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If you're new to NETWise, we strongly recommend you go back and listen to the series from the beginning, starting with episode 1. It will give you a solid grounding in the basics of neuroendocrine tumors and how they're treated. You can find the whole series at NETRF.org/podcast and wherever you get your podcasts.

Do you have a story to tell about your own NET journey? If you're a NET patient who would like to participate in a future episode, please email us and let us know! podcast@netrf.org

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Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert in formation and patient perspectives. My name is Elyse Gellerman, from the Neuroendocrine Tumor Research Foundation.

On today's NETWise, we're going to dive into the relationship between cancer and genetics. There's still a lot we don't know about how the genetic code you are born with affects the likelihood that you will develop neuroendocrine cancer, but there are some cases where we can identify a very clear connection. This can have very important implications for treatment strategies, prognosis, and the health of other members of your family.

To understand this, let's start with some basics about the relationship between cancer and DNA. Cancers begin in the body because of some kind of genetic mutation, a modification in a cell or group of cells that allows them to multiply and form a tumor. Often, this mutation doesn't cause cell multiplication, exactly, but rather turns off a mechanism that *prevents* cell multiplication. Here's Gretchen Thone, a genetic counsellor at Geisinger Medical Center in Danville, Pennsylvania:

> ***Thone:*** *"So they're supposed to be acting in a certain way, almost like a brake on like a car to say, 'Okay, this cell is not functioning. It's not doing what it's supposed to be doing on a day-to-day basis. It's a little out of control. So what's going on with it?' And that gene is supposed to stop that and say, 'Okay, this cell, we need to look at it and need to handle it in some way.' But if there's a genetic change that actually impacts the way that that gene is functioning, it's not going to be able to stop that cell from growing. So then it grows out of control."*

These mutations can be grouped into two large categories: hereditary mutations – also called "germline" mutations – which are passed down from parents to children, and "somatic" mutations, which pop up sporadically in a person's body, unrelated to their DNA at birth. Here's Dr. Lauren Fishbein, an endocrinologist at the University of Colorado:

> ***Fishbein:*** *"Most neuroendocrine tumors are sporadic, meaning they do not have a hereditary genetic component. In those cases, what happens is one cell in the body develops a*

change in the DNA that we call a mutation, but just one cell – let's say in the pancreas or the small intestine, that develops a mutation and develops in the tumor. So that's a somatic, tumor-specific change."

And, unfortunately, in the case of most NETs, we really don't know what causes the somatic mutations that result in their growth.

Fishbein: *"It's different than lung cancer, where we can attribute a lot to smoking – melanoma or other skin cancer, where we can contribute a lot to DNA damage from the sun's UV rays. For neuroendocrine tumors, we really don't know the answer to that."*

In some cases, though, we're able to point to a particular germline mutation as a primary factor in someone developing NETs. To the best of our knowledge, some kind of hereditary mutation causes up to 15% of pancreatic NETs, and 30-40% of pheochromocytomas and paragangliomas, rarer NETs that grow in the body's adrenal system.

Fishbein: *"The hereditary mutations, they're caused by changes in our DNA that we are born with. So those changes in the DNA are present in every cell of our body, and they predispose us to get one of these neuroendocrine tumors. It doesn't mean the person will get a neuroendocrine tumor. It just means they're at higher risk to potentially develop one."*

We describe people who have an identifiable germline mutation that affects their health as having a genetic "syndrome," and there are several syndromes that have been identified as causes of NETs. Let's talk about some of the most prevalent, one by one.

All of these are rare conditions. The most common is called Multiple Endocrine Neoplasia, Type 1, or "MEN-1," which affects around 1 in every 30,000 people.

> ***Fishbein:*** *"The gene is called MEN-1, and it makes a protein called 'menen.' And there's still a lot of research going on for exactly what menen does, but one of its roles is as a modifier for how our chromatin – which is our DNA, folds and is controlled in our cells. And so, if there's a mutation in the MEN-1 gene, the menen protein can't function properly. And we're okay with having just one copy of menen in our cells – so, remember, we inherit two copies of every gene and protein: one from Mom, one from Dad – and if someone's born with predisposition for MEN-1, that means every cell in their body is missing one copy already. And, luckily, our cells still function with just one good copy, but if a particular cell in our body – by chance, that good copy of MEN-1 gene – gets damaged, then that cell can't operate correctly because it's missing menen, the protein from MEN-1 gene. And so that is what predisposes to tumors. And there are certain cells or tissues in our body that are more susceptible. And that's where we find the tumors like*

in the pancreas is more susceptible. The parathyroid glands are more susceptible, et cetera."

Here's Dr. Mark Lewis, an oncologist at Intermountain Healthcare in Utah. As we heard in an earlier episode of this series, he is himself a NET patient with MEN-1.

Lewis: *"Problems that MEN-1 patients deal with sometimes are remembered by the mnemonic, 'the three Ps.' So it's three organs are affected, and they're all the midline, or pancreas, parathyroid, and the pituitary. So all of us will have parathyroid problems – in almost every MEN-1 patient by the age of 50, but potentially much younger will have problems with hyperparathyroidism. Some of us will have pancreas problems, and probably the minority of us – doesn't mean everyone will have the pituitary problems, but those are the three Ps."*

The first and most prevalent of these "three P" problem areas for MEN-1 patients is the parathyroid, specifically a condition called "hyperparathyroidism." While this isn't itself a NET condition, it's one that NET patients with MEN-1 absolutely need to be aware of, because, as Dr. Lewis said, nearly all of them will develop this condition sometime in their lives. At its core, it's an imbalance in the way the body handles calcium.

Lewis: *"98% of our calcium at any one time is stored in our skeleton. And that's great. That's what gives us form. Otherwise, we'd be sort of a puddle on the floor. But 2% of our calcium at any given time is in the bloodstream. And*

> *it's an extremely careful balance. There's four parathyroid glands; they're the drivers of how quickly calcium is released from your bones into your bloodstream. Hyperparathyroidism just means that at least one of them is overactive."*

Out of control activity in one or more of these glands can cause calcium to move too quickly out of the bones and into the bloodstream – causing problems like kidney stones when the excess calcium builds up in places it shouldn't – and also compromising the health of the bones.

> ***Lewis:*** *"Not only does your blood calcium go up, but your bone calcium goes down. So when I was actually found to have MEN-1 at age of 30, I already had osteoporosis, and that's a condition a lot of people associated with aging, but it can happen in very young people if the parathyroid balance is out of whack."*

Around 40% of MEN-1 patients also develop the second of those characteristic "Ps" – pancreatic neuroendocrine tumors. We've talked about PNETs a lot in this series, and we need to spend some more time with them here, because the PNETs caused by MEN-1 have some very distinctive characteristics. First, they often form what we call "multifocal" primary tumors. This means that, rather than one single primary tumor that then might metastasize and form secondary tumors elsewhere, many small tumors develop all at once in the original site.

> ***Fishbein:*** *"It's very common to see in those who have MEN-1. They can have a single pancreatic neuroendocrine tumor, but it's not uncommon to see multiple small M – pancreatic neuroendocrine tumors in those with MEN-1, and that can be challenging. And that's partly why the guidelines for the pancreatic neuroendocrine part of MEN-1 suggests kind of watching and monitoring when those tumors are very small, because we know that a lot of patients will have these multiple small tumors that maybe will hopefully never grow or change. And so we can watch them over time. The only way to cure someone when they have multiple would be to remove the whole pancreas, which is a big surgery and can have a lot of consequences. [It] can be done, and patients can live very well without a pancreas – luckily, we can replace the enzymes and the hormones needed. But, you know, we want to avoid that if we can. And so guidelines really do recommend surgery at certain sizes that the pancreatic neuroendocrine tumors get to, especially when there's multiple of them."*

People with MEN-1 are also more likely to develop gastrinomas of the pancreas: functional PNETs that produce excesses of gastrin, a hormone which causes the body to make stomach acid.

> ***Fishbein:*** *"And so there can be gastrinomas in patients who don't have MEN-1, but if there is someone who has a gastrinoma, their chance of having MEN-1 is a little bit higher. And so gastrinomas can form from cells in the pancreas and also cells in the duodenum at the end of the stomach, beginning of the intestine, and those gastrinomous*

tumors can make very high levels of gastrin, causing severe, severe heartburn. That can be very difficult to control. We can use antacid medicines like proton pump inhibitors, PPIs, to help control the acid. But for some people, even with high dose of those medications, it can be difficult to control the acid levels. And so this can be a challenge for patients with MEN-1, especially if they happen to have multifocal disease, because then, which one of these little tumors is the one that's over-making gastrin? And so that can be challenging sometimes from a therapeutic standpoint as well."

About a third of MEN-1 patients also develop a cancer called Pituitary Adenoma, which is the third of those three "Ps." And other tumors are possible as well.

Fishbein: *"There are other conditions associated with MEN-1, including other neuroendocrine tumors. And so people with MEN-1 can be at increased risk for developing lung or bronchial neuroendocrine tumors, as well as thymic neuroendocrine tumors. They can also be at increased risk for developing adrenal nodules or tumors, which tend to be benign. And there's also discussion of whether breast cancer is at increased risk for those with MEN-1 or not; uh, that data and that research is still ongoing."*

MEN-1 and some of the other hereditary syndromes we'll discuss in this episode are conditions of constant surveillance, making people who have it need frequent scans and lab tests throughout

their lives in order to be on the lookout for any of the many types of cancer that may occur.

Metzcar: *"My name is John Metzcar. I am 40 years old. I am in Bloomington, Indiana, and I have MEN-1. It really starts with my sister. In the mid two-thousands, my sister was having problems in her abdominal region. And, you know, just no solution, no solution, not sure what's going on, not sure what's going on. And then the results came back positive for pancreatic neuroendocrine tumors. And then she already pieced together from my mom's history of having parathyroid adenoma and pituitary adenoma that we must have MEN-1 in the family. So that's kinda how we found out. That was in 2008. And then things kind of accelerated over a couple of years as, as like, my mom got into screening and surveillance, and extensive disease was revealed at that point in time, in terms of pancreatic neuroendocrine tumors. You know, I got involved in surveillance eventually and then was shown to have, you know, at least a couple problems in 2010. But I was reluctant to get it. My sister really pushed everybody, actually, to get this looked at, to have the best care possible. Even though it's scary to know all of this, it can feel scary to know all of this, you know, at least now I have choices. I can go in informed and make the best choices that are available to me.*

And I've had several of the manifestations of MEN-1. So I had a bronchial carcinoid that was diagnosed in 2010 and then was removed with a surgery. And at the same time that

I was diagnosed with a bronchio – a bronchial carcinoid, and while that was of the most concern to the care team, it was also apparent that I had pancreatic neuroendochrine tumors. And so I had a distal pancreatectomy in 2014. in terms of treatment, I'm looking at I get six months serial PET CTs. So that's the Netspot, the gallium dotatate scans. And so then basically a treatment decision is made every six months. Right now I am on everolimus. I started on a lanreotide and that wasn't getting the control that my endocrinologists wanted. Then I tolerated it well after we had a little bit of a dose reduction. That was, that was, it was hard at first, but I mean, you know, working with the team, we got it dialed in and I don't have, I have almost no problems. And so then next up will probably be PRRT, is what I assume."

In addition to MEN-1, there's another, rarer genetic condition called MEN-2, which affects a different gene and presents a different set of problems.

Lewis: *"So MEN-1 and MEN-2, it's almost unfortunate, in my mind, that they are named so similarly, because they really are very, very different conditions. And I think, unfortunately, there's a lot of confusion even among physicians about how related or unrelated they are. Just like MEN-1 has this dominant hyperparathyroidism, the dominant feature of MEN-2 is medullary thyroid cancer. Some of those mutations are so scary and threatening that the*

risk of cancer starts almost at birth. And you really have to consider doing thyroid surgery within that first year of life, which is a huge decision for parents to make, as you might imagine, but sometimes a lifesaving one for that affected child. The other aspects of MEN-2 can include hyperparathyroidism again, and then a nasty problem called pheochromocytoma…"

Pheochromocytoma, and a related kind of cancer called paraganglioma – often referred to as "pheos and paras" – are types of neuroendocrine tumors that develop in and around the body's adrenal system: Pheos growing inside the adrenal glands themselves, and paras elsewhere in the body. They're very often functional tumors, producing excess adrenaline in the system, which creates a distinct and challenging set of symptoms.

Lewis: *"You can end up with extremely high blood pressure. Imagine being sort of in a fight or flight situation all the time and unpredictably. And so patients get a horrible pounding in their chest, their heart just palpitating. They can get very, very sweaty and get horrible headaches from elevated high blood pressure."*

Pheos and paras can be caused by MEN-2, and also by a number of other genetic syndromes. Here's Dr. Joseph Dillon, an Endocrinologist at the University of Iowa:

Dillon: *"About 40% of pheos and paras have a genetic predisposition; in all, upwards of 20 genes have been have been isolated. Now some of those genes have been isolated*

in only, you know, one or two families. So, of the other genes that have been isolated that drive pheos and paras, one of the big groups of genes is called the 'SDH genes.' And those, of the 40% of people who have pheos and paras with genetic abnormality, probably about 15% have, have SDH genes. And there are five known SDH genes: A, B, C, D, and AF2; I'm not sure why they didn't just call it "E," – but of these group of genes, the SDHB genes tend to have more pheochromocytomas, and abdominal and chest paragangliomas; upwards of 30% of them can be can metastasize, be typical malignant cancers. Whereas, if you look at the SDHA, or the SDHC – people who have those genetic abnormalities more frequently get paragangliomas of the head and neck area, and they do not tend to be malignant or metastasize widely. So, so very different behavior from genes that are even closely related, because they're all related to this SDH, which is which is an enzyme within the mitochondria of these cells. Up to 85% of people will, who have specific SDH genes will get some pheochromocytoma or paraganglioma during their lifetime."

The last genetic condition we'll describe in detail today is call Von Hippel-Lindau Syndrome, or VHL. VHL affects around 10,000 people in the United States at any given time, and can be the cause of a number of neuroendocrine cancers, including pancreatic NETs, pheos, and paras.

Fishbein: *"Similar to MEN-1, we all have two copies of our VHL gene, and someone who has VHL is born with just one functional copy in all their cells. And, again, luckily*

enough, that one copy's enough, but if some particular cell picks up a mutation in the one good copy, that can lead to a tumor. The VHL gene is involved in controlling the hypoxia pathway in our cell. So it regulates what is called a 'hypoxia inducible factor.' And that hypoxia inducible factor goes on to regulate a whole set of genes in the cell. So VHL is kind of a master regulator of this hypoxia pathway. And so, when that VHL protein isn't working, because there's a mutation, that can lead to cells growing and tumors forming."

Karle: *"My name is Doug Karle, I live in Minnesota and I'm 48 years old. My diagnosis of VHL was at age 43. [I] woke up on a Saturday morning. My wife and the kids were out of town, and my right leg was completely numb. I was doing some work in the house and I figured, you know what, I pinched a nerve or I did something. So, started driving to the grocery store to get some food for breakfast. And then my left hand went completely weak, just nothing, it just… dropped. And so, you know, drove myself to the emergency room, and I'd had eight bilateral strokes. And so, I go through this three-month misdiagnosis period. Yeah, maybe it's lymphoma, could be leukemia, could be acute, could be chronic; had multiple biopsies that took place during that time. And during this, they identified some masses on my adrenal glands. And within, you know, two weeks, they had it figured out and it was bilateral pheochromocytoma. And so I got my testing done, got the results back, and I have VHL. The best way that I can characterize VHL is cancer for*

life. Someone, unfortunately, gets, you know, a normal cancer and you know, then they get to their five-year all-clear and they're good to go. For us, these tumors continue to pop up and grow in different areas of the body. So I just had spinal surgery to remove an angioblastoma on my spine, I had a T-10 to T-12 laminectomy. The – and then there's other smaller items that are on my spine as well. I've got lesions on my pancreas, one kidney, and liver. I've got a paraganglioma and, you know, literally, I mean, it's like, once a year I'll go through and just chart down, like all the stuff that's on the list and the size of it, and you know, where it's currently graded. It's been an interesting emotional journey. You know, the reality of, you know, what people refer to as "scanxiety" is there. Every year I go in for, you know, three MRIs… and, you know, the first couple of years, it was really difficult. And over time, it's like, I don't sweat what the results are going to be. It's gotten to the point – and it's going to sound silly, but – I sweat inconvenience of sitting in the tube for three, four hours, you know, however long it is to get to get all these things done. So, you know, that part has gotten easier. Where, where it becomes more difficult is my soon-to-be 12-year-old son, he also has VHL. And my sister, one of my sisters has VHL as well. And so after I got tested, then the kids got tested. My mom got tested, and all my siblings; my dad passed away in 2000. And he appeared to be the carrier. And so, the caregiver side, I think, is the hardest because you can't control what they have to deal with. So my son, uh – this will

actually be his first year going into the tube. And that's a tough thing."

Thone: *"We do recommend testing children for MEN-1 and VHL; screening guidelines start fairly early. We start looking at prolactin and insulin and glucose at like five. So, and we even recommend a head MRI at five years of age. And that's hard for parents. And I have a few right now that I am, it's an ongoing conversation and, you know, you're just as supportive as you can. And, as – for me, I know I've definitely recommended, like – even if you don't want to do testing, like, let's just get this recommended, the screening guidelines, like what they say, let's just start that. We can take this one step at a time, but like, we need to make sure that everything is okay and they're safe. But, yeah, it gets tricky for sure. And there's a lot of different reasons. I mean, sometimes a lot of it is guilt, too, like – they feel so bad about their child inheriting this genetic change. And I just really talk to them a lot about how there's nothing that they could have done. So, really, just addressing the whole family as one and, you know, helping to support them through that whole process of testing, and then, if it comes back positive, you know, being supportive in the next best step with like, the specialists they would need to see and the screening options that they have. So it's, it's definitely a lot."*

Dr. Lewis's son also has MEN-1:

> ***Lewis:*** *"Yeah, I mean, essentially, you know, so – we tested him when he was two… obviously that was not when we told him, but essentially… I don't know about you, I can sort of start to remember things maybe when I was around four? And so we basically, when he started going to the doctor at that age, just made it a part of his checkup, and that way it wasn't something so foreign to him. And I really hate the phrase 'new normal,' I think I've heard that way too much during covid – but, again, normalizing for him an abnormal condition is the way I put it."*

Even for families who don't realize they carry this condition until all the children are grown, this is an emotionally difficult situation for parents and children alike.

> ***Metzcar:*** *"My mom is receiving treatment. My impression is that, you know, there was some element of, of sorrow, of grieving, and doubly for her, because of course this isn't the kind of thing that you want as a parent to have for your children. And then, you know, as the, as the carrier of the mutation, that, I think, was even harder on her. And at the same time, I think she really reflected on all the joy that she had at, you know, being a parent and having children, having successful children that, you know, of course I don't, I don't think she would have done it any other way. And I think that that reflects the, this experience that we all have, where it's a mix of, of, sometimes it's a mix of the best of things and the worst of things. And, and it, you know, it's hard, it's, it's, it's life in some, in some aspects, there's ways in which – not*

to be too hyperbolic about it, but – there's some aspects of which having this kind of chronic disease that we know isn't going to go away… it can highlight everything. So I believe that's reflected in her experience as well."

Perhaps the toughest set of decisions is for a person who has received a diagnosis of a serious hereditary condition and doesn't yet have children of their own. Should they have kids, knowing they have a 50% chance of those children being born with this syndrome?

Metzcar: *"And everybody approaches this differently. You know, my wife and I decided to end up having children. I think, right after my diagnosis, I was reluctant. I had been interested in, in having children and I was, I was reluctant to, after that. So I have a child, I have a daughter; she's negative for the mutation. So, certainly simplifies her life, but we would have been ready to handle it. I mean, that's the, that's the decision that we, you know, we had to be comfortable with either outcome. And I think that our take on it was that the treatments had been successful, and that, when we looked at other members of the community, they'd had, they've lived good lives. And, in fact, we're continuing to live good lives. And, furthermore, that, when it came to some of the most pernicious aspects of MEN-1, like the malignancies, that treatments were improving. That there was something more every day, and that we could, we, we could see that my mom had been successfully treated. And so we just decided that it was, it was worth it, and that we would be without*

regrets. So I guess another way to put it is: we might be with more regrets if we didn't go with children."

There are also options for potentially having children without sharing this particular gene with them, such as conceiving by in-vitro fertilization and pre-testing the embryos, but these can be complicated, expensive, and fraught with ethical issues. It's a subject for careful conversations with your family and care team.

Overall, the case for being screened for these conditions when you know there is a history of them in your family is fairly clear: knowing you have a syndrome like MEN-1 or Von Hippel-Lindau as early as possible can improve your long-term care enormously.

Fishbein: *"For all these genetic hereditary conditions, the key, I think, is knowledge, and knowledge is power. So, if someone knows they have a genetic predisposition of some sort, then it allows them, with their providers, to do the appropriate screening so that these associated conditions can be picked up early. And, again, this is true for all of these hereditary conditions. And the key is early diagnosis so that there can be surgical cures when it's still at a relatively – no surgery is easy, but relatively – easier time for tumor removal."*

But what if you have a tumor that *might* be caused by a hereditary condition, such as a pancreatic NET or a

pheochromocytoma, but don't have a known history of one of these conditions in your family? Should you be screened for them, just in case? That's a more complicated question.

> ***Fishbein:*** *"Only maybe 10, maybe 15% of everyone with a pancreatic neuroendocrine tumor is going to have a hereditary predisposition. And so there are guidelines from the American College of Medical Genetics, and they recommend that just having a pancreatic neuroendocrine tumor alone is not enough to necessarily screen for one of these hereditary conditions. However, if you have a gastrinoma type – the one that's making the high gastrin and causing that severe acid and heartburn – then those people should be screened for MEN-1. Or, if you have a pancreatic neuroendocrine tumor, and one of the other features of either MEN-1 or VHL, et cetera, then they should be tested for it. But, usually, a single pancreatic neuroendocrine tumor alone, without any of these other features, is not usually enough to trigger the need for genetic testing. And for pheo/para, it's as high as 40% of those. So for pheo/para, we do recommend that anyone with pheo/para be screened for a genetic cause."*

We live in a time when home genetic testing has become very available. One thing we strongly recommend is to not try to interpret genetic risk factors without the help of doctor or genetic counselor who really understands what the results mean, and can help you determine what is a genuine cause for concern and what is not.

Thone: *"If someone is interested in knowing about themselves, then that's, that's their right. But, also, I really, really encourage people to have some kind of physician or genetic counselor that they can talk to about what these results are, 'cause I feel like – people go into, like, direct consumer testing and they have no idea what could come up from it. And there's so many things that are looked at, and they're just little risk factors, and it's going to mean a different thing for a different person. They're just looking at little changes that, you know, could even be seen in the general population that just increase your risk. But it's not, it's not anything that I would want a patient to stress over. Like, I would really want them to come and, like, talk to us and have that support person to go through those results."*

Fishbein: *"I am a huge proponent for genetic testing. I do believe knowledge is power. But we do have to use it in a thoughtful way so that we know what we're looking for, and we can deal with the potential incidental findings. So we do need to be thoughtful about how we do our genetic testing."*

All in all, there's still quite a lot we don't know about genetic causes of NETs, and it's quite possible that there are hereditary conditions that we have not yet discovered. And, as researchers learn more and more, it may open the doors for new

knowledge – and new treatments – for NET patients with genetic syndromes.

> ***Fishbein:*** *"Now, we do know that sometimes there are families that seem to have the same small intestine tumor in the families, but they do not have a known genetic predisposition or a germline mutation. So there probably are genes or causes that we have not identified yet as scientists and physicians that do lead to hereditary conditions that we don't know about yet. And so this is an ongoing field of research and discovery."*

Thanks for listening to NETWise. My name is Elyse Gellerman from the Neuroendocrine Tumor Research Foundation. This episode was produced by David Hoffman of CitizenRacecar, assisted by Garrett Tiedemann and Charlotte Moore. It was made possible by the generous support of Ipsen Biopharmaceuticals and TerSera Therapeutics. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. This is a production of the Neuroendocrine Tumor Research Foundation, where we're committed to improving the lives of patients, families, and caregivers affected by neuroendocrine cancer by funding research to discover cures and more effective treatments and providing information and educational resources. Please visit us at NETRF.org.

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