* Majority of patients who get pancreatic cancer, actually close to 90% actually die from the disease.

7:30

* And that really has a host of different reasons. Usually at this point in the class we go around and we sort of ask people to think about what are the.

7:36

* Reasons they would think a cancer would have high mortality. You know, why would one particular cancer lead to more cancer deaths than than others.

7:45

* And usually what happens when we do that is people name a whole host of different things, which I'll show you on the next slide.

7:54

* That could be for any cancer type right that are not necessarily specific to pancreatic cancer. And they're just general things that could lead to high mortality from a cancer.

8:01

* But pancreatic cancer checks all of the boxes, meaning all of the things that people mentioned and it really does have essentially the highest mortality of any major cancer type.

8:07

* So as you might think, there's a number of things on this list. So there's a limited number of predisposition factors that we know of and they're mostly lower penitence risk factors.

8:21

* The early warning symptoms and signs are relatively nonspecific. Something we've been thinking more about lately is how we use these things in aggregate to try to find patients in the general population who are developing this disease.

8:32

* We don't really screen for pancreatic cancer. Although I'll show you a couple of examples now where we're starting to, and I think that's starting to raise some hope that if we can identify people at higher risk.

8:47

* That we actually can find it early with screening tests that we may improve, survival. And again, I'll give you a couple of examples where that's starting to be done.

9:01

* Pancreatic cancer spreads very early. So most cancer types, many of the other GI cancers that I take care of like colon cancer, it's a pretty stereotyped small tumor, bigger tumor, lymph nodes get involved, becomes metastatic.

9:06

* And 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 and it will sometimes just skip the nodes altogether and develop the task to seize.

9:27

* So the problem is it spreads quite early. And it's development. Except biologic reasons for that at the molecular level are not that well understood yet, but it's very invasive and it tends to invade into both lymphatics and the Venus system very early on.

9:40

* I mean, this may be part of the reason why it's spread so early. And then people get really sick.

9:51

* With this disease. This is a cancer where people lose a lot of weight. They can't eat or drink well.

10:01

* They get a lot of fatigue. They get nausea vomiting other issues. And actually that sometimes really causes us problems and it prevents us from being able to treat the disease as a aggressively as we would like.

10:07

* And as I'll show you, patients with pancreatic cancer, about half the patients in the United States.

10:19

* If they develop metastases from their pancreatic cancer, get only one line of therapy and then they pass away.

10:25

* Right, and that's again in sort of modern age of. Oncology care that's quite uncommon right you can in women with metastatic breast cancer use 10 different therapies over in multiple different years.

10:32

* And pancreatic cancer, we just don't have that. Our momentarium in the same way.

10:44

* And that sort of goes to the next point, which is this tends to be pretty refractory to the treatments we have.

10:49

* They're not a lot of chemotherapies that work. And immunotherapy, which we think of a lot now for other cancers don't work in pancreatic cancer, at least the immunotherapies we have today.

10:54

* A lot of work going on to try to change this. 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 or because of new targeted drugs that have been able to say in like EGF army and lung cancer, keep people alive for many years or help cure the cancer after tumor reception.

11:04

* And that's been difficult in pancreatic cancer so far. I'm not going to talk a lot about it, but there's a sea change coming, which is that 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.

11:27

* That are gonna hopefully change some of this in pancreatic cancer. Alright, so to start with one of the main issues we talked about is that this disease presents late, right?

11:46

* So it tends to present it in advanced stage. It spreads very early. So if you look at this, you can sort of see that on the bottom is your AJCC stage.

11:57

* So stage one and 2 mean it's localized to the pancreas. No evidence of metastases.

12:07

* And it doesn't invade blood vessels around the tumor that prevent reception. This is really the stage or stages one and 2 that we can cure in some instances.

12:13

* In fact, 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.

12:22

* 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.

12:33

* Larger tumors that invade vessels, blood vessels, which is locally advanced disease or metastatic disease.

12:43

* And you can see on the Y axis is the 5 year survival rates, they get very low very fast, right?

12:48

* As the stage gets higher. And so really once you end up even with a localized tumor that gets bigger or has lymph node involvement or a tumor that invades blood vessels, you really don't care a lot of those patients.

12:54

* So really 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.

13:02

* I'm at the time of their diagnosis. So really a sea change is needed in addition to new therapies moving things to earlier diagnosis.

13:21

* So I thought I would start off with. A couple of groups for which we do actually do some sort of surveillance or screening.

13:30

* For pancreatic cancer there's really 2 groups like this One of those that have a very strong family history and or known genetic inherited mutation and another are patients that have cystic lesions of the pancreas.

13:38

* If you add this up, it's about a quarter of patients with pancreatic cancer. The problem is who ultimately get pancreatic cancer.

13:52

* The problem is many of these patients are not known and I'll show you there are a number of genetic mutations related to this, but there's quite a number of families that don't know they have these mutations and you only know you have a cystic lesion if you've had some sort of scan that showed it often for other reasons because the sister often asymptomatic.

13:57

* So although there's about a quarter where we could potentially do surveillance, most of these are not actually found by surveillance.

14:17

* But let me give you a little sort of discussion of the, on genetic risk, cause this is where some of the data has started to emerge really just in the past 2 or 3 years.

14:24

* Suggesting that screening may be useful if you can find a high enough risk group that it is, appropriate.

14:34

* So this is a study now it's a few years old, published in, Journal of the American Medical Association, from a Mayo clinic study where they basically took 3,000 patients with pancreatic cancer and they did panel sequencing of the germ line and what they were trying to do is identify what were germline mutations that were in patients with pancreatic

14:41

* cancer. The ones on the top, these first 6 were ones that were statistically significantly different than when they compared to sort of a population database called Nomad.

15:03

* And what they saw is a few of these mutations were in jeans that we know about, right?

15:14

* For other cancers, really all of them, right? So BRCA one, BRCA 2, ATM, and others that predispose to other cancer types, right, to breast cancer, ovarian cancer, and others.

15:15

* And this really wasn't the first study that had done this, a number of studies, including a couple of studies we published from Dana Farber, but this was the biggest.

15:30

* I mean, it really, again, emphasize that there are a number of inherited mutations. That are related to development of pancreatic cancer.

15:37

* This is then led to a host of recommendations about the potential for screening. This is a review article that we wrote.

15:47

* Leah Billers, a junior faculty member at Dana Farber. That talked about these different syndromes, right, based on the genes that are known to be inherited that have pathogenic mutations and relate to pancreatic cancer.

15:56

* 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.

16:04

* Sort of follow-up we have of these patients to try to suggest and and sort of make the case that screening may be useful if you can find the right people to do it in.

16:18

* So what was done for these individuals, people with familial risk of pancreatic cancer, either because of inherited mutations or also multiple first degree family members within the same family was a combination of 2 types of imaging tests.

16:33

* One was an endoscopic ultrasound. You place a probe through an endoscopic down someone's throat into the stomach and then around through the small intestine, the duodenum, which is here.

16:48

* And the probe then looks at the pancreas and it's trying to find small lesions in the pancreas.

16:59

* That's sort of what this is denoting what this is denoting. And you can find small cancers this way, before they have spread.

17:05

* But it is invasive, right? It's an endoscope that requires an invasive procedure.

17:14

* Procedure requires some sedation. So we also have been using MRI, which obviously does not require sedation.

17:18

* This is a procedure where you use, magnetic resonance imaging together with what's called an MRCP just to pick up the ductile structures.

17:26

* Again, where you can now start to delineate the anatomy and try to find where the pancreatic duct is sitting where the pancreas is sitting and then identify small tumors.

17:34

* So we've been doing this for a little while, but the efficacy of it was not really that well understood.

17:44

* And so this is a relatively recent article. That has started to show along with a couple others actually that there may be benefit to doing surveillance among individuals who have high risk.

17:50

* Because of genetic mutations or familiar risk. This is called the CAPS protocol. And 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.

18:02

* I mean this was a study that looked at around 1,700 individuals. 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.

18:10

* Could you find early cancers? This is not a randomized study. It's really a sort of surveillance follow-up study where each of the institutions followed a similar surveillance program.

18:30

* And I think what you can see here in the box is that yes, there were cancers that were found.

18:42

* There were 26 actually pancreatic cancers. And stage one and 2, like we talked about are really the stages where cure can be possible, mine where we have the ability to do surgery, chemotherapy, and try to remove the tumor.

18:47

* And 3 quarters of the patients who were, sort of faithful to the screening program doing this every other year approach.

19:01

* We're found with early stage cancer. And you can contrast that to what we talked about before where that really sits more at 15 to 20% in the population.

19:09

* And then there were a set of individuals who sort of fell out of surveillance for whatever reason.

19:19

* They stopped coming. It's actually not as you might suspect the easiest thing. To stay in surveillance when you have to do these types of procedures once a year.

19:26

* It's easy over time for people to sort of say, I'm gonna stop doing this.

19:30

* But if that happened, 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.

19:38

* And then if you looked at survival, there's 3 curves here on the Kaplan Meyer curve for survival.

19:52

* The top curve is actually where several patients that were found. To have a pre invasive lesions in the pancreas, sort of like DCIS of the breast or a polyp in the colon and those patients had those removed and those were almost universally cured, right?

19:58

* This is overall survival. They did not develop disease. They died from something else the individual passed away. So you could find 3 million, and those people could be cured.

20:15

* And then you could also with the blue line in the screen detected patients. Those are individuals who had a blue line in the screen detected patients.

20:25

* Those are individuals who had a blue line in the screen detected patients. Those are individuals who had early stage disease.

20:33

* The cure rate was much, much higher and patients did much much better than those here in the red line.

20:34

* Who, who had their cancers diagnosed outside of surveillance? So the 5 year survival rate among those who had prema ligna lesions was a hundred percent.

20:40

* For those who had the screen detected cancers, which are mostly stage one and 2. Is almost 3 quarters and unfortunately like we usually see in regular practice no patients were alive at 5 years if they had their cancer diagnosed outside of screening.

20:50

* So there's now, they're now probably 2 or 3 studies like this that start to suggest.

21:05

* If you can look in a high risk population and use some imaging tests that we have available even now, we can push.

21:10

* The staging to earlier stage disease and potentially find disease early. Okay, the problem though as we mentioned is 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.

21:18

* Because of this and a couple other studies, germline testing is now recommended. So looking for inherited mutations in every patient who's diagnosed with pancreatic cancer.

21:32

* That obviously doesn't help that patient. Right have the disease found early they've already you know developed the cancer but what we now do is what's called cascade testing, whereas all of the first degree family members, if the pro band, the person with cancer is found to have a mutation.

21:43

* All of those family members are then offered germline testing. And if they have the mutation, they then end the type of screening program that we just described.

21:56

* With the hope that this will then allow us to start to find more and more individuals who should undergo screening.

22:09

* The other, and I'm not gonna spend much time on this, but the other. Place, the other population where we will do some screening or surveillance is among those that have cystic lesions of the pancreas.

22:16

* Again, these are mostly asymptomatic and they're not things that we would know about unless people had scans for another reason for the most part.

22:25

* There's a lot this paper if you're more in if you're interested there are a number of different guidelines around how to manage system lesions in the pancreas just quite complicated.

22:36

* This is a European set of guidelines. Really to highlight there are a number of different kinds of SIS.

22:46

* They're not all the same. But the one that you most often hear about is an IPMN, which is an introductory papillary mucinous neoplasm.

22:51

* The most important thing about IPMS is they themselves are not invasive, right? They're not an invasive tumor that will spread to other areas of the body.

23:00

* However, they have the ability to transform to become an invasive cancer. And that's really the important piece is how do we manage these either by follow-up or ultimately by surgical removal to prevent cancer from ever developing, meaning invasive cancer.

23:08

* And so you can see among, again, a number of different guidelines that exist. You either end up in, you don't need follow up or you should get MRIs and US is just like actually what we talked about with the familial risk.

23:24

* Or you should go to surgery. And again, this is an opportunity. And a window for us to try to find people who should have a pre-molignant lesion removed.

23:38

* Again, very much like what a colonoscopy does in colon cancer. These lesions are related to about 10% again as we talked about at the beginning of pancreatic cancers and many people don't.

23:48

* No, they have them, but again, it is another place where we can start to find this disease earlier and try to treat it more effectively.

24:00

* Alright, so if we then think, well, what happens in the other 75%, right? Why do these people get pancreatic cancer and what can we do to try to find the cancer earlier, which really is what we need to do in order to cure more patients.

24:08

* So there are a host of different features and Laura, I mentioned a couple of these in the sort of lead into this.

24:23

* That are related to pancreatic cancer risk and we'll sort of review them. I tend to put them in sort of larger categories that help us think through some of the biology of the risk factors.

24:30

* But among the initial set are demographics, right? So there are groups of individuals that we know are at higher risk of pancreatic cancer in the population.

24:41

* I think to start with 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.

24:50

* Colin cancer gets a lot of or colorectal cancer gets a lot of attention. For that, but pancreatic cancer is actually doing the same.

25:06

* But generally speaking still, it is a cancer that tends to be an older individuals. The median diagnosis is around the age of 70.

25:14

* 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.

25:22

* As we talked about, those are known risk factors for pancreatic cancer and they do tend to be enriched in the Ashkenazi Jewish population.

25:35

* And it tends if you look worldwide it tends to be more in Western culture cultures than Easter.

25:43

* In the US, if you look at populations within the United States, African-americans have the highest risk.

25:48

* And so you can see from the 2 figures here you can see again as the rate per 100,000 individuals by age.

25:51

* You can see that there's a substantial increase as you hit 45 to 50 and then a very steep increase that seems to mostly continue.

26:02

* As people age. Slightly higher in men than in women. That's the green versus the blue.

26:06

* Right, and then if you look at men and women by race ethnicity, again, black Americans tend to have higher risk.

26:18

* In both men and women compared to their counterparts of other races.

26:25

* So if we think beyond some of the demographics, what are some of the other risk factors that that predispose individuals to get this disease.

26:31

* Laura, I mentioned at the beginning that what I would sort of put into this category of altered metabolism.

26:41

* There are a number of features related to systemic metabolism, how we process nutrients, weight, exercise that are risk factors for pancreatic cancer, particularly obesity, physical inactivity is a little less consistent, but seems probably to be related.

26:46

* And then also diabetes. And if we start to think a little bit, well, what are the relative risks? Right?

26:57

* We talked to the beginning, part of the issue for some of the risk factors we do know. Is that the penitence, meaning the likelihood that they get the cancer, when they have this risk factor tends to be pretty low.

27:07

* So there's not really like a smoking and lung cancer relationship here. These are much more attenuated relative risks than you would see in a circumstance like that.

27:21

* So if you look at obesity and this is sort of long term obesity, what you can see is the relative risk is about one and a half to 2 fold.

27:30

* If you're in the obese range versus the healthy weight range. And if you have diabetes, again, this is now long term.

27:38

* So at least 5 years or longer, what you see is the relative risk is between 2 and 2 and a half.

27:42

* 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.

27:52

* Which we'll talk a little bit more about. So people, if you do a case control study and you look at the time of diagnosis, patients with pancreatic cancer will often be underweight in comparison to their counterparts without pancreatic cancer.

28:02

* And again, that's usually happening as you approach the time of diagnosis. Interestingly, diabetes does the same thing.

28:16

* And this is really a quite a unique feature of this kind of cancer. You don't see this really in any other cancer type.

28:20

* So that paper from. And the MD Anderson and Mayo Clinic group, I'm led by Cress Charity.

28:30

* And what he studied over a number of years and we've done some work in this area too is that yes diabetes over, you know, a decade or longer is clearly a risk factor for pancreatic cancer again with the relatives we talked about.

28:37

* But the other thing that occurs is the cancer itself, just like it causes. Weight loss also actually causes hypoglycemia.

28:50

* The exact mechanism of this is not totally clear. We have a number of studies going on trying to figure out why this is.

28:59

* Happening at the molecular level. But this, figure is showing, which is a, from a paper from, You can see on the y-axis is their mean fasting blood glucose.

29:06

* And on the x-axis is actually the time before the patient is diagnosed with pancreatic cancer here, time 0 is over here to the right.

29:19

* That's the blue, right, of the people who have who develop pancreatic cancer. And then the red are the people who don't develop pancreatic cancer.

29:28

* This is a matched. Case control design. And what you can see is that people with pancreatic cancer, particularly in the 2 to 3 years before they're diagnosed, start to develop hypoglycemia and the blood sugar rises.

29:34

* And this is not something you tend to see in patients without pancreatic cancer. And in fact, if you look at a population level in the United States, it's about half a percent of people who develop diabetes.

29:45

* After they turn 50 so older than the age of 50 who actually have pancreatic cancer as the cause of their diabetes.

30:04

* Right? And so lots of diabetes is for all the reasons we know, right, not related to cancer at all.

30:07

* But about one in 200 to one and 2 50. It's actually from an underlying pancreatic cancer that's just not been diagnosed yet.

30:13

* Because of this, there's some large studies going on now. And that's a combined effort between the endCI and NIDDK to try to study patients with new onset diabetes.

30:25

* Of older age to try to see whether we can use that as a potential population for screening. I mean, there's a number of studies going on and we've been involved in some of those too.

30:36

* But again, a very unique feature of pancreatic cancer that it actually causes diabetes in addition to diabetes being a risk factor.

30:47

* Yeah, please.

30:57

* Brian, can I see a quick question? This is Laura. I'm just on the figure that you showed.

30:58

* Is, is there any suggestion that at the time of the initial onset of hypoglycemia that the tumor was actually there but just not diagnosed yet or is it really that the the cancer is developing and growing within that 36?

31:00

* 30 to 36 months.

31:17

* Yeah, so it's a great question. So. One of the troubles we have with this disease is that We there are times that the cancer is there, but very hard to see.

31:19

* The pancreas is among the most difficult organs to image in the body. So scans have a hard time sometimes picking it up.

31:30

* We have Well, I would say Sresh Charlie did a really interesting study where they went back and tried to find scans from the time that people became hyperglycemic.

31:32

* And in some instances, they actually could see a small mass that was missed when the patient had the scan.

31:49

* But that they obviously had this scan for some reason, right? It wasn't for pancreatic cancer at that time because they didn't know they had pancreatic cancer.

31:55

* So it was a scan that was done incidentally. But yeah, sometimes you can. What we see though is that As the tumor is growing and the as it gets bigger, you're more likely to become hypoglycemic.

32:03

* So it does seem to be correlated with the size of the tumor. Which then obviously it has implications for diagnosis.

32:16

* 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.

32:25

* If you go back and look, that might have been missed. And then there's some been a couple of really interesting studies recently.

32:33

* Using machine learning and radiomics to try to look whether you can see. On CT scans.

32:36

* 18 months before someone was diagnosed, Are there differences in the pancreas that may not have conglomerated yet to make a visualized mass?

32:44

* And the answer to that is yes, there's actually been a couple of very high profile papers, including one recently in Nature Medicine that did this.

32:54

* And so I think that when they're getting hyperglycemic, the cancer is there.

33:03

* I'm not sure always will be able to see it, but if you did serial scans, I think you would because it will eventually show up.

33:08

* Is that answer, that what you were thinking about?

33:16

* Yeah, absolutely. That's fantastic. Thanks.

33:19

* Okay, yeah, I think it's very a very cool area. I'll show you a study that we did recently where we also were using CT scans.

33:21

* We collected from before diagnosis. 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.

33:24

* Alright. So another feature that we usually think about related to risk factors for pancreatic cancer are things that lead to inflammation and they can be sort of inflammation in the pancreas, they can be systemically, but really inflammation in the pancreas in particular.

33:42

* And it's interesting in a number of different mouse models of pancreatic cancer. This type of inflammatory insult is almost required in order to see the tumor develop.

33:59

* So there's clearly an interplay between inflammatory issues in the pancreas. And the development of the cancer.

34:08

* There's a few on this list here as we're sort of going through and talking about risk factors that are we think related to inflammation.

34:15

* One is cigarette smoking, 2 is heavy alcohol use, and then 3 is chronic pancreatitis, which is by definition a in chronic inflammatory condition of the pancreas.

34:23

* And again, these all have relative risk modest, but relative risk for pancreatic cancer, that are in sort of the one and a half to three-ish kind of range.

34:35

* For smoking, this is the range you tend to see for current smokers versus never smokers 2 to 2 and a half.

34:45

* Again, you smoke more, you smoke longer, the relative risk tends to be higher. I mean, it's been actually really interesting.

34:51

* We're in the middle of doing a study around this now. You don't when you sequence pancreatic cancers at the DNA level.

34:58

* You don't see mutational signatures of cigarette smoke, right? So they've been many studies that have shown in cancers like lung cancer or had a neck cancer, we have direct exposure of epithelium to the toxin, in this case the toxins in smoking, you get stereotype DNA mutations that develop that you can pick up when you sequence the tumor.

35:05

* In pancreatic cancer, we don't see that. So meaning that it does not seem to be a direct toxic effect of the carcinogens in the smoke on the DNA in the tumor.

35:27

* And so what we've been studying now is 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.

35:37

* And so we've been trying to figure out can we start to look at this by looking at pancreatic cancers in the lab both at the DNA level to figure out well what mutational spectra do they have and then also by looking at among smokers compared to non-smokers, what's the micro environment the tumors are living in?

35:48

* Is there more evidence of inflammatory insults around the tumors? So I think this is an interesting area where the reason smoking is related to pancreatic cancer is different than you might think for some other cancer types.

36:06

* And then alcohol and chronic pancreatitis, they these may work similarly. I think as folks likely know, people who drink a lot of alcohol do get pancreatitis.

36:19

* And so there may be something here that's linking those 2. And then chronic pancreatitis, which can happen from a number of different reasons.

36:28

* It can be stones in the pancreatic duct, it can be medications. Again, it can be heavy alcohol use.

36:35

* There's inherited forms of pancreatitis. These all are related to an increased risk of pancreatic cancer.

36:41

* I would say chronic pancreatitis also has this same interesting relationship that diabetes does.

36:49

* And obesity versus weight loss does. Which is that a tumor in the pancreas sometimes causes pancreatitis.

36:55

* So as you can sort of get a sense of reverse causation in studies of pancreatic cancers really important to think about.

37:02

* So if you look at people who've had a cue pancreatitis, they actually have a substantially higher risk of pancreatic cancer much more than 2 to 3.

37:05

* In the next 12 months. But that's because the cancer caused the pancreatitis. So what sometimes happens is pancreatitis can happen from blocking of the ducks that drain enzymes out of the pancreas into your small intestine, which is one of the main jobs that the pancreas does.

37:16

* The tumor will sometimes impede the flow of the enzymatic fluid out of the pancreas and when that happens they get pancreatitis.

37:34

* 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, and 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 that caused the pancreatitis.

37:40

* 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.

38:00

* Right, I see. Yeah.

38:12

* And I'm sorry, Brian, there's a question in the chat. How do you differentiate?

38:13

* This in terms of causal inference. Maybe you address that kind of already, but.

38:17

* Yeah, so I agree. It is important. I think at the end of the day some of this has been defined using model systems in the lab, right?

38:20

* And and then some of them have been you defined using human data. I would say one thing to go back to the diabetes one interesting piece and then I'll keep going is one of the ways we've been able to tell from human data that pancreatic cancers cause diabetes has been that when you remove the tumor, so patients that have a localized tumor They got diabetes

38:30

* in the year or 2 before their diagnosis. The diabetes actually goes away. Which is pretty cool, right?

38:54

* That's really strange. You wouldn't have thought that, right? You would have thought if it was all risk factor.

38:59

* That as the pancreas malfunctions, right, because the pancreas makes insulin.

39:07

* 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.

39:12

* 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, which is really telling you that there's almost like a parity of plastic syndrome.

39:16

* The tumor is actually causing dysfunction. Some of it's in the pancreas, some of it is actually peripherally that's causing the diabetes.

39:32

* And so by putting sort of different lines of evidence together, we've been able to determine that there is this sort of bimodal distribution where there's a risk that comes when you have diabetes for a long period and then a risk that comes right up against the time of diagnosis.

39:38

* And we've also done some studies where we've measured markers of insulin resistance and among individuals before diagnosis where we have blood samples and again we can see this you shaped.

39:51

* Curve, which again has supported the fact that it is again has this differing biology.

40:06

* Alright, so.

40:13

* And then I'd say the last big bucket here, right? So we talked about the demographics of the disease.

40:17

* We talked about some of the exposures that are risk factors for pancreatic cancer, right?

40:22

* Things that are inflammatory related like cigarette smoking, alcohol, things that seem to be metabolically related like physical activity, obesity.

40:27

* Some of these also fall, if you think about sort of comorbid conditions, again, diabetes, pancreatitis, cystic lesions we talked about at the beginning.

40:35

* So the other big bucket then really is is inheritance, right? So either strong family history.

40:41

* Or inherited mutations. And we talked a bit about some of the rare inherited mutations. Just to review this again from this study from Mayo Clinic and mostly the thing I wanted to point out is what are the actual relative risks, right?

40:51

* We talked about what the relative risks are for smoking and obesity. What are they for genetic mutations?

41:05

* And so you can see among these most of them are between 5 and 12 fold risk, right? CDN, CDK and 2 A is.

41:11

* One of the genes that has the highest risk for pancreatic cancer, that actually is a gene that leads to familial melanoma syndrome.

41:19

* So these patients get both melanoma and pancreatic cancer. I've had a number of patients in my clinic where I talk to them and they say, oh yeah, my dad in Melanoma, I had melanoma.

41:26

* And then when we do the genetic testing, they have one of these genetic mutations that predispose them also to the pancreatic cancer, which is why I'm seeing them.

41:36

* And then you can see a number of the mutations we think about, PRCA 2 is about a six-fold, ATM about a six-fold, P.

41:44

* 53 is the cause of leaf, And MLH one is the cause of Lynch syndrome, one of the genes that cause lynch syndrome.

41:52

* That have higher risks. And you can see BRC ones actually a little bit lower. 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.

41:59

* Actually these individuals had even a higher risk than was listed here. This is purely based only on mutation.

42:13

* Those studies actually required you have at least one family member with pancreatic cancer also. And so those patients we think had at least a tenfold risk of pancreatic cancer.

42:20

* 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.

42:31

* That really expands the population, right, because there's quite a number of people we now know of, PRC one and 2 mutations.

42:42

* Most of them do not have a family history of pancreatic cancer. And so whether they should also be undergoing pancreatic cancer screening is not that well-defined.

42:47

* And this is something that's now being studied to try to figure this out. Again, it may allow us to find more cancers early if we expand.

42:57

* The screening population, but certainly there's also then more complexities, right? We could cause more problems by doing them cause issues with the endoscopy where someone has a reaction to.

43:05

* To the sedation or we find some random finding an MRI that leads to, you know, having to do all this workup that turns out not to be cancer.

43:16

* So there are certainly drawbacks to expanding the screening population. And we're trying to look at how we would do that in a safe way.

43:21

* Alright. People often ask, do we know about common variance? And these are often identified in genome mind association studies or G.

43:34

* That people have. Pancratic cancer is again substantially less common than some of the other cancer types that cause a lot of mortality less common than some of the other cancer types that cause a lot of mortality.

43:43

* So it's been much harder to do these studies. Also these patients tend to not live long, right?

43:54

* So if you need to have banks specimens, banked blood samples, buffy coat, normal DNA has to come from somewhere to do these studies.

43:58

* It's not as easy to get those samples for patients with pancreatic cancer than say prostate cancer or breast cancer where there are now, you know, hundreds of these variants that have been identified.

44:07

* In pancreatic cancer, we have a couple dozen that have been identified through a series of genome might association studies that have been done over the years.

44:17

* These are actually worldwide studies. You really need studies from all over the world to do this. I'm in order to aggregate enough cases and controls and you can see that these studies that have led to the variance over here again have had a little over 10,000 cases and close to 20,000 controls.

44:25

* There's a study that's going on right now called PAN Scamp 4, which will more than double these numbers.

44:38

* I mean, those, samples are mostly sequenced. And you can see again, I think as an important point and as folks probably know from looking at these studies.

44:50

* 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.

45:00

* So any individual variant that you find is not going to allow us to screen, right, a particular group of individuals.

45:06

* However, what's now started to move forward in other diseases, maybe someday in pancreatic cancer.

45:13

* Is 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 of the score overall.

45:21

* I might say there also are some interesting genes on this list that have the variance nearby, right? These studies are not looking for a particular gene, right?

45:33

* They're looking for a polymorphism, but 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 which has been sort of an interesting in road to try to understand why some of these cancers may be developing.

45:38

* The one at the top actually has some of the best data and R 5 A 2 is actually a transcription factor that helps delineate self fate in the pancreas and there have been a number of really quite interesting studies that the gene dosage effect of NR 5 A 2 actually changes the self fate within the pancreas, particularly after an inflammatory insult.

46:01

* And so again, 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.

46:21

* Alright, so maybe to sum up some sort of thoughts from the risk factor aspect and then can maybe see if folks have other questions or thoughts.

46:30

* But what I would say a number of the factors we talked about and and Ed's done quite a bit of work along these lines really relate to overall sort of health and healthy lifestyles, whether it be obesity or smoking or alcohol use.

46:32

* Diabetes and there have been a number of studies that have suggested that if you an aggregate can have a population that has a healthier set of behaviors along these lines.

46:46

* That it does look like we would prevent some pancreatic cancer from developing, right? And it may not actually be a small percentage.

47:03

* There could be a substantial percentage. So this is important, right? It's hard to get people to change their lifestyle because of pancreatic cancer.

47:07

* It's a rare disease. But certainly as other public health interventions lead to healthier lifestyles, you would hope that we may also have an effect on pancreatic cancer.

47:15

* A second is that there are now a couple defined populations for which surveillance is considered appropriate and and actually now I would say considered a standard thing we should be doing.

47:26

* Although most places in the country still don't do this. So it usually means going into a major academic center.

47:36

* If you have a strong family history, or genetic risk to then do the screening. And these MRIs are complicated to read.

47:46

* You need somebody for who does the endoscopic ultrasound who really knows how to do this in the familiar risk population.

47:54

* There's some complexities in that population in particular. But if we can identify these individuals in the population, it does seem like we can stage shift.

48:00

* And again, back to that cup study where 3 quarters of patients when they underwent this screening at stage one or 2 disease, which we generally speaking only see in 15 to 20% of patients otherwise.

48:10

* So this really, I think, has led to some, some conviction that doing this type of screening can be useful.

48:23

* There's a lot of work going on now in pancreatic exists, which is I think really interesting.

48:30

* We don't do this work in my own group, but I think it's quite cool. And it really is trying to get it this issue that as we get more and more CTs and MRIs and things as a population, we will find more and more of these CIS.

48:34

* The vast, vast majority will never become cancer. But we know a subset will. So how do you figure out what that subset is?

48:48

* So you get rid of the SIS early. I mean, there's been some really interesting studies using cell free DNA from the cyst fluid.

48:51

* So aspirating the cyst. And looking for mutations that would signify invasive disease. And then using other markers within this is fluid and then a host of clinical factors too to try to make these decisions.

49:03

* Presumably that will be the more and more the future, right, as we understand how to restatify these CIS.

49:16

* 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.

49:21

* But the better we are at this, the more we can remove things that prevent people from getting pancreatic cancer in the first place, which would be an important thing.

49:28

* And then we talked about, about a number of different risk factors. For the disease.

49:37

* And one of the issues we've run into and we've done a number of studies around this and others have too is that individually none of these right are sufficient, right?

49:44

* You can't set up a program for pancreatic cancer screening. Around smoking like you do for lung cancer, right?

49:52

* The penitence is not high enough and you end up having very poor predictive values because the prevalence is so low.

49:57

* And even when you try to combine these, You don't really get to risk levels high enough, right?

50:03

* 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 and when you sort of play out the numbers for positive predictive value that's about what we need.

50:09

* You really can't get there either. So really what this has made us start thinking about is other ways to try to define risk, including some of the reverse causation and I'll show you some of that.

50:21

* In a second. But maybe I'll stop for one sec and see if there's any questions or Comments.

50:33

* Yeah, people have questions just raise your hand or just speak up. Specifically.

50:43

* Hi.

50:49

* Or just use it as an excuse to drink some water, but you guys go for it. Yeah.

50:50

* Good.

50:51

* I actually know a question. But. In regards to diabetes. So I know there is an uptick with the use of GLP one agonist, especially like with Gov.

50:52

* Do you think We'll see maybe like a decline. And pancreatic cancer as a result.

51:05

* Yeah.

51:14

* Potentially or do you think there is some unknown long term consequences of using these. Medication.

51:15

* Yeah, that's a great question. I don't know the exact answer. 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.

51:20

* Maybe we would see a reduction in incidents over time. 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.

51:38

* 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.

51:51

* And a lower rate. In fact, you know, the rate of pancreatic cancer has increased a lot in the past 10 to 20 years.

52:03

* And some of that has been thought to be due to obesity and diabetes, right? That is playing some role.

52:16

* Because smoking is going down. Right. And so we're seeing less lung cancer, but year over year, substantially more pancreatic cancer.

52:23

* So whatever it is, it's whatever benefit we're getting from a little less smoking is being outweighed by other features, maybe obesity and diabetes among.

52:27

* So it's a interesting question.

52:34

* Thank you. Caroline, you can go ahead and. I see.

52:41

* Yes, hi. Also, I'm in a cafe, so I apologize for the music in the background.

52:44

* But I thought it was so interestingly talking about this link between melanoma and increatic cancer.

52:49

* Do you think it would be? Worth it for people with melanoma to regularly be screened for this gene.

52:56

* That may lead to their system pancreatic cancer.

52:57

* Yeah, it's a great question. So You know, I think and I have to admit I'm not sort of studied that question at all myself.

53:05

* I think it would need to be based on what the prevalence of the gene mutation would be among all of the melanoma carrier, you know, all the folks who develop Melanoma in the US.

53:15

* So my understanding is it's a pretty small number of people with melanoma who have a CDK into a mutation.

53:25

* And so I think at the population level we would need to decide, you know, does that make sense?

53:33

* I think to your point though, of all of the genes on the list. That we talked about.

53:40

* All of them so far as we discussed have really required that there be a family member with pancreatic cancer to do screening.

53:46

* That is actually not been the case for CDC. A because the risk is so high. Even if there's not a family member, those patients have still undergone screening.

53:54

* And in fact, screening has been, if anything, a little less effective in that population because that disease seems to be more aggressive.

54:04

* 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, which is really disappointing and upsetting when that happens because you're trying to screen and you still don't find it.

54:13

* So I think your question is really interesting because I think that is a population that screening we would do.

54:29

* Even if there wasn't a family history of pancreatic cancer itself but i don't know the answer specifically because I haven't really looked at that directly related to melanoma alone.

54:37

* Melanoma is common.

54:47

* Thank you.

54:50

* Alright, so.

54:55

* One more.

54:57

* I was, oh sorry, sorry, go ahead.

54:58

* Okay.

55:02

* There's one more question in the chat. Thank you. I can read it out loud or Maria, if you want to speak up, has there been any surveillance on how 4 month therapy use could either lessen or increase the development of

55:03

* Yeah. There's been a little bit of work on that. You know, women have a slightly lower risk of pancreatic cancer than men.

55:14

* It may be some of the risk factors like smoking and other things may be more prevalent in men, particularly historically, but, but the data have been a little bit mixed in terms of hormone therapy, whether that may reduce or You've made that reduce the risk of pancreatic cancer.

55:20

* There's actually a instructor in, in my group, Anababak who's very interested in that question is in the process of actually doing an analysis around those ideas in the Harvard cohort studies where there's an older study that, Eva Shurnhammer did quite a long time ago.

55:42

* But that was with very small numbers of cases. And so that's now sort of an area that she's interested in, and so that's now sort of an area that she's interested in, again, particularly around some of these.

55:53

* Sex specific differences and incidents and trying to understand why some of that may be, I think is a very interesting question.

56:05

* Alright. Oh wait, hold on, I think I'm seeing one more. Oh, you're welcome.

56:15

* Okay, so let's keep going. Alright, so. The next thing I wanted to talk a bit about was.

56:22

* We've gotten quite interested lately in the idea that There are actually features that the cancer will present.

56:31

* 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.

56:40

* And so we've gotten interested in these in this. Idea over the past I'd say 5 Maybe 5 to 10 years, for a number of different reasons.

56:55

* One is this is the Yaki Center. This is where we one of the one of the sites we see patients at Dana Farber.

57:01

* And so when you see these patients in clinic, patients with pancreatic cancer, they don't develop symptoms or issues the day before they're diagnosed.

57:12

* Alright, so often what they'll tell you is 9 months ago I had this that happened and 8 months ago I felt like this and 6 months this happened and what you realize is there are a lot of things happening, particularly in the one to 2 years before they're diagnosis.

57:23

* That are probably related to the cancer. But that those things weren't aggregated in a way that told the clinicians that they should look for pancreatic cancer.

57:39

* 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.

57:50

* And I think from our own work in that space and Suresh's work, I think what it shows you is again the hyperglycemia is happening at 2 to 3 years in some patients before they're diagnosed.

58:03

* 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.

58:18

* And then we've done a series of studies ourselves together with Matt Vander Hyden's lab.

58:28

* Matt is an oncologist at Dana Farber and, runs a lab at MIT. She's also the head of the Coke Center at the, at MIT.

58:33

* And so we've had a series of papers over about the past 10 years. Where we've gone back and forth between people and mouse models and shown that there again are a lot of changes happening in both before cancer is diagnosed and that this may provide a window for diagnosis.

58:41

* Early. And really what I'll show you is where this ends up going. Is the idea that we could combine some of these features together with risk factors in sort of higher order models to allow us to pull people out of the general population and I'll show you a manuscript we published recently around these ideas.

59:00

* So if you think then about pancreatic cancer risk, yes, there are risk factors. And then there are a bunch of cancer associated features.

59:20

* And as you start to aggregate these things together, you realize there are quite a number of these features that are occurring in the one to 2 years before diagnosis.

59:26

* These can be symptoms, right? Things that people are telling you. But again, people often have abdominal discomfort from pancreatic cancer.

59:35

* That doesn't happen the day before they're diagnosed. That can happen many months before. They can actually have issues with their diet, including changes in their food preferences, malabsorption, because one of the jobs of the pancreas is to make enzymes to absorb food.

59:42

* Again, we talked about new diagnosis like diabetes. It's also the cancer that really has among the highest rate of Venus thromboembolic events like Venus, the leg being the most common.

59:56

* I'll show you a study we did that some of this you can aggregate into changes in medicines that people take and that actually has predictive ability.

1:00:09

* Lab changes, imaging features. So really there's a wealth of information, particularly as medical records have become digitized.

1:00:17

* And we're putting all of this stuff into the medical record. There's really a lot of information here that maybe allow us to take what we learned and talked about over here.

1:00:25

* And added together to come up with a way to find people at risk. So we did a couple of proof of principal studies around some of these ideas.

1:00:35

* I thought I'd just show you a couple. This one was done by Ian Zhang, who's, a PhD student working with Ed now, who actually worked a bit with us prior to starting his PhD.

1:00:43

* 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 medical record and one of the things that has become very structured in the medical record as medications.

1:00:53

* Right, whenever we write medications now, they took away our prescription paths, right? When I started, I would just scribble something on a prescription bed and hand it to the patient.

1:01:06

* And then a bunch of years now they like forcefully removed it from my hand and wouldn't let me use that anymore.

1:01:14

* And so now in order for me to write a medicine, I can only type it in the medical record, right?

1:01:19

* So every medicine goes into the medical record. The dose is known the day it starts is known, the day gets refilled is known.

1:01:24

* So there's really a lot of information. So we decided we would do a proof of concept study using a couple of the Harvard cohort studies and the nurse's health study and health professionals follow study where some medication data has been collected and in some instances that medication data can be collected every 2 years.

1:01:29

* And you could actually ask. Over each 2 year period over time, what change did people make in their medicines?

1:01:50

* And so if you ask and say the questionnaire started here and then 2 years later, 4 years later, 6 years later, and then they got their cancer diagnosis here, time 0.

1:01:52

* What happens if we went back to the last questionnaire? That they had before their cancer was diagnosed.

1:02:08

* And the one before that. Right, so on average, that's about a year before their cancer is diagnosed.

1:02:15

* And 3 years before their cancer is diagnosed and then ask what changed. Right, what medications did they take differently, either starting a new medicine or stopping a medicine?

1:02:20

* And we went in with a few hypotheses about what medicines we thought people would start and stop.

1:02:30

* And then what you did is ask, well, could this predict risk of pancreatic cancer in the next 2 years.

1:02:36

* After you see what medicines they changed. And the answer was yes, and I'm just gonna present you one, you know, one figure from this, but in particular, as we just talked about, if you newly started diabetic medicines, medicines for diabetes, particularly insulin since the diabetes that people get related to pancreatic cancer in a year or 2 before is often rapid.

1:02:43

* meaning their sugar goes up very quickly. Much more so than often you see sort of in standard run to the mill diabetes and they get more hyperglycemic.

1:03:05

* So it becomes harder to control and these patients more commonly end up on insulin. So starting of insulin was one, although any diabetes medicine actually predicted risk.

1:03:14

* Anticoagulants like we just talked about these patients are at risk for clots and sometimes the clot actually precedes their diagnosis of cancer.

1:03:24

* 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 because those are often in place because they were somewhat overweight.

1:03:33

* Which raised their blood pressure. And you could start to make a matrix of medication change and say, well, if they start this one and stop this one or what if they start and stop both of these and you can start to see that this actually predicts risk.

1:03:41

* In an unadjusted sense if they had a couple of these different changes upwards of 5 fold.

1:03:58

* And if you adjust for some of the other risk factors, we already know more like threefold. But this started to clue us in.

1:04:03

* Again, that there's a lot of latent data in the medical record that could be useful in predicting risk.

1:04:10

* That's not causation, right? It's not that the antiquated medicine is causing their cancer.

1:04:16

* It's an effect, right? It's the reverse causation and that that may be useful. Then we did another study.

1:04:21

* In this one we were looking actually at CT scans. This goes back a little bit to Laura L's question, where we were actually taking CT scans from people before their time of their pancreatic cancer diagnosis actually was a similar design to how Suresh Chari did.

1:04:27

* One of the studies that I mentioned. And this is actually a study we did together with Michael Rosenthal, who's a study we did together with Michael Rosenthal, who's a radiologist.

1:04:46

* At the Brigham and Dana Farber. And also a computer scientist. And so what we did is we made, AI algorithms, machine learning algorithms, to take a CT scan and be able to, in an automated manner, segment all the organs in the ab, right?

1:04:53

* Not all, many of the organs in the. So for example, The yellow is the liver.

1:05:09

* So ground truth means we had a radiologist go through and segment it, meaning they went through the images and pixel by pixel on the images said, liver, liver, liver, this is liver, right?

1:05:16

* And that's colored yellow. And then we trained the computer to basically do that. And then what you can see is the prediction is what the computer says is liver.

1:05:26

* And the ground truth is what the person initially said was liver. And then we went through and systematically did this for a lot of different, markets.

1:05:36

* Liver, spleen, pancreas, kidneys. And some others. And so what you could start to do with that information was start to ask well what's the distribution of these organs in the general population and then what happens in the time before someone is diagnosed with pancreatic cancer.

1:05:44

* So in this paper, what we did was actually skeletal muscle. We quantified skeletal muscle on the CT and also fat, so adipose tissue.

1:06:04

* And this was based on some of the work we had done with Matt Vander Hunt's lab in the past where what we had seen both in mouse models and some preliminary data in people is that it seemed like 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.

1:06:13

* 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 if you were a particular age, a particular sex or a particular race.

1:06:32

* And then together with Anababic I mentioned before, looked at CT scans from before diagnosis and patients with pancreatic cancer and match controls who do not get pancreatic cancer.

1:06:49

* And what we could show is that as you get closer to the time of your pancreatic cancer diagnosis, which is this direction.

1:06:59

* You see that the skeletal muscle, this is showing muscle that we see somewhat similar things with, adipose tissue.

1:07:07

* That the amount of skeletal muscle goes down. And what we can show is that, again, there are these differences happening in patients before their cancer is diagnosed that are actually detectable either by seeing say patterns and medication use.

1:07:14

* Or patterns on CT scans and that these may be useful. And that then takes us to sort of some of the next steps.

1:07:30

* So one of these is now to use the electronic medical record. And machine learning models that tries to take into account all this information, right?

1:07:37

* Feeding this different information to then predict who's going to get risk of pancreatic cancer.

1:07:47

* In the first paper doing this that we published was last year together with chisander who's at Dana Farber in Harvard medical school and Sauron Brun who's in Denmark.

1:07:49

* And we started out somewhat simpler. This was a just using ICD codes from the medical record.

1:08:04

* So as folks who are more clinical may know every time we see a patient in clinic, you have to bill for the visit, right?

1:08:11

* So you have to say you did XY, and Z and that's why the insurance company should give you a hundred bucks for whatever you just did.

1:08:17

* So to do that, you have to put a code, which is a international, disease code, ICD code.

1:08:25

* That says what the diagnosis were that you were treating. And so it turns out you have millions and millions of these codes sitting behind the medical record for all of the visits that people have had.

1:08:32

* And that this ICD code structure as it gets changed over time has become more and more complicated. And so there are now tens of thousands of different codes.

1:08:45

* So 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 for pancreatic cancer in different time frames and we chose a number of different time frames.

1:08:54

* I'm a what I would say is this, to a degree actually worked. In fact, work better than I think we suspected that there is now just a tremendous amount of information in the medical record.

1:09:12

* And you can start to leverage this. Ideally where we would like to go for early detection, right?

1:09:24

* You pick out again an individual who's at risk for the disease in the next year or 2 years.

1:09:30

* That relative risk is high enough that it justifies doing an MRI or an which is where this is heading in the follow up studies that we're working on now are trying to incorporate lots of other types of information.

1:09:36

* This was sort of the initial proof of principle with ICD codes, but now using lab tests and medications and blood.

1:09:49

* I just said that test blood tests, imaging, other things, to try to help us put this together.

1:09:57

* Then the last part to this I just wanted to say. Is you can also think about this beyond a single disease, right, beyond pancreatic cancer only.

1:10:03

* And so we got interested in the idea that weight loss can be seen in other cancer types, not just pancreatic cancer.

1:10:12

* And could you use this as a way to again pull people out of the population who should undergo some sort of cancer screening.

1:10:20

* I mean, this was a study that Charlie Wong also worked with and also now works with us as a post-doc did that was just published recently if you're interested in reading more where she used weight change again in the nurse's health study and health professionals follow up study to actually predict risk of cancer in the next year.

1:10:21

* It's not causation, right? It's not causing the cancer. It is a consequence of the cancer.

1:10:48

* But it turns out there are some cancers that do this and many cancers that don't. And 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 that a further evaluation should be done.

1:10:53

* And she explores a number of ways to try to do that in the management. Alright, why don't I stop again for a second?

1:11:08

* See if folks have questions and then I don't think there's too much more time left. I may have to go quick through the rest.

1:11:17

* If you remind me how long this goes.

1:11:23

* Yeah, it goes until 3 30. So you have 18 min.

1:11:25

* Okay, all right, not much. Other questions folks have or anything we should discuss before I'll quickly go through the rest

1:11:28

* I have a good question. Oh, sorry. Go ahead, Jen.

1:11:37

* Hi. Okay, thank you. I want to ask that could medication and behavioral risks such as smoking or weight change and obesity, increase the expression of the mutated.

1:11:38

* So let me just see if I understand. So you're asking. People who smoke or, are the mutations in the tumor different or do they synergize with inherited mutations to cause the cancer?

1:11:52

* Or neither if I didn't get it right. And either one of us. Okay.

1:12:05

* Yeah, like in inherited things because like, obesity actually puts our body in a low rate inflammatory state.

1:12:06

* So that could I alter the micro environment and alternative gene expressions.

1:12:14

* So yes, so there's been some really interesting work. Mostly in mice that have tried to understand why obesity is a risk factor, molecularly for pancreatic cancer.

1:12:21

* And one of the most interesting studies show that there's actually interactions between the epithelial cells, the acider cells that make the enzymes.

1:12:35

* In the hormone producing cells. Alpha beta cells in the pancreas. And obesity changes the communication.

1:12:45

* 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.

1:12:55

* So, yes, I would say you're, I would totally agree with you that. Obesity is working by some mechanism, right?

1:13:13

* It is doing something within the pancreas that's causing this and that you can decide for that at the molecular level.

1:13:20

* Thank you.

1:13:28

* Hey there, are you just had a quick question about the, the slide that you're just on about the predictive modeling or booking.

1:13:31

* Do you know if the top of your head what algorithm seem to predict. The best

1:13:38

* Yeah, so. We used actually a number of different machine learning models. Which you can go to the paper to see this specifics.

1:13:45

* You know, ultimately I think, we needed a, we needed models that took into account time series.

1:13:48

* So I think one of the advances of that paper and I'm not a computer scientist, so this wasn't me and my specific insights, but I think one of the advances of that paper was that it wasn't just the ICD codes you had.

1:14:03

* It was actually the order in which you had them and the timing in which they related to one another. And so 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.

1:14:18

* And Laura, I mentioned this actually in her question at the beginning, which we had a study a few years ago.

1:14:35

* 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.

1:14:41

* 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.

1:14:48

* And we can see that in these models because you can see that some of these factors are going together within the model to increase risk.

1:15:01

* So, but certainly if you have, you know, more interest in the actual models, the paper goes into quite a lot of detail describing the different models that were used.

1:15:11

* Cool, super interesting. Thank you.

1:15:20

* Yeah. Alright. So let's see, we made it through the first bullet point. That wasn't very good.

1:15:23

* Prediction of timing on my part. So let's let's go relatively quickly through the rest.

1:15:27

* Alright, so I'm gonna skip that. Let's skip some of this stuff.

1:15:36

* Let's talk a little bit more about this. Cause I think this is relevant to what we talked about.

1:15:42

* So again, there are a number of symptoms that people get from this disease. We talked about a number of these because now we're really thinking about how to leverage them for earlier diagnosis.

1:15:46

* These are things like weight loss, early satiety where people can't eat as much at one time.

1:15:56

* They can get nausea or vomiting or upset of their bowels. One of the things we've been studying a lot is how pancreatic enzyme secretion, which is what breaks down the food in your bowel, goes down in patients who have an early tumor.

1:15:58

* And this is now something we're leveraging to try to again try to find these tumors early.

1:16:15

* But there are these symptoms that can occur. Anyone individually may not tell you there's a cancer, but as you start to think about biologically how they go together, I think can be useful.

1:16:20

* Signs means what the doctor can see, right, when they. When they examine the patient.

1:16:31

* These are usually later. Stage stuff, right? So once you can feel, say, a It's not usually a good sign, right?

1:16:40

* These are usually things that are a bit later in terms of the development of the cancer. I think more helpful is going to be some of the symptoms that we describe.

1:16:47

* And then these 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.

1:16:56

* I mean, ultimately you need a biopsy where you must buy up to either the tumor in the pancreas or the metastasis to define what's going on.

1:17:06

* And then you can stage these tumors, which we talked about, right? So there's more limited stage or stage one and 2.

1:17:14

* There's what's called locally advanced stage 3 and stage 4. They sort of fit into these 3 categories.

1:17:17

* Which we mentioned at the beginning. And then we talked about this fact that there's so few. Right, who have localized disease at diagnosis that this really is something that we need to be working on, to change.

1:17:23

* And not only do 80% present with advanced disease. Alright, either metastatic or locally advanced, but among those 80% the median survival is quite short, right?

1:17:39

* So it's less than a year. I'm and again that goes back to what we talked about at the beginning that there aren't that many effective therapies.

1:17:51

* So again, it really highlights the need to find this disease earlier. Alright, so I'll just spend a couple of minutes then on how we manage the disease.

1:17:56

* 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.

1:18:01

* That you know, you are fortunate living in Boston. There are a lot of really good cancer centers in Boston and there's a lot of oncologists.

1:18:17

* And so really trying to spend some time either collaborating with an oncologist who treats the disease you're interested in.

1:18:25

* Or even spending some time in clinic, I think is important because it really helped you. Understand the disease you're trying to, do research on and also what patients go through.

1:18:32

* So I'm gonna skip this part. Let me do. Let's do this.

1:18:45

* Why don't we just talk about one patient just to give you a sense of that? And then I think we'll finish.

1:18:51

* So this was a gentleman who I took care of. It's a 53 year old guy.

1:18:56

* He had a couple of respectors like we talked about, he was overweight. Definitely smoked and drank a bit too much.

1:19:02

* And actually in one of those episodes when he was doing a little bit of that too much he actually fell and he broke his ankle.

1:19:10

* And when he went to go get surgery, orthopedic surgery to repair the ankle.

1:19:13

* They saw that his liver tests were abnormal. And he did not at that point have symptoms of a pancreatic cancer per se, but they notice that his liver tests were somewhat off.

1:19:21

* And because of that, they then did a scan to try to figure out, well, what's going on with his liver.

1:19:31

* They did an abdominal scan and they actually saw a mass in the pancreas. It was only in the pancreas.

1:19:33

* 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.

1:19:41

* And then he had the ultrasound we talked about to biopsy the mass. And that mass was add no carcinoma.

1:19:51

* And I know carcinoma is between 90 and 95% of pancreatic cancer.

1:19:57

* As you guys know, it's a histologic description of a gland forming tumor.

1:20:02

* We always do a special kind of CT scan for pancreatic cancer called a pancreas protocol CT.

1:20:06

* That's what helps us do surgical planning to make decisions. And I'll show you his scan in a second.

1:20:12

* But he had a 2 cm mass. In the pancreas. That's actually top level.

1:20:17

* Size for a T one tumor. Right. So the small tumor. But it abutted a couple of the veins that run near the pancreas.

1:20:23

* We had to put in a port, which is an IV that goes under your collarbone.

1:20:31

* It's semi permanent. It can come out, but it can also stay in for years if you need it.

1:20:35

* And we started him on. Chemotherapy right away. He got 2 months of chemotherapy.

1:20:40

* We shrunk the tumor and he went for surgery. 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.

1:20:45

* Economic center where they do hundreds of these a year, not a small place. And again, he fortunately had a small tumor.

1:20:54

* He had no lymph nodes that were positive. We gave him 4 more months of chemo because 2 months is really just not enough.

1:21:04

* To get rid of this. Disease with the hope that by doing this, we would cure him, right?

1:21:06

* So this is just what we see and it goes back again to some of the points we talked about. That this tumor is not easy to see.

1:21:16

* This is the tumor. Right here that I'm circling if you can, I hope you can see my pointer.

1:21:21

* I mean the yellow is the era. Right, and then this is the vein that it's up against, the superior Mesenteric vein is right here that's the bright.

1:21:24

* Sort of blob. And that's the tumor. That's what was biopsyed and shown to be cancer.

1:21:36

* This is something we see a lot of, which is that early on with early tumors, you see dilated pancreatic ducts, which is this dark stripe.

1:21:39

* In the middle of the pancreas, the rest of this sort of fish shape thing is the pancreas itself.

1:21:49

* This is part of what some of these machine learning algorithms are picking up is that you see this dilated doctor early on.

1:21:56

* And then just as comparison, this was the tumor again here. And then after we gave 2 months of chemotherapy, you can see it's largely gone, right?

1:22:03

* This is the stent. This circle thing that's propping up the bile duct. But you know longer see that tissue, that dark tissue here next to the vein.

1:22:12

* Okay. 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, unfortunately.

1:22:22

* And he developed a new lung nodule, in 2,018, so this is now 3 years.

1:22:26

* You have 3 years, we had no cancer. 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.

1:22:36

* And it wasn't, unfortunately, was his pancreatic cancer. We're able to wait another year actually before many new ones showed up.

1:22:44

* And then eventually had to give him chemotherapy and he was on chemotherapy for about a year, before he passed away.

1:22:52

* I mean, we didn't really talk about this much, but we now sequence the DNA in the tumor in every patient.

1:22:59

* We look for a number of different characteristics. And we did sequence to look if he had any inherited mutations because all patients should have that done.

1:23:05

* And just to give you a sense, this is a chess CT scan. Some of you are probably quite familiar with this, but this was his initial recurrence in 2,018.

1:23:12

* This is the recurrent lesion. All of the black is the normal lung.

1:23:20

* In the middle is the media style. And this is the, the great vessels in the Media Steinem.

1:23:26

* But this is the one we removed by surgery because we weren't entirely sure what it was.

1:23:32

* And then this a year later are the recurrences. This is another nodal in the long.

1:23:33

* This is another one here. And then eventually he had more and more. That grew and ultimately he passed away because the disease.

1:23:42

* Became refractory to chemotherapy. Alright, why don't I stop there?

1:23:50

* Maybe I'll just say again in summary and then try to have a couple of minutes, at least we can.

1:23:56

* Have other questions but. Tough disease, right? Third most common cause of death from cancer in the US.

1:24:02

* Really I think prevention and earlier detection are really important. Right to try to improve survival from this disease.

1:24:05

* It's hard, right? 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.

1:24:14

* We talked about risk factors including smoking, obesity. Obesity, diabetes, pancreatitis.

1:24:25

* We talked about, and then family history. We did a little less discussion about treatment, just given time.

1:24:32

* 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.

1:24:39

* And then trying to treat it as it recurs. And then genetic testing is now recommended for all patients with pancreatic cancer for the reasons we describe.

1:24:47

* And then we didn't talk much about this today, but ultimately we do a lot of clinical trials at Dana Farber where we're testing new therapies or testing new detection approaches.

1:24:57

* We have a new trial we just open for patients that have familial risk. Trying to use these new multi-cancer early detection tests with sulfur DNA to try to see if we could do better by using that in addition to scans.

1:25:08

* And ultimately it's really only by doing these trials, right, by trying new things and having sort of patients be willing to try those things with us that we make progress.

1:25:22

* So. I don't know, I stop and I'll stop sharing and thanks for everyone's attention.

1:25:31

* Thank you. Let's open it up for any, comments from, our students.

1:25:38

* I have a question that, When it comes to understanding those pictures that or shown, the cities can.

1:25:46

* Are we supposed to as public health children? Are we supposed to understand them?

1:25:56

* 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 that I would.

1:26:01

* Expect if you have no medical training that you're supposed to be able to read a CT.

1:26:11

* Okay, thank you.

1:26:16

* Right, I wonder just in terms of the descriptive epidemiology, and looking sort of where pancreatic cancer has been rising.

1:26:20

* It feels like it's popping up even more so in women than men, even though men still are at greater risk.

1:26:26

* I wonder what your general thoughts are in terms of. Is that a real thing? Our pancreatic cancer is also vulnerable to sort of this earlier onset that we're seeing for other GI cancers, but just if you talk a little bit about the genetic epidemiology.

1:26:35

* And what you see in clinic too.

1:26:47

* Yeah, so it definitely does seem like pancreatic cancer is increasing in young people. You know, in some ways not too dissimilar from colorectal cancer, although the prevalence of pancreas is obviously lower.

1:26:54

* And that now has been shown in actually multiple studies in multiple countries that that is true. You're right that some of those data, not all, some have suggested that some of the increase in younger individuals is more in women than in men.

1:27:09

* You know, in clinic, actually I've been seeing that a lot. Lately. I would say over the past couple of years, I have now been pretty routinely seeing patients in their thirties and forties with pancreatic cancer, which I just I can't remember that 15 and 20 years ago.

1:27:30

* I mean, maybe I did, but I don't really remember that the way I'm seeing it now.

1:27:48

* I had I had a stretch a few months ago, right? I met 3 people in their thirties in 2 weeks.

1:27:53

* And that's just not normal. That's just not the way it used to be. So something is, I think, different, you know, in terms of what's happening.

1:28:00

* You know the ideology of that's not that clear right why exactly that is just like in colorectal cancer it hasn't been so clear either.

1:28:10

* I think we did have some work and others have shown this to that. There does seem to be. When you have these risk factors, they do seem to matter more in younger individuals than older.

1:28:17

* 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.

1:28:29

* Right, still the overall prevalence is much higher as you as you age. And we've actually been doing some work looking at this now trying to understand that by actually looking in tumors.

1:28:37

* And trying to see how age related mutation patterns differ. Compared to risk factors that you have.

1:28:48

* Because there are ways to find signatures in the tumor itself that tell you what's own was exposed to.

1:28:56

* And that's part of the problem is it can be hard to see in the tumor, you know, did the obesity as that really interesting question one of the students asked like, oh, how's that actually working?

1:29:02

* Right? Why is obesity related to risk? We can start to do this with some risk factors by understanding the tumor and trying to find signatures of what they were exposed to that led to that tumor to develop.

1:29:07

* 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.

1:29:27

* 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.

1:29:33

* Great. Thank you so much. Any other final comments or questions?

1:29:41

* Yeah.

1:29:47

* I got a final question. Doctor, do you think, or what do you think is the importance of the familiar pancreatic cancer syndrome?

1:29:48

* And surveillance. And high risk patients for pancreatic cancer screening.

1:29:54

* D the importance meaning should we do it or maybe tell me a little more what you mean.

1:30:01

* And more in terms of the number of patients, the, first, patients, or formulas that actually have the disease.

1:30:06

* For instance, we know that familiar. Cinder is more than 2. Should we, should we keep these number, this threshold number or probably, should we reduce it?

1:30:15

* Do you have a comment about that?

1:30:27

* Yeah, and when you say 2, you mean the number of relatives in the family. Just trying to make sure I answer your question.

1:30:30

* Yes, correct. Yes. Yes.

1:30:36

* I see. Huh. Okay. Yeah, so, you know, so far from the studies that have been done, it looks like people who have Just one first degree relative have a pretty modest increase in risk, a relative risk more around the 2 to 3 range.

1:30:38

* Which seems not to be sufficient to recommend screening. So right now, people have one first degree relative are not being recommended for surveillance.

1:30:53

* Unless they have a genetic mutation that they inherited. Right, so if they have one first of your relative that relative had a BRCA 2 mutation and they inherit that PRC 2 mutation, then the risk is much higher because the penitence is much higher when you have not just one family member.

1:31:02

* But you actually have a known genetic event that's predisposing the family to get the disease. So in that circumstance, we would recommend it.

1:31:18

* You're right. That in families that have multiple relatives. But don't have a known genetic mutation.

1:31:27

* 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.

1:31:35

* First degree relatives in the family with pancreatic cancer that all of the first degree relatives around them Get screened.

1:31:45

* And that's because the relative risk seems more like it's in the 5 to 6 range, which is higher.

1:31:52

* And seems more appropriate. However, there have been a couple studies that have shown If you look at people who have a genetic mutation in their family and you look at those who just have the familiar risk.

1:31:56

* The penitence is clearly lower among those that have 2 family members and no genetic mutation than those that have even one family member with a genetic mutation.

1:32:12

* And so there continues to be debate as I think you're alluding to. About whether we should be using family history alone.

1:32:22

* Without a genetic mutation. At this point we still do and those people still qualify for these.

1:32:29

* 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?

1:32:31

* At which surveillance would be appropriate. And then what are all the different ways you get to that level? Right, I don't really care, right?

1:32:48

* If it's these 2 things or these 4 things that get you to a risk level, great. If it's these one or 2, fine.

1:32:56

* But it's really trying to define risk in a way that can be clinically actionable. That's important.

1:33:02

* Well, thank you so much, Brian. This has been really amazing and, This is just, yeah, thank you again.

1:33:11

* Let's give Brian. Our, thanks and wish we could have been in person but great to see you.

1:33:18

* ExcellentThank you