

December 2015-Genetics Web

Maren Scheuner:

I'm very happy to be able to join you all today and I appreciate the opportunity. So in preparing for this presentation, I spoke with some of the folks at the Blue Cross Blue Shield Association and the idea of this presentation is to give you a sense of an approach to genetic testing, genetic testing strategies. I have lots of clinical examples. I touch on next generation sequencing panel but it isn't necessarily the focus of this discussion and I think perhaps you will be having another talk on that as well. So let me just move forward here with the slides.

So I wanted to give -- I know you've had -- this is now your seventh webinar on this topic so very briefly, just to kind of set the stage, there's a couple slides on some basic principles around genetic testing, and then jump into some case examples to try and illustrate the pre-analytic phase or process that is involved in thinking about selecting a genetic test. This is a slide showing some common reasons for genetic testing. I think you all are probably familiar with this. I'm going to focus my comments today on arriving -- or trying to arrive at a diagnosis of a genetic disorder and what I mean by that is an inherited, single-gene, Mendelian disorder. I'm not going to talk about multifactorial conditions and gene associations, et cetera. There are lots of reasons to try and make a genetic diagnosis, you know. Maybe it's a patient whose already had signs and symptoms and you suspect a specific condition so ordering a genetic test or tests then helps confirm the suspected diagnosis and, you know, many talk about ending that diagnostic odyssey and sometimes there are definite changes in management downstream from that. And then the other area is if there's a family with a suspected genetic condition and there's an unaffected family member for whom understanding their predisposition would be helpful in guiding surveillance, prevention, management options. Prenatal diagnosis is another subset of diagnostic workup. It's just in a fetus. I'm not going to touch on any examples today around that. Carriers, screening for recessive conditions to inform reproductive decisions. I don't have examples for that today. And then there's a whole area of pharmacogenetics, pharmacogenomics to inform response to certain treatments and to inform prognosis of either an inherited or acquired condition.

So genetic testing is pretty fundamental to genetic diagnosis although it's not always necessary but it is being used, I would say, more and more as we discover more and more of the genes that cause Mendelian disorders of which I think now there are about 6,000 to 7,000. We've identified, I think, 2,500, 3,000 of the genes contributing to those conditions. There are different types of genetic tests. I think most commonly we all think of molecular genetic tests that interrogate DNA or RNA and those assess genotype. We also look at a higher level and look at chromosomes and order a karyotype. And then, of course, we can look at metabolites and proteins that are the product of these genes or involved in the biochemical processes and just [inaudible]. Today -- there's a little bit of noise on the phone and I don't think it's me but I wanted to make sure it's not just me hearing it. I just want to interject there.

So today I'm going to focus on the molecular genetic testing for the most part. So here is a list of some common molecular techniques that I think you may have heard about. [inaudible] analysis, Sanger sequencing is the "old fashioned" approach where we do one gene at a time. Now we, for the last couple of years, have had massively parallel sequencing technologies. It's

called Next generation sequencing. This is similar in terms of it's a sequencing process but it can be done on thousands to millions of pieces DNA all at one time and so we get lots of throughput, lots of output on one patient and it [inaudible] and improve the efficiency of testing and reduce the cost of testing. The deletion duplication complementary typically to sequence analysis so that if the condition, the gene you're looking at, if there isn't a point mutation or involving just a few nucleotides but larger deletions or duplications of [inaudible] gene, you need to do some other type of test to investigate that. On the single gene level, [inaudible] types of studies. I've listed this example here, MLPA, and then if you want to look across the entire genome, there is a range in hybridization that can look for copy number variants.

And then, of course, we still use very often targeted mutational analysis. So this is important when there is a known mutation in a gene that's causing a disease in a family. You would like to try and exclude that in an at-risk family member, for example. But there are also common mutations in genes that are, for the most part, based on a person's ancestry that can be tested or targeted initially. Now here I have what's called the eighth framework. This framework -- I got this image from the CDC's website and this is the analytic validity, clinical validity, clinical utility, and ethical legal social issues to consider when you're evaluating a genetic test. And I know that the Blues and many health plans think about this framework when they look to the literature for evidence of, you know, these issues around validity and utility. I'm not going to go over this with you. I think perhaps you've heard about this. Maybe we can talk more about it afterwards but I think what I wanted to point out is this middle here, this bullseye, where we have a disorder and setting.

So the context is extremely important when you're trying to apply a genetic test clinically. Of course we need to understand the analytic validity, the clinical validity, the clinical utility, but it's also important when you're using it for [inaudible] disorder for which you're testing and the setting and I think primarily these are patient characteristics and provider characteristics. So, for example, with regards to the disorder and genetics, there are common pieces -- how should I say, common tenants, common principles that need to be considered like penetrance. If I have a gene mutation, what's the probability I'm going to develop the disease in my lifetime? Also, variable expressivity. If I have a gene mutation associated with a diagnosis, what types of conditions am I at risk for because typically it will be more than one manifestation. So these are important things to consider. And as I mentioned, the patient's characteristics, their age, their gender, their preferences, and the provider that's involved in offering the testing, what is their expertise? How familiar are they with the condition that's of concern, but also the genetic testing technologies that can be utilized to investigate that disorder? So with that, let's see, I think this is my last introductory slide and then we can get into some clinical cases.

This is a diagram that I've used to try and illustrate what happens in a genetic evaluation. I'm a clinical geneticist. I get referrals from primary care, from specialists to help evaluate a genetic diagnosis in a patient. I'm a physician trained in genetics, also trained in internal medicine, and I often times -- I work together with genetic counselors and I wanted to differentiate what the medical geneticist's or clinical geneticist's role is and a counselor's role. So in this line here would be the physician's responsibility and again, this is the more traditional model of a geneticist working with a genetic counselor, but there's also an emerging model of genetic consultation and evaluation where a non-geneticist works together with a counselor or a non-

geneticist works on their own to kind of achieve these goals that I've outlined here on this slide. So I think that again gets back to who is providing these services.

Now the key thing in my mind is coming up with a differential diagnosis. That's what we do in medicine. So we have to consider all this stuff over there, the medical history, family history, developmental history is sometimes very important with genetic conditions, reproductive history, habits, et cetera, et cetera. Physical exam, sometimes looking for specific stigmata associated with a known genetic syndrome, and of course, reviewing labs, procedures, imaging, et cetera. Then with that information we can look to see if there are genetic tests available that could address that differential diagnosis and maybe it's one diagnosis, one gene, or many genes and a series of decisions that are made, or we do a panel or an exome, and it kind of depends. Now the clinical decision making really relates to, you know, how will management change? Is there a specific treatment that's available? Will there be surveillance that will be ongoing for this patient or are there preventive options available, and then reproductive options. If the patient is still of reproductive age, then if we make a genetic diagnosis, this could be relevant to their future offspring and they may want to know about it and make decisions either not to have children, to adopt, to use a donor sperm, donor egg, or if they get pregnant, think about prenatal diagnostic options.

The genetic counseling and education side is sometimes very important. It's not always but for complex genetic testing, it typically is a critical piece where we consider patient's motivations for understanding a diagnosis, cultural norms, beliefs, educational level, what's going on in their family, what they've experienced. All of this comes into play in terms of what they can understand and how they relate to what this diagnosis may mean. And then when it comes to their decision making, you know, their preferences, values, their knowledge, risk perception. All of these things will play into their decision about having a genetic test or entering into certain intervention or surveillance programs and it should be a shared decision.

Okay. So let's -- I do have a couple more slides here I think, so -- introductory slides. So genetic testing errors. Lots of studies done. Genetics is no different from any other laboratory tests. Most of the errors are made in the pre-analytic phase, before we order a test, because we don't have enough information about the patient to select the right test, or because we might have the right diagnosis but we don't know enough about the genetic tests and their limitations and we select the wrong test. This results in --inappropriate test selection could result in, you know, a compromised informed consent process which is very important to patients, overutilization of tests that aren't indicated which leads to misdiagnosis and [inaudible] and then, of course, underutilization of indicated tests which could result in delayed or missed diagnoses. So I have two cases I wanted to present that illustrate the importance of getting the differential diagnosis right and I think you're all, as I understand, physicians, clinicians, and I don't think this will be too much of a big surprise, that this is a really key step. But I can't emphasize it enough and it doesn't really get discussed enough, as far as I'm concerned.

So I have -- this is not unusual. I'm pretty much a gatekeeper for all the genetic testing services where I work. I get referrals from physicians of all types requesting genetic testing for their patients. And here's an example of a case I recently saw. The patient is a 38-year-old male. He was referred from the gastroenterology clinic and it said genetic testing desired. And this case

was from a resident probably, or a fellow submitted the case. He said it was discussed with the biliary attending and they described a patient who may have chronic pancreatitis and they were requesting hereditary pancreatitis gene testing -- requesting a panel specifically of the genes listed here. So I met with the patient. This is the family history I ascertained. So here he is at age 38. He also has some reflux and it looks like, at least on imaging and by history, he has some pancreatitis but never really hospitalized with acute bouts. And then his brother has "pancreas problems" and I've shaded him a little lighter blue, not sure if he's similarly affected. But the father dies from abdominal cancer at age 66 and we always worry about that because pancreatic cancer is increased risk in people with chronic pancreatitis so possibly that's related. The other history that was interesting to me is that there's this cousin over here with pretty early onset type 2 diabetes, we clarified, but otherwise -- and mom has diabetes at a later onset but nothing else too exciting is going on here.

So in reviewing his labs and so forth, you'll see here everything looks pretty okay except his renal function is not so great for a young guy with no history of any reason to have any kidney problem, but I saw [inaudible] again, there's this agenesis of the pancreas from [inaudible] calcifications, common bile duct normal. Nothing else going on there. But there are these multiple bilateral renal cysts and the liver, spleen, and adrenals looked okay. So in talking about that and the family history, I thought, "Okay, this is unusual." You know, he's got agenesis of the pancreas. This is not acquired. It is most likely congenital and there [inaudible]. He's got bilateral renal cysts with renal insufficiency, and he has this maternal family history of diabetes of early onset in a first cousin. So these are the things that were of, you know, that kind of popped out at me and I thought well, could these all be related. And I thought well I know of something that could, you know, account for all of these. And let me go look it up again and so I did and I remember that yup, you were right. Renal cysts and diabetes of early onset, there's a condition called MODY 5, or maturity-onset diabetes of the young 5. It is due to heterozygous mutations in the HNF1B gene. It features all of the stuff that we saw. My patient doesn't have diabetes, however, but he does have this dorsal agenesis of the pancreas with pancreatitis and renal disease. And so there were a couple of other things that I found in kind of looking at the databases that might explain some of these features, but not all of them, including the hereditary pancreatitis and these other things could just be a red herring.

So in thinking of a genetic testing strategy, rather than doing what the G.I. doc requested, I said, "You know, I think we should look into this MODY 5. I talked to the patient about it. He was on board and if that was normal, then we could talk about testing for hereditary pancreatitis and the test [inaudible] includes sequencing and deletion duplication testing." And so [inaudible] lo and behold the patient has a pathogenic mutation in the HNF1B gene. Essentially the entire gene from exon 1 to the [inaudible] has been deleted. It's missing. So this is a huge deletion and there are many other cases in the literature that are described that have this phenotype and are diagnosed with MODY5. So for this patient, implications, and management, whatever is going on here in his agenesis of the dorsal part of the [inaudible] is, I would say, due to this HNF1B gene mutation. He's at risk for diabetes so we sent him to the endocrine clinic. He's at risk for exocrine pancreatic dysfunction. The renal [inaudible] -- I sent him to nephrology. He has never seen a kidney doctor. This is likely coming from the maternal side of the family and now we have other family members we could test for to determine if they have the same condition. So that was the first [inaudible].

**Male Speaker:**

I want to interrupt just because there's somebody on the line who hasn't muted and it's becoming quite difficult to hear you so if everybody could make sure they're muted, that would be great.

**Maren Scheuner:**

Okay. Thank you. Great. This next case, Mr. SH, he's a 54-year-old male. He's referred by primary care and the patient himself requested genetic testing. He informed his primary care doctor that his brother recently "screened for defects" due to arrhythmia and his information is as follows: He has Arrhythmogenic right ventricular cardiomyopathy. The other information that was provided is here. Lots of PVCs but no specific arrhythmia aside from that was known. He had sleep apnea and the brother provided the specific test that was performed and his accession number because if any family member wanted to get tested, they're going to need this number. So I met with this patient and he was just expecting to get his blood drawn and I said, "No, no, no. I need to go over the history with you and really understand what's going on and make sure you yourself don't have similar symptoms, et cetera." So I spoke with him and he himself, my patient, really is doing really well. No cardiac symptoms whatsoever, very active. He had not had an echo but he does have a normal EKG and in further questioning, he offered yes, my brother has a large heart and my uncle said we all have it because we're all athletes. We were wrestlers. My brother's doctor recommended an ICD after his genetic test and then he saw a specialist at Johns Hopkins and he was told something different.

So then we looked at the family history and this is what I marked. So here is my patient here. He is unaffected, age 54. It's his younger brother, age 46, who has this "enlarged heart" and ARVC diagnosis and it's the other history that is of concern is the father who died at 72. The family thought it was from a stroke but it is known that he had a pacemaker and had some kind of arrhythmia. So something may be going on here, possibly paternally inherited although hard to know for sure. So we then -- I was able to get the brother's test results. The patient brought them with him and he said, "This is his test report. And this is what his doctor ordered, was the next gen sequencing panel with these genes on the panel and my brother is heterozygous for a variant of uncertain significance, so in the RYR2 gene." So I explained to the patient that this variant, the lab is not calling it pathogenic. They don't know if it's the cause of anything. It's like it could be a polymorphism, it could be pathogenic. They just don't have enough information to really interpret it as pathogenic and this patient, you know, it's not appropriate to test other family members who, you know, certainly those who are not affected because it couldn't change anything. It really has no clinical significance right now, this variant. We don't know enough.

And so I explained that there and the other thing is -- so there's no genetic testing. My patient came wanting a test, expecting his blood to be drawn. I said, "No, there's no reason to do that. What's more important is that we really understand what is going on with your brother. You know, does he have a cardiomyopathy? What is his arrhythmia? I need to review his medical records to really understand what he has so I can understand if you are at risk." So the one thing I did is I ordered an echo because of his history of cardiomyopathy and we didn't have information and then I said I'll follow up with you in a couple of months. So that's case number two illustrating that maybe it's not the patient himself with the genetic diagnosis, but it's

something in the family and before we go ordering tests, we need to really understand what is going on in the family and make sure we understand the phenotype. Okay. So selecting the right test depends on the right diagnosis and it requires a synthesis of all this information as I discussed before.

So now we'll go on to selecting the right test. So this is kind of the next step, I would say, kind of in the pathway or the pre-analytic phase before the informed consent process, which we won't get into. So I have, I think, three or four cases here and they're all kind of quick and then I think we'll have plenty of time to answer questions. So case three is Ms. T. So she's 47 years old, referred by primary care and she has just been diagnosed with invasive lobular carcinoma of the right breast and I learned from the referring physician that her maternal aunt also had breast cancer. And so when I met with a patient, or I think the counselor met with the patient, she was diagnosed with invasive lobular adenocarcinoma and, as I said, she had two foci but it was small together no more than 15 millimeters, and she elected to undergo bilateral mastectomy with reconstruction just because of her own personal history of this happening and she does have some family history. She had a sentinel node biopsy negative and her tumor was ERPR positive and her HER-2/neu negative.

So in talking to the patient about what are your expectations, what do you understand about genetic testing, and what would you do with that information, the patient said, "If it's positive, I would get everything taken out." And what she meant by everything was her, you know, uterus, her fallopian tubes, and ovaries. She reported that she's had this problem with adenomyosis. She has had a lot of vaginal bleeding and she said it would just be better to get everything out instead of just the hysterectomy, which was planned as we understood -- or at least on the table. So this is her pedigree. So here she is. We knew about this breast cancer. We don't know the age at diagnosis of this maternal aunt. She died in her 70s. That's the extent of it, but she's alive. And the mother is age 66. No cancer history that we knew of. Her father -- this should have a slash here, died at age 32 from a primary brain tumor of some kind. We don't know more than that but it was an early death from brain tumor and probably not metastatic disease, probably a primary. And then it's the maternal aunt over here also had breast cancer in her 50s. She is currently 71. No one else in the family had ever undergone genetic testing and there is no Jewish ancestry. We always ask about Jewish ancestry with breast cancer because of three common mutations in BRCA 1 and 2 and if we are to offer a patient testing, we would start there and if that were normal, we would think, you know, is it worthwhile to do any additional testing. In this case, the patient was not Jewish.

So in terms of a differential diagnosis, given her somewhat early age at onset under 50 and multifocal lesions with, you know, this invasive lobular cancer, she could have hereditary cancer and it may be, you know, I'm more suspicious of the paternal -- the father's side of the family given his cancer diagnosis with brain cancer in his sisters than the maternal side but it could be coming from either if it is genetic, if it is hereditary. And then if it is hereditary breast cancer, we know of a number of genes these days that do contribute to breast cancer. Some are of higher risk than others and I want to point out that CBH1 is associated with lobular breast cancer specifically, which our patient had, and also diffuse gastric cancer whereas I'm sure you're familiar with BRCA1 and 2, it can be early onset. Typically it is ductal but it could be lobular and of course, there's an increased risk for ovarian cancer. So because the patient had bilateral

mastectomy, you know, her decision making about dealing with any increased risks from these genes related to that, that decision has already been made. So testing would really potentially be helpful to understand her risks for other cancers and then to offer her other preventive and surveillance options depending on those test results.

So we went forward with testing and we found that she had a BRCA2 gene mutation pathogenic. At position 1929, there's a deletion of a guanine G nucleotide and that leads to an early stop in the production of the amino acid chain and so this is known to be a pathogenic mutation. And it has been observed in the literature and other families, it's actually likely a founder mutation from northwest England. I hadn't even looked back to see which -- so here her grandfather is from England. You know, this is the first time I put two and two together on this. So it is likely that this is paternally derived possibly from this grandfather, although we don't know the country of origin of these maternal grandparents but just thought I'd throw that in there. So anyway, for this patient, she has maximally reduced her risk for another breast cancer with the mastectomy. But we did recommend that she remove her tubes and ovaries to reduce her ovarian cancer risk. We referred her to G.I. because of BRCA2, there is an increased pancreatic cancer risk and there are some surveillance options, although again, you know, how well they do at detecting pancreatic cancer at an early stage is debatable. There is also an increased risk for melanoma with BRCA2 and we advised her about that. And of course, we recommended that she speak with family members. And in follow-up, we learned that she had a hysterectomy with bilateral salpingo oophorectomy. She was seen in G.I. clinic and did have endoscopic ultrasound and her mother and both sisters have tested negative so yes, it's coming from the paternal side of the family. So good news there for mother and sisters.

The next case is Ms. CJ. She's 30 years old, referred by primary care. She's got a family history of early onset breast cancer and genetic testing was desired to evaluate for her risk of breast and ovarian cancer. Specifically requested was testing for BRCA 1 and 2. And we were informed by the primary care doc that she would consider preventive surgery after childbearing. So let's show you a little bit more about this patient. So here she is, age 30. She is currently preg -- no, no. That's the next slide. She's not pregnant at this time. She has a paternal first cousin, a female cousin, with breast cancer diagnosed recently just at age 28. That's really the extent of the history here. We have lung cancer in this paternal grandfather so if this is hereditary, and it sounds like it. When you see breast cancer at 28, that's a huge red flag. And we did verify that was an invasive ductal carcinoma as I recall. So this could be -- there are three uncles here. So men can certainly carry these mutations. They have a much lower risk for developing cancer as a result. And so you can see pedigrees where it's male to male to male and then eventually a daughter inherits it and you see breast cancer or ovarian cancer or whatever.

So this definitely is assigned. But now this is a third-degree relative to our patient. And so -- and always -- we always want to identify the mutation in the affected family member rather than offering her testing first because a normal test result would be somewhat reassuring especially given the distance -- the genetic distance of this history. But it just would be so much more informative if we would know this cousin's genetic test results. It so happens the cousin lived in Germany and my patient thought well do they have genetic testing in Germany? And I said, "Yes, they have genetic testing in Germany." So she corresponded with her cousin and her cousin did undergo testing and so this is reflected here in this slide. The conversation that we

had -- the testing strategy is to hold off on our patient and see if her cousin would undergo testing. And her cousin did test and now my patient is pregnant which kind of was a little bit of a wrinkle and most women don't really want to know about this stuff while they're pregnant. But her cousin has the BRCA2 mutation.

Now we also learned that her cousin's mother, unrelated to my patient, died from breast cancer at an early age so now I strongly suspect that this woman's mother was the person who transmitted this BRCA2 mutation to this cousin. But I can't prove that and because I have a known familial mutation, we offered our patient that test. It would have been good for her dad to test but it's hard to get men tested. So -- the insurers typically will not pay so we offered this familial mutation to our patient. And the good news is that no mutation was detected. So that was good news all around for her. So she's not at increased risk for breast and ovarian cancer. There's no indication for enhanced surveillance or prevention. And there's no risk to transmit this familial risk to offspring. So this illustrates the importance of, you know, if you have someone at risk, to try and work with that family to get that familial mutation known. And sometimes it takes a while and it takes effort and lots of clinicians don't have that time, but that's something that we often do in genetics.

Okay, case number 5. Mr. MC. A 46-year-old man referred by G.I. clinic and all they said was possible Lynch syndrome so let's see. This is his story. He was diagnosed with synchronous colorectal cancer at 2 centimeters and 18 centimeters on his first colonoscopy at age 46. I believe he had his colonoscopy because he has a family history in his father and paternal aunt. So he had it at an earlier age than typical. Both tumors were screened for Lynch syndrome so maybe you've had some discussions about Lynch syndrome. We know that there are at least four mismatched repair genes that code for these proteins that fix mismatches that occur during DNA replication. If you have a mutation in one of these genes, you can't fix these mistakes and mutations accumulate in tissue becoming a tumor. And so immunohistochemistry can be done looking at the proteins that are made from these genes and if there's absent staining of a protein, it suggests that there's lots of heterozygosity. It suggests that there's a germ line mutation in the gene where there's lots of protein expression.

We also can do microsatellite instability testing and in my hospital, we tend to do both, especially in a case like this where what ends up happening is the immunohistochemistry was normal so we went on to do microsatellite instability testing and there all five markers -- these are molecular markers, showed high instability and there was no promotor methylation of the amylase 1 gene, which could be a somatic reason for having the MSI high phenotype. So I know this -- I went a little bit into Lynch syndrome. It's a lot of detail, maybe more than you needed, but just wanted to kind of explain the process there and those results. These are the other problems. He's currently smoking, which is a problem, especially with the cancer history, of course. And then we have some family history. So here's what he told us. He has a sister from home. He is estranged. He hasn't spoken with her in quite a while. His mother died at age 40, maybe from cancer or possibly AIDS. He knew nothing about his maternal family, only that his grandparents were white. His father, he knew, died at 54. He had colorectal cancer diagnosed at age 38. His father's sister also is deceased possibly. He wasn't even sure if she was alive or dead but he had heard that she had colorectal cancer as well but doesn't know the age or anything. So he's kind of estranged from his family. He doesn't have a lot of information but

enough here, especially with his own history, which is sufficient, to be concerned about an inherited predisposition to colorectal cancer.

So genetic testing strategy for him, given his personal family history, it is consistent with Lynch syndrome. He meets what are called these Amsterdam criteria where you have three family members -- I could go back to the pedigree -- three family members first-degree relatives to one another and at least one of them diagnosed before age 50 with colon cancer. Now I know this is a question mark but he said his aunt did have colon cancer. He just didn't know at what age and if she's even living. But if we go by this history and the fact that his tumor had microsatellite instability, it meets clinical criteria for Lynch syndrome which is the most common cause of hereditary colorectal cancer. But there are many other hereditary colorectal cancer syndrome that could feature this but we could never exclude Lynch syndrome because it meets these clinical criteria. And furthermore, making the genetic diagnosis with a molecular test isn't going to impact his cancer surveillance or prevention. We're going to have to recommend that he follow kind of the Lynch syndrome recommendations for surveillance, which are listed here. We emphasized for him to quit smoking, to start aspirin. There was a big study that showed taking aspirin reduces the incidence of colorectal cancer in these patients. So in this case, we didn't do genetic testing because the clinical phenotypic information was sufficient to make a diagnosis.

I think I might have time for one more case. Maybe this is the last case anyway. A 33-year-old female referred by G.I., again. Lots of referrals from G.I. She had colonoscopy today so the day of they sent the consult in for rectal bleeding. Lots of polyps removed, two more than 1 centimeter. Grandmother had breast cancer. Question of whether we should be sending the polyp for some special testing. That was what was on the consult request. So here is some more history. Abdominal pain. She had been passing clots and they did the colonoscopy and nine polyps were found throughout the colon. She also had a cyst removed from her back and with these hereditary cancer syndromes, we're always asking about dermatologic findings and other things that could be related. The migraine, acne, and back pain, I don't think, are related. These are her meds. She's taking a vitamin, not aspirin, not smoking, drug, or alcohol use. And she walks every day in terms of exercise. So here's her pedigree. She's an only child. She has a son age 13. Unfortunately her mother died from a drug overdose at age 37. She is estranged from her maternal aunt. This is the grandmother with breast cancer of Guatemalan ancestry. Grandfather was African-American and her grandparents on the father's side are both African-American. Dad is 59 and had a normal colonoscopy and she doesn't know much about these four uncles and this paternal aunt over here.

So the family history really isn't that helpful. You know, this could just be -- I mean, having nine tubular adenomas at such a young age is definitely concerning, I would say, for a polyposis phenotype. Clearly it's not classical familial adenomatous polyposis because she doesn't have hundreds to thousands of polyps which you would expect at age 33 and the classical familial adenomatous polyposis, but she could have an attenuated form of familial adenomatous polyposis due to a mutation in the APC gene, or she could have MUTYH-associated polyposis. MUTYH is another gene. The phenotype looks exactly the same as APC but it's due to recessive inheritance so that it would mean that the father and mother were both carriers, she inherited the two abnormal gene copies, and now she's at risk for developing multiple adenomas. It's also possible that she has Lynch syndrome because we do see polyps in Lynch syndrome, adenomas,

much more frequently than the average. Even though it's been called non-polyposis colon cancer, clearly the colorectal cancers develop in polyps and patients do have multiple of them.

So there is a relatively broad differential diagnosis for her and again, I've listed that here. There really wouldn't be much utility to test her adenomas for Lynch syndrome as I described in the previous case. It's pretty low yield. So if we wanted to arrive at a genetic diagnosis for her, the best thing would be to order, you know, a series of genes one at a time or to do a gene panel that has a combination of the genes that I've mentioned to you to try and sort this out. And it would be important because, for example, the APC gene is associated with other malignancies, a little bit of pancreatic cancer risk, thyroid cancer, but really gastric and small bowel. Those are the areas that we would be mostly concerned about. MUTYH-associated polyposis, there are some other cancers associated with this but less is really understood about this particular one and of course with Lynch syndrome, we know that women would have a very significant increased risk for endometrial cancer, ovarian cancer, also gastric cancer, ureter cancer. Several other cancers are increased with Lynch. But I think if we were to diagnose Lynch syndrome with genetic testing, then we would advise her at some point she needs to have her uterus and tubes and ovaries removed as a preventive measure.

So we ended up with a panel of genes. You'll see a lot of genes on this panel. That's because the laboratory that we have a contract with -- in order to get the genes of interest, this was like the best approach for us and it, you know, there are some of these genes that, you know, really don't pertain at all and I wouldn't even think are relevant like CHEK2 or CBH1, but they just happen to be on the panel. But when you do panel testing, as in this case, you see here we did find a pathogenic mutation in the APC gene and we also found a variant of uncertain significance. So these variants, they, you know, we need to explain them to our patients and we need to tell them that they can change over time and sometimes family studies can be done to inform what these variants mean. In this case, I guess you could say we were lucky because we found a pathogenic mutation that we suspected and it helps us with making the diagnosis of attenuated FAP for this patient. So here are the, you know, what we recommended to her in terms of surveillance, et cetera, and of course now there's a test for her son and relatives to understand, you know, who else is at risk in the family. And she may be the first in the family. She may be a de novo mutation but certainly her son would be at risk and when he's older could look into this.

So I'm at the end now so I have at least 15 minutes for discussion. So selecting the right test, I want to emphasize that if you think about that ace framework and the disorders and setting that's in the middle of all of that, you know, the clinical context is so important. It's so important to understand the patient characteristics that are going to contribute to the diagnosis and differential diagnosis, the characteristics of the genetic disorder that you're contemplating and they're listed here, inheritance pattern, the prevalence, penetrance, variable expressivity, the clinical heterogeneity so that it might look genetic but it might be "non-genetic" or there may be a lot of genetic genes or genetic diagnoses that have the same phenotype, genetic heterogeneity. The genetic test that you might want to order to kind of work this up, you know, it depends on if there even a genetic test available. Even in this day and age, even though we know a disease is Mendelian, is hereditary, there may not be a clinical test. And then this idea of targeted versus comprehensive testing, one gene at a time or panels, axons, and understanding the limitations of

all of that, and then the provider. You know, who's arriving at this differential diagnosis and how much do they really understand about the disease of concern and how much do they understand about the genetics and the limitations of genetic testing and what it can really offer.

So in summary, genetic diagnosis can end a diagnostic odyssey. It can help guide management and surveillance recommendations. It can inform reproductive and life planning decisions for the patient and it can have health and reproductive implications for the family members. Making a diagnosis can be complex and it relies heavily on genetic testing these days. And selecting the right test relies on the accurate diagnosis, et cetera. So I --

[end of transcript]