Reporting the Research: What's Real News in Breast Cancer and Ovarian Cancer?

National Teleconference & Webinar Transcript

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Presented By

SHARSHERET

Sharsheret – Your Jewish Community Facing Breast Cancer

With generous support from
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I. Introduction
Shera Dubitsky, MEd, MA, Clinical Supervisor, Sharsheret

Shera Dubitsky: Good evening, everybody. Thank you so much for your patience. We were having some technical difficulties but we are on our way. I want to thank you for joining Sharsheret's National Teleconference and Webinar Reporting the Research: What's Real News in Breast Cancer and Ovarian Cancer?

The teleconference tonight is made possible with the generous support from Genomic Health and GlaxoSmithKline.

I'm happy to announce that Sharsheret was recently awarded a generous grant from the Federal Government from the Centers for Disease Control and Prevention, the CDC, to enable us to develop and launch *Thriving Again: Life After Breast Cancer for Young Jewish Women*, a program that will address the support needs and education for thousands of young Jewish cancer survivors.

As part of Thriving Again, Sharsheret will create unique, culturally tailored resources and support programs that best serve Sharsheret's young survivor population. We will provide urgently needed support services and education for young survivors and their families.

We are also going to share key lessons that we've learned with healthcare professionals, other national organizations and the public. If you know someone who is a breast cancer survivor or if you yourself are a breast cancer survivor and would like more information about participating in this new program, please contact us via email at info@sharsheret.org or by phone at 866.474.2774.

To listen to the teleconference, I guess hopefully you're on. Okay, we're having some difficulty with the slides. Sorry.

Let's start off with just giving you a brief overview about Sharsheret.

Sharsheret (inaudible). We are a national not for profit organization supporting young women and their families of all Jewish backgrounds facing breast cancer. We are supporting young Jewish women facing breast cancer at every stage before, during and after diagnosis, and we are helping women connect to our community in a way that feels most comfortable taking into consideration their stage of life, diagnosis or treatment, as well as their connection to Judaism. We also provide educational resources, offer specialized support to those facing ovarian cancer or are at a high risk for developing cancer.

The Jewish perspective on research is that we have a Jewish imperative which is to choose life. We are charged with seeking out all available options to guard our health and to protect our well being. It is a strong Jewish value to educate ourselves to engage in the proper and responsible research in order to gain knowledge that will help us in decision-making; and it's also our nature to be curious and ask questions.

Every day that passes, we are fielding calls from women seeking to gather and clarify information, and the conversations that we're having with women calling Sharsheret often begin with "I just saw in the news", "is it true that", "somebody I know told me the doctor said", "my doctor told me that the treatment for breast cancer is not the same as when my mother was diagnosed, how is it so different?"

Tonight we are going to try to address that. We are hearing you loud and clear and we have decided to get a panel of experts who will share and explore the latest research in screening techniques, genetics, fertility options, breast cancer treatment and ovarian cancer treatment.

In the years that I have been at Sharsheret, I have seen many changes in the detection and treatment of breast cancer and ovarian cancer. When my mom was diagnosed with breast cancer 34 years ago, the emphasis was on saving a woman's life regardless of her quality of life. But today, there is tremendous push for women to not only survive but to thrive and lead full lives as a breast cancer or ovarian cancer survivor.

I have spoken to women who are excited by the advancement in technology and treatment and other women who are expressing ambivalence about the new technology, new surgery, new interventions even though the results are well established and offer a better quality of life for a woman.

For many women calling Sharsheret the overriding question always comes down to: how can I trust that I'm making the right decision?

Our goal tonight is to discuss current options before, during and after treatment, and to explore what's on the horizon in the world of breast cancer and ovarian cancer. There will be an opportunity for participants to pose questions to the panelists during the live question and answer session following the presentation.

II. Genetics Updates
Elsa Reich, MS, CGC, Genetic Counselor, New York University School Of Medicine and NYU Langone Medical Center

Our first speaker is Elsa Reich. Elsa has been a genetic counselor at NYU for 37 years and has provided care for patients with a wide variety of genetic concerns. She has been the genetics consultant to the Institute for Reconstructive Plastic Surgery since 1975 and has provided prenatal consultations, pediatric and adult consults for a variety of heritable conditions.

She began to provide genetic counseling to individuals concerned about hereditary predisposition to cancer in the mid-90's. She has taught in the Sarah Lawrence Human Genetics Program and the Genetic Counseling Program at Mt. Sinai Hospital and extensively at NYU. She has spoken at numerous conferences and outside venues both to the lay public and to professional groups and has also spoken for Sharsheret. She has been an active professional as a member of the American Board of Genetic Counseling, a board member of the National Society of Genetic Counseling and New York Genetics Task Force. We are very honored to have Elsa on Sharsheret's Medical Advisory Board. So Elsa, I'm handing the floor over to you.

Dr. Elsa Reich: Thank you very much and I wanted just to say that I'm going to be talking about a few old things and a few new things so let's move ahead since we're a little bit late tonight. We've lost some of the slides, I'm sorry to say.

The frequency of hereditary cancer is relatively modest to moderate when compared to the small number of cancers. So, among women with breast cancer, only about five to ten percent are actually hereditary, related to a single gene. For ovarian cancer, it's also roughly five to ten percent, although in some populations, namely the Jewish population, it's a little bit higher. For endometrial cancer, it's less than five

percent and for colorectal cancer, it's also less than ten percent and in some cases, less than five percent. Next slide, please.

Most cancer is not hereditary but when it is, it's important for everyone in the family to know and this is one of the things I'd like to emphasize in my talk tonight and we'll come back to why that's the case. Next slide, please.

Now, you can see this lovely shadow of a tree and just like this tree, the family tree has many branches and there's both the mother's side and the father's side. Let's always remember that. Let's go ahead.

You should try to learn as much as you can about the health of your extended family members, especially the history of cancer, the type of cancer and the age and/or ages at the time of the diagnosis. Likewise, and I can't emphasize this enough, it's very important to share your own personal history of cancer with your family members including your children, both the men and the women, and to let them know whether you're considering testing for the presence of a mutation and whether they want to know your results. If your children are adults, you should be respectful of their adulthood and share that information with them. You should be willing to share the results of your testing with them, if they wish. You may actually be saving their lives. Go ahead.

Now, here we have a special situation in genetics, a little bit more so than in many specialties because for us, the patient is always the family and when we're talking to an individual, we always see the family sitting behind our patients. Next slide, please.

Now, is the fathers' family important? Why, it really is. We all know that the mother's family history is important but what about the father's? A recent article showed that referrals for genetic consultation were five times more common because of the maternal history of breast cancer and ovarian cancer as opposed to that of the father. Next slide. Let me show you a couple of examples. Go ahead.

Now, this is our diagram of a family history and the blue circles are women who've had breast cancer, the yellow circles are those who've had ovarian cancer, squares are male, circles are females. What you can see in the center of the slide is a woman diagnosed at 32 years of age with breast cancer, very early. She has a BRCA1 mutation and that means that she has up to an 85 percent risk of breast cancer. She's already had breast cancer but for someone who has not had cancer, it's a lifetime risk of up to 85 percent and about a 20 to 45 percent risk of ovarian cancer.

Now let's look at her family. Her mother had breast cancer. Her maternal grandmother, with the yellow circle on the upper right, was diagnosed with ovarian cancer at 52. On the left side of the family, her father's side of the family, his mother had ovarian cancer at a relatively early age. We don't know exactly how old. There's no one else in the family with breast cancer but we want to know which parent is the BRCA1 carrier because there can be implications for other family members. Next slide please.

Now, you can see here we're a little bit surprised because we would have assumed it came from the mother's side. After all, there's breast cancer and ovarian cancer on that side. But in fact, it came from the father's side of the family. He's a carrier. Subsequently, we found that other members of his family were also carriers. So, this information has been very useful to this family. I didn't put all of the members of the family but his brother, who is the last figure on the left, has a daughter and she

turned out to be a carrier. So she was able to institute some important surveillance. Next slide please.

Here's another, and this is a demonstration of that as I was just telling you, that he found out that actually, it was his granddaughter who had it. His son had a BRCA1 mutation but his granddaughter did not. So we're able to help people understand what their chance is to develop breast cancer and ovarian cancer, if they're positive. Go ahead, please.

Now there are many genes contributing to hereditary breast cancer and ovarian cancer and most of you have heard about BRCA1 and BRCA2 and I'm not going to take too long to talk about other genes but there are several of them and let's move on to the next slide.

Now, here we're showing some of the more common ones and you may not be familiar with this, and I'm not going to go through the whole thing as we are pressed for time a little bit, but there are several and they're much less common than BRCA1 and BRCA2. There's one condition that I'd like you to be a little bit more familiar with and that's on the next slide.

That condition is what we call Lynch Syndrome and Lynch Syndrome is a hereditary cancer syndrome that predisposes to multiple different types of cancer including colon and uterine cancer which are the most common, gastric, urinary tract and others, but it also predisposes to ovarian cancer. So, in 2.6 percent of BRCA1 and BRCA2 negative tumors, that is to say, women who have been tested and are negative, have a mutation in one of the— actually it's only one of the first three genes because I didn't include the last two, predisposing to ovarian cancer. So we can't forget that we have other genes that also are responsible for hereditary ovarian cancer and breast cancer. Next slide please.

So I'm not going to talk about all the new genes associated with breast cancer but one of the ones that's gotten some publicity lately is called RAD51C and it accounts for somewhere between 1.5 and five percent of high-risk breast and ovarian risk families.

Now, in the United States we're not currently providing routine genetic testing because its frequency and associated risks are not yet completely defined, although we have sent some samples out to Europe to have some testing. There are variants in other genes that can interact with high-risk genes to modify the likelihood of developing cancer and one of them is FGFR2 and this is a gene that is frequently known because it's associated with certain craniofacial disorders but it may modify the age of onset of cancer in BRCA2 carriers. So we're learning a lot about the effects and interactions of these genes with other genes. Next.

There are multiple large studies that have been done by extensive collaborative groups to identify variants within the genome that appear to be associated with either an increased or decreased risk of breast cancer and ovarian cancer in both BRCA carriers and non-carriers. Now the GY studies, that means the genome-wide association studies, that's what we call the next generation sequencing, some of these groups have also looked at variation in known genes that are in the pathway of the BRCA1 and BRCA2 and will identify variants that potentially contribute to modify the age of onset in carriers. Go ahead.

Now, are we using the results of these studies to help patients? Well, not yet. There are so many different variants that we haven't established a paradigm by which we

can make some of these predictions but we're learning all the time. So some of the studies have revealed some very interesting findings but at the moment, we're not able to use this to predict with accuracy the age at which an individual may develop cancer. Someday, we may be able to. Go ahead.

How has research expanded our knowledge and thereby our ability to treat these cancers? Well, understanding the pathway of the normal BRCA1 and BRCA2 genes has helped to elucidate the potential role of other genes contributing to an increased risk of breast cancer and ovarian cancer, and has also allowed researchers to utilize treatment and take advantage of the failure of these genes to correct the DNA damage and ultimately cause cell death thereby, killing the tumor cells. Next slide, please.

Now, many of you know that BRCA1 associated tumors are most frequently triple negative, meaning that they're estrogen and progesterone receptor-negative and also HER2-negative. There are also non-BRCA1 tumors, especially in young women, in which the normal BRCA1 gene has been turned off, that are also triple negative and have what we call BRCAness. They don't have a mutation in all of their cells but preliminarily, these tumors appear to respond to some of the same medications. Next slide.

Now, intensified surveillance for breast cancer and other preventive treatments such as risk reducing surgery, some of these are the benefits of having genetic testing so that you know what to do. Treatment, BRCA carriers have a high response rate to PARP inhibitors following more traditional therapy and this is still in clinical trials. BRCA carriers are more sensitive to platin compounds like cysplatin and carplatin. Some sporadic or non-hereditary breast cancers are also sensitive to these substances but need to be identified for specialized testing. One of the benefits is also reproductive options, embryo freezing, oocyte freezing and pre-implantation genetic diagnosis. Next slide, please.

Information for family members, daughters, sons, brothers, sisters, husbands, et cetera, some may find that they're carriers and should begin intensified surveillance. Some may find that they're non-carriers and they follow age-appropriate surveillance and learn that their children do not have to be tested. Knowing one's carrier status may be lifesaving.

I'd like to emphasize at this point, if there's no purpose in doing genetic testing, that is to say if there's no utility, if it doesn't help anybody to do anything, there's no purpose in having it but if there's a benefit to you or your family members, then it's worth doing. Next slide.

I just wanted to mention this because maybe the person who's asking about fertility will mention this. Pre-implantation diagnosis, very briefly, is a procedure that allows a woman or a man who is a known carrier to avoid transmitting a mutation to her or his child or children without having to make a decision to terminate a pregnancy. This is a procedure that is acceptable to the orthodox rabbis. Next slide.

I'm not going to discuss this because perhaps that will be discussed later. Next slide.

So what can you do? Know your family history and share it with your close and distant relatives. Ask you doctor for a referral to a genetic counselor to learn about the chance that you are of carrier. If you are a carrier, ask your physician about treatments that may be beneficial. Keep talking with your doctor about new developments. Stay connected to Sharsheret to learn and to help each other. Next.

What can you do tomorrow? Call a genetic counselor or call me for a referral near where you live or contact me for further discussion of your situation and maybe I can help you. There are many knowledgeable genetic counselors in the United States and abroad who can help you in many ways. Next slide.

Here's my email address at NYU. Here's my telephone number so please don't hesitate to copy it down and you can get my number from the people at Sharsheret if you don't do it now. Thanks so much for having me.

Shera Dubitsky: Elsa, thank you so much. Genetics is certainly on the minds of many of our participants tonight. I think that you shared some very valuable information that our callers can now take home and share with their families. And Elsa will be on later to answer some questions for us.

III. Fertility Updates
Kutluk Oktay, MD, FACOG, Fertility Specialist. New York Medical College/Westchester Medical Center

Shera Dubitsky: We're going to switch the order because Dr. Oktay is going to need to leave early, so I'm going to introduce him. Dr. Oktay is one of the world's foremost experts in fertility preservation as well as ovarian stimulation and in vitro (inaudible).

Dr. Oktay has devoted his professional life to the science of fertility preservation and infertility treatment. He is a world renowned researcher, a gifted medical educator, and a skilled clinician dedicated to his patients.

Dr. Oktay was invited to the President's Cancer Panel as an expert on fertility issues of cancer patients and fertility preservation. Furthermore, he was named the Co-Chair of the American Society of Clinical Oncology Committee for Fertility Preservation (inaudible) for people with cancer.

In 2008, after a ten-year career at the Weil Medical College of Cornell University, Dr. Oktay became a Professor of ObGyn and the Director of Division of Reproductive Medicine and Infertility at New York Medical College, Westchester Medical Center, and he founded the Center for Reproductive Medicine and Institute for Fertility Preservation. He was also named a consultant position at Memorial Sloan Kettering Cancer Center and a consultant for Cancer and Allied Diseases at Memorial Hospital.

Dr. Oktay has published extensively in medical journals and he regularly lectures around the globe and has repeatedly received top doctors' awards around the country.

Dr. Oktay actually addressed this issue for Sharsheret in 2004 and we are very fortunate to have him back to provide fertility updates. So Dr. Oktay, the floor is yours.

Dr. Kutluk Oktay: Thank you very much. Can you hear me well, there?

Shera Dubitsky: We can hear you. Just let us know when to move the slides along.

Dr. Kutluk Oktay: Okay. Well, thank you very much for the opportunity. I'm going to try to summarize the options for preserving fertility as well as some of the options that apply to those of you who may be concerned about fertility issues before and after breast cancer, and

other cancers related to, especially, BRCA. If you could advance the slide for me, please. Next slide, please.

Among the new items that I would like to discuss with you is what's new about how chemotherapy affects ovarian reserve and what can we do in the situation of estrogen-sensitive breast cancer in terms of preserving fertility, how pregnancy relates to history of breast cancer, and a couple of new approaches to preserving fertility, and also some new information about BRCA carriers and specific to their future fertility. Next slide, please.

As it has been mentioned, in 2006, Haskell released guidelines, more of recommendations, of fertility preservation in young people with cancer and this is a valuable document, and there is an accompanying patient document as well which you can get through ASCO that summarizes pretty well the situation. These guidelines are now being updated and hopefully in a year or so, it will reflect the fast developing field. If you have any difficulty obtaining this, you can also contact me or email me. You can contact me through the FertilityPreservation.org website. Next slide, please.

One of the major issues in women who are faced with breast cancer and ovarian cancer is chemotherapy side effects. We have learned in our recent research that several of the agents that are used in the treatment of, especially breast cancer, are quite damaging to ovarian reserve. This has been known for a while, that agents that are called alkylating agents are damaging in that they can reduce the egg reserve significantly. But we have now found that additional drugs that are used in the treatment of breast cancer, such as doxorubicin, are also quite toxic to ovarian follicles. Next slide, please.

Women are born with a set number of eggs so what chemotherapy does is that it takes away a chunk of the egg reserve thereby advancing so-called ovarian age and making the menopausal age sooner. So this graph shows you the natural curve of the decline in egg reserve. When women get to about 51, 52, all egg reserve is exhausted and as a result, menopause occurs. What chemotherapy does is to accelerate this process. Next slide, please.

We are looking at a count of eggs from ovaries of women who were exposed to chemotherapy versus women who were not. What this slide tells you is that those who were exposed to chemotherapy have egg numbers comparable to those who are ten years older than themselves. So in other words, overall, when chemotherapy is given, especially those combining agents that are known to be damaging the ovary, ten years of reproductive life might be lost. Next slide, please.

Considering this, we have come up with certain guidelines of when to recommend fertility to preserve eggs. The previous speaker mentioned about embryo or oocyte freezing. But, depending how old you are and how much delay there will be because of chemotherapy or tamoxifen treatment, and some patients may not receive chemotherapy but they may be on tamoxifen for five years, depending on how many children you may want to have in the future, fertility preservation may be necessary even in very young patients. If you could please advance to the next slide?

For example, many of us think that a 30-year old might not necessarily need fertility preservation after chemotherapy because most women of that age will retain their menses. But if you consider the information I gave you, a 30-year old may now have an egg reserve of a 40-year old woman after chemotherapy and if she's asked to delay child-bearing for five years because she's on tamoxifen, then her egg reserve

will be reduced comparable to that of 45-year old women, at which time, the probability of pregnancy is very, very low.

So if you are faced with a chemotherapy situation, you should really get competent advice on how and what kind of approach should be used for fertility preservation regardless of your age. Next slide, please.

In the past, there have been suggestions that the hormonal suppression with agents called GnRH analogs could preserve ovarian function. But recent randomized studies are showing, like the one here, GBG 37 ZORO study, that this approach is not beneficial. So far, there is no medical hormonal approach to preserving fertility. Next slide, please.

The current approaches, therefore, involved cryopreservation of embryos, oocytes or ovarian tissue. Next slide, please.

The most established method of preserving fertility is embryo freezing, followed by egg freezing or oocyte freezing, both of which require about two weeks of ovarian stimulation and office-based egg collection procedure. Next slide, please.

Because timing is very important, it's also very important that patients are referred very early in the process. In a recent study, we show that if women are referred before breast surgery, they would be able to get in and be able to undergo at least two cycles of ovarian stimulation and start chemotherapy at least a month early. So, this response often falls upon the shoulders of breast surgeons so that these patients can be referred early in the process. Next slide, please. We can pass that next slide.

One of the other problems in trying to do fertility treatments in women with breast cancer is that fertility drugs increase estrogen levels and this is usually not considered safe in women with estrogen-sensitive breast cancer. To get around this, we've used a medication called Letrozole which blocks estrogen production, at the same time stimulating ovaries. Next slide.

With that treatment, we found that—next slide please—and you're going to take a look at the last column before it says P value. That kind of treatment keeps estrogen levels close to natural levels and results in a number of eggs and embryos comparable to standard stimulation protocols. Next slide. Next slide please. Let's pass these. We'll pass this, as well.

This protocol also gives very high success rates and some of the patients may consider gestational carriers. As a matter of fact, more than half of these patients who freeze their eggs or embryos, many of them do so because they don't want to wait until the end of the five-year tamoxifen treatment. Next slide. Next slide please.

Also, we have been following these patients who underwent ovarian stimulation before breast cancer treatment to freeze their eggs and embryos and this slide shows that the green line representing those who underwent fertility treatment with breast cancer history and the purple line representing a control group, there is no significant difference between those two groups. In other words, women who underwent IVF treatment did not seem to have higher risk of cancer recurrence. Next slide.

Overall research indicates that women who conceive after breast cancer do not have increased risk of breast cancer recurrence and some studies indicated they want the benefit of conceiving even though some suggested that this could be because

healthier women attempt pregnancy, by some studies controlled for that. Next slide, please. We can pass these. Thank you. Next slide. Next slide, please.

Now, one of the very interesting things we found about treating women with BRCA mutations with infertility and fertility preservation procedures—next slide—is that what we have found was that women with BRCA mutations produced a lower number of eggs in response to fertility drugs. As you can see from this table, compared to BRCA mutation-negative, BRCA mutation- positive patients produced at least three or four eggs fewer. Next slide.

They're much more likely not to respond to fertility treatments sufficiently.
The BRCA mutation-positive patients had a poor response, lower response to fertility treatments: one out of three times whereas this was only one out of 33 times in BRCA mutation-negative patients.

Also, (inaudible) studies show that if you look at blood markers, women with BRCA mutations have lower oocyte egg reserve. Also there's some data that women with BRCA mutations experience menopause earlier. Therefore, it seems that women with BRCA mutations may have some disadvantage in terms of ovarian reserve but further research will be needed.

As was discussed during the first talk, there are ways to test BRCA mutations in embryos by what's called pre-implantation genetic diagnosis which requires in vitro fertilization and biopsy of embryos by removing one or two cells and detecting these mutations.

Some patients prefer to do gender selection only preferring male gender because of the perceived higher risk in women but perhaps this is not necessarily a completely protecting approach as conditions associated with BRCA mutations are being revealed in both genders. Next slide, please.

One final thing is that we have always spoken about cryo-preservation of eggs as an inferior method. Next slide. Recent research indicated that with the current methods of oocyte freezing—next slide—success rates have approached to that of doing IVF with fresh eggs, and pregnancies can occur until the age of 44 with frozen eggs. Therefore, egg freezing appears to be a much more attractive choice, which is a choice for women without a partner or who don't want to use donor sperm to freeze embryos. Next slide. We can pass this, please. And we can pass this.

Finally, ovarian tissue freezing is the most experimental procedure that we do for fertility preservation which is reserved for women who don't have sufficient time to undergo ovarian stimulation. Recently, this procedure has evolved to be performed by robotic ovarian transplants, giving us further options.

In conclusion, in terms of fertility preservation and fertility issues, earlier referral is essential, especially pre-chemotherapy but even with those who had chemotherapy and who have recovered from that, their egg reserve is now lower and they should not waste time and they should be considering conception as early as possible and seek help from a fertility specialist as soon as possible. Thank you.

Shera Dubitsky: Thank you, Dr. Oktay. I know that some of the issues that you brought up tonight are certainly in response to questions that we get everyday here at Sharsheret about fertility. So, I want to thank you for sharing your insights with such clarity and I know that you won't be here for the question and answer but perhaps people will be able to email us questions and we can get them to you.

IV. Sreening Updates
Thomas Kolb, MD, Radiologist, Private Practice

Shera Dubitsky: Our next speaker is Dr. Thomas Kolb. Dr. Kolb is widely regarded as a leader in the field of women's healthcare and imaging. For 15 years, he served as Assistant Clinical Professor of Radiology at Columbia University College of Physicians and Surgeons, and is in private practice in New York City specializing in the detection and diagnosis of breast cancer in young, predominantly high-risk, menopausal women.

Dr. Kolb has achieved double board certification having received his training in Pediatrics at the Albert Einstein College of Medicine in the Bronx and in Diagnostic Radiology at the Columbia Presbyterian Medical Center in New York City.

Dr. Kolb has been on the faculty of numerous medical educational meetings and he has lectured throughout the United States and internationally on the topic of breast cancer detection and diagnosis. He holds positions on the Board of Directors of the Breast and Prostate Cancer Research Foundation in New York, the Medical Advisory Committee for Young Survivor Coalition, and the Susan G. Komen Foundation and for Sharsheret.

Dr. Kolb is an original founder of a New York breast cancer study and was co-author of its research publication *Breast and Ovarian Cancer Risk Due to Inherited Mutations in BRCA1 and BRCA2*.

Dr. Kolb has investigated and published original research detailing the use of multiple new technologies including infrared and electrical impedance imagery specifically for the detection and diagnosis of breast cancer.

So with that, Dr. Kolb, the floor is yours.

Dr. Thomas Kolb: Shera, thank you very much. I hope you all can hear me. In my time allotted, I thought I'd do something pretty ambitious and have decided to talk about the entire screening mammography debate on a single slide in one or two minutes. It seemed to be a very Jewish thing to do and then we'll take a trip through the strengths and weaknesses of screening (inaudible) examinations that are currently available or may be available in the near future. So let's move on to the next slide and you'll see.

We'll start talking about mammograms just for the beginning of this talk and we'll move on to something that you may have heard that's coming down the pike right now: 3D mammography or tomosynthesis. We'll talk about that. We'll talk about ultrasound use of the screening methods of detecting breast cancer. Then, something that I'm very interested in, a research setting icon which I think you'll hear a lot more about which is adding automated screening ultrasound to tomosynthesis of 3D mammography and having a conjoined examination.

We'll bypass MRI for the moment and go to molecular breast imaging which includes breast-specific gamma imaging, PET scanning of the breast called pattern positron emission mammography. Then, we'll finish up with infrared technology. I'll tell you all my thoughts about the strengths and weaknesses of all these technologies and we'll end up with a very hot topic that concerns dense breasts. So let's go the next slide.

Starting with the mammogram and let me start with a fact. The fact is that the only screening method that we're going to talk about tonight or that exists for the detection

of breast cancer that has a clear survival benefit showing mortality reduction, elongation of life, is a screening mammogram. Physical examination done by a physician or a self-breast examination done by the patient, ultrasound, MRIs, have never been shown to have a survival benefit. We'll talk about that.

So the issue with mammograms is really the question of degree of benefit versus the degree of harm. So, most of the randomized controlled trials done from the 1970's to the 1990's showed approximate 30 percent survival benefit in women above the age of 50 down to a 15 percent survival benefit in women that are younger, between 40 and 49. There have been many investigators that have evaluated these results, hundreds of thousands of women over the course of seven very large studies that won't be replicated anytime soon and have corroborated those results.

However, coming into question is how do these results now fare in the modern era where there is now better treatment available? Perhaps survival is due to better treatment. There's been some people that have (inaudible) at the methodology of the original studies to assess that where it had weaknesses and, therefore, they use mathematical models instead of being able to repeat patient studies which don't look like they will be done anytime in the near future, plugging in assumptions about cancer incidence and cancer activity with different types of therapies plugged into mathematical models and results are looked at that way.

Some have found a lesser benefit for screening mammography from the United States Preventive Service Taskforce that was talked about in 2009, a couple of years ago extensively to yesterday in The New York Times where the benefit of the mammogram is felt to be, by some, less than what was originally proposed.

Be that as it may, no one disagrees that there is a benefit to screening mammograms. They have to weigh that against the cost of doing mammography, widespread screening, the false-positive rate which has been dictated by physicians and I do think that women have to be part of this debate, over-diagnosis and this is talked about a lot today. However, there's no way, in advance, to know in a mammogram if there is a cancer, whether it's a cancer that will be aggressive and lethal or whether it will be indolent and just sit there for a number of years. So, without actually biopsying it, there's no way to know. When discussing over-diagnosis, while it is a truthful statement, doesn't help a woman in terms of prolonging her life. Finally, there's the theoretical radiation myth.

So those are the issues and we have to weigh out the benefits versus the harms. No matter what the numbers are in any studies that you look at, it really comes down to that and to just quote the USPSTF study that was published in 2009 that recommended we change our guidelines which were not changed, they said that while there was a clear benefit to mammography, they find the benefit was inefficient—finding these cancers were inefficient. So there were other motivations to suggesting new guidelines which have not been adopted, for the most part, in this country. Next slide, please.

So now, moving away from mammography and going to 3D, you may be hearing about this soon. I have to give you a disclaimer that I'm principal investigator for a very large tomosynthesis trial, the GE North American Tomosynthesis Trial and with that disclaimer, let me tell you what 3D mammograms are.

They're basically a CAT scan of the breast. Think about a pamphlet that has ten pages printed on very thin paper. If you hold it up to the light there will be many words and many punctuation marks and many letters and it's our obligation to find

the cancer among all those symbols. Well, basically a cat scan of the breast takes apart each page so you can look more carefully for cancer detection and we can obtain multiple one-millimeter images through a single sweep of the x-ray gantry through the breast. So instead of having one picture, one two-dimensional picture of a three-dimensional breast, we have 60 pictures, let's say, of the breast to look through to scroll through to find a breast cancer. It's the same dose of radiation as a conventional mammogram.

In the United States, only one manufacturer has been FDA-approved and in Europe there's at least two that are being sold. I have to tell you that we have to view 3D mammography with some caution because of the claims of increased sensitivity which means finding additional breast cancers over and above conventional 2D full-field digital mammogram as well as better specificity. There are no peer-reviewed studies in the United States that have been published by the vendor that had the FDA clearance yet. We only know what they submitted to the FDA.

So I think we're really in a holding pattern now in terms of 3D. I don't know anybody that should really be rushing out. The concept here is very good but by reducing structural noise, by obtaining these very thin images of the breast, you would be able to find additional cancers and decrease the recall rate—decrease the false-positive rate of mammograms. But I really do think we need more research before we go running out to try to get a 3D versus 2D examination. Next slide, please, is an example of what I just said to you. Next slide. Let's move on.

This is an example of what 3D can do. On the left is a typical full-field digital mammogram which there's really no distinct abnormality identifiable but when you look at a very thin section of the breast, you can see there's a little architectural distortion shown by that blue line on the bottom and that is a typical deforming small cancer. Next slide, please.

You can see calcifications very well on the thin images. On the left is a conventional digital mammogram. On the right is a 3D mammogram. Next slide, please.

You can see the better resolution of and identification of additional calcifications and distortion on the 3D images. Next slide, please.

One final example, a typical full-field mammogram on the left and on the right. You can see the mass just pop right out at you and this is a typical example of what you can see, it's possible to see on 3D imaging. Next slide, please.

We'll talk about ultrasound for a minute here. Ultrasound is utilized as a screening examination. Next slide, please. I'd like to point out to you something that you may already know. We grade breast density from 1 being a non-dense breast meaning predominantly a fatty breast to grade 4 on the top row there which is a very dense breast with very little fat in it and you can see the sensitivity of the mammogram the top numbers. Statistically significantly decreases in a non-dense breast, 98 percent mammograms are excellent detectors of breast cancer in non-dense to below 50 percent in very dense breasts, and the number is even lower than that if you factor in other detection methods like MRI. Approximately 60 percent of cancer will not be seen on a mammogram in a woman who has extremely dense breasts. Who has dense breasts? Two-thirds of premenopausal women and 25 percent of post-menopausal women have breasts that are dense enough to decrease the sensitivity of the mammogram. Next slide, please.

Can you move the slide ahead? Mine's frozen. So basically conventional, back one slide, just one second here. If you look at the middle row, if you use mammography and physical examination which are conventional means of screening for breast cancer and, again, I'll repeat there's no mortality benefit to physical examination whatsoever no matter who examines you, your gynecologist, breast surgeon or if you examine yourself.

You'll see that in very dense breasts, again, cancer detection is 63 percent using conventional methods. If you switched out and substituted ultrasound for physical examination, we find far more cancers than utilizing physical examination instead of us. Next slide, please.

Now, this slide is very important because it talks about false-positives or the flip side of a positive biopsy. If you look at the box on the bottom of the screen, the box on your right, you'll see that the positive biopsy rate, PBR, of screening breast ultrasound is approximately ten percent. That means, for every ten masses you biopsy, one mass will be cancerous and the findings that I present on screening ultrasound have consistently been found by other groups throughout the world including a multi-institutional study in the United States. The one fault they find in finding all these additional cancers by using ultrasound is that the positive biopsy rate is too low. It's only ten percent. I'm not sure most women would agree with that. I think most women would like to have an early stage cancer found since biopsy in this day and age refers to a needle biopsy with some local anesthesia in the skin that takes about two minutes to perform.

But you'll see that even if you incorporate screening breast ultrasound—the bottom right box—with the conventionally screened group on the left, you'll see that the top box is a large group of patients, over 27,000 patients, that were screened with mammography and ultrasound and the positive biopsy rate is 25 percent which is entirely acceptable. So this is a very viable way of screening for breast cancer. Next slide, please.

It actually finds a 73 percent increase in detection of non-palpable invasive cancers by 73 percent. So we're talking about finding a very large number of additional cancers using ultrasound. Next slide, please.

Now, one of the problems of using ultrasound is that it's hard to corroborate the examination. There's intra-observer variability. Basically, it's dependent on who does the ultrasound. In an effort to automate it, there is a company that has put out a device where a panel where the ultrasound ray is incorporated within and three different pictures of the breast are performed. One is the medial part of the breast which is the inner part, one is the lateral part and one is the central part, and these images are basically stitched together into a panoramic view of the breast.

It is a step in the right direction and I think it is important. It's not, I don't believe, ready for prime time yet although it is being sold and used throughout the country. I think there are too many false-positives where we have to revert back to handheld ultrasound in dealing with the automated type scan. I'll propose to you a better method. Next slide, please.

I think that if we are able to use 3D mammography and during the single ompression we scan the breast with ultrasound as well,then within ten seconds we'll be able to obtain both the mammographic or x-ray data as well as ultrasound data at the same time and we would be able to know exactly where in space a mass is if the mammogram showed an abnormality. So that you'd be able to sit at a viewing

station, see a possible abnormality on a 3D mammogram, put a cursor on it and the ultrasound data would come up and it would show you that it's either a meaningless finding, a benign mass such as a cyst, or it could be something that's suspicious like a cancer that needs further attention. Next slide, please.

This is a prototype of this type of system which I think appears to be very 1990's or 2000 and not 2K11 but it would significantly enhance streamlining cancer detection and this prototype is in use and, hopefully, we'll have more data to present in the near future about this type of conjoined imaging. Next slide, please. Next slide, please.

Let me move on to molecular breast imaging. You may have heard about it. This is a call that I'm sure typically comes up at Sharsheret. It certainly comes up in my office. I just had a breast-specific gamma imaging examination and they found something, what should I do?

Well, it is a problem what to do with a finding on BSGI. What is BSGI? It's an injection of a radioactive material, it's technetium-99 (Tc99m). It's called sestamibi. It was used in cardiac studies and serendipitously shown that cancers in the breast lit up with this tracer as well.

But the major stumbling block to this technology, which is not widely publicized and explained, is the dose to the breast is 20 to 30 times the radiation of a single mammogram. Now, there are attempts to decrease that dose of the radio tracer that is injected into the body through an intravenous injection to half that but you'd still be talking about 10 to 15, even if that was possible, at least 10 to 15 times the radiation dose of a single mammogram and I find that I don't think that it would be reasonable that there could be mass screening done with this technology with these radiation levels.

So I think it is a problem. We're talking about this as a screening test not a diagnostic test. While the published results are encouraging that it is similar to MRI in finding breast cancers but more specific in finding breast cancers and better in that way, the results are limited to a very, very few centers, not widespread whatsoever and the stumbling block of radiation is certainly there. Next slide, please.

Another molecular breast imaging technique is positron emission mammography; it's PET scan of the breast. Again, it's an injection but this time, a radioactive sugar compound, FDG, same increased dose to the breast. Right now, it's being used for staging breast cancer after one was detected. It certainly is not being used as a screening examination nor should it be touted as one. Next slide, please.

Finally, infrared technology, which I looked at about 15 to 20 years ago, breast thermography. Basically, this is the only test I can tell you to stay away from. The FDA has approved it. It sounds too good to be true and it is. There's no radiation. It's non-invasive and it looks at differences in infrared head emission or the heat pattern. There are no good peer-review studies in the literature comparing infrared technology versus mammograms, ultrasounds, MRIs and so on and that tells you something about the technology. So if it sounds too good to be true, it usually is. Next slide, please.

Let me spend one minute here on dense breasts. Dense breasts is a hot topic now because of recent legislation in certain states which I'll tell you about. The two important facts for you to know are that women with dense breasts have an increased risk of developing breast cancer significantly so, four to six times above the

normal risk woman. This has been known for about 30 years. It's nothing new. There's also decreased accuracy of the mammogram in women with dense breasts that I showed you on a study that we did a few years ago that has been corroborated by multiple groups across the world.

What are dense breasts? It's the lack of fat. Non-dense breasts are mostly composed of fat. Dense breasts have very little fat in them and the only way you could know whether you have dense breasts or not is by looking at the mammogram. You can't inspect or palpate your breasts and know whether your breasts are dense or non-dense.

So should a woman know their breast density? Is it important for them to know that? Well, I think it's critically important since it affects the accuracy of the mammogram. I would argue that it's unethical to not to tell a woman what her breast density is. While you're telling one patient whose breasts are non-dense that her mammogram is normal and you may be 98 percent correct, telling another woman whose breasts are extremely dense that her mammogram is normal, you're only 40 percent certain that she doesn't have breast cancer if she, in fact, really had it.

So Connecticut and Texas have mandated radiologists, just recently since 2009, to report breast density directly to the patient. It's a contentious issue.

California vetoed a bill. There is a bill in the New York State Senate pending. I think they're going to vote on it in December or January. There's a movement to put together a federal bill as well to inform women of their breast density and to ask them to speak to their doctors to see what they can do about it and we've discussed certain screening examinations that can be performed.

It's somewhat of a complex issue. The American College of Radiology, in fact, is against telling women their breast density, routinely telling women their breast density in letters to the patient. So while a woman does get a letter mandated by the Mammography Quality Assurance Act, which is a federal law, that tells them whether their mammogram was normal or abnormal, she does not get along with that, information that tells her how accurate the mammography report really is. Next slide.

So we've talked about 3D mammography. I think we need to go very slow with that now. I don't think anyone should be really rushing out to get it. We're in the very early incubation stages of that technology. Screening ultrasound is relatively mature. It's been studied for about 10 or 15 years right now. We're moving into the automated ultrasound era. If we can couple that together with tomosynthesis or 3D, I think that would be a major advance for conventional breast cancer detection.

We talked about the nuclear medicine cancer detection examination, gamma imaging and PET scanning of the breast where the radiation at risk is just there and not being publicized by centers that do offer it to patients which I think is an issue. Thermography, which really has not been proven viable in my mind at all and we've discussed a little bit about dense breasts which I think you'll hear a lot more about very soon.

Thank you to Sharsheret and the audience as well and, hopefully, we'll take up some questions in the Q&A.

Shera Dubitsky: Great. Thank you, Dr. Kolb. As you said, we are hearing so much about screening in the media and we're hearing here at Sharsheret from our callers that it really is an emotionally charged topic. We very much appreciate you handing over the

knowledge so clearly and giving ultrasound a better understanding of what the options are that are available to women, it sounds like, depending on their own set of variables. So thank you for that.

V. Breast Cancer Updates
Ruth Oratz, MD, Medical Oncologist, The Women's Oncology & Wellness Practice

Shera Dubitsky: Our next speaker is Dr. Ruth Oratz. Dr. Oratz is a medical oncologist specializing in the treatment of breast cancer. She is Clinical Associate Professor of Medicine at the New York University School of Medicine and Director of the Women's Oncology and Wellness Practice.

Her research interests are focused on breast cancer clinical trials and the genetics of breast cancer. Dr. Oratz has been practicing medical oncology for more than 20 years and established the Women's Oncology and Wellness Practice, a unique environment that provides state of the art medical care in an intimate, personal and private setting.

Dr. Oratz is especially committed to helping the women facing cancer continue to live her life actively and fully. Her practice addresses women's concerns about family life, career, relationships and sexuality.

Dr. Oratz is a Diplomat of the American Board of Internal Medicine, is board certified in Internal Medicine and Medical Oncology. She is a Fellow of the American College of Physicians. She's on several advisory boards of organizations dedicated to education and support for women and their loved ones as they cope with the breast cancer experience.

She is the Chair of the Medical Advisory of the Susan G. Komen Greater New York and also is on the medical boards of BreastCancer.Org, Living Beyond Breast Cancer, Cancer Care and our very own Sharsheret and the Metastatic Breast Cancer Network of New York.

Dr. Oratz has always been very generous in terms of fitting Sharsheret into her schedule and for this, we are very grateful. With that, Dr. Oratz, the floor is yours.

Dr. Ruth Oratz: Thank you very much, Shera. You gave me a big assignment in a short amount of time tonight which is to cover what's new in the medical therapy of breast cancer. Let's go to the next slide, please.

Just very quickly, as you all know, breast cancer is the most common malignancy in women. This year, more than 200,000 women will be diagnosed with invasive breast cancer in the United States.

We've actually made a lot of progress in breast cancer. We've seen a decrease in the incidence of new cases, particularly in older women that may be a little bit related to the hormone replacement therapy story. But since we're focusing on young women, I think that what's very important to acknowledge is that we really are seeing a decrease in death and mortality from breast cancer in women who are diagnosed at age less than 50 and I think this is in part due to better screening and early detection as well as to significant advances in our treatment of breast cancer. So things really are different now than they were a few decades ago. Next slide, please.

There are, as I always like to tell my own patients, some underlying principles to the treatment of breast cancer and I like to think of things in two big categories. The first is local control, that means how do we deal with the tumor that's in the breast, and we have many modalities for treating the primary tumor in the breast using surgery, whether that's a mastectomy or a lumpectomy. We need to evaluate the lymph nodes associated with that tumor. That can be done by a sentinel node biopsy, by imaging or lymph node dissection at the time of surgery. We also use radiation therapy to control disease in the breast and chest wall and nodal areas.

But the medical treatment of breast cancer is really focused on systemic control and that is about preventing the cells from the primary tumor from spreading to other parts of the body. Or if they have already started to spread, to treat that cancer so that we reduce or prevent the risk of recurrence or progression of disease.

We have many modalities for treating breast cancer and these include chemotherapy, hormonal therapy, targeted biologic agents and, of course, the new treatments that we're looking at in clinical trials. Next slide, please.

So until very recently, the way that we approach making treatment decisions was based on what I'm referring to here as the old paradigm and that was using the tools that we had available to us until recently, a microscope and a ruler. So we would look at the size of the tumor, whether or not there was lymph node involvement and whether or not the cells had spread and that's that TNM staging system. A lot of people are concerned about what's the stage of my disease, 1, 2A, 3C. What does all of that mean?

The stage is just a rough way for us to get a sense of how much cancer is there. Stage, in and of itself, is not as important as we used to think it was and I'm going to spend a little time explaining that in a few minutes.

The other kind of information that we used to get from our microscope was a description of what those breast cancer cells looked like. So based on this somewhat qualitative and subjective interpretation by the pathologist and an estimate of how much cancer was present, oncologists would then make treatment decisions about what would be the best therapy for a patient following surgery or even before surgery.

We now know that we really have to make our treatment decisions based on a new paradigm and that new paradigm is looking at the molecular biology of the tumor cell, the DNA. Not that we inherit from our parents necessarily, but the DNA inside that cancer cell. What's making that cell tick? What's making that cell behave in a malignant fashion?

We know that there are many markers we can look at that give us a handle on the biology of the tumor cell and this is where we've now come to understand that the biology of the tumor is more important, in many respects, than the stage. You can have a very, very small tumor but it may be very aggressive in its' behavior. On the other hand, there can be tumors that get to be very large but may be very slow growing and very indolent and not aggressive and that's what we mean by biology trumps size.

Many of the factors we look at in this biologic paradigm are familiar to you. The type of cell of origin, ductal or lobular, whether the estrogen and progesterone receptor, the hormone receptors are expressed, the HER2/neu status and then some other issue like the proliferation index for Ki-67 which tells us how quickly that cell is growing. Next slide, please.

We now know that breast cancer is not just one disease but that there are many subtypes of breast cancer and there are at least five distinct molecular subtypes that we look at in a common way and this is a graph that shows that these different subtypes have very different biologic outcomes. Next slide, please.

So the decision about treatment, especially in early stage breast cancer, is who needs hormonal therapy, who needs chemotherapy, who needs biologic treatment? The data that we have used up until now for giving us information about making these decisions came from prospective randomized trials that have been done over many decades and we are extremely grateful to the women who have given of their time and their energy and have participated in these clinical trials to help advance the field.

But it's important to understand that when we look at clinical trials data, we're really looking at the results of what happened to large groups of women and that the information from a clinical trial cannot predict the outcome for an individual. It can only guide us about what happened to groups of women who may have had similar clinical presentations.

So, for example, in an early stage breast cancer which is estrogen-receptor Positive, we now know that not all women need chemotherapy and that in fact, even though the group of women in prior clinical trials seemed to do better if they had chemotherapy than the group of women who didn't, not every single individual benefited from that chemotherapy. So we want to be able to determine who are the people who really need that treatment? Next slide, please.

So we now want to tailor therapy to the individual patients to understand the biology of the tumor cells from the tumor in her body and then choose treatment that is effective at the same time that we're minimizing toxicity and promoting a full recovery. Next slide, please.

We now have available to us a number of assays that are called genomic assays and these are being used in early stage breast cancer. So far, these assays have been most helpful in cases where the estrogen receptor is positive and here, what we're trying to do is sort out, using either the Oncotype test or the MammaPrint test which are commercially available, which tumors really also need chemotherapy in order to be sure that we're preventing recurrence as much as possible. All patients with estrogen receptor positive disease will also receive hormonal therapy. Next slide, please. Next.

So, in choosing hormonal therapy as our first modality, we have to think a little bit about the biology of the whole female system and where that estrogen is coming from. In the pre-menopausal woman, most of the estrogen in the body is produced by the ovaries and the ovary gets a signal from the brain that says "make estrogen". That estrogen then circulates around the body and if there are cells that have estrogen receptors, the estrogen binds to those receptors and in the case of a cancer cell, sends a message to that cell which says, "whoa". In post-menopausal women, estrogen is still produced in the body, not so much in the ovaries, but in other tissues, predominately the adrenal glands and also in fat cells. I'll come back to that a little bit later on.

So when we look at options for hormonal therapy—next slide please—we have to look at the status of that woman. Is she pre- or post-menopausal and what would be

the best way of approaching turning off that message that estrogen is sending to the estrogen receptor?

In pre-menopausal women, we know that we can block estrogen action on the receptor using a class of agents called selective estrogen receptor modulators and tamoxifen is the drug that we use most commonly in this setting. It's a very, very effective drug. It's been around for a long time and we know how to use tamoxifen safely and effectively.

Another option in pre-menopausal women is to shut down the function of the ovaries to turn off that message that the brain is sending. We can do that medically by interrupting that signal using medicines like Zoladex or Lupron or triptorelin. There are a number of these that we give once a month by injection that can put the ovaries to sleep and shut down estrogen production by the ovaries. If we do that, we also have to use tamoxifen or an aromatase inhibitor and these are the agents that have been used in post-menopausal women to further reduce the amount of estrogen that's being produced.

There are a number of important clinical trials: the TEX trial, the SOFT trial and the Purchay (sp) trial which are, hopefully in the next few years, going to give us a lot of information about what is the best hormonal therapy for a young woman. Is it tamoxifen alone? Is it tamoxifen combined with ovarian ablation or is it one of the aromatase inhibitors combined with ovarian ablation? So there's still a lot of information that we need to learn about how to use hormonal therapy in young women.

There are other drugs out there that we can use, particularly once someone has already had tamoxifen or once someone has become post-menopausal, or in women who've had their ovaries removed. And sometimes, we do recommend that young women consider having an oopherectomy or removal of the ovaries particularly if there is a BRCA mutation and we're concerned about the risk of ovarian cancer. But there might be other circumstances as well when we consider removing ovaries in a pre-menopausal woman. In that case, we have the opportunity of using agents that down-regulate the estrogen receptor director and the drug that we use most commonly for that is called Faslodex or fulvestrant.

There are a lot of clinical trails going on now looking at the combination of other biological agents and Bortezomib (sp) is one of them, in combination with hormonal therapy, that may make these hormonal treatments work more effectively. Next slide, please.

Here's just an example of one of the drugs that we're looking at in combination with tamoxifen and the aromatase inhibitors. It's a drug called RAD-001 or everolimus. This medicine has already been approved by the FDA for treatment in other types of cancers, particularly kidney cancer, and now we're looking at combining this biologic agent, which shuts down different pathways in the cancer cell, with hormonal therapies.

In one important study called the TAMRAD trial that was done in women who had advanced breast cancer, we saw that the addition of everolimus to tamoxifen was superior to tamoxifen alone. In this study, there was an improvement in overall survival as well as in doubling the time to progression of disease. So that's a really important hint to us that maybe this combination would be useful in earlier stage disease even, perhaps, in preventing recurrence.

We're also looking at the combination of everolimus with aromatase inhibitors. This is a very promising agent and you'll be hearing more about it. The main side effects are that it can cause some rash on the skin and a little bit of diarrhea and some fatigue. But in general, it's pretty well tolerated. Next slide, please.

Chemotherapy, of course, is still a mainstay of treatment. Next slide. We use chemotherapy particularly when the estrogen receptor and progesterone receptors are negative or even if the estrogen receptor is positive. And by looking at that patient's individual tumor, we feel that there's a real benefit to chemotherapy, either based on a genomic assay or some other information we have about that cancer cell.

I'm not going to talk about the standard chemotherapy agents that we've been using but I just want to mention that within the last year or so, there are several new agents and combinations that have been FDA-approved and that we're using with great efficacy in the clinic. Eribulin or Halaven is one of those drugs. Ixempra, ixabepilone Exapolone is another one that shows a lot of promise and has already been used in women with advanced breast cancer. We're seeing excellent responses particularly when we combine Ixempra with Xeloda.

Of course, we're very interested and we've been hearing a lot about PARP inhibitors over the last few years. PARP inhibitors are biologic agents that work together with chemotherapy, not instead of chemotherapy, and seem to enhance the efficacy of chemotherapy in some settings. But there's a little more work that we have to do before these drugs are approved and become commercially available.

There's a big pipeline of agents that are still under investigation and I think that we'll hear some exciting results about new chemotherapy drugs that are being developed as well. Next slide, please.

In patients who have HER2-positive breast cancer—next slide—we have a number of ways of approaching the treatment of this disease. We very often give chemotherapy in the setting of HER2-positive disease and that chemotherapy is combined with trastuzumab or Herceptin.

Herceptin was the first treatment that was developed that targets this HER2/neu receptor and it is an extraordinarily effective treatment. There are other drugs that we know can help target the HER2/neu receptor, Tykerb or lapatinib is an oral drug. It's a pill that is very effective when used either with chemotherapy or in combination with Herceptin. Right now, Tykerb is used in the setting of recurrence but we're looking at it in the adjuvant setting that is in preventing recurrence, as well.

There are a number of new agents that are under investigation. Pertuzumab is a monoclonal antibody like Herceptin. It may work very well when it's combined together with either Herceptin or chemotherapy, and another oral drug called Neratinib that we're currently studying, as well, for targeting the HER2 molecule.

A drug that has recently been reported and will, I think, very soon come to FDA approval is T-DM1 and I'm sure many of you have heard this data already. T-DM is an antibody that sort of linked up with the chemotherapy drug and we already have excellent data that this agent is very, very effective when it's given to women who have HER2-positive breast cancer. In fact, it performed better than the combination of Herceptin and Taxotere in a phase II clinical trial. I won't go through the numbers here but you can come back and look at them on the slides. In the interest of time, I'll move to the next slide.

This slide is just a quick demonstration of where these different agents work at the cell surface. I'm not going to spend time on these chemical mechanisms but perhaps we'll save that for another teleconference. Next slide, please.

This is a recent update that was just published about two weeks ago in the New England Journal of Medicine and I think it's very important that we get this information out. This is an update on the very first trial that we've done looking at the question of Herceptin in early stage breast cancer in the adjuvant setting and Herceptin in this study was tested with two different chemotherapy regimens. One of them, the first regimen was the Adriamycin, Cytoxan and Taxol regimen, ACT, and that worked very, very well with Herceptin. The other chemo combination was called TC, in this case, Taxotere and carboplatin together with Herceptin.

There had been, I think, some bias and some concern that maybe the Adriamycin arm was better and that women with HER2-positive cancer should always get Adriamycin. But, in fact, this most recent update published by Dr. Dennis Slamon, the man who actually discovered or invented Herceptin, if you will, really showed in this study that TCH was absolutely equivalent to the Adriamycin treatment arm. It performed absolutely as well and there were fewer side effects. There was a lower incidence of heart damage from the treatment arm and there was a lower incidence of leukemia related to chemotherapy.

Now, let me just say that the incidence of heart failure and leukemia are very, very small to begin with. These are not major problems. Nonetheless, it looked like the TCH arm was, perhaps, a little bit safer and certainly equally as effective. Next slide, please. Next.

So I've been focusing a lot on drugs earlier throughout this talk but there is a lot that you can do actually to prevent recurrence if you've been diagnosed with breast cancer and maybe even to reduce your risk of getting breast cancer in the first place.

The number one risk factor that you have control over is your diet. We know that obesity is a significant risk factor for the development of breast cancer, particularly as women get older. If you've gained 45 pounds or more from the age of 18 until you get older in your adult life, that doubles your risk of breast cancer.

So those pounds creep up. With each decade, with each pregnancy, with each event in life we have to be very, very careful not to let those pounds add on and the reason for that is that fat cells produce and store estrogen and it also turns on other pathways in the body that have to do with insulin, with diabetes, with changing the balance of other hormones that act like growth factors that turn on inflammation pathways.

All of these things can stimulate the growth of cancer. It's really, really serious. This is not a joke. This whole conversation about the obesity epidemic in America is real and it's important for breast cancer, as well. So maintain a healthy weight. You can do that by diet and exercise.

Alcohol is another big risk factor, probably because it's related to the way estrogen is metabolized in the body and it's also really fattening so don't drink alcohol every day.

The other things that you can do just in terms of maintaining your own health and preventing recurrence if you have been diagnosed with breast cancer is to maintain good bone health. There's some controversy about whether or not maintaining a normal bone density actually will help prevent metastasis to the bone but we do know

that if the disease has already spread to the bone, it's important for us to keep those bones very strong and that does help prevent further progression in the bones. Next slide, please.

So I went through this very quickly. We don't have too much time left and we've already gone over. I want to leave a few minutes for Dr. Poynor so I'll let you take over now.

Shera Dubitsky: Dr. Oratz. Thank you very much. You know, there is so much information out there and women are saying it's just so overwhelming so I think that your discussion tonight really gives women an understanding that at the end of the day, treatment will really be determined by her own unique set of variables. So thank you for sharing that.

VI. Ovarian Cancer Updates
Elizabeth Poynor, MD, PhD, FACOG, Gynecological Oncologist, Private Practice

Shera Dubitsky: Our next speaker is Dr. Elizabeth Poynor. Dr. Poynor is a gynecologic oncologist and pelvic surgeon who focuses on the comprehensive surgical management of gynecologic cancers, and works with medical and radiation oncologists to facilitate a compassionate, multi-disciplinary approach to the management of women's cancers.

She has special expertise in the complex management of women and their families who have a genetic predisposition to developing breast cancer and gynecologic malignancies. As a surgeon scientist, Dr. Poynor's work focused on translating basic science principles into clinically meaningful treatments and she served as Director of Translational Research for the Gynecology Service at Memorial Sloan Kettering Cancer Center.

She has also served as an investigator in numerous clinical trials relating to surgical, medical and biological treatment of gynecologic cancers. We are also very privileged to have Dr. Poynor on Sharsheret's Medical Advisory Board and Dr. Poynor, the floor is now yours.

Dr. Elizabeth Poynor: Thank you so much for allowing me to review with you this evening and update you on the more recent treatment of ovarian cancer. Next slide.

Worldwide, there are approximately 240,000 women who are diagnosed with ovarian cancer each year and approximately 125,000 deaths. In the United States, there are approximately 21,000 who are diagnosed with ovarian cancer each year and approximately 16,000 deaths.

The average risk for a woman to develop ovarian cancer in her lifetime is 1.6 percent. However, women who have a personal history of breast cancer or a family history of multiple members with breast cancer or ovarian cancer may be at significantly elevated risk to up to 44 percent.

The five-year survival for ovarian cancer currently ranges from 30 percent for women who are diagnosed with advanced stage disease to 92 percent for women who are diagnosed with ovarian cancer confined to the ovaries. Unfortunately, currently still, approximately 75 percent of women who are diagnosed with ovarian cancer will have the disease which has spread beyond the ovaries at the time of diagnosis rendering the five-year survival up to 75 percent. However, the overall cure rate's lower at 30 to 30 percent. Next slide, please.

Surgery, combined with chemotherapy, remains the cornerstone of treatment for women who are diagnosed with ovarian cancer. Surgery for ovarian cancer is typically referred to as debulking surgery and is usually performed first with the goal to leave no residual disease behind and to extirpate all of the tumor including, many times, both ovaries. However, for younger women, we will sometimes preserve fertility and retain one ovary and the uterus.

The standard drugs for ovarian cancer treatment have remained over the past 15 years, up until quite recently, platinum combined with taxol and this has been established as the best treatment. We are now beginning to combine biologics in with this regimen.

Ovarian cancer is a very chemo-sensitive disease and approximately 80 percent of ovarian cancers will respond to upfront platinum and Taxol chemotherapy and up to 40 to 60 percent of women will have a complete response rate, meaning all residual tumor is dissolved with this type of chemotherapy. Next slide, please.

The new treatments related to ovarian cancer include screening, early diagnosis, and prevention strategies. Initial treatments are now, in addition to surgery, up front, neoadjuvant therapies in which chemotherapy is given up front in order to decrease the complexity of the surgery and decrease the side effects to the patient.

Antiangiogenesis treatments are now entering into upfront treatment with ovarian cancer and we'll review this in a minute. New techniques also involve the prevention of relapse with biologic treatments or extended cytotoxic chemotherapy. New treatments are also relating to the treatment of recurrent disease with incorporating more targeted or biologic treatments and we are now beginning to investigate BRCA1 mutation and BRCA mutation-specific treatments with the investigation and incorporation of PARP inhibitors. Next slide.

The PLCO trial was recently published in the United States and this is the prostate, lung, colorectal and ovarian cancer screening trial in which many women throughout the country were enrolled. The trial looked at yearly CA-125 combined with ultrasound screening for ovarian cancer and the trial basically found that the survival from ovarian cancer in early detection rate was not improved with yearly or annual screening with a CA-125 and an ultrasound.

Other trials including trials from the United Kingdom have really looked at the rate of rise of CA-125 over time, combined with ultrasound screening, also combined with risk stratification of a patient, to look at and determine if we can decrease the mortality from ovarian cancer with a combination of CA-125 and ultrasound screening.

These trials have been more promising and warrant further investigation. So currently, we still recommend for elevated risk individuals to have an ultrasound every six months along with the CA-125 over time. However, we need to look at the rate of rise of CA-125 over time and not absolute cutoff values.

There has been an increased focus on the identification of elevated risk individuals to develop ovarian cancer. Since 1984, when BRCA1 and BRCA2 genes were cloned, there's been a realization that we can actually begin to prevent ovarian cancer through prophylactic surgery, through the identification of women who are at significantly elevated risk.

It is also important to remember that ovarian cancer is a component of a Lynch Syndrome which Elsa also touched upon, in which we see colorectal cancers, other GI cancers, urologic cancers and endometrial cancers, along with ovarian cancer in the family.

This syndrome is due to mutations in mismatch repair genes and women who are numbers of Lynch families may have an up to ten percent change of developing ovarian cancer. More recently, mutations in the RAD51 gene which is a gene which is also involved in DNA repair similar to the BRCA1 and BRCA2 genes have also been identified in women who have ovarian cancer. It is currently estimated that women who harbor a RAD51 gene may have an elevated risk to develop ovarian cancer of approximately ten percent based on early risk estimates. So these would be women that we would also begin to talk to about heightened surveillance and potentially prophylactic surgery and its hopeful that we'll begin to have a genetic assay for mutations in this gene in the next few years in this country.

There's also been a real focus over the past five years on the realization that ovarian cancer, which was commonly thought of as a silent killer, actually has associated early warning signs and symptoms and is actually a disease that whispers. Many women who have ovarian cancer will report up to approximately a year before the diagnosis of their disease that they had subtle symptoms such as pelvic pain, pelvic pressure, maybe bladder pressure, urinary frequency, abnormal bleeding and sometimes, excessive fatigue reported before they were diagnosed.

So by getting the message out to not only women in the community but also physicians who care for women and healthcare practitioners who care for women, we need to listen to women a little bit better in terms of the early warning signs and symptoms of ovarian cancer and actively investigate symptoms which are persistent and new for a patient that don't resolve over a brief period of time.

Those people are really beginning to get this message out and so this is hopeful that we'll perhaps begin to pick up ovarian cancer earlier. Indeed, individuals in the United Kingdom who are running large screening trials are actually incorporating a questionnaire for early warning signs and symptoms of ovarian cancer in their screening programs and they have currently demonstrated that this is feasible. Next slide.

In prevention strategies, there's been an increased awareness of elevated risk for women to develop ovarian cancer and practitioners are really beginning to question women about their family histories. Women really need to be aware of their family histories for three generations so that they can review with their healthcare practitioners their individualized risk to develop the disease.

There has also been an increased acceptance amongst the medical community in performing genetic testing. Approximately six years ago, when I left Sloan Kettering, the only places that genetic testing were really being performed was at the academic institutions. Now, individuals and in private practice, not only in oncology, but also in general ObGyn and internal medicine practices are beginning to review with their patients their risk for developing ovarian cancer and breast cancer and reviewing with individuals genetic testing.

There's also an increased acceptance of prophylactic surgery. When I performed my first prophylactic surgery at Lenox Hill approximately six years ago, I was questioned why there was no pathology in the specimen of the ovaries that I was removing and had to answer to a pathologist and I told him that was a good thing that this was

prophylactic surgery. And since that time, there's been an increased awareness of prophylactic surgery amongst the medical community over the past five or six years.

Important questions, however, remain. These include who should counsel women? Should it be a genetic counselor, a nurse practitioner specialized in genetic counseling, a physician in an academic center or a community setting? And it's important that we educate our healthcare practitioners and individuals in our community so that they can be well aware of how to counsel women appropriately.

Elsa also touched on the question of: can we identify other risk factors that affect the penetrance of a BRCA1 or BRCA2 mutation? As you're well aware, not all individuals who have a mutation will go on to get cancer and indeed, only approximately 15 percent of BRCA2 patient women will go on to develop ovarian cancer in some families.

More recently, we're now beginning to question the type of surgery which is performed for ovarian cancer prevention. Next Slide.

Typically, prophylactic surgery has been removal of the ovaries and the fallopian tubes which leads to a surgically induced menopause and this can be quite life-altering for women who are premenopausal and those women who are not candidates for hormone replacement therapy after surgical removal of the ovaries.

We now are finding that ovarian cancer or a subset of ovarian cancer may actually arise in the distal end of the fallopian tube. A large study that was published in 2009 demonstrated that of the six percent of women who had cancer found at the time of prophylactic surgery, all of those women actually had the origins of the cancer in the distal fallopian tube.

So the etiology, or the origins, of ovarian cancer has actually been quite elusive because the cancer is usually more advanced by the time we find it and also, the ovaries are very difficult to look at. It's not like a colonoscopy where we can pick up a preclinical phase but we are now, based on these prophylactic specimens from women who have undergone surgery, beginning to question whether there is a subset or a significant portion of ovarian cancer which actually arises in the distal end of the fallopian tube.

If that's the case, we may be able to perform salpingectomies instead of oophorectomies. The fallopian tube does not produce hormones and this would allow women to retain their hormonal function after prophylactic surgery. Indeed, it's been hypothesized that we could prevent up to 20 to 30 percent of ovarian cancers in this country if women actually had their fallopian tubes removed at the time of hysterectomy if the ovaries are left behind and also, at the time of tubal ligation. So, not ready for prime time, yet, but definitely something that individuals and investigators are beginning to think about. Next slide.

Now, initial treatments of ovarian cancer have been primarily debulking surgery before the initiation of chemotherapy. However, some individuals might not be able to optimally debulked or down to residual disease of not being visible or less then one centimeter. This may be based on tumor characteristics such as location and extent of tumor or the patient may not be able to tolerate extensive surgery.

More recent data has suggested that chemotherapy, prior to planned surgery, is not inferior to surgery first. So it allows us to shift our paradigm a little bit and offer chemotherapy to women first in order to make the surgery perhaps less debilitating to

them. This is becoming a more accepted upfront treatment of ovarian cancer. Next slide.

(Inaudible) and taxane-based chemotherapy regimens remain the standard and have remained the standard for the past 15 years. Delivery of those regimens has changed, however. Approximately six years ago, a landmark paper was published which demonstrated that intraperitoneal therapy or belly wash chemotherapy for women with ovarian cancer actually led to a prolonged survival for women. So for women who can now tolerate the more intense chemotherapy and we prefer to delivery it via the intraperitoneal route combined with the intravenous route. Some women, however, are not able to tolerate this because it's associated with more side effects.

Japanese investigators have also looked at alternative ways to employ standard drugs and weekly Taxol which is actually an antiangiogenic agent, may be more effective than our (inaudible) Taxol that we give currently. More recent strategies in upfront treatment have targeted angiogenesis. Next slide.

Bevacizumab which targets the VEGF receptor has been used as a key target in the biologic treatment of ovarian cancer. Avastin or bevacizumab has been demonstrated to be a very active agent in ovarian cancer. In GOG 218 which is a large cooperative group trial from the United States, it was demonstrated that there was a better progression-free survival when Avastin was combined with chemotherapy and initial treatment, and extended for approximately ten months after the initial treatment.

ICIB7 which, again, is another very large international multi-institutional trial also demonstrated a survival benefit in patients who were not only optimally debulked but who were suboptimally debulked at their initial surgery.

These two large trials also demonstrated that the toxicity of Avastin is acceptable in individuals with ovarian cancer and now the current question remains on how we combine Avastin with our other treatment options with IP therapy or using Avastin combined with weekly Taxol or with other biologic agents. Next slide.

Investigators have also focused on prevention of relapse because we know that approximately 50 percent of women who have a complete response with advanced stage disease will relapse within approximately two years of their initial chemotherapy. We've looked at the extension of cytotoxic chemotherapy which has demonstrated some progression-free survival but not necessarily overall survival. However, biologics with less or lower side effects actually offer a new opportunity to prevent relapse. Investigators are actively looking at vaccine therapies, antiangio-genesis therapies and other targeted therapies such as PARP inhibitors. Next slide.

Chemotherapy has been the standard treatment of recurrent disease. However, there's an increasing recognition throughout the community that surgery actually may be a good option for some women who have a prolonged disease-free interval or who have disease which can be completely removed.

The goals of surgery for recurrent disease as for upfront treatment include complete removal of all tumors in an aggressive fashion. Questions remain how do we provide surgery and secondary and tertiary debulking surgery with newer biologic agents? Next slide.

Bevacizumab or Avastin has also become very promising in the treatment of recurrent ovarian cancer and recently, lead investigator Carol (inaudible)

demonstrated that treatment of the current disease was platinum-based therapy combined with gemcitabine or Gemzar, and Avastin was actually better than carboplatin and gemcitabine alone, leading to a longer progression-free survival.

As with upfront treatments with Avastin as an antiangiogenis treatment in ovarian cancer, we still don't know how this prolongs progression-free survival translates into overall survival.

Other promising drugs in the treatment of ovarian cancer include PARP Inhibitors, especially for those women with a BRCA1 or BRCA2 mutation, potentially women who have a RAD51 mutation when they're with other tumors that demonstrate a decreased expression of BRCA1 and BRCA2 proteins.

CI3 kinase inhibitors are also promising in the treatment of recurrent disease as well as mTOR inhibitors. Next slide.

Molecular targets are really where we are moving in the treatment of ovarian cancer. Drug resistance is a very large question in these treatment strategies and how do we overcome this? Because the way, a cancer cell that is wired is very complex and there is a redundancy in the signaling pathways and this redundancy can lead to the large problem of drug resistance. A specific mutation can develop which can overcome the efficacy of a drug. Alternative signaling pathways can also be turned on when you shut down one pathway with a biologic agent and another pathway may take over allowing the cells to continue to grow out of control.

So now we know how some biologic agents which we know are active in ovarian cancer and the question is how do we combine them with other biologics or other cytotoxic chemotherapies? Investigators are looking at what we call horizontal strategies are targeting multiple pathways at once, or vertical strategies where we interrupt one signaling pathway at multiple points.

One of the questions that also remains is how do we assess the treatment success of these biologic treatments? We've looked at shrinkage of tumor and as a response criteria that we measure for cytotoxic chemotherapy but we have to reset our minds that stability of tumor for biologics for ovarian cancer actually may be a signal of success. Next slide.

So, improvement in treatment has been incremental with ovarian cancer. Fifteen years ago, we discovered that platinum Taxol was the way to treat ovarian cancer. We are now moving into the world of biologics where we're seeing a better survival with women who are treated with antiangiogenesis drugs including Avastin. We are currently at a point where we can characterize the molecular aspects of a tumor and we now realize that not each ovarian cancer is the same and it is actually a heterogeneous disease with a different molecular profile for each tumor.

Now that we realize that ovarian cancer is heterogeneous and each has its own specific molecular footprint, we can now leap into the future and we can transition from what we call oncogenomics, where we're actually describing things, to mechanism-based (inaudible), which are targeted to specific aberrations in the tumor.

Questions which are currently being investigated for ovarian cancer is how do we best incorporate angiogenesis inhibitors in biologic agents and how do we overcome drug resistance? We're going to answer these first with Avastin which is the most well studied, then with the PARP inhibitors, and then with other biologics after this.

So thank you for allowing me to give a summary this evening.

Shera Dubitsky: Thank you Dr. Poynor. We get phone calls from women saying that the information about ovarian cancer seems to be very scarce and difficult to come by so we appreciate you shedding light and bringing the information about ovarian cancer to the forefront. And I'm glad that people will be able to access that and not just this evening but when our transcript is posted. So thank you for your time.

VII. Question & Answer Session

Shera Dubitsky: Due to the late hour, we have actually received many questions but I'm going to actually try to merge them into one question and perhaps, each one of the panelists can share their thoughts. It's interesting that I'm seeing a trend in the questions and a lot of them actually have to do with the next generation. So I was wondering if everybody on the panel can comment on it in terms of the focus of your discussion.

So we are getting questions about at what point should the next generation and at what age should children be tested for the BRCA? At what age should adult daughters who have a family risk get screened? At what age should we be talking about these risks? I think, Dr. Oratz, that you were referring to at what age should we be discussing these things with the next generation?

So if each one of you can comment on that because that seems to be the trend and all the other questions that we've received, we will forward them to the panelists and we will post the answers when we put up the transcript.

So Elsa, I guess we'll just do it in the order that we spoke. Elsa, maybe if you can just really very briefly address that issue?

Ms. Elsa Reich: I'd be very happy to and it's something that I think a great deal about because more and more, I'm seeing a lot of young women who are considering, and I underline considering, genetic testing and I rarely see young women who are under the age of 20. I think that's early.

But I think it's important thing that a parent or other relative should be talking with the young women in the family and helping them to understand that even though this can be an anxiety-provoking situation, it has a benefit and because we recommend that surveillance start at about 25 years of age, that's the current recommendation, I think that a young woman should at least discuss genetic testing.

Now, some of the other panelists may not agree with me on my point of view but I believe that a young woman has a choice that she can make. She doesn't have to have genetic testing when she's 25 years old. But if she has a 25 or 50 percent chance to be a carrier, I would strongly recommend that she, at least, initiate the appropriate surveillance because at that point, I'll take a flying leap and say, I don't think that people will be recommending that she remove parts of her body. But it's very important that she be followed and especially if there's very early onset of cancer in her family.

However, some women have told me that they're having the testing at that point, not because they really want to, but because they want the benefit of the encouragement from knowing that they're a carrier, for example, to do the screening. Because they're afraid that if they don't know and they can say to themselves "well maybe I'm not really a carrier", they won't do the screening as we recommend.

So I think that it's important to share that information with your daughters, help them understand and to encourage them to consider it for themselves.

Shera Dubitsky: Great. Thank you, Elsa. Dr. Kolb, what are your thoughts about that in terms of screening for the next generation?

Dr. Thomas Kolb: In terms of high-risk patients, we start screening 10 to 15 years before the age of onset of cancer diagnosis in the primary family member, whether it's the mother, generally there's a sister, or so on. We don't start below the age of 25 to 27.

So in women that are very high risk and that are young, meaning that they meet the American Cancer Society criteria of 20 to 25 percent risk of developing breast cancer, those women would have annual MRIs. So those women, again, who are above the age 25 to 27, at least over 27, I would say, they should have mammograms yearly if they're dense and the majority of those women will be dense. They should have a bilateral breast ultrasound at the same time as the mammogram to reduce the false negative rate of mammography.

Six months after that I would do a breast MRI. Again, if she meets the American Cancer Society criteria and then alternate mammogram and sonogram with MRI at six-month intervals.

For those patients who drop out or don't want to have MRI for various reasons, financial reasons if insurance is not covering it, claustrophobia, not wanting an intravenous injection and so on, I do substitute ultrasound at six months, as well, and those patients will have an annual mammogram and two screening ultrasounds, one at the time of the mammogram and one additional one at six months.

So that's basically the scheme that we use for high-risk women.

Shera Dubitsky: Okay. Thank you. Unfortunately, Dr. Oratz had to go but Dr. Poynor, perhaps you can take it from the perspective of an oncologist. At what point should these women be having conversations with I guess maybe their teenage daughters or adult daughters, about proper self-exams, proper screenings, just in terms of proper lifestyles? At what point should they be having those kind of conversations?

Dr. Elizabeth Poynor: I think every individual is different and every family is different. I think the maturity level of the young women and the relationship that the younger women has with her mother or other family member will really set the appropriate time for that individual.

It can cause a lot of anxiety in younger women who are undergoing these discussions and testing but I also point out that it can provide them a wealth of information so they're able to initiate their best cancer screening earlier and their ovarian cancer screening. From my standpoint, it also allows them to initiate family planning earlier.

Because we don't have great screening techniques for ovarian cancer early detection, women who are delaying child bearing who are at high risk to develop ovarian cancer, are at risk for developing the disease while they're delaying their child bearing.

So typically, what I would do with my family members is have a conversation with the parent of the child and then we come up with a plan at what age do they feel that it's appropriate for their specific children. Certainly, by the age of 22, those conversations

have really coalesced and have come to fruition by the age of 22. Because we begin to initiate screening at the age of 25, certainly by the age of 25, if an individual is going to consider genetic testing, those very serious conversations should occur.

I think that if a woman doesn't understand her risk, it actually provides a little bit of a disturbing sense in terms of her ability to plan her family because the lack of screening technologies for ovarian cancer prevention strategy, for ovarian cancer in very elevated risk women, unfortunately, is to remove the ovaries currently. So hopefully, those discussions have occurred in a very earnest fashion by the age of 25.

VIII. Teleconference Conclusion
Closing Remarks

Shera Dubitsky: Great. Thank you very much and thank you to all our panelists.

As we conclude, we request that you complete the online evaluation that you will be receiving in your emails. We grow our programs and services based on the valuable feedback that we receive from you and, in fact, tonight's event is a direct result of responses from prior evaluations and conversations with our staff. So we really want to thank all of you for partnering with us in this endeavor.

Finally, we invite you to visit Sharsheret's newly updated website at www.sharsheret.org. We're very excited by the new look and also by the fact that it's interactive and, more importantly, by how we can support you online.

One woman shared the following email,

"Last night, I was sleepless and could not stop my mind from racing. I went on to the Sharsheret's website which kept me company all night long. By morning, I had found the strength and courage to keep going."

We hope that you have all found strength, courage and insight this evening and, again, we want to thank our esteemed panel for their generosity of wisdom and time, and we want to thank all of you for joining us this evening.

Have a good night. Take care.

IX. Speaker Bios

Shera Dubitsky, MEd, MA is the Clinical Supervisor at Sharsheret. Shera assists women newly diagnosed and at high risk of developing breast cancer, provides supportive counseling to women living with metastatic breast cancer, and lectures nationally on topics addressing the needs of women facing serious illness. Prior to joining the Sharsheret staff, Shera worked as a researcher at Memorial Sloan-Kettering Cancer Center.

Thomas M. Kolb, MD, is widely regarded as a leader in the field of women's health care and imaging. For 15 years he served as assistant clinical professor of Radiology at Columbia University College of Physicians and Surgeons and is in private practice in New York City specializing in the detection and diagnosis of breast cancer in young, predominantly high-risk premenopausal women. Dr. Kolb has achieved double board certification, having received his training in pediatrics at the Albert Einstein College of Medicine in Bronx, New York, and in diagnostic radiology at the Columbia-Presbyterian Medical Center in New York. Dr. Kolb has been on the faculty of numerous medical educational meetings, and he has lectured throughout the U.S. and internationally on the topic of breast cancer detection and diagnosis. He holds positions on the board of directors of the Breast and Prostate Cancer Research Foundation in New York, and the medical advisory committees for the Young Survivors Coalition, the Susan G. Komen Foundation (NY) and Sharsheret. Dr. Kolb is an original founder of the New York Breast Cancer Study and was co-author of its research publication "Breast and Ovarian Cancer Risks Due to Inherited Mutations in BRCA1 and BRCA2". Dr. Kolb has investigated and published original research detailing the use of multiple new technologies, including infrared and electrical impedance imaging specifically for the detection and diagnosis of breast cancer.

Kutluk Oktay, MD, FACOG, is one of the world's foremost experts in fertility preservation as well as ovarian stimulation and in vitro fertilization for infertility treatments. Dr. Oktay has devoted his professional life to the science of fertility preservation and infertility treatment. He is a world-renowned researcher, a gifted medical educator, and a skilled clinician dedicated to his patients. Dr. Oktay was invited to the President's Cancer Panel as an expert on fertility issues of cancer patients and fertility preservation. Furthermore, he was named the co-chair of the American Society of Clinical Oncology Committee for Fertility Preservation Guideline for People with Cancer. In 2008, after a 10 year career at the Weill Medical College of Cornell University, Dr. Oktay became a Professor of Obstetrics & Gynecology and the Director of Division of Reproductive Medicine & Infertility at New York Medical College/Westchester Medical Center and founded the Center for Reproductive Medicine and Institute for Fertility Preservation (CRM-IFP). He also was named a Consultant Physician at Memorial Sloan-Kettering Cancer Center, and a Consultant for Cancer and Allied Diseases at Memorial Hospital. Dr. Oktay has published extensively in top medical journals, such as the New England Journal of Medicine, Lancet, JAMA, and Journal of Clinical Oncology. He regularly lectures around the globe and has repeatedly received the Top Doctors awards around the country.

Ruth Oratz, MD, FACP, is a medical oncologist specializing in the treatment of breast cancer. She is Clinical Associate Professor of Medicine at the New York University School of Medicine and Director of the Women's Oncology and Wellness Practice. Her research interests are focused on breast cancer clinical trials and the genetics of breast cancer. Dr. Oratz has been practicing medical oncology for more than 20 years and established The Women's Oncology & Wellness Practice, a unique environment that provides state-of-the-art medical care in an intimate, personal and private setting. Dr. Oratz is especially committed to helping the woman facing cancer continue to live her life actively and fully. Her practice addresses women's concerns about family life, career, relationships and sexuality. Dr. Oratz is a Diplomate of the American Board of Internal Medicine, is board certified in Internal Medicine and Medical Oncology. She is a Fellow of the American College of Physicians. She is on several advisory boards of organizations dedicated to education and support for women and their loved ones as they cope with the breast cancer experience. She is the Chair of the Medical Advisory Board of Susan G. Komen Greater New York and also is on the medical boards of breastcancer.org, Living Beyond Breast Cancer, CancerCare, Sharsheret, and the Metastatic Breast Cancer Network of New York.

Elizabeth Poynor, MD, PhD, FACOG is a gynecologic oncologist and pelvic surgeon who focuses on the comprehensive surgical management of gynecologic cancers and works with medical and radiation

oncologists to facilitate a compassionate, multidisciplinary approach to the management of women's cancers. She has special expertise in the complex management of women and their families who have a genetic predisposition to developing breast cancer and gynecologic malignancies. As a surgeon scientist, Dr. Poynor's work focused on translating basic science principles into clinically meaningful treatments and she served as Director of Translational Research for the Gynecology Service at Memorial Sloan-Kettering Cancer Center. She has also served as an investigator in numerous clinical trials relating to surgical, medical, and biological treatment of gynecologic cancers.

Elsa Reich, MS, CGC, has been a genetic counselor at NYU for 37 years and has provided care for patients with a wide variety of genetic concerns. She has been the genetics consultant to the Institute for Reconstructive Plastic Surgery since 1975 and has provided prenatal consultations, pediatric and adult consults for a variety of heritable conditions. She began to provide genetic counseling to individuals concerned about hereditary predisposition to cancer in the mid-90s. She has taught in the Sarah Lawrence Human Genetics Program and the Genetic Counseling Program at Mt. Sinai Hospital and extensively at NYU. She has spoken at numerous conferences and outside venues both to the lay public and to professional groups. She has been active professionally as a member of American Board of Genetic Counseling, a board member of the National Society of Genetic Counseling and New York Genetics Task Force.

X. About Sharsheret

Sharsheret, Hebrew for "chain", is a national not-for-profit organization supporting young women and their families, of all Jewish backgrounds, facing breast cancer. Our mission is to offer a community of support to women diagnosed with breast cancer or at increased genetic risk, by fostering culturally-relevant individualized connections with networks of peers, health professionals, and related resources.

Since Sharsheret's founding in 2001, we have responded to more than 24,000 breast cancer inquiries, involved more than 1,400 peer supporters, and presented over 200 educational programs nationwide. Sharsheret supports young Jewish women and families facing breast cancer at every stage—before, during, and after diagnosis. We help women and families connect to our community in the way that feels most comfortable, taking into consideration their stage of life, diagnosis, or treatment, as well as their connection to Judaism. We also provide educational resources, offer specialized support to those facing ovarian cancer or at high risk of developing cancer, and create programs for women and families to improve their quality of life.

Sharsheret offers the following national programs:

The Link Program

- *Peer Support Network,* connecting women newly diagnosed or at high risk of developing breast cancer one-on-one with others who share similar diagnoses and experiences
- *Embrace*, supporting women living with advanced breast cancer
- *Genetics for Life,* addressing hereditary breast and ovarian cancer
- *Busy Box,* for young parents facing breast cancer
- *Best Face Forward,* addressing the cosmetic side effects of treatment
- *Sharsheret Supports*, developing local support groups and programs
- *Family Focus*, providing resources and support for caregivers and family members
- *Ovarian Cancer Program*, tailored resources and support for young Jewish women and families facing ovarian cancer

Education and Outreach Programs

- *Health Care Symposia,* on issues unique to younger women facing breast cancer
- *Sharsheret on Campus,* outreach to students on campus
- *Facing Breast Cancer as a Jewish Woman*, an educational resource booklet series

XI. 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.

The information contained in this document is compiled from a variety of sources ("Information Providers"). Neither Sharsheret, nor any Information Providers shall be responsible for information provided herein under any theory of liability or indemnity. Sharsheret and Information Providers make no warranty as to the reliability, accuracy, timeliness, usefulness or completeness of the information.

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