The Clearity Foundation: Revolutionizing Ovarian Cancer Treatment Through the Use of Tumor Profiling

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Abstract: This case study discusses the Clearity Foundation, a nonprofit organization dedicated to improving treatment options for women diagnosed with ovarian cancer. Laura Shawver, a career cancer researcher who herself was diagnosed with ovarian cancer, created the Clearity Foundation to revolutionize ovarian cancer treatment through the use of molecular tumor profiling, which is the analysis of the tumor genome to reveal specific abnormalities. Shawver challenged the trial-and-error approach to ovarian cancer treatment, advocating instead for an individualized treatment approach using tumor profiling as a way to give ovarian cancer patients the best treatment based on each woman's unique tumor characteristics. Though there were many challenges to establishing the Clearity Foundation, Shawver's biggest hurdle came in the form of criticism from gynecological oncologists, who were skeptical of tumor profiling and resisted Shawver's assertions that it could improve outcomes for women with ovarian cancer. This case illustrates the challenges of advocating for novel treatment within a medical system that has structural barriers that slow the adoption of new discoveries. More broadly, this case explores the role that scientifically based nonprofit organizations like the Clearity Foundation play in advancing medical care, as well as the factors that necessitate the existence and intervention of these types of organizations.

Laura Shawver and the Clearity Foundation

Laura Shawver walked out of the Society of Gynecological Oncology Meeting feeling shocked yet determined. She had just presented the mission and plan for her foundation, the Clearity Foundation, to a group of thirteen gynecological oncologists, all of whom were leaders in the field (L. Shawver, personal communication, October 31, 2017). Shawver had started the Clearity Foundation to improve treatment options for women diagnosed with ovarian cancer; she hoped to achieve this largely by providing women with access to molecular tumor profiling, which currently characterizes protein biomarker expression as well as specific gene abnormalities of tumors to predict the treatment that will be most effective in targeting those specific abnormalities (The Clearity Foundation 2018). As a lifelong cancer researcher who had faced her own ovarian cancer diagnosis, Shawver was passionate about the mission of the Clearity Foundation and strongly believed tumor profiling to be a crucial step in ovarian cancer treatment (L. Shawver, personal communication, October 31, 2017). She was convinced that by starting the Clearity Foundation she was providing oncologists with a way to access tumor profiling and use the results to improve outcomes for their patients (L. Shawver, personal communication, October 13, 2017). Instead of supporting the goals of her foundation, however, the gynecological oncologists at the meeting raised numerous concerns, questioning the scientific support for tumor profiling and

asserting that tumor profiling was not yet correlated with a treatment outcome (D. Zajchowski, personal communication, December 4, 2017). Despite her knowledge of the limitations of the existing data supporting tumor profiling in ovarian cancer, Shawver felt that there was scientific rationale behind the approach and was taken aback by such strong criticism from the very individuals whose collaboration she would need if the individualized tumor profiling data the Clearity Foundation could provide was ever to be used in determining treatment options for patients (L. Shawver, personal communication, October 13, 2017). Medical professionals would need to incorporate tumor profiling into their decision-making in order for the Clearity Foundation to realize its mission of personalized treatment to improve outcomes for women with ovarian cancer (Benson 2016). Caught between her vision for the services that the Clearity Foundation could provide and the realities of working within the medical system that actually provides women with care, Shawver had to determine the future of the Clearity Foundation and its role in advancing the adoption of tumor profiling.

Laura Shawver: Cancer Researcher

Laura Shawver has been a cancer researcher for most of her career, working mainly at biotechnology companies. She has more than 25 years of experience developing small molecule drugs for cancer and other serious diseases. She received her B.S. degree in Microbiology in 1979 and her Ph.D. in Pharmacology in 1984, both from the University of Iowa. She started her biotechnology career at Berlex Bioscience, where she began as a research scientist in the Department of Molecular Biology in 1989 and became the Director of Cell Biology and Immunology in 1991. She moved to SUGEN, Inc. in 1992, which focused on understanding key molecular pathways of cancer cells. She spent ten years working at SUGEN in various managerial roles before eventually becoming President in 2000. Shawver developed an understanding of tumor profiling and its role in cancer treatment after profiling tumors from clinical trials for years at SUGEN. From 2002 to 2010, Shawver worked at Phenomix Corp in San Diego as the Chief Executive Officer and Director (L. Shawver, personal communication, October 31, 2017).

Shawver attributes her career success to hiring and working with the right people, yet she does not necessarily describe collaboration and listening to the opinions of others as a crucial aspect of her leadership. She appreciates when her colleagues challenge her and she certainly values the specific areas of expertise that they provide, but when the scope of the discussion broadens to decisions relating to the overarching goals of the organization, she listens to input only "when [she] agrees with it" (L. Shawver, personal communication, December 1, 2017). Her strength lies in her persistence, her ability to deal with ambiguity, her conviction, and most of all in her confidence when faced with adversity. She believes that "you have to act as if things will work out even if you are not sure that they will," which was especially important in her work creating the Clearity Foundation, though perhaps even more pertinent to her cancer diagnosis (L. Shawver, personal communication, December 1, 2017).

Laura Shawver was diagnosed with ovarian cancer on August 31, 2006. Nothing in her career, including her years as a cancer researcher, could have prepared her for the shock of receiving this diagnosis and the panic as she tried to come to terms with the ramifications. She realized early on that everyone needs an advocate when faced with a cancer diagnosis. An advocate is someone who attends appointments, asks questions, and provides a support system. Shawver's advocate was her partner Tracy, who is now her spouse. Shawver is blunt, pragmatic, and generally unflappable, but after her diagnosis Tracy had to hold her hand when Shawver was used to being the hand-holder (L. Shawver, personal communication, October 13, 2017).

Ovarian Cancer: Prevalence, Treatment, and Tumor Profiling

Ovarian cancer is a common gynecologic malignancy. It is the fifth leading cause of cancer death in women in the United States (National Cancer Institute 2018). There have been an estimated 22,440 new cases of ovarian cancer in 2017, which represents 1.3 percent of all new cancer cases, and there were approximately 14,080 deaths due to ovarian cancer in 2017, which represents 2.3 percent of all cancer deaths. The percentage of women who survive for five years with an ovarian cancer diagnosis is 46.5 percent. The survival rate for ovarian cancer is startlingly low in comparison to other types of cancers such as breast cancer, which is due in part to the fact that most ovarian cancers are detected in advanced stages because there is currently no effective screening method for ovarian cancer and the symptoms are often mistaken for stomach and digestive issues (National Cancer Institute 2018). The 10-year survival rate drops to 15 percent when ovarian cancer is detected as an advanced-stage disease, indicating the need for more timely diagnosis of ovarian cancer (Palmirotta et al. 2017).

Scientists have historically characterized ovarian cancer as a cancer that begins in the tissue that covers the ovaries, but recent research indicates that the most common type actually originates in the fallopian tubes (National Cancer Institute 2017). Ovarian cancer can also spread from the peritoneum (the membrane lining the cavity of the abdomen) (National Cancer Institute 2018). It usually occurs in post-menopausal women, but young women are also affected. Recent studies have grouped ovarian cancers into two subtypes, known as type I and type II (Palmirotta et al. 2017). Type I ovarian cancers are low-grade tumors and make up 25 percent of all ovarian cancers. Low-grade tumors include serous, endometrioid, clear cell, and mucinous, and they are characterized by slow growth and resistance to conventional chemotherapy. Type II ovarian cancers are high-grade and represent more than 70 percent of all ovarian cancers; they are characterized by aggressive growth but a high sensitivity to chemotherapy (Palmirotta et al. 2017).

The typical treatment for ovarian cancer is surgery followed by a first-line chemotherapy (Palmirotta et al. 2017). The surgery is called a debulking surgery to remove the tumor, and the chemotherapy is generally a platinum-based drug combined with a taxane that is used to get rid of any cancer cells still present in the body after surgery. The platinum causes the cancer cell to die, while the taxane prevents the cells from dividing and growing (Palmirotta et al. 2017). Evidence indicates that this generalized treatment has vastly different outcomes depending on the subtype of ovarian cancer. Though this combination is generally effective as an initial therapy, it becomes less effective over time as cancer cells continue to divide and develop resistance to the treatment. Approximately 75 to 80 percent of ovarian cancer patients will relapse, and their oncologists are left to decide between a number of approved chemotherapy drugs (The Clearity Foundation 2018). Without a standard-of care to choose the most effective drug, treatment regimens are determined on a trial and error basis, costing women valuable cycling through treatments as their cancer progresses (The Clearity Foundation 2018; UNM Health 2016).

In 2006, molecular tumor profiling was just beginning to emerge as a strategy to address this deficit in care (Palmirotta et al. 2017). At the time, molecular tumor profiling consisted of testing for and measuring specific protein biomarkers, which are proteins in tumors that are indicative of abnormalities. Now, it also involves analyzing the tumor genome and sequencing genes to identify alterations. As a result, molecular tumor profiling is generally defined as the molecular analysis of alterations in DNA, RNA, and proteins (ACCRF 2018). By determining the molecular composition of a tumor, treatment can be tailored to the specific mutations that are present in that tumor. Understanding the molecular characteristics of a tumor can enable doctors

to prioritize drugs that are more likely to be effective for an individual patient (The Clearity Foundation 2018).

One of the first journal articles discussing tumor profiling was published in 2004 (Cross and Burmester 2004). The article offered a positive outlook of the future impact of tumor profiling in cancer treatment, but also discussed several barriers to the incorporation of tumor profiling into diagnostics and treatment. These barriers included the cost of the technology, the special handling procedures required, and the need for standardization within the research community (Cross and Burmester 2004). Due to these issues and the fact that tumor profiling was just emerging as a focal point of cancer research with little data available about its effectiveness, hospitals in 2006 did not profile tumors regularly. Most oncologists did not have access to the technology necessary to profile tumors and many did not understand the potential clinical benefits of tumor profiling.

Laura Shawver: Ovarian Cancer Treatment

The first significant milestone of Shawver's cancer treatment was surgery to remove the tumor on September 8, 2006. As a cancer researcher, Shawver understood the treatment process for ovarian cancer and the importance of the surgery, but she still balked at the thought of receiving such an invasive procedure. Shawver discussed the surgery with her oncologist and surgeon, trying to convince them that the incision should be performed in a more cosmetically appealing way. The removal of ovarian cancer tumors requires an incision from the navel to the pubic bone, and the patient must be completely opened up so that the surgeon can remove the entire tumor in one piece. This procedure is not appealing to many women, and some attempt to bargain with their surgeons to receive a less invasive surgery. However, the women who receive this minimally invasive surgery have a higher mortality rate, so Shawver's surgeon insisted that she be operated upon in the standard manner and Shawver eventually agreed. She had a grapefruit-sized tumor that needed to be removed. Her surgeon was not sure if there was intestinal or liver involvement, which would have made the surgery more challenging.

Shawver received the operation and her tumor burst during surgery. The tumor cells spilled everywhere, and her doctors did not know how to stage her. Staging occurs when doctors perform additional steps during surgery to determine the extent of the cancer, which was necessary in Shawver's case because her surgeon was unsure how far her cancer had spread. Her doctors ended up performing numerous peritoneal washings during surgery; they used salt-water solution to wash Shawver's abdominal cavity, and then they removed the solution to check for cancer cells. Despite the complication, the peritoneal washings allowed her doctors to determine the extent of her cancer, so her surgeon was able to remove the entire tumor (L. Shawver, personal communication, October 13, 2017).

Early in her treatment, Shawver discussed tumor profiling with her oncologist, since she had been doing tumor profiling at her previous company, SUGEN, with patient tumors from clinical trials. Shawver insisted that her oncologist take a slice of her tumor and test it to determine its characteristics. Despite profiling tumors for years in her professional capacity as a cancer researcher, when it came to Shawver as a patient, she could not have her tumor profiled. While Shawver was able to profile tumors in a research setting, hospitals had not yet incorporated tumor profiling into treatment and did not have a mechanism to test tumor samples from patients. Her oncologist told her that tumor profiling did not exist for ovarian cancer. This was extremely frustrating for Shawver because she knew that, especially for her type of ovarian cancer, molecular tumor profiling was necessary to determine the most effective course of treatment. Knowing the genetic mutations of Shawver's tumor could have enabled her oncologist to choose the most

appropriate chemotherapy drugs for her specific subtype of ovarian cancer, instead of just using the standard chemotherapy drug combination which was likely less effective (L. Shawver, personal communication, October 13, 2017).

After surgery, Shawver's tumor was sent to a pathologist, who determined Shawver's subtype of ovarian cancer. Shawver was diagnosed with clear cell ovarian cancer, a rare histology which has particularly poor outcomes compared to other types of ovarian cancer. It is known to exhibit little response to typical ovarian cancer treatments (Friedlander et al. 2016). Shawver sent the slides of her tumor to three different pathologists to confirm the diagnosis and then sent her pathology report to six different oncologists, many of whom were her friends in the field, to determine if chemotherapy was necessary. As someone in the cancer field, Shawver knew the physical and emotional toll that chemotherapy would take; much like with the surgery, she tried to convince her oncologist and those who reviewed her pathology report that chemotherapy was not necessary. In fact, she did need chemotherapy, and she received chemotherapy of carboplatin and paclitaxel, the standard drug combination of a platinum-based drug and a taxane, starting in October 2006 and ending in March 2007. When discussing the chemotherapy, Shawver stated that "it is not easy, but you get through it" (L. Shawver, personal communication, October 13, 2017). Laura spent six months recuperating after she finished chemotherapy, which is customary for those who undergo chemotherapy due to the numerous and severe side effects of the treatment. This recovery period gave Laura time to consider her options as she anticipated the recurrence of her cancer.

The Inspiration for Clearity Foundation

The inspiration for the Clearity Foundation came in the six months during which Shawver recovered from chemotherapy. One day at breakfast, Shawver had a discussion with her spouse Tracy, who asked Shawver what she was going to do if she had a recurrence of her cancer. Both Shawver and Tracy knew that there was a very high chance of recurrence due to the nature of her cancer diagnosis, and Shawver had become increasingly concerned about the possibility of recurrence and what she would do if that happened. Shawver replied that she would need to have her tumor profiled. At this point, Shawver knew that getting her tumor profiled through her oncologist was not an option since there was no mechanism to do so. Tracy told her that she should start a company to do tumor profiling. When Shawver dismissed this suggestion by citing the fact that there was no money to make for investors, Tracy suggested that she start a nonprofit company and told her to call it the Clearity Foundation, a name that she had created in reference to Shawver's diagnosis of clear cell ovarian cancer. That same day, Shawver decided to start the Clearity Foundation (L. Shawver, personal communication, October 13, 2017).

The Mission of the Clearity Foundation

Shawver's initial motivation to form the Clearity Foundation was entirely personal; she was desperate to figure out what to do when her cancer recurred. Despite her years of work in cancer research and her belief that tumor profiling could have improved her outcomes by identifying the chemotherapy drugs with the highest success rate for her type of cancer, she received the same treatment as everyone else with ovarian cancer. She felt deeply angered by what she deemed to be the failure of the medical system to provide her with the best care, and she was determined to ensure that should her cancer recur, she would be able to access tumor profiling in order to receive the appropriate treatment for her cancer.

Shawver describes that while Clearity Foundation "started out of fear, it quickly became a calling" (L. Shawver, personal communication, October 13, 2017). Though she had initially framed the mission of Clearity Foundation around the idea of providing women with tumor profiling, her true commitment was providing women with the best ovarian cancer care in whatever way she could. Shawver stated that "we help in whatever way that we can. You know, there are some ovarian cancer organizations that provide blankets to take to chemotherapy. That is not what we do. If people need help identifying treatment options, that is what we do, whatever that looks like" (L. Shawver, personal communication, October 13, 2017). Shawver felt that tumor profiling was the main avenue to do this, but she acknowledged that tumor profiling would not always be possible. Shawver expanded her mission to include getting women access to the right chemotherapy drugs, determining the best way to sequence the drugs, and getting women on the correct clinical trial if that was the best way for them to access treatment. It was also important to Shawver that she remove the cost component from care; she committed to covering the cost of tumor profiling if it was not covered by insurance (L. Shawver, personal communication, December 1, 2017).

Shawver's mindset as she determined the concrete goals for the Clearity Foundation was one of stubborn resolve. She said that "I think that maybe because I am a scientist and I am trying to understand things that are not understood, or discover things that nobody knows, or create something that nobody has done in the past, it is more natural to me to be forward-looking" (L. Shawver, personal communication, December 1, 2017). Shawver did not want to think about how she could reinvent what was already being done in cancer treatment; she wanted to think about what could be done differently. "I have a favorite quote," Shawver stated:

> That 'the difficult we do immediately, but the impossible takes a little longer.' I love that because I have seen in my career the impossible happen all the time. The things that we think are impossible are probably really not" (L. Shawver, personal communication, December 1, 2017).

Shawver knew that starting the Clearity Foundation would be an immense challenge, but she believed that it needed to be done and she was convinced that her experience and personal history made her the best person to start the foundation (L. Shawver, personal communication, October 13, 2017). In doing so, she was immersing herself in a field that was only beginning to recognize the value of personalized cancer treatment, and she was choosing to address a cancer with a particularly limited body of research and supporting data.

Ovarian Cancer: The Silent Killer

Innovation in ovarian cancer has been historically inadequate. There are several possible explanations for this. The first is that while ovarian cancer has a very high mortality rate, it has a lower prevalence than other types of cancers, which has made it less of a priority in the medical community (National Cancer Institute 2018). Additionally, women's health has been historically neglected in research, public policy, and clinical settings; only within the last 20 years have these deficits been acknowledged and addressed, albeit not completely (Blumenthal 2011). As a result, it is important to note the role that ovarian cancer being a cancer that only impacts women plays in the lack of available research, though this has been largely unaddressed in the literature regarding ovarian cancer (Jansen 2009). The second explanation centers around the language used to discuss ovarian cancer. Up until fairly recently, ovarian cancer was considered a silent killer; it

was an insidious cancer that had no identifiable causes, signs, or effective treatments. The medical discourse around ovarian cancer made it seem like the diagnosis was a death sentence, and this was how many physicians perceived ovarian cancer (Jansen 2009). Since the prognosis was grim, little was done to address ovarian cancer, especially in comparison to the work done to address other types of cancer. There was also a startling lack of information about ovarian cancer in medical publications in the 20th century. Many medical textbooks failed to mention the symptoms of ovarian cancer at any stage, and the ones that did only discussed the symptoms of advanced ovarian cancer. This left medical professionals without any basis for recognizing symptoms in their patients. Additionally, and perhaps unsurprisingly given its lack of inclusion in the medical literature, ovarian cancer symptoms were rarely addressed in cancer awareness campaigns aimed at the public (Jansen 2009).

Given the lack of public discourse about ovarian cancer, women had a limited ability to recognize ovarian cancer symptoms, little knowledge with which to interpret an ovarian cancer diagnosis, and a minimal understanding of the prognosis and treatment regimen for ovarian cancer. One consequence of this is that women had to be completely reliant on their oncologists for care since they did not have enough information about ovarian cancer to be involved in their own treatment decisions. Up until the women's health movement in the 1980s and 1990s, women would just do what their doctors said and they would not try to educate themselves (Jansen 2009). Women did not know to ask the right questions or insist that their doctors fight for them, and they had limited power to demand more information (L. Shawver, personal communication, October 13, 2017). All of these factors played a part in minimizing the sense of urgency for ovarian cancer research.

Molecular Tumor Profiling: Summary of Data

In 2007, research in ovarian cancer was only beginning to catch up to the body of research available for other types of cancer. One of the most promising areas of research in ovarian cancer was an assessment of the molecular profiles of tumors to develop targeted treatment strategies for each subtype of ovarian cancer. This was a novel way to approach cancer because it represented a movement away from the traditional manner of treating cancer based on the tumor's origin, with no consideration of its specific attributes (Cross and Burmester 2004). The first step to achieve targeted therapies was molecular tumor profiling (Palmirotta et al. 2017).

In the research community, where Shawver had spent the majority of her career, there was a general consensus that molecular tumor profiling represented the future of cancer care. Numerous journal articles published between 2003 and 2005 explored the potential benefits of tumor profiling, highlighting early developments in the research (Iqbal and Lenz 2003; Trainer 2004; Wadlow and Ramaswamy 2005). All of these articles predicted that tumor profiling would one day revolutionize cancer diagnostics and treatment, and it was simply a matter of time before tumor profiling was supported by enough data from clinical trials to be incorporated into routine cancer treatment. Though these articles also mentioned barriers to the widespread adoption of tumor profiling (mainly that use of this technology was incredibly dependent on proof from clinical trials), the prevailing attitude seemed to be that the implementation of tumor profiling was inevitable; it was a matter of when it would be used, not if it would be used (Iqbal and Lenz 2003; Trainer 2004; Wadlow and Ramaswamy 2005).

While leading cancer researchers found tumor profiling to be promising, there was not yet enough data to illustrate a definitive correlation between tumor profiling and improved treatment outcomes, making oncologists weary of adopting tumor profiling as an initial step in treatment

selection. The only research that was available was from data collected retrospectively. Researchers collected data from women with ovarian cancer who were treated with chemotherapy drugs that work by inhibiting the activity of specific cellular proteins or enzymes. Then they tested the women's tumors for a few specific protein markers, which is one part of a tumor profile, and they determined the rate of success for women who took chemotherapy drugs based on the amount of specific protein markers expressed by their tumor. This study, despite illustrating a correlation between tumor profiling and better treatment outcomes, had been done on women who were already treated, so it did not definitively illustrate that using tumor profiling to determine treatment in advance significantly improved outcomes (D. Zajchowski, personal communication, December 4, 2017). To Shawver, the results from the retrospective data analysis were sufficient to demonstrate the value of tumor profiling in cancer treatment, but the oncologists did not see it this way.

The particular study that likely would have swayed oncologists' perceptions of tumor profiling is called a prospective clinical trial. To do this type of trial, researchers must gather a group of women with ovarian cancer and profile their tumors. Then, they need to assign half of the women to a clinical trial for a specific drug based on the results of the profile and assign the other half to a standard of care drug randomly. After the women receive treatment, researchers have to compare the results; the group of women who got the drug that matched their profile should exhibit better results than the women who did not get a profile-matched drug. The idea is to do this before assigning treatment to determine if the treatment selected based on the tumor profile truly resulted in better outcomes.

The reason that this type of study had not been done is that the study would need to be very large, and thus expensive. There are numerous possible biomarkers and therapies to test, more so than other types of cancers, and the trial would require an unusually large number of patients. Additionally, studies this large involving cancer patients have strict ethical requirements, which further complicates the design of the clinical trial and increases costs (Nardini 2014). The medical community is largely dependent on pharmaceutical companies to advance research in promising areas. No pharmaceutical company wanted to pay for a trial of that magnitude with chemotherapy drugs (D. Zajchowski, personal communication, December 4, 2017). Pharmaceutical companies spend money on clinical trials for the products that they believe will bring in the most money, which provides a fundamental barrier when clinical trials are necessary to advance products or technologies that will not necessarily provide significant revenue for the specific company paying for the clinical trial. Tumor profiling, though incredibly promising, was challenging to advance because unlike a drug, this innovation was not in the hands of only one pharmaceutical company, making it a risky investment with limited potential benefit to the company yet with enormous potential benefit for the consumer. Outside of grant funding, there is no system in place to advance novel technologies like tumor profiling, and the free market discourages pharmaceutical companies from investing in a technology that will not bring them exclusive returns (Herzlinger 2006). While this lack of funding for a clinical trial was the most significant hindrance to the widespread adoption of tumor profiling, it was by no means the only one. Even if data from a prospective study had been available to demonstrate correlation, there were still numerous other barriers to incorporating tumor profiling into routine care.

Barriers to Tumor Profiling

The most obvious barrier was that even if the Clearity Foundation could profile tumors, there were not many approved chemotherapy drugs that actually acted on specific molecular

alterations of tumors, and very few had been specifically studied in ovarian cancer. The first cancer drugs based on molecular alterations were Herceptin for breast cancer and Gleevec for chronic myelogenous leukemia. Ovarian cancer research had much farther to go to develop viable drugs to act on the specific genetic alterations discovered by tumor profiling (Benson 2016). The lack of approved drugs meant that there were two options for getting chemotherapy drugs based on tumor profiling information. One option was to persuade doctors to use an off-label drug, which meant that the drug had been approved for another cancer but not for ovarian cancer. Doctors needed to have a high level of confidence that the drug would work to consider this option, which was often not the case. The other option for targeted treatment was getting women into clinical trials. This posed another set of issues, however, since there were only a limited number of clinical trials and doctors could not recommend their patients for clinical trials if they were unaware of their existence or if they believed that standard of care options were more likely to provide benefit (D. Zajchowski, personal communication, December 4, 2017).

Physicians therefore represented a fundamental barrier to incorporating tumor profiling into cancer care. Even physicians who believed in the benefit of tumor profiling often did not want to have their patients' tumors profiled (Benson 2016). It is possible that this discrepancy is due to the fact that most physicians reported that tumor profiling would result in more time necessary to discuss treatment options, which is in opposition to the standard of efficiency that characterizes hospitals with high volumes of clients. It is also possible that this hesitance was because they did not understand tumor profiling, were uncomfortable explaining genomic concepts to patients, or felt that they had a limited ability to make treatment recommendations based on the data (Benson 2016).

This last point is particularly important, and it was a significant criticism of tumor profiling at the time. The success of tumor profiling is completely reliant on the ability of oncologists to analyze the data from tumor profiling and utilize this analysis to choose an appropriate combination of chemotherapy drugs. If oncologists do not have enough information or training to use tumor profiling data to assess treatment options, then there is simply no value in providing oncologists with tumor profiling data, since it will not influence treatment decisions (Benson 2016). Given that tumor profiling was a relatively new technology, it is possible that oncologists required training to appropriately analyze tumor profiling data in order to make treatment recommendations. When Shawver described how familiar doctors were with tumor profiling, she stated that "they did not understand it at all, it was futuristic to them" (L. Shawver, personal communication, October 13, 2017).

The adoption of tumor profiling also required oncologists to have a certain level of adaptability and flexibility in their treatment decisions, which was a significant departure from the formulaic method of ovarian cancer treatment utilized by oncologists. Shawver said that tumor profiling "was not going to change what [oncologists] did or the sequence of how they would order treatment" (L. Shawver, personal communication, October 31, 2017). Sticking to a formulaic treatment process minimized liability for oncologists, which was steadily rising each year; malpractice lawsuits and the costs associated were severely impacting the latitude that doctors had to go beyond standard treatment regimens, which made tumor profiling a risk for doctors (Brenner and Smith 2004).

Many studies about molecular tumor profiling also raised concerns about using molecular tumor profiling without a standardized system in place. Nearly every laboratory that profiles tumors does this process differently (Nguyen and Gocke 2017). While studies continue to suggest that third-party tumor profiling is the best option until tumor profiling becomes widely used by

oncologists, it was clear in 2007 that before oncologists could adopt molecular tumor profiling it had to be standardized to provide consistent results across laboratories (Benson 2016).

Starting the Clearity Foundation

Shawver incorporated the Clearity Foundation on August 31, 2007, just five months after finishing chemotherapy for her ovarian cancer. The goal of the Clearity Foundation was to help ovarian cancer patients and their physicians make better-informed treatment decisions through the use of molecular tumor profiling (The Clearity Foundation 2018). After profiling, which Shawver thought should occur at diagnosis or after the first cancer recurrence, Shawver hoped to use this information to help women receive the appropriate drugs, either by using approved drugs, persuading oncologists to provide off-label drugs, or by getting women into clinical trials. Over the summer, Shawver reached out to her friends with expertise in areas that she deemed necessary, such as law, public relations, and genetics (L. Shawver, personal communication, October 31, 2017). One of the most important people she contacted was Deborah Zajchowski, a cancer biologist who became the Scientific Director of the Clearity Foundation and was pivotal in the early work of the foundation.

Shawver knew that one of the main challenges of establishing the Clearity Foundation was finding laboratories to profile tumors. Shawver reached out to individuals to discuss her dilemma, and during the summer and fall of 2007, she met with Tom Grogan, a founder of Ventana. Ventana made instruments to automate the process of taking thin slices of tumors, placing them on a slide, and staining them, which was a key advancement in the technology available to profile tumors. Tom Grogan was affiliated with the Arizona Cancer Center at the time, and after hearing what she was doing, he offered to profile Shawver's own tumor in his laboratory. He also wrote a report about her tumor so that she could go to other labs that did tumor profiling, show them the report, and say that she wanted to do this for other women with ovarian cancer. Having this example of a tumor report from Tom Grogan's lab allowed Shawver to demonstrate to other laboratories how she wanted the results of the tumor profile to be presented, since this was not yet a standardized process. This strategy was a success, and she ended up finding several laboratories that could profile the tumors that she sent them (L. Shawver, personal communication, October 13, 2017).

The next step in the laboratory search was performing a pilot study to determine the best laboratory to use for tumor profiling. This pilot study began at the end of 2007. One of the most important laboratory factors was reproducibility of the data, and the lab needed to be CLIA (Clinical Laboratory Improvement Amendments) and CAP (College of American Pathologists) certified, which was a standard to ensure quality laboratory testing. To determine the best laboratory, Shawver and her scientific advisors, led by Zajchowski, did an analysis to see what the results looked like from each laboratory. They wanted to ensure that the results were consistent between labs, and they also wanted to determine which labs could offer data that the other labs could not, since tumor profiling does not necessarily include all of the same tests. They knew that they wanted labs that could test for a few different proteins, including HER2, a marker for breast cancer that they thought would also be important for ovarian cancer, and also the estrogen receptor. Once they determined the series of tests that wanted, they found the lab that could do the most reproducible testing and provide them with the largest number of tests. Since they wanted to do as much testing as possible in the fewest number of laboratories, they decided at the end of the pilot study to initially use only one lab called Clarient, which they began working with in 2008 (D. Zajchowski, personal communication, December 4, 2017).

Shawver had applied for 501(c)(3) status in the fall of 2007 and it was granted in the spring of 2008, making her nonprofit status official. Shawver was committed to covering the costs of tumor profiling, saying that "we really wanted to take that potential criticism out of the equation" (L. Shawver, personal communication, December 1, 2017). Given the nature of her company, she needed to be funded through donations, but initially it was challenging to get donations because most potential donors had a very limited understanding of tumor profiling. As a result, she started Clearity with a grant from herself, and she was the main source of funding for the foundation for the first few years. This added another layer of stress to her work starting the Clearity Foundation, and she says that "it felt like a lot of weight on [her] shoulders" (L. Shawver, personal communication, December 1, 2017). She was committed to doing whatever she could to allow Clearity to succeed, which required not only an emotional commitment but also a financial one.

After finding a laboratory to profile tumors, Shawver set up a system to coordinate with the laboratory and drafted a plan for the foundation. At this time, she was also trying to find someone to pay for a prospective clinical trial to prove the efficacy of tumor profiling. She knew that having this data would provide support for her assertions that tumor profiling was correlated with positive treatment outcomes. She reached out to pharmaceutical companies but was met with resistance. These would be expensive studies with limited possibility for economic return, and potentially even a loss of profits if the findings would relegate their product to just a small subset of tumors. As a result, Shawver was unable to find anyone to pay for a prospective clinical trial, and she eventually put aside this strategy to concentrate on her plans to launch Clearity and garner support for tumor profiling.

She formally launched the Clearity Foundation in September 2008. The next step for the Clearity Foundation was attending a Society of Gynecological Oncology Meeting, where all of the leaders in the field would be gathered. Shawver intended to present her plan for Clearity Foundation to a group of gynecological oncologists at the conference in the hopes that they would provide support for her mission (L. Shawver, personal communication, October 31, 2017).

Society of Gynecological Oncology (SGO) Meeting

The Society of Gynecological Oncology Meeting was in February 2009. Shawver was scheduled to present to a group of thirteen gynecological oncologists. She was accompanied by her Scientific Director, Zajchowski. Going into the meeting she felt confident; her foundation would revolutionize ovarian cancer care while placing very little burden on oncologists. It was clear to Shawver that molecular tumor profiling was the future of oncology, and she was providing a way for oncologists to access tumor profile data at no cost in order to better treat their patients. At the meeting, Shawver presented her plan for what Clearity was going to do and how they were going to accomplish their mission (L. Shawver, personal communication, October 31, 2017). Specifically, she discussed the results of the pilot study, demonstrating that they had found a laboratory, Clarient, that could profile tumors consistently. Shawver also explained the types of tests that they could do and demonstrated the potential impact of these tests on treatment by highlighting several case studies that indicated the positive treatment outcomes associated with tumor profiling (D. Zajchowski, personal communication, December 4, 2017).

Instead of enthusiasm for what she presented, Shawver received an overwhelmingly negative response to the Clearity Foundation's vision and plan. The gynecological oncologists at the meeting accused her of advocating for tumor profiling when there was no proof that it was correlated with a treatment outcome (L. Shawver, personal communication, October 13, 2017). They were referring to the fact that the supporting data for tumor profiling, including that data that

Shawver provided, was taken retrospectively and did not demonstrate causation. Zajchowski recalls that their main concern was that "no prospective clinical trial [had] proven that the testing that we do actually predicts responses to therapy" (D. Zajchowski, personal communication, December 4, 2017). The gynecological oncologists asserted that the Clearity Foundation was unethical because nothing that the Clearity Foundation did would influence their treatment decisions. They told Shawver that "you are taking advantage of people who need to have hope and you are giving them false hope" (L. Shawver, personal communication, December 1, 2017). This meant that oncologists would not use results from tumor profiling even if the Clearity Foundation provided them; they did not believe that tumor profiling would help them determine treatment any more effectively than the methods they were currently using to select treatment, and they felt that Shawver was overly optimistic about the potential that tumor profiling had to improve outcomes for women with ovarian cancer.

After the meeting, Shawver talked to Zajchowski, who interpreted the events of the meeting as a signal of the end of the Clearity Foundation; she did not think that they would be able to continue after such a harsh criticism of their mission from leaders in the field (L. Shawver, personal communication, October 31, 2017). Zajchowski says the she told Shawver that "this is going to be really hard," and she asked her, "is this even something that we can do?" (D. Zajchowski, personal communication, December 4, 2017). Both Shawver and Zajchowski were expecting the gynecological oncologists to be excited about the Clearity Foundation and to embrace their vision; neither anticipated the harsh criticism, even though both knew that "scientifically [they] were going to have a big hurdle" (D. Zajchowski, personal communication, December 4, 2017). Zajchowski says that after the meeting, "I could see why the key opinion leaders said that to us, and I know that [Shawver] could too" (D. Zajchowski, personal communication, December 4, 2017). At the same time, Zajchowski says that Shawver, more so than her, recognized that if they did not do this, no one else would. There was no single pharmaceutical company motivated to fund a prospective clinical trial, and without an organization advocating for tumor profiling and providing the profiling to patients, using profiling results to select treatment would never become the standard of care for ovarian cancer (D. Zajchowski, personal communication, December 4, 2017).

Was the Clearity Foundation simply too far ahead of its time? Ultimately, given the circumstances, what was the best strategy Shawver could employ to provide women with the quality of ovarian cancer care she envisioned within the constraints of the current medical system? How can one advance clinical practice and promote new approaches to care when there is no pharmaceutical industry sponsor to fund the studies physicians are accustomed to seeing before adopting new technologies? How can a scientifically based nonprofit foundation change the treatment paradigm when they are not the physician selecting the treatment or the pharmaceutical company studying and promoting a specific product in which they are economically vested? Given the norms of our medical system and the various players with sometimes competing objectives, what is the role of patient-centered organizations like the Clearity Foundation?

Epilogue

It was shortly after the SGO meeting that Shawver received a call from a woman whose daughter would become the Clearity Foundation's first patient. The woman's 11-year-old daughter had alveolar soft-part sarcoma, which is a rare, usually occurs in young patients, and has a much poorer prognosis than ovarian cancer (Folpe and Deyrup 2006). When the woman learned that Shawver knew how to access molecular tumor profiling, she called Shawver to ask for her help.

Though this young girl would not be a typical patient for the Clearity Foundation, Shawver knew what she needed to do; receiving this call from someone in desperate need of molecular tumor profiling, who could not access this care through the normal medical system, reinforced for Shawver all of the reasons why the Clearity Foundation was necessary (L. Shawver, personal communication, October 13, 2017). Shawver pushed forward with the Clearity Foundation despite the negative feedback from oncologists, and she did so with her mission and strategy unchanged.

The Clearity Foundation began profiling tumors regularly and was persistent in trying to persuade oncologists to adopt tumor profiling. Though it took several years for the foundation to gain traction within the medical community, the Clearity Foundation continued to advance its mission and made incremental progress in providing women with access to improved and targeted treatment for ovarian cancer. After several years of funding the Clearity Foundation herself, Shawver succeeded in generating interest from donors; gaining this donor funding was an important milestone in legitimizing the Clearity Foundation and it lifted a weight off of Shawver's shoulders, allowing her to focus on the operation of the Clearity Foundation (L. Shawver, personal communication, December 1, 2017).

While initially Shawver found it immensely challenging to convince oncologists to use the tumor profile results that the Clearity Foundation provided, tumor profiling has now become far more widely used in ovarian cancer treatment and is utilized at most major teaching hospitals. In fact, at this point, many oncologists order tumor profiling for their patients without the intervention of the Clearity Foundation. Shawver stated that "it is amazing now, eight years later, that people have largely bought into this" (L. Shawver, personal communication, December 1, 2017). The shift toward the use of tumor profiling in cancer treatment occurred slowly in response to a growing body of evidence and pressure from those in the research community. The success of tumor profiling to treat other cancers such as breast cancer likely contributed to its use in ovarian cancer, and it seems that as data continue to accumulate, tumor profiling will begin to assume an even more prominent role in cancer treatment. Interestingly, a prospective clinical trial proving the efficacy of tumor profiling in improving treatment outcomes has still not been performed (D. Zajchowski, personal communication, December 4, 2017).

Though molecular tumor profiling is certainly more prevalent now, there remain several issues with the way that the technology is currently being implemented. While the medical community recognizes several tests within the tumor profile, there are some tests that oncologists will not even consider when determining treatment (D. Zajchowski, personal communication, December 4, 2017). Additionally, the use of tumor profiling at hospitals is very tumor specific and therefore focuses on the more prevalent types of cancers, meaning that it is less prominent in ovarian cancer. It is also important to note that tumor profiling is still not usually done as an initial step in treatment; it is most often used when a woman fails multiples treatments, which minimizes the effect that tumor profiling can have on improving treatment outcomes (L. Shawver, personal communication, December 1, 2017). As the mission of the Clearity Foundation evolves in response to developments within the medical community, these issues remain at the forefront of the work that the Clearity Foundation does to promote tumor profiling as a means to improve treatment options for women with ovarian cancer.

The growing acceptance and availability of tumor profiling within the medical community has allowed the Clearity Foundation to expand their mission; while their early work centered around getting women access to molecular tumor profiling, they are now more focused on helping women consider their options for treatment given the results of their specific profile, and their website features one of the best search engines to help women determine the appropriate clinical

trial based on the results of their tumor profile (L. Shawver, personal communication, December 1, 2017). Today, the Clearity Foundation continues to play an important role in the ovarian cancer community; it is backed by committed donors and board members, and it is fueled by the continued passion and contributions of Shawver and Zajchowski, in addition to many others who have been involved since the inception of the Clearity Foundation.

Shawver succeeded in founding and sustaining the Clearity Foundation not because the idea behind the Clearity Foundation was unassailable or the benefits of tumor profiling were irrefutable. She succeeded largely because of her unwavering belief in the goals of the Clearity Foundation and her steadfast conviction that what she was doing was essential for improving ovarian cancer outcomes. It was her conviction that allowed her to persevere when faced with opposition, and it is her conviction that continues to drive the Clearity Foundation forward today.

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