Pancreatic cancer has essentially the highest mortality of any major cancer type. Majority of patients who get pancreatic cancer, actually close to 90% actually die from the disease. There are a number of things that could lead to high mortality from a cancer, but pancreatic Cancer checks all of the boxes. Pancreatic cancer spreads very early. There's a limited number of predisposition factors that we know of and they're mostly lower penitence risk factors. We don't really screen for pancreatic cancer. Although I'll show you a couple of examples now where we're starting to. Pankretic cancer doesn't really follow that paradigm like many other cancers. You can have quite small tumors in the pancreas and already end up with distant metastases. It will sometimes just skip the nodes altogether and develop the task to seize. And then people get really sick. This is a cancer where people lose a lot of weight. Pancreatic cancer tends to be pretty refractory to the treatments we have. They're not a lot of chemotherapies that work. immunotherapy, which we think of a lot now for other cancers don't work in pancreatic cancer. A lot of work going on to try to change this. There are a whole host of drugs out there now that inhibit an oncogene called KRAS that are either in the in the preclinical space for now just hitting phase one trials. That are gonna hopefully change some of this in pancreatic cancer. And then the last is, you know, some of the tumors we've seen improvements in treatment and lower mortality has either been because of immunotherapy. If you find a stage one tumor, which is a small tumor with no node involvement, you actually can cure over half of these people with surgery and aggressive chemotherapy. But the problem is this is a very small, in this case, 5% or less of patients. Most patients either present with larger tumors that haven't spread. Larger tumors that invade vessels. If you want to to cure more people we're gonna have to move leftward more towards the green right in this diagram than we are in the blue in the yellow currently where over half of patients even present with distant metastases. So really a sea change is needed in addition to new therapies moving things to earlier diagnosis. Many of these patients are not known and I'll show you there are a number of genetic mutations related to this. Suggesting that screening may be useful if you can find a high enough risk group that it is, appropriate. But let me give you a little sort of discussion of the, on genetic risk, cause. The study was published in the Journal of the American Medical Association. It looked at 3,000 patients with pancreatic cancer and did panel sequencing of the germ line. And what they saw is a few of these mutations were in jeans that we know about, right? For other cancers, really all of them. There are a number of inherited mutations. That are related to development of pancreatic cancer. This is then led to a host of recommendations about the potential for screening. And there's now screening recommendations by age and how to do this screening. So let me just tell you what the screening is and then I just wanted to show you some of the data from the largest. Sort of follow-up we have of these patients. People with familial risk of pancreatic cancer, either because of inherited mutations or also multiple first degree family members within the same family. One was an endoscopic ultrasound. You can find small cancers this way, before they have spread. But it is invasive, right? It's an endoscope that requires an invasive procedure. This is called the CAPS protocol. It's based at Johns Hopkins, includes a number of different academic centers, in this case 8 of which Dana Farber has been one for many years. And look to see if someone stayed in this screening program, which is primarily once a year doing either the endoscopic culture sound that we talked about or the MRI. There were 26 actually pancreatic cancers. 3 quarters of the patients who were, sort of faithful to the screening program doing this every other year approach. And then there were a set of individuals who sort of fell out of surveillance for whatever reason. They stopped coming. It's actually not as you might suspect the easiest thing. The rate of finding early stage disease, stage one and 2 for the people who fell out of the surveillance program were just what you would have expected in the general population, which is again in that 15 to 20% rate. And then if you looked at survival, there's 3 curves here on the Kaplan Meyer curve for survival. The 5 year survival rate among those who had prema ligna lesions was a hundred percent. The cure rate was much, much higher and patients did much much better than those here in the red line. If you can look in a high risk population and use some imaging tests that we have available even now, we can push the staging. There's very few patients we know of in the general population who have a risk like this and we'll come back to that idea. Because of this and a couple other studies, germline testing is now recommended. The hope is that this will then allow us to start to find more and more individuals who should undergo screening. IPMS is an introductory papillary mucinous neoplasm. IPMS is not an invasive tumor that will spread to other areas of the body. However, they have the ability to transform to become an invasive cancer. These are mostly asymptomatic and they're not things that we would know about unless people had scans for another reason. These lesions are related to about 10% of pancreatic cancers. And again, this is an opportunity. And a window for us to try to find people who should have a pre-molignant lesion removed. It is another place where we can start to find this disease earlier and try to treat it more effectively. The most strong risk factor for pancreatic cancer is age, right? This is tends to be an age of older adults, although that is changing as people have likely heard. GI cancers in particular seem to be rising in younger individuals. Colin cancer gets a lot of or colorectal cancer getsA lot of attention. The median diagnosis is around the age of 70. It tends to be a higher rate in men in Ashkenazi Jewish individuals, which may have something to do in part with the familiar inheritance of BRCA mutations. In the US, if you look at populations within the United States, African-americans have the highest risk. There are a number of features related to systemic metabolism, how we process nutrients, weight, exercise that are risk factors for pancreatic cancer. Physical inactivity is a little less consistent, but seems probably to be related to diabetes. Black Americans tend to have higher risk. In both men and women compared to their counterparts of other races. There's not really a smoking and lung cancer relationship here. These are much more attenuated relative risks than you would see in a circumstance like that. One of the paradoxes of this, which Laurel I mentioned in her question is that patients with pancreatic cancer tend to lose weight as they approach the time of their diagnosis. Diabetes over a decade or longer is clearly a risk factor for pancreatic cancer again with the relatives we talked about. Weight loss also actually causes hypoglycemia. The exact mechanism of this is not totally clear. We have a number of studies going on trying to figure out why this is. Happening at the molecular level. People with pancreatic cancer start to develop hypoglycemia in the 2 to 3 years before they're diagnosed. This is not something you tend to see in patients without the disease. About half a percent of people who develop diabetes in the U.S. after they turn 50 have cancer as the cause of their diabetes. A very unique feature of pancreatic cancer that it actually causes diabetes in addition to diabetes being a risk factor. We there are times that the cancer is there, but very hard to see. The pancreas is among the most difficult organs to image in the body. As the tumor is growing and the as it gets bigger, you're more likely to become hypoglycemic. Which then obviously it has implications for diagnosis. What I would say though is as you start to get within a year or 2 before diagnosis, You can sometimes start to see evidence of a mass there. If you go back and look, that might have been missed. There's some been a couple of really interesting studies recently. Using machine learning and radiomics to try to look whether you can see. differences in the pancreas. And so I think that when they're getting hyperglycemic, the cancer is there. I'm not sure always will be able to see it, but if you did serial scans, I think you would. inflammation in the pancreas in particular. This type of inflammatory insult is almost required in order to see the tumor develop. There are clearly signatures of the cancer that you can see before they're diagnosed where there's a window I think that early detection could be possible. In pancreatic cancer, we don't see a direct toxic effect of the carcinogens in the smoke on the DNA in the tumor. You don't when you sequence pancreatic cancers at the DNA level. So they've been many studies that have shown in cancers like lung cancer or had a neck cancer, you get stereotype DNA mutations that develop. There's been this thought that this is an inflammatory insult, but there's not a lot of data yet to show that there's some data in mouse models as I was mentioning, but not so much in humans. So we've been trying to figure out can we start to look at this by looking at pancreatic cancers in the lab. And then alcohol and chronic pancreatitis, they may work similarly. Chronic pancreatitis can happen from a number of different reasons. It can be stones in the pancreatic duct, it can be medications. There's inherited forms of pancreatitis. These all are related to an increased risk of pancreatic cancer. It has this same interesting relationship that diabetes does. And obesity versus weight loss does. The tumor will sometimes impede the flow of the enzymatic fluid out of the pancreas and when that happens they get pancreatitis. So I will sometimes see patients in clinic who 3 months ago presented to the hospital they had acute pancreatitis, their everything was inflamed, they didn't know what was going on. Then they end up doing a repeat scan to check on things and now they see the mass and they actually had a pancreatic cancer. So again, reverse causation in this disease related to a number of these risk factors is really important. And biologically, I think quite interesting too as we think how to leverage these things for early detection. Pancreatic cancers cause diabetes, but when you remove the tumor, the diabetes goes away. If you removed the tumor in a bunch of someone's pancreas, they should become more diabetic, not less, because you're actually removing beta cells. That's really strange. You wouldn't have thought that, right? There's almost like a parity of plastic syndrome. The tumor is actually causing dysfunction. Some of it's in the pancreas, some of it is actually peripherally that's causing the diabetes. And their ability to decreed insulin should go down. But in this case, you're removing the tumor and they're diabetes is getting better. Risk factors for pancreatic cancer are inflammatory related like cigarette smoking, alcohol, things that seem to be metabolically related like physical activity, obesity. Some of these also fall, if you think about sort of comorbid conditions, again, diabetes, pancreatitis, cystic lesions we talked about at the beginning. One of the genes that has the highest risk for pancreatic cancer, that actually is a gene that leads to familial melanoma syndrome. The studies I showed you where screening was effective, we think, although again, not randomized, but where we think we're able to catch some of these cancers early. This is purely based only on mutation. Those studies actually required you have at least one family member with pancreatic cancer also. This is now a big source of debate. I'm in the field is should you require individuals to have a family history or should everyone with a BRC one or 2 mutation get screening. Pancratic cancer is substantially less common than some of the other cancer types that cause a lot of mortality. So it's been much harder to do these studies. Also these patients tend to not live long, right? So if you need to have banks specimens, banked blood samples, buffy coat, normal DNA has to come from somewhere. In pancreatic cancer, we have a couple dozen that have been identified through a series of genome might association studies. You really need studies from all over the world to do this. The relative risk for each minor allele or each risk allele is very low right so it may be 1.2 or 1.1 9. There are some genes near these polymorphisms that biologically have been studied and do relate in in mouse models and preclinical work to the development of pancreatic cancer. This has been an interesting in road to try to understand why some of these cancers may be developing. If you aggregate these, you can generate risk scores that do allow you to segregate relative risks such that the extremes have much higher risk. The gene dosage effect of NR 5 A 2 actually changes the self fate within the pancreas, particularly after an inflammatory insult. Some of these may be interesting biology to study, but still have quite a bit of work to do before this would be useful in a clinical setting. There are now a couple defined populations for which surveillance is considered appropriate. Most places in the country still don't do this. It usually means going into a major academic center. If you have a strong family history, or genetic risk to then do the screening. It's hard to get people to change their lifestyle because of pancreatic cancer. There's a lot of work going on now in pancreatic exists, which is I think really interesting. And these MRIs are complicated to read. You need somebody for who does the endoscopic ultrasound who really knows how to do this in the familiar risk population. But if we can identify these individuals in the population, it does seem like we can stage shift. The better we are at this, the more we can remove things that prevent people from getting pancreatic cancer in the first place. So how do you figure out what that subset is? So you get rid of the SIS early. Some of them will ignore and say you're fine. Some will need surveillance and some will need to go directly to the operating room. Pancreatic cancer screening is difficult because the prevalence is so low. You don't really get to risk levels high enough. If you think we need a risk level higher, a relative risk in the 8 to 10 fold range most likely to simulate what we're seeing in the familiar risk. There has been also some concern that those drugs may actually lead to some inflammation in the pancreas and be a potential cause of pancreatic cancer. So I think You might suspect, as you said, that If we had ways to Reduce obesity and reduce hyperglycemia that we think are risk factors for this disease maybe we would see a reduction in incidents over time. There's been a number of studies trying to look at this, which have been not definitive at all, but so I think it we will have to see over time, but I do agree with you that you might suspect interventions that can reduce obesity and diabetes would have a positive effect. And a lower rate. People with melanoma who have a CDK into a mutation. That may lead to their system pancreatic cancer. Do you think it would be. Worth it for people with Melanoma to regularly be screened for this gene? That's a great question. I think at the population level we would need to decide, does that make sense? A because the risk is so high. Even if there's not a family member, those patients have still undergone screening. And in fact, screening has been, if anything, a little less effective in that population because that disease seems to be more aggressive. So what we sometimes see is. They have a CDK in 2 a mutation. We're doing scans every 12 months and they actually develop a cancer 6 months in in between. Women have a slightly lower risk of pancreatic cancer than men. The data have been a little bit mixed in terms of hormone therapy, whether that may reduce or increase the risk. There's actually a instructor in, in my group, Anababak who's very interested in that question. There are actually features that the cancer will present. That occur in the time period before the cancer is diagnosed. And if that happens enough in advance and you can aggregate some of these things together, it may allow you to actually pull people out of the population who should undergo surveillance. And so that's now sort of an area that she's interested in. Patients with pancreatic cancer, they don't develop symptoms or issues the day before they're diagnosed. And that really just comes from listening to patients as you see them in clinic. A second is this is Sir Ashtari who I mentioned before, you know, he has really spent a long time, 20 years trying to think about an elucidate some of the relationships between diabetes and pancreatic Cancer. The hyperglycemia is happening at 2 to 3 years in some patients before they're diagnosed. And so again, there's a window there where something is happening that we think is due to the cancer, but they're not diagnosed with cancer. And really what I'll show you is where this ends up going. Pancreatic cancer can be diagnosed in one to two years before diagnosis. People often have abdominal discomfort from pancreatic cancer. They can actually have issues with their diet, including changes in their food preferences. The idea is to combine some of these features together with risk factors in sort of higher order models to allow us to pull people from the general population. Cancer has among the highest rate of Venus thromboembolic events like Venus, the leg being the most common. Some of this you can aggregate into changes in medicines that people take and that actually has predictive ability. Lab changes, imaging features. So really there's a wealth of information, particularly as medical records have become digitized. Every medicine goes into the medical record. The dose is known the day it starts is known, the day gets refilled is known. So there's really a lot of information in the record. And what I, in wanted to do, which I thought was a really interesting study is, you know, there's again lots of data in the medicalrecord. The study used data from Harvard cohort studies and a nurse's health study. It asked people what medications they took before and after their cancer was diagnosed. It also asked what medications did they take differently, either starting a new medicine or stopping a medicine? The study is a proof of concept study. The study looked at what medicines people started and stopped. And then what you did is ask, well, could this predict risk of pancreatic cancer in the next 2 years. And the answer was yes, and I'm just gonna present you one, you know, one figure from this, but in particular, if you newly started diabetic medicines. There's a lot of latent data in the medical record that could be useful in predicting risk. Anticoagulants like we just talked about these patients are at risk for clots and sometimes the clot actually precedes their diagnosis of cancer. And then there are weight changes and what we see in clinic is that patients often have stopped or reduced the doses of their anti hypertensive medicines. The study looked at CT scans from people before their pancreatic cancer diagnosis. It's not that the antiquated medicine is causing their cancer, it's an effect, right? It's the reverse causation and that that that may be useful. The yellow is the liver. Not all, many of the organs in the liver are yellow. The study looked at the distribution of organs in the general population and then what happens in the time before someone is diagnosed with pancreatic cancer. We quantified skeletal muscle on the CT and also fat, so adipose tissue. And then we went through and systematically did this for a lot of different, markets. Liver, spleen, pancreas, kidneys. As people were getting closer to their time of pancreatic cancer diagnosis, they were wasting skeletal muscle and also adapostic, mean they were losing them. So what we did then is ask, what was that in the population? Across entire population by age and sex and race and created essentially, standard curves for what that should be. There are these differences happening in patients before their cancer is diagnosed that are actually detectable either by seeing say patterns and medication use. Or patterns on CT scans and that these may be useful. And that then takes us to sort of some of the next steps. So one of these is now to use the electronic medical record. There are now tens of thousands of different codes. The question of this study was, could you take these codes? Look at them over time in relation to both each other and the diagnosis of pancreatic cancer and predict who's at risk. I'm a what I would say is this, to a degree actually worked. There is now just a tremendous amount of information in the medical record. And you can start to leverage this. You pick out again an individual who's at risk for the disease in the next year or 2 years. That relative risk is high enough that it justifies doing an MRI or an. There are some cancers that do this and many cancers that don't. When patients come to clinic to see their doctor, seeing that their weight has changed could be a signal that a cancer is coming in. And she explores a number of ways to try to do that in the management. There's been some really interesting work. Obesity actually puts our body in a low rate inflammatory state. So that could I alter the micro environment and alternative gene expressions. If you remind me how long this goes. Yeah, it goes until 3 30. So you have 18 min. Obesity is working by some mechanism, right? It is doing something within the pancreas that's causing this. And in the setting of obesity it actually has a signal that originates from some of the alpha beta cells that essentially promote it's almost like the repair and growth response within the asthma cell compartment. We used a number of different machine learning models. The transformer models were some of the best for that that took into account not just what codes were there, but the time in which they developed in their relationship with one another. And Laura, I mentioned this actually in her question at the beginning, which we had a study a few years ago. That the new onset diabetes that happens from the cancer when it's paired with weight loss the risk of pancreatic cancer goes up dramatically. The paper goes into quite a lot of detail describing the different models that were used. Either one alone has less risk, still some risk, but less. And so I think those types of studies will show you that it's the combination of factors that are happening. And we can see that in these models. Some of these factors are going together within the model to increase risk. Signs means what the doctor can see, right, when they examine the patient. Once you can feel, say, a It's not usually a good sign, right? These are usually things that are a bit later in terms of the development of the cancer. We talked about a number of these because now we're really thinking about how to leverage them for earlier diagnosis. Patients all get sort of a standard workup, including CT scans. They may get the endoscopic culture son that we talked about because you also can buy up see the tumor that way. I mean, ultimately you need a biopsy where you must buy up to either the tumor in the pancreas or the metastasis. I would very much say that as you guys. Study particular cancers that you really learn how those cancers are treated and how patients experience those cancers. There are a lot of really good cancer centers in Boston. And so really trying to spend some time either collaborating with an oncologist who treats the disease you're interested in. Or even spending some time in clinic. A patient who I took care of had a mass in the pancreas. There was not cancer and other organs. He had some evidence early evidence of obstruction of the bile duct and had a procedure to open that. And he did not at that point have symptoms of a pancreatic cancer. He had a 2 cm mass. In the pancreas. That's actually top level. Size for a T one tumor. We had to put in a port, which is an IV that goes under your collarbone. It's semi permanent. It can come out, but it can also stay in for years if you need it. This is a whipple procedure which is as folks may have heard as a large complicated kind of surgery, definitely a surgery you want done in a big. Economic center where they do hundreds of these a year. And again, he fortunately had a small tumor. He had no lymph nodes that were positive. We gave him 4 more months of chemo because 2 months is really just not enough. To get rid of this. Disease with the hope that by doing this, we would cure him, right? This is something we see a lot of, which is that early on with early tumors, you see dilated pancreatic ducts. And then after we gave 2 months of chemotherapy, you can see it's largely gone. So that was great. And we really hope he was going to be cured and he was for a while, but his tumor eventually did come back. Because he's a long term smoker, we actually did surgery to remove it because we had to make sure it wasn't lung cancer. We're able to wait another year actually before many new ones showed up. And then eventually had to give him chemotherapy and he was on chemotherapy for about a year, before he passed away. Cancer is the third most common cause of death from cancer in the US. Early detection is a hard problem, but there are now, I think, a number of avenues that are moving forward to try to do this. We talked about risk factors including smoking, obesity, diabetes, pancreatitis. Dana Farber: We did a little less discussion about treatment, just given time. But the patient I showed you is sort of a, an example of trying to use chemotherapy and radiation or chemotherapy and surgery to try to cure the tumor. And then trying to treat it as it recurs. Genetic testing is now recommended for all patients with pancreatic cancer. Pancreatic cancer has been rising. It feels like it's popping up even more so in women than men, even though men still are at greater risk. I'm certainly not going to tell you what you need and not need to understand, but I would say I show you that more as just so you see what clinicians are looking at less. Pancreatic cancer is also vulnerable to sort of this earlier onset that we're seeing for other GI cancers. You know, in some ways not too dissimilar from colorectal cancer, although the prevalence of pancreas is obviously lower. And that now has been shown in actually multiple studies in multiple countries that that is true. There does seem to be. when you have these risk factors, they do seem to matter more in younger individuals than older. That if you're obese or you smoke, that it increases the relative risk of cancer at younger ages more so than at older ages. Still the overall prevalence is much higher as you as you age. There are ways to find signatures in the tumor itself that tell you what's own was exposed to. But I think at this point, I don't really know the answer aside from it does seem like obesity diabetes do matter more when you're younger. And that that may be what's in part playing a role. And then there may be other exposures we have that we don't know yet. D the importance meaning should we do it or maybe tell me a little more what you mean. And more in terms of the number of patients, the, first, patients that actually have the disease. And high risk patients for pancreatic cancer screening. Cinder is more than 2. Do you have a comment about that? The exact cut point at which to say you should do surveillance is not that clear. We generally now will recommend people who have 2 or more. First degree relatives in the family with pancreatic cancer that all of the first degree relatives around them Get screened. And that's because the relative risk seems more like it's in the 5 to 6 range. There continues to be debate about whether we should be using family history alone. At this point we still do and those people still qualify for these. Problems and trials that, that we are doing. But I think my last part would be I think the way you're thinking about it is exactly how I think about it too, which is what's the risk level? "We're trying to define risk in a way that can be clinically actionable. That's important," he says. "This has been really amazing and, This is just, yeah, thank you again. Let's give Brian. Our, thanks and wish we could have been in person but great to see you"