

Kaylene Ready:

Okay, so thank you to Dr. Belinson [spelled phonetically] and Dr. Brown [spelled phonetically] for inviting me today to speak to you. I am Kaylene Ready. I'm a genetic counselor at Counsyl. Prior to joining Counsyl, I worked at MD Anderson Cancer Center for five years in the Breast, and now at Counsyl, I am the Director of Inherited Cancer. We won't be talking too much about cancer testing today. Rather, we want to provide an overview of genetic testing: who should have genetic testing and why would people pursue this type of testing.

So, the main objective today is to understand the population in whom genetic testing is performed and why. And what we're going to do is cover three main topics. The first is the difference between a clinical and a molecular diagnosis. The second is the types of testing, such as the differences between diagnostic, prognostic, and therapeutic testing, as opposed to discussing things like the difference between sequencing or genotyping. And finally, the third topic, we will discuss who to test, including when it makes sense to test somebody who is presenting with symptoms, versus when you might want to think about testing a family member. And as we go through this, you might recognize that the overview presented here will very closely mirror the BCBSA context policy entitled "General Approach to Genetic Testing."

So, first, let's discuss a clinical versus a molecular diagnosis. Before I get too far into this, I really want to point out that clinical utility is the key to all of this. And that is whether and how a genetic test will influence medical management. In this instance, genetic testing is much like any other medical test. The important question to ask is "What am I going to do with the results of this test?" And if the answer is "Nothing," or "I don't know; I'm not sure," then testing may not be necessary. If the test is needed to confirm a diagnosis when there's uncertainty, or if the test will be used to make medical management decisions, then testing might make a lot of sense. So, important questions in thinking about clinical utility include can the diagnosis be made on critical features alone, and then secondly, how will the molecular testing aid in prognosis or treatment?

So, an excellent example of when a clinical diagnosis may be enough versus when a molecular diagnosis may be needed can be seen by looking at achondroplasia and Down syndrome. Achondroplasia is the most common form of dwarfism. And you may be familiar with this. Affected individuals have short arms and legs. They have a large head, very characteristic facial features. And I'm showing a picture of somebody who has achondroplasia on the left. And genetic testing is widely available for achondroplasia, but in most cases, the diagnosis can be made based on clinical and radiographic findings. Importantly, the management and treatment are really based on clinical findings, such as monitoring bowing of the legs or kyphosis.

In contrast, on the right, you can see a baby with Down syndrome, and molecular testing is very commonly used to confirm a diagnosis of Down syndrome. This is primarily because not all babies with Down syndrome have all of the characteristics associated with Down syndrome, and many of the symptoms that can be present at birth, like low muscle tone or a flat facial profile or excess space that can happen between the large and the second toe, some of those things can be present in babies who don't have Down syndrome. It's also useful to know if the baby has Down syndrome because of an extra whole copy of chromosome 21 in every cell, or if the baby could be mosaic, meaning that some of the cells have an extra chromosome and some do not.

This information is really helpful for prognosis because we want to know if the baby is going to maybe have more severe learning disabilities or maybe not as severe if they were mosaic. And finally, the baby could have Down syndrome because of translocation, and that can be inherited from a parent, as opposed to occurring sporadically. And that is important to know because it can affect the parent's risk to have another child with Down syndrome.

Next, we'll talk a little bit more about the different types of testing. So, there are several major categories that we're going to go over. I've listed those categories here. Again, they may look familiar, as they'll be similar to the ones you see in the BCBSA concept policy entitled "General Approach to Genetic Testing." I'm going to review most -- I'm going to review four categories. You might notice in the concept policy that there is a fifth, and the fifth is reproductive testing. And while reproductive testing is a category of testing, we're not going to focus on that today, since it will be discussed in later detail on a different -- in detail in a later webinar. And you'll also notice that some of these categories can be further divided into diagnostic, prognostic, and therapeutic indications, and where relevant, I'll discuss and provide examples of each of those sub-categories.

So, the first category we'll discuss is germline testing in affected individuals. And the first reason that germline testing might be used is to confirm or possibly exclude a particular genetic diagnosis. So, imagine that you have a young child who presents with café au lait spots and axillary freckling. These are common symptoms of neurofibromatosis type 1, but maybe the child doesn't fulfill any of the other diagnostic criteria besides having these café au lait spots and axillary freckling. What's interesting, despite what I learned commonly in genetic counseling school, is that the café au lait spots and axillary freckling, they can be associated with a number of different conditions. They can be associated with neurofibromatosis type 1, but they can also be associated with Legius syndrome, with constitutional mismatch repair deficiency, and a number of other things. And the clinical management of each of these conditions can be very different. In particular, like I've noted in the slide here, the risk for tumors can be vastly different with each of the different conditions.

So in this case, genetic testing can be useful to determine an accurate diagnosis, and therefore, appropriate management because we really want to figure out -- you know, if this kid has neurofibromatosis type 1, we're going to be monitoring for a very different set of tumors than we might be looking for if the child had constitutional mismatch repair deficiency, where they could be at increased risk for both colon and brain cancer in childhood, versus in the middle with Legius syndrome there's really no risk for tumors. And then, obviously, you know, we wouldn't need to be monitoring for that type of outcome.

The next reason that germline testing might be used is in a prognostic setting, and that means that we want to predict the natural disease course, such as disease aggressiveness, recurrence, or risk of death. So, the best example here is to think about Long QT syndrome, and Long QT syndrome is a really great example of thinking about using genetic testing for prognostic purposes. It's a cardiac disorder. It's associated with syncope and possible sudden cardiac death, and it can be caused by 15 or more different genes. But it's been discovered that different genes are associated with different triggering events. So, for example, in Long QT syndrome type 1, we typically see symptoms that are triggered by exercise, while in Long QT syndrome

type 2, usually, we see emotional stress or auditory stimuli triggering particular events. And then finally, with Long QT syndrome type 3, symptoms can occur during sleep.

So, if we look at specifically LQT1 and LQT2, we can look at those individuals and make recommendations about things that they might want to avoid, depending on what type of LQT syndrome they have. So, for LQT1, we typically would avoid strenuous exercise, especially swimming, without supervision. For LQT2, then, we would want to recommend a reduction in loud noises; so, maybe, avoidance of alarm clocks or loud phones ringing. And those things can really make a difference in the prognosis of those patients.

The final reason that somebody might consider germline testing in an affected individual is for therapeutic purposes. And the example that we're going to give here is genetic testing of the P450 gene. In particular, there's a drug that you may have all heard of called Plavix, and patients with certain genetic variants in a gene called CYP2C19 have been found to have lower levels of the active metabolite, and therefore, less platelet inhibition, and then, therefore, a greater risk of major adverse cardiovascular events like heart attacks, stroke, or death. So, in the case of Plavix, testing for CYP2C19 polymorphisms can actually identify patients who may not respond adequately to the standard regimen and may actually need to look at alternate treatment strategies.

The next major category of testing that we're going to discuss is germline testing, but to benefit a family member. This is testing that we can use to figure out who else we need to test in the family; so, maybe not the affected relatives themselves, but figuring out whether testing is useful in asymptomatic relatives. And we're able to do that by testing the person who actually presents with symptoms and identifying the pathogenic mutation. So, the example here is familial adenomatous polyposis, or FAP, and this is, you know, again a good example of how testing can be used in an affected individual to actually benefit the family member. So, FAP is really a fairly easy diagnosis to make based on clinical criteria because patients typically present with hundreds or even thousands of polyps in the colon. And the risk for colon cancer is nearly 100 percent given this very heavy polyp load.

So, testing may not influence the affected individual's management, but it can really help figure out what to do with at-risk family members. And this is primarily because if the mutation is going to be identified, you are most likely to find it in the person who presents the symptoms. And if you're able to find it in the person who presents the symptoms, then you can figure out whether offering testing to family members is going to be helpful. And so, if you find mutation in the first person, then you offer testing to that person's relatives, and you can figure out which of those relatives would benefit from surveillance. This is important because surveillance can really reduce the risk, if not prevent the risk, of colon cancer. And surveillance can even be extended to an affected person's children, who may have to undergo colonoscopy as early as age 10 if they are found to carry the familial mutation.

The next category of testing is germline in unaffected -- germline testing in unaffected individuals. And this has really gained a lot of steam in the past few years thanks to Angelina Jolie. You may have read her articles in The New York Times. And when we think about testing in unaffected individuals, it's testing for individuals that have some kind of family

history, but who don't have any personal history or features of the condition. Generally, this type of testing is most appropriate if the condition is one in which life expectancy is reduced or the disorder is one that is associated with moderate to severe morbidity or disability. Again, it's really clinical utility that plays an important role here. The main question to ask yourself is "Will the results of the test impact management and in a way that affects health outcomes?"

So, hereditary cancer testing and, specifically, testing of the BRCA gene is really maybe the best example of when germline testing of an unaffected individual can be useful. So, in the case of Angelina Jolie, she had a significant family history of breast and ovarian cancer in her mother and a maternal aunt. And once she was identified as having a BRCA1 mutation, she pursued both prophylactic mastectomy and oophorectomy, significantly reducing her breast and ovarian cancer risks; in fact, to less than that of the general population. And, as I mentioned before, she wrote about that experience in The New York Times, really in an effort to make people aware of the testing and really was hoping to write from the perspective of a patient who's gone through this and bring light to the choices available to women identified with these mutations.

The fourth category of testing is DNA testing of cancer cells. And the first reason that this testing might be used is for diagnostic purposes; for example, in a patient who maybe presents with a cancer of unknown primary. It is important to know the type of cancer so that the best treatment for that particular type of cancer can be used. So, if we can figure out what the primary tumor is, and if the primary tumor can be identified, then treatment can be based on that type of cancer. And in these cases, testing could involve looking for expression or perhaps lack thereof of certain genes known to be associated with particular types of cancer.

The next reason that DNA testing of cancer cells might be used would be for prognostic purposes. And prognostic testing of cancer cells can be used to determine the risk of cancer progression or even recurrence risk. So, you may have heard of Oncotype DX. I think they're pretty famous for this test at this point. That's a very good example of prognostic testing of cancer cells. This test is designed to determine which early stage cancer patients will benefit from chemotherapy. So, you can actually look at the tumor itself, look at the cancer cells, and they determine a risk score to determine whether adjuvant therapy and patients with ER-positive, HER2 negative early stage invasive breast cancer would be useful. And it provides an individualized and quantitative risk assessment that identifies the patient's 10-year risk of distant recurrence. Oncotype now also has, I believe, tests for both colon and prostate cancer as well, but they kind of became famous for their breast cancer tests.

The final reason that somebody might actually use DNA testing on cancer cells is for therapeutic purposes. And this is an area that is gaining steam, but I will use an example that is used quite commonly in clinic right now, as opposed some of these samples that are perhaps more in the research realm at this point. So currently, the treatment for non-small cell lung cancer, we use testing to look for genes EGFR and ALK. And those are two genes that can be mutated in non-small cell lung cancer. It turns out that EGFR mutations are present in about 10 percent of Caucasian patients and up to 50 percent of Asian patients, and they are sensitive to a very particular type of chemotherapy called TKI. In contrast, ALK mutations are present in about 2 to 7 percent of patients with non-small cell lung cancer. And these patients who have ALK mutations, they're resistant to TKIs; they need treatment with a completely different type of

chemotherapy. So, as you can imagine, it's really important to know if you have a patient that's presenting with non-small cell lung cancer do they have EGFR mutations, do they have ALK mutations, so that the physician can choose the appropriate therapy.

Of course, the final question is really who to test, and this is an important question to think about. We've talked a lot about testing the proband, and that is the person who has presented with symptoms. But once you find a mutation in a proband, you have to begin thinking, because of the genetic testing, in which case does it make sense to also test the proband's relatives? And there are several factors which may influence the risk to relatives, including mode of inheritance, degree of penetrance, as well as de novo mutation or new mutation rate. The mode of inheritance and de novo rate will help determine exactly who in the family is at risk and how high their risk is, whereas the degree of penetrance will help determine the clinical utility or usefulness of testing anybody at risk. And of course, as we go along this route, ideally genetic counselling is provided to at-risk family members so that they can understand the risks, as well as the risks and benefits of testing, and they can make an informed decision about whether pursuing testing is appropriate for them.

So, I'm providing two examples here to really illustrate these two points about when testing makes sense in relatives or not. The first example is Li-Fraumeni syndrome. Li-Fraumeni syndrome is an autosomal-dominant, hereditary cancer syndrome. It's primarily associated with breast cancer, sarcoma, lung cancer, and adrenal-cortical carcinoma, but really just about every cancer under the sun has probably been seen in patients with Li-Fraumeni syndrome. Since it's autosomal dominant, there's a 50 percent chance for first-degree relatives to have the same mutation. And initially, the condition is highly penetrant. There is a 90 percent or greater risk for cancer, but fortunately, there are also management guidelines. So, we know what to do if somebody presents with a P53 mutation, which causes Li-Fraumeni syndrome. So, in the case of Li-Fraumeni, it makes sense to offer testing to close relatives to determine their risk so that they can benefit from additional cancer screening or potentially even surgery.

In contrast, if we think about Rett syndrome, we might make a different decision. So, Rett syndrome is an X-linked dominant condition. These children typically present with normal psychomotor development during the first six to 18 months of life, but then they have a short period of developmental stagnation, and then rapid regression. They lose all of their language and motor skills that they had developed during the first six to 18 months, and then, that kind of levels out. It's actually -- it's really kind of a tragic condition. But interestingly, the condition has a more than 99 percent de novo or new mutation rate. So, while it is genetic, typically these children present sporadically, and that means most of the cases occur by chance. So, in this case, testing of relatives is unlikely to be beneficial because we wouldn't expect any of the relatives to test positive.

So, again, I just want to reiterate that whether and how a genetic test will influence medical management is really the key. And fortunately, in that sense, genetic testing is very, very much like other testing. If you know what you're going to do with the results of the test -- specifically how the test will better help with a diagnosis, a prognosis, or perhaps a choice of therapy -- then it's likely to be beneficial. So, with that, I will thank you again for your time and open it up to any questions. [end of transcript]