Women at Risk: Genetic Susceptibility to Breast Cancer

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I. Introduction

Tiffanie Burnett: [Not Transcribed]

Lisa Mullineaux: My name is Lisa Mullineaux. I am going to give you a general background on genetics and the inherited risks of breast cancer. And then Dr. Oratz is going to talk about syndromes associated with breast cancer, BRCA1 and 2, and then we are going to talk about the San Luis Valley.

Most people who develop breast cancer don't have an inherited risk of breast cancer. Only about 10 percent of people who have breast cancer have some inherited risk. I'll give you some background on genetics. Cancer is a genetic disease, so all cancer has genetic components. If you look inside a tumor, there are problems of genes in that tumor. But not everyone that has cancer has an inherited risk.

For general background, the genes inside your body are blueprints for your body to function. And they are recipes to make a particular type of protein. Each gene has a unique protein that it makes. Most people who have tumors start out with normal cells and then carcinogens and normal cell division can cause mutations in cells and lead to a tumor. Most people don't inherit a mutation. Most people have normal cells and then a tumor develops. Most people start out with normal cells, and over time those cells might accumulate mutations, and that forms a malignancy.

An inherited risk is when there is a mutation in a gene that you actually inherit, so every cell of your body will have that mutation. Either the egg or the sperm has a mutation and so every single cell of this person's body has that mutation. The previous slides, where we looked at the steps for cancer, instead of starting with normal cells, you are starting one step ahead of the process, so every cell in your body has a mutation. It is more susceptible to getting cancer.

The types of genes that are usually associated with inherited risk are called tumor suppressor genes. Has anyone here ever had a sunburn? What happens to your skin when you have a sunburn? It peels. That's dead skin. A tumor suppressor gene did that. A tumor suppressor gene produces a protein that kills damaged cells. When you do sun damage to yourselves with a sunburn, the tumor suppressor gene says, "Let's get rid of that cell because there's too much damage."

In summary, a gene is a recipe to make a protein, and when a tumor suppressor gene is normal, it helps protect your body from getting tumors. And when it's abnormal, when you have a mutation that you've inherited, then you are at high risk of getting cancer.

What do we look for in terms of inherited risk? What sort of keys do we say, "Well, if these things occur, maybe we should consider additional genetic counseling?" Some of the indicators are having an early age of onset of cancer. For men, if they have prostate cancer diagnosed less than age 55, that is pretty young. A woman diagnosed with breast cancer less than age 50, that's pretty young.

If we see the same type of cancer in many generations, that is also an indicator. So it seems like there is a clustering in a family. Sometimes we see a unique pattern of cancers. For example, with hereditary colon cancer, we see colon, uterine, and ovarian cancer in those families. If we see those kinds of cancers together, that pattern, we consider maybe this is an inherited risk. For breast cancer, sometimes we see breast and ovaries. Sometimes we see breast and thyroid. Sometimes we see breast and childhood cancers. Those are unique patterns that make us say, "That may be related to something inherited."

The other things that make us believe that there could be inherited risk is if we see a person who has more than one cancer (e.g., both breast and ovarian cancer, both colon and uterine cancer, maybe they have melanoma and pancreatic cancer). If they have more than one cancer, that makes us think that things could be inherited. If we see cancer in both of a pair of organs – like bilateral breast cancer – or bilateral kidney cancer – we might consider that could be inherited. If we see more than one cancer in the same organ, what we call multifocal disease, that is also an indicator. A lot of times, in hereditary colon cancer, there is a higher risk of developing more than one colon cancer in the colon.

Now I am going to switch gears to breast cancer and breast cancer risks. For some people who have breast cancer, it runs in their family. If it runs in their family, then we think perhaps that could be an inherited risk. This slide shows you there are a lot of genetic predispositions to breast cancer. You probably all have heard about BRCA1 and 2, and the reason that you've probably heard about it is that it makes up a majority of inherited risk that we can actually test for. But you see [in the slide] that there's a big part there -- we've got 15 percent that's familial. That's cancer that we know runs in families, but we don't know the genetic causes of it. A lot of times when we do genetic testing, it looks like it's running in your family, but we don't have positive answers about why it is running in your family. And that's because we just don't know everything about inherited risk.

Dr. Ruth Oratz: We are going to talk a little bit about what some of the clinical syndromes are that are associated with the inherited risk of breast cancer. Lisa explained to you a little bit about the basic background of genetics. Let's now focus on breast cancer in women in the United States.

This year, more than 200,000 women will be diagnosed with breast cancer. And in the State of Colorado, we'll see about 2,500 new cases. Because so many women present with early stage disease, and our treatment is becoming more and more effective and we are seeing so many women surviving their breast cancer, we now have several million breast cancer survivors in the United States. This is really a huge group of people that we are talking about.

Breast cancer has now become the leading cause of death in young women in America, between the ages of 40 and 55. It is very, very important that we begin to understand what is causing the increased incidence of breast cancer, and how we can intervene not only in terms of early detection and treatment, but hopefully prevention.

We are here tonight to talk about the genetic links to breast cancer. We are going to talk about some of the other risk factors. But one of the things that's important to understand is that our genetics is related to our family histories, and that's why we ask about family history. But our genetics is not necessarily our destiny. And what we are learning is that if we can understand what these inherited susceptibility factors are, with more research as we move forward – we are not quite there yet – we'll be able to identify people who are at increased risk and intervene early, hopefully with better interventions than the ones that are available to us now, to actually prevent cancers. We can also use this

information to help us develop new treatments that are targeted to correct these genetic abnormalities.

It's also important to realize that the genes we inherit interact with our environment. So even if you have inherited a gene that gives you a predisposition to developing cancer, it is not 100 percent that every person gets that cancer. It's a high percentage, and I'll show you some of those statistics. But it's not 100 percent. So we know that these genes interact with other genes, that still have to be identified, and with the environment as well.

Breast cancer is not one single disease. There are lots of different versions of breast cancer. Breast cancer in young women is a little bit different than breast cancer in older women. If any of you have had experience with breast cancer yourselves or with someone close to you, you know that we, the doctors, get very interested in exactly what kinds of cancer cell is this. Does it have estrogen receptors? Does it have other molecular markers? We now understand that there are many, many different subtypes of breast cancer, and those molecular differences which are determined by the DNA in the tumor cell help guide us to choose appropriate treatments. Breast cancer is really a spectrum of different diseases.

Some of the risk factors aside from family history that are important are environmental factors and also biological factors. The first thing is age. The incidence of breast cancer increases with each decade of life. The older we are, the more likely we are to get breast cancer. Like gravity, that just comes with the territory. [Laughter] We also know that the hormonal environment in the body is a contributing factor. And when doctors ask questions like, "How old were you when you had your first menstrual period?" or "Have you ever been pregnant, and if so, how old were you when you had your first period?" or "When did your period stop? When did you enter menopause?" -- the reason we ask those

questions is that that gives us some information about what's been going on with estrogen in your body, and how much estrogen has been there, and how long has the estrogen been around. The earlier you are at the age of menarche, first menstrual period, the older the age of menopause, that's a longer time of having estrogen. Why is that important? Estrogen is a growth factor for breast tissue. When puberty begins and the breast begins to develop and grow, that's under stimulation from estrogen.

100 years ago, or 150 years ago, most girls didn't start developing until the age of 14, 15, 16. That was the normal age of menarche. Today, it's normal for young girls to start having their menstrual periods at age 10 or 11. And that has to do with diet and with food. So here in America and other affluent countries where we have a lot of food and a lot of our food comes from animal protein and dairy products, young children are reaching a bigger size at an earlier age. And in fact it's body mass that sends the message to the brain and says, "OK. Now we are ready for the next phase of life," which for women is the reproductive phase of life. Diet is related to this because it leads to this earlier menarche. It's very important that we try to understand these environmental issues as well and how diet comes into play here. Dietary factors are very important. We also know that the daily use of alcohol – if you have more than two drinks a day every single day – that is associated with breast cancer.

The only real environmental exposure that we have been able to identify with certainty is ionizing radiation. That is data that came to us originally from the atom bombs in Japan – Hiroshima and Nagasaki. We followed that population and saw that people who survived did develop cancers 10, 15, 20 years later. And the women who were young at the time of exposure were at increased risk of developing breast cancer.

We know that women who have X-ray treatment for Hodgkin's Disease or Non-Hodgkin's Lymphoma when they are in their 20s or in their late teens are at a very high risk of developing breast cancer many years later. When they get radiation treatment to those lymph nodes, there is a low dose scatter to the breast. And it is that sort of low dose X-ray that does increase the risk of breast cancer.

That raises the question – and it's an important question – is there then a risk from getting mammograms or other diagnostic X-rays? And the answer is no. The reason is that it is not enough radiation. It has to be a higher dose over a longer period of time. And having an annual mammogram – and sometimes even when they do a six-month in between – that's not enough of a dose to be a risk, but something to bear in mind.

Let's switch gears back to the family history issues and the genetic factors. We've known for a very, very long time that breast cancer ran in families. In fact, even in ancient Rome, physicians noticed that there were families that had clusters of women who had breast cancer. And the very famous French physician in the 19th Century Dr. Broka [phonetic] described one family that had 10 women who had breast cancer in four different generations. And as Lisa said, one of the hallmarks of an inherited susceptibility for cancer is if we see lots of individuals in the family in many different generations.

It took 100 years for us, after that observation, to identify the gene that may be related to this breast cancer susceptibility and so far we've identified 2 of those genes. They are called BRCA1 (that stands for Breast Cancer 1) and BRCA2. There are undoubtedly many other genes which regulate the inherited susceptibility to breast cancer and other cancers. We are looking for them. We are still doing research. But these are the genes we've identified so far.

When we as clinicians meet with patients we try to figure out, “Is this someone who might be from a family where there is a risk of an inherited susceptibility?” What do we look for? We look for lots of individuals in many different generations. We look for early age onset – someone very young when they were diagnosed. We look for the connection – the link – between breast and ovarian cancer, particularly in this situation. Bilateral breast cancer – in both breasts.

And there is a significantly higher incidence of inherited susceptibility to breast cancer in Jewish women. The reason for that is that once the genetic mutation is introduced into the population, if everyone in that population just keeps marrying one another, or staying together, that gene is going to stay in the population. If you marry more widely, than the gene gets diluted in a larger population. Just as a historic phenomenon, Jewish people tend to marry other Jewish people, so once that mutation got in the population, it stayed there. There are other populations around the world where we find this similar clustering. In Denmark there are clusters like this; in Greenland; probably in Ireland as well. And these are populations were people were geographically isolated. Again, they tend to marry the people who are around them. If you are on an island, you don’t have a lot of options. That is why we see these genetic clusters in certain populations. And sometimes by studying these small, in-bred populations, we get information that is translatable to the larger population.

Another clue when we are thinking about breast cancer genetics is when we see a man with breast cancer. Male breast cancer is rare. But it is not that rare if it’s a genetic, familial, inherited form of breast cancer, and I am going to show you why that is. Here is an example of the kind of work that Lisa does all day long. Any of you who have had the chance to meet with her knows that she is very busy drawing these charts, and circles, and squares. What does it all mean? Well, the circles are women and the squares are men. And what you can see is that each line that we go down is a different generation – so we have lots of

generations in this family. And anyone who is in red [on the slide] has cancer. So in this family, which has a BRCA mutation, we see a very young woman, age 36, who is diagnosed with breast cancer. Her father was the one who carried the genetic mutation. That is what the yellow stripes are; they are carriers. He never got sick because he was a man and because, even with the mutation, it is unusual to develop cancer, although he may be at increased risk of prostate cancer. But he never got cancer. When we talked a little bit more about the family, we learned this sister died of ovarian cancer, and going up in the family we see that his mother – she was OK, she was healthy – but she was a carrier, because her sister died of breast cancer at a young age. And then we see going down another sister who is a carrier, and her daughter affected.

When we do these big family trees, we really want to try to map out everyone in the family. Everybody counts – not just first degree relatives, which means parents, and siblings, and children – but grandparents, aunts and uncles, cousins. The more information we can get about the family, the bigger the picture is, and the more we can fill in this family tree, it helps us understand the way the gene may be traveling in the family.

It is also really important to remember that this gene –the BRCA1 and BRCA2 gene – can travel through the male side or the female side. This is not a gene that is limited to the women in the family. The men tend not to express it. They tend not to get sick. So it is silent. But it can be inherited and passed down. Each individual who is a carrier can pass that gene on to each child with a 50-50 risk. For example, this father who carried the gene has two children, and there is a 50-50 chance that each one of those daughters could have inherited that abnormal gene.

What happens if you are one of these carriers? Is there an increased risk of developing cancer? You can see at the bottom of this curve the risk of

developing cancer in the general population, and it increases with age. And you can see that for people who are carriers of mutations in BRCA1, the top 2 curves, the risk of developing cancer over time is much higher. And the other thing we notice about these curves is that the cases start much earlier – younger age of onset, higher risk of developing cancer.

What are the cancers that we see in association with BRCA1 mutations? We see breast cancers with a range of about 50 to 85 percent chance that if you inherited a mutation in BRCA1, you might get breast cancer. We see a 40 to 60 percent chance of this being bilateral, meaning it will affect both breasts. We see a lower risk of ovarian cancer, but certainly a significant risk – 15.5 percent risk. BRCA1 mutations may be associated with other malignancies, particularly prostate cancer in men.

Here's a BRCA2 family. This is the other gene, the second breast cancer gene. The diagram looks very similar. What I would point out that is a little bit unique for the BRCA2 mutation is that we tend to see more male breast cancer, possibly a little more expression of prostate cancer in males. Again, with BRCA2 mutations, we see a 50 to 85 percent lifetime risk of breast cancer, not as much bilateral breast cancer, a little bit lower risk of ovarian cancer with this mutation, and a higher expression in the males. About 6 percent of BRCA2 mutation carriers will develop male breast cancer.

Here's what the genes look like. They are very large genes. There are more than 400 mutations which have already been identified in these 2 genes. There are lots of ways that the genes can be abnormal, can be broken. But we do know that there are three mutations that are very, very common. They are listed up here. That's the code for the way we identify where on the gene the abnormality is – whether there is an insertion or deletion. These three specific abnormalities are found very, very often in the Jewish population. Until recently,

we thought these abnormalities were found in what we call the Ashkenazi Jewish population, which are Jews who lived in mostly Eastern Europe – Germany, Russia, Poland, Northern Europe, that part of the world. But we are going to hear some interesting information historically that's going to tell us that maybe these mutations in fact are much older, and may be traveling around the world in other folks as well.

The clinical syndromes again are that we see early onstage breast cancer. We see the median age is 42 years old for BRCA1 mutations. The BRCA2 mutations may come on a little bit older, a little bit later in age. We see a lot of bilateral breast cancer and often the cancer develops without us seeing the pre-malignant phase, which we sometimes see in the other 85 percent of people who develop breast cancer, where we see in situ carcinomas or pre-malignant lesions, abnormal mammograms, and atypical biopsies before the actual cancer develops. Sometimes with this inherited kind of breast cancer, we just see more aggressive cancer that grows more quickly.

Are there differences in outcomes? Differences in prognoses? It's not 100 percent clear. I think that when we see each individual patient, we still want to look at what's going on with her specific tumor. Just because you have an inherited form of breast cancer, doesn't necessarily mean it's worse or better. There are some aspects that may make it more favorable, and some aspects that make it less favorable. Again, with each individual patient, we need to look at the full clinical spectrum and have your doctor sit down and go through with you what the best treatment should be.

Lisa is now going to talk to you about a very interesting finding here in Colorado, in the San Luis Valley, where we were doing some population studies to try and understand where else this mutation lives. Not just in the Jewish population – but where else in the population.

Lisa Mullineaux: I first started doing genetic counseling in 1994. In 1994, there weren't many genes discovered yet. There was a gene discovered for hereditary colon cancer that is pretty rare. And Myriad labs came to us and said, "We would really like it if you could send us some samples of people because we would like to launch this product." We set up a psycho-social study at the University of Colorado regarding hereditary breast and ovarian cancer. One of the people that I saw was of Spanish-American descent. That person got tested for BRCA1 and 2 and she was found to have a mutation in BRCA1 that is common in the Jewish population. And I said, "That's kind of odd. She's Spanish American." I remember her telling me a story about her dad playing guitar in Santa Fe. And I said, "Where exactly are you from?" And she said, "My family is from Southern Colorado and Northern New Mexico." I kept that in my mind, and thought this was a little unusual. I did a literature search and found that in Spain there seemed to be some of this Jewish mutation also found in their population. So I put that in the back of my head. When I came to Rocky Mountain Cancer Centers, I saw two additional families that – from that day on, I asked, "I know that you are Spanish American. Where exactly are you from?" One of the clues is that people from the San Luis Valley do not say they are Mexican. They say they are Spanish. Some of them say they are Caucasian and Spanish. There is definitely a tie to being Spanish in the San Luis Valley. So I always ask, "Where exactly in Colorado? Did you come from Spain?" We found three total families. And then I asked around, and we decided to publish this paper and look back at our data and find out how many people of Spanish ancestry did we test and what was the situation. I can tell you that when I asked people about their ancestry – I'm from the East. And in the East, everyone identifies themselves by what ethnic group they're from. When you meet someone, it's not rude to say, "Who are you? What are you? What ethnicity?" When I came to Colorado a few years

ago, I realized that was a rude question. I have to ask it in genetics because ethnicity makes a big difference in the way you look at things.

These are the collaborators on the study. There were also some physicians who were involved in the study. Our scientific advisor is still working on this study. She is doing some additional work, and she is at the Eleanor Roosevelt Institute, which is now a part of the University of Denver. It used to be a part of the University of Colorado. You might recognize some of the names of the other genetic counselors. There are a couple of Rocky Mountain Cancer Center doctors who have also participated in this study.

What we found was that in these families—and there were really significant family histories. I would say they were some of the most significant families that I have seen in terms of family history of breast and ovarian cancer. We found that these people originate from the San Luis Valley. They have this mutation in the BRCA1 gene. The old way we used to name it was 185; the new way is 187 delAG.

When we looked back at our study, all the people we tested that were of Spanish American descent – we didn't test that many. It was surprising. We looked back several years, I think from 2001 back, and we had only 19 Spanish Americans, which isn't very many. If you look at the percentage of the population that is Spanish American in Colorado, the percentage of people that we tested is much smaller. And there are some barriers to testing.

Ten of them had mutations in BRCA1 or BRCA2. Six of them were from the San Luis Valley. And all six of them had this Jewish mutation. Four of them weren't from the San. Luis Valley, they were from Puerto Rico, or of some Latin ancestry, and they had different mutations. When we asked them if they had Jewish ancestry, "Could you be Jewish?," they said, "No, I couldn't be Jewish. I'm not

Jewish. I'm Spanish American." One person, when I told her we were going to publish this information, she went back to her family and they said, "Maybe we were Jewish." So one person said, "Well, maybe I had Jewish ancestry."

The types of families that we saw at the center were fairly typical of breast and ovarian cancer families. Some of them – the mutation came from the father's side. Some – it came from the mother's side. Some had breast cancer and had a family history of breast cancer. One family had male breast cancer in their family. One person had bilateral breast cancer, and breast cancer in other family members. One woman had breast and ovarian cancer, and breast and ovarian cancer in her family. These were examples of everything you see. They were pretty significant family histories.

Have we found the 185 or the 187 delAG in other populations? As Dr. Oratz said before, yes, we've seen that in the Jewish population, 1 percent of people with Jewish ancestry will have the 185 or 187 delAG. And like I said before, when I did a literature search, there were people in Spain. What we know about the BRCA1 mutation is that it's a dominant condition, which means that offspring of people who have this mutation have a 50 percent chance; the risk for second breast cancers are pretty significant; there is a fairly high risk for ovarian cancer; and there is a risk for prostate cancer.

What are other studies that have been done? In Spain, there's been a lot of studies done, and I actually got an e-mail from someone who bet me a beer about whether or not we were going to find the same things they did. What they did was they tested -- Dr. Diaz, from Spain, he's been involved in many studies. And in the literature, there are about 17 people of Spanish descent from Spain who have this mutation, and of those 17, two people think they were Jewish and they were Sephardic Jewish, is what they indicated, and three gypsies. Then Dr. Diaz performed some additional testing. There's a way to genetically figure out if

the mutation occurred in a same ancestor – it's called the haplotype analysis. And it's like forensics. It's like looking at markers to determine if this came from the same person. They did this haplotype analysis on 13 of 17 people who have this mutation, and 12 of them had the same exact haplotype. So it came from the same Jewish ancestor as what is called the Ashkenazi Jewish ancestor. One of the 13 had the same thing with some additional information.

This gives us the idea that something is going on with our population in the San Luis Valley. Dr. Oratz is going to tell you some more about the history in the Valley.

Dr. Ruth Oratz: Who are these families in the San Luis Valley and are they related to people who have the same genetic mutation? Is it possible that, in fact, they are Jews? How did these mutations get into the population? One of the ideas is that we are looking at the Founder Effect – that if we go back in time, we can identify the original ancestor, who then over the generations propagated this mutation. One of the theories is that the founder in the San Luis Valley populations was a Jewish person who came from Spain to Mexico in the 1500s and then traveled up to Colorado to New Mexico. And the Jews who were living in Spain at this time were called Sephardic Jews, and it was felt that they were a group that had separated off from the Jews who were living in Europe. There was this idea that maybe about 2,000 years ago, at the time of the Roman Empire, there were Jews who moved up from Palestine in the Middle East to Italy and then up into Europe, and then some that traveled across North Africa up into Spain and Portugal. Those two groups had diverged, and maybe even diverged genetically. And the reference of the separation is the Ashkenazi Jews -- the European Jews – and the Sephardic Jews. "Sephard" is the Arabic word for Spain. And that refers to the individuals who lived in the Moslem world, traveled with Islam across North Africa up into Spain and Portugal, and into the Middle East as well – Iran, Iraq, and that part of the world – Turkey, Greece. Those are the Sephardic Jews.

There was this huge Jewish population in Spain. But then in the 1300s and 1400s, things weren't going so well for them. And the Inquisition started. And we know that by 1492, there was the expulsion from Spain. A lot of Jews went to Portugal, but then they were expelled from Portugal. There is some evidence that Christopher Columbus himself may have been Jewish. There is certainly evidence that there were Jews with him on his ship coming to the New World.

So we know that even in the very first expedition to the New World from Spain and Portugal, there were Jews on those ships. Unfortunately, the Inquisition followed them to the New World and it followed about 100 years later. But there was a response to the Inquisition, and what happened to the Jews who were living in Spain was that they had a couple of choices. They could voluntarily convert to Catholicism, and that way avoid being persecuted. And many individuals did that. There were some individuals who converted but only on the surface – they really didn't mean it. They were still in their private lives, in their family lives, practicing in some respect Jewish tradition and had Jewish faith, but on the outside were living as what were called New Christians – again, trying to hide from the Inquisition. There were some people who just became atheists and said, "I'm not having anything to do with any of this stuff, but I don't want to get into trouble with the Inquisition." And we see all these different kinds of individual responses. And then some people just said, "I'm going to get out of here and travel to the New World and maybe we will be safe there."

As I said, the Inquisition unfortunately followed them to the New World, and there were thousands of people who were persecuted. The Inquisition was in fact very active in Mexico and in Peru. There were a lot of individuals who settled in Mexico. One family, called the Carvajal family is very interesting, and there is a wonderful book written about this family. Luis de Carvajal was, in fact, the governor of Mexico, a huge area in Mexico, and he was Jewish. His family was Jewish. Luis de Carvajal had converted, but many of his other family members had not converted and a number of them were persecuted in the Mexican Inquisition. We know that that family is there. And we know that there were several hundred Jewish families in Mexico in the 16th Century. So in 1598, there was a big expedition that went from Mexico north, into what we call New Mexico and Colorado, and there was then the Spanish taking over New Mexico. San Luis itself, in Colorado, was a city that was founded in 1851, but the population was already very well established from the 1600s.

In that first expedition, there were 129 soldiers, and there may be another 600 or 700 people who traveled from Mexico up into Colorado and New Mexico, and then those individuals over the generations grew into this much larger population in the San Luis Valley.

Another possibility for how this genetic mutation got to the San Luis Valley is not only that it could have come with the Spanish who came to Mexico, but in the 18th and 19th Centuries, when America was being settled and people were landing on the East Coast from Europe, and then traveling west across the U.S., there were some Jewish people who landed also. And they came from the so-called Ashkenazi Jewish population. A lot of these people traveled west. And we find in Santa Fe, in the 1800s, lots of people with Jewish ancestry, people who came out with everyone else for the Gold Rush. They came out for trade. They came out to settle the west. So there was also an Ashkenazi community that started developing here in New Mexico and Colorado. And many of these people were men – individuals, single men – and there weren't a lot of women around whom they could marry. So there was in fact a great deal of intermarriage with the local population, in particular with the Spanish women. We could postulate that this mutation has entered into this population because of the migration of European men, who came and brought this mutation with them and married into the group. We know that this mutation is found in about 1 percent of Ashkenazi Jewish people, and we know that it is also found in Spain. There are some studies that have been done in the Middle East that show that it is also present in some populations from Iran and Iraq and Turkey as well. This is probably a very ancient mutation. It was probably present in the Jewish population before that split into the two parts of Europe, and it is seen in other populations as well.

There is, though, this very interesting connection to the so-called Crypto-Jews in Colorado and New Mexico. These are the individuals who now are beginning to uncover the fact that even though they had been living as Catholics, as Christians, here for the last three or four centuries, they have this evidence in their family that they may be of Jewish ancestry. There are traditions and practices in the family that are linked to Jewish traditions and Jewish practices, and there is a huge body of literature now that is uncovering these practices.

If we look at other people of Spanish descent, who live in this part of the country, are we seeing breast cancer? The answer is yes, we do see breast cancer in other Hispanic individuals here. There is a little bit of an earlier age of onset in Hispanic women. We do see more advanced stage at the time of diagnosis, so this may be reflecting barriers to access to health care and to public health education. We need to understand the genetics of this population as well as what the sociological, political, environmental factors are for treating breast cancer.

So where do we go with all of this? Well, we are just at the very beginning of understanding the genetics of breast cancer. We reviewed with you this evening the two most common breast cancer genes that have already been identified. We are doing lots of research to try and find other genes. Sometimes we test families expecting that we are going to find a mutation because they fit all those criteria, and then when we test them, we don't find a mutation. What does that mean? Something's going on. Certainly, there is a genetic risk. It just hasn't been identified yet. We need lots more research to identify other genes that are involved, to understand the interactions between these genes and the environment, and to understand the sociology and anthropology of where these genes reside in our different populations, and how they traveled over time to different parts of our community to help us predict risk and then ultimately, as I

said at the beginning, to come up with ways that will lead us not only to better breast cancer treatment, but ultimately prevention.

Rochelle Shoretz: If you are joining us this evening, chances are you are one of three types of families. You could be a family that knows you are at high risk of breast cancer – you may not have known the scientific details before tonight's presentations, but you have seen more than one family member affected by breast cancer in a pattern that raises genuine suspicion. You could be a family that, until this evening, had no idea what hereditary breast cancer was – never heard of it, not a clue. Or you could be part of a family who falls somewhere in the middle – you've heard something about genetics, maybe even read something about genetics, but at the time you did, the subject didn't seem urgent enough to register.

I was 28 years old when I was diagnosed with breast cancer, and I fell into the third category – I knew something about the breast cancer genes - can't remember if I knew precisely what they were called, but I certainly didn't know enough to consider genetics when the doctor told me the tumor was malignant. Ultimately, it was my stepmother, who lost her own mother to breast cancer at a young age, who pulled me aside and asked if I had considered genetic testing before my surgery. Well, none of the doctors had suggested it, despite my young age and some family history of breast cancer. But ultimately, I chose to put off surgery until I had the results of a genetics test to help me determine if I was a candidate for a lumpectomy, or could benefit from a bilateral mastectomy.

Over the past 2 years, I have spoken with hundreds of women and their family members about hereditary breast cancer, genetic counseling and genetic testing as the founder and executive director of Sharsheret. Sharsheret is a national not-for-profit organization, blessed to have Dr. Oratz as a member of our Medical Advisory Board, that provides culturally sensitive peer support for young Jewish

women facing breast cancer. But we've received many calls from women of varied cultural and religious backgrounds, concerned about genetics, who understand that almost all of the Ashkenazi Jewish women Sharsheret serves are concerned about genetics, too. And I'd like to touch on some of those concerns, because it is important to validate the questions that many of us have about hereditary breast cancer and breast cancer genetics – and we will have an opportunity to address many of those questions shortly during the Question and Answer Session.

Women who have been diagnosed with breast cancer, and those who already know that they may be at high risk, want to discuss the blood test you can take to check for BRCA1 and 2 mutations: where to take it, how long until the results come in, who will help interpret those results. They want to discuss their fear of the test results – what it will mean to their daughters, to their sisters, to their mothers. They want to talk about the consequences of not taking the test, or of taking the test but not sharing the results with their loved ones. They want to discuss the fear they have that knowledge about hereditary diseases in their family will affect their children's ability to marry, a genetic "taint" that will mark them as an unsuitable family. And they want to discuss the difficulty they are having in tracing their family history. For many of the women at Sharsheret, for example, much of their family history was obliterated during the Holocaust, and creating a complete and accurate genealogy can be a difficult, if not impossible, task.

Family members of those affected by breast cancer face another series of concerns. And I'd like to highlight some of those concerns by sharing with you an e-mail we received just two months ago. I've altered some of the details out of respect for the writer's privacy.

"My wife is a 55 year-old breast cancer survivor. Our daughter is 26 years old. My wife is undergoing genetic testing at this time, but we are in disagreement as to what to share with our daughter in the event that the test comes back positive. Because my wife's mother is a two-time breast cancer survivor, my wife has been extremely vigilant in looking for cancer and has prepared our daughter well. With two generations ahead of her, I believe our daughter will be similarly vigilant – frequent checkups and mammograms at the appropriate age. My contention is, therefore, that it is unnecessary to burden her with the fear that she is any more genetically predisposed than she already knows, IF there is no further action she can take. 'Condemned' or 'defective' is the message I fear her perceiving. I do not want her to fear having children or whatever other reactions she might have. My question is: Have these ethical issues been discussed anywhere? Is there any guidance you can share with my wife and me?"

Ultimately, the writer's wife tested negative for genetic mutations, and he wrote to tell me that he was relieved that he and his wife did not need to make the important decision of how much to share with their daughter. But I am certain that for many of you here this evening, those questions loom.

So where do we go for answers? You all received an information packet this evening with some of the many resources available to those who are interested in learning more about hereditary breast cancer, genetic counseling, and genetic testing. And I'd like to highlight some of those resources for you. First, genetic counselors. It seems obvious, as we sit here tonight, but I've found that we often overlook their professional guidance when we consider genetics. Very often, we think of "genetic testing," and forget that there is an entire process of "genetic counseling" that comes before any blood is ever drawn. A genetic counselor can review your family history, discuss whether genetic testing is even necessary, and review the benefits and concerns you may have about learning the results.

Please consider Sharsheret another valuable resource for peer support. Sharsheret can connect you with other women at risk of developing breast cancer or who have already been diagnosed with breast cancer. We can link you with someone who has addressed the concerns you may have now – someone who had to make the difficult decision about whether or not to get tested, or someone who has already opted for the kind of prophylactic surgery you may be considering. We can also help you locate the resources you may need over time. Sometimes, it helps simply to speak to someone who understands what you are going through because they have gone through it, too.

FORCE: Facing Our Risk of Cancer Empowered is another wonderful resource for women at increased risk of breast cancer. They have an extensive website, and have begun a peer support hotline, like Sharsheret's Link Program, to connect women with similar concerns.

And Rocky Mountain Cancer Centers, here in Colorado, offers consultation with certified genetic counselors, like Lisa, and consultation with physicians to discuss the clinical aspects of genetics. Their website address is www.cancercolorado.com.

For some, genetic counseling and genetic testing will lead to action – prophylactic surgery, chemo prevention, or even increased surveillance – being watched by health care professionals who understand your risk. For others who are already vigilant about their medical care and are not prepared for prophylactic measures, genetic counseling and testing may mean information that can seem more frightening than useful. I'd suggest one simple action that we can all take, regardless of how prepared we feel to pursue genetic testing: Know your family history. Look back and begin to piece together the genealogies that many of our families have long ignored. Let's pass information on to our older children so that they are educated about their risks, and can choose for

themselves whether counseling or testing is meaningful preparation. In understanding our past, we can continue to protect our future.

Thank you.

ROCHELLE SHORETZ: It is now my pleasure to introduce what is probably the most exciting part of the evening – the question and answer session. I'm going to begin with the first question for Lisa.

Lisa, could you start by telling us a little bit about the process of genetic counseling and genetic testing from a patient's perspective? What is the first phone call like? What is the first meeting like? Give us the nuts and bolts from the perspective of a person who is going to meet you, a genetic counselor, for the first time.

LISA MULLINEAUX: What usually happens is that a physician who sees a patient notices that they have a family history and they might give them a copy of a family history form to fill out. Actually, that's one of the hardest parts, filling out the family history form, because it requires that you contact some family members that maybe you don't want to contact. So that can actually be a pretty scary process for some people. But it helps us figure out what is going on. When I receive a family history form, I look to see if this family seems like a family of inherited risk. Then an appointment is made, and I sit down with the patient and sometimes several family members. Sometimes we have too small a room. We talk about what the pros and cons of genetic testing are. Sometimes people make a decision that this is appropriate for them and it will help them. Other people may not be ready for it. I've had people come back to me several years down the road, after I've done some genetic counseling, to say, "OK. Now I'm ready. I wasn't ready three years ago, but I am ready now." And some people – it's not going to be helpful for them, and it's not information they want to know. You have to really be ready to receive the information to get testing.

ROCHELLE SHORETZ: Dr. Oratz, can you discuss a little bit about the relationship between sisters and being tested? What does it mean if one sister tests positive or negative, for example, in relation to other siblings in the family?

DR. RUTH ORATZ: That's a great question, and it's a loaded question. I'm going to answer the easy part of it first. What is the actual risk if one sister has a mutation that her sister or her brother can have a mutation? What I want you to remember is that when we talk about family members, the men can get it. So any risk for a woman in terms of inheriting a mutation is true for her brothers, father, and sons. This is not a mutation that is limited to women.

Let's say a woman comes to see me and she has breast cancer, and she falls into a category where we think there might be a genetic risk – again, we see a family history, or she's very young when she's diagnosed. And she decides to go ahead and have genetic testing and learns that she carries a mutation that has contributed to the development of her breast cancer. What does that mean for her family members? Well, if she has that mutation, that means she inherited it from one of her parents. It could have been from her mother; it could have been from her father. So again, we do that complete family history, trying to trace back on our map where it may have come from. The next thing that we would do is try to identify anyone else in the family who does have cancer – breast cancer or ovarian cancer – figure out the relationship and test that individual. So we try to test people who already got cancer. And if we see that we can trace the mutation in the family and where it's traveling, that's very important information for us. We don't always have access to those people. They may live very far away. They may have died a very long time ago. We may not be able to get that information about other family members who have a diagnosis of cancer.

What about the people who don't have cancer? What is their risk? If the individual – my patient – has a mutation for breast cancer, and she has siblings –

sisters or brothers – each sibling has a 50/50 chance of having inherited that same mutation from either parent. Sometimes we know which parent it comes from, sometimes not. Again, we could figure that out with our map, or by doing more testing.

Let's say that woman – my patient – had children. Each one of her children – her sons and her daughters – has a 50/50 chance of inheriting that mutation. So this is what we call a dominant gene. It is autosomal, which also means it is not on the X chromosome. It is not just an issue for women.

ROCHELLE SHORETZ: Lisa, a lot of questions have come up to the front about health insurance. How much does it cost to get genetic counseling or testing? Does insurance cover it? What about insurance discrimination claims?

LISA MULLINEAUX: I wanted to add one thing to the [previous] question for Dr. Oratz. Sometimes we find discrepancies in test results between sisters, and there can be survivor guilt for a sister who does not have a mutation.

There are 40 states in the United States that have insurance discrimination legislation to protect people against genetic discrimination. And most of them deal with health insurance. There is some protection. State laws apply to state-regulated insurance. Nothing's really been tested in courts, but there has been a survey of actuaries and people who offer insurance. The one really important type of insurance that there will never be legislation about because it is not considered a right -- it is considered a luxury -- is life insurance. And I've had some patients who have actually purchased life insurance before they actually get their blood drawn.

DR. RUTH ORATZ: I do want to elaborate on the hard part of the question that was asked to me, and that Lisa brought up, which is the emotional impact when

parents or siblings or children are tested. We talked about, "What does this mean to my sibling if I have a mutation?" And I think that is why we do genetic counseling before we do genetic testing. Nobody just pops into the office for a blood test to find out whether or not there is a mutation in BRCA1 or BRCA2. First we torture you [laughter] – you spend hours talking to us, talking to Lisa, talking to the doctors – so that you really understand, as Lisa said, what this information means not only to the individual who is being tested, but what the implications are for the family members.

Let me share with you a story that happened today. I took care of a young woman while I was practicing in New York, about five or six years ago, who was diagnosed with breast cancer when she was 28 years old. I encouraged her to have genetic testing at the time, and she was very reluctant to have it. She was about to be married, and she was going through her chemotherapy and her treatment, and she decided not to have the testing. She really just wasn't ready for it at this point in her life. And today I got a phone call from her mother. She called the office, and she asked, "Do you remember who I am?" And I said, "Of course." She told me that her daughter was fine, she is healthy, she is doing well. She said, "But you know, I am very upset." And I said, "What's going on?" And she said, "I have ovarian cancer." And of course, that was very upsetting news. I know the doctors who are taking care of her and reassured her that she was in very good hands and that everything was being done to take care of her. And I said to her that when she was finished with getting her treatment and so on that it was really critical now that she and her daughter, and the rest of the family, really think about this issue. She said to me, "How much more cancer can this family take?" And my answer to her was, "That's what we need to find out. We need now to identify who the people are at risk and perhaps intervene to prevent these cancers. The interventions are very difficult ones. I'm not going to say that doing traumatic surgery is easy for anyone to accept. But if this woman knew three years ago that she was a mutation carrier, she may have decided to have

her ovaries removed. And she may not have been diagnosed with Stage III ovarian cancer.

That's a true story. That phone call came in at 3 o'clock this afternoon. And that's where we are at right now with genetic testing. We need to do better, and we do need better intervention and better prevention other than this radical surgery that we talked about. And there might be some other options that women have for prevention or for increasing the surveillance. But that's why this information is important.

ROCHELLE SHORETZ: Dr. Oratz, two part question. What do we do with this information? For the family member who tests positive, what are the options? For the family member who tests negative, what are the options in terms of screening –MRIs, mammograms, in terms of diet, in terms of surgery?

DR. RUTH ORATZ: I think it's important to think about this in four ways. Having a mutation; not having a mutation; having already been diagnosed with cancer; or not having yet had cancer. If the individual already has a diagnosis of cancer, and we learned that he or she has a mutation, that may have an impact on further intervention. Some women elect to have a prophylactic, contra lateral mastectomy – removing the opposite breast if they've already had breast cancer in one breast and they have a mutation, because there is a 20 percent chance of getting cancer in the opposite breast. As women get a little bit older, they may think about having their ovaries removed because of that risk of ovarian cancer, depending on which mutation they have and depending on the family history. Sometimes we get a clue about how many people in the family are carriers and actually get cancer. Remember: it's not 100 percent.

For people who are at risk and get tested and learn that they do not have a mutation, that doesn't mean your risk is zero. That means it's probably not as

high as the people who have mutations, but we are still going to watch very carefully. What does watching very carefully mean? Mammography is still the gold standard for imaging the breast. The recommendations are to start having screening 10 years before the youngest person in your family got cancer. If the youngest person was 45 at the time of diagnosis of breast cancer, we are going to start looking at that next generation when they are younger. Rochelle told us she was 28 when she got breast cancer. Does that mean we are going to start with an 18 year old? No, probably not. But it depends. With each generation, what we are also seeing is an earlier age of onset that may be because of gene-environmental interaction.

For individuals who have genetic mutations, we increase their surveillance dramatically. We start at a very early age and many of those individuals will take as options prophylactic surgery. For people who don't have mutations, we still watch them very closely. Their risk is not as high, but it's not zero. It's probably something in between. Mammography is still the gold standard. We sometimes use ultrasound of the breast to help us if we think that there might be something that could be seen better by ultrasound, but not everyone needs an ultrasound all the time. MRI is a new technology, which particularly in younger women or in women with very dense breasts can sometimes show us things mammograms can't show us. There are a lot of different ways to image the breast. Self-exam, of course, is very important. And physician exam is important. And we are also now starting to use PET scans, which is another kind of X-ray picture to look at metabolic activity in the cells. Each individual woman has to sit down with her clinician, look at her risks, understand the meaning of the results of her genetic testing, and then map out a program for what her follow up is going to be. And there are lots of different options.

There are also a number of clinical trials that are going on that are looking at new prevention strategies, either using medications or using specific surveillance programs or dietary interventions that we are trying to look at to reduce this.

ROCHELLE SHORETZ: Lisa, are there any distinguishing characteristics between women who are carriers of a genetic mutation for women who are older versus younger?

LISA MULLINEAUX: Not that I know of. There doesn't seem to be any distinguishing characteristics. With BRCA1, we see estrogen receptor negative tumors more often. 80 percent of the time with BRCA1, it's estrogen receptor negative tumors. With BRCA2, we are more likely to see estrogen receptor positive tumors, but there isn't really any difference in the type of cancer in young and older women who have mutations. With BRCA1, the age of onset of breast cancer tends to be a little younger than BRCA2. And that's true of ovarian cancer. The recommendation for people with BRCA1 mutations that are considering having their ovaries removed, we recommend around age 35. For BRCA2, we recommend age 45.

ROCHELLE SHORETZ: Can testing be done anonymously? That's a big concern for many of our Sharsheret callers.

LISA MULLINEAUX: I've done some anonymous testing. The benefit some people think they have is that their insurance company won't know and that will be helpful. We've done some of that testing. The downside of that is the continuity of care issue. If we don't have information about your genetic testing in your records, maybe a doctor will not treat you the way they should be treating you because they don't know what your test result is. It can be an issue because of your ongoing medical care, not to have the information in your chart. Some

people feel it is going to protect them to do it anonymously, and they pay for it themselves. And we do support that in our group.

ROCHELLE SHORETZ: Under what circumstances might one want to persuade a family member to undergo genetic counseling? When, for example, would it make more sense for a relative to undergo counseling than for the individual to go him or herself?

DR. RUTH ORATZ: Well, I couldn't convince my young patient five years ago herself, and perhaps if I had persisted with her mother and her father, we may have had better information. The woman who now has ovarian cancer has a daughter with breast cancer. They have another son and daughter. And that woman herself has siblings. So that family really needs this information. They are feeling now that they need it as emergency.

It's very, very individual, and these are very delicate and difficult conversations for family members to have with one another. Sometimes people haven't seen each other in a long time, or they are estranged, or there are other issues in the family. We all have family stuff. Tolstoy wrote in the very first sentence of *Anna Karenina*, "All happy families are alike. Each unhappy family is unhappy in its own way." We are all there. These are really complicated, difficult issues, and that's why genetic counseling and these lengthy discussions are very important.

ROCHELLE SHORETZ: As we near the end of the symposium, I want to note that Dr. Oratz and Lisa will be available to answer questions as people are leaving. Some of the questions that have come up are more personal in nature, so I would encourage you to approach them privately.

As we close, what is new on the horizon? Is there any new research regarding other breast cancer genes? Is there a BRCA3 gene coming down the line? And will these genes be discovered in time for us to react to them?

DR. RUTH ORATZ: There is a huge amount of research going on. I think the research that Lisa did with families in the San Luis Valley illustrate that by just being observant and smart, we are going to uncover other information epidemiologically that is very important. There are huge databases of families where we think there is a risk, we haven't found a genetic abnormality, but that DNA is banked, and researchers are looking for these new genes – BRCA3 and BRCA4. Molecular biologists in the lab are working on trying to understand the interaction of different genes with each other and that interaction between genetics and the environment is very, very important. Lots and lots of research going on in treatment, early detection, and hopefully, eventually, a cure.

LISA MULLINEAUX: There is a BRCA3, but it is controversial whether it's really true or not. Some researchers believe that the researcher that found it is right, and some believe that it is not right. So we are not doing a BRCA3 test yet. There are a few other things that are weak genetic components that are being looked at. We don't do clinical testing right now for those weaker susceptibility genes, but there is some research going on right now. About half of inherited breast cancer is associated with BRCA1 and 2, so there is a half missing piece.

DR. RUTH ORATZ: If you have the opportunity to participate in a clinical trial, and these open and close all the time, please participate in clinical trials. That is the only way that we can collect information that is organized, uniform in the way we look at the data, and that will allow us to make progress going forward.

ROCHELLE SHORETZ: Thank you very much Dr. Oratz, Lisa. Thank you all for joining us. I would like to thank our sponsors again: Rocky Mountain Cancer

Center, Rose Women's Organization, Myriad, Amgen, Sharsheret. If you have any remaining questions, we will be here to address them. Thank you again.

VIII. Disclaimer

The information contained in this document is presented in summary form only and is intended to provide broad understanding and knowledge of the topics. The information should not be considered complete and should not be used in place of a visit, call, consultation, or advice of your physician or other health care professional. The document does not recommend the self-management of health problems. Should you have any health care-related questions, please call or see your physician or other health care provider promptly. You should never disregard medical advice or delay in seeking it because of something you have read here.

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