Core biopsies are usually preferred to permit grading of the tumour.
Calcitonin, fine-needle aspiration biopsy (FNAB)	Used to evaluate lymph nodes in individuals who have medullary thyroid carcinoma to determine if the cancer has spread to the lymph nodes
Electrolytes (fecal)	Sometimes called a fecal osmolality test, a stool sample is evaluated for levels of electrolytes such as sodium, potassium and magnesium, to help determine the cause of chronic diarrhea
KI-67 antigen	A test that is performed on a sample of tumour tissue to determine how quickly the tumour cells are dividing and increasing in number (proliferating). The result of this test is sometimes referred to as the *proliferation rate* and – when evaluated alongside many other factors – it may provide an insight into how quickly a disease is progressing. This test is critical to the grading of a NET.

* 5-HIAA = 5-hydroxyindoleacetic acid; ACTH = adrenocorticotropic hormone; CT = computed tomography; EGD = esophagogastroduodenoscopy; EUS = endoscopic ultrasound; FDG = fludeoxyglucose (18F); FSH = follicle-stimulating hormone; GI = gastrointestinal; GH-RH = growth hormone releasing hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; MIBG = iodine-123-meta-iodobenzylguanidine; MR = magnetic resonance; MRI = magnetic resonance imaging; PET = positron emission tomography; PPI = proton pump inhibitor; PTH = parathyroid hormone; SRS = somatostatin receptor scintigraphy; TSH = thyroid-stimulating hormone; VIP = vasoactive intestinal polypeptide.

† Prior to undergoing any tests or procedures in the U.S. or elsewhere, be sure to determine the total costs that may be incurred.

‡ Avoid eating avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts for 48 hours prior to the start of urine collection. Coffee, alcohol and smoking should also be avoided during this period. Drugs such as acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (in some cough syrups) and phenobarbital can also increase 5-HIAA levels.

Gallium 68 Scan (Ga68)

The Gallium 68 scan, used with functional PET imaging, is a nuclear medicine scan that relies on the overexpression of somatostatin receptors to visualize tumours. NETs typically express several somatostatin receptor subtypes in a unique pattern based on tumour type, origin and grade of differentiation.

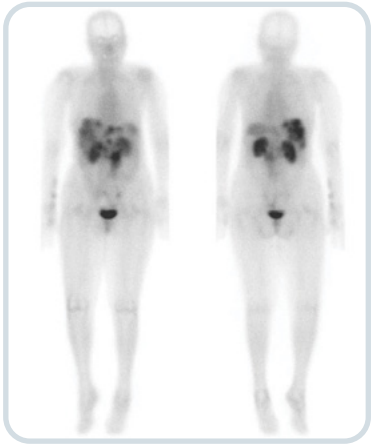
Ga68 scans offer advantages that include better detection of small lesions, higher image resolution, ability to make lesion measurements, better guidance for doctors when choosing treatment and dose, and exposure to less radiation. In addition, this scan offers a major advantage to patients because it can be completed in less than 2 hours compared to 2 days for other types of scans, such as Octreoscan or MIBG scan.

Tumours that may be visualized with a Ga68 scan include:
bronchial tumours, gastroenteropancreatic (GEP) tumours; pheochromocytoma, paraganglioma, neuroblastoma, medullary thyroid carcinoma and others.

Prior to receiving a Ga68 scan, ask your doctor whether or not you should discontinue somatostatin analog therapy. The radiopharmaceutical will be administered intravenously and the scan will be performed. The substances used to perform the Ga68 scan are rapidly cleared from the blood; therefore, no radioactivity is detectable in the blood or urine within four hours.

Clinical experience with Ga68 scans in NETs is rapidly expanding. This important diagnostic tool is now approved for use in Canada. Speak to your treatment team about access to this scan.

Octreotide Scan (also called an OctreoScan or somatostatin receptor scintigraphy)



Octreotide is a hormone-like substance that is used to both treat certain types of NETs and to diagnose or monitor them using scanning techniques. In an OctreoScan procedure, octreotide is bound to radioactive indium-111, which, when injected into the bloodstream, attaches to tumour cells that have receptors for somatostatin. Because many neuroendocrine tumours have somatostatin receptors on their surface, the octreotide is able to target these receptors, which then allows doctors to see images of the targeted neuroendocrine tumours and any metastases (areas of cancer spread) that might be present.

Patients being treated with somatostatin analogs (long- or short-acting octreotide or lanreotide) need to advise the imaging facility personnel before being scheduled for an octreotide scan. The timing of this scan may need to be determined according to the medication schedule.

Octreotide scans are also used for evaluating the next steps in treatment, such as determining if peptide receptor radionuclide therapy (PRRT) might be a reasonable treatment option.

For more information on the use of octreotide as a *treatment*, please see page 28 in the section on somatostatin analogs.

MIBG Scan (also called a metaiodobenzylguanidine scan)

The MIBG scan uses a substance (metaiodobenzylguanidine) that is attracted to neuroendocrine cells. When MIBG is bound to a radioactive material, usually a radioactive isotope of iodine-123, it can help identify certain types of tumours throughout the body. Similar to the OctreoScan, MIBG technology is used to treat, diagnose and monitor patients with NETs. Frequently, an MIBG scan is used to confirm the presence of pheochromocytoma, paraganglioma, or neuroblastoma tumours and is helpful in identifying patients who are not candidates for surgery but might benefit from targeted radionucleotide therapy instead.

Having an MIBG scan is a two-part process: first, the MIBG is injected and, after a period of 24 hours the scan is performed. This delay is necessary to allow the tumour adequate time to accumulate the MIBG, enabling it to be seen on an imaging screen.

After being injected into the bloodstream, approximately 40% to 85% of functioning malignant NETs will accumulate the MIBG. The ability of a tumour to "take up" the MIBG is referred to as being "MIBG-avid," and this ability varies widely depending on the type of the primary tumour. For example, if a primary tumour is located in the pancreas, metastatic tumours will rarely show up on an MIBG scan.

When an MIBG procedure is used to deliver treatment to a tumour, it is attached to a different type of radioactive isotope of iodine, commonly iodine-131. Treatment is often administered at three- to six-month intervals but protocols may differ between cancer treatment centres.

Protect Your Thyroid!

If you undergo an MIBG scan, you will be required to take a medication called **potassium iodide** beforehand to protect your thyroid gland. Potassium iodide prevents the thyroid from absorbing radioactive material. You will likely start taking the medication **one or two days prior to the MIBG injection** and **continue taking it for two to seven days**. Your healthcare team will be able to advise you on the most appropriate regimen for you.

Staging and Grading of Neuroendocrine Tumours

As part of your NET diagnosis, your doctors will have performed several tests to evaluate the characteristics of your tumour and learn how advanced it is. The "stage" of a tumour describes the extent of cancer throughout the body. It often includes information such as the size of the tumour and whether it has metastasized (spread).

The "grade" of a tumour is an assessment of the cancer cells that make up the tumour. By examining these cells under a microscope, a pathologist can determine how quickly the cells are growing and dividing, which can provide information on how likely the cancer is to spread.

Different staging and grading systems are used for different types of cancer. In the case of NETs, the classifications are based on where in the body the tumour is located, with many other factors taken into account. Owing to the complexity of NETs, the staging and grading systems are frequently re-evaluated by the best international experts in the field.

What does it mean if a tumour is "well-differentiated" or "poorly differentiated"?

When examined under a microscope, "well-differentiated" tumours have cells (and cell organization) that look closer to normal tissue. These tumours tend to grow and spread at a slower rate. On the other hand, "poorly differentiated" or "undifferentiated" tumours have abnormal-looking cells with abnormal tissue structures. Generally, undifferentiated tumours are associated with more aggressive behaviour. The pathologist uses this information on differentiation to assign a particular numerical grade to a tumour.

Prognosis

In a study of over 35,000 patients with NETs, it was shown that there is great variation in the expected time of survival following diagnosis. The main factors influencing expected outcome appear to be the type of tumour, its location in the body, and the stage and grade of the tumour. Other factors that play a role include age at diagnosis and sex. In this analysis, women had longer survival durations than men with similar disease characteristics.

Today, new surgical approaches, therapies and medications have significantly improved the course of disease for many patients, and new treatments are always on the horizon. Although there are no guarantees, your doctor may be able to give you some helpful information based on your test results.

Remember – *only* your healthcare team can advise you on your particular tumour status and expected outcome.

Treatment Options for Neuroendocrine Tumours

Many factors influence the type of treatment that doctors recommend for managing NETs, the most important of which is the specific type of tumour that is involved. Treatment plans are designed with several considerations in mind: stage of the disease, grade of the tumour and the type of hormones (if any) that are secreted by the tumour. Some common options for managing NETs are discussed below:

Generally, the goals of treatment are to: eliminate the tumour or reduce its size; control the effects of hormones produced by the tumour; manage complications and symptoms caused by the disease itself or hormone secretion.

Surgical Options	
Curative surgery	Complete removal of the tumour and surrounding tissue
Cytoreductive surgery	Involves the removal of a large portion of the tumour or cancerous cells to potentially increase the effectiveness of chemotherapy or radiation therapy that will follow. Cytoreductive procedures are also called debulking surgery.
Palliative surgery	Surgical procedures that are aimed at controlling symptoms caused by a tumour when maintaining quality of life is the primary goal

Ablative Techniques	
Radiofrequency ablation	During this procedure a special probe is introduced into the body through a small incision. The probe uses electrodes that emit energy to kill cancer cells.
Cryotherapy	This technique uses liquid nitrogen or liquid carbon dioxide to freeze abnormal cancer cells. The procedure may be performed during surgery or via laparoscopy, which involves only a very small incision through the skin.

Liver-directed Therapies (embolization techniques)	
Embolization techniques	A variety of therapies, all intended to achieve a similar end result, exist in this category. They include: • Bland embolization, • Chemoembolization, and • TheraSphere (Y90 radioembolization). Each type of embolization uses a specific technique to block or reduce the flow of blood through the hepatic artery to the liver. The hepatic artery is the main blood vessel that transports blood to the liver, so blocking it prevents the cancer cells from getting nutrients that they require to grow. These techniques are also used to deliver chemotherapy or radiation directly to the tumour site, and are often preferred for patients with liver metastases who are not candidates for liver surgery. **Administration** Hepatic arterial embolization involves injection into the hepatic artery. In this procedure, a thin and flexible tube called a catheter is put into an artery through a small cut in the inner thigh. A dye is usually injected into the bloodstream at this time to help the doctor monitor the path of the catheter.

Chemotherapy

A treatment that uses powerful chemicals to damage fast growing cancer cells so they stop growing and multiplying. The aims of this treatment are to:

- Kill as many cancer cells as possible without substantially affecting healthy cells
- Increase the chances of killing cancer cells
- Lower the chances that cancer cells will become resistant to certain drugs

As with other NET treatments, the success of chemotherapy depends greatly on the type of tumour and its characteristics. Chemotherapy has proven beneficial for some patients with pancreatic NETs, whereas treatment response has been limited in other patients with NETs.

Drugs

Poorly differentiated NETs are usually treated with chemotherapy medications that can be used alone or in combination. These drugs include:

- Capecitabine
- Cisplatin
- Platinum-based drugs*
- Streptozocin
- Temozolomide

Capecitabine and temozolomide are often used in combination, known as the CAPTEM regimen, which is a promising treatment option for metastatic NET patients.

* Most commonly used combination regimes that include platinum-based drugs are: carboplatin + etoposide, carboplatin + paclitaxel, and cisplatin + etoposide

Administration

The route of administration (taken by mouth or injected into the bloodstream or spinal fluid) will depend on the type of cancer being treated.

Only your healthcare team can advise you whether chemotherapy might be a suitable option for you.

- **Cycles** Chemotherapy is usually given at regular intervals called cycles. Each cycle is commonly followed by a rest period that can last several days or weeks. The rest period allows normal cells to recover.
- **Schedule** The length, timing, and number of cycles depend on the drugs used and the type of cancer. The schedule is usually set by your doctor at the start of treatment and may change according to the response. Treatment time can range from 3 to 12 months.

Radiation Therapy	
External Beam Radiation	A machine outside the body directs radiation, in a focused beam, toward the tumour or cancer cells
Brachytherapy	A radioactive substance is contained in a seed, wire, needle or catheter that is then implanted in the body, directly inside the tumour or as close to it as possible
Radionuclide Therapy	A nuclear medicine technique using radioactive substances that bind to tumours when injected into a patient, delivering radiation directly to the tumour. • The most common form of this treatment is called peptide receptor radionuclide therapy (PRRT), which uses a radiolabelled somatostatin analog that specifically binds to NETs. • Radiolabelled MIBG is also occasionally used to treat some types of NETs.
PRRT (Peptide receptor radionuclide therapy)	**Principle** Similar in principle to other radionucleotide therapies, PRRT uses a radioactive material that binds to certain receptors on neuroendocrine tumour cells. Several radioactive substances may be used, including Indium-111, Lutetium-177, and Yttrium-90, to label a somatostatin analog such as octreotide or octreotate. These substances are combined with a bonding molecule such as DOTA and are referred to as DOTATATE or DOTATOC. **Prior to Therapy** Prior to being considered suitable candidates for PRRT, patients must be evaluated via OctreoScan or Gallium-68 PET scan to ensure that octreotate can bind effectively to cell receptors and deliver highly targeted radiation to the NETs. The higher the density of receptors, the greater the uptake of radioactivity into the tumour, which typically results in a better treatment outcome.

PRRT (Peptide receptor radionuclide therapy)	**Use** Primarily, PRRT has been successfully used in patients with gastroenteropancreatic (GEP) tumours with metastases, including functioning and non-functioning endocrine tumours of the pancreas. However, it has also been used in patients with pheochromocytoma, paraganglioma, neuroblastoma, medullary thyroid carcinoma, pulmonary (as part of a clinical trial), and bronchial NETs. Suitable candidates for PRRT usually have progressive well-differentiated or moderately differentiated NETs. LUTATHERA® lutetium (177Lu) oxodotreotide is the first and only therapeutic radiopharmaceutical indicated for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETS) in Canada. **Administration** The PRRT treatment process involves intravenous administration of amino acids, which have the ability to protect the kidneys from the effects of radiation. Following the amino acids, 177Lu octreotate is administered intravenously. Later, a scan will be performed to validate that the radioactive substances have bound to the NETs, as expected. Ask your doctor about potential effects on fertility and contraceptive precautions that must be taken. Pregnancy should be avoided for at least six months after treatment.

Before receiving PRRT, patients may be required to adjust somatostatin analog therapy as it can interfere with effective receptor targeting. Be sure to ask your doctor if it will be necessary for you to discontinue therapy before undergoing PRRT. Each time you meet with your healthcare team, remember to bring a complete list of all your medications, including somatostatin analogs, and your medication treatment schedule(s).

Biologically Targeted Therapies (everolimus, sunitinib)

Targeted therapies work by focusing on specific cancer genes, proteins, or other substances that are necessary for particular cancer cells to grow and divide. The aim of all targeted therapies is to attack the cancer cells, while limiting damage to normal cells. Some of these medications block (inhibit) the biological signals that cancer cells receive – signals that tell them to multiply at an uncontrolled rate and form tumours.

For select patients with pancreatic neuroendocrine tumours, medications from the mTOR inhibitor (everolimus) and tyrosine kinase inhibitor (sunitinib) drug classes have shown promising anti-tumour activity. Everolimus has also proven to be an effective treatment for select patients with neuroendocrine tumours that originated in the lung or gastrointestinal tract.

Administration

The route of administration of biologically targeted therapies is by mouth, taken once daily.

Somatostatin Analogs (lanreotide, octreotide)

To date, in appropriate patients, somatostatin analogs are the only proven therapy for the management of hormonal symptoms resulting from NETs. In addition, clinical evidence has led to the approval of somatostatin analog treatment to help stabilize disease in patients with NETs. Clinical trials with somatostatin analogs have shown that they have antiproliferative properties which can stop the growth of cancer cells, confirming their benefit for patients with well-differentiated advanced disease.

Administration of Lanreotide

The route of administration of the lanreotide gel long acting formulation is via deep subcutaneous (under the skin) injection.

Administration of Octreotide

The route of administration is usually via one of three different routes: subcutaneous (just under the skin) injection; continuous subcutaneous infusion delivered with the use of a pump; and a long-acting, slow release formulation delivered intramuscularly. Each option has advantages and disadvantages, which your doctor can discuss with you. Since the immediate-release form of octreotide remains active in the body for only a very short time, long-acting release formulations have been developed to allow some patients to receive an intramuscular injection only once per month.

Somatostatin Analogs (lanreotide, octreotide) con't.

Long acting release formulations of somatostatin analogs are now considered the "standard of care". Treatment is always modified to meet the patient's specific needs, based on the recurrence of symptoms (if any) and the results of hormone level testing.

Short-acting somatostatin analogs play an important role in patient care. When administered intravenously, they may be used for the prevention and management of carcinoid crisis – a potentially life-threatening disorder that causes patients to experience extreme flushing, dangerous fluctuations in blood pressure, respiratory spasms, rapid heart rate and mental confusion. **Carcinoid crisis** can be triggered by anesthetics used during surgery, chemotherapy, or any invasive procedures that may stimulate the tumour.

Interferon Alpha Therapy

This medication is sometimes used in cases where octreotide alone has failed to provide an adequate treatment response.

Telotristat Etiprate Therapy

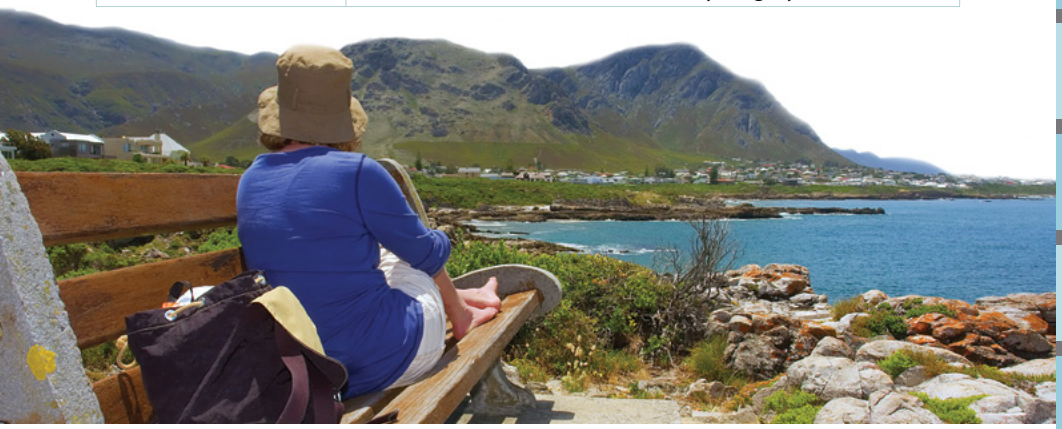
Telotristat ethyl is used for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone.

This medication is designed to reduce the production of serotonin which can be measured by u5-HIAA.

Administration

The route of administration of telotristat ethyl is by mouth, taken three times daily with food.

Symptom Management	
Ascites A buildup of fluid in the abdomen causing bloating and discomfort	**Diuretics** This class of oral medications may be used to help the body get rid of extra fluids
Blood Glucose/ Blood Pressure	**Alpha-adrenergic blockers and beta blockers** These two classes of medications are generally used to regulate blood pressure and heart rate. They are commonly taken orally or by intravenous injection. • *Alpha-blockers* are often used to manage potentially life-threatening blood pressure fluctuations in patients undergoing surgical or invasive procedures. • *Beta-blockers* may be used to control a fast or irregular heart rate. Depending on the type of NET a patient has, alpha- and/or beta-blocking medications may be prescribed as long-term treatment. **Diazoxide** A blood pressure oral medication that also inhibits insulin secretion and can therefore be beneficial for maintaining blood glucose balance in patients with insulinomas. It may be used as a short-term therapy in patients scheduled for surgery and as a long-term therapy in those who have tumours that cannot be removed by surgery.



Cushing Syndrome	**Adrenostatic agents** (ketoconazole, mitotane) This class of oral medications is used in the treatment of adrenocortical carcinoma. These drugs work by suppressing the adrenal cortex and reducing levels of cortisol in the body. Ketoconazole is used to control excessive levels of steroid hormones secreted by benign or malignant adrenal tumours and in patients with specific types of Cushing syndrome.
Diarrhea	**Cholestyramine** An oral medication that is used for the treatment of bile acid-induced diarrhea. It may be particularly relevant for patients who have NETs that cause abnormal absorption of bile salts in the intestine. **Diphenoxylate/atropine, Loperamide** These are oral medications that are used in the treatment of diarrhea. They may be used in combination with other therapies such as fluid and electrolyte therapy, which are important in preventing patients from becoming dehydrated due to diarrhea. **Pancreatic enzyme replacement** Pancreatic enzymes are oral medications that are used to help the body break down foods. They are often used for patients who experience reduced fat absorption as a result of the disease or the treatment. Different mixtures may be used to improve food digestion and absorption of nutrients.
Lack of Appetite/ Weight Loss	**Dexamethasone** An oral medication that may be used to stimulate appetite in patients. This medication is generally given in low amounts as short-term therapy.
Pain	**Narcotics** This class of medications, also called opioids, is used to help control moderate to severe pain. They may be taken orally or by intravenous injection, alone or in combination with other medications to relieve pain.

Nausea and Vomiting	**Antinauseants** Antinauseants are a class of medications used to prevent or control nausea and vomiting. They are most often taken orally, by rectal suppository, by intravenous injection, or by intramuscular injection. These medications are generally used in combination with other drugs and may be given before the treatment starts. **Prokinetic agents** (domperidone, metoclopramide) This class of medications is generally used to relieve stomach and intestine symptoms. They help the stomach empty more rapidly.
Stomach Acid	**Proton pump inhibitors (PPIs)** (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) PPIs work by limiting the amount of stomach acid that can enter the stomach, thereby decreasing the overall amount of gastrin. These medications can be taken orally or by intravenous injection. Patients with a gastrinoma should be advised that it is dangerous to stop PPIs without medical supervision. Furthermore, it must be noted that gastrin levels and chromogranin A levels will be falsely elevated in patients taking PPIs. Ask your doctor if you should discontinue PPI therapy before any tests and, if so, when you should stop taking this medication.
Your doctor may refer you for additional supportive care to help with physical, practical, emotional, and spiritual challenges	

Alternative Therapies

The use of alternative therapies for the treatment and management of NETs is controversial among many healthcare professionals and patients alike. If you decide to explore alternative therapies, be sure to discuss it with your treating physician and other members of your healthcare team. This is important because it's possible that natural or herbal therapies could affect other treatments you might be receiving (drug interactions). In addition to this concern, it's in your best interest to examine the scientific evidence behind any therapy you might consider, as well as the qualifications of those who support its use.

Enrolling in a Clinical Trial – An Important Option

Clinical trials are scientific studies that are conducted to develop new medications or other important therapies. The purpose of a clinical trial is twofold: to evaluate the effectiveness of a new treatment, and to assess its safety. All new medications available in Canada and the U.S. (and most other countries) start out in clinical trials. If the treatment is found to be safe and effective, then it can become a treatment option for a particular disease and made available to patients.

Clinical trials are designed in steps called phases. Each phase evaluates a different aspect of the drug, for example: efficacy, dosing, safety, or ideal duration of treatment. If you look for clinical trials, you will often see them identified as "phase I, II or III studies."

Many patients choose to participate in a clinical trial because it may allow them to try a medication that would not otherwise be available. Clinical trials also enable researchers to develop a better understanding of the disease, thereby helping other patients — both present and future. Rest assured that the medical researchers who conduct clinical trials are required to follow a strict code of ethics that is designed to protect the health, safety and privacy of all participants.

Visit the Following Websites for Additional Information:

Canadian Cancer Trials

www.canadiancancertrials.ca

(Clinical trials in all Canadian provinces)

U.S. National Institutes of Health

www.clinicaltrials.gov

(Clinical trials in Canada, U.S. and around the world)

National Cancer Institute

www.cancer.gov/clinicaltrials/search

(Clinical trials in Canada, U.S. and around the world)

The Canadian Cancer Society provides information about specific clinical trials

Call the toll-free Cancer Information Service at 1-888-939-3333.

For certain patients, enrolment in a well-designed clinical trial may be considered a good option. Clinical trials may give people with cancer access to the newest types of treatment.

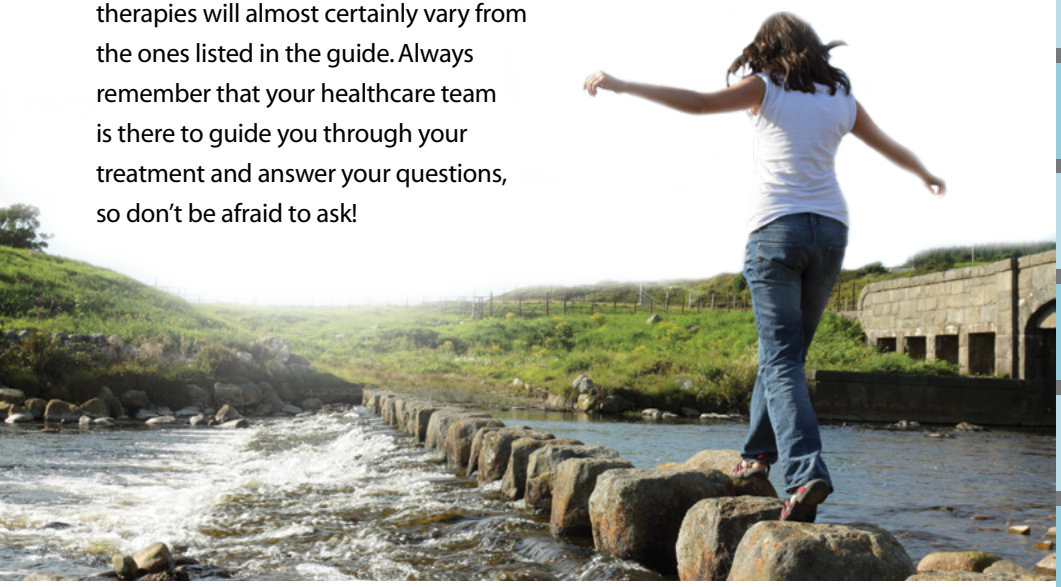
Your Navigation Guide

What To Expect And When

Almost everyone fears the unknown. Whether you're four years old and going to school for the first time, interviewing for an important new job or facing a health crisis, moving into uncharted territory likely gives you cause for concern.

The Navigation Guide was developed to help reduce some of your concerns. As you come to terms with your NET diagnosis, knowing what to expect every step of the way can help ease some of the uncertainty you may feel.

The guide may help you maintain a sense of control from the time of diagnosis all the way through the long-term treatment period. Bear in mind that your experiences will differ from those of other patients with NETs due to the broad scope of the disease. Similarly, your tests and therapies will almost certainly vary from the ones listed in the guide. Always remember that your healthcare team is there to guide you through your treatment and answer your questions, so don't be afraid to ask!



Navigation Guide

1 Diagnostic Tests

The range of tests your doctors order will vary depending on the type of NET you have or are suspected of having. Please refer to the section entitled *Tests That Your Doctors May Perform* on pages 12–17 for a brief description of the many tests used in the diagnosis and management of NETs. After diagnosis, it's important to follow your doctors' recommendations for regular follow-up testing as this will allow your disease to be carefully monitored.

2 Diagnosis and Staging

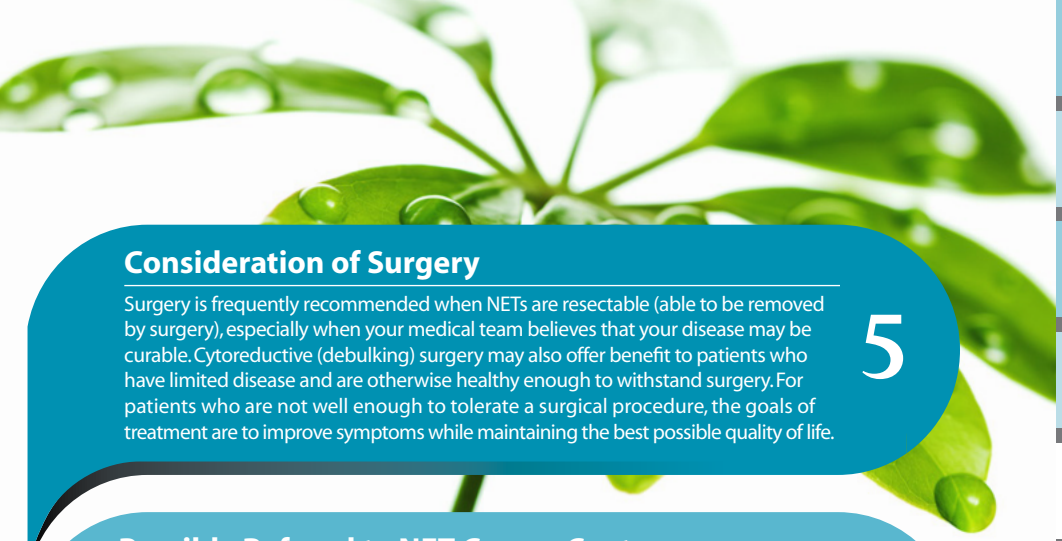
For many patients with NETs, obtaining a diagnosis is a long and often frustrating process since symptoms may be non-specific, especially initially. Once you have obtained a diagnosis, all efforts can be focused on finding the best possible treatment. Staging of your disease is an important next step, since treatment approaches will vary based on the exact type of NET you have and whether it has metastasized (spread) throughout your body.

3 Pathology

Pathology is the examination of tissues and cells (often from a tumour) under a microscope to diagnose disease and learn the characteristics and features of a particular tumour. Nowadays, as more is being learned about the role that genetic factors and cellular characteristics play in cancer (and other diseases), pathology analyses are more important than ever. A better understanding of a tumour's "genetic blueprint" and unique features may provide valuable insights into its likely response to a particular therapy.

4 Referral and Treatment

Once your NET has been evaluated and its functional status revealed, you will be referred to a physician who is a specialist in managing your particular type of NET. He or she will discuss the frequency and severity of your symptoms, the stage and grade of the tumour, and examine you for evidence of complications that can accompany certain types of NETs. Next, you and your doctor can begin to formulate an individualized treatment plan.



Consideration of Surgery

Surgery is frequently recommended when NETs are resectable (able to be removed by surgery), especially when your medical team believes that your disease may be curable. Cytoreductive (debulking) surgery may also offer benefit to patients who have limited disease and are otherwise healthy enough to withstand surgery. For patients who are not well enough to tolerate a surgical procedure, the goals of treatment are to improve symptoms while maintaining the best possible quality of life.

5

Possible Referral to NET Cancer Centre

Given the specialized nature and complexity of neuroendocrine cancers, very few small or local hospitals will have the expertise necessary to optimally manage NETs. It is widely accepted that the involvement of an expert multidisciplinary team represents the ideal scenario for the diagnosis, treatment and ongoing evaluation of a NET patient. Highly specialized NET cancer centre experts will be able to offer you guidance on the best course of treatment and provide support resources for you and your family.

6

Before You Start Treatment

Regardless of the type of NET you have or your expected prognosis, make sure you fully understand all of your treatment options, including possible enrolment in a clinical trial. Be sure to ask your doctor any questions that you may have about your disease and its management. Your healthcare team can help you understand what to expect during treatment, including potential side effects of therapy.

7

Follow-up Care

Your multidisciplinary team will regularly evaluate levels of hormones, peptides, amines and a range of other substances secreted by certain types of NETs. These results will enable doctors to determine how well a treatment is working and, in some cases, can indicate disease recurrence or the development of metastases. In addition, your NETs will be monitored with the use of anatomic and molecular imaging tools such as CT scans, angiography, MRI, MIBG scans, PET scans and others.

8

Getting to Know Your Healthcare Team

A Multidisciplinary Team is Essential for Managing NETs

Family Physician or General Practitioner – A medical doctor whose practice is not limited to a particular specialty.

Endocrinologist – A doctor who specializes in the diagnosis and treatment of disorders of the endocrine system (the glands and organs that produce hormones).

Medical Oncologist – A doctor who specializes in diagnosing cancer and treating the disease by using chemotherapy, hormonal therapy and/or biological therapy. This physician is often the main healthcare provider for patients who have been diagnosed with a NET. Medical oncologists also provide supportive care and may coordinate treatment given by other specialists.

Surgical Oncologist – A surgeon who specializes in treating cancer by performing surgical procedures (e.g., removing tumours, growths or malignant cells).

Radiation Oncologist – A doctor who specializes in using radiation therapy to treat cancer.

Nuclear Medicine Physician – A doctor who uses radionuclides to diagnose and treat patients.

Interventional Radiologist – A doctor who uses minimally invasive, guided-imaging procedures to diagnose and treat patients.

Nurses (Oncology, Primary, etc.) – Healthcare professionals, some of whom specialize in cancer care, who are trained to care for people with illnesses or disabilities.

Cardiologist – A doctor who deals with the structure, function and disorders of the heart.

Gastroenterologist – A doctor who specializes in diagnosing and treating disorders of the digestive system.

Psychologist – A specialist who can counsel patients and their families about emotional and personal matters, and can assist them in making important decisions.

Occupational Therapist – A healthcare professional who is trained to help people with cancer or other illnesses learn to better manage activities involved in daily living.

Radiation Therapist – A healthcare professional who administers radiation treatment in the hospital or clinic.

Pharmacist – A healthcare professional who is trained in the science of preparing and dispensing drugs.

Dietitian – An expert in food and nutrition who helps patients achieve their health-related goals.

Pain Specialist – A healthcare professional who is an expert in devising pain management strategies.

Patient Navigator – A person who helps patients liaise with healthcare clinics, administrative systems and support services related to patient care.

Palliative Care Specialists – A team that provides care to improve the quality of life of patients who have a serious or life-threatening disease.

Only you can decide how involved you want to be in managing your disease.

Some patients prefer to take a hands-on, proactive role, while others are comfortable relying on their medical team to guide their healthcare decisions. Many patients feel that learning as much as they can about NETs, tracking their test results and joining a support group gives them a sense of empowerment over their illness. There is no "right" or "wrong" approach, as long as you fully understand and follow your doctor's directions on important diagnostic and treatment choices.

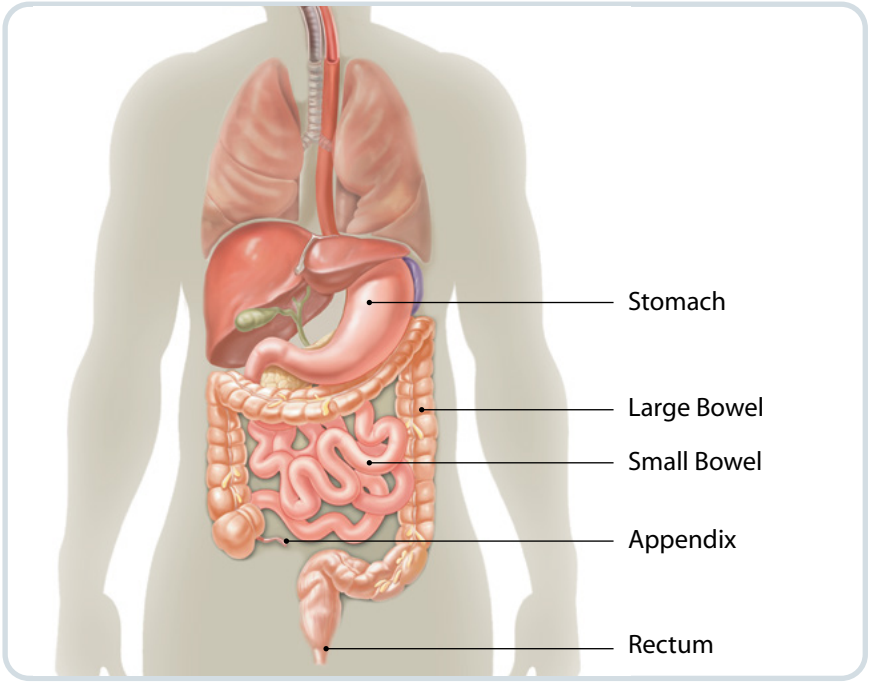
As you face the challenges of managing your illness, you may find comfort in knowing that you are not alone. In fact, you will be supported every step of the way by a group of medical professionals, each of whom is dedicated to keeping you as healthy as possible. Although everyone's medical needs are different, the team of healthcare professionals listed in this booklet is typical for many people being treated for NETs.

Discuss with your oncologist the personal healthcare team that he or she is considering for you. If you feel confident and comfortable with your team, it will make it easier for you to ask any questions that may arise.

Many patients also seek the help of a family counsellor, social worker, member of the clergy, dietitian, registered massage therapist, licensed acupuncturist or a NET patient group, for additional support.

Neuroendocrine Tumours of the Gastrointestinal Tract

Sites Where Gastrointestinal (GI) Neuroendocrine Tumours Can Occur



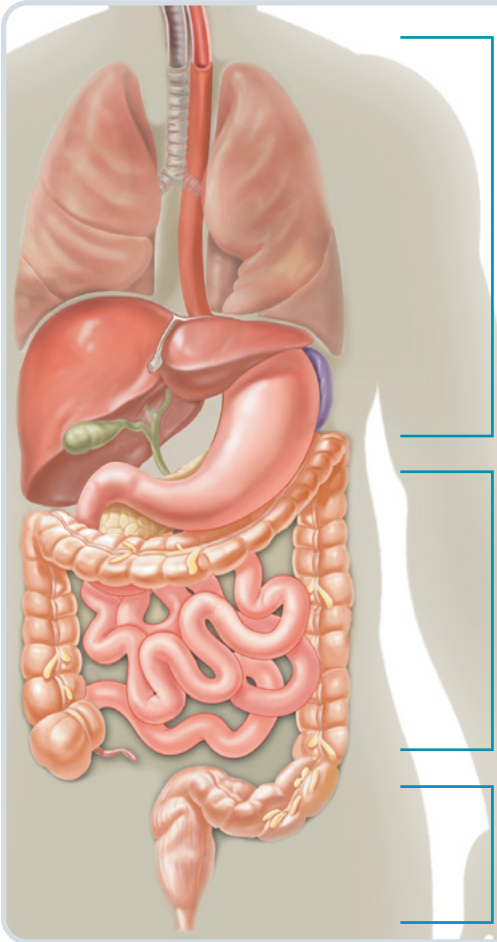
Gastrointestinal NETs are the *most prevalent* group of NETs, and include:

• Gastrinoma • Neurotensinoma • Serotonin-producing NETs (carcinoids)

Symptoms of these NET subtypes are discussed on page 43.

NETs are usually classified by the site in the body where they originated, the tumour cell's characteristics under a microscope and the type of hormone the tumour secretes.

A Word About Gastrointestinal Tumour Location



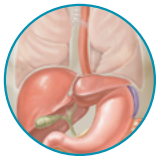
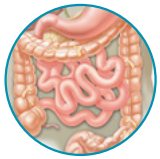
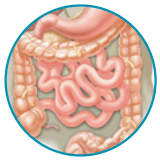
Foregut
- Thymus
- Bronchus
- Esophagus
- Lung
- Stomach
- Proximal duodenum
- Pancreas*
- Hepatobiliary (liver, gallbladder, bile ducts)*

Midgut
- Jejunum (middle section of the small intestine)
- Ileum (third section of the small intestine)
- Appendix
- Ascending colon

Hindgut
- Transverse colon
- Descending colon
- Rectum

*The pancreas, liver and gallbladder are not considered to be part of the gastrointestinal tract but are classified as *accessory organs of digestion*. However, gastrointestinal and pancreatic neuroendocrine NETs are often referred to together and are called *gastroenteropancreatic* or GEP NETs.

In pathology and medicine today, there is a gradual shift away from the traditional system of classifying NETs by where they occur in the gut and away from using the term "carcinoid" to describe a NET. A new approach categorizes NETs by the characteristics that certain groups of cells share, such as how they divide, multiply, and respond to the body's chemical and hormonal signals.

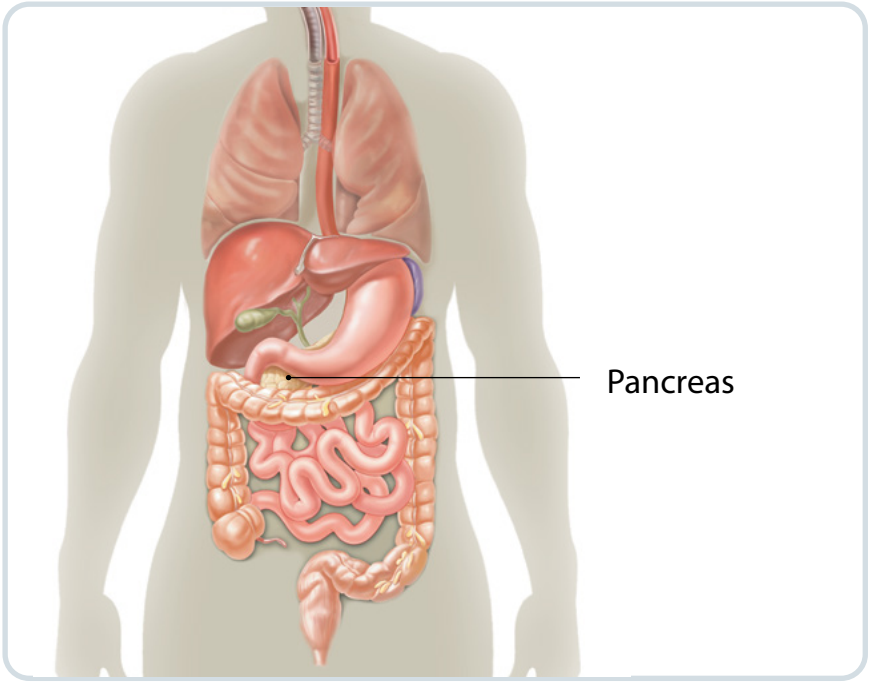
Common Sites	Tumour Type	Associated Symptoms
 Foregut & duodenum	**Gastrinoma**†	(Zollinger-Ellison syndrome) Symptoms are related to increased levels of gastrin (stomach acid): peptic ulcers, stomach pain or bleeding, severe heartburn, vomiting, weight loss, severe diarrhea and fatty stool, low red blood cell count. See important warning below (†) about proton pump inhibitor therapy
 Midgut	**Neurotensinoma**	The effects of elevated levels of the peptide neurotensin in patients with NETs are poorly understood. Symptoms such as severe watery diarrhea, diabetes, low levels of potassium in the blood, low levels of stomach acid and weight loss make it virtually indistinguishable from the VIPoma syndrome. Other symptoms may include swelling, low blood pressure and flushing.
	Serotonin-producing NETs (carcinoids)	Symptoms are typical of the **carcinoid syndrome** – facial flushing, diarrhea, intermittent abdominal pain, asthma, heart palpitations or right-sided heart failure. Some patients may also experience watering eyes and increased nasal secretions.
 Midgut & appendix	**Goblet cell**‡	Since goblet cell NETs occur almost exclusively in the appendix, the typical presentation is acute appendicitis, with symptoms such as abdominal pain and swelling, loss of appetite, nausea and vomiting, constipation or diarrhea, and/or fever. Other, less common signs can include bowel obstruction, GI bleeding, inflamed lymph nodes in the abdomen or iron deficiency anemia.‡

† If you are being evaluated for a suspected gastrinoma, it is essential that you do not take proton pump inhibitor (PPIs) medications at the same time. PPIs will cause gastrin and chromogranin A levels to be falsely elevated and, therefore, many doctors recommend that PPI therapy be discontinued prior to testing. Before undergoing any tests, ask your doctor for explicit instructions on when to stop taking this medication.

‡ The classification of Goblet Cell Carcinoma (GCC) as a NET is controversial, due to the fact that this type of tumour shares cellular features of both a NET and an adenocarcinoma. It is recommended that GCC tumours be meticulously examined by a pathologist to determine the best course of treatment and prognosis.

Neuroendocrine Tumours of the Pancreas

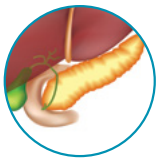
Sites Where Pancreatic Neuroendocrine Tumours Can Occur

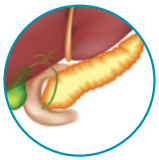


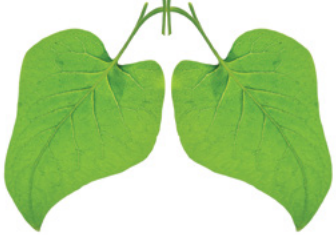
Pancreatic NETs include:

- Insulinoma
- VIPoma
- Glucagonoma
- Somatostatinoma
- ACTHoma
- PPoma

Symptoms of these NET subtypes are discussed on pages 45–46.

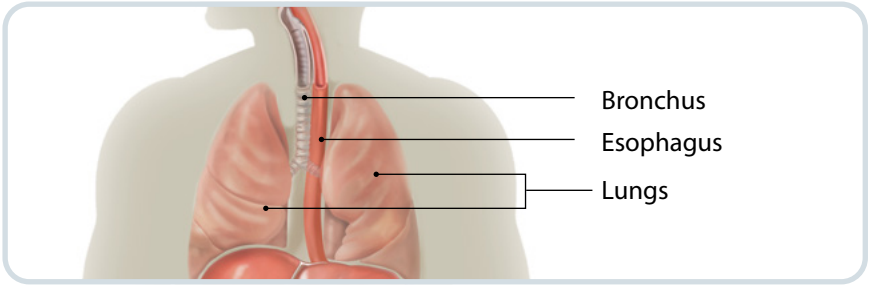
Common Sites	Tumour Type	Associated Symptoms
 Pancreas	**ACTHoma (adreno-corticotropic hormone–secreting tumour)**	Symptoms are typically those seen in Cushing syndrome that result from high levels of cortisol: weight gain, a full, rounded face, muscle weakness, high blood pressure, mood changes, excessive hair growth, abdominal obesity, purple-coloured lines on the skin, an unusual build-up of fatty tissue between the shoulder blades or just above the collarbone, high levels of glucose or low levels of potassium in the blood.
	CCKoma (cholecystokini-noma)	Symptoms may include non-watery diarrhea, severe weight loss, gallbladder disease and the presence of peptic ulcers *without* the high gastrin levels usually associated with peptic ulcer disease.
	Glucagonoma	Symptoms are related to *high* blood sugar: diabetes mellitus, mouth sores, blood clots in the leg or lung, diarrhea, depression, extreme fatigue or a skin condition called necrolytic migratory erythema that may appear as a red, swollen, painful or itchy rash – most commonly on the buttocks, legs and groin.
	Insulinoma	Symptoms are related to *low* blood sugar: confusion, irritability, sweating, dizziness, weakness, rapid heartbeat, periods of unconsciousness. Some symptoms may improve upon eating. Other symptoms may be related to an excess of catecholamines – substances such as epinephrine, norepinephrine and dopamine which elicit a "fight or flight" response, such as rapid heartbeat and increased blood pressure.

Common Sites	Tumour Type	Associated Symptoms
 Pancreas	**PPoma (pancreatic polypeptidoma)**	Symptoms may not be evident in the early stages of disease but when they occur, will often include abdominal pain and occasional watery diarrhea. Examination may reveal an enlarged liver or metastases (spread of cancer) in the liver.
	PTHrPs (parathyroid hormone-related protein-secreting tumours)	Symptoms generally present as bone abnormalities, similar to those seen in patients with high levels of parathyroid hormone. Other symptoms may include kidney stones, peptic ulcer, and neurological or psychiatric disturbances.
	Somatostatinoma	Symptoms are related to an increased level of the hormone *somatostatin*: diabetes mellitus, gallstones, weight loss, diarrhea and fatty stool, abdominal pain, nausea and vomiting, appetite loss and low levels of stomach acid.
	VIPoma (vasoactive intestinal peptide)	Symptoms are related to an increased level of the hormone *vasoactive intestinal peptide*, which increases intestinal activity: severe watery diarrhea, very low levels of potassium in the blood, low levels of stomach acid, muscle weakness and cramping, lethargy, flushing, heart rhythm disturbances, abdominal pain and dehydration. Other symptoms may include high levels of glucose or calcium in the blood.



Neuroendocrine Tumours of the Lungs

Sites Where Lung Neuroendocrine Tumours Can Occur



Lung NETs are the *second most prevalent* group of NETs, and include:

- Typical and atypical NETs
- Small cell carcinoma
- Large cell neuroendocrine carcinoma

Symptoms of these NET subtypes are discussed on page 48.

- "*Typical*" lung NETs rarely spread beyond the lungs as they generally grow more slowly. Nine out of 10 lung NETs fall into this category.
- "*Atypical*" lung NETs are much less common but are generally more aggressive in their growth rate and tendency to spread.

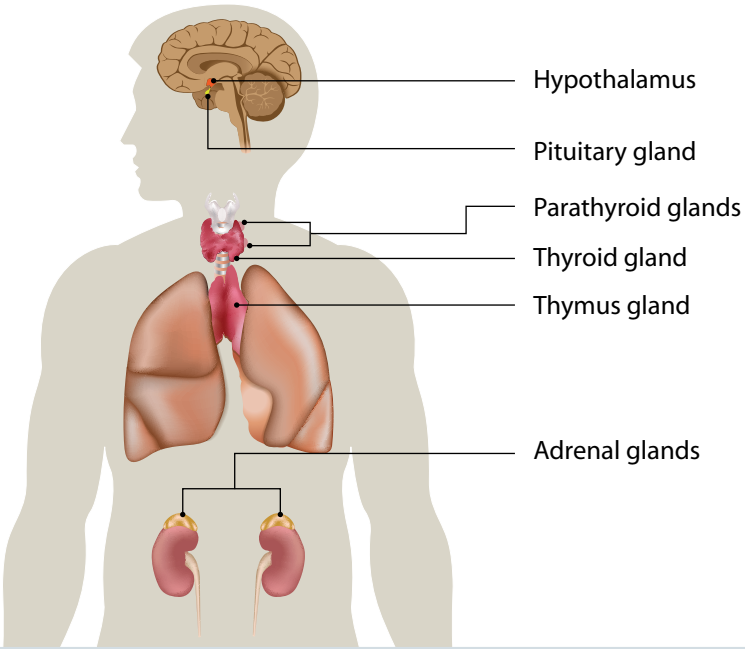
Typical vs. Atypical NETs. What's the difference?		
	Typical NET	**Atypical NET**
Patient has high levels of serotonin in the blood	✔	✗
Patient has high levels of chromogranin-A in the blood	✔	✗
Patient has high levels of 5-HIAA in the urine	✔	✗
Tumour can produce 5-HTP	✗	✔

Adapted from American Society of Clinical Oncology, 2012.

Common Sites	Tumour Type	Associated Symptoms
 Lungs & Pancreas	**GRFoma (growth-hormone releasing factor)**	Primary symptoms include the rapid and abnormal growth of bones and cartilage, a disorder known as *acromegaly*. Patients may experience excessive growth in the bones of the hands, feet, head and face. GRFomas are often associated with gastrinoma or certain genetic syndromes.
 Lung	**Large cell neuroendocrine carcinoma (LCNEC)**	Symptoms for LCNEC are typically the same as those for small cell lung cancer (SCLC) and it has a similar prognosis, but LCNEC is less common. Confusingly, LCNEC is considered to be a type of non-small cell lung cancer (NSCLC) and is treated accordingly.
	Small cell lung carcinoma (SCLC)	Cough, blood in the sputum, chest pain, hoarseness, weight loss, shortness of breath, recurrent bronchitis or pneumonia, wheezing, tiredness or weakness. Symptoms such as bone pain, jaundice, lumps in the neck area, headache, numbness, balance problems or seizures may indicate the cancer has metastasized (spread) to other organs throughout the body.
	Typical and atypical lung NETs	Symptoms may differ depending on tumour location and tumour size: **Centrally located** tumours may cause a cough, blood in the sputum, wheezing, shortness of breath, pneumonia or chest pain. **Peripherally located** tumours rarely cause symptoms.

Neuroendocrine Tumours of the Endocrine Sytstem

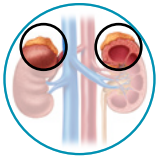
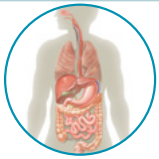
Sites Where Endocrine System Tumours Can Occur

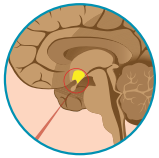
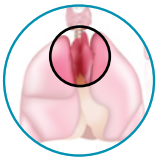


Endocrine System NETs include:

- Adrenocortical carcinoma
- Pituitary adenoma
- Thyroid medullary carcinoma
- Parathyroid neuroendocrine cancer
- Thymus neuroendocrine cancer
- Neuroblastoma
- Pheochromocytoma or paraganglioma

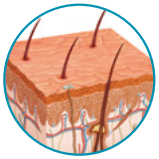
Symptoms of these NET subtypes are discussed on pages 50–51.

Common Sites	Tumour Type	Associated Symptoms
 Adrenal glands	**ACCs (adrenocortical carcinomas)***	Symptoms may be evident depending whether the tumour is functioning or non-functioning. Either type of tumour may cause a lump or a feeling of fullness in the abdomen as well pain in either the abdomen or back. Functioning tumours may cause symptoms related to the release of cortisol, aldosterone, testosterone or estrogen: weight gain, changes in hair growth, high blood pressure, excessive thirst and urination or menstrual irregularities in women. Patients with certain genetic syndromes are at an increased risk of developing ACCs.
	Neuroblastoma*	Neuroblastoma is a NET that often appears in early childhood, with symptoms that may include a lump in the neck, chest or abdomen, bulging eyes, bone pain, and weakness or paralysis. In infants, painless blue-coloured lumps can sometimes be seen under the skin, and a distended stomach and breathing difficulties may also be present. Less common symptoms include fever, easy bruising or bleeding, high blood pressure, severe diarrhea, uncontrolled muscle or eye movements, or swelling throughout the body.
	Pheochromo-cytoma (arises from chromaffin cells of the adrenal medulla)*	Symptoms include high blood pressure that does not respond to medication, headache, sweating, rapid or irregular heart rate, feeling shaky or extreme paleness.
 Head, neck, abdomen & pelvis	**Paraganglioma** (arises from sympathetic ganglia cells outside the adrenal glands and is often called extra-adrenal paraganglioma)*	General symptoms may include high blood pressure, headache, rapid heart rate, sweating or flushing, an enlarged mass in the neck, dizziness, ringing in the ears or vision problems. However, symptoms will vary widely depending on the location of the tumour, since only certain tumours secrete substances that give rise to symptoms.

Common Sites	Tumour Type	Associated Symptoms
 Pituitary gland	**Pituitary tumours** (general)	Symptoms will vary depending on the type of hormone or other substance that is secreted by the tumour cells (somatostatin, ACTH, thyroid, etc.). Additional, rare symptoms may include vision problems, or abnormal movement of the eye or eyelid, accumulation of cerebrospinal fluid around the brain or leakage via the nose.
 Thymus gland	**Thymus neuroendocrine cancer**	Symptoms may not be evident in the early stages of disease. However, as the tumour increases in size patients may experience cough, chest pain and symptoms related to compression of the superior vena cava, a large vein that leads into the heart. These symptoms might include facial swelling, headaches, visible veins in the face, neck or chest, or dizziness. In addition, thymic NETs are often associated with endocrine disorders that release hormones, which in turn, can cause other symptoms.
 Thyroid gland	**Parathyroid neuroendocrine cancer**	Symptoms are generally related to increased levels of parathyroid hormone (PTH), resulting in a condition called hyperparathyroidism. Patients may experience vocal cord paralysis and a lump in the neck may be present. Other signs include high levels of PTH and calcium in the blood, along with kidney or bone disease that can result from elevated PTH.
	Thyroid medullary carcinoma*	Symptoms may not be evident in the early stages of disease. At later stages, patients may experience difficulty breathing or swallowing, hoarseness and a lump in the neck may be present.

* Although the majority of NETs are not hereditary, these types of NETs can be associated with inherited syndromes. Please see page 54–57, where you will find detailed information on inherited syndromes associated with NETs.

Other Types of Neuroendocrine Tumours

Common Sites	Tumour Type	Associated Symptoms
 Skin	**Merkel cell carcinoma**	A neuroendocrine carcinoma of the skin, most common in older people and those with a compromised immune system. The first symptom is usually a painless flesh-coloured or bluish-red raised nodule (lump) on the head, neck, arms, legs or trunk. Even though most nodules appear on sun-exposed skin, they can occur anywhere on the body.
 Unknown primary	Generally, NETs of unknown primary origin occur within the following three broad categories: low-grade neuroendocrine carcinoma; small cell carcinoma; or poorly differentiated[††] neuroendocrine carcinoma, each of which has its own unique characteristics.	If a cancer has spread to one or more locations throughout the body but the site where it originated remains unknown, it is called a *cancer of unknown primary (CUP).*

[††]Please refer to page 21 for more information on tumour differentiation.

Less Common Neuroendocrine Tumours

Certain types of NETs affect only a small percentage of the population. However, if you have been diagnosed with a less common subtype, it's more important than ever to have accurate information at your disposal. Please refer to page 69, where you will find a list of resources that may provide access to the information you need.

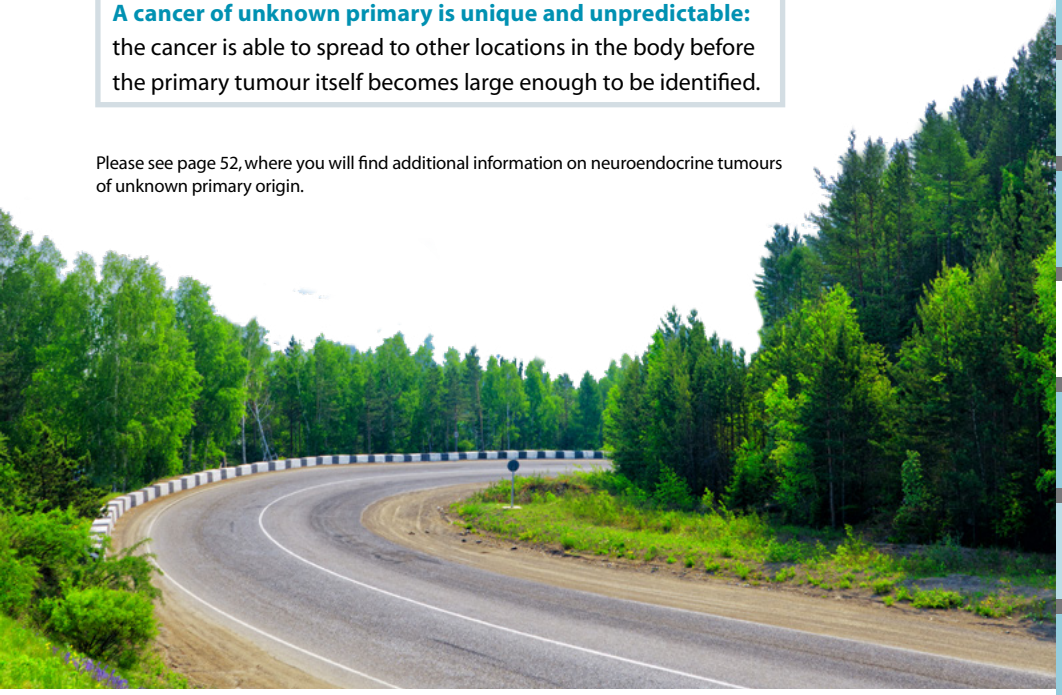
Neuroendocrine Tumours of Unknown Primary Origin

When someone is diagnosed with a NET, or any other type of cancer, it's only natural to want answers. First and foremost, questions such as "What type of cancer do I have and where did it start?" will come to mind. Unfortunately, the answers to these questions are not always straightforward.

Although most types of NETs can now be identified with the use of advanced pathology techniques, a few types resist classification by site of origin. Your healthcare team will do their best to identify and classify your tumour, since certain NETs respond well to specific chemotherapy or other treatment options.

A cancer of unknown primary is unique and unpredictable: the cancer is able to spread to other locations in the body before the primary tumour itself becomes large enough to be identified.

Please see page 52, where you will find additional information on neuroendocrine tumours of unknown primary origin.



Hereditary Conditions and Neuroendocrine Tumours

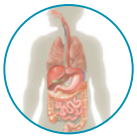
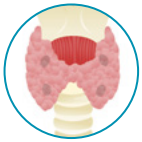
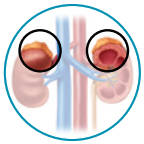
Some families have a higher-than-normal incidence of certain types of cancer. This sometimes happens because a family member carries an abnormal gene, called a genetic mutation, which passes from one generation to the next, causing cancer to develop in certain individuals.

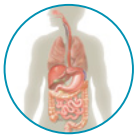
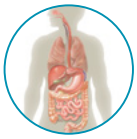
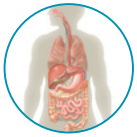
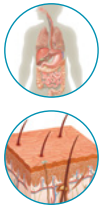
It's important to remember that it is the *gene* that is inherited not the disease. Not every member of a family will inherit the abnormal gene. If you have been diagnosed with an inherited type of NET, ask your healthcare team if genetic screening would be appropriate for other members of your family.

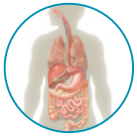
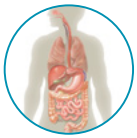
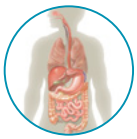
It is important to know that the majority of NETs are ***not*** hereditary. The risk factors for NETs are poorly understood and most NETs occur without any known cause.

Inherited Syndromes Associated with NETs

- MEN1 syndrome
- MEN2A syndrome
- MEN2B syndrome
- MEN type 4 syndrome
- Carney complex
- Neurofibromatosis
- Neuroblastoma
- Tuberous sclerosis
- Von-Hippel Lindau syndrome
- Hereditary paraganglioma-pheochromocytoma

Common Sites	Inherited Syndrome	Additional Information
 Parathyroid gland, Pancreas, Pituitary gland, Adrenal glands, Small intestine, Stomach	**Multiple Endocrine Neoplasia Type 1 (MEN1)**	(Formerly known as Wermer syndrome) MEN1 results from a mutation on the *MEN1 gene*. Symptoms will vary widely depending on the type of hormone or other substance that is secreted by the tumour cells and may include: abnormal milk production and menstrual disorders in women, excessive growth in soft tissues, excessive production of gastrin (Zollinger-Ellison syndrome), diabetes, skin rash, watery diarrhea, bone pain, fractures or kidney stones.
  Thyroid, Parathyroid gland, Adrenal glands	**Multiple Endocrine Neoplasia Type 2 (MEN2)**	MEN2 results from a mutation on the *RET* gene. MEN2 is classified into three subtypes based on symptoms: **MEN2A** • Medullary thyroid cancer • Pheochromocytoma • Parathyroid tumours **MEN2B** • Medullary thyroid cancer • Pheochromocytoma • Benign tumours of nerve tissue on the tongue and lips • Digestive disorders • Muscle and joint problems • Spinal disorders • Characteristic facial features include swollen lips and eyelids **FAMILIAL MEDULLARY THYROID CANCER (FMTC)** • Medullary thyroid cancer in four or more family members • No evidence of pheochromocytoma or parathyroid tumours

Common Sites	Inherited Syndrome	Additional Information
 Parathyroid gland, Pituitary gland, Multiple organ systems	**Multiple Endocrine Neoplasia Type 4 (MEN4)**	The discovery of mutations in the *CDKN1B* gene led to the recent identification of the MEN4 syndrome. The initial presentation resembles the MEN1 syndrome *but* MEN1 mutations are not found. Similarly, the main characteristics are parathyroid and pituitary adenomas, with the most common clinical feature being primary hyperparathyroidism (PHPT). Generally tumours occur in two or more endocrine glands, although MEN4 tumours can also develop in nonendocrine glands or in other organs. NETs of the cervix, carcinoids in the bronchi and stomach, and gastrinoma have also been observed.
 Brain, Eye, Spinal cord, Multiple organ systems	**Von-Hippel Lindau syndrome (VHL)**	VHL results from a mutation on the *VHL* gene. The VHL syndrome is associated with blood vessel tumours on the brain or spinal cord (hemangiomas), or eye (retinal angiomas). Presence of the *VHL* gene increases the risk of developing kidney cancer or pheochromocytoma. Pancreatic cysts, genital lesions in men and ear tumours (which may cause hearing loss) may also occur.
 Multiple organ systems	**Carney complex**	Initial signs of the condition are connective tissue tumours in the heart or other heart problems, and skin pigmentation abnormalities. Patients may notice spotty patches on the lips, around the eyes and in the genital area. Frequently, patients will also experience the symptoms associated with Cushing syndrome, such as thyroid abnormalities, facial swelling, weight gain, diabetes, high blood pressure, excessive hair growth or bruising. Patients with Carney complex are at a higher risk of developing adrenocortical tumours.
 Skin, Multiple organ systems	**Neuro-fibromatosis Type 1 (NF-1)**	This hereditary condition involves abnormal cell growth throughout the nervous system. Symptoms may include: skin pigmentation abnormalities, such as multiple light-brown coloured birthmarks (café au lait spots), tumours that develop along nerves on the skin or throughout the body, freckles in the armpits or groin area, bone deformities and eye lesions. NF-1 patients have an increased risk of developing carcinoid NETs, pheochromocytomas, paragangliomas, gastrointestinal stromal tumours and pancreatic NETs.

Common Sites	Inherited Syndrome	Additional Information
 Skin, Brain, Kidneys, Multiple organ systems	**Tuberous sclerosis (TSC)**	Although NETs have been reported in patients with TSC, they are not considered to be a major feature of this inherited disorder. Nevertheless, pituitary tumours, parathyroid tumours, gastrinomas, insulinomas, carcinoid NETs and pheochromocytomas have all occurred in rare instances. The main symptoms associated with TSC include fibrous tumours (abnormal formations of normal tissue) that may form on the face, in the brain, eyes, skin, heart, lungs or kidneys; seizures; and intellectual or developmental disabilities.
 Adrenal glands, Multiple organ systems	**Neuroblastoma**	Neuroblastoma is a type of cancer that develops from immature nerve cells called neuroblasts. Approximately 1% to 2% of neuroblastoma patients have a family history of the disease, and these patients are frequently diagnosed in infancy. Research has shown an association between those with a genetic abnormality on chromosome 6p22 and an aggressive type of neuroblastoma. Other genes have been linked to lower-risk types of neuroblastoma tumours. Commonly, the first evidence of neuroblastoma is a mass in the abdomen, with or without associated pain, but symptoms often vary depending on the location and characteristics of the tumour. Other symptoms may include diarrhea, bone pain, bulging eyes, bruising around the eyes, breathing difficulties, fever, high blood pressure or anemia.
 Multiple organ systems	**Hereditary paraganglioma-pheochromo-cytoma**	People with hereditary paraganglioma often develop more than one paraganglioma, which may include pheochromocytomas. Extra-adrenal paraganglioma are more likely to become cancerous than other types of paraganglioma or pheochromocytoma. At least four gene mutations have been identified that play a role in the development of this heritable disease, with each one giving rise to particular characteristics. For example, people with type 1, 2 or 3 hereditary paraganglioma usually develop paragangliomas in the head or neck region, while those with type 4 are more likely to develop paragangliomas in the abdominal area with a higher risk of metastatic spread.

Coming to Terms with Your Diagnosis

Everyone has his or her own way of coping with a cancer diagnosis. Out of necessity, each person will find a way to make sense of the changes and uncertainty that surround them. During the turbulent times immediately following diagnosis, it may help to have an open and honest discussion with your family about how you're feeling. Remember, it's perfectly natural to feel angry, fearful, sad, resentful and a range of other powerful emotions. In some cases, speaking with a psychologist or counsellor can also be helpful.

Once you've had time to process your diagnosis, you may wish to learn everything you can about your disease and its treatment. Many patients with NETs find that having information empowers them and allows them to take a more active role in important treatment decisions.

Your new reality. As you mentally process and learn to accept your NET diagnosis don't underestimate the value of a patient support group. People who are facing similar challenges can be an important source of guidance, information, and when necessary, calming reassurance.

Sharing Your Diagnosis with Others

How much information you wish to share about your disease is a highly personal decision. However, it can take a great deal of energy to try and maintain a strong front – a situation that might leave you feeling isolated and exhausted. Staying in open and honest communication with your friends and family allows you to express your emotions and perhaps draw strength from each other during challenging times.

Opening up to your friends makes it easier for them to support you in practical matters as well. Don't hesitate to accept offers of help around the house, meal preparation, an evening out or the support of having a trusted friend accompany you to doctor's appointments.

Talking About Your Disease with Young Children

When a serious illness occurs, the entire family is profoundly affected. Even very young children can sense that something is amiss and need to be reassured that they will always be loved and cared for. By explaining your illness in simple, age-appropriate language, children will feel included in this important family matter. Most importantly, they will understand that your disease is not their "fault," a common response among young children to any family crisis.

When you talk to your children, convey your messages with honesty, while assuring them that your doctors are doing everything possible to make you well. Encourage your children to ask you any questions they may have about your disease or treatment.

Lifestyle Tips for Managing Flushing

For many patients, repeated episodes of flushing are the first indication that they may have a NET.

Flushing is defined as a visible, sometimes sudden, reddening of the skin, often accompanied by a sensation of warmth.

Approximately 8% to 28% of patients with serotonin-producing carcinoid NETs will experience classic "carcinoid syndrome" symptoms, of which flushing is the primary characteristic. In fact, more than 90% of patients with carcinoid syndrome will experience flushing at some point during their disease. NETs that originate in the small intestine or appendix are more commonly associated with carcinoid syndrome. Other symptoms of carcinoid syndrome include intestinal disturbances such as diarrhea (80%), heart disorders (40%) and bronchoconstrictive conditions such as asthma (15%).

In patients with NETs, flushing (and diarrhea) are believed to be the result of various hormones and substances secreted by the tumours themselves, predominantly serotonin, histamine or tachykinins. Some medical experts recommend that, in addition to taking appropriate medications to help manage flushing and other symptoms, patients avoid the "Five E's" listed below:

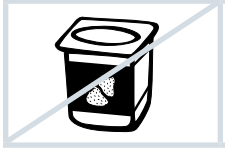
Avoid or Limit the Five E's...

Epinephrine (a common ingredient in allergy medications and local anesthetics)

Emotion (stimuli such as anger, embarrassment or pain can trigger symptoms)

Exercise (or any type of exertion that exacerbates your symptoms)

Ethanol (alcoholic beverages)



Eating certain foods, such as fermented foods

For tips on choosing foods that can help control symptoms, please refer to *The Importance of Diet and Nutrition*, on page 63.

Lifestyle Tips for Managing Stress

Without a doubt, life can be stressful enough without the added challenge of a cancer diagnosis! Almost everyone has commitments and activities that are an important part of leading a busy, productive and enjoyable life. However, many people feel that they're running on "overdrive" much of the time. When you're faced with a serious illness it may be time to slow down, regroup and come to terms with the situation – your new reality. So where do you begin? While it's unrealistic to suggest that lifestyle modifications can alleviate all the stress-related emotions you feel, even small changes may help you cope just a little bit better.

People with cancer often say that they feel better and have more energy when they participate in regular physical exercise. Many people have found stress relief by participating in the following activities:

- Joining a support group for NET patients
- Yoga or tai chi
- Visualization techniques
- Meditation
- Art, music or reading
- Deep breathing exercises
- Spending time with a pet
- Exploring spiritual faith
- Keeping a journal or diary
- Physical exercise, such as swimming, walking or biking*

* Before starting any exercise program, *be sure* to check with your doctor to establish a level of activity that is safe and beneficial for you.

The Importance of Diet and Nutrition

Although proper nutrition is important for everyone, certain patients with NETs can face unique challenges when planning and maintaining a healthy diet. Many foods contain amines which are naturally occurring substances that increase as a food ripens or ferments. Unfortunately, amines are the same substances that can trigger symptoms in certain people with NETs, particularly patients who have high levels of serotonin in their blood.

In some cases, patients with NETs will require increased protein and niacin in their diet, while others will need to focus on starchy, digestible carbohydrates and reduced fats to help manage diarrhea. Although consuming the widest variety of foods possible is generally considered ideal, every individual must do what is best for them, based on their own experience learned through trial and error.

Be sure to initiate a discussion about diet and nutrition with your healthcare team.

Foods with VERY HIGH levels of amines	Foods with MODERATELY HIGH levels of amines
Aged cheeses	Raspberries
Alcoholic beverages, particularly red wines	Chocolate in large amounts
Smoked, salted or pickled fish	Some nuts (peanuts, Brazil nuts)
Cured or smoked meats (salami, sausage, pepperoni, bologna)	Coconut
Yeast extracts (found in many processed foods) and Brewer's yeast	Caffeinated beverages in large amounts (coffee, colas)
Broad beans (Fava beans)	Bananas
Fermented foods (sauerkraut)	Avocado
Some soy products (miso, tofu, soy sauce)	

Adapted from Hassell *et al*. Nutrition and Carcinoid, Providence Cancer Center.

Understanding and Managing Fatigue

Feeling fatigued at the end of a long day or after a strenuous task is something that almost everyone has experienced, regardless of age or health status. However, for patients with NETs or other malignancies, fatigue often exceeds simple "tiredness." Among patients with NETS, those who have tumour types that disrupt blood sugar levels, such as glucagonoma, often experience severe fatigue.

Medical professionals characterize cancer-related fatigue as a persistent, distressing state of physical, emotional and cognitive exhaustion that interferes with normal daily functioning and is out of proportion to recent activity.

If this describes how you've been feeling, it's essential that you discuss your fatigue with your healthcare team.

After doing a thorough examination, your doctors will not only want to offer you immediate treatment, but also monitor and manage your fatigue on an ongoing basis. Many factors play a role in the development of fatigue, as shown in the list on the following page, and *many* are treatable!

Treatable Factors That Can Contribute To Fatigue		
Anxiety or depression	Nutritional deficits	Pain
Calcium or magnesium imbalance	Sodium or potassium imbalance	Organ or neurologic dysfunction (cardiac, kidney, liver, lung, etc.)
Sleep disorders	Emotional distress	Infection
Alcohol or substance abuse	Side effects of medications	Anemia

Adapted from National Comprehensive Cancer Network, Cancer-Related Fatigue Guidelines, 2013

Your doctor will reassure you that fatigue is a very common side effect of many treatments. It's essential to understand that treatment-related fatigue is not necessarily an indicator that your disease has progressed. As you work with your healthcare team to manage your fatigue, try these tips:

- Structure your daily routine
- Set priorities and schedule activities for times of peak energy
- Allow your family and friends to help
- Delegate tasks to others until your energy levels increase

Tips for Caregivers

There are few things in life that affect a person more than the diagnosis of a serious illness. The impact is often felt not only by the patient but also by their entire family. As everyone adjusts to the diagnosis, the immediate and overwhelming desire is to do everything possible to provide care and support to the patient, and the weight of this responsibility is often borne by the spouse, partner, children, relatives and close friends.

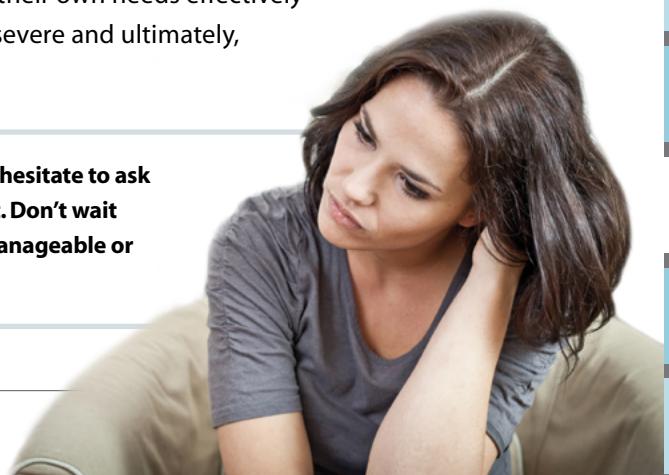
Today, patients generally stay in hospital for shorter periods of time and many treatments are administered on an outpatient basis. That means the role of the at-home caregiver is more important – and more demanding – than ever. Right from the start the caregiver is a vital part of the patient's healthcare team. The problem is, who is caring for the caregiver?

The Following Tips May Help Caregivers Meet The Challenges of Their Essential Role:

- If you are working outside the home, speak with your employer about taking a leave from work. Some government programs allow Family Medical Leave, which enables individuals to care for a loved one, while ensuring the protection of their job in their absence.
- Provincial government agencies may offer employment insurance benefits to people who are away from work temporarily, providing care to a family member.

- Seek support from cancer organizations and caregiver groups, where you can discuss your concerns with other people who are facing similar challenges.
- Before you feel overwhelmed, consider seeking the advice of a counsellor, psychologist or other mental health specialist. Know that you're not alone – many caregivers will experience depression or other psychological distress at some point in their journey.
- Some caregivers find value in turning to a leader in their religious or spiritual community.
- Reach out to members of the multidisciplinary healthcare team if you feel like you do not have the knowledge to handle certain care-related tasks.
- Ask the healthcare team to teach you techniques for moving the patient safely and decreasing the risk of falls. Knowing how to keep your patient comfortable will help decrease your stress.
- Learn how to recognize a medical emergency and what to do, should one occur.
- Avail yourself of the services of home-care nurses, therapists, aides and social workers.
- Attend education and information sessions whenever possible and understand that the role of a caregiver changes as the patient's condition changes.
- Do your best to maintain and protect your own health while performing your caregiver role.
- Don't feel guilty about taking time out to "recharge your batteries." Caregivers who manage their own needs effectively have the strength to persevere and ultimately, be a better caregiver.

Most importantly – don't hesitate to ask for help when you need it. Don't wait until things become unmanageable or overwhelming for you.



Tracking Your Health

Many people with NETs like to keep track of their health-related information over the long-term. You'll find an example of a suggested *"Tracker"* template shown below. You can create individual trackers to chart appointments, prescribed medications, over-the-counter medications, side effects, results of blood tests and scans, your physical activity, blood pressure or diet.

If you choose to regularly monitor your vital health information, take your trackers with you to your doctors' appointments. Your healthcare team may use the information you've recorded as a guide for setting future healthcare goals.

Date	Test or Scan	Doctor's Name/ Instructions	Results	Follow-up

Information Resources

The organizations listed below can provide information on NETs and offer support. Learning more about the diagnosis and treatment of NETs may help you manage your illness more effectively.

www.cnets.ca
Canadian Neuroendocrine Tumour Society (CNETS)

www.carcinoid.org
The Carcinoid Cancer Foundation

www.carcinoidawareness.org
Carcinoid Cancer Awareness Network

www.caringforcarcinoid.org
Caring for Carcinoid Foundation

www.thenetalliance.com
The NET Alliance, a global organization

www.netpatientfoundation.org
NET Patient Foundation, based in the United Kingdom

www.cancer.ca
Canadian Cancer Society

www.canceradvocacy.ca
Cancer Advocacy Coalition of Canada (CACC)

www.ccanceraction.ca
Canadian Cancer Action Network (CCAN)

www.raredisorders.ca
Canadian Organization for Rare Disorders (CORD)

www.unicornfoundation.org.au
The Unicorn Foundation

www.amend.org.uk
Multiple endocrine neoplasia disorders (MEN1 & MEN2)

www.netcancerday.org
International Neuroendocrine Cancer Alliance (INCA)

www.pancan.org
Pancreatic Cancer Action Network

www.pheoparatroopers.org
(pheochromocytoma & paraganglioma)

Drug Reimbursement

People who have been diagnosed with NETs frequently require a wide range of medications – drugs to treat the cancer itself, supportive care medications and other therapies. In Canada, once a patient leaves the hospital, each individual province or territory controls the reimbursement of cancer medications. As you know, drug coverage plans vary widely across the country.

Some private insurance plans may provide coverage for cancer medications, but it is up to the individual to determine which medications are covered. When speaking with your health insurance provider, be sure to ask how much you will be required to pay (the co-pay amount).

It is an unfortunate fact that many cancer therapies are very expensive and are not covered by private, provincial or federal insurance programs. Be aware that some pharmaceutical companies have developed valuable patient assistance programs to assist eligible patients who require specific cancer therapies, which may be another avenue to explore.

Participation in a clinical trial may be one way to gain access to a new therapy, but this decision must be made in consultation with your healthcare team.

Visit **www.drugcoverage.ca.** A helpful database that provides information on prescription drug reimbursement throughout Canada.

Questions to Ask Your Healthcare Team

1. What type of NET do I have?

2. What stage is my disease at and what is the usual prognosis?

3. What treatment options or combination of treatments do you recommend, and why?

4. Are there testing or treatment options currently not available in Canada that I should consider? If so, will my provincial health insurance program pay for these tests or treatments and will I require pre-approval? I'll want to know all the costs that will be incurred.

5. What is the usual timeline for the treatment(s) I'll be receiving?

6. Can you explain the side effects that I may experience as a result of this treatment?

7. **Would I be a potential candidate for inclusion in a clinical trial of my type of NET?**

8. **What lifestyle changes should I make to stay as healthy as possible before, during and after treatment?**

9. **If my type of NET has a hereditary component, should my children or other family members undergo genetic testing?**

10. **After treatment, what type of regular follow-up tests will I require and for how long?**

11. **Can you recommend any support services or organizations that could provide information and guidance to my family and me?**

12. **To whom should I speak to about health insurance or financial concerns?**

Other questions:

Terminology Used In This Booklet

5-HIAA
5-hydroxyindoleacetic acid

5-HTP
5- Hydroxytryptophan – an amino acid produced naturally by the body. 5-HTP is converted into serotonin, a neurotransmitter, which transmits signals between brain cells.

Ablative
Techniques that use ablation – the removal or destruction of a body part or tissue or its function. Ablation may be achieved through the use of surgical procedures, radiofrequency, cold, heat, medications, hormones or other methods.

ACC
Adrenocortical carcinoma

ACTH
Adrenocorticotropic hormone

Adenocarcinoma
Cancers that begin in glandular (secretory) cells. Glandular cells are found in tissue that lines certain internal organs. They produce and release substances in the body, such as mucus, digestive juices and other fluids.

Adrenal cortex
The outermost layer of the adrenal gland that is responsible for producing androgen and corticosteroid hormones.

Adrenal glands
Two small endocrine glands, located just above each kidney, function interactively with the hypothalamus and pituitary gland in the brain. The adrenal glands secrete important hormones, including adrenaline and noradrenaline, which play a role in controlling blood pressure, heart rate, muscle relaxation and other body functions.

Adrenaline
A hormone and neurotransmitter. Also called epinephrine.

Appendix
A small, fingerlike pouch that sticks out from the cecum (the first part of the large intestine near the end of the small intestine).

Benign
Not cancerous (nonmalignant). Benign tumours may grow larger but do not spread to other parts of the body.

Biopsy
The removal of cells or tissue for examination by a pathologist. The tissue samples (specimens) will be evaluated under a microscope and additional tests may be performed. There are many different types of biopsies, including: (a) incisional biopsy, in which only a sample of

tissue is removed; (b) excisional biopsy, in which an entire lump or suspicious area is removed; and (c) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is used, the procedure is called a fine-needle aspiration biopsy.

Bronchi
The large airways that lead from the trachea (windpipe) into the lungs. (Singular: bronchus).

Carcinoid
A type of slow-growing NET that usually occurs in the small bowel or appendix, and sometimes in the lungs or other sites. Carcinoid NETs may spread to the liver or other sites in the body, and they may secrete substances including serotonin and many others. Today, there is a shift away from describing these tumours as "carcinoid," to using the term neuroendocrine tumours or neoplasms. It is now recognized that "carcinoid" inadequately describes the characteristics of many NETs.

CCK
Cholecystokinin, a peptide hormone

Cerebrospinal fluid
The fluid that flows in and around the hollow spaces of the brain and spinal cord, and between two of the meninges (the thin layers of tissue that cover and protect the brain and spinal cord).

Cervix
The lower end of the uterus that forms a canal between the uterus and vagina.

Chronic
A disease or condition that persists over a long period of time.

Colon
The longest part of the large intestine, a tube-like organ connected to the small intestine at one end and the anus at the other. The colon consists of the ascending colon the transverse colon, the descending colon and the sigmoid colon. The function of the colon is to remove water, nutrients and electrolytes from partially digested food. The remaining solid waste (stool), moves through the colon to the rectum and leaves the body through the anus.

Cortisol
A glucocorticoid hormone made by the adrenal cortex (the outer layer of the adrenal gland). Its function is to enable the body to use glucose, protein and fats.

CT
Computed tomography

Curative
Treatment (usually surgery to remove all cancerous tissue) that is intended to cure a disease. Curative surgery works best for localized cancer.

Cytoreductive
The surgical removal of as much of a tumour as possible. Also called "debulking surgery," it may increase the effectiveness of other therapies or help relieve symptoms in select patients.

Differentiation
Describes the processes by which immature cells become mature cells with

specific functions. In cancer, this describes how much or how little tumour tissue looks like the normal tissue it came from. Well-differentiated cancer cells look more like normal cells and tend to grow and spread more slowly than poorly differentiated or undifferentiated cancer cells. Differentiation is used in tumour grading systems, which are different for each type of cancer.

Diffuse
Not localized or confined to one area; widely spread.

Duodenum
The first part of the small intestine that connects to the stomach.

EGD
Esophagogastroduodenoscopy (also known as upper GI endoscopy) – a test that introduces a small, flexible camera down the throat to examine the lining of the esophagus, stomach and first part of the small intestine.

Electrolyte
A substance that, when it is dissolved in water or body fluids, breaks up into ions (electrically charged particles). Some examples of ions are sodium, potassium, calcium, chloride and phosphate. These ions help move nutrients into cells, help transport waste out of cells, and allow nerves, muscles, the heart and the brain to function normally.

Embolization
The blocking of an artery by a clot or foreign material. Embolization can be performed as treatment, using a variety of techniques to block the flow of blood to a tumour.

Epinephrine
A hormone and neurotransmitter. Also called adrenaline.

Erythema
Redness of the skin.

Esophagus
The muscular tube that enables food to travel from the throat to the stomach.

FNAB
Fine-needle aspiration biopsy

FSH
Follicle-stimulating hormone

Functional tumour
A tumour that is found in endocrine tissue and produces hormones. Also referred to as a "functioning" tumour.

Gastrin
A hormone that is released from cells in the lining of the stomach after eating. Gastrin signals the stomach to release an acid that helps digest food.

Gastrointestinal
Also referred to as the "GI" system, it refers to the stomach and intestines.

Gene
Genes are pieces of DNA that occupy a specific location on a chromosome. Most genes contain the information for making a specific protein that will determine a particular characteristic of an individual. Genes are the functional and physical units of heredity that are passed from parents to children.

GEP
Gastroenteropancreatic. Refers to the gastrointestinal and pancreatic systems, collectively. Gastrointestinal and pancreatic neuroendocrine NETs are often referred to together as "GEP NETs."

GH-RH
Growth hormone releasing hormone

Glucose
A type of sugar that provides the main source of energy for many of the systems and processes in any living organism.

Gn-RH
Gonadotropin-releasing hormone

Grade
Pathologists commonly describe tumour grade by four degrees of severity, based on the microscopic appearance of cancer cells: grades 1, 2, 3 and 4. The cells of grade 1 tumours are often well-differentiated or low-grade tumours, and are generally considered the least aggressive in behaviour. Conversely, the cells of grade 3 or grade 4 tumours are usually poorly differentiated or undifferentiated high-grade tumours, and are generally the most aggressive in behaviour.

GRF
Growth-hormone releasing factor

Hepatic
Refers to the liver.

Hepatobiliary
Refers to the liver, bile ducts and/or gallbladder.

Hereditary
Transmitted from parent to child by information contained in the genes.

Hormone
One of many substances produced by various glands throughout the body, which circulate in the bloodstream and stimulate or regulate certain cells or organs.

IGF
Insulin-like growth factor

Ileum
The part of the small intestine beyond the jejunum and before the large intestine (colon).

Interferon
A biological response modifier (a substance that can improve the body's natural response to infections and other diseases). Interferons interfere with the division of cancer cells and may help slow tumour growth. There are several types of interferons, including interferon-alpha, -beta and -gamma. The body normally produces these substances but they can also be produced in the laboratory to treat cancer and other diseases.

Invasive
A medical procedure that invades (enters) the body, usually by incising or puncturing the skin or by inserting instruments into the body. Minimally invasive procedures are used whenever possible – requiring only small incisions, using small laparoscopic instruments and necessitating fewer stitches.

Islet cell
A cell found in the pancreas that produces hormones (e.g., insulin and glucagon) that are secreted into the bloodstream to help control the level of glucose (sugar) in the blood. Also referred to as endocrine pancreas cell and islet of Langerhans cell.

Jejunum
A part of the small intestine that is located approximately half-way down the small intestine between the duodenum and ileum sections.

Lanreotide
A drug similar to the naturally occurring growth hormone inhibitor somatostatin. Lanreotide is used for the treatment of enteropancreatic neuroendocrine tumours in adult patients to delay progression, and the treatment of adult patients with carcinoid syndrome.

LAR
Long-acting release

LCNEC
Large cell neuroendocrine carcinoma

LH
Luteinizing hormone

Localized
Describes disease that is limited to only a certain part of the body, and has not spread to nearby lymph nodes or other organs.

Malignant
Cancerous. Having properties that enable cells to invade and destroy nearby tissue and/or spread (metastasize) to other parts of the body.

Mediastinal
Refers to the mediastinum – the area between the lungs. The organs in this area include the heart and its large blood vessels, the trachea, the esophagus, the thymus and lymph nodes, but not the lungs.

MEN
Multiple endocrine neoplasia

Metastasis
The spread of cancer from one part of the body to another. A tumour that is formed by cells that have spread is called a "metastatic tumour," a "metastasis" or a "met." The metastatic tumour contains cells that are like those in the original (primary) tumour. The plural form of metastasis is metastases.

MIBG
Iodine-123-meta-iodobenzylguanidine

MRI
Magnetic resonance imaging

mTOR
Also referred to as "mammalian target of rapamycin," it is a protein that helps control several cell functions, including cell division and survival, and binds to rapamycin and other drugs. Since mTOR may be more active in some types of cancer cells, blocking mTOR may cause the cancer cells to die.

Multidisciplinary
A term used to describe a treatment planning approach or team that includes a number of doctors and other healthcare professionals who are experts in different specialties (disciplines).

Mutation
Any change in the DNA sequence of a cell. Mutations may be caused by abnormalities that occur during cell division or they may be caused by exposure to DNA-damaging agents. Mutations can be harmful, beneficial or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

Neoplasm
A mass of abnormal tissue that develops when cells divide more rapidly than they should. Neoplasms may be benign (not cancer) or malignant (cancer). Neoplasms are also referred to as tumours.

NET
Neuroendocrine tumour

Neuroendocrine
Interaction between the nervous system and the endocrine system in which certain cells release hormones into the blood in response to stimulation of the nervous system.

Neuroendocrine tumour
A tumour that develops in specialized cells that release hormones into the blood, in response to signals sent from the nervous system. Neuroendocrine tumours may produce higher-than-normal levels of hormones, which can cause a range of different symptoms.

Neurologic
Refers to the nerves or the nervous system.

Neurotensin
A substance found in small intestine and brain tissue; it induces vasodilation and hypotension; in the brain it is a neurotransmitter.

NF-1
Neurofibromatosis type 1

Non-functional tumour
A tumour that is found in endocrine tissue but does not produce additional hormones. Also referred to as a "non-functioning" tumour or an "endocrine-inactive" tumour.

Noradrenaline
A substance produced by certain nerve cells and the adrenal gland. It can act as both a neurotransmitter (a chemical messenger used by nerve cells) and a hormone (a chemical that travels in the blood and controls the actions of other cells or organs). Noradrenaline is released from the adrenal gland in response to stress and low blood pressure. Also called norepinephrine.

Norepinephrine
See noradrenaline

NSCLC
Non-small cell lung cancer

Octreotide
A drug similar to the naturally occurring growth hormone inhibitor somatostatin. Octreotide is used to treat diarrhea and flushing associated with certain types of tumours.

Ovary
One of two female reproductive glands in which the ova (eggs) develop. The ovaries are located in the pelvis, one on each side of the uterus.

Palliative
Care and treatment provided with the main intent being to improve the quality of life of patients who have a serious or life-threatening disease. Also referred to as supportive care.

Pancreas
A glandular organ located in the abdomen. It produces pancreatic juices, which contain enzymes that aid in digestion, and also produces a range of important hormones, including insulin.

Parathyroid glands
Two pairs of parathyroid glands, located beside the thyroid gland in the neck, release parathyroid hormone, which regulates calcium levels in the blood. The parathyroid hormone stimulates the release of calcium from the bones into the blood, absorption of dietary calcium via the intestines, and conservation of calcium by the kidneys.

Peptide
A molecule that contains two or more amino acids. Amino acids are the molecules that join together to form proteins. Peptides that contain many amino acids are called polypeptides or proteins.

PET
Positron emission tomography. May also be an acronym used to describe a pancreatic endocrine tumour.

PET scan
A nuclear medical imaging technique that uses positron emission tomography (PET) to produce three-dimensional images of functional processes in the body.

Pineal gland
A very small organ in the brain (cerebrum) that produces melatonin. Also referred to as the pineal body or pineal organ.

Pituitary gland
A small, three-lobed gland, attached to the hypothalamus of the brain, that produces hormones which control other glands throughout the body and regulate many vital physiological roles, including growth, reproductive functions and absorption of water into the blood by the kidneys.

PNET
Pancreatic neuroendocrine tumour

PP
Pancreatic polypeptide

PPI
Proton pump inhibitor, a type of medication used to reduce the production of gastric acid.

Prognosis
The likely outcome or course of a disease, including the likelihood of recovery or disease recurrence.

Proximal
Refers to a part of the body that is closer to the centre of the body compared with another part. For example, the hip socket is proximal to the ankle. The opposite of proximal is distal.

PTHrPs
Parathyroid hormone-related protein-secreting

Rectum
The last segment of the large intestine closest to the anus.

Retroperitoneal
Refers to the area outside or behind the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen).

SCLC
Small cell lung cancer

Small intestine
The segment of the digestive tract that is located between the stomach and the large intestine.

Somatostatin
A hormone that regulates the rate at which other important pancreatic hormones, such as growth hormone, gastrin and insulin are released into the blood.

Spleen
An organ that is part of the lymphatic system. The spleen makes lymphocytes, filters the blood, stores blood cells and destroys old blood cells. It is located on the left side of the abdomen near the stomach.

Sputum
Mucus and other matter expelled from the lungs by coughing.

SRS
Somatostatin receptor scintigraphy

Stage
The extent of a cancer in the body. Staging is usually based on the size of the tumour, whether lymph nodes contain cancer and whether the cancer has metastasized (spread) from the original site to other parts of the body.

Supportive care
Care and treatment provided to improve the quality of life of patients who have a serious or life-threatening disease. The goals of supportive care are to proactively prevent or treat the symptoms of a disease, side effects caused by treatment, and to address the psychological, social and spiritual problems related to a disease or its treatment. Also called palliative care or symptom management.

Testes
Two egg-shaped glands located inside the scrotum that produce sperm and male hormones. Also called testicles.

Thymus
An organ, located in the chest behind the breastbone, that is part of the lymphatic system, in which T lymphocytes grow and multiply.

Thymic
Refers to the thymus gland.

Thyroid
A gland located beneath the larynx (voice box) that produces thyroid hormone and calcitonin. The role of the thyroid is to help regulate growth and metabolism. Also called the thyroid gland.

Tracer
A substance (such as a radioisotope) used in imaging procedures.

TSC
Tuberous sclerosis

TSH
Thyroid-stimulating hormone

Tumour
An abnormal mass of tissue that results when cells divide more rapidly than they should or do not die when they should. Tumours may be benign (not cancerous), or malignant (cancerous). Also referred to as a neoplasm.

Tyrosine kinase inhibitor
A substance that blocks the action of enzymes in the body called tyrosine kinases. Tyrosine kinases are a part of many cell functions, including cell signalling, growth and division. These enzymes may be overactive or found at high levels in certain types of cancer cells and blocking them may help keep cancer cells from growing. Some tyrosine kinase inhibitors are classified as targeted therapy and are used to treat cancer.

Vasoactive
Refers to something that causes blood vessels to constrict (become narrower) or dilate (become wider).

VHL
Von-Hippel Lindau (syndrome)

VIP
Vasoactive intestinal polypeptide

NOTES

Maureen Coleman

Passed away at the age of 65 on August 31, 2013

We would like to dedicate this publication to our Founding Past President of CNETS.

After being diagnosed with a neuroendocrine tumour in 2000, Maureen initiated the first support meeting of Canadian NET patients in Toronto, Ontario, in May 2001. Along with this small group of patients, Maureen forged ahead over the next six years, developing the foundation for the organization that became incorporated as CNETS in 2007 and attained charitable status in 2008. Maureen was the President of CNETS from incorporation until December 2012.

Under her leadership, CNETS became a prominent organization for the cause of patients with NETs and has achieved national and international recognition.

Maureen touched the lives of many. She was a passionate, inspiring and outgoing advocate for NET cancer patients and a generous friend to many around the globe. Maureen provided support, information and guidance, and will be remembered as a fighter and a true champion for those who suffered from NET cancer. She dedicated herself unselfishly to CNETS and to our cause. She was a remarkable and irreplaceable woman who is deeply missed by her colleagues at CNETS and her many friends around the world.

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CANADIAN NEUROENDOCRINE TUMOUR SOCIETY