Program Title: Genetics and Genomics of Ovarian Cancer

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Guest Speaker: Dr. Melissa Frey, MD, Assistant Professor of Obstetrics and Gynecology in the division of gynecologic oncology at Weill Cornell Medicine.

Dr. Frey specializes in all aspects of gynecologic oncology. Her research focuses on genetics and genomics in gynecologic cancer. She has presented her research at national and international meetings and has more than 50 publications in peer-reviewed scientific journals. Much of Dr. Frey's research has focused on genetic syndromes that predispose to gynecologic cancer including hereditary breast and ovarian cancer (BRCA1/BRCA2) and Lynch syndrome.

Dr. Frey graduated magna cum laude from Duke University and earned her medical degree from Weill Cornell Medical College, graduating with honors in research. She completed her residency in Obstetrics and Gynecology at Weill Cornell Medicine / NewYork-Presbyterian. She subsequently completed her fellowship in gynecologic oncology at New York University Langone Medical Center. Dr. Frey has received numerous awards for her clinical excellence, surgical expertise and medical research, as well as many teaching awards.

Program Description:

This webinar addresses the following topics pertaining to Genetics and Genomics of Ovarian Cancer:

- The latest research on genetics and genomics for ovarian cancer
- How does your genetics affect treatment?
- The importance and role of genomics as it pertains to treatment
- PARP Inhibitors
- The importance of genetics for family members

NOTE: You may find it helpful to view and listen to the slides from this webinar (which are posted on our website and YouTube channel) while reading through this transcript.

Robin Perlmutter: Good afternoon. I'm Robin Perlmutter, peer counselor here at Support Connection. I'd like to welcome you all to our nationwide webinar on genetics and genomics of ovarian cancer with Dr. Dr. Melissa Frey. Remember that Dr. Frey is sharing her expertise. Any information from tonight -- or today, or questions pertaining to individual concerns should be discussed with your doctor.

It's with my great pleasure that we have Dr. Dr. Melissa Frey, Assistant Professor of Obstetrics and Gynecology in the Division of Gynecologic Oncology at Weill Cornell Medicine. Dr. Frey specializes in all aspects of gynecologic oncology. Her research focuses on genetics and genomics in gynecological cancer. Much of her research is focused on genetic syndromes that predispose gynecologic cancer, including hereditary breast and ovarian cancer and Lynch syndrome. Dr. Frey has received numerous awards for her clinical expertise, surgical expertise and medical research, as well as many teaching awards. Thank you for sharing your time and expertise with us.

Dr. Melissa Frey: Thank you very much for inviting me to be here today with you. I'm going to be talking about genetics and genomics of ovarian cancer.

So we'll just start with definitions and a little bit of background. Cells are the building blocks of the body. They make up all of our organs and tissues. Every cell has DNA. DNA is the hereditary material for our bodies, or sort of the code for building and maintaining cells. And then sections of DNA together are called genes, and these are instructions for our cells. And then many genes

together form chromosomes. And every person inherits two pairs of chromosomes; 23 from his or her mother and 23 from his or her father.

This would be sort of a line of DNA, and then a lot of DNA together makes a gene, and the genes are found in chromosomes. Chromosomes are found inside of our cells. And when something is -- so there's a problem or a mistake in our DNA, and that causes the gene not to function or the protein not to function correctly, that's called a mutation. There are two types of mutations you may have heard of: germline and somatic. And germline means it's present in every cell in our body. So if this is a woman with ovarian cancer, if she had a germline mutation, for example a BRCA mutation, it would be present in all of her cells, including in the cancer cell. It would have been inherited from one of her parents, either her mother or her father, and she would have a 50% chance of passing this on to each of her children.

This is in contrast to what we call a somatic mutation. So if we again take a woman with ovarian cancer, if we looked at her cancer and found a mutation in the cancer that was not present anywhere else in her body, we would call that a somatic mutation. That's not inherited from parents, so it cannot be passed on to children.

When we think about ovarian cancer, both germline and somatic mutations are very important. You can see that about a quarter of ovarian cancers are caused by germline mutations, meaning mutations passed from parent to child. About 6% are caused by somatic mutations. And then the remainder are not caused by mutations, and we're still uncertain for many of these cases as to what caused the cancer.

How are genes shared in families? So if we take a woman, she has 23 pairs of chromosomes, and she has a mother and a father, each of whom have their own chromosomes. And that means that she inherited one chromosome from each parent for her 23 chromosomes. So if we're speaking about let's say this one pair of chromosomes, she inherited the blue from her father and the green from her mother. And let's say she then has a partner, and they go on to have children together. Each of these children will have 50% of his or her genetic material from their father and 50% from their mother, and so it may look something like this.

And now if you think about a BRCA mutation, how does that work? So let's say that this woman's mother had a BRCA mutation on what in this diagram is her green chromosome. So she inherited that chromosome from her mother, so unfortunately, she inherited that BRCA mutation. And then whichever children of hers also have that green chromosome, they also will have that BRCA mutation. So you can see this patient passed on a BRCA mutation to one of her daughters and one of her sons. The important takeaway from this is that mutations like BRCA can be inherited from either a mother or a father. It's not just that it goes down a maternal lineage. And that also all you need, unfortunately, is one copy of the gene that's not functioning to cause a cancer.

So kind of going back to this diagram, if we know that about 25% of ovarian cancers caused by mutations that they're passed from parent to child, if we delve into that group, we know that about 75% are at the BRCA1 and 2 genes and 25% are other genes. So now we're going to look more closely at these genes.

So let's first think about BRCA1 and 2. What cancers are women with BRCA1 and 2 at risk for? Well, we know breast cancer, there's more than a 60% lifetime risk for breast cancer. Of course, ovarian cancer. Now, we separate the BRCA into BRCA1 and 2, and BRCA1 seems to carry the higher risk of

ovarian cancer, about 40% to 60% lifetime risk, versus about 15% to 30% lifetime risk for ovarian cancer with BRCA2. There also is an increased risk for pancreatic cancer more pronounced in people with BRCA2 mutations. And there may be an increased risk for melanoma and in men for prostate cancer.

So this may lead you to ask, for a woman who has ovarian cancer, what do we learn by finding a BRCA1 mutation? So why is it important that women get genetic testing? Well, first of all, treatment implications. Some of you may have heard about PARP inhibitors. This is probably the most exciting advance in the treatment of ovarian cancer in over two decades. The PARP inhibitors are a targeted therapy that seek to work especially well for women with BRCA1 and 2 mutations.

Currently, there are three clinical scenarios for which a woman with ovarian cancer could be prescribed a PARP inhibitor. The first is what we call frontline maintenance. So if a patient has a diagnosis with ovarian cancer and has either surgery or chemotherapy or most often a combination of the two, when that woman completes her chemotherapy, we can offer her what's called maintenance therapy in the front line. And that means that we think there's no evidence of disease when we use a PARP inhibitor to maintain her without disease or keep her from getting the disease again. So that's the first indication of probably currently the most commonly used in patient.

There's also treatment for recurrence. So if a person has ovarian cancer that went into remission but then returns, and then gets treated again with chemotherapy, we can also use this to maintain in that person without cancer after she finishes her chemotherapy. So this is what we call maintenance following recurrence.

And then finally, for people with more advanced disease who've sort of been through or run out of standard chemotherapy treatment options, we can use this as treatment. So not maintaining someone without disease, but for someone we know has active cancer, we can use it for treatment.

Again, the sort of most commonly and most efficacious scenario in which to use this now is this frontline group. And PARP inhibitors actually have been used -- have been approved for all women with ovarian cancer for frontline therapy, all women with advanced ovarian cancer. So it's not only limited to women with BRCA1 or 2 mutations, but we know that it tends to be most effective in women with BRCA mutations, whether that's germline or somatic. And the workflow that we use at our office and I think a lot of oncologists are using now is that every person with a new diagnosis of ovarian cancer should get genetic testing, starting with the blood or the germline testing, because if we find a BRCA mutation, then we know that that person's an excellent candidate for a PARP inhibitor. But even if that testing is negative, then we have to go to the next step, which is test the tumor because we know that in about 5 or 6% of women, we'll find a mutation just with their tumor.

And really our goal is to identify all women who could benefit from a PARP inhibitor. And why is this so important? Well, we know that this therapy, when given as maintenance, can improve progression-free survival. So it can lengthen the time until a cancer returns. And we're hopeful that it may improve overall survival. Although we don't have the data yet, I think many of us are very excited about this drug. But importantly, this relies on -- in order to find who the best candidate is for this relies on genetic testing. And so that testing, I would argue, should be done when someone is diagnosed. So it's really something you need to think about right away with diagnosis.

Kind of back to what can we learn from genetic testing. Well, we can learn about treatment

implications. We can also learn about risk of other cancers. And so even though our patient or a woman, they already have ovarian cancer, it doesn't mean that she can't get one or the other BRCA-associated cancers like we talked about, breast cancer, pancreatic cancer, melanoma. So it's important to kind of allow a woman to be at risk of -- informed about what she's at risk of and also for us to do cancer screening.

And then finally, risk for family members. First degree relatives will have a 50% chance of sharing this same mutation. And so a lot of my patients ask me, "Why would I want to tell -- why don't I get tested and find out I have a mutation and then have to tell my daughter that she might have this mutation and tell her that she's inevitably going to get breast and ovarian cancer. This will just cause her stress without benefiting her." And I think what I'd like to kind of debunk today is that myth that we can't act and benefit from this information. And that really the whole goal is that if we have this information, we can save lives and prevent cancer; not just inform people of their risk of cancer.

So how can we do that? What options are there for risk reduction for BRCA1 and 2 mutations? Well, for breast cancer, there's a lot of options. Starting at age 25, we recommend clinical breast exam and a breast MRI every 12 months. And then starting at age 30, we use both mammogram and breast MRI, do every 12 months so that every 6 months someone has one of the imaging studies. We can discuss option for risk-reducing surgeries. So women do have the option of having a mastectomy to prevent breast cancer. And there's also oral medications, like something called tamoxifen that can decrease the risk of breast cancer.

What about ovarian cancer? Well, we recommend risk-reducing surgery, taking out the tubes and ovaries, usually starting at 35 to about 40 years. However, for women with a BRCA mutation, it is reasonable to wait a little bit longer. We offer ultrasounds of the ovaries and CA125, which is a blood test. But I think it's very important to note that this has not been proven to be beneficial. Unfortunately, we have no good way of screening for ovarian cancer, and that's why we still rely on surgery to remove the organs to prevent the cancer.

We know that oral contraceptive pills can reduce the risk of ovarian cancer. So for a young woman who's not ready to have her ovaries removed and tubes removed, she could consider taking oral contraceptive pills. We also discussed the option of hysterectomy, because there's some evidence that BRCA mutations, especially BRCA1, may increase the risk of uterine cancer. And then also, there's something called salpingectomy, which we're going to talk about for a moment, which is just removing the fallopian tubes.

So just to review the anatomy, these are the ovaries and the fallopian tubes that connect the ovary to the uterus. Really the main role of the fallopian tube is to allow a fertilized egg to travel from the ovary into the uterus to allow for pregnancy. When we operate on women to prevent ovarian cancer, we take out the fallopian tube and the ovary, which is very effective at preventing the cancer. It's standard of care, but it also causes menopause. And so a woman who's 35 or 40, we're putting her into menopause 10 to 15 years earlier than she would have otherwise gone through menopause. And we know that that can be terrible for quality of life, but also for health. There's significant implications for heart health and bone health and cognition. So it's not a decision to take lightly, but of course, we want to prevent ovarian cancer.

There's some new data that actually the majority of ovarian cancers are not ovarian cancer at all, but actually are fallopian tube cancer that starts in one specific part of the fallopian tube, which is

the end of the fallopian tube that's closest to the ovary. And if this is the case, then really, maybe we don't need to be removing the ovary. Maybe we can just take out the fallopian tube and save the ovary, and that's called salpingectomy. I'll tell you, this is not yet standard of care because we don't know that it's safe from a cancer or an oncologic standpoint. But there is a serious benefit, which is that there's no surgical menopause. And there are currently four or five ongoing clinical trials trying to better evaluate this, because if we do find that this is safe, this will be a major benefit for women who are trying to prevent ovarian cancer, but who do not want to undergo early menopause.

So, just continuing on to how can we prevent cancer in women with BRCA mutations. For pancreatic cancer, we now have some protocols that seem to be effective for pancreatic cancer screening. However, I would advise that this really should be done at high volume centers because this is relatively new. And then finally for melanoma, we recommend skin checks and eye checks so that if a melanoma does develop, it's caught early.

We're now going to switch gears and talk about Lynch syndrome. We kind of covered BRCA1 and 2. Now we'll talk about Lynch syndrome. Lynch syndrome is a different cancer predisposition syndrome that's caused by a mutation of one of five genes, either MLH1, MSH2, MSH6, PMS2 or EPCAM. The main cancers that are associated with Lynch syndrome are colorectal cancer. There's about a 50% to 60% lifetime risk. And endometrial cancer with the risk ranging about 30% to 60%. But there does seem also to be an increased risk in ovarian cancer for some of these genes approaching 40%, and then also various other cancers with lower risks. So we know Lynch syndrome has many associated cancers.

You could ask the same question. For a woman with Lynch syndrome, what do we learn by finding a mutation? Well, there are also treatment implications. So if someone has Lynch syndrome and an ovarian cancer, she may be a candidate for immunotherapy. We know that many of these tumors in Lynch syndrome are exquisitely sensitive to immunotherapy. There's also the risk of other cancers. So if a woman develops an ovarian cancer, we'd want to know if she's also at increased risk of developing colon cancer or uterine cancer. And then finally, the risks persist for first degree relatives. So a 50% chance of all first degree relatives having the same mutation, a 25% chance for second degree relatives and so on.

What are the options for a person with Lynch syndrome if we find this out before cancer? How can we reduce that person's risk of cancer? Well, for uterine and ovarian cancer, we can do ultrasounds and biopsies, but then really the standard mainstay of treatment is a risk-reducing surgery. So that's -- for these people, that's removal of the uterus, tubes and ovaries. For colon cancer, we perform regular colonoscopies and endoscopies. We can perform pancreatic cancer screening and skin screening.

So kind of moving away now from those specific syndromes, we're going to talk about ovarian and breast cancer a little more in general. So do genes contribute to ovarian and breast cancer? Well, we went over already that many ovarian cancers are caused by mutations either in genes that are inherited from parent to child or just something in the specific ovarian cell that stopped functioning properly.

What are the genes? We talked about BRCA1 and 2 contributing to ovarian cancer, but we're actually learning that there are some others, like the Lynch syndrome genes. And then also these are three genes, RAD51C, RAD51D and BRIP1 that you may hear more about. And these are genes

that we know can also run in families and can increase the risk of ovarian cancer. Additionally, there are some genes that we're currently studying, so PALB2 and ATM. We may find with more research that these also significantly contribute to ovarian cancer. So you can see all of these genes may be related to ovarian cancer, and so it's important that we evaluate for this in any woman who has ovarian cancer.

What about breast cancer? We know that in breast cancer, about 10% of cases are due to mutations that run in families. And which genes can cause breast cancer? Well, again, BRCA1 and 2 certainly can cause breast cancer, but there are a bunch of other genes that have a known association with breast cancer and then a couple of genes that we're currently studying that may cause breast cancer.

So kind of going back to a woman with ovarian cancer, what are the implications of genetic testing? Well, we said if you find a mutation, it will clarify the cause of her cancer, which can be very helpful for someone. It can inform her of her risk of other cancers. It can allow us to use sort of the best and newest targeted therapy. Usually that's going to be PARP inhibitors.

But then there's one more implication that I've alluded to earlier, but I think that we often as physicians don't pay enough attention to and that we really need to start thinking about, and that's called cascade testing. What is the cascade? Cascade is a process whereby something, typically information or knowledge, is successively passed on. And in genetics that means if I find a person with a BRCA mutation, I have to offer her relatives who are also at risk of carrying this mutation the option for genetic assessment. That's sort of part of my responsibility as a clinician.

What would be sort of the ideal way that we carry out cascade testing in this country? So if I see a woman who's diagnosed with ovarian cancer, I will immediately offer her genetic testing. And if we find a mutation, we can offer her targeted therapy with PARP inhibitors, and we can also allow her to prevent other cancers with breast screening, et cetera. But really simultaneously, we should be reaching out to her relatives, offering all of them testing if they're interested, identifying those who have the same mutation that's in our patient, and then allowing those people to benefit from cancer prevention. And this is how I would really see the ideal way of sort of use of genetics for ovarian cancer. Unfortunately, we know that less than 30% of relatives end up getting tested, which is really sort of a dismal number because we know that these relatives can have up to a 70% or 80% risk of developing cancer in their lifetime.

So why is it that less than 30% of relatives end up getting tested? Well, I think it's actually not that surprising when we think about it. Currently, we place the burden entirely on women with newly diagnosed cancer. So we tell a woman you have ovarian cancer. You have to cope with your cancer diagnosis. You have to prepare for surgery and then recover from surgery when it's finished. You have to prepare for chemotherapy. You have to navigate time off work. Consider the financial toxicity of cancer and cancer treatment. Consider risk for other cancers.

But while doing all of this, you have to be the sole person who's responsible for cascade testing of your families. You have to contact your relatives, some of whom you may not be close with or may be estranged from. You'll have to disclose your own cancer diagnosis and your own mutation. You'll have to explain to them how this works, how very complex genetics function. And then they're going to ask you, "Okay, how do I get tested? You're telling me I have this risk. What should I do next?" So I think when we place this whole burden on our patients, it's not surprising that it's too much, that this is not a system that's going to function, and we have to find alternatives.

So we have some research going on at Weill Cornell where I practice that's trying to have the clinician or the medical team take on this burden. What we're doing is we're actually working with our patients, and if they want our help, they'll tell us, these are my relatives. You're allowed to contact them. We'll contact relatives by telephone. We'll offer them videos by email. And if they want to have genetic testing, we can actually accomplish that through a kit that's mailed to their home. So a relative never even has to leave his or her home. The relative can live in a different state. All of this can be done by telephone and mail.

Our goal is to transfer this burden away from our patients and put it on us, the medical team, because we think we have some more resources to deal with this, and really prioritize the convenience of our patients and our relatives. And just to show you one example of what this looks like, this is one of the first patients who was enrolled in our pilot study. This was a 36-year old woman who had Stage 4 ovarian cancer, and we found a BRCA mutation. She had a very big family who was very invested of course in her care, but also she said to us, "We're all family members. How do we get tested? We don't have a doctor that knows how to do testing or we may not have health insurance or may not have time to get to the doctor right now. What can we do to get testing?"

And so we spoke with all these relatives on the phone, and for relatives who were 18 and older, we offered them testing. And we explained to them your risk is 50% of carrying this. And among the six relatives who we spoke to, all underwent testing, and we found that four of them actually had the same mutation. And within six months, all four of these relatives had undergone either a medical appointment, a screening, a mammogram, some of them even a risk-reducing surgery. So we know this is effective and we know it can work. And that's something that we're continuing to study at Cornell because we really would like to create a paradigm shift where everyone offers is standard of care where the medical team helps our patients and it's not just in a research setting.

So I think -- I've tried to explain to you why I think it's critical that we find out who among women with ovarian cancer has a BRCA mutation or a Lynch syndrome mutation. It can affect treatment, but it can also sort of help us prevent cancers in relatives. So let's think about this now on a population base level. So if we think about for each cancer, we're going to go over the number of cases, the number of deaths, the percentage that are due to a condition, and then how many we prevent.

So let's think about breast cancer. There were almost 300,000 cases in 2020. There were about 40,000 deaths. If we think that 10% of these cases were due to BRCA mutations or Lynch syndrome mutations, that's almost 30,000 cases that could have been prevented or caught earlier had we known about the BRCA mutation. For ovarian cancer, there are about 20,000 new cases a year, about almost 14,000 deaths, and we know that let's say about 20% of those are due to genetic causes. That's over 4,000 cases we could prevent had we known about all of these women in advance and offered them a risk-reducing surgery. And then finally for uterine cancer, there are about 65,000 cases a year. Only about 3% are genetic, but that's about 2,000 cases a year that we could prevent or diagnose early if we had this information. So if we sum this all up, that's about almost 35,000 cancers that are due to mutations each year, 30,000 female cancers that could be either prevented or caught early if we had this genetic information.

So a lot of people when I give this talk ask me, "Well, I had genetic testing, but I think it was a few years ago. Should it be repeated? Or once I had it, am I good if I don't have a mutation at the end of

the day?" I think the first thing I ask is what type of genetic testing did you have? So what are the types? I think most physicians and most patients are aware that there are different types of testing. So there's something called single site. Especially before recently, if you knew there was one mutation that ran in your family, we could test for just that mutation. And so if you had testing, we can't tell you what's going on in all of your genes, but we know that you don't carry this one mutation that let's say your sister or mother or brother had.

There's a very common form of testing, it's called the Ashkenazi Jewish 3-site testing. So this is looking for the three most common BRCA1 and 2 mutations that are found in Ashkenazi Jewish people, and this again is very commonly performed. There's something called single gene testing where we just look at BRCA1 and 2, but we're looking at the full genes; not just specific sites in those genes. And then the most recent form of testing is called multigene panel. We can look at big panels of genes, often exceeding 50, 60, 70 genes, and we're looking at all of them at the same time. And really, we can do it all for the same cost and the same time as we can do single site testing, so this is how the majority are tested by now.

The next question I'll ask besides what type of testing someone had was when was the testing completed, because that will give us some information on what type of testing someone had. So for this, I'm just going to quickly look at a history of commercial genetic testing. So we know BRCA1 was cloned in 1995, BRCA2 in 1996. Sometimes I'll have a patient tell me that her mother had ovarian cancer and passed away in the 1980s, unfortunately, but her genetic testing was negative. It's important to know that we didn't have this genetic testing before the mid-1990s. And so anyone who was diagnosed and passed away before that time really could not have had genetic testing.

The way that we test BRCA1 and 2 really changed dramatically in 2006 with something called BART testing. And so for someone who didn't have testing after 2006, we definitely consider retesting because we know we're catching many more people with mutations when we use that method of testing.

In 2010, there was a new method of testing called next-generation sequencing. And this sort of happened around the same time as the Supreme Court case. There was a Supreme Court case in 2013 that basically invalidated single gene patent. So before then, there was one company, Myriad, that was the only company that could offer genetic testing. It was good that we knew that everyone who got testing got very high quality testing through an excellent lab. The problem was it was very expensive. It was often exceeding $3,000 for testing, so that really limited testing. After 2013, there had been many, many companies that offer testing. And this sort of heralded a ship where we went from just BRCA1 and 2 testing to testing these larger panels. And so if I had someone who had testing prior to 2013, I usually recommend repeat testing with a larger panel.

So kind of in summary, is repeat genetic testing ever indicated? I would say yes. Sometimes we should update testing based on changes in technology, based on changes in family history or based on changes in knowledge of genetic syndromes. And then also -- but I think this requires really thorough genetic assessment by an oncologist or genetic counselor to really work through exactly what the family history was or what the prior testing is.

Then in summary for the whole talk, inherited mutations account for 20% to 25% of ovarian cancers. Information about a genetic mutation has many health implications. It has implications for cancer treatment, risk for other cancers and risk for cancer among relatives. Genetic testing is

complex and dynamic. Sometimes updated or repeat genetic testing is warranted. And for those with mutations, communication with family members is critical and something that we, the medical team, should facilitate and work with you on.

I want to just thank Support Connection for inviting me to speak today and also my team at Weill Cornell. And I invite any and all questions.

So the first question I think has to do with some of the PARP inhibitors and risk of blood cancers like leukemia. So I think we're all very, very excited about the PARP inhibitors. And some of you may know those as the names are Lynparza or RUBRACA or ZEJULA. But there is this risk of blood cancer. There's risk of secondary cancer with any cancer treatment, any chemotherapy, but we think the risk may be a little higher with these PARP inhibitors. And the risk that we currently appreciate is probably about a 1% to 2% risk of getting a blood cancer from these PARP inhibitors, and that seems to be pretty consistent across trials. But I would tell you that while that's scary, we know the risk of an ovarian cancer coming back is significantly higher than 1% to 2%. So I tell my patients, if I think they're a good candidate for a PARP inhibitor for maintenance, I would be very excited and encouraging about using that.

Okay. The next question, "I'm a BRCA2 positive ovarian cancer patient. I've been on Lynparza for almost two years. What is your recommendation about continuing on the medication or stopping?" This is a question that's coming up now. It's going to -- I think we're going to learn more about this soon. And I think the issue is that this drug is relatively new, and so we don't have a lot of long-term data. Currently, I think most providers are considering stopping the mediation at two years, unless we think that a woman is getting clinical benefit. So if there is evidence that there's some disease, but it seems to be stabilized by the medication, then we would continue it. But if someone has no evidence of disease, our hope is that there's some women who are going to be cured, and so there's no reason to continue on this drug for years and years and just collect toxicity risk without changing cancer recurrence rate. But it's of course impossible to know who's been cured and who hasn't, but currently, most people are considering stopping the mediation at two years.

"When did the idea of germline or somatic testing start? Is it standard protocol for ovarian cancer surgery?" The idea of germline testing has been around since the discovery of the BRCA genes in the mid-90s. But I can tell you -- and really, it's been over -- I think that the Society of Gynecologic Oncology in the early 2010s, maybe 2014, had an official recommendation that everyone should have germline testing. But I recently have reviewed the literature from across the country and across the world, and the majority of people with ovarian cancer still do not get genetic testing, despite multiple organizations, including the Society of Gynecologic Oncology recommending it. So I can tell you that even though it's standard, the majority of people are not getting this.

And then as far as somatic testing, that's not current -- there's currently different workflows at different practices. I think many oncologists are including that in their workflow, and I think it's something that can be helpful. But as far as when that should happen and whether it's absolutely standard, that's still yet to be determined.

"Is there anything on the horizon that will improve longevity beyond existing PARP inhibitors?" There are always things on the horizon, and there are multiple, multiple ongoing clinical trials. Many trials are looking at immunotherapy. Although I would say overall the results of immunotherapy in ovarian cancer have been a little bit disappointing. But I think there are many, many trials. There are many PARP inhibitors. There are many combinations of drugs that we've

used in the past with PARP inhibitors. So I think there are things that are exciting, but not anything that I can specifically name right now.

So someone asked if they -- so another drug that's used as maintenance is called Avastin. Another name for that is bevacizumab, and that's also been used as maintenance. And some people asked what are the advantages of Avastin versus a PARP inhibitor and what are the risks of Avastin. So, there actually now are trials of using both Avastin and a PARP inhibitor together, and so some clinicians are doing that. Other people are concerned that that's just too many side effects, too much toxicity. If someone has been on Avastin for eight years, and I think that's exciting that it's been successful for eight years and preventing the disease from coming back. Avastin does have some pretty serious side effects. It can cause very serious high blood pressure. It can cause blood clots. It can cause problems with the intestines. But I think for someone who's tolerating it well, that's great. And I think we've never had a study that I'm aware of that has sort of a head-to-head comparison of a PARP inhibitor versus Avastin. I would tell you in my practice, if someone has a BRCA mutation either in their blood, so something inherited, or in their tumor, I am favoring PARP inhibitors because I think that really, the studies are exciting. But I think Avastin is also a great option for many patients.

"How long does someone have to stay on a PARP inhibitor who has ovarian cancer?" I think this, as someone else asked this question, this is really something that we're all struggling with right now. And we think these trials are all relatively young, so we don't have great long-term follow up. And that's something that hopefully we'll learn about in the coming years. But the question of when did the benefits of that medication start to be outweighed by the potential toxicity, like the leukemia that you mentioned, no one knows yet. I think we do have this statement or kind of practice that we sort of reevaluate after two years to see. But there's no absolute rule, but the two years is when I reevaluate and consider stopping.

"Can you speak to what a woman of childbearing years with BRCA2 can do to limit getting -- future offspring from getting the gene?" Okay. This is a really important question, and it's something that should happen when someone has genetic testing and is bound to have mutations, this is a critical part of the counselling. It's important to tell relatives because it can affect their ability to prevent cancer, but there's also reproductive options. Women who are planning to get pregnant, who feel strongly that they do not want to have a child who shares this mutation can use assisted reproductive technologies, so in vitro fertilization. And can sort of remove oocytes, eggs, fertilize them, and then check the embryo prior to being re-implanted to make sure it doesn't have mutation. Now I think -- I don't recommend this because this is a moral and ethical decision; not a medical decision. And of course one thing to consider is that the woman who's thinking about making this decision herself had this mutation, and so of course if her parents had decided to use this technology, she may not be here, kind of however you conceptualize that. So I think it's important to let people know this is an option, and we certainly at Weill Cornell have a very large fertility center and have many, many women each month that come through our center who are using in vitro fertilization for this reason. But it's a personal decision. It's not always covered by insurance. Often not covered. So it could be a financial decision for some people. But it certainly is an option.

I think it's important that we inform people of this option, especially because many women may have to use IVF, in vitro fertilization for other reasons. A woman may have infertility for other causes, and so she may want to know if she's already doing this process, if she could also only use embryos that she created that don't have a mutation, that's a possibility. So thank you for that

question. It's very important.

"We always talk about having conversations with our daughters, but given increased risk of prostate cancer, too, should we have the same conversation with our sons and have them do genetic testing?" I think the answer is absolutely. There's risks for prostate cancer. There's risk for pancreatic cancer, which can happen in both men and women. And especially for BRCA2, there's a risk of male breast cancer. Additionally, relatives, male relatives may have children. And so they then have the possibility of passing this gene on to their sons or daughters, and so they may also want to consider some of the reproductive technology to prevent that if it's what they want to do. So I think it's critical that we discuss this with both sons and daughters and remember that this can be passed to us from either our mother or our father. But I think there's this misconception that's understandable that this always comes from the maternal side. And it's really 50/50 whether it came from a mother or a father.

"Is it fair to suspect that being on a PARP is also prevention from breast cancer recurring?" That's a great question. I don't think we know that. There are a lot of studies now currently ongoing with PARP inhibitors for treatment of breast cancer. And I think the same would be said for ovarian cancer. If a woman is on a PARP inhibitor for breast cancer treatment and still has her ovaries, does that reduce the risk of ovarian cancer? And I think we all like to think yes, but we don't know that yet. And I think that leads to the next question of, "Will we ever use PARP inhibitors as preventative measures?" So for a woman who doesn't have cancer who's at high risk. I don't think we have that data yet, and that's going to require some careful consideration of possible benefit versus possible side effects and toxicity. But again, very, very good question.

Another patient asks, "I had BRCA testing 2013. I was negative. In 2014, I was diagnosed with ovarian cancer. Should I get gene tested again?" Great question. The first step I think would be to meet with a genetic counselor or an oncologist and bring a copy of the testing, because the copy of the testing will say exactly what testing someone had. So if the test was just BRCA1 and 2, then I would recommend getting retested. Because we know about a quarter of the mutations that we find in ovarian cancer patients are in genes other than BRCA. For example, those Lynch syndrome genes or maybe talk about RAD51C, RAD51D, BRIP1. And so there's certainly a chance we're going to find something. I think it's less likely because we know that BRCA1 and 2 are the most common, but it's certainly possible. And most genetic counselors would recommend updated testing, and insurance is often covering it for that reason. So I think it's worth at least having the discussion and talking about it.

"You mentioned oral contraceptives can reduce ovarian cancer. I've been told they increase the risk of breast cancer. Is that true?" Thank you for another really important question. There is some concern that taking extra estrogen can increase the risk of breast cancer. But I think that while we have some signal of that, the finding is not so strong, and so that's not an absolute certainty. We have very, very strong evidence that women who take birth control pills, especially for 5 to 10 years, have a significant decreased risk in ovarian cancer. Approaching 40% to 50% decreased risk of ovarian cancer. And so I think for young -- and I'll also say, I'm very biased because I'm a gynecologic oncologist, so I treat ovarian cancer. So my mind is always on ovarian cancer, and I think less about breast cancer. But I would argue even despite my own biases, breast cancer is something we have screening for, and breast cancer is something that can be cured when it's found. Ovarian cancer has no screening, and ovarian cancer often cannot be cured once it is found, or it's a lot more difficult to cure. So my bias is always towards preventing ovarian cancer over breast cancer, but of course, you can't say that it comes with no risk.

"What's the recommendation for how to do contrast dye CAT scans following surgery, chemotherapy and PARP inhibitor use?" This is a good question. I think that -- I don't know of any specific guidelines. I think in general for women who aren't on treatment, when they finish treatment, we're not doing what we call surveillance scans, meaning that you don't have to get a CAT scan every three or six months. For women on PARP inhibitors, some people would say you don't have to get a CAT scan and just follow a blood test, whether it's CA125 and follow exams. Some providers are getting regular CAT scans. For women who are getting this on a clinical trial, they most likely will be getting regular CAT scans as part of the trial, but there's no absolute recommendation at this point.

Unidentified Speaker: What is the significance of a CA125, which is increasing in terms of the number?

Dr. Melissa Frey: CA125 is sort of a complex part of ovarian cancer screening and treatment. I've given a whole hour lecture on that for women with ovarian cancer because it's so complex. But I'll tell you, we use it for a few scenarios. We use it when a woman, if someone comes to be and has an ovarian mass, we'll get a CA125, and if it's very high, that will kind of raise my suspicion that there's a cancer. For women who have high risk of cancer, either because of a family history or because of a mutation like a BRCA1 or 2, we do check CA125; however, I can tell you that we've never shown that that's an effective way to screen. We do it because we think it's relatively low cost and relatively convenient for patients because it is a blood test, but we don't have great evidence.

Where it really has been approved and where it's most useful is we have -- if there's a woman who has ovarian cancer and you're getting treatment, we can often -- the CA125 will drop as the cancer responds to treatment. So it's very good surrogate marker for treatment being effective. And also for a woman who had ovarian cancer, if we're worried about it returning or just want to kind of follow her, we can check that on a regular basis. And often a CA125 will rise either just as the cancer returns. So for some women, it kind of correlates very well with their cancer, but the issue is for some women, it correlates poorly. So you could have one of two scenarios. We have women who have very elevated CA125 because maybe they have pancreatitis or maybe they have a gastrointestinal infection or any kind of inflammation can increase CA125. We also have women who may have cancer, even a very advanced cancer where the CA125 is total normally. So I think the CA125 fails on both extremes, but we use it because it's sort of the best that we have right now.

Unidentified Speaker: Thank you very much.

Dr. Melissa Frey: "Have existing PARP inhibitors been ranked based on efficacy and time of successful treatment?" So currently there have been no head-to-head evaluation of different PARP inhibitors, so comparing one to the other. There are currently three that are approved for use in ovarian cancer. And often the way I choose them is not all that are approved in the exact same scenario, so one might be approved just for BRCA mutations. One might be approved for everyone in a certain scenario. So sometimes that drives what I prescribe. The other thing is side effect profile. So even though we don't have a study comparing all three, we know from individual studies, this specific mutation may be more problematic for people who have low platelets. Or this specific medication may interact with other medications that that person is on. So I think it's an individualized discussion with someone's oncologist about which is the best PARP inhibitor for you, but we don't know that one is better than the other.

"Following surgery and treatment, how would one know if ovarian cancer has returned?" So one of

the things we can do is a CA125, and we can check that. Often we're checking that every few months. The other is just regular exams, because unfortunately if this does return, usually we'll either go to something on exam or women will feel symptoms. So the symptoms they feel like when the cancer was initially diagnosed. So for a lot of people that's abdominal bloating or feeling like one's getting full very quickly, like you take a couple bites of food and then you're full. For other people that's nausea or vomiting or fatigue, or sometimes that's shortness of breath if it's cancer in the lungs. We can use CA125 for this, and there actually have been some very good studies that show that actually the CA125 will often go up before someone has symptoms, but it's usually only a few weeks before. And so I think whether someone wants that CA125 done for that reason or not, it's a very personal decision, not a medical decision, because it doesn't affect how well we treat people, how long people live. And so I think the most common way when we find this is symptoms.

"Is it possible to talk where for women that were on SOLO-1, trials of Lynparza, that progression-free after five years?" Okay. So the question, I think this is the question that we're all asking. There have been some really exciting studies. One of them is called SOLO-1. That was one of the first study published looking at women who completed their treatment for ovarian cancer and then were put on a PARP inhibitor. And this is where we're getting this exciting information. These PARP inhibitors really work in people with BRCA mutations.

But the question is what happens after five years? We were so excited about these results. They published them before we have all of the follow-up data, and that's because we want to get this information out. Well, we don't know yet as far as how does this affect how long people live in general. We know that people are having long, long periods with no disease, exceeding 20 months, which is great. But we don't know what's happening two, three, five, seven years from now for everyone.

And I think the way to -- how do we know -- how do we learn from this? I think we're hoping that this data's going to be published, and before it's published, it will be presented at our meetings. And I know that many of the ovarian cancer kind of wonderful groups like this group, as soon as they have information like that, we have experts come and talk about it and put that information out. But currently, we don't have all that information yet.

"Will PARP inhibitor costs go down? Avastin options -- Avastin treatment option costs are much lower than PARP inhibitors." This is a major issue that I appreciate. And Avastin is also very expensive. And I think it depends on specific insurance carriers what's affordable and what's not affordable. And of course we're very hopeful that PARP inhibitors go down. But I think if financial toxicity or financial issues are a barrier for the one getting PARP inhibitors, it's worth discussing it with either your oncologist or social worker at the office, because I know that many of the companies that offer PARP inhibitors have really powerful patient assistance programs. And so there often is help available if you ask for it and look at it. And that might mean switching to a different PARP, or that might mean just using a resource that you didn't know existed. But I think each of these drug companies has people who are specifically designed to help patients who are having trouble with the cost of the PARP inhibitor. That's not going to be the answer for everyone, but for many women that can be helpful.

Robin Perlmutter: Does Weill Cornell have a surveillance program?

Dr. Melissa Frey: Yes. So as --

Robin Perlmutter: So that if you're not a patient, but you want to send someone there. Like what you were saying that the clinicians are getting more involved in helping patients with their family members, can family members just come to your center?

Dr. Melissa Frey: Yes, absolutely. So one of the things -- we have four gynecologic oncologists in our group, and each of us has sort of a different clinical niche or area that we do the most. And I do the most of the cancer genetic syndromes. So families with BRCA or Lynch or RAD51 genes. And so one of the things I do is not just treat my patients, but I treat family members, and even family members who are not my patients. And I team closely with our clinical genetics program, and we actually have registries here. So basically, if I see a women with a Lynch syndrome or a BRCA mutation or RAD51C, I will see her and I will take care of all her gynecologic issues, even when she doesn't have cancer. My goal is to prevent cancer.

But then I also will basically create a network for her and providers here who are very aware of the mutation and what has to be done, then we all meet as a group. And so we have gastroenterologists who can do pancreatic cancer screening or colon screening. We have breast surgeons and breast medical doctors who can help work on the breast screening. We have nutritionists. We have genetic counselors. We have all that sort of built in. We have dermatologists for skin checks, ophthalmologists for eye checks. We're in Manhattan, so we're not -- because of real estate we're not all in the same building, but we're all very, very connected. We can try to sort of make the appointments as convenient as possible so that people can have this all taken care of in a way that's very coordinated. And then as a group, we meet frequently as a whole group to discuss all the patients to make sure that nothing slips through the cracks, so basically kind of creating sort of a registry so that everyone's followed.

Robin Perlmutter: Terrific. Thank you.

Dr. Melissa Frey: "My daughter has been seeing Dr. Cigler for the last seven years for surveillance. She has the BRCA2 gene." So Dr. Cigler is one of the most prominent members of our BRCA and hereditary cancer team. Her name's Tessa Cigler. She's one of the breast medical oncologists here. And so again, I think anyone who's seen here that wants to be a part of multidisciplinary care absolutely can be.

And we're trying to be innovative also as far as how to make our care more patient centered. So an example, and the Lynch syndrome is a little less common in woman with ovarian cancer, but there may be people that this group serves that have Lynch syndrome. In woman with Lynch syndrome, the medical community recommends a colonoscopy and an endometrial biopsy every year. Endometrial biopsies are very uncomfortable, and having to do that every year at a gynecologic oncologist's office is terrible. And so one thing we offer here now is we do them together at the time of the colonoscopy. So people are getting a light anesthesia for the colonoscopy. Why can't we just do the endometrial biopsy while someone's already sort of sleeping comfortable? It sounds easy, but that actually took years of planning to be able to have a room that could do both. But that's sort of the type of thing that I'm interested in both clinically and from a research perspective, how can we really make things more patient centered and easier for our patients.

Robin Perlmutter: There's another question.

Dr. Dr. Melissa Frey: "I came late to the meeting. Where are you located?" So I'm one of four gynecologic oncologists at Weill Cornell Medicine. We're at New York Presbyterian Hospital in Manhattan, on the upper east side of Manhattan on 68th Street.

Robin Perlmutter: That's about it. And Dr. Frey, thank you so much for such an outstanding presentation, your passion, dedication and commitment to the cancer community. And especially now more than ever, a heartfelt thank you for all that you're doing during these challenging times. And to all of you for taking the time to become educated on this very important topic. Have a great day, everyone. Thank you.

Dr. Melissa Frey: Thank you.

Unidentified Speaker: Thank you.