



Precision oncogenomics in pediatrics: a personal reflection

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Abstract Cindy Campbell, a bereaved parent who lost her son to a rare pediatric brain tumor, shares her experience and frustration over the lack of treatment options and minimal research funding in pediatric oncology. She invites Dr. Jeffrey P. Greenfield to reflect on the situation and share his professional experiences pertaining to advances in oncogenomics and pediatric brain tumors. They share a passion for making this technology available to all pediatric brain tumor patients in the future and using data to inform treatment protocols and improve outcomes.

INTRODUCTION

Pediatric brain tumors are the most common solid tumors found in children, and they are the leading cause of cancer-related deaths among children 14 years old and under (Guerreiro Stucklin et al. 2018). Approximately 2800 children are diagnosed with brain cancer in the United States each year, and some types of brain tumors, such as diffuse intrinsic pontine glioma (DIPG), have a 0% survival rate (Ward et al. 2014). These poor statistics reflect the challenges faced due to anatomic constraints of disease in the central nervous system—including difficulties such as getting chemotherapy or targeted agents across the blood–brain barrier, and the often-inoperable location of many tumors. Long-term effects from toxicity—including effects on cognitive, endocrine, and neurologic development secondary to current standards of care (surgery, chemotherapy, radiation)—are the price paid for those who do manage to survive the poor odds (Dang and Philips 2017).

Genome and epigenome profiling is becoming integral in redefining both the way pediatric brain tumors are categorized and how they are increasingly being treated, as molecular alterations are emerging as powerful prognostic markers and targets. They are now frequently being used to stratify patients within traditional pathologic diagnoses and tailor therapies as new targeted agents become available (Dang and Philips 2017). As genetic and epigenetic data change the way pediatric brain tumors are diagnosed, new guidelines for how treatment outcomes are analyzed are emerging, and molecular targets are being used to develop novel therapies (Dang and Philips 2017). Scientific and technological advances that were unavailable to most children less than 10 years ago are now being integrated into therapeutic treatment protocols, and the landscape for pediatric brain cancer therapy is just beginning to realize the potential predicted by precision oncogenomics at the dawn of the sequencing boom in oncology. These changes have created a new environment, one in which parents with a child newly diagnosed find

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themselves navigating a very different landscape than the one a parent might have encountered in 2010.

A PATIENT'S STORY

In August of 2010, I could tell something was wrong after my family returned home from a long vacation and my 2-year-old son, Ty, was unusually restless. Always a terrible sleeper, we assumed he just needed to readjust to his routine. On the third sleepless night, he was crying in discomfort and he could not tell us what was wrong. I knew in my gut that it was not normal, that this was not a problem with him acclimating to his regular routine. My husband and I suspected that he was experiencing head pain due to increased pressure when he was lying down.

It was sunrise and our spunky, agile, athletic little boy had slept less than 2 hours by the time we arrived at the hospital. Dressed in a yellow tee, gray shorts, and flip-flops, he hopped on the scale, laughed at the blood pressure cuff, took a needle like a champ, and held up two fingers when asked how old he was (“two half” he would say, instead of “two-and-one-half”). The team seemed puzzled over why we came. Ty had not a single sign of neurological distress and his bloodwork was fine. My husband and I were convinced something was wrong and demanded they perform an MRI, regardless.

On the screen before us, a monster revealed itself. At the base of his skull behind his nose, was a growth that resembled a quarter-sized knob, pushing up against his brainstem like a playground bully. In that instant, my life was ripped into a “before” and “after” that most others cannot comprehend. I started grieving the loss of my life before diagnosis and I knew I would never be the same. A fierce need to save Ty consumed me completely from that day forward.

Ty had the first of many tumor resections, and 90% of the tumor was removed; however, it took 6 weeks for the pathology to come back—an excruciating wait that began our “this is unacceptable” list; at that time we had no idea how long the unacceptable list would grow.

The first report we obtained from Johns Hopkins pathology review suggested that it was likely an epithelioid sarcoma. For 2 weeks, I frantically Googled “epithelioid sarcomas” while scribbling stream of consciousness notes. Then another opinion we sought from Dana Farber/Boston Children’s Hospital identified the deletion of INI-1 in a genetic analysis, thereby reclassifying the tumor as a non-rhabdo rhabdoid tumor. To complicate matters further, Ty’s tumor originated in his skull base around the clivus, but it had penetrated the dura mater, leaving residual tumor on the brainstem. We did not know if we were treating a sarcoma or a brain tumor, and no one could give us a clear answer.

When we arrived at Memorial Sloan Kettering Cancer Center (MSKCC) for consultation on treatment, Ty’s disease was suddenly being referred to as an atypical teratoid rhabdoid tumor (AT/RT). Our heads were spinning—what were we treating, anyway? It was there that we first met pediatric neurosurgeon Dr. Jeffrey Greenfield, who became a trusted advisor throughout the course of treatment. Dr. Greenfield is on the faculty of Weill Cornell Medicine, and he treats patients at both New York-Presbyterian and MSKCC.

At that point we did not know yet that precision medicine was an area of research interest for Dr. Greenfield. But my husband asked, “Can’t we do what Steve Jobs did? I’ve been reading about genetic sequencing and precision medicine, can we do that? We need that for Ty.” If we could sequence the tumor and come up with targeted therapy, the pathology would not matter. We could more strategically treat the tumor itself, rather than the tumor classification. That was when we started talking about precision medicine—its promise, and its failures for children—with Dr. Greenfield.

Unfortunately, at the time the field of precision medicine was just beginning to evolve, but not quickly for children and not nearly fast enough for Ty. As much as we lobbied and advocated and screamed, there just were no good treatments options available to us.

In 2011, our son was declared NED (no evidence of disease) after two small metastases were found and surgically removed from his cerebellum. But we understood that metastatic brain cancer would return, and we refused to sit around waiting for the other shoe to drop. With each disease-free day he was growing stronger, and we were desperate for ways to suspend that shoe forever. Why could we not try something that might stop the inevitable recurrence? Why could we not do anything?

We exhausted our standard of care and found ourselves desperate for options. Our frantic searches for clinical trials came up completely empty. Nothing. We begged the team to look at his cancer genome to reveal clues to ways in which he could be more effectively treated with targeted therapies. We wanted extreme measures, we demanded access to cutting-edge therapies, but we were met with silence and empty stares from every medical team we consulted with. Our hands were tied.

Without critical genetic information to guide Ty's treatment, doctors did the best they could to respond to his symptoms. But nothing they did was effective in the long run.

“These obstacles remain true to this day, and my desperate search for options opened my eyes to the harsh realities of pediatric cancer research.”

In October 2012, our son relapsed and died because of the lack of treatment options available to him. Clinical trials for Ty were absent. Cutting-edge therapies showing efficacy in adults were denied to pediatric patients often because of liability concerns from the pharmaceutical companies. Federal research dollars for pediatric cancer research fell grossly short of what was needed to advance potential cures. These obstacles remain true to this day, and my desperate search for options opened my eyes to the harsh realities of pediatric cancer research.

- Therapies that are currently being used often leverage adult hand-me-down agents that are overly toxic for children, and these agents are not designed to treat the unique biology of children's cancers.
- In the realm of today's clinical research, progress is too slow and promise too rare, often taking 5 years or more before research discoveries are tested in humans.
- When pediatric patients are concerned, this timeline is delayed even further because a limited patient population might fail to reach accepted research standards (e.g., large-scale, multicenter, single-treatment, placebo-controlled, narrow eligibility criteria).
- Federal funding falls tremendously short, and that amount gets smaller as it is distributed across various cancer types specific to children. The funding gap is left to nonprofits, private foundations, and individual families to fill.

In many ways, it is the parents who are driving change in this arena. They are running marathons, baking cookies, and riding bicycles cross-country to raise funds for research. On one hand it hurts to know that this is a reality for parents who should otherwise be home caring for their sick children, but on the other hand, their determination and unbreakable hope is what inspires me to work so hard on their behalf.

My husband and I co-founded the Ty Louis Campbell Foundation (<https://www.thetlcfoundation.org/>) to fund strategic research. The only way I can continue to parent and care for my son is to dedicate my time toward advancing progress in his memory.

I will never forget the day that we were called to a meeting at Weill Cornell Medicine and Dr. Greenfield presented us with the concept for funding a laboratory to support the inception of The Children's Brain Tumor Project (<http://weillcornellbrainandspine.org/childrens-brain-tumor-project>). The excitement in the room over the prospect of bringing precision medicine and potential clinical trials to children who otherwise do not have options was palpable. My husband and I did not hesitate to partner on this exciting initiative, and we have been funding a fellowship at the laboratory ever since.

My story is not unique. I am speaking on behalf of the 30,000 parents per year in the United States who have to become experts in the specifics of their child's disease in order to properly advocate for the best treatment options. It simply should not be this way, and I hold tremendous hope knowing that, in time, it will not be.

It may not be a single moment when we notice it, but slowly and surely we are witnessing a changing tide, and gradually approaching that moment in pediatric cancer history when we will all finally agree to use a new adjective—acceptable.

DR. JEFFREY P. GREENFIELD

When I first met Ty in 2010, he was standing up in his hospital bed and his bouncing blonde curls had yet to fall out. He was just starting high-dose chemotherapy for a brain tumor that had already been aggressively resected, and his treatment road map called for radiation following chemotherapy. No additional surgery was likely required, and I assumed I would not see him much. I was very wrong about that.

There are fewer than 200 full-time pediatric neurosurgeons practicing in the United States, and I have come to realize that we all share a very similar passion for "fixing" things. We also share the frustrations and emptiness that inevitably emerges after meeting a patient with an inoperable brain tumor. Knowing that a child harbors a tumor that I cannot "fix" surgically has always been part of what inspires me to stay so invested in growing my scientific efforts; my passion for research in precision oncogenetics is truly inseparable from my surgical efforts. Until we can cure every child, they should remain inseparable as the two halves inform each other.

Ty's parents were always challenging us to present better options. They wanted to have access to the same technology they were reading about, specifically the successes in adult cancer such as melanoma and lung cancer, and they screamed about the unfairness of it all. Pediatrics was not a research priority for precision oncogenomics, and they were right. It was and is completely unfair and unethical.

It does not seem that long ago, but in 2011 we simply did not have the bandwidth to sequence every pediatric brain tumor, and we were just starting to understand what it might mean if we did (the cost of sequencing started to drop in 2008). Sequencing technology for genomes and epigenetic information was becoming more readily available, and the cost of data collection/analysis was decreasing drastically (National Institutes of Health: National Human Genome Research Institute 2016), but it was also becoming clear that the link between data analysis and targeted treatment decisions was anything but a straight and obvious line. I was working at MSKCC, one of the largest providers of pediatric oncology care in the United States, and I was starting my Weill Cornell research laboratory, but we did not have protocols to uniformly acquire, preserve, bank, and study tumor tissue straight from the OR, let alone provide sequencing that could inform targeted therapies.

Ty's treatment protocols were failing him every step of the way. After several VP shunt malfunctions and two relapses that were addressed via additional tumor resections, I had become an integral part of the team treating Ty. Over the course of 2 years, however—and only through the lens that years of reflection can afford—it had become obvious that many of the

treatments we offered to treat Ty ended up hurting him. He suffered infections from being so chronically ill, spontaneous brain hemorrhage from chemotherapy, and radiation necrosis that left him paralyzed from swelling in his brainstem. It was heartbreaking to witness the cost of the “cure.”

If ever there was a need for safer, less-toxic treatment options that work, it is in the sphere of pediatric neuro-oncology. The current protocols in frontline therapy have debilitating effects on the developing child and highlight the need for molecularly targeted treatments with reduced toxicity to help decrease the severity of long-term side effects (Northcott et al. 2017). In fact, >65% of children who survive 5 years or more are reported to have a serious/disabling or life-threatening chronic health condition as a result of treatment (Hudson et al. 2013), and radiation, a vital component of long-term survival for children with malignant brain tumors, is proving to have severe late effects including increased mortality in adulthood as a result of the treatment toxicity (Bandopadhyay et al. 2014).

We have to do better than this, and I strongly believe precision oncogenetics is a large part of the way forward. I have promised myself that I will continue to push my research efforts with the help of my patients, their families, my institutions, and growing national collaborations to the point where the efficacy and accessibility of this technology will be available for every pediatric brain tumor patient.

I knew that we were not yet prepared to deliver potentially lifesaving options to Ty’s family via precision medicine. I knew I was not going to save their son in the end. I also knew that I was going to put actions into motion to accelerate the process and ensure that children like him would gain access to this and other developing technology in the near future.

I partnered with my colleague, Dr. Mark Souweidane, to create the Children’s Brain Tumor Project—a research program that is powered by families—to fund a new laboratory specific to researching rare pediatric brain tumors. It is extremely difficult to secure funding from government agencies (<4% of the National Cancer Institute budget is allocated to research of all childhood cancer; NCI Portfolio 2016), and there is little to no profit for pharmaceutical companies (Scudellari, 2015) to investigate rare pediatric brain tumors. Therefore, our support comes from individuals and parent-founded organizations, like the Campbell’s, who want to advance research into rare and inoperable brain tumors and help to address the unmet needs of each and every child faced with these life-threatening diagnoses. We would not exist without the support of these families and pediatric brain cancer nonprofits who fill the funding gap.

Since 2012 we have moved from borrowed benches in other research labs into our own dedicated pediatric neuro-oncology laboratory. In addition to sequencing of DNA, RNA, and methylation analyses, we are also growing cell lines from patient’s biopsies and creating avatar animals—close replicas of the children’s masses in a mouse model that we can study. We work closely with the Englander Institute for Precision Medicine to sequence every pediatric brain tumor that we see here and perform high-throughput screening to help identify promising drugs that may be effective against an individual patient’s tumor. I want to leverage what I learned from Ty’s experience to help inform my research and make it all widely available to the clinical community so others can learn from our work. We do this by collaborating with any and all open-access sequencing and cloud-based storage platforms and communities to share and disseminate the information widely and immediately.

Thankfully, we are far from alone in these efforts. Collaboration and information sharing among established research institutions—such as Stanford University, the University of San Francisco, and MSKCC—is increasing rapidly with the development of consortiums such as the Pediatric Brain Tumor Consortium, the Pacific Neurooncology Consortium, and, most importantly, the Childhood Brain Tumor Tissue Consortium. Rare tumor samples and viable cell lines are being shared among research institutions for genetic data

sharing, and the development of “big data” resources, such as Cavatica (<http://cavatica.squarespace.com/>), help to map viable agents to target mutations.

“The new clinical trial is really an N of 1, where the only drug that is right is the drug that is right for your tumor, not what is slightly better for a bunch of similarly looking tumors.”

Similar to the TLC Foundation, family foundations such as Christian Rivera Foundation, Chad Tough, the McKenna Claire Foundation, and Solving Kids’ Cancer are making targeted and strategic funding investments that make this progress possible. Without family-founded and community-funded efforts such as these, the needs to advance the research of pediatric brain tumors simply would not be met.

With the growing use of precision oncogenomics across the country, we can learn so much more from an individual patient than we ever have before. Upon sequencing the tumor, we can dig even deeper by looking at specific proteins and building our findings into the clinical framework so we can identify the right drugs for an individual patient that might yield better results. The new clinical trial is really an N of 1, where the only drug that is right is the drug that is right for your tumor, not what is slightly better for a bunch of similarly looking tumors. New findings are also informing basic research projects examining the molecular underpinnings of why these cancers occur, their developmental links, and the growing understanding of the crucial role of the children’s immune system in how we can fight these varied and unusual brain cancers.

Thanks to the advocacy of parents like the Campbells and many other pediatric brain cancer families who have supported research, we are hopeful that the implementation of precision medicine will quickly become a standard of care around the world—rather than the exception.

Competing Interest Statement

The authors have declared no competing interest.

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