The Significance of Unknown Significance

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AS A PEDIATRIC hospitalist, I performed the red reflex as part of a routine eye exam on hundreds of infants and children before I found one that was abnormal. I made the discovery not at the bedside of a newborn but on the floor of my own living room. For a week, I had intermittently noticed a yellow discoloration in the back of my youngest son's right eye. It was visible at certain angles in low light, but then he would look away or his pupil would constrict, and it would be gone. But when our nanny mentioned it, I pulled out my old medical school ophthalmoscope. It was not even charged; I had only used it once or twice in the past few years to look in my older son's throat or to serve as a prop for my daughter's stuffed animal checkups. Once the device was charged, I crawled around trying to catch the attention of my son Elliot, then 8 months old, our indestructible third child.

My husband, a psychiatrist, looked on expectantly as I checked, rechecked, adjusted the light, and checked again, hoping each time I was making some sort of mistake in my physical exam. A fiery orange glow reflected back from his left eye, but from his right—nothing. The next day, Elliot was diagnosed with retinoblastoma.

My husband and I took Elliot to the pediatric ophthalmology clinic in the children's hospital where I worked. The appointment started with the typical banter of colleagues, the ophthalmologist relaying an anecdote about smartphone camera flashes causing an uptick in referrals for leukocoria. We did not discuss the differential of an abnormal red reflex, but it hung heavily in the air. The attending had a student with him whom he let do the exam first, gently correcting her technique and making teaching points as she looked in Elliot's eyes. When he took his turn at examining, there was a perceptible stiffening in his body language. They left the room under the pretense of needing to wait for Elliot's eyes to dilate before making a diagnosis. I would later learn that the attending was canceling a meeting with his chairman to stay with us through a diagnosis of cancer. When they returned, the student would no longer make eye contact with me. For me, that was when I learned my son's diagnosis: before a word was even said. In that trainee's face, I saw my own early experiences delivering bad news to families, and I remembered how hard it had been to look them in the eyes. I started to cry, whispering in Elliot's ear, "I'm so sorry, buddy. I'm so sorry." The ophthalmologist only got out half the statement—"I think your son has retinoblastoma"—before he started crying himself.

The week that followed Elliot's diagnosis was a whirlwind of opinions and second opinions, consultations and team meetings. The stress was punctuated with surreal moments of crossover between being a pediatrician and a parent. A medical school classmate found out about Elliot's diagnosis when the case was discussed at a tumor board. Eventually my husband and I were presented with 3 treatment options: enucleation of the eye, systemic chemotherapy, or intra-arterial chemotherapy (IAC). There was no single protocol to follow. Though I had helped my patients and their caregivers navigate treatment options many times before, I had never had to make such a serious choice for my own family.

With the help of our son's team, we chose IAC delivered directly to the retina by a neurointerventional procedure. As parents, it seemed a near-miraculous option because it would help our son avoid the adverse effects of systemic chemotherapy. As physicians, it was unsettling because we knew that not all experts embraced this therapy, and it had not yet been studied with the time and rigor we might have liked. But it was cancer, and something had to be done. I told myself that in the end we would know that we did the best we could with the information we had. Still, I could not get rid of the fear of one day looking back and thinking that I made the wrong choice.

Our next experience with uncertainty—prognostic uncertainty—was more difficult. Elliot had genetic testing for a mutation in the *Rb1* gene as a standard part of his retinoblastoma assessment. He had one tumor in one eye only, so we thought he was unlikely to carry a germ-line mutation. In the initial flurry of treatments and checkups, we lived happily with that assumption. Eight weeks into his treatment, however, we were accidentally given his genetic results over the phone. A familiar children's hospital number came up on my cell phone, so I picked up, assuming it would be another appointment reminder. The genetic

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counselor we had met only once was on the line, calling to follow up on Elliot's test results and see what questions we had. My response—"What results?"—was met with an uncomfortable silence. The seconds waiting to hear the answer seemed to carry the same life-changing weight as the seconds before the ophthalmologist first said the word "cancer." Elliot had a "variant of unknown significance," a single base pair substitution resulting in a single amino acid change in the *Rb1* gene. On one end of the spectrum was hereditary retinoblastoma, a cancer predisposition syndrome carrying with it up to a 400 times greater chance for future cancer compared to the general population. On the other end of the spectrum was a sporadic tumor—a solitary cancer that carried no increased risk for future disease. Somewhere in the middle was my son, whom I wanted to imagine as an 80-year-old man surrounded by his children and grandchildren. On good days, I could see him as that aging man. But there were bad days too, where my hand grazed a black dress in my closet and I imagined myself wearing it to his funeral.

Until Elliot was diagnosed with cancer, my experiences with serious childhood illness had always been as a pediatrician, not as a parent. As I tried to process the upheaval in our lives, the most readily available coping mechanisms I had were those I used in my professional life. I scoured the literature, looking for evidence to support a benign interpretation of my son's genetics. I got frustrated when presented with any contradictory information, so I would search again. Finally my husband convinced me to deactivate my medical library access. I repeatedly consulted experts. Each time we met with a member of Elliot's team, I asked the same questions; I dissected every gesture and every word choice as they answered. I tried to micromanage, offering to contact the genetics lab myself to see if there were any updates on my son's variant.

Now I can see that nothing in my bag of coping tricks was going to change the fact that I did not know what would happen to my son. I had to learn to live with it. As time has passed, the peaks and valleys of emotion have smoothed out somewhat, and the questions live in the background, a dull hum. They swell with less frequency and urgency—I can tune them out more easily. Grappling with the unknown significance of Elliot's genetic testing has been, for me, the most significant lesson of all.

As we have moved through this process with Elliot, his team has been honest that his genetic variant makes their recommendations about his care more complicated. Elliot's oncologist, ophthalmologist, and geneticist were all comfortable saying "we don't know" as an admission of the lack of certainty in medical science. As a physician, I understood that this type of uncertainty is unavoidable. As a physician, I could be forgiving of that reality. As a parent, I was less forgiving. I often felt stuck filling in the gray areas myself, and I would usually fill them with unhealthy thoughts and predictions about Elliot's future cancer risk. I wished someone would have said not only "we don't know" but also "we don't know and that must be really hard for you to live with." Recognizing the burden of the uncertainty would have made it less powerful.

Elliot ultimately required 5 cycles of IAC, then several months of laser and cryotherapy to treat residual tumor. He still undergoes monthly eye exams under anesthesia to monitor for tumor recurrence or any new tumors, a routine that will continue for the foreseeable future. He has had general anesthesia 30 times and counting. With each passing month of no new tumors, it feels less likely that he has hereditary retinoblastoma, but I continue to struggle with that unknown.

In the early days of Elliot's cancer diagnosis, I sometimes wondered what I would look like on the other end of this experience. There are hints of a silver lining to an experience I never wanted to have. As a mother, I understand better what it feels like to be present with my family in the moment, mostly because that was the only way I could get through these intense and scary times. When Elliot was in the midst of chemotherapy and we waited month to month to see how his tumor was responding, the moment was the safest place to be. This presence is one gift his cancer gave me. But I am still trying to understand how I have changed as a pediatrician. I know I cry more readily with colleagues and trainees who share their stories of difficult diagnoses and poor outcomes because I have touched those feelings as a parent. I am more respectful of the wide and sometimes conflicting range of emotions created by illness in a child because I have been the mother laughing in the preop area with the anesthesiologist, then sobbing in the hallway 5 minutes later. When my patients and families are forced to tolerate diagnostic or prognostic uncertainty, I recognize it and engage them in dialogue about their fears. These subtle practices are the way I try to lend significance to my son's diagnosis—and the way I try to negotiate my new identity as a pediatrician as well as a mother of a child with cancer.