MARGO THELANDER: This is the second of two talks on cancer genetics. The first talk was given earlier in 2015 by Dr. Shoba Kankipati.

My name is Margot Thelander, and I'm one of two licensed genetic counselors specializing in hereditary cancer risk assessment at John Muir Health.

I was trained in molecular genetics and genetic counseling at UC Berkeley with clinical training at UCSF, Children's Hospital Oakland, and Kaiser Genetics in San Francisco in Oakland. And I have been with John Muir Health for almost 11 years.

The focus of a cancer genetic counselor is to identify hereditary cancers syndromes in your patients and their family members, syndromes for which there are proven measures that can be taken to reduce the chances of cancer developing or to detect it in the earliest stages.

Unfortunately, too many of our patients are referred to us by surgeons or oncologists after a diagnosis of cancer. To be effective in preventing cancer, we count on our primary care physicians to recognize when a patient has a family history that suggests a possible cancer predisposition syndrome.

Referring these patients for a genetic evaluation is the most important step you can take in preventing cancers in your patients and secondarily in their family members. If your patient has an inherited predisposition to cancer that can be identified by genetic testing, they can then be armed with the information they need to be proactive and take preventive measures to decrease the odds of cancer developing or to catch it in the earliest stages.

In part one of the Cancer Genetic CME talks, Dr. Kankipati reviewed some of the more common cancer syndromes and discussed the recognition and management of patients with these syndromes.

Today, I want to focus on the primary care provider's role as the gatekeeper for patient risk assessment and prevention of disease. This will include a review of the optimal strategies for assessing which patients may have hereditary cancer risk, and a review of best practices for family history documentation.

I'm also going to present some of the recent developments in our understanding of genetic factors underlying cancer risk and the resulting complexity of a genetic evaluation.

And lastly, I'll address the benefits and risks of genetic testing for your patients. And how the choice of who to test first in a family can significantly change the risk to benefit ratio.

I'm sure you're all familiar with family histories documented in standard pedigree format. The patient identified with an arrow, males represented by squares, and females by circles, etc.

Here's a case that represents a missed opportunity to prevent an aggressive, potentially lethal, breast cancer in a young woman with two children. The patient has a very strong family history of early onset breast cancer and ovarian cancer.

The breast cancer is represented by the blue icon, ovarian by green.

But it was not until her own recent breast cancer diagnosis that her breast surgeon referred her to genetic counseling, essentially to help with surgical and treatment decisions.

Considering the full extent of her family history, it was not surprising to find that she carries a BRCA1 mutation and has hereditary breast and ovarian cancer syndrome. This patient's breast cancer could have been prevented.

First, if the patient's mother with ovarian cancer, or her maternal aunt with breast cancer at age 30, had been referred to genetic counseling in accordance with clinical guidelines, and the familial BRCA1 mutation had been detected at that time, this young woman could have found out her own genetic status earlier and could have taken risk reducing measures to avoid her current breast cancer diagnosis.

But there are still ample opportunities to prevent further breast and ovarian cancer in this family. There are three unaffected adult females in the family, who are identified with blue stars, who should consider testing for the family mutation. If they're negative, they can gain significant peace of mind. And if positive, they can undertake the appropriate risk reducing measures and not let family history repeat itself.

This pedigree shows a young man of 35, indicated by the arrow, who has come to see his primary care physician for a routine checkup. He mentions to his physician that his sister was recently diagnosed with ovarian cancer at age 40. The doctor already knows the patient's father had colon cancer at a young age, and that a paternal aunt had endometrial cancer in her 30s.

He had recommended that his patient begin colon screenings soon due to familial risk for colon cancer. Current guidelines for colon screening in patients with a first degree relative with colon cancer specify starting screening colonoscopies 10 years before the earliest diagnosis of colon cancer in the family and repeating at three to five year intervals. However, with these other early onset gynecologic cancers in the family, there could be a cancer syndrome in the family that would change screening recommendations for this patient.

If you attended the first talk on this subject, what syndrome might you suspect in this family? Yes, the answer is Lynch Syndrome, the most common hereditary cause of colon and endometrial cancers.

What would be the best step to take to find out if your patient has Lynch Syndrome?

So the ideal family member to evaluate first is the father, as he had cancer at an unusually young age and is in the direct line of descent between the other affected family members. If the father was deceased, the aunt with endometrial cancer would also be a good candidate due to her early age of diagnosis. The sister would be acceptable, although her ovarian cancer could also have been caused by a maternally inherited gene.

If the father and aunt are deceased or unable to come in for genetic testing, we can often obtain a tumor block or slides from their cancer surgeries. That can be used to screen for Lynch Syndrome at the protein level and indicate what genetic testing would be appropriate for your unaffected patient.

As a quick review, about 10% of cancer patients have an inherited mutation in a single gene causing a hereditary predisposition to specific types of cancer. Because of the multisystemic nature of the cancer risk, the patient is said to have a hereditary cancer syndrome.

In these patients, the family history usually shows multiple relatives with cancers, one or more diagnosed at an early age. Sequential generations are usually affected and some family members may have more than one primary tumor.

It is critically important to identify our patients who have these hereditary cancer syndromes as they, and their family members, may be at risk for more than one kind of cancer. And there are often preventive measures that can be taken to eliminate the risk or increased surveillance for early detection and a much better outcome.

On this pie chart, notice the relative wedge sizes of hereditary versus familial cancer risk. Patients are labeled as having familial risk for cancer when they have a family history, but we cannot find an underlying genetic cause. As you'll see later, the hereditary wedge of the pie is gradually increasing in size and the familial wedge is decreasing as we discover new cancer susceptibility genes and offer more up-to-date testing to patients in the familial group.

This slide shows a small fraction of the known hereditary cancer syndromes. Over 200 hereditary cancer susceptibility syndromes have been described. The majority of which are inherited in an autosomal dominant manner. That is, a single gene mutation inherited from only one parent causes the syndrome.

Although many of these are rare syndromes, they account for approximately 10% of all cancer, amounting to a substantial burden of morbidity and mortality in the human population.

One of the things you may notice is that a given type of cancer, such as breast cancer, occurs in a number of these syndromes. In fact, in five of the syndromes on this slide alone.

This is why obtaining a complete history of all cancers in the family is important. It allows us to determine which syndromes to include in our genetic differential diagnosis. And therefore, which gene or genes to test. As you can see, all hereditary breast cancer is not due to the BRCA1 and 2 genes, nor is all hereditary ovarian cancer.

This slide shows the genes that are associated with these syndromes. I'm sure you all have some familiarity with hereditary breast and ovarian cancer caused by mutations in the BRCA1 and 2 genes. Other genes in the same cellular DNA repair pathway as BRCA1 and 2 are also known to increased risk for breast and ovarian cancer when mutated and are therefore considered part of the same clinical phenotype. Although the degree of cancer risk has not been well quantified for some and clinical management guidelines are a work in progress.

With all the media focus on the breast cancer genes, it may surprise you to know that Lynch Syndrome is twice as common as hereditary breast and ovarian cancer syndrome, but less often recognized in patients. Because the cancers associated with Lynch Syndrome are mostly preventable once the syndrome has been recognized in an individual and the screening and prevention guidelines are followed, the CDC has taken up Lynch Syndrome screening as a major public health issue.

In spite of the fact that we have genetic testing to confirm the diagnosis of many hereditary cancers syndromes, our most important tool for cancer risk assessment is the family history. This is the starting point for assessing whether your patient is at risk of having a hereditary cancer syndrome and whether or not genetic testing is a good idea for the patient.

An accurate family history is also crucial for interpreting most genetic test results. Most of your patients who undergo genetic testing will have negative results, but interpreting that negative result properly must be done in the context of an accurate family history. So I'm going to go over a few important things to keep in mind when you take a family history.

The accurate and up to date family history can be a tricky thing to get in a world where families are, more often than not, spread across the country or the globe. Patients very often have not had discussions about health issues with aunts, uncles, and cousins they rarely see. As a result, when you ask your patients if they have any family history of cancer, they often really don't know, unless they go home and start contacting relatives they haven't spoken to in years.

For this reason, it can be very helpful if your patients receive a family history questionnaire at the time their appointment is scheduled with the clear expectation that they complete it, and bring it to their appointment, and that you consider it important. The history should include at least three generations and both maternal and paternal lineages.

Then, ask if there are any new diagnoses in the family as a routine part of each visit. This needs to be incorporated into the normal workflow in your practice to be effective.

As genetic counselors, we insist that patients do this homework before their first appointment. And it is often very different from what is in their medical record, where we're likely to read no family history of cancer.

Over time, things can change, so family histories are dynamic. This young woman initially presented with a family history of colon cancer in her father and no other known cancer in her family. Her calculated risk of having a hereditary cancer syndromes, such as Lynch Syndrome, was only 5%. And she was not considered a candidate for genetic testing by any of the criteria used by her health insurance.

Two years later, however, her sister had developed endometrial cancer and her brother had developed colon cancer, both under age 50. Her calculated risk of having Lynch Syndrome is now 49% and evaluating the family for Lynch Syndrome would be highly recommended.

If she was your patient, would you proceed to test your patient for Lynch Syndrome at this point? What would be the most informative strategy to finding out her cancer risks?

And the answer is to test an affected family member. And if the affected family member has a negative result, then screen their tumor block for evidence of mismatch repair deficiency. If their result is positive, then test your affected patient for the family mutation.

When asking a patient about family history, one thing that cannot be emphasized enough is that the structure of the family is as important as cancer history. You need to know the size and gender composition of each side of your patient's family to be able to assess the likelihood of hereditary risk for cancer.

Here's the pedigree of a young woman being assessed for hereditary breast cancer risk because of her early age of diagnosis. Because there are a sufficient number of females on each side of the family in the preceding generation, none of whom had any cancer and are all still living, there's a very low probability that her breast cancer at age 41 has an underlying hereditary cause.

In general, the larger the family size, assuming no cancers in most relatives, the lower our index of suspicion for hereditary cancer syndrome. And the more likely it is that the patient has a sporadic cancer.

Does anyone have any questions about why this patient is being evaluated for a hereditary breast cancer risk when she already has been diagnosed with breast cancer?

And there are three reasons. First of all, a positive genetic test result often impacts surgical and treatment decisions, such as the decision to undergo bilateral mastectomy instead of lumpectomy. If she has a cancer syndrome, she may have cancer risk to other organs, such as her ovaries. And if we can identify a genetic and underlying genetic cause of her breast cancer, then the risk to her family members and children can be further elucidated.

There are several factors that can result in an individual who does have hereditary predisposition to breast cancer, having no family history of either breast ovarian cancer, and this pedigree demonstrates two of them.

First, there are few females on the paternal side of the family. And secondly, there is an early death in the paternal aunt that precluded the possibility of developing cancer. Since there are no females living past 30 on one side of the family, we cannot rule out hereditary breast cancer risk.

Any of the males on the paternal side, her father, two paternal uncles, and her paternal grandfather, could be silent carriers of a genetic mutation that increases risk for breast cancer and ovarian cancer. A limited family structure therefore raises the index of suspicion for a hereditary syndrome simply because the lack of information that might convince us otherwise.

So if your patient says no family history of cancer, ask how many aunts and uncles they have on each side of the family.

Other factors that can make it difficult to tell whether a patient has hereditary risk for cancer include surgeries that remove an organ that might otherwise have developed a malignancy.

For example, if female relatives have ever had a complete hysterectomy, that could mask hereditary risk for ovarian or endometrial cancers. Family members who are adopted and have no knowledge of their biological family history or loss of contact with family members after divorce or emigration, resulting in incomplete family history.

Another reason one might not suspect high risk for cancers is if family members are already adhering to an increased level of screening and removal of precancerous growths, such as colon polyps, due to a prior family history of cancer.

In this family, the four adult children whose father had had colon cancer were undergoing rather regular colonoscopies at three to five year intervals. Two of the brothers had developed polyps and had them removed but no cancers had developed in this shorter screening interval.

This is, of course, a good thing. But it also had the effect of concealing possible hereditary risk to the 20-year-old daughter of one of the polyp prone brothers.

It was therefore quite a shock when the daughter developed colon cancer at age 22 and was subsequently found to have Lynch Syndrome due to a genetic mutation she inherited from her father. This patient lost her battle with colon cancer at age 24.

So to summarize, a good strategy for documenting your patients family histories, tell your patients upfront that family history is taken very seriously in your practice. And tell them to do their family history homework before coming in to see you. Get history on both sides of the family, as well as the number of aunts and uncles and any early deaths.

Ask for any changes in the family history at every follow up visit as a matter of routine. And keep a current copy of the NCCN Guidelines for Hereditary Cancer Syndromes handy so you always know which patients need a genetic evaluation.

Now Dr. Kankipati talked about Lynch Syndrome in part one. However, because I think the primary care physician plays such an important role in the early identification and proper management of our patients with Lynch Syndrome, I'm going to discuss it again from the standpoint of what you can do to recognize patients who might have the syndrome, as well as the kind of multidisciplinary management these patients require.

Lynch Syndrome is the underlying cause of 5% of all colon cancer cases and a major cause of hereditary endometrial cancer as well. In addition, the syndrome is characterized by an increased risk of cancers of the ovaries, the stomach, small intestine, bile ducts, upper urinary tract, pancreas, and sebaceous glands all due to a single genetic mutation that can be passed down through successive generations in a family.

The gene mutations involved in Lynch Syndrome cause a deficiency in the cell's ability to repair DNA mismatches that occur during DNA replication. While we generally think of it as a colon cancer syndrome, a female with this syndrome often develops endometrial cancer before or instead of colon cancer. And family members can present with any one of these other cancers instead of or prior to colon cancer.

It has been estimated that approximately 600,000 people in the United States have Lynch Syndrome but only about 5% are aware of it. This is a huge missed opportunity for cancer prevention since colon and endometrial cancers are largely preventable if Lynch Syndrome screening and prevention guidelines are followed. As a primary care provider, you will usually be concerned about cancer risk in an unaffected patient with a family history of cancer.

So I'm just going to make a couple of important points that aren't on the slide. Genetic testing of your unaffected patient is rarely informative with respect to the patient's own cancer risks unless a close family member with a cancer diagnosis has previously been tested with positive results. In which case, your patient should be testing in a targeted way for the specific mutation found in the family.

Therefore, the best risk assessment for your patient can only be done by working with the family as a whole, which is what genetic counselors specialize in.

Your unaffected patient has a lower probability of carrying a cancer related mutation that may be in his or her family. And a negative genetic test result in an unaffected patient can be interpreted more than one way and definitely does not mean the patient does not have hereditary cancer risk.

Possible interpretations of negative results could mean that some family members carry a Lynch Syndrome related mutation that your patient just did not inherit, which is the best case scenario.

It could mean that affected family members have Lynch Syndrome due to an undetectable mutation, so that it also would not be picked up in your patient. And we have other ways to detect to screen for Lynch Syndrome in that case.

Or it could mean that the cancers in the family are due to a genetic factor that has not yet been discovered, so also would not be picked up in the testing that was done on your patient.

A much more informative strategy for determining whether your patient has Lynch Syndrome can be very time consuming, but this is what genetic counselors do all day. And we are always happy to work with our primary care providers to evaluate patients for Lynch Syndrome.

Our strategy would be to obtain a tumor block from an affected family member to screen by immuno-histochemistry for a mismatch repair protein deficiency and use that information to determine whether genetic counseling is indicated, as well as to interpret any negative genetic test results.

If there are discordant results between tumor testing and germline genetic testing, the genetic counselor will pursue somatic mutation testing of the tumor block to discriminate between patients with Lynch Syndrome who have an undetectable mutation and the occurrence of two somatic mutations causing the tumor.

A patient like the unaffected 45-year-old woman right here in this pedigree has a family history that definitely suggests Lynch Syndrome. But because no one in the family had a cancer diagnosis under age 50, she does not meet screening criteria that miss about 40% of patients with Lynch Syndrome.

Those are called the Amsterdam criteria. And the Amsterdam criteria are used by many health insurance to cover genetic testing.

Therefore, if family history alone is used to determine who should have genetic testing, many Lynch Syndrome diagnoses will be missed and many patients and their family members will go on to develop additional cancers that could have been prevented.

Fortunately, as I mentioned, there are these other means available to prescreen patients for this genetic syndrome if they have any personal or family history suggestive of the syndrome.

And, as I mentioned, these other ways of prescreening are based on testing tumor tissue for features that indicate that the mismatch repair genes aren't functioning properly and that one of them may contain a germline mutation.

So individuals with Lynch Syndrome are said to have mismatch repair deficiency. And we currently know of four genes that encode the mismatch repair proteins. As well as a stretch of DNA called the EPCAM locus that can actually disrupt expression of one of the mismatch genes.

The normal function of these proteins is to repair mismatch errors that occur during replication of DNA as cells divide. And a mutation in any one of these genes usually results in the absence of the corresponding protein in tumor tissues, which we then can detect through immuno-histochemistry.

So if the unaffected family of 45-year-old woman was your patient, what strategy would you use to assess her risks for cancer?

You would ask whether there was any available tumor block from either her sister or her father, and or whether either of those family members was available for genetic testing. Also, I would get the phone number for the oncologist of both the sister and the father to inquire about whether tumor screening was already done or if genetic testing was already done.

Since 2012, we've been performing universal Lynch Syndrome screening of all colon and endometrial tumors from suit surgeries performed at John Muir Health to determine which patients should undergo genetic testing for Lynch Syndrome.

Universal tumor screening is recommended by the Centers for Disease Control because it compliments screening for Lynch Syndrome on the basis of family history. Family history picks up about 60% of cases and, combining it with the IHC, this results in close to a 100% detection rate.

If a patient undergoes genetic testing and a mutation is detected in one of the four mismatched repaired genes, this confirms a diagnosis of Lynch Syndrome. This slide shows the current guidelines for surveillance and preventive measures.

So a colonoscopy at age 25, repeated every one to two years, prophylactic hysterectomy, and bilateral salpingo-oophorectomy is a risk reducing option for women who have completed childbearing. Screening for ovarian and endometrial cancers is not currently recommended. Both transvaginal ultrasound and endometrial biopsies can be considered at the clinicians discretion, but data do not support their efficacy.

If there's a family history of gastric or small bowel cancers, consider upper endoscopy for those beginning at age 30, depending on the gene involved and the family history. Also, consider annual urinalysis for urothelial cancer starting at age 25 to 30.

Recent studies have also shown that young female cancers with Lynch Syndrome, who are not yet ready to have the risk reducing gynecological surgeries can benefit significantly by having their colonoscopies coordinated with simultaneous endometrial biopsies while under sedation.

Also, early studies show evidence that progestins may be useful for reducing the risk of endometrial cancer in women with Lynch Syndrome. And that aspirin is likely to reduce the risk of colon cancer in both genders. More studies are currently underway to confirm this risk reduction and the optimal dosage.

Identifying patients who have Lynch syndrome leads to dramatic decreases and more ability and mortality, as is illustrated by this 2005 paper in the European Journal of Gastroenterology. This paper describes the long term effects of early and more frequent surveillance in 22 families that were identified as having Lynch Syndrome.

The authors followed these families over three generations. And just to quickly summarize the study, the incidents of colon cancer fell from almost 60% in the first generation down to only 8% within two generations. Solely due to identifying which family members had the syndrome and having them undergo increased colon screening and removal of precancerous polyps.

So in addition to knowing your patients current family history, you can go to the current NCCN and website and download the current guidelines for Lynch Syndrome screening to help you assess which patients should be evaluated for Lynch Syndrome.

The NCCN guidelines for managing patients with Lynch Syndrome are also found on the web site and are updated annually.

And, of course, if your patient has a diagnosis of colon or endometrial cancer, check the pathology report for results of IHC screening of the tumor, which will also indicate whether a genetic evaluation is recommended.

There been some important changes in the last few years regarding hereditary breast and ovarian cancer syndrome, including an expanded list of genes that can cause it. The most clinically relevant information can be found on the NCCN website under Guidelines for Detection, Prevention, and Risk Reduction. And under Genetic High-risk Assessment for Breast and Ovarian Cancer.

Of the 10% of breast cancer patients who have a hereditary predisposition to breast cancer-- that is detectable by our current technology-- about half have a mutation in BRCA1 or BRCA2. Another 30% have mutations in a variety of other known breast cancer genes, such as TP53, CHEK2, PALB2, BARD1, BRIP1, FANCC, RAD51C, RAD51D, PTEN, CDH1, and ATM. And about 20% are believed to have an unknown but highly penetrant breast cancer gene based on their strong family histories that demonstrate an autosomal dominant pattern of inheritance.

So what are these other breast cancer susceptibility genes? To a large extent, the other known breast cancer susceptibility genes normally function along side of BRCA1 and 2 in what is known as the fanconi anemia BRCA pathway of double stranded DNA repair.

Keeping the DNA in good repair is critical to maintaining the integrity of the cell cycle and avoiding the transformation of normal cells to cancer cells. As you all probably remember from biochemistry, a block in any step of a biochemical pathway due to mutation of the corresponding gene can lead to a similar clinical phenotype.

In the case of the fanconi pathway, mutations in some of these genes leads to a very similar risk profile, as we see with BRCA1 and 2 mutations. While others lead to more moderate risks or risk for breast cancer and cancers other than ovarian.

Some of the genes in this pathway, such as TP53 and PTEN have been well-characterized, and we have had management guidelines for over a decade. Whereas several of the genes in the pathway were made available for clinical testing based on their clear association with specific cancer risk, but before clinical guidelines were agreed upon.

In the event that a patient is found to have a mutation in a gene for which no guidelines yet exist, patient management is based on a combination of what is known about the specific gene combined with the patient's family history, with the expectation that consensus guidelines are a work in progress. And I'll show you an example of that shortly.

Occasionally, a patient will come to genetic counseling and tell me, my doctor doesn't think genetic testing is going to change my family history that shows I have a very high risk for cancer. To try to dispel the assumption that one's family history is one's inevitable fate, let me tell you about the three sisters in this family, indicated with the blue stars down here.

The three sisters have a very strong family history of both breast and ovarian cancer, often in the same individual. The sisters are concerned about their own cancer risks after their mother and three maternal aunts were diagnosed with both breast and ovarian cancer, as well as several other maternal relatives with either breast or ovarian cancer.

The three sisters were assumed to be at high risk for breast and ovarian cancer due to their strong family history. All three were advised to have preventive removal of their ovaries and to increase screening for breast cancer.

One sister followed this advice, while the other two decided to consult a genetic counselor before making any decisions about surgeries. At the end of a genetic counseling session attended by the sisters and their mother, the mother consented to having blood drawn for genetic testing of the BRCA1 and 2 genes.

As I'm sure you know by now, finding the underlying genetic cause of her cancers is the important first step in a genetic evaluation of her daughters. It was no surprise to find that the mother carries a pathogenic mutation in the BRCA1 gene, which explained the high incidence of breast and ovarian cancers in the family.

Once the familial mutation had been detected in the mother, each of her daughters could then be tested for that specific mutation, each having an independent 50/50 chance of having inherited it. Subsequent genetic testing of the three sisters showed that two of them had not inherited the family mutation, and therefore had the general population risks for both breast and ovarian cancers in spite of the family history.

Unfortunately, one of the sisters who had tested negative had already undergone a bilateral salpingo-oophorectomy, putting her unnecessarily into menopause in her 30s. The sister who tested positive for the BRCA1 mutation began planning the steps she would take to reduce her high cancer risks.

So this family story illustrates why assessing a patient's cancer risk solely on the basis of family history is not usually the best approach. In cases where an affected family member is living and consents to genetic testing, the whole family benefits.

For this reason, it is always important to start any genetic evaluation with an affected family member. And this can be facilitated by a genetic counselor who is trained to work with the family as a whole.

As you all know, advances in technology often drive advances in clinical practice and genetic testing is no exception. The old gold standard for DNA sequencing called Sanger sequencing has rapidly been replaced by Next Generation DNA sequencing, which allows a molecular diagnostics lab to sequence multiple genes simultaneously with greater accuracy and no increase in cost. In fact, the costs have been declining significantly.

As a result, if a patient has a paternal family history that has a lot of breast cancer in it, and a maternal family history with a lot of colon cancer, we can test simultaneously for any suspect genes in the differential with a single multigene panel test.

Before I address the potential downsides of this approach to testing, let's look at the benefits.

More patients with clear evidence of inherited cancer risk are having a mutation detected that explains the pattern of cancers in their families and leads to changes in their medical management. And secondly, depending on the indication for testing, up to 9% more patients have a pathogenic mutation detected, many of which are clinically actionable under today's NCCN guidelines. And these guidelines are continually evolving to incorporate the new data on other cancer genes.

This slide shows the 2015 version of the NCCN guidelines for managing patients with hereditary breast and ovarian cancer syndrome. And I've added the 2016 changes in red.

The guidelines now recommend-- in a second column over-- the addition of an annual breast MRI for women with mutations in nine different genes. In the third column over, a risk reducing bilateral salpingo-oophorectomy for women with mutations in 10 different genes, and discussion of risk reducing bilateral mastectomy for women with mutations in six different genes.

So you can see just in a six month period how these guidelines are changed.

For several other genes being tested on the multigene panels, the guidelines state-- as you can see in the blue box-- that there is insufficient evidence for intervention. But that intervention may still be warranted based on family history or other clinical factors.

So for example, if you had a breast cancer patient with a PALLB2 mutation, which warrants a risk reducing bilateral mastectomy, the guidelines do not specifically recommend removing her ovaries. But if she has a sister with ovarian cancer, the intervention is still warranted based on family history.

Clearly, the optimal management of these patients is a work in progress. And we can expect to see a lot of changes in the guidelines to keep up with the rapid adoption of multigene panels by most genetic centers across the country.

On the downside, pretest counseling, informed consent, and result interpretation are all more complex and time consuming with multigene panels. Also, even when testing one or two genes at a time, a certain percentage of patients will be found to carry genetic variants of uncertain significance that may take months to years to be reclassified either as benign variants or pathogenic mutations. One of the downsides of multigene panel testing is the increased number of patients with variants of uncertain significance.

In order to find out whether a genetic variant has clinical significance, the ordering clinician needs to go a lot further than ordering the test and reporting the results. Receiving a result with a variant of uncertain significance requires that the clinician communicate with the testing lab regarding enrolling specific family members in research on the variant and then facilitate this research testing.

It's also a very good idea if the patient enrolls in a research registry devoted to studying genetic variants of uncertain significance. And it's imperative that the clinician follow up with the patient as new information on the variant is received from the lab or other research.

Let's look at a couple of patients who've benefited from Next Generation testing. This is the pedigree of a patient I first saw in 2009. Here she is down here.

She has a personal history of bilateral breast cancer, and a family history of a sister with both breast and ovarian cancers. Paternal grandmother with bilateral breast cancer, paternal aunt and cousin with breast cancer in their 50s and 60s. No maternal family history other than lung cancer in a smoker.

In 2009, we tested both the patient and her sister for BRCA1 and 2 mutations, and both had negative results.

The patient returned for further testing of other genes in 2015, and we found that she and her sister carry a mutation in the PALB2 gene, one of the genes in the fanconi BRCA pathway.

PALB2 mutations are associated with a fourfold increased risk for breast cancer, with limited evidence suggesting an increased risk for ovarian and pancreatic cancers. Fortunately, my patient has already undergone a full hysterectomy due to her sister's history.

The benefits to my patient from having pursued this extra testing are that she now knows the reason for all the breast cancer in her family, and they have a defined marker that can be used to find out if other family members are at high risk or not. She's got two sisters, multiple nieces, and paternal cousins who all will benefit from this information.

Here's the pedigree for a male patient who presented at age 56 over here with an aggressive prostate cancer.

The maternal side of his family is very small due to his mother having been an only child. So we can't tell if there might have been more extensive maternal history beyond his mother's early breast cancer.

On the paternal side, there's a lot of cancer. Father with kidney cancer at 40 and a glioblastoma at 63, uncle with prostate cancer in his 60s, another uncle with colon cancer at 64, two cousins with breast cancer, one of whom also had colon cancer, and grandparents with prostate cancer and an unspecified brain cancer.

This patient is a good candidate for a multigene panel test because the genetic differential includes at least three syndromes. His paternal family history of colon, brain, and kidney cancers suggests Lynch Syndrome. The combination of colon, breast and prostate cancers is suggestive of a mutation in the CHEK2 gene, another gene involved in maintaining the integrity of the genome. And his maternal family history of early breast cancer, combined with his early prostate cancer, suggests hereditary breast and ovarian cancer due to a BRCA1 or 2 mutation.

So a custom panel of genes was ordered to cover all these possibilities and results showed that he does indeed carry a mutation in the CHEK2 gene that is known to double risks for colon, breast, prostate, kidney, and thyroid cancers. Absent NCCN guidelines for CHEK2 mutation carriers, screening recommendations were based on the extensive data on CHEK2 in the literature combined with his family history.

Some of the screening recommendations were things he was already doing, such as colonoscopies at three to five year intervals. However, due to his twofold risk for thyroid and male breast cancer, his annual physical exam will now include special attention to these issues.

I want to close by thanking our primary care providers for all you do. And invite you to use your John Muir Health genetic counselors as resources to help identify patients with hereditary risk for cancer.