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Shannon's Story

By John Barry, her father

I've always considered myself fortunate to have stumbled into the CRO industry when I joined PPD back in 1992. Even after 27 years, I still think myself fortunate to be part of this incredible R&D ecosystem. Like most professionals, my journey has taken me in and out of different organizations along the way. In 2010, I found myself back at PPD after a two-year stint at Quintiles. I'll never forget the call my wife and I received from my daughter, Shannon, then a 23-year-old wife and mother of a 2-year-old son, Landen. At the time, she was living in Snow Hill, NC, a two-hour drive from our home in Wilmington, NC but very close to her 18-year-old sister, Shelby, a freshman at East Carolina University.

On the call, Shannon told us that she had mentioned to her GP that she was having some memory lapses and fatigue. She was sometimes unable to collect her thoughts and occasionally had slurred speech. Her physician thought it was nothing, chalking it up to the pressures and sleepless nights of new motherhood, but to be safe, scheduled her for an MRI. The MRI had been performed earlier that day and a follow-up visit scheduled for two weeks later. Shannon was calling to let us know that, before she even got home from the MRI, her physician was calling to tell her she needed to see her first thing the next day. Shannon wanted to know what this call might mean. All we could offer was that she was about to get some really bad news.

My wife, Barb, a Duke-trained nurse practitioner, and I were unable to clear our schedule for Shannon's appointment the next morning, so we called her sister Shelby and told her to clear her class schedule and go to the doctor with Shannon. All we could offer Shelby was that Shannon was likely about to get some bad news and that she needed to be there with her for support. We all anxiously awaited the visit, set for 8 a.m. the next day. I was on a conference call when texts from Shelby started coming in. Shannon had a tumor about the size of two golf balls at the back of her right frontal lobe.

Despite the worst-case scenario planning my wife and I had done the night before, I was stunned. I was no longer an executive; I was a father in desperate need of direction, so I do the only thing I could think of: send an email to PPD's CEO, Dr. Fred Eshelman. Prior to PPD, he had been an accomplished clinical researcher at GSK. He was well known in R&D and medical circles and I hoped he might give me some advice. He quickly replied and

Shannon (at left) with her family

asked for a few minutes to make some calls. Within minutes, Dr. Ernie Mario, PPD's Chairman of the Board, walked into my office at PPD with Dr. Alan Friedman, Duke's Chief of Neurosurgery, on the phone. As it turned out, Dr. Mario had been on Duke's Board of Trustees. After a quick chat, Dr. Friedman was set to see Shannon that next Monday morning.

It's not lost on me how lucky I was that I was able to make that call to Dr. Eshelman, that I had someone in my network who had those connections and that I could call. At the time, I wasn't thinking about all the people who find themselves in a similar situation but can't make that call and, just as important, wouldn't get that answer. I don't know how other dads, who have their own Shannon, would be able to navigate this complicated ecosystem of ours. I just knew that, within four days of hearing the news, Shannon would be in the hands of a preeminent surgeon at one of the world's leading brain cancer centers, and that was all that mattered to me.

2010 was a tough year. Shannon had a craniotomy in early March and spent the next six months recovering her left-side motor skills. Dr. Friedman explained that they were able to resect most of the tumor but, as it was an infiltrative tumor, he was not able to get the whole thing without causing permanent damage. Shannon had a 70% chance that the tumor would come back and, if it did, there was a 50% chance the tumor would advance in grade, so a 35% chance the tumor would become malignant. As a grade 2 glioma, any progression would likely be very slow. We learned that gliomas are not uncommon but that they usually occur later in life and cause few problems before the patient dies from other causes. The gliomas are then discovered on autopsy. We considered our odds pretty good and settled back into a normal life.

In late 2014, almost five years after Shannon's original diagnosis, she returned for routine follow-up MRIs. She had remained asymptomatic, so we were expecting good news. It was her chance to restart her life as "cancer free." To our distress, her tumor had started to regrow. A biopsy the next week confirmed it has also progressed to a high-grade glioma (grade III). She now officially had cancer and, in addition to a second craniotomy, she would also need standard-of-care treatment: radiation and a decades-old chemotherapy drug, Temodar.

By this point, my career had taken me to Merck, so imagine my surprise when I learned that Temodar was a Merck product. Also imagine my frustration that Merck's most promising new drug, Keytruda, was years away from consideration as a brain cancer treatment.

I started looking for clinical trials, particularly with the new wave of immunotherapies in development, and found limited effective options. R&D companies need to make decisions about which tumors to investigate and when. While brain cancers make the list, high-grade gliomas that aren't yet glioblastoma (GBM) have few clinical study options. Companies like Merck typically start by targeting cancers like metastatic melanoma that are aggressively lethal to gain approval. They then use these results and commercial returns to help inform and fund trials for other cancers on their list. Common cancers like lung, breast and colorectal usually have higher priority than brain cancer. Professionally, I understood this but, personally, I struggled with the reality that Shannon would have to depend on a standard of care treatment that was not considered curative until a new treatment became available. It's an industry dilemma that we need to put these patients on treatments we know will likely fail while promising new agents are being tested on other diseases.

GBM options are now becoming available. For example, UNC Chapel Hill currently has a GBM first-line treatment study that includes a triple-combination therapy of standard of care, an innovative plasmid technology, and immunotherapy. That's a trial we would have jumped on in 2015, but we had to settle for standard of care.

After a quick family trip to Disney World over Christmas, Shannon had her surgery at Duke, and started six weeks of concurrent Temodar and radiation therapy, followed by seven months of Temodar alone. I was fortunate to have access to oncologists at Merck who knew everything about the compound. I could share my fears and concerns with them, ask them about possible side effects, and dive deeper into the specifics of treatment efficacy. We knew that Shannon's treatment would not be curative, but at this point, our job was to keep her alive until a cure did become available. We believed that her cure had already been discovered and it was just a matter of keeping her here until we could get it for her.

If 2010 had been a hard year, 2015 was even harder. Aside from the short period it took to regain her motor function back in 2010 — which seemed long at the time — Shannon had been largely asymptomatic up to 2015. She had never looked like a cancer patient. Now she had the hair loss, fatigue, nausea, vomiting and a nasty lower GI infection brought on by the indiscriminate immune suppression. Her son, now 7, became aware that his mother had a horrible disease and began to worry about her future. He had to grow up fast.

For most of 2015, I was traveling back and forth between Pennsylvania and North Carolina, trying to be both the patriarch of my family and an executive for Merck. Fortunately, Shannon's husband, Charlie, was there for her to lean on.

In late 2015, as expected, Shannon went into remission. Her remission lasted a little over a year. She then progressed again in the spring of 2017. This time though, as she had failed standard of care, I was optimistic she might finally qualify for one of the more promising treatments now in clinical trials. This was good news until her biopsy revealed a new tumor: grade III anaplastic astrocytoma (AA), a less common form (7%) of brain cancers.

While a number of trials were targeting GBM, only two were actively recruiting for grade III AA. One trial was being conducted by Orbus Therapeutics out of Palo Alto; the second was being conducted by Tocagen. As it turned out, Duke was a participating center on the Orbus trial, so Shannon could enroll straight away. Imagine my surprise when I learned that Dr. Mario, PPD's Chairman, was also the Chairman of the Board of Orbus. It's a small and interconnected world.

The open-label Orbus trial was investigating eflornithine against lomustine, a standard-of-care drug more commonly used outside the United States. As an open-label trial with 1:1 randomization, we knew Shannon had a 50:50 chance of randomizing into the active treatment arm, so it was with some disappointment that we learned Shannon randomized into the control arm, a standard of care that may not actually have been as good as the standard of care she had already failed. As a clinical research professional, I am proud of the work we do. I know the data from control arms is every bit as important as data from active arms, but as a dad, I must admit I was disappointed.

I explained to Shannon that, all along, we'd been lucky. While it might have seemed like, if she could get a bad diagnosis, she got a bad diagnosis, she had also had the mildest symptoms possible for each diagnosis. She'd had a terrific life throughout this journey. We'd celebrated birthdays, holidays and special events. She was young, otherwise healthy, full of energy, and had a loving family to support her. She was a perfect trial candidate and I asked her to be true to the clinical research paradigm, to be true to the work we do, and enroll into the control arm. I let her know she'd be watched carefully and that we could always tap her out at any time. True to form, Shannon enrolled into the control arm and, six months later, completed the trial and again went into remission. Nevertheless, I'll always wonder whether enrolling in that trial that was the best decision for Shannon.

At this point, I knew there was a strong probability that Shannon would soon progress again, so I started looking for a job that would take me back to North Carolina. I was lucky to find a role as the Chief Operating Officer of Pharm-Olam, a mid-size CRO with operations

headquarters in Research Triangle Park, NC. After joining, I was surprised to learn that Pharm-Olam was the CRO running the trial on behalf of Orbus. It was humbling to know that my daughter was a trial patient in our system and her data was in our database. It's a revelation that rebalanced me, as I now knew one of those anonymous subjects we study.

In July 2018, Shannon had progressed again. This time, though, we learned of the progression after she had had two significant seizures on July 4th, which prevented her and Charlie from joining us at a family wedding in Syracuse. Landen was with me, Barb and the family in Syracuse. It was difficult to keep the news from him, but we did.

Soon after the wedding, we returned to Raleigh to meet with the Duke team. The night before our appointment, we met Shannon and Charlie for a quick dinner at a local restaurant to let Landen know what was happening. Even at the young age of 10, he knew that a seizure was an ominous sign and, when he learned that his mom had had two seizures just four days earlier, his heart sank. We'll all be haunted by the sadness that overcame him that night. It was the first time he fully realized his mother was now fighting for her life.

Initially, there was some confusion at Duke over whether Shannon had actually progressed to GBM. While her MRI revealed significant tumor growth, Dr. Friedman looked at her and told us he did not think she had glioblastoma. She simply did not "look like a glioblastoma patient." His comments reminded us that, except for 2015, Shannon had never "looked" like a cancer patient. Dr. Friedman was pretty certain she did not have GBM and recommended a third craniotomy. Clinical care and clinical research now came into conflict: If Shannon had GBM, surgery would eliminate her most promising option, Duke's poliovirus trial, a vaccine featured on *60 Minutes* back in 2015.

If Shannon still had AA, surgery would eliminate an Agios trial that was still recruiting for grade III AA patients, a trial that would require surgery but not until after four weeks of treatment. Both the GBM and AA trials required the presence of tumor mass, so surgery would take both trials off the table. We were fortunate to be aware of the options as we discussed next steps with the Duke team. Dr. Friedman wanted to minimize the number of invasive procedures that needed to be performed by performing one surgery to both resect and biopsy the tumor. His focus was on clinical care. After a couple of days and another MRI, he agreed to do just the biopsy first. We're grateful that Dr. Friedman was willing to listen and change course. This experience reminded us all that, in the end, it's still the patient, with support from her family, who has control of her journey.

As we waited for the biopsy and its results, minutes felt like days. We appreciated Dr. Friedman's experience, but his assessment, while based on decades of experience, conflicted with the rapid tumor growth rate. There was an upper limit to the tumor size for Duke's poliovirus trial, and we were concerned Shannon would "size out" of this study.

Shannon finally had her biopsy and, later that afternoon, Dr. Friedman came into her room with the initial results. He opened with an apology, as her tumor pathology did, in fact, suggest Shannon had transformed from glioma into GBM. She still did not look like a glioblastoma patient to him. The GBM bad news was offset by the good news that Shannon was now eligible for Duke's poliovirus vaccine, one of the most promising experimental treatments available. Shannon's tumor had grown from 2.7 cm to 4 cm and counting, so we were concerned she would soon exceed the 5.5 cm cutoff for the trial.

The logistics over the following days were herculean, as the calendars for over 18 medical professionals had to be coordinated. For the first patients enrolled in the study, this coordination took around 30 days, but they had been able to shrink that down to 10 to 12 days. The trial involved three different experimental procedures: the intra-tumoral delivery, the vaccine, and the contrast dye to image the vaccine after it was applied.

The consent form was nearly 30 pages long. From the perspective of the patient, it was an ominous document. There were questions like, "If you die, will you donate your brain to science?" It's tough to sit there and walk through these questions with your daughter. Nevertheless, Shannon signed the informed consent. The study-entry MRI found Shannon's tumor was now 4.9 cm, so she had qualified with only a few days to spare and no room for delay.

It was now the day of the infusion. The treatment catheter had been inserted into Shannon's brain. The study nurse walked into the room with the infusion solution. We were less than 30 minutes away from the start of the six-hour infusion when Shannon had a 3.5-minute seizure that might qualify as an exacerbation of symptoms, an exclusion for the trial.

The study nurse packed up the infusion solution and started to walk out of the room. Charlie leaped into her path, yelling, "This is her life! Don't take it away from her!" He literally blocked the door to prevent her from leaving.

I understood, scientifically, why Shannon's pre-treatment condition was important, but as a dad, I knew we were running out of options. After much discussion, the Duke team concluded that, while it was a long seizure, she never lost consciousness, so it wasn't more significant than her previous seizures and would not be considered an exacerbation. They proceeded with the infusion.

The procedure was like a biopsy, so Shannon was able to go home the next day. The side effects were minimal; this was not like classic chemotherapy where the patient is up all night vomiting. On the other hand, there was no way to tell if the treatment was working so, for four weeks, we waited.

One morning in the first week of September, we went back to Duke for an MRI. That afternoon, the Duke team came into the exam room. They couldn't contain their excitement. Casey, the nurse practitioner, put the MRI up on the screen. All the layperson needs to know about cancer MRIs is that black is good and white is bad. There were huge black holes in Shannon's tumor. There was far more black than white. The tumor was dying. I remember walking back to the car and Charlie saying, "For the first time in nine years, I feel like I'm going to have my wife back." After nine years, I felt like I was going to have my daughter back.

The week eight MRI showed almost no change from week four. Then, in early December 2018, we went back for the week 12 MRI. The news was devastating: Not only had she progressed, but the cancer had now spread to the leptomeningeal membrane around her brainstem, giving her less than six months to live. Leptomeningeal disease (LMD) was exclusionary in almost every brain cancer trial. Compassionate use immunotherapy for LMD was not an option because of the high risk of a lethal side effect. We were devastated that we were left with carboplatin and Avastin as Shannon's only treatment option.

We were out of options at Duke, so we began looking for other possibilities. Once again, I reached out to my network, this time to Dr. Roy Baynes, Senior VP of Global Clinical Development at Merck. Dr. Baynes put me in touch with several oncologists at Merck. I learned that LMD is an end-stage progression more commonly found in breast cancer patients. Because of the advances we've made in treating breast cancer, these patients now live long enough to get LMD. It's less common in GBM patients, likely because patients don't live long enough to get it. Most of the LMD trials I found required a specific primary tumor type, in most cases breast.

ClinicalTrials.gov, an important source of information for me over the previous nine years, remained difficult to navigate but, with Merck's help, I found an investigator-initiated trial at Johns Hopkins (JHU) for LMD disease that did not mandate a specific primary tumor type.

The Merck team put me in touch with the JHU team, and Shannon's results were evaluated by the JHU tumor board.

Shannon's options were closing in. The JHU trial required an LMD lesion of at least 2 mm, which Shannon didn't yet have. Alternatively, she could have had a spinal tap to see if cancer cells were present, but her Avastin use precluded that procedure. At the same time, she also needed to maintain a strong mental and physical cognition score. In other words, to get into the JHU trial, Shannon's condition had to deteriorate, but only in one particular way. This brings me to today, in March 2019, when we are waiting for disease progression but without a deterioration of symptoms. Could Shannon thread one more needle?

In January 2019, *Scientific American* published an article noting that most oncology trials fail because of a lack of patients. It also noted that almost 75% of oncology patients are never given the option to participate in a clinical trial. The patients and the trials are out there but it is no easy matter for many patients to find the right studies, even with expert and dogged support.

In our journey, we have had the good fortune to have access to people like Drs. Eshelman, Mario, Friedman and Baynes, and the countless others who have supported us through Shannon's clinical journey. We will forever be grateful for their help. Knowing they were there for us gave my family the confidence that, if an option was out there, we would find it. Every treatment option was more complicated than presented here, but we knew we were doing all we could do to keep Shannon alive, mostly healthy, and in good spirits. The journey has been almost unbearable, but it could have been much worse.

As we near the end of Shannon's journey, I am left thinking about less fortunate patients and families who live their story with fear instead of hope, with despair instead of optimism.

As an industry, we can do better. We must do better. To our patients and their families, a clinical trial is more than tests, procedures and data. To them, it also gives them hope that their dark passage will eventually emerge into the light. I think we would all agree that, regardless of the final outcome, living with hope is a much better way to live.

So, was Shannon able to thread one more needle? Sadly, no. After a valiant nine-year battle, Shannon McHone passed away peacefully on April 11, 2019, at the age of 32. She left behind a loving husband, Charlie, an 11-year-old son, Landen, and countless others who journeyed with her or were otherwise touched by the story I share with you today. She will never be forgotten.

To learn more about Shannon's journey against the odds, please visit www.caringbridge.org/visit/shannonmchone. To support other teachers who are battling cancer or who have an immediate family member who is fighting this disease, please visit http://www.flunkcancer.com/home.html.

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