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What You Need to Know About NENs  
Transcript

Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. I'm Jessica Thomas, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

If you're new to this show: welcome. You're in the right place.

Maybe you've been recently diagnosed, or maybe you're a longtime patient. Maybe someone you care about has neuroendocrine cancer. In any case, you probably have questions. What exactly is this disease? What is it doing in your body right now? And what should you be doing about it?

This series will help you find answers to those questions. We'll speak with some of the best experts on neuroendocrine tumors from all around the world, and you'll hear NET patients share their experiences. We'll explain what neuroendocrine cancer is, how it spreads, and explore current best practices in diagnosis and treatment.

This is a revised version of our very first episode. We've made some updates to reflect new terminology used to describe different kinds of neuroendocrine cancer.

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Let's start with the basics. What exactly is a tumor, and what is cancer?

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To understand the answer to that question, you first have to understand something about the structure of our bodies. Every part of your body is made out of cells - tens of trillions of them. Each one of the cells that make up your body is an identical copy of your DNA, a molecule that lays out the blueprint for building...you! The biological recipes for making your organs, bones, hair, everything, are completely defined in your DNA.

When you get injured, your body repairs itself by making copies of healthy cells to replace the damaged ones. This is also how we grow and make things like hair and blood. Every cell in your body has this capacity to copy itself. But every time a cell divides, there's a small chance that it won't go exactly as planned. That can result in an abnormal cluster of cells somewhere in your body. We call this cluster a tumor.

Here's Dr. George Fisher, an oncologist at Stanford University Medical Center:

**Fisher:** *So, if you were to imagine that any cell that's capable of cell division all of a sudden acquired the capability to divide without control, meaning one cell becomes two, two become four, four become eight, eight become sixteen, then that lack of control of cell division would allow that individual cell to become a lump, and that lump is basically what a tumor is.*

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Now, "tumor" can be a scary word, but many tumors actually aren't such a big deal.

**Fisher:** *And this little mass, or lesion, or bump - however you'd like to imagine it - is composed of abnormally-growing cells that might not have acquired the biological characteristics that would allow them to spread. So they just grow like a little lump, and they might sit there and they might become a mole on your skin.*

And so benign - meaning non-cancerous - tumors can sometimes be uncomfortable, or can sometimes even make you sick and need to be dealt with. But they are called "benign" because they basically mind their own business. They grow in one place and only one place, and when they're removed or destroyed, that's the end of it.

But sometimes we develop a tumor that has other ideas. This tumor has developed a glitch in its DNA that inspires it to copy itself uncontrollably, and to cause other cells it comes in contact with to do the same. This causes chain reactions of uncontrolled cell growth to spread wider and wider around your body. This is called cancer, and it IS a big deal, because it can often mean that these out-of-control clusters of dividing cells can grow in such a way that they prevent your organs from functioning properly. Here's Dr. Pamela Kunz, an oncologist at the Yale Cancer Center.

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**Kunz:** *Tumors develop because cells, the cell of origin, tend to divide out of control, and they become a cancer when they develop the potential to spread to other places.*

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Your cancer happens to have started in a kind of cell called a neuroendocrine cell. Everyone has these all over their body. These cells make up a system that controls several important bodily functions - things like heart rate, blood pressure, air flow, digestion, and lots of other things. They do this by acting as the meeting points for two different kinds of signaling systems that keep your body running.

These two systems are the endocrine system and the nervous system. To break that down a little: some cells communicate with each other by sending and receiving chemical signals, such as hormones, which are produced by the endocrine system. Other cells, such as the cells in your brain, run on an entirely different system of electrical signals - sending sparks of electricity between the different neurons. Neuroendocrine cells can communicate with both systems. These cells are unique in this way - most cells can only receive one kind of signaling.

Here's Dr. David Metz. Until his retirement in 2021, he was a Professor of Medicine in the Department of Gastroenterology at the University of Pennsylvania, and Co-Director of their Neuroendocrine Tumor Program:

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**Metz:** *So, there are cells in the body that are neurons, they're nerves, and there are other cells in the body that are endocrine cells that form parts of glands, and these are all essential for normal function. The adrenal gland makes cortisol, so when you get a fright, your cortisol goes up as your fight or flight hormone, for example. So there are all these hormones around the body that are there to keep you controlled.*

*Similarly, the nerves in your body also have a feedback role. So if I have a nice big lunch today, and I stretch up the lining of my stomach so I get a little distended and a little bit uncomfortable, a message goes to my brain along the vagus nerve saying 'I'm feeling a little bit bloated', and that sends another message down the other side of the vagus to the valve at the bottom of your esophagus to relax so that you can have a burp. Those are nerves responding to a big meal. So those cells are all over our body. You've got millions and millions of these kinds of cells that do regulatory functions of hormonal balancing and control, nervous function, sensory, and motor, and keeping everything together so that we are functioning normally.*

And in many of these places, such as in the glands that make those hormones, there's a need for a group of cells that can bridge the gap between these two kinds of signaling - receiving an electrical message from the nerves and turning it into a

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chemical message. That's where your neuroendocrine cells come in. Here's Dr. Fisher:

**Fisher:** *It's a translator. So it translates a neurologic - which is really an electrical - communication to a hormonal - which is a molecular - communication, where a molecule is released by a cell and goes and attaches to a different cell and in so doing sends a message to that cell to do something.*

And because neuroendocrine cells are everywhere in your body, neuroendocrine tumors can form just about anywhere. About a quarter of primary neuroendocrine tumors begin in the lung. More than half begin somewhere in the gastrointestinal tract - 12% in the small intestine, 9% in the pancreas, and 29% elsewhere, including the stomach lining, appendix, and rectum. Other sites or primaries of unknown origin account for the remaining 21% of primaries.

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*My name is Wendy Knoll. I live in Raleigh, North Carolina. I am 37 years old.*

*My story started a really long time ago. I was in vet school, I was 25 years old, and I started coughing, actually while holding a dog, while working. The veterinarian that I worked for was kind of getting upset with me. He was like, "Well, stop coughing." I was like, "I*

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*can't. I can't." He listened to my chest with his stethoscope, and he's like, "Good God, Wendy. You sound awful." I was like, "Well, I'm not sick. I don't feel sick. This is so weird." He said, "Go to urgent care right now."*

*I ended up going to urgent care, and the physician there sort of said the same thing like, "Your lungs sound awful. Let's take an X-ray." He sort of diagnosed me with walking pneumonia. From the X-ray, he said that there was a little spot there, and he wasn't quite sure what it was. He put me on antibiotics. And then he told me, "You need to go see a pulmonologist," and I did. The story continued there that the pulmonologist said, "You're 25, I don't think that spot is anything. It's probably a lymph node. Let's go ahead and test you to see. Maybe you have asthma." So I had a whole bunch of breathing tests. He put me on steroids and inhalers. I'd have like sporadic coughs. For months I would use the inhaler, and I wouldn't get better, so I was getting really frustrated.*

*So then it got to the point that I was even like coughing and I would have bloody sputum. I got really upset. I went back to him and I said, "With all due respect, I'd like to get a CAT scan. I'm really scared about this spot in my lung." He was like, "Wendy, you're really young. This is not anything to worry about." He sort of was upset with me because he thought since I was in veterinary school I sort of knew everything. Then he sort of, not angrily, but just*

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*wrote the script to get the CAT scan. I went and had the CAT scan done. Literally, I just walked out the door from getting the CAT scan done and he called me and he said, "I need to see you in my office right away." I knew it. I knew that it just wasn't normal.*

*Anyway, we went back into his office, and he said, "There is a tumor there. It's probably nothing. I'm going to schedule for you to have a biopsy." I said, "Okay, let's do it as soon as possible." At that point, they had told me that it was a carcinoid, so I went crazy looking for information*

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As we learn more about this cancer, the words we use to describe it have become more accurate and precise.

For example, in Wendy's story we just heard the word "carcinoid." That's because neuroendocrine tumors *used* to be called "carcinoid" tumors - the term means "cancer-like." This word was used to describe neuroendocrine tumors when they were first discovered. This was because the first kinds of neuroendocrine tumors identified grew very slowly. So slowly, in fact, that when they were originally discovered, it was thought that they might not actually be cancer at all - just *like* cancer, hence the term "carcinoid."



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But this term is outdated, and we don't use it anymore. We now know that neuroendocrine cancer DOES behave like other cancers - just at a different pace. Here's Dr. Eric Nakakura, a surgeon at the University of California, San Francisco:

**Nakakura:** *Neuroendocrine tumors, in general, you often hear the description as being 'cancers in slow motion', because even neuroendocrine tumors that have spread to other parts of the body, such as the liver, can be indolent and not grow for months or even years. And so, this is in contrast to many other types of cancers that have spread to the liver where week by week, month by month, there's clear, gradual growth.*

And partially because of the old "carcinoid" label, physicians until very recently tended to misunderstand just how dangerous these tumors actually are. Here's Dr. Kunz, followed by Dr. Metz:

**Kunz:** *Neuroendocrine tumors, even as recently as ten to fifteen years ago, were actually all classified as being benign. I think this stems from the word 'carcinoid' that was coined over 100 years ago and meant 'cancer-like'. And I think that pathologists for a long, long time called these benign, and thus so did doctors taking care of these patients, and so then patients had this belief that these cancers would never come back. And we now know that these in fact are cancers, and they can grow and spread, and*

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*therefore they need to be treated as such. They need to be treated like cancers, and therefore patients need to have appropriate surgeries and treatments, et cetera.*

**Metz:** *In my mind, I think neuroendocrine tumors, in general, are all malignant. They all have malignant potential. The number we usually quote is 60-90%. I think they all have the potential for malignancy if you leave them alone long enough.*

We left behind the word "carcinoid," but as our understanding of neuroendocrine cancer increases, the language we use to describe it continues to change.

For a long time, we referred almost exclusively to neuroendocrine tumors, or "NETs." This is where the name of this podcast, NETWise, comes from. But since the term NETs became popular, we've learned that there is not just one type of neuroendocrine cancer - there are two. There are neuroendocrine tumors, or NETs, and there are also neuroendocrine carcinomas, which are called NECs.

These are both kinds of cancer that can develop from mutations in neuroendocrine cells, so in order to talk about BOTH NETs and NECs, we've started using the term "neuroendocrine neoplasm." Here's Dr. Thor Halfdanarson, an oncologist at the Mayo Clinic in Minnesota:

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***Halfdanarson:** Probably the most important thing in terms of the terminology now is that we talk about the neuroendocrine neoplasms. We've always been talking about NETs, so neuroendocrine tumors, but that leaves out the fast-growing neuroendocrine carcinomas.*

A neoplasm is an abnormal growth of cells. So "neuroendocrine neoplasms" or "NENs" is an umbrella category for any unusual growth of neuroendocrine cells, which encompasses BOTH NETs and NECs.

The differences between NECs and NETs is that NECs - the carcinomas - are much less common than NETs, and NECs grow much more quickly.

***Halfdanarson:** And it can spread locally where it actually grows through, let's say it starts in the colon, and now it like grows through the wall of the colon or the small intestines into adjacent organs or structures.*

In a nutshell, NETs and NECs are both kinds of cancer that can arise from neuroendocrine cells. And in order to talk about both at once, people have started to use the umbrella category "NENs."

This may sound complicated, but it's a sign of how much more we understand about neuroendocrine cancer than we used to. And the

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words we use will likely keep changing as we learn more and more.

Because most neuroendocrine neoplasms are tumors, you're going to hear us use the terms NENs and NETs almost interchangeably, but we'll specify when we're talking about NECs.

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Now, back to the basics of neuroendocrine cancer.

We know that this cancer can occur in any organ. So how do we talk about its location, and the way it spreads?

First of all, if you're diagnosed with neuroendocrine cancer, the disease will be named for its "primary" site - the place where the very first tumor appeared. But that location is just the beginning. Like all cancers, NENs have the potential to spread throughout the body. That tendency to spread is called "malignancy," and the new tumors that form are called "metastases" or "metastatic tumors." All neuroendocrine tumors have the potential to spread, given enough time.

The first place that most tumors spread is into the lymph nodes near the primary site. Lymph nodes are a kind of gland that work as filters for harmful substances in the body. They carry oxygen and other nutrients and remove waste products that flow out of the cells.

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Here's Dr. Dan Halperin, a medical oncologist and researcher at the MD Anderson Cancer Center at the University of Texas in Houston:

**Halperin:** *So a lymph node is basically a docking station of immune surveillance, as fluid tracks back to the circulation from really any end organ. So as blood pumps into any organ, the fluid pressures basically push some of the water out into this space - the lymphatics - and then that will drain back through these little docking stations where we find these immune cells.*

This lymphatic system is the way cancers most often travel from one place to another.

**Halperin:** *And the presence of cancer in lymph nodes is a way of saying that the cancer cells have made their way into that lymphatic network and are moving and surviving within that lymphatic network, and so the presence of cancer in the lymph node is an indicator that that cancer has the ability to travel.*

The more a cancer spreads, the more serious it is - and managing and treating the spread generally becomes more urgent than dealing with the original tumor.

**Halperin:** *We typically think of cancer in terms of what we call a TNM hierarchy, or 'tumor, node, metastasis'*

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*hierarchy, and this is how we stage the cancers. We consider them sort of in order of importance, so the tumor is the initial site; and then if it moves to the lymph nodes, that's more important than what's going on at the local tumor. And similarly, if it moves and metastasizes, and we're dealing with disease in the liver or the bone or somewhere else, that really takes precedence over what's going on in the nodes or the primary tumor, particularly from a, say, prognostic standpoint.*

How far the cancer has spread from its primary location is referred to as the cancer's "stage". This is an important metric in determining how it should be treated:

**Kunz:** *'Stage' refers to where in your body is the cancer. So let's use, as an example, a pancreatic neuroendocrine tumor - so that, just by definition, would mean that it started in the pancreas, and that could be a Stage 1, 2, or 3, depending on where it is in the pancreas and whether there are lymph nodes involved. Once it spreads far outside the pancreas, so for example to the liver or to the lungs, that by definition would be a Stage 4. There are only four stages, so four would be the most advanced stage, and by definition that means it is metastatic, or has spread.*

The metastases of many neuroendocrine tumors grow much bigger and faster than the primary tumor. This is very unusual. Here's Dr. Xavier Keutgen, a surgical oncologist from the University of

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Chicago Medical Center and director of their Neuroendocrine Tumor Program, followed by Dr. Metz:

**Keutgen:** *Classic cancers usually have a larger primary tumor and then a small amount of lymph node metastases or distant metastases. Neuroendocrine tumors, it's a little different - often we see very small primaries, especially for small bowel, but a really significant amount of lymph node metastases and an even higher burden of distant metastases.*

**Metz:** *Neuroendocrine tumors are upside-down tumors, in which the primary is tiny, the lymph nodes are a little bit bigger, but the spread to the liver and bones and everywhere else is formidable.*

Metastases happen in places that pieces of the primary tumor can find a way to get to. For example, with NEN primaries in the small intestine and pancreas, metastases can occur in the abdominal cavity that surrounds these organs. Here's Dr. Fisher:

**Fisher:** *Neuroendocrine tumors that arise in the pancreas and the gut can literally just go through the wall of the colon or the appendix or fall off of the pancreas and land in the fat in the abdomen and find a place to grow there. We call that 'intraperitoneal seeding.' It's really the simplest kind of spread, because if you can imagine the tumor that makes it through the wall of whatever organ it's*

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*in, and then seeds from that tumor individual cells can literally fall off and just land anywhere in the abdomen. If they survive the fall and land in a place that's fertile ground, and if they can then recruit a blood supply to feed them, then that individual seed can become a tumor of itself.*

But the most common way for these seed cells to travel is the way most things travel around the body - through the bloodstream. Because of this, the most common site for small intestine and pancreas NENs to metastasize is your liver, because that's the first place blood from the small intestines and pancreas goes. This is because one of the liver's most important jobs is to be a filter for nutrients after they are extracted from the food that is digested in the small intestine.

One of the things the liver does with those nutrients is to combine some of them with enzymes that are made in pancreas in order to finish that digestion - things like insulin to help process sugars. So, the blood and lymph flow from those two places is steered directly to the liver, and those cancer seeds tend to follow the same path.

Here's Dr. Ed Wolin, an oncologist who is the Director of the Center for Carcinoid and Neuroendocrine Tumors at Mt. Sinai in New York:



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**Wolin:** *Neuroendocrine tumors that start in the pancreas (or) the intestine preferentially go to the liver when they metastasize. The tumor cells go into the blood supply that leaves the pancreas and leaves the intestine, which is called the portal vein, and that vein goes directly to the liver to filter the blood. So it's a bypass track that takes the tumor to the liver, so the liver gets a big dump of cancer cells before the rest of the body. And that's why you see people with neuroendocrine cancers sometimes that have 20, 30, 40 liver metastases and don't have much else in their whole body.*

And because of the strange, "upside down" nature of NETs, the metastases are generally much bigger than the primary tumor that seeded them - and it's very often these liver metastases, not the primary tumors, that cause the biggest health problems.

**Keutgen:** *So, the number one cause of a decreased lifespan in neuroendocrine tumor patients are liver metastases that become so overwhelming that the patient gets into liver failure.*

Other kinds of NENs, like lung NETs for instance, metastasize differently, because the blood flow is different.

**Wolin:** *Lung neuroendocrine tumors, when they metastasize, don't go directly to (the) liver the same way that intestinal and pancreatic ones do. The lung, when it*

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*metastasizes, the cancer cells go into the bloodstream, they go all over the body, and you don't necessarily find a lot of cancer in the liver if you don't have a lot of cancer everywhere else.*

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*So, this was 2005. I had three-fourths of my right lung removed.*

*After that, I went on to live my life. I got checked every three months, then every six months, then every year via CAT scan of my chest, and everything came out clean. I got married to a wonderful handsome man. I had a beautiful daughter eight years ago. Then I had another beautiful daughter two and a half years ago.*

*There was a point where in between my first daughter and my second daughter, it was my seven-year checkup. I went and had my CAT scan, and I got a new oncologist. He said, "You know what, Wendy? It's been seven years. This cancer is not going to come back." He's like, "We don't even need to do these CAT scans on you anymore. Probably let's do it every five years." I was like, "Whoa, that's awesome but so scary and I'm not comfortable with every five years." He's like, "Okay, how about every three years?" I said, "Okay, let's do three."*

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*Three years went by and I went and had my CAT scan done. He said, "Wendy, I see some changes, and there's something in your liver, and also some lymph nodes are larger. Let's get an MRI." They fit me in that day. And then I called the doctor and he called me back that night. He said, "You have tumors all over your liver. There's also some in your pelvis, in your spine, and all throughout your lymph nodes." And then the biopsy came back and it was determined that it was the same cancer as my original tumor, but now they were calling it neuroendocrine tumor.*

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Wherever a primary NET appears, and wherever it metastasizes to, NETs can be difficult to diagnose and very often misdiagnosed. This is also closely related to their bizarre upside-down nature. Because the primary tumors can be much smaller than the eventual distant metastases, NENS are often not discovered until after they've spread, which might be many years after they first began. Here's Dr. Fisher:

**Fisher:** *The problem with neuroendocrine cells is that we don't really see the benign cells. We don't have a way of detecting them, and oftentimes when they've grown they've already spread by the time we can first diagnose them, so they tend to be diagnosed at a point when most patients already have spread of the disease.*

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Often, NENs aren't discovered in the body until they begin to cause symptoms. One way they do this has to do with the fact that some NENs are what we call "functional" tumors. This means that they have the ability, like healthy neuroendocrine cells, to produce hormones. These extra, unwanted hormones can cause a whole different range of problems in your body. Here's Dr. Kunz:

**Kunz:** *The other really important feature of neuroendocrine tumors is that about 40% of them can secrete hormones. Going back to the terminology - neuroENDOCRINE, they have the word 'endocrine' because they share these endocrine features of secreting hormones. One of the classic examples of that for small intestine NETs is that the tumor can secrete a hormone called serotonin, and serotonin can cause things like flushing of the face, which is sort of a periodic redness of the face, or really watery diarrhea.*

These functional NENs can be referred to by the name of the hormone they produce - so a NEN that produces the hormone gastrin, for instance, can be called a "gastrinoma", or one that produces glucagon could be called a "glucagonoma".

That particular set of hormonal symptoms that Dr. Kunz just mentioned is called "carcinoid syndrome" and can be typical in NENs that have metastasized to the liver. We'll talk about functional NENs and the various syndromes they cause in depth later in this series. But for now, there's a big problem here in terms of diagnosis. Those symptoms - diarrhea and redness of the

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face - could be caused other things that are much more common than a neuroendocrine tumor. This is true for most of the symptoms associated with NENS - stomach pain, jaundice, persistent coughing - all of them could be caused by something that most doctors would see in a patient every day, rather than NENS, which they might never have seen before in their entire career. Here's Dr. Fisher followed by Dr. Metz:

**Fisher:** *You know, to be honest, neuroendocrine tumor is a rare cause of diarrhea. There are far more common causes of diarrhea. And so, you know, if you go to see your internist and you say 'jeez, I have diarrhea' and he'll say 'well, how many times a day', and you say 'three or four times a day' and he'll say, 'well, go ahead and take some Imodium', or they'll do a stool test to see whether you have an infection, or they might even do a colonoscopy and look for inflammation of the bowel and decide that you don't have any inflammation and therefore you're OK, and just take these medications - when, in fact, the diarrhea is due to tumor that might be in the liver that's releasing hormones that tell your gut to make more fluid, and when your gut makes a lot of fluid it comes out watery, and you end up with diarrhea that gets progressively worse, sometimes over a timeframe of years.*

**Metz:** *So it's not often that you make a diagnosis of gastrinoma, but you see a whole lot of ulcers. It's not often that you make the diagnosis of carcinoid syndrome,*

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*but you'll see a whole lot of middle-aged women who are menopausal and have flushing and diarrhea. So the patient gets labeled as having irritable bowel syndrome and maybe being perimenopausal when they really are showing the carcinoid syndrome, or the patient gets labeled as having a typical ulcer and heartburn and reflux disease when they've really got Zollinger-Ellis syndrome and a gastrinoma.*

So, symptoms are commonly mistaken for other conditions such as irritable bowel syndrome, colitis, asthma, or menopause. Misdiagnosis is extremely common, and on average, people have symptoms for five years before learning they have a neuroendocrine tumor. When it takes so long to obtain an accurate diagnosis, cancer can spread to other organs. More than half of NETs spread beyond the primary site before they are diagnosed.

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*My name is Marilyn Kline, and I'm a neuroendocrine patient, cancer patient. I was diagnosed in June 2017.*

*I'm pNET, pancreatic NET in the tail with mets to the liver. That is my official diagnosis. My story is not unsimilar to many others I've heard where I had symptoms of not feeling correct for a number of years. But for me, it actually started Labor Day 2016 where I had an internal bleed.*

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*I ended up in hospital with something called Dieulafoy lesions, which I had never heard of. I had to look it up. They went in and clipped it and shut it and then they said, "Oh, you're fine, you're healthy, nothing to worry about." I didn't believe that. So I asked for a GI consult, which I got, who also told me I was fine, healthy, nothing to worry about. My questions, of course, were "Well, should I change my diet? Should I be exercising more? Should I have a colonoscopy more frequently?" I had all these questions. But this GI doctor said, "No, you're perfectly healthy." I did have a pain on my left side which now I figure was the primary tumor in the pancreas.*

*But again, this is a story that I hear a lot from other NET patients is that they would go to doctor after doctor after doctor and everybody would say, "Well, you look fine, you look healthy, you look great, nothing wrong with you," until you get the CT scan or the PET scan or both, and they show up with the metastasis.*

*It was another nine months, sadly. The first diagnosis from my GI doctor was "I'm not happy." Let me see if I can get this verbiage, if I remember this verbiage right. "I'm not happy with the way the scan looks. I'm going to get another one." So I had another test. The first was an ultrasound. The second was a CT scan. After the CT scan, he said, "Well, it looks like you've got lymphoma, but I want to verify." So then I had a PET scan, and then he said, "Oh,*

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*I'm really sorry, Marilyn. You actually have liver cancer." That's the point I said, "Doctor, I really think I need to see an oncologist. I would like an oncologist consultant. That needs to happen in the next 24 hours." And he said, "Oh, I'm not sure." I said, "It needs to happen in the next 24 hours." He got it. I mean I called about five times, but I got to an oncologist in the next 24 hours. That's who got me the biopsy, got me the right PET scan, and got me the correct diagnosis.*

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Another way a NEN might cause the symptoms that allow it to be diagnosed is through what's called "mass effect", meaning that the size of the tumors get to the point where they're physically blocking something. Here's Dr. Nakakura

**Nakakura:** *So the prototypical small intestine neuroendocrine tumor is a neuroendocrine tumor of the ileum, that part of the small intestine just before the large intestine. And what happens with these tumors is that they're frequently diagnosed very late, only when patients start having symptoms, such as abdominal pain, or they can actually have blockage or obstruction of the intestine, where they're vomiting and unable to eat.*

*And what happens is that the tumor starts in the wall of the intestine, spreads to the lymph nodes in the region, and causes a scarring reaction, what we call a mesenteric*



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*mass. It's actually a ball of tissue that's very, very hard. And that mesenteric mass then kind of kinks and buckles the intestine, causing a blockage. And it's the development of this blockage that leads to abdominal pain, often when they eat large meals or food that's hard to break down into small pieces. And ultimately, when they get blocked, that's when they end up in the hospital, when they're vomiting.*

That's just one way a mass effect might occur - anywhere that a blockage might get in the way of some important bodily function can be a place that a NEN may cause symptoms. These could range from a tumor in the liver blocking a bile duct, and thereby causing jaundice, to a tumor in a lung blocking a bronchial tube and causing persistent coughing.

As we heard, the liver is a hot spot for NEN metastases, and ironically, the natural resiliency of your liver can often work against the discovery of metastatic NENs. Here's Dr. Fisher again:

**Fisher:** *Another curious thing about neuroendocrine tumors is that you can sometimes see large lumps in the liver, sometimes the size of several softballs, occupying valuable real estate in the liver and crowding out normal liver. What then can happen is that the normal liver, which has the ability to grow to replenish itself, can get bigger and bigger and bigger as the tumors occupy more and more space,*

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*and the person can have a lot of disease in the liver and still have completely normal liver function and feel perfectly well.*

That may seem crazy - that a tumor could grow bigger than a softball before someone notices that it's there - but no one is going to look for a tumor unless they have a reason. And with many NETs, the noticeable symptoms that would cause a doctor to look for a tumor don't appear for a long time, or not at all.

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Because of these challenges, one of the most common ways that NENs are diagnosed is by accident. Imaging technology platforms like CT scans and MRIs are being used more and more routinely, and because of that, it's getting more and more frequent for a NEN to be picked up on a scan that was being done for an entirely different reason.

**Halfdanarson:** *So these are patients who come in, have a scan for a kidney stone and we find a pancreatic neuroendocrine tumor which might have been there for years, and could have been there for another 10 years without anyone knowing, but just because we're doing so many more scans, we pick up so many more tumors.*

**Fisher:** *So we get so many scans now, CT scans in emergency rooms, for people who ate a bad taco, come in with a belly ache, and they get a scan, and they may see that there's a*

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*spot on the pancreas, or they may see that there's a spot in the liver, or multiple spots in the liver, and they get a biopsy and then they're told that they have a neuroendocrine tumor that has spread. It's always a scary thing, and to imagine that all of a sudden you're diagnosed with a terrible disease when you feel pretty well must be terrifying and confusing.*

It's not only scary and confusing to have been misdiagnosed or accidentally diagnosed with something like cancer, it's also frustrating. How could my doctors miss something so important?

A popular metaphor that is often taught in medical school is "when you hear hoofbeats, you should think horses, not zebras." And this makes sense, generally speaking. As a primary care doctor, you are orders of magnitude more likely to be dealing with something other than an uncommon cancer when someone comes in complaining of diarrhea, stomach cramps, a persistent cough, or flushing.

But the problem, of course, is that zebras do exist. And NEN patients are zebras. The good news is that there are more fellow zebras out there than you might think.

While a new diagnosis of a NET is much less common than many other kinds of cancer, this slow-motion pace means that there are a lot of people living with NETs - more, even, than with much more well-known diseases.

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**Halfdanarson:** *They are actually common in terms of how many patients are out there with neuroendocrine tumors. We don't have a ton of new diagnoses per year, but just because patients with neuroendocrine tumors live long compared to many other cancers, the number of patients with neuroendocrine tumors at any given time is fairly high.*

**Halperin:** *So there are hundreds of thousands of people walking around the United States right now with neuroendocrine tumors, so while not that many people will get diagnosed with it, it's not as uncommon to meet someone who's living with a neuroendocrine tumor as you might think.*

**Wolin:** *That's more than the number of Americans with stomach cancer plus pancreas cancer added together, which is phenomenal because everyone knows about stomach cancer and pancreas cancer, but they don't think about neuroendocrine cancer.*

But because of those numbers, more and more people are becoming aware of this disease, and more and more researchers are joining the fight against it. This means that there are actually quite a few treatment options that are available for NET patients - from surgery to medicine to nuclear medicine - so NET patients are surviving, and even thriving, for longer than ever.

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In episode 2, we talk about how your doctors learn all they can about your particular tumor, and how that information will determine a course of treatment. Then in the following episodes we look at popular treatments options, and give you as much information as we can about how they're best used and when and why, and what you can expect if you receive them.

So stay tuned for all of that and more about living your best life even while you're living with neuroendocrine cancer.

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Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education for the NET Research Foundation.

The original version of this episode was written and produced by David Hoffman and Laran Hyder. This update was written and produced by Anna Van Dine; post-Production by José Miguel Baez; Production Manager, Gabriela Montequin. Executive producer, David Hoffman.

This podcast is made possible by the generous support of Boehringer Ingelheim and Novartis.

If you would like to join NETRF in our mission to fund research for NET cancer or help support educational programs like this NETWise podcast, please go to [netrf.org/donate](http://netrf.org/donate).

Special thanks to everyone we interviewed for this episode. We are grateful for your expertise.

And a note: Marilyn Kline, whose story we heard, passed away in 2019. She was an active participant in NETRF's patient education

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programs. We are forever grateful to Marilyn for sharing her story.

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