**Speaker**

**AB** Welcome. My name is Amanda Brandt. I am a Genetic Counselor at the University of Texas MD Anderson Cancer Center.

**KR** Hello. My name is Kaylene Ready. I’m also a Genetic Counselor.

**AB** Today, we are going to review a few case studies that involve hereditary breast and ovarian cancer. And, we’ll go through some of the difficult decisions that may need to be made in regards to some of the testing and screening for your patients.

**AB** In this module, you will be able to describe the various cases when genetic testing is indicated; think critically about how to interpret the test results based on a patient’s personal and family histories; and understand the potential difficulties that may arise during the genetic counseling process and testing process.

**AB** So, in Case 1, we have a 31-year-old woman who is unaffected. She’s coming in questioning her family history of cancer and is concerned whether or not she would have a high risk. She has a sister, who is 38, diagnosed with breast cancer at the age of 31. She has twin sisters, who are 46 years old, one of whom was diagnosed with breast cancer at the age of 33. Her other sister diagnosed with breast cancer at the age of 34. On her paternal side of the family, you will see she has an aunt diagnosed with breast cancer at the age of 23, who passed away at the age of 29. Related through her paternal grandmother, she had a great-aunt who was diagnosed with breast cancer at 35 and died at the age of 40.

**AB** In this case who --- what would you do first? A) Recommend testing for your patient. B) Recommend testing to an affected family member. C) No testing would be recommended. Or, D) Run the Gail model to assess the breast cancer risk. The answer is B: Recommend genetic testing to an affected family member.
So, now, let’s say we decided to do testing on her affected sister. And the test results show that she is positive for a BRCA1 mutation. What is your next step? A) Recommend testing for your original patient. B) Recommend testing for all maternal and paternal family members. C) Recommend testing for all siblings and paternal relatives based on family history. Or, D) No testing recommended. The answer is C: We would recommend single site genetic testing for all of her siblings and paternal relatives based on the family history that we originally saw on her paternal side of the family.

Now, let’s go back to your original patient. Let’s say she tests positive for the BRCA mutation that we previously identified in her sister. What screening or risk reduction options would you recommend to her? A) No increased cancer screening, she does not have hereditary cancer. B) Increased breast cancer screening only, based on her family history of breast cancer. C) Increased breast and ovarian cancer screening based on her positive BRCA1 results. Or, D) Recommend prophylactic surgery to be performed as soon as possible. The answer would be C: Increased breast and ovarian screening, based on her positive BRCA1 and BRCA2 positive results. We would also discuss prophylactic surgery as an option. But it’s not something that would need to be performed as soon as possible.

Now, let’s consider when your patient tests negative for the known BRCA1 mutation in the family. What would you recommend to her now? A) No increased cancer screening, she does not have hereditary cancer. B) Increased breast cancer screening only, based on her family history of breast cancer. C) Increased breast and ovarian cancer screening based on positive BRCA1 results. Or, D) Recommend prophylactic surgery to be performed as soon as possible. The answer is A: No increased cancer screening would be necessary because she did not inherit the BRCA1 mutation in the family. And, she would have the general population risk of cancer and should be screened accordingly.

In summary, this case illustrated that it is important to test an affected family member first to give us the most amount of information whether or not the family has
hereditary breast and ovarian cancer, and tested positive for a BRCA1 or BRCA2 mutation. You only need to order single site testing for family members if we have identified a BRCA mutation in the family. We also want to make sure that you’re referring to the NCCN Guidelines™ for the most up-to-date information and current screening recommendations for patients who have BRCA mutations.

Okay, I'm going to go through the second case with you. This case is a little different than the first. We see here that our proband is a patient who is 41 years old and was diagnosed with breast cancer at age 38. She reports a family history of a sister, who is age 52, and has a history of breast cancer diagnosed at age 40. Additionally, she has a paternal aunt who is in her seventies and has a history of breast cancer diagnosed at age 55.

So, considering this family history, what would you do first? Would you, A) Recommend genetic testing to your patient. B) Recommend genetic testing to an affected family member. C) No genetic testing is recommended. Or, D) Run the Gail model to assess breast cancer risk. The correct answer is A: You would recommend genetic testing to your patient. Your patient is an appropriate genetic testing candidate because she has breast cancer. And, she has breast cancer at an early age.

Imagine that these are the results you receive for your patient. You can see here, no mutation is detected. BRCA1 sequencing and 5-site rearrangement analysis has been performed. And, BRCA2 gene sequencing has been performed.

Now, given the results I just showed you, what would you do next? A) No further genetic testing is required. B) Consider BART analysis or BRACAnalysis® Rearrangement Testing. C) Test the affected sister. Or, D) Recommend risk reducing bilateral salpingo-oophorectomy. The correct answer is B: Consider BART analysis. As you saw on the previous slide with the results, BART™ analysis has not yet been performed. And, so, it makes sense to consider doing BART™ analysis, just to make extra sure that there is not a mutation in this family.
Now, imagine you performed the BART™ testing and your patient receives negative BART™ results. What risk management recommendations would you make for your patient, given these results? A) Risk reducing bilateral salpingo-oophorectomy? B) Review recommendations for contralateral breast cancer risk including prophylactic mastectomy and screening. Or, C) No recommendations should be made since the patient had negative test results and is not at high risk for another breast cancer. The correct answer is B: You need to review the recommendations for contralateral breast cancer risk including prophylactic mastectomy and screening. This is an --- this is an important consideration as the patient still may have an increased risk of breast cancer, given both her personal and family history. And, this is the case even though she tested negative for a BRCA1 or BRCA2 mutation. It’s important to consider the family history when making recommendations for contralateral breast cancer risk.

Imagine now that your patient asks what recommendations you would make for her unaffected sister and daughter. Would you, A) Recommend genetic testing. B) Recommend general population breast cancer screening. C) Recommend high-risk breast cancer screening. Or, D) Recommend high-risk breast and ovarian cancer screening. The correct answer is C: You would recommend high-risk breast cancer screening. Again, even though a BRCA1 or BRCA2 mutation was not identified, women in this family could still have an increased risk of breast cancer, based on the family history. So, it’s important to recommend high-risk breast cancer screening for any unaffected females in the family.

Now, imagine you go ahead and recommend high-risk breast cancer screening for the unaffected sister and daughter. What exactly do you recommend and how frequently would you screen? A) Recommend semi-annual mammogram alternating with breast MRI, beginning at age 28. B) Recommend semi-annual mammogram alternating with breast MRI, beginning at age 40. C) Recommend annual mammogram beginning at age 40. Or, D) Recommend annual mammogram beginning at age 28. The correct answer is A: Recommend semiannual mammogram alternating with
breast MRI, beginning at age 28. Again, this family is considered to be high-risk, based on the family history. So, we need to recommend high-risk screening which typically involves screening every six months. And, we recommend screening at age 28, as that is 10 years earlier than the earliest diagnosis in the family. But, of course, screening recommendations may change over time. And, it is important to continue to consult the NCCN Guidelines™ for the most up-to-date recommendations.

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Now, imagine for a moment that if you have the same family history and you do genetic testing, and you receive a variant of uncertain significance. What do you do then? A) Stop there. No further testing in this family is necessary. B) Test all family members for the VUS or Variant of Uncertain Significance. C) Order comprehensive BRCA1 and BRCA2 genetic testing for other family members with a history of breast or ovarian cancer. D) Enroll the family in the Myriad® Variant Reclassification Program to determine testing candidates in the family. The correct answer is D: You would enroll the family in the Myriad® Variant Reclassification Program to determine testing candidates in the family. However, you may have also thought that C is an appropriate answer, where you would order comprehensive BRCA1 or BRCA2 genetic testing for other affected family members. Certainly, C could be considered, and it would be an appropriate option. However, enrolling family in the Myriad® Variant Reclassification Program is a slightly better answer, as Myriad® will help you determine the best testing candidates in the family. And, additionally, Myriad® may offer testing to family members at no additional cost. So, we would recommend enrolling the family in the Reclassification Program first. And, if the family didn't want to do that, I think the next best step would be to do C and order comprehensive BRCA1 and BRCA2 genetic testing for other family members who are affected.

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Now, which of the following recommendations would be incorrect for your patient and/or her family if a variant of uncertain significance were found? A). Recommend risk reducing bilateral salpingo-oophorectomy? B). Discuss the option of bilateral mastectomy. C). Recommend high-risk breast cancer screening for unaffected women
in the family. D). Recommend family follow up with a physician to discuss clinical significance of the variant on an annual basis. The --- the incorrect option is A: To recommend risk reducing bilateral salpingo-oophorectomy. In some cases, people feel like, if you find a variant of uncertain significance, that that may be similar to finding a natural mutation. And, they may recommend risk-reducing bilateral salpingo-oophorectomy, but that is incorrect. Most variants in the long-term are reclassified as negative, benign polymorphisms and they are not mutations. So, you would not want to recommend risk-reducing bilateral salpingo-oophorectomy in a family that does not truly have hereditary breast and ovarian cancer. The remaining options are correct. It would be appropriate to discuss the option of bilateral mastectomy, to recommend high-risk breast cancer screening for unaffected women in the family or to follow up with a physician to discuss the clinical significance of the variant on an annual basis. Again, this family does have a significant family history of breast cancer so high-risk breast cancer screening makes sense. The follow up with the physician also makes sense as variants do get reclassified from time to time. And, it would be important for the family to learn about a reclassification by visiting with you on an annual basis.

So, in summary, it’s important to realize that BART™ analysis is not automatically performed on all patients. So, when you receive results, and particularly negative results, they need to be reviewed to determine if BART™ testing was performed. If BART™ testing was not performed, then you may need to consider ordering BART™ testing so that your family has the most up-to-date testing available. Additionally, it’s important to remember that not all families with a strong history of breast cancer are explained by BRCA1 and BRCA2 gene mutations. You then have to look at the family history and make recommendations for your patient as well as family members, according to that family history. That means you need to consider the number of relatives affected, as well as the age of onset of breast cancer diagnoses in the family. You also need to consider whether this is a family that’s affected by breast cancer only, or whether it’s a family affected by breast and ovarian cancer, as that may influence your screening and
prophylactic surgery recommendations.

KR It's also important to consider whether there are other family members that may be more informative to test. In this family, we tested a person who had breast cancer and who had breast cancer at an early age. But, even if she tests negative, it may still be appropriate to offer testing to other family members who had a history of breast cancer. It's also important to refer the family to appropriate research studies, as we demonstrated with the finding of a variant of uncertain significance. The laboratory can help you determine appropriate research studies or, in some cases, with the Reclassification Program, may have research studies of their own that may help the family in the long term. And, finally, it's important to let patients know that they need to continue to follow up with you on a long-term basis. Cancer genetics is a rapidly evolving field and the results as well as testing options may change. Thank you for listening to our presentation about hereditary breast and ovarian cancer case studies. We welcome your feedback.