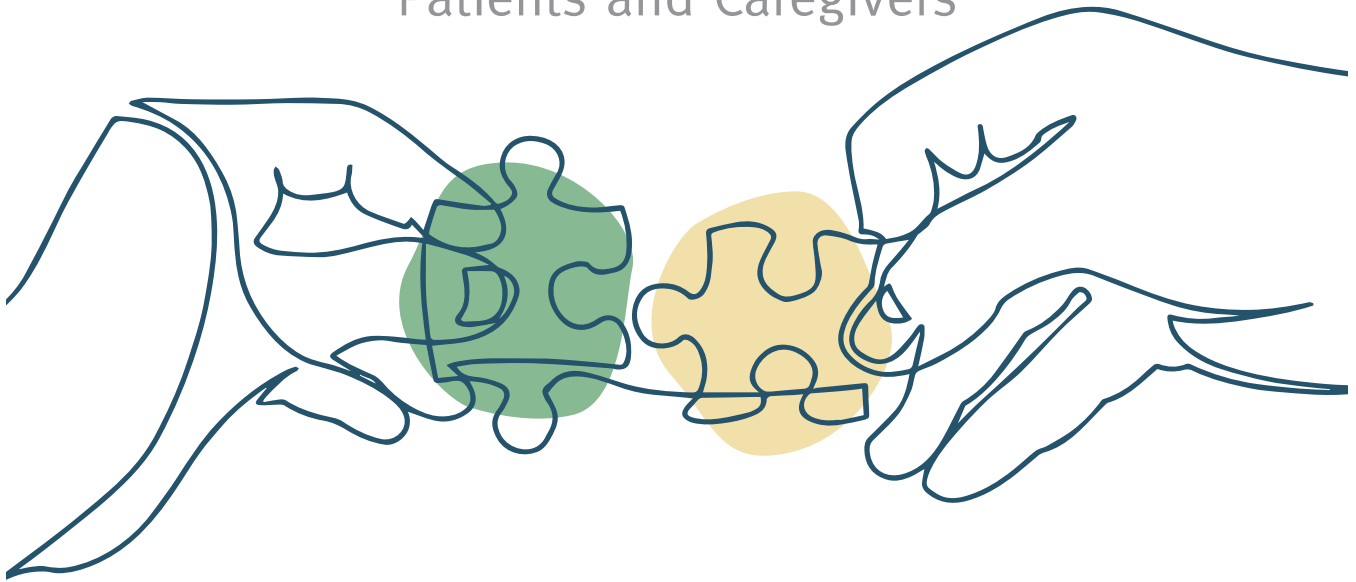


HIGH-GRADE NEUROENDOCRINE CANCERS

A Guide for
Patients and Caregivers



OUR MISSION

*To optimize the care of those
with neuroendocrine cancer
through the education of and
collaboration among physicians,
health care providers, patients,
and caregivers*



Dedicated to
Larry Sylvan

I dedicate this work to my late husband, Larry Sylvan, who was diagnosed with High Grade NEC in November of 2012. Just days before he passed away on September 7, 2013, he said, “Please do not let anyone else fight this disease alone.” After his 9-month cancer journey, I formed the online High Grade Neuroendocrine Carcinoma (Aggressive) Group. My goal was to get the best information available to all new patients and caregivers as soon after diagnosis as possible. Dealing with this awful disease is daunting and receiving guidance can empower the patient with knowledge and determination. —Susan Meckler Plummer

Dedicated to
Craig A. Cook

My dad, Craig Allen Cook, exercised every day at 6 am and was the healthiest 71-year-old I knew when he was diagnosed with Stage 4 NEC in December 2018. Our family believes we got an extra year with our dad based on all that I learned from Susan Meckler Plummer and the High Grade Neuroendocrine



Carcinoma (Aggressive) Group she runs plus my own external research. It was so confusing initially because most of the research is on the low-grade version of this disease, which behaves very differently and requires different treatment. We went against our primary oncologist’s recommendation that he go into hospice care in June 2019. Instead, Craig chose to try a different treatment recommended by the specialist we consulted. In June 2020, when his doctors recommended hospice again, we all agreed it was time. We are eternally grateful for that extra year. We were able to have several trips with him and a bonus Christmas, plus special normal moments like going for a swim, watching golf, and just drinking a cup of coffee together. I know for sure that his positive attitude and hopefulness lengthened his life and forever inspired me. When you are having a really hard day, maybe you can remember Craig, whose motto was “Never, Ever Give Up Hope,” and be inspired and carried through by some of his strength. —Natalie Eckdahl

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**The information on medical topics in this guide does not constitute medical advice.*

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Introduction

Healing NET Foundation’s mission is to optimize the care of those with neuroendocrine cancer through the education of and collaboration among physicians, health care providers, patients, and caregivers. This publication has been developed to support you as you face high-grade neuroendocrine cancer. Contributors include fellow patients and caregivers as well as physicians who are working hard to better understand and more effectively treat neuroendocrine carcinoma and high-grade neuroendocrine tumors. We combine these perspectives and types of knowledge to create a more complete picture.

Most patients have never heard of neuroendocrine cancer at the time of their diagnosis. People often think of cancer as related to a specific organ, but a neuroendocrine tumor in the pancreas is not what we typically think of as pancreatic cancer (adenocarcinoma). Rather it is cancer of the neuroendocrine cells located in the pancreas. There are many types of neuroendocrine cells, some making different hormones in many different parts of the body, thus the cancers arise in a variety of locations and can cause a wide range of symptoms or effects.

Here you will find information about the assessment and treatment of Grade 3 NET and poorly differentiated NEC, the more aggressive “high-grade” forms of neuroendocrine cancer. Though both have a Ki-67 index greater than 20, it is important to note that Grade 3 NETs and NECs are treated differently, and within each type there is significant variation in growth rate and behavior. This guide contains general information about high-grade neuroendocrine cancer assessment and treatment. The information here is not a substitute for a thorough medical evaluation from a healthcare provider but can give context to the diagnosis. Your care will need to be tailored to you specifically—there is no “one size fits all” approach. Please note: It is not likely, but some Grade 3 NET patients with a lower tumor growth rate may find the information in *Navigating the NET Patient Journey* (www.thehealingnet.org/navigating-nets) relevant to their situation.

This guide is designed to help you, patients and caregivers alike, find the support and resources you need during one of the most difficult and demanding periods of your life. We have included quotations from patients and caregivers about how they or their loved ones have faced this disease, which they have shared in the hope of helping you. Share this guide with your friends and family to build a greater understanding of your situation. Your healthcare providers, members of support groups, and many others want the best for you. You are not alone in facing cancer and in seeking the best quality of life.

NEUROENDOCRINE CANCER TERMS

Neuroendocrine cancer is really a class of cancers that originate in neuroendocrine cells, which are found throughout the body. They are in every organ that produces or secretes the many different hormones that control body processes. Thus, neuroendocrine cancers may originate in various sites, such as lungs, intestines, cervix, or pancreas, and the malignancies typically spread (metastasize) to other parts of the body. Some neuroendocrine cancers can be very quiet and indolent, while some can be extremely aggressive and grow fast.

NEUROENDOCRINE NEOPLASM (NEN)

is an umbrella term used by medical professionals that refers to any abnormal growth of neuroendocrine cells. These malignant growths are divided into two categories of neuroendocrine cancer:

NEUROENDOCRINE TUMOR (NET)

When examined under a microscope, NETs look “well differentiated.” That means the tumor cells and how they are organized in a tissue appear similar to normal cells and tissues.

NEUROENDOCRINE CARCINOMA (NEC)

At the microscopic level, NECs are “poorly differentiated.” They contain abnormal-looking cells and may lack normal tissue structures. NECs are divided into “large-cell,” “small-cell,” and otherwise undefined types, all of which tend to be aggressive in their growth.

Note: Patients can, but rarely do, present with tumors that are essentially two tumors in one—such as neoplasms that are a mixture of neuroendocrine and non-neuroendocrine cells (miNENs) or adenocarcinomas with neuroendocrine features.

WHAT DEFINES NEUROENDOCRINE CANCER AS HIGH-GRADE?

The World Health Organization classifies diseases to improve the tracking and analysis of data, and these classifications evolve over time. The most recent (2019) classification of NENs is organized by grade (growth rate) and type.

NENs are graded according to how many cancer cells are in a phase of cell division called mitosis. This is called the mitotic rate. The Ki-67 index, which measures levels of a protein that can be detected in dividing cells, is a marker of how quickly a cancer may be growing.

- NETs are placed in three ascending grades. Grade 3 NETs are the fastest growing with a mitotic rate and Ki-67 index greater than 20.
- NEC is classified as high-grade by virtue of its rapid growth and typically high Ki-67 index.

	TYPE	MITOSES	KI67
LOW GRADE	Well-differentiated NET Grade 1	< 2 mitoses per 10 high-power fields (HPF)	< 3%
	Well-differentiated NET Grade 2	2-10 /10 HPF	3-20%
HIGH GRADE	Well-differentiated NET Grade 3	> 20 /10 HPF	> 20%
	Poorly differentiated NEC	> 20 /10 HPF	> 20%

CHAPTER ONE

CHOOSING A PHYSICIAN

With this diagnosis, you will want to take action to find the best care. It is likely that the oncologist or other physician who diagnosed your cancer does not have much experience with high grade NET or NEC. As a first step, ask your physician how many patients with NEC or high-grade NET he or she has treated. If the answer is very few, don't hesitate to ask for a referral to someone with more experience—at least to get a second opinion. Find a physician who is an expert in high-grade NET and NEC—one who has treated many patients with this disease or is part of a center that has. One advantage of a specialized neuroendocrine tumor center is access to a multidisciplinary team of specialists with experience in assessing and treating neuroendocrine cancers. In addition, there are usually professionals who can improve your experience by addressing side effects and other aspects of care, such as a dietitian, pharmacist, social worker, and palliative or supportive care team.

Some organizations provide directories of doctors known to treat neuroendocrine cancer patients (see, for example, netrf.org/for-patients/neuroendocrine-tumor-doctor-database and carcinoid.org/for-patients/treatment/find-a-doctor). It may help to find out what the experiences of other patients have been. For example, you may want to check online reviews posted on websites such as healthgrades.com or on cancer center websites. Keep in mind that some patients respond better to the



personality of one physician over another so decide what's most important to you and do your homework accordingly.

It is best to be seen by an experienced neuroendocrine cancer specialist for a thorough assessment and an effective treatment plan. You will want to find a doctor who thinks ahead. Even if your cancers shrink during the first course of treatment, they will likely start growing again, and you want a physician who's already plan-

WHEN THERE ARE BARRIERS TO SEEING A SPECIALIST:

Specialists in neuroendocrine cancers, particularly NECs and high-grade NETs, are not found in every cancer center. Traveling to see a specialist may not be an option due to economic, health or logistical reasons. For example, insurance networks may dictate which physicians you see (see Chapter 5 for more information on insurance). Some neuroendocrine specialists are doing telemedicine. Consider contacting them to determine if this is an option for you. An alternative to seeing an out-of-town specialist is to seek a local physician who is willing to do research on your behalf, review the latest guidelines, set up consultations and send medical files and imaging to a specialist for review. Find a provider you trust who communicates clearly.

ning the next step of therapy. Your treatment and monitoring can be a coordinated effort between a specialist and your local physician.

Once you have chosen the provider to direct your care, stay engaged. You will benefit from being an active participant in all aspects of your care. Don't ever be afraid to ask questions. Knowledge is power and building your knowledge really can make a difference.

Some practical considerations:

- Prior to your first meeting with the specialist, ask if you can bring a family member or friend along, especially if you'd feel more comfortable having a second set of ears. If your friend or support person can't come with you in person, ask if they can attend the meeting virtually, via Zoom or Facetime.
- Ask for a number you can call or a portal you can access so you can leave a message if you have questions about your care.

Keep track of information from testing, appointments, and insurance. See "Communication and Organization Tools" at thehealingnet.org/patient-resources.

If your relationship with your doctor is challenging, it will benefit you to find someone else. Your goal is to create a positive, collaborative relationship, and if the doctor you are seeing isn't interested in building such a relationship, find someone who is. You know best what feels supportive and respectful. The best doctor for you is one who admits he or she doesn't have all the answers and still has a lot to learn from this disease—and from you.

"Patients have told me, 'I don't feel my doctor is listening to me. He says it's all in my head.' You're not crazy. You need to find a new doctor. Let's face it: it's a ton of paperwork to change doctors midstream when you don't have any energy to do that. I get that, but the biggest thing is getting to the right doctor quickly and getting the facts you need."

—Gil Schaezle

"We asked if anyone knew another family dealing with this type of cancer we could talk to, but it was so rare that none of the doctors or other staff could offer any personal connections for us. Yet the surgeon kept insisting that he absolutely knew how to treat it and we needed to trust him fully. He insisted that we stay off the internet and not do any research on neuroendocrine cancers because it would only serve to frighten us, and he had everything under control. We finally did what we should have done in the beginning: we went online. We found a group on Facebook for women with the same type of cancer who connected us with the right doctor."

—Sally Turnage Gustin

CHAPTER TWO

GETTING A THOROUGH ASSESSMENT

One of the reasons it is so important to find an experienced physician, or a physician willing to consult with one, is that you need a thorough assessment based on your initial diagnosis. Each patient is different from the next in both obvious and subtle ways. A thorough assessment provides the information needed to develop an effective treatment plan for your specific situation. Factors that need to be determined include cell differentiation, grade, stage, and whether the tumors are functional (release excess hormones). A personalized approach is always key in determining what diagnostic tests are needed, what therapy is chosen and whether changes are needed over time.

Your oncologist may want to conduct genomic testing of the cancer cells to uncover more treatment options. In some cases, your physician may also want to do genetic testing of your normal cells to understand whether a genetic mutation contributed to your cancer or could be associated with other health risks.

GRADING: THE IMPORTANCE OF PATHOLOGY

The pathology report describes what is observed in the microscopic analysis of tissue removed during a biopsy or surgery and is critical to making an accurate assessment. A biopsy is a tiny piece of tissue collected at a particular spot at a certain moment, a snapshot, so it offers only a specific window into what's going on.

Pathologists identify the rate of mitosis and the Ki-67 index to determine the grade of the cancer, which greatly influences treatment decisions. Several factors can impact the accuracy of the report, from varying assessment protocols to differences seen in the tumor itself. If you are being evaluated at a center where there are not many neuroendocrine cases, it is reasonable to ask that your biopsy sample be sent to a larger center for another assessment.

Request and review copies of your pathology reports. You have a right to see them, and it should become a habit to collect all your information. It's important that you or your caregiver examine the pathology reports to make sure no mistakes have been made that could adversely affect the treatment you receive. If you've been diagnosed with NEC but your Ki-67 index is in the 30s or 40s, for example, you may actually have a well-differentiated Grade 3 NET. These two different forms of neuroendocrine cancer may demand different treatments.

“I always ask for my pathology report. I’ve caught stuff twice on my pathology reports because of reading them ... Doctors don’t know that with this disease every little thing is suspect. You need to pay attention. You need to read your pathology report, and you need to get your scans on a disc. It only takes them five minutes to run a copy for you. I do that with everything. You can’t trust that your stuff will get from one place to another, so you have to take everything with you.”

—Christa Sonsire

“Think of a biopsy as hunting for a blueberry inside a blueberry muffin using a needle. If the blueberry is very small and deep inside or in a challenging location, you may not get it or you may get only a small piece.”

—Chandrikha Chandrasekharan, MBBS

STAGING: THE IMPORTANCE OF RADIOLOGY

The chart below outlines the various imaging technologies and their uses in assessing neuroendocrine cancers. Imaging is used to detect the extent of the cancer on a scale from Stage 1 (has not spread) to Stage 4 (spread to other organs or parts of the body). By the time of diagnosis, the disease may already have spread, or metastasized,

SCAN TYPE	DESCRIPTION	USE IN NEUROENDOCRINE CANCERS
MRI <i>magnetic resonance imaging</i>	Uses magnets and radio waves to produce 3-D images of organs and tissues	Especially useful for finding liver metastases.
CT <i>computed tomography</i>	Uses x-rays to make 3-D images of body structures (bone, vessels, soft tissues)	Often the initial assessment for staging and for surgical planning. Can help identify primary tumor.
PET <i>positron emission tomography</i>	Uses very small amounts of radioactive substances to detect biological features of a tumor (often combined with CT to gather info in one procedure)	PET-CT scans, particularly FDG-PET and PET-DOTATATE scans (below) are often used—possibly in combination—to assess neuroendocrine cancer
FDG-PET	Uses fluorodeoxyglucose (FDG), a radiopharmaceutical that emits electrically charged particles called positrons	To identify which tumors (lesions) are “hot,” rapidly dividing, and which are “quiescent,” not showing much growth. Useful with NEC.
DOTATATE-PET Gallium 68 (Ga-68) or Copper 64 (Cu-64)	Ga-68 and Cu-64 are positron-emitting radioisotopes that bind preferentially to somatostatin receptors (SSTR).	May be done with a well-differentiated Grade 3 NET to determine if the tumors are expressing somatostatin receptors on their surface, in which case PRRT (peptide receptor radionuclide therapy) might be a treatment option. Generally not useful with NEC.
OCTREOSCAN <i>a type of SPECT: single-photon emission computed tomography</i>	Radioactive octreotide is injected into a vein and travels through the bloodstream to tumor cells with somatostatin receptors. The SPECT scan makes images of the tumor cells.	This is an older scan; newer technologies provide more detailed pictures of NETs and are performed over several hours rather than several days.

throughout the body. NETs and NECs typically metastasize even when the original/primary tumors are relatively small and even when they have been surgically removed (resected) with clear margins, meaning that no visible cancer is left. Radiological imaging, including CT and MRI, can detect the extent to which the cancer has spread throughout the body. Two types of PET scans provide valuable information for assessing the growth rate of the tumors and whether somatostatin receptors (SSTRs) are present. SSTRs are proteins on the surface of neuroendocrine cells that bind the hormone somatostatin, and they can have diagnostic, prognostic, and potentially therapeutic value.

FUNCTIONAL AND NONFUNCTIONAL TUMORS

Some NETs are called functional because they release excess hormones into the body. Such hormonal imbalances can cause various syndromes, each with their own constellation of challenging symptoms, such as diarrhea, flushing, heartburn, wheezing, excessive sweating and others. Nonfunctional tumors release very small amounts of hormone or none, but they could possibly become functional

over time. It is quite rare for neuroendocrine carcinomas or high-grade NETs to be functional, but if you are having symptoms, you can work with your doctor to manage them.

TESTING FOR MUTATIONS

Increasingly physicians are conducting genomic testing (next generation sequencing, molecular testing) of tumor cells from the patient's blood or tissue biopsy. Results of such testing could expand the treatment options. Genomic testing provides a read-out of the cancer genes to uncover specific targetable mutations, including but not limited to MSI, TRK, FGFR, HER-2, BRCA, RET, high tumor mutational burden (TMB) and others, for which there could be existing approved applications or a potential clinical trial or novel drug in development. NEC tends to have a higher percentage of potentially targetable mutations as compared to NET.

Some forms of neuroendocrine cancer may run in families, meaning that it may be passed down through mutations in genes. This is an incredibly rare occurrence but if your diagnosis is thought to possibly be hereditary, you may want to consider formal genetic testing.



CHAPTER THREE

GETTING THE RIGHT TREATMENT

There is no cookbook with recipes to follow when it comes to treating a person with high-grade neuroendocrine cancer. Each patient's unique situation requires careful consideration before a treatment plan is implemented. The treatment information in this chapter is general and may not apply to your particular situation. However, because there are some significant differences between the general treatment approach to poorly differentiated NEC and to well-differentiated high-grade NET, this chapter is divided into three parts:

- Part 1 describes typical treatment approaches for poorly differentiated NEC
- Part 2 focuses on treatment of high-grade well-differentiated NETs
- Part 3 outlines beneficial treatments for both NET and NEC

Doctors keep learning more, but you will find some consensus opinions in this chapter about what treatments are most beneficial and when certain interventions make the most sense. Remember that no two patients are alike, and this general outline may not be appropriate in your case.

You or people close to you can stay on the lookout for the latest information about your disease. You or your caregiver will need to advocate effectively on your behalf and from time to time may even have to push to get the care that you need when you need it. On the other hand, you may

wish to avoid certain treatments because you think they will diminish your quality of life too much. An important element of your care is to think about what you most want your life to be like. That self-awareness can help you make difficult treatment decisions.

PART 1: TREATMENT APPROACHES FOR NEUROENDOCRINE CARCINOMA

Aggressive tumor growth requires timely intervention with the best available treatments. Though it takes time to gather all the necessary information to plan treatment, your doctor is unlikely to suggest a “wait and see” approach regarding treatment itself. Medical research continues to open up new treatment options and clinical trials. Your doctor must be able to identify the most effective treatments for you, obtaining them through clinical trials and compassionate use programs if necessary.

CHEMOTHERAPY

Each patient should be evaluated according to his or her individual cancer biology (what the cancer looks like and how aggressively it is spreading). In general, however, the standard, first-line treatment for NEC with a high Ki-67 index is a chemotherapy combination called the platinum “doublet” (cisplatin or carboplatin with the partner drug etoposide).

Cisplatin and carboplatin are similar in their anti-cancer effect, but they differ in their side-effect profiles. The appropriate agent should be selected based on the individual patient. Cisplatin can cause more nausea, kidney problems, nerve pain, hearing loss, or numbness (neuropathy), whereas carboplatin

COPING WITH CHEMO

Once chemotherapy begins, don't suffer from side effects in silence or try to be stoic or brave. Cancer chemotherapy is going to cause side effects because it targets fast-growing cells and does not differentiate between normal and malignant ones. Patients commonly experience hair loss, fatigue, nausea and vomiting, loss of appetite and weight loss, anemia and an increased susceptibility to infection. Your doctor can prescribe medications to help minimize the side effects of chemotherapy.

Frequent needle sticks required to inject chemotherapy into the veins in the arm are uncomfortable, and chemotherapy drugs can damage the tissue around veins, making injection sites increasingly difficult to find. If one is not offered to you, request a chemo port (also called a port-a-cath), a small reservoir placed under the skin near a large vein, usually in the upper chest. Blood can be drawn and chemotherapy drugs can be injected into the port, eliminating the need for needle sticks and often reducing infusion time.

“Losing her hair was a given, but she was constantly dehydrated and had chills. I would find her sitting in the yard with a heavy coat on in 90-degree weather. We made many trips to the hospital for fluids. She lost her taste for most foods and had terrible sores in her mouth.”

—Sally Turnage Gustin (caregiver)

tends to cause more blood count abnormalities (lower numbers of red and white blood cells). Overall carboplatin is relatively better tolerated with fewer side-effects. It is often preferred in the treatment of metastatic disease as preserving a patient's quality of life is paramount. Etoposide is a long-standing chemotherapy drug that is used in combination with platinum and treats many types of cancers. The common side effects include lowered blood counts, vomiting, loss of appetite, diarrhea, hair loss, and fever.

The good news is that NEC is very sensitive to the platinum doublet. Treatment with cisplatin or carboplatin will cause dramatic shrinkage of the carcinomas in about 50-70% of patients. Some patients are suffering from severe symptoms caused by widespread disease at the time of diagnosis. By shrinking the cancer, an initial course of chemotherapy may relieve their symptoms and improve their quality of life. They may go from being bedridden to feeling like themselves again.

The bad news is that the cancer-shrinking effects of a cis- or carboplatin doublet generally last for only a few months and then the carcinomas start growing again. That is why it's important for your doctor and you to decide on a next step even as you begin your first round of chemotherapy. As a second line therapy, some doctors recommend topotecan, which is used to treat recurrent or metastatic small-cell lung cancer, ovarian cancer and uterine cancer. Like cisplatin, however, topotecan has a lot of side effects and its benefit in terms of shrinking cancers is modest. Other chemotherapy drugs such as 5-fluorouracil based therapy (FOLFIRI, FOLFOX), capecitabine/temozolomide, taxane agents, or a combination of these drugs may also be suggested by your treating physician.

IMMUNOTHERAPY

Many NEC patients are receiving immunotherapy after platinum doublet chemotherapy, but increasingly the immunotherapy drugs are being added to the platinum doublet chemotherapy (as part of the first line treatment), particularly for patients with small cell histology. Immunotherapy drugs stimulate the body's immune system to attack abnormal cells. Immunotherapy drugs in current use include nivolumab (Opdivo), ipilimumab (Yervoy), pembrolizumab (Keytruda), and atezolizumab (Tecentriq).

Immunotherapy doesn't work for every patient, and even when it does work, the drugs must be given over the course of several weeks before they begin to show positive effects. Patients who respond to immunotherapy may continue to experience positive anti-cancer effects after the treatment has been stopped. That's because these drugs unleash the power of the immune system. Many neuroendocrine cancer specialists are enthusiastic about immunotherapy because it holds out the possibility of increasing survival time for the NEC patients who respond. Immunotherapy with other combination treatments remains an active area of research.

NEC AND PEPTIDE RECEPTOR RADIONUCLIDE THERAPY-PRRT

PRRT has an extremely limited, if any, treatment role for patients with poorly differentiated neuroendocrine carcinomas. A recent analysis suggests the only subset of patients with NECs in whom PRRT may meaningfully slow disease growth is the minority with somatostatin receptors (proteins on the surface of cells that bind to the hormone somatostatin).

SURGERY AND NEC

Surgery is not recommended for treating metastatic NECs. If the disease is localized to a particular area or is causing symptoms, it could be beneficial; however, this is usually decided after a tumor board discussion.

PART 2: TREATMENTS FOR GRADE 3 NEUROENDOCRINE TUMORS

SURGERY FOR GRADE 3 NETS

Surgery can be considered in Grade 3 NETs on a case-by-case basis. It may be warranted in early-stage disease before the cancer has become disseminated throughout the body, when the cancer(s) can be removed easily and when there is a high likelihood that the surgeon will be able to remove it all. Surgical debulking may play a role to "reset the clock" with regards to the burden of disease. When the cancer is more advanced, surgical removal of a piece of it can help make the diagnosis. Surgical removal of large cancerous growths that are causing symptoms by impinging on nerves, obstructing the intestines, or pressing on the liver can relieve pain and avoid other complications.

G3 NETS AND PEPTIDE RECEPTOR RADIONUCLIDE THERAPY-PRRT

PRRT has been helpful for patients with low-grade NETs and could be considered, though it has not yet been proven to have benefit, in treating patients with well differentiated Grade 3 NETs. PRRT is the equivalent of a "heat-seeking missile" for tumors with somatostatin receptors. A radiation-emitting

material called a radionuclide is piggybacked onto a synthetic piece of protein (peptide), which is injected into the bloodstream. PRRT delivers a high dose of radiation specifically to receptor-bearing cancer cells wherever they are in the body. Currently Lu-177 dotatate (Lutathera) is FDA-approved for use in well-differentiated gastroenteropancreatic NETs with somatostatin receptor expression. These treatments are given as an intravenous infusion every two months for a total of four doses.

The best way to check for the presence of somatostatin receptors is either the Gallium-68 or the Copper-64 DOTATATE scan. Your doctor may also request a FDG PET scan in this situation to see how rapidly the tumors are growing before suggesting PRRT. Because of the faster growing nature of the high-grade neuroendocrine tumors, your doctor may recommend more frequent imaging to check for tumor growth between PRRT treatments than is traditionally done for Grade 1 or 2 tumors.

CHEMOTHERAPY WITH NETS

Factors that are usually considered while initiating chemotherapy in NET patients include primary location of the tumor, side effects from the tumor, burden of tumors, their behavior over time and your own health factors. Some patients with a well differentiated Grade 3 NET may be offered systemic treatments that are conventionally used in Grade 1 or 2 well differentiated NETs, such as octreotide or other targeted oral drugs. Usually when a more aggressive clinical presentation is noted or the burden of the disease is concerning, your clinician may recommend the combination of oral chemotherapy pills called capecitabine and temozolomide, often

referred to as CAPTEM, especially for patients with a tumor arising from the pancreas. Some other chemotherapies, such as the cis- or carboplatin doublet, oxaliplatin or irinotecan may also be discussed.

PART 3: BENEFICIAL CARE FOR ALL HIGH-GRADE PATIENTS

PALLIATIVE CARE

Palliative care relieves and manages symptoms to improve your quality of life. By relieving symptoms, palliative care supports your overall treatment plan. Anyone with a life-threatening illness can benefit from palliative care. It can help you cope, endure, and marshal the energy needed to undergo treatments. Relief from symptoms also makes it easier on your caregiver because no one wants to see someone they love suffer.

Most medical institutions have full time palliative care teams that typically include an attending physician, a nurse or nurse practitioner, a clinical social worker, and a pastoral care professional. Palliative care is most effective if started at the time of diagnosis, but you may begin at any time.

“Palliative Care does not mean the patient is dying. It is not the same as Hospice. IF/when there are no treatments left, or the patient does not want additional treatments, the Palliative Care team can help transition to Hospice.”
—Jennifer A. O’Brien in *The Hospice Doctor’s Widow: A Journal*

Palliative care is holistic or multi-faceted and therefore a valuable ally regarding your overall quality of life. It accounts for a patient's wishes as it addresses a full range of needs—physical, social, emotional, spiritual. Perhaps your diagnosis has spurred you on to do things that you had been putting off, such as completing a big hike or visiting a faraway place. Your care team can help you anticipate your needs and plan with you to achieve your goal. Work with your medical care providers to live fully.

COMPLEMENTARY MEDICINE

There are additional treatment modalities that are not typically part of conventional medical care in the United States but that may be used in conjunction with mainstream medicine to reduce symptoms and improve quality of life. Complementary medicine is the term used to describe using alternative therapies alongside conventional medicine. Don't be surprised if the physicians treating your cancer suggest some complementary treatments for you to try in an effort to manage pain, reduce stress, or generally improve quality of life.

Yoga, chiropractic manipulation, and meditation are popular complementary therapies, and there is a wide range of such mind and body practices: acupuncture, massage, tai chi, qi gong, mindfulness-based stress reduction, relaxation techniques (such as breathing exercises and guided imagery), hypnotherapy, and dance, art or music therapy. Traditional medicine, such as Ayurvedic medicine, traditional Chinese medicine, homeopathy, and naturopathy, can also complement Western medicine. Dietary supplements are used by many Americans, but since they can interact with drugs,

“Being pain-free made an incredible difference in Lety’s ability to function fully. Her psychiatrist put her on an antidepressant and anti-anxiety medication, both of which helped her tremendously. This is something that may seem counterintuitive, and many doctors don’t seem to understand. So many of Lety’s cancer sisters have been denied proper meds and are on disability and in immense pain. Their pain often isn’t managed until they reach hospice. A stage 4 cancer patient is technically dying, they just don’t know when. Worrying about addiction is ridiculous. Lety never abused any of her medication, never took more than she was prescribed, but the meds made all the difference in managing her secondary symptoms.”

—Sally Turnage Gustin

check with your doctor first. Cannabis (marijuana) is a plant that contains chemicals called cannabinoids that are being studied for medical use. Federal law does not allow possession of marijuana, but more and more states have approved its medical use. Cannabis products, including CBD, are commonly used by cancer patients to relieve pain, nausea, and anxiety. Make your medical team aware of any complementary approaches you are using.

Read more by the National Center for Complementary and Integrative Health at nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name

CLINICAL TRAILS

Participation in clinical trials, or studies in humans, can provide access to off-label or investigational therapies that are not yet on the market or covered by insurance but might benefit you. Ask your doctor to keep track of clinical trials that might be appropriate for your situation. For example, your doctor may recommend testing your cancer for the presence of mutations because you may qualify for clinical trials of new immunotherapies or other targeted therapies.

Phase 1 clinical trials enroll a very limited number of patients in order to study the safety of the drug first. They may be testing a new drug for the first time in human subjects. Sometimes a phase 1 study involves combinations of existing drugs that do not have established safety data for the combination approach. Phase 2 studies often enroll larger groups of patients. The primary purpose of a phase 2 study is to check if the dose determined to be safe in the phase 1 trial has meaningful activity against this cancer. Typically phase 1 and phase 2 studies do not have a placebo arm (use of a non-drug in some study subjects for comparison). Phase 3 clinical trials usually enroll patients by the hundreds. They may compare two different types of drugs or combinations and are often randomized into groups where one set of patients receives a treatment slightly different from the other set of patients. These trials may also involve use of a placebo. Clinical trials focusing on neuroendocrine tumors, especially phase 1 or phase 2, are more likely to be available in larger academic centers or high-volume centers that see more neuroendocrine tumor patients.

It is important to ask your treating physician early on about clinical trials if you are interested in pursuing that option. ClinicalTrials.gov and TrialsToday.org (a shortcut to search the government site) are reliable sources listing clinical trials. Review any trial options you find with your treating physician, who can help assess your eligibility or provide other guidance.

Compassionate Drug Use

Sometimes patients do not qualify for a clinical trial or may not live close enough to the trial site to participate. According to the American Cancer Society, “Compassionate drug use means making a new, unapproved drug available to treat a seriously ill patient when no other treatments are available.” Drugs may be made available under expanded access programs (EAPs) or the Right to Try Act, but it is not always possible to get access. Read more about compassionate use here: cancer.org/treatment/treatments-and-side-effects/clinical-trials/compassionate-drug-use

Memorial Sloan Kettering Cancer Center provides information about herbs and cancer treatment, including a searchable database: mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs

MONITORING

Monitoring is watching existing disease by comparing the results of new tests and scans to prior results. Cancer can change over time; information gathered about the changing cancer landscape is essential to planning the most effective care to rein it in.

How you are monitored will depend on your specific cancer. It will include CT or MRI imaging scans and more rarely may include nuclear medicine scans, such as the FDG-PET scan or gallium or copper DOTATATE imaging in the case of Grade 3 NET. You may be concerned about possible side effects related to radiation exposure from frequent scans, but the benefits of this effective tool to monitor your cancer far outweigh any risks. Scans measure in one or two dimensions the size of cancerous growths so your doctor can tell if the cancer is growing or shrinking. It may be more effective to track changes with a series of scans than by doing repeat biopsies: however, sometimes a repeat biopsy can be useful to test for a change in growth rate, which could mean a change in the treatment approach. Blood or urine tests for biomarkers that are shed by cancer cells, like Chromogranin A (CgA), serotonin, or pancreastatin, are sometimes used in low-grade NETs but their use with Grade 3 NET is under debate. They are not used for monitoring NEC.

Another way to monitor treatment is the Karnofsky Performance Status (KPS). Developed by two clinical oncologists in the late 1940s, the KPS scale measures the ability of cancer patients to carry out daily activities. Changes in functional status over time can be used to compare the effectiveness of different therapies, determine prognosis and decide whether a patient qualifies for a clinical trial.

The disease can stabilize for a time, and it can progress and change at varying rates and in different ways. Monitoring at regular intervals provides valuable information to inform treatment decisions.

CARING FOR YOUR WHOLE SELF

Some patients become consumed by the illness, the treatments, and the side effects. Your medical care needs to be broad enough to address other aspects of your health beyond your cancer care. Perhaps you need the support of a nutritionist or a sleep specialist. A big consideration is your psychological wellbeing—attend to your emotional and mental health needs. Ask for help! A counselor can address added challenges that may accompany the cancer diagnosis. For example, you may have waited a long time for your diagnosis, or you may have been misdiagnosed and thus spent time being treated for the wrong condition. Perhaps you are experiencing emotional fallout from that. This is likely the first time you are facing your

“When you know you have this hanging over your head, mentally I think that really breaks a lot of people down. It’s been like a roller coaster. I think I’m OK with it and then I’m not.” —Christa Sonsire

own mortality. There are no classes on how to deal with a life-threatening illness.

It can be even harder when those around you, your friends and loved ones, don’t understand the gravity of your situation, or when they try to minimize your illness, fatigue, and anxiety. Under such circumstances, it is easy to feel isolated. Or perhaps your loved ones are suffering so much under the weight of the diagnosis that you are very worried about them. Most cancer patients will benefit from pastoral or professional care.

“The word ‘cancer’ was so hard for us to say for so long. I’m not sure why. Maybe we just didn’t want it to be real. I remember being terrified beyond anything I had ever experienced in my life.” —Sally Turnage Gustin

It is not selfish to prioritize self-care and your quality of life. Here are some ideas for caring for yourself and focusing on the best of life:

- Spend time with the people you most enjoy.
- Find solace in small things, whether it is a beloved pet or quiet time in your garden. Give yourself permission to take a few minutes every so often to refresh and do nothing.
- Studies have shown that prayer, meditation, or connecting with a higher power can improve patient outcomes. If your faith is important to you but you are unable to attend religious services, ask if you can arrange visits to your home by members of your congregation, or connect with your faith community and attend services online.

- Look for centers that offer services like massage, individual or group therapy sessions, or yoga and meditation classes. These are good ways to relieve stress and connect with others.
- If you are feeling up to it, exercise. Walk, ride a bike, or go to the park.
- If you're able, keep up your hobbies. If you like to fish, ask a friend to take you out on the water. Spend time making music. Read a good book.

“There was a patient in Florida—he wasn’t going to let his cancer stop him from living. His dad bought a fishing boat because this is what they loved to do, and he was on the water every day. People who have a zest for what they do in life, they do better.”

—Susan Meckler Plummer

- If you are having trouble getting enough sleep, ask your doctor if some of your medications may be keeping you awake. Check out good sleep hygiene tips suggested by organizations such as the Sleep Foundation.
- Eat well. Don't fill up on junk food. Beware of ads for dietary supplements and treatments that promise miracle cures. If it sounds too good to be true, it usually is.
- If you haven't done this yet, think about what you'd like to give to others who are important to you, including letters, photos and other precious possessions that will remind them of you. Maybe you'd like to prepare a scrapbook of memories or a video sharing stories or your thoughts and feelings for your loved ones.

“If I don’t get out of this house soon, he is not going to live to die of cancer and I will do life without parole.”

*—Jennifer A. O’Brien in *The Hospice Doctor’s Widow: A Journal**

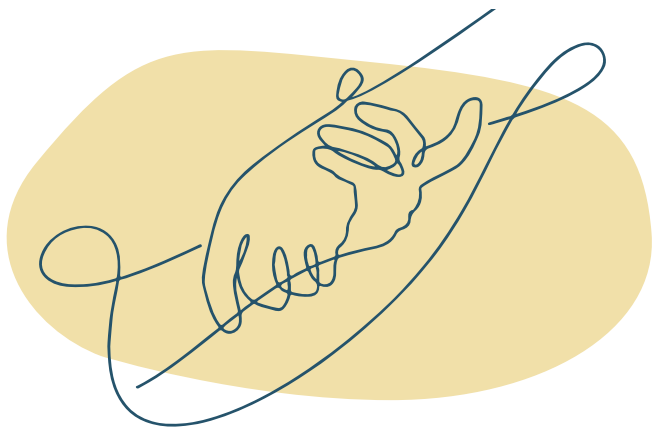
SELF-CARE AND SUPPORT FOR CAREGIVERS

Self-care is as important for caregivers as for patients. You also need time to refresh and restore. For ideas about taking care of yourself, see “Self Care for the Caregiver” at thehealingnet.org/caregiving-hub

It's important for caregivers to think ahead about the types of support they may need along all parts of their caregiving journey. While so intensely caring for a loved one, caregivers will rely on the patient's larger support circle. Caregivers can create their own circle of care through relationships that provide emotional support, assistance, and distraction. Adding forms of support, perhaps therapy or pastoral care, can help smooth the transition to hospice or help you adjust when the patient you have been supporting passes away. After such an intense focus on the patient, caregivers may find strength by connecting with and helping others in a similar situation, such as by participating in a grief support group.

“The other members of our group (and I say ‘our’ because we are all now a part of each other), didn’t cure my son’s cancer but they explained how to better care for him, offered experiences to help us determine what questions to ask, acted as a sounding board, helped us locate resources to serve us as caretakers and our son as a patient, held our hands virtually when the end came and continue to value our insight and experiences in the hope of helping others.” —Lisa Foley

- Perhaps most important, don't let your pride or reluctance or fear of rejection prevent you from asking for and accepting help from others. You will be giving your caregivers a gift—the gift of serving you.



CHAPTER FOUR

FIGURING OUT WHO IS ON YOUR TEAM

CAREGIVERS

Caregivers are unpaid loved ones who help with the details that can make treatment more stressful. They'll take you to your appointments and stay with you if you need them to. They'll bring you meals (and make sure you eat them). They're quick to respond when you call. You can count on them even in the worst of times. You can talk to them about anything, and they won't judge you.

Usually, your family and close friends will support you and want to be central caregivers or members of your care team. You can generally expect to rely on those closest to you, and they are often a valuable element of working with your medical team. Sometimes, however, you may find that those closest to you are not your best resource. Perhaps you've already had this rude awakening: family members who don't understand what you're going through and friends

who drift away, full of excuses for why they cannot be there when you need them.

A diagnosis of cancer, especially this cancer, may change your relationships with others. Family members may not understand how the disease and its treatments have made it difficult for you to work or to function the same as you used to. Or perhaps you've always been the independent one, happy to live alone, far away from family and old friends. Now that you're sick, being so independent may not seem as attractive anymore.

While some people may not be there for you, you will find that others are quick to offer help. Once you have found those who want to help you, it may be hard to establish responsibilities and boundaries, but it will help you and your caregivers alike to be clear and direct. Caregivers are not professionals, of course, and this may be the first time that they've engaged so intensely in the care of a person with a serious, life-threatening illness. That is why it is helpful for them to have some guidelines. Be open and honest in your conversations with your caregivers. They will thank you for it.

Some things to think about:

- Establish boundaries. For example, how much information about your circumstances, including your diagnosis, treatment, side effects and prognosis do you want your caregivers to share with others?
- Be specific about what kind of support you need. Caregivers can become frustrated if they constantly have to ask you, "How can I help?" If you enjoy cooking but it's difficult for you to get to the grocery store, for example, give your caregiver a shopping list and invite him or her to help you prepare a meal and dine with you.

- Assign different roles based on the unique strengths of your care circle. If you are having trouble understanding what your doctor is suggesting, ask a caregiver who is good at taking notes and researching medical journals and websites to come with you to your next appointment and later to go over the specifics of your treatment plan with you. Perhaps you want to create an audio or video message for loved ones and have a friend who can help you produce it. Maybe someone would enjoy doing some housekeeping to help you.

If you want to share your experience, consider using social media so that your friends and loved ones can follow your journey—even from halfway around the world. You could begin a personal health journal on caringbridge.org, for example. Check what options you have to create privacy settings so you can choose who will be able to access the information you share.

See the Healing NET Foundation website for more information for caregivers and about caregiving: thehealingnet.org/care-giving-hub

In some ways, choosing your care circle is as important as choosing your doctor. In fact, if you don't have a support system, your doctor may think twice about beginning aggressive treatment that is likely to cause significant side effects. Some side effects, which vary by treatment type, could lead to life-threatening complications. Your doctor will describe any risks. In addition, treatment is an incredibly involved process. You'll need to come to the clinic early for your blood work. Then you'll meet with the doctor and go to the infusion room to receive your che-

motherapy. You might have to stay there longer than anticipated if you have a reaction to the infusion. Afterwards, you may feel woozy from the anti-nausea medications you were given. All of this is difficult to navigate on your own.

BE A BETTER CAREGIVER

As a caregiver, you may feel overwhelmed and unsure of how best to support your loved one. Here are some ideas to consider:

- Learn the medical terms related to symptoms, assessments, and treatments so you can ask educated questions and better understand what the doctor is telling you.
- Utilize communication and organization tools to involve others in circles of care
- Instead of asking "How do you feel today?" you might consider asking "How can I help you today?"
- Sometimes the only—and best—gift you can give is to be a comforting presence and simply be still and listen.
- It's OK to empathize but it will make you a less effective caregiver if you immerse yourself in the patient's suffering, which is distinct and different from your own.

For more on caregiving, see thehealingnet.org/caregiving-hub

SUPPORT GROUPS

Support groups can be a great help. They can connect you to others who understand what you're going through and who can offer valuable tips for coping and finding the resources you will need. Making so many decisions is hard, especially when you're tired and scared. Perhaps you feel you can't think straight. Maybe you can't see the best next step for you. People in these groups can help you find clarity. They stand ready to offer a shoulder to cry on

and a hand to help you up when you stumble. If you are traveling to see a specialist in another city, you may want to connect with a local support group there. Perhaps a group member can pick you up at the airport or sit with your caregiver while you are undergoing tests or procedures.

In addition to providing emotional support, support groups often share valuable information. They invite experts to their events (virtual or in-person) to field questions. Support group members can talk about their experiences with different doctors or treatments. They may expand your understanding of the disease in general or provide insight into your specific diagnosis. Support group members often share information about clinical trials. They offer advice as to what to ask your physician, what tests should be ordered and what needs to be done at different steps along your cancer journey. Just remember that some treatment advice or other advice you find online or get from others may not be accurate or medically appropriate. Anything you consider for your medical care should be thoroughly discussed with your trusted medical team.

“These were the first human beings ever that we were able to talk to about our journeys and the loneliness and isolation of dealing with this beast of a disease. It was incredible! It was the start of a new family. We found ourselves talking and texting with them in the middle of the night, sometimes about trivial things, but often about fears and pain and things you can’t share with many others. When Lety was dying, these were the people who got me through the early days.” —Sally Turnage Gustin

ONLINE SUPPORT GROUPS DEDICATED TO HIGH-GRADE NEUROENDOCRINE CANCER

These private Facebook groups are administered by Susan Meckler Plummer, co-author, who took care of her husband when he was diagnosed with NEC. You must ask to join:

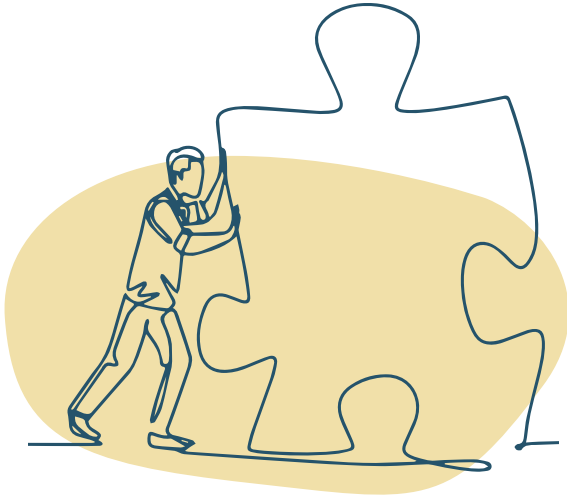
High Grade Neuroendocrine Carcinoma (Patients and Caregivers)
(for Grade 3—with a Ki-67 over 20)
facebook.com/groups/1920986924817967/

Zebra Caregivers Talk NETS (Caregivers Only)
facebook.com/groups/295352687612082/

Zebra Angel Support (Bereavement)
facebook.com/groups/249342105213278/

You can find groups by searching online or on Facebook for neuroendocrine carcinoma or neuroendocrine tumor support groups. Several neuroendocrine cancer organizations have listings of support groups—see thehealingnet.org/patient-resources to find links to those listings. Joining a support group (or multiple support groups) can be part of building a care team wherever you are. Because a high-grade diagnosis is even more rare than a diagnosis of well-differentiated Grade 1 and Grade 2 NETs, you may not always find patients or caregivers with a similar diagnosis in every support group.

Note: Support groups are not for everyone, as important as they are to so many people. Try some different support groups, but only participate if the experience is beneficial to you.



CHAPTER FIVE

PAYING FOR CANCER CARE

It is unfortunate, but any discussion about cancer care is not complete without asking who is going to pay for it. Having access to quality insurance coverage is vital to someone diagnosed with cancer in the U.S., and you or your advocate will need to work quickly to become educated about your health insurance plan. Unexpected bills for testing and treatments add up fast. Cancer patients in active treatment frequently meet their full deductible each year. The maximum out-of-pocket for any non-Medicare insurance is set nationally, and for 2021 the amount is capped at \$8,550. This chapter contains advice for addressing challenges you may encounter.

KNOW YOUR RIGHTS

AFFORDABLE CARE ACT

The current law governing all individual and group insurance plans (with a few exceptions) provides several rules important to cancer patients. First and foremost, the Affordable Care Act (ACA) protects your right to obtain coverage despite pre-existing conditions, and companies cannot cancel an existing policy after a person

is diagnosed. The ACA also removes lifetime caps or coverage limits.

High-grade patients should not have to wait for weeks to hear whether their health insurance plan is going to cover a certain procedure, scan, or treatment, but the reality is that insurance claims do not always proceed automatically or smoothly through the system. Denials are not uncommon in NETs. Financial toxicity—stress about current and future financial problems related to cancer care—is a real fear when an insurance company denies coverage of a request by the patient or provider to pay for health care services. Obtaining access to what you need—and finding ways to cover or avoid a high price tag—will sometimes require exceptional creativity on your or your advocate’s part AND on the part of your health care providers.

Under the Affordable Care Act, you have the right to appeal decisions made by your health insurance company. An initial denial doesn’t mean denied—it’s not the end of the road. Denial means that you (or your advocate) will need to be persistent. Many private insurance companies are offering case managers (often nurses) or patient navigators to help their insured navigate care and coverage issues. These services can be very helpful in streamlining the pre-approval process that your doctor or hospital is required to obtain. Call your plan’s administrator to inquire whether case manager services are available and determine if they can be helpful for your NET care. You can also find help through nonprofit organizations like the Patient Advocate Foundation, patientadvocate.org, which helps patients with chronic, life threatening, and debilitating diseases access the care and treatment recommended by their doctor.

EMPLOYMENT PROTECTIONS

Depending on your circumstances, you may need to research employment protections and laws pertaining to people with cancer and/or their families. These programs are governed by both state and federal statute so what is available to you will depend on where you live. The Family and Medical Leave Act (FMLA) is a federal program that provides leave protections for patients and family (caregivers). Laws pertaining to (patient) employment protections as well as resources available for cancer patients are listed by state at the Triage Cancer website, tragecancer.org.

COBRA

If your cancer diagnosis results in a change in employment (you resign or are laid off or let go), under federal law you are entitled to COBRA benefits (Consolidated Omnibus Budget Reconciliation Act of 1985). Rules vary from state to state as to the length of time you can carry COBRA coverage. COBRA plans are available for a fixed number of years and match your employer's coverage.

SOCIAL SECURITY DISABILITY INSURANCE (SSDI)

You may qualify for benefits if you are no longer able to work, you have worked long enough and recently enough, and you paid Social Security taxes on your earnings. Refer to this government website for all the details: ssa.gov/benefits/disability.

MEET INSURANCE CHALLENGES

DENIALS

You must follow up on all denials to learn exactly what the issue or situation was that caused it.

Here are some common scenarios—

- **Wrong code:** A billing office may have entered the wrong diagnostic or treatment code and you can find this out by a phone call to your insurance company or you may see it noted on your Explanation of Benefits (EOB) statement. Sometimes a simple re-filing of the claim with the correct diagnostic code is all that is needed.
- **Not medically necessary:** When a test or treatment is deemed not medically necessary, you or your doctor will need to appeal. Keep in mind: Your insurance is a business contract, and you need to understand what that contract or policy covers, what your rights are, and how the appeals process works. Keep your complete statement of coverage on hand and request one if you cannot locate it.
- **Experimental:** Sometimes when a treatment or diagnostic tool is approved by the FDA, it takes time for insurance companies to “catch up.” Often the private carriers wait for Medicare to approve a new treatment or procedure before they consider it established. Reversing this denial will likely require the help of your doctor or further steps to prove the treatment or procedure is no longer considered to be experimental (or in clinical trial).

“You have to be persistent. Many times, the people making these decisions have no medical background. Deny doesn't mean deny; deny means you have to work harder...File an appeal; it'll probably get denied and then your doctor will do a peer-to-peer with their medical director.”

—Christa Sonsire

PEER TO PEER

Peer to peer requests are calls between your doctor and a doctor from the insurance company to discuss why the testing, imaging or treatment prescribed is medically necessary. These requests can occur after insurance denials or occasionally prior to further action by the insurance company. You and your doctor have the right to request that the “peer” from the insurance company be knowledgeable about NETs and/or have comparable expertise as your doctor. In some cases, an insurance company case manager or patient navigator may be able to offer preliminary assistance to help you avoid these requests and coverage denials.



APPEALS

Your insurance contract will stipulate what you need to do to appeal a decision to deny coverage. Know exactly what your appeals process is before you make the phone call or write the email or letter as most appeal processes have specific time limits for each step once an appeal has started. Note that there is a regular appeal process and expedited appeal. For a patient with high grade NEC, it is always an expedited appeal process. Don't be caught off guard. This appeals information and what your insurer is contractually required to cover is contained in your full policy.

There are steps you can take and resources that can assist you as you navigate the appeal process:

- Write a great appeal letter. Examples of appeal letters and more information about navigating coverage denials are available online. [See Laurie Todd's website, theinsurancewarrior.com, for examples.]
- Search NET organizations online for educational articles and videos regarding denials and appeals. The information can help you better understand the appeals process and how to get the coverage that you have paid for and that you have a right to receive.
- Learn more about insurance related issues and legal rights of people with cancer on the websites of nonprofit organizations like the Cancer Legal Resource Center, thedrlc.org/cancer.
- Contact your state's Insurance Commission for difficult issues and concerns relating to your coverage. The insurance commissioner is a state-level position in all 50 states, and duties vary state to state, but the general role is to serve as a consumer protection advocate and insurance regulator. See trriagecancer.org/cancer-resources-and-educational-information/stateresources for state-by-state information.

PINCH YOUR PENNIES

MEDICARE PART D DRUG PLANS

Medicare Part D drug coverage comes from private insurance companies, with Medicare paying a portion of the costs. Seventy percent of people on Medicare have a Part

D plan. You need to sign up as soon as you're eligible—if you don't, you may have to pay a late enrollment penalty later when you do enroll. Be sure the drugs you need are on the Part D plan you select, or you could face thousands of dollars in out-of-pocket costs.

NON-MEDICARE DRUG COVERAGE

For those not on Medicare, most insurance plans will cover prescription drugs; however, the copays, deductible, and out-of-pocket maximums can vary from policy to policy, and year to year. Check your drug coverage at renewal time for changes in coverage if you have some choice in the coverage.

ASSISTANCE WITH DRUG COSTS

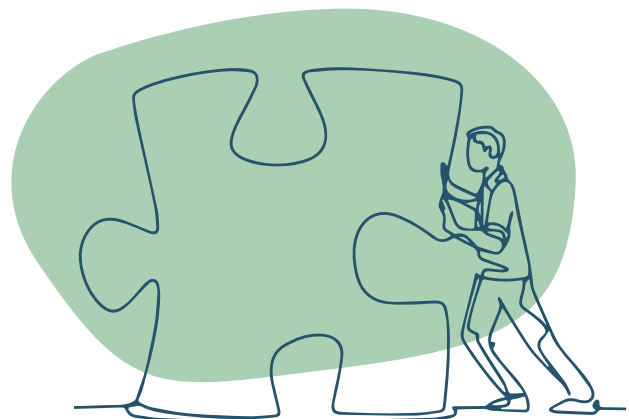
- Ask your doctor's office, your pharmacy, your insurance company or the drug manufacturer if any savings programs are available.
- Check your prescriptions. By switching to generics for regular medications that aren't part of your treatment for NEC or high-grade NET, you might be able to cut your drug costs. For generic drugs, and limited brand name drugs, you may wish to use a program like GoodRx, goodrx.com, that may provide the drug at a lower cost than what your insurance will provide. You just have to be sure you don't use Medicare to pay at the same time.
- Most brand name drugs will have some type of copay assistance program offered by the manufacturer that reduces the cost of the drug to typically under \$50. You may need to do a web search to find the program for the drug you are considering (enter the drug name and "patient assistance" to begin).

These plans may have little or no income verification but in general are not available to those on Medicare.

- You may also find additional financial support for medication and care through private foundations. One such program providing foundation assistance specifically for NET patients is the Lois Merrill Foundation, thelmf.com.
- NeedyMeds, needymeds.org, is a national nonprofit organization that connects people to programs that will help them afford their medications and other healthcare costs.

INDIRECT COSTS

Indirect costs of care can add up as well, especially if your specialized care is not close to home. The American Cancer Society's Hope Lodge Program provides low-cost lodging near some major medical centers. See cancer.org/treatment/support-programs-and-services/patient-lodging/hope-lodge. Many hospitals have lists of hotels near them that offer hospital rates to patients and families—ask for more information from the hospital's information services or your referring physician. Mercy Medical provides long-distance transportation to patients with financial need, mercymedical.org.



UNBIASED HELP IN CHOOSING MEDICARE COVERAGE

State Health Insurance Assistance Programs (SHIP) are available in every state. They provide local, independent, government counselors who can assist you in choosing the right plan for you. To find a SHIP counselor in your area, go to shiptacenter.org.

One of the most helpful services on the Medicare.gov website is the Medicare Plan Finder. This interactive tool will help you find every plan offered in your area and provides in-depth comparison information. To narrow your search, you may isolate your search to drug coverage under Part D plans or you can plug in your medications and get immediate information on which plans offer the best value and coverage for your needs. To access this tool, go to medicare.gov/find-a-plan

MEDICARE—AVOID POTENTIAL PITFALLS

- Everyone 65 and older is eligible for Medicare (as is anyone who has been on SSDI for two years). See Medicare.gov for the best in-depth and accurate information. If you are becoming Medicare eligible at the time of a NEC or high-grade NET diagnosis, you or your advocate will need to become educated on the options in choosing Original Medicare or a Medicare Advantage plan. If you opt for Original Medicare, you will likely add Medicare Supplemental Insurance (aka a Medigap plan) which will cover expenses that original Medicare does not, such as the 20% coinsurance responsibility.

Medicare Senior Advantage, the HMO component of the program, promises no out-of-pocket

co-pays, but like commercial health maintenance organizations it can have a restrictive network, meaning you are restricted in the choice of physicians covered under the plan. If you have doctors in different locations, Original Medicare offers the widest possible network (basically the entire U.S.) for eligible care. This could also ensure that consultations with NET specialists are easier to obtain. Be aware you can only join or switch Medicare plans during certain times, called enrollment periods, so you should invest a lot of time on the front end to make sure you have the right plan for you starting out. If you are on a Medicare Advantage plan and want to move to Original Medicare, you may find it cost prohibitive to get a supplemental (Medigap) policy. You can be subject to medical underwriting, which is always a risk for cancer patients. Medical underwriting is when insurance companies try to figure out your health status to make decisions about what coverage to offer at what price and with which exclusions.

READ THE FINE PRINT!

Regardless of what type of Medicare policy you have, if you are handed a form at the doctor's office or clinic with a box that indicates you will be responsible for whatever Medicare doesn't cover...
DO NOT CHECK THE BOX.

All Medicare providers agree ahead of time to take whatever Medicare pays. If you don't check the box, you're still going to receive the care and they can't legally bill you or charge you for the balance. But if you check that box, you most certainly will get their bill.

CHAPTER SIX

END OF LIFE PLANNING

When people are suddenly confronted with a cancer diagnosis, particularly one with so many unknowns and such variation, it may feel paralyzing. It will likely take some time to get your feet under you again but exploring end of life questions sooner than later can free you up for living. In this chapter you'll find advice on handling some very practical matters, on clarifying what you want for yourself, and on understanding hospice care (living well while you are dying).

“As a Financial Advisor I have seen what happens when people do not have their affairs in order. I insist my clients have the tough conversations and put things in writing”. —Cindy Poole

EASING THE BURDEN WITH ADVANCE PLANNING

There are things that you need to do upfront in addition to seeking the best treatment. Update your will, for example. **Every adult in a family should prepare advance directives** in case of sudden impairment due to accidents or serious illness.

Advance directives allow you to communicate the type of medical care you want if you become unable to make decisions or state your wishes. They help your physicians know more about your preferences and goals in life and enable them to make treatment recommendations honoring these wishes. Think of preparing these documents as a gift to your family members. Without advance directives,

they might have to decide what is best for you without your input. You can expect to be asked if you have these documents when you go in for a surgery or a procedure requiring anesthesia.

- A **living will** states your wishes should various medical scenarios occur, like stroke or coma.
- A **medical or healthcare power of attorney** (sometimes known as a durable power of attorney) names someone as your health care proxy or representative to make healthcare decisions for you when you are unable to speak for yourself. A proxy can be a family member or trusted individual who will carry out your wishes. Your proxy is allowed to access your medical records—make sure your proxy is aware of this.

You should also let those close to you know where your important papers are stored and what your wishes are for burial, memorial services, or celebrations. This does not mean you are giving up. Making some of these difficult decisions upfront can be a great relief to you and your loved ones. It will help you conserve your energy and summon your strength for treatment and for decisions to come.

All of us know that at some point our lives will end; what we don't know is if we will die from NETs or from some other cause. When we interact and share our stories with fellow NET patients, we quickly realize that some live with extreme quality of life issues and others lead fairly normal lives. There is no single outcome that is the same. We are all different. I believe it is important to have hope and at the same time be grounded in reality, knowing there will likely be challenging times on our journey with NETs. —Denny Organ

“I just had a conversation with a ‘death doula.’ I have started that process with her because it’s too difficult for my friends. These are hard conversations. I need to have them, but I don’t want to tax the people around me. My advice is to get a notebook and write it all down. What do you want to happen? What do you want them to do? This is the biggest gift you can give people.” —Christa Sonsire

WHAT IS A DEATH DOULA?

The term is based on the doulas who are hired to assist with births and to support mothers of newborns. A ‘death doula’ or ‘end-of-life doula’ assists the dying and their families. They supplement rather than replace other support like palliative care and hospice care.

According to the National Hospice and Palliative Care Organization’s End-of-Life Doula Advisory Council, “They provide a wide range of holistic services, including physical, emotional, spiritual and practical support [and] may work with families from initial diagnosis through bereavement.”

nhpco.org/about-nhpco/committees-and-councils/end-of-life-doula-council/

More Practical Steps to Consider

- Put accounts and property in the name of your partner or trusted family member (if appropriate to your circumstances)
- Make sure beneficiaries are listed correctly on retirement plans, life insurance, and other such accounts

- Help your loved ones learn how to take over the tasks and responsibilities that have usually fallen to you
- Provide a loved one with passwords to all devices (e.g., computers, cell phones)
- Make decisions about communication—Who should be notified of the illness? What information should go in an obituary?
- Go through things you own and make provisions regarding certain belongings

DIFFICULT CONVERSATIONS

Eventually you are going to have this conversation with yourself: What do I want out of life? Becoming aware of your own thoughts and feelings forms the basis for the decisions you make and the conversations you have with others.

Your doctor can help you find your way through hard choices. What is the status of your disease? Is your cancer tamped down by a course of treatment, at least for the moment, or is it ramping up again? Are you early in your disease or worn out by treatments that haven’t worked? Your doctor can help you weigh the pros and cons. If your cancer is spreading rapidly and causing a lot of symptoms, enrolling in a Phase 1 study of a new experimental treatment may not serve you well. What about aggressive chemotherapy? Your doctor can lay it out for you: this is how much more time the treatment is likely to give you, and these are the toxic drug side effects that you may experience. The decision whether or not to proceed with treatment is yours, but you will have input and support from your care team.

Decision-making is deeply personal. Everyone has a different way of looking at the options and a different calculation of risk versus benefit. A treatment may feel worth trying to one patient but not to another.

Will I feel best if I make every effort to try to prolong my life? Do I want to be fully present for the loved ones around me and able to savor every moment I have with them? How will I tolerate the possibility that my mind and memories may be clouded by “chemo brain” (an effect of the treatment drugs)? How much pain and how many courses of treatment can I endure? When it comes to clinical trials, how much uncertainty can I cope with?

“Have open conversations because it’s very important to know whether you want to be part of an experimental session. Do you even want chemo? Those are super, super important conversations. No matter how painful they are, they have to happen, especially in a high-grade situation. The patient should always have the say, whether it’s a child or your grandparent. They should have the say in what happens next.” —Gil Schaenzle

Each patient needs the space to process and make difficult decisions in a way that feels best to them.

Some of the most difficult conversations will be with your loved ones. If you are the patient, you may fear people’s reactions and possible resistance to your wishes. Maybe you want to

enter hospice care, but your wife doesn’t want to hear of it. If you are the caregiver, maybe your husband is holding fiercely onto life, even though he is suffering horribly. Is he doing that for himself, or is he doing it because he doesn’t want to leave you all alone? If you are having trouble facing these conversations because the emotions are too raw, you can seek a friend, mediator, therapist, or clergy member to facilitate the difficult conversations for you. Perhaps your doctor is the best person to guide such a conversation. Having that difficult conversation just might clear the air and give you or your loved one a measure of peace.

*“It’s tough, a very difficult conversation. My husband did not want to go to hospice. He was in horrible pain. The [hospice team] left and he looked at me, and he said, ‘I don’t want to do that.’ We talked it through. I said, ‘It’s OK. You’re not giving up. You don’t have to stay there.’ I got him to at least consider it. He ended up doing it. He actually passed away three days later.”
—Susan Meckler Plummer*

If your child is the patient, it’s important that you be as honest and open as you can—taking into consideration how old they are and where they are developmentally. Try to achieve the difficult balance of being as truthful as you can while offering hope and encouragement. “I don’t know” is an acceptable response, but don’t lie. You are one of the few people in the world your child trusts without reservation or hesitation, and you don’t want to weaken that bond of trust. It’s important for you to listen and ask what your child really wants. Is he or she willing to undergo another course of chemotherapy or to enroll in a clinical trial of an

experimental drug? Or would it be better for both of you to recognize that treatment is doing more harm than good and that now is the time to simply hold each other close?

*“Hope for the best and prepare for the worst.’ The ‘best’ and the ‘worst’ change over time. At first the best may be a cure and the worst is death. Then, the best may become laughter and appreciation and the worst is pain and suffering.” —Jennifer O’Brien in *The Hospice Doctor’s Widow: A Journal**

HOSPICE CARE

One of the hardest choices you will ever have to make is when to acknowledge that you have reached the end of the road—at least this one here on earth. This will require a huge change in your mindset and expectations and in the course that you plotted long ago for your life. Gene Lovelace, who served as a hospice chaplain for many years, shares the following thoughts from the perspective of his professional role and from the perspective of a caregiver to a NET patient.

MEANING OF HOSPICE

The word hospice derives from the Latin term “hospes,” which means both “host” and “guest.” Since Biblical times, it has referred to a place of hospitality, a “safe house” where travelers and pilgrims could find rest and refuge. And so it is today, a place of safety and rest for the weary who are now near the end of their journeys.

“How many years on this earth is enough? That is a very difficult and hard question to answer, is it not? I heard a story about a young reporter asking millionaire John D. Rockefeller about wealth, “Mr. Rockefeller, you have worked to gain so much money, exactly how much is enough?” He paused, then answered, “How much money is enough? I would say a little more is enough.” For most of us, we appreciate and enjoy the life we have been living before our illness and hope for better and MORE days ahead. Yet, there comes a time when many of us are faced with our physician suggesting that we move from a curative mode of care to pursue only palliative care and even hospice care.

What do you mean my treatments are not working any longer? Are you sure there is not one more thing we can try? Why can’t I qualify for an experimental trial? Why have my days been cut short?

This transition can be especially difficult for a teen or young adult, a parent of young children, someone with many family responsibilities, or a person whose illness has moved very rapidly. How do we face, and then accept, that the illness cannot be cured? How can any of us accept being told that this cancer will soon end my life on this earth?

“After my quarter-century as a hospice professional, I wish that I had a good answer to those questions. I wish that I could give you steps you could take or a process that you could follow to reach the place where you can accept the reality that cancer will soon take your life or the life of someone you love and care for. I do not have a plan for you, yet I can share that the great majority of my patients were able to reach some point of acceptance of this reality

and then begin to work on building a new way of living. I often think of this quote, “We practice dying DAILY, so we learn to fully live.” This is easy to quote and harder to practice, but it may be worthwhile to consider how facing death can contribute to life. I remember in my early years in hospice care, I was taken aback by the wisdom and directness of one of our social workers, a self-described “old hippie woman,” who said, “If we can make peace with the reality that we are all going to die, the rest of life can be easy.” Getting to a point of acceptance can take time for a patient as well as their loved ones and friends. The acceptance comes at a different pace for everyone involved, and many times my patients reached acceptance much earlier than their family members or friends.

“I remember the journeys of many of the children I helped care for in hospice. Almost universally, the child would reach a place of acceptance that they were not going to recover from the illness much earlier than their parents. In fact, I would say that many, if not most, parents rarely reached the point of acceptance that there was not a treatment or something else that could be tried to save their child’s life. Many times, the children were the ones who spoke out, sometimes adamantly, that they did not want to continue hospitalization or the exhausting and time-consuming routines of the treatments. They were tired of living with cancer and treatment, tired of not living fully. Knowing that their days were very limited, they just wanted to go outside, ride their bicycle, and play with their friends. Many of them would prefer to live life now as fully and normally as possible, like their friends, and then die with the expectation that they will gather on the

other side of this life with a grandparent, a loved one, or a friend they met in cancer treatment who had died before them.

“It’s like you’re a commercial fisherman. If your boat is going down, you have to acknowledge that fact. If you don’t, your brain won’t be freed up to do the things you need to do. Hospice isn’t giving up. Hospice is helping you change your goal. The focus has changed, so they help you with that. They help you navigate that difficult change in course.”

—Gil Schaenzle

“When is it time to ask a local hospice to get involved in your care? I have never had a patient or family say, “We really got hospice involved a little too early.” What I’ve heard many families and patients tell me was that they sure wished they had invited hospice into their lives sooner.

“There are many reasons patients delay moving to hospice care, but the biggest reason is that they may not fully understand the benefits. Many times, a patient or family member thinks of hospice as the last thing we can do in the final days of our life. Inviting hospice to get involved may invoke feelings of giving up or not fighting this illness that has so seriously changed their world. However, hospice care is not about giving up; it is about shifting our focus from exhaustive treatment regimens to catching our breath, taking stock of where we are, and trying to have as many good and pain-free days as possible.

HOW HOSPICE WORKS

Hospice provides a medical team, equipment, home or inpatient treatments, hospice pharmacy, assistance with personal care, grief, end of life planning, spiritual guidance, and counseling. Hospice supports not only the patient, but also the people in their surrounding circle of care. The core hospice team typically includes a hospice physician, nurse, social worker, chaplain, care partner, and a volunteer. Some hospice programs provide music, pets, massage, aromatherapy, or other complementary therapies. Most hospice care is provided in your home or that of a loved one but might include care in a hospital, nursing home, or a hospice facility if available.

“Most patients who begin hospice care are simply exhausted and so are their family members. Treatments, surgery, hospitalization, not getting adequate sleep or nutrition, and the stresses of illness take their toll on everyone. So, what happens if you stop the aggressive treatments you have been taking to try to beat this illness? It varies based on your particular diagnosis and stage in the illness. Hospice care does not provide curative treatments. Yet, hospice patients tend to live better days and even more days. Since 1983 in the U.S we have had a Medicare Hospice Benefit which has given us almost 40 years of insurance reimbursement and data related to end-of-life care. An article several years ago in the Journal of Pain and Symptom Management showed that hospice care produced 29 more days than non-hospice cancer care for five specific cancers. Hospice care heart patients lived 88 days longer than those without hospice involved. And if hospice does not work out for you or meet your current needs, you can return to the care plan you were on before hospice began.

“None of this is easy, it is never easy, especially if you are young and suddenly feel robbed of the many years you anticipated, or if the illness has been a recent diagnosis, and your end seems very near. You will face the total range of human emotions, mostly sadness, disappointment, and anger. Yet, hospice care and staff will walk alongside you and your loved one to assist you. Hospice will do all that they can for you to be comfortable, alert, and help you enjoy life as much as possible. Hospice patients tend to feel happier because they regain some of the control of their daily life that may have been lost during the routines of aggressive curative treatments. Family members and friends may feel more comfortable during visits. Patients may feel better if they can spend their days in their homes, with their pictures on the walls, their pets in the room, and the familiar smells and contentment of being home. Hospice workers pay attention to the quality of the days that you can have. They help you know how things will likely progress with your illness and what the next few weeks and months may typically be like. They will also tell you how the hospice team will help you manage the changes that lie ahead of you. Hospice care does not cure the underlying illness, but hospice care can provide a different type of healing: the joy of living life each day as fully and pain free as possible.”

—Chaplain R. Gene Lovelace, MDiv

“When he dies, we’ll say, ‘He was loved and will be missed.’ We WON’T say he lost.”

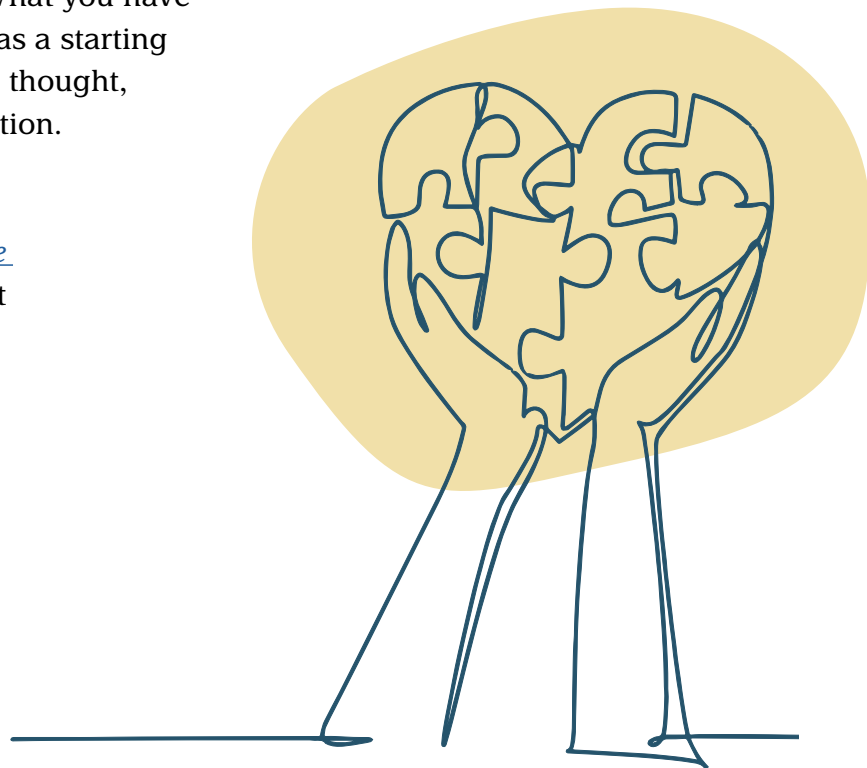
*—Jennifer O’Brien in *The Hospice Doctor’s Widow: A Journal**

WHERE NEXT?

Those of us involved in developing this publication strongly feel that you deserve the best possible care, and we hope you have found ideas to help you advocate for yourself, such as seeking the best physician(s) for you, understanding the full range of available care, engaging with support groups, helping loved ones, building a care circle, making practical decisions, and managing insurance matters. This general overview will not necessarily apply to your specific medical situation or your own personal experience, but the many people who contributed to this guide hope that you have found helpful information and that you feel the support of a caring community of strangers.




From the earliest conversations that were the basis for this guide on high-grade neuroendocrine cancers, the goal has been to bring information together in one place that covers not only assessment and treatment approaches but also the human experience of facing the diagnosis. What you have read will hopefully serve as a starting point for further learning, thought, conversation, and connection.

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