Program Title: Molecular Profiling As A Guide To Ovarian Cancer Treatment. For women who are diagnosed at stage 3 or 4, and women who are dealing with a recurrence.

Presented by:
Support Connection, Inc. (*With funding from The HERA Women's Cancer Foundation)

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Guest Speaker: Laura Shawver, PhD., The Clearity Foundation:

- A biotechnology entrepreneur with 25 years of experience in cancer research and drug development.
- Has spent more than two decades studying cancer-causing proteins. States: "I've learned that cancers are very different, even if they look the same under a microscope. This 'uniqueness' factor underscores what all oncologists know today: there is no 'one size fits all' cancer treatment."
- Active member of the American Association for Cancer Research
- Has served on Hollywood's Stand Up 2 Cancer scientific advisory committee since its inception in 2008.
- An ovarian cancer survivor, diagnosed in 2006.
- In 2008, founded the Clearity Foundation to help women with recurrent and refractory ovarian cancer obtain access to molecular profiling.

Topics:

- What is molecular profiling?
- Why should I consider molecular profiling and when is it not right?
- What are the potential benefits?
- Examples of how testing has helped patients and research.
- How does testing work: cost, process, timeframe, test results?
- What is my next step?
- How will this information be used by me, by my doctor?
- How can Clearity Foundation help patients through this process?

Robin Perlmutter: … possible. Remember that Dr. Shawver is sharing her expertise. Any information from tonight or questions pertaining to individual concerns should be discussed with your doctor. It is with my great pleasure that we have Dr. Laura Shawver, who is a biotech entrepreneur with 25 years experience in cancer research and drug development. Dr. Shawver is also an ovarian cancer survivor, diagnosed in 2006. In 2008, she founded The Clearity Foundation to help women with recurrent and refractory ovarian cancer obtain access to molecular profiling. Clearity's mission is to help women live longer, healthier lives. Thank you, Dr. Shawver, for sharing your time and expertise with us tonight.

Laura Shawver: Great, Robin, thank you. Can you hear me okay?

Robin Perlmutter: Yes.

Laura Shawver: Okay, great. Well, good evening everyone. I'd like to start off by thanking Robin and Support Connection for this opportunity. It's also great to see some familiar names pop up, and thanks very much to everybody for joining. Tonight, I hope to tell you about molecular profiling as a guide for ovarian cancer treatment, and I'm going to go through some of the slides quite quickly. But, as you probably appreciate, the slides and a transcript will be available shortly after this evening, maybe a couple of weeks later, on the Support Connection website, and I'd also like to make myself available offline to address any questions that you might have. And of course, it's particularly special to me to do this during Ovarian Cancer Awareness Month, which was the month that I was diagnosed nine years ago.

Robin, if we could go on to slide 2, you already mentioned the mission of the Foundation, to improve the survival and quality of life of women with ovarian cancer through molecular profiling, and by doing so, giving hope to women and their families.

On the next slide is a high-level view of the three buckets by which we do that: supporting patients who are in the fight; increasing awareness about the value of molecular profiling; and igniting research, so more women can have access. If we go on to slide 4, I've bulleted here under each of these main buckets, the activities of the Clearity Foundation. I don't have time, unfortunately, to review those with you this evening, because the focus for tonight will be to provide you information about molecular profiling, and how we hope and personally, I hope, to support women in the fight, and that's the purpose of tonight's overview.

Robin, if we go on to slide 5, this is the outline and the topics to be covered. Where I want to first review the current treatment paradigm, I know that most of you know that, but I thought I'd start by comparing and contrasting it to another cancer, to see how things have shifted in other types of cancer, and how it needs so desperately to also be shifted in ovarian cancer. And that's what Clearity Foundation does. We really seek to change the treatment paradigm. We hope to address the questions on this slide: what is molecular profiling; why should I consider it; what are the benefits. I'm going to give a couple of case examples, but we have more if you'd like to explore those offline. What can I expect, how does the testing work, what's the cost, the process, the time frame, how do I get the test results, what's my next step, and how will I use this information? And importantly, how Clearity Foundation can help you through this process. And for those of you who are in the fight, or know somebody that is, Clearity Foundation would really like to provide any help that we can.

On slide 6, I thought I would give you an overview of what's happened in lung cancer, which has changed so dramatically over the last ten to 15 years. Just like ovarian cancer, it's broken down into different histologies, as you can see from the pie chart on the upper left. But, in lung cancer, automatically if you're diagnosed they go on to do molecular profiling to break it down into various molecular subsets, as you can see on the pie chart on the bottom. And many of you are already familiar with breast cancer, which is typically divided into three main subgroups, and of course, molecular profiling perhaps originated when we understood that certain subtypes of breast cancer are estrogen receptor-driven, and if you're ERPR positive you should be treated with an anti-estrogen.

And, in lung cancer, if we go on to slide 7, it's interesting how, based on these molecular alterations, that determines the treatment, that people don't automatically go on a chemotherapy. Sometimes they do, as shown on the right for first-line treatment. People go on a platinum doublet, but not always. Based on the molecular alteration, people can go on an EGF receptor inhibitor, or an ALK inhibitor, and even maintenance treatment, second-line and third-line treatment, can be different based on the histology of -- but most importantly on the molecular biology.

If we go on now to ovarian cancer, on this slide, it's also many different diseases, and in fact, ovarian cancer is really 30 different subtypes. But, the predominant subtype is epithelial ovarian cancer, and I'm going to be limiting my remarks tonight to epithelial ovarian cancer and the main histological subtypes. And if we go on to the next slide, you see that these main histological subtypes, which is in the first row -- HGSC on the top there stands for High-Grade Serous, and then the next column is Clear Cell Carcinoma, the next one is Endothelial, the next one is Mucinous, and Low-Grade Serous. And then, if you go down to the row that I've circled there on the molecular genetics, this is taken from a review article by Bookman. You can see that the molecular alterations are different across these histological subtypes, just like they are in lung cancer, just like they are in breast cancer.

However, if we go to the next slide, unfortunately, independent of the histology, independent of the molecular biology, we almost all receive the same treatment. We have the cytoreductive surgery, to have

our ovaries and uterus and anything else that we don't need removed. Following that, we will receive a platinum doublet, a platinum taxane doublet, typically Carboplatin and Paclitaxel, or Taxol. Mostly this is IV, but lately sometimes it's an IV/IP regimen.

And unfortunately, following surgery and chemotherapy, 25% of us either don't respond or we go on to relapse very quickly after treatment, 25%. But the reason that this chemotherapy doublet is used, is because 75% of the time we do achieve remission, and following that, there is a surveillance period. Unfortunately, as most of you appreciate, 75% of the time then people do recur and this is where the difficulties begin in terms of what are the next treatments, how do we choose those treatments, and why should we take particular treatments, and that's really what I'd like to focus the rest of the talk on.

On the next slide, I am just overviewing why I believe that it's time for a paradigm shift in ovarian cancer. Clearity Foundation, as Robin mentioned, was launched in 2008, and we -- I know that being a nine-year survivor, having never recurred, that I'm one of the lucky ones, and I'm very dedicated to pushing molecular profiling as a way to prioritize treatment options and to improve the outcome for women battling ovarian cancer.

On slide 12, you can see that we launched in 2008 to, as I said earlier, improve the survival and quality of life of women with ovarian cancer, but more importantly bring molecular profiling to the forefront of ovarian cancer diagnosis and treatment, just like it is for breast cancer, just like it is for lung cancer, and many other cancers, as well. And, to not only help you, but help doctors identify a therapy that's now informed by your tumor molecular profile rather than pick out of the hat or trial and error, which is the current process. And, to thereby increase the probability of success for new drugs to use molecular profiling either for off-label use, or to get people on the right clinical trial.

What we have done since 2008 is followed over almost 500 patients and more than 500 profiles. We've created the largest database of its kind, where not only do we have clinical history information, but we have the molecular biology of each woman's tumor and most importantly, we track the outcome. You can see that we can divide the database by histology, which is shown on the top, you see papillary serous there, 71%, which of course if the predominant histology in epithelial ovarian cancer. There's other features that we can track as well, like platinum response. Importantly, however, what we're doing is, we're utilizing the database not only to help you as an individual make a more informed decision about what your next treatment should be, but also to help understand on a population basis, what profiles match to which drugs in the best fashion.

On the next slide, I want to talk a little bit about the process, and how Clearity works. We really are a bit of a clearing house, where we provide physician and patient education. We coordinate the testing, although we don't do any testing ourselves, and I'll talk a little bit about the laboratories that we utilize later on. Our database is HIPAA compliant, and a secure database, where once the data goes in we have a way to interpret the profiles, and provide a report to you and to your physician, and help to -- to help you, and help the physician, understand what the prioritization of treatment options are.

If we go on to slide 15, what is needed, then, is a biopsy or surgical sample of your tumor. One of the things that's very important is that we have a proximal sample, meaning it's close to the time of doing the profiling. We published a study back in 2012 that demonstrated that in ovarian cancer, tumors change over time, and with treatment, so we don't go back to an archived block from your surgery. We need a biopsy that's near to the time where the profile is done. Your doctor will order the biopsy, and the pathologist assigned to your case stores the sample in something called a FFPE block. This is standard pathology lingo, and it stands for Formalin-Fixed, Paraffin-Embedded. For those of you that have had a recent surgery, we can use that sample. It's not always possible to get a biopsy and I'm going to talk about that a little later on.

We will work with your oncologist to provide requisitions to the testing laboratories, and then the laboratories will request your FFPE block from the pathologist, and the laboratories will provide the results to your doctor and to us, and because we are utilizing three different laboratories, we consolidate the results from the testing laboratories and will provide a consolidated report to you and your doctor.

Profiling is not for everyone. Our focus is on recurrent disease, when a surgical sample or biopsy specimen is available. As I mentioned, sometimes when treated with Carbotaxol it doesn't work right out of the gate. In that situation, we can go back to the surgical specimen and a new biopsy isn't required. And that can be helpful to prioritize which chemotherapy one receives next.

If you did achieve remission, then we would need a profile, if you were one of the people that recurred, that would be the time to have a profile to help prioritize the next treatment. I will say that often times, people come to us after two or three or four, sometimes more, recurrences, and that doesn't mean we cannot do the profiling. We will, but I will just comment that the more treatments that an individual has had, the more heterogeneous the tumor becomes, and the more difficult it is to identify a treatment that may provide a long-lasting benefit. We really encourage people to have a profile during their first or second recurrence.

If we go on to the next slide, not always is tumor profiling appropriate. Here are some statements that you can see, do they match to you.

"I'm having a recurrence since my first diagnosis, and my doctor has planned another surgery or biopsy to remove tumor tissue." Oftentimes, if you've had a long-term remission, let's say two or three years or more, your oncologist will recommend that you have a second debulking surgery. If so, we'd be happy to profile from that, from a FFPE block from that surgery.

Another statement: "I've had a recurrence since my first diagnosis, and another surgery or biopsy was performed to remove tumor tissue during the last year." That's really the cutoff that we use. Ideally, we would like to have a tumor tissue that's from a surgery or biopsy within six months of the time we do the profile, but we will extend it out to a year.

Lastly: "I've had a recurrence or my cancer progressed within the first year of my first diagnosis." Those are the people that are platinum-refractory or platinum-resistant, where we can go back to the primary surgical sample. Next slide?

For recurrent ovarian cancer, and I think some of you know this all too well unfortunately, there is multiple treatment choices for recurrent disease. There's multiple types of chemotherapy, such as Doxil, as Gemcitabine, Topotecan. If you've been more than a year from your first treatment, you're going to get carboplatinum again. There's new investigational agents. I'm not going to talk a lot tonight about clinical trials, but I'm a big advocate of clinical trials and understanding your choices of clinical trials at first recurrence, rather than waiting until you have failed all available chemotherapy. And finally, there's new drugs approved in other cancers, that might be considered for your ovarian cancer, and that's the role of molecular profiling, that it may help to prioritize these choices.

If we think about this in a flowchart, which is shown on the next slide, we have two main marker panels to prioritize chemotherapy or clinical trial. We have a chemotherapy marker panel, and a targeted therapy marker panel, as well as a gene panel, and that can help select your next chemotherapy. It can help select a clinical trial with the targeted agent. Or, it may help select a chemotherapy agent for combination with a targeted agent in a clinical trial.

The markers that we use for the chemotherapy panel is shown on this slide, and this is a standard test panel that aims to help prioritize drugs that are on the NCCN guidelines for the treatment of recurrent ovarian cancer. Some of you probably know that that's how physicians think about treatment, is the

NCCN guidelines. I'm not going to go into great detail tonight about the biomarkers, which are in the first column. There's a lot of information on our website, if you would like to know those, and to dive into the details, but each of those biomarkers are associated with a drug class which is shown on the second column. And then, specific drugs on the third column. And each of these has a particular target inside the cell.

For example, if we look at Liposomal doxorubicin, which works on a target called TOPO2, if your tumor doesn't express TOPO2, there's no way that that drug can work because the target is not there to interact. This is the biomarker panel that we run to help prioritize choices amongst the various chemotherapy options for recurrent ovarian cancer.

On the next slide, I'd like to go through the results interpretation. Again, I won't go into a lot of detail this evening, because we have a lot of information on our website which I've outlined here. But, for the chemotherapy panel, it's a protein panel where we're measuring it by something called immunohistochemistry, or IHC, and we compare your results to all of the women that have already had the test and are in our database. And the results are interpreted using clinical research evidence that correlates the marker with the drug response, and all of that clinical research evidence is on our website.

And the chemosensitivity markers are called out if they're high, if they're in the high end of the range, above the 75th percentile, and in two slides I have an example of that. Chemoresistance markers, on the other hand, are called out if they're in the low end of the range, below the 25th percentile. Sometimes the best way to explain this is to do a case study, and that is shown on slide 22.

This is a woman that was diagnosed back in 2005 with Stage IIIB papillary serous carcinoma, this is a fairly typical diagnosis. She had surgery, and then she had typical carboplatin and paclitaxol treatment, but she also had maintenance Taxol for 10 months. And she was in remission for two-and-a-half years. Upon recurrence, the doctor -- her oncologist prescribed carbotaxol again, not surprising since she had responded to it the first time. This is a pretty typical treatment paradigm right now for ovarian cancer. If you responded the first time with a long remission period, you will receive it again. Unfortunately, this time, she progressed while on treatment. They added Avastin on top but she continued to progress. They changed the chemotherapy regimen to Doxil, but she progressed while on Doxil, presented with a bowel obstruction for which she had surgery. And that's where Clearity Foundation came in, and we did a profile. This was back in 2011, now, and we prioritized gemcitabine, pemetrexed, and anti-estrogens, I'll show you the data on the next slide, and not surprisingly, the oncologist prescribed gemcitabine because that's a pretty standard treatment for recurrent ovarian cancer. And she remains tumor-free to this day.

Now, you can go on, Robin, to slide 23. This is the actual data for those that are interested, and when I talk about the 75th percentile and above, and the 25th percentile and below, these are the data that I look at and Dev Zikowsky (ph), our Scientific Director, looks at as we're interpreting the results. If you look at anti-estrogens, aromatase inhibitors are on the top. That square was the actual patient data, and this is a box plot where the whisker on the top represents the 75th percentile and above, and the whisker below the box represents the 25th percentile and below. We look at where every person's red dot falls on the graph, and that helps us to call out particular drugs.

And importantly, the way that I look at this, is that she probably should have gotten gemcitabine when she first recurred. She would not have had to receive carbotaxol again, Avastin and Doxil, because all of that was toxicity without benefit.

I'd like to now turn to the targeted marker panel, which is shown on the next slide. Here now, we -- in 2012, when Foundation Medicine launched their -- when they launched their services in a clear manner to do next-gen sequencing of certain genes that matched particular drugs, we actually -- Clearity Foundation was their first customer, because we believe that in certain circumstances, that there are agents that benefit other cancers that can be used in ovarian cancer. And on the left-hand side, again, this is on our

website, and you can go and study it at your leisure. I'm just going to give an overview here, where we think of these different treatments in buckets, as shown on the right hand side, where specific molecular alterations would call out one of these molecular targeted agents.

And that's shown on slide 25, actually in somebody's report, where there's a summary of agents associated with benefit that sometimes these drugs are approved in other cancers. If you go to the second row down, where it says KRAS, NF1, we call out Trametinib. This is a drug that's approved in melanoma, for patients that have KRAS and BRAF mutations, and could potentially be used in ovarian cancer if one has that molecular alteration.

If we go on to the next slide, I'm going to give another case study now utilizing the -- both the chemosensitivity panel as well as the molecular targeted panel. Here now, we have a rare histology. This is a clear cell carcinoma. This woman was diagnosed in stage IIIC and she only had three months in remission, following surgery and carbotaxol treatment. That's pretty typical of some of these uncommon histologies where they are known to be chemo-refractory.

During the profiling, looking at chemosensitivity, chemoresistance, topoisomerase I inhibitors were prioritized and she went on a clinical trial with topotecan and an AmGen drug called AMG386. And she had stable disease for 17 months. Now, in clear cell, stable disease is considered a win because most people progress while on treatment.

She did elect at that time to have surgery to remove residual disease, and she wanted to understand the choices for maintenance treatment. By this time, we were doing the next gen sequencing panel at Foundation Medicine, and we identified PIK3CA as a mutation, which correlates with everolimus as a potential treatment. And she did continue on with another TOPO1 inhibitor, irinotecan and everolimus, and remained in remission for 18 months. And her actual profile is shown on the next slide, where the pathway that drives protein synthesis is -- and her alteration of this PIK3CA mutation is shown in the green box, and why potentially everolimus or another drug, temsirolimus, would be effective on somebody with this molecular alteration. And indeed, it was in her situation, and the clinical evidence does support the use of mTOR inhibitors in combination with chemotherapy agents.

What we have on our website, which is shown on the next slide, is the ability to identify clinical trials based on a particular molecular alteration. There's a dropdown menu where you can just select mTOR, and it will pull up all of the clinical trials that in ovarian cancer for these mTOR inhibitors. And if you'd like any help with this, it's pretty easy and self-explanatory to use, but if you'd like any help with it we're happy to do that.

In summary, on slide 29, we really are trying to change the paradigm, and we're doing that by trying to help people in the fight today. And, help you prioritize your treatment decisions from all the available treatments out there, not only what is in the NCCN guidelines, not only what's in clinical trials, but also potentially off-label use. And, at the same time, you're very important to helping the next person that comes in by providing your profiles to us, by providing your follow-up information. This allows us to do analysis to see how successful we are in matching a treatment with a -- how successful we are with matching treatments to molecular alterations. Next slide?

What makes us different from the laboratories that conduct these tests, Caris, Clarient, and Foundation Medicine? We utilize these labs for testing, but we're different. We're not-for-profit, and we're not running these tests to make money. Our goal is to find the right predictive tests for patients, rather than to run tests. I can tell you that what we do today in 2015 is not what we did in 2008. We've learned some things that work and some things that don't. We are a quality monitor, and we have an evergreen panel, and we are only focused on ovarian cancer. And, very focused on finding the right molecular targeted agent to combine with the right chemotherapy, and that requires multiple modalities. That's why we use three different laboratories, and we're the only ones that integrate testing for both. Next slide?

I thought it was important to talk about some of the perceived barriers to profiling. They're listed here. One that comes up a lot is the evidence for each target is limited to preclinical or retrospective clinical research, and mostly in cancers other than ovary. Another perceived barrier, and sometimes these are real barriers, it may not be possible to obtain a surgical specimen or safely obtain a biopsy. We know that we can't always provide a profile to people that want one, because we can't get the right surgical sample or a biopsy. The tests cost too much, and insurance won't pay. And, another barrier is that sometimes, the drugs that are suggested by these tests are off-label, and insurance or Medicare will not reimburse.

Let's talk specifically about the costs. First of all, a little bit about the process. I'm not going to go into great deal of detail about this. Everything is online. Either you or your physician completes the paperwork. We arrange for the tumor specimen to be sent to the labs. It takes three to four weeks. We receive the results and generate a summary. We provide consultation to you and to your physician, if she or he would like it, and our patient support services are free of charge. The profiling costs are covered by many insurance plans, but sometimes they're not, and we do provide financial assistance for profiling costs. We do have a short, one-page grant application to fill out, and we've never turned anybody down. That can include costs for a copay, if need be. Next slide?

We've taken it one step further, however, in that we recognize that certain types of ovarian cancer, particularly these uncommon histologies, do not respond to standard treatment. And the profiles can identify drugs that are used to treat other cancers with similar genetic alterations. Unfortunately, right now, it's true that insurance does not often pay for these off-label drugs, and we have initiated a pilot program designed to reduce the costs for these treatments, and really our goal is to help women access these more promising treatments and to provide an opportunity to show effectiveness of new drugs and ovarian cancer, and energize clinicians for larger-scale drug trials to change clinical practice. Next slide?

Here are some case studies that demonstrate that in these uncommon histologies when there are these specific molecular alterations as noted in the second column, that there are drugs that match to these that are approved in other diseases, that actually do have benefit in ovarian cancer. And I'll just call out in the second column, this Castro, et. al. paper was a clear cell patient that went on Trametinib and Metformin. This was one of our case studies that we recently published, that I didn't have time to talk about tonight, but I'm happy to send a reprint of that paper to anybody that would like it. Next slide, please?

This is just to demonstrate where, on our website, to find the background forms, the consent forms and authorization for release of medical information, so we can be a broker on your behalf and move your tumor around and get the results. Next slide?

I know we're just about out of time, here. I want to leave time for questions. I only have three more slides. I wanted to just briefly talk about the forms that need to be provided. It's a background form that you fill out online, there's a consent form that needs to be printed and signed, the authorization for release of medical information, we need a copy of your insurance, and if you're requesting it, the financial assistance form, which is also online. Next slide?

In summary, we're here to help. We want to help you with access to molecular profiling, we want to help prioritize treatment options including chemotherapy, clinical trials, off-label use, particularly if you get on a clinical trial, we'd like to help you be on one that matches your profile, to help you with questions for your doctor, and that there are -- there's no costs for Clearity services, and we help with profiling costs when needed. And as I mentioned, we've launched a pilot program to supplement drug costs with a profile matched to rare histologies when an oncologist agrees to prescribe, and for anybody that would like the details on that program, I'm certainly happy to provide it.

Finally, on slide 38, we have launched a patient portal. The goal, and you can see the link, you can have -- there's a link here to the patient portal. It's a way to not only store your medical records all in one place, but it's a way for us -- we have not -- it's still in beta testing, but it will be a way for us to get the report to you, to get the report to your doctor, where it's all accessed online. We also have educational content, news, tutorials and resources, and we hope it can be a forum for social support as well.

And, I'd really like to thank you for participating tonight, and I'm really looking forward to addressing your questions.

Robin Perlmutter: Okay, thank you so much, Dr. Shawver. That was really terrific. Caller # 1 has a question. Her question is, "I am a little confused, please excuse me, but I was diagnosed with Stage IIIC-platinum refractory adenocarcinoma. Would I be eligible for profiling? I am BRCA negative."

Laura Shawver: Hi, Caller # 1. Yes, you would be eligible for profiling. I would like to understand when you were diagnosed, and how long it's been, how many treatments you have been on. If you are recently -- if you've only been on Carbotaxol and you recurred, either while on the Carbotaxol or within six months of taking that drug, we can go back to when you had surgery. If you've gone on to receive either single-agent Doxil or gemcitabine, we probably would want a new biopsy, but absolutely you would be eligible for profiling.

Robin Perlmutter: Okay. Caller # 2 asks: "How does your approach compare to the approach of Patrick Soon-Shiong in California?"

Laura Shawver: Right, he's an incredible person, and I hope that he will make a difference for many types of cancer going forward. I'm not aware that at this time Patrick and his company is doing real-time analysis. What they -- their approach, I believe, I'm not completely familiar with it, is to do what's called big data, and to analyze data from a population. And our approach is to help each individual, and by doing so and collecting data, we can also help a population at large. But, I will say that it's going to take all of us, too -- I'm a big believer in finding a cure for ovarian cancer, and I know that it's a horrible disease, it's many different diseases, it will require different drugs for each histology and molecular biology, but I think it's going to take many people working on this problem in order to get each woman their cure. And that's our collective goal.

Robin Perlmutter: Okay. Caller # 3 asks: "If all hospitals and doctors encouraged their patients to go to Clearity for profiling, do they do this profiling for their patients? And, if they're doing it in-house, are they sending it to one of the three labs that you mentioned?"

Laura Shawver: Great question. I can tell you that over time, there has definitely been more doctors that are working with us. And in 2008, when we first launched, in our first kind of KOL meeting that we had -- that stands for Key Opinion Leader -- we had a bunch of gyn-oncs in the room, we said, "This is what we're going to do." They said, "Well, we would never do a biopsy, and therefore, we would never profile." And because of the fact that colon cancer and lung cancer are treated now based on biopsy and doing molecular analysis, most gyn-oncs are on board, and almost never do we hear anymore, "I can't do a biopsy."

However, we do hear that their treatment, their choice of treatment for you won't change based on the profile. It's very frustrating, to me. I would say if you have one of these uncommon histologies, like clear cell, endometrioid, mucinous, low grade serous, carcinosarcoma, I would go to the mat and insist to have a profile, because they're very chemo-refractory cancers and we need to be our own advocates. And we also have to recognize that some of the doctors -- this is complex science. They don't understand it, and we have to help them get there. I know from experience that it can be difficult to get a physician to talk to me the first time, but once they understand what we're doing, it's easy for them to work with us the second time.

One of the things that happened early on is that they didn't appreciate that we were removing the cost barrier by paying for it, and some doctors thought we were taking advantage of patients by having them pay for the profiling or pay us to do our work, and once they understood that we're -- we remove the cost barrier, they're a lot more receptive. I'll just say that we have to be our own advocates, and sometimes push our doctors to do this.

Robin Perlmutter: Okay. Caller # 4 would like to know, "If I had my surgery and front-line chemo within the last year, but haven't recurred, would there be a benefit to having profiling within the year even if I haven't recurred?"

Laura Shawver: Yes, and another very good question, and as -- like, I certainly appreciate that we all want to do everything possible to be prepared in case of a recurrence. But, it actually doesn't make sense to have a tumor profiled if you're still in remission, because the likely scenario is that you will stay in remission for long enough that any profile that we did today would be irrelevant when you recurred, and it would have to be repeated. I would say sit tight, and sending all positive energy your way so that you won't recur ever.

And we'll be here in case you do.

Robin Perlmutter: A question, we have a question from Caller # 1. "I received a full course of IV/IP cisplatin and Taxol, I'm scheduled to receive my second Doxil treatment next week. I would need a new tissue sample, is that correct?"

Laura Shawver: How -- I would need to know, Caller # 1, how long it was in between your platinum Taxol treatment and your Doxil treatment. If -- well wait, Caller # 1, you said you're platinum -- you said you're platinum-refractory? No, we would be able to go back to your surgical sample even though you've had a Doxil treatment. We should talk offline, Caller # 1.

Caller # 1: Thank you. I'm just overwhelmed. I'm sorry to ask you to repeat.

Laura Shawver: Oh no, no worries. We would not need a new biopsy. We could go back to your surgical sample because you're platinum-refractory.

Caller # 1: Okay. How can we talk offline?

Laura Shawver: I'm going to make sure that Robin sends my e-mail around to everybody, and you can send me an e-mail, set up a time to talk, and I'll connect you to our patient coordinator at the Clearity office who can help you through all of this.

Caller # 1: Thank you so much. I feel so hopeless, and this has been a wonderful, inspiring webinar.

Laura Shawver: You're welcome, Caller # 1, and we know how difficult it is, and you're exactly the type of person that should be profiled, right now.

Caller # 1: Thank you.

Robin Perlmutter: Okay, [question from Caller # 5] … "LGSC [Low Grade Serous Carcinoma] I had surgery in April and I am on anastrozole. No recurrence so far. My CA125 is 20 as of last week. My cancer is ER and PR positive. Should I get profiling, given my current situation?"

Laura Shawver: I think not. Low-grade serous is fairly indolent and slow-growing, and it is one of those -- it has a very different -- it's very different than high-grade serous. It's actually, of all of the ovarian cancer histologies, probably the only one that can really benefit from an anti-estrogen, or in this case an aromatase inhibitor, and I would continue on the anastrozole and keep me posted on your CA125. I'd be interested to know

what your CA125 was at the lowest after your surgery, if you wouldn't mind telling me. Or, we can talk offline.

What I would want to know in this case is, if -- like my CA125 was never high, and like my CA125 today is probably 15 and has probably been somewhere between 10 and 15 for a number of years. I don't know how to interpret 20 without knowing what it was in April. If it was 2, and now it's 20, I would want to know what it is a month from now and track it pretty closely. But, if it was always 8, 10, 12, then 20 may not be as important, but we can talk offline, Caller # 5.

Caller # 5: Can you hear me?

Laura Shawver: Oh, now I can hear you.

Caller # 5: Okay, good. It was 334 before I had the surgery, when I still had the tumor, and the first month after it was 90, and then the second month after it was 45, and then last week is 20.

Laura Shawver: Oh, you're going in the right direction, congratulations!

Caller # 5: Yeah.

Laura Shawver: All right. No, I would absolutely keep on that.

Caller # 5: Just keep on what I'm doing?

Laura Shawver: Yeah, I'll send you all positive energy too, because you're going in the right direction.

Caller # 5: Yes, I'm with Dr. Leiserowitz at UC Davis.

Laura Shawver: Oh, okay.

Caller # 5: You know who he is?

Laura Shawver: I don't, but --

Caller # 5: A lot of research on this as well, and that's just the first thing he suggested. He said, you don't need chemo.

Laura Shawver: Yeah, that's excellent, and if it ever does start to go back up, I mean, you probably -- you should -- you should then be profiled because I can pretty much guarantee you that you have a mutation in either the MAP Kinase or the PI3 Kinase pathway, and we have other low-grades that we're dealing with who are on these other agents and do fine where chemotherapy doesn't really do anything, as your oncologist pointed out.

Caller # 5: Right, are they on the MEK inhibitors, those?

Laura Shawver: They, one of -- that's right, they are.

Caller # 5: Yeah.

Laura Shawver: The MEK inhibitors, those are like, trametinib.

Caller # 5: Yeah.

Laura Shawver: And that's right.

Caller # 5: If I recur, we'd try that probably?

Laura Shawver: Probably, yes. I would want to know if you had a PIK3cA mutation because then I'd go on everolimus rather than trametinib, but some people have only a KRS (ph) mutation, some have only a PIK3cA mutation, and some have both. There are different pathways, so you want to think differently about the drugs.

Caller # 5: Right. The only DNA mismatch repair proteins, you know, that they did after the surgery, was the MLH1, MSH2, MSH6 and PMS2.

Laura Shawver: And your doctor did those?

Caller # 5: I had surgery at Stanford, and they did those, as just you know, right -- right after the surgery or during the surgery, and then they --

Laura Shawver: Did you have any alterations?

Caller # 5: No, no.

Laura Shawver: Okay. Because --

Caller # 5: But those aren't any of the ones you were talking about.

Laura Shawver: No, no, they're not. And I'm surprised they just did those, but there's an interesting line of thinking right now, that alterations and mismatch repair could potentially predict response to immunotherapy such as Keytruda and Opdivo, the PD-1 PD-L1s. We're tracking that, and it could be that that's why they looked at that. They should have looked at others, though.

Caller # 5: Yeah, I was wondering why they didn't do it right then, just the whole thing.

Laura Shawver: Some people are getting onboard, and -- about doing it regularly, and some are not.

Caller # 5: Uh huh. Doing it regularly like during the -- during a regular --

Laura Shawver: Well, if you have breast cancer, lung cancer, melanoma, colon cancer, when you have surgery you just get profiled, boom. I mean, it's standard operating procedure to do that. Ovarian cancer, it's not yet.

Caller # 5: I see.

Laura Shawver: It's very institution-specific.

Caller # 5: Uh-huh. Huh. Okay. Thanks.

Laura Shawver: Sure.

Robin Perlmutter: Okay, Caller # 6 has a question. “Is it safe to biopsy lymph nodes in the neck?”

Laura Shawver: Well, Caller # 6, I can't advise you on that because I'm not a medical doctor, and you'll have to ask your oncologist about that. That being said, I know that we have profiled lymph nodes from the neck region, but it just depends on where they are, and you'll have to ask your oncologist if they would -- if they can safely remove them. If they can safely remove them, then we can profile.

Robin Perlmutter: Okay, and Caller # 7's question is-- she has two questions: "Is there any difference between the analysis that is done by the three labs? And, do you have people that are using immunotherapy as a result of their profiles?"

Laura Shawver: Hi, Caller # 7, so great to talk to you, thanks for the questions. Caller # 7 and I go way back. On the -- the different, the three laboratories do different things. There's very little overlap. However, that being said, whenever we implement a new test, we will often duplicate it at two different labs because we want to understand the concordance or the lack of concordance. We do have one test that we continue to test at two different labs, because it's a noisy assay. Foundation Medicine does the Next-Gen sequencing. Caris does the chemosensitivity/chemoresistance panel on the vast majority of the biomarkers, but they don't do all of them, and we use Clariant to round them out.

Immunotherapy, great question, comes up a lot now. Right now, there are no markers that correlate to response to the PD-1 PD-L1 inhibitors, with the exception of the MSI, micro satellite instability in colon cancer, where it was shown that the response to I think it was Keytruda went from zero to 60% if you had micro satellite instability. Very hot area of research, because unfortunately, in ovarian cancer these immunotherapies have not been as exciting as they have been in melanoma or lung cancer. The responses have been underwhelming, with the possible exception of clear cell.

Robin Perlmutter: Okay. Oh, I'm sorry, go ahead?

Caller # 1: (inaudible) are you talking to me?

Robin: Do we have a question from someone?

Caller # 1: Yes, can you hear me?

Laura Shawver: Yes, we can.

Caller # 1: Oh, I'm sorry. I guess -- and maybe my question is inappropriate, but if this is -- you know, directly targeted towards a specific tumor, your individual tumor, I don't understand -- I go to a major -- it's rated fourth in the country, cancer center, and I don't understand, why isn't this done routinely? You know, you go through hell and back getting the cisplatin and the Taxol, and then I find out, well, it didn't even work. I guess I'm a little angry, and I have no idea if this Doxil is working or not. I'm not eligible for any clinical trials because it's an adenocarcinoma except for a folate receptor, which I don't even know if -- my tumor's not back, the test isn't back yet to see if I have folate receptors.

Laura Shawver: Uh huh. That would be a good one, Caller # 1, if you -- because you probably do have folate receptors, if you could get on that clinical trial. That's a great clinical trial to get on.

Caller # 1: It's a Phase I trial.

Laura Shawver: Well okay, again, we can talk offline, because Phase I sometimes, I believe that that trial is through the dose escalation, and they're expanding, so they know their dose. But, even so you have an adenocarcinoma?

Caller # 1: High-grade serous, right.

Laura Shawver: Yeah, papillary serous adenocarcinoma, and you're BRCA-negative, you said.

Caller # 1: Yes.

Laura Shawver: It's harder for that histology to identify something that would match -- right now, it's harder to do. There's -- everybody's working to try to understand the BRCA genes, in other words, what gene alterations might make you sensitive to a PARP (ph) inhibitor, even if you don't have a BRCA mutation itself. But, it's more difficult right now for your histology. If it was me, I would want to be profiled to understand potential chemotherapy choices, and some -- I would have to understand a little bit more about who your physician is, and maybe why they wouldn't want to do this. But, let's talk offline.

Caller # 1: Thank you so much.

Laura Shawver: Sure.

Robin Perlmutter: Okay. Thank you so much, Dr. Shawver. I'm just going to share a couple of comments from some of our women. Caller # 8 wanted to thank you, she is so grateful for the Clearity Foundation, and Caller # 9 -- I'm sorry, and --

Laura Shawver: Thank you very much, thank you.

Robin Perlmutter: One of our other ladies also wanted to comment, Caller # 9 commented that she pushed -- "I pushed for the tumor sample analysis and Clearity was very, very helpful in facilitating the process after my recurrence. I am currently exploring a clinical trial, thank you so much for what you do."

Laura Shawver: Oh, great, Caller # 9, thank you. and I -- I hope you get on that clinical trial and keep us posted on how you do, and I think for people that have been through the process, they know that we're here, we've been talking with some women since 2008, and we try to work through, continue to help work through, if new issues arise.

Robin Perlmutter: Okay, well, I want to thank you, Dr. Shawver, for your passion, dedication and commitment to the ovarian cancer community, and to all of you, very enthusiastic participants who came out tonight to become educated on this very important topic and tool, as Dr. Shawver so generously offered, I will be sharing with you her e-mail address so that you can correspond with her further, or if you have any additional questions. And again, this webinar will be posted to our website within the next several weeks, and you'll get a notification on that, as well. Thank you again, everyone, and have a great evening.

Unidentified Participant: Thank you so much.

Laura Shawver: Yes, thank you. Thanks, everyone. Nice talking to all of you.

Unidentified Participant: Thank you.

Laura Shawver: Okay, 'bye.

Unidentified Participant: Goodnight.

Unidentified Participant: Goodnight.