Providing Molecular Profiling for Patients With Ovarian Cancer: An Interview With Laura Shawver, PhD, of The Clearity Foundation

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The Clearity Foundation was launched in 2008 to help patients with ovarian cancer and their physicians make better-informed treatment decisions based on the molecular profiling of tumors. The Clearity team includes scientists, physicians, and volunteers who feel passionately that the paradigm for recurrent ovarian cancer treatment needs to change from a trial-and-error approach to one that individualizes therapy selection based on the molecular profile of each patient's tumor. This nonprofit organization provides patient support services including lab test coordination, tumor blueprint interpretation, and clinical trial identification completely free of charge to the patient. Clearity also advocates for expediting the clinical development of novel targeted agents for ovarian cancer and has created a database that is correlating tumor molecular profiles with treatment outcomes.


Laura K. Shawver, PhD

The Clearity Foundation creates a molecular profile for women with recurrent ovarian cancer by measuring a wide range of markers. The molecular tests of Clearity's standard panel are protein assays, and the information from these helps patients prioritize from the approved cancer drugs. Recently, Clearity expanded the panel by incorporating the analysis of more than 200 genes, most of which are correlated with new therapies being tested in clinical trials. The combined information from the panels allows patients to prioritize from both chemotherapy agents and the molecular targeted agents being tested in clinical trials.

In addition to providing access to molecular profiling tests, Clearity also provides a summary report providing a consensus interpretation of results based on published evidence from clinical research studies as well as their own ovarian cancer database, with the intention of educating both patient and physician as to how this information can be used to prioritize treatments that may be most appropriate for that patient.

Advocacy groups such as The Clearity Foundation are playing a large role in the adoption of personalized medicine techniques. *Personalized Medicine in Oncology* (*PMO*) recognizes this role and welcomes groups such as this to the personalized medicine community. We were pleased to speak with Dr Laura Shawver, biotechnology entrepreneur, The Clearity Foundation founder, and ovarian cancer survivor, about the challenges in profiling ovarian cancers, translational research, and her experience as a patient.

Dr Shawver is the Founder of The Clearity Foundation and Chief Executive Officer of Cleave Biosciences, which is focused on developing novel drugs for difficult-to-treat cancers. She is a biotechnology entrepreneur with 25 years of scientific experience.

PMO Thank you so much for speaking with us, Dr Shawver. To begin, can you describe how physicians access their patient's molecular profiling?

Dr Shawver To summarize our services, when a patient works with Clearity, the first step is to gather all the necessary documents. For example, for patient consent to participate in our database, they provide authorization and release forms, and we fill in laboratory test requisitions. If a woman needs help with payment for the tests or help with her co-pays, she also fills in a simple grant application form. Our patient coordinator fills out most of the forms, often in collaboration with the oncology nurse from the physician's office.

Next, we coordinate the shipping of the tumor block from the pathology laboratory to the CLIA [Clinical Laboratory Improvement Amendments]-certified testing facilities to ensure timely analysis of the specimens. In addition to tumor specimens, we may be able to conduct profiling on a cell pellet from peritoneal ascites fluid or pleural effusions.

It's worth noting that we utilize CLIA-certified laboratories and the latest technologies for molecular profiling. These laboratories and the composition of our testing panel evolve as new evidence becomes available. Our Web site provides the list of our current tests and laboratories.

After all the tests have been completed, we provide an easy-to-read report that summarizes and provides a consensus interpretation of the results from multiple laboratories to the physician. The Clearity Foundation offers assistance or consultation to interpret the information on the reports. We also track patient results and outcomes to enable improvements in results interpretation.

PMO How well or weakly established is the practice of accessing patients' molecular profiling among oncologists?

Dr Shawver Molecular profiling in its simplest form has been used for many years to help choose the appropriate treatment for certain cancers and is now routine. Examples include estrogen receptor protein for breast cancer: antiestrogens and aromatase inhibitors; HER2 protein and copy number for breast cancer: trastuzumab; and *c-Kit* status for gastrointestinal stromal tumor: imatinib and sunitinib. And more recently, the adoption of testing for *EGFR* mutation for lung cancer coupled with *KRAS* status: erlotinib; *KRAS* status for colon cancer: cetuximab; *ALK* translocations for lung cancer: crizotinib; and *BRAF* status for melanoma: vemurafenib.

However, the measurement of a comprehensive panel of markers/genes to generate that profile and identify all therapy options that match the molecular characteristics of the tumor is not routine. A comprehensive panel is especially important in ovarian cancer because we are all so different.

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Protein expression measured by immunohistochemical tests can also be utilized to help understand sensitivity and resistance to chemotherapy agents such as topoisomerase I (topotecan, irinotecan), topoisomerase II (anthracyclines such as pegylated liposomal doxorubicin), thymidylate synthase (antifolates such as pemetrexed), and ribonucleotide reductase M1 (nucleoside analogues such as gemcitabine).

Unfortunately, the use of molecular profiling to prioritize treatment choices – whether it's FDA-approved agents or clinical trial agents – for recurrent ovarian cancer is limited. Oncologists have multiple choices for treatment when ovarian cancer recurs, but that choice is typically trial and error without a means to prioritize among those choices.

PMO What are the challenges to this process – either in the community or academic setting?

Dr Shawver The first challenge is that many doctors believe treatment for recurrent disease is only palliative. Therefore, when faced with a woman battling recurrent ovarian cancer, they believe that any treatment will buy time, but that most women will die of the disease. Es-

sentially, they give up on searching for a cure, at least for an individual. At Clearity, we want to help doctors change this by providing treatment that is prioritized based on the testing. Even chemotherapy works by interacting with specific targets in the cell. If that target is not present, the chemotherapy drug will not work. Sometimes, if the target is present at a level that is too high, not enough of the drug can be delivered to the tumor to provide sufficient inhibition of this driver of cell growth, and the tumor is unaffected. So, our tests measure the levels of those targets with the aim of ruling out drugs that might not work and ruling in the drugs that have a better chance. By using this information to prioritize treatment options, we hope that more women will benefit and avoid drugs that would result in all the toxicity associated with those agents but provide no benefit.

Clinical trials will be needed, and the goal is to show preliminary evidence using our database that will establish the testing parameters for clinical trials.

Another challenge in this approach is that despite considerable clinical research evidence to support the correlation of expression levels of these chemotherapy targets with patient responses to those drugs, there have been no prospective clinical trials to prove that they are indeed predictive of response in ovarian cancer. As a result, physicians are reluctant to use these tests as a basis for their decision making. But, in the 5 years that we have been providing profiling assistance, we have seen an increasing number of physicians who are using these results to inform their decisions. We are collecting patient results and outcomes in our database.

I would also like to mention that outside of chemotherapy drugs, there are drugs in clinical trials for ovarian cancer that may be better choices for some women. The 200+ gene panel helps us provide information that can be used to identify such a clinical trial agent so that a clinical trial can be selected based on the patient's tumor profile rather than choosing a trial just because it is at her doctor's institution, which is how most doctors recommend clinical trials for their patients.

PMO How definitive or conclusive is the knowledge obtained from molecular profiling relevant to the diagnostic and the treatment process for patients with ovarian cancer?

Dr Shawver Each of the targets in the standard panel that Clearity tests for at our partner labs has considerable clinical evidence for its association with treatment benefit or lack thereof. These studies can be found on our Web site (www.clearityfoundation.org/healthcare-pros/drugs-and-biomarkers-staged.aspx). However, some of the evidence is for cancers other than ovarian. This is one reason that Clearity is keeping a database and tracks women over time so that we can better establish the relevance of each of these tests. Ultimately, clinical trials will be needed, and the goal is to show preliminary evidence using our database that will establish the testing parameters for clinical trials. In contrast to the standard panel of tests, the evidence for drug responses for the markers tested in the 200+ gene panel is less robust because only some of them have been shown to be associated with drug response. We continually monitor the results reported for clinical trials so we can provide patients and physicians with the most up-to-date, relevant information about the tests that may predict responses to drugs in clinical development.

PMO Is it more challenging to obtain genetic signatures in ovarian cancer than in other cancers?

Dr Shawver The actual laboratory testing is the same as for other cancers. One of the challenges, however, is in obtaining an appropriate specimen for testing. Dr Zajchowski and colleagues have shown that the results from a recent specimen are likely to be different from the primary tumor or an older specimen [Zajchowski et al. *Mol Cancer Ther*. 2012;11:492-502]. Therefore, we will not conduct the profiling on an archived tumor block unless it has been obtained within 1 year. Second surgeries for ovarian cancer are not common – although a recent study published at ASCO [http://meetinglib

rary.asco.org/content/117950-132] provides support to do this – and while doctors are becoming more accepting of obtaining a tumor biopsy at the time of recurrence, it is sometimes too risky because of the tumor location.

PMO What strategy is Clearity following to raise the healthcare literacy of practicing oncologists and patients to accelerate the process of obtaining molecular profiles in ovarian cancer?

Dr Shawver The Clearity Foundation has been providing access to molecular profiling for 5 years. When we first started, it was very controversial, and we faced an uphill battle. However, because several recently approved drugs are associated with specific molecular alterations that identify patients who have a high likelihood of benefit from that agent, it is becoming standard practice in breast, lung, colon, and skin cancers to conduct molecular analyses. As a result, physicians are more likely to consider using a molecular profile to inform their treatment decisions. Thus, we have been helped in our mission to bring this approach to women battling ovarian cancer. Unfortunately, ovarian cancer patients are much more heterogeneous, and the number of tests that are needed to prioritize a treatment or a clinical trial is greater. This means a greater cost. Part of Clearity's mission is to remove the cost argument for not conducting these tests. We get the word out in different ways – presenting our findings at the various oncology meetings, speaking with doctors and patients one-on-one, and providing educational forums.

PMO Does the founding of Clearity suggest that the cancer healthcare system alone is insufficient for meeting the special needs of ovarian cancer patients? If so, what is primarily "missing" from the paradigm? What fuels this oversight? And what is your remedy for correcting it?

Dr Shawver The numbers are just against us. Almost every woman diagnosed with epithelial ovarian cancer gets the same treatment, ie, a combination of a platinum (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel), following surgery to have her ovaries and uterus removed, along with anything else they need to take out to optimally remove all the tumors. Of the women diagnosed with stage III or stage IV cancer, which represents 75% of the diagnoses, 80% will get to remission where no tumor is detected. This is truly remarkable, so it is difficult to think about how to give a different agent when one has an 80% chance of a response. Here comes the other astounding fact: of the women who get into complete remission, 80% will recur, most in the first 2 years. So while the agents initially work and work very well, their effects are short-lived. However, even The Clearity Foundation cannot focus on how to find the 20% of women who will not respond to standard of care because it is hard to justify given the 80% complete response rate. Clearity helps women when standard of care does not work or when they recur following treatment – as most do. With the multiple drugs that are used to treat recurrent ovarian cancer, there is less than a 20% chance that the agent will work. Our remedy is to increase this really terri-

Dr Shawver addresses the audience at a Clearity Foundation educational event.

Of the women diagnosed with stage III or stage IV cancer, which represents 75% of the diagnoses, 80% will get to remission where no tumor is detected.

ble statistic from less than 20% to something that gives both the woman battling this disease and the physicians treating it hope that she can have a cure the second time around.

Unfortunately, patients and doctors often do not approach us until they have had a second, third, or fourth recurrence. To give the best chance, we believe that every woman with recurrent ovarian cancer should be profiled on her first recurrence.

PMO Regarding translational medicine, how successfully do oncologists tend to apply research findings into practice?

Dr Shawver Translational medicine is not the focus of The Clearity Foundation. This is a very important aspect when developing a new drug. Clearity is focused on doing better with the drugs we already have by providing tests that can prioritize these treatments. Personalized, or precision, treatment is a better buzzword for what Clearity provides.

The more research that is carried out to elucidate the drivers of subsets of ovarian cancers, the more possible it will be to cure this disease.

PMO The obstacles to making translational medicine claims, it would seem, include the multitude of research studies, the incomplete scope of the process of care involved in treating any given disease state, and the reconciling of any study's findings against the backdrop of NCCN [National Comprehensive Cancer Network] Guidelines and pathways. How well does the medical profession understand what it takes to distill research findings into clinical practice?

Dr Shawver I'm glad that you asked this question. Most of what Clearity provides to physicians is a way to prioritize among the agents that are in the NCCN Guidelines for the treatment of recurrent ovarian cancer. These include the platinum agents, the taxanes, pegylated liposomal doxorubicin, gemcitabine, topotecan, and pemetrexed. For the majority of patients, our tests prioritize only 1 of these agents. The usual agents that doctors prescribe for a first recurrence, either as a single agent or in combination with a platinum, are paclitaxel, pegylated liposomal doxorubicin, and gemcitabine. If there is less than a 20% chance that an agent will work, I don't understand why everyone is not *insisting* on a test that can help prioritize. There is considerable clinical research evidence for each of the markers for these agents (which are posted on our Web site [www.clearityfoundation.org/healthcare-pros/drugs-and-biomarkers-staged.aspx]) and the other 2 agents in the NCCN Guidelines that are less commonly used, topotecan and pemetrexed. For some drugs, good tests do not exist, and we need to acknowledge this as well. For example, there are not good markers for predicting responses to platinum. Therefore, we utilize more standard clinical determinants such as how long the patient was in remission following treatment with a platinum agent. If it is longer than 6 months, she would likely receive 1 of the drugs in combination with platinum rather than as a single agent.

PMO Is the practice of translational medicine in ovarian cancer research increasing, static, or being confused by the explosion of research data?

Dr Shawver Indeed, there is an explosion of research data. The findings of the recent comprehensive genomic analyses of ovarian cancer, exemplified by those from The Cancer Genome Atlas project, have helped classify ovarian cancers in ways that enable us to match new drugs in clinical trials to specific patients. Without those results, the interest in ovarian cancer as an indication for some of these novel drugs would not be as high. The more research that is carried out to elucidate the drivers of subsets of ovarian cancers, the more possible it will be to cure this disease. The 200+ gene panel is used to identify those patients for whom these novel drugs may be the best choice.

PMO How closely or loosely aligned is translational medicine and NCCN Guidelines?

Dr Shawver Our core panel is designed to be exactly aligned to the best that it can be. As I mentioned be-

fore, not all of the drugs have good tests where we rely on the clinical response data.

PMO How has your personal experience of surviving ovarian cancer changed your professional perspectives on translational research?

Dr Shawver As a scientist, translational research is finding ways to enrich patient populations for a response to a particular drug. Being a patient has made me much more focused on the urgency of this and on each individual as a real person with a family that cares if a drug works for them. I become impatient when I see drugs being developed for a population when it is well known that only a fraction will benefit. It makes me so mad. I think we should do better.

PMO What was the *single* most important unmet need you sought to fill when you founded Clearity?

Dr Shawver The standard paradigm for women who have recurrent ovarian cancer is to go from one chemotherapy to the next to the next and have a poor quality of life, and they ultimately succumb to their disease. Clearity was founded to change this paradigm and show that women with recurrent ovarian cancer can be cured. Cure is a big word, and we are often criticized for using it. However, as we frequently say, *someone* has to believe in a cure and help both patients who are fighting for their lives and doctors who have only seen incremental changes in this disease over the past 40 years.

PMO Since Clearity's founding, has this need remained constant, or have priorities shifted?

Dr Shawver The need has remained constant. We have had anecdotal successes, but the key is to provide data that show what we do is working. Clearity is now focused on how to get more women with recurrent ovarian cancer and their doctors aligned with molecular profiling to prioritize their treatment choices so that not only can we continue to help on an individual basis, but we can provide the appropriate data.

PMO How closely aligned is Clearity's mission to the growth of personalized medicine?

Dr Shawver Yes, this is what Clearity is focused on. However, it is more difficult for ovarian cancer because we do not neatly fall into big buckets. For breast cancer, there are 3 big buckets, and 2 of these buckets align to treatment choices that are associated with better outcomes. For ovarian cancer, we are still sorting this out, but we may need 100 buckets to do so.

Several members of Clearity's Board of Directors at the Someone Lived fund-raiser.

PMO What effect is Clearity's work having on healthcare disparities in ovarian cancer?

Dr Shawver We are proud that we have provided access to molecular profiling for women without health insurance. The tests are costly, however, and not all insurance companies reimburse the test, which puts everyone, including Clearity, in a difficult situation. If all insurance companies paid for the tests, we could focus our resources more on people without insurance.

Being a patient has made me much more focused on the urgency of this and on each individual as a real person with a family that cares if a drug works for them.

PMO Clearity seeks to improve competency among several stakeholders through systems changes. I'd like to throw out several different stakeholders and get your insights as to what changes are needed within that group to improve ovarian cancer outcomes. To start, what can patients do?

Dr Shawver Patients should insist on understanding why a drug is the right one for you. Educate yourself on the value of testing your tumor and be able to ask your doctor to provide these tests and explain the results.

PMO Researchers?

Dr Shawver Focus efforts on understanding how to select patients that will benefit from the new drugs being developed; don't accept that a drug can get approved in an all-comers trial because it works in 20% to 30% of patients and therefore statistical significance can be obtained. This is negatively affecting the lives of 70% to 80% of people in your trials.

PMO Payers?

Dr Shawver Insist that your ovarian cancer patients have a Clearity test. Insist that the doctors follow up with us to provide follow-up data. We will provide you all of the data for analysis on cost-effectiveness.

PMO Medical associations?

Dr Shawver We need your help to collect the appropriate data. Encourage women to participate and ways to validate profiling effort. Encourage cooperative efforts to place women in the most appropriate clinical trial.

PMO Pharma?

Dr Shawver Many of your drugs under development for other kinds of cancer will likely work in subsets of ovarian cancer. Create a consortium among companies so that patients can be funneled into each of your trials with only 1 centralized test. Clearity is willing to help by providing the tests to the consortium.

PMO What lessons does Clearity's experience have for the rest of the cancer community?

Dr Shawver The Clearity model can be used as a template for other difficult-to-treat cancers. The types of tests are similar, often the same. We should all be collecting the appropriate data to prioritize treatment decisions, which provides actionable hope for people battling cancer.

PMO It was such a pleasure to speak with you. Your story is quite an inspiring one. Please accept our best wishes for continued success. ◆

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