Hello. My name is Maureen Mork and I'm a Certified Genetic Counselor in the Clinical Cancer Genetics Program at The University of Texas MD Anderson Cancer Center. I'll be lecturing today on the Cancer Genetic Risk Assessment.

After my lecture, I hope that you'll be able to identify features of families that are suggestive for hereditary cancer syndromes; to discuss the implications and impact of hereditary cancer on families and patients that we see; and to describe the benefits, limitations, and risks of genetic testing for hereditary cancer syndromes.

So as a genetic counselor, I'm really actually only focusing on a small percentage of all cancer which is the hereditary component of cancer. Most cancer, approximately 70 to 80% of cancer, is considered to be sporadic and not associated with hereditary cancer predisposition genes. Individuals with sporadic cancers tend to be diagnosed at older ages. These cancer diagnoses may be related to risk factors. And we don't typically see these families with cancer running through them. Another category of cancer risk is familial clustering of cancer or multifactorial cancers. These represent approximately 15 to 20% of cancers. And in these families, we see more cancer than we would expect to see in the sporadic cancer families. But these families may have the clustering of cancer due to a number of factors which can include shared environment and lifestyle factors. These families may also have some shared genes in common. But these genes are considered to be low penetrant or subtler acting genes than what we would typically see in the hereditary cancer families. Hereditary cancer families constitute about 5 to 10% of cancers. And families with hereditary cancers have cancer risks that are caused by a single high impact or highly penetrant gene. In these families, we typically see people in the family with young ages of cancer diagnosis. There may be multiple members of the family with the same type or related types of cancer. And we may see families that have individuals with more than one type of cancer.

And with the discovery of these hereditary cancer genes that constitute the 5 to 10% of cancer, genetic testing is now available to us as a tool to identify patients who are at high-risk for certain types of cancers. And you as healthcare providers have an important role to inquire of these patients, you know, what is their family history of cancer, to know what red flags you should be looking for in the family history, and to refer appropriate patients to genetic counseling for further workup, risk assessment, and genetic testing, if appropriate.

So the first step, of course, is inquiring about the family history. And it's important to know what questions you need to ask and of what family members you need to ask.

It's important to ask about a three generation pedigree that you ask about both maternal and paternal families. We want to make sure that you don't focus just on one side of the family. And inquiring about cancer history should include the type of cancer of family members, the ages at onset, and personal risk factors. For example, if a patient has a relative that's had an endometrial cancer, it'll be important to ask if that --- if that relative has had certain risk factors, for example, obesity that could have contributed to
that cancer risk as opposed to a hereditary cause. In addition to asking about relatives affected with cancer, it’s also important that you ask about unaffected relatives, asking about their ages at death or current ages. And this will help to give a context about how big the family is and within that family how many individuals in that family developed cancer.

And a very important concept to be aware of for these hereditary cancer syndromes is the mode of inheritance. The majority of hereditary cancer syndromes are inherited in an autosomal dominant way with incomplete penetrance. And what that means is that an individual in a hereditary cancer family is equally likely to have inherited this, whether it’s a man or a woman in the family, and then his or her sons or daughters are also equally as likely. So there’s no --- no bias or no selection, no inheritance pattern based on the sex of the individual. And this is passed down in a 50/50 manner meaning that if an individual is affected that his child --- his or her children have a 50% risk to have inherited the cancer susceptibility gene mutation and an equally likely 50% chance to not have inherited that mutation. However, it’s important to note that the penetrance of these conditions of these genes is often incomplete. And what that means is that because an individual carries a gene mutation this doesn’t mean that that individual is guaranteed to develop a cancer. And this is what is meant by incomplete penetrance. And because of this incomplete penetrance of cancer, the cancer itself may appear to skip generations. But an important concept to know is that the cancer, while appearing to skip generations, does not represent the gene mutation. The gene mutation is not skipping generations, but is passed through with that 50/50 chance but the cancer itself is expressed incompletely. And individuals are not inheriting the cancer, but they’re rather inheriting the genes that predispose to cancer.

And this brings us to the Two-Hit Hypothesis which was first described by Alfred Knudson in 1971. And this describes why individuals with a hereditary cancer predisposition gene are developing cancer at younger ages than an individual that does not have this predisposition mutation. These cancer predisposition genes come in pairs, as most of our genes do. An individual who does not have a hereditary cancer syndrome like this individual here will have two copies of a gene mutation --- of a gene that has no mutations. But if we look over to an individual here that has a cancer predisposition mutation, one of their two genes already has a mutation which is considered to be the first hit. And his or her daughters are then at risk to have inherited this hit again. However, just because this individual’s child has inherited the first hit in their germline this does not necessarily lead to cancer. What leads to cancer is when this individual develops or acquires a second hit in the other copy of the gene and this is the second hit of the two hit hypothesis. Once this individual identifies develops the second hit that leads to tumorogenesis and cancer. And it is this reason why an individual who has inherited a cancer predisposition gene often develops cancer at younger ages than an individual who is born with no gene mutations. For this individual here, she will not develop cancer unless two hits are acquired. And this is usually at later ages.
So, when you are reviewing your patient’s family history, the red flags that you should be looking for that may warrant a referral to genetics include clustering of the same cancer in close relatives. And you want to make sure that these are on the same side of the family. Unless a parent’s --- Unless a patient’s parents are related to each other, cancer on opposite sides of the family isn’t typically an associated risk factor. You’re also looking for early age of cancer onset, typically below the age of 50. If you see a patient or --- or his or her relatives with two or more primary cancers in a single individual, this is also a red flag for hereditary cancer. Individuals with --- with hereditary cancer may also have bilateral cancer impaired organs or multifocal cancers. When you are taking the family history, if you see that successive generations are affected, this is potentially evidence of autosomal dominant inheritance and could also warrant a referral to genetics. And finally, if you yourself are familiar with any of the hereditary cancer syndromes and you see a family history that seems to be consistent, this also may be an appropriate family for genetics.

So, now, that we have reviewed some basics of cancer genetics I will provide an overview of some common syndromes.

And I’ll talk about three specifically. There are over two dozen hereditary cancer syndromes. So I won’t be discussing each of those. Of the hereditary breast cancer syndromes, the most common is hereditary breast and ovarian cancer or HBOC. And this is caused by mutations in the BRCA1 and BRCA2 genes. You may also hear these referred to as BRCA1 and BRCA2. Moving to the hereditary colorectal cancer world, there are two syndromes that you may run into. The first is Lynch syndrome, which is also referred to as hereditary nonpolyposis colorectal cancer or HNPCC. And this condition is caused by mutations in the DNA mismatch repair genes. And this is considered to be the most common hereditary form of colorectal cancer. Lynch syndrome is contrasted with familial adenomatous polyposis or FAP, which is caused by mutations in the APC gene, and causes individuals to develop hundreds to thousands of --- of colorectal polyps. And therefore, causes an incredibly high lifetime risk for colorectal cancer nearing 100%. These three conditions are some that you may --- that you may encounter in clinic. The other hereditary cancer syndromes tend to be quite rare so I won’t be reviewing those today. And today I’ll specifically be focusing on hereditary breast and ovarian cancer.

So as I previously stated this is causative for the majority of hereditary breast cancers and is caused by a germline or inherited mutations in the BRCA1 and BRCA2 genes.

And mutations in these genes cause quite elevated lifetime cancer risks. Women with these mutations have up to a 50 to 85% risk for breast cancer over their lifetime. And they also have a risk for a second primary breast cancer after their first breast cancer of 40 to 60%. Women also have an elevated risk for ovarian cancer between 15 to 45%. And it’s important to note that this isn’t exclusively to the ovaries. This includes fallopian tube cancers and primary peritoneal cancers. In families with BRCA1 and BRCA2 mutations, we also see elevated risks for male breast cancer, prostate cancer, and for men and women with BRCA2 mutations, in particular pancreatic cancer.
So if we take those red flags that I discussed previously that was kind of a general overview for cancer genetics and focus it in on hereditary breast and ovarian cancer, you'll be able to see that families with multiple individuals with ovarian cancer or breast cancer should be a red flag for --- for hereditary breast and ovarian cancer. You should also be looking out for young age of onset of breast cancer, which is typically under the age of 50 or when women are premenopausal. Women may also have bilateral breast cancer. This should be a red flag. In addition to women who develop triple negative breast cancer, that is, estrogen, progesterone, and HER2/Neu negative on their tumor markers. If --- If a woman has both breast and ovarian cancer, that should also be a red flag. Women who are of Ashkenazi Jewish ancestry and men of Ashkenazi Jewish ancestry may also raise a red flag. The reason is that individuals of Ashkenazi Jewish ancestry have BRCA1 and BRCA2 mutations at a higher carrier frequency than the general population. Male breast cancer, which is quite rare in the general population, is also a red flag for hereditary breast and ovarian cancer.

And here is a pedigree or a family history that is demonstrating a family with some typical features of hereditary breast cancer --- breast and ovarian cancer and this family has a BRCA1 mutation. Here, with the arrow, is the first patient that presented to genetics or the ProBand. She has breast cancer at 36. And you'll see that there are a number of other individuals in the family who have had breast cancer at young ages and also have ovarian cancer. And the individuals that are shaded in orange represent individuals that carry the BRCA1 mutation and have been affected with cancer. And you can see that this is demonstrating the autosomal dominant inheritance with successive generations being affected. And, this also demonstrates incomplete penetrance with these individuals here with the white with the blue stripe. These individuals are carriers of the BRCA1 mutation in the family, but are personally unaffected with cancer. For our patient’s father here, we often do see men with BRCA1 or BRCA2 mutations who are unaffected with cancer simply because the cancer risks for men are lower than that of women. If we move up to our patient’s father’s aunt, she is 86 and has never developed a cancer. But her daughter developed a breast cancer and she is a carrier of the BRCA1 mutation. She did have a risk-reducing surgery in her 40s, a total abdominal hysterectomy and bilateral salpingo-oophorectomy which could explain why she is 86 and has never developed any cancer.

So for these families at high-risk for breast and ovarian cancer, we do discuss a number of management options with them. And these are the management recommendations that are put forth by the National Comprehensive Cancer Network Clinical Practice Guidelines in --- Guidelines in Oncology. For breast cancer, women have the recommendation of increased surveillance, including a breast self-exam beginning at age 18 and then mammogram plus breast --- breast MRI every six --- [I'm sorry] --- every 12 months and this would be rotating mammogram every six months, then breast MRI six months later, then back to mammogram every six months, so that this --- so that these women are having breast imaging every six months with alternating modalities. Women are also recommended to have clinical breast exams every six to 12 months, all of this beginning at age 25. Women also have the option of taking
tamoxifen or similar drugs for chemo prevention. And women also have the option of undergoing a risk-reducing bilateral mastectomy. For ovarian cancer, there is no proven benefit to surveillance for ovarian cancer. But women may wish to undergo transvaginal ultrasound along with a CA-125 blood test for ovarian cancer marker every six months beginning at age 30. Chemopreventative options include oral contraceptives and women are recommended to undergo to consider a bilateral salpingo-oophorectomy. And all of these different options are typically discussed with women at a high-risk clinic.

So a summary of the implications of hereditary cancer on families. These families have unique family history features with young onset cancers in multiple family members. These families are recommended to undergo increased cancer surveillance and management typically beginning at younger ages and with an increased frequency over the general population. And these family members have a range of management options which are which can be discussed at high risk cancer management clinics, if available.

Next, we’ll move to discussing the genetic counseling and testing process.

Genetic counseling is a process of providing information about an inherited condition to an individual or family, providing supportive counseling to these families, and providing these families with resources. And genetic counseling is typically provided by a highly specialized board certified genetic counselor.

And when a genetic counselor, like myself, meets with a family we make sure to do a number of things with the family. First, risk assessment. As part of the risk assessment, we will generate a multi-generation pedigree making sure to find out who in the family has had cancer, who in the family has not had cancer. And we may need to obtain clarification or documentation of the reported cancer family history. As part of this risk assessment, we also identify the appropriate family member to test. For example, a patient that is sitting in front of me may not be the appropriate family member to test. There may be a mother, a sister, an aunt, or an uncle that is better and would provide the most informative genetic test result for the rest of the family. Genetic counselors also interpret the genetic test results and impart this information to the patient and their family. And through this process several issues, including psychosocial issues and insurance issues, may arise and genetic counselors help address those. Genetic counselors as part of the patient’s health care team also help to provide individual individualized screening recommendations.

So an important concept to know about genetic testing and genetic counseling is that not all patients that are seen by a genetic counselor are offered genetic testing. So a referral to a genetic counselor means that a patient will receive a comprehensive risk assessment and recommendations. But those recommendations may not include genetic testing. For example, a patient may have a relatively low-risk family for which genetic testing is not appropriate. There may not be a gene that is known that can explain the family cancer history. And therefore genetic testing isn’t available or, as I
had stated previously, there may be someone else in the family that’s more appropriate for genetic testing. But once, the appropriate patient has been identified that patient will be provided pre-test genetic counseling, including the implications of a positive or negative or an inconclusive result. These patients will undergo the informed consent process. And after the test has been sent off, the genetic counselor will follow up with the patient to disclose results and provide post-test counseling and follow-up, which very often includes not only the patient but his or her family members.

In 2010, the American Society of Clinical Oncology updated their policy statement regarding genetic testing for cancer susceptibility and stated that personal and family history features suggestive of a hereditary cancer syndrome is an indication for genetic testing. It’s important that any test that is offered be adequately interpreted and that the results of the testing will aid in the diagnosis and medical management for the patient. In addition, genetic testing should be done in the setting of pre- and post-counseling.

In addition to thinking about the logistics of genetic counseling and genetic testing, there are also other considerations to think about. One of them is the wide range of possible emotional reactions from the patient and his or her family. Some families may be quite assured reassured by the information that they receive why other family members and patients may be quite distressed. And it’s important to anticipate and be able to address all of those possible reactions. Something else that’s important to discuss with the patient is how will the patient and their family actually use this important information that you are providing to them. It’s a discussion that we have is sharing test results with family members. And also to discuss how the test results may change that patient and family and family’s cancer screening and health management. A lot of patients are concerned about the cost of genetic testing and insurance concerns as well as genetic discrimination. And I’ll be going into that in a little bit.

So, “what are some benefits of genetic testing?” Genetic testing can provide information about an individual’s cancer risk. It can also help determine cancer risk for family members and may assist in making decisions about cancer screening or management depending on the results of genetic testing. It can also provide relief from uncertainty. For example, if a family has been identified to have a gene mutation that causes an increased risk for cancer and a family member tests negative for that mutation that’s been in the family, he or she may be quite relieved because they don’t have the same cancer risk as the rest of of the family with the mutation and would be at the population level risk for cancers. And this goes back to the final point, it may identify individuals who are not at risk in families with known mutations.

However, there are certainly limitations in this process. Going back to the point I made before about incomplete penetrance, if someone tests positive for a genetic mutation, this does not determine with certainty if a cancer will develop, what type of cancer will develop, or when a cancer will develop. In addition, a negative test result cannot rule out an increased cancer risk. For example, there may be someone better in the family
that needs to be tested so a negative test result doesn’t necessarily rule out a mutation in the family. Or, the family may be at an increased risk due to the multifactorial or the family clustering of cancer and therefore this test result --- a negative test result doesn’t always provide reassurance that there is a --- a lower cancer risk. In addition, the screening and prevention measures that are available for hereditary cancer are not 100% effective. So even if individuals undergo the recommended screening, they may still unfortunately develop a cancer. In addition, all individuals have a background risk for cancer. So even in a family in which an individual tests negative for the BRCA1 mutation in the family, he or she is still at the background risk for cancer. And for example, a woman in that situation would still have the 12% lifetime risk that a woman has in the general population to develop cancer. So these are important concepts to discuss with patients.

So in the genetic counseling process, we need to determine what type of test is most appropriate for the patient that you are seeing. And this includes full gene analysis, known mutation testing, and multi-site testing. The first type of test was --- is full gene analysis, [it] involves analyzing the entire gene for mutations through sequencing of the gene and deletion and duplication testing of the gene. This is typically recommended to patients when there has been no previous genetic testing in the family. And, you need to have the most comprehensive look at the gene to see if you can find your answer. However, the limitations of this is that it may not identify all mutations. Our technology isn’t perfect. And it may identify uncertain variants for which the clinical significance is unknown and not well understood. For known mutation testing, this is recommended for individuals in a family in which a mutation has already been identified in the family. And this involves testing that individual only for the specific gene mutation that has been identified in the family as opposed to the comprehensive look at that gene. And this is the best method once the family mutation has been identified. And it has a 100% accuracy for family members. So if a family member tests negative for the mutation that’s been in the family, he or she can be quite reassured of this information. However, if an individual tests positive then he or she is aware of the cancer risk and recommended screening. And finally, multisite testing involves testing for a panel of specific mutations. And this is typically recommended, for example, in individuals of Ashkenazi Jewish ancestry for the BRCA1 and BRCA2 genetic testing. There are three common mutations in that population. So for individuals who are Ashkenazi Jewish as opposed to doing comprehensive genetic testing, we’ll typically start off by testing for those population-specific founder mutations.

Now, once the appropriate genetic test has been recommended, the patient decides to undergo the testing, and the test is sent off, there are several different test results that can come back and have imp --- an impact on the patient and his or her family. These two results, positive and true negative, are pretty straightforward and have some very clear cut answers for the family. The first is a positive result. This means that a deleterious or disease-causing mutation has been identified in the gene that is associated with the increased cancer risks. This confirms the diagnosis of the cancer syndrome in the family and other family -- family members can definitively clarify their risk to inherit the specific cancer syndrome. And this is done through predictive genetic
testing. The second very clear cut result is called a true negative and this is a result that would come from the single site or the known mutation testing. So if you have a family member who is being tested for the mutation that’s already been identified in the family and he or she has no mutation detected, meaning that they have tested true negative for the mutation that’s already been found in the family, this is very reassuring that the individual has not inherited the cancer syndrome in the family. And the cancer risks are not 0%. They return to the general population risk. But they are not the elevated cancer risk that we see in the hereditary cancer syndromes.

These last two results, uninformative negative and uncertain variant or variant of uncertain significance, provide some uncertainty and are somewhat inconclusive for these families. The first result on this slide which is an uninformative negative comes as the results of the comprehensive genetic testing, which looks at the gene through the sequencing and deletion duplication testing. And this is when a --- a --- no mutation has been identified in the family. So there’s no previous genetic mutation known and no mutation is detected when you test your patient. There’s a number of different possibilities for the reason for this uninformative negative result. It could mean that there is no mutation in the family that can be found at all, because the family doesn’t have a hereditary cancer syndrome or because our genetic testing technology is not perfect and may have missed it. There may be some role in considering testing in another affected family member. And we would work with the family to help identify the appropriate person next. And typically the cancer risk management is based on the family history of cancer in these cases. Finally, the uncertain variant result, also called a variant of uncertain significance means that the laboratory has identified a DNA change, but the clinical significance of that DNA change is unknown. That is to say that the laboratory is unsure whether this DNA change is contributing to cancer risk or if it is just a benign change or a polymorphism. In this case, we do not typically clinically recommend to test other family members, because we do not want family members to make decisions about their health care based on the presence or absence of this uncertain variant. Some laboratories or research programs may recommend testing affected family members to determine segregation with cancer. But this, again, is not typically a clinical recommendation that we’ll make. And again, cancer risk management is based on the family history of cancer rather than the genetic test results.

And for these patients regardless if that patient pursues genetic testing as part of their health care team, we make sure to discuss individualized cancer screening based on the personal and family history, preventative measures including discussing the national guidelines, and medical management options including referrals to appropriate specialists. And these recommendations are based either on positive genetic test results or on the patient’s family history of cancer.

Finally, I will review the Genetic Information Non-Discrimination act of 2008 also referred to as GINA 2008. Many patients ask me about the risk for insurance discrimination or about employment discrimination based on undergoing genetic counseling or genetic testing. I find that they are reassured when I review with them
GINA, which is federal legislation that was signed into law in 2008. And it prohibits discrimination for individuals who have undergone any kind of genetic workup for their health coverage and employment based on genetic information. And in this law, genetic information is defined as an individual or family member's genetic tests, family history, and genetic counseling, genetic testing, or education by that individual or anyone in their family. For more specific information about the GINA legislation, you can visit this website which is listed down below which is the National Human Genome Research Institute.

So in summary, not everyone who comes for genetic counseling for a risk assessment is offered genetic testing. There may be someone more appropriate, if there's anyone appropriate in the family at all. There is an emphasis as --- as recommended by ASCO on pre- and post-test counseling. And not all genetic test results are unequivocal. Not all genetic test results are straightforward. So this is where genetic counselors are important to help make recommendations. Genetic --- Cancer risk assessment is based on positive test results or family history. We need to make sure to consider the emotional and psychological impact on the family and there is federal and state legislation for genetic discrimination. This is the conclusion of my talk today. Thank you for listening and I hope that at the conclusion that you'll be able --- that you've learned how to identify families that are at increased risk for hereditary cancer syndromes and the impact that this can have on families. Of course, we'd welcome any feedback and I thank you again.