WNPR Radio: Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers with the director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer.

Dr. Winer: November is Pancreatic Cancer Awareness Month, a time to raise awareness about one of the most challenging cancers to diagnose and to treat. You may not know that pancreatic cancer is currently the third leading cause of cancer-related deaths in the United States. It's estimated that over 64,000 Americans will be diagnosed with it this year. But there is some good news, including advances in early detection and some new innovative therapies that are both here and about to be here, as well as supportive care strategies that have evolved for patients.

To help us better understand pancreatic cancer, there is no one better than Dr. Joe Lacy. Dr. Lacy is a well-known medical oncologist, researcher, and professor of medicine at Yale School of Medicine. And although Dr. Lacy has been involved in many different aspects of cancer care, she really focuses on gastrointestinal cancers and specifically pancreatic cancer. Her work has contributed significantly to improving outcomes for patients facing pancreatic cancer. Dr. Lacy is someone who both succeeds in individual patients' rooms, where she helps individuals and their families, but also, through her research, has tried to have a much larger impact on all individuals with pancreatic cancer. Joe, thanks so much for joining us tonight. Dr. Lacy: Well, thank you, Eric, for that kind introduction. Pancreatic cancer is indeed a challenging cancer, and I think the statistics tell the story. Dr. Winer: So you mentioned that there are 64,000 cases diagnosed per year. There are 52,000 deaths per year from pancreatic cancer. So the death rate almost approaches the incidence. That simply reflects the sobering lethality of pancreatic cancer. And that's really quite different from a lot of other malignancies. For example, breast cancer has over 300,000 cases and 43,000 deaths. So a woman, and occasionally a man, diagnosed with breast cancer stands a pretty good chance of not losing their life to it. On the other hand, you hear a diagnosis of pancreatic cancer, and in 2025, it's still, unfortunately, far more common than not—far more common than not—that someone will ultimately lose their life. Dr. Lacy: Yes, that is all true. The five-year survival for this disease, although it's tripled over the last two decades—which is an accomplishment—still sits under 15%. And for those patients who present with advanced disease, very few are long-term survivors, with less than 2% making it to five years. Dr. Winer: What are some of the reasons for this? These are very discouraging statistics, and we'll talk more about this. Dr. Lacy: There are a number of challenges we're facing with pancreatic cancer. First and foremost is that, for most patients, the diagnosis is made late. Most patients—70 to 80%—are diagnosed when the disease is already locally advanced and inoperable, or metastatic and inoperable. Thus, these patients are not curable. Now, we can treat these patients with advanced pancreatic cancer, but even with the best treatments in 2025, the prognosis really remains limited. Dr. Winer:

So when people come in with locally advanced or even more advanced pancreatic cancer, what are the kinds of symptoms people have? And I guess the other question I have is, how long have those symptoms been going on? Dr. Lacy: Really, the question is, why are so many patients diagnosed so late? And there are a couple of reasons for that. First of all, we do not do routine screening for pancreatic cancer in the general population, so we don't have that opportunity for early detection. The presence of symptoms, in most cases, is what prompts a workup that leads to the diagnosis. The pancreas is an organ that lies deep in the abdomen, so there aren't any lumps, bumps, or masses. These tumors tend not to cause any symptoms until the disease is advanced. And the symptoms are often quite nonspecific: a little bit of indigestion, discomfort after eating, maybe a change in bowel habits, maybe a little weight loss. These are common symptoms that we all experience here and there. Oftentimes, these symptoms have been present, in retrospect, for many months, even a year or longer. Now, a few patients—about a third—will present with an alarm symptom of what we call jaundice, yellowing of the eyes and the skin and darkening of urine. That is the setting where we often do make the diagnosis earlier, when the tumor is operable. Those are some of the challenges with making an early diagnosis of pancreatic cancer. Dr. Winer: And does that presentation with jaundice occur more frequently depending on where in the pancreas the cancer is? Dr. Lacy: Yes. Jaundice occurs when the tumor is in what's called the head of the pancreas. In that area, the bile duct that carries bile from our liver to the intestine traverses through the pancreas. As the tumor grows—and it doesn't need to be very large—it starts to narrow that bile duct and obstruct it. Now, there are a lot of other challenges. I'll mention a few more with pancreatic cancer. Second, these tumors, even when diagnosed early, have often already disseminated to other organs before detection. Surgery alone, in those patients who are operable, cures less than 10% of patients. Even in those presenting with small, stage 1 disease, only about a third are cured with surgery alone. Now, we improve upon those statistics with the addition of chemotherapy, but still, we're only at about a 45% cure rate in patients who present with localized operable disease. Finally, there's the inherent, very complex biology of pancreatic cancer. This not only contributes to the early dissemination but also renders this tumor exceptionally resistant to many drugs—not only traditional chemotherapy but also immunotherapy drugs and targeted therapies.

Dr. Winer: Good evening again, and welcome back to Yale Cancer Answers. I'm Eric Winer, and tonight we're talking with our guest, Dr. Joe Lacy, an expert in pancreatic cancer. Because November is indeed Pancreatic Cancer Awareness Month, we were just talking about KRAS, which is an oncogene that is present in—or mutated in—over 90% of pancreatic cancers. We were discussing the fact that there are new drugs that inhibit what KRAS does in terms of promoting

the growth of pancreatic cancer. I want to stay on this topic for just another minute or two and then talk about some other issues.

Dr. Winer: So these drugs will come out. Undoubtedly, there will be patients who have extraordinary responses. And then, as is often the case with new drugs in most cancers—particularly complicated cancers—some people will benefit from them, and then their cancers will manage to outsmart the drugs. To what extent are people getting ready to look at resistance mechanisms to KRAS inhibitors? Dr. Lacy: Well, that research endeavor is well underway. We're learning a lot about resistance mechanisms. There are a number of mechanisms that contribute to resistance, and research is already underway, looking at ways in which we can delay or overcome resistance. That will probably involve combination therapies. But people were prepared for this based on experiences with other drugs targeting oncoproteins or oncogenes. So I think we're ahead of the game with respect to that question in pancreatic cancer and KRAS. Dr. Winer: Well, that's good because, of course, trying to figure out what will be next after KRAS inhibitors for those who benefit but then stop benefiting is going to be really critical. Can we talk a little bit about risk factors? Pancreatic cancer is one of the cancers that's seen with increased frequency in the setting of certain germline mutations—cancer genes that people inherit from their mother or father. And, of course, as a breast cancer doctor, I'm most familiar with BRCA2. But can you talk a little bit about the increased risk of pancreatic cancer in the setting of inherited mutations? Dr. Lacy: Sure. Since we're on the topic of risk factors for pancreatic cancer, I would start by saying that the majority of patients with this diagnosis have only one risk factor, and that's advancing age. Like many cancers, the incidence of pancreatic cancer goes up sharply after the age of 60. Forty percent of patients are over the age of 70. Many are in their 80s, and another 40% are in their 60s. In terms of modifiable lifestyle choices, such as smoking, obesity, and heavy alcohol consumption—yes, these do impact the risk of getting pancreatic cancer, but the impact is actually quite modest, about one-and-a-half to twofold. Now, this compares to a 25-fold increase in the risk of lung cancer in smokers. So what I tell patients is, you have this cancer, and it's nothing that you did or didn't do in your life. This is just something that happens, and in most cases, it's simply related to getting into your 70s and 80s. There are a couple of other risk factors. Recurrent bouts of pancreatitis or chronic pancreatitis is a significant risk factor. And interestingly, a recent diagnosis of adult-onset type 2 diabetes is a risk factor. In fact, what we think happens is that pancreatic cancer itself can cause insulin resistance and diabetes. However, the vast majority of patients who are diagnosed with adult-onset diabetes do not, and will never, get pancreatic cancer. So we are not screening those patients with a new diagnosis of diabetes now. Dr. Winer: And longstanding diabetes doesn't seem to increase the risk very much? Dr. Lacy: That's correct. Longstanding diabetes has a very minimal impact on risk, with only about a one-and-a-half-fold increase. Dr. Winer: And of course, the reason this is of interest to people is that insulin is produced in the pancreas, so there's a natural connection here. But it sounds like the connection is far

less significant than what one might imagine. Dr. Lacy: Yes, diabetes can be what we refer to as a paraneoplastic syndrome. It's an effect of the cancer itself on glucose metabolism. Dr. Winer: And with respect to genetics, hereditary factors are extremely important in pancreatic cancer. Probably about 20% of patients' risk for pancreatic cancer is familial, genetic, or hereditary, correct? Dr. Lacy: Yes, that's right. We are able to identify cancer-causing genes in about 5% to 10% of patients with this diagnosis through germline genetic testing. The most common gene that causes pancreatic cancer is one that you're very familiar with, and that's BRCA, or BRCA. While we associate BRCA with breast and ovarian cancer, it is also the most common genetic cause of pancreatic cancer, increasing the risk anywhere from about four- or five-fold to as much as 20-fold, depending on the specific BRCA mutation. Because of this, it's now recommended that all patients with this diagnosis, regardless of age, stage, or family history, undergo what we call germline genetic testing to determine whether they carry a gene such as BRCA that they inherited from their mother or father and that causes this cancer. Dr. Winer: Why is this testing important? Dr. Lacy: First, it's important for family members. First-degree relatives can be tested, and if they carry the gene, they can go into a pancreatic cancer screening program because they are known to be at high risk. It also has implications for the patient. We know that pancreatic cancer associated with a BRCA mutation responds very well to the FOLFIRINOX regimen, so we would want to use that. Additionally, we now have a targeted drug called olaparib, which is used widely in BRCA-mutated breast cancer, that can be used after the patient's initial chemotherapy to maintain their response or remission. Dr. Winer: And you see somatic mutations—mutations arising just in the tumor, not in every cell of the body—in pancreatic cancer as well, correct? Dr. Lacy: Yes, absolutely. We do see somatic mutations in BRCA2, but it's not yet clear whether that confers the same sensitivity to FOLFIRINOX or PARP inhibitors. That's still a work in progress. Dr. Winer: And are there other inherited gene mutations besides BRCA that are associated with pancreatic cancer? Dr. Lacy: Yes, there are. ATM mutations and CHEK2 mutations can be associated with pancreatic cancer. It can also be associated with Lynch syndrome, which is more commonly linked to colon cancer, though it accounts for less than 1% of pancreatic cancer cases. However, it's important because patients with Lynch syndrome-associated pancreatic cancer may respond well to immunotherapy.

Dr. Winer: Since we're on the topic of genetic testing, that identifies a group of people at very high risk. Let's talk now a little bit about screening. Where are we with screening methodologies? Dr. Lacy: This is a very important topic because I think we all feel that earlier diagnosis of pancreatic cancer will result in better outcomes for patients. We don't screen for pancreatic cancer in the general population, and it's not recommended by professional societies or covered by insurance. This is in contrast to breast, colon, lung, prostate, and cervical cancers, where screening is recommended and has been shown to improve cancer-related outcomes and save lives. The reason we don't screen for pancreatic cancer is multifaceted. First, it's costly to screen the entire popula-

tion for a relatively uncommon cancer. Many tests would need to be done to detect the cancers. Second, the screening tests are still somewhat imperfect. A simple CT scan is not sensitive enough; we often miss pancreatic cancer on CT scans. MRI is better but more costly and difficult for patients. The best test for early detection is an endoscopic ultrasound, a minimally invasive procedure requiring some sedation. What we're really hoping for is a simple, accurate blood test. There's a lot of research into blood-based screening for many cancers, and while we're not there yet, I think we will get there.

WNPR Radio: Dr. Jill Lacy is a professor of medicine and medical oncology at the Yale School of Medicine. If you have questions, the address is CancerAnswers@Yale.edu. Past editions of the program are available in audio and written form at YaleCancerCenter.org.

WNPR Radio: Funding for Yale Cancer Answers is provided by 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.