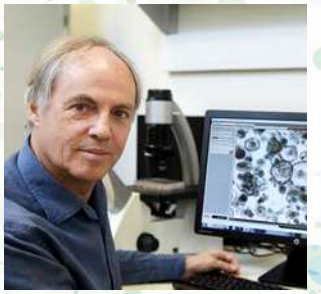
NEUROENDOCRINE CANCER

A guide for patients and families









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NEUROENDOCRINE TUMOR RESEARCH FOUNDATION

We are here today, for your tomorrow.

Visit **netrf.org** to learn about the promising neuroendocrine cancer research we fund, find more educational resources, and learn about ways to support NETRF. Sign up for our newsletter using the QR code and follow us on Facebook, Instagram, LinkedIn, X, Bluesky, and YouTube. We hope to be an essential and helpful part of your life as you navigate neuroendocrine cancer.

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About the Neuroendocrine Tumor Research Foundation (NETRF)

Nancy Lindholm founded NETRF (originally called the Caring for Carcinoid Foundation) in 2005 after being diagnosed with metastatic neuroendocrine cancer at age 29. 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 scientific advisors. She also gathered others with personal or family experience with neuroendocrine cancer to form a Board of Directors.

Today, NETRF honors Nancy's legacy by serving as the largest global funder of groundbreaking neuroendocrine cancer research, driving innovation worldwide to advance our understanding and treatment of this complex and formidable disease.

For more than 20 years, NETRF has remained committed to our mission of transforming hope into breakthrough science, and those breakthroughs into new and improved treatments. NETRF has invested more than $43 million to accelerate neuroendocrine cancer research – supporting emerging investigators and established scientists while fostering collaboration among hospitals and academic institutions.

NETRF is making the once impossible, possible by advancing leading-edge research in early detection and personalized treatments, empowering patients and their loved ones with solutions today and the promise of brighter tomorrows.

Educating and Empowering Patients

We work to improve the lives of patients, families, and caregivers affected by neuroendocrine cancer with educational resources, including:

- NET Knowledge Center
- Monthly NETRF News
- NETWise podcasts
- Extensive YouTube library with videos about diagnosis, treatment, research, and living with neuroendocrine cancer
- Thrivership resources
- Patient and caregiver education conferences
- Searchable directory of providers and multidisciplinary treatment programs

How to Use this Guide

At NETRF, we recognize that every patient's journey is unique — whether you or a loved one is newly diagnosed, exploring treatment options, or navigating long-term management strategies. We also understand that everyone begins this journey at different stages and has different information needs along the way.

That's why we've designed this guide to be easy to use. Our mission is to support, educate, and empower patients, caregivers, and families, ensuring you have the information and resources needed to navigate this complex condition with confidence.

Consider this guide as a supportive companion to consult before and after doctor's appointments. Gaining a deeper understanding of neuroendocrine cancer can help ease some of the uncertainty and give you the knowledge needed to navigate your diagnosis and treatment options.

To make the best use of this guide, simply skip to the sections that matter most to you at this point in your journey, jot down notes and questions for your doctor, and share information with those involved in your care. Small steps like these may help reduce the anxiety that comes with managing neuroendocrine cancer.

You are not alone in this journey, and we are here to help every step of the way.

NETRF would like to thank the following people for their valuable review and insightful contributions to this new edition of our Patient Guide:

- Elyse Gellerman, NETRF Chief Executive Officer
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- Tobi Walsh

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Medical Disclaimer: This guide 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)

FOREWORD

In 2012, tumors in my husband's liver were diagnosed as neuroendocrine. At that time, there was little information about neuroendocrine cancer and few treatment options available. Today things are changing and having this publication is part of that change. I want to thank NETRF for assembling this Guide and keeping it up to date. The Patient Guide reflects the many recent advances in research and treatments, and now also includes information on neuroendocrine carcinoma.

My husband, Vince Taylor, lived well with neuroendocrine tumors (NETs) for six years, and we learned a lot about neuroendocrine cancer 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, race or gender-based assumptions, and geographic distance. My husband and I were fortunate to have many advantages, but there were times when I believe racial bias slowed provision of some treatment and when busy doctors' schedules meant that outreach to neuroendocrine cancer specialists by our medical team was delayed. Part of the reason I wanted to write this foreword is to encourage you to learn enough information about neuroendocrine cancer to really advocate for yourself and your family.

Here are several lessons we learned:

- Connect with medical professionals experienced in neuroendocrine cancer. As these cancers are uncommon and varied, 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 guide 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 neuroendocrine cancer 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 at a time when funding for critical research is being cut and when medical best practices are being questioned. This means that it is more important than ever to find trusted sources and advocate for yourself. I know it is hard to do when you are also dealing with medical symptoms and the pressures of daily life, but it is absolutely essential.

NETRF is the most trusted global resource for neuroendocrine cancer information and the largest funder of neuroendocrine cancer research. Read this Guide, go onto the NETRF.org website to listen to the podcasts that combine medical information along with patient insights, and search the provider directory to find a neuroendocrine cancer specialist who can work with you.

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 – all the while – enjoyed friends and cooking and music. He was a wonderful role model, and his love remains a force in our lives.

You can live life to the fullest as well! This guide will help you get your footing as you learn how this uncommon disease may affect you. So, take that deep breath and then know we are in this together!

Suzanne Ludlow
NET patient spouse
Vice President, NETRF Board of Directors
Silver Spring, Maryland

FACING NEUROENDOCRINE CANCER

Receiving a neuroendocrine cancer diagnosis can be overwhelming and may feel isolating. It's natural to have questions and concerns, especially when faced with unfamiliar medical terms and complex treatment decisions.

From the moment of diagnosis, you may find yourself navigating a maze of new tests, procedures, medical jargon, and abbreviations that may seem like an alphabet soup of letters and numbers. You might encounter terms like "Ki-67 score," "dotatate scan," "Cu-64 scan," and "peptide receptor radionuclide therapy," wondering what they may mean for you. This guide aims to demystify these terms and provide clear explanations of tumor sites, diagnostic tests, and treatment options – empowering you to engage more confidently with your health care team.

Because neuroendocrine cancer is uncommon, finding the right medical expertise can be challenging. The "Finding Care" section of this guide offers practical advice on how to locate specialists who are experienced in diagnosing and treating these tumors, ensuring you receive the highest quality of care available.

UNDERSTANDING NEUROENDOCRINE CANCER: A COMPLEX BUT NAVIGABLE LANDSCAPE

Neuroendocrine cancer is a broad term used to describe various types of tumors that develop from neuroendocrine cells — specialized cells found throughout the body that help regulate many essential functions by releasing hormones. Some medical societies or physicians may use the term “neuroendocrine neoplasms” to refer to neuroendocrine cancer.

As you read through this guide, you will come across different terms such as neuroendocrine cancer, neuroendocrine tumors (NETs), and neuroendocrine carcinomas (NECs). In this guide, we use the term neuroendocrine cancer to cover information that applies to both NETs and NECs. When details apply to only one type, we will specifically refer to either NETs or NECs.

WHAT THE TERMS MEAN

Neuroendocrine cancer includes both neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). The words "tumor" or "carcinoma" describe how the cancer behaves and how aggressive it may be. These terms can be confusing, so here's a quick breakdown to help clarify them.

- **Neuroendocrine cancer:** A type of cancer that develops from neuroendocrine cells, which are specialized cells that have characteristics of both nerve cells and hormone-producing endocrine cells. These cells are found throughout the body, especially in organs like the lungs, pancreas, gastrointestinal tract, and adrenal glands. The tumors were previously known as carcinoid tumors or carcinoid cancer; while current classification schemes for lung NETs still include the carcinoid terminology, it is not a commonly used term.
- **Neuroendocrine tumors:** These tumors are well-differentiated, meaning their cells look and act more like normal neuroendocrine cells. They usually grow slowly and may not cause symptoms right away. Many people live for years with NETs, especially with careful monitoring and treatment. You might think of NETs as the "slow and sneaky" form of neuroendocrine cancer. Of note, a subtype of NETs called Grade 3 NETs does have potential to grow fast and be aggressive.
- **Neuroendocrine carcinomas:** These are poorly differentiated, meaning the cancer cells look very different from normal cells and grow much more aggressively. NECs often require urgent and intensive treatment. They're best described as the "fast and fierce" form of neuroendocrine cancer.

Understanding Your Diagnosis — is it a NET or NEC?

A neuroendocrine cancer diagnosis can feel overwhelming. One common source of confusion is not being told right away whether it's a NET or a NEC.

This distinction matters. It can impact your treatment plan, prognosis, and next steps.

If you're unsure which type you have, we encourage you to speak with your health care provider. Understanding your specific diagnosis is a key part of taking charge of your care. You deserve clear answers, so please don't hesitate to ask.

What are the differences between NETs and NECs?

Neuroendocrine tumors (NETs):

- Well-differentiated
- Grade 1, 2, or 3
- Often slow-growing
- Not classified as large-cell or small-cell

Treatment for NETs

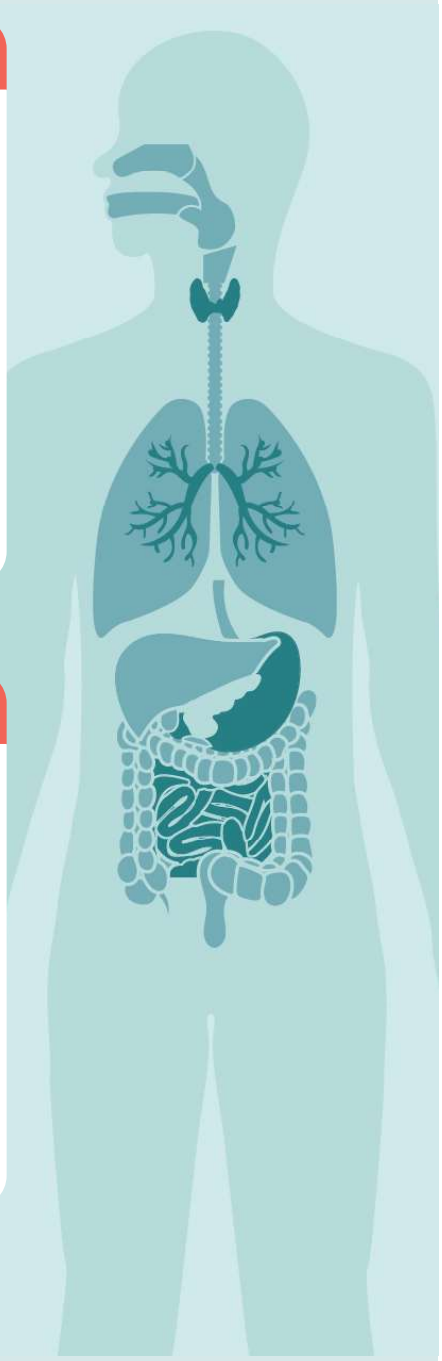
- Can often be effectively treated for many years
- Common treatments include surgery, somatostatin analogs, chemotherapy, targeted therapies, and radiation therapy
- Other treatments include PRRT

Neuroendocrine carcinomas (NECs):

- Poorly-differentiated
- Always high-grade
- Always aggressive
- Can be classified as large-cell and/or small-cell

Treatment for NECs

- Treatment options are limited
- Treatment typically starts with a chemotherapy regimen, and can also include immunotherapy
- Many patients also explore clinical trials



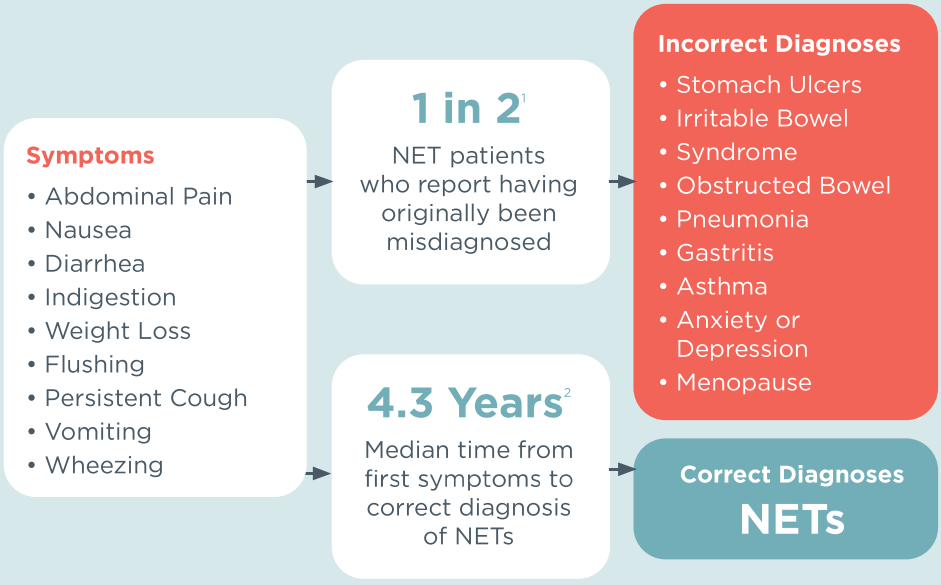
ABOUT NEUROENDOCRINE CANCER

Fast Facts About Neuroendocrine Cancer

- More than **248,000 people** in the U.S. are living with neuroendocrine cancer.
- More than **28,000 people** in the U.S. are diagnosed with neuroendocrine cancer each year.
- There was a **5.2-fold increase** in incidence between 1975 and 2021.
- **4.3 years** is the median length of time that passes from the first symptoms to diagnosis.
- Up to **58% of patients** had metastases at diagnosis.
- The increase in the number of people diagnosed with neuroendocrine cancer is attributed in part to **improvements in diagnostic techniques** and **greater awareness** of neuroendocrine cancer.
- Before receiving a NET diagnosis, patients see on average **five health care providers during 12 visits**.

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.

Neuroendocrine cells

Neuroendocrine cells are specialized cells in the body that have features of both nerve cells (neurons) and endocrine (hormone-producing) cells. Like neurons, they can receive signals from the nervous system. Like endocrine cells, they can release hormones into the blood.

These cells act as a bridge between the nervous system and the endocrine (hormonal) system, helping regulate many body functions.

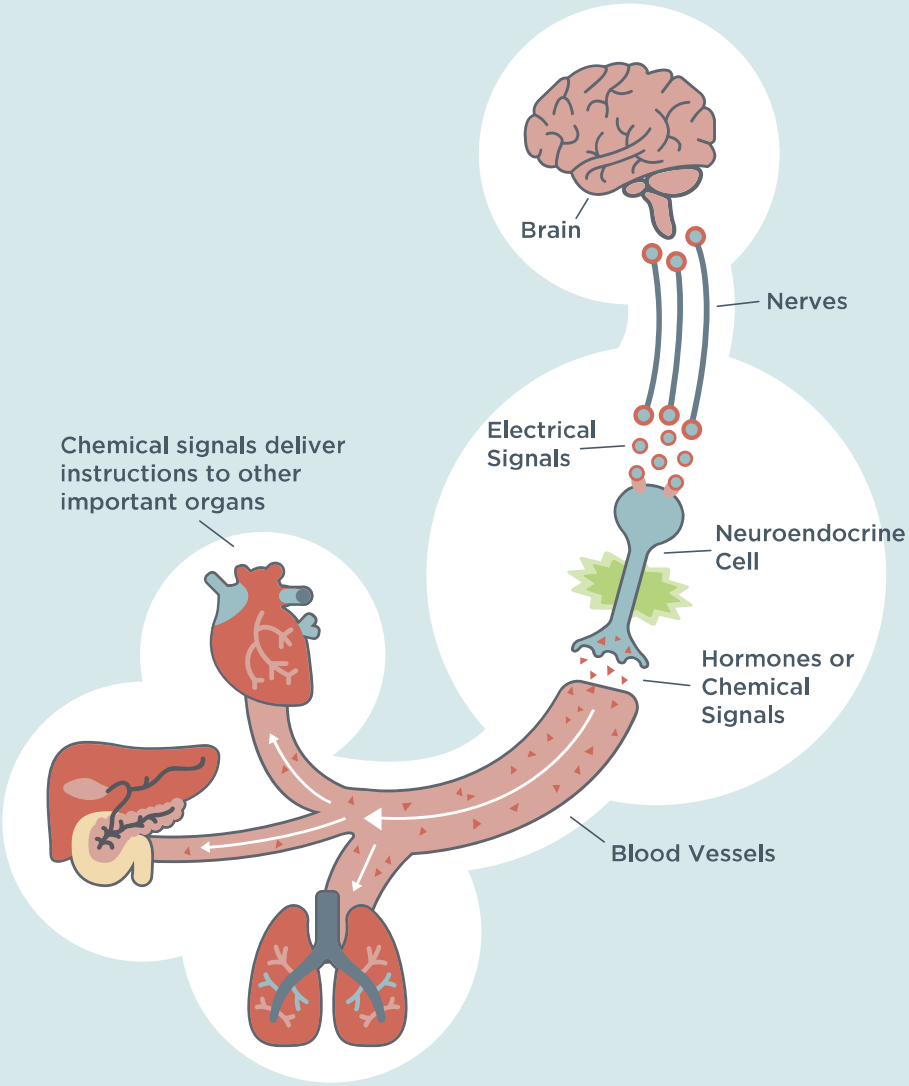
These hormones can also control body functions like blood pressure, heart rate, digestion, breathing, and blood sugar levels.

Neuroendocrine cells are found in many different organs, including, but not limited to:

- Gastrointestinal (GI) tract (small intestine, rectum, stomach, colon, esophagus, appendix)
- Gallbladder
- Pancreas
- Thyroid
- Lungs
- Pituitary gland
- 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.



ABOUT NEUROENDOCRINE TUMORS

Neuroendocrine tumors (NETs) are cancers that arise from neuroendocrine cells. Unlike neuroendocrine carcinomas (NECs), NETs are well differentiated and tend to grow slowly, though some can behave more aggressively.

Because of their gradual growth, NETs may not cause symptoms for years and are sometimes found incidentally during imaging or surgery for another reason.

NETs can develop almost anywhere in the body. The most common sites include:

- Gastrointestinal (GI) tract, especially the small intestine, appendix, and rectum
- Pancreas
- Lungs
- Adrenal glands

Some NETs produce hormones that can lead to a variety of symptoms depending on which hormone is released and where the tumor is located.

Because NETs vary widely in behavior and symptoms, diagnosis often requires specialized imaging and blood or urine tests that detect hormone levels or tumor markers. A biopsy confirms the diagnosis and helps determine the tumor grade and differentiation. Tumor stage is determined primarily by imaging.

ABOUT NEUROENDOCRINE CARCINOMA

Neuroendocrine carcinoma (NEC) is an aggressive type of cancer, described with terms like "high-grade," "poorly differentiated," or "highly proliferative." These all point to the same idea: the cancer grows and spreads quickly, and the cells look very disorganized under a microscope. They are defined as either small cell or large cell.

The lungs account for the vast majority of NECs. Other sites include:

- Cervix
- Bladder
- Gastrointestinal (GI) tract
- Skin (Merkel cell carcinoma)

NECs can develop in many other parts of the body as well. Despite where they begin, most NECs behave similarly, growing quickly and often spreading before they are diagnosed.

What are the symptoms of a NEC?

Symptoms depend on where the cancer starts and where it spreads. However, many people experience:

- Rapid, unintentional weight loss
- Fatigue
- Loss of appetite
- Pain, especially if the cancer spreads to bones
- Neurologic symptoms, if it spreads to the brain
- Changes in bowel or bladder habits

Unlike some NETs, NECs rarely produce hormones that cause symptoms. However, in some instances NECs can cause electrolyte abnormality or muscle weakness.

How are NECs diagnosed?

Diagnosis starts with imaging scans — often covering the whole body — and a biopsy to examine tumor cells under a microscope. Pathologists can also use special lab tests on the biopsy tissue, using markers such as synaptophysin and chromogranin A (and sometimes INSM1), to help confirm the diagnosis.

How are NECs treated?

Treatment for metastatic NECs usually begins with chemotherapy and may be combined with immunotherapy such as immune checkpoint inhibitors. This treatment approach may shrink the cancer and relieve symptoms, but it's not a cure. Many people with a NEC require ongoing treatment or new therapeutic approaches if their cancer worsens.

MiNENs

In addition to "pure" NECs, some tumors are mixed, meaning they contain neuroendocrine and non-neuroendocrine parts. **Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs)** are rare tumors that contain both neuroendocrine and non-neuroendocrine (typically adenocarcinoma or squamous cell) components, each making up at least 30% of the tumor. The neuroendocrine component is most often a high-grade, poorly differentiated neuroendocrine carcinoma rather than a well-differentiated neuroendocrine tumor. They are most often found in the gastrointestinal tract or pancreas, though they can occur in other organs, and can be challenging to diagnose, usually requiring a detailed pathology review after biopsy or surgery. Treatment is typically based on the stage of cancer and directed toward the more aggressive component, which is often the neuroendocrine carcinoma, and may involve platinum-based chemotherapy, surgery, or a combination of approaches. Because of their aggressive nature, MiNENs tend to have a poor prognosis, but outcomes vary depending on the tumor's behavior, location, and stage at diagnosis.

Cell Transformations

Transdifferentiation refers to a process in which a tumor changes from one cell type to another, often as a form of resistance to treatment. In certain cancers, such as prostate adenocarcinoma, long-term treatment with androgen deprivation therapy can lead to the tumor evolving into a partial NEC. This phenomenon, sometimes called treatment-emergent neuroendocrine prostate cancer (t-NEPC), results in a more aggressive, poorly differentiated tumor that no longer responds to hormone therapy. Similar transformations have been observed in other cancers, such as lung or colorectal cancer, typically after targeted therapies or chemotherapy. These transdifferentiated NECs often have a worse prognosis and require different, more intensive treatment approaches, such as platinum-based chemotherapy, similar to other high-grade NECs.

Notes

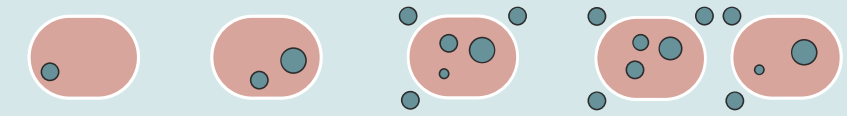
GRADE, DIFFERENTIATION, AND STAGE

Understanding the grade, differentiation, and stage of a neuroendocrine cancer is important for your doctor to develop an effective treatment plan. These factors are based on the results of your diagnostic tests.

Stage, Differentiation and 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



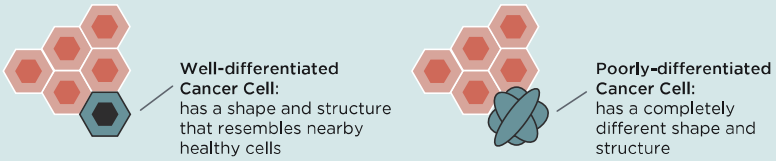
Stage 1
Tumor is small and hasn't spread

Stage 2
Tumor is large but hasn't spread

Stage 3
Tumors have spread to neighboring lymph nodes

Stage 4
Tumors have spread to other organs

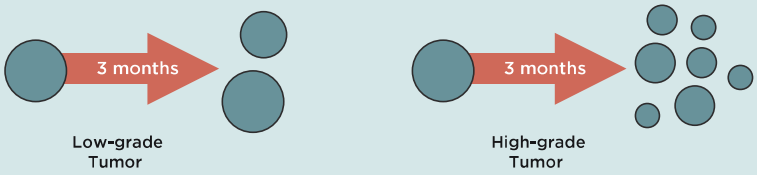
Differentiation | Tells how abnormal the tumor cells look when compared to the surrounding healthy cells



Well-differentiated Cancer Cell:
has a shape and structure that resembles nearby healthy cells

Poorly-differentiated Cancer Cell:
has a completely different shape and structure

Grade | Tells how quickly the tumor cells are dividing



Low-grade Tumor

High-grade Tumor

What is tumor grade?

Tumor grade is defined by evaluating how aggressively the tumor is likely to grow and spread, which is determined by its proliferation activity. This is primarily assessed using two key methods:

- **Ki-67 index:** This is a percentage that shows how many tumor cells are actively dividing. Ki-67 is expressed on a scale of zero to 100 percent. It is measured through immunohistochemistry (IHC) staining of a tumor biopsy sample.
- **Mitotic count:** This involves counting the number of cell divisions (mitoses) seen under a microscope within a specific area of tumor tissue on stained slides.

A pathologist will analyze tumor samples using these measures to classify the tumor's grade. Generally, a lower grade indicates a slower-growing tumor and better prognosis. Higher-grade cancers grow more quickly and require more aggressive treatment. The grade will play a critical role in guiding treatment decisions.

Classification and grading criteria for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs according to World Health Organization 2019

Terminology		Differentiation	Grade	Mitotic Rate (mitoses/2 mm^2)	Ki-67 (%)
NET G1		Well differentiated	Low	< 2	< 3
NET G2			Intermediate	2-20	3-20
NET G3			High	> 20	> 20
NEC	Small-cell type (SCNEC)	Poorly differentiated	High	> 20	> 20
	Large-cell type (LCNEC)				
MiNEN		Mixed neuroendocrine and non-neuroendocrine differentiation	Variable	Variable	Variable

NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; NEN: neuroendocrine neoplasm; MiNEN: mixed neuroendocrine–non-neuroendocrine neoplasm; SCNEC: small-cell neuroendocrine carcinoma; LCNEC: large-cell neuroendocrine carcinoma

What is tumor differentiation?

Doctors describe neuroendocrine cancer as either well-differentiated or poorly differentiated based on how the cancer cells look under a microscope.

- **Well-differentiated** tumors have cells that look and behave more like normal, healthy cells. The structure of the tissue may also resemble normal tissue. These tumors usually grow and spread more slowly. All NETs are well-differentiated.
- **Poorly differentiated** tumors have cells that look more abnormal and often lose the structure seen in healthy tissue. These types of tumors tend to grow and spread much more quickly. All NECs are poorly differentiated.

Low-grade neuroendocrine cancers (Grade 1 or 2) are well-differentiated NETs with a Ki-67 index below 20%. These tumors tend to grow slowly and are generally less aggressive. High-grade neuroendocrine cancers (Grade 3) have a Ki-67 index above 20% and may be either well-differentiated or poorly differentiated. Poorly differentiated Grade 3 tumors are classified as NECs. These are fast-growing, more aggressive cancers that require different, often more intensive treatments than lower-grade NETs.

In contrast, well-differentiated Grade 3 NETs are more aggressive than Grade 1 and 2 NETs but not as aggressive as NECs. They are typically treated with therapies used for NETs, such as somatostatin analogs or peptide receptor radionuclide therapy (PRRT), but research to determine the most effective treatment strategies for Grade 3 NETs is ongoing.

This distinction helps doctors understand how aggressive the cancer is and guides treatment planning.

The thoracic versus digestive World Health Organization terminology and criteria for neuroendocrine neoplasms.

Thoracic WHO 5th Ed, 2021		Digestive WHO 5th Ed., 2019 / WHO 2022 terminology		
Terminology	Criteria: Mitotic counts per 2 mm²	Terminology	Criteria:	
			Mitotic counts per 2 mm²	Ki-67
Typical carcinoid	<2	NET, grade 1	<2	<3%
Atypical carcinoid	2–10 (or necrosis)	NET, grade 2	2–20	3–20%
–	–	NET, grade 3	>20	>20%
SCLC and LCNEC (NEC)	>10	NEC (small cell or large cell)	>20	>20%
Combined NEC and NSCLC		MiNEN		

LCNEC: large cell neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-non-neuroendocrine neoplasm; NEC: neuroendocrine carcinoma; NET: neuroendocrine tumor; NSCLC: non-small cell lung carcinoma; SCLC: small cell lung carcinoma.

What is a cancer stage?

Cancer staging describes how far the cancer has progressed, based on the size of the tumor and whether it has spread to other parts of the body (a process called metastasis). Understanding the stage of your NET or NEC helps your doctor understand the extent of disease, plan the most effective treatment, and identify any clinical trials that may be appropriate for you.

Cancer is often grouped into Stages I through IV, with Stage I being early and localized, and Stage IV indicating that the cancer has spread to distant parts of the body. It's common for neuroendocrine cancers to be diagnosed at a more advanced stage, after they have already spread. However, even with Stage IV disease, there are often treatments available to help manage or control the cancer.

If your cancer shows signs of progression, such as growing, spreading, or returning after treatment, your doctor may perform additional tests to "restage" it. In cases where treatment is very effective, you may hear the term, "no evidence of disease" (NED), which means that no signs of cancer are detectable using current testing methods.

Notes

DIAGNOSTIC TESTING

Testing plays a crucial role in helping your doctor determine the specific characteristics of your tumor type and develop a treatment plan for your neuroendocrine cancer.

Imaging tests

Imaging tests are an important part of diagnosing and monitoring neuroendocrine cancers, which can sometimes be challenging to detect. Because these tumors often behave differently from other cancers, your doctor may recommend specialized scans designed to specifically locate and track them.

Talk with your doctor about which type of imaging test is best for you and what to expect before, during, and after the scan. If your test involves a contrast (a special dye or radioactive material), ask about any necessary precautions or aftercare. Be sure to let your care team know if you feel anxious or claustrophobic during scans, as there may be options available to help you stay comfortable.

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 more clearly on the scans.

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 help differentiate tissue types and detect abnormalities such as tumors and metastases. MRI is also the imaging modality that best detects pituitary neuroendocrine tumors (PitNETs).

Positron emission tomography (PET)

Positron emission tomography (PET) uses radioactive material and a special scanner to detect neuroendocrine cancers. Examples of PET imaging studies include Gallium-68 (Ga-68) or Copper-64 (Cu-64) scans, FDG (fluorodeoxyglucose) scans, and MIBG scans.

- **Gallium-68 (Ga-68) or Copper-64 (Cu-64) PET scans** use radioactive tracers that bind to somatostatin receptors on neuroendocrine tumors. After the tracer is injected, the scan can detect NETs throughout the body, but only if the tumors express somatostatin receptors. Since NECs rarely express these receptors, Ga-68 and Cu-64 scans are generally not effective for detecting NECs and are not routinely used for that purpose.
- **FDG (fluorodeoxyglucose) PET scans** are often used to identify more aggressive neuroendocrine cancers, and they are especially helpful in high-grade disease, including many poorly differentiated NECs. A small amount of FDG, a type of radioactive sugar, is injected into a vein, and a PET scanner creates images of where the body is using the sugar. Cancer cells appear brighter in the picture because they are more active and consume more sugar than healthy cells.
  - Functional imaging, especially PET/CT using 18F-FDOPA and 18F-FDG, is an important tool in the evaluation and management of medullary thyroid carcinoma (MTC). It is particularly effective for detecting metastases in patients with elevated calcitonin (CTN) levels.
- **MIBG (metaiodobenzylguanidine) scans** are primarily used to detect pheochromocytoma and paraganglioma as well as a pediatric neuroendocrine cancer, neuroblastoma. The scan involves injecting a radioactive iodine drug, MIBG, which is absorbed by certain NETs. These scans can take 1-3 days because it takes time for the radioactive material to be absorbed by the tumor(s) before they can be imaged.

Single Photon Emission Computed Tomography (SPECT)

Octreoscan is a type of nuclear medicine scan that uses a radioactive form of octreotide (a somatostatin analog) to detect tumors that express somatostatin receptors. A small amount of Indium-111-labeled octreotide is injected into a vein, allowing it to circulate through the bloodstream and bind to somatostatin receptors on tumors. A gamma camera then captures images of the radioactive signal to show where tumors are located in the body. Although Octreoscan was widely used in the past, many centers now prefer more advanced imaging techniques such as Gallium-68 or Copper-64 DOTATATE PET/CT scans, which provide greater sensitivity and image clarity.

Endoscopy

Endoscopy is a medical procedure that uses an endoscope, a flexible or rigid tube equipped with imaging capabilities, to view the lining of various organs in the body. This tool not only allows for visualization of internal areas but can also enable small surgical procedures. Endoscopy can be used to visualize tumors in the lungs and GI tract, including the small and large intestines and rectum. In some cases, an ultrasound probe may be attached to the end of the endoscope to perform an endoscopic ultrasound, which can be particularly useful for looking at adjacent organs like the pancreas.

Colonoscopy

Colonoscopy is a procedure that uses a thin, tube-like instrument (colonoscope) with a light and lens to look inside the rectum and colon for abnormal tissue or cancer. A colonoscope can also include 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, also known as esophagogastroduodenoscopy (EGD), is used 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 (duodenum).

Bronchoscopy

Bronchoscopy is used to look inside the trachea and the large airways of the lungs for abnormal areas. A bronchoscope — a thin, tube-like instrument with a light and a lens — is inserted through the nose or mouth and down into the trachea and lungs. This device may also include a tool for removing tissue samples, which are then examined under a microscope for signs of cancer.

5-HIAA test

5-Hydroxyindoleacetic acid (5-HIAA) is a breakdown product of serotonin, a hormone released by some NETs. Because serotonin levels fluctuate throughout the day, using a 24-hour urine collection to measure the 5-HIAA byproduct provides a more accurate assessment of daily hormone levels. Some medical centers now offer a blood test for 5-HIAA, which simplifies the process by eliminating the need to collect urine. This test is used by doctors to diagnose and monitor certain types of NETs.

Foods to avoid

The following are some foods to avoid for 48 hours before a 5-HIAA test:

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

Medications may also affect your test results, such as certain pain relievers or antidepressants. 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)

CgA is a protein stored and released by neuroendocrine cells and is commonly used as a blood-based biomarker for monitoring NETs. It is measured through a blood test and monitored over time, ideally at consistent intervals after the administration of a long-acting somatostatin analog (SSA). However, CgA has limitations, including the risk of false-positive results. For example, levels can be elevated by factors unrelated to NETs, such as the use of proton pump inhibitors—medications commonly taken for heartburn. As imaging techniques improve, the reliance on CgA tests may decrease. Importantly, chromogranin A is a tumor marker, not a hormone, and is not used for diagnostic purposes.

Blood chemistry tests

Blood chemistry tests measure certain substances such as glucose, enzymes, fats, and proteins. These tests give essential information about how well a person's kidneys, liver, and other organs are working. Results that are either high or low can be a sign of an underlying disease.

Fasting serum tests

Fasting serum tests measure the amount of gastrin, sugar, glucagon, VIP, or somatostatin in the blood. Patients may need to fast for at least 8 hours before these tests.

NETest

The NETest is a blood test that looks for molecular evidence of tumor activity. It may be more sensitive than other tumor markers, such as CgA. Recent published studies suggest that a positive NETest result after tumor resection can predict the likelihood of a cancer's recurrence.

Tissue tests

Your doctor may remove a piece of tumor tissue to examine it under the microscope. Testing this tissue will help to confirm the diagnosis, tumor grade and differentiation, and the most effective treatment options.

Before you undergo a tumor tissue test, consider learning about tissue donation and how your tissue may help researchers develop laboratory models of neuroendocrine cancer.

Learn about tissue donation

Procedures for removing tissue samples

A biopsy involves the removal of cells or tissues for examination. The specific biopsy technique used depends on the location of the tumor. Each method aims to safely and accurately extract tissue samples for diagnostic testing.

Endoscopic and fine-needle biopsies

Endoscopic ultrasound-guided fine-needle aspirations (EUS-FNA) involve using an endoscope equipped with a biopsy needle and integrated ultrasound probe. The ultrasound helps generate images of internal organs and tissues, guiding the placement of the biopsy needle to extract tissue samples for examination under a microscope.

Fine-needle aspiration (FNA) is used to biopsy the lungs. This technique involves using a thin needle to remove tissue or fluid identified by CT scan, ultrasound, or other imaging techniques. After making a small incision, the biopsy needle is inserted into the abnormal tissue or fluid to collect samples. These are then analyzed by a pathologist to look for cancer cells. A chest x-ray is performed after the procedure to make sure no air is leaking from the lung into the chest.

Immunohistochemistry

Immunohistochemistry (IHC) uses antibodies to check for specific antigens in a tissue sample. The antibodies create a visible color or glow, letting doctors see where the target is in the tissue under a microscope. Pathologists often use IHC to test for tumor markers such as chromogranin A and synaptophysin, among others, to accurately diagnose NETs and differentiate tumor types such as a Grade 3 NET from a NEC.

IHC is also a standard method used to assess the proliferation rate, the Ki-67 value, of NETs and NECs, which helps determine tumor grade and guide treatment.

Notes

FINDING CARE

People diagnosed with a neuroendocrine cancer can face challenges to get an accurate diagnosis and specialized care. Since symptoms may mimic those of other common conditions such as irritable bowel syndrome, menopause, or asthma, many people are at first misdiagnosed. Some physicians may not have diagnosed or treated a patient with a neuroendocrine cancer. As such, patients and their families often need to advocate for appropriate and specialized care within a complex health care system.

Finding a specialist

A standard piece of advice you will hear frequently is to find a neuroendocrine cancer specialist and build a multidisciplinary care team based on the type of cancer you have and your specific needs.

A multidisciplinary approach involves a team of different types of doctors and health care providers who regularly convene — often at meetings called "tumor boards" — to review a patient's medical history and test results. This team leverages its collective expertise to develop a treatment plan that aligns with a patient's preferences and goals. The composition of this multidisciplinary team can vary depending on a person's unique medical needs.

The task of finding a physician can seem daunting, but NETRF has worked to make it easier for people to find doctors who specialize in the treatment of neuroendocrine cancer. NETRF has a directory of U.S. neuroendocrine cancer providers on our website as well as a listing of multidisciplinary neuroendocrine cancer treatment programs.

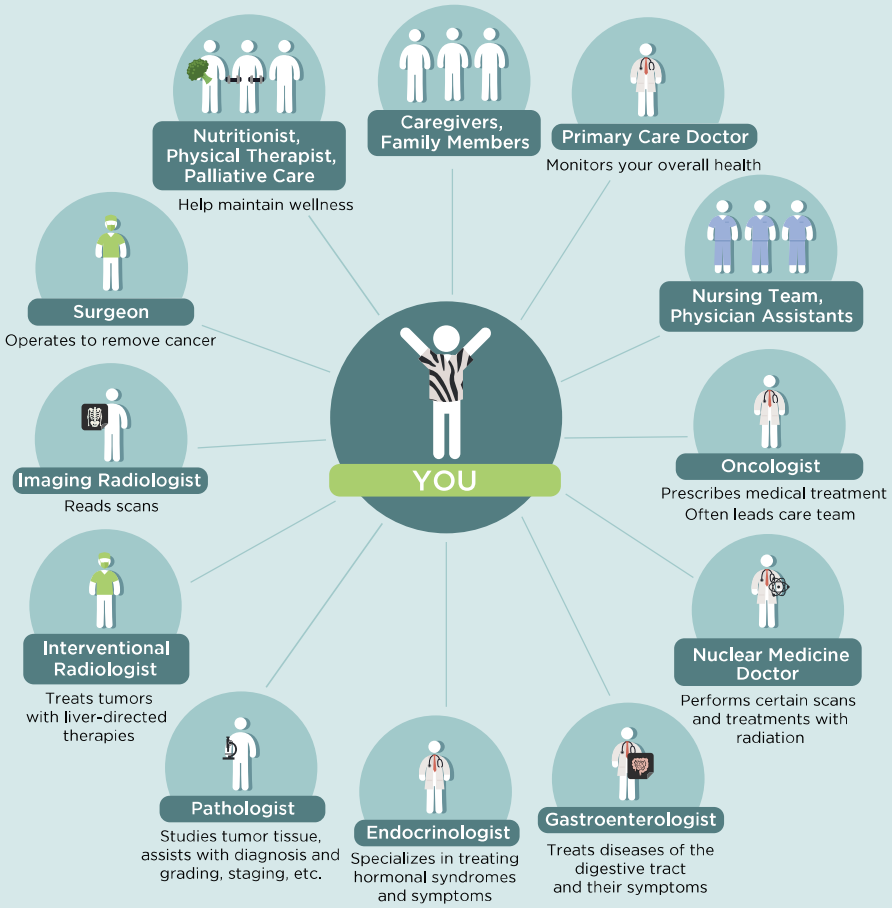
NETRF's YouTube channel features talks by health care providers who specialize in neuroendocrine cancer. Looking at these videos may also help you find a specialist.

NETRF YouTube Channel

NET Provider Directory

Your Care Team

Neuroendocrine cancer is 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 specialist

Patient Support Groups

Check out neuroendocrine cancer advocacy and patient support groups to find specialists. These groups, run by patients and caregivers, meet in communities across the world, both in person and virtually. Organizers and participants typically know a lot about the physicians in their areas.

Physician Organizations

Explore professional associations for physicians who focus on neuroendocrine cancer, including:

- 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 neuroendocrine cancers may also be conducting 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 neuroendocrine cancer clinical trials on NETRF's NET Trial Finder.

NET Trial Finder

Talking with your doctor

Finding the right doctor is a crucial step in your treatment journey. Once you have identified a suitable specialist that meets your needs, establishing a good rapport and maintaining open communication is essential. Ask your chosen specialist how they will communicate with all the members of your care team, even if they are not within the same health system.

Doctor appointments can sometimes be overwhelming, packed with complex information that may be difficult to fully absorb or comprehend. It might also feel like there's never enough time to address all your questions. To optimize your appointments, consider the following tips.

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, bring a copy of your current medications and ask what other medical records you need to bring.
- If possible, make multiple appointments on the same day, especially if you have to travel a long distance to see a specialist.
- 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 NCF, 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 communication 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.

Because neuroendocrine cancer is uncommon, it's not unusual for patients to have doctors in different institutions or even in different states. It's important to keep your entire care team informed about your test results, imaging scans, and treatment plans. You may need to take an active role in sharing records or transferring scans between offices. Although this can sometimes be a logistical challenge, staying organized and ensuring everyone has the same information helps your team coordinate care and make the best treatment decisions for you.

Telemedicine and Technology

The increased use of telemedicine has created new opportunities for neuroendocrine cancer patients. Virtual appointments are now enabling some patients across the country to consult with specialists and maintain regular contact with their physicians. However, there may be licensing limitations on whether an out-of-state physician can conduct a virtual visit with you, and insurance companies vary in their coverage of telemedicine services. It's worth inquiring about telemedicine options, especially if traveling a long distance for an in-person appointment would be necessary.

Ask if your physician offers a patient portal. Some portals allow you to message your health care provider directly, request changes to appointments, see test results, or refill prescriptions. Additionally, download any necessary telehealth apps on your phone or tablet and familiarize yourself with these digital tools to maintain effective communication with your care team.

Establishing and maintaining good communication with your care team is crucial to building trust. Being more informed and involved in your care makes it easier to stick to your care plan and work toward the best possible outcomes.

Notes

TUMOR SITES

One of the defining characteristics of neuroendocrine cancers is their high variability — no two tumors are exactly alike. These tumors are often described by doctors as "heterogeneous," which means they can differ in their location, growth rate, and whether they cause symptoms.

Neuroendocrine cancer can develop almost anywhere in the body, but they most commonly begin in the gastrointestinal (GI) tract, lung, or pancreas. The initial location where a neuroendocrine cancer first forms is called the primary site. However, by the time they are diagnosed, over half of neuroendocrine cancers have spread, or metastasized, to other parts of the body such as lymph nodes, bones, or the liver.

The signs and symptoms of neuroendocrine cancers can significantly vary depending on the tumor's primary site. Complicating diagnosis further, 1 in 2 patients with NETs are initially misdiagnosed with other conditions, such as irritable bowel syndrome, gastritis, or anxiety, reflecting the complexity and non-specific nature of their symptoms.

Sometimes the original location of a neuroendocrine cancer cannot be identified. In some studies, this occurs in up to 20% of cases, which can complicate treatment and management decisions.

If testing shows that a neuroendocrine cancer has metastasized but doesn't reveal where it started, the cancer is said to be of "unknown primary."

GI Neuroendocrine Cancer

The most common sites for neuroendocrine tumors in the gastrointestinal (GI) tract are the small intestine and the rectum.

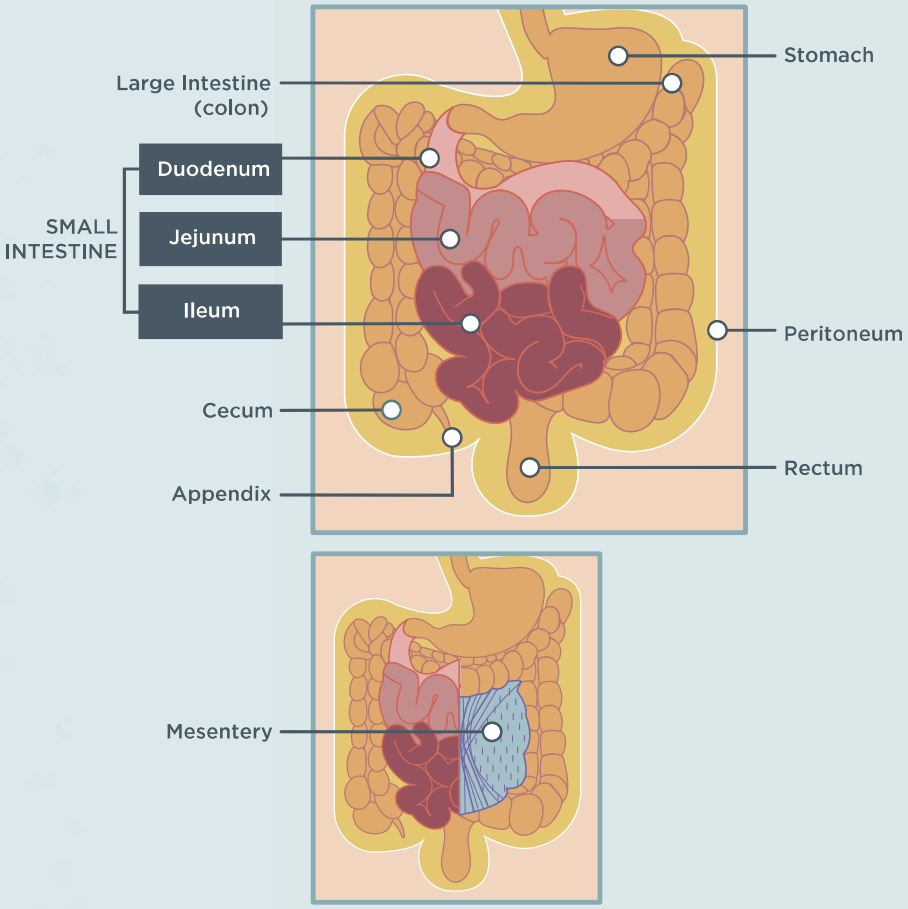
What is the GI tract?

The GI tract consists of organs that help digest food. Each part of the GI tract has a specific role in the digestion process:

- **Stomach:** The stomach stores swallowed food and liquid, mixes them with digestive juices, and slowly releases the mixture into the small intestine.
- **Small intestine:** Muscles in 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 consists of three parts – the duodenum, jejunum, and ileum.

- **Large intestine:** The large intestine continues to break down food, absorbs liquids, and forms waste material (stool). The colon is a major component of the large intestine.
- **Rectum:** The rectum stores stool until it is pushed out during a bowel movement.

Parts of the Gastrointestinal Tract



Symptoms vary by tumor location

Some GI neuroendocrine cancers may not cause any signs or symptoms. Others may cause symptoms if they overproduce and release hormones into the bloodstream or grow large enough to cause blockages in the GI tract.

The symptoms of a neuroendocrine cancer in the small intestine may include:

- 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
- Fatigue
- Mental confusion

The symptoms of a neuroendocrine cancer in the large intestine may include:

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

The signs and symptoms of a neuroendocrine cancer in the stomach may include:

- Abdominal pain
- Weight loss
- Nausea/vomiting

Pancreatic neuroendocrine cancer

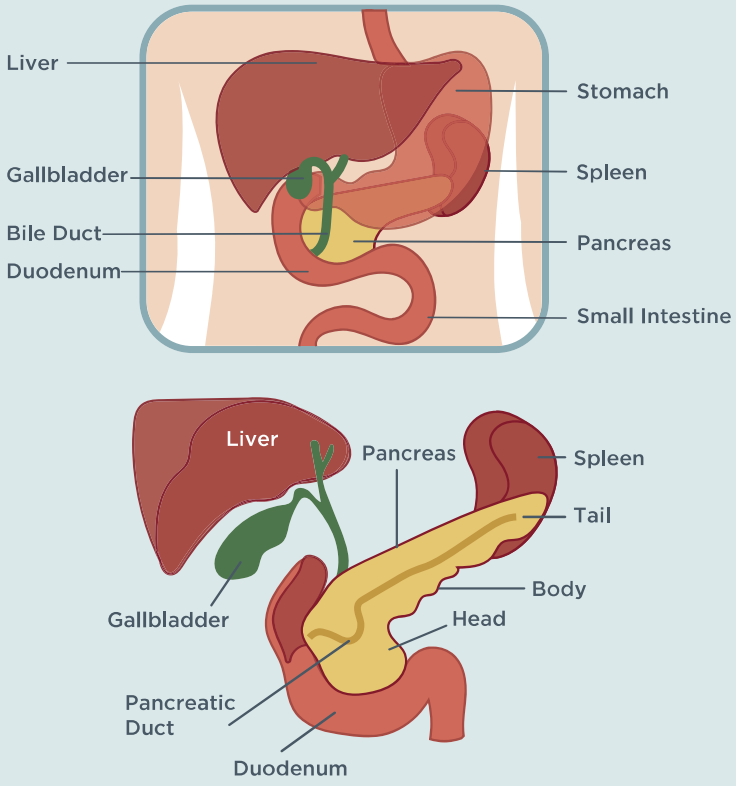
Pancreatic neuroendocrine tumors are sometimes called pNETs or PanNETs. About 9% of NETs occur in the pancreas. Pancreatic NECs (PanNECs) make up 20% of gastrointestinal NECs.

Where is the pancreas?

The pancreas is located 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, gut movement, and acid production in the stomach (endocrine cells)

Pancreas Location and Structure



Symptoms of Pancreatic Neuroendocrine Cancer

While some pancreatic neuroendocrine cancers may not cause any signs or symptoms, pancreatic NETs can sometimes overproduce hormones, leading to a range of symptoms that vary depending on the specific hormone involved. PanNECs don't typically secrete hormones. Some of the symptoms include:

- Diarrhea
- Skin rash
- Fatigue
- Nausea
- Hypoglycemia
- Abdominal pain
- Digestive problems
- Gallbladder problems
- Weight changes
- Jaundice (yellowing of skin and the whites of the eyes)

Risk factors for pNETs

Most pancreatic neuroendocrine tumors are not inherited, but certain inherited syndromes can run in families and increase a person's risk of developing a pNET.

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

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

Pancreatic Neuroendocrine Cancer vs. Pancreatic Cancer

Pancreatic neuroendocrine cancer is not the same as "pancreatic cancer," which usually refers to pancreatic adenocarcinoma. Although both cancers develop in the same organ, they are different types of cancer.

Pancreatic adenocarcinoma and neuroendocrine cancer differ in terms of:

- Causes
- Symptoms
- Tests
- Treatments

Pancreatic adenocarcinoma

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

Pancreatic neuroendocrine cancer

- Starts in the endocrine cells
- Less common (<5%)
- Better prognosis (pNET); but PanNECs may have poorer prognosis

Lung Neuroendocrine Cancer

The lungs are a common site for NETs and NECs. About 30% of all NETs develop in the lungs. They may not cause symptoms in their early stages and may be incidentally discovered during screenings for unrelated diseases.

Lung neuroendocrine carcinoma makes up approximately 91% of all neuroendocrine carcinomas and approximately 14-16% of all lung cancer. Lung NECs are classified as either small cell lung cancer, which accounts for 98% of cases, or large cell neuroendocrine carcinoma, which accounts for 2% of cases.

Lung neuroendocrine cancers can be categorized based on their location within the lungs.

- **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

Types of Lung Neuroendocrine Cancer

Lung neuroendocrine cancers can be classified based on how quickly they grow and how likely they are to spread. Some of the terms are different from the way neuroendocrine cancers in the rest of the body are classified. The main types include:

- Typical carcinoid (TC): These tumors tend to grow slowly and are less likely to spread beyond the lungs.
- Atypical carcinoid (AC): These grow somewhat faster than typical carcinoids and have a higher chance of spreading outside the lungs.

Small cell lung cancer (SCLC): This is the most aggressive type of lung neuroendocrine carcinoma and is strongly associated with smoking.

Large cell neuroendocrine carcinoma (LCNEC): Another high-grade, fast-growing form of neuroendocrine cancer, LCNEC shares characteristics with both small cell and non-small cell lung cancers and is also considered aggressive.

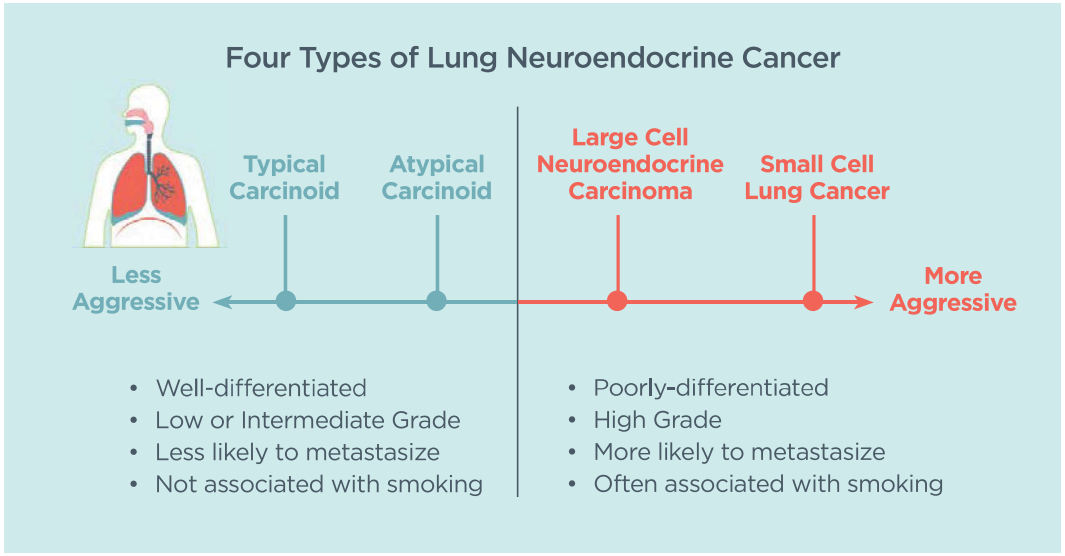
Another type of condition is diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, or DIPNECH, a rare, pre-malignant lung condition characterized by the abnormal proliferation of pulmonary neuroendocrine cells. Initially, DIPNECH may or may not cause symptoms. Over time, DIPNECH may be associated with, and in some cases progress to, lung NETs. When lung NETs co-occur with DIPNECH, they are more often typical than atypical, although reported proportions vary across studies.

Symptoms of lung neuroendocrine cancer

Lung neuroendocrine cancer can cause symptoms when it blocks an airway. These symptoms may include:

- Cough
- Wheezing
- Shortness of breath
- Chest pain
- Coughing up blood

A functional lung neuroendocrine cancer, which releases hormones into the bloodstream, may cause additional symptoms such as Cushing's syndrome.



Adrenal Gland NETs

What are pheochromocytomas and paragangliomas?

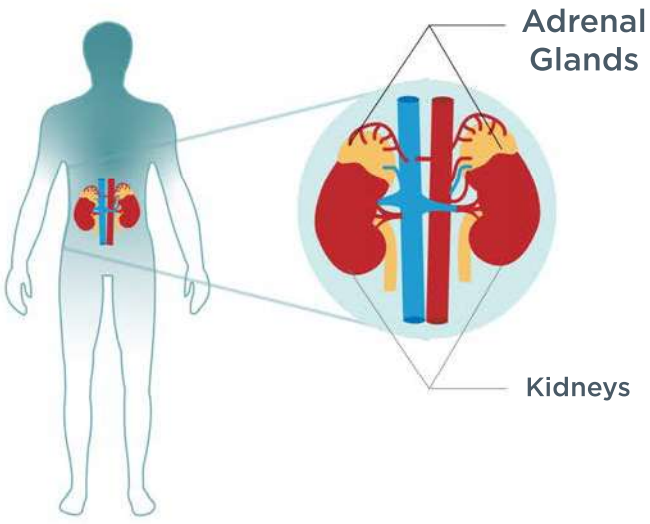
- **Pheochromocytomas** are rare tumors that arise from specialized cells in the adrenal medulla, the inner part of the adrenal glands located on top of the kidneys.
- **Paragangliomas** are rare neuroendocrine tumors that originate from paraganglia, clusters of specialized cells found outside the adrenal glands along the autonomic nervous system.

Both pheochromocytomas and paragangliomas can produce excessive amounts of adrenaline and related hormones. These hormones are part of the body's "fight-or-flight" response and usually released in response to stress.

Where are the adrenal glands?

The body has two adrenal glands, each situated atop a kidney in the back of the upper abdomen.

These glands produce hormones that control blood pressure and blood sugar levels, helping the body respond to stress.



Pheos and Paras

Pheochromocytoma	Paraganglioma
Occurs in the adrenal glands	Occurs outside the adrenal glands, most often in the head and neck, chest, abdomen, or pelvis
These are very rare NETs. Every year there are only between two and eight new pheo or para diagnoses for every one million people. The majority of these are pheochromocytomas. • Some pheochromocytomas and paragangliomas produce excess stress hormones such as adrenaline, which can cause symptoms like high blood pressure, sweating, headache, and feelings of anxiety or nervousness. • Both are strongly associated with genetic syndromes.	

Pheo and para symptoms

Pheochromocytoma and paraganglioma symptoms may be triggered by:

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

The signs and symptoms of pheochromocytoma and paraganglioma may occur after:

- 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)

Pheo and Para Risk Factors

Certain syndromes or gene changes passed down in families can increase the risk of developing pheochromocytoma or paraganglioma. 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

SDH Mutations

Mutations in *SDHB*, one of the subunits of succinate dehydrogenase (SDH), are strongly associated with a high risk of malignant paraganglioma and pheochromocytoma. In contrast, *SDHD* mutations are primarily linked to hereditary head and neck paragangliomas, often manifesting with multiple tumors but generally showing very low metastatic potential.

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.

Other Primary Sites

While most NETs and NECs arise in the gastrointestinal tract, pancreas, lungs, or genitourinary tract (such as the bladder, prostate, or cervix), they can also occur in less common sites. These include the thymus, larynx, breast, skin (Merkel cell carcinoma), thyroid (medullary thyroid carcinoma), and even the biliary tract or gallbladder. Though rare, tumors in these locations often present unique diagnostic and treatment challenges due to their atypical behavior and limited research data.

Metastatic Sites

NETs most commonly metastasize to the lymph nodes and liver, with about 50% of patients showing liver-only metastases. Less commonly, NETs can spread to the bones, lungs, and peritoneum, among other sites. NECs, which are more aggressive, tend to spread earlier and more extensively, but often follow a similar pattern of metastatic spread. Although rare, both NETs and NECs can also metastasize to areas such as the brain, breast, and even the heart.

Notes

FUNCTIONAL AND NONFUNCTIONAL NEUROENDOCRINE CANCER

Some neuroendocrine cancers can release hormones that cause a variety of disruptive symptoms. These are called **functional** neuroendocrine cancers. Conversely, neuroendocrine cancers that do not produce hormones are called **nonfunctional**. The majority of neuroendocrine cancers are nonfunctional.

Most functional tumors are NETs, which are more likely to produce hormones. Functional NETs are generally found in the gastrointestinal tract, pancreas, or lungs. In contrast, NECs are typically nonfunctional and rarely secrete hormones.

Notably, carcinoid syndrome is the most common functional syndrome and affects about 20% of patients, in particular those with metastatic midgut NETs. Specialized testing is used to determine if a tumor is producing hormones. While most NECs are nonfunctional, some NECs — especially small cell lung cancer — can present with paraneoplastic syndrome, a group of symptoms caused by an abnormal immune response and/or by hormone-like substances produced by the tumor.

Nonfunctional and functional GI neuroendocrine cancers

Many nonfunctional gastrointestinal (GI) neuroendocrine cancers can grow silently for a long time without causing any noticeable symptoms. However, they may still cause issues if the tumor grows large enough to block part of the GI tract, leading to symptoms like pain or digestive problems.

In contrast, functional GI neuroendocrine cancers produce hormones that are usually broken down by the liver as blood flows from the gut. But if the tumor spreads to the liver, the liver may no longer be able to break down the excess hormones. When this happens, high levels of hormones, such as serotonin, can build up in the body, potentially leading to carcinoid syndrome, a condition with symptoms such as flushing, diarrhea, and wheezing.

Carcinoid syndrome

The signs and symptoms of carcinoid syndrome include:

- Flushing of the skin and face with or without sweating
- Abdominal pain
- Feeling bloated
- Diarrhea
- Wheezing or other trouble breathing
- Fast heartbeat
- Blood pressure fluctuations
- Carcinoid heart disease (e.g. heart murmur and 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, with up to one-third of those affected developing carcinoid heart disease which includes thickening of the cardiac valves. 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 are available that can help alleviate the symptoms of carcinoid syndrome. Additionally, lifestyle changes, such as avoiding alcohol and certain foods, may also help in managing symptoms, as certain foods and stress can trigger them.

Carcinoid Crisis

Some patients experience severe, sudden, and even life-threatening symptoms called a carcinoid crisis. This condition affects a person's blood pressure and heart rate and typically occurs during surgery, invasive procedures, or in times of severe stress. Preventing a carcinoid crisis is possible with hormone therapy. To avoid complications, medications may be needed to manage hormone production before surgery or other procedures.

Nonfunctional and functional pNETs

Functional pNETs can overproduce and release large amounts of hormones into the bloodstream, depending on the specific type of endocrine cell from which they originate:

	Hormone secreted	Effect
Insulinoma	Insulin	Lowers blood sugar levels by promoting glucose uptake into cells. Excess insulin causes low blood sugar, which can lead to symptoms like sweating, confusion, shakiness, and even seizures.
Glucagonoma	Glucagon	Raises blood sugar by stimulating the liver to release glucose. Overproduction leads to high blood sugar and is often associated with weight loss, diabetes, and a distinctive skin rash called necrolytic migratory erythema.
Gastrinoma	Gastrin	Stimulates the stomach to produce excess gastric acid. This results in Zollinger-Ellison syndrome, characterized by severe ulcers, abdominal pain, and chronic diarrhea.
VIPoma	Vasoactive intestinal peptide (VIP)	Regulates water and electrolyte secretion in the intestines. Excess VIP causes profuse watery diarrhea, low potassium, and dehydration.
Somatostatinoma	Somatostatin	Inhibits the release of several other hormones (e.g., insulin, glucagon, gastrin). Overproduction can cause diabetes, gallstones, fatty stool, and digestive problems due to widespread hormonal suppression.

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

- Diarrhea
- Indigestion
- A lump in the abdomen
- Pain in the abdomen or back
- Jaundice (yellowing of the skin and whites of the eye)

Nonfunctional and functional lung neuroendocrine cancers

Nonfunctional NETs in the lungs can cause a range of symptoms such as coughing, wheezing, shortness of breath, and chest pain.

Nonfunctional NECs in the lungs cause similar symptoms to lung NETs:

- A cough that does not go away or gets worse
- Coughing up blood
- Chest pain that worsens with deep breathing, coughing, or laughing
- Hoarseness
- Loss of appetite
- Unexplained weight loss
- Shortness of breath
- Feeling tired or weak
- Infections that don't go away or keep coming back
- Wheezing

Functional Lung NETs

Functional lung NETs are rare but can produce biologically active hormones that lead to distinct clinical syndromes. The most common hormone secreted is serotonin, which may cause carcinoid syndrome, characterized by episodes of flushing, diarrhea, and wheezing.

Unlike gastrointestinal NETs, lung NETs can cause carcinoid syndrome even without liver metastases, as hormones released in the lungs can enter systemic circulation directly. Some lung NETs may also secrete adrenocorticotropic hormone (ACTH), resulting in Cushing's syndrome, which can occur when the body has too much cortisol, a hormone that helps regulate stress and metabolism. This can cause weight gain, high blood pressure, and elevated blood sugar, among other symptoms. These hormone-related symptoms can be early clues to diagnosis and guide further testing and management.

Functional Lung NECs

Functional lung neuroendocrine carcinomas, particularly SCLC and, less commonly, LCNEC occasionally produce hormones leading to paraneoplastic syndromes. Although most NECs are nonfunctional, some SCLC tumors can secrete ACTH, causing Cushing's syndrome, or antidiuretic hormone (ADH), leading to SIADH (syndrome of inappropriate antidiuretic hormone secretion).

These syndromes can result in significant clinical symptoms such as muscle weakness, confusion, high blood pressure, or high blood sugar levels, and may precede the cancer diagnosis. Recognizing these hormone-related syndromes is important, as they often reflect a high tumor burden and may complicate treatment.

Notes

INHERITED RISK FACTORS

For many people diagnosed with neuroendocrine cancer, the exact cause remains unknown. Most neuroendocrine cancers appear sporadically, meaning they develop without a clear inherited or environmental trigger. However, research has shown that some neuroendocrine cancers have a genetic component and may run in families. This is particularly notable in certain subtypes, where the genetic vulnerabilities are more prevalent.

Studies suggest that about 10% of pancreatic neuroendocrine tumors and 35% of pheochromocytomas and paragangliomas are linked to inherited genetic factors, highlighting the importance of genetic evaluation in these cases. Similarly, while most small and large intestinal neuroendocrine cancers occur spontaneously, some are also associated with inherited syndromes.

NET Type	% Hereditary (Approx.)	Common Syndromes
Pancreatic NETs	10–20%	MEN1, VHL, NF1, TSC
Pheochromocytoma/ Paraganglioma	30–40%	SDHx, VHL, MEN2, NF1
Medullary Thyroid Carcinoma	25%	MEN2 (RET mutations)
Small Intestine NETs	<5%	Rare familial cases
Lung NETs	Rare (<1%)	MEN1

NECs are typically sporadic; however, in rare cases, NECs can arise in individuals with hereditary cancer syndromes, such as Lynch syndrome or Li-Fraumeni syndrome.

When diagnosing and evaluating neuroendocrine cancer, doctors consider both your personal medical history and your family's history. The presence of a known genetic mutation in a close relative, such as a parent or sibling, can play a crucial role in determining whether your neuroendocrine cancer may have an inherited cause. Additionally, the occurrence of two or more related medical conditions or syndromes in a family member may indicate an underlying genetic predisposition for neuroendocrine cancer.

While knowing about an inherited genetic risk factor may not change your treatment plan, it can significantly influence how your doctor monitors your health over time. If a hereditary risk is confirmed, your doctor may recommend regular screenings to detect potential related conditions early, allowing for timely intervention. Furthermore, knowledge of a genetic syndrome may also guide testing or monitoring

of family members, ensuring that any genetic predispositions are managed proactively.

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 Pituitary neuroendocrine tumors Parathyroid adenoma Adrenocortical tumors Lipomas	MEN1	Gastrinomas Insulinomas VIPomas Glucagonomas Somatostatinomas Other NETs (lung, gastric, thymic)
MEN2: Multiple endocrine neoplasia type 2[a]	MEN2A syndrome (cutaneous lichen amyloidosis, Hirschsprung disease) MEN2B syndrome (mucosal neuromas, marfanoid habitus)	RET	Pheochromocytoma Medullary thyroid carcinoma
MEN4: Multiple endocrine neoplasia type 4[a,f]	Overlaps with MEN1, primary hyperparathyroidism (PHPT)	CDKN1B	Pituitary neuroendocrine tumors Pancreatic neuroendocrine tumor
VHL[b]	Von Hippel-Lindau disease (renal cell carcinoma and hemangioblastomas)	VHL	Pheochromocytomas Paragangliomas Pancreatic NETs
GCHN: glucagon cell hyperplasia and neoplasia[g]	Mahvash disease	GCCR	Pancreatic NETs
SDHx-related syndromes[a]	Hereditary paraganglioma-pheochromocytoma syndrome Carney-Stratakis syndrome	SDHD SDHA SDHAF2 SDHC SDHB	Paraganglioma Pheochromocytoma
TSC: Tuberous sclerosis complex[b]	A wide spectrum of benign tumors, skin abnormalities and behavioral/cognitive problems	TSC1 TSC2	Pancreatic NETs[b]
NF1: Neurofibromatosis type 1[a]	von Recklinghausen disease Neurofibromas Malignant peripheral nerve sheath tumor (MPNST) Optic pathway glioma	NF1	Paragangliomas Pheochromocytomas Gastrointestinal tract and pancreatic NETs[b] Duodenal/periampullary somatostatinoma

If you or a family member has been diagnosed with a neuroendocrine cancer, discuss genetic testing with your doctor to see if it could provide useful insights to your care. 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.

Table notes

a. Schernthaner-Reiter MH, Trivellin G, Stratakis CA. MEN1, MEN4, and Carney complex: pathology and molecular genetics. Neuroendocrinology. 2016;103:18-31.

b. National Cancer Institute. Pheochromocytoma and Paraganglioma Treatment (PDQ®)–Health Professional Version. cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq Accessed October 9, 2018.

c. National Cancer Institute. Genetics of Endocrine and Neuroendocrine Neoplasia (PDQ®)–Health Professional Version. cancer.gov/types/thyroid/hp/medullary-thyroid-geneticspdq#link/_767. Accessed October 9, 2018.

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f. Alrezk R, Hanah-Shmouni F, Stratakis CA. MEN4 and CDKN1B mutations: The latest in MEN syndromes. Endocr Relat Cancer. 2017. 24;(10):T196-208

g. Mete O, Chetty R. Pancreatic endocrine neoplasia: familial syndromes. Diagn Histopathol, 2017;23:8, 378.

Genetic tests

If your medical or family history suggests a potential inherited risk, your doctor might recommend genetic testing. This testing, which can be performed using blood or saliva samples, helps identify specific gene mutations.

Who should be tested?

Genetic testing looks for mutations in specific 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 or monitoring. Genetic counseling can help you consider the risks, benefits, and limitations of genetic testing.

Genetic counseling is a key component of the genetic testing process. It involves a thorough review of your personal and family medical history related to potential cancer risks. 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 testing may not be covered by all insurance plans, or coverage may be subject to specific criteria. It's important to contact your health insurance provider to understand your coverage and confirm any out-of-pocket costs before proceeding with testing.

Ask your doctor if there's a genetic counselor they recommend or look for a genetic counselor here: findageneticcounselor.nsgc.org/

NEUROENDOCRINE TUMOR TREATMENTS

Treatment can reduce the number and size of neuroendocrine tumors as well as reduce some of the symptoms caused by tumors. Common treatments include:

- Surgery
- Somatostatin analogs
- Targeted therapies
- Chemotherapy
- Radioligand therapy (PRRT)
- Interventional radiology
- Clinical trials

Surgery

Surgery is a common treatment for neuroendocrine cancer, often used to remove tumors or reduce the size of more advanced tumors to alleviate symptoms and improve quality of life. The type of surgery performed depends on the tumor location, grade, stage, and overall disease burden (the severity of disease and its impact on daily life) as well as a person's age, health, and other coexisting conditions.

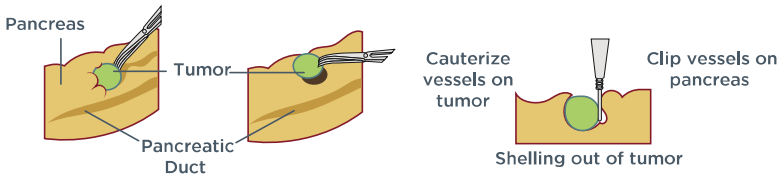
Pancreas

- **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.
- **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 person's condition determines which organs are to be removed during this procedure.

Surgery for Pancreatic Neuroendocrine Cancer

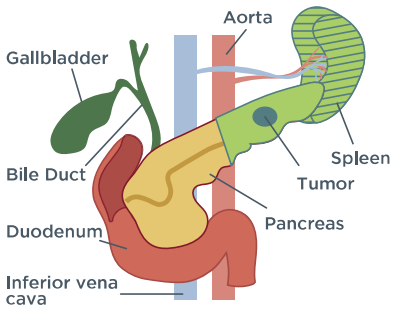
Enucleation

Removes ONLY the tumor itself



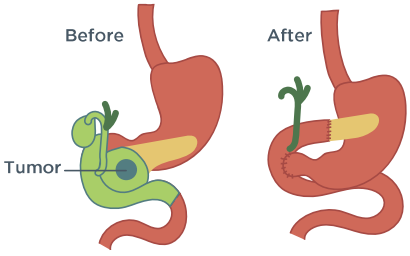
Distal Pancreatectomy

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



Pancreatoduodenectomy ("Whipple Procedure")

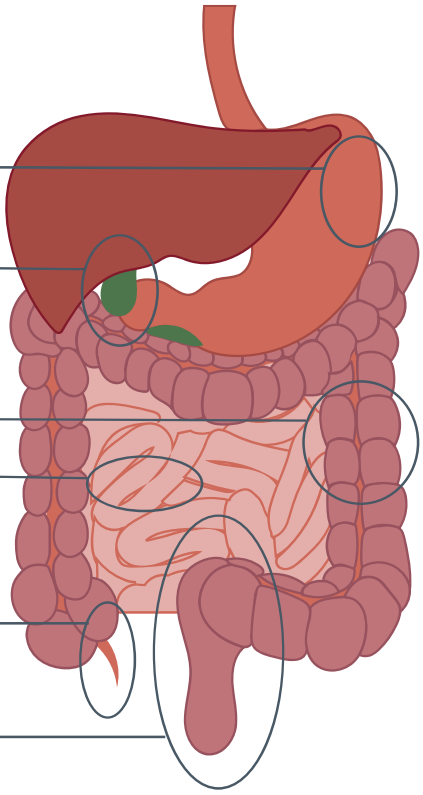
Removes the head of the pancreas, the gallbladder, nearby lymph nodes, and parts of the stomach, small intestine, and bile duct. The remaining parts of these organs are then reconnected in a new way.



Gastrointestinal tract

- **Appendectomy:** Removes the appendix
- **Cryosurgery (or cryotherapy):** Uses an instrument to freeze and destroy neuroendocrine cancer tissue. The doctor may use ultrasound to guide the device.
- **Endoscopic resection:** Removes certain small tumors from the inner lining of the GI tract using an endoscope
- **Gastrectomy:** Removes all or part of the stomach
- **Liver resection:** Removes 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:** Removes 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 intestine resection:** Removes all or part of the small intestine, often along with nearby mesentery and lymph nodes
- **Abdominoperineal resection (APR):** Removes the anus, rectum, and part of the sigmoid colon; a permanent colostomy is created through the abdominal wall

NET Surgeries in the Gastrointestinal Tract



Gastrectomy:
Removes all or a portion of the stomach

Cholecystectomy:
Removes the gallbladder

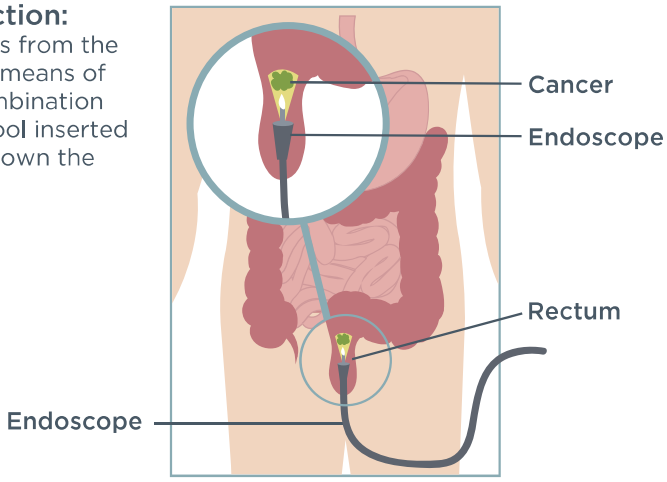
Resection Hemicolectomy:
Removes a portion of the large intestine along with nearby blood vessels and lymph nodes

Small Intestine Resection:
Removes all or a portion of the small intestine along with nearby blood vessels and lymph nodes

Appendectomy:
Removes the appendix

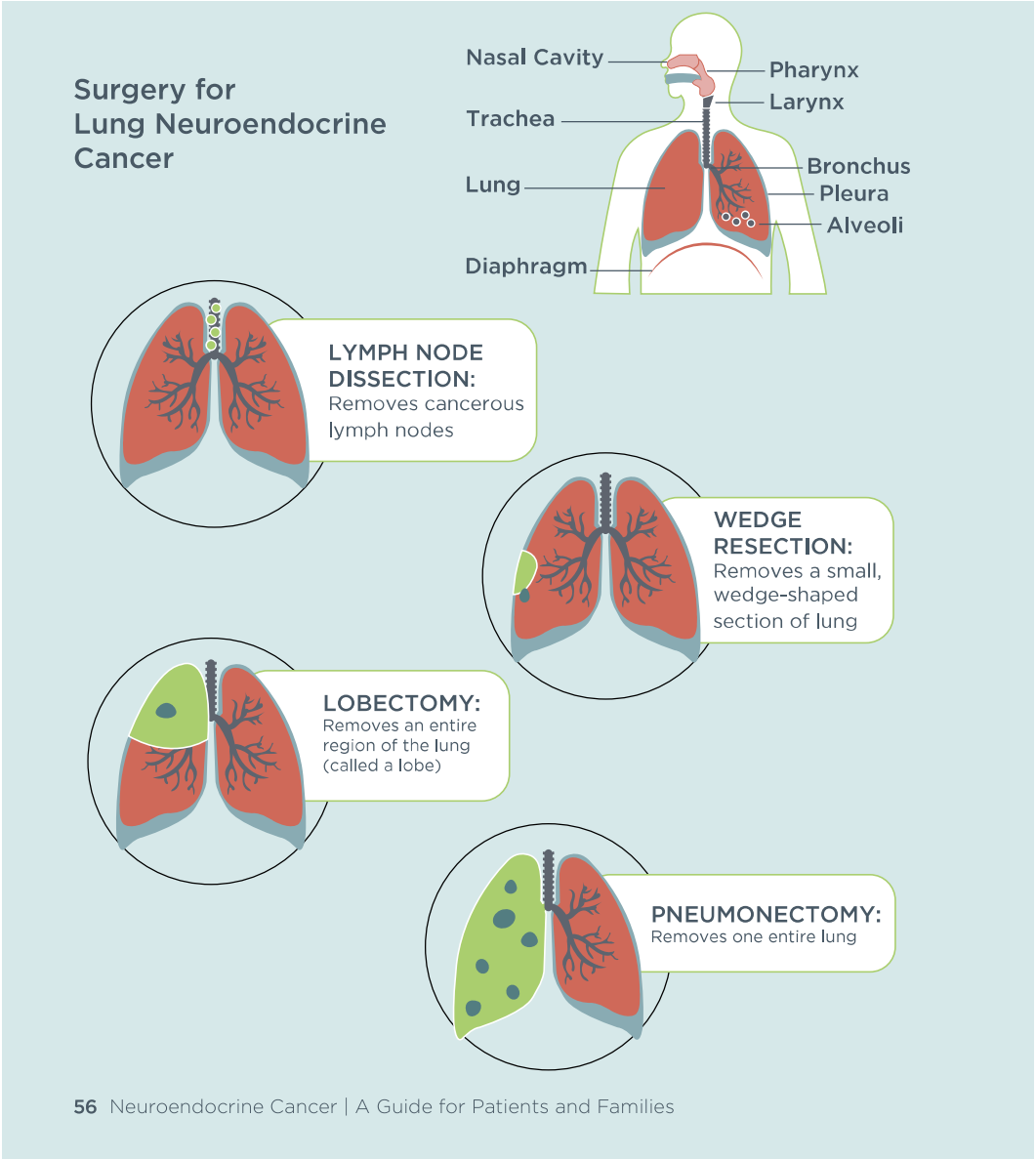
Abdominoperineal Resection:
Removes part or all of the anus, rectum, and sigmoid (lower) colon

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



Lungs

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



Liver transplantation

Liver transplantation is a rare but carefully considered treatment option for people with NET liver metastases. It may be considered when the liver is the only site of metastasis, the primary tumor has been controlled, and the disease is slow-growing and well-differentiated. Strict criteria are used to identify candidates who are most likely to benefit, as outcomes can vary. While not commonly performed, studies have shown that in carefully selected patients, liver transplantation can lead to long-term survival and improved quality of life. It is not recommended for patients with a grade 3 NET, NECs, or rapidly progressing disease.

Therapies

There have never been more treatments for neuroendocrine cancer. In 2005, only two treatments were approved for neuroendocrine tumors. As of this publication, there is a range of treatments available for NETs and NECs. Treatment options depend on the tumor's location, grade, and whether it has spread. Common therapies include somatostatin analogs to slow tumor growth and control hormone-related symptoms. Targeted therapies, such as everolimus, cabozantinib, or sunitinib, may be used for certain advanced NETs, depending on the tumor's site of origin and how quickly it is growing. Radioligand therapy (e.g., PRRT) is another option for advanced NETs that express somatostatin receptors. In some cases, chemotherapy may be used, especially for higher-grade or rapidly growing tumors.

Somatostatin analogs

Somatostatin analog therapy may reduce excess hormone release from some neuroendocrine tumors, which can improve symptoms and quality of life. These injections may also help slow tumor growth in some patients, but they are generally used to control the disease rather than cure it. The side effects of somatostatin analogs are generally mild and may include nausea, cramping, loose stools, abnormal stools (steatorrhea), and changes in heart rate. Somatostatin analogs are available in long- and short-acting formulations and include:

- Octreotide
- Lanreotide

Somatostatin analog injections are typically administered by a healthcare provider. Talk to your doctor about providers in your area who have experience giving the injections.

Targeted therapy

Targeted therapy is a type of cancer treatment that uses drugs designed to specifically target certain molecules involved in the growth and survival of cancer cells without affecting most normal cells. Unlike traditional chemotherapy, which attacks all rapidly dividing cells, targeted therapy works by interfering with specific proteins, receptors, or signaling pathways that are more active or abnormal in cancer cells.

In NETs, targeted therapies commonly used include:

- **Everolimus:** Blocks a protein called mTOR, which helps cancer cells grow and divide
- **Sunitinib:** Inhibits proteins involved in tumor blood vessel growth (angiogenesis), and is particularly used in pancreatic NETs
- **Cabozantinib:** Blocks multiple proteins that tumors use to grow and spread, including those involved in blood vessel formation, cell growth, and resistance to treatment
- **Belzutifan:** Blocks HIF-2α, a protein that helps tumors grow and survive in low-oxygen environments, thereby slowing tumor growth and reducing the formation of new blood vessels, and is particularly used in pheo/para and VHL-associated pNETs

Targeted therapy can help slow tumor growth, prolong progression-free survival, and sometimes reduce tumor size, especially in patients with advanced or inoperable NETs. It is typically given as a pill and may be used alone or in combination with other treatments.

Other types of targeted therapies are being studied for the treatment of neuroendocrine cancers.

Chemotherapy

Chemotherapy works by using drugs that kill fast-growing cells, a hallmark of many cancer types. These drugs circulate through the bloodstream and target cells that divide quickly, like cancer cells, by interfering with processes such as DNA replication, cell division, or protein synthesis. However, because chemotherapy doesn't distinguish perfectly between cancer cells and other fast-growing healthy cells, it can also affect:

- Bone marrow (causing low blood counts)
- Hair follicles (causing hair loss)
- Digestive tract lining (causing nausea, diarrhea, or mouth sores)

Chemotherapy can be effective in certain situations — especially for pancreatic NETs, high-grade NETs, NECs, or when the disease is progressing rapidly. Taken orally or through IV infusions, these drugs enter the bloodstream and reach cancer cells throughout the body. Sometimes, a combination of chemotherapy drugs is used to enhance effectiveness. Among the chemotherapy drugs used to treat NETs are:

- CAPTEM (capecitabine + temozolomide): A chemotherapy regimen used particularly in pancreatic NETs and sometimes in higher-grade disease
- 5-fluorouracil
- Streptozocin

Radioligand therapy

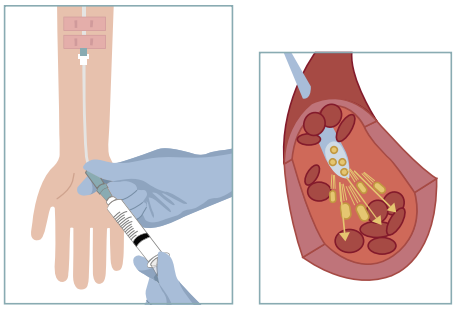
Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is a targeted treatment for NETs that express somatostatin receptors. It works by delivering a radioactive particle directly to the tumor using a somatostatin-like molecule, allowing for focused radiation that damages cancer cells while sparing most healthy tissue. PRRT is most often used in advanced or metastatic NETs, particularly when other treatments have not been effective.

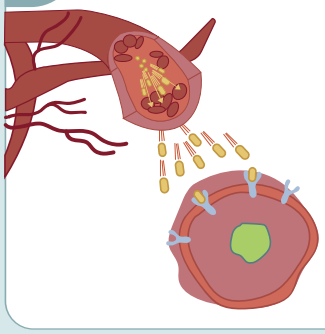
The most commonly used radionuclide, the unstable molecule that emits radiation, in PRRT is Lutetium-177 (Lu-177). Studies have shown that PRRT can increase progression-free survival and, for some, decrease tumor size to ultimately relieve symptoms and improve a patient's quality of life.

PRRT for NETs

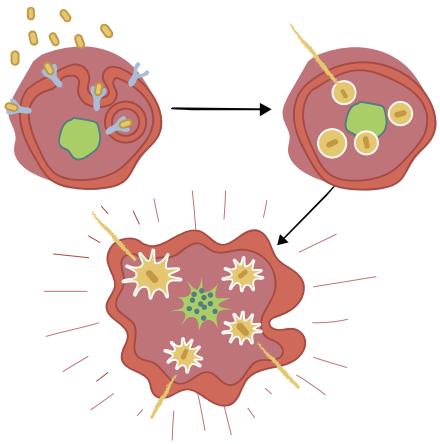
1. PRRT treatment is injected into the bloodstream and seeks out somatostatin receptors on NETs.



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 antinausea medication at the time of treatment.

Less common but more serious side effects of PRRT include damage to the bone marrow or kidneys. Research shows a 2-3% risk of developing a blood cancer, such as leukemia or myelodysplastic syndrome (MDS), after PRRT. However, this risk may increase to as high as 20% in patients who have previously received alkylating chemotherapy agents like streptozocin or temozolomide. These findings highlight the importance of considering the cumulative effects of treatment when planning the sequence of therapies for NETs.

The future of PRRT is focused on enhancing its effectiveness through several innovative strategies. Research is exploring the use of alpha particle therapies, such as actinium-225 and lead-212, which may deliver more potent and precise radiation to tumor cells with less damage to surrounding tissue.

Additional approaches include combining PRRT with other treatments (like radiosensitizers or immunotherapies) and modulating somatostatin receptor type 2 (SSTR2) expression to increase tumor uptake of the radiopharmaceutical, potentially improving outcomes for more patients. For tumors that do not express somatostatin receptors, research is underway to identify and validate new targets for treatment. NETRF actively supports research in these areas, funding studies aimed at enhancing PRRT efficacy.

Neuroendocrine Cancer with Weak or Absent Somatostatin Receptors

Somatostatin receptors are proteins found on the surface of some neuroendocrine tumor cells. They act like “docking sites” that allow certain scans and treatments to find and target the tumor.

Not all neuroendocrine tumors have enough of these receptors. When receptor levels are low or absent, treatments that rely on them, such as somatostatin analogs and peptide receptor radionuclide therapy (PRRT), may not work as well.

This is more common in some higher-grade or more aggressive neuroendocrine tumors, and it can also be seen in some lung NETs, particularly when receptor expression is lower or uneven across different tumor sites. For these patients, treatment may rely more on:

- Chemotherapy
- Targeted therapies
- Clinical trials

Researchers are actively studying new biomarkers, surface targets, and next-generation radioligand therapies to expand treatment options for this group.

Liver-directed Therapies

Liver-directed therapies are treatments used to target neuroendocrine cancers that have spread to the liver, especially for well-differentiated neuroendocrine tumors. Many of these procedures are performed by specialists in interventional radiology.

Some liver-directed therapies work by blocking the tumor's blood supply, while others work by destroying tumors directly.

Treatments that block the tumor's blood supply

Hepatic Arterial Embolization

This treatment reduces or blocks blood flow to liver tumors. The liver receives blood from two main sources: the portal vein and the hepatic artery. Hepatic embolization specifically targets the hepatic artery, reducing its blood flow while the portal vein continues to supply necessary blood to the liver.

Main types of hepatic arterial embolization include:

- **Bland embolization:** Tiny particles, such as beads or gelatin sponge material, are injected to block blood flow to the tumor.
- **Transarterial chemoembolization (TACE):** Combines embolization with chemotherapy delivered directly into the hepatic artery.
- **Transarterial radioembolization (TARE or Y-90):** Tiny beads containing radioactive yttrium-90 are injected into the hepatic artery to deliver radiation directly to liver tumors.

Treatments that deliver treatment directly into the liver

Hepatic Arterial Infusion (HAI)

This treatment delivers chemotherapy directly into the hepatic artery. By delivering treatment directly to the liver, HAI may allow higher chemotherapy concentrations to reach tumors while limiting exposure to the rest of the body.

Treatments that destroy tumors directly

Radiofrequency Ablation (RFA)

Radiofrequency ablation is a minimally invasive procedure used to treat small, localized NET metastases, especially in the liver. It uses heat generated by high-frequency electrical currents to destroy cancer cells. The procedure involves inserting a thin probe directly into a tumor, usually under image guidance. The probe emits radiofrequency energy, creating frictional heat in the tissue. This heat raises the temperature of the tumor cells, causing cell death.

Histotripsy

Histotripsy is a newer, noninvasive treatment used for certain liver tumors. It uses focused ultrasound to mechanically break down tumor tissue without needles, radiation, or surgery. Histotripsy is not available at all cancer centers.

During the procedure, a physician uses a specialized device with real-time imaging guidance to direct ultrasound energy at the tumor. This creates tiny bubbles in the targeted tissue that rapidly expand and collapse, breaking down the tumor. Over time, the body gradually clears the treated tissue.

Histotripsy is still being studied, but it may offer advantages for some patients, including precise treatment and real-time monitoring during the procedure. The U.S. Food and Drug Administration (FDA) authorized this technology for liver tumors in 2023.

NEUROENDOCRINE CARCINOMA TREATMENTS

Systemic chemotherapy is the mainstay of treatment for NECs. The most commonly used regimen is a combination of platinum-based chemotherapy (cisplatin or carboplatin) with etoposide, similar to protocols used in small cell lung cancer. This is often the first-line treatment for both localized and metastatic disease. Second-line chemotherapy regimens include FOLFIRI (5-fluorouracil, leucovorin, and irinotecan), FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and CAPTEM (capecitabine and temozolomide).

Surgery may be considered for localized tumors if complete removal is possible and the person is in good health. However, most patients present with advanced disease, limiting surgical options.

Radiation therapy can be used in combination with chemotherapy for local control or to relieve symptoms, especially in cases of bone or brain metastases, or spinal cord compression.

Immunotherapy is under investigation for NECs. Early studies using immune checkpoint inhibitors (e.g., PD-1 or PD-L1 blockers) have shown some promise, particularly in tumors with high mutation burden. Currently, the combination of ipilimumab and nivolumab is used in extrapulmonary NEC patients, and atezolizumab or durvalumab is used in SCLC. Next generation immunotherapies, including DLL3-targeted bispecific T-cell engagers (BiTEs), are now FDA approved for use in SCLC and are also showing promise for extrapulmonary NEC patients.

Ask your physician about new targeted therapies that may be in clinical trials. Genomic profiling may identify actionable mutations (e.g., in BRAF, KRAS, or MSI status) that could guide personalized therapy. Because treatment options for neuroendocrine carcinoma can be limited, taking part in a clinical trial may offer access to promising new therapies and help advance future care for others.

Supportive and palliative care are essential components of treatment, aimed at managing symptoms and improving quality of life.

WHY RESEARCH MATTERS FOR NETS AND NECS

Research is essential to improving how neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) are diagnosed, monitored, and treated. For many patients, these diseases can be difficult to recognize early because symptoms may be vague, varied, or mistaken for other conditions. Even after diagnosis, treatment responses can differ significantly from one person to another.

These challenges can affect outcomes. Delayed diagnosis may allow the disease to progress before it is found, reducing the opportunity for a surgical cure. While some currently available therapies can help control tumor growth or manage symptoms, many do not cure the disease. That is why continued research is so important, to help patients get diagnosed earlier and to develop more effective, personalized treatments.

Research also helps answer some of the questions patients and families ask most often:

- How can NETs and NECs be found sooner?
- Why do some treatments work better for some patients than others?
- How can new therapies be developed to improve outcomes and quality of life?

How Research Leads to Better Care

Biomedical research generally happens in three stages, and each plays an important role in improving patient care.

Basic research focuses on understanding how tumors form, grow, and behave. Scientists study tumor cells and use laboratory and animal models to better understand the biology of NETs and NECs.

Translational research takes discoveries from the laboratory and helps move them toward patient care. This includes developing promising new approaches, such as biomarkers, imaging tools, or treatment strategies, so they can be tested more effectively.

Clinical research includes studies and clinical trials that evaluate new therapies, diagnostic tools, and treatment approaches in people. Clinical research helps determine whether new interventions are safe and effective for patients.

Together, these stages of research create the path from scientific discovery to better diagnosis, better treatment options, and, ultimately, better outcomes for patients.

How NETRF Supports Progress

Because research requires time, expertise, and resources, funding is critical to advancing discoveries. NETRF supports research across the full spectrum, from early laboratory studies to work that helps bring promising ideas closer to patient care.

NETRF is the largest global funder dedicated to neuroendocrine cancer research, with a focused mission to discover cures and develop more effective treatments. Since 2005, NETRF has awarded more than $43 million to support hundreds of research projects at research institutions worldwide.

By funding high-impact research, NETRF helps accelerate progress in the areas most likely to improve the lives of patients and families affected by NETs and NECs.

NETRF's Research Roadmap

To guide this work, NETRF has developed a Research Roadmap focused on three key areas: Early Detection, New Therapeutic Development, and Precision Medicine.

- **Early Detection** aims to identify tumors at an earlier, more treatable stage by improving biomarkers, imaging, and risk-prediction methods.
- **New Therapeutic Development** focuses on discovering and advancing innovative treatments that can improve outcomes, overcome treatment resistance, and build on the therapies available today.
- **Precision Medicine** seeks to better understand the genetic and molecular features of each tumor so that treatment can be tailored more specifically to the individual patient.

By investing in these priority areas, NETRF aims to improve patient outcomes, enhance quality of life, and increase the potential for more effective, individualized care, and ultimately, cures.

For more information about NETRF's research portfolio and funded projects, visit netrf.org/for-researchers/about/.

CLINICAL TRIALS

Clinical trials play a vital role in testing the safety and effectiveness of new therapies for neuroendocrine cancer. Trials are also essential for advancing medical knowledge and improving care for future patients. Participation is always voluntary, and each trial follows strict safety protocols with close monitoring. Talking with your care team can help you decide whether a clinical trial is a good fit for you.

What is a clinical trial?

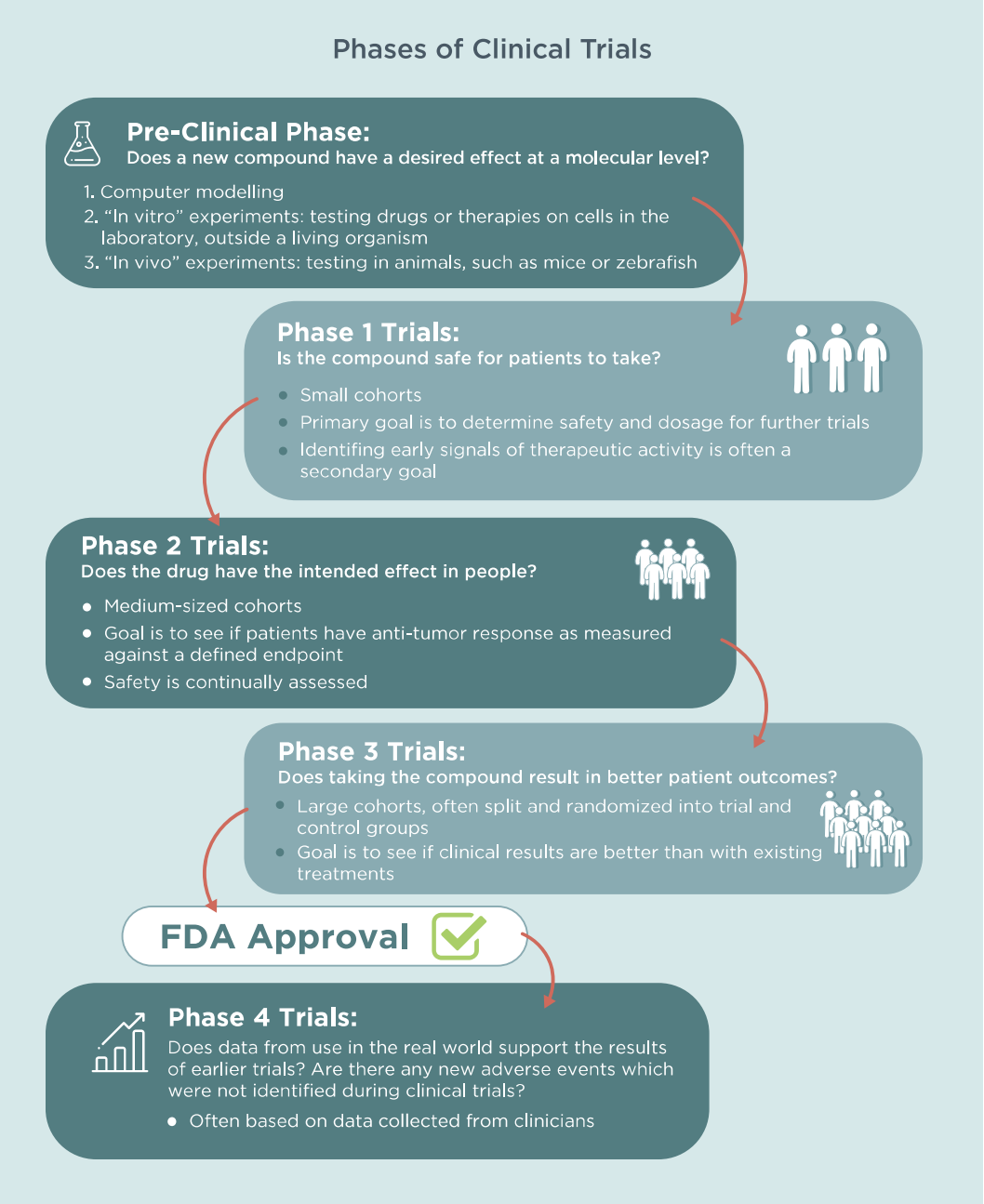
Clinical trials are research studies that help improve how we understand, diagnose, and treat diseases such as neuroendocrine cancer. A clinical trial represents the culmination of a lengthy research process that starts in a laboratory. Before testing new treatments on humans, researchers spend many years discovering new treatments and studying the effects of them on cell cultures or animal models. This initial research helps them determine the most effective doses, potential side effects, and how the new treatment compares to existing therapies. Typically, it takes about 10-15 years from the conception of a new drug to the initiation of its first clinical trial.

Clinical trials are conducted in phases, typically Phase 1, 2, and 3, each designed to answer specific research questions. Once a new treatment is successful in one phase, it may proceed to the next phase. Typically, if a new treatment is shown to be safe and effective in Phase 3, regulatory agencies, such as the U.S. FDA and the European Medicines Agency (EMA), may approve it for patient use, after which it can become available.

Not all trials test new drugs; some focus on other important parts of care and research. Here are a few common types of clinical trials and what they aim to do:

- **Treatment trials:** Test new therapies or combinations to see if they are safe and effective
- **Biobanking studies:** Collect tissue, blood, or other samples to help researchers study the biology of neuroendocrine cancer
- **Natural history or observational studies:** Follow patients over time to learn how the disease progresses
- **Imaging or diagnostic trials:** Test new scans or tools to find or monitor tumors more accurately
- **Supportive care trials:** Explore ways to manage symptoms or improve quality of life during treatment

Each trial phase helps advance care, and clinical trials may be an option at different points in treatment, including at diagnosis, during treatment, or after treatment.



How to Find a Clinical Trial

Clinical trials have specific criteria that determine who can take part, based on factors like your cancer type, stage, prior treatments, and overall health. Some people are interested in clinical trials because they offer access to promising new treatments, especially when standard options are limited or no longer effective. Others join to contribute to research that may help improve care for future patients. If you're considering a clinical trial, talk with your doctor because they can help identify trials that may be a good fit for you and guide you through the process of finding one that matches your individual needs and goals.

NETRF NET Clinical Trial Finder

NETRF, in partnership with Ancora.ai, offers a user-friendly NET Clinical Trial Finder designed to help patients with neuroendocrine cancer discover clinical trials that may be suitable for them.

How to Use the NETRF NET Clinical Trial Finder:

1. **Access the tool:**



Visit the NETRF NET Clinical Trial Finder.

2. **Enter your information:** Provide details about your diagnosis, such as tumor type, grade, and any previous treatments. This information helps tailor the search results to your specific condition.
3. **Review matching trials:** The tool will generate a list of clinical trials that align with your provided information, including details about the trial's purpose, location, and eligibility criteria.
4. **Consult your healthcare provider:** Discuss the list of potential trials with your doctor to determine which ones may be appropriate for you. Your healthcare team can assist in evaluating the options and initiating the enrollment process if you choose to participate.

This tool aims to simplify the process of finding clinical trials, making it more accessible for patients seeking new treatment options or contributing to research efforts.

Questions to ask your doctor about clinical trials

If your doctor suggests a clinical trial as the next step in your care or if you have an interest in taking part in a clinical 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 is the clinical trial treatment potentially better than my current treatment?
- How long will I be in the trial?
- What kinds of tests and treatments are involved in the trial?
- What is the new treatment being compared against?
- How will I know if my disease is responding during the trial?
- 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?
- Would receiving the treatment in this trial limit my treatment options after the trial?

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?

Learn more about clinical trials

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

- **NETRF:** Highlights new clinical trials in the monthly NETRF News newsletter and explains clinical trials in this episode of the NETWise podcast. Subscribe to NETRF's newsletter and listen to our podcasts here:

NETRF News	NETWise Podcasts
	

- **National Cancer Institute:** Offers basic information on clinical trials cancer.gov/about-cancer/treatment/clinical-trials

MANAGING YOUR SYMPTOMS

Discovering that you have neuroendocrine cancer is life changing. For some, this diagnosis comes after years of dealing with persistent, unexplained ailments. Others may find out they have cancer incidentally during routine medical exams or while being treated for another condition, which can be shocking.

A person with neuroendocrine cancer can have symptoms for many reasons:

- A tumor may release hormones into the bloodstream.
- Cancer treatment has side effects.
- Tumors may cause blockages or affect organ function as they grow.
- Diabetes can be caused by certain neuroendocrine cancers, most directly by pancreatic NETs through their hormone effects, and it can also develop as a side effect of treatment.
- Gallbladder problems, such as gallstones or inflammation, can occur with some treatments.
- Surgery for a GI or pancreatic neuroendocrine cancer can affect digestion.
- Tumors may cause pain in other parts of the body by affecting nerves or pressing on the spinal column.

As a result of these complex challenges, 92% of patients make one or more lifestyle changes to better manage their symptoms and improve their quality of life. 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 to recommend modifications or treatment options to alleviate any symptoms.

Palliative care is specialized medical care focused on improving quality of life for people living with serious illness. It is not the same as hospice and does not mean that treatment is stopping. Palliative care can be provided at any stage of neuroendocrine cancer and alongside treatments such as chemotherapy, targeted therapy, or PRRT. A palliative care team helps manage symptoms like pain, fatigue, shortness of breath, nausea, diarrhea, anxiety, and sleep problems, and also supports patients and families with emotional and practical concerns. Many people find that involving palliative care early helps them feel better and stay more active while continuing their cancer treatment.

To learn more about palliative care, please listen to this episode of our NETWise podcast.

Diarrhea

Diarrhea is a frequent and challenging symptom for many people with neuroendocrine cancer. This condition may arise from the disease itself or as a side effect of treatments. There are a few steps you can take to try to reduce the severity and frequency of diarrhea. In addition to limiting certain kinds of food and drinks (see Nutrition chapter), 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 people whose symptoms are not adequately controlled by somatostatin analog therapy.

To learn more about symptom management, please listen to this episode of NETWise.

Fatigue

Fatigue is one of the most common issues faced by people living with neuroendocrine cancer, manifesting both physically and emotionally, making it difficult to manage. There are a few things you can do to help manage your cancer-related fatigue:

- Plan activities for the time of day when you have the most energy.
- Schedule rest during low-energy times.
- Avoid overscheduling and pace yourself.
- Establish a sleep routine, going to bed and getting up at the same time each day.
- Aim for 7-8 hours of sleep per night.
- Develop a bedtime relaxation routine, such as taking a bath, reading, or whatever helps you wind down from the day.

- Use your bed only for sleep and intimacy.
- Keep your bedroom cool and dark.
- Limit daytime naps to less than 30 minutes.
- Exercise to gradually increase your energy.
- Address any underlying anxiety, stress, or depression that may affect your energy levels.

Additionally, talk to your care team about your fatigue. There may be other tests or treatments that can help.



To learn more about fatigue and fatigue management, listen to our NETWise episode on understanding fatigue in neuroendocrine cancer.

Integrative care

Integrative care combines mind-body practices, natural products, and lifestyle changes with conventional cancer treatments. Up to 80% of cancer patients use integrative medicine approaches such as acupuncture, yoga, massage, mindfulness, meditation, and hypnosis to manage pain and improve quality of life.

While some practices like acupuncture, yoga, and meditation are proven safe and effective, others may not be beneficial or could be harmful depending on your ongoing treatments. Be sure to talk to your care team before starting any new integrative, complementary, or alternative medicine therapies to ensure they are safe and won't interfere with your cancer treatment.

NUTRITION

Proper nutrition plays a vital role in supporting your overall health during cancer treatment. It can help you maintain strength, improve your quality of life, and reduce nutrition-related side effects. By paying attention to what, when, and how you eat, you may be able to ease some of the troublesome symptoms caused by neuroendocrine cancer.

Since every patient is unique, there is no one-size-fits-all approach to nutrition. In fact, 64% of people who have neuroendocrine cancer adjust their diets as a result of their disease.

Here are some tips to find what works for you:

- Listen to your body; what you can tolerate may change over time.
- Trial and error is normal; some foods may cause discomfort one day but be easier to digest another time.
- Cooking can make a difference; some people tolerate certain foods when cooked but not when raw.
- Choose gentle foods and drinks that are easy on your digestive system, such as white rice, oatmeal, bananas, toast, plain chicken, among others.

When and how to eat to help manage your symptoms

- Making adjustments to when and how you eat can help reduce diarrhea.
- Try smaller, more frequent meals instead of large meals, especially if large meals worsen your symptoms.
- Some people find it helpful to drink fluids between meals instead of with meals.
- Stay hydrated by drinking fluids regularly throughout the day. Ask your care team how much you should drink if you have ongoing diarrhea or a medical condition that affects fluid intake.
- Prioritize food safety to reduce the risk of food-borne illness:
  - Refrigerate or freeze perishable foods promptly.
  - Discard expired or spoiled items.
  - Refrigerate leftovers and discard them after 48 hours.

If you are experiencing digestive issues, consider avoiding highly processed foods, carbonated beverages, and 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

Seeking nutritional advice

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 neuroendocrine cancer. Working with your care team to create a personalized nutrition plan can help support your overall health and well-being.

Your medical history and any other health conditions will play a key role in determining the best dietary choices for you. It's important to adjust your diet based on your own needs and experiences.



To learn more about nutrition and neuroendocrine cancer, please listen to this episode of our NETWise podcast.

Enzymes and Other Supplements

Some people who have surgery for pancreatic neuroendocrine tumors may develop a condition called exocrine pancreatic insufficiency (EPI). This happens when the pancreas no longer produces enough enzymes to properly digest food, leading to symptoms like bloating, diarrhea, or greasy stools.

Pancreatic enzyme replacement therapy (PERT) can help manage these symptoms by replacing enzymes needed to digest fats, proteins, and carbohydrates. Most PERT products are pig-derived and are taken with meals and snacks. If you've had pancreatic surgery or notice digestive changes, ask your care team whether PERT might be right for you.

Religious groups have granted dispensation for pork-derived medicines like PERT, recognizing them as essential treatments. Individuals with pork allergies should discuss alternatives with their doctor.

People who have had surgery for other GEP-NETs may need to address deficiencies such as Vitamin D, B12, niacin, and iron caused by malabsorption, carcinoid syndrome, or treatments like SSAs. Supplements may include vitamins (A, D, E, K), calcium, probiotics for diarrhea, and antioxidants. Talk to your doctor before taking any supplements.

THRIVERSHIP — ADJUSTING TO THE NEW NORMAL

Thrivership is not just about surviving; it's about flourishing in your new normal after cancer diagnosis and treatment. Understanding what you need on your personal journey to thrive is crucial, especially when navigating life with neuroendocrine cancer.

Each day presents an opportunity to lead a meaningful and productive life. In this section, we will explore various strategies and practical steps that can help you make the most of every day, tailoring a survivorship plan that resonates with your unique circumstances and goals.

Managing emotions

People face many emotions when living with neuroendocrine cancer, with 60% of patients saying their disease had an impact on their emotional health. 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 neuroendocrine cancer for many years.

Those who have cancer may experience:

- 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. Your care team may be able to suggest names of counselors with experience in treating cancer survivors. Many patients benefit from attending patient support groups where they can share concerns and solutions with others who are facing the same cancer. You may also find support through online forums and virtual communities, which can be helpful if you prefer to connect from home.

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.

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.

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, relaxation exercises, and being out in nature or taking a walk 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 find fulfillment by volunteering for a worthy cause. Community involvement can offer social, professional, and emotional benefits. Whether you volunteer for a neuroendocrine cancer-related organization like NETRF or causes that are not related to neuroendocrine cancers, 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

A neuroendocrine cancer diagnosis can reshape what you once considered "normal." Instead of returning to life as it was, you may find yourself adjusting to a new normal, one that includes routine scans, ongoing medications, and long-term symptom management. Many patients experience the stress of regular monitoring including CT scans, injections, and infusions to track tumor growth or prevent cancer progression.

Yet even with these challenges, you can still lead an active and meaningful life. Each person finds their own way forward, adapting to changes in work, relationships, and daily routines – sometimes in ways that bring unexpected strength and resilience.

Most importantly, you are not alone. The neuroendocrine cancer community is strong and supportive, filled with people who truly understand what you're going through. Even if you've never met another person with neuroendocrine cancer before, you can easily connect with others who share similar experiences, symptoms, and concerns. While neuroendocrine cancers are uncommon, the community of patients, caregivers, and advocates is vibrant, offering encouragement, resources, and support at every step of your journey.

NETRF has a growing library of thrivership resources covering an array of topics to help you live your best life with neuroendocrine cancer.



To learn more about navigating your new normal, please listen to this episode of our NETWise podcast.

IN SUMMARY

Living with a NET or NEC can feel overwhelming, but there is hope and help at every step of your journey. Advances in research are leading to new treatments and more personalized care than ever before. We encourage you to stay informed, work closely with your care team, and explore all available options, including clinical trials.

At NETRF, we are here today, for your tomorrow. We are dedicated to supporting you with credible information and educational resources. NETRF is funding neuroendocrine cancer research around the world so scientists can develop new treatments and cures for it.

We hope this Guide has been helpful to you and your loved ones. We welcome feedback and your suggestions for future versions of this book.

Knowledge is power, and NETRF is here with you as you continue learning about neuroendocrine cancer. We offer additional information and resources across a wide range of topics, including symptom management, treatments, disease state education, research, the financial impact of cancer, caregiving, thrivership and more.

Please find these resources and more at:

NETWise podcast

NET Knowledge Center

Your Feedback Matters

NETRF greatly appreciates the support and insights of patients, caregivers, family members, friends, and medical professionals to ensure that our patient guide is accurate and meets your needs.

Please share your feedback with us, including information we may consider in future editions of the guide. Please send your feedback to info@netrf.org.

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