[WNPR] Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers. The director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists on the forefront of the battle to fight cancer. Here's Dr. Winer. [Dr. Winer] November is Neuroendocrine Tumor Awareness Month. I actually just learned that it's technically November 10th as Neuroendocrine Tumor Awareness Day, but they've spread out to the whole month, and we'll be focusing on this relatively rare and often misunderstood category of cancers. Neuroendocrine tumors, or sometimes called NETs, arise from cells of the neuroendocrine system. And our guest will describe to us what that is. They are responsible for producing hormones in the body. These tumors can occur in a variety of places, perhaps most commonly in the abdomen, so either in the gastrointestinal tract, the pancreas, but sometimes also in the lungs. And they present unique challenges when it comes to diagnosis and treatment. Joining us this evening is Dr. Pamela Kunz. [Dr. Winer] Dr. Kunz is an internationally recognized medical oncologist and researcher specializing in neuroendocrine tumors. She's the director of the Center for Gastrointestinal Cancers at Smilow Cancer Hospital and at the Yale Cancer Center. Her work has not only advanced our understanding of neuroendocrine tumors, but has also helped the quality of life of many patients, many patients both in her own practice but far beyond. [Dr. Winer] So, Pam, thanks so much for being here with us this evening. [Dr. Kunz] Thanks, Eric. [Dr. Winer] Maybe you could just tell us a little bit before we even start with any questions about the cancer spread, about the neuroendocrine system. And these cancers arise from cells that that are fundamentally neuroendocrine. So what are neuroendocrine cells? [Dr. Kunz] That is right. Well, neuroendocrine cells can be scattered throughout our entire body. And, you know, they are part of our normal system, and they get their name endocrine because some of them can secrete hormones. So, for example, in the pancreas, those endocrine cells are important in secreting insulin, and that's an important part of what the pancreas does. But throughout the body, if they become abnormal or develop mutations or divide abnormally, they can become tumors or cancers, and thus they can originate in almost any part of the body. [Dr. Kunz] And you already named the most common locations, including the small intestine, the pancreas, and the lungs. [Dr. Winer] And do these tumors ever arise in other than the pancreas? In other what we think of as endocrine glands, so the adrenal glands or the pituitary? [Dr. Kunz] They can indeed. So in the pituitary gland, most commonly it is benign growths called a pituitary adenoma. But that's actually very much related to these kinds of neuroendocrine growths. In the adrenal gland, some of our listeners may have heard of cancers called pheochromocytomas, also related paragangliomas. Those can secrete hormones that can actually cause lots of challenges, including high blood pressure. And so, yes, in fact, other endocrine organs can be involved. [Dr. Winer] And for patients who come to medical attention with these cancers, what are some of the most common symptoms that patients may experience? I realize that, of course, there are occasional patients who may just not have any symptoms and be diagnosed almost by happenstance. But for those who are presenting with

symptoms, what are they coming to see their doctor about? [Dr. Kunz] So symptoms probably fall into two main categories: symptoms from tumor bulk, meaning they block something. So and that will depend entirely on where the tumor is located. So if the tumor itself is in the pancreas or the head of the pancreas, it can block a bile duct and a patient may present with jaundice, which is yellowing of the skin. [Dr. Kunz] If a patient has a tumor in the small intestine, they may present with a tumor with an intestinal blockage, and then there may be symptoms of hormone excess. So one of the classic neuroendocrine hormonal syndromes is called carcinoid syndrome. That is related to a hormone called serotonin. And we measure that in the blood or in the urine as something called 5-HIAA. [Dr. Kunz] And that hormone can cause facial flushing, upper chest flushing, and/or diarrhea. And so patients may present with those symptoms as well. But those can also overlap with many very common medical diagnoses, such as menopause or just normal types of diarrhea. And so it gets very complicated diagnosing that. [Dr. Winer] So I'm sure there must be patients who have had symptoms for months or even years. Symptoms of flushing, symptoms, you know, lots of things cause diarrhea. And only when it gets really, really bad or they happen to see a particularly astute clinician does it get unraveled. [Dr. Kunz] That is exactly right. And in fact, the large majority of patients, especially with metastatic neuroendocrine tumors who have some of these symptoms, are often misdiagnosed or have delayed diagnoses. And we could have a whole other conversation around trust and rare diseases. And that is a real challenge for the field. [Dr. Winer] And I'm sure there must be some proportion of patients who don't have any symptoms related to the release of a hormone. How common is that with a neuroendocrine tumor? That someone has the tumor but they don't have these symptoms of flushing or diarrhea or some of the other symptoms from other sorts of hormones? [Dr. Kunz] Only about 30% of patients with NETs have hormone secretion. We actually call that having a functional neuroendocrine tumor. And about 70% of patients are nonfunctional. [Dr. Winer] And any difference in prognosis between the two? [Dr. Kunz] No difference in prognosis. It may mean that patients are brought to attention sooner. And typically we think that patients with metastatic NETs are the ones who have more obvious hormone secretion. It has to do with more kind of tumor volume. [Dr. Winer] Yeah. So you've already talked a little bit about the different types of neuroendocrine tumors. What are the most common of these? [Dr. Kunz] The most common are in the small intestine and in the lungs. And in terms of primary site, in terms of hormone secretion, by far the most common is the small intestine NET that secretes serotonin. Pancreatic NETs can also secrete hormones, and they are related to really one of the primary jobs of the pancreas. So we can see insulin secretion. [Dr. Kunz] So when insulin is secreted, we can see lowering of blood sugar. And there are also some other less common hormones that the pancreas can secrete. [Dr. Winer] But I want to talk to you about the lung neuroendocrine tumors in a second. But let me just, sort of going back to something we were talking about before, for those with these small bowel tumors, how do these cells wind up in the small bowel? [Dr. Kunz] That's an excellent question. I'm not even sure I know the answer to,

Eric. I mean, I think these neuroendocrine cells are normal throughout, really, our entire body. They're epithelial cells. So they kind of live in the lining of a lot of our organs. And as long as they're not misbehaving, we don't generally know that they're there. [Dr. Winer] And they don't really have a purpose in the small bowel. They're just there. [Dr. Kunz] Right. [Dr. Winer] Right. Got it. So tell me for a minute about these lung cancers—or they're not really lung cancers. They're neuroendocrine cancers in the lung. These are relatively common. And are they easier to treat or are they more difficult to treat than the others? And they're, of course, very different from standard lung cancer. [Dr. Kunz] Yeah, very different. And I think a good way for our listeners to think about this is that, you know, this is actually a type of lung cancer. And for example, if I think about the pancreas, it is a type of pancreatic cancer. But really what differs is how the cells look like under the microscope. [Dr. Kunz] And I think that broadly in oncology, we're learning that there are very different histologic types that we have to treat differently. And so lung neuroendocrine tumors probably comprise fewer than 5% of lung cancers. So they are not very common, but they are very different. And neuroendocrine, and probably using the term neuroendocrine neoplasm is better because we have the slower-growing, well-differentiated tumors and then we have higher-grade, faster-growing neuroendocrine carcinomas. [Dr. Kunz] And that's true really across all primary sites. But for the lung specifically, some of our listeners may have heard of small-cell lung cancer. That is a very aggressive form of lung cancer that is actually a type of neuroendocrine neoplasm. [Dr. Winer] So that's the kind of faster-growing kind, the slower-growing neuroendocrine tumor patients may have for years, it may go unrecognized. And even if a patient has a metastatic low-grade lung neuroendocrine tumor, they may still have years ahead of them. [Dr. Kunz] And we have very different treatments that we would use to treat the lung adenocarcinomas, which is the other kind. [Dr. Winer] And there's the small cell cancers, which are neuroendocrine, are typically classified as more standard lung cancer. [Dr. Kunz] That's right. [Dr. Winer] Whereas these others are typically thought of more as neuroendocrine tumors arising in the lung. [Dr. Kunz] That's right. [Dr. Winer] It's a funny distinction we have. [Dr. Winer] And for the non-small cell cancers, what kind of hormone secretion do you see in those patients in the lung? [Dr. Kunz] Yes. So the lower-grade neuroendocrine tumors of the lung can also secrete serotonin, interestingly. So they can have flushing, diarrhea. They can actually also have bronchospasm, so almost presenting like asthma. Some of them can secrete a hormone called cortisol, which can affect our sort of overall metabolism and weight, and sort of how we metabolize muscle and fat. So that can be a challenging one to treat. [Dr. Winer] And what role does imaging have in diagnosing these cancers? Because my sense is that the imaging can sometimes be a little complicated. [Dr. Kunz] It is. I mean, imaging is really critical. A couple of pearls to pass along to our listeners. So we use standard imaging like CT scans and MRIs all the time like we do for other solid tumors of different organs. One key for the CT scans is that we use a CT scan called a multiphase CT scan. In particular, the arterial phase of that scan is important, and that's because the slower-growing NETs

are very hypervascular. [Dr. Kunz] So when we are taking pictures of these tumors on a CT scan, when the contrast is going through the arteries, that is actually very diagnostic for this type of tumor. We also use a type of PET scan called a DOTATATE PET scan. The more common one is called gallium-68 DOTATATE PET, and then there's a copper-64 scan that is a little bit less common. [Dr. Kunz] And those are really important because they demonstrate to us if a patient has a special receptor on the surface of their cell, which lights up like a light bulb, where the tumor cells are located. [Dr. Winer] And if these cancers are localized, meaning they haven't spread elsewhere, the initial approach is typically surgery. [Dr. Kunz] Exactly. [Dr. Winer] And that can be curative. [Dr. Kunz] And that can be curative. And that is the goal. And in fact, even for some patients with limited metastatic disease, we can sometimes still cure those patients. [Dr. Winer] And in patients who have more advanced metastatic disease, is there ever a role for surgery to try to eliminate some of the tumor volume in terms of its ability to cause symptoms or— [Dr. Kunz] Absolutely. [Dr. Winer] —to get rid of, you know, by getting rid of tumors, you get rid of some of the hormone production that makes people feel unwell. [Dr. Kunz] Yes, definitely. Both for hormone secretion and for tumor bulk. And it depends a little bit on the biology of an individual patient's tumor. So we want to make sure that it is slow-growing and is not fast-moving and not going to other places. But we think of what we call cytoreductive surgery or removing as much tumor as we can see visibly. Our surgical colleagues will do that, and we really think that that helps reset the clock. [Dr. Winer] Okay. Well, we're going to have to take just a brief break. When we come back, we'll talk about some of the treatment options that are available and some of them newly available for patients with neuroendocrine tumors. We'll be right back. [WNPR] Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where patients diagnosed with pancreatic cancer are provided easy access to specialized care, including innovative treatments and clinical trials. Learn more at SmilowCancerHospital.org. [WNPR] Genetic testing can be useful for people with certain types of cancer that seem to run in their families. Genetic counseling is a process that includes collecting a detailed personal and family history, a risk assessment, and a discussion of genetic testing options. Only about 5 to 10% of all cancers are inherited, and genetic testing is not recommended for everyone. [WNPR] Individuals who have a personal and/or family history that includes cancer at unusually early ages, multiple relatives on the same side of the family with the same cancer, more than one diagnosis of cancer in the same individual, rare cancers, or family history of a known altered cancer-predisposing gene could be candidates for genetic testing. [WNPR] Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers such as Yale Cancer Center at Smilow Cancer Hospital. More information is available at YaleCancerCenter.org. [WNPR] You're listening to Connecticut Public Radio. [Dr. Winer] Good evening again and welcome back to Yale Cancer Answers. Eric Winer, your host. And if you're joining us now for the second half, we're talking about neuroendocrine tumors in recognition of Neuroendocrine Tumor Awareness Month. That is November. Our

guest tonight is Dr. Pamela Kunz, a leading expert in the diagnosis and treatment of these neuroendocrine tumors, otherwise called NETs. [Dr. Winer] So what are the main treatment options available for patients with neuroendocrine tumors, and how do you determine the best approach? I guess we've already talked about the role of surgery for localized disease and surgery to occasionally remove a large amount of tumor to decrease symptoms, but there's much more than surgery. [Dr. Kunz] That's right. So we think of, I would say, managing both the tumor itself and managing the hormones. So for that subset of patients that have hormone secretion, there are actually treatments that we have directly to lower the hormone levels. Primarily, we use a class of treatments called somatostatin analogs that includes octreotide and lanreotide. Those are more of a hormone therapy than a chemotherapy. [Dr. Kunz] They affect the hormones of NET tumor growth, not related to male or female hormones. And those are a monthly injection. There is actually a relatively new medication approved for carcinoid syndrome diarrhea that directly blocks an enzyme that's responsible for that called telotristat. So that was a trial that I helped participate in a few years ago and is now an FDA-approved drug, which is very exciting for that subset of patients that have diarrhea-predominant carcinoid syndrome. [Dr. Kunz] The other major bucket is really thinking about how we treat and prevent tumor progression and hopefully help prolong life and quality of life for patients with NETs. And there are four main categories. So the somatostatin analogs that I already mentioned actually also help slow down tumor growth. So octreotide and lanreotide as a monthly injection. [Dr. Kunz] The second major bucket are considered biologics, and these are typically oral treatments that block a specific tumor growth pathway. The ones that we have, we have at least three FDA-approved treatments right now. I should also mention, Eric, we've just really—these FDA approvals have all been since 2011. So in less than 15 years, we've seen just an explosion of research and FDA approvals in this field, which has been very exciting and I think very helpful for our patients. [Dr. Kunz] So that second bucket are biologics. We have one medication called everolimus, another called sunitinib, and another called cabozantinib that was just FDA approved in April of this year. [Dr. Winer] And can I just say, these aren't standard chemotherapy drugs. [Dr. Kunz] They're not. [Dr. Winer] These are more targeted. [Dr. Kunz] That is exactly right. Yep. So they target specific features of neuroendocrine tumor growth and take advantage of that. And I'm sure you can speak to this too. This has really been widespread throughout oncology, of using more targeted therapies as opposed to cytotoxic chemotherapies, and very exciting. And there are a number of other drugs in this space that are in clinical trials and being evaluated. So that's bucket two. [Dr. Kunz] Bucket three are standard chemotherapies. [Dr. Winer] I was about to ask you about that. [Dr. Kunz] Yes. Well, I have a special love for one particular combination because I helped lead a trial of capecitabine and temozolomide versus temozolomide for patients with pancreatic NETs. And I think, Eric, you can probably speak to this, you know, chemo gets a bad rap. And I think not all chemotherapies are the same. And these are all oral chemotherapies and are actually very well tolerated in the spectrum of chemotherapy. [Dr. Kunz] And

that clinical trial demonstrated that on average, patients had about two years of stability and had about a 40% chance of tumor shrinkage, which was actually the highest that had been reported to date for that particular patient population. [Dr. Winer] And it is true that both of those drugs individually or given together are pretty well tolerated. [Dr. Kunz] Yep. And, you know, I think sometimes people forget that we also have the ability to adjust doses. And so if the, you know, initial dose that we start is just has too many side effects, we can usually decrease the doses. And for the most part, we can decrease doses in somebody who's had side effects without compromising the effectiveness of the drugs. [Dr. Winer] That is exactly right. [Dr. Kunz] Yeah. [Dr. Kunz] And then I'll leave one of the best for last. So the fourth bucket of treatments is something called radioligand therapy. We also call it theranostics, and it's probably one of the most exciting directions that we've seen for neuroendocrine tumors. So the word theranostics, if people are wondering, is a combination of the words therapy and diagnostic. [Dr. Kunz] So basically, we're using an imaging tool to help identify a target, and then we have a treatment that goes to that exact same target. And so the FDA-approved treatment in that is called lutetium dotatate. It takes a treatment dose of a radioisotope, in this case, lutetium-177, attaches it to a protein, and that protein knows to come in on this receptor that the PET scan shows us. [Dr. Kunz] And it basically is targeted radiation delivered directly to the cancer cell. So we've had a series of trials. We're now on our third series of trials called the NETTER Trials. And I've had an opportunity to participate in and lead a number of those that have shown, again, almost a two-year what we call progression-free survival, which is essentially a two-year period of stability for patients after they receive that treatment. [Dr. Kunz] It's a treatment course of four total doses. So one of the nice things is it's an IV treatment, I should mention, and it's a finite treatment. [Dr. Winer] So you get it, and you're done. [Dr. Kunz] You get it, you're done. And which is, I think, a really nice thing for patients who have a metastatic cancer. I talk about strategic breaks and how we give treatments for patients with metastatic NETs that those breaks are really critically important for them to get back to life and pause on treatment. And patients can do well off treatment for a while after that. [Dr. Winer] And can you give it again? [Dr. Kunz] So that's an excellent question. So that is an active research question. There are several research trials open on giving two more doses. In fact, we can often do that outside of a trial. We're starting to look at newer forms of these radioligand therapies with different radioisotopes and different proteins. So stay tuned. Lots of new research in this space. [Dr. Winer] And are these radioligands somewhat similar to another class of drugs that we're talking about these days a lot, which are antibody-drug conjugates, where you have an antibody that delivers the payload, which is typically a little bit of chemotherapy, ideally directly to the cancer? [Dr. Kunz] Yeah, I mean, I think the principle is really the same. Like we want to get the drug directly to the cancer cell. [Dr. Winer] To the right place. [Dr. Kunz] To the right place. So then, to your point, we're then ideally eliminating the toxicity or side effects to normal tissues if we can get it closer to where the tumor cell is. So absolutely, that's the goal. [Dr. Winer] So these

advances, of course, arise because of clinical trials. And we know that clinical trials are really critical in advancing cancer treatment. What are some of the most exciting trials that are going on right now? [Dr. Kunz] So we participated at Yale in one trial that just finished, but I can't wait for the results. So it was called the ACTION-1 Trial, and it was looking at one of these new forms of radioligand therapy with a different radioisotope called actinium-225. [Dr. Kunz] So, Eric, I had to go back and revisit physics and really relearn some of this. So the difference with this radioisotope is it emits a particle of energy called an alpha particle, as opposed to the lutetium, which emits a beta particle. Alpha particles have higher energy and travel only micrometers, so a much shorter distance, so in theory have a chance of being more effective and less toxic. [Dr. Kunz] So we've just finished that trial in patients with gastroenteropancreatic NETs after they'd already had a standard course of the lutetium-dotatate. So this, in fact, was a retreatment trial, which is also good to look at. And so we hope to have results in the next year or so. So that will be exciting. [Dr. Kunz] Another clinical trial that is a national clinical trial we are also soon to open—back to your comment about can we bring the drug closer to that tumor cell—this is called a non-peptide drug conjugate, where we are really attaching a small molecule with a chemotherapy that goes directly to that somatostatin receptor. That receptor on the surface of the cell that we can identify with the PET. [Dr. Kunz] So those receptors, because they are expressed in over 90% of patients with well-differentiated NETs, are a perfect target for drugs. [Dr. Winer] Wow. Sounds cool. [Dr. Kunz] It's cool. Yeah. [Dr. Winer] So for patients who are living with chronic or more advanced neuroendocrine tumors—so the cancer has obviously spread outside of its original location—people are living with these tumors for years and years and years. How do you maintain quality of life and minimize symptoms? How often are these people coming in to see you in the clinic, and what's their life like? [Dr. Kunz] Yeah, that's a great question. And I think I have a special interest in survivorship for patients with metastatic neuroendocrine tumors. So these are patients who may live years, like many years, could be 5, 10, depends on the patient. But with that comes the chronicity of treatment, the chronicity of getting scans every 3 to 6 months. [Dr. Kunz] And I think that these are really important areas for us to study as physicians in the field. So I typically will see patients who get scans every three months, usually if they're on a treatment. And one exciting thing is that we are actually developing a neuroendocrine tumor survivorship clinic to really focus on this. [Dr. Kunz] So it will focus both for patients who have curative intent treatments and for patients who have metastatic disease. And there are unique features of every survivorship kind of program depending on the tumor. But for patients with NETs, it may be thinking about hormones. It may be thinking about having had a bowel resection, in which case we need to monitor for specific vitamin deficiencies. [Dr. Kunz] So there are lots of opportunities. And then the mental health piece that I think you alluded to, which is dealing with the uncertainty of scans and really the uncertainty of a chronic cancer diagnosis. [Dr. Winer] You know, and one of the things that I think people need to keep in mind, because if you're 40 or 45 or 50 or even 60 and you hear that the

prognosis is that you can live five years, you can live ten years, maybe you can live a little more, it still doesn't sound like enough, right? And I think people have to remember that the pace of discovery continues to accelerate. [Dr. Kunz] That's exactly right. I could not have said it better. And I've had patients that have benefited from ongoing trials in their lifetime. And I think that that's really helpful. [Dr. Winer] And people who benefit from things that they didn't remotely expect to benefit from. [Dr. Kunz] Exactly. [Dr. Winer] That would be incredible. [WNPR] Dr. Pamela Kunz is a professor of internal medicine and medical oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at YaleCancerCenter.org. [WNPR] We hope you'll join us next time to learn more about the fight against cancer. [WNPR] Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.