Ovarian Cancer Research Breakthroughs

National Webinar Transcript

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Presented by:

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About Sharsheret

Sharsheret, Hebrew for “chain”, is an international non-profit organization, that improves the lives of Jewish women and families living with, or at increased genetic risk for, breast or ovarian cancer through personalized support and saves lives through educational outreach.

With regional offices in the Midwest, Northeast, Southeast, West, and Israel, Sharsheret serves 275,000 women, families, health care professionals, community leaders, and students. Sharsheret creates a safe community for women facing breast cancer and ovarian cancer and their families at every stage of life and at every stage of cancer - from before diagnosis, during treatment and into the survivorship years. While our expertise is focused on young women and Jewish families, approximately 25% of those we serve are not Jewish. All Sharsheret programs serve all women and men.

As a premier organization for psychosocial support, Sharsheret works closely with the Centers for Disease Control and Prevention (CDC) and participates in psychosocial research studies and evaluations with major cancer centers, including Georgetown University Lombardi Comprehensive Cancer Center. Sharsheret is accredited by the Better Business Bureau and has earned a 4-star rating from Charity Navigator for four consecutive years.

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

- Thriving Again®, providing individualized support, education, and survivorship plans for young breast cancer survivors
- Busy Box®, for young parents facing breast cancer
- Best Face Forward®, addressing the cosmetic side effects of treatment
- 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
- Sharsheret Supports™, developing local support groups and programs

Education and Outreach Programs

- Health Care Symposia, on issues unique to younger women facing breast cancer
- Sharsheret on Campus, outreach and education to students on campus
- Sharsheret Educational Resource Booklet Series, culturally-relevant publications for Jewish women and their families and healthcare Professionals

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Transcript:

Jenna Fields:

We're going to get started and more people will be joining us I know in the next few minutes. I'm Jenna Fields. I am the Chief Regional Officer of Sharsheret, and we will be presenting tonight's webinar; Ovarian Cancer Research Breakthroughs with Dr. Beth Karlan.

Tonight's webinar is an early kickoff to Sharsheret Summit. Sharsheret Summit brings together thousands of people for virtual and in-person education all across the country

from September 26th to October 31st. Please visit our Sharsheret Summit website to learn more, and to sign up for any of our amazing upcoming webinars that feature top experts in the fields. My colleague is going to put the link for that in the chat.

Tonight's webinar is sponsored by Merck and we're grateful to our Sharsheret Summit sponsors; Merck, AstraZeneca, Novartis, Pfizer, Lilly, Daiichi-Sankyo, City of Hope, Eisai, and GSK. Before we begin, just a few housekeeping items.

Tonight's webinar is being recorded and will be posted on Sharsheret's website along with a transcript. Participants' faces and names will not be in the recording, and if you want to remain private, you have the option to turn off your video and rename yourself, or you can call in to the webinar.

We also have closed captioning available. To display live captions, click on the bottom bar, click on captions, and then click on show captions. You may have noticed that you were muted upon entering the Zoom, please stay muted during the call. We will hold a Q&A at the end of the presentation. If you have any questions, please type them into the chat box and we'll get to as many as we can during the Q&A.

I want to remind you that Sharsheret is a not-for-profit supporting cancer organization and does not provide any medical advice or perform any medical procedures. Our full medical disclaimer is in the chat.

A quick program spotlight for all of you. If you're interested in giving back to Sharsheret, we're looking for new bakers to join our annual Pies for Prevention Thanksgiving Bake Sale, supporting the Stephanie Sussman, Ann Nadrich Memorial Jewel, and Sharsheret's Ovarian Cancer Program. You can become a baker and bake alongside over 40 sales across the country. Visit our website to learn more and sign up.

Most importantly, if you're currently facing an ovarian cancer diagnosis, please remember that Sharsheret is here for you and your loved ones. Sharsheret provides emotional support, mental health counseling, and other programs designed to help navigate you through the cancer experience. All are completely free and confidential. Our contact information is in the chat box below.

And if you are a member of our Embrace Program, someone who's facing advanced ovarian cancer, we invite you to stay on the Zoom following the Q&A for a more intimate breakout session with Dr. Karlan.

At Sharsheret, we know that ovarian cancer isn't just a diagnosis, it's a journey. Whether you're living with it or supporting someone who is, tonight's webinar is designed to give you the latest updates from one of the most esteemed ovarian cancer researchers in the

country, Dr. Beth Karlan. Now, before we welcome Dr. Karlan to the screen, I'm pleased to welcome Lori to share her story. Lori, thank you so much for being here.

Lori Cohen:

Thank you for having me. So, I will keep this short. So, my name is Lori Cohen. I am a very, I hope I don't cry. I wasn't expecting that. I'm a very grateful two-year survivor of Stage 3 ovarian cancer. Looking back, I think the symptoms that led me to it are very simple.

When we look at that BEACH acronym, I had some bladder discomfort, pelvic pain, all things I didn't really think were anything significant, but when I did go finally get to my doctor, they found a mass. It was unclear what it was. Fast-forward, imaging, surgeons, they scheduled me for surgery. When I woke up, I woke up to a diagnosis of ovarian cancer. I'm very grateful for my surgeons, my doctor and everyone, especially this organization.

Once I came out of the initial shock of it all and I started going into research mode, Sharsheret was one of the organizations that I came across immediately. And I remember doing a deep dive into old webinars and joining every Facebook group that you had, I think even ones that I shouldn't have been in. I was just looking for knowledge and others to help answer questions and just read other stories and hear other just stories of hope.

Somebody from the Sharsheret organization, a genetic counselor, Rachel, put me in touch with, because I had a lot of questions coming out of my genetic testing because I have children, I have a daughter, I have a sister, I have nieces. So, that was a great free resource. I was on a Zoom with a genetic counselor answering all my questions, really helping fill in the gaps of what I didn't fully understand from my doctors, so that was really helpful.

It's been a journey; surgery, chemo, I cold capped. I'm HRD positive, so I am on Lynparza, so a PARP inhibitor, which has been very, very grateful for that drug. So, that's where I currently am. I'm about 15 months into what I believe will be a two-year dose of that of Lynparza, and I'm thriving.

I go for my scans, I meet with my doctor, but I am living, I still am very research-based. So, I'm constantly listening to new things and I'm very grateful for Sharsheret for sharing webinars such as this with cutting edge information. Because you always just give me questions to go and ask to my doctors, so I can keep up with the latest and meet people and give them hope. So, that's my story.

Jenna Fields:

Thank you so much, Lori, for sharing your story. I'm really glad that you're doing well, and sharing your story makes a huge impact. So, thank you for being so open with us tonight.

We're now honored this evening to welcome Dr. Beth Karlan, who is a professor and vice chair in the department of Obstetrics and Gynecology at the David Geffen School of Medicine at UCLA. She holds the Nancy Marks Endowed Chair in women's health research and is the director of Cancer Population Genetics at the UCLA-Jonsson Comprehensive Cancer Center.

Her research focuses on early detection and precision prevention for ovarian and other gynecologic malignancies, as well as on identifying biomarkers to personalize treatments and improve patient outcomes. Recognized as an authority on inherited cancer risk, Dr. Karlan has contributed to the development of treatment guidelines and novel therapies for patients. And she's authored more than 500 peer-reviewed research publications.

In addition to her many accolades, Dr. Karlan is a member of Sharsheret's Medical Advisory Board. I've personally known her for over nine years and have seen firsthand why Dr. Karlan is so beloved by her patients and her colleagues. It's now my pleasure to introduce Dr. Karlan.

Dr. Beth Karlan:

Lori, you're not alone. Now Jenna's going to make me cry too before I even start. So, thank you Jenna for the wonderful introduction. Thank you to all of Sharsheret for all that you do. As Lori mentioned, building community that is supportive, that is knowledgeable, really does help survival. And there've been many studies actually looking at randomized groups and interventions of just this type of support. And women and men, but the women do live longer, live better, and I think have a much better quality of life. So, thank you to all of you from Sharsheret.

Big, big shout out to everyone who's on the Zoom this evening. For you, empowering yourself with knowledge, the opportunities to ask questions and find out what else you can do to live longer and live better. It says you have a rich life, a life with purpose, and one you want to save and savor.

So, Jenna gave me the task of 35 to 40 minutes to bring us up to speed. I've tried to include some of the hot topics. I can't go into everything in depth obviously, but why is that not working? Let's see. There we go. Here. So, this is the outline. We'll go over some of the current numbers and trends, so you get a sense of that. They're dry, but there's some exciting news there too.

Really highlight that ovarian cancer is not one disease, and knowing about your own ovarian cancer, what subtype you have has real clinical implications more and more with our targeted therapies. Go over some highlights of current standards of care, the use of heated intraperitoneal therapy, genetics and PARPs, really what's on the horizon.

Some clinical trials, the really new advent of antibody drug conjugates that we'll touch bases on. Some comments about survivorship, and then salpingectomy and prevention. So, that's the outline, and I'll get going.

Why are we here this evening? Because of our families, because of our will to live, because of the long list of things we still want to get done. This is a very dear patient of mine for over a decade with her husband and her daughter, who was in graduate school and decided to start this run in her honor, it went over 10 years. And her daughter Kelly, now works with us in development and in our Simms Mann center at UCLA to help with survivorship, but she really started that legacy.

Here's a clear cell ovarian cancer patient of mine at five years. And I told her we were going to celebrate that by making it across the finish line that defined future successes in life.

Here is a dear patient of mine whose mom I took care of. Her mom passed away from ovarian cancer. She had a BRCA1 gene, had risk-reducing surgery and she brought her daughters in, because she wanted them to have care too. So, it's really about generations and knowledge and being active, and I think that's what I'm here tonight to try to give you some more information to do that.

So, where are we in 2025? About 20,000 new cases are estimated according to the American Cancer Society. About 12,700 deaths are predicted. For those of you who have looked at these statistics over years, and I hope you have and I just have, ovarian cancer is now down here at number seven. It used to be up at number three or four.

There really are positive trends for ovarian cancer despite the unfortunate increase in uterine cancers, colorectal cancers and pancreas cancers that continue to go up, especially in women under 50. But our survival is improving.

Overall now, there's almost a quarter million women in the US who are living with ovarian cancer. You see some age breakdown here, but again, more of a reason for you to be here, to find out how do you live longest, live best, and be able to make the most of every day.

A piece of good news. When you look over these last 20 years or so, 15 years shown here, the long-term trends for both the new cases and deaths are decreasing for ovarian cancer. As I mentioned it in the last slide, but here you see from SEER from a national registry of data, the blue are the new cases, the green are the deaths. Both are decreasing.

In thinking about this a good deal, some of it is due to the greater use of birth control pills, which do decrease the risk of ovarian cancer with cumulative use in our premenopausal years. We're not saying use them after menopause, in the premenopausal years, they really do decrease the risk of ovarian cancer up to 50% by 10 years of use.

The greater availability and knowledge about genetic testing in women who find out they carry an inherited predisposition to ovarian cancer, the fact that they act on it and have risk-reducing surgery. And again, the increased use of opportunistic salpingectomy that I'll touch on in our prevention section.

Mortality is better because we have better treatments, we have better chemotherapies, better trials, better targeted therapies. We've really begun to have really more individualized approaches beyond one size fits all, same treatment for every woman with ovarian cancer. And of course we have better medical and surgical care to support women through their journey. Whether it's growth factors, so you don't get sepsis if your blood counts go low with chemotherapy, but really we have to keep going obviously, but we have made some progress.

This was the highlight from a National Academies of Medicine meeting we held almost a decade ago now to really stop thinking ovarian cancer as one disease. These subtypes of epithelial ovarian cancer, the most common kinds, are really very different. They have different genetic predispositions, they have different molecular biologies, they have different risk factors and can have different treatments.

In fact, most of them don't begin on the ovary. The most common ovarian cancer, of course, is the high-grade serous ovarian cancer. Most likely begins in most cases in the fallopian tube. Those are the cells whose native epithelium, the native lining is serous cancer. It undergoes transformation becoming malignant due to the constant insults, if you allow, of ovulation. Where the rupture of the egg from the follicle has growth factors in the enzymes that cause stress on those cells and cause them to become malignant.

Low-grade serous cancer may have the same last name of serous cancer, but they're very, very different. They're related in that they're both ovarian cancers so to speak, but very different risk factors, biology and treatments now, and FDA-approved treatments.

Clear cell cancers and endometriotic cancers both likely begin from endometriosis. Again, different cancers, different treatments. Mucinous cancers we're not quite certain whether they come from the gastrointestinal tract like the appendix or colon or elsewhere, but they too are very different.

What does that say? I'll go over, you don't need to have all the details. Really, this is one of my slides that I use with some of my scientific lectures. But each of these major groups of low-grade cancers, high-grade serous and endometrial cancers, clear cell and mucinous are really different. They have different genes, whether it's BRCA, CCNE1, I am not trying to just give you word salad here, but each of these are specific targets with specific types of therapy.

When you go to the low-grade cancers, you see different things. You see estrogen receptor, progesterone receptor, PI3 kinase. And again, the names are not as important as to understand that knowing the type of ovarian cancer you have can help you find a clinical trial. Can help you understand what are the new FDA-approved treatments as new FDA-approved treatments for low-grade cancers, clear cell cancers, and these are all coming down the pipe.

So, we need to stop thinking of ovarian cancer as just one size fits all, one disease, but these really are very specific. Similar if you follow things at all with lung cancer, we know there are many different kinds of lung cancer that have specific targeted therapies on a pie chart being cut up into many different pieces. Each one can have improved survival if you get the right target. If you have that target and there is a treatment available.

It is important research cures cancer. It's the ongoing partnership in research by both patients, clinicians and investigators to have this bidirectional path. From questions at the bedside, to women being participants in trials of being willing to allow their tissues at surgery or elsewhere to be studied. That we can then make the discoveries, bring them back to the clinic and iterate back and forth. I've seen this from my own lab and from others that this is really where we need to go.

Standard of care 2025. When a woman discovers that she likely has advanced ovarian cancer, there needs to be a tissue diagnosis. Either we'd like it to be more than just tapping the fluid that may accumulate from the ascites and cytology, but having a biopsy. And with consultation by a gynecologic oncologist decide whether or not is it most appropriate based on her disease distribution and her other health indicators, comorbidities and other things she may have going on in her body, whether she should have surgery or whether she should initially have her debulking with chemotherapy.

So, neoadjuvant chemotherapy is often used to kill the cancer cells prior to what we call an interval debulking surgery. They have equivalent outcomes whether you have your primary debulking surgery or interval debulking surgery after chemo, the overall survivals are the same. That really has a caveat. That's after being evaluated by someone who, like a GYN oncologist, who understands both ways to treat this in terms of the surgical capabilities and not.

So, it's your imaging, your CT scans, your PET-CT scans, what that shows to determine which tact is best, but the two both need to be evaluated. So, the decision should be made by a gynecologic oncologist. If you have the neoadjuvant chemotherapy, sorry for the word salad, but otherwise letters get so small on here, so I'll try to repeat what they stand for.

But if you have neoadjuvant chemotherapy and then interval debulking surgery, there's shorter hospital stay, fewer surgical complications, less bowel resections or colostomies. So, in many cases that is better for patients, but it depends on each woman and each woman's disease.

The most important standard that we need to uphold is getting down to what we call R0; no visible residual disease. If your primary debulking surgery is not going to be able to get out everything, then you're better off having chemotherapy prior to surgery. Really, we know that the overall survival, how many years that woman is going to live is correlated with getting down to no visible disease.

The other thing that we're discussing more and more, and I'll show you some trials, is the use of heated intraperitoneal chemotherapy. This is at the interval debulking surgery if they can get the tumor out to use this methodology, and I'll show you a picture of it in a moment, where you heat the abdomen and heat the chemo to about 42 degrees. That really seems to knock out any of those residual cells. You still need to finish your chemotherapy after surgery, but it seems to give you at least an extra year of survival, and I'll show you that in a moment.

Also, standard of care is to make sure you get both germline testing done, so in testing to see if you have inherited predisposition, as well as testing your tumor, which is HRD testing, as Lori said she had done. And that should be offered to everybody with ovarian cancer independent of which type you have.

The standard of care is still in the upfront setting to use carboplatin and paclitaxel for six cycles every third week. And then you and your doctor can decide whether or not the use of bevacizumab, which is an anti-angiogenesis agent, should be used in your case.

The way I think of it is the chemotherapies are like your lawnmower cutting off the top of a field of weeds. The bevacizumab attacks the blood vessels, the roots underneath, so that the blood vessels that would feed the ovarian cancer cells that remain would be also cut off. So, again, there is pros and cons and risks that need to be individualized, but this is what would be in a textbook for standard of care today.

As Lori mentioned, she did have HRD. So, in her case, I'll show you beautiful survival curves, beautiful evidence of response. A PARP inhibitor, and PARP is a polyadenosine ribose polymerase inhibitor, which is why we call it PARP, does provide significant improvement in terms of both progression-free survival and also overall survival. And really is a standard of care for women with advanced ovarian cancer, either carry BRCA, germline mutation, or have HRD.

HIPEC. So, basically what you do is you do your interval debulking surgery, you get all the tumor out, and then you take catheters. The perfusionists as we call them, are the same people who do cardiac bypass perfusion. This is not just a little thing. It really is a big thing and they use the same type of machine that would be used if you're having cardiac bypass and everything is going through.

What you do is we use cisplatin. The chemotherapy is heated up to about 46 degrees, and then you put it into the abdomen for about 90 minutes. The heated chemo opens up the cells, makes them more susceptible, and you sit there, literally I often have my residents and my fellow, you basically have to just volley back and forth the abdomen and the fluid and keep it circulating. You just do this back and forth for the 90 minutes and then take it out.

It's a high dose, so you need to make sure there's protection for your kidneys and that you don't have nausea and all afterwards. But what you see here on my right, I think it's your right too, this was a Phase 3 randomized controlled trial. So, these patients had neoadjuvant chemotherapy, interval debulking surgery, half the group got HIPEC and half did not.

The red line of those that got the HIPEC and they lived longer, about a year longer overall if they had the HIPEC. Now we still need no therapies, and I'm going to get into some of those targeted therapies, antibody drug conjugates and where else. But this is a sign of something we can do 90 minutes extra.

I often sit down during that time and let the resident and fellow help with the agitation of the abdomen. But I think it's definitely, I think any of us here to buy another year of life for 90 minutes it sounds like the best deal there ever is. So, something else to consider if that might be right for you.

Germline genetic testing. This is for the inherited predisposition to ovarian cancer that runs in families. About 20%, about one in five ovarian cancer patients, may have one of this. Most of them are due to BRCA1 and BRCA2, although there are other genes, as you see listed here, also associated with it.

One point, Lori I'm using you, I hope it's okay, using your story as a way to... Thank you, sweetheart. I appreciate it. I got the thumbs up from her. These genes are not on the X and Y chromosome. They are what we call autosomal genes. So, they are the same type of genes that you can inherit eye color or other things with. So, I know you mentioned the importance of being tested and your female relatives are the ones you called out.

Part of the, I won't call problem, part of the issue is men are just as likely to carry and pass on one of these variants as are women. The men who carry these genes also have risk of

pancreas cancer, or prostate cancer, or male breast cancer, or in some cases colon cancers.

So, I think that when we talk about this, whether it's around Rosh Hashanah, whether it's around Thanksgiving, when families gather, men don't follow through on their testing. They're really great, even my physician colleagues. They'll say, "I had my wife and my daughters tested." I said, "Well, what about you?" They said, "I don't need to worry about that." Please encourage the men you love as well to consider if this would be appropriate for them.

I bring this up because despite the now 15 years since the National Guidelines, National Comprehensive Cancer Network guidelines have recommended genetic testing that every woman with ovarian cancer, we're barely, barely at 35%. It's covered by insurance, it's covered by Medicare. It might allow you to have the access to PARP inhibitors, which not every patient has access to, because they're not FDA-indicated any longer.

So, please discuss this with your physician. Even if you're on here, even if you're 80, even if you've been in remission for five years, if you've not had this done yet, please ask. One thing patients sometimes get confused about, and I'll go through it in a moment. Even if you had genetic testing when you were per se pregnant and you had carrier screening, that's very different in a different type of genes. So, please ask specifically about this.

Not testing, as I said, missed opportunities for targeted therapies. Unfortunately, you can have second cancers. Lightning with one of these genes can strike twice. So, you can have an ovarian cancer and then get a breast cancer or something else, and it would be good to know that you should have high risk prevention there too. Think of all those family members you could help save their lives.

I have dear patient who's a nurse practitioner and every year, I see she's out now more than seven years with her ovarian cancer. But she brings me in pictures every year of the growing group of people in her family that she keeps getting tested, and it makes me smile.

So, as I said earlier, it can improve ovarian cancer survival. Over half of ovarian cancers are susceptible to PARP, either due to inherited mutations, that could be close to 15%. You can have it a tumor mutation, like it sounds like Lori has with her HRD. Or you can have what we call methylation or other things that can alter the expression of these genes.

When you know that you have access to PARP inhibitors, maybe immunotherapies depending on the alterations, and there's a growing list of these specific targeted treatments based on what gene you have altered in your tumor.

So, I think even if you've initially been diagnosed, when you have your surgery, whether it's upfront or whether it's an interval debulking surgery, it's important to get the somatic testing. I think one of the things I find with my patients as they live with ovarian cancer is often knowing what's next. If it is to come back, do I have additional treatments? What else is out there?

Every year, every two years you live with ovarian cancer, we're having more discoveries. This is really becoming more accelerated FDA approvals for ovarian cancer. So, please have as much information as you can.

You guys may have seen this in past years, I just think it's important to bring up again. And that's really how transformative PARP inhibitor maintenance therapy has been. It's a whole class of drugs. Lori mentioned she's on Lynparza, which is Olaparib. There's niraparib and rucaparib that are also FDA approved for ovarian cancer.

When these curves separate, it shows benefit in the treatment arm. The blue one, every case it's significantly separated. With the most data for Olaparib, because it started the earliest. So, SOLO1 is the trial, we now have seven, eight-year data. But here, this was only at seven and a half years and there was a three-and-a-half-year benefit.

These women had advanced ovarian cancer, all got to remission, and they were randomized to either placebo or Olaparib. Those in the Olaparib arm at six and a half years had a three-and-a-half-year survival improvement. So, again, it's not a cure, but it's allowing you to get to that next stage, that next step to go onto the next treatment that can get you another three years, and another three years, and another three years.

As an ovarian cancer community, I am proud of what we've been able to bring forward into the oncology community. That the implications of PARP inhibitors, and they're not all the same PARP inhibitors, now have FDA approvals in breast cancer, pancreatic cancer, and prostate. Cancer, all stemming from studies that began and what we were able to demonstrate ovarian cancer.

So, this is going to be the way forward. That we are going to be able to really not just throw a grenade in to kill every growing cell, but to really target specific mutations, so that we can have less toxicity and have women live longer and better.

I know I've thrown around terms tonight, germline, somatic, epigenetic. Just some quick things because there's more stuff coming along the line with someone asked about the Signatera test and things, and I'll get to that.

So, germline genetics is what you have from either a blood test or a buccal smear or saliva. It's a test. It's looking for a gene that you inherited, so it's been in you since before you were

born. It's when the sperm and egg met. Could come from your dad or your mom. It's in every cell of your body. It can be passed on to your kids by either men or women, as I said.

A somatic change is due to, and we don't know exactly why. Part of it is due to ovulation perhaps, part of it may be due to other hormones, to antibiotics, to infections, but they are acquired over a lifetime. Somatic mutations increase as we get older. We're living longer. Ovarian cancer is not one that's associated with UV light, but we know that skin cancer is increased because of the DNA damage from UV light. Things like smoking causes DNA damage in those tissues.

So, these are not inherited. They are acquired during our life. It's things we're trying to figure out what leads to this so we can prevent it. But they will define your cancer, so they'll be part of the targets.

Now, as cancer cells grow, just like every other cell, they're growing really fast and their DNA repair is not very good, because they're cancer cells. So, the cells break off and they get into the bloodstream, the cells die, they burst. The DNA gets into the bloodstream. We now understand that we call it an analyte, something to study, to analyze. You can look at circulating tumor DNA, circulating tumor cells, which is CTCs. Exosomes are little blebs that pop off.

So, sometimes we'll say, "Maybe your tumor's recurred and you didn't have a biopsy. We don't have a tissue from before. We can do a liquid biopsy." Which is to take a tube of blood to look for that tumor DNA, and to do the same type of somatic analysis as we would've done with a tissue biopsy. And that too, we may say, "Has your tumor changed? Is there now a target that we can get to?"

There's also ways to look at unique fragments of DNA, and these are really bespoke tests to your tumor. When I talk about this, these are the pathology slides and blocks that are held by most departments, most hospitals, departments of pathology for a couple of decades. So, they should be able to go back to your archival tissue and get one of those blocks. They look at the DNA fragments that come out of your specific tissue.

And then over time, that becomes your bespoke, like we use a CA-125 traditionally, bespoke test to look for minimal residual disease. How early can we find that your tumor may be rearing its head again, so that we can intervene perhaps a bit earlier? MRD testing, Signatera type testing, which was one of the questions folks asked about, and they're just one brand. So, that's for these circulating tumor DNA tests can be used to follow things over time.

I forgot, I'm sorry, I lost that. It'll come back to me. But it is something that you need to ask for and it would be done after your tumor was diagnosed and can be used over time. We

don't have yet for ovarian cancer specific national recommendations, although my patients have had no problem having them reimbursed by their insurers, but it's not yet in the national guidelines. Stay tuned, it should be coming.

Antibody drug conjugates. If you guys haven't heard about it, this is I think an exciting advance in our treatment of all cancers. I'm optimistic ADCs may replace chemo even. This is basically a smart bomb. This is targeted chemo. So, as you see over here, we have our cancer cell and we have all these receptors, antigens, things on the surface.

So, what an ADC is it's an antibody that targets one of these. Many of you may have heard of Herceptin in the past, that was an antibody that just targeted these. But what we've done now with an antibody drug conjugate, we take our antibody, we have a little linker molecule that links the antibody to a drug. This drug could be, again, it could inhibit DNA, could kill the cells in a number of different ways, similar to chemotherapy in general.

This has really, I think, revolutionized so much of the future for oncology care, in that we don't just give you platinum or a taxane to kill all the rapidly growing cells, that you lose your hair and things like that. These drugs are really much more targeted to those cells that have this receptor. The beauty of them, one of the additional things is, so they bind on the cell. The complex, the antibody drug conjugate, is taken up by this endosome, that piece where it's bound is pinched off into a little vesicle.

It lysis so the toxins can kill the cancer cell that they're within. But when that cancer cell dies, that toxin is still there. So, you get this halo effect, well, maybe not halo, but at least it kills the other cells nearby that may not have had the receptor. So, it really is a way to get even further effects of the drug with less toxicity.

So, these smart bombs to attack ovarian cancer, there's some that are FDA approved, some in clinical trials. Here's a list of some of the ones that are the most promising that are in trial. I'll go over two of them right now, but there's a lot more coming and stay tuned. It's really very exciting. Again, they all have cancer cell, a little target, an antibody, a cleavable linker, and a drug that we call the payload.

So, the first one to talk about, and many of you may have heard about, is mirvetuximab, which is also known as Elahere. This is an FDA approved ADC specifically for ovarian cancer, that binds the folate receptor alpha. That is on 90%, 80% to 90% of ovarian cancers, and it's not on the normal cells.

So, it has its FR alpha binding antibody. It has this cleavable linker. And here the payload, the toxin is what we call DM4. It's a tubulin targeting agent that doesn't let the cells reproduce. As I say, it's on 80% to 90% of ovarian cancers and limited on normal tissues. It's even on the low-grade tumors. This is really, really exciting.

I won't bore you, but again, clinical trials are so important. And looking at the data critically is important, because Mirvetuximab has been around for a long time. Even got to a Phase 3 trial called FORWARD a decade ago that was negative. But it wasn't thrown out because they went back and they said, "There's a signal here. Something is looking good, but we can't show in a randomized fashion that it's working."

So, they changed the cutoff, they changed the asset. They used ideal body weight and launched new trials, and it got accelerated FDA approval, now full FDA approval, based on randomized controlled trials. I'll show you that here. This is the MIRASOL trial. Again, these were women who had platinum-resistant ovarian cancer.

A place that's really hard since platinum is the most effective chemotherapy. Once you become resistant, you don't see improvements like this. In this trial, again, it's not a cure, but we did see this significant improvement in progression-free survival in those women who got the Mirvetuximab, the Elahere. Really for someone with platinum-resistant disease, many of these women had been had on 5, 6, 7 prior treatments. It really was a game changer.

Indeed, the FDA gave accelerated approval for anyone who had platinum-resistant epithelial, ovarian, fallopian tube, or peritoneal cancer. There's ongoing trials now looking at platinum sensitive patients, also showing excellent response, and really bringing into the upfront setting. I'm talking too long. Let me go fast.

Another one here, this is DESTINY2. This is an antibody drug conjugate that targets the HER2 antigen, similar to what was being done with breast cancer patients with Herceptin. This is now an antibody drug conjugate using the same antigen, the HER2, and this time linking it with something that's called a topoisomerase, a chemotherapy type drug.

It's been looking at pan-cancer, so cervical, endometrial and ovarian cancer has been looked at as well as others. And we really saw a great response for ovarian cancer. So, another option again for someone right now with platinum-resistant disease.

Here is just a long list of antibody drug conjugates, and this is just a partial list and different targets that are coming forth. So, something to think about, to discuss with your physician, to look at the NCI website to see whether or not this is right for you.

Some examples of beyond these other cases, so specific genetic alterations. CCNE1 is common in about 20% of high grade serous ovarian cancers, often difficult to target. RAS mutations and these different subtypes that we now have chemotherapies, immunotherapies and targeted therapies that are really demonstrating improved outcomes. There's other novel immunotherapies ongoing looking at vaccine approaches, T-cell therapies, and new types of antibodies that look at two different targets.

The good news is patients are living longer with cancer, and our cancer death rate has significantly fallen these years. They call it a silver tsunami because it is really we're seeing more than two-thirds of these patients over 65, who continue to be able to alive with ovarian cancer.

We need to think about ovarian cancer survivorship along a continuum. Even previvorship, those women who find out they have a high risk and are BRCA1 or 2 or any of the genes and don't yet have a diagnosis, they need to be thought about too. Those individuals, women from the time of diagnosis, you're a survivor.

What does that mean? What can you do to improve your journey through chemotherapy? Prevent or take care of your neuropathy, chemo brain symptoms, et cetera. And then ongoing, the anxiety for a next recurrence. What does it mean? This really needs to be incorporating to our standards of care.

Issues that need to be addressed, of course, are menopause management, sexual concerns, fatigue, neuropathy, so many different things. Recognizing there's PTSD that goes with this journey that needs to be addressed. There may be accelerated aging with some of the cognitive issues, and really also the financial toxicities. The things that you need to put aside, because you need to pay for treatments, and that needs to be taken into our survivorship plans as well.

Many things we can be doing better by really understanding how they work. Stress reduction. Physical activity, there's multiple studies now coming out about exercise. Really there was a randomized trial recently in young colon cancer patients. How randomized are just being told to exercise versus given a coach for two years significantly improved survival. Diet, having a genetic testing.

I'm an advocate. I've been talking about trying to launch a new sub-specialty just like we have now, palliative care physicians, physical medicine rehab physicians. I think we need to have a whole group of folks trained in survivorship to really take this on as not just the last two minutes and go see the nurse practitioner.

I love my nurse practitioners, so please, that's nothing negative. They just often have more time. We really need real clinical trials to understand what works, what doesn't work, so we can give guidance to patients.

I'll just call out one of our physician's assistants, Rachel Frankenthal, has been very active in this. She's a certified yoga instructor and provides a series of 8 to 10 week yoga classes for our patients. Can be done on Zoom. And the surveys we have really show improved brain fog, fatigue, sleep, and these are ongoing for folks who can log in. They are free of charge as well.

I'm getting there, Jenna, I promise. An ounce of prevention is worth a pound of cure. The last section I just have to, please allow me to say almost better than curing cancer is never getting cancer at all.

So, I think we now understand that most ovarian cancers do begin in the fallopian tube. I say most, we think maybe some of the low-grade serous and the mucinous may not, may begin elsewhere. But now when we recognize this discovery, it really shifted the focus to risk-reductive types of surgery versus screening. We still are doing a number of screening studies, but so much has been invested. Hundreds of thousands of women have been-

I can keep going. I'm going to just keep talking.

Okay. Basically really this is the most effective way and it really will reduce the risk of ovarian cancer. Both not just in the BRCA population, but this is really being looked at for women across the globe as a way to have an opportunistic salpingectomy to prevent ovarian cancer. So, whether it's a GYN surgery, whether it's a tubal ligation, or desire for one at cesarean section or other surgeries, that when you remove the fallopian tubes, you significantly reduce the risk of ovarian cancer.

So, this was a large study done in Canada. Women who had opportunistic salpingectomy versus those who had surgery but did not have their tubes removed. This was the predicted number of ovarian cancers one would've seen. But when you looked at the comparison from expected number of cases versus those that were observed, for the high-grade serous cancers, zero ovarian cancers versus those that were expected.

When you looked at all epithelial cancers, those were reduced. Whereas the breast cancer and colon cancers were not changed. So, this really does seem to be having an impact.

There's a number of campaigns now to try to get this more widely embraced by both gynecologists and even talking to non-gynecologic surgeons to consider there. We've mentioned genetic testing and the need to do that. Remember that if you do carry one of the high-risk genes, to have your risk-reducing surgery by the specific ages. I think those women we see with these mutations who have their risk-reducing surgery 10 years later in their fifties or sixties, do have a higher risk of having a cancer found at the time of diagnosis.

Lastly, I mentioned earlier cascade testing. Telling your family if you carry one of the high-risk genes about it. And helping them also understand the risks and that they too can have prevention interventions for themselves. This is just an example of this, what it means for your relatives. Most folks don't talk about this with their relatives. Families are complicated.

It may sound easy. You haven't spoken to your sister, you don't know that cousin, but it's something that you really can have an impact on lowering the risks. We're actually working to put together an AI bot that can be your Siri that, hi, I recently found out, what does this mean? Can you help guide me? What do I do next? And give you scripts and support of what you can tell your family members, how it's done, and give them information as well.

So, I think what do we do now, and I'll stop for questions after this. Really implement efforts to broaden genetic testing, cascade testing for primary prevention. We've already pushed the survival curve significantly, but when I was in training, women with ovarian cancer, the median survival was 18 months and we're now close to 70 months.

So, we're doing better, but we need to have more cures. We need better treatments, especially since resistance happens to platinum, to PARPs, et cetera. We need more drug approvals, better insurance coverage, more funding, better ways to get patients paired up with funding. Follow the national guidelines. They were there based on data. And really help train the next generation of scientists and clinicians to keep this coming. So, September, it's Ovarian Cancer Awareness Month.

Jenna, I hope your symposium can be pushed back to start on September 8th and not till just the 26th, because we're starting it, we're kicking it off tonight. But talk, educate, advocate, live. Thank you for your attention. Thank you to Sharsheret for all that you do. Sorry if I went over a few minutes, I just wanted to try to get in as much information as I can for everyone who's made the time to join us tonight. So, thank you.

Jenna Fields:

Thank you so much, Dr. Karlan. This was just so informative, and I've got your whole alphabet soup written out. So much information that is really critical for all of us here. Thank you.

Just two things I want to mention. One is that Sharsheret's genetic counselors are available to help guide you in talking with cascade testing with your family. So, please don't hesitate to utilize Sharsheret's resource in addition to the resources at your local medical center. Genetic counselors are a great tool to help you communicate with your family about reducing their risk.

The other thing I want to mention is we are having a webinar on October 29th with Seth Cohen of City of Hope, Orange County, who is going to talk about managing the side effects of ovarian cancer treatment, in addition to a speaker who will be speaking about breast cancer side effect treatment. So, please register for that webinar. I put the information about it in the chat if you're interested.

Dr. Beth Karlan:

Jenna, Seth is the urologist, you know that?

Jenna Fields:

Yes.

Dr. Beth Karlan:

But he's talking about side effects of ovarian cancer.

Jenna Fields:

Yes. And he's going to talk about urogynecologic side effects.

Dr. Beth Karlan:

Okay. Okay.

Jenna Fields:

Yeah.

Dr. Beth Karlan:

His twin brother, Josh, is GYN oncologist.

Jenna Fields:

Yes, the twin brothers who are both in the same field. We're very lucky to have them both. Lots of questions. I'm going to combine a few and I'm going to stick to more general questions. So, there was some chat early on when you talked about HIPEC, about if you can use it for recurrence as a tool? And then follow up question about how people can find a provider that will offer it as a procedure, because it sounds like some providers won't.

Dr. Beth Karlan:

Okay. So, the best data we have from randomized Phase 3 trials published in the New England Journal of Medicine, which again is a very controlled situation, was looking at doing it at interval debulking surgery. If you are in a situation where your tumor has recurred, and it's amenable and appropriate to have a secondary surgery or a tertiary surgery, and they're able to get the tumor out, I think it's something to discuss with your physician.

Typically, in those situations, you are not platinum-resistant, you are still platinum sensitive. That's one of usually the indications that you're doing the surgery. And HIPEC, we

have done it for recurrences. I just wanted to provide the strongest evidence for why I think it is worthwhile.

I started studying heated intraperitoneal chemo, believe it or not, it's been around, oh, goodness, I don't want to tell you, but it was in the seventies. We were looking at it then, and it really does have a lot of biologic background to it. So, I think, yes, think about it.

Most academic medical centers, larger health centers will have access to HIPEC. If they do cardiac bypass, they should have perfusionists, so that could be another thing. So, I think you can ask around in almost any zip code and find someone.

Jenna Fields:

Great. Can you speak to the prevention aspect? You spoke about fallopian tube removal. I know that so many people want to know when is that magical screening going to be coming down the pipeline? What is the latest on prevention and detection?

Dr. Beth Karlan:

Okay. Again, the current evidence continues to grow demonstrating opportunistic salpingectomy will prevent ovarian cancer, whether or not you have inherited the predisposition or not. The age that is right for you depends on have you completed your childbearing? What is your future? If you have a BRCA gene, just for that group, do you intend to have pre-implantation genetic testing, so that you don't carry a BRCA baby? If so, you're going to need assisted reproductive technology.

I've had medical students here at UCLA, they have a BRCA gene, they say, "I want to have only BRCA-free babies." We've done their salpingectomy to reduce their risk at age 25. I've had other women who are 38, they have BRCA2. They really don't want to go through early menopause and they just found out, and we'll take out their tubes then.

If you have a BRCA gene or any of the other genes, I'm just using that as a grab bag, you still need to have the oophorectomy done at the ages that are indicated in the guidelines, but it's a really good first step.

Other things that can lead to prevention, I said birth control pills. There are some trials being done with vaccine therapies. I think those are still really early, but coming down the pipe. We don't want just cutting body parts out to be the only way to prevent cancer. We'd like to have some medical interventions that are easy, like a vaccine.

Screening trials are ongoing. There's a new one being launched. Ovarian cancer, as I said, is decreasing. It's harder and harder to have a positive screening trial. I still believe I'm still helping to participate in a number of the screening trials, but it's still, I think I've said too

many times it's going to be five years away and I don't know when at this point. So, I'm really trying to focus on primary prevention right now.

Jenna Fields:

For our folks who are facing clear cell adenocarcinoma, are ADCs available for them, or are there any maintenance drugs for it?

Dr. Beth Karlan:

Sure. So, yes and yes. Well, okay. Yes and yes. So, maintenance therapy currently can and should be an aromatase inhibitor. Medicines that are often used for breast cancer, the anti-estrogens is what aromatase inhibitors are. There are good data, again, that going on an aromatase inhibitor in the maintenance phase can prolong survival. So, that's something important to consider there.

ADCs depend on your target. So, I only went through the mirvetuximab and the one that targets HER2, the name is also very, very long, those can be on clear cell tumors. The other targeted therapy for clear cell cancer is while immunotherapies, drugs, checkpoint inhibitors like Keytruda, typically are not very effective for ovarian cancer.

Many times with clear cell cancers, and there's more and more trials, looking at combinations of checkpoint inhibitors for clear cell cancers. I can think of more than a handful of women in my practice with advanced clear cell cancers who've had a complete remission and are still there by using combinations of checkpoint inhibitors that were used initially for melanoma.

So, subtype specific therapies are really important. Understanding what are the best targets in your tumor, and then what you and your doctor are most comfortable with. Definitely hope for everybody there.

Jenna Fields:

Great. Thank you. I know there's so many more questions in the chat that we're not going to be able to get to tonight. Dr. Karlan, thank you so much for this informative webinar. Lori Cohen, thank you for sharing your story with us this evening.

Tonight's webinar is sponsored by Merck and we're grateful to our Sharsheret Summit sponsors; Merck, AstraZeneca, Novartis, Pfizer, Lilly, Daiichi-Sankyo, City of Hope, Eye-zai, and GSK.

Please remember that Sharsheret is here for you and don't hesitate to contact us if you need any support. We are putting our evaluation link into the chat right now. Please take a second to evaluate our webinar, so that we can get you more of what you need.

In a second, we are going to be staying on with our community of Embrace Women, those who are facing advanced ovarian cancer. Dr. Karlan is going to offer a private Q&A for that population. We appreciate those who fit that description to stay. And we appreciate those who do not to say goodbye.

We will be sending out our Zoom, our recording, and transcript as soon as it's ready in the next couple of weeks. So, thank you again for filling out the evaluation and have a wonderful evening.