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Good morning. So, we're going to talk about, genetic susceptibility to G.I. Cancers today. As Dr. Brand just said, the first part will be about colon syndromes, and then he'll talk to you a little bit about pancreatic syndromes as well. So this is interactive, I'm going to give you guys some case scenarios, and ask you to tell me what you think the genetic syndrome is, so please participate. Alright, whoops, sorry.

So just a little bit of an overview for you first. This is information that you may already know, but just if you are seeing a patient and thinking about whether or not they may have a hereditary predisposition to cancer. These are the sorts of things that you would want to keep in mind, so young age of cancer diagnosis typically before age 50, if there are multiple people in the family that have had either the same or genetically related types of cancer, people with more than one cancer diagnosis, people with unusual types of cancer, and then of course from a colon perspective, people who have lots and lots of colon polyps.

We all know that about 10% of cancers are considered due to a hereditary cause. It's pretty general across the board. It does apply to both colon cancer and pancreatic cancer. So if I am seeing a patient, this is what I would do. So I would first collect their pedigree, I would ask about at least 3 generations of the family, and draw that out and then I would look for those features that we talked about just a moment ago. And then, if you're doing these things, you may or may not ask about 3 generations of family, but certainly if you see things that look suspicious to you, we welcome referrals for these patients.

Most of the hereditary G.I. Syndromes are inherited in a dominant fashion, there are a couple that are recessivly inherited. So this is just a review of dominant inheritance, you know there's one mutation, and there's a 50% chance to pass it on to each child.

If we do genetic testing for a patient that we see, obviously there are a variety of different test results that we may get, so we may find a mutation we would consider that to be a positive result. So in that case, we would have some idea of what cancer risks might be associated with that mutation, we would have screening guidelines that we could implement for our early detection and prevention, and we would also at that point be able to offer testing to other people in the family.

We could get a negative result, no mutation is detected. There's already a mutation that's been identified, in that family, then obviously that's very good news, because now that person is that the general population risk for cancer. If there has not yet been a mutation identified in the family, that may or may not be reassuring depending on the level of concern that we have to start with, about the family history. But, it would certainly reduce the likelihood of a single gene predisposition. And then, we could also get a variance of uncertain significance, meaning something is identified that there's currently not enough data to interpret.

So usually, we don't use that result for clinical purposes. OK I'm not going to go over this slide in a lot of detail, because most of the slides that follow this are expanded discussion. But, this is just a nice 1-slide summary, of the hereditary syndrome associated with an increased risk for colon cancer, that we are currently aware of, and have at least some clinical testing for. So, the syndrome, the associated genes, the risk for colon cancer, whether or not there are other cancers associated, and what those risks may be.

OK, so here's our first genetic condition. So, this is a 68-year-old man who had a past medical history significant for a papillary transitional cell carcinoma of the bladder, at age 62. And in 2011, he had a colonoscopy done with 2 small polyps, that being 1 of them. And then 5 years later, he had a repeat colonoscopy and he had a 3 centimeter mass in the cecum, that was biopsied, and found to be cancer. So, does anybody have any thoughts? So a relatively small number of polyps, a cancer that developed within 5 years, on the right side of the colon, past history of a urinary tract cancer.

Lynch, good job. So just to expand on that, this might have given you some more clues if you weren't quite sure yet. Here's his family history. So our probe end is here with the arrow pointing to him. And then, on his father's side of the family, you can see that there are several family members that have had colon cancer. His grandmother was diagnosed before age 50, there's also a pancreatic cancer, in one of his paternal aunts. So this family history does look consistent with an autosomal dominant pattern of transmission. We've got 3 generations, we've got young ages of diagnosis, and we've got Lynch-related cancers.

So he had surgery, this is his right hemi-colectomy pathology. So it does have mucinous features, which is another feature of microcephaly instability, which should suggest the possibility of Lynch Syndrome. And, you can see they had immunized chemistry studies for the mismatch repair proteins performed, that's done as you probably know, on every colon resection at UPMC. And, he had loss of PMS2 expression.

So all of this is coming together, to suggest that there's a pretty good likelihood that he has inherited mismatch repair gene mutation. And, so we can potentially, try to figure that out in a couple of ways. So we can establish a clinical diagnosis of Lynch Syndrome, using the Amsterdam criteria. This patients family does meet the Amsterdam criteria, because there are at least 3 people in the family, that have had a Lynch related cancer. So colon in this case, 1-2-3, at least 4.

They are happening in at least 2 generations of the family, and at least one of the diagnoses is under age 50. So they meet Amsterdam criteria, so we could establish a clinical diagnosis, without any genetic testing. But obviously, it would be nice to know i we can identify the mutation, for the benefit of other family members.

So he did under undergo germline testing for PMS2, since his tumor studies indicated that, that would be the most likely gene that he might have a mutation in. And, he was found to have a likely pathogenic variant in PMS2, so we have our molecular explanation for the family history.

So this is just a reminder of the cancer risks that are associated with Lynch Syndrome. Obviously, the highest risk is for colon cancer. We do know that people who have lunch syndrome, that develop colon cancer have a higher risk of an attack or misdiagnosis. So continuing colonoscopies is obviously important.

These are the current

NCCN guidelines for Lynch Syndrome. I'm not going to go over all of this in a lot of detail, but this is just for your reference. The most important thing from a G.I. perspective, is that we start colonoscopies at a younger age, 20 to 25, and we do them more often, every 1 to 2 years. Typically, our patients, we suggest, annual colonoscopies after age 40. And you guys I'm sure know, that's because if you do develop polyps, if you have Lynch Syndrome, there's a more rapid progression to cancer. And so we need to be doing colonoscopies often enough, to find those polyps while they are benign.

From a G.I. Perspective, there is some guidance for upper G.I. Surveillance, but it's not particularly helpful. Basically, they say we don't have enough data to make a firm recommendation, but it could be considered for people who have a higher risk for upper G.I. cancers. So people who are of Asian descent would potentially benefit from routine surveillance, and people who have a family history of an upper G.I. cancer. We suspect they may have a higher risk, than those that don't have a family history. So for those people, we typically suggest surveillance every 3 to 5 years, beginning around age 30. For everybody else in our clinic, we typically suggest, obese lineup or endoscopy at 30, or at the time we identify the mutation. And, Dr. Brand normally does biopsies for H-pylori and treats if necessary.

OK, so there's also some recommendations for the other, extra colonic cancers as well.

And then, if you remember this man had a family history of pancreatic cancer, in a 2nd degree relative. And so that raises the question of whether or not he should have any sort of pancreatic cancer surveillance. Dr. Brand will talk about this more, this is just an excerpt from the American College of Gastroenterology Guidelines for Management of Hereditary G.I. Syndromes. And, they do suggest the possibility of surveillance, for people who have mismatch repair gene mutations.

If they have a 1st or 2nd degree relative with pancreatic cancer, typically that is either endoscopic ultrasound, or MRI starting at age 50, done on an annual basis.

So this is what we told this gentleman, have a colonoscopy every year, consider annual endoscopic ultrasound, annual urinalysis to screen for urinary tract cancers, annual physical exam, and considering daily use of an 81 milligram aspirin, for preventive purposes. Any questions? OK.

Next case. So this is a young man's colonoscopy. I think he's in his early 20s, if I remember correctly. And, he has a lot of polyps in his colon, and as you can see. And the biopsies were all adenomas he did have a cancer as well.

Good job. This should be the easiest one. OK so, obviously this is an example of classic FAP, so we're seeing hundreds to thousands of adenomas, beginning in adolescence. You know there's also attenuated FAP, where we see a milder Fener type, usually between 10 and 100 adenomas that start developing at a somewhat later age. We do typically see upper G.I. polyps, for these people.

There is also some increased risk for extra colonic cancers and benign tumors. So thinking about outside of the colon, this is this man's upper endoscopy, so he's got a lot of fundic polyps in his stomach, as you can see. And then he also had some periantilary adenomas, identified both of those things being classic with FAP. And then, he had a relatively large desmoid tumor, as you can see from that imaging.

And then, we also know that people with FAP have a somewhat increased risk for thyroid cancer. There's a very specific histology that's generally associated with FAP, it's the cribiform-morular variant of papillary thyroid cancer. And with people who have FAP, it's often multifocal. So if you ever were to see a pathology report, that indicated that, as this one does, that person probably should have a colonoscopy, because it's relatively likely that they're going to have FAP.

So most people with classic FAP have mutations in the APC gene which is dominantly inherited, but there is a relatively high de novo mutation rate. So the absence of family history should not exclude the possibility of FAP, from your differential. And then some people also have mutations in the mute-white genes which is recessively inherited. So we got another reason not to exclude things based on the absence of family history.

This is just a table from a publication a few years ago, that indicates what the likelihood of finding mutations in these genes, based on the number of adenomas that someone has in their colon. So you can as the polyp number gets higher, the likelihood of an APC mutation increases.

There are some other more newly identified genes, that have also been associated with poly-posic to varying degrees. So the Pole genes are typically associated with an attenuated FAP phenotype. There have also been upper G.I. polyps seen and maybe brain tumors and endometrial cancer. So some families that meet Amsterdam criteria, that look like Lynch syndrome, actually are found to have mutations in these genes. GRIM-1 is a gene again associated with Poly-posic, sometimes we see mixed types of polyps, this means there's one particular mutation that seems to be limited to the Ashkenazi Jewish population. So not something that we see very often, but occasionally.

AXIN2 2, again, attenuated poly-posic. The other thing that often families with AXIN2 mutations have is a fair number of missing teeth or Oligodontia. So if you see a person that has polyps and they say, oh, I don't have 7 of my teeth and maybe they have an AXIN2 mutation. And then lastly NTHL1, this is the most nearly described of these genes, it's also recessively inherited, so mutation NTHL1 are one or the 2 recessive conditions. And it seems to be associated with Poly-posic. There's probably some other types of cancers associated as well. But it's really too recent to say for sure what the whole picture of this gene is.

OK so, this person underwent genetic testing, going back to our lots of polyps picture, and did have a mutation identified in the APC gene, no surprise there. So we have, again, an answer for his diagnosis. Obviously people with classic FAP need to have their colons removed, but we do need to recognize that after that happens, there's still more to be done as far as management is concerned. So whatever portion of their lower GI tract remains, needs to be looked at every once and awhile. Also if they didn't have their rectum removed, that needs to be evaluated every 6 to 12 months. If they had a pouch or an ostomy that needs to be evaluated everyone 1 to 3 years. And then upper G.I. surveillance obviously is also very important. We determine the frequency of that using this Spigelman classification.

OK, so now we have a 51-year-old woman who has had 3 colonoscopies over 5 years, and she has had a total of 23 tubular adenomas removed. One Serated adenomas and 18 hyper-plastic polyps. And this is one of her colonoscopies, you can see a reasonable number of polyps there. So 51, a little older, 23 adenomas. What do you think?

Sure for what would be the most likely diagnosis? Of- So we've got mostly adenomas and less than 100 but more than 10, attenuated FAP. So she actually underwent a panel, looking at a number of the genes associated with colon cancer risk, and she was found to have 2 mute-white mutations. So this is mute-white to associate a poly-posic. So she does fit what we typically expect to see with mute-white mutation. She's got an attenuated phenotype, you know so fewer number of polyps presenting at a later age, although we can see variability within that spectrum as well.

So these are the guidelines for mute-white associated pol-posic. They're identical to the guidelines for attenuated FAP. So if you looked at both of those within NCCN and they would be exactly the same. So, typically we would suggest colonoscopies every 1 to 2 years, based on polyp burden. Obviously, some of these people may need to have surgery to remove some, or all of their colon, if they've got too many polyps to manage endoscopically. That's just a case by case basis, depending on what each person looks like. And then, we do also typically suggest upper endoscopy again, using the Spigelman classification, and an annual physical exam.

This is not yet part of NCCN guidelines, but we have also seen that a reasonable number of people with mute-white mutations have Thyroid involvement as well. And so, we do typically suggest for our patients that they have a baseline thyroid ultrasound. So for everybody that we have with mute-white mutations, that has had a baseline ultrasound has had something identified.

So for this patient we recommended annual colonoscopy with consideration of surgery if necessary, an upper endoscopy at the time of her next colonoscopy, baseline forward ultrasound, an annual physical exam. So she had a baseline upper endoscopy, she did have some fundic gland polyps. But nothing was identified in the duodenum and then on her thyroid ultrasound, she had a 1.6 centimeter nodule, that's being followed. So she's undergoing continued evaluation for that.

OK, this is another one that hopefully will be easy for you. So this is somebody small bowel, and as you can see there's a lot of ugly looking polyps there. Most of them as you can see being in the jejunum.

So this person did not have this feature but a lot of people with this genetic condition have freckling of their lips, and inside their mouth, Puetz-Jeghers. So Puetz-Jegher Syndrome, obviously associated with hammered home with is GI polyps the most common location is in the jejunum. And so this makes sense for this individual. So 2 classic features that we just talked about the polyps, and then also then he could cutaneous hyper-pigmentation.

This gentleman was actually interesting his mutation in SDK11 was identified through a multi-gene panel. And that picture that I showed you of his endoscopy, was actually done after he was found to have the mutation. Before the mutation was identified, he had, had kind of a mixed bag of colon polyps, but not any classic features of Puetz-Jegher syndrome.

So he had testing and was somewhat surprisingly found to have a deletion of the entire SDK11 gene, so obviously that's harmful. But it was found in a mosaic state. So it wasn't identified in all of the cells that they analyzed. So presumably some of his cells have this mutation, but not all of them do. And so that may be the reason why he had a somewhat unusual presentation. But obviously when he had an upper endoscopy, we found that at least his small bowel is pretty classically involved.

So there are a number of cancer types associated with Puetz-Jegher syndrome, even outside of the GI tract, but for GI surveillance, upper GI surveillance and colonoscopy is important. There's also a relatively high risk for pancreatic, cancer so endoscopic ultrasound is also a component of care, for these people with Puetz-Jegher Syndrome. And the frequency of the GI surveillance, is obviously somewhat dependent on findings.

OK so, this one's a little tricky, but it's not a repeat of something we've already talked about, so I'll give you that clue. So this is a 31-year-old woman, whose medical history is significant for a total abdominal colectomy at age 24, due to the finding of over 100 polyps and an early stage cancer. And then that's a picture of some of her polyps actually after her colectomy that's in her rectum. She also reported that she had frequent heavy nosebleeds.

So I'm not telling you what kind of polyps she had, because that would give it away, but does anybody-- can anybody think about the combination of colon polyps and nosebleeds, and what that might mean? I've stumped you, OK so they were juvenile polyps. So she has juvenile poly-postic syndrome, and we know that people who have mutations in this SYN4 gene, which is one of the genes that can cause juvenile poly-postic is usually also have features of hereditary hemorrhagic telangiectasia, nosebleeds are the most common feature of that. So that one was tricky.

So this is the pathology from her surgery. So as you can see, an early stage cancer in the background of juvenile poly-postic. And you can see here, greater than 100. So juvenile poly-postic syndrome, obviously characterized by the presence of juvenile polyps throughout the GI tract, sometimes just in the colon but sometimes, in the upper GI tract as well.

Typically we see juvenile polyps, but we can also see hyper-plastic polyps and adenomas in people, that have juvenile poly-postic syndrome. We talked about SYN4 already that's one of the genes that can cause juvenile poly-postic, the other one is BMPR1A. It is not associated with HHT that's only smart form. But only about half of people with a clinical diagnosis of juvenile poly-postic, will have mutations in 1 of these 2 genes. There are a lot of people that we do genetic testing for and we don't find an explanation, even though they still have the clinical diagnosis. It is dominantly inherited but, a fair number of people do not seem to have a family history, so probably a genetic mutation.

So this individual also underwent a multi-game panel we were confident that she was going to have SYN4 mutation, but for insurance purposes that was the easiest way to go about it. And she did in fact have us SYN4 mutation. So these are the guidelines for juvenile poly-postic posts under management. Obviously, lower and upper surveillance is recommended, at a pretty closed interval, starting in the teenage years. And we usually also refer people with SYN4 mutations to the HHC clinic, that's hearing Presbyter. OK this is off-center.

Alright so, this is a person who had a colonoscopy, I am and thinking that I must be missing something, there we go. So 55-year-old woman who had a colonoscopy, she had ganglia neuromas hamertomas, leipomas and 1 tubular adenomas. Thoughts?

OK, let me tell you about her past medical history, an maybe this will give you some more clues. She's had a trickle adenomas removed, she's also had a papillary keratosis removed, and an angio-fibroma, she's got a multinomial nodular goiter, she had hemangioma, and she has a big head. Alright, it's Cowden Syndrome.

So if you're thinking about Cowden Syndrome, and you're only thinking about somebody GI tract, it might look exactly the same to you as juvenile poly-postic syndrome. The presentations are often very similar. But if you ask about people's non-GI tract, then you're going to start seeing other things, if they have Cowden syndrome. And this person has had a lot of the features that we would expect. So macro-cephally, thyroid cancer, or some sort of thyroid nodular disease. There's also an increased risk for breast cancer and uterine cancer, maybe also kidney cancer and melanoma. And then those skin findings that she had the trichilemmomas is the classic feature of Cowden syndromes. So if you ever see that, that should alert you to the possibility of Cowden Syndrome. The other thing that you should always know is associated with Cowden Syndrome is lower might duclose disease, which is a benign hemangioma in the brain. In adults it's basically patho-pneumonic for Cowden Syndrome.

So this woman had P10 testing, because that's the gene that's associated with Cowden syndrome, and she did have a mutation identified. She also happens to be mosaic, which is not something we actually find that often, I just picked 2 mosaic examples for you.

But in this case, we obviously don't know which cells are involved and which aren't, so we would follow her as if she has Cowden syndrome. And so these are the guidelines for Cowden Syndrome, a lot of them are focused on the breast cancer risk for women, and the endometrial cancer risk for women. But from a GI standpoint, they do suggest colonoscopy starting at age 35 unless there's something that would prompt earlier surveillance, like symptoms or a family history. And then screening every 5 to 10 years. But in my experience a lot of people with Cowden Syndrome need to have colonoscopies more often, because they do tend to develop a lot of polyps.

OK, now I'll let Dr. Brand talk to you, unless you have any questions for me.

OK it's going to be hard to follow up, after Beth's excellent talk. We obviously, the majority of this talk is focused on the colon, because of the I would say, well over 80% of our referrals for hereditary GI tumor clinic, are colon related. My personal research interests and my personal interests has always been pancreatic, and hereditary pancreatic cancer. Dating back to seeing patients with Henry Lynch, from the Lynch syndrome.

When I was a junior faculty member at Nebraska, the most famous of all of the hereditary pancreatic cancer patients, of the families, is actually President Carter's family. Where all 3 of his siblings, and his father, and some people debate whether his mother had pancreatic cancer as well. But, to the best of my knowledge at least they have not identified the genetic syndrome, as you know he actually, no they have not identified the genetic syndrome, that I know of at this point, or he may have been retested. I know you're implying because of the melanoma that occurred in his brain. I do not know who will come across that, with one of the conditions of whether he has that or not.

There's, when we talk about hereditary pancreatic cancer, there's 2 definitions you need to know. First of all, there's a hereditary predisposition for dealing with known genetic syndromes and Beth went through a couple of them, that are GI related. I'll go through the list here before. But the most common ones are actually more with the breast cancer genes. And then there's this condition, and this gets confusing, just like hereditary pancreatitis gets confusing.

When you start, many years ago the term was coined familial pancreatic cancer, and really what that means it's a family that has 2 or more cases of pancreatic cancer, and at least 2 of those cases are directly related. And then that family is considered to have familial pancreatic cancer, and that's important because what we are doing gene searching, these are the types of families where there's an increased risk. Keep in mind there's only 1.5% lifetime risk of getting pancreatic cancer, which is I think now like 1 in 67 individuals. So you know it's pretty rare to have 2 family members have pancreatic cancer.

When you have clustering of pancreatic cancer cases, risk goes up. If you have 3 or more 1st degree relatives, with pancreatic cancer your risk is 17-fold, compared to the general population risk again 1.5% so you're getting around the 20-25% range. The one first degree relative, and 2 first degree relatives, these are in families. So this isn't just having 1 first degree relative, these are families that meet criteria for familial pancreatic cancer.

So you could be a parent and a grandparent, you would still meet criteria for familial pancreatic cancer. If you were related, if you were the child to that, then you would only have 1 relative. If you were a brother, you know it was your brother and your dad, who had pancreatic cancer, than you would have 2 first degree relatives. So to me, I always say a 4 to six-fold risk. And to me, it doesn't make a difference as long as you are at least one first related, to one first degree relative.

I think some of this is the numbers are small, and I think if we continue to expand, you'll see it probably become closer to normal. But then those that have a lot of excess cases probably do have a greater risk.

If you get pancreatic cancer or younger in these families, there seems to be greater risk, than when your later age onset. If you're a smoker, and that's I think because you're magnifying the risk, hereditary wise. And keep that in mind. That's true with a lot of the colorectal cancer syndromes, and especially Lynch, that smoking's bad anyways, but smoking when you have a hereditary disorder is really bad because you get cancer at an earlier age. And you get it more and more at risk for developing it.

With keeping that-- when we look at these, it used to be in the old days, when I would go to conferences, and particularly when Henry Lynch would talk about it, he would be big into doing these pedigrees and pattern recognition, because we didn't have these panels of gene genes that we could test at that point in time. A large part these panels didn't even start developing historically until the Supreme Court 2012, right you know, earlier this decade, I think it is around 2012. Ruled against Myriad Genetics that you can patent genes, and so that, so now all of a sudden you can put all of the genes on a panel. You could patent the technology to identify the genes, so you'll see different platforms that have to be licensed. But you can't patent the gene itself. So you look for things like melanomas, and pancreatic cancer early, and particularly early age. I don't know, we may think familiarly typical multiple mole melanoma, and I think that's where we'd be suspicious for President Carter's family, to have. If you see breast cancer in and pancreas you think of the BRCA mutations, are probably 2 in ATM can also give you breasts. And so a lot of these syndromes now, that we're seeing in a lot of our referrals actually come from people that are being tested for other reasons, with these big panels, and then incidentally are found. So panel testing has really changed how we care for patients with hereditary GI disorders, because when you saw that Amsterdam criteria, that was only picking up 50, 60% of Lynch Syndrome. But we had no other way of doing it. Now we made pick-up Lynch Syndrome because someone did a panel and they find it, and it was for even something which is very low, not very common in it, breast cancer it's debated. We will get a referral for that. So we get surprises now because, and we used to think that MLH1 and MSH2 were by far the most common, that's because the most penetrant for colon. But MSH6 and MSH2, they're not their phenotype isn't as strong, in their patterns aren't strong, but they're actually more common than what we thought before.

So we have to keep that in mind with all these, and all the different malignancies. So it becomes very important with panels. And then the risk we're trying to figure out. Now the easiest way is to figure out, we we're always with the BRCA mutations because there's a lot of breast cancer, there's a lot of patients that you can follow in registries. Thankfully, most people don't die immediately from breast cancer, so you get some natural history with them.

You have a pancreatic cancer registry, that you're following patients for it's hard to follow them for the development of a secondary malignancy, you know because most of these patients as you know, will be dead within a couple of years. But with colon and with breast, you can you have that ability to see what else is going to develop with.

The highest risk is actually with Puetz-Jegher Syndrome. And so that ever shows up as a board question, many years ago I know it was a board question, when I did my renewal at 1 point. Hereditary pancreatitis, you know if you're a smoker can put up over 100-fold, but it's up there as well.

All right so here's a family, and presented to us in melanoma, and then develop pancreatic cancer at 45, melanoma at 39, brother with melanoma 40, and their father dying of pancreatic cancer and melanoma. And, that's their, what syndrome are you thinking of? FAM, so familiarly typical multiple mole melanoma. These are just examples of a bunch of atypical anevi.

This was a patient that Dr. Lynch had the opportunity to meet, when he was when he was a junior faculty member at M.D. Anderson, and it was always, exciting because I would hear him lecture about this, or we would go meet with families that had this, when he was first, before it was commercially done, we had a research interest in this. And Dr. Lynch back before HIPAA, was able to go on what he called family information sessions, where we would just go to a city, and would be almost like a little reunion. And we would educate all the people there, and then we would draw their blood, and individually counsel them on issues. So I got to have the ability to go with him on at least 3 or 4 different visits.

And this one I went to Seattle, because I had always heard the story about this guy showed up, and gave him his family history of everyone having young age melanoma, a couple of pancreatic cancer cases, and he himself had already had 3 melanomas. And so Dr. Lynch examined him said you know I don't see anything that concerns me, and the guy said you know you're the 1st doctor to ever see me that didn't suggest a biopsy. And my wife was convinced that this little lesion right here, was changing. So back then things weren't as busy, he walked them down the hall to one of the surgeons, who removed it, it was the guy's 4th melanoma.

So these things just need really very close follow up with dermatologists. So we went to Seattle, and actually one of the first times that a Dr. Wickham, companies were there for another reason. I was at University of Nebraska. He was at Pittsburgh here. He actually came in with us to see this family as well, and I came to, the guy lifts up his shirt there and they were like almost all these moles had faded here, and I was so disappointed.

It was good for him. I mean, he hadn't developed a melanoma in years, and apparently it was Dr. Lynch telling me this, so I take it as gospel, because I'm biased. Obviously, he had a lot to do with my career in genetics. But you know he says at times you can see loss of expression, of some of these phenotypes as they grow older, so. You know, that was, I was so looking forward to that. Maybe he was diagnosing his 9th melanoma, but it was good to have it.

So Fam, keep in mind that we do see early-age onset melanoma, but we don't necessarily see early age onset pancreatic cancer. Most of these hereditary syndromes, when you compare the age of onset, to the age of onset you get with sporadic cases, you don't see a difference in the age. So that age is not a good clue for hereditary onset.

The, it is caused by the CDK into a, we used to use the old term P16 mutations. When you hear that, that's the same. You know, there's about a 2% chance at least if you live in Italy, I'm just looking at sporadic pancreatic cancer, as all-comers of having a CDK come into a mutation. Where other ethnic backgrounds were tests 0%, so there seems to be some founder mutations,

in some of the populations

So just like colon, we do the same exact thing for hereditary pancreatic cancer patients, and look for these clues on the pedigree. Now if you take the small subset of familial pancreatic cancer cases, and we think there's about, there's about a 5% occurrence, of when you look, we look at our pager registry, that you guys are all familiar with. At least in the 1st years will become familiar with, where we try to identify patients with pancreatic cancer, into our research study. The pancreatic adenocarcinoma gene environment registry. It's sort of the one that you may see my coordinator's in the GI lab for, you may see, we always appreciate a referral for pancreatic cysts, for other neoplastic processes.

If you look at that about 4.6 to 5% will have a newly diagnosed pancreatic cancer, will have a 1st degree relative with cancer. So they'd then meet criteria for familial pancreatic cancer. And if you do genetic testing, on that subset of the patients, then you get about a little bit more than 20%, that we know recognized genes. So in theory, if you ran a panel on those families your hit rate should be about 20%.

We've just completed or in the process of evaluating the data from looking at consecutive sporadic pancreatic cancers. It was a multi-center trial with Beth Israel, and Boston, and us and Virginia Piper and Arizona. And we enrolled 300 consecutive, newly diagnosed pay-grade cancer patients, within 90 days. To avoid any bias they were, instead of just showing up in the registry, like our other ones do, not necessarily meeting with it, you know Beth and in our other genetic counselor Eve, I met with them, you know Pittsburgh put in almost 200 to 300 patients a year, so we see a lot of pancreatic cancer here.

And you know those results will come out, but you know whether we start testing sporadic people, were just crunching the data now, and actually have a phone call this afternoon to see, and so that will be coming out. So it maybe that will be broadening recommendations for doing genetic testing. And this of course, is important because if you find something, you can use that information.

Not necessarily for screening for pancreatic cancer, that we could debate about all day long. But for associated cancers with syndromes and, if this person's newly diagnosed pancreatic cancer, there's a good chance that the cancer may come back, and may allow you to target their therapies.

So PARP inhibitors, if you find a BRCA mutation, or in some of these others ATM, PARP-2 work through DNA repair mechanisms. So there may be some targeted therapies that will work more effectively if we found a Lynch syndrome, which we sometimes do. So that's something to keep in mind. We're trying to make it more simple to think, when you refer a patient for genetic counseling. And so, with colorectal cancer we do universal testing.

In some of the reasons why universal testing is effective, is because it's not, it will become more common, is that just the 3% that we detect that have Lynch Syndrome. But 15% of these tumors, will be MSI high. So only 20% have of those Lynch Syndrome. Most of the others will be just acquired, mimicking Lynch Syndrome. But they'll be candidates for treatment, if needed with checkpoint inhibitors you know, and there's been some great responses for that.

So it's just again part of targeted therapy, genetics is important. That's why I encourage you guys to come to our clinic, because you need to understand these reports and how to think about it.

So here's a case with some excess pancreatic cancer, you see 3 cases here. There's breast cancer here, and that's not what the clue comes from. The clue comes from actually right here, with an early onset breast cancer. And so we actually tested this individual and they had a BRCA mutation. And that was able now, to use that information to get rid of half of the people that you need to do surveillance in.

So based on guidelines, you know these, I think this was just was shown by Beth. These are the people that we consider at risk, for developing pancreatic cancer, and in terms for surveillance we suggest 1st or 2nd degree relatives, because the penetrance isn't great enough. And so if we take all comers with BRCA, the risk may only be 4-fold. But, if we take the subset that have a 1st degree relative or a 2nd degree relative, that risk goes up to maybe around 15-fold. And so were, we presented that in abstract form and we're finally in the process of writing that paper up as well.

And we start again with surveillance as Beth said, at the age 50 or 10 years younger, but for Puertz-Jegher we suggest at age 35, because their cancers come earlier. And now with colonoscopies I have them, I do screening colonoscopies on demand, as all the GI doctors do, and that's because you know that screening makes a difference right? If you take 100,000 individuals and they get screening colonoscopies, and you compare it to 100,000 people who didn't, less people will die of colon cancer who got their screening colonoscopy. That's a successful screening test.

We don't suggest doing surveillance of the pancreas in the general population. First of all, like most cancers it's too low incidence. So you're never going to have a test that has a good enough performance status, that you're not working up too many false positives. The second thing is we don't have a test that's ever been shown, to make a difference. So expert opinion, would recommend that these people be screened at centers like ours, where we're studying it, and trying to understand it. And we use endoscopic ultrasound on an annual basis. And we also offer them trials. We participate in the CAPS trial, so at least those that are screened at Shadyside will get Secretin and I'll collect pancreatic juice afterwards. That's a multi-center trial that's run out of Hopkins.

And so we are constantly, so if you come across a hereditary pancreatic cancer family, please send them our way, because we'll offer them genetic testing if appropriate, or at least counseling. But I always meet with these people in our clinic, because they have to be honest with them about the limitations. Because when you look at it, and you put all the cases together worldwide, that we have found green, detected pancreatic cancer cases. And really screens not the right word, surveillance detected, because screening in a high risk population, there's less than 300 cases that have been found. If you throw all the major groups together, which we do on an annual basis at DDW. I meet with them, so we don't have a lot of experience, and many of those patients will unfortunately still die of their disease.

I do think that we find more receptacle stages. Alright so again, we're happy to see them, they should be taking care of these patients that are at risk, and I just want to go and just be sure I can wrap up here, with some family here now with a lot of gastric cancer, and mostly diffuse gastric cancer.

And, this is the probe end, in one of those families, you guys recognize who that is I hope. So Napoleon his family, he's part of a hereditary GI gastric cancer family. And so we now know the mutation that's responsible for it. It's a mutation in the ECHO HEREN or CDH1 gene. It's a huge risk for gastric cancer and this comes down to, we don't recommend prophylactic pancreatic-ectomies for patients with pancreatic cancer, because that will give them brittle diabetes. There's a 1% to 2% chance of dying from it. And we don't know, because the penetrance isn't to the level like it is here for hereditary gastric cancer. Where you can get risk as high as over 80%.

And then we look for associated cancers, and I have to say now more CDH1 mutations are found, not because of hereditary gastric cancer, but because of breast cancer, lobular breast cancer. They find it on panels. So we get our referrals, and it actually puts you in a tough situation, because we don't see her gastric cancer, in a lot of these pedigrees. And so it's a hotly debated topic, on whether we should be doing close surveillance on these individuals, or recommending gastroectomy. And we counsel them, have them meet with the surgeon, and it's gone both ways in terms of doing it.

We have had people, and I've know branches of these families are being cared for at other sites, where they've operated on these families and all of a sudden have found some small force of cancer in their stomachs, even without a history of it. So we tend to try to be a little bit more aggressive, and encourage prophylactic gastroectomy just because there isn't a very reliable way of doing surveillance. These on the bottom here, some other associated syndromes with the increased risk for stomach cancer. And again, this just shows a family that we cared for, actually the initial person who found the CDH1, was a young lad who unfortunately had a kidney transplant, a kidney disease, and then developed gastric cancer. And so we actually tested his mother, and she ended up being a carrier, and ended up being found a asymptotically to have gastric cancer, when we did a prophylactic gastroectomy on her.

So testing criteria, families with 2 or more patients with the gastric cancer, and in any age, 1 confirmed to be diffuse gastric cancer. So diffuses at the m that type intestinal. Intestinal usually tends to go more with H-Pylori infection. And if you have both families with lobular breast cancer, that's the other clue to look for. And look for, this is an early age of cancer as well. And there seems to also be in association with cleft lip and palates, and then signet ring, so Carcinomas too, with the CDH1 mutation.

We try to get people through the age of 20, so they got their growth and achieve it before we consider doing a prophylactic gastroectomy. So If you end up doing surveillance on them, this is not proven, they used to suggest using dye trying to pick a precursor lesions, you don't do that with upper GI tract lesions now because concerns about absorption, and side effects from the dies.

But you have to do at least 30 biopsies. I use jumbo forceps when I do these, so not small ones, because really trying to get as much volume, in as deep as you can. And we've had them pick up a couple of cells on that one lady, the mother the one patient I showed you, we actually picked that up on one of the 30 biopsies. And then we were able to prove it. And we have to go from 5 different, 6 different sites, 5 biopsies at each site.

And then we start breast cancer surveillance at age 35, we send our patients to the high risk breast clinic, so they can discuss with them care. And then there is some thought that there may be an increased risk for colon cancer. So if there's any family history of colon cancer, we start colonoscopy a little bit earlier, at 40, and we'll go every 5 years.

And so with that opening up for any questions.

So for pancreatic EUS versus MRI, what's the thought process versus a non-invasive test?

So that's a good question. So just to repeat it for the tape the question was MRI versus EUS, invasive versus noninvasive, you know why one or the other. I think that the MRI's are great for picking up little cystic lesions, and I think we became in vogue, when we were first dealing with cysts. And you can probably pick up a few more tiny little cysts. And tiny little cysts, and these cysts we all worry about EPM ends, but what we've learned is that the cancers themselves even in the hereditary families, when you've taken the system, you've done total pancreatic-tectomies, on those and they've done it. What they find is the system cells may not actually even have high grade dysplasia, but they actually found the other precursor lesions these Panin lesions, scattered throughout the pancreas.

And that they may actually be developing more solid cancers, in the setting of smaller cysts. So there are some cysts that will progress, and so larger cysts are of concern. So anecdotally, which you hate to make decisions on here, I do think you see smaller solid lesions better, with EUS.

And we have a patient with that same exact thing happened, where I was following them closely, she was in her 80's and she only wanted to be operated on, if we can prove that it was cancer. And she actually had a huge cyst, and she had 4 family members die of pancreatic cancer. And, when we tried to talk her into Whipple, she said no, you know I want you to follow it. And so as I was following it, in her junction, her body and tail she developed a small little solidly lesion. Couldn't see it by MRI, because I said I can't see her, doing a EUS every 3 months.

And so I tried to do with an MRI, and by the time I got to 9 millimeters, I was finally able to prove that little solid thing was cancer. She's now out 6 years after total -pancreatic-ectomy, and is doing very well. I mean she's on an insulin pump because we had to take it all out, and so she was right. That was early in our experience. First of all now, if we subject any hereditary patient, I totally push for a total pancreatic-ectomy and we're not always as anxious to operate on the cyst, and remove a dominant cyst, because of the field effect. So you have to be prepared to do a total pancreatic-ectomy. So I think that is the long winded answer to say, that I don't think MRI picks up these small solid lesions as well.