A Two-Way Street: Investigating Pediatric Cancers

Among babies with Beckwith-Wiedemann Syndrome, scientist are identifying which genetic changes are more likely to cause cancers.

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When Megan Miller was twenty weeks pregnant, the doctors at Children's Hospital of Philadelphia (CHOP) noticed her baby was unusually large for his gestation age. After further examination, Megan was informed that he likely had a condition known as Beckwith-Wiedemann Syndrome—a diagnosis she had never heard of. Naturally, the expecting mother consulted Google, where she found alarmingly little information. "The only place that had good scientific facts," she recalls, "was CHOP's website."

Thanks to Damon Runyon Clinical Investigator Jennifer M. Kalish, MD, PhD, founding director of the Beckwith- Wiedemann Syndrome Clinic, CHOP was one of the few hospitals in the country where the term "Beckwith-Wiedemann Syndrome" (BWS) was a familiar one in 2015. The nation's leading BWS researcher was in the delivery room just after Finn was born—six weeks early and eight pounds, seven ounces. Genetic testing confirmed the diagnosis Dr. Kalish gave on sight.

Beckwith-Wiedemann Syndrome is a genetic condition that affects roughly one in 10,000 babies and causes overgrowth in certain parts of the body. The affected region on chromosome 11 contains "imprinted genes," meaning the copies inherited from the mother and from the father are normally expressed differently. On chromosome 11, "grow" signals are activated on the father's copy (in the interest of a robust baby) but silenced on the mother's copy (in the interest of a safe delivery). In BWS, the process of imprinting goes awry, and the child ends up with two active copies of the genes that behave like the father's, causing the syndrome's characteristic overgrowth. This misfiring of growth signals also puts patients with BWS at increased risk of developing cancers of the kidney and liver during childhood. Why some cases develop into cancer and others do not, however, remains poorly understood.

When Finn was born, Megan and her husband, Travis, were reassured to learn that their son's genetics put him at comparatively low risk for cancer. Then, just as the pair was getting ready to bring eight-week-old Finn home, the doctors found a tumor on his liver. "I was sitting in the NICU with him, and Dr. Kalish came in late at night," Megan remembers. "And I just knew. But I was so glad it was her, and not a stranger, telling me the news."

A Patient-centered Approach

For Dr. Kalish, the relationship between research and clinical work has always been a two-way street: her patients informing her research questions as much as her discoveries inform their treatment. A geneticist by training, she was originally drawn to study BWS as an imprinting disorder. But another research question soon arose. “When one of my patients developed a tumor, I went to the literature,” she says. “And found nothing about how the syndrome transitions to cancer in some kids.”

Unraveling a biological mystery like this requires a huge amount of data from patients, clinical information as well as blood and tissue samples. In 2014, no such database existed—so Dr. Kalish established the country’s first (and only) active BWS patient registry and biorepository at CHOP. The research was still in its early stages when she met Finn, who had a liver tumor despite what was considered a low-risk genetic profile. After that latenight conversation in the NICU, Dr. Kalish asked Megan if she would be willing to enroll Finn in the growing patient registry. “Obviously I was one hundred percent on board,” Megan says. “I have said from the beginning—anything she needs from Finn or me, we want to do, because it helps everyone.” From then on, anytime Finn had blood drawn or underwent surgery, they sent “a little extra” to the lab.

Coming Together

Over the past six years, thanks to patients like Finn and their families, and Dr. Kalish’s ongoing efforts, BWS research has come a long way. Scientists can identify which genetic changes are more likely to cause kidney cancers and which are more likely to cause liver cancers. Regular screenings are now recommended until the age of seven regardless of genetic profile, a change for which Dr. Kalish personally advocated. And last December, her team unveiled the first human cell-based model of the syndrome, developed using cells from patients in the registry.

Dr. Kalish also organizes a biannual conference at CHOP for patients, families, and providers from around the world to gather and share their insights and experiences with BWS. This year, the conference drew nearly 200 participants from 14 countries.

When asked what has changed since her son was diagnosed, it is the growth of this community that stands out to Megan. “The network is so much bigger now,” she says. “There’s even a Facebook group where people ask questions. We give them Dr. Kalish’s email, and—no joke—she calls them back half an hour later. That never happens. Not even your pediatrician!”

Megan herself remains active in the BWS community, offering support to other families online and in person. She has spoken at the CHOP conference multiple times, and joins Dr. Kalish’s class each year to talk with first-year medical students (to whom Finn passes out packets).

In the meantime, Finn has grown into a sweet and loving six-year-old, the middle of three brothers. This summer, he was eagerly anticipating first grade. “He’s so excited. He loves school. And he’s

playing baseball this year. Right, Finn?" she confirms with Finn, who grins in response. It has been exactly six years since his last day of chemotherapy.

"Our whole lives would be so much different if Dr. Kalish hadn't known to screen him," Megan says, as her voice hitches.

Supported by her Damon Runyon award and buoyed by recent successes, Dr. Kalish's team continues to investigate the links between BWS and childhood cancers. "Once we figure out the pathways that lead to overgrowth and tumorigenesis, we can figure out how to intervene," Dr. Kalish explains. "Then we can do screenings, but also provide a treatment to prevent the transition. That's the ultimate goal."

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