Breast Cancer Genetics
Impact on the Jewish Woman and Her Family

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Sharsheret

Linking Young Jewish Women in Their Fight Against Breast Cancer

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I. Introduction

Rochelle Shoretz: Thank you for joining Sharsheret at our third annual symposium, "Breast Cancer Genetics: Impact on the Jewish Woman and Her Family." My name is Rochelle Shoretz and I am the Founder and Executive Director of Sharsheret, which is Hebrew for "chain," a national organization supporting young Jewish women facing breast cancer.

I will soon have the pleasure of introducing our distinguished speakers, all of whom will share their insights into what has become an urgent topic for the men and women of Sharsheret - breast cancer genetics.

I want to welcome those who are joining us here in New York, as well as those participating via teleconference and webcast. We have participants from more than 15 states across the country tonight and many more certain to join us, as the webcast remains available online after tonight's event.

I'd like to begin by thanking those who have made this important event possible. A generous grant from The Jewish Women's Foundation of New York enabled Sharsheret to bring us all together this evening. The Foundation was committed to ensuring the broadest possible access, and their support has given this New York event a truly national audience. I'd like to acknowledge many of the Foundation's trustees and staff who are here with us this evening. Beth Israel Medical Center opened their doors and I'd like to thank Cindy Turkeltaub in particular for her assistance in coordinating the details of tonight's event. Thank you to all of our symposium supporters - FORCE, Hadassah, Supersol, and our technical provider, Globix.

Sharsheret's staff and volunteers have worked tirelessly and in particular, I'd like to recognize Elana Silber, our Program Coordinator, and Shera Dubitsky, who coordinated this remarkable event. Their contributions to the women of Sharsheret cannot be measured.

When I was diagnosed with breast cancer a little over 3 years ago, I was overwhelmed with concerns. What type of surgery should I choose? What course of treatment should I pursue? Will I lose my hair? Will I live? 28 years old and raising two young boys at the time, I was overwhelmed with information and decisions.

In the midst of the chaos, a family member asked if I had made an appointment to speak with a genetic counselor, and it was then that I began to consider for the first time the role genetics may have played in my own diagnosis.

Some of you with us today may be in the same place - newly diagnosed, in the midst of treatment, or even a few years beyond diagnosis. Some of you may be

otherwise healthy, but face the risk of breast cancer nonetheless, perhaps with a significant family history of cancer.

And many of you may have the same questions that I had --

- What do I need to know about breast cancer genetics and its impact on me, a Jewish woman of Ashkenazi descent?

- What are the risks and downsides of genetic counseling and testing?

- What impact will this information have on the other members of my family - my mother, my sisters, my daughters?

Our speakers tonight have volunteered their time to address these important questions and more. And they have also agreed to shed light on areas of breast cancer genetics that have received little prior attention - the impact of hereditary breast cancer on Jewish women of Sephardi descent, and some of the unique concerns faced by Orthodox and Chasidic families considering counseling and testing.

We will then hear from representatives of support organizations that address the needs of Jewish families at risk of breast cancer. And finally, all of the speakers will take questions from our audience, including those of you participating via teleconference.

But before we begin, I would like to highlight Sharsheret as an available and valuable resource for those of you participating this evening.

When Sharsheret was founded three years ago, we began as an organization that would provide support for young Jewish women who were newly diagnosed. But the phones began to ring with calls from younger, healthy women who were concerned about their risks of developing breast cancer because their mothers or their sisters had been diagnosed.

They wanted to speak to other women who had grappled with the same decision-making - whether to get tested and what to do with the results. And we quickly began to recognize that the very same peer support that proved invaluable to the woman struggling through treatment was invaluable to the woman coping with a family history of breast cancer. Both wanted to speak to someone who could simply understand.

Sharsheret now offers three programs --

1. Our **Link Program** connects women across the country in one-to-one conversations with peer supporters who share the same background and concerns.

2. Sharsheret's **Quality of Life Programs** are designed to enhance the quality of life for younger women living with breast cancer, with initiatives like the *Busy Box* for parents of young children and *Best Face Forward* to address the cosmetic side effects of treatment.

3. And finally, our **Education and Outreach Program** educates health care professionals and those in the Jewish community about the issues impacting young women and Jewish women facing breast cancer.

Over the past 3 years, one of the most urgent topics for those reaching out to Sharsheret has been the subject of tonight's symposium. Our goal is to answer some of the critical questions you've brought to our attention, raise new ones, and generate discussion about the ways in which breast cancer genetics impacts the Jewish woman as an individual, as a family member, and as part of a broader community.

This is the first of what is certain to be an ongoing conversation, and we encourage you to stay involved as the Sharsheret, the chain, continues to grow in the years ahead.

II. Genetics For Jews: What Every Jewish Woman and Family Needs to Know About Breast Cancer Genetics

It is now my pleasure to introduce Jessica Mandell, the principal genetic counselor and research coordinator of the *New York Breast Cancer Study*. The study investigates the genetic and environmental links to breast and ovarian cancer in the Jewish population, and you will find a summary of the article Ms. Mandell co-authored on the subject in your information packets.

Ms. Mandell will start us off this evening with a fitting overview, "What Every Jewish Woman and Family Needs to Know About Breast Cancer Genetics." Please join me in welcoming Jessica Mandell.

Jessica Mandell: Hello. Thank you for having me here tonight. I'm very pleased to be here and to introduce this discussion for all of us this evening.

Specifically, what I'd like to talk about tonight is an overview of inherited breast cancer: What it really means to have not only breast cancer in your family, but to have it be recognized as a genetic condition or a predisposition in your family and how this impacts families, particularly of Jewish descent. And also, I'd like to present the data that has come from the *New York Breast Cancer Study*. This is the abstract from the paper that was published in *Science* in 2003, which was a landmark project coordinated through many centers here in the New York metropolitan area on Jewish women with breast cancer to understand these inherited factors.

To start off, I really just wanted to give everyone an overview and to just get it down to the basics.

When we think of breast cancer, it's a pretty common condition in the general population of women and the majority of cases, 90% of cases, are really sporadic cases caused by our environment, our diet, our hormones, things that are not related to inheritance in our family. However, 10% of the population of breast cancer does have a genetic or an inherited factor that's predisposing us. It's something passed on in our family.

So what really are these genetic or inherited factors? Specifically, what we have been able to discover, just in the past 10 years, are these two genes called BRCA1 and BRCA2, which you may have heard of as BRCA genes. It's the same thing. BR stands for breast, CA for cancer, and gene 1 and gene 2 for when they were discovered.

And really, if you think of DNA as the human blueprint that makes up who we are and directs our development, each gene in our body is just a piece of the DNA.

So if the DNA is a book, each gene is a page in the book. BRCA1 and 2 are just two pages of the book. They are normal, natural parts of our bodies. We all have them. Men and women have them the same. We pass them on to our kids the same.

The significance is that if you have a mutation or a mistake inside of the BRCA1 or 2 gene, a chemical that's deleted or inserted in the wrong place, that can turn off the function of the gene. It's these mutations in our bodies that give us an increased risk to develop breast and ovarian cancer.

A lot of people say, "I have the breast cancer gene." It's not that we carry the gene, because we all have the gene. It's that you have a particular mistake or mutation in your gene, which now, since that gene isn't working, gives you these increased risks of cancer.

And how does this impact the Jewish population?

Specifically, what we have discovered is that there are three mutations - two in BRCA1 and one in BRCA2 - that are most common among people of Ashkenazi Jewish descent and we suspect that they're carried by about 1 in 40 Ashkenazi Jewish individuals.

So how is it that the Jewish population came to carry these genetic mutations most frequently?

It's not really that the Jewish population only has inherited breast cancer, because a lot of populations have inherited breast cancer due to other mutations in the BRCA genes as well, but it's just like with other areas of genetics, certain populations from different ancestral backgrounds have a particular genetic component to their bodies that's different from people of different ancestral backgrounds and this is what we have discovered about Jewish people with the BRCA genes as well.

And really, what we have discovered is that about 2,000 years ago we think these gene mutations arose, probably in populations in Eastern European countries, and in a very small subset of that population these genes existed. These gene mutations existed, but over time, due to historical events, isolation of the Jewish population, migration of the population once the population became very small, those mutations all of a sudden became a larger portion of the population. And then, as we migrated again and our population expanded, the gene mutations have spread out so that now more Jewish people carry those same mutations that were, at one point, very, very rare.

The other thing that's important to understand is that since these are normal parts of our bodies, these genes, they're carried by men and women. We can

inherit these gene mutations from our fathers just as we can from our mothers, which some people haven't understood in recent times and also, the idea that a mother or father can pass it on to their sons and daughters.

But what you'd tend to see is, because we're talking about breast and ovarian cancer specifically, the women in the family will show the condition, whereas the men in most instances, or in many instances, can carry these genetic mutations without much significant medical affect on their own bodies. There are some cancer risks to men, which I will mention, but in general you'll see that a parent will pass it on to their child and the women will be affected, whereas the men can continue to carry these mutations in their bodies and possibly pass it on to the next generation.

So what are these real risks that we're talking about?

If you look at this, the yellow bars are just the general population risks for what we expect of breast and ovarian cancer. This is just United States population information. About a 12% lifetime risk is what we expect for a woman in the general population to develop breast cancer. That at some point in her life, from 0 to 70 or 80, 12% chance that she'll get breast cancer.

If you carry a mutation in BRCA1 or 2, the risk is increased to what we suspect to be around an 85% lifetime risk. That's very significant - for people to find out this information - certainly by an impact on their health. It's important to understand this isn't a 100% risk. It's not that you will automatically get breast cancer, but it's a very increased chance that you will.

With ovarian cancer, these risks are also increased with BRCA1 and 2, which is also important to understand. These are called breast cancer genes, but they correspond to an increased predisposition for breast cancer and ovarian cancer in women who carry these same mutations.

Ovarian cancer is very rare in the general population. It's about a 1 to 2% lifetime risk. With the BRCA1 mutation, however, that risk is increased to about 60% lifetime chance and with BRCA2 it's a bit less, to about a 20% lifetime chance. But it's also very significant if you can learn this about yourself through genetic testing.

Now, what this graph also doesn't show us are the other risks of certain types of cancers that can be related to BRCA1 and 2. Specifically in men there is slightly increased risk of prostate cancer for both of these gene connections. For BRCA2 there are also increased risks of male breast cancer, about a 5 to 10% lifetime risk, which is increased over about a less than 1% risk, very rare in the general population.

We also see in some families an increased risk of pancreatic cancer, skin cancer, throat cancer, and stomach cancer that's associated specifically with BRCA2. So certainly that's not in all families with these gene mutations. But if we see that in a family with some other indications, then it sort of matches what we would expect and that's also important - that anyone who's found to carry a gene mutation in BRCA2 or BRCA1 understand these extra cancer risks as well.

So how do you know if you really have one of these gene mutations in yourself or in your family?

Primarily what we look for are families that have multiple cases of breast cancer, breast cancer going from generation to generation, more cases in a family than you would normally expect to occur just by chance. You also tend to see earlier onset cancer, cancer occurring in a woman - 20's, 30's, 40's, even 50's, some were premenopausal - as opposed to 60's or 70's or even 80's, which is more typical for a general population type of cancer. You see a combination of breast cancer and ovarian cancer in the same family in some instances and also in the same woman in some instances. And also a flag is the bilateral breast cancer. These are two singular cancers in the same woman. Not a spreading of one cancer to another per se, but two separate primaries that just occur in each of a woman's breasts because all the cells of her breasts are susceptible to getting cancer at some point in her lifetime. So she has an increased risk to get breast cancer again, even if she's already had it one time.

Being Ashkenazi Jewish does not automatically mean that there is a gene mutation in your family. But if you're Jewish and you have these other factors in your family, then certainly it's something to be looked into. And male breast cancer, because it is so rare in the general population, when you see it in a pattern with these other factors as well, increases the likelihood that there's a genetic mutation responsible for the family history.

So here I just want to reiterate what a person does when they recognize a lot of these patterns in themselves and in their family. The next step really is to contact your doctor, or specifically your genetic counselor, to go over exactly what it means, what your family history means, what this pattern means, so you can explain if this is really an inherited situation or not. It's been shown in the literature that a lot of people today, a lot of women and Jewish women in particular, because of all the media that we see and all the research studies that are coming out, have very high expectations of their own personal risk of breast cancer and the fact that there could be a genetic inheritance in their family. But, in fact, when they sit down with a counselor or a doctor and really go through their family history and their medical history and their personal risk assessment, they realize that their risks are probably a lot lower than they originally expected and that maybe they don't even need genetic testing. But for a lot of people who

go through genetic counseling, it really shows them exactly what their risks are and shows them that they're a candidate for genetic testing.

And in this, it's important to review what the pros and cons of testing are. Not just that you're a good candidate - okay, fine, the statistics support genetic testing for you - but personally and medically for you: Do you want genetic testing? Is it really what's going to be helpful for you? Do you want to know this information? Is it going to impact you positively, in a medical way and in a personal way?

And in a medical way, one of the primary benefits of genetic testing is that if we can identify somebody who is at higher risk of these cancers, we can offer them options for breast and ovarian cancer screening and prevention, and possibly some other types of cancers as well that they would not otherwise be able to access.

Those things include screening options, like mammograms, MRI, and ultrasounds are becoming more popular for breast cancer screening. There is ovarian cancer screening, which is helpful for a certain population of women. Chemo-prevention, taking a drug therapy like tamoxifen to reduce your risk of breast cancer, before you even have cancer. Prophylactic surgeries, risk-reducing surgeries, such as having your breasts removed or your ovaries removed before developing cancer, which can reduce your risk of getting these cancers by potentially over 95%. And then also lifestyle changes, dietary factors, exercise, decreased smoking, decreased drinking - things that maybe genetic testing or genetic counseling would serve to help you change in yourself that's going to help reduce your cancer risks.

The process of genetic counseling can be very important in identifying for you not only that you're a good candidate medically and statistically, but personally if this is information that's really going to be helpful for you.

So to shift gears a little bit, I want to talk about the *New York Breast Cancer Study* and what we found and how we can now apply the information from this study to the general population. Specifically, when we set out on this study, we were just going to assess, as basically as we could, what are these BRCA genes doing in a population of women with breast cancer? How many women carry these gene mutations? What kinds of risks are associated? What sort of environmental factors are at play to either exacerbate or reduce our risk?

And so what we did was we tried to create what we think is one of the largest population studies to date in this area. We took Jewish women, specifically from the New York metropolitan area - New York, New Jersey, Connecticut - similar environmental background, all diagnosed with invasive breast cancer.

We didn't differentiate on how old they were when they were diagnosed. It didn't matter to us what their family histories were. We were just really looking to see what was in the general population and we specifically picked Jewish women as a population 1) because there are a lot of Jewish women in this area who have breast cancer, and 2) because of these three mutations that are most common among Jewish individuals, it's very easy to do genetic testing and to tell, "yes you have this," or, "no you don't." We did pre- and post-test genetic counseling for every woman for free and we offered them genetic testing for free for these three mutations and then tried to see what we would get.

What we also were able to do was, when we found a woman who actually had a gene mutation, we opened the study up to invite her entire family into the project. We offered them, as well as all of her relatives, pre- and post-test genetic counseling and genetic testing for free. We not only got her information from just her reports of her family history, but in actuality how this mutation was being passed on in her family, what types of cancers it was causing, etc.

So what did we find? We enrolled 1,008 women who were Jewish, who had invasive breast cancer. Of those 1,008 women, 103 or 10% carried one of these three mutations. That statistic matched what we had generally suspected from previous reports of general population inherited breast cancer.

The next thing we found, which was significant, was that the breast cancer risks - the chances of getting breast cancer if you carry one of these gene mutations - really matched all the previous reports. Which was helpful because some more recent studies had suggested maybe these risks really weren't so high. But in our study, the risks were as high as suspected, up to an 82% lifetime risk to get breast cancer for those women who carried a BRCA1 or BRCA2 mutation.

Similarly, for ovarian cancer, we found the same increased risk. BRCA1 carried a risk of 54% lifetime. BRCA2 carried a 23% lifetime risk. This is for ovarian cancer, specifically in women who have these mutations. So, again, these statistics matched what we had seen in other studies.

One of the other interesting things that we found was that among women who actually carry these genetic mutations, there wasn't -- I mean, we all suspect you have the same mutation in your body, you should have the same biological predisposition. But we actually found that there were differences, even among this group of similar women. One of the differences, specifically, was the incidence of getting breast cancer, based on when these women were born. Women who were born before 1940 - so we're talking 60, 70, 80 years ago - those women who developed breast cancer had a lower incidence of getting breast cancer than women who were born in more recent years, from 1940 to the present, say, in the past 50 or so years.

If you're thinking, "Well, we have the same lifetime risk, why is there a difference?" you have to think of environment and lifestyle differences among women who were born before 1940 and after 1940. Women in more recent decades are exposed to a lot of different things in their environment: More hormones in their bodies through food and through drug therapies, more toxins in our environment, different diets, different reproductive patterns, different smoking and drinking patterns - all things that we now recognize as potential environmental factors that may increase risks of breast cancer.

This points to the idea that it's not just the breast cancer genes alone that are causing breast cancer, but that they work with our environmental factors to actually bring the cancer into development. Specifically, in breaking down those environmental factors, we had women fill out a very extensive questionnaire, from everything we think of related, from their childhood to their adult life, about all the factors from diet, exercise, smoking, anything related to potential breast cancer risks. And the most significant factors we found were exercise, having an active life, and having a normal body weight for your size. But not so much as when you were an adult, more when you were a teenager.

For women who carried these gene mutations when they were teenagers, those women who had a more active lifestyle, did sports in school and things like that, and had a more normal body weight at that time, had a lower risk of breast cancer when they were adults. On the flip side, women who had a less active lifestyle, a more sedentary lifestyle, and had a higher body weight when they were teenagers had a higher breast cancer risk when they were adults.

This factor, yes, it tells us that certainly exercise and lifestyle factors and dietary factors are important. This information isn't necessarily going to impact a woman who is now 50 years old, has breast cancer, and has a gene mutation. She can't go back and change what she did as a teenager. But this is certainly important information for our daughters and the younger generations in our families and specifically for a woman who knows she has the mutation, who has children, has female children. They don't know that they're carriers or not yet. They're too young to be tested. But she can instill in them healthy lifestyle behaviors that potentially can help reduce their risk of breast cancer as adults. It's a way to be proactive going forward, which can be very helpful.

One of the final things that we learned from the study, too, which was very interesting, is just the idea that this inheritance comes from both sides of the family. It's not just your typical pattern that you would see in a family that indicates a genetic mutation in the family.

This is a woman – the woman who's filled in, in black. She was our initial participant, breast cancer at 42, certainly young age of onset, Jewish. However, when we initially saw her, no family history to speak of. So we counseled her

with the idea that it was very unlikely we would find something in her family. She did carry a gene mutation in BRCA2 and it turns out that it was inherited from her father's side of the family.

Of the 103 women who had a gene mutation, exactly 50% inherited it from their father and 50% inherited it from their mother. So it's very important in testing your own family history, when your doctors are working with you and your family histories, to recognize your paternal and maternal sides of your family.

Here it just so happens that none of the relatives in her family carried a gene mutation. Just by chance these things happen. You don't necessarily have to have a very strong family history for there to be a gene mutation in your family. Maybe your family is too small. Maybe there are no women in your family or maybe just nobody inherits it.

This doesn't mean that every Jewish woman should go out and get genetically tested. It just means that if you're Jewish, if you've had early onset breast cancer, if there are a few things that make you wonder, "Do I really fit this pattern?" that maybe seeing a genetic counselor would be a good idea for you to see if you really are a good candidate for testing. And then, just on the flip side - and this is something Dr. Offit will address more specifically - these were a bunch of families that we also enrolled: Very early onset cancer, breast and ovarian cancer, male breast cancer, multiple relatives affected. None of these families carried one of these gene mutations.

So the idea is, well, then, what's behind all of these other families? If they are 90% of our population with breast cancer, a lot of them had strong family histories, there's got to be something else out there. These three mutations certainly are not the only answer for inherited cancer in Jewish women and certainly in other populations as well.

I just want to recognize – these are all the medical institutions, the doctors and genetic counselors, some of which are here today, that helped us on the *New York Breast Cancer Study*. We couldn't have done it without them and certainly the Breast Cancer Research Foundation here in New York, which supported our research. And I thank everyone for being here tonight.

Rochelle Shoretz: Thank you, Jessica. Your work is critical to the well being of Jewish women everywhere and your remarks helped set the stage for the remainder of our discussion tonight.

You will all have an opportunity to submit questions for Ms. Mandell during the Q&A session at the end of the presentations this evening. In the meanwhile, I encourage you to write your questions on the index cards you should have received in your information packets and we also have volunteers circulating in

the audience with additional cards, should you need them. For those of you participating via teleconference tonight, you'll have an opportunity to submit your questions to the operator later on in the program.

Dr. Kenneth Offit has been on the cutting edge of cancer research as Chief of the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center. He has advocated tirelessly for the education of men and women who want to learn more about hereditary breast cancer. I know, because I have had the privilege of hearing him speak at more than one late night event.

Although hereditary breast cancer is only a small percentage of breast cancer overall, most lectures on cancer genetics focus on the woman who tests positive for a genetic mutation. Tonight, Dr. Offit will address the often-overlooked concerns of a majority of those who have submitted for genetic testing – the implications of testing negative. Please join me in welcoming Dr. Kenneth Offit.

Dr. Kenneth Offit: The question that was asked is an interesting one: Is there new research about women that have tested negative for BRCA mutations? The answer is, well no, actually, there isn't. So what we did, in anticipation of this talk, was to do the research. It's an interesting and an important topic and I will share some data with you that are not published. And one of the opportunities and one of the privileges and responsibilities of doing this kind of work is that if you ask a question and you don't know the answer you have to get it, do it yourself.

We've been talking about the genetic evolution in medicine and cancer and just to remind you that breast cancer goes back pretty far, the family history of breast cancer.

This is not a Jewish event. What is striking is that in the Ashkenazi population the proportion of ovarian and breast cancer that is hereditary is greater than what you see in this slide here and goes up to 40% for ovarian cancer and 30% for breast cancer.

The causes of hereditary susceptibility -- and this is really the question today. If you look at the right-hand side of that pie chart you see that for families with breast and ovarian cancer, we think that BRCA1 and 2 account for virtually all, but not all, that 5%, is that tricky 5%. And for families with site-specific cancer, we think that BRCA1 and 2 do not account for the majority of cancers. In fact, we think that probably a third to a half are not due to BRCA1 or 2.

And so the question that we often come to be asked is, if you're in a family with breast cancers and you've tested BRCA-negative, what about your ovarian cancer risk? And we'll give you some data for that today.

This was already alluded to by Jessica and the *New York Breast Cancer Study*. And I actually put these numbers in to just show you that, in fact, what the *New York Breast Cancer Study* did was confirm what we had suspected. That these penetrants (ph) were high. This is a mutation that I discovered in 1996. It's the most common BRCA mutation right now, I think, in the world and it's in the Ashkenazi group, in 1.5% of Ashkenazis together. One of the three mutations seen in 1 in 40 of the Ashkenazi population.

And great, they were focusing on outside of the Ashkenazi population. We know there are 13 million Jews in the world and we know that we've got a million more here than in Israel and we're all pretty much Ashkenazi here. But not in Israel, where it's half or less Ashkenazi.

And this is just giving you a statistic. These are numbers that I've calculated and nobody's ever questioned me on this, but it's daunting if you think that we're 2% of the population in the United States and yet we account for, I think, a quarter to a third of all the BRCA mutation carriers in the country. And that's amazing, isn't it, when you think of that? Okay and you won't see the numbers laid out for you quite like that.

And if you're an Ashkenazi Jewish woman and you're affected with breast cancer before the age of 40, you've got a 30% chance, roughly, of having one of these mutations and I just told you that ovarian cancer number, which is staggering. Every Jewish woman with ovarian cancer and I believe with breast cancer should have this testing.

Jessica already showed you the slide. I can give you my sort of historical take on this. This is the real thing. The population of Jews by 1700 had decreased to 10,000. It's incredible, isn't it, to think that the population was that small in size in the center of Europe?

And then Catherine the Great came and protected us in 1710 and then we were able to increase in population from 10,000, in 1710, to 2 million by 1800 and up exponentially to 1939. And this, of course, is where we were, where Catherine the Great protected us and this, of course, is how we came to be that near extinction population that led to that extraordinary emergence of those rare mutations that Jessica indicated.

She's pointed out to you the risks of the cancers. We've done a lot of these studies. You know it's important to understand. Because of the Ashkenazi simplicity of testing, we get our ice cream in three flavors, not the Baskin-Robbins' huge number.

We can do this testing on archival material and a lot of the literature that has been written about extra breast risk, for example our study on prostate cancer this year showing a 5-times risk in BRCA2, not BRCA1 carriers, all done in the Ashkenazi population and that's important. Colon cancer risk, not increased in BRCA carriers, despite what's written.

Also in the Ashkenazi population we have some extraordinary events that can happen, that probably will not happen in any other group. If a woman and a man both carry a BRCA2 mutation and they marry each other, they may have a child with leukemia and brain tumors. And this is a very rare circumstance that we reported for the first time and raises, really, the prospect of prenatal testing for BRCA2 mutations in the Ashkenazi group, if you happen to have a rare BRCA2 mutation. And I wrote about this is JNCI and is something that I think merits further discussion within the genetics community.

This is the slide that Jessica showed you, but I'm going to embellish a little bit on the clinical aspects of this, because I think I noted in the panel that this is often not done and would not be done this evening if I didn't.

One of the things that I believe very strongly is that the genetic counseling for this particular syndrome needs to include interaction with practitioners, oncology practitioners. The kind of counseling that you get will vary according to the range of experiences of the person you're in the room with and our view is often going to be different.

And I can just say from experience that perhaps the reason that our uptake of surgery for the ovaries was so much greater at our center than others was because I cared for a lot of people with ovarian cancer. And I also saw what the actual morbidity and mortality was for laparoscopic surgery and could share that one-on-one, as a physician, with individuals.

Just getting the options is not enough. You've got to actually go through this as a thought experiment to truly empower - to steal the word of a great organization on the panel tonight - the individual.

So I've mentioned to you what the strategies are. I'm going to give you a little bit more data on the screening. Ovarian screening with ultrasound and C125, we recommend. But, as you know, our group has been very strongly committed to screening up to performing or discussing the preventive ovarian surgeries. Which was the paper that we have published in the *New England Journal*, showing the detection of early ovarian cancers in 3% of the BRCA mutation carriers who had the so-called preventive surgery.

Tamoxifen data is there. It's somewhat contradictory at the current time. Is tamoxifen protective in BRCA mutation carriers? Two studies that are offsetting. We think the stronger of the studies by Stephen Narod in *Lancet* actually leads us to think that there is a protective effect, certainly in BRCA2 and possibly in BRCA1.

Oral contraceptives, also offsetting. In Israel the study was negative. Perhaps the use and dosing of oral contraceptives was not as great as it is at the current time. Also, because of the concern of increased risk of breast cancer due to oral contraceptives, this is not universally recommended.

Prophylactic mastectomy, the two large series in Rotterdam and Mayo Clinic. This is still the "Gold Standard." But as I was at surgical grand rounds this morning and Pat Borrigan said we would like to see the day when this type of surgery is made obsolete. There are big differences, cultural differences in surgery practice in Europe. This prophylactic surgery is much, much more common, particularly in Northern Europe than here in the United States.

MRI. This is a mammogram miss and an MRI pick up and in our series that we did at Sloan-Kettering we found that we missed half of the cancers with yearly mammogram screening in BRCA mutation carriers. That's nothing to be proud about. The MRIs, however, have a much greater sensitivity.

This is an editorial that we wrote just a few weeks ago in *JAMA*. Two landmark studies have come out and I would recommend you read the editorials and read these studies. These are very important. We recommend it in this article and hopefully this will become policy that MRI be reimbursed for BRCA mutation carriers.

The sensitivity is an order of magnitude greater than that is for mammography and the key number, which I calculated from these studies, the percentage of lymph node positivity in these studies. And you'll notice in this Warner, the Canadian study, it's down to 9% and all of those studies, all of those 9% that have positive lymph nodes were at the time of the first screen, the prevalence screens. And I can go through this with you in Q&A. I don't have time now.

But in the incidence, in the 2- and 3-year, those numbers were zero. That's very important data. I commend you to read that editorial. BRCA mutation carriers at our institution get an MRI, six months, alternating with mammography and ultrasound. Each of these modalities offers a little bit that the other modality doesn't.

For DCIS, the pick up is still better with mammography. This is our *New England Journal* paper. This is laparoscopic surgery. This is a microscopic ovarian cancer. 3% of BRCA mutation [carriers] will have this microscopic surgery. Now we didn't make a big deal about it in the paper, but I could tell you offhand that 70 to 75% of women were Ashkenazi Jewish in this, okay. It's irrelevant because the results are the same. They're universal results.

So what about women with a family history of breast cancer that test negative?

The most important thing here is if you test negative in a family where you have a mutation. That's a true negative. So you're negative and you are a population risk of breast cancer, you may be lower than population risk of breast cancer, so you had better get that straight.

But what about if you test in a family where you don't know if there is a mutation and you've got multiple cases of breast cancer?

Should you still do ovarian ultrasound? Should you have your ovaries removed because there could be another gene causing you to have ovarian cancer risk?

How about the other genes that are associated with these? These are very, very rare, P-53, P-10 - these you'll never seen in practice.

BRCA testing -- and so here is the data we did. From '94 up to 2002 we pulled all of our cases, with three cases of breast cancer in the same lineage. One of the breast cancer cases diagnosed before age 50, no ovarian in the lineage, and no BRCA mutation.

Most of our cases, where we have negative three Ashkenazi, we go on and do the full sequence, because we've reported the founder/non-founder frequency in this group is not insignificant. It's probably around 5 to 6% and so we say go ahead and do that.

205 suspected male probands met the criteria for the analysis that was done for the organizing of this conference. 166 - 81% - completed a questionnaire. We actually did a survey by mail. We had an incredibly high response rate. That's 81% without even trying hard. That's how motivated the women are in our studies.

Mean follow-up of 40 months, so that's not bad, right? That's over three years. 7 of 161 probands in 12 to 85 first- or second-degree female relatives had a new breast cancer, so there you see there's a lot of hereditary breast cancer that's not BRCA1. But no proband and one first-degree relative had ovarian cancer, 2,540 woman-years of follow-up and that's no different than what would be expected.

So that's actually interesting and what it tells us is that the ovarian cancer rates are not higher in these families with breast cancer in a negative BRCA mutation and this is kind of cool. Those of us aficionados in the field, they said that's useful, you know we can use that and you can use that, but not until we publish it, okay. I haven't even submitted it.

Risks of cancer in non-BRCA carriers -- and then, oh yeah, we looked at other cancers too - melanoma, pancreas, prostate. This is in this BRCA negative group and the numbers are tiny, but nothing is staring out at you and as Jessica mentioned and as we told you from our research, prostate cancer increased in BRCA2 mutation carriers. Pancreatic cancer increased, particularly in BRCA2 mutation carriers.

So anyway, these are the key points --

- Genetic testing can identify some individuals at risk.

- Models are available to do this type of risk estimation.

- Efficacy data are available for some but not all of the medical interventions that are available for BRCA1 or 2.

- And I've told you about this recent explosion of information on MRI.

If you're thinking of MRI, like I said with genetic cancer, genetic counseling, it's good to go to places where you have multidisciplinary cancer genetic counseling with a psychologist, oncologist, genetic counselor, as well as surgeons and others.

In this area, MRI is very operator-dependent and right now we have a sponsored study. Good centers for MRI you know about in the United States, for example Philadelphia is a strong one; Toronto, where they published this data.

But you've got to be careful, because if you have an inexperienced reader in MRIs right now you have a very high false positive rate. It's a sharp learning curve. But the data are impressive. That's been our experience at Sloan-Kettering.

Now I put this [slide] on. I know it's a political season and we can all go boo for my friend Bill Fritz (ph), okay, who I went to school with. I'm going to convince you now that actually Bill did a good thing. So, as a conservative - some would say reactionary - Republican, he got together with Daschle and a year ago this week he got this thing through the Senate.

And I asked him to do this at a college reunion - I kid you not - and he said it was a piece of cake. He said this was bipartisan. This has got to be done. Bill is very, very tuned in to this particular issue and he did this.

But the sad news is, I'm told, this is not going to go through the House of Representatives. And of all of the issues that we touch on, I wanted to be sure that we did touch on this particular issue.

Because until we get this done, all the way done, not just through the Senate but all the way through, to make a law out of this, 40% of the women that we see have a major concern about genetic discrimination. Not only for them, but for their children. If you have breast cancer, HIPAA protects you. You know you have Federal protection, but not your daughters, not yet, not until this gets done.

Thanks a lot.

Rochelle Shoretz: Thank you Dr. Offit for sharing with us all of that tremendous research. I'm sure that many of those with us tonight and those of you participating via teleconference will have questions about the work that we saw

tonight and future research that may be on the horizon for families affected by hereditary cancer. And again, we'll have time for those questions later on this evening.

When Sharsheret had the privilege of working with our next speaker, Dr. Ruth Oratz, in presenting a symposium on genetic susceptibility to breast cancer in her new home state of Colorado, we knew we had to bring Dr. Oratz and her research back to New York for at least one more night.

For years, breast cancer research has focused primarily on the Ashkenazi Jewish woman, with almost nothing written about women of Sephardi descent.

Dr. Ruth Oratz is an Associate Professor of Clinical Medicine at the New York University School of Medicine and an oncologist specializing in breast diseases in Colorado. Tonight, she will share with us her emerging research on "Sephardi Jews and the Genetic Susceptibility to Breast Cancer." Please join me in welcoming Ruth Oratz.

IV. Emerging Research on Sephardic Jews and Genetic Susceptibility to Breast Cancer

Dr. Ruth Oratz: Thank you, Rochelle. It really is a pleasure for me to be back in New York and any excuse to be here, especially to join you here at Sharsheret, is a wonderful one.

It is ironic that it took me to go to Colorado to become interested in the genetics of Sephardic women and as I present some of this data to you, I'll tell you the story about how that actually happened when I arrived in Denver.

At NYU, I collaborate with Dr. Harry Ostrer, who is the Head of the Clinical Genetics Program there. He published an interesting paper in 2001, which looked at a historical survey of the genetics of Jewish populations. Dr. Ostrer has postulated that Jewish people originated in the Middle East a long time ago, more than 2,000 years ago, and then as we all know, migrated to other parts of the world.

There were several populations that had been established in the Middle East, in the Persian Empire, along the whole Mediterranean Basin, down into the Indian subcontinent and then up into both Eastern and Western Europe. And more recently, of course, Jews have migrated all over the world to East Asia, Australia, South Africa and so on.

We're going to be thinking historically about those older communities. We know that some of the Jewish communities retained real geographic stability. Both Jessica and Dr. Offit talked to you a little bit about that idea of founder mutations and communities that were in one place that allowed growth of the mutation within that population. We know that Jews were linked by common language, religion, social customs and marriage and that within the Jewish community we could identify who was Jewish and who wasn't Jewish.

Historically, three Jewish communities have emerged that are kind of geographic, based on patterns of migration and based on these historical traditions of language and customs. The oldest Jewish population is probably the group of Jews who have stayed in the Middle East and are referred to as "Middle Eastern" or "Oriental" Jews. We think that they first settled or first developed in this part of the world in the second century BCE - Israel, Palestine, and the communities in Iran, Iraq, Central Asia, Arabian Peninsula, Yemen and so on. Those Jewish populations, who have been there consistently for 4,000 years, are probably the oldest populations and the founder populations.

We then saw a migration in the early Middle Ages of Jews across the Mediterranean Basin, traveling across North Africa, maybe stopping in Italy, in the Balkans and Turkey, and then traveling up into Spain and Portugal, the

Iberian Peninsula. We see a large Jewish migration, which followed, actually, the spread of Islam through the Middle East, across North Africa, and up into the Iberian Peninsula.

Then, a little bit later in the Middle Ages, we see Jews disbursing from that Oriental/Middle Eastern population probably up through the old Roman Empire, up through Rome and so on, into Eastern Europe - the founder population for the current Ashkenazi Jewish population. You saw that map of where those people settled in Eastern Europe and have since migrated throughout Europe and other parts of the world.

So these are the three communities that we're going to be thinking about historically. And as Dr. Offit said, there are about 13 million Jews in the world today, with a very large proportion of Jews living in the United States. The second largest group, of course, lives in Israel.

Here in the U.S., 90% of the Jewish community is Ashkenazi. In Israel, though, we still have a very large percentage of that original founder population. About 23% are Oriental Jews and again, these would be Jews from countries like Yemen, Saudi Arabia, Jews who were in Palestine and never left, in Lebanon and never left, and other Sephardic populations. These might be Jews whose families had gone to the North African countries - Algeria, Morocco, Egypt - into the Iberian Peninsula, Spain and Portugal. Some of the Jews who went up into Turkey, they would be part of that Sephardic population and then, of course, the Jews who came back to Israel from Europe, the Ashkenazi Jews who are about half of the Israeli Jewish population.

So what does that mean genetically? Well, Jewish religious law defines who is Jewish according to religious law. But what we are interested in is how we are related in our DNA. There are people who have joined the community. There are people who have left the community and we still may somehow be related.

There are two ways that we can look at that relationship and one thing that's been very interesting is studying the Y-chromosome, which is the chromosome that defines being male. Males have Y-chromosomes, females don't. We can look at the Y-chromosome to find linkages that may tell us if we're related to one another. And we can look at mitochondrial DNA, which is another kind of DNA that's in our cells. Mitochondria lives in the cytoplasm of our cells and we inherit this mitochondrial DNA only from the female side. So there are some tricks that geneticists can use to try and understand how populations are related to each other. Let's look at these different Jewish populations. In addition to using these tricks, we can look at diseases that are genetically linked, that are prevalent in populations, and see if we can identify genetic conditions in these populations.

We know that there are probably more than 40 genetic conditions, which are associated with Jewish identity. And as you've heard earlier, some of these can be identified as founder mutations, which means they were present a long time ago in the population and have stuck in that population.

Some of these conditions are very rare. Some of them are only found in one Jewish group and not in the others and that's what we're trying to now understand with respect to the BRCA1 and BRCA2 genes. Can we date the age of these mutations? Can we correlate the patterns of geographic migration with the presence of a mutation in a community and how does this all get put together?

Let's focus on a different BRCA mutation, the one on the BRCA1 gene, 185delAG mutation. Dr. Offit showed you this on the timeline that he flashed up there. He showed you that the BRCA2 mutation probably was introduced in Eastern Europe sometime in the late Middle Ages - and I will show you some data that I think supports this notion - is a very ancient mutation and may in fact even have been present in the original Oriental Jewish population in the Middle East. This mutation has been identified certainly in the Ashkenazi population, but it is also seen in other Jews, in Iraqi Jews and in Moroccan Jews. I'm going to show you some really interesting data about other groups who carry this mutation who are not Ashkenazi.

So, what's the evidence that this is an ancient mutation? Well, there's some anecdotal data. This is a paper that was first published from some work done in the Rambam Medical Center in Haifa in 1998. In this study they looked at Israeli individuals, Israeli women who had breast cancer and ovarian cancer and they looked at both Ashkenazi and non-Ashkenazi populations. In 1993, in Israel, the rate of breast cancer per 100,000 Ashkenazi women was 89.8. For the Oriental or Asian born Jewish women with breast cancer, the risk was 70.7, so a little bit lower. For the North African - this would be Moroccan, Algerian women - the risk was 55.6. That was the rate of breast cancer in those populations. In the women who were studied - so this is Ashkenazi, Jewish women who had breast or ovarian cancer, in Israel - about half of them had a 185delAG mutation, a very large percentage of the Ashkenazi women with breast and ovarian cancer in this particular clinical trial. There was selection, because a lot of them came in for testing because they had family history in addition to having breast or ovarian cancer, unlike the *New York Breast Cancer Study* where women were not selected for family history. That may be why this rate is a little higher - high rate of finding mutations.

There was an estimate, looking at these family histories, that this mutation was very, very old, at least 46 generations old and may have originated before the 1200's, maybe in Europe, maybe not in Europe. But these investigators also

found the same mutation in non-Jewish women and I will also show you that they found this mutation in non-Ashkenazi Jewish women.

There was an analysis done on more than 600 Iraqi Jews and this mutation, the 185delAG mutation, was found at about the same rate. These were not people with breast cancer. These were just Iraqi Jews and there was about a 0.47% incidence in the unaffected population of Iraqi Jews.

In non-Ashkenazi Jewish women with breast and ovarian cancer - and there were 112 women tested - 12 of them had the 185delAG mutation, about a little bit less than 10% - the same rate that we would see in an Ashkenazi similar population and here's the breakdown. They were Turkish, Yemeni, Iraqi, Moroccan, Greek, Syrian, Indian, and Egyptian from that whole Oriental and Sephardic group.

So, overall, we can say that the general mutation rate for 185delAG in non-Ashkenazi Jews, unaffected, was about the same as in the Ashkenazi population and this is all in that Bar-Sade paper. I think the study gives some credence to the notion that this is a very old mutation that is, in fact, not restricted to Ashkenazi Jews and may have arisen before the Diaspora from the Middle East.

Is there any other data to support this notion? Well, there's been some work done in Spain looking at whether or not BRCA1 mutations are present in Spanish women with breast and ovarian cancer. These are not necessarily Jewish women. This is just data coming out of different medical centers in Spain. This is a letter published in 1998.

These investigators looked at 87 women who were living in Spain who had breast and ovarian cancer in their families and 4.5% of those who were studied had this BRCA1 mutation. Two of those were the 185delAG mutation. There were some other BRCA mutations noted in the other two families. One of the other very interesting findings was that these investigators did that trick of looking at the Y-chromosome in these families and saw that the families shared common ancestry with Ashkenazi Jews.

It's raising this question of maybe these people had Jewish descendants living in Spain. One family actually said, "Yes, we are descended from Jews who were living in Spain and Portugal," even though now they were Christians and had converted because of the Inquisition.

Other data in Spain shows, again in breast cancer patients and their families, that BRCA mutations are identified and in this study 51 families were looked at. There were 7 mutations identified, 4 of which were specifically 185delAG.

This is a paper that came from a family that was living in Chile. This was a woman who had early onset breast cancer and she was not Jewish. She was of Spanish descent. She was living in Chile. She was tested. As you see, she had early onset breast cancer. Her sister had early onset ovarian cancer. They knew of a paternal grandmother who had had breast cancer, another paternal aunt who had breast cancer. This is a very typical family for looking for a BRCA mutation. In this family, the 185delAG mutation was identified, again raising the question of, did this family who migrated from Spain to Chile have Jewish ancestry in their background?

I arrived in Colorado and I began to practice at Rose Medical Center and on the second day that I was in the office, I met our genetics counselor. And Lisa Mullineaux said, "You know, we've made this very interesting observation. There are Hispanic women living in Colorado who have breast cancer and a lot of family history with breast and ovarian cancer in their families and when we've tested them, we've been finding this 185delAG mutation."

And I said to her, "Oh, they're Jewish." She looked at me like I was completely crazy. I said, "No, I'm sure that's what it is." She said, "No, they're living in the San Luis Valley. They've been there for 500 years."

This is how they got there. As you know, when the Inquisition in 1492 became law in Spain, many Jews left Spain. The first migration was to Portugal and then there was a huge migration, including individuals who traveled with Christopher Columbus, a documented, huge migration of Jews from Spain and Portugal to Mexico. Then there was travel from Mexico up into what is now Northern New Mexico and Southern Colorado and there happens to be these two mountain chains. We have a lot of mountains out west, getting to know them well, and there's a valley in between these two chains of mountains called the San Luis Valley. This de Oñate expedition came up, with a whole bunch of people from Mexico. They settled in the San Luis Valley and they stayed there for 500 years and because they were caught between these two mountains, they never went anywhere and they just kept marrying each other. And it's in that group of individuals that the 185delAG mutation was found.

In the study that Lisa and colleagues published from the San Luis Valley ancestry, we saw 19 breast and ovarian cancer patients. They all consider themselves Spanish. None of these people told us that they were Jewish and they met the criteria that we would use for wanting to do genetic testing. They underwent complete sequencing of both of the genes and here's the data from that paper, which was published last summer in *Cancer*. Of the 10 patients who tested positive for a mutation, 6 of them had the 185delAG and 5 of those women had breast cancer, 1 had ovarian cancer, and these were the other mutations that were seen in BRCA1 and BRCA2. Two of them are known to be

associated with disease-causing mutations, 2 of them were variants of unknown significance.

None of these individuals knew of any relationship between their families. They didn't think they were related to each other. But we now believe that this is representative, this pattern in this community, is representative of the founder effect and we've been doing some ancestry studies and actually have sent in some anthropologists.

The genetic counselors have gone back and we are beginning to identify that there is relationship between these families and in fact, there probably is a common ancestor for these families in which the mutations are found. So far, with this ongoing research, we have found a common ancestor in 3 of 6 of the families. Here's why they didn't leave the valley, because of these big mountains.

These are the individuals who've done this work. David Salazar is an anthropologist and a genealogist. Tess Castellano is a genetic counselor. And they've gone back down to the valley, talked to these families and figured out these relationships. What we have also figured out - and there's a big sort of anthropological database for this - is that many of these individuals are in fact Crypto-Jews. Even though they deny Jewish ancestry and Jewish heritage and they're practicing Christians, they think that they know that maybe along the way their ancestors were Jewish. They have interesting family rituals like the family dinners on Friday night and not on Sunday night and candles are put on the table. They don't eat pork. They sometimes don't eat pork after sundown.

There are two very important holidays that are observed. This was well documented during the Inquisition, that Jews who wanted to continue to observe found that it was difficult to observe the Sabbath and difficult to observe holidays because that was recognized. But if you fasted, that wasn't so easy for an outsider to notice that you were doing something observant. The two fasts that were traditionally observed were the Fast of Esther in the spring, right around the time when we celebrate Purim, and of course the fast in the early fall for Yom Kippur. Again, in these Crypto-Jewish populations, we see observance of these fast days as well. There's this anthropological database and as we've been studying these populations, this information is coming out.

What we're trying to do now is to collect more data, identify additional families that may carry mutations, to determine whether or not these families are in fact related and to look at the larger Hispanic population in Colorado and in New Mexico. There are a number of studies going on there, and in addition, as I said to include this Y-haplotype study.

This is just some of the data that Sharon Graw, who is a geneticist who worked on the trial looking at these different subjects, was able to come up with the idea

that there was consistency with Ashkenazi Jewish haplotypes and that these families had some relation. In general, this data I think points to the fact that the 185delAG mutation on BRCA1 may be a very ancient mutation and is undoubtedly present in Jewish populations who are not Ashkenazi.

So where do we go from here? We move on to do some more research. As Ken said, when we have this idea we have to do the work to answer the questions. Dr. Ostrer and I have been collecting DNA from all kinds of Jewish populations. I went out to Deal [New Jersey] this summer and got 110 samples from Syrian Jews. We're collecting some more DNA from other Sephardic populations here in the New York area who can easily identify themselves and where we can get good family histories and so on. We're looking at the Y-chromosome haplotypes and we will also be opening a study looking specifically at affected individuals - women who have breast and ovarian cancer who are of Sephardic ancestry to see, as we did in the *New York Breast Cancer Study*, focusing now only in the Sephardic population, if we can identify the incidence and prevalence of these genetic mutations and get a little more information about other populations.

Thank you.

Rochelle Shoretz: Thank you, Dr. Oratz. It is always a pleasure to have you back in New York, and I know that your emerging research will be important to women in the Sephardi community in the years ahead. Again, all of our participants here in New York and those participating on the teleconference will have an opportunity to submit questions to all of our panelists during the Q&A session later on this evening.

Genetic counseling and testing can raise a series of anxieties for any woman and family. For those in the Orthodox or Chasidic communities, the cultural and religious implications of genetic counseling and testing can make this subject even more difficult to approach. Dr. Sheldon Feldman and Dr. Stewart Fleishman of Beth Israel Medical Center have been working with health care professionals and Jewish leaders in these particular communities to address with sensitivity the needs of Orthodox and Chasidic families affected by breast cancer.

Dr. Feldman is Division Chief of Breast Surgery and Dr. Fleishman directs the Cancer and Support Services Program right here at Beth Israel. Please join me in welcoming Drs. Feldman and Fleishman.

Dr. Stewart Fleishman: Thank you. I'll go first and then hand the microphone over to Shelly. Thank you again to everybody, Cindy as well, for getting us involved in this very interesting area. And I must say that it is a real comment on the Jewish Diaspora when Dr. Oratz has to go to Colorado to find our Sephardi roots. It's really amazing information and I'm glad that you could share it with us.

My job here is to catalog a few of the issues that you're all living with every day and you know about in a much more personal way than I do and hopefully this will be a springboard for discussion. But first I must make a confession. I'm really from a mixed Jewish family in that my mom's family had come to the United States in 1784, though Jewish, from Manchester, England, and my dad's family, after a pogrom in Russia in 1907. And a result of that is sort of a real yin and yang in that they looked at things in entirely different ways. My maternal grandmother spoke English and no Yiddish and my paternal grandmother spoke Yiddish and no English. How they communicated I'm not certain, but it really sort of set the stage for looking at issues like this from two very diverse points of view.

Knowing that yin and yang, I wanted to just catalog some of these issues for us to discuss later. There are a number of issues that we are concerned about when looking at genetic information or test information for which we are really scared about getting the results.

My paternal grandmother said, "Don't go to hospitals, don't go to doctors, because no one ever leaves the hospital and you always get bad news." My maternal grandmother was happy to go to find out that she was fine. And that's sort of the dilemma that we face when looking at these kinds of predictive tests for heritable illnesses, as we've been discussing tonight.

The political issue and the cultural issue certainly merge when looking at the idea that as a community we've often been told that we have bad genes. We've heard this a number of times through history and in spirit, not necessarily identifying I guess genetic information during the Inquisition and maybe not during the pogroms, but certainly during the Holocaust. We were told that we carried bad information and bad "stuff" and I think that underlies our fears of learning a lot about what runs in our families and what doesn't. We could be picked out and identified and that's really hard to be able to live with and so pass on to our children.

Also, the fear that there's nothing we can do. We've seen, in modern life and through cancer especially, my paternal grandmother said, "Don't touch cancer, because if you have an operation it spreads." But she said that in Yiddish and I really didn't need an interpreter. But we do know that there are things that we

can do. People have enumerated some of these issues already, whether it's more frequent imaging studies, whether it's thinking about tamoxifen or a similar drug for hormonal treatment, whether it's prophylactic mastectomy or oophorectomy. There are a number of things that may be possible to do to help us live long and healthier lives. But those are difficult, difficult decisions. Because by doing those things, you're cutting down on some of the other opportunities in life, like having a large family. The privacy and confidentiality issues Dr. Offit alluded to, with the discrimination issues - that's the heart of the discrimination issue. Is the information that we get going to be kept private and confidential and will this be passed on to other people who don't necessarily have our consent, be those current insurance companies, future insurance companies? Though we are still not able to find a case of actual discrimination in the insurance world for patients who have tested positive for a variety of heritable illnesses, that's a fear that we all harbor and is still a question for the future.

The stigma of having our children live with the idea that cancer is in their family, that they may develop cancer at some point in their lives. If they do marry the wrong husband or the wrong wife they may actually pass this on to their kids is something that also colors our decision about to learn, to not learn. Will we have to be tested? Won't we be tested? And that really runs in the background of all of the decisions that we're making tonight.

In addition, for those families who do use the services of a matchmaker, this is not a selling point - to have cancer running in the family - and it makes the match less desirable. All health issues are sensitive. We do know that from all of our patients. The government, in an unusual sort of way, acknowledges that with the HIPAA guidelines or the privacy guidelines that we all live with. But this is not particular to the Ashkenazi community or the Sephardi community or any of us, but it's particular to everybody.

I guess part of the problem is that in our communities, our Jewish communities, privacy and modesty are much more of core values than in many of the other communities. My paternal grandmother would have been out there with a placard, though it would have been in Yiddish and no one would have understood it, and my maternal grandmother wouldn't have said a word to anybody because she'd be afraid to be stigmatized. We're still living with this duality and it is kind of hard to put together at this point.

However, there are a number of realities in that you may not get pregnant because you're so worried about all this. If you get treated with tamoxifen you may go through early menopause. If you choose to have a prophylactic oophorectomy then you may not be able to have as large a family as you wanted.

The results are somewhat confusing even to us. We know it's confusing to you. We're learning more and more about this as the days and the years go by. And that really colors our decision to have testing and to learn the results and then to act on them. And if you have a lot of kids, then you've affected more people than if you have just a few kids. When you put all these cultural issues together it makes it particularly difficult for an Orthodox or Chasidic family to make this decision rather than for a different family.

Dr. Feldman and I put together a summary of the kinds of issues that people face if they find out that they have cancer and they choose genetic testing for themselves and for their family. It may optimize decision-making, as we've spoken about before, whether it's for preventive purposes or a decision about how many times to get pregnant. There may be a more accurate risk assessment for the kids, because they may get a positive test or a negative test, as much as we know what that means. We certainly can advocate a proactive approach to health and wellness, based upon the things that I mentioned before.

But I think one of the things that is hardly acknowledged is that if you are negative and you do come from one of those families that Dr. Offit described, there should be some relief in that you'll be okay and your kids will be okay and that something good that can come out of all of this. Again, based upon today's information, and I know you'll say, "But what if you learn in the future that's not so?" and that's something we really don't have an answer for today.

If there is a positive, if there is cancer, if you yourself have cancer and there is testing in yourself and your family, there will be increased distress for everybody in the family. There may be the stigma that I addressed before, certainly reduced fertility either out of worry or because of the hormonal treatments or the surgeries you may have less kids. And you're adding that on top of the usual burdens of cancer that we face in the modern world, the complications of ambulatory care. The fact that you don't have treatment in the hospital but out of the hospital and we've off-loaded the burden of treatment onto the patient and to the family.

The worry. About I'm going to die. How disabled will I be? Won't I be able to enjoy myself? How much pain will I be in? All these are things that everybody else worries about, on top of the cultural and particular things that we're discussing tonight.

Financial issues. Again, back to the discrimination, as well as the fact that cancer treatment is expensive and sometimes not knowing is cheaper. It may be in the short run, but not in the long run.

And the guilt. Did I pass this on to my family? Have I given my children a legacy that they may not particularly be thankful to me for in the future? It's a very, very difficult thing to have to live with.

If there's no cancer in the family, similarly, a more accurate risk assessment, if there's a positive. If the individual herself does not have cancer, a more accurate risk assessment for the family and optimizing early detection through increased surveillance, as we've described.

The MRI issue. I think that's a really important point. Not everybody can do MRIs of the breast. If that's going to be suggested for you, you need to go to somebody who does it all the time and has a good track record - really, really important – and not just where your insurance company sends you.

Implementation of prevention strategies, as I said before.

And certainly better family planning. And if you yourself don't have a cancer diagnosis or the identified patient doesn't have a cancer and there's a negative test and more worry for everybody and the guilt of perhaps passing something on.

These lists look awfully similar because they are. This is certainly one of those yin or yang questions that we really haven't been able to answer yet. But these issues are out there and they descend all at once when somebody is faced with the idea that they may have cancer and there may be cancer in the family and they need to do something.

Again, I present the kinds of issues that you're living with really as a summary for the discussion later and now I will turn the microphone over to Dr. Feldman.

Dr. Sheldon Feldman: Thank you, Stewart. Thank you all for being here and I appreciate the opportunity to speak to this group.

About six months ago, a group of us, largely sponsored by Rochelle's work and through Myriad and people who work in the breast cancer field and in genetics, we came together for a little bit of a group meeting.

We all live with frustration about having information and technology available that we think can really benefit our patients but that is not readily accepted by a group of people who really are at significant risk. [It was] more of a brainstorming session to see what are the things that we could do or begin to make initiatives or inroads into this.

And I think meetings like this are really a huge step towards this. I think the work of Sharsheret is fabulous in terms of providing the kind of support that's required for these sensitive issues.

I saw a patient today, earlier this morning, who is a 47-year-old woman whose mother and sister have both died from breast cancer in their late 40's, who has a large family, has 8 daughters. And for about the fourth time, we talked about the possibility of talking with a genetic counselor about her for accurate risk assessment. These conversations are difficult.

And she said to me, "Well, so what will I do if I get the information I'm gene positive?"

So we talked about the usual strategies. "Well, you're getting near menopause. Prophylactic oophorectomy is something you could consider."

"Well, the Rabbi would never go for that."

"Well, who is your Rabbi?"

Well, she told me who her Rabbi was.

I said, "Well, I know your Rabbi and we've had some conversations and you know what? I think he actually might. He won't make that decision for you, but I think he might encourage you to move in that direction, if it's an informed decision with you and your health care providers."

I think that's where the relationship has to grow. And some of the strategies that we look at for communities with heritable cancer - certainly culturally sensitive education and educational materials need to be developed and provided. And again, forums like this I think are a great springboard to doing this.

The belief "information is power" - I think that we all believe that. And I think beginning to translate this into reality and to proactive change for our patients and devising this relationship between physicians and health care leaders and the rabbinical community is an important relationship that we need to continue to develop so that we can benefit more patients.

I think the kind of work that's being done through FORCE, through Chai Lifeline, and through Sharsheret again moves us greatly towards this.

Now, one thing I just, in a few minutes, wanted to talk about was the success of existing programs for Tay-Sachs Disease called Dor Yeshorim. It's confidential and private. It is sanctioned by rabbinical authorities. They are educational

support mechanisms in place and it can affect matchmaking efforts and family planning.

Now, Jewish law does recognize genetic importance of disease and also does provide advice for families to possibly avoid matches with other families where disease may be transmitted. So this is, I think, pretty well established.

Dor Yeshorim is the Committee for the Prevention of Jewish Genetic Diseases and as I read a little bit more to prepare for this talk, I learned that this actually was founded by Rabbi Eckstein in 1974 after he lost 4 of his 5 children to Tay-Sachs Disease.

Shortly after Rabbi Eckstein came forward with this, there was a large outcry from the Orthodox Chasidic religious community and strong opposition to this concept, because of concerns about increased abortion rates, distress to the families, which might lead to lower fertility, and also to possible discrimination.

As the program evolved in the '70's, the testing became truly voluntary, anonymous and the idea of testing younger adults - not who were preparing to get married but who were high school students or seminary students so that the information would be obtained not at the last minute, right before the match was going to happen, but well in advance – would allow this service to grow and to mature.

And I have a quote I just wanted to read from Rabbi Moshe Feinstein from around this time, when he was asked about whether it was advisable for a boy or girl to be screened for Tay-Sachs Disease.

His answer was that, "It is advisable for one preparing to be married to have him or herself tested. It is also proper to publicize the fact via newspapers and other media that such a test is available."

Pretty strong statement. So if we thought about this today, in the context of BRCA1 or 2 testing, I think that maybe there is some common ground here to something that we could move forward.

He also goes on to say, "It's clear and certain that absolute secrecy must be maintained to prevent anyone from learning the results other than the physician."

I think this concept does potentially help us conceptually towards learning from the success of this important program. Worldwide there have been several million young adults now tested through this program. Thousands of couples have been found to be high risk. The screening has been expanded to other "Jewish genetic diseases," including cystic fibrosis, certain types of anemia, and

familial dysautonomia. Genetic counseling can then be provided to couples who are “incompatible.”

I think this is a strategy which can be very effective in the Orthodox Chasidic population. In the very fabric of the communal life of this portion of our population there are specific morays related to marriage and procreation that this has adopted very well into becoming sort of a standard operating procedure.

BRCA testing clearly is different and the information that we obtain is different. But I think we get back to the same concept that information is power, that there are strategies that we can take. And we can advise patients to be proactive in terms of risk reduction strategies, heightened surveillance techniques, which really can impact on saving many, many lives from both breast and ovarian cancer.

I think it certainly is a provocative area to consider. I think we need to do better and certainly one of my goals here at Beth Israel is to continue to develop good working relationships with community leaders, advocates, and with the rabbinical community, so that we can help educate each other about what are the special ways we can communicate this information and in the long run come up with better strategies to help our patients.

I’d be happy to answer questions about this and I appreciate your attention. Thank you.

Rochelle Shoretz: Thank you, Doctors, for beginning this important conversation.

I actually want to take this opportunity to note that Sharsheret has just published *Breast Cancer Genetics and the Jewish Woman* with a generous grant from the Greater New York City Affiliate of the Susan G. Komen Breast Cancer Foundation.

You should all have received a copy of that booklet tonight in your packets and those of you participating via teleconference or webcast will either receive one in the mail or can call our office ask that some be sent. For those of you who want to take back additional copies for your office, I believe we have extra copies available as well. The booklet is sensitive to the concerns of Jewish women of all backgrounds and will be available in Yiddish for distribution to Yiddish-speaking communities.

Through their presentations this evening, our speakers have left us with a lot to digest and often, that is where the anxiety begins. What do I do with all this information and am I the only one out there considering these important questions?

Beth Israel is fortunate to have Cindy Turkeltaub, who in her many hats, has fielded many of these questions from the women and families with whom she meets. Ms. Turkeltaub coordinates social work services at the hospital and also serves as an informal liaison for many Jewish organizations addressing breast cancer in Jewish women.

She will present our next panelists, who will share with us some of the support options available to you and your loved ones and the ways in which women cope with a genetic susceptibility to breast cancer.

Please join me in welcoming Cindy Turkeltaub.

Cindy Turkeltaub: I want to welcome everybody.

Before I introduce the panel, I want to say that I meet a lot of the women, especially Shelly's patients and the other physicians in the breast service, when they first get diagnosed. And I would expect to hear the reaction, "Oh my God! What am I going to do? What's it going to be like? Will I die? What's going to happen?" And that doesn't happen.

One of the very first responses, from what I always call "my ladies" is, "Will it affect my kids' Shidduchim? Will they get married?" And the first time I heard that I was stunned. They don't worry about themselves. They don't worry about that. They're worrying about their children. The more I hear it the more I have come to accept that this is really what it's all about.

They're worried about how does it affect their children and there's a tremendous amount, as Dr. Fleishman talked about, guilt with a legacy. And I think that that is really very poignant in their ambivalence about their testing.

From what the women have explained to me, it's that they go back and forth. If they don't get tested and they don't know, then they can go along with the belief that it was an aberration. It just kind of happened.

But if they get the results, then they have to face the fact, like Dr. Fleishman said, there's something in their genes. And then if somebody asks about a Shidduch, they have to face it. And then they actually have to come up with the answer of, "Am I mandated to say something or not," and that's a very real issue and this is what they talk to me about all the time. "If I don't get tested, then I'm not mandated to say anything because I really don't know anything as a fact. But if I know something as a fact, then I have to say something."

And that's really what's been a tremendous issue for them and we struggle with it. I spend a lot of time working with the women individually and with their husbands and sometimes with the children, especially the older children who are at the ages of Shidduchim. That's if the parents, and if the mothers, tell their children of their diagnosis.

I very often rely on community agencies to help with the support that the families need. I've relied on Sharsheret for the women who need buddies, because very often women really need somebody in a very similar situation. I've relied on Chai Lifeline who offers anonymous telephone support groups, because the Orthodox women are not going to come to a support group. They don't want to see

anybody in their community because then, “I know that you know that I know that you know” and there goes the confidentiality.

I’ve relied on a lot of other organizations that can offer support in the context of their own community where they feel safe. And I’m going to now [introduce] the panel, which are some of the organizations out there that I’d like you to learn more about, so that you can avail yourself of some of those services.

Rivi Katz is a social worker who serves as the Link Program Coordinator of Sharsheret. Ms. Katz works both with newly diagnosed women and with those at high risk of developing breast cancer, and assists with the development of programs benefiting the women of Sharsheret.

I’d like to introduce Ms. Katz and ask you to please talk about your work with Sharsheret, which supports women with breast cancer.

Rivi Katz: My purpose today, this evening actually, is to share with all of you here what Sharsheret can offer women who have a strong family history of breast cancer, whether or not they have been diagnosed with the disease.

As Rochelle mentioned earlier this evening, although Sharsheret was originally founded to serve the needs of young Jewish women newly diagnosed with breast cancer, we quickly discovered that there were many women who, because of a strong family history, were anxious and fearful about their risk of developing breast cancer or of the impact of family history on their treatment decisions if they had already been diagnosed.

Like many of you here today, my mother was diagnosed with breast cancer in 1986, at the age of 46. At the time, I was 24 and my sister was 20. The genetic mutation specific to Ashkenazi Jewish women had not yet been identified.

Today, at the age of 43 with two daughters of my own, ages 15½ and 18, I have been giving a lot of thought to the possibility of genetic counseling and testing and to the impact my decision would have, not only on me, but on my daughters who will soon be entering young adulthood.

Speaking to the women of Sharsheret has helped me realize that I am not alone and that, as someone whose mother was diagnosed with breast cancer at a young age, I do have options.

I am currently the Link Program Coordinator at Sharsheret. As Rochelle mentioned earlier, the Link Program is the core of Sharsheret’s services and pairs both newly diagnosed women and those who are facing the risk of breast cancer with volunteers who share their personal backgrounds and concerns.

Sharsheret is a national organization, and we have volunteer Links all over the United States. Many of you may feel more comfortable speaking with women who live outside your own communities. Conversations between you and your Link take place over the telephone and are completely confidential. You can feel safe expressing your concerns freely, and you don't have to worry about the reactions of your friends or family.

How does Sharsheret address the needs of women with a strong family history of breast cancer, both those who have been diagnosed and those who have not?

First, Sharsheret can provide resources on breast cancer and genetics. An excellent resource, which was also mentioned earlier, is the newly published booklet by Sharsheret, entitled *Breast Cancer Genetics and the Jewish Woman.*

This booklet, made possible by a grant from the Greater NYC Affiliate of the Susan G. Komen Foundation, can be found in the packets you received today. The booklet contains frequently asked questions about Breast Cancer Genetics. Some very common questions we have received from our Sharsheret callers include --

- What can a genetic counselor do for me?
- What if I choose not to be tested? What are my options?
- What impact will genetic counseling or testing have on the other members of my family?

Second, Sharsheret can offer support to those facing the risk of breast cancer through our Link Program. If you have a strong family history and are concerned about the possibility of an increased risk of breast cancer, you can speak with someone with a similar background who struggles with some of the same concerns.

You may want to speak with someone who went for genetic counseling and/or testing about her decision-making process and about the emotions she experienced during this time. You may also want to speak with someone who decided to undergo prophylactic surgery about her decision and about the procedure itself.

You can also speak with someone about discussing the issue of family history with your children, spouse, or significant other. The matches we make through our peer support program are tailored to your concerns.

Finally, Sharsheret addresses the needs of family members by providing information and resources and access to the Link Program, whereby family

members at increased risk of developing breast cancer can speak with others who face a similar risk.

There are many emotional reactions to the prospect of genetic testing, some of which were mentioned earlier this evening by some of the speakers. For those of you who opt to be tested and receive a positive result, you may feel comforted by a genetic explanation for your breast cancer. You may feel that genetic testing can increase your treatment options. You may also feel guilty about carrying a genetic mutation and worry about passing it onto your children.

For those of you who test negative, you may feel anxious that you don't have a specific explanation for getting breast cancer at an early age. You may also experience a sense of guilt, if you are part of a family where other members have tested positive. You may say to yourself, "Why was I spared? Why my sister and not me?"

Some of you may decide that you don't want to go for genetic testing. You may feel that your breast health is already being carefully monitored, and you don't want to be burdened with the added anxiety of knowing you have a genetic mutation.

It is very common for women with a strong family history of breast cancer to feel anxious. Sharsheret can help you sort out these various emotions and concerns. At Sharsheret, young women can connect and share their stories.

I would like to conclude by sharing an e-mail Sharsheret received from a husband who was deeply affected by the prospect of hereditary breast cancer in his family.

And the e-mail went as follows --

> "My wife is a 50 year old breast cancer survivor. Our daughter is 24 years old. My wife is undergoing genetic testing at this time. 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, seeking mammograms by 30, meeting with an oncologist, etc.
>
> 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?"

Sharsheret was able to give this man the guidance he was seeking by directing him to resources that could address many of his questions and by offering him a supportive and sensitive venue in which to discuss his concerns.

Sharsheret provides women and their family members who are facing the risk of breast cancer with valuable resources about breast cancer genetics as well as a confidential and safe environment in which they can share their anxieties and concerns with others who have been there.

Our contact information can be found on our website, www.sharsheret.org. You are not alone in your concerns, and we hope that you will feel comfortable calling Sharsheret for guidance and support. We'd love to hear from you.

Cindy Turkeltaub: Thank you, Rivi. That was a very powerful e-mail, very powerful.

I'd like to now introduce Dr. Susan Friedman.

Dr. Friedman is the Founder and Executive Director of the national non-profit organization FORCE, which is Facing Our Risk of Cancer Empowered, a national consumer organization devoted to serving individuals affected by hereditary breast and ovarian cancer. Dr. Friedman is a veterinarian by profession - I love animals - and a 7-year cancer survivor.

I'd appreciate it if you could come and tell us a little bit about your work at FORCE and about the way you offer support to Jewish women and their families at risk for breast cancer.

Dr. Susan Friedman: Okay. I'm not known for speaking quickly, but I will.

This is the mission of FORCE and really FORCE started as an Internet-based, non-profit organization. And also because I am a carrier of a BRCA2 mutation, I want to thank Dr. Offit for helping to isolate the mutation and for the research that all the researchers on the panel have contributed. On behalf of the high-risk community, we really appreciate it.

I started my journey with breast cancer and as a breast cancer survivor who then later found out that I carried a mutation. There were a lot of areas that I couldn't find support specific to and there was no FORCE at the time and there was no Sharsheret at the time. And so I, founded FORCE specifically to address the issues that go along with hereditary breast and ovarian cancer, both for those

who have had cancer and those who haven't yet been diagnosed or had a hereditary predisposition.

We started as an Internet-based organization and last year we started a telephone help line with the University of Pennsylvania. Both our website and our help line provide anonymous support so that people can call in. We're very respectful and acknowledge the issues of privacy that are of concern to those who may carry a mutation or who are at high-risk.

The name FORCE, Facing Our Risk of Cancer Empowered - we chose the name carefully. I call risk the "un-diagnosis."

What we found is that particularly the high-risk community faces some issues --

Living with uncertainty. The idea of your risk for cancer is higher but you may or may not ever get cancer in your lifetime. The exact amount of risk is unclear and I really appreciate the fact that they're really closing in on what the risks for breast and ovarian cancer are in the carriers. But there's still that unclear -- usually people are given a risk range, rather than being told for sure if they're going to develop cancer in their life. That can lead to uncertainty and the need for support.

The recommendations for risk management often aren't standardized and it just really -- I can't tell you how much I appreciate Dr. Offit mentioning MRI and the importance of it and the research that they've done to show that MRI is an effective tool in their right hands for early diagnosis.

Friends and family are often unsympathetic. And that is that particularly people who haven't been diagnosed with cancer but carry a mutation are at high risk, often times they are reassured by their family members and their friends, "If you haven't had cancer, why are you worried?" Or sometimes there's proselytizing going on, "You need to go out and get this test." Sometimes that type of pressure can be very uncomfortable for people and can lead to the need for support. That's what we address at FORCE.

As far as what's in the name "Empowered," for many patients information is empowering. You've heard that over and over again on that panel. Genetic testing may not be the right choice for everyone. But for some people they do choose it and it is the right choice for them.

People can only make informed decisions if they're receiving the most accurate and up to date information. That's my little plug for people seeing a genetic counselor or a specialist in cancer genetics, so that they know they're getting the most up to date information when they're making these decisions.

Just knowing that their fears are justified, through being a part of a community - even if it's an online community or through a Link program or through our telephone help line - just knowing that you're not alone can be very helpful.

I just wanted to read a post from one of our members, real quickly, because I love this post and it speaks to the issue of risk.

And she wrote this --

> "Okay, I have to admit I need a label. Do we have one? You know, those of us that have the gene but have not had cancer, the ones going through all this research and deciding on prophylactic surgeries or not. We need more of a voice and a label, a name. I've never been one hung up on labels, but a lot has changed for me since this process began. I feel if we had a label we could begin to have more of a voice. What are your thoughts?"

My immediate thoughts were that the medical community already had a label and that label is "Unaffected Carrier." And really, I think unaffected carrier doesn't even begin to describe what people who are going through genetic counseling, looking at their family history, genetic testing, and the choices that they're faced with after going through the process.

So we came up with the term "Previvor," which is survivor of a predisposition to cancer. We like it better because, in my book, anybody who's faced family history of cancer and/or genetic counseling and/or genetic testing and the choices, is a survivor in every sense of the term.

That really concludes what I was going to say. But since Dr. Offit did mention legislation, I did want to say that because Congress has not passed legislation, it was passed in the Senate but not in the House of Representatives, it'll be another year. The National Society of Genetic Counselors and FORCE have developed a brochure on genetic discrimination, "*Genetic Information and Discrimination and Privacy: What You Need To Know*." That will be available next week and people can find it by contacting FORCE.

Thank you.

Cindy Turkeltaub: Thank you. I love that new name.

I'd like to introduce Beth Murphy.

Beth Murphy is the Founder and President of Principle Pictures where she produces, directs, and authors documentaries for television and radio news. Ms. Murphy's production, "Breast Cancer Legacy," which many of you have seen

outside during registration, explores breast cancer genetics and is going to air this Thursday evening on the Discovery Health Channel - pretty impressive.

I'd appreciate it if you could come up tell and us what compelled you to do this.

Beth Murphy: Thank you very much. Thank you everyone, for coming out tonight and for being here.

The program is called "Breast Cancer Legacy." It's an exploration of what it means to have a family history of breast cancer and what you can do to protect yourself if you have one, while also looking toward the future and what the future of genetic research promises in terms of prevention and even a cure some day.

About three years ago I produced another program and did a book with that called "Fighting For Our Future." And the purpose of the project was to focus on young women with breast cancer, really an awareness that, yes, young women in fact can and do get breast cancer.

In producing that program, I learned that young women are more likely to be genetic mutation carriers and I really wanted to know why. This project is very much an outgrowth of that original project. I also have a family history of breast cancer and it was really after my mom's re-diagnosis that I started investigating what that family history means for myself and my three sisters.

What I learned about young women and genetics is that there's something known as "anticipation in genetics" and maybe you've seen it in your own families. What it means is that if there is something coming down through the generations it will reveal itself earlier and earlier in each generation. Maybe your grandmother was diagnosed with ovarian cancer in her 60's, your mom was diagnosed with breast cancer in her 40's, and you may be facing breast cancer in your mid-20's.

In producing this program, I was fortunate enough to work very closely with Sue Friedman of FORCE and I also collaborated with the Young Survival Coalition and it was really a wonderful experience, because Sue introduced me to a family of Previvors: Four sisters who reminded me very much of my own family and had never been diagnosed with breast cancer but were dealing with extraordinary, I would call it, trauma. They faced enormous psychosocial issues. They had disagreements among themselves about who wanted to know what, when, and the pressure within the family, watching their mother who passed away with ovarian cancer. And all of these issues were really very raw and at the surface. The oldest sister taught me an awful lot about the stages that people go through and are comfortable with experiencing as time goes on. At the very beginning, because their mom had ovarian cancer, "That's it. I want the ovaries out. Take them out." Never considered having prophylactic mastectomy

and it's only now, years later, you're saying, "Well, you know what? I think I'm ready to take that step as well."

In terms of just how different people face the decision-making process, there are enormous medical questions on the table during the testing process, but even more psychosocial issues, I found, in talking to these women. And one thing that really rang true throughout - and I did dozens of interviews that never made it into the documentary - but one thing that really I found - I don't know that it surprised me, but I was impressed by it - and that is the extraordinary hope that the women that I talked to felt about the future of genetic research.

I think that there is great cause for hope. We interviewed the U.S. Surgeon General for the documentary who said what we're doing now and what the medical community is researching now was science fiction when he was in college. And when you look at it at that way, it is really impressive some of the studies that are going on right now with gene therapy to address these issues. Some of the things that the future of genetic testing promises is gene therapy, which could include targeting a cell and fixing the problem that exists in the cell, fixing the mutation, or making the cell stronger to have a better reaction or better effect from the chemotherapy, or inserting "suicide genes" into the cell so that you actually cause the cancer cell to self-destruct. These are all tests that are going on right now and they are exciting. They hold exciting possibilities and I was very impressed by how much hope the women that I talked with had in the future.

Thank you.

Rochelle Shoretz: Thank you Cindy, Sue, Rivi, and Beth for those informative presentations. Information about all of the support organizations featured here this evening can be found in the information packets you received.

I'd like to welcome back all of our speakers for the Q&A session, which is usually the best part of the evening for a lot of you. It's an opportunity for all of us here to submit questions to our distinguished speakers.

To those of you here with us this evening, please submit the questions you've written on index cards and we've got extra index cards that can be circulated around. Please submit those questions to the volunteers who will be wearing little pink ribbons on their lapels.

And for those of you participating via teleconference, please press star-1 and you will be placed in the queue to submit your questions to an operator. Given the hour, we likely won't have time to address every personal case or circumstance, so please keep your questions general in nature.

I'm going to start with the first question for Dr. Offit.

Question: Dr. Offit, how old must a woman be to submit to genetic counseling and testing? Can teenagers be tested and who in a family affected by cancer would be the best candidate for testing?

Dr. Kenneth Offit: In answer to the first question, we don't test kids. We start at 18 and that's arbitrary. There's no law against testing kids. It's just the right thing to do. There's no intervention that we'll put in place before age 18 and ethically the feeling in the community of practitioners is not to do that. There are other pediatric conditions that cause hereditary breast cancer, which are rarer, that we didn't talk about tonight, such as -- well, I won't go into them because it'll confuse you. But we do actually test children for some of these rare hereditary conditions, but not for BRCA mutations, so "no" for kid testing.

In terms of the best person to start to test in a family - and that's a good question, because that's a very important one - we like to test the affected individual, someone affected by breast or ovarian cancer, at the earliest age in the family. And that's where all of the effort should go in, and in fact, even where the resources should go in to even pay for the testing, if you can get that particular individual on board in the family.

That's what you use to inform the testing for the rest of the family. That's a critical, critical juncture and that brings in all the questions of family communication, psychodynamics, and these other issues that have been alluded

to this evening. But if you can begin with an affected individual, then the information is more powerful, because the negative test then becomes the true negative test in the family.

Rochelle Shoretz: Thank you. Dr. Oratz, for you - whom would a Jewish women of Sephardi descent contact if she wanted to participate in some of the research that you've begun? Is there an opportunity for such participation at this point in time?

Dr. Ruth Oratz: Well, right now the study that we have open is looking at unaffected Sephardic individuals and we're just doing some general background epidemiological genetic information. BRCA1, the 185delAG mutation, is only one of the genetic markers that we're looking at.

We are also looking at Y-haplotype and some other genetic markers in males and females just to try and establish the relatedness amongst these communities and between the communities. We will actually be doing a lot of outreach into the specific subset Sephardic communities.

Once the second protocol is open, which hopefully will be open some time in the spring, we will be reaching out to affected Sephardic women with breast or ovarian cancer or males, if they have breast cancer, to come in specifically to see whether or not those individuals carry mutations.

They could contact, here in New York, Dr. Harry Ostrer at NYU Medical Center to get more information about that or, if they have a question, they could contact me and Sharsheret can provide that contact information.

Rochelle Shoretz: Thank you. For Drs. Feldman and Fleishman - how do some of the Orthodox and Chasidic patients you see get beyond some of the cultural and religious concerns regarding genetic testing and counseling? I know you've seen and counseled some families. What has the process been like for those families?

Dr. Sheldon Feldman: Well, it can be a long process. It takes, I think, several meetings and discussions, sharing educational materials, conversations with the Rabbis. And it's an ongoing discussion. There's no, I think, real formula.

I think it is -- you know I always try to stress that this is not an emergency decision that needs to be made, that it is a dialogue, which the field continues to develop and unfold. It reminds me a little bit, sometimes, about the conversations we have with patients about tamoxifen for risk reduction.

Someone who has had a diagnosis, for example, of lobular carcinoma in situ, whose risk is now elevated because of that information, we know that tamoxifen

can reduce the risk, but we're talking about lifetime risk. So if someone's ready to make a decision and feels comfortable and has enough information, fine. If not, we continue to talk about it. It can be a pretty organic, long-term decision.

Stew, any --?

Dr. Stewart Fleishman: Yes, just one other point. I think that sometimes we over-generalize and over-simplify and say that the Rabbis are unified in their decisions and approach and it's anything but. I think that there are some pro, some against, and some that are uncertain. We shouldn't over-generalize that the rabbinical community has a uniform view of all this, because they certainly don't and that's something to keep in mind.

Rochelle Shoretz: Thank you. Some of the questions that are coming up from the audience are questions of recommendations. The women and the men here want to know what they need to do, screening-wise and surveillance-wise, if they have a family history of breast cancer.

And the questions are coming twofold --

1. What do you recommend for women who have already submitted for testing and have tested positive?

2. What are the current recommendations for women who are testing negative?

And I'll leave this question open for Ms. Mandell or for Dr. Offit to walk us through those recommendations.

Dr. Kenneth Offit: If I look tired, it's because I was, at 7:00 this morning, doing the same thing to a bunch of surgeons and I [have] to say you guys are a lot more informed than the surgeons. Don't tell my colleagues I said all that. Why do they start so early? Because they have to go in the operating room, I guess, after that.

So, yes, that's a big question and Judy Garber and I and Stephen Narod and I, we've written a couple of reviews in the *Oncology Journal* that'll come out in the next couple of months. I've written a book, if you want to get more of the details.

But let's see. Well, let's do this. For the mutation carriers, it's a moving target, right? And as I think I've alluded to, we've tested in our cohort studies, we've got, I think close to 4,000 women that have been tested, 500 carrying mutations, all of them in a prospective dialogue with us. We're learning as we go along.

The genetics got out in front of the medicine on this and so we started, as oncologists, Ruth and I, to do what we thought would be the best, hoping that it would prove to be okay. And what we've seen over the last decade -- by the way, this is the 10th anniversary of BRCA1, so we should all nod our heads this evening for that momentous [unintelligible].

It was October of 1994 [when] the BRCA1 was first identified. And in that decade, what we've worked out is what I'll tell you now is pretty much the best we have for BRCA mutation carriers. The breast screening has changed. It's changed in the last, really, few months. The MRI screening program that I identified is an investigational approach to BRCA mutation carriers. If you have a family history of breast cancer and you don't have BRCA mutation, we address the ovarian part of your question. But if you have multiple breast cancer cases, even without a BRCA mutation, you probably should also be managed, breast cancer-wise, the same way because half of hereditary breast cancer is not BRCA1 or 2. That's what we showed in that pie chart.

We have to be careful about that and I have to be more careful about that, as we try to get insurance companies to pay for MRIs - not to restrict it just to the BRCA mutation carriers, but to hereditary breast cancer by some definition that we agree to, multiple cases at early onset.

Just to speed it up, so the MRI screening, mammography, ultrasound.

I gave you what our protocol is for the breast –

- Discussion or preventive surgery. We call it risk-reducing because it's not absolutely prophylactic for the breast.

- Chemo prevention, tamoxifen and hopefully soon raloxifene, if that trial comes down.

- And aromatase inhibitors, we hope, will be next in terms of hormonal risk-reduction for breast cancer.

For the ovaries --

- Ovarian ultrasound and CA-125 on a six-month basis for BRCA mutation carriers. We reported our results for this in the *Journal of Clinical Oncology*. We have good results.

- We do the CA-125s and ultrasounds and our track record is actually pretty reasonable. But the Gilda Radner registry is published there. It's dismal in terms of finding early ovarian cancers.

- The risk-reducing surgery of course is what we recommend in the setting of the ovarian cancer risk.

- And then I've spoken to you a little bit about oral contraceptives data.

So that is essentially the highest risk recommendations.

If you're in the familial group and you're negative, we do the same screening of the breast as we would do in the BRCA group.

What's tricky are those families, that 5% sliver where it's ovarian and breast in the family and BRCA negative and then you're stuck, because you have to assume that there is still, even there, a residual ovarian cancer risk that you can't really quantify. And we've actually taken, even some of those women, have elected to do the preventive surgery.

One little thing that I'll mention, which is a detail of the management but is profound in the counseling, and that is the greatest terror of women with the surgery is surgical menopause. And one of the pieces of data that'll come out over the next year from our group, from Narod's group and other groups, it was just not surprising - is that if you do, if you have your surgery and you're premenopausal - you can take hormones --

Dr. Ruth Oratz: I'd like to add a few comments along the issue of management. I'll come back to the -- well, I won't -- the hormone thing I think is what it is and I would certainly agree with those recommendations.

I would also encourage women to seek participation in clinical trials. There are a large number of national studies going on. There are also institutional studies going on.

So the GOG, the Gynecologic Oncology Group, has opened a very large ovarian cancer screening and prevention trial for women at high risk. You do not necessarily have to be a mutation carrier. You can just have family history. You have, in that study, the option but not the requirement to have an oophorectomy, to have the surgical removal of the ovaries. If you elect not to have surgery, then there is a detailed screening protocol and some other experimental components to that and women will be followed prospectively. I certainly would encourage women to participate in that clinical trial if they're eligible.

There's another NCI-sponsored clinical trial that is open at NYU. Dr. Fishman is running that trial and that is also an ovarian cancer early detection program.

Look into the programs that are available. It's very, very important for your participation in these studies, so that we can come back next year with

information that's meaningful to you about what interventions and what modalities actually are going to help us. For early detection, our prevention studies - and we talked about some of the chemoprevention studies. There will be other studies, hopefully, that we'll be able to develop that will be less toxic and our goal is 10 years from today, when we have this conference, that we won't be talking so much about surgery.

Rochelle Shoretz: Ms. Mandell, if you could take us back a few steps. For some people here, the issue of genetic testing is one that has been tossed around in the family. They've given it considerable thought. They know a lot about it. But some of the questions that have come up here are questions about the actual nature of genetic testing.

What is genetic testing? How does one receive genetic testing? What's the counseling like? Are there costs associated with it and any insurance implications that you may know of, as a counselor?

Jessica Mandell: I think that it's important to recognize that with genetic testing there are different modalities that is being achieved when individuals are having genetic testing and there isn't an exact guideline as to how it should be addressed, although amongst the general medical community, there is an idea of how it is best achieved.

Basically, genetic counselors serve as particular medical specialists who help individuals go through the process of genetic testing. Not all genetic testing is processed through an actual genetic counseling visit. Some doctors will provide the genetic counseling on their own or other medical specialists can provide genetic counseling as well and order tests as well. And it can be appropriate in some settings. I think that genetic counseling, in general, when it is performed by whatever type of specialty, it is a separate visit than just your general medical assessment and physical examination. It's really sitting down, going through your family history, drawing out what we call "a pedigree" or a family tree of the history in your family, so that we can really assess who has cancer, at what age it was diagnosed and any other factors that might contribute to the idea if something is inherited or not.

It is a process that also goes through looking at a woman's personal background, her reproductive history, her hormonal history, other factors in her life that may be impacting on her own personal breast cancer risks, which may be different than her family history risks. And then also, just processing the information about, as we have all been talking about, is genetic testing right for you, even if you meet the criteria, the threshold for genetic testing as it stands. Are you really a good candidate, personally? Do you think that all of these medical options are going to be useful to you or not? Do you think that it's going to affect your family in a positive way or perhaps a negative way?

Genetic counseling is a consenting process and understanding process as much as it is just deciding if you want to know what the actual test is going to be. For some people, genetic counseling is a long-term process. In other people, it is just a one time visit.

In general, most genetic counseling sessions, when you come in, will be an hour, maybe two hours. If you see several medical specialists on a given day, it could be even longer than that. In general, you will have to pay for these services. There is insurance coverage in a lot of instances for these services. That is separate charges than your actual genetic testing.

The genetic testing itself is a blood draw, a standard routine blood draw from your arm. They take a sample. They send it off, in most instances. There's a company called Myriad Genetic Laboratories, which performs BRCA1 and 2 testing. If you're going to be doing genetic testing for other relationships to breast cancer, as we have talked about, some other genes, they would be performed in other laboratories.

The testing does certainly cost money that you can either pay for out of pocket or that, in some instances, insurance will cover for you. According to the information on genetic discrimination, some people prefer to pay out of pocket. It goes back to, again, how you want to go through this process, what's going to be best for you.

And if your family decides that one person in particular in your family is the best person to approach for the testing, perhaps it's not you but it may be a relative of yours, families come up with ways of going through that process, getting the counseling and the testing covered for that individual.

In general - the testing - if you go for just the three mutation testing, if you're a Jewish individual, that's often the first step. Because if those are the most common genetic mutations then they will rule those out and that will be a less expensive test, a fast test to do. If that test comes out negative, you may then choose to go on for further BRCA1 and 2 analysis, which is called full sequencing, where they actually go through the entire gene to try and find any other genetic mutations that you may carry that are related to cancer. And then you may find that you're in the position where they don't find anything and then you have to go into the further discussion, as we've been talking about.

Rochelle Shoretz: Thank you. Dr. Friedman, a lot of questions have been coming to the front about insurance, generally. What's covered, what isn't in terms of counseling and testing, issues of discrimination, questions about whether or not you can test anonymously through your insurance company. I

was wondering if you could speak just briefly about resources that are out there for people with questions about insurance.

Dr. Susan Friedman: Okay. Yes, I can address some of them. And as far as discrimination goes, we're coming out with a brochure, which will be available on the FORCE website and also the website of the National Society of Genetic Counselors that does have a list of resources and is an overview of the laws, because the laws are a little bit confusing.

There are some federal laws that can protect against insurance discrimination, but there are also state laws that are often times stronger and they vary from state to state and it's the same thing with employment discrimination.

My understanding, too, is that coverage, for instance in anyone 65 or older, that Medicare now covers genetic testing with some guidelines that usually qualify quite a few people. And so sometimes that may make it easier for the family to have an identified mutation found in that family and then other people to be able to do the test for the single site.

As far as testing anonymously, I do know that it happens. I know that people do it and there are issues that can be associated with that. What I strongly encourage people to do is have that discussion with a genetic counselor so that you can decide what's the best decision for you and your family.

Because there are issues that may come up, where if you are asked by an insurance company if you've had genetic testing and you've had genetic testing anonymously and you end up putting "no," that could be insurance fraud. So you have to be really careful about it.

And you know I want to say one other thing and that is that although there's a pervasive fear about genetic discrimination on the basis of a predictive test, for those who've already been diagnosed with cancer there's already a cancer pre-existing condition. And for those who haven't - there are really - at this point, documented cases are exceedingly rare of genetic discrimination.

A lot of times, the fear is really just based on legend and lore and I'm not saying that there's not potential there. But once again I think it's important that people weigh out the benefits versus the downside for them and their family and the best way to do that is to speak with a qualified health care provider.

Dr. Ruth Oratz: I think it's very important that we don't fall into this trap of anonymous testing is the safety net. It is very important for the health care professionals, the doctors, the genetic counselors, the people who are going to be taking care of you and your family to know if there's a mutation and what the

mutation status is for individuals. And that really does need to be part of the medical record.

Your medical record is protected under the Federal HIPAA legislation. Your medical record can't be given to anyone other than your treating physicians without your consent. So there is other protection in terms of having this information as part of your medical record and there are very, very important reasons why that information should be part of your medical record.

I think that I agree with your comments that this notion of discrimination is much more of a fear that is not based on reality and there are very strong arguments against anonymous testing.

Beth Murphy: I just wanted to add one thing and that is that the fear, it's been really interesting, because a third of the people who are offered the genetic testing are actually turning it down because of this fear, even though across all 4,000 genetic conditions, there really are very few cases of any genetic discrimination.

The fear of it is really palpable and I've met doctors who refuse to put the information in the patient's records. One of the women in the documentary didn't want to use her real name in the documentary even though she appeared in the documentary. She was afraid of discrimination.

But at the federal level, this patchwork of federal legislation, the American with Disabilities Act and HIPAA together do provide some protection, but not really enough protection. Right now not all 50 states have laws on the books to protect people. There are just over 30 states that have that kind of legislation. Really what's needed is something at the national level.

Dr. Kenneth Offit: I'll add two cents. There are a couple of lawyers here. I obviously like to be sure that we get the right laws.

There's a New York State civil rights law that overrides HIPAA in New York, which we should be aware of and HIPAA defers to the state laws. So New York actually is not good or does not have a law for genetic discrimination, which other states do. But we have a very, very --

Dr. Ruth Oratz: But we do have another --

Dr. Kenneth Offit: We have a very tight privacy law, which actually precludes the release of genetic information to anybody without written, informed consent, and that actually overrides HIPAA. HIPAA defers to -- this is just New York.

Dr. Ruth Oratz: Right.

Rochelle Shoretz: Any advice for a man who carries a mutation? That's probably one area that we haven't discussed and in general is a question that has come up more than once. What are the implications for the men in the family who are carrying a mutation, for their own screening but also the implications for testing for the broader family?

Dr. Kenneth Offit: I saw actually a fellow today and I didn't mean to insult him. He's carrying a mutation. I feel, you know, it was like a pride, this is all my family, since, you know, responsibility and your group describes the mutation, so I welcome them all in. He was a heavy fellow and I don't remember the adjective that I used to say you look like you've got a little oomph there, because we can do mammograms with men, if they've got enough to squeeze up there. And so he could have - this guy definitely could have had a mammogram.

We do that for the men. The men have risks for male breast cancer with BRCA2 mutations particularly and of course they can examine themselves, because you should be able to feel very easily in a male. It's just right against their chest wall. But they don't, for some reason, think about it so they often present with axillary nodes, just because men aren't thinking along those lines.

And then the other male risks I think I told you. The prostate cancer risk we showed in this study, which we published this year, is probably the most stable estimate - because it's large numbers and it's Ashkenazi so it's relative to this - was between 4 and 5 times relative risk increase for prostate cancer in males. It was not an earlier onset of prostate cancer in our series, which is encouraging.

So we still actually say, "Start the PSAs [Prostate Specific Antigen test] at age 40, but really there's no strong evidence that the guys need to start the PSAs earlier than 50. The general population for prostate cancer risk and then colon cancer was there for both men and women. We just didn't see that for either the men or women, with the common BRCA mutations.

And for guys, that's pretty much it. There's a pancreatic cancer tie that goes with BRCA2 when you see that in families and we actually have, again in a research setting, we're doing MRIs, a research study for pancreatic screening. But we're restricting that for families in which we see those pancreatic cancers and that's not a common occurrence. So the main thing for the guys is male breast cancer and the prostate.

Dr. Ruth Oratz: There is another pancreatic screening study that I think is open in either -- I think it's at Johns Hopkins, which is an endoscopic ultrasound study. Again, BRCA2 positive families who already have pancreatic cancer in the family, those family members might be eligible for that.

Dr. Sheldon Feldman: The flip side to that is that if we see men who are diagnosed with breast cancer, that there may be a genetic predisposition. So it comes the other way as well, where often a man presenting with a breast cancer becomes sort of the index case in terms of detecting the genetic abnormality.

Rochelle Shoretz: I have time for about three or four more questions and so here they go in a minute or less each one. A lot of questions coming up to the front about hormones, pregnancy, fertility, tamoxifen, HRT, estrogen-positive tumors, estrogen-negative tumors.

If one of you could sort of synthesize whatever we know now currently about the effects of hormones coursing through the body at various times, either through medications or just biologically and their affects on carriers, those who test positive, and obviously those who do not, that would be great.

Dr. Kenneth Offit: I'll just amplify the comments that I made before, which got the hoots with the estrogen. I mean, certainly estrogen deprivation, the sooner you start it in a BRCA mutation carrier, the lower the breast cancer risk. I don't want to make any beef about that.

And the other thing is if you do an oophorectomy and you go through surgical menopause, one of the things I've learned from the endocrinologists that I work with is a significant proportion of women will have no symptoms at all after a surgically induced menopause. And it might be as high as 40%, okay.

As I said, I'm very sympathetic toward -- in fact, estrogen replacement even in the recovery room temporarily in women post most of these oophorectomies. So the estrogen issue - I mean, clearly estrogen promotes breast cancer risk in the BRCA mutation carriers and the less estrogen the better.

Now, having said that, there's a lot that we don't still know and I alluded to in the slide that tamoxifen is an open question in terms of its role. BRCA1 tumors tend to be estrogen receptor negative. BRCA2 tend to be estrogen receptor positive. So you know that if it's a BRCA2 mutation carrier then you would have more of an expectation of benefit to a tamoxifen type of intervention.

It's not clear and I think all of us in the field are trying to get together to pool data as best as we can, over the next couple of years or hopefully sooner, to really flesh out the question of whether or not we'll get protection. I won't go into the theories of tumor genesis and BRCA, but there may be a hormone-sensitive critical period in the course of these tumors.

I think I've tried again to go at the hormone issues.

Ruth?

Dr. Ruth Oratz: Well, I want to just take the fertility issue. For our young patients, we certainly -- again, this is very specific to each individual woman and to how old she is when she learns this information. But if she is of childbearing age and she does not have cancer, we encourage those women to become pregnant and have children.

Pregnancy, in and of itself, does not increase the risk of either breast or ovarian cancer and if she is healthy and wishes to have children, we currently would encourage her to go ahead with her pregnancies and have her children, and then afterward, think about the question of oophorectomy at that time, after she's done with her childbearing. Certainly for women in their late 20's and 30's who wish to continue having children, that is a very reasonable option for them.

The question of whether or not a mutation carrier wants to, somewhere in that timeframe, investigate prophylactic mastectomy, if she feels that that's the risk reduction she wants to make for her breast cancer intervention, she certainly can have breast surgery and still go ahead and have normal pregnancies and healthy children.

Dr. Kenneth Offit: Or at the least get your screening started early.

Dr. Ruth Oratz: Right.

Dr. Kenneth Offit: You've got your pre-pregnancy mammograms, MRIs. You can't do either of those and you really can't get gadolinium when you're pregnant, but you can get ultrasound through pregnancy. I had three consults this week on recently pregnant young ladies. One where the rabbi called - that was interesting - and said he wanted me to tell him so he could tell her whether she should terminate that. And I said, "Rabbi, why don't you just send her to me directly?"

Dr. Ruth Oratz: Right.

Dr. Kenneth Offit: He said, "Okay."

Dr. Ruth Oratz: And physical examinations. Of course stay in very close contact with your doctors and make sure that you're followed closely.

Rochelle Shoretz: In terms of being followed closely, a few questions have come up about MRI generally and I know that they were discussed. But one question in particular: is there a benefit to having an MRI done at a facility that can't do a MRI-guided biopsy? Another question about PET scans, CAT scans, all kinds of scans. Could someone comment on that?

Dr. Kenneth Offit: Well, we were just down at the Institute of Medicine earlier this week and at the Institute of Medicine we did a thing on breast cancer imaging last year - a good book on this if you want to read through this on that.

Most of the biopsies done under MRI are done after the sonogram localizes the lesion on MRI. You know in the series it tells you only about 40 to 50% of those lesions could be visualized, in the Canadian study, but ultrasound.

We have the ability in our shop to do the MRI guided biopsies. You definitely want to ask that question when you're getting MRIs. You don't want to see the thing and then not be able to biopsy it.

Now, MRIs do have a false positive rate which is significant, and this is a struggle and this is the learning curve with MRIs right now and the technology may sort itself out a little bit better. But even in its nascent stage, at this point, the sensitivity is greater. What else?

Dr. Ruth Oratz: We're not using PET scans and CAT scans routinely for early detection.

Dr. Kenneth Offit: Yes, PET scans -- nuclear imaging, gamma counters just in general - whether its technetium or PET scans, don't have the resolution to see the sub-centimeter sized lesions that we're talking about. PET scans can be useful in staging for treatment.

Dr. Ruth Oratz: Right.

Dr. Kenneth Offit: But for detection they tend not to work. CT scans, similarly, don't have a role in breast cancer screening.

Participant: How often that MRI?

Dr. Kenneth Offit: My feeling about BRCA tumors, which I've published, is that the major issue is the kinetics of these tumors. I feel - this has to be proven - that six-month imaging is where we need to go, because in our series we had interval cancers between annual screening.

I'm not convinced that even MRI, with its increased sensitivity, where we're going from 80 to probably 95% on an annual basis, will actually hit the home run. I think some type of six-month imaging. What we're doing on a research study is mammogram six months, MRI six months, mammogram. That's what we're doing in a research setting. I can't say that should be standard practice. I would say, though, at this point, an MRI on an annual basis is what has been published with increased sensitivity and that's what's actually in the literature.

Rochelle Shoretz: The last question I'm actually going to take myself. "Can we get a copy of this evening's wonderful presentation on a video?" Thank you for the question and definitely an appropriate way to close.

Sharsheret will make tonight's presentations available on a webcast that will be up and running probably within a day or so and that webcast will be available for 90 days. I'll tell you a little bit more about that as I close.

As we wrap us this evening, please join me in thanking all of our speakers for generously offering their time and expertise this evening. I'd also like to thank our sponsors once again for bringing us all together - the Jewish Women's Foundation of New York for the grant that made this symposium possible, and our symposium supporters - they deserve it - Beth Israel Medical Center, Hadassah, FORCE, Supersol, and our technical provider, Globix.

Please be sure to complete the evaluation forms you have received. Your feedback is important to us and we use it to help us design future Sharsheret events.

Thank you all for joining us this evening, those of you here in New York and those all across the country participating via teleconference and webcast. Since Sharsheret's founding, we've heard from women across the country who want to discuss a critical concern that unites all Jewish women facing the risk of breast cancer - genetics. Tonight, we brought together those very women, their families, and the health care professionals who care for them.

The webcast of this event will be available for 90 days, so please let others know that they can still take part in this important symposium. And a transcript of the event will appear on Sharsheret's website, www.sharsheret.org, in just a few weeks.

We look forward to continuing this important conversation about breast cancer genetics and its impact on the Jewish woman and her family, and hope to explore new research with you in the years ahead.

Good night and thank you.

IX. 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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