Thank you Rocky. I want to do a little disclaimer here, after you heard those 2 other excellent talks that were really based upon a lot of data in some cases millions of colonoscopies and 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 study so it’s really a totally different magnitude. This is not necessarily ready for primetime 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 into the business? Rocky mentioned that I went to Nebraska after my fellowship at UC San Francisco and that’s where I met Henry Lynch. Henry Lynch had all these families that were developing pancreatic cancer. 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 you know he was always very proactive with the hereditary predispositions and he wanted to do surveillance and so we stared 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 and so the thought was 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 3 of his siblings died of pancreatic cancer. And unlike other cancers keep in mind all these family members we don’t see, we don’t have big survivor benefits for pancreatic cancer. So I’m just going to give you a couple pedigrees in 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 of 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 the 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 proband right now developed pancreatic cancer at 45. So how do we counsel this family? Do we recommend any gene testing? You saw they had both melanoma and pancreatic cancer in it so keep that in mind during the talk here and we’ll allude 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 where 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 in pancreatic cancer so you know where we’re standing. Try to define hereditary pancreatic cancer for you. Go over some of the risks for developing pancreatic cancer and then give you right now what I think is a current status of pancreatic cancer surveillance in 2013. So in the U.S. 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 of the decline in smoking by 2020 if it keeps at the current rate it’ll 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 adenocarcinomas which are responsible for about 90% of the 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, 5 year survival rates are dependent upon what stage you’re found at. So less than 10% of patients are found in localized stage when it’s containment in the pancreas and no negative and those people have a little bit better outcome. But unfortunately about half of these long term 5 year survivors will still die of disease.

There’s known precursor lesions so you’ve 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 2 mucinous cystic neoplasms or IPMNs; 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 they’re at panIN 3 a sort of carcinoma in situ and or 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, serous cyst, mucinous cyst, and occasionally some are solid pseudopapillary tumors in young women and this just schematically gives you an idea of the different types of cysts. This is a microcyst which is totally benign and a pseudocyst which is an inflammatory typically after an episode of pancreatitis. And then we have side branch IPMN and this is the main pancreatic duct and we get what’s main duct IPMN and sometimes you’ll hear the term mixed side branch main duct when both there’s dilation involvement of the main duct and the side branch and then we have the mucinous cystic neoplasm which are solitary usually occur in the body and tail and often in women middle aged.

So in terms just to reinforce IPMNs because this is a precursor lesion that we’ll discover in surveillance studies and what our concern is is that it arises and causes cystic dilation of the main pancreatic duct and like I said there’s 3 variants. They’re often within the head of the pancreas and they can progress to invasive adenocarcinoma. It’s a whole other talk in cystic neoplasms but in terms of what we’re doing with them because they’re overwhelming our healthcare system with 600,000 cysts a year being diagnosed.
So how do you define hereditary pancreatic cancer? Well there’s 2 different scenarios. The first one is it’s a recognized 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 is defined as having at least 2 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 5-10% of pancreatic cancer cases are related to hereditary factors and this has been shown from a study from Louisiana and if you could see they’re having, 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’s probably a lot of them that are, I you have to have the right correct environmental hits but so clearly and if you have a history of pancreatic cancer your risk is even greater. This was confirmed in Montreal and when 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 50 or about 80% 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 familiar atypical multiple mole melanoma which is caused by P16 germline mutation.
So if you have cases of melanoma usually cases of multiple cases at a younger age, there at substantial risk of pancreatic cancer and I’ll show you that, be sure to keep in mind case number 1. Then we talked about familiar 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-Telangectasia is an autosomal recessive condition and so it’s fairly rare and that was found to be associated with an increased risk for pancreatic cancer. As you’ll see and I’ll just briefly allude to, we now know that if you just carried 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 we recently been reported by Hopkins that just carrying a mutation in a TM gene itself does increase your risk of developing or 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 Terry Brentnal studies in the University of Washington which Dr. Wickum and their group collaborated on to report that there was a mutation in pallidin. This does not seem to be a major factor in most of our familiar pancreatic cancer cases. We now about the mutations responsible for about 15% with these known syndromes so the majority of the familiar 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 3 or more family members, 2 or more family members or what about early age onset pancreatic cancer? So heres the list again of the syndromes and you can see it ranges depending on what your mutation is. Actually
if you look at registries of familiar breast and ovarian cancer patients for example the risk for any BRCA1 or 2 mutation carriers is actually less than 5 fold. We are in the process of writing up our data here where if you select outpatients 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’re a first degree relative and 15 fold with secondary 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 of these individuals, well it depends on where they fall in the pedigree. But if you have 3 or more first degree relatives your risk could be as high as 17 fold. Now keep in mind this is all in the setting of familiar pancreatic cancer where they’ve met that definition of two first degree relatives and they fall on this registry. This is from Hopkins group. One first degree relative and two first degree relatives are about the same, they all can get familiar pancreatic cancer so that’s probably like having a father and a grandfather, you know the children are potentially at the 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 a greater risk and same with if you smoke.

So what’s if we don’t see a recognized syndrome when we counsel these patients, and they just present with 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 infected 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 cases in them. Pancreatic cancer is about the third most common cancer in hereditary breast/ovarian cancer situations. Lynch syndrome is rare, less than 1%. PALB2 which is also it gives you excess cases of breast cancer it’s about 3% and then that ataxia telangetasia mutation that I mentioned is responsible for about 3-4%.

So there’s really no current guidelines available for genetic testing in hereditary pancreatic cancer kindreds. 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. So right now what I would recommend what you do is you review the pedigree and this is what we do when patients come in they’re seen with the 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’re participating in a multi-center trial trying to better determine the yield of these panels, I don’t have those numbers now. At times we may order them if they’re 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 screening is testing and the study of an asymptomatic general population. So we heard great examples in the earlier talks today about colonoscopy in that setting. Surveillance is testing an asymptomatic high risk individual. Many of the studies that you’ve see about for yields for detecting pancreatic cancer done in a diagnostic setting where that’s where these patients come in with symptoms. So to make an (inaudible) would be if they came in with either an iron deficiency anemia or a change of bowel habits or blood. You’re not doing 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 into this in the 90’s I was naïve and in retrospect it looks like you know 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 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 1,000 false positive 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 enrich it 10 fold and we make the age adjusted incident rate about 120 per 100,000 and we
apply that same biomarker, at least there we’re getting to a positive predictive value of about 12% and so no one knows that correct number. I’ll leave it to smarter individuals that myself to try to model it out but most people would say at least a 10% rate that they use that often for genetic testing to apply a study. So I think it is if you enrich the population it is worthwhile. So really what we use to enrich it is these hereditary cases, that’s the only 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 6 years studying 1,000 patients and they did see 19-9 which is a marker you’re all familiar with and they used a cut off of greater than 37 and guess what? They had a substantial number of patients who became positive but their positive predictive value was only 0.9% and that study so 1 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 with 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 age of 65 and they die at 67 they lived 2 years with the diseases. 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 can 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 and point this out as we look for earlier stage disease.

I don’t think there’s anything regarding indolent pancreatic cancer. If you have that unlike prostate cancer you can feel quite confident in treating it. So what can we do, so Meme Canto first, so Terry Brentnal first reported doing screening mainly based with ERCP and then she tried EUS and then Meme 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 IPMNs and one of them actually had carcinoma in situ, so they studied a lot of patients and they found about 10%. In Europe they found 44 individuals who did a first time endoscopic ultrasound and they actually found 3 pancreatic cancers. Makes you debate whether these were truly asymptomatic high risk individuals but regardless, 2 of them were stage 2 B which would be regional. We already saw that that doesn’t have as good of outcome so this really you know I have to full disclosure, you know it’s tough to say whether you made a difference. Some of them had IPMNs. 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 panIN 3 lesion which is carcinoma in situ, cancer or malignant or premalignant cyst such as an IPMN or an MCN that if you use surgery to validate it there’s about a 6 % yield with 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 if you took them all as being mucinous cysts then you may get that yield up to 13% for finding something. But the problem is when you take the 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 about there’s been only to summarize this there’s been 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 that have both clinical and surgical diagnoses but keep in mind that some of these that we removed, that we don’t do a great job determining on these cystic lesions or even these solid lesions they remove and find out they were like splenic venules.

So I want to give you a little personal example of screening. So this is a family that came to see me pretty soon after I came here and was actually this sister was the initial proband and she came in and said look I had my mother and 2 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 wasn’t able to find a BRCA mutation on her and she underwent an endoscopic ultrasound and she had about a 2.6 cm cyst. I was concerned about it at that time we were still early on with the cystic things but it was well over 2 cm and I know it doesn’t meet the criteria everyone thinks about with 3 cm so we suggested she get
operated on. And she said her daughter lived in Chicago and said no I want her to move to Chicago and so she’d be closer for recovery because she was 81 and she went to Chicago there was a delay in her seeing, and I had set her up with because I had 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. So the third sister then of course seeing her other sister die came rushing 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 a small cyst it measured about 1.5 cm not even over 2 cm. Well I just went through this other experience with the other sister here so we had a conference about her, we had her go to talk to the surgeon and she said 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 well 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 head or the tail of her pancreas and everything looked fairly normal, the body of the pancreas at that time. And then about 6 months later she developed this little thing by the splenic artery on a follow up and this is in the body of the pancreas now not in the head where I showed you where that cyst was and we were debating about between doing a Whipple which a lot of centers just resect the part there versus a total pancreatectomy which can make you a brittle diabetic. So I stuck this was 6 mm, 7 mm 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 into here with this and 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. She says no unless you show me it’s cancer, I don’t know what this is. I
said alright. So 3 months later I said I can’t follow you with 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 we don’t see anything else in looking at the body and tail. 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 on endoscopic ultrasound within a month after her MRI and I needled that and now I get adenocarcinoma, and so this was 3 years ago. She accompanied her older sister to a recent clinic visit, she underwent a total pancreatectomy and had it was actually a stage 2 lesion that was 9 mm 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. With these cysts themselves we know are at 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 EUS can identify small tumors or premalignant 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 resectable stage and without resection you do not have an opportunity for long term survival or cure. In our site at least over 80% of our patients, the one patient who I used full disclosure, there was a
delay in 6 moths she’s the only patient to date that we’ve ever found in a screening say that we recommended surgery that wasn’t found at a resectable 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 the cystic lesions but I think these small solid lesions are important as well and I think that was evidence by this case because I’ve gone back to radiologists with full disclosure on where the tumor is on 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 is 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 other things in like smokers. We only like to test if we, if it comes from a known genetic syndrome we will only do it if they agree to have testing and they’re mutation carriers.

So by this point in time everyone is worried they’re going to get pancreatic cancer. Here are just some tidbits that have never been proven. But avoid smoking, healthy diet of fruits and vegetables,
exercise regularly, weight reduction if necessary and there’s some debate about an increased intake of vitamin D 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.