Program Title: The Latest in Treatments for Ovarian Cancer
Presented by: Support Connection, Inc.
Moderator: Robin Perlmutter, Support Connection Peer Counselor
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Guest Speaker: Elena Ratner, M.D.: Dr. Ratner is a Board Certified Gynecologic oncologist with special interests in chemotherapy targeted drug development, patient quality of life programs and early cancer detection. Her credentials include: Associate Professor of Obstetrics, Gynecology and Reproductive Sciences at Yale New Haven School of Medicine; Co-Chief, Section of Gynecologic Oncology, Director and Founder of Sexuality & Intimacy in Menopause Program, and Director of Discovery To Cure, at Yale New Haven Health Cancer Center, Smilow Cancer Hospital; Director of Early Ovarian Cancer Detection Program, Director of Gynecologic Oncology, at Stamford Health.

As a gynecologic oncologist, Dr. Elena Ratner partners with women throughout their cancer journey, delivering comprehensive, personalized care. Dr. Ratner helps her patients experience a high quality of life throughout treatment and into survivorship by fitting treatment around their lives and providing targeted therapies with as few side effects as possible. She works hard with each patient to preserve a sense of normalcy and to prevent cancer from taking over their lives. As the founder of the Sexuality & Intimacy in Menopause Program, she helps survivors of cancer reconnect with their bodies using a multidisciplinary approach, including counseling, hormone therapy and other techniques.

Dr. Ratner practices bench-to-bedside research, examining her patient's tumors and identifying their specific types of cancer. This allows her to design an effective, individualized treatment plan for each patient. In her lab, she also works to develop new chemotherapy and cancer drugs that effectively treat cancer and improve quality of life for her patients. As a result of her commitment to gynecologic cancer care, Dr. Ratner has received many awards for her teaching, research and patient care. Most recently, she was given the Yale University Smilow Cancer Center Award for Clinical Excellence.

Topics:

- The newest info on the development of drugs for advanced ovarian cancer
- The role of personalized medicine
- Targeted therapies
- PARP Inhibitors
- Quality of life issues
- Sexuality and menopause
- Question and answer period

Robin Perlmutter: Remember that Dr. Ratner is sharing her expertise tonight, and any information or questions pertaining to individual concerns should be discussed with your doctor.

It is my great pleasure that we have Dr. Elena Ratner, a board-certified gynecologic oncologist with special interest in chemotherapy-targeted drug development, patient quality-of-life programs, and early cancer detection. Her long list of credentials include Associate Professor of Obstetrics, Gynecology, and Reproductive Sciences at Yale New Haven School of Medicine, Clinical Division Director Section of Gynecologic Oncology at Yale Cancer Center, Director and Founder of the Sexuality and Intimacy and Menopause Program, and the Director of Discovery to Cure.

Thank you, Dr. Ratner, for sharing your time and expertise tonight.

Elena Ratner: Great, thank you, Robin. Thank you for this opportunity. I am so excited with that we are on this call today. I am very excited to share this talk with you and, hopefully, we can make this interactive and beneficial for all of us.

So what I would like to talk with you today about how the paradigm of ovarian cancer has changed, and how it is certainly likely to continue changing and improving. So we're going to talk about a personalized approach to management of ovarian cancer, and we will take some time to talk about quality of life and issues of sexuality and intimacy.

So ovarian cancer, unfortunately, continues to be prevalent and to, unfortunately, be deadly; 22,000 women get diagnosed, 14,000 women lose their fight. And among cancers for women, it is not towards the top, but it is still important because of how difficult this cancer continues to be. And that is why so much research is dedicated to this cancer to try to find its cure.

The reason for why this cancer continues to be so challenging is multifold. Towards the end of the talk or towards the middle of the talk, we will talk about difficult mechanisms of this cancer and how this cancer, unfortunately, is really smart and learns how to resist the therapy that we try to kill it with and what we now do to be able to arm ourselves against it.

But it's also very challenging because these cancers continue to be diagnosed at later stages. We used to say that ovarian cancer is a cancer that whispers; that there's no symptoms, and that is why most women still, unfortunately, get diagnosed in later stages.

There is some new literature now that talks about how long these cancers have been present prior to diagnosis as long as 18 to 24 months, and that women, unfortunately, see multiple providers before they are actually and finally diagnosed appropriately. So because of that, and because of bad delay in diagnosis and because the symptoms are so vague, is these cancers still are diagnosed at late-stage.

But we know now that that's actually not necessarily the truth. Ovarian cancers do not necessarily whisper, it's that nobody is listening. Some very good studies by Barbara Goff show that, of course, a great majority of women with stage 3 and 4 cancers have symptoms as high as 97% but as high as 89% of these women had symptoms in stage 1 and 2. But these symptoms were so vague that women and, more importantly, their providers attributed them to hormonal changes, and those symptoms were not addressed earlier.

What separates the symptoms that women get who subsequently develop ovarian cancer versus those who are just normal hormonal symptoms of menopause or peri-menopause is that the symptoms that women get happen every single day for two weeks. And for those women who have hormonal changes and hormonal symptoms, those symptoms come and go.

So, so much of what is being done right now in ovarian cancer research and prevention has to do with education and awareness and efficacy. And we are educating women to listen to their bodies, to pay attention to their symptoms, and when they do feel like they have symptoms and when they do feel that something is not right to demand the care that they deserve and not to take no as an answer and not to be listened to.

And so much of what we do is educating the providers about identifying the symptoms in diagnosing these cancers early because most of these women at the beginning of their presentation actually do not go to the gynecologist. Instead, they go to a urologist and gastroenterologist and

even chiropractors. So those are all the providers that need to be educated about the symptoms because that is so important.

So for women who do develop ovarian cancer, who are these women? In the older days, a couple of years back, we used to say that, you know, a very small percentage, you know, maybe 10% or so of these cancers were genetic or hereditary. And then a great majority of them are something called "spontaneous," which means there is no predisposition in the genes.

We now know that that number is high. Women with BRCA mutation, and women with Lynch syndrome, it was some other genetic syndromes have a higher risk of developing these cancers. But, yes, overall, most women who develop it do not have a gene that predisposes them to this cancer. And the lifetime risk of getting ovarian cancer is approximately 1.4%. That number, of course, is higher for women who have genetic mutation.

So the risk factors for ovarian cancer is older age. Average age diagnosis is 63. Women who have never been pregnant, women who had infertility, BMI more than 30, and personal history of breast cancer. And things that are protective is having a tubal ligation. You know, nowadays, there's actually a lot of thought and a lot of literature that a lot of ovarian cancers are actually not ovarian cancers. No, indeed, they are fallopian tube cancers. So in my institution we no longer do tubal ligation if somebody doesn't want to have children. Instead, we take out their tubes entirely. And taking out tubes is something that we do now routinely for women who are at high risk to decrease their risk of ovarian cancer.

Women who have hysterectomy, women who have multiple pregnancies, anybody who has had five children and breast fed each child for one year has a 50% reduction in ovarian cancer and, more practically speaking, is birth control pills. Birth control pills significantly reduce the risk of ovarian cancer. Anybody who takes birth control pills for five years decreases their risk by 50%. Anybody who takes it for 10 years decreases it for as high as 80%. So the reduction in risk is significant, and that goes for women who have genetic predisposition as well, such as BRCA mutation, and that reduction in risk is proportional. So let's say somebody has a 20% chance of developing ovarian cancer, but they take birth control pills for five years, their risk becomes five years or, you know, down by 50%.

So big advice that I always give to everybody not just patients and not just their families, but all my friends and girlfriends is that at some point during your lifetime try to get in five years of birth control pills to decrease your risk of ovarian cancer.

So how is ovarian cancer treated? Right now the paradigm continues to be such that treatment for ovarian cancer is a combination both surgery and chemotherapy. Now, remember there are many different ways of doing the treatments, and there's different order of the treatments. Sometimes we do surgery first, sometimes we do chemotherapy first. The goal of the surgery and the chemotherapy is to leave nothing behind at the time of surgery. So anything that has to be done for that has to be accomplished, and that's why frequently we would give chemotherapy before surgery to increase the chance of leaving nothing behind in the surgery and also to decrease the chance of having a very big surgery with a hard recovery. So it is very common to give some chemotherapy before the surgery to melt away a lot of the tumor and then surgically remove everything possible.

So the goal of surgery is to remove all visible disease. You know, and surgeries nowadays are done both laparoscopically or robotically and also through the normal, old-fashioned way. And the

benefit of the old-fashioned way that we are able to use our fingertips to be able to feel the nodules. And the benefit of laparoscopic or robotic surgery, which I do quite a bit, is to shorten the recovery time and to allow women to get back to their normal lives and to be able to get back to chemotherapy. So either way that this is done is acceptable as long as all tumor that could be seen or could be felt is removed.

In the older days we used to talk about that with the surgery you want to leave behind nothing more than a centimeter, nowadays that number is zero millimeters. We now want absolutely nothing left behind.

And then following the surgery, women would get more chemotherapy, and that chemotherapy could be both intraperitoneal or intravenous and there's multiple different ways, and we will talk about that in a few minutes, how chemotherapy is so drastically changing; how a couple of years back everybody would get the same chemotherapy but nowadays the paradigm is such that we are able to truly provide personalized therapy, personalized care, according to the mutations that the women have. That as important as what kind of cancer they have but, more importantly, what kind of mutation.

Some of the recent literature says that women with ovarian cancer do much better if they are taken care of by specialists in this field, by gynecologic oncologists and providers and facilities that have high volume. That these women have a better prognosis and better outcomes. And that's, of course, not surprising.

So the benefit of leaving nothing behind you in surgery is very important. It has to do with the thought that there are certain cells in these tumors that are called stem cells, and stem cells cannot easily be killed by chemotherapy. That's why those kinds of cells, we call them general cells or cells that are very difficult to destroy can only be removed with surgery. And that's why surgical debulking with surgical removal of tumor is so important.

So the way that this usually works is that women have symptoms, they get diagnosed, they get chemotherapy followed by surgery or surgery followed by chemotherapy. And in the older days we would just finish the treatment and then wait and watch and check with the CAT scans or blood tumor markers every three to six months to watch to see if the cancer cells would come back.

Nowadays, some of the thoughts are changing, and one of the greatest advances over the past couple of years has been maintenance therapy, and maintenance therapy is using central treatment when there is no active cancer cells present. And we'll talk about that in a few minutes.

We do know that, unfortunately, even though most ovarian cancers respond really well to chemotherapy up front, that a majority of them do come back. And when they come back, we just continue treating them as we are and stabilizing them and giving more vacation time in the region of therapy but then coming back to the chemotherapy after that. So that's why it is so important to try to extend the period of time in between chemotherapy, something that we call progression-free survival, which means that the woman would not be on active therapy but would be on something that would be much more easily tolerated. So, so much research has been done to try to find a way to expand that period of time.

So we have done research in ovarian cancer for a very, very long time. And you can see that the summary of some of the team research advances in the field of ovarian cancer and you probably see many drugs on there that you're familiar with but, more importantly, even seeing that from

1960s to mid-2014, mid-2015 there really has not been great advances in ovarian cancer, and that's not from lack of trying but just because of the complexity of the cancer.

In particular, a lot of research over the years has been dedicated to trying to find an effective and easily tolerable way to find this maintenance therapy, to find a way to extend the period of time between active chemotherapies. And we have looked at many things. We have looked at antibodies and injections and pills but, unfortunately and solutionally, we have never been able to find anything that was effective. And that is why what happened in 2017, 2016 is so exciting.

So a few things happened. In 2014, first of all, there was a drug called Olaparib or Lynparza, which was the first PARP inhibitor that came on the market. And Olaparib was a perfect example of a personalized targeted therapy that was specifically for women with BRCA mutation. Around the same time, chemotherapy with addition of Bevacizumab, or Avastin, also came on the market and again it was exceedingly exciting because it was not tied to toxic chemotherapy, it didn't have too many side effects, and it worked on the blood vessel and additional Bevacizumab appeared to prolong progression to survival as well.

In the next couple of years, as the PARP inhibitors came on the market, Niraparib and Rucaparib. So as I was saying, that in 2014, Olaparib, Lynparza came out to the market, and it was an incredibly exciting drug, incredibly exciting concept of using targeted personalized therapy specifically for women with BRCA mutation. And it was incredibly exciting, but it was, at the time, only for small category of women who had the BRCA mutation. And as I mentioned to you before, that proportion of the population is, at the most, 15%.

So what follows next was even more exciting. Multiple other PARP inhibitors came on the market, Niraparib and Ricaparib. And what made them so exciting not only did they also have incredibly positive results, but that they weren't just for the women with BRCA mutations, they were for all comers, and I'll talk in a few minutes about what that implies. In case if you're not hearing me, I will repeat also that around the same time, Bevacizumab, or Avastin, came on the market, and that also was a very exciting advance because similarly it was not a type of toxic chemotherapy, but it was a special medicine that worked on blood vessels that showed to improve this progression free survival.

So, overall, as you can see, not many things happened for many decades, but then starting in 2014, some really, really exciting things that happened, and I'm going to show you exactly what.

So the complexity of ovarian cancer is such that it is very complex field. You know, there's many different ways that these cancers learn how to resist therapy and, you know, five years ago, seven years ago, I used to give this talk, and I used to show you these aspects and tell you that ovarian cancer is so complex because of the genetic and cellular and molecular levels. And it's complex as to what turns on and turns off the controls of this cancer.

And I will show you this graph, and I will say, you know what? This is why it's so hard. This is why we're struggling with finding cures and treatments, because there are so many different aspects of this cancer that we need to take into account. But this is now the new slide, and this is something that is not totally established, and we're still in the infancy, but it is incredibly exciting that out of the challenges of this cancer, out of the challenges of the resistance and the complex mechanisms, comes opportunity to attack this cancer better and smarter.

So for all these challenges and limitations of complex mechanism, we now have a way to be able to target them, to hit them, to kill them, in a much more specific and much more targeted way. So you see the PARP inhibitors, as what I was talking about before the work on DNA repair and VEGF signalings that I mentioned, too, before with Bevacizumab as well as many, many other different targets that we now use. And when I give this talk to you in a couple of years, this graph is going to be way more complex and way more busy because half of those things we did not have a year ago. And that is how exciting and how fast this field is moving at this time.

So nowadays, the way that we treat this cancer, it is much less about the type of cancer, but it's more importantly about specific functions of the cells. So sometimes we treat ovarian cancer how I would treat thyroid cancer or how I would treat melanoma because in this day and age, I care much less about what kind of cancer this happens to be, but I care more about what kind of mechanisms and what kind of ways this cancer, what kind of weaknesses this cancer has that I can attack.

And this is in many different ways of opportunity for us to use different targets. This one, in particularly, for the PARP inhibitors. So Bevacizumab is what I mentioned to you before is very -- a great advance. It is used for first-line ovarian cancer treatment and maintenance and also very active and successful in recurrent disease. I use it a great deal in my practice, and some of my women on Bevacizumab for three to five years during their treatment.

This is now all the literature that came out over the past couple of years to show you the great advances in, particularly, all Bevacizumab and of PARP inhibitors in the maintenance setting(inaudible). And the results were quite astounding. You know, the results of these PARP inhibitors was unlike anything that we have ever seen before. What these studies have shown that using PARP inhibitors in women with BRCA mutations showed incredible benefits.

So 21 months versus five months when women were not on PARP inhibitors, and this wasn't benefit just for -- it wasn't just for the women who had BRCA that was hereditary, that was genetic, that was in their blood, but it was also for women who had normal -BRCA in their blood, and they genetically did not carry the mutation and genetically did not pass it on to their children but had BRCA mutation in their tumors, and that number is actually much higher than the 15% that I told you before of the women who have the germline mutation.

And we now routinely, every single one of my women who has ovarian cancer gets not only their blood tested for this mutation but, more importantly, has a tumor tested for this mutation because I know that the additional 20% will have additional mutations, and I will know that they will benefit from these drugs. But even in addition to PARP inhibitors, I look for 380 mutations in the tumors, so I know how to attack them better and smarter.

But, so, unquestionably, we know that for women who have BRCA mutations, again, whether it's germline or just in the tumor, the benefit of PARP inhibitors is really astounding with numbers that we have not seen before as you see here again (inaudible) into 20 months. But what about women who do not have the BRCA mutation? Because even if we say that maybe 30% have it, still 70% of women do not.

So these are different studies -- these are different studies that look at different PARP inhibitors and this is, kind of, how these studies are a bit different but, essentially, I am just showing you that some of these studies were for women who just had the BRCA mutations and other studies were much more open. They were for all comers, they for women who had the BRCA mutations and those who did not.

And it shows that for women who had the BRCA mutation, they had benefit that was very profound. Again, not to mention before 20 months versus five months, but even for women who did not have the BRCA mutation, which, again, are the women that we did not know whether they would respond or not, we can see for those women also had a substantial benefit of longer than 9 months versus 3.9 months in those who did not take this drug.

And what's even more important is two things. One is that now we are so much smarter that we are able to really look at the tumor and study the tumor and understand the genetic makeup of these tumors. And understand who is likely to respond to these medicines and who is likely not. So I am able to study the tumor and understand whether the mechanisms of daily repair as such that these women are likely to respond or not. So it's truly personalized and individualized treatment.

But also very importantly, you can see that even for women that did not have any mutations for whom I would not have expected the response to be very good, or very long, 20% of these women still had no cancer at 24 months. And in a better group 31% of these women.

So not only do these new drug's work in our sessions, but as important or even more important that to some of these women, and this is a nice percentage, you know, it's one-third or one-fifth of these women, this response is not just profound but also long-lived and they benefit from these drugs for many months and many years. So that is quite incredible.

And this is just some of the many examples from this new targeted therapy and, again, it always seems from being able to check the tumor, study the tumor, and send the tumor and then being able to offer this multiple new targeted therapy in a very personalized way.

So the way that this is done by institutions is, again, we very much believe as personalized medicine because cancer is a genetic disease and specific targeted treatment is needed. So personalized medicine allows for the tailoring of the medical treatment to the individual characteristic of the patients and the benefit of that is not only will the therapy work better but also the side effects will be less and women are able to live their life easier and better while we are controlling their cancers in a personalized individual way.

So this is how it's done at my institution, like I mentioned, we study, we have a -- during surgery we take a piece of tumor, we study the tumor, we look at 380 mutations inside the tumor, and then in our labs we establish the cell line for these tumors and for tumors that are hard to treat, they're complex, we put them into mice. And then we treat these mice with therapy and for the therapy's benefit, the mouse will then bring it over to the patient so it benefits her.

Additionally, we are looking at cells circulating tumor DNA cells in the blood that tells us whether the tumor inside is dying or is still alive. So those are just some of the examples of this new personalized approach, which is very much changing the course and the nature of this disease.

So, in conclusion for this part, ovarian cancer continues to be difficult. We have to be diligent, we have to be aware, we have to talk to each other, we have to be advocates for the disease and make women aware of the early symptoms and empower these women to demand and receive the care that they need, and they demand for these cancers to be diagnosed early.

A truly personalized approach is needed and is upcoming and is exciting and is changing the nature of this disease. And this extends to surgical care and therapy. We now are able to do very

complex, very big surgeries laparoscopically and when in the older days the patient would be in the hospital seven to 10 days. Now they go home same day or next morning. I mean, that is changing the nature of this disease.

And now, more importantly, a treatment that we cannot treat all cancers the same. We have to be smart, we have to be proactive, we need to study these tumors, we need to understand them. These tumors are smart and complex, and we need to be the same. We need to use this complexity of the tumor not as a challenge but as an opportunity to target this disease and target these cancers not only to make it work better and improve the efficacy of our treatment but, as important, to provide good quality of life and to provide the ways for women to live their life relatively uninterrupted. I gave you the examples -- PARP inhibitors, immunotherapy, and Bevacizumab as examples of these new targeted approaches of which there are many.

I'm going to talk briefly now about quality of life. As you can tell from my talk, quality of life -- I believe quality of life to be extremely important. Ovarian cancer very much is and becoming even moreso a chronic disease, which women live for many, many years, and has become like diabetes or heart disease. So it is very important that we not only concentrate on early detection and cure of these cancers, but that we concentrate on quality of life and optimizing everything that we can.

So sexuality, intimacy, menopause is something that women with ovarian cancer very frequently suffer from. It has to do with many aspects, a lot of them having to do with the cancer itself, with the treatment itself, with a surgery itself and, hence, this is a very common side effect of the treatment.

There's many, many cancer survivors, and that number is expected to grow exponentially. One-third of all men and women who live today will be diagnosed with some sort of cancer during their lifetime. A lot of these cancers are curable, and a lot of these cancers, there's many survivors and that is why we need to know how to deal with the side effects.

Sixty-five percent of survivors have cancers that affect sexual organs, and ovarian cancer certainly is one of those. Females suffer with this a little bit more than males. For women the distress of these concerns grows longer, grows higher as they have more acute distress, so women are very affected by this. And we know, you know, we used to think that breast cancer was the cancer most affected by these symptoms, but we now know that gynecologic cancer is even moreso.

I'm not going to go too much in the definitions, but there are specific definitions of the sexual dysfunction -- pain during sexual intercourse, hypoactive sexual disorder, or orgasmic disorder, sexual pain disorder, and they are kind of self-explanatory. So hypoactive sexual desire, having very low desire for intercourse, sexual arousal, an inability for arousal. And orgasmic disorder, inability to have an orgasm and then sexual pain disorder, which is very, very common is pain during intercourse.

The prevalence of this is very high. This is not for women and men with cancer. This is for general population. So there was a very big study of 40 million American women outside the study of all the adults in the US, ages 18 to 59. And from the study we found out that 40 million of American women who are affected by some sort of sexuality dysfunction that affects women more than men, 43% to 31%. And it increases as women age and, for men, it stays exactly the same.

And you can imagine the number is so high, for general population that number is higher for women and men with cancer. And the numbers of the dysfunction really spread themselves

equally. So 43%, 32% have lack of sexual interest; 28% unable to achieve orgasm; and 21% pain during intercourse. So for men and women with cancer that number is much higher. The number is as high as 80% for women who have gynecologic cancers and 90% of men with prostate cancer.

And the causes are very complex. They include both physiologic and psychologic. So I want to stop for a second at this slide because I think this slide is one of the more important slides of this talk. Just to show you how common sexual dysfunction or intimacy dysfunction is in gynecologic cancers. It is complex and there's many different reasons for this. But it is talked about so little in this field that I think many times women don't appreciate how common this is and, again, in my practice this is just commonly addressed and discussed and it's part of our normal exam and normal questionnaire because we know how common it is and that helps us open up our conversation.

So I'll just say it briefly because this is such a big part of the psychologic aspects of the sexuality and intimacy is just one quick word about the (inaudible) model called the Basson model. Prior to Rosemary Basson, the model of female sexuality was very similar to the model of male sexuality. We used to say that it was similar, it was excitement until orgasm and resolution and, you know, there's a couple of other different attempts at this that really just equated female sexual cycle to the male. But Rosemary Basson had a most beautiful model that showed that for women sexual intimacy and sexuality actually has to do much more with emotional intimacy than it does with actual steps of the sexual act.

And she showed that for women there was many different ways to increase sexuality but all of them really had to do with increasing intimacy. And a few things for women that actually improved their desire to be with their partner was either having a new partner or when their partner was away for longer than two weeks. So those were the two things that predisposed women for being more sexual towards their partners as a model, which I think is actually very interesting and very funny.

So women with cancer there's many different aspects that predispose them to this difficulty and this dysfunction, and it has to do with cancer, it has to do with treatment such as surgery, radiation, chemotherapy. Women with breast cancer suffer a great deal with this because of their hormone management as well as because of the surgery they have had that change their bodies and make them feel different and frequently make them feel like they lost their femininity and makes it more difficult. This was the study to discuss with that.

So from the sexuality perspective, we got to address this from different aspects. Women with gynecologic cancers have had surgery and that surely contributes to their hormonal status. That hormonal lack of estrogen contributes to decrease in sex drive. It contributes to pain with intercourse. What they have gone through in their cancer diagnosis and through the treatment also contributes greatly to the psychologic aspects of their cancer.

And this relationship is very complex. Age plays a large role, menopause, symptoms of menopause, quality of life and sexuality. And these five are very much intertwined and really kind of have to be addressed all at once. And some of these symptoms are easy -- or relatively easy to manage. Having vaginal dryness is a very common symptom under those circumstances. And that is usually very easily manageable with either herbal medicines but also with hormonal management, which is very safe because for vaginal estrogen a very small amount actually gets absorbed.

Systemic symptoms are more difficult. Things like hot flashes, things like difficulty in sex drives, difficulty concentrating, poor sleep, those are much more difficult and systemic hormones are a

little bit more difficult discussion where we really need to discuss pluses or minuses, benefits and risks, also.

Many different medicines and medical conditions contribute to this, and those have to be addressed very carefully when diagnosis is being made. And then, most of all, achievement, what can be done? So psychologic counseling plays a very big role both individuals, couples and groups, medical, which includes hormone achievement, medications, medical devices and surgery. And the approach that I argue for, which is the integrative medical and psychologic approach, and that is the approach that we use in my institution.

I will stick to these because there's a little bit more detail of those but, in summary, of all these symptoms vaginal discomfort and pain are the most common symptoms that women experience with cancer diagnosis. And, as I mentioned, there's a lot of lubricants that can be used. There's vaginal estrogen that can be used, there is herbal medicines that can be used. Things for sex drive, which is testosterone can be used, especially if the cancers do not have hormone receptors, and we use testosterone as well as estrogen for the sex drive.

Interestingly, women can use Viagra, just like men use Viagra, and that particularly benefits women who have diabetes and also who have cervical cancer for who the nerves, the clitoris (inaudible) are somehow damaged and not functioning. And also for the women for cervical cancers who had big surgeries there may be mechanical devices they can use to try to improve orgasms and try to improve their response.

But, most importantly, and this is just the pain options that I was discussing with you before, which is vaginal estrogen, which is safe, but systemic estrogen, which has more potential side effects and really has to be considered after other entities are exhausted.

But in overview of this, the most important point that I wanted to share with you before is how important quality of life is and what a big role sexuality and intimacy plays in this and also how absolutely common and prevalent it is. And many of the discussions that I have with my women and my patients is really just acknowledging that this is all part of the normal course of this cancer and the treatment and is incredibly common but should not be accepted as the norm and we always try to think of specific issues that can be targeted, and I would encourage you to do exactly the same with your providers. If there is something in particular that you feel could be optimized, it certainly can and should be, and this should be very much part of the normal achievement and optimization that you go through for your treatment.

I'm going to save some questions -- some questions, we have 15 minutes, so I'm going to pause here.

Robin Perlmutter: Thank you so much, Dr. Ratner, that was terrific. Dr. Ratner, is Lynparza the best drug for BRCA2 ovarian cancer? I've been on it for six months now if so I'm interested in what super foods work well with it. Besides grapefruit what should I avoid? And any other significant findings related to Lynparza in terms of what to do and not to do?

Elena Ratner: So Lynparza is a wonderful drug. That was the drug I showed to you before, Olaparib. That's the drug that's the strongest for women with BRCA mutation -- or the literature is the strongest. But, yes, all these PARP inhibitors are actually very similar in terms of how they work, they all have (inaudible) very similar efficacies, which is great because if you're not tolerating one drug, then you

can have a sister drug or a cousin drug that also will work very well but will give you different side effect profiles.

So if you are on the Olaparib for six months, that's wonderful news. That means you're tolerating it, and it means that it's working. And, yes, this is a wonderful, wonderful drug for BRCA 2 mutation.

In terms of food, it's, you know, a question for the ages. There's a lot of older thought about sugars and, you know, avoiding that. The current thought, really, is that it is very important to eat well and exercise. And that is more important than anything, and I always tell my patients do not -- if you really like to eat, and you need to have a piece of chocolate in the evening time, do not let yourself not have it. You know, there's absolutely no literature that is so absolute. It is more important to eat well and exercise and have a good functional status, and that has been very much connected to better prognosis.(inaudible).

Robin Perlmutter: Okay, thank you. Another question in the chat is "Can you discuss T-cell trials and NOTCH 1 and T-53 repair research?"

Elena Ratner: Yes, so this is part of this new approach, which is targeted therapies. And this is part of what I showed you on the graph a couple of slides back. Yes, this all has to do with targeted therapies. It's not for everybody. Similarly, the tumors have to be studied, and they have to be appropriate mutations. But if those mutations exist then, yes, this is a great new approach of targeting these cells and have your immune system fight the cancers, and there's some positive preliminary data but only in women who have specific targeted mutation.

Caller #1: Dr. Ratner, I finished chemotherapy five weeks ago. It was dosed dense for 18 weeks every week and my doctor talked about putting me on Lynparza. But I don't have a BRCA mutation. Two other mutations were discovered in my tumor and I don't have the paperwork with me, so I really don't know what they are, I don't remember what kind they are except that they had to do with methylation. My doctors told me that there is a conference at the end of this month in Barcelona, the European --

Elena Ratner: Yes.

Caller#1: So you know about that conference?

Elena Ratner: Of course.

Caller#1: Do you know and have you heard anything about the results that are going to be discussed there in terms of Lynparza for non-BRCA women? That's what my doctor is waiting for.

Elena Ratner: Yes, so those questions are more complex. Yes, I am very involved with that literature. No, of course, I don't know, I won't be able to tell you what this one that's going to be said. This is a big conference that comes up in the next couple of weeks, and there's going to be a lot of very important information that's going to come out.

You must have -- one of the mutations that you must have must be the BRCA mutation that I was mentioning before in the tumor. But your doctor would not have been able to offer you Olaparib if (audio break) you did not have that kind of mutation. So what's going to come out in ESMO in Europe is something called results of the PRIMA study. This is going to be very, very important

results, and it's going to talk about benefits of PARP inhibitors in women who do not have BRCA mutations after they complete chemotherapy.

So, yes, this is a study we are all very much waiting for. The literature for use of Olaparib or pretty much any PARP inhibitor in the adjuvant setting. So after you finish chemotherapy (inaudible) if you have the BRCA mutation. It sounds really positive, really, really wonderful results. So now we are eagerly awaiting to see the results of the PRIMA study to see if that benefit also similar for women without BRCA mutation. So, yes, in a couple of weeks we will know that information.

Caller #1: Okay, thank you.

Robin Perlmutter: We have another question in the chat. "Why do drugs such as PARP inhibitors eventually stop being effective?"

Elena Ratner: That's a wonderful question. So it has to do with that complex thing I told you before how ovarian cancers are so smart that they learn how to resist chemotherapy or PARP inhibitors (background noise). So similarly to how chemotherapies only work for a period of time and then the tumors learn how to resist them by different alternation in their mechanisms. Similarly, they learn the same kind of mechanism resistance to PARP inhibitors. So there's something called DNA repair. This is how they work. It's called homologous recombination, and the cells, unfortunately, learn how to resist it.

But that's not to say that we're not thinking of the next step. You know, right now there's a lot of research as to what can be done and what should be done to try to reverse the resistance and, you know, a lot of labs are doing -- my lab, we are doing research on trying to reverse the resistance and finding a way to give women who are no longer sensitive to PARP inhibitors, PARP inhibitors in combination with another drug, which will potentially reverse that resistance.

Robin Perlmutter: Someone is asking that she has a recurrence of granulosa cell tumor. "How do I know if my doctor has tested my tumor for important mutations?" Her tumor was sent to FoundationOne.

Elena Ratner: So that's an excellent question. So granulose tumor is a bit different from everything else we talked about today, so kind of take everything that we discussed with a grain of salt, because it's a little bit different mechanism and different everything. But, yes, if your physician sent it to FoundationOne then she has information she needs. FoundationOne is what you need to genomically subtype the tumor. So that would be sufficient.

Caller # 1: Okay, thank you.

Robin Perlmutter: More questions, folks?

Caller #2: I have a question.

Robin Perlmutter: Go ahead.

Caller #2: In talking about recurrences and genetics FoundationOne testing. Doesn't this tumor profile change from recurrence to recurrence?

Elena Ratner: Yes, absolutely. Another excellent question. Yes, the tumors change with time, and like we mentioned before they become resistant so, yes, recurrence to recurrence these tumors change.

Usually not one recurrence with a next recurrence but, overall, yes. So it is usually a few times that I would say check the genomic foundation for these tumors doing the course of treatment because the tumors, you know, three, four, five years out from their recent diagnosis are very different, indeed, from the tumors that we study at diagnosis.

Caller #2: Yes, I have a second part to that. What if there is a recurrence but not enough to biopsy to test for a mutation or a change in the makeup?

Elena Ratner: Yes, another excellent question. And that happens and, you know, I really don't recommend biopsying it a lot at all because biopsies now could have side effects. (background noise) If the tumor is too small to biopsy, I just wouldn't do it. I would just treat and look at the tumor 3-5 and look at the CAT scan and let that be determination whether the drug is working and whether the tumor is different. Only tumors big enough or if it's not responding, that would be my cue to actually again do the genomic testing. But I wouldn't do it if it's too small to biopsy.

Caller #2: Thank you.

Robin Perlmutter: Okay, we have a question in the chat. "Does the literature also suggest that Lynparza works to prevent breast cancer from showing up?"

Elena Ratner: Yes, I see that question. If a woman has BRCA mutation, then, yes. And the BRCA mutation is not just in the tumor but in her blood and something called germ line, so through all the tissues then, yes, conceptually, even though there's no indication right now for use in breast cancer, but, yes, conceptually, it would also work on that. But I'm hesitant to say because there's really no evidence-based studies or medicines made to really quote it. But, conceptually speaking, I think that's the right idea. There's no literature to support it.

Robin Perlmutter: Okay, thank you. More questions, folks? Okay, we have a question in the chat. "If you have chemotherapy before surgery, can you still get information from the pathology to individualize your treatment?"

Elena Ratner: Wonderful question, and I'm sorry I didn't mention it before. So, yes, some of the mutations are not altered by chemotherapy. So things like BRCA, things like homologous recombinations, things like PDL-1 or MSI, things that make you candidates for PARP inhibitors, for immunotherapy are not altered by previous chemotherapy. Some things are, but not anything that's clinically pertinent to choose the drug. An excellent question.

Caller #3: I was positive for a BRCA gene, and my daughter was tested, and she also is positive although she has had no disease at all. They are watching her carefully, but does she need to be treated with Lynparza or just do they need to be particularly sensitive when my daughter goes for her testings?

Elena Ratner: Oh, yes. So definitely not Lynparza, please do not let me confuse you.

Caller #3: Okay.

Elena Ratner: I was talking with PARP inhibitors, Lynparza one of them, I am only talking about (background noise) the treatment of cancer. Absolutely no literature using any of these drugs as preventative drugs. But your daughter does need to be seen by specific physicians who have expertise in this. You know, depending on what kind of BRCA mutation it is, they have to provide her with a specific personalized plan of surveillance, whether it's ultrasound or a blood test. And, usually, when she's

done with childbearing, depending again on what kind of BRCA it is, we do recommend that either fallopian tubes or fallopian tubes and ovaries are removed (background noise) but that doesn't usually happen until 35 or 40 years of age, again depending on what kind of BRCA mutation it is.

So, yes, she needs to be seen by specialists, she needs to be seen by people who understand what this mutation entails. And then it would be, again, a very specific personalized individualized plan according to her mutation, her age, and her (inaudible) life circumstances.

Caller #3: Okay, thank you. All that is being done. I just wondered if there was more, but she's seen very extensively.

Elena Ratner: Good, that's great.

Robin Perlmutter: Okay, folks, this concludes our webinar tonight. And, Dr. Ratner, I want to thank you so much for your passion, dedication, and commitment to the ovarian cancer community and to all of you for coming out tonight and taking the time to become educated on this very important topic. Have a great night, everyone.

Elena Ratner: You, too. Thank you.