SPEAKER 1: Well, thank you, Rocky. I want to do a little disclaimer here. After you heard those two other excellent talks that were really based upon a lot of data, in some cases millions of colonoscopies in other cases hundreds of thousands, when we talk about pancreatic cancer, we're talking about suggestions and recommendations that are based in the thousands of patients studied.

So it's really a totally different magnitude. This is not necessarily ready for prime time as you'll see from our approach but should be really limited to centers that study this. So that's a little disclaimer. Now how did I get in the business? Well, Rocky mentioned that I went to Nebraska after my fellowship at UC San Francisco. And that's where I met Henry Lynch. And Henry Lynch had all these families that were developing great cancer.

And the question was in the early 90's, what do you do for them? Do we just ignore them because we have no data? Or he is always very proactive with the hereditary predispositions. And he wanted to do surveillance. And so we started doing endoscopic ultrasound just based solely on at that time MRI really was not available for the abdomen. But based on the fact that you could pick up small neuroendocrine tumors.

So the thought was to pick them up as small as we can. This is an example of one of the most famous pancreatic cancer prone families that we have. And that's actually President Carter's family where both his father and all three of his siblings died of pancreatic cancer. And unlike other cancers, keep in mind, all these family members, we don't have big survivor benefits for pancreatic cancer.

So I'm going to give you a couple pedigrees and families just for you to keep in mind. Hopefully, by the end of this talk, you'll be able to answer how to manage them. Here's a family that came to see us right here. This was a woman that had melanoma, a couple cases here. I saw they live in actually Henry Lynch was taking care of them. And they were talking about getting screened. And then all of a sudden, we got this frantic call because they wanted to get everything taken care of with their business. And life insurance back like that in the 90's. And then there's this sister right here of our proban right now developed pancreatic cancer at 45.

And so how do we counsel this family? Do we recommend any gene testing? You saw they had both melanoma and pancreatic cancer. So keep that in mind during the talk here, and we'll elude to it. Is this family at increased risk for pancreatic cancer and should surveillance be performed on unaffected family members?

Here's another family, and this is a little bit more common in what we see were all these stars signify pancreatic cancer cases. And so how do you deal with this type of family where there's no obvious hereditary predisposition? So do we recommend any gene testing in this circumstance when there's no glaring thing like a melanoma pancreatic cancer?

Are these family members at increased risk for developing pancreatic cancer? And what recommendations, if any, should be made regarding prevention or surveillance strategies? So today, I'm just going to sort of hit on some background of pancreatic cancer, so you know where we're standing at. Try to define hereditary pancreatic cancer for you, go over some of the risk for developing cancer, and then give you right now what I think is the current status of pancreatic cancer surveillance in 2013.

So in the US in 2013, there's going to be over 45,000 patients diagnosed with pancreatic cancer. And the majority of these patients, unfortunately, will die of this disease. It's presently the fourth leading cause of cancer related mortality in the United States. With projections and because the decline in smoking, by 2020, if it keeps the current rates, it will become the second leading cause of cancer death in the United States.

Worldwide, it's also a problem. And keep in mind that this discussion is really sticking to adenome carcinomas which are responsible for about 90% of cancers. What do you have to keep in mind for pancreatic cancer is, and why do we have such a dismal prognosis? And, in part, that's because we find the majority of our patients when it's either regional, which means lymph nodes are involved, or distant and you can see survival rates, five year survival rates are dependent upon what stage you are found at.

So less than 10% of patients are found in the localized stage. But when it is contained within the pancreas and no negative, those people have a little bit better outcome. But, unfortunately, about half of these long term five year survivors will still die of disease.

There's known precursor lesions. So you heard a great talk about the importance of adenomas. So we know adenomas are precursor lesions for colon cancer. Well, we have those same type of precursor lesions in the pancreas. The majority of them about 85% go through what we call PanIN lesions, Pancreatic Intraepithelial Neoplasias.

And then the other two are mucinous cystic neoplasms or IPMN's, Intraductal Papillary Mucinous Neoplasms. And they're responsible for about 15%, maybe up to 20% of pancreatic cancers. This is just a schematic showing you the changes along the lining of the pancreatic duct where the ducts become more dysplastic. And by the time there a PanIN through that sort of carcinoma in situ. And corresponding to these changes in dysplasia, you would get more and more molecular defects.

In terms of cystic neoplasms, keep in mind that only about a small minority of pancreatic cysts are neoplastic. There's different types of cysts, sera cysts, mucinous cysts, and occasionally some rare solid pseudopapillary tumors in young women. And this just schematically gives you an idea of the different types of cysts. This is a microcysts which is totally benign and a pseudocyst which is in an inflammatory typically after an episode of pancreatitis.

And then we have a side branch IPMN. And this is the main pancreatic duct. And then we get what's a main duct IPMN. And sometimes you'll hear the term mixed side branch main duct when both there's dilation involvement in the main duct and the side branch.

And then we have a mucinous cystic neoplasim which we are solitary usually occur in the body and tail and often in women middle-aged. So in terms just to reinforce IPMN's because this is a precursor lesion that we'll discover in surveillance studies. And what our concern is that it arises and causes cystic dilation of the main pancreatic duct, and like I said, there's three variants.

There often within the head of the pancreas. And they can progress to invasive adenoma carcinoma. It's a whole other talk on cystic neoplasm. But in terms of what we're doing with them because they're overwhelming our health care system with 600,000 cysts a year being diagnosed.

So how do you define hereditary pancreatic cancer? Well, there's two different scenarios. The first one is to recognize genetic syndrome such as hereditary breast, ovarian cancer with a known germline mutation, so we know it's caused by BRCA1 or 2 mutation that has an increased risk for developing pancreatic cancer. And we'll go through the syndromes associated with that.

The other one is what we call familial pancreatic cancer. And that has defined as having at least two cases of pancreatic cancer with at least one directly connected so either parent, child, or siblings. It could be more cases as you saw in my pedigree. So 5% to 10% of pancreatic cancer cases are related to hereditary factors. And this has been shown from a study from Louisiana. And if you could see there's an increased risk of developing pancreatic cancer from having a history of any cancer in your family. And that makes sense. And the more we learn from the sequencing of tumors that there does appear to be common genetic mutations throughout it.

And these are just the ones that are known. There are probably a lot of them that are yet to have the right correct environmental hits. But so clearly if you have a family history of pancreatic cancer, your risk is even greater. And this was confirmed in Montreal. We've looked at our own registry here, we find that about 5% of our pancreatic cancer cases have a first degree relative. So similar to what other centers have seen. And about 8% of ours have at least a first or second degree relative.

This is just a list of syndromes that are associated with an increased risk of pancreatic cancer. You can see here familiarly typical multiple mole melanoma, which is caused by P16 germline mutation. So if you have cases of melanoma usually often multiple cases at a younger age, there is a substantial risk of pancreatic cancer. And I'll show you that. [INAUDIBLE] keep in mind case number one.

And then we talked about familial breast ovarian cancer, there's a PALB2 mutation which is a gene involved with fanconi anemia, FAP, hereditary pancreatitis, and cystic fibrosis has a mild to modest increased risk.

Ataxia-telangiectasia is an autosomal recessive condition. And so it's fairly rare. And that was found to be associated with an increased risk of pancreatic cancer. As you'll see, and I'll just briefly allude to, we now know that if you just carry one of those genes, remember with an autosomal recessive condition, you need to have copies from both parents for it to really express itself.

But it has recently been reported by Hopkins that just carrying a mutation in an ATM gene itself does increase your risk of developing seems to predispose to getting familial pancreatic cancer. I should say. It doesn't have much to do with sporadic pancreatic cancer and non-familial.

And then there's this famous Family X that Terri Brentnall studies in the University of Washington, which Dr. Whitcomb and their group collaborated on to report that there was a mutation in Paladin. This does not seem to be a major factor in most of our familial pancreatic cancer cases. We know about the mutations responsible for about 15% with these known syndromes. So the majority of the familial pancreatic cancer patients, we do not know the gene responsible.

So what is the risk when you have a known germline mutation, or if you have three or more family members, two or more family members, or what about early age onset pancreatic cancer? So here's a list, again, of the syndromes. And you can see it ranges depending on what your mutation is. And actually if you look at registries of familial breast and ovarian cancer patients for example, the risk for any BRCA1 or 2 mutation carrier is actually less than five-fold.

We're in the process of writing up our data here where if though you select out patients that have a family history, a case of pancreatic cancer in this and is a known mutation carrier, that that risk is actually 20 fold if they are a first degree relative and 15 fold if they are a second degree relative.

And you'll see that type of information is reflected in our recommendations. So here's that family again with multiple cases of pancreatic cancer, what's the risk for these individuals? Well, it depends where they fall in the pedigree. But if you have three or more first degree relatives, your risk can be as high as 17-fold. Now, keep in mind, this is all in the setting of familial pancreatic cancer where they met that definition of two first degree relatives and they followed this registry.

This is from Hopkins Group. One first degree relative and two first degree relatives are about the same. They all admit familial pancreatic cancer. So that's probably like having a father and a grandfather, you know the children are potentially at same risk as having a father and a brother who had pancreatic cancer.

So I think first and second degree relatives, two first degree and one first degree relatives are about the same. If you have pancreatic cancer at a little younger age, there seems to be at greater risk. And the same with if you smoke.

So if we don't see a recognized syndrome when we counsel these patients, and they just present with an excessive number of cases of pancreatic cancer, what is the chance of finding a mutation? So if you have two first degree relatives or more than two first degree relatives, there is a slight increase chance of finding a mutation.

These are patients who have been affected with pancreatic cancer that are being tested. So remember, this is not an unaffected member. And you can see with the BRCA2 seems to cause many of these cases without even having breast or ovarian cancer cases in them. Pancreatic cancer is about the third most common cancer in hereditary breast ovarian cancer situations.

Lynch syndrome is rare or less than 1%. PALB2, which is also gives you excess cases of breast cancer, it's about 3%. And then that ataxia-telangiectasia gene mutation that I mentioned is responsible for about 3% to 4%.

So there's really no current guidelines available for genetic testing in hereditary pancreatic cancer candidates. I can tell you I sit on the ACG guideline committee. And we're in the process of updating our genetic testing and surveillance guidelines or actually creating them for it. And we're going to have gastric cancer, pancreatic cancer, along with a lot of the colon cancer and polyposis syndromes.

And so right now what I would recommend when you do is you review the pedigree, and this is what we do when patients come in, they're seen with a genetic counselor. If melanoma is present, we consider testing for FAM. We look for, see if they meet Amsterdam criteria, which has to do with Lynch Syndrome. We look to see if they meet hereditary breast ovarian cancer guidelines.

And then keep in mind the yield for testing increases with the number of first degree relatives. And there's now the availability of panels out there now that the cost has gone down. We were participating in a multi-center trial trying to better determine the yield of these panels. So I don't have those numbers now. At times, we may order them if they are covered by their insurance policy from case to case basis and their anxiety after we counsel them. But I certainly wouldn't recommend it for any pancreatic cancer case out there.

So who should be screened for pancreatic cancer? So let's first of all understand what we mean by screening. So screenings is testing in the study of an asymptomatic general population. So we've heard great examples in the earlier talks today about colonoscopy in that setting.

Surveillance is testing in an asymptomatic high risk individual. And many of the studies that you see about for yields for detecting pancreatic cancer is done in a diagnostic setting where these patients come in with symptoms. So to make it analogous to colon would be if they came in with either an iron deficiency or anemia or change in bowl habits or blood, you're not done screening at that point or surveillance, you're doing a diagnostic test to work it out.

So can we screen the general population for pancreatic cancer? I got in this 90's, I was naive. In retrospect, it looks like if you just sat down and calculated this out, we would see that it's impossible to screen for the general population for pancreatic cancer. It's too rare. The age adjusted incident rate in the United States is about 12 per 100,000. There's about a 1.4% lifetime risk of dying of pancreatic cancer. If you had an incredible performing biomarker with a 100% sensitivity and 99% specificity, you'd be able to detect all 12 pancreatic cancer cases. But at the same time, you'd be working up over 100,000 false positives studies. That's about a 1% positive predictive value.

So it's not feasible to screen the population. You have to enrich it. So what happens if we enriched tenfold? And we make the age rate, adjusted incident rate about 120 per 100,000, and we apply that same biomarker, at least there we're getting to about a positive predictive value of about 12%. And so no one knows that correct number. I leave it to smarter individuals than myself to try to model it out.

But most people would say at least a 10% rate, they use that often for genetic testing to apply a study. So I think it is if you enrich the population that it is worthwhile. And so really what we use to enrich it is these hereditary cases. That's the only one case right now that we have. There are people looking into new onset diabetics over the age of 50. And there are other areas there right now. But they still need a little bit more work before we're ready to at least apply it in a more clinical setting like we do now for these hereditary cases.

So how should someone be screened for pancreatic cancer? So just to show you that my numbers weren't totally off base. The Koreans back in 2004 invested in studying for six years, 71,000 patients. And they did C199 which is a marker you're all familiar with. And they use a cut off of greater than 37. And guess what? They had a substantial number of patients that became positive. But they're positive predictive value was only 0.9% in that study.

So one out of 100 patients that were positive for that test ended up having pancreatic cancer. So that was very predictable if you think about it. The other issue that we have to deal about particularly pancreatic cancer since we know it's so difficult to find it at a stage that we can cure or see is this issue of lead time bias.

So if you diagnose a patient at the age 65 and they die at 67, they live two years with the disease. Now I say I want to come and do surveillance on them. And I diagnose them at 62. But they still die at 67. Did I really make a difference in their life? No. But if they died at 85, then I think you could start feeling comfortable that you did. So this is something very hard to deal with in terms of if you made a difference or not. But I just have to be in full disclosure point this out as we look for earlier stage disease.

I don't think there's anything set call regarding the indolent pancreatic cancer. If you have that unlike prostate cancer, you can feel quite confident in treating it. So what can we do? So Mimi Canto first, Terri Brentnall first reported doing screening mainly based with ERCP and then she tried EUS. And then Mimi Canto sort of compared them both with CT scans. And this was her first cap study. And what she found was that 10% of patients in this setting had IPMN's. And one of those actually a carcinoma in situ.

So they studied a lot of patients. And they found about 10%. In Europe, they found 44 individuals. They did a first time endoscopic ultrasound, and they actually found three pancreatic cancers. Makes you debate whether these were truly a symptomatic high risk individuals. But regardless, but two of them were stage 2B which would be regional. We already saw that that doesn't have as good an outcome.

So this really I have to full disclosure you know it's tough to say whether you made a difference. Seven of them had IPMN's. If you take all comers, and you pull everything together, and the most recent studies, and we're probably up to about 2,000 reported patients in the literature now. You can see that for high risk, which is defined as a PanIN3 lesion, which is carcinoma in situ, cancer, or pre-malignant cyst, such as an IPMN or an MCN that if you use surgery to validate it, there's about a 6% yield within endoscopic ultrasound or in some cases CT or MRI.

If you look at in terms of clinical diagnosis, where a lot of the centers say, well we saw a cyst. And when the cysts are small, it's often difficult to say whether they're mucinous or not mucinous. But when you took them all as being mucinous cysts then you may get that yield up to 13% for signing something. But the problem is when you take patients to surgery and you operate on them about up to 40% of the time, at least in our early experience, what we removed was benign.

So there's been only, to summarize this, there's about 1,500 high risk patients studied to date. About 49% are found to have abnormalities to be obtained by surgical proof. You can be up to 23% of the population, you have both clinical and surgical diagnoses. But keep in mind that some of these that we remove, that we don't do a great job with determining on these cystic lesions, or even these solid lesions they remove and they find out they were like splenic venules.

So I want to give you a little personal example of screening. And so this is a family that came to see me pretty soon after I came here. And actually this sister was the initial pro band. And she came in and said, look, I had my mother and two of my aunts died of pancreatic cancer, older age. I'm getting older age. I'm worried about dying of pancreatic cancer.

So I talked to her about surveillance. And as she was walking out the door, she said, you know my sister here who's had ovarian cancer and breast cancer, she was just diagnosed when they were following up her cancer with a cyst in her pancreas. And the doctor told her, don't worry about it, come back in a year or two. I said wait a second. More than you, I need to see your sister. And we ordered genetic testing and wasn't unable to find a BRCA mutation on her.

And she underwent an endoscopic ultrasound. And she had about a 2.6 centimeters cyst. I was concerned about it. At that time, we were still early on with the cystic things. But it was well over 2 centimeters. I know it doesn't meet the criteria everyone thinks about with 3 centimeters. So we suggested she get operated on. And she said, her daughter lived in Chicago, said no, I want her to move to Chicago. So she'll be closer for recovery. Because she was 81.

And she went to Chicago. There was a delay in her seeing it. I'd set her up there because I'd just moved from Chicago. So I set her up with a good pancreatic cancer surgeon. For a variety of reasons, she delayed. Six months later, they took her to the operating room. And they found that she had metastatic disease.

And so the third sister then, of course, seeing her other sister die, came rushing tests to see us. And this is the one I'm going to show you our experience with her. So we first scoped her, and she had a cyst. And you can see it's small cyst. It measured about 1 and 1/2 centimeters, not even over two centimeters.

Well, I just went through this other experience with the other sister here. So we had a conference about her. We had her go talk to the surgeons. She says, look, I do not want to be diabetic, run that risk. I don't want a major operation. You haven't shown that it's cancer. I said that's fine. We're going to have to follow you pretty closely here. Because I've already gotten burned once in your family.

So this is just a picture of the tail of her pancreas and everything looked fairly normal. The body of the pancreas at that time. And then about six months later, she developed this little thing by the splenic artery in a followup. And this is in the body of the pancreas now, not in the head where I showed you that cyst was. And we were debating about between doing a whipple, which a lot of centers just recect the part there versus a total pancreatectomy which can make you a brittle diabetic.

So this was six millimeters, seven millimeters in size. I stuck a needle into it. You can see, it may not show well with the lighting, but there's a needle tip going right in here with this. We got some atypical cells. So now I said, you've got that cystic lesion there. And you know she went and saw one of our surgeons. We're going to have to take out your whole pancreas. Says no, not unless you show me it's cancer. You know I don't know what this is.

I said all right. So three months later, I said I can't follow you endoscopic ultrasound all the time. So I'm going to do an MRI on you. And so they do an MRI, and they say, we see that cyst. But we don't see anything else and looking at the body and table. And then I take her back, and you can see that there's the cyst there.

But there's now she has more of a nodule in an endoscopic ultrasound done a month after her MRI. And I needle that, now I get adenocarcinoma. And so this was three years ago. She accompanied her older sister to a recent clinic visit. She underwent a total pancreatectomy. And had actually a stage 2 lesion that was nine millimeters in size. Because it had grown through the pancreas, nodes were negative.

But she's doing well after a total pancreatectomy at this age. But it goes to tell you, she was actually the smart one. Because we may have done a whipple surgery on her. She still needed surveillance and the tumor develops elsewhere. So we've learned a lot from this. And her sister is probably the same case. Where the cysts themselves we know our risk for developing pancreatic cancer. But they can develop cancer anywhere in the pancreas.

And so when we take our patients to the OR now, we have a very low threshold for recommending total pancreatectomies in this setting.

So in summary, US can identify small tumors or pre malignant cysts. Cystic lesions may just be a marker of increased risk of pancreatic cancer in these patients who are at increased risk. Very important is that there's no data at this time demonstrating that surveillance of pancreatic cancer decreases the risk of dying from this disease.

But we do feel that there's more patients found at a respectable stage and without resection, you do not have an opportunity for long term survival or a cure. And in our site at least over 80% of our patients, the one patient who I used full disclosure there was a delay in six months. She's was the only patient to date that we've ever found in a screening study that we recommended surgery that wasn't found at a respectable stage. And I don't know if the delay dealt with any of it or not.

The choice of imaging is of some debate. I favor endoscopic ultrasound. I think MRI is great for these cystic lesions. But I think these small solid lesions are important as well. And I think that was evident by this case. Because I've gone back to radiologists with full disclosure on where the tumor is and those MRIs and none of them can find it.

So what's our approach? So unlike colonoscopies, where I'll have them show up across the hospital here in the GI laboratory without me ever meeting them, we will not do screening or surveillance on an individual until we bring them into our office once, discuss with them the current status or limitations, we tell them that everything right now is based on expert opinion and the consensus of expert opinion, it should be done in centers with active research so we can learn from our experience.

We don't know when to start. We typically start at the age of 50 or 10 years before the youngest age of onset of pancreatic cancer for the familial cases. For the ones with the genetic syndromes, we factor in other things like smokers. We only like to test if it comes from a known genetic syndrome, we only do it if they agree to having testing and they are mutation carriers.

So by this point in time everyone's worried they're going to get pancreatic cancer. Here are some tidbits that have never been proven. But avoid smoking, healthy diet, and fruits and vegetables, exercise regularly. Weight reduction if necessary. And there's some debate about an increase in taking vitamin D and as well as baby aspirin.

So the possibility now exists to identify high risk individuals based on family history. The role of genetic testing is not known outside of known genetic syndromes associated with an increased risk of pancreatic cancer. But we may find in these familial pancreatic cancer patients that we can offer them a panel. These patients are appropriate candidates for surveillance at least based on expert opinion. And so with that I'll conclude. Thank you.