Program Title: Toll-Free Teleconference for Women with Ovarian Cancer

Presented by: Support Connection, Inc.

Originally Recorded on: September 18, 2012, 8 pm - 9 pm (NY time)

Guest Speaker:
Michael V. Seiden, MD, PhD of Fox Chase Cancer Center in Philadelphia: President and CEO; Principal Investigator for their NCI-sponsored comprehensive cancer center grant; Principal Investigator for the NCI-funded ovarian SPORE grant shared by Fox Chase and the University of Pennsylvania. Before joining Fox Chase, Dr. Seiden served on the faculty of the Dana Farber Cancer Institute, Harvard Medical School, and Massachusetts General Hospital where his research interests included translational research in gynecological malignancies with a focus on ovarian cancer.

Topics:

- Evolving knowledge about different sub-sets of ovarian cancer
- The move towards treatment based on serous, muceneous, clear cell and low-grade tumors
- The potential for individualized therapy through molecular profiling
- Recent reports on clinical trials e.g. Avastin, PARP inhibitors
- "BRCAness" – i.e. traits some cancers share with those occurring in BRCA1 or BRCA2 mutation carriers.
- Question and Answer period

Robin Perlmutter: I'd like to welcome you all tonight to our Fifth Annual Ovarian Cancer Educational Teleconference. I am Robin Perlmutter, the Clinical Director and peer counselor here at Support Connection. We have over 35 women here tonight from across the nation, from both coasts and in between.

Just a few housekeeping points before I introduce Dr. Seiden. You will notice that your lines are muted. After Dr. Seiden's presentation, you will have the opportunity to ask questions. I will just ask at that point that you hit star, 7, if you have a question for him, and that will unmute your line. Everyone else, if you're not asking a question, please keep your line muted so that we don't have any background noise. Please do keep your questions brief specific to the topic so that we can allow some more questions. Remember that Dr. Seiden is sharing his expertise tonight, and any information from tonight or questions pertaining to individual concerns you should be discussing.

It is with my great pleasure that we have Dr. Michael Seiden, President and CEO of Fox Chase Cancer Center in Philadelphia, with us tonight. Dr. Seiden is principal investigator for the NCI-sponsored Comprehensive Cancer Center grant, and he also serves the same role for the NCI-funded ovarian SPORE grant. Thank you, Dr. Seiden, for sharing your time and expertise with us tonight.

Michael Seiden: Oh, you're welcome, and good evening, everyone. It's a real pleasure to spend an hour with you. And I thought I would take about, oh, 30 minutes or so to talk a little bit about where we are in the treatment of ovarian cancer, and do it a bit in the form of a story that will touch on a number of the topics that were passed out in the outline.

I think, really, the science that we are unraveling in ovarian cancer now links back to a clinical observation and that is (inaudible) cancer survivors are probably very familiar with it, and that is how a woman does with ovarian cancer. And in particular (inaudible) very, very different. There are some women who are cured with the disease, there are some women who enjoy remissions that are many, many, many years in duration, and there are some women who have very short remissions or, even in a few cases, don't have a remission. And the question that has really been one of the center -- the most important sort of centerpieces for the scientific community to figure out is why is that?

And one of the very early observations that were made in the late 1990s was that young women who were diagnosed with ovarian cancer, particularly women in their 40s or 50s who had family histories of ovarian cancer and breast cancer, and who had mutations in BRCA1 or BRCA2 -- these are two important genes; everyone is born with two copies of these genes. But women who were born with a defective copy of one of these genes, if they developed ovarian cancer, and they were at very high risk for ovarian cancer, even though they were at high risk of

getting the cancer, as a group, they seemed to do much, much better after they received platinum chemotherapy than other women with ovarian cancer. They tended to live years longer. That intrigued scientists. In fact, we noticed this observation even before we knew what BRCA1 and BRCA2 did.

Scientists continued to do some research and discovered that the BRCA proteins were both important in repairing DNA, and they work together to repair DNA in a very special way.

Let's, for simplification, say there's two ways to improve and to fix DNA: way A and way B, and both of these proteins repair DNA through a pathway called way A. And repairing DNA in cancer cells is actually important. The DNA in cancer cells is pretty messed up, and the cancer cells became cancerous because the DNA is pretty messed up, but if the DNA gets too messed up, the cancer cells die.

So, some very smart scientists said, well, these women who have BRCA mutations, they can't fix their DNA by way A, what about by way B? If we could block that other way of fixing DNA, the cancer cells would have no way to fix the DNA and they would die. And these clever scientists figured out that a drug, or a family of drugs called PARP inhibitors, could paralyze that second way that cancer cells could fix their DNA. So that for women who had BRCA mutations, giving these cancer cells, or exposing these cancer cells to a PARP inhibitor led to the cancer cells dying very, very quickly in the testing. And this led to a series of experiments that started about four or five years ago, where women were being given PARP inhibitors.

And during the very early parts of the clinical trials, it was given to a lot of different people who had cancer, but about halfway through the first trial they said, well, let's selectively give this to some women with ovarian cancer who have known mutations in the BRCA genes. And in some of these women, indeed, many of these women in these early trials, there was evidence of dramatic responses to the PARP inhibitors.

And some women, they received multiple prior types of chemotherapy including platinum chemotherapy where their tumors had been resistant to standard chemotherapy, many of these women had very nice responses to PARP inhibitors. Some women had 90% or greater drop in their CA-125. These were oral medications. In general, their side effects were less severe than chemotherapy. That led, in the, oh, three or four years ago, maybe two, three years ago, a lot of enthusiasm around the use of PARP inhibitors.

Now, as some of you, or maybe most of you know, PARP inhibitors are not yet widely available. And indeed no PARP inhibitors are FDA approved, which has been frustrating to clinical investigators and to ovarian cancer patients.

There have been a couple of reasons for that. One has been a technical reason. The first drug that came out was a drug called olaparib. That was a drug for which there was the most amount of data, and it was initially formulated in a capsule. And it just ended up that the right dose was taking 8 capsules at a time, and taking 8 capsules at a time, especially if you're taking the drug every day or twice a day, is pretty onerous. So, the company decided they really couldn't do that. They had to switch from manufacturing it from capsules to tablets. And it took longer to do that than they anticipated, and the appropriate dose of the tablets ended up being a little bit different than the dose for the capsules. So, there were definitely some technical slowdown.

The other thing, unfortunately, is ovarian cancer is not that common. For women who have epithelial ovarian cancer, that's maybe 20,000 women diagnosed a year. But if you say, well, how many of them have BRCA mutations, that's only 3,000, 4,000 a year at most. And unfortunately pharmaceutical companies, when making decisions, have to ask themselves, well, we have a lot of different things we can invest in, will there be a large enough demand for this particular drug to put it at the top of our priority list?

So, there has been, at least in some of the pharmaceutical companies some ambivalence to how important this drug would be in their entire portfolio of medications that they sell. So, that has led to some disincentives.

But the other thing is, people with BRCA mutations, they can't repair their DNA well, tend to be pretty sensitive to a lot of chemotherapy drugs, and in fact, the pharmaceutical company had done a small trial where half the women got a PARP inhibitor and half the women got Doxil. Maybe some of you have had that drug. It's a commonly used drug in ovarian cancer. And in that trial, the women who received the PARP inhibitor did very, very well. But because people with BRCA mutations (inaudible) therapy, the women who received Doxil also did pretty well.

So, there wasn't a giant difference, which told the pharmaceutical company that to get this FDA approved would take a much bigger study, much more expensive, would take longer time. And that also discouraged some of the pharmaceutical companies.

And the third issue, which might be an issue, but we don't know for sure, is normal cells have to repair DNA damage, too. And there is some concern that people on PARP inhibitors for a long period of time might accumulate some DNA damage in their normal cells that they can't fix. And it might lead to an increased risk of other cancers, and that's always a very concerning thing to the FDA and pharmaceutical companies.

But for a bunch of different reasons, the PARP inhibitors remain in clinical trial. There still is a lot of enthusiasm about them in the clinical trial (inaudible), but it might not be a really speedy road to FDA approval.

I want to add one other little bit to the PARP inhibitor story, because I think it's important. These two proteins, BRCA1 and BRCA2, repair DNA, but they need a lot of partner proteins to repair DNA. And a couple of groups have said, well, we know if BRCA1 is mutated, or BRCA2 is mutated, the PARP inhibitors often help; what happens to some of the partner proteins that are broken or mutated?

So, with the ability now to sequence genes much faster and at a much lower price, some groups have begun sequencing many, many other genes that might be important in partnering with BRCA. And they found that in a significant minority of patients, these other DNA repair genes are mutated, and they probably lead to an increased risk in families of having BRCA mutation.

So, if some of you have, say, a family history of breast cancer or family history of ovarian cancer and you've been tested to see if you have a mutation in BRCA1 or BRCA2, and the doctor said we checked, those genes are fine, we are now finding there are some partner genes that are also sometimes mutated. And soon, in fact they're already becoming available, but I think soon there will be a much larger collection of genes that will be tested besides BRCA1 and BRCA2. And these will help inform families of potential risks in sisters and/or daughters, but they also might indicate that their BRCA pathway is broken, and those people might also be sensitive to PARP inhibitors.

And that's led to a new term that talks about how well the BRCA, not proteins, but pathways, a repair pathway, works, and it's been sometimes called BRCAness. Meaning that BRCA pathway worked well or did not work well. And if in your tumor it doesn't work well, that would suggest, that would predict that your tumor might be sensitive to a PARP inhibitor.

And there are a group of scientists across the country now looking for tests not to sort of measure the BRCA1 and 2 protein, but to measure BRCAness with the theory that if you have a BRCA low tumor, you might be sensitive to PARP inhibitors.

But this has led to a whole new field. If problems with the BRCA pathway might identify a woman as being a good candidate for PARP inhibitor, could you find other genes that were either over-expressed or under-expressed or mutated within your tumor that would help the physicians pick the best drug for you?

For some of you who perhaps survive with recurrent ovarian cancer, perhaps you had many chemotherapy drugs and perhaps when you've gone to meet with your oncologist he or she has said, well, I can give you this drug or that drug, and perhaps it hasn't sounded particularly scientific as to which one he or she was picking.

So, there has been a hope that if you could really understand how your tumor, a tumor that came out of your body was genetically different than other people's tumors, could you better select the drugs that might best manage your tumor? This has sometimes been called personalized medicine, or precision medicine.

And to help, again, to answer that, the National Cancer Institute funded a very large study where they took about 400 women who had serous ovarian cancer, or sometimes called papillary serous ovarian cancer, which is the most common type of ovarian cancer in women in their middle ages, and they sequenced thousands of genes in these women to try to understand was this one disease or a bunch of different diseases. And what they learned was almost every one of these women had tumors that had about 100 different genes that had mutations in them.

But if you looked at two different women, say, Mrs. Smith and Mrs. Jones, they both had 100 mutations, but the 100 mutations in Mrs. Smith were different than the 100 mutations in Mrs. Jones. In fact, 99 out of 100 mutations

in Mrs. Smith's tumors were different than the ones in Mrs. Jones' tumors. The only mutation they tended to usually have in common was to a gene called P53, which we don't really have good drugs for yet.

So, the good news was that we could learn a huge amount relatively quickly, not terribly cheaply yet, but much, much cheaper than a few years ago of the detailed, detailed molecular characteristics of a woman's tumor. But the challenge was that when you looked at serous cancers, it looked like almost everyone's tumor was slightly to moderately different than everyone else's tumor, which made it very difficult to make global recommendations.

And I think, as many of you who might be survivors on the call, I suspect many of you had Taxol and carboplatinum, or something like Taxol and carboplatinum sometime in your history. But you might say, well, why is everyone getting Taxol and carboplatinum if everyone's tumor is different? Shouldn't everyone be getting something slightly different based on the genetics of their cancer?

I think the answer 10 years from now, or maybe a little more than 10 years from now is yes, they probably all should get something different, but in 2012, we're still wrestling with, well, what would be better for a woman with these 100 mutations as compared to a woman with a different set of mutations.

Scientists are working on that. We are collecting more and more genetic information on ovarian tumors. We're beginning to try and sort out, do some of these genes predict what drugs might work best, but it's still early. I'd say we're collecting information very quickly. We'll undoubtedly have a lot more information a couple of years from now. In fact, companies are beginning to pop up that will do molecular characterization of your tumor.

Foundation Medicine has a test, a test in California by a company called [Claris] that does the test. So, there are groups that are beginning to do detailed analysis of this, and I think that information is important to scientists as we learn more and more about the genes in individuals' tumors.

I think there is still a little bit of caution for how important it is for patients, because it's like we're learning new languages that underlie ovarian cancer and our ability to interpret this genetic language and how to translate that genetic language into best drugs is still early, in its infancy. And as the technology becomes faster and more accurate and cheaper, we will learn a lot more in the next several years. But it's still early days.

One other thing for some of you who might be listening who has less common tumors, the other thing we have learned is that people who have clear cell cancers of the ovary, people who have something called low-grade ovarian cancer, people who have something called mucinous ovarian cancer, these are totally different tumors. They are as different as kidney cancer is from ovarian cancer, or colon cancer is from ovarian cancer. They happen to show up in this organ we call the ovary, but they are from totally -- they have totally different genetics. And the best, best treatments for those in the next several years will be dramatically different than the best treatments for serous cancers.

But, unfortunately, in the 1980s and the 1990s, because these tumors were even rarer, people used to just lump them into the serous ovarian cancer trials. But now many of the groups, both in the United States and in Europe, are now beginning -- and in Asia, are now beginning to treat these tumors on totally different protocols than serous cancer.

The tumors are rare. There are not thousands of women who can go onto these studies, so unfortunately the studies take a long time, they move slowly. There's not enough women in the world to check 50 different drugs out at the same time. You can only kind of pick one or two trials at a time to do. But we are beginning to think of these as totally different cancers, and are beginning to look at the genes that are mutated in these less common ovarian cancer types and chart totally different treatment strategies.

I want to just, before I open it up to questions, just talk about two other avenues which have gained some interest in the last couple of years and I predict will gain a lot more interest. That is one of the things which has frustrated clinicians, and probably even more so the patients, such as yourself, is because all of these tumors are genetically a little different than each other, there's been -- it's been discouraging in some ways that we would ever find sort of a magic pill that would work great for everyone's ovarian cancer.

If you think about it, if everyone's ovarian cancer is slightly different or moderately different, we might find a pill that's great for Mrs. Jones but won't be useful for anyone but Mrs. Jones. And perhaps if any of you have been in ovarian cancer support groups or maybe even in yourself, you'll find that some people will go on drugs, like Doxil

or maybe Alimta, and they will be on it and do great for a year or two. And there's other people who will go on the exact same drug, exact same dose, and it won't work at all. So, we've already begun to see that there is no one drug that works well for everyone. And if all these tumors are different, maybe targeting the tumor will be very difficult.

So, there's been a new strategy, and that's been, well, let's not target the tumor. What do tumors interact with or need? And one thing, of course, all tumors need regardless of what genes are messed up in the tumor, as tumors grow they need oxygen and they need glucose, and they need nutrients. I mean, tumors do need sort of oxygen and nutrients to grow larger, and that oxygen and those nutrients are delivered by blood vessels. And the blood vessels aren't cancerous; they're normal blood vessels. And there are new baby blood vessels that are sprouting into these tumors, which are very much like -- if you think of a new city popping up in some rural area, the bigger and bigger the city got, the more gasoline and electric you would need. So, as the tumor metastasis and starts as a little speck and gets bigger and bigger, it needs more and more blood vessels to bring to it the oxygen and energy it needs to support a growing tumor.

So, there's also been a very big interest in understanding what sort of molecules or hormones are needed to support new blood vessels. And this has led to the study of a couple of different drugs. The one of which has gotten the most discussion in ovarian cancer has been Avastin, or bevacizumab.

This is an antibody, it's not a chemotherapy. Perhaps some of you have had it. It's given IV. When given by itself, it has none of the typical chemotherapy side effects. It sometimes can cause a little bit of hoarseness. If you take it for a long time it usually causes a little bit of increased blood pressure. There are rare but scary side effects including blood clots, and probably the scariest one of perforation of the intestines.

But for most women, 95% or so, it's an easy drug. It works very different than chemotherapy. And we have found in some women whose tumors are very, very resistant to chemotherapy, this drug can be effective when given by itself.

It's a pretty versatile drug. If you give it with chemotherapy and following chemotherapy, when you are first diagnosed, your remission is likely to be longer. If you didn't get it during your initial chemotherapy but your tumor comes back and the doctor decides to retreat you, or retreat the tumor with platinum again, and for the second time around your physician adds bevacizumab to the standard chemotherapy, your remission is longer than if he just gave you the chemotherapy without the bevacizumab.

And we just recently heard at this year's ASCO a study called the AURELIA study, where if your tumor was really resistant to a bunch of different chemotherapies, if the doctor went to pull that third or fourth different chemotherapy off the shelf and give it to you in treatment of your cancer, if he added Avastin to it, the ability -- the chances your tumor would shrink was higher if he or she added Avastin. And the amount of time that chemotherapy worked was much, much longer.

So, there's a lot of Avastin being used. It's still not FDA approved. There's still not been any convincing data that women are living longer. There is good evidence that when they get the Avastin during a discrete episode of chemotherapy, the chances of that particular chemotherapy will work longer is pretty good, but still not compelling data that women live a lot longer because of it. And the drug is expensive, many thousands of dollars per month of treatment, and in 1 in 20 women it can cause very, very significant side effects.

So, that has generated concerns in people who have to pay for healthcare. It has caused concerns that we might be doing harm to a small subset of patients. But I think it's fair to say that most medical oncologists who take care of women with ovarian cancer feel like Avastin is important.

There is a variety of opinions about is the best time to use it right away, right after the first surgery, or is it better to hold it in reserve, maybe at the second time you use chemotherapy, or to keep it farther back in your back pocket and use it when you're running out of chemotherapy options. And there are smart people that can take different sides of that debate. The debate's not over.

It is clear it has an important role in ovarian cancer management, but I think that professional groups have not yet come to a consensus of when the best time to use it, how long it is to be used once you're on it, should it be stopped. There is still a lot of important questions regarding Avastin that need to be answered. And there are some

new questions about should other molecularly targeted agents be mixed with Avastin. So, still a very, very active area of research.

The other area which is not as active yet, but I predict will become much more active soon, and for those of you who maybe have access to large centers that are interested in research, that you might keep an open ear about is immune-based therapies. And there has been pretty good data for the last decade that there is a pretty hostile battle between the immune system and a woman's ovarian cancer. And obviously in most women with advanced ovarian cancer, the cancer is slowly but surely [deeding] out their own immune system. But as we've learned more about immunology and learn more about how we can rev up the immune system, new treatments have become available that seem to be effective.

And, in fact there were two studies that were recently published in the *New England Journal of Medicine* and another couple of studies that were published two years ago, which have shown that there is some very interesting immune-based therapies that -- one of which is now FDA approved in melanoma, and another one, which is not quite as effective, which is approved in prostate cancer.

The data which just came out in the *New England Journal of Medicine* showed some very fantastic and very long-lived responses in individual lung cancer, some of which have been individuals whose tumors have been slowly but surely shrinking for now two-plus years. And some of these new antibodies turn on or off important molecules in the immune system which allow them to recognize tumor cells within the body that had previously been camouflaged.

There have been a handful of women with ovarian cancer who have been treated with these. There is a small handful of women -- small, maybe less than a dozen, but still an important dozen -- who have had some, what might be considered "oh, my God" responses, where without chemotherapy the tumors had shrank and remained under good control for many, many months, and in a few cases in excess of a year or so.

There is some definite [hints] here, and I do think that in the next year or two there will be a rapidly increasing collection of trials that look to better evaluate some of these immune-stimulating strategies, particularly in women who perhaps finish surgery and chemotherapy either the first time around or the second time around, and the physician or surgeon or patient is pretty sure there's no small amount of tumor left. Perhaps their 125 was normal, perhaps their CAT scan is normal, but maybe they've already had a recurrence of their tumor. There is a high suspicion there is still some small tumor around.

I think this group will be a very important group of individuals to explore how these immune-stimulating agents might keep in check or even potentially eradicate these tumors. And these strategies might work in larger groups of patients even if each individual's tumor is genetically quite distinct in other women who have a tumor that we call ovarian cancer but in reality each of these ovarian cancers are a bit different from each other.

I'm going to close so that we can take some questions. I am going to just summarize by saying a couple of things. The good news is -- there's two pieces of good news, there's one piece of challenging news. I think the good news is we know -- we've learned more about what makes ovarian cancer, ovarian cancer in the last five years. We've learned more in the last five years that we learned in the 1900 years before that. So, the speed at which we are gathering new knowledge about ovarian cancer is getting faster and faster. And I suspect in the next five years we will learn at least twice as much as we learned in the past five years. So, I do think it is realistic to think that there will be a massive amount of new knowledge in ovarian cancer in the next few years, and that's good news.

The challenging piece is one of the things we've learned with all of this news, is this is a relatively uncommon tumor, ovarian cancer, but in reality it's not one cancer; it's lots and lots and lots and lots of genetically distinct cancers. So, the frustrating thing is, it makes it unlikely that one magic pill will be the perfect solution for everyone who is alive today with the diagnosis of ovarian cancer. Many of these women will need very individualized solutions, and that's frustrating, that we're not likely to, at least in the short term, trip across that magic pill that eliminates ovarian cancer for everyone quickly.

But to close on a positive note, there are a massive number of molecules in clinical trials, and many, many of these are not just another chemotherapy drug. There are immune-stimulating drugs, there are blood vessel-blocking drugs, there are drugs which I haven't talked about that work on totally different strategies than the sort of tired old chemotherapy drugs.

I would encourage all of you to -- if your personal situation has something to do with dealing with ovarian cancer, the next time that there is a therapeutic decision that needs to be made, ask your physician, is there a clinical trial I am eligible for? If he or she says no, you have the wrong kind of cancer, or no, not here, be persistent. Say, well, okay, if not here, how about somewhere else? There's a big center down the street, or there's a big center 30 miles from here, would they possibly have something? Or could I inquire?

And probably all of you know there is a website called clinical trials.gov, which is pretty user-friendly, that you can go to and you can sort of type in ovarian cancer in the state you live in and what type of ovarian cancer you have, and whether your disease is recurrent or not, and it will give you a printout of trials that are available with phone numbers and contact people. It's not always 100% up-to-date, but it does give you at least a starting point if the physician doesn't seem to have that sort of information at his or her fingertips. With that, I'll stop and hopefully some of the things I told you have been useful, and if not, I'm happy to take some questions.

Robin Perlmutter: Thank you so much, Dr. Seiden. Folks, if you have a question, please hit star, 7, to unmute your line, and you can just announce yourself with your first name and ask the question.

Susan: Okay, do you have to call on us or --

Robin Perlmutter: No, no, you can just announce yourself one at a time and ask your question.

Susan: Okay. This is Susan. Thank you for all this information. One question I had is, you referred to the study with Doxil and the PARP inhibitor having the same results, and I wondered, if it has the same results as Doxil, isn't it good enough for the drug companies or for the FDA to approve a drug that has less side effects and certainly more user-friendly and doesn't have such a negative impact on our quality of life, if we just take a pill instead of infusion?

Michael Seiden: Yes, that's a great question. So, there are lots of drugs that have gotten FDA approved, not because they beat the best drug, but because it was a tie and they were less toxic or gave people a different choice. So, the challenge was, when this trial was conducted, it was relatively small. I don't remember the precise size, but maybe 50 people got Doxil and 50 people got a PARP inhibitor. I think what happened was the pharmaceutical company was hoping that the PARP inhibitor would really tremendously outperform Doxil. And it ended up looking a little bit more like a tie, and usually pharmaceutical companies -- I mean, the FDA would consider approving a drug on a hundred person study if it was much, much better than the standard drug, or if the standard drug didn't work at all. But if you're trying to prove its equivalent, at least in the eye of the FDA, they don't want sort of 50 versus 50; they want sort of 500 versus 500.

So, when this study ended as a tie, it was clear that to get past the FDA, the company, AstraZeneca, would likely need to repeat the study and make it about tenfold bigger to prove beyond a shadow of a doubt that perhaps the PARP inhibitor was a little better or at least equally effective and didn't have any weirdo side effects. That was going to cost a lot of money. And I think if you're a woman with a BRCA mutation and ovarian cancer, it's money very well spent. But presumably for some other reasons, the pharmaceutical company decided it was not money that they could afford to spend or wanted to spend, or couldn't afford to spend right at this minute. And I don't have any particularly inside knowledge as to what they were thinking that they have not gone forward with that larger study, at least at the moment.

Susan: I see. Thank you. But I know that there seemed to be an awful lot of trials with veliparib, and I'm actually in one of those now. And so are they similar or are they almost the same drug as veliparib?

Michael Seiden: Right. So, olaparib got out of the gate first, and veliparib came along later. The feeling is veliparib should be similar to olaparib, and those studies in women with BRCA mutation either by itself -- veliparib by itself or veliparib with chemotherapy are underway right now. And they have not yet been completed and reported. The hope is that veliparib will look as good or maybe even better than olaparib.

And then the gynecology/oncology group already has plans to do a multi-hundred person ovarian cancer study as soon as some of the early trials -- and perhaps you're on one of those early trials -- have been finished and

evaluated. And hopefully a large randomized veliparib study will be up and running sometime in the next year or so.

Susan: Okay. Thank you.

Robin Perlmutter: Okay, thank you. Next question?

Gail: My name's Gail. My question is --

Michael Seiden: Hi, Gail.

Gail: Hi. Clear cell ovarian cancer you're saying is very rare, and then surviving that is more rare?

Michael Seiden: Right.

Gail: Because I'm a 27-year survivor or clear cell, Stage III.

Michael Seiden: Right. Wow! First of all, good for you. Congratulations. So, clear cell carcinoma is a tumor which, first of all, is developing a very strong link to endometriosis, which is not true with serous carcinoma. And it ends up that about half of the women who have clear cell cancer of the ovary have a very specific mutation in a gene called ARID, A-R-I-D1A, which is a gene that is important in how this very long strand of DNA is wound up in a cell. And it's assumed that these mutations probably arise in a little pocket of endometriosis and unfold the DNA so that the gene or a couple of genes that are normally off, get turned on and cause the cancer. And this mutation, ARID1A mutation, is essentially never, ever seen in the more common type of serous cancer.

And it suggests that for women who have clear cell cancer, since the genes that are turned on are totally different than the genes that are turned on in serous cancer, then the best treatments for those cancers will be quite different. So, just by comparison, there's about 22,000 cases of ovarian cancer in the United States a year, and about 13,000 or 14,000 of those, about maybe 1,000 to 1,500 are clear cell.

Gail: They weren't going to consider me for any of the studies because of the type of cancer I had, but they were interested in my longevity. And since now, when they test me, they find out I don't have heart problems, blood problems, kidney problems, and I don't have osteoporosis. So, they like studying me for that part.

Michael Seiden: Yeah, I want to tell you that one wonderful thing that any of you who take part in advocacy can be very proud of is one of the programs which received significant support because of the advocates is the Department of Defense Ovarian Cancer Research Program. And that program receives between $10 million and $20 million a year from Congress that is targeted to ovarian cancer. And the ovarian cancer research program has decided just this year to fund one large national study that would look to collect tumors that were stored in, say, wax block from women who were diagnosed with ovarian cancer, say, more than 5 or 10 years ago who are doing well.

And there are now techniques where you can take those tumors, even if they were removed 10 years ago or 20 years ago, and look at thousands of genes to try to unlock why is there a small but meaningful proportion of women who, despite the fact that they're diagnosed with Stage III or IV disease, are alive and well 10 or 20 years later. Where unfortunately the majority of women who are diagnosed with Stage III or IV disease experience a recurrence of their tumor much sooner than that.

Gail: Right. Because, like I said, there are several especially -- different doctors, they go, "I want to know what you've done," because I've never had a recurrence and I've been fortunate on that. And they go, "You don't even look like you've ever had ovarian, but here it is in your record." And they see what all's in there and they go, "Oh, my land, what have you done?" And they're curious as to what was going on as to what I did to get this kind of result.

Michael Seiden: Yeah. I think we need to learn more from people like yourself and the genes in your tumor to try and unlock some secrets as to why your history is so much different than many of your colleagues.

Gail: Now, that was the Department of Defense Research, right?

Michael Seiden: Yeah, the Ovarian Cancer Research Program.

Gail: Okay, thank you.

Michael Seiden: You're welcome.

Unidentified Participant 1: Hi. I've got some information that came up from Support Connection that really caught my eye, and that was that the numbers of changed. It was like 1 in 70 several years ago over a lifetime that a woman could possibly get ovarian cancer, and in their information they've got 1 in 57. Is that because of the Baby Boomer generation aging, or is there something else going on?

Michael Seiden: There is -- not exactly. Definitely the population is aging, so that may be part of it. The other thing is, there are also a couple of possible worrisome trends. One is having multiple babies starting at an early age is protective of ovarian cancer, and the average age at which women marry and have first births are getting older. So, that trend in itself will increase the risk of breast and ovarian cancer.

The other thing is, there is a weak but real association with body weight and the risk of ovarian cancer. And as the American population becomes a little more obese, the incidents of ovarian cancer is likely to go up. If you look at the women who are -- you sort of break women into sort of the lowest body mass, the lowest quarter versus the highest quarter, the one-fourth of women in the highest body mass index, or BMI, have a rate of ovarian cancer that is 60% higher than the group that has the lowest BMI.

And the other thing is, there has been a trend to try to reduce the dose of hormone in birth control pills. And there is at least a little bit of concern that that may be a little less protective of ovarian cancer than the old birth control pills.

So, later age of first birth, possibly the changing use of birth control pills, and the changing formulation of birth control pills, increasing body weight in all Americans on average, and the increasing age that women live to, many of those trends will conspire to tend to push the ovarian cancer incidents rate up a bit.

Unidentified Participant 1: Okay. And the other question I had, quickly, there was like 30 subtypes of ovarian cancer. Is that still about the same?

Michael Seiden: Well, it depends a little bit of whether you are a lumper or a splitter. If you're a splitter, you could argue everyone's serous cancer is unique, and then there's --

Unidentified Participant 1: Right.

Michael Seiden: -- 15,000 different types. But even if you're relative conservative, a lot of different techniques have been able to separate serous cancer into many different subgroups. We mentioned there is clear cell cancer, mucinous cancer, there is low-grade cancers, there is transitional cell cancers, there is mixed cancer. So, I wouldn't say all the pathologists have agreed on whether it's 30 different types, 20 different types or 100 different types. What is becoming clear is there is a lot of genetic diversity that really calling it ovarian cancer is really an over-simplification. In fact, I just finished writing a book chapter that will be coming out soon, and I didn't even call it ovarian cancer, I called it cancers arising in the ovaries.

Unidentified Participant 1: I liked what you said last year at the OCNA Conference, gynecologic cancers of the ovary.

Michael Seiden: Yes.

Unidentified Participant 1: I thought that was absolutely dead on.

Michael Seiden: Right.

Unidentified Participant 1: So, thank you very much.

Unidentified Participant 2: Hi. I have the BRCA1 gene and I got a hysterectomy five years ago because my sister's had breast cancer and I figured that was a good, just a preventive thing to do. But then I have -- I was just newly diagnosed with ovarian cancer without ovaries.

Michael Seiden: Right. How does that work, right?

Unidentified Participant 2: I don't have a tumor, Doctor. In other words, they're doing the chemotherapy first. I have the ascites.

Michael Seiden: Yeah, right.

Unidentified Participant 2: And then they're going to --

Michael Seiden: Yeah. So, what we learned is that in women who have BRCA mutations, if they have their ovaries and fallopian tubes removed, they reduce their risk of ovarian cancer by about 90% to 95%. Now, I think the first question is, well, wait a minute, if I don't have ovaries, how does it not lower the risk by 100%?

Unidentified Participant 2: Right.

Michael Seiden: And there is a couple different theories for that. One is the cells that make up the ovaries actually when you are an infant start way up by your kidneys. And as you develop as a fetus in the uterus, those cells drift down from up where the kidneys are to where your ovaries are. And there is a thought that some of these ovary-like cells, almost like dandelion seeds, kind of drop off somewhere in the middle of your abdominal cavity. And while 99.99% of those ovary-like cells end up in your ovaries, there is a few of them that sort of fall off that train track as a developing fetus. And when the surgeon goes in and removes your fallopian tubes and ovaries, some of those early ovary-like cells are still left higher up in your abdomen and they can occasionally turn into cancers that have high CA-125 and ascites, and under the microscope look exactly like ovarian cancer.

The other theory is these tumors might not even start in the ovary; they might start right next to the ovary, in the fallopian tube. And it is possible that some of these precancerous cells fall off the fallopian tube and land somewhere other than the ovary a couple of years before they turn into full-blown cancer. So that you come in, you remove the ovaries and the fallopian tubes, say, when you're 40 or 45, but some already precancerous cells have escaped, and given time, another year or two or three or five, a couple more mutations occur and something that really looks like regular ovarian cancer develops. And it is usually called primary peritoneal cancer, but biologically acts very much like ovarian cancer.

Unidentified Participant 2: But, see, he first diagnosed me as primary peritoneal cancer, which has a very bad survival rate, but then he rediagnosed me with ovarian.

Michael Seiden: Well, they have similar survivals, the two of them, but because of -- but what's more important than what you call it is the genetics. So, if you have BRCA mutation, that should mean that you're more likely than not to have a good response to chemotherapy that has platinum in it, and most of the PARP inhibitor trials are very willing to take people with primary peritoneal cancers that have BRCA mutation.

Unidentified Participant: (Inaudible)

Michael Seiden: (Inaudible)

Unidentified Participant: Yeah, if just your tumor has the mutation. I was analyzed that for people on the call by the Clearity Foundation --

Michael Seiden: Right.

Unidentified Participant: -- their mission is to have tumors analyzed --

Michael Seiden: Right.

Unidentified Participant: I believe they use Foundation Medicine up in Cambridge.

Michael Seiden: Right. So, for women who have BRCA mutations within the tumor but they didn't inherit it, so the so-called somatic mutations, it's very likely that those individuals will be sensitive to the PARP inhibitors. There [has] really been a large trial that has specifically pulled that group of women out to answer that question specifically. But from what we understand about the biology, we would think that they would have a BRCAness that would suggest that they should have a reasonable likelihood of responding to a PARP inhibitor.

Unidentified Participant: Thank you.

Robin Perlmutter: Okay. Thank you so much, Dr. Seiden. I really appreciate you spending the time this evening with us all. I really can't thank you enough for helping support our mission of educating women with ovarian cancer. So, I appreciate you being on the line tonight and hope you found this most helpful. Please join us again. We will keep you posted as to any further educational teleconferences, and have a good evening.

Michael Seiden: All right. Thank you.