Breaking Boundaries: Vaccine Breakthroughs in BRCA and Breast Cancer Prevention

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Presented by:

SHARSHERET®
The Jewish Breast & Ovarian Cancer Community

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Jenny Stein: Thank you guys so much for joining tonight. I know we're still letting people into the room, but wanted to get started just because we have a lot of material to cover and want to make sure that we're able to get to everything. I'm Jenny Stein. I'm the Midwest Regional Director for Sharsheret. Thank you so much for joining us this evening for our webinar **Breaking Boundaries: Vaccine Breakthroughs in BRCA and Breast Cancer Prevention**. This is our opening webinar for our 2024 Sharsheret Summit, which brings together thousands of people, virtually and in person, throughout the US and Israel from October 9th through November 10th. We hope you'll be able to join our national and virtual webinars on the hottest topics in breast cancer and ovarian cancer, attend or host an in-person education or awareness raising program with one of our community partners, learn more about screening guidelines, and access the most up-to-date data and materials in our digital resource packet. However you choose to participate in our Sharsheret Summit, it is the source for the latest information on breast cancer and ovarian cancer.

So I want to first start by thanking our Sharsheret Summit's sponsors, AstraZeneca, Daiichi-Sankyo, Merck, Pfizer, City of Hope Orange County, Eisai, Northwell Health Center Institute, and RMA of New York and Long Island. We now have a special message from our Sharsheret Summit lead sponsor, Daiichi-Sankyo.

Stephanie, we can't hear.

Hold on one second. Sorry about that.

Gissoo Decotiis: Of our entire team. My name is Gissoo Decotiis. I'm the Global Head of Advocacy and Strategic Relations at Daiichi-Sankyo. On behalf of our entire team, we are honored to partner with Sharsheret year round and be part of its National Summit. Sharsheret's model to provide emotional support, educational resources and financial assistance ensures those living with breast and ovarian cancer have the knowledge and support needed to make informed decisions about their care. This includes vital genetic testing for Jewish women and their families who understand their risk while also advocating for precision medical treatments that could potentially alter their outcomes. Sharsheret's commitment to personalized support for those living with cancer mirrors Daiichi-Sankyo's mission to contribute to the enrichment of quality of life around the world while addressing diverse medical needs. Together we share a deep compassion for patients and by combining our strengths, we empower those at increased genetic risk to not only manage but thrive in their health experiences. Thank you for allowing us to be part of this essential work as we continue making a meaningful difference in the lives of those affected by cancer.

Jenny Stein: Thank you so much. Along with our Sharsheret Summit partners, I want to also just take a moment to thank our Summit national partners who have really partnered with us to help spread the word and educate around breast and

ovarian cancer. So thank you so much. And before we begin, just a few housekeeping items. Our webinar is being recorded, and it will be posted on Sharsheret's website along with a transcript. Your faces and names will not be in the recording. If you would like to remain private, you can turn off your video and rename yourself or you can call into the webinar. My colleague is putting those instructions in the chat box now. You may have also noticed that you were muted upon entry. We do ask that you stay muted throughout the presentation. If you have any questions, please put them in the chat box either publicly or click on Sharsheret, and you can send us a private question.

We already received some questions prior to the webinar and we anticipate that there'll be more in the chat box, and we'll do our best to answer all the questions. Please make sure if you are putting a question in the chat box that it's a general question as we can't offer any specific medical advice. As we move into the webinar itself, I also want to remind you that Sharsheret is a national, not-for-profit cancer support and education organization, and we do not provide any medical advice or perform any medical procedures. So the information that you guys will hear tonight, it's not a substitute for any medical advice or treatment for any specific medical condition, and you should not be using this information to diagnose or treat any health problem. If you have any questions that are specific to your medical care, the speakers tonight will not be able to address those specifics. And therefore, we would advise that you speak to your medical provider and always seek the advice of your physician or a qualified health provider with any questions you have regarding a medical condition.

And now we are so honored to learn about cancer vaccines from three incredible women, Kristen Dahlgren, Dr. Betsy Levick, and Dr. Susan Domchek. Unfortunately, Dr. Kiran Dhillon, the Executive Director of the Cancer Vaccine Institute at University of Washington, was unable to join us this evening, but we are gratefully appreciative of Dr. Levick for her flexibility tonight to be here. So Kristen Dahlgren is an award-winning journalist turned breast cancer advocate and founder of the nonprofit Cancer Vaccine Coalition. The Cancer Vaccine Coalition partners with the nation's top vaccine and cancer researchers with the goal of bringing a breast cancer vaccine to market in five to 10 years.

Dr. Betsy Levick is a recently retired radiation oncologist from the Oncology Hematology Care in Cincinnati, which is a multidisciplinary cancer treatment center that serves the tri-state area of Ohio, Kentucky, and Indiana. She's specialized in the treatment of women's cancers. She's currently the Chairman of the Board of Directors at Oncology Hematology Care overseeing 40 physicians and is on the Board of the Cancer Vaccine Coalition. And Dr. Susan Domchek is the Executive Director of the Bassar Center for BRCA at the Abramson Cancer Center, as well as the Director of the Mariann and Robert MacDonald Cancer Risk Evaluation program, which are both through the University of Pennsylvania. Dr. Domchek's work focuses on genetics and the treatment of people with an increased hereditary risk for cancer. So each of our speakers will give a

presentation, and then we will have time at the end for a question and answer session. So I'm going to turn it over now to Kristen Dahlgren.

Kristen Dahlgren: Thank you. And I'm so happy to be with everyone. I never thought I would be included in this amazing group of physicians talking about curing cancer. I still ask myself every day, what is a journalist doing talking about cancer vaccines? This was me a few years ago as an award-winning journalist for NBC News. I traveled the world reporting. And then on January 30th of this year, I did something crazy. I went on the Today Show and announced that I would be leaving my dream job that I'd worked so hard to get to because I needed to do something to help accelerate breast cancer vaccines.

Why? This was me in 2019. I was diagnosed with stage two breast cancer. I went through eight rounds of AC-T chemo. I had a double mastectomy, did 25 rounds of radiation. Since then, I've had six surgeries including LVA deep flap, a revision of that, a flap removal, implants, and more revisions. It's definitely been a journey. Today I am still feeling the impact of breast cancer. Probably like many of you out there, I have no feeling in my chest, my abdomen, part of my lower leg is numb. When I lift my arm, it's really difficult. I have limited shoulder mobility, some lung fibrosis from the radiation, and I'm in chemically induced menopause, which is not really all that much fun. And I'm one of the lucky ones. One in eight of us in this country will be diagnosed with breast cancer, but I really feel like it's been normalized.

And if you look at these stats every two minutes, someone in the US is diagnosed with breast cancer. One in 40 is a woman's chance of dying from breast cancer in this country, and one in three new female cancers in the US will be from breast cancer every year. And so there really is nothing normal about breast cancer. Through my reporting on NBC, I was lucky enough to be introduced to Dr. Nora Disis at the University of Washington's Cancer Vaccine Institute, and she really blew my mind in our conversation and started me down this path. She told me that breast and other cancer vaccines are in development, that many of them are already in clinical trials. She has many cancer vaccines already in phase two clinical trials. And that researchers like her predict that with the right support, we actually could have breast cancer vaccines to market within five to 10 years.

But key in that statement is “with the right support”. Without it in the current system, we've unlocked the science and cancer vaccines are very likely coming, but it could be 25 to 30 years. And so for me, that was just too long to wait. She told me about some of the trials they're doing, and I know Dr. Levick will get into this more, but we know that breast cancer vaccines are already saving lives. At the University of Washington, 10 years ago, they did a study, a phase one clinical trial of 66 women with advanced HER2 positive breast cancer. They looked again at 10 years after that vaccination. 85% of those who got the most effective dose are still alive. They actually had a reunion, and these are some of the pictures

from that reunion when the median survival rate for that late stage, HER2 positive breast cancer is only five years. So really some incredible results in a small study.

So we asked what do we need to do to advance the science? And really quickly, we brought these top researchers together. So we have Kiran Dillon and Dr. Disis from the University of Washington, Dr. Larry Norton from Memorial Sloan Kettering, Beth Mittendorf from Dana Farber, Powell Brown, and Paula Pullman from MD Anderson, Tom Budd from Cleveland Clinic and Shipra Gandhi from Roswell Park all coming together as part of our coalition. We've since then had one of Dr. Domchek's colleagues, Julia Chu from UPenn who wants to be a part of it and told us about her research. I'd like to invite Dr. Domchek to join us as well and talk about the vaccines that she's developing. All of these researchers get together every few weeks. They talk about the science, they make suggestions, and by working together, by collaborating, I think we really could move things forward.

At Cleveland Clinic, they're also working on cancer vaccines, trialing them in BRCA positive patients as well. And they're working a little bit differently than the University of Washington with the retired protein hypothesis. So the idea is that with age, we retire proteins that we no longer need like pigment. Many of them are organ specific and associated with reproduction so breast, ovary, testes, and prostate. These organs are ones that of course have high incidence of cancer. And so the conditions provide a strategy for autoimmune based cancer vaccines according to the Cleveland Clinic. So they're working with something called alpha-lactalbumin, which is a protein in human milk produced by the mammary gland and only during lactation after our childbearing years, there's little risk of expression in healthy women. But they notice that in many breast cancers, especially in early triple negative breast cancer, they're seeing significant levels of alpha-lactalbumin.

And so they decided that that meets the criteria for an antigen in an effective cancer vaccine. So that's what at Cleveland Clinic they've been trialing in both metastatic triple negative breast cancer and also for BRCA positive patients. So a lot of researchers across the country have been working on this type of thing. You may ask why now, and there are a few reasons. One is we have a better understanding of the immune system than we ever have. We know which parts of the cancer can be targeted to teach our immune systems to fight it. And then thanks to the COVID vaccine development, we now have safe and approved vaccine delivery methods like mRNA. So this moonshot idea is happening. The UK is already placing 10,000 cancer vaccines through clinical trials by 2030. It's a massive national effort in many different cancer vaccines, and we've seen a lot of headlines both from the UK and from Europe.

The World Economic Forum is calling this a historic leap in cancer vaccines. They're touting the world's first lung cancer vaccine trial. So the University of

Washington has already been working on lung cancer vaccines. This is a growing field in cancer research. Glioblastoma, that you can see there on the bottom right, something that we never thought that we would be able to see these effective treatments they're developing for vaccines for as well as in prostate cancer as well. So what we want to do, this idea of the Cancer Vaccine Coalition, is can we do what the UK is doing here and how do we do that? And we think of ourselves kind of as a hub. So we've got the researchers who are working on it, coming together talking about it. We're bringing in industry to support what they're doing. Industry, ultimately, pharmaceutical companies have to manufacture and scale these vaccines.

We want to get trial participants aware of what's out there so that we can fill trials really quickly when we are able to fund them. So we're also raising the money to try and bridge this gap, what's often called the Valley of Death for vaccines in the phase two area. So if we can fund some of those trials, we'll move them through much quicker. And then the government, I've been to the White House twice in the past year. I've talked to the NIH and the NCI trying to get the government also to play a role in moving these things quicker, much like they're doing in the UK. So it's streamlining the pipeline, taking established concepts, things that are already into clinical human trials, enrolling the studies quickly, deciding quickly go, no-go decisions, whether something's working and then working with the FDA to try and provide a road map for approval like they did during COVID.

Again, COVID was a great example of how collaboration took 10 years of science into eight months. We think we can do the same thing in cancer vaccine research. So if we did that, if we got a breast cancer vaccine to market in 2030 instead of 2050, according to what the predictions are for the current system. That is 860,000 lives saved in the U.S. alone. If you know someone who has breast cancer, if you are someone who has breast cancer, those statistics really mean something because those are real people that we could save. Someone said to me recently, and I've adopted this quote, "If we lost a small commercial jetliner every day, we would find a better way to fly the plane. We lose 114 lives to breast cancer every day. That's the equivalent of that small commercial jetliner. So we really need to find a better way to fly this plane." And we hope that's what we're doing. So a lot of people are asking...

Jenny Stein: Sorry if you just don't mind trying to wrap up your comments. I know you have a video you want to show too, but just to make sure we have time for everyone. Thank you.

Kristen Dahlgren: Got it. So this is my last slide, and then we have that video. So the question you ask a lot of times when you're diagnosed is why me? And the answer ultimately is, well, why not you? And so I say that same thing with finding a cure for cancer. Why me? Why a journalist? Well, why not any of us? And together, I really think that we can do that. So here's a picture of my eight-year-old. She's the reason

why I really want to create a cancer-free future. And then, sorry, let me start this over. This is one of our volunteers and someone who is part of this “Give us a Shot” campaign that we're really proud of. And it's women telling their stories and men with breast cancer.

Alli Leonard: I'm Ali Leonard. I was diagnosed December 2023, two weeks before my 39th birthday. That was the first thing that I thought, what about my kids? What are they going to do without their mom? She finally broke down and told me, I just miss the way you used to be, mom. Yeah, I miss that person too. And I think that's the hardest part is that you know that you're never going to be truly that same person again. At what point will I ever not be thinking about cancer? A cancer vaccine would give me a shot at getting my peace back. It's mind blowing. That's a thing that I had never heard of. I want a shot at watching my kids grow.

Kristen Dahlgren: So we all deserve a shot. We're inviting people to make their own videos and send them to us. And we're really looking forward. Tag us and thank you for listening.

Jenny Stein: Thank you so much, Kristen. And we'll now hear from Dr. Levick.

Dr. Betsy Levick:: Hi, thank you. I'm honored to be here tonight and I'm trying to simplify vaccines in about 10 minutes, so hang with me if you will. All right, let's start, Jenny. What we're going to talk about this evening is the goal of vaccines and the prevention and treatment of cancers. And obviously, vaccines have had a profound impact on human health. In polio, in smallpox, we've practically eradicated the diseases. HPV vaccines, we are going to get rid of many of the HPV driven diseases such as cervical cancer and some head and neck cancers and some anal cancers. So many diseases that cause serious harm or death 50 years ago have almost been eliminated. This is the important line. Vaccines can also train the immune system to recognize cancer as a threat and create a tumor destructive immune response. Remember, vaccines are going to be working on your immunity and your immune response as opposed to chemotherapy. Next slide.

Kristen touched on this. We're at a tipping point for cancer vaccines. We know the type of immune response we now need to kill cancers. We know what parts of a cancer cell can stimulate the immune system. So if you look at these little yellow creatures on the outside of the cell and the inside of the cell, that's what we're targeting. And finally, we have new vaccine technology, which makes immunization much more effective. Next slide.

How do we create these vaccines? Well, it's important to know that cancers have proteins that drive cancers to be cancers. They drive cancers to grow, they drive cancers to do all sorts of bad things. We need to predict which protein segments have the right response. And then we barcode for the effective cancer vaccine that can really go after some of these driver proteins, some of these

proteins that are making these cancers bad actors. We then look at multi antigen cancer prevention and treatment vaccines. You'll see as we go through the slides. Initially we were targeting one bad protein, and now we're working on targeting more proteins with each vaccine. Next slide please.

Vaccines for the most common and deadly cancers in clinical trials, we touched upon breast cancers being trialed, ovarian cancer, lung cancer, we have good vaccines for melanoma. We're working on colon cancer, bladder and prostate. So what is the role of vaccines in cancer? They're going to be used to treat cancers, prevent cancer from recurrence in patients who have had cancer. We don't want this recurring, and overall prevent cancer from occurring in the first place. So high risk patients, how do we prevent a cancer from occurring? Next slide, please.

The vaccine to prevent breast cancer recurrence. This is I think a great slide. And this is the study that Kristen briefly talked about. If you look at breast cancers, whenever anyone's diagnosed with breast cancer, there is at least three things we always test for, so there's a myriad of testing going on. We look at estrogen and progesterone receptor status as well as whether or not HER2 protein is being expressed. And if you look at a normal cell to the left, it only has a few HER2 receptors, and two HER2 genes. If you look at the cell that is over-expressing HER2, there's lots of these little green things on the outside of the cell, plus there's more HER2 genes present. So if we can come up with a HER2 vaccine that is an ICD, remember it's an immunogenic cell death, this may be incredibly helpful in HER2 positive cancers.

And there was a very good phase one clinical trial done that looked at patients with stage three and four HER2 over-expressing breast cancer. And they enrolled 66 patients with either no evidence of disease on scans after they had completed therapy or limited metastasis to the bones. They received three doses. And these are done, the vaccines are given just like any shot is for three months. And a phase one trial, if you recall, is meant to say, is this vaccine safe? That is the main goal of a phase one trial. In addition to safety, they looked at immune response. And we check immune response usually with blood work to see if your T-cells are responding and has there been a clinical response?

Next slide please. In this study, 98% of the side effects for vaccines from this HER2 positive vaccine were minor. They were similar to what you get with flu and COVID, like a sore arm, red arm, a welt, maybe a little bit of malaise, being a little tired, maybe a few flu-like symptoms. Remember, they tested three different doses, and all doses had immune response as measured in the patient's blood work. And amazingly, 75 to 80.

Unknown: Yep, for sure.

Dr. Betsy Levick: And we'll talk about 75 to 85% of patients... I have no idea who muted me. Can you hear me now?

Jenny Stein: Yeah, we can hear you, Betsy.

Dr. Betsy Levick: Someone muted me. I don't know who. Okay, 50% of. If you look at the results of this study, 75 to 85% of the patients are alive at 10 years after their vaccines and 50% of the patients have not had a recurrence. And multiple studies are in the development for HER2-positive breast cancers. Someone is not on mute, but it's not me.

Speaker 5: As it used to be called.

Dr. Betsy Levick: Next slide, please.

Speaker 5: Love you.

Dr. Betsy Levick: There's a way to target cancer stem cells, which are sort of early stage cells to prevent breast cancer. We can train our immune system to recognize these stem cells. What we worry about is you could get resistance to any therapy including developing recurrent disease or metastatic breast cancer. So in comes the STEMVAC DNA vaccine and in mice STEMVAC prevented breast cancer in about 60% of mice. Next slide please. STEMVAC has become an important vaccine that's being tested, and it generates strong immune responses in different clinical trials, including in this phase one clinical trial. And this took patients with stage three and four hormonal receptor-positive disease or triple negative disease. And if you look at it, I think about 75% of the patients had hormonal receptor-positive disease. There were 30 patients, they were given the same three shots, plus they were given boosters. And what happened is by blood work, they detected immune responses.

And what the STEMVAC does, it doesn't just target one protein, it targets five different proteins that can drive the cancer. So they found immune responses in the patient's blood work to all five stem proteins, the stem cell proteins that they were targeting, and patients who got boosters had increased levels of response. These patients are in follow-up, and we're going to see if we can prevent breast cancer in high-risk women. Next slide, please. STEMVAC can also be effective in other diseases. Kristen mentioned, GBM or glioblastoma, lung cancer. They're trialing some pancreatic cancer. So for any clinical trial we ask that you discuss it with your oncologist, plus you can go to CLINICALTRIALS.GOV for a lot of different trial updates and what's ongoing. Next, please.

Moving on to ovarian cancer, and that's been a little bit harder to target with vaccines. But here's one trial looking at the prevention of ovarian cancer. And there's this thing called STIC, which is really, it stands for serous tubal intraepithelial carcinoma. And it's a precursor to ovarian cancer. And it has been

found in women who undergo oophorectomies or removals of their ovaries who are genetically high-risk or it has been found in hysterectomy patients as well. And we know that by just doing a preventative removal of the ovaries, it probably stops ovarian and fallopian tube cancers in the 80 to 85% of the patients. But there's always a small risk of recurrence. And the question that came up is can they develop a vaccine for STIC to prevent ovarian cancer?

So what they looked at, and this is sort of a big word, but essentially it's an insulin-like growth factor-binding protein. Again, it's another protein that can drive cancers. And it looked at the IGFBP-II vaccine to target this protein to see if they could get an immune response in patients with advanced stage ovarian cancer. And as noted, almost all the patients had increase in responses, plus compared to historical models, the progression-free survival and overall survival was improved. Currently, they're working on developing again, a vaccine that targets STIC, and it will target multiple proteins including the ones listed above. Next slide please.

What's our vision? Our vision at the Cancer Vaccine Coalition is to eliminate cancer. And we just happen to, we were working on breast first. We're looking at intermediate risk patients. And what's that mean? You're an intermediate risk, and we're looking at vaccines for people with chronic inflammation. And obesity is just one example. And it's vaccines to target risk factors to prevent cancer. We're also looking at vaccines that would target "high risk individuals," those with genetic mutations or precancerous lesions like DCIS. And we want to develop vaccines to intercept or prevent cancer. And finally, in this equally important group, we want to target very high risk individuals who have breast cancer and may have a high risk of recurrence or may be living with breast cancer. Can we develop vaccines to both treat cancer and to prevent recurrence? Next slide, please.

So I just really want to thank everyone. These are Dr. Kiran Dhillon's slides. And it's been my honor, and I'll stay on to hopefully answer any questions this evening.

Jenny Stein: Thank you so much. I'll now pass it over to Dr. Domchek.

Dr. Domchek: Well, I thought I was unmuted. I keep un-muting myself, and I get re-muted. I'll be following up on the last talk to just talk about this concept of cancer immunointerception that was on one of the slides. And I'll just talk about that a little bit more what we mean by it. In the situation that we're doing at the University of Pennsylvania, we're really focusing on the preventing or intercepting cancers - so not developing a cancer in the first place. You've heard about different vaccine approaches, sort of therapeutic vaccines when we give them to treat cancer in the advanced setting. There's vaccines to prevent recurrence when you've already had a cancer, and you're trying to reduce the risk of the cancer coming back. And here we're talking about vaccines to try to

prevent the cancer from developing in the first place. And there's multiple different approaches, some of which you've heard, but I want to define this term, cancer interception.

This was initially coined by Liz Blackburn who won the Nobel Prize a number of years ago and coined this as cancer interception is an active way of combating cancer and carcinogenesis at earlier and earlier stages. So this is fundamentally different from prevention. Prevention is a situation where, for instance, you don't smoke so you don't cause damage in your lungs, which increases your risk of developing lung cancer. You don't spend time in the sun, so you don't develop those lesions that develop into melanoma. This is really suggesting that the cancer has started, but you're going to take care of it before it becomes clinically apparent. And we do have a paradigm which is in colon cancer, having a colonoscopy and removing polyps, that's a form of mechanical interception. You're removing pre-cancerous lesions which have the opportunity to become cancer.

And so that is an example that we give. But when we talk about individuals with genetic susceptibility, individuals with BRCA1 or BRCA2I mutations, and there are other gene mutations, but largely you're born with one bad copy and when a cancer develops, the second copy is lost. So that's the way you move from the left part of the curve to the right where you've now lost both copies in a cell of BRCA1 or BRCA2. Then abnormal cells start to develop. Eventually, this becomes an early stage cancer that can be detected. And finally, it can develop metastatic disease which spreads outside the breast and obviously becomes a major problem. And when you talk about standard drug development, we generally start at metastatic disease, and then we move into the earlier and earlier stages. But when you think about it, the biology is actually quite different in metastatic disease and early stage disease and even in these pre-cancerous lesions. So we're very interested in this concept of biologically-informed disease interception. We are particularly for BRCA1 and 2 and other genetic conditions.

We're targeting this area of maximal impact when the second copy of the gene is lost, and the first abnormal cells have developed. But you couldn't find the cancer using any of the traditional techniques. So there's a couple of different approaches one can take when you talk about cancer interception. But the idea is this, that if you take your average twenty-five-year-old who even if they have a BRCA1 or 2 mutation has a very low risk of cancer. Over the next say 15 years, slowly you develop abnormal cells. And if periodically you could do something to get that risk back to baseline, to weed the garden if you will, or to erase the dry erase board and take away things and set it back to normal, you can imagine a situation where you could just never develop cancer in the first place because you periodically intercept the disease.

And so that is the general concept that we're trying to think about. And there's multiple different things you could think about potential interception trials or

strategies in known BRCA mutation carriers. And we're using BRCA carriers as an example. That's not the end goal, but it's an example where we understand the biology. So there are other trials underway, something called with RANK-Ligand inhibitors and pending trials with PARP inhibitors. But really I'm going to focus for today on this concept of immune interception. So you've already heard that immune prevention of infection was the prior great immune revolution. Childhood vaccinations though are for prevention, not treatment. Once you get polio, giving a vaccine does not help. And so in infection post-exposure, vaccination generally does not work. But we know that immunotherapy is really now standard to treat many, many cancers at least in different components, less so in breast cancer than other cancers, although it is important particularly in early-stage triple-negative breast cancer.

But we know the immune system can be activated to help treat cancers. And therefore, it really goes to the next step is that it could also be used to help prevent them in the first place. We have taken a bit of a different approach, which is work that has spanned a few decades has looked at the prospect of something called TERT as a universal tumor engine. So TERT is, it's called the catalytic subunit of telomeres. And what I'll show you here - that these are your chromosomes, and on the tip of the chromosomes are telomeres and they help the chromosomes basically maintain their ends. And the example that's often given is the tip of the end of a shoelace to prevent the shoelace from unraveling. So telomeres are important in this regard, but it also is over expressed and aberrantly expressed, meaning it's expressed in a weird way in cancers. And it's immunogenic, so it is in the cell, it's kind of gobbled up. And then it's presented on the outside of the cell in something called the MHC groove.

And even though it's expressed like that in cancer cells, it has a very restricted expression in normal cells, which provides a potential therapeutic window, meaning that you wouldn't necessarily hurt normal cells but you would hurt their cancer cells. Another important component about telomerase, which we find compelling is that it has a really critical functional role in oncogenesis. And by this we mean that in cell lines, if you get rid of telomerase, the cancer can't be a cancer anymore. And one of the things that we're always aware of with cancer vaccines is that the potential that if you target something on the outside of the cell that can be shed, that maybe the cancer will just shed it, and it still is the cancer. These are all theoreticals by the way. There's pros and cons to every approach that we're discussing. But this potentially would limit a mutation or deletion as a means of the immune escape as we call it.

We've done studies over the years, and again, this is where it was alluded to, but vaccine technology has changed quite a bit over the years. The first trials that we did were what we called dendritic cell vaccines where we took cells out of a person's body, exposed them to proteins and then put them back in. It's a very hard technology to use. We then moved into peptides, which we're making specific peptides. The challenge with peptide-based vaccines is that it has to

match your white cells because certain peptides match up with certain white cells. That's called HLA restriction. So we did peptide-based vaccines in metastatic breast cancer. We showed that there was immune response without toxicity, and that individuals who had an immune response had improved overall survival. But still this was, it is always harder in metastatic disease to get robust immune responses in breast cancer.

So the next study that was done by my colleague at Penn, Bob Vonderheide looked at a new technology, which is DNA, plasmid-based technology. This was developed initially at Penn and licensed by a company called Inovio. And that is the company that we've been working with. So this was a trial. Now we've talked about that metastatic space, therapeutic vaccines, and now we're into the space of giving a vaccine to try to prevent cancer from coming back. So these are almost 100 people with different types of cancer, breast, ovarian, pancreatic prostate, because again, this particular endogen is over expressed in 95% of human cancers so it's pretty unrestricted. And these were all people who had high-risk, but early-stage disease, they were vaccinated four times. Because this is a DNA vaccine, you have to use a pulse of electricity. That's why this device is used. And even though there is electrical shock in your arm, people are very motivated and return.

And what's shown here is just that with the vaccine, there was a development of an immune response. This is the way the immune response is measured. And importantly, if you look at individuals who have pancreatic cancer, which is a very difficult cancer, these individuals kind of did better than expected. We always are very careful not to over-rely on historical controls to say things worked, but this was promising. So we actually, because of my very specific interest in genetics and trying to offer something to high-risk patients, we then have taken this into the setting of known BRCA1 and 2 mutation carriers. This particular DNA plasmid encodes not only TERT but WT-I and PSMA. This is a product that Inovio had, and there was reasons PSMA and WT-1 are expressed in breast cancer, PSMA in prostate cancer. And so we were interested in BRCA 1 and 2 carriers.

So we have been doing the study now. It's just at Penn. Our first cohort were 16 patients, all with BRCA 1 and 2 mutations, the first 16 patients had had prior cancer. And then our second cohort are healthy individuals with BRCA 1 and 2 mutations. Half in each cohort gets sort of the vaccine alone, half gets the vaccine with something called IL-12, which is just a way to rev up the immune system a little bit more. We've completed the cohort of cancer patients, and we've completed the first arm of our healthy carriers and are well on our way. We actually have a wait list. So we will anticipate completing this clinical trial by the end of the year. And so this is, so far patients have been very interested, they've been very motivated, which is always very humbling because these are experimental vaccines that we're giving to patients.

We've seen what we call injection site reactions, which is just like it hurts where we give the shot, but otherwise nothing that's been clearly associated with the vaccine. So this is one other approach. DNA technologies here, mRNA technologies here, so lots of different vaccine technologies and different things to put in the recipe to try to generate the immune response. So again, our goal is to have a potential vaccine as one of our cancer interception techniques. And this is just sort of to say that these trials are really, really hard to do, but they're important. And the other thing is that we really do need to understand the biology of that pre-malignant state. You heard about these STIC lesions and these lesions in the fallopian tubes. The more we understand about that and the immunology of that, the more that we'll be able to develop effective vaccines. I work with a lot of people at Penn and other places. So I'll thank you for your attention, and I think we wanted to make sure to have time for the panel. Thank you.

Jenny Stein: Thank you so much, Dr. Domchek. And thank you so much too to Kristen and Dr. Levick. So before we get into some questions, I know there were some in the chat as well as some ahead of time, I just want to remind everybody that the information provided tonight is not a substitute for medical advice or treatment of any health problem. And if you have any questions that are specific to your medical care to please discuss it with your physician or qualified health provider. So one of the questions that has come up a couple of times is if it's possible, if it's even in the works yet, could these vaccines potentially for breast cancer patients be used for patients if they're ER positive, so do not need to go on hormone therapy? I don't know if that's something yet that's in development at all, but a lot of questions.

Dr. Betsy Levick: I think most of the studies currently are looking at vaccines in addition to standard of care treatment. Eventually, we may get there in prevention or in low risk, but right now I don't think we have a lot of evidence for withholding standard of care treatment in many of these trials. Now some of the vaccines are being given neo-adjuvantly meaning before standard treatment. So I think that's the way most of them are going. Do you have anything to say, Dr. Domchek?

Dr. Domchek: Yeah, I want to be clear that even though the things that we have for treatment of breast cancer have clear side effects, they've been highly effective. And the mortality rate from breast cancer is down 40%. And so we are trying to figure out how to give people less. But right now we are far away from having people withhold standard therapy right now. Sorry.

Jenny Stein: No, thank you so much. I know people have asked where they can find out about clinical trials. You can go to clinicaltrials.gov that was mentioned earlier, but you can go there to see what trials are open and they would talk about the eligibility to see what you're eligible for. But what about if people are in Canada or is there

another place also besides here in the US besides clinicaltrials.gov to see if there are clinical trials open?

Kristen Dahlgren: That's a question that we get asked a lot. And I was actually just at the American Academy of Cancer Research today talking about how difficult it is to find clinical trials. Clinicaltrials.gov is your best bet to find all of the trials, but it can be a little bit cumbersome. So that's something I think that people are working on is pooling what these trials are and what's available. Part of what we'd like to do is to help enroll trials quickly. So we are trying to keep a database, but it is by no means comprehensive of people that reach out to us, and we'll try and keep people updated on the trials that we're funding and what we see is available. But right now clinicaltrials.gov is the place that has everything listed. And as far as Canada, it would list trials in Canada as well. And there is a hope that some of these trials could be international at some point that we're working on, but we're not there yet.

Jenny Stein: I know we talked a lot about particularly the Cancer Vaccine Coalition, your guys' goal is to get a vaccine to market in five to 10 years. Realistically, are we there yet or what else would need to be done to try to get us to that point? Or when do you think a vaccine could be available?

Kristen Dahlgren: Yeah, that's what the scientists are saying. And look, it's not likely that it's going to be one single vaccine for breast cancer. I mean there are the things that Dr. Domchek's working on. There's different subtypes of breast cancer. The University of Washington has had some successes and thinks that if we can move the process along quicker, that means funding trials, enrolling them quicker, and then also working with the FDA on both accelerated approval and just having clear endpoints to these trials. Betsy, I'll let you if you have anything to add to the timeline.

Dr. Betsy Levick: Yeah, I think it's important to realize historically it can take 25 years to take a drug to market after it goes through the three phases. And I think what we are trying to do is having collaboration between the researchers. In fact, one study we're going to get going is going to be done at two different centers in different parts of the U.S. So if we work on a collaboration and education, we can get patients to enroll in clinical trials hopefully more quickly. And the third big component which Kristen mentioned is these trials are incredibly expensive and how do we fundraise to get the clinical trials up and going? I do think, or maybe it's my profound wish that if the phase two trials are positive, Pharma is going to jump in larger numbers and with a lot more money and help fund these trials. I mean, we will need manufacturers of vaccines. We'll need money to run these trials, so we are going to need help. But right now if we can get these phase two trials up and going and see the results, it may be incredibly promising and I hope it is.

Dr. Domchek: I do want to differentiate the different types of vaccines and how likely it is that they'd be an approval for those vaccines. So for instance, in the metastatic setting, you don't need as much time to figure out whether something works or not. In the adjuvant setting, it takes years to enroll in the trial and years of follow-up, just being very realistic. And these have to be randomized or you don't know that they work or not. So I think that once you get into the adjuvant setting and in the prevention setting, it's even harder still. So I think that there is a process unfortunately that has to happen even if the science is there, the clinical trials do take time and you can't assume things work. We have many examples in cancer unfortunately, where we thought things worked, but we hurt people and we didn't help them. And that's the reason why we're so grateful for volunteers who join the studies because it's the only way that we know whether things work or not.

Dr. Betsy Levick: And in fact, that's why a lot of the trials have started with triple negative because you can find out your results somewhat more quickly. And I totally agree. And despite trying to move, get vaccines moving more quickly, you have to go through the phases. And you have to do them ethically and morally and have great data behind them.

Kristen Dahlgren.: One of the things that also came up at the conference that I was at is the endpoints. And can we at some point with robust data start using things like CT DNA, which is developing circulating tumor DNA as an endpoint or as indication of disease. In multiple myeloma, they've now approved that. And so there is the possibility that as things like that develop, we could start to see those used to give us more information about where the disease, how much of a disease burden someone might have.

Dr. Domchek: I think another point to play off of is that if you have cancer, you can develop a personalized cancer vaccine related to the neoantigen as we call them, the chewed up little pieces of DNA that can generate an immune response based on the tumor you have. But if you are looking at a prevention vaccine, you don't have a cancer. So you actually have to target something that is common. And so that's why it'll be faster to develop vaccines in people who already have cancer much faster than in people who have not yet had cancer. So that's why I always like to differentiate kind of three types of vaccines, just to keep it clear that there are really different study designs and there are actually often different technologies that we use.

Jenny Stein: And on the topic of technology, do you think that AI would be able to help with this process of vaccines for cancer?

Dr. Domchek: Yeah, I think that it will allow us to interrogate things much better to be able to see whether or not there are these shared neoantigens. And also to be able to, right now they use risk prediction models for what the antigens will be that will generate an immune response. And the better we get at that, the better. So we

talk about AI, but it's just about sometimes it's just sort of a catchphrase for just improved bioinformatics.

Jenny Stein: Okay, perfect. And then one last question, this is more for Dr. Domchek. You had mentioned about the gene copy and how it's lost once the cancer comes. I'm wondering, I know you said that was for BRCA 1 or 2 and just wondering is that specific to that mutation or is that for all genetic mutations?

Dr. Domchek: It's a pretty complicated question. So it depends on the gene. And so mostly for BRCA1, BRCA2 and PALB2. Some of the other gene mutations, CHEK2, it's much more complicated. So I'll have to leave it at that for this session.

Jenny Stein: Okay, no problem. I definitely understand that. And I just wanted to thank you guys so much for joining us. Thank you Kristen and Dr. Levick, Dr. Domchek for educating us on the cancer vaccines and the progress within breast cancer, ovarian cancer, and the BRCA mutations. I know we weren't able to get to all of the questions, but hopefully everyone is leaving with a little bit more knowledge than you came here with. Like I said at the beginning, this webinar is being recorded and it will be posted on our site either the end of this week or next week with a transcript as well. We do ask that you take a moment to fill out a brief evaluation survey that we're going to be putting in the chat box now. Our evaluations really do help us to inform our future programming. And so we'd be really appreciative if you take the time to fill out that survey for us.

As always, we would love to stay connected with you. Sharsheret does have a social media site where we post information about our events such as these and other program updates. And we would also encourage you to join us for other webinars during our 2024 Sharsheret Summit. Like I said, the Summit is running through November 10th. We're putting the link into the chat box now where you can find out more information including our upcoming webinars. Our next webinar will be on Tuesday, October 15th at 5:00 PM Pacific 8:00 PM Eastern. The title of that webinar is **Fact to Fad: Breast Cancer and Ovarian Cancer Screening Options Beyond the Hype**, which will discuss current screening recommendations for people at average risk as well as those at high risk. And as a reminder, our Summit brings together thousands of people virtually and in person throughout the country and in Israel.

And we hope that you can join another webinar on the latest hot topics in breast cancer and ovarian cancer, attend or host an in-person education or awareness raising event with our community partners, learn about the latest screening guidelines, and access the most up-to-date data and materials in our digital resource packet. However you choose to participate, like I mentioned earlier, this is the source for the latest information on breast cancer and ovarian cancer. I want to thank again our sponsors for today's webinar, AstraZeneca, Daiichi-Sankyo, Merck, Pfizer, City of Hope Orange County, Eisai, Northwell Health Cancer Institute, and RMA of New York and Long Island, as well as our

Summit national partners. Please never forget that Sharsheret is here for you and your loved ones. We provide emotional support, mental health counseling, and other programs designed to help you and your loved ones navigate a cancer experience.

All of the services we provide are free, completely private and personalized. You can reach out to us at 866-474-2774, and you can also email us, which my colleague is going to put this information in the chat as well, at clinicalstaff@sharsheret.org. We are here and available to help each and every one of you no matter where you are in your cancer journey or if you have BRCA mutation or you just have questions or calling for a loved one. So our social workers and genetic counselors are available for you. You guys are our priority, so please do not hesitate to reach out. And my colleague is going to be putting in some links as well to find out more about Sharsheret as well as the Cancer Vaccine Coalition. So thank you guys so much for your time this evening, and have a nice rest of your week.