



A guide for patients and families

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ABOUT THE NEUROENDOCRINE TUMOR RESEARCH FOUNDATION (NETRF)

In 2005, NET patient Nancy Lindholm founded NETRF (originally called the Caring for Carcinoid Foundation) after being diagnosed with metastatic neuroendocrine cancer at age 29. Determined to learn what she could about her diagnosis and knowing the importance of research for a rare cancer that received little governmental funding or attention from the pharmaceutical industry, Nancy recruited some of the best scientists in the Boston area to become volunteer scientific advisors. She also gathered others with personal or family experience with NETs to form a Board of Directors, with many of those members continuing to serve NETRF.

Today, NETRF honors Nancy's legacy through its mission to fund research to discover cures and more effective treatments for neuroendocrine cancers. NETRF has invested tens of millions of dollars in research to help build the field of neuroendocrine cancer research by funding young investigators and those with established research programs and by fostering collaboration between hospitals and academic institutions.

EDUCATING AND EMPOWERING PATIENTS

We work to improve the lives of patients, families, and caregivers affected by neuroendocrine tumors (NETs) with informational and educational resources, including:

- NETWise Podcasts
- Extensive YouTube library with videos about diagnosis, treatment, research, and living with NETs
- Patient and caregiver education conferences
- Searchable databases of NET doctors, multidisciplinary treatment programs, and support groups

GET INVOLVED

Visit netrf.org to learn about the promising NET research we fund, find educational resources, and learn about ways to support NETRF. Together, we can make a difference.

Notes

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Medical Disclaimer: This booklet is not intended as and shall not be relied upon as medical advice. The Neuroendocrine Tumor Research Foundation does not represent that any information provided here should supplant the reasoned, informed advice of a patient’s oncologist, physician, or appropriate qualified health professional. Always consult your doctor about your treatment options.



Suzanne Ludlow (center) with husband Vince Taylor (right) and son Langston Taylor (left)

Foreward

In 2012, my husband was diagnosed with a neuroendocrine tumor (NET) cancer. At that time, there was little information and few treatment options available. Today things are changing and having this publication available to you is part of that change. I want to thank NETRF for assembling this booklet and supporting critical NET research, which has made amazing advances in recent years.

My husband, Vince Taylor, lived well with a NET cancer for six years, and we learned a lot about NET medical care during that time. It took us several years to understand that we needed to see a NET specialist rather than only relying on our otherwise excellent oncologists. I want others to understand the complexities of this uncommon disease faster than we did, so that all can seek out the best care for themselves in a timely manner.

As someone who has been there, let me suggest that you first take a deep breath. Then, read through the materials here, and write down questions for your doctor.

Any serious medical condition is challenging and can be complicated by many issues including insurance rules, limited funds, language barriers, racial bias, and geographic location. My husband and I were fortunate to have many advantages, but there were times I believe racial bias slowed the provision of some treatment and when busy doctors' schedules meant that outreach to NET specialists by our medical team was delayed. Part of the reason I wanted to write this Foreward is to encourage you to learn enough about NETs to really advocate for yourself and your family.

Here are several lessons we learned:

- Connect with medical professionals experienced in NETs. As NETs are unusual, and the treatment options related to them are changing rapidly, you must be connected to the right people. This is really important!
- Keep learning. Besides this booklet and your medical team, there are websites, podcasts, support groups, and a whole social media community available to you and your advocates.
- Trust yourself and what you are feeling. Because of the relative rarity of NETs and the uniqueness of every individual, share what does and doesn't work for you with your medical team. This is always a good thing to do, but it is more important when dealing with an uncommon medical condition. If you feel better when you eat donuts and worse when you eat shrimp (like my husband!), share that information with your doctor. It has value and will help your medical team learn how to help you.
- When you have a choice to do or not do something, focus on what would make you happiest. My husband chose to assist with some research efforts but also declined several clinical trials that required multiple hospital visits that would keep him from working. I appreciated that his doctors respected his choices without pressure.

This updated guide is being issued two years after the start of the COVID-19 pandemic. We now have a greater appreciation of the value of scientific research and we have seen first-hand how health information can change as more is learned. Most importantly, we have learned to say “I love you” often because life is precious.

Vince taught me the importance of living life to the fullest. Although he was living with cancer, he focused on the “living” part. He worked, saw our son graduate from college, and kept on enjoying friends and cooking and music.

You can live life to the fullest as well! NET research is making progress and this guide will help you get your footing as you learn about how this uncommon disease may affect you. I wish you the best. We are in this together!

Suzanne Ludlow

NET patient spouse

Member, NETRF Board of Directors

Silver Spring, Maryland



About Neuroendocrine Tumors (NETs)

FAST FACTS

- 175,000+ people in the U.S. are living with a NET.¹
- More than 12,000 people in the U.S. are diagnosed with a NET each year.¹
- NET incidence has increased 6.5x from 1973 to 2012.²
- The median length of time that passes from first symptoms to diagnosis is 4.5 years.³
- Up to 58% of patients had metastases at diagnosis.⁴
- The increase in the number of people diagnosed with NETs is attributed in part to improvements in diagnostic techniques and greater awareness of NETs.¹

Facing a NET diagnosis

Having neuroendocrine cancer can be an isolating and scary experience.

Upon diagnosis, many people are bewildered by the names of tests and treatments. You may hear new abbreviations of both letters and numbers that sound strange or seem like alphabet soup. This booklet explains things such as a Ki-67 score, Cu-64 scan, and PRRT therapy. Knowing more about tumor sites, diagnostic tests and treatment approaches may make it easier for

you to ask questions about your NET and understand the answers from your health care team.

Use this booklet as a guide before and after doctor's appointments. Learning as much as possible may help you cope with the uncertainty of neuroendocrine cancer and better understand your diagnosis and treatment options. To make the best use of this booklet, skip around to the sections that matter most to you at this point in your journey. Make notes of questions to ask your doctor or share information with those involved in your cancer care. All of these steps are simple ways to make the experience feel less isolating and less scary.

It may be hard to find physicians who are experts in the care of these tumors, because it is an uncommon cancer. The "Finding Care for NETs" section of this booklet offers practical advice about finding a NET specialist.

What is a neuroendocrine tumor (NET)?

A neuroendocrine tumor (NET) – in some instances also referred to as a neuroendocrine neoplasm – is an uncommon cancer that forms in neuroendocrine cells. (Previously, NETs were called carcinoid tumors or carcinoid cancer.)

NEUROENDOCRINE CELLS

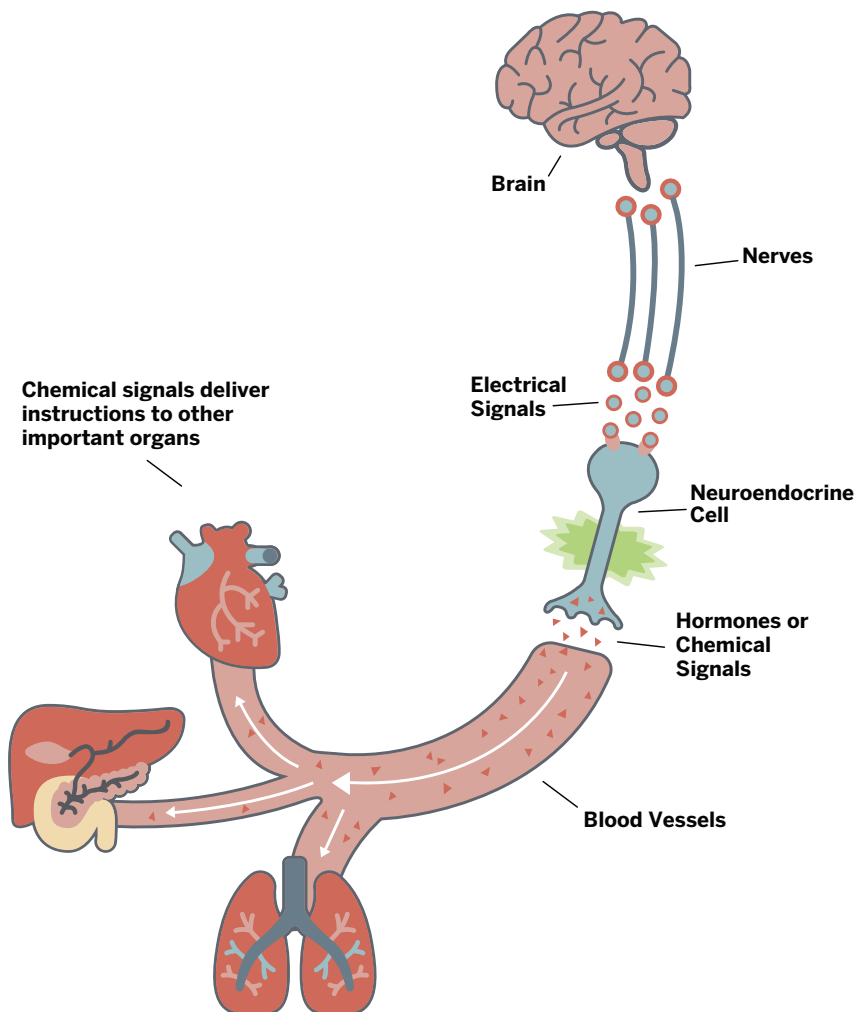
Neuroendocrine cells carry messages from the nervous system to the endocrine system. In response to these messages, the endocrine system makes and releases hormones into the bloodstream that control body functions like blood pressure, heart rate, digestion, breathing, and blood sugar levels.⁵

Neuroendocrine cells occur in many different organs, including:

- Gastrointestinal (GI) tract (small intestine, rectum, stomach, colon, esophagus, appendix)
- Gallbladder
- Pancreas
- Thyroid
- Lungs
- Pituitary glands
- Thymus
- Kidneys
- Prostate
- Skin
- Cervix
- Ovaries
- Testicles

Neuroendocrine Cells are Translators

They take electrical signals from your brain and translate them into chemical signals that can be understood by the other organs in your body.



Notes

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Tumor Sites

FAST FACTS

- 58% of NETs spread beyond the primary site by the time of diagnosis.⁴
- 1 in 2 patients with NETs are first misdiagnosed with another condition such as irritable bowel syndrome, gastritis, or anxiety.⁶
- Most NETs occur in the lungs, appendix, pancreas, small intestine, and rectum.⁷
- A primary tumor site cannot be found for 15% of NETs.⁸

One of the first things to learn about NETs is that no two tumors are alike. Doctors often say these tumors are “heterogeneous,” meaning the NETs can vary by site, how fast they grow, and whether they cause symptoms.

NETs can occur almost anywhere in the body, but most commonly start in the gastrointestinal (GI) tract, lung, or pancreas. The place where a NET first forms is called the primary site.

From its primary site, a NET can spread to other places, such as the lymph nodes or the liver. When a tumor spreads, it is called metastasis.

Sometimes testing will show where neuroendocrine cancer has spread in the body but not where the tumor started (the “primary site”). In such a case, the cancer is said to be of “unknown primary.”

The signs and symptoms for NETs vary depending on the primary site of a tumor.

GI NETs

The most common places for NETs to form in the GI tract are:⁹

- 39% in the small intestine
- 15% in the rectum
- 7% in the appendix
- 5% to 7% in the colon
- 2% to 4% in the stomach

Small bowel NETs are increasing in incidence and are now the most common primary malignancies of the small intestine.¹⁰

WHAT IS THE GI TRACT?

The GI tract consists of organs that help digest food, which are:¹¹

- **Stomach:** The stomach stores swallowed food and liquid, mixes the food and liquid with digestive juices, and slowly empties it into the small intestine.
- **Small intestine:** The muscles of the small intestine mix food with digestive juices from the pancreas, liver, and sometimes the gallbladder, while absorbing vitamins and nutrients from food. The small intestine is made up of three sections: the duodenum, jejunum, and ileum.
- **Large intestine:** Helps to break down food while absorbing liquid from the materials and forming waste product (stool). The colon is part of the large intestine.
- **Rectum:** The rectum stores stool until it is pushed it out during a bowel movement.

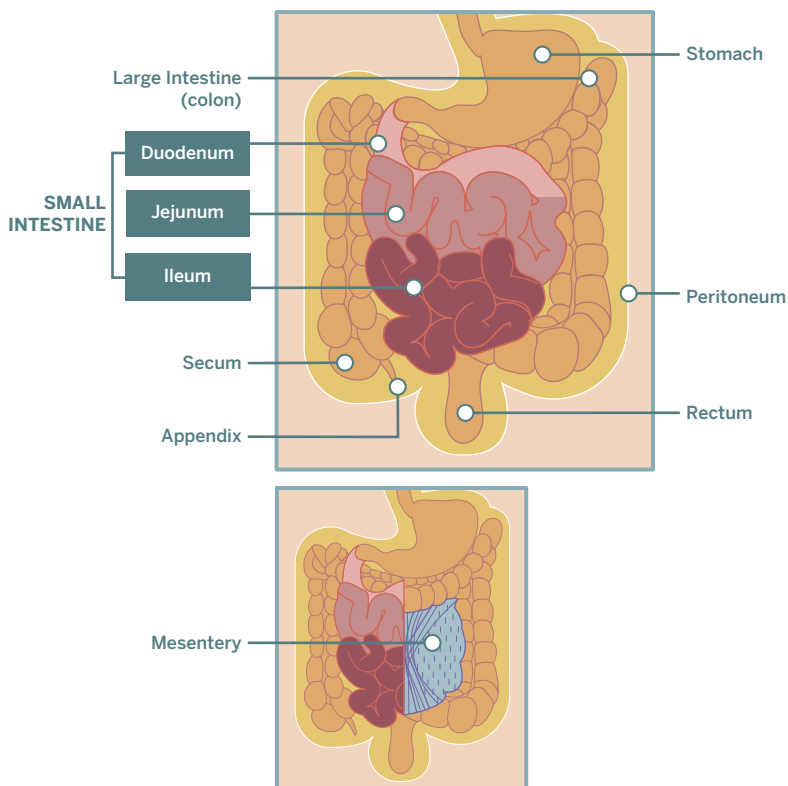
SYMPTOMS VARY BY TUMOR LOCATION

Some GI NETs may not cause any signs or symptoms. A GI NET may cause symptoms when it overproduces and releases hormones into the bloodstream or grows large enough to cause blockages in the GI tract.

The symptoms of a NET in the small intestine may include:¹²

- Abdominal pain
- Constipation
- Diarrhea
- Blood in the stool (or dark and tarry stool)
- Nausea
- Vomiting
- Jaundice from blockage in the bile ducts (yellowing of the skin and the whites of the eyes)
- Rash
- Weight loss

Parts of the Small Intestine



- Fatigue
- Mental confusion

The symptoms of a NET in the large intestine may include:¹³

- Abdominal pain
- Pain in the rectum
- Weight loss
- Diarrhea
- Blood in the stool
- Constipation

The signs and symptoms of GI NETs in the stomach may include:¹⁴

- Abdominal pain
- Weight loss
- Nausea
- Vomiting

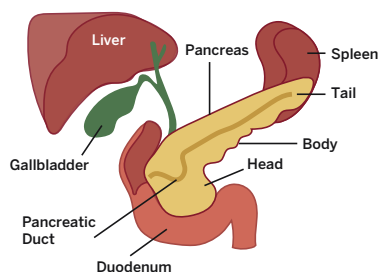
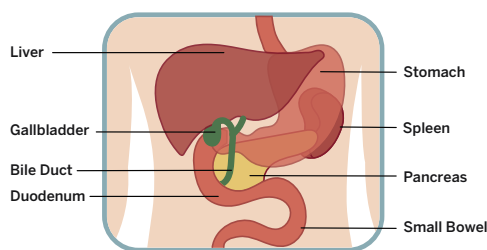
Pancreatic NETs

About 7% of NETs occur in the pancreas.⁸ Pancreatic NETs are sometimes called pNETs.

WHERE IS THE PANCREAS?

The pancreas is in the upper abdomen behind the stomach. It has two essential functions:

- Produce enzymes that break down food in the small intestine (exocrine cells)
- Produce hormones that regulate blood sugar, the movement of the gut, and acid production (endocrine cells)



SYMPTOMS OF PNETS

Some pNETs may not cause any signs or symptoms. But pancreatic neuroendocrine tumors may overproduce hormones and cause a range of symptoms, depending on the hormone.¹⁵ Some of the symptoms include:

- Diarrhea
- Skin rash
- Fatigue
- Nausea
- Hypoglycemia
- Abdominal pain
- Digestive problems
- Gallbladder problems
- Weight changes
- Jaundice

RISK FACTORS FOR PNETS

Most pNETS do not appear to be inherited but some risk factors can run in families. A few different syndromes can increase a person's risk of developing pNETs, including:¹⁶

- Multiple endocrine neoplasia type 1 (MEN1)
- Von Hippel-Lindau (VHL) disease
- Tuberous sclerosis complex
- Neurofibromatosis type 1 (NF1)

Having one of these risk factors does not mean you will develop a NET; it simply increases the likelihood.

PNET vs. pancreatic cancer

Pancreatic neuroendocrine cancer is not the same as “pancreatic cancer,” which usually refers to pancreatic adenocarcinoma. Though they occur in the same organ, these are two different types of cancer.

Pancreatic adenocarcinoma and neuroendocrine cancer differ in terms of cause, symptoms, tests, and treatments.

PANCREATIC ADENOCARCINOMA

- Starts in the exocrine cells
- More common (more than 90%)¹⁷
- Poorer prognosis

PANCREATIC NEUROENDOCRINE TUMOR (PNET)

- Starts in the endocrine cells
- Less common (approximately 7%)¹⁸
- Better prognosis

Lung NETs

About 30% of NETs occur in the lungs.⁸ A lung NET may not cause symptoms in its early stages. Lung NETs are sometimes discovered when patients are screened for unrelated diseases.¹⁹

Lung NETs may be further described based on where they occur in the lungs.¹⁹

- **Central:** forms in the walls of large airways near the center of the lung
- **Peripheral:** develops in the narrow airways toward the edge of the lung

In addition to the lungs, a lung NET can form in the bronchial system (the air passages that lead to the lungs).¹⁹

TYPES OF LUNG NETS

Depending on how fast a lung NET is growing, it may be further classified as:²⁰

- **Typical carcinoid (TC):** may grow slowly and are often centrally located.
- **Atypical carcinoid (AC):** may grow a little faster and are more likely to spread beyond the lungs. They are often peripherally located.

The most aggressive lung NET is small cell lung carcinoma, which is almost always related to smoking.

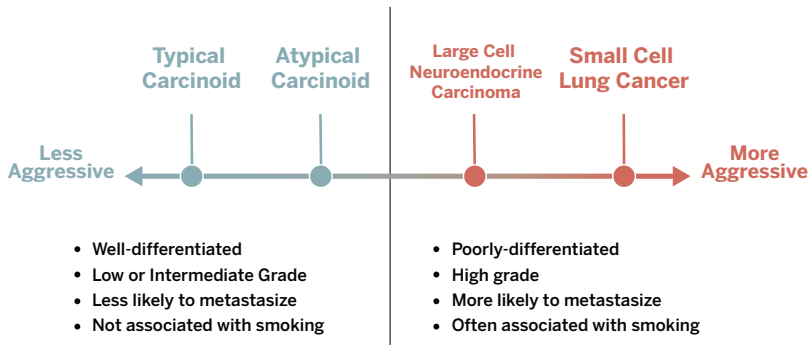
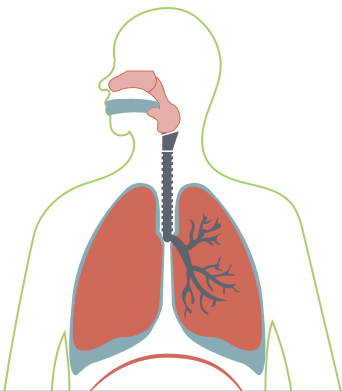
SYMPTOMS OF LUNG NETS

Lung NETs can cause symptoms when they block an airway, such as:²¹

- Cough
- Shortness of breath
- Wheezing
- Chest pain

A functional lung NET, which releases hormones into the blood, may also cause a few other symptoms such as Cushing's syndrome.²¹

Four Types of Lung NETs



Classifications of lung neuroendocrine tumors

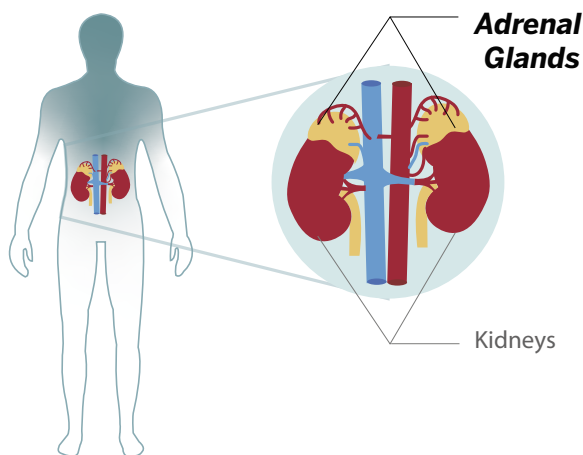
| | Typical Carcinoid | Atypical Carcinoid | Small Cell Carcinoma | Large Cell Neuroendocrine Carcinoma |
|---|-------------------|-----------------------|----------------------|-------------------------------------|
| Grade | | | | |
| Prevalence (% of all lung tumors) | Low 1-2% | Intermediate ~0.2% | High 10-15% | High 2-3% |
| Associated with smoking | No | No | Yes | Yes |
| Overall survival at 5 years | >90% | 50-80% | 5% | 15-40% |

Source: Hung 2019

Adrenal gland NETs

Pheochromocytoma and paraganglioma (also called Pheo/Para) are rare NETs that occur either inside or outside of the adrenal glands. These tumors affect approximately 1 in every 3,000 people.²²

“Pheos” and “Paras”



Paraganglioma

Can be anywhere in the body, most often in the torso, neck, and head

Pheochromocytoma

Only found in the adrenal glands

- * These are very rare NETs. Every year there are only between two and eight new pheo or para diagnoses for every one million people in the United States. The majority of these are pheochromocytomas.
- * Both can cause overproduction of adrenal hormones, resulting in symptoms like high blood pressure, sweating, headache, and feelings of anxiety, nervousness, or anger.
- * Both are strongly associated with genetic syndromes.

WHERE ARE THE ADRENAL GLANDS?

There are two adrenal glands, located on the top of each kidney in the back of the upper abdomen.

Adrenal glands make hormones that control blood pressure and blood sugar to help the body respond to stress.

What are pheochromocytomas and paragangliomas?

- **Pheochromocytomas:** occur in nerve tissue inside the adrenal glands and near certain blood vessels and nerves.
- **Paragangliomas:** occur outside the adrenal glands.

Pheo/para produce excess amounts of adrenaline and related hormones, which are the “fight-or-flight” hormones usually released in response to stress.

Pheo and para symptoms

When pheo and para tumors release too much adrenaline or noradrenaline, it may cause:²¹

- High blood pressure
- Headache
- Heavy sweating without any known reason
- A strong, fast, or irregular heartbeat
- Shakiness
- Extreme paleness

The signs and symptoms of pheo and para may occur after:²¹

- Strenuous physical activity
- Physical injury
- Emotional stress
- Childbirth
- Undergoing anesthesia
- Surgery (which may include surgery to remove the tumor)
- Eating foods and drinks that are high in tyramine (such as red wine, chocolate, and some meats and cheeses)

Risk factors for pheochromocytoma and paraganglioma

Sometimes specific syndromes or gene changes passed down in families can increase the risk of pheochromocytoma or paraganglioma.²¹ These risk factors include:

- Multiple endocrine neoplasia 2 syndrome types A and B (MEN2A and MEN2B)
- Von Hippel-Lindau (VHL) disease
- Neurofibromatosis type 1 (NF1)
- Hereditary paraganglioma syndrome (succinate dehydrogenase mutations)
- Carney-Stratakis dyad
- Carney triad

Having someone in your family with one of these risk factors does not mean you will develop this type of cancer; however, it increases the likelihood.²⁴



Nonfunctional and Functional NETs

FAST FACTS

- About 60% of NETs are non-functional.⁸
- Carcinoid syndrome is a manifestation of some metastatic midgut NETs.

Some NETs release hormones, which can cause a lot of disruptive symptoms. When a NET produces hormones, it is called a “functional” neuroendocrine tumor. When a NET does not produce hormones, it is called “nonfunctional.” Nonfunctional and functional tumors are generally associated with gastrointestinal (GI),

pancreatic, and lung NETs. Testing can help determine whether a tumor is functional or nonfunctional.

Nonfunctional and functional GI NETs

Although many nonfunctional GI NETs may grow for a long time without causing signs or symptom, some nonfunctional tumors may cause signs or symptoms if the tumor blocks parts of the GI tract. In functional GI NETs, the hormones released are usually metabolized as the blood flows from the gut

to the liver. If the tumor has spread to the liver and the liver enzymes cannot destroy the extra hormones made by the tumor, high amounts of these hormones may remain in the body and cause carcinoid syndrome.⁴⁸

Carcinoid syndrome

The signs and symptoms of carcinoid syndrome include:^{9,49}

- Flushing of the skin and face (without sweating)
- Abdominal pain
- Feeling bloated
- Diarrhea
- Wheezing or other trouble breathing
- Fast heartbeat
- Blood pressure fluctuations
- Heart murmur
- Lower extremity swelling (if the hormones affect the right side of the heart and its valves)

RISKS AND COMPLICATIONS OF CARCINOID SYNDROME

Carcinoid syndrome can lead to heart damage or heart disease.⁴⁸ Up to one-third of those with carcinoid syndrome may develop thickening in their cardiac valves.⁵⁰ Talk to your doctor about any carcinoid syndrome symptoms you experience, as it is important to manage carcinoid syndrome to reduce risks and prevent complications. Treatments can help alleviate the symptoms of carcinoid syndrome. Lifestyle changes, such as avoiding alcohol and certain foods, may also help in managing symptoms, as certain food items and stress can trigger them.⁵¹

CARCINOID CRISIS

Some patients experience severe, sudden, and even life-threatening symptoms called a carcinoid crisis. A carcinoid crisis, which affects a person's blood pressure and heart rate, typically occurs during surgery, invasive procedures, or in times of severe stress.⁴⁸ A carcinoid crisis can be prevented and treated with hormone therapy.⁵² To prevent problems, you may need to take medication to manage hormone production before surgery or other procedures.⁴⁸

Nonfunctional and functional pNETs

Although nonfunctional pNETs can grow for a long time without causing signs or symptoms, the size of the tumor may cause:¹⁵

- Diarrhea
- Indigestion
- A lump in the abdomen
- Pain in the abdomen or back
- Jaundice (yellowing of the skin and whites of the eye) if a bile duct is blocked

Functional pNETs can overproduce and release large amounts of these hormones into the bloodstream, depending on the endocrine cell of origin:⁵³

- Insulin: lowers the levels of sugar in the blood⁵⁴
- Glucagon: increases the levels of sugar in the blood⁵⁴
- Gastrin: gives a signal to the stomach to produce more stomach acid⁵⁴
- Vasoactive intestinal peptide (VIP): helps control water, salt, enzyme, and gastric acid secretions in the body. It also plays a role in the relaxation of smooth muscle in the digestive tract, heart, and blood vessels⁵⁵
- Somatostatin: helps regulate other hormones in the body⁵⁴

When a pNET releases hormones, it may also be called:⁵³

- Insulinoma
- Glucagonoma
- Gastrinoma
- VIPoma
- Somatostatinoma

Nonfunctional and functional lung NETs

Functional NETs in the lungs can cause a range of symptoms such as flushing, diarrhea, or wheezing.⁵⁶

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, or DIPNECH, is a rare lung condition characterized by the abnormal proliferation of pulmonary neuroendocrine cells. DIPNECH may or may not cause symptoms. Over time, DIPNECH may progress to a lung NET. The cause of DIPNECH is not known. NETRF is funding research to better understand this rare condition.

Notes

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Diagnostic Testing for NETs

FAST FACTS

- 1 in 2 U.S. patients reports being diagnosed with other conditions along with neuroendocrine cancer.²⁵
- The average time from a person's first symptom to a diagnosis with a NET is approximately 4.5 years.³
- NETs are often found when people have x-rays or medical procedures for other reasons.²⁶
- Patients saw an average of 5 healthcare professionals before receiving their diagnosis.²⁵
- Only 1 in 5 U.S. patients thought their symptoms could be cancer.²⁵
- Less than half of those with NETs feel they have enough information at the time of diagnosis.²⁷

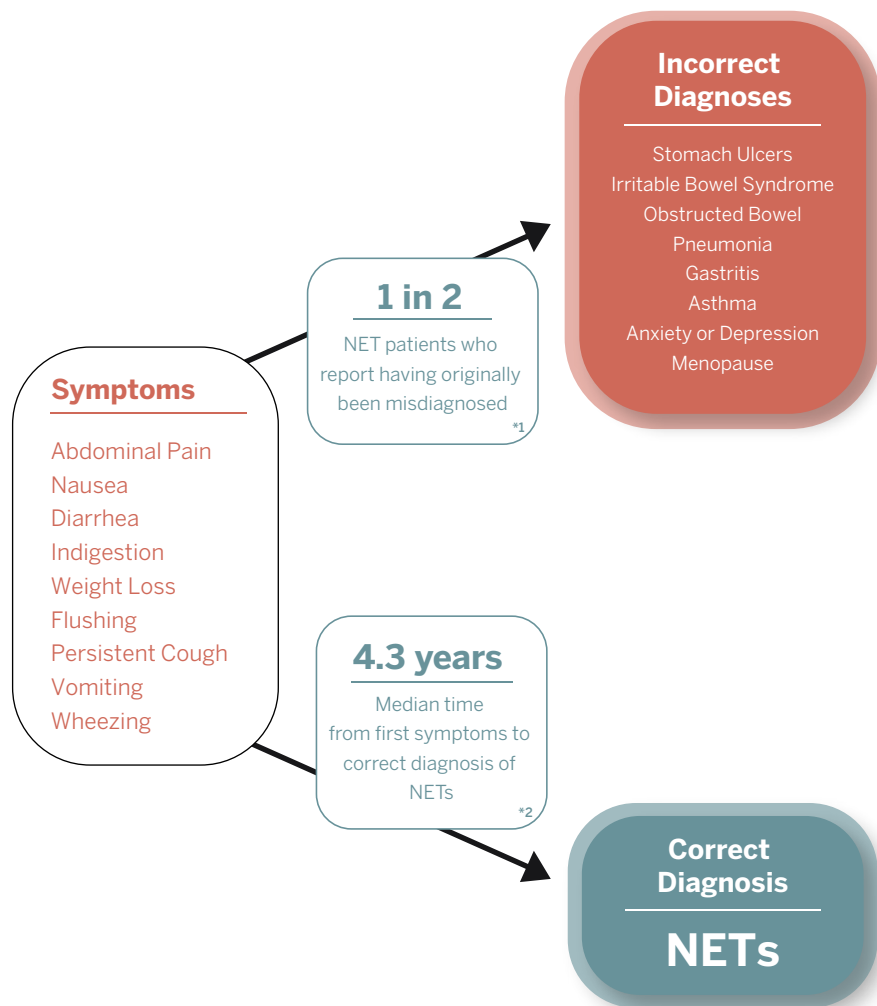
Testing can help your doctor understand the specifics of your tumor type and develop a treatment plan for your neuroendocrine cancer.

Imaging tests

Imaging tests diagnose and monitor NETs. Since NETs can sometimes be hard to “see,” your doctor may use different scans than those used for other types of cancer.

Misdiagnosis of NETs

The symptoms of neuroendocrine tumors are often mistaken for those of more common conditions



^{*1} Wolin EM, Leyden J, Goldstein G, et al. Patient-reported experience of diagnosis, management, and burden of neuroendocrine tumors: results from a large patient survey in the U.S. *Pancreas*. 2017; 16(5):639-647.

^{*2} Singh S, Granberg D, Wolin E, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETs. *J Glob Oncol*. 2016;2(1):43-53.

COMPUTED TOMOGRAPHY (CT)

Computed tomography, or CT, uses a highly specialized x-ray machine and computers to create multiple cross-sectional images of the body. A CT scan can generate images of different body tissues as well as help detect tumors. A dye may be injected into a vein or swallowed to help the organs or tissues show up on the scans more clearly.

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging, or MRI, uses radio waves, a powerful magnetic field, and a computer to generate detailed (i.e., two- or three-dimensional) images of the body. These images are useful in contrasting different types of tissue as well as detecting abnormal growths in the body like tumors. MRI can be useful for locating and measuring metastases.

POSITRON EMISSION TOMOGRAPHY (PET)

Positron emission tomography (PET) uses radioactive material and a special scanning device to detect NETs.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY

Gallium 68 (Ga-68) or Copper-64 (Cu-64) scan

This imaging test uses a radioactive tracer called Gallium-68 (Ga-68) or Copper-64 (Cu64) to bind to a tumor's somatostatin receptors. Patients undergo a PET scan after an injection of the tracer (Ga-68 or Cu64). The images from the scan can show NETs located anywhere in the body if the tumors have receptors for the tracer.

Octreoscan

Octreoscan uses a radioactive substance that can bind to and illuminate any somatostatin receptors in a tumor (not all tumors have somatostatin receptors). In this test, a tiny amount of radioactive octreotide is injected into a vein so it can travel through the bloodstream. Octreotide then attaches to the tumors and a special camera that detects radioactivity shows the sites in the body in which the tumors are located. In many centers, the Gallium or Copper-64 scan is preferred to the octreoscan.

FDG (fluorodeoxyglucose) scan

A FDG-PET can find fast-growing neuroendocrine cancer cells in many aggressive tumors. A small amount of FDG, a type of radioactive sugar, is injected into a vein. The PET scanner rotates around the body and constructs a picture of where the body is using the sugar. Cancer cells appear brighter in the picture because they are more active and take up more sugar than healthy cells. FDG is commonly used to detect tumors that are high grade and/or poorly differentiated.

MIBG scan

An MIBG scan is used to find pheochromocytoma and paraganglioma. A tiny amount of a radioactive substance called MIBG is injected into a vein so it can travel through the bloodstream. The scan can then detect NET cells that take up MIBG. These scans may be taken over a period of 1-3 days.

ENDOSCOPY

Endoscopy is a medical procedure that uses an endoscope to view the lining of multiple organs in the body. An endoscope is a flexible or rigid tube with imaging capabilities that can enable small surgical procedures. Endoscopy can be used to visualize tumors in the lungs and GI tract, small/large intestine, and rectum. Sometimes, an ultrasound probe is put on the end of the endoscope to perform what is called an endoscopic ultrasound, which can be particularly useful for looking at adjacent organs like the pancreas.

Colonoscopy

Colonoscopy is a procedure to look inside the rectum and colon for abnormal tissue or cancer. A colonoscope is a thin, tube-like instrument with a light and a lens to inspect the rectum and colon. The instrument may also have a tool to remove polyps or tissue samples, which are then analyzed under a microscope for signs of cancer.

Upper GI Endoscopy

An upper GI endoscopy or esophagogastroduodenoscopy (EGD) is a procedure doctors use to diagnose and treat problems in the upper GI tract, which includes your esophagus (food pipe), stomach, and the first part of your small intestine (the duodenum).

Bronchoscopy

Bronchoscopy is a procedure to look inside the trachea and the large airways in the lung for abnormal areas. A bronchoscope is a thin, tube-like instrument with a light and a lens that is inserted through the nose or mouth and down into the trachea and lungs. The bronchoscope may also have a tool to remove tissue samples, which are then checked under a microscope for signs of cancer.

5-HIAA tests

Hydroxyindoleacetic acid (5-HIAA) is a breakdown product of the hormone serotonin, which NETs can release. Since serotonin levels go up and down throughout a typical day, a 24-hour urine collection of the 5-HIAA byproduct is more reliable in measuring the daily amounts of the hormone. Some centers now have the capability of doing this test with a blood sample, eliminating the need to collect urine. Your doctor may use the 5-HIAA test in diagnosing and monitoring some neuroendocrine cancer.

FOODS TO AVOID

The following are some food items to be avoided for 48 hours before a 5-HIAA test:²⁸

- Avocados
- Bananas
- Cantaloupe
- Eggplant
- Grapefruit
- Dates
- Hickory nuts
- Honeydew melon
- Kiwi
- Pecans
- Pineapple
- Plantains
- Plums
- Tomatoes and tomato products
- Walnuts

Other items may also affect your test results. Before starting your urine test, be sure to ask your doctor for a complete list of the foods and medications you need to avoid.

Blood tests

CHROMOGRANIN A (CGA)

Chromogranin A (CgA) is a protein commonly released by NET cells. A blood test is used to measure CgA. Serial CgA measurements during follow-up should be performed at approximately the same intervals after the administration of a long-acting SSA. False-positive levels of CgA may occur due to several issues such as the use of proton pump inhibitors (medications to treat heartburn).²⁹ As better imaging techniques have been developed, there may be less utilization of CgA tests. Chromogranin A is a tumor marker and not a hormone; it is not part of diagnostic testing.²⁶

BLOOD CHEMISTRY TESTS

Blood chemistry tests measure certain substances such as glucose (sugar), enzymes, fats, and proteins. Blood chemistry studies give essential information about how well a person's kidneys, liver, and other organs are working. An unusual (either higher or lower) result can be a sign of disease.³⁰

FASTING SERUM TESTS

Fasting serum tests measure the amount of gastrin, sugar, glucagon, vasoactive intestinal peptide (VIP), or somatostatin in the blood. For these tests, patients may need to fast for at least 8 hours.⁶

NETest

A blood test called the NETest looks for molecular evidence of tumor activity. It is more sensitive than other tumor markers. Recently published results on the NETest following surgery have been promising, showing that a positive NETest following resection can be a predictor of recurrence.^{31,32}

Tissue tests

Your doctor may remove a piece of tumor tissue to study it in the laboratory. Tumor tissue testing will confirm if a tumor is cancerous and can identify treatments that are most likely to help treat the cancer.

Before you undergo a tumor tissue test, consider learning about NET tissue donation and how your tissue may help researchers develop laboratory models of NETs. NETRF works with Pattern.org to collect excess tissue for research into the causes and treatments of NETs. This excess tissue is a very small amount and does not affect your diagnosis or tumor typing. For more information about tumor tissue donation, visit pattern.org.

PROCEDURES FOR REMOVING TISSUE SAMPLES

During a biopsy a physician removes cells or tissues for testing. The method used to do a biopsy depends on the location of the tumor.

ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATIONS (EUS-FNA)

Endoscopic ultrasound-guided fine-needle aspirations (EUS-FNA) involves taking a sample of tissue to examine it under a microscope. An endoscope is a thin, tube-like instrument with a light and a lens and a biopsy needle at the end. An integrated ultrasound probe bounces high-energy sound waves off internal organs and tissues to create a picture on a monitor. This picture helps the doctor see the location where the biopsy needle is to be placed.

BIOPSIES FOR LUNGS

FINE-NEEDLE ASPIRATION (FNA)

Fine-needle aspiration (FNA) is a biopsy of the lung that involves removing tissue or fluid with a thin needle. A CT scan, ultrasound, or other imaging procedure first finds abnormal tissues or fluid in the lung. A small incision is then made in the skin and the biopsy needle is inserted into the abnormal tissue or fluid. A sample is then removed with the needle and sent to a laboratory where a pathologist will view the sample under a microscope to look for cancer cells. A chest x-ray is done after the procedure to make sure no air is leaking from the lung into the chest.

LABORATORY TESTS FOR TUMOR TISSUE SAMPLES

IMMUNOHISTOCHEMISTRY (IHC)

Immunohistochemistry (IHC) uses antibodies to check for specific antigens in a tissue sample. The antibody is usually linked to a radioactive substance or a dye that causes the tissue to brighten under a microscope. This type of test may be used to tell the difference between the types of cancer. Typically, pathologists will test tumor tissue for chromogranin A and synaptophysin, among other markers.



NET Grade and Stage

FAST FACTS

- More than 1 in 3 patients with a NET do not know their tumor grade.²
- 91% of patients with NETs report their grade as 1 or 2.⁴

Your test results help your doctor to classify your tumor grade and cancer stage, which are important for establishing the plan for your treatment.

What is a tumor grade?

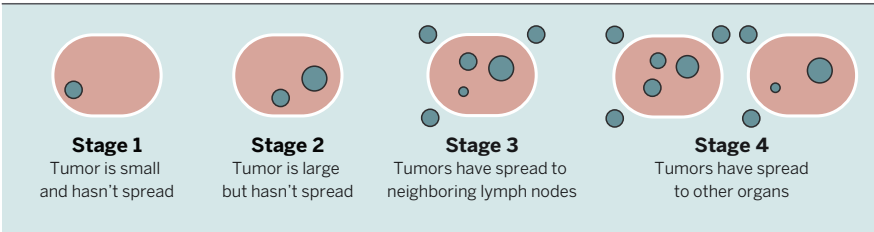
Tumor grade is based on how abnormal cancer cells and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread.

Laboratory analysis by a pathologist will determine tumor grade. Generally, a lower grade indicates a better prognosis.³³ Usually, higher-grade cancers grow more quickly and require more aggressive treatment.

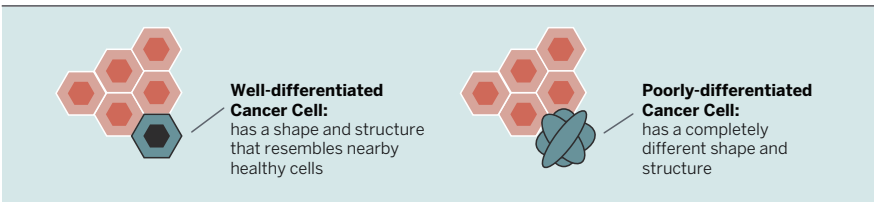
Stage, Differentiation, & Grade

These are easily confused, but are actually very different metrics that say very different things about a tumor

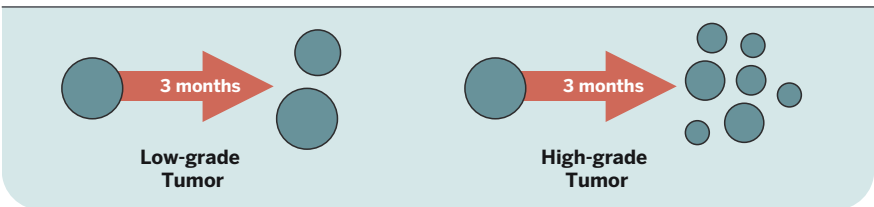
Stage | Tells **how far** cancer has travelled from the site of the original tumor



Differentiation | Tells **how abnormal** the tumor cells look when compared to the surrounding healthy cells



Grade | Tells **how quickly** the tumor cells are dividing



DIFFERENTIATION

- Well-differentiated: The tumor's cells and the organization of tissue in the tumor resemble nearby healthy cells and the organization of normal tissue. Well-differentiated tumors tend to grow and spread slowly.³⁴
- Poorly differentiated: These tumors have abnormal-looking cells and may lack normal tissue structures. Poorly differentiated tumors tend to grow quickly.³⁴

You should speak to your doctor for more information about your tumor grade and how it affects your treatment options and prognosis.

KI-67

Ki-67 is a protein that indicates cell division, or proliferation. Pathologists use tumor tissue samples to test for Ki-67. This test can show the number of cells that are dividing and the number of cells that are dormant. The level of Ki-67 in cells increases as cells prepare to divide. If there is a high percentage of cells in a particular area of tumor tissue with a high Ki-67 level, this means the cells are quickly dividing.^{34,35} The results of a Ki-67 test help to establish a grade for a tumor, which indicates how fast cancer may be growing. Ki-67 is expressed on a scale of zero to 100 percent.

HIGH-GRADE NETS

The World Health Organization classifies NETs, as well as neuroendocrine carcinomas or NECs, based on how much cancer is present and how aggressive the cancer is. Among the determining factors in the grade of NETs is the Ki-67 index and whether the cancer is well-differentiated or poorly differentiated.

Low-grade NETs, grade 1 or 2, are defined as well-differentiated tumors with a Ki-67 index of less than 20%. These tumors are not as aggressive. High-grade tumors with a Ki-67 index of more than 20% are classified as grade 3. Grade 3 tumors can be well-differentiated or poorly differentiated. Poorly-differentiated Grade 3 tumors are referred to as NECs. These tumors grow faster, are more aggressive and are treated differently than lower-grade NETs.

If you have a high-grade NET or NEC, it is important to see a NET specialist with experience treating these more aggressive tumors. For more information on high-grade NETs, go to NETRF's NETWise podcast (netrf.org/podcast). The HealingNET Foundation also has a publication with more information about high-grade neuroendocrine cancers (thehealingnet.org/high-grade-neuroendocrine).

What is a cancer stage?

Cancer stage refers to the extent of your cancer, depending on how large the tumor is and how far it has spread (metastasized).³⁶ Knowing the stage of your cancer helps your doctor:

- Understand how serious your cancer is
- Plan the best treatment for you
- Identify clinical trials that may be treatment options for you

STAGES I-IV

Doctors often use Stage I-IV to describe stages of cancer.³⁷

If cancer comes back or spreads to other parts of the body, your doctor may “restage” your cancer. If treatment is successful, you may also hear the phrase “no evidence of disease” or “NED,” which means that current testing methods cannot detect any signs of cancer in the body.³⁸



6

Finding Care for NETs

FAST FACTS

- The likelihood of being diagnosed at a NET specialist center has increased in recent years.²⁵
- NET patients most frequently see oncologists/hematologists, followed by general practitioners and surgeons.²⁵
- On average, patients travel an average of 30 miles to see a NET provider.²⁵

People who have a NET can face challenges to get an accurate diagnosis and find specialized care. Since NET symptoms may mimic those of other common conditions such as irritable bowel syndrome, menopause, or asthma, many people are at first misdiagnosed.⁴ Some physicians have never seen a patient with a NET. Patients who have an uncommon cancer like a NET and their families often must advocate for themselves to receive specialized care in a complex health care system.

Finding a NET specialist

A standard piece of advice you will hear frequently is to find a NET specialist. If you have a NET, it is important to build a care team based on the type of NET you have and your specific needs.

The term “multidisciplinary” describes an approach to treatment planning that relies on a team of different types of doctors and health care providers. This team meets regularly, sometimes at conferences called “tumor boards,” to review a patient’s medical history and test results. Members of the team offer input based on their specialized experience and training. With the input of the experts and an understanding of the patient’s wishes and goals, the team comes up with a treatment plan. The makeup of a multidisciplinary team can vary depending on a person’s medical needs.

The task of finding a physician can seem daunting, but NETRF makes it easier for people to find doctors who specialize in the treatment of neuroendocrine cancer. NETRF has a database of U.S. NET specialists on our website as well as a listing of U.S. cancer centers that have multidisciplinary NET treatment programs.

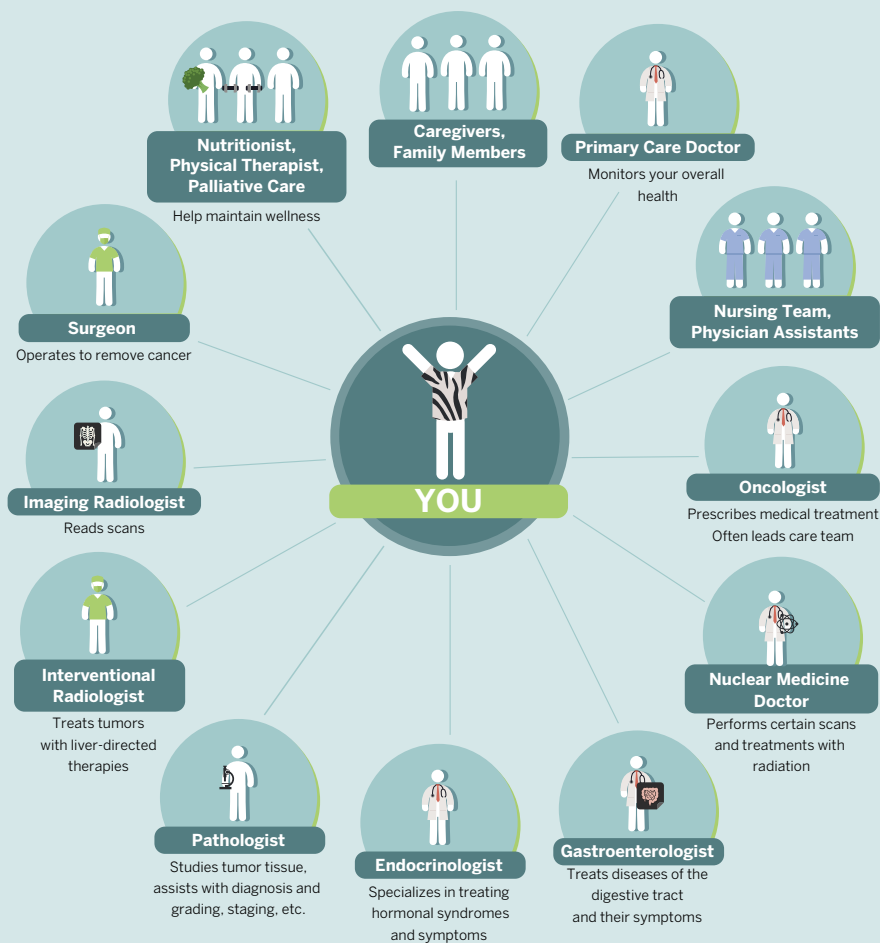
NETRF’s YouTube channel ([YouTube.com/c/NETRF](https://www.youtube.com/c/NETRF)) features talks by health care providers who specialize in NETs. Looking at these videos may also help you find a NET specialist.



www.netrf.org: Find a NET Specialist

Your Care Team

NETs are a complicated disease, and successful care and treatment requires the input of a lot of different specialists. These might include:



More ways to look for a NET specialist

PATIENT SUPPORT AND ADVOCACY ORGANIZATIONS

Check out NET advocacy and patient support groups to find NET specialists. These groups, run by patients and caregivers, meet in communities across the U.S., both in person and virtually. Organizers and participants typically know a lot about the physicians in their areas. NETRF has a list of U.S. patient support groups (netrf.org).

PHYSICIAN ORGANIZATIONS

When looking for NET specialists, check out the professional associations for physicians who focus on NETs. Looking at the physicians who are active in these societies can be another way to identify a physician specializing in NETs.

- North American Neuroendocrine Tumor Society (NANETS)
- European Neuroendocrine Tumor Society (ENETS)
- Society for Nuclear Medicine and Molecular Imaging (SNMMI)

PUBLISHED RESEARCH

Physicians who specialize in NETs may be conducting clinical research. You can search on PubMed or Google Scholar for scientific articles about your diagnosis. Look at the names and institutions of the authors or look for physicians conducting NET clinical trials at clinicaltrials.gov.

Talking with your doctor

Once you find the right doctor, it is important to build rapport and maintain good communication.

Doctors' appointments can at times be overwhelming. You may hear so much information that it is hard to take it all in or understand all of it. During visits, it may seem like there is never enough time to ask all your questions. To make the most of your appointments, consider some of the following suggestions.

Preparing for doctors' appointments

- Write down your questions in order of importance. Don't leave out something you think may be considered silly; list all the concerns you have.
- Keep track of any symptoms or side effects that you experience in a symptom diary. As you do so, don't forget to include the details about how long you have been experiencing problems, when they usually occur, how severe your symptoms are, and whether they interfere with your ability to carry on with daily activities.
- When going to a new health care provider or specialist, bring a copy of your current medications list and ask which other medical records you need to bring beforehand.
- If possible, make multiple appointments on the same day.
- For any routine testing, ask your doctor if imaging centers or laboratories close to your home can be used.
- Start a notebook, file, or something else to organize all your medical information. Check out NET Vitals from LACNETS (lacnets.org/netvitals), a tool to collect all the key information about your diagnosis and treatment in one document.
- Let your doctor know in advance if you need an interpreter due to language or communications differences.
- Try to figure out transportation, directions, and parking in advance to make your arrival as smooth as possible. For large institutions, find out what entrance and elevator you need to take to get to the right floor.

TELEMEDICINE AND TECHNOLOGY

The increased use of telemedicine, which has accelerated during the COVID-19 pandemic, has created new opportunities for NET patients. Virtual appointments are now helping some NET patients across the country to reach out to NET specialists and stay in contact with their own physicians. There may be licensing limitations on whether an out-of-state physician can have a virtual visit with you and insurance companies have different rules on whether they will cover telemedicine. That said, it is worth asking about telemedicine, especially if you would need to travel a long distance for an in-person appointment.

Ask if your physician has a patient portal. Some patient portals allow you to message your health care provider and request appointment changes or prescription refills. Download any needed telehealth apps on your phone or tablet. Get familiar with these digital tools so you can use them to maintain communication with your care team.

It is important to establish and maintain good communication with your care team to build trust. By being more informed and involved in your care, you may find it easier to follow your care plan to work toward the best possible results.



Treatment of NETs

FAST FACTS

- Before receiving a NET diagnosis, patients see on average five health care providers during 12 visits.²⁵
- 72% of patients with NET have surgery.²⁵
- 91% of patients with NET want a wider range of treatment options for ongoing management of their NETs.²⁵
- 76% of patients with a NET feel they know about the available treatment options.²⁵

Treatment can reduce the number and size of NETs as well as reduce some of the symptoms caused by tumors. The most common NET treatments are:

- Surgery
- Somatostatin analogs (hormone)
- Targeted and chemo therapies
- Interventional radiology
- Nuclear medicine
- Clinical trials

Surgery

Surgery is a common treatment for NETs, with 72% of patients reporting having surgery.²⁵ The type of surgery depends on the tumor site, grade, stage, and disease burden (the severity of disease and its impact on daily life). Surgeons also consider a patient's age, overall health, and any other

chronic diseases as criteria for surgical treatment options. Surgery can sometimes remove early-stage tumors that have not spread, offering patients the possibility of a curative treatment.³⁹ In advanced cases, surgery can reduce tumor bulk to treat symptoms and improve the quality of life.⁴⁰

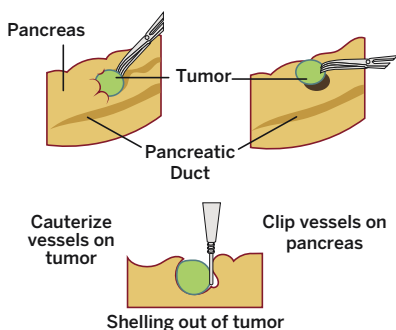
PANCREAS⁴¹

- **Distal pancreatectomy:** Removes the body and tail of the pancreas. The spleen may also be removed if cancer has spread to the spleen.
- **Central pancreatectomy:** Removes the neck and part of the body of the pancreas. The procedure spares the tail to help maintain the function of the pancreas.

NET Surgeries in the Pancreas

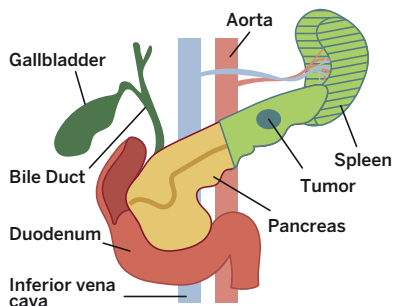
Enucleation

Removes ONLY the tumor itself

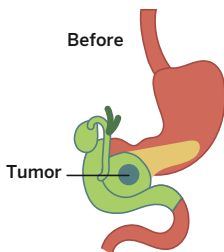


Distal Pancreatectomy

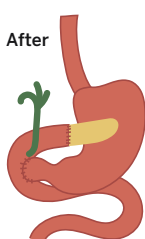
Removes the tail and/or body of the pancreas (and sometimes also the spleen with lymph nodes)



Before



After



Pancreatoduodenectomy ("Whipple Procedure")

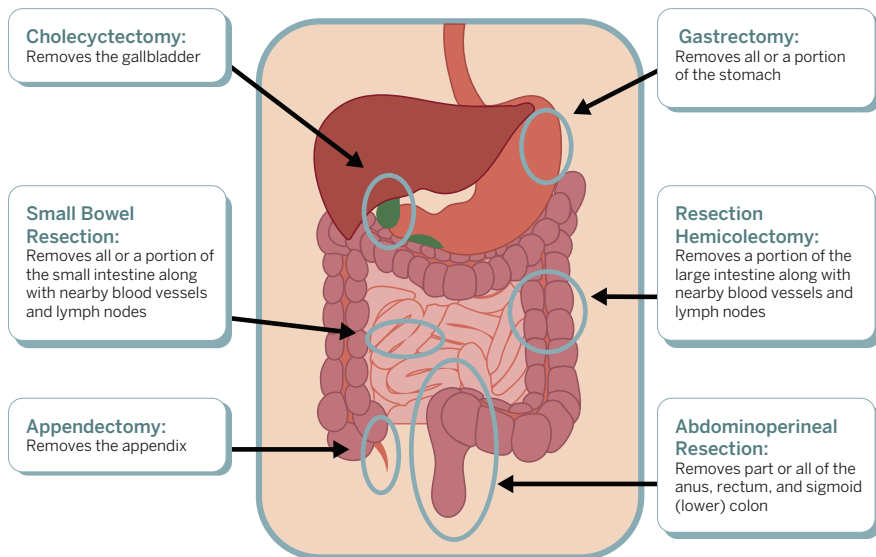
Removes the head of the pancreas, the gallbladder, nearby lymph nodes, and parts of the stomach, small intestine, and bile duct. The remaining parts of these organs are then reconnected in a new way.

- Enucleation: Removes the tumor only. This surgery may be done when cancer occurs in one place in the pancreas.
- Pancreatoduodenectomy (Whipple procedure): The head of the pancreas, gallbladder, nearby lymph nodes, part of the stomach, small intestine, and bile duct are removed, although enough of the pancreas is left to make digestive juices and insulin. The patient's condition determines which organs are to be removed during this procedure.

GASTROINTESTINAL TRACT^{42,43}

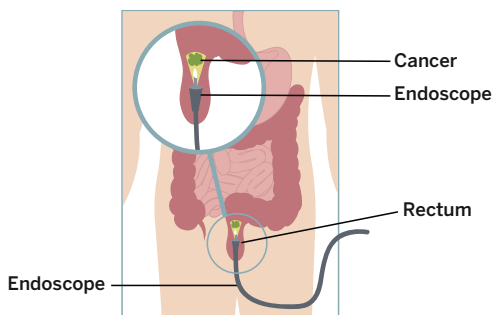
- Appendectomy: Removes the appendix
- Cryosurgery: Uses an instrument to freeze and destroy the NET tissue. This type of treatment is also called cryotherapy. The doctor may use ultrasound to guide the device.
- Endoscopic resection: Removes a small tumor that is on the inner lining of the GI tract. An endoscope is inserted through the mouth and passed through the esophagus to the stomach and, sometimes, the duodenum.
- Gastrectomy: Removes all or part of the stomach
- Liver resection: Remove portions of the liver where cancer can be found
- Liver transplant: Removes the whole liver and replaces it with a healthy donated liver
- Local excision: Remove the tumor and a small amount of healthy tissue around it
- Resection: Removes all or part of the organ that contains cancer. Nearby lymph nodes may also be removed.
- Segmental colon resection or hemicolectomy: Removes part of the colon as well as the nearby tissue, blood vessels, and nearby lymph nodes
- Small bowel resection: Removes all or part of the small intestine and the nearby organs where cancer may have spread

NET Surgeries in the Gastrointestinal Tract



Endoscopic Resection:

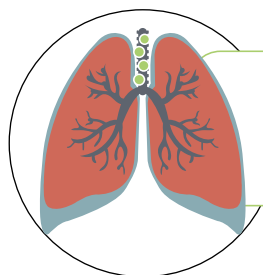
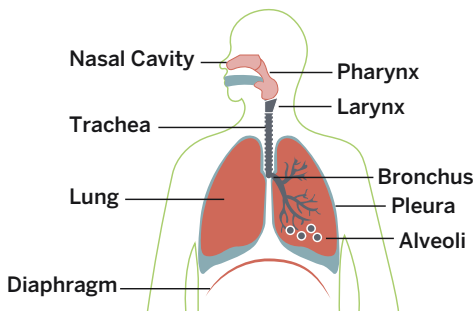
Removes small tumors from the colon, or stomach by means of an endoscope – a combination camera and cutting tool inserted up the anus or down the throat



- **Abdominoperineal resection (APR):** Major surgery using different approaches to remove the anus, rectum, and part of the sigmoid colon through an incision made in the abdomen. The end of the intestine is attached to an opening in the surface of the stomach, and the body waste is collected in a disposable bag outside of the body. This opening is called a colostomy. Lymph nodes that contain cancer may also be removed during this procedure.

- Lobectomy: Removes a whole lobe of the lung
- Pneumonectomy: Removes one whole lung.
- Sleeve resection: Removes the tumor and part of the bronchus (airway).

NET Surgeries in the Lungs



LYMPH NODE DISSECTION:

Removes cancerous lymph nodes



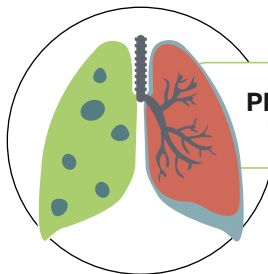
WEDGE RESECTION:

Removes a small, wedge-shaped section of lung



LOBECTOMY:

Removes an entire region of the lung (called a lobe)



PNEUMONECTOMY:

Removes one entire lung

- **Wedge resection:** Removes a tumor and some of the healthy tissue around it in the shape of a small wedge. If a larger amount of tissue is taken, it is called a segmental resection.
- **Lymph node dissection:** Removes lymph nodes to check for or prevent the spread of cancer

Sometimes surgeons may recommend surgery to take out some of a tumor, even if it is not possible to remove all of it. This is called cytoreduction or debulking surgery and can be a treatment option for liver tumors.

Therapies

Different therapies or drugs are used to slow or stop the growth of neuroendocrine cancer cells. Close to half of patients who have a NET report using drug therapies other than chemotherapy, including somatostatin analogs.²⁵ Fewer patients (about 1 in 5) reported being treated with chemotherapy.²⁵

SOMATOSTATIN ANALOG THERAPY

Hormone therapy with a somatostatin analog may stop an excess of hormones from being released by NETs, which can improve quality of life.⁴⁵ Somatostatin analog injections may improve symptoms and, in some patients, may help slow tumor growth but cannot cure them. The side effects can be relatively mild and may include nausea, cramping, loose stools, abnormal stools (steatorrhea), and changes in heart rate.⁴⁴ Given by injection, somatostatin analogs are available in long- and short-acting formulations and include:

- Octreotide
- Lanreotide

TARGETED THERAPY

Targeted therapy uses drugs or other substances to identify and attack specific cancer cells without harming healthy cells. Targeted therapy changes the way cancer cells grow, divide, and spread. For example, they may block or turn off signals to make more cancer cells. For NETs, a few targeted therapies have been approved by the U.S. Food and Drug Administration (FDA), which are:

- Everolimus
- Sunitinib

Other types of targeted therapies are being studied to treat NETs.

CHEMOTHERAPY

Chemotherapy can stop the growth of cancer by either killing cancer cells or stopping their division. Taken by mouth or injected, chemotherapy drugs enter the bloodstream and reach cancer cells throughout the body. Sometimes, one or more chemotherapy drugs may be used together. The way the chemotherapy is given depends on the type of tumor being treated. Some of the chemotherapy drugs used to treat NETs include:^{45,46}

- Capecitabine
- Carboplatin
- Cisplatin
- Dacarbazine
- Doxorubicin
- Etoposide
- 5-fluorouracil
- Oxaliplatin
- Streptozocin
- Temozolomide

IMMUNOTHERAPY

Immunotherapy involves using a patient's own immune system to fight cancer. At present, immunotherapy is more commonly used in other cancer types. NETRF is funding studies to learn more about the role immunotherapy can play in treating NETs.

INTERVENTIONAL RADIOLOGY

Interventional radiology is a minimally invasive approach to treat neuroendocrine cancer that has spread to the liver. Often called liver-directed therapy, this approach starves liver tumors by denying them the nutrients they require to grow.

HEPATIC ARTERIAL EMBOLIZATION

Hepatic arterial therapy reduces or blocks the flow of blood to stop cancer cells from getting the oxygen and nutrients they require to grow. The sources of blood to the liver are the portal vein and hepatic artery.

Hepatic embolization blocks or reduces the flow of blood in the hepatic artery to kill cancer cells growing in the liver. The portal vein continues to supply blood to the liver. There are two types of hepatic embolization:

- Bland embolization: injection of embolic particles, such as tiny gelatin sponges or beads to reduce blood flow
- Chemoembolization (TACE): injection of embolic particles (to reduce blood flow) that are mixed with chemotherapy (to kill tumor cells) or the direct infusion of chemotherapy in the artery by use of a catheter

RADIOEMBOLIZATION

Radioembolization combines embolization with radiation therapy to kill tumor cells in the liver. A doctor injects millions of radioactive microspheres (or microscopic beads) into the hepatic artery, which then emit radiation to kill tumor cells.

RADIOFREQUENCY ABLATION (RFA)

Radiofrequency ablation (RFA) uses an electrical current to destroy tumor cells. RFA involves placing a small probe into a tumor to raise the tumor temperature and destroy it. RFA can be done laparoscopically but is more commonly done in combination with liver resection.

Nuclear medicine therapy

PEPTIDE RECEPTOR-RADIONUCLIDE THERAPY (PRRT) / RADIOLIGAND THERAPY

Radioactive drugs to treat NETs were available in Europe for many years and peptide receptor radionuclide therapy (PRRT) was approved there in 2017. The following year, the U.S. FDA approved Lutetium-177 (Lu-177) to treat NETs in the GI tract and pancreas, and iobenguane i-131 (i-131) to treat advanced pheochromocytoma or paraganglioma. These radioactive drugs are delivered intravenously to target specific characteristics of NET cells. This therapy is also known as radioligand therapy.

PRRT is a method of delivering radioactive drugs through the bloodstream. Unlike healthy cells, some NET cells have proteins (called receptors) on their cell surface that can bind to hormones. PRRT targets and kills tumor cells by releasing radioactive compounds, called radiopeptides, that can bind to these receptors and then emit radiation to kill NET cells.

BENEFITS OF PRRT WITH LU-177

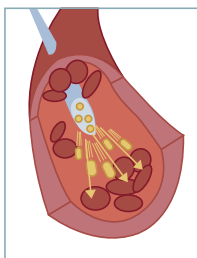
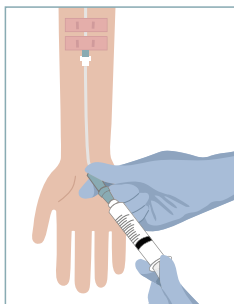
Studies of Lu-177 have shown PRRT can:

- Increase progression-free survival
- Improve a patient's quality of life
- Relieve symptoms
- Decrease tumor size

PRRT for NETs

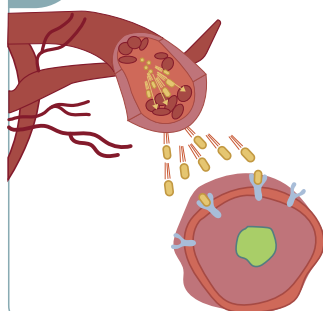
1.

PRRT treatment is injected into the bloodstream and seeks out somatostatin receptors on NETs.



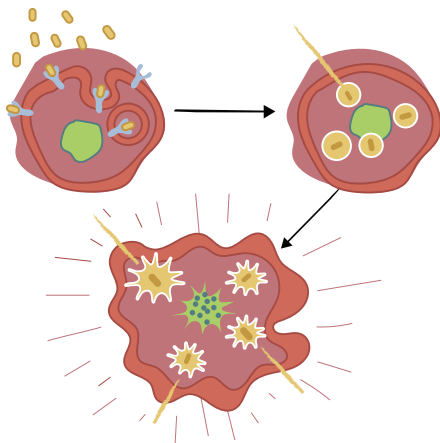
2.

PRRT finds and binds to the cell's receptors.



3.

Radioactive material enters the tumor and kills cancer cells.



4.

Remaining radiation is flushed from the body.



SIDE EFFECTS OF PRRT WITH LU-177

Although generally well tolerated, PRRT with Lu-177 may have side effects such as:

- Nausea
- Vomiting
- Decreased blood cell counts
- Increased liver enzymes
- Decreased blood potassium levels
- Increased blood glucose

These common side effects are often mitigated or avoided by taking amino acids, fluids, and anti-nausea medication at the time of treatment.

Less common and more serious side effects include bone marrow or kidney toxicity. Studies have shown there is a risk of less than 2% of developing blood cancers such as leukemia or myelodysplastic syndrome.

NETRF has funded research to study new nuclear particles to be used in PRRT, as well as combinations of PRRT and existing drugs that may make the treatment more effective.

Clinical trials and research

Clinical trials test the safety and effectiveness of new therapies. By participating in a clinical trial, patients may get early access to the latest treatment options. Clinical trials also help improve care for other patients.

WHAT IS A CLINICAL TRIAL?

Clinical trials are the final step in a long process that begins with research in a lab. Before any new treatment is used in people in clinical trials, researchers work for many years in the lab to understand its effects by testing it first on cells or in animals. They then work to determine the best dose for treatment, the side effects the drug may cause, and how the effectiveness of the drug compares to current treatments. It can take 10-15 years to develop a new drug to the point of a first clinical trial.

Clinical trials occur in phases. Once a new treatment is successful in one phase, it may proceed to the next phase.⁴⁷

Phases of Clinical Trials



Pre-Clinical Phase:

Does a new compound have a desired effect at a chemical level?

1. Computer modelling
2. "In Vitro" experiments: testing isolated chemicals in the laboratory
3. "In Vivo" experiments: testing in animals, such as mice or zebrafish

Phase 1 Trials:

Is the compound safe for patients to take?

- Small cohorts
- Primary Goal is to determine proper dosage and frequency of administration for further trials
- Identifying early signals of therapeutic activity is often a secondary goal



Phase 2 Trials:

Does the compound have the desired chemical effect in humans?

- Medium-sized cohorts
- Goal is to see if patients have anti-tumor response as measured against a defined endpoint



Phase 3 Trials:

Does taking the compound result in better patient outcomes?

- Large cohorts, often split and randomized into trial and control groups
- Goal is to see if clinical results are better than with existing treatments



FDA Approval



Phase 4 Trials:

Does data from use in the real world support the results of earlier trials? Are there any new adverse events which were not identified during drug development?

- Often based on data collected from clinicians

How to find a clinical trial

Clinical trials have strict criteria for eligibility. Speak to your doctor about your interest in clinical trials. Your doctor will be a good resource to help you determine what is best for you.

QUESTIONS TO ASK YOUR DOCTOR ABOUT CLINICAL TRIALS

If you are thinking about taking part in a clinical trial, ask your doctor: “Is there a clinical trial that I can join?” If your doctor does offer you a trial, the following are some of the questions you may want to ask:

Questions about the trial

- What is the purpose of the trial?
- Why do the researchers believe that the treatment being studied may be better than the one being used at present? Why may it not be better?
- How long will I be in the trial?
- What kinds of tests and treatments are involved in the trial?
- How will the doctor know if the treatment is working?
- Who will be in charge of my care?
- Can I talk to someone who has been in the trial?

Questions about risks and benefits

- What are the possible side effects or risks of the new treatment?
- What are the possible benefits?
- How do the possible risks and benefits of this trial compare to those of the standard treatment?

Questions about your rights

- How will information related to my health be protected?
- What will happen if I decide to leave the trial?

Questions about costs

- Will I have to pay for any of the treatments or tests?
- What costs will my health insurance cover?

Questions about daily life

- How often will I have to come to the hospital or clinic?
- Will I have check-ups after the trial?

Questions about comparing choices

- What are the other treatment choices available to me, including standard treatments?
- Will I know if I'm receiving the treatment being studied or a placebo?

Cancer.net offers additional questions you can ask your healthcare team about clinical trials and offers a link to a mobile app (cancer.net/cancer-types/neuroendocrine-tumors/questions-ask-health-care-team).

LEARN MORE ABOUT CLINICAL TRIALS

Learning more about clinical trials may make it easier for you to talk to your doctor about possible studies. Some resources for learning about clinical trials include:

- ClinicalTrials.gov – to search for available trials
- National Cancer Institute – offers basic information on clinical trials (cancer.gov/about-cancer/treatment/clinical-trials)
- American Society of Clinical Oncology – provides an introduction to cancer research for patients (cancer.net/research-and-advocacy/introduction-cancer-research)
- NETRF – highlights new NET clinical trials in the monthly e-update newsletter and explains clinical trials in an episode of the NETWise podcast. You can subscribe to NETRF's e-update newsletter at netrf.org/for-patients/ and listen to our podcasts at netrf.org/podcast/.



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Notes



Inherited Risk Factors for NETs

FAST FACTS

- Most small and large intestine NETs occur spontaneously, but some are associated with an inherited syndrome.⁵⁷
- 35% of pheochromocytomas and paragangliomas are associated with a hereditary syndrome.⁵⁸

We don't know what causes many NETs. Most seem to develop sporadically. Even though the causes of NETs are not largely known, we do know that some risk factors for neuroendocrine cancers can be passed down in families.

Researchers estimate that inherited factors may be associated with 10% of PNETs⁵⁹ and 35% of

pheochromocytomas and paragangliomas.⁵⁸ Other rates vary depending on the primary site and subtypes of tumors.

Your medical history and your family's medical history are part of the evaluation process. Having a first-degree relative with a known mutation also plays a vital role in establishing a clinical diagnosis. In some cases, the presence of two or more associated medical conditions or syndromes may indicate an inherited genetic condition.

| Inherited Risk Factors for NETs | | | |
|--|--|--------------------------------|--|
| Name | Associated Syndromes and Conditions | Affected Gene(s) | Related NETs |
| MEN1: Multiple endocrine neoplasia type 1 ^{a,b,c,d} | Zollinger-Ellison syndrome ^e Pituitary adenoma Parathyroid adenoma Adrenocortical tumors Lipomas | MEN1 | Gastrinomas Insulinomas VIPomas Glucagonomas Somatostatinomas Other NETs (broncho-pulmonary, gastric, thymic) |
| MEN2: Multiple endocrine neoplasia type 2 ^a | MEN2A syndrome (familial medullary thyroid cancer, hyperparathyroidism) MEN2B syndrome (cutaneous lichen amyloidosis, Hirschsprung disease) | RET | Pheochromocytoma |
| MEN4: Multiple endocrine neoplasia type 4 ^{a,f} | Overlaps with other MEN syndromes, pituitary adenoma, primary hyperparathyroidism (PHPT) | CDKN1B | NETs (pancreatic, lung, gastric) ^b |
| VHL ^b | Von Hippel-Lindau disease (renal cell carcinoma and hemangioblastomas) | VHL | Pheochromocytomas Paragangliomas Pancreatic NETs |
| CGA: glucagon cell adenomatosis ^g | Mahvash disease | GCCR | Pancreatic NETs |
| SDG: succinate dehydrogenase ^a | Hereditary Paraganglioma Syndrome Carney-Stratakis syndrome Pituitary adenoma, GIST, RCC | SDHD SDHAF2 SDHC SDHB | Paraganglioma |
| TSC: Tuberous sclerosis complex ^b | A wide spectrum of benign tumors, skin abnormalities and behavioral/cognitive problems | TSC1 TSC2 | Pheochromocytoma Pancreatic NETs ^b |
| NF1: Neurofibromatosis type 1 ^a | von Recklinghausen disease Neurofibromas Peripheral nerve sheath tumors Optic glioma | NF-1 | Paragangliomas Pheochromocytomas Gastrointestinal tract and pancreatic NETs ^b |

Being aware that you have an inherited genetic risk factor will not always have an impact on your treatment plan but it may affect how your doctor monitors your health. If a genetic mutation is confirmed, your doctor may order additional testing regularly to look for other problems associated with that risk factor.

There are many different types of gene tests, which use a range of technologies. The gene testing kits advertised on TV (also known as direct-to-consumer testing) will probably not identify risk factors for NETs. Your doctor can order a test to look for specific mutations.

Genetic tests

Your doctor may order genetic testing if your medical or family history indicates that you may have an inherited risk factor. Doctors can test for inherited mutations using blood or saliva.

WHO SHOULD BE TESTED?

Genetic testing looks for specific genes as well as certain changes in those genes. It is essential that your care team guides any decisions about genetic testing so the test results are reliable, accurate, and meaningful.

Genetic testing may not always be appropriate, especially if the results will not affect treatment planning. Genetic counseling can help you consider the risks, benefits, and limitations of genetic testing.

Genetic counseling includes a detailed review of an individual's personal and family medical history that is relevant to the possible cancer of risk.

Counseling also includes discussions about issues like:

- Whether genetic testing is appropriate
- Which specific test(s) might be used
- The technical accuracy of the test(s)
- The usefulness of the test in making health care decisions
- The psychological risks and benefits of learning one's genetic test results

Genetic tests may not be covered by all the insurance plans or may be covered only based on strict criteria. Contact your health insurance plan to learn more about your coverage and inquire about the costs before making any decisions about genetic testing.

Ask your doctor if there's a genetic counselor who works with their team or look for a genetic counselor here: nsgc.org/page/findageneticcounselor

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| | |
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|--|---|



9

Managing Your Symptoms

FAST FACTS

- 92% of patients with NET make one or more lifestyle changes due to their condition.⁴
- 56% of patients with NET report general fatigue/muscle weakness.⁴
- 48% of patients with NET experience diarrhea.⁴
- 20% of patients with NET seek counseling for emotional symptoms.⁴

People who have a NET can lead meaningful, active, and productive lives. Learn how you can make the most of every day.

Managing symptoms of NETs

There is no doubt that life changes the instant you learn you have a NET. For some, the news comes following years of persistent, unexplained ailments. Those who have no symptoms or whose tumor was

discovered incidentally during routine medical care or while being treated for another condition may be shocked to learn they have cancer.

A person with neuroendocrine tumors can have symptoms for the following reasons:

- A NET may release hormones into the bloodstream

- Cancer treatment may have side effects
- Tumors may cause blockages or affect organ function as they grow
- Diabetes is connected to some pancreatic NETs
- Gallbladder problems are common
- Surgery for a GI or pancreatic NET affects digestion

Tell your doctor about any symptoms or side effects that you may be experiencing. To explain the frequency and seriousness of any side effects, keep a log of your symptoms and share it with your care team. This may help your doctor in recommending modifications or treatment options to alleviate any symptoms.

DIARRHEA

Diarrhea is a common and troublesome symptom in many people who have a NET. There are several reasons that could explain the diarrhea, from the disease itself to side effects from the treatment. There are a few steps you can take to try to reduce the severity and frequency of diarrhea caused by NETs. In addition to limiting certain kinds of food and drinks (see Nutrition chapter on page 67), it is important to talk to your doctor about other ways to treat your diarrhea. For example, a medication called telotristat ethyl is approved to treat carcinoid syndrome diarrhea in combination with somatostatin analog therapy.

CANCER-RELATED FATIGUE

Fatigue is one of the most common issues faced by people living with NETs.⁴ Beyond physical exhaustion, fatigue may also cause emotional exhaustion. This makes fatigue tough to tackle. There are a few things you can do to help manage your cancer-related fatigue, including:

- Schedule activities for the time of day when your energy level is usually highest.
- Schedule rest when your energy level is usually low.
- Avoid overscheduling and pace yourself.
- Establish a sleep routine for going to bed and getting up at the same time each day.
- Sleep 7-8 hours a day.
- Prepare for sleep with a relaxation routine such as taking a bath, reading, or whatever helps you wind down from the day.
- Use your bed for sleep and sex only (don't read, watch TV, or use electronics in bed).
- Keep your bedroom cool and dark.

- Limit daytime naps to less than 30 minutes.
- Exercise may gradually increase your energy.
- Consider the role that anxiety, stress, or depression may play on your energy level.

Additionally, talk to your care team about your cancer-related fatigue. There may be other tests or treatments that can help resolve the issue.

Integrative care

Integrative care for people who have cancer includes mind-body practices, natural products, and lifestyle modifications in conjunction with conventional cancer treatment. Upwards of 90% of patients who have cancer use integrative medicine approaches like acupuncture, yoga, massage, mindfulness, meditation, hypnosis, and massage for pain management and enhanced quality of life.

Some complementary and alternative medicine approaches like acupuncture, yoga and meditation have been studied and are considered to be safe and effective. Other approaches, however, may not be beneficial and may actually be harmful, depending on the treatment you are receiving.^{60,61} Be sure to talk to your care team about any integrative, complementary, or alternative medicine therapies you are considering to ensure those therapies are safe and will not negatively interfere with your cancer treatment.

Managing emotions

People face many emotions when living with a NET, with 60% of patients saying their disease had an impact on their emotional health.⁴ It is challenging to live with the uncertainty of the diagnosis. The upheaval may seem never-ending. It can be a marathon of tests, treatments, symptoms, and syndromes. Some patients may experience symptoms daily. Emotions can change from day to day and week to week, which is true for both newly diagnosed patients and those who have been living with a NET for many years.

Those who have cancer may experience:⁶²

- Feelings of being overwhelmed
- Anger
- Fear and worry
- Hope
- Stress and anxiety

- Sadness and depression
- Guilt
- Loneliness
- Gratitude

EXPRESS YOUR EMOTIONS

Share what you are feeling with those you trust. Talk to your family and friends about your feelings. If you have a faith community, consider reaching out to a faith leader for support. One in five NET patients seeks counseling for the emotional aspects of the illness.⁴ Your care team may be able to suggest names of counselors with experience in treating cancer survivors. Many patients living with a NET benefit from attending patient support groups where they can share concerns and solutions with others who are facing the same cancer.

If you are not yet ready to talk, consider other ways to express yourself. Some people keep a journal of their thoughts and feelings. Engaging in any creative art form – like painting, woodworking, music, film, poetry, or photography – may help you identify and understand your feelings.³¹

KEEP LEARNING

Fear and worry can sometimes take over. In these situations, it helps to be informed. Most people feel better when they learn the facts, as they feel less afraid and are aware of what to expect. Play an active part in your care by learning as much as you can about NETs.

FIND OUTLETS FOR RELAXATION

Anxiety, fear, and worry can tighten muscles and make your mind race. It helps to find ways to let go of the tension. Meditation, guided imagery, and relaxation exercises may help you.

BE AS ACTIVE AS YOU CAN

Getting out of the house to do something can help you focus on things besides cancer and the worries it brings. Exercise, gentle yoga, and stretching can help, too.

GET INVOLVED

Some people living with NETs find fulfillment by volunteering for a worthy cause. Community involvement can offer social, professional, and emotional benefits. Whether you volunteer for a NET-related organization like NETRF or causes that are not related to NETs, helping others can be emotionally uplifting.

LOOK FOR THE POSITIVE

Sometimes, looking for the positive in a situation means looking for the good even in a bad time or trying to be hopeful instead of imagining the worst. Try to use your energy to focus on wellness and what you can do presently to stay as healthy as possible.

MAKING THE MOST OF EACH DAY

Being diagnosed with neuroendocrine cancer may change all that you have come to know as normal. Instead, you may need to discover a “new normal.” As part of the new normal, many patients undergo the stress of routine scans to check for the growth or recurrence of tumors. You may take medication for years to manage symptoms or reduce the risk of your cancer progressing.

In between injections, infusions, and CT scans, you can still lead an active and meaningful life. Each person finds his or her way forward. Yes, your life will be different – your work and relationships may change, sometimes for the better.

We want you to know there is a tight-knit and supportive NET community. Even though you may have never met another person with neuroendocrine cancer, you can easily find a robust community of NET patients who are experiencing the same symptoms, challenges, and fears. While NETs are uncommon, people touched by this disease have found many ways they can come together to help one another.

Notes



10

Nutrition and NETs

FAST FACTS

- Patients with NETs reported issues with nutrient absorption, vitamin deficiency, and hyperglycemia.²⁵
- 64% of patients with NETs reported making lifestyle changes related to nutrition.²⁵

Eating well with NETs

Proper nutrition helps support your cancer treatment by helping you maintain your general health throughout your treatment, enhancing your quality of life, and minimizing nutrition-related side

effects. By paying attention to what, when, and how you eat, you can ease troublesome symptoms caused by NETs. NETs and NET patients vary quite a lot from one to the next, and the best approach to improving your nutrition varies just as much.

A majority of patients who have a NET say they need to make dietary changes as a result of their disease.²⁵ Pay attention to your body's response to different foods and what you can and cannot tolerate. Finding what you can and cannot eat can be a process of trial and error. Your ability to tolerate certain foods can change from time to time. Some people with NETs find they can eat a certain food when it is cooked, but not when it is raw. As a rule of thumb, choose foods and drinks that are gentle on your digestive system.

When and how to eat to help manage your symptoms

Minor adjustments related to when and how you eat can help alleviate diarrhea for those who have NETs.

- Eat small and frequent meals.
- Don't drink while you are eating; drink 30-45 minutes before a meal.
- Drink 6-8, 8-ounce glasses of fluid a day. Spread your fluid intake out during the day by taking regular sips. When you have diarrhea, drink no more than 4 ounces at a time.
- Pay close attention to food safety to avoid food-borne illnesses. Freeze food items right away. Dispose of old, expired items. Throw out leftovers after 48 hours.

What to avoid if you have NET symptoms

To reduce the frequency and severity of gastrointestinal symptoms, try to reduce or cut the consumption of the foods you find irritating. As your triggers for symptoms may differ from other patients, it is helpful to keep a food diary until you identify the foods that are irritating or helpful for you. If you are experiencing digestive problems, avoid highly processed foods and carbonated beverages as well as foods that are high in:

- Fiber (insoluble fiber)
- Amines (chemicals found in fermented, charred, overripe, and overcooked foods)
- Fat
- Sugar
- Salt
- Heat/hot spices (capsaicin)
- Alcohol
- Caffeine
- Aged cheeses and meats

Foods to eat when you have a NET

Talk to your doctor about your diet and consider asking for a referral to see a registered dietitian with expertise in nutrition for patients who have a NET. Work with your treatment team on a personalized nutritional plan to support your health. Your medical history and any other health conditions will drive your daily food choices. Some of the food choices others have found helpful are included in the chart below, but work to develop modifications based on your personal experience.²⁹

| EATING WELL WITH NETs | | |
|-----------------------|--|---|
| | EAT THIS | CONSIDER AVOIDING THIS |
| Vegetables & Fruit | Peeled, cooked vegetables (potatoes, squash, carrots, parsnips, zucchini, summer squash, turnip) | Tomatoes and tomato products |
| | Cooked vegetables (asparagus, string beans, peas, shallots, onions, green onions, red bell pepper) | Corn, cruciferous vegetables (broccoli, cauliflower, cabbage, brussels sprouts) |
| | Raw vegetables (leafy greens, celery (with ribbing peeled), cucumber (peeled and seedless)) | Raw onions Pickled vegetables |
| | Peeled fruits [apple, pear, peach, nectarine, mango, papaya] | Dried fruit, canned fruit in heavy syrup |
| | Blueberries, strawberries | Pineapple |
| | Grapes | Overripe bananas |
| | Cantaloupe/honeydew melons | Watermelon |
| Grains | Oatmeal | Wheat |
| | White rice | Dried beans (red, black, pinto) |
| | White bread | |
| | Quinoa | |
| Dairy | Lactose-free (if lactose intolerant) rice or almond milk | Aged cheese |
| | Low-fat dairy products | |
| Protein | Skinless chicken | Bacon, processed meat (luncheon meat) |
| | Fresh fish, seafood | Fatty fish |
| | Eggs, egg substitute | Nuts |
| | Lean meats | Smoked meats |
| Fats and Oils | Unsaturated fats (canola, safflower, sunflower) | Saturated fats (butter, shortening, coconut oil) |
| | | Fried food |
| | | Chips |
| | | Pastries |
| | | Avocado |
| Beverages | Water, flavored water | Caffeinated beverages like coffee, tea |
| | Diluted sports drinks | Alcoholic beverages |
| | Diluted fruit juice | Fruit juice |

Resources

There are a number of resources that may help you on your journey with a NET. Sign up for our newsletter and follow us on Twitter, Facebook, YouTube, and Instagram. Check out the resources on our website, including our NETWise podcast, and consider joining us for our patient and caregiver conferences. We hope to be an essential and helpful part of your life with neuroendocrine cancer. NETRF is here for you.



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 **@CureNETs**

 **@NETRF**

 **NETRF**

 **@netresearch**

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