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Childhood cancer, often in the shadow of adult cancers, garners sympathy from all, but drug development from few.

By Laura Beil

Not too long after her 15th birthday, Callie Caylor finished a high school basketball game with the feeling that her heart was gripped in a vise. Eventually, her breathing found its normal cadence, the pain quieted, and the Texas high school freshman was given a diagnosis of asthma.

Life went as usual the next few weeks. Then one morning after a track meet, the chest pain was so excruciating Callie could not lift herself out of bed. She would soon find out that her 120-pound frame carried a tumor in her torso the size of a football.

Doctors at Children's Medical Center Dallas—a little over an hour from her hometown—diagnosed Callie with Ewing's sarcoma, a rare malignancy arising from the bone, which disproportionately affects children and young adults. Treatments melted away her cancer, and for more than a year, Callie returned to a teenager's universe of school, movies with friends, and as always, athletics.

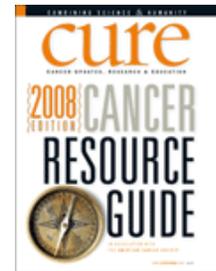
Until the day a scan found a dime-sized spot of tumor in her remaining lung. That is when Callie's parents made a surprising discovery: their daughter's choices for backup treatment came from a shallow pool. In the race to develop better drugs to treat cancer, children have often been left at the starting gate.

The problem, at least in dollar terms, is that most children are healthy. In the health consumer market, big patients simply overpower little ones. In any given year, more than one million adults will learn they have cancer, but less than 13,000 children under age 19 will get the same diagnosis.

To makes things worse, at least for the bottom line, the common cancers—breast, prostate, colon, and lung—occur rarely, if at all, in minors, who tend to suffer leukemias and brain, bone, connective tissue, and nervous system malignancies. For drug companies wanting and needing robust sales, and even taking into account orphan product allowances, children's cancers are often too infrequent to be profitable.

Donna Caylor, Callie's mother, understands the business sense, but asks government decision makers and pharmaceutical executives to consider one other reality. "They need to be in those hospitals and looking at those children," she says.

Not just her daughter. Two-thirds of all medications used in kids—drugs for any condition—have not been tested and labeled for pediatric use, according to data reported last year. (One in five adult prescriptions across conditions is off-label.) But oncology may feel the deepest urgency, since cancer remains the most fatal illness of childhood.



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Progress With Hand-Me-Downs

"It's a real problem getting pharmaceuticals specifically for children," says Jessica Boklan, MD, of Phoenix Children's Hospital. Mostly, they get the hand-medowns. "It's pure economics."

Beyond economics, she says, the logistical and ethical demands of clinical trials have also worked against children. The small number of patients, especially for some of the more deadly cancers, makes it more difficult for researchers to gather enough participants for trials with statistical muscle. Also, ethical guidelines have historically discouraged the testing of experimental medications in children. How does all this play out? One study last year in the *Archives of Internal Medicine* reported that 93 percent of children with cancer receive at least one drug not approved for pediatric use.

Pediatric oncologists have tried to make clinical trials almost a standard part of treatment. Only about 3 percent of adults with cancer are treated through clinical trials, compared with approximately 50 percent of children. And since 2000, the Children's Oncology Group—a network of hospitals that collaborate on pediatric cancer research—has combined children worldwide to conduct studies with greater statistical power.

"Children will never represent a market force," says Greg Reaman, MD, chairman of the Children's Oncology Group. But using drugs without the benefit of formal testing—though it is a practice born of necessity—leaves doctors and families navigating uncertainties. Lacking the prescribing information from clinical trials, physicians are left to calibrate doses and schedules based on the known adult information, the biology of the cancer, and past experience.

"We've been successful, but we've been lucky," says Patrick Leavey, MD, clinical director of the Center for Cancer and Blood Disorders at Children's Medical Center Dallas. Perhaps in a testament to the persistence and teamwork of those who care for children, the Centers for Disease Control and Prevention recently reported that death rates from pediatric cancer fell 1 to 3 percent per year since 1990. Even relying on off-label adult drugs, five-year survival rates for childhood cancers approach 80 percent. Still, that leaves 20 percent of children needing something more.

Despite frustrations, oncologists and patient advocates are heartened by recent signs of a shifting research and legal landscape, driven in part by federal legislation that has tried to make pediatric drug development both attractive and required.

Insurance companies have largely accepted that pediatric oncology might not operate like the adult world, but issues still arise. Four-year-old Aaron Juarez of Avondale, Arizona, developed an allergy to one of the main medications necessary for treating his leukemia. Unfortunately, the new medication his doctors recommended, Erwinia, was only manufactured in Europe. The family's insurance carrier balked.

"The insurance company doesn't even know what Erwinia is," says Aaron's mother, Tamra. As a result, the hospital is absorbing the cost of the drug, and Aaron's leukemia appears to be under control.

Despite frustrations, oncologists and patient advocates are heartened by recent signs of a shifting research and legal landscape, driven in part by federal legislation that has tried to make pediatric drug development both attractive and required. For these and other reasons, more pharmaceutical firms appear to be paying attention to children early in the development process.

In one notable case, the leukemia drug Clolar (clofarabine) came on the market in 2004. Clolar, which treats children whose cancers don't respond to

previous drugs, was the first cancer drug in two decades to reach the pediatric market ahead of adults. "This is a major exception," Dr. Boklan in Phoenix wrote in *Molecular Cancer Therapeutics* in 2006, "as approval of new cancer drugs for pediatric patients is typically an afterthought to their development and approval for treating adult cancers."

The drug's manufacturer, Genzyme Corporation, has long taken interest in uncommon diseases, and children's cancer seemed like a natural extension of company philosophy, says Michael Vasconcelles, MD, Genzyme's vice president of clinical research. Clolar had been tested and carried to the regulatory finish line by the small San Antonio-based firm Ilex Corporation. Genzyme acquired Ilex, along with the drug, just before approval. (Clolar is now in the final stage of testing for leukemia in adults.)

"For Genzyme, this was a usual and customary program to inherit," Dr. Vasconcelles says. "We're used to identifying unmet needs."

Government Steps In

For drug companies that do not have a business strategy built on rare diseases, lawmakers are using persuasion in the way only the government can. The federal Food and Drug Administration first tried in 1998 to require pediatric testing of drugs. The rule was invalidated in 2002 on the grounds that the FDA had overstepped its authority, leading Congress to pass the Pediatric Research Equity Act in 2003. In late 2007, Congress reauthorized the law along with another measure called the Best Pharmaceuticals for Children Act, which rewards drug companies who seek pediatric labeling with a six-month extension of exclusive marketing.

But opinions vary on the degree to which these laws have helped children. In May 2007, the Government Accountability Office reported that between 2002 and 2005, the FDA asked drug companies to study 214 patented drugs for pediatric use. In 173 cases—including 28 cancer drugs—the manufacturers agreed. Some findings have given doctors pause. GAO's Marcia Crosse told Congress that "pediatric drug studies conducted under BPCA have shown that the way that some drugs were being administered to children potentially exposed them to an ineffective therapy, ineffective dosing, overdosing, or previously unknown side effects—including some that affect growth and development." None of the 41 remaining drugs have been tested, even though the FDA asked for some to be examined by the National Institutes of Health. In addition, the GAO reported, "few of the off-patent drugs identified by NIH as in need of study for pediatric use had been studied."

An analysis published in 2007 in *Nature Reviews Drug Discovery*, from Asher Schachter, MD, of Children's Hospital Boston, found that the government rule change in 1998—the early attempt to require pediatric studies—appeared to accelerate the time for pediatric approval from seven years to around four years. However, the flow of new pediatric drugs submitted for approval overall did not significantly increase.

In general, companies have little incentive to study their drugs in children, Dr. Schachter says. With few officially approved alternatives, physicians will use the drugs regardless, prescribing them off label. However, because the drugs are officially considered unapproved in pediatrics, companies "are not culpable because they say on their label 'not for use in children.'"

"Delaying the performance of pediatric clinical trials until a drug's patent is approaching expiration places the risks of off-label prescribing entirely on children," Dr. Schachter wrote in the journal.

He has a simple suggestion: grant an exclusive patent extension only if the pediatric clinical trial data are submitted within one year of approval in adults. "You can't do it seven years later; you have to do it within one year," he says. "I think if that happened, it would have a huge impact."

While some researchers have hesitated to include children in early clinical trials, off-label use, he says, is "to my mind much more experimentation. What you get is everyone coming up with their own dose."

Studying Kids

When it comes to medicine, children are not pintsized adults. Their growing

bodies and immature organs can tolerate some drugs at higher doses than adults, while some drugs reach toxicity at lower thresholds. Or, children might metabolize some chemotherapy treatments too rapidly, leaving them with all the side effects and few of the benefits.

To make clinical trials more efficient to conduct, some experts propose a change in structure that could make vital information easier and faster to obtain with fewer participants. The idea, described early this year in the *Journal of Clinical Oncology*, is known as the “rolling six” design, and it aims to get quicker answers once pediatric testing is under way. (A 2003 report to Congress noted that pediatric phase I safety trials typically don’t get started until two years after adult studies.) The framers of the rolling six idea predict it will be included in study protocols later this year ([see sidebar](#)).

And some initiatives are aimed at streamlining the process even before drugs reach the clinical trial stage. A program based at St. Jude Children’s Research Hospital in Memphis has, since 2004, been sifting through dozens of adult drugs looking for those that hold promise in children. Funded by the National Cancer Institute, the project identifies compounds that attack malignant cells in a way that might apply to childhood cancers. Once the compounds are flagged for testing, researchers begin looking for anti-tumor activity in mice.

“We’ve been doing this for nearly 30 years at St. Jude on a much smaller scale,” says Peter Houghton, PhD, who heads the Pediatric Preclinical Testing Program. He and his colleagues in Memphis and several other sites can examine about a dozen drugs a year. “Our objective is to attempt to identify drugs that should be prioritized for pediatric cancers,” he says. In doing so, the investigators may also gain more insight into the biology of pediatric cancers.

Since the vast majority of oncology drugs are developed for cancers that don’t strike children, the program is a way to find drugs that might be otherwise overlooked in pediatrics. Preclinical testing has already had some positive findings, including favorable signs for an experimental class of compounds called insulin-like growth factor 1, or IGF-1, inhibitors. The hormone IGF-1, a cousin of insulin, is thought to have a role in many types of cancer. But among those that may be acutely dependent on IGF-1 is Ewing’s sarcoma—Callie Caylor’s cancer.

Roche, the maker of one experimental IGF-1 inhibitor, says it plans to include children early in the testing process. Catherine Wheeler, MD, the company’s medical director for science, says in her industry career, “it’s gone from a situation in which it was considered not ethical to be doing investigations in children to more ethical to do investigations first.”

If industry is treading cautiously, it is because pediatrics has a slate of considerations beyond market forces, she says. Babies to teenagers fall under the heading of children, which affects dose and formulations. Also, since the treatment comes at the beginning of a hopefully lengthy life, the distant side effects, including infertility, cardiac problems, and second cancers, are of particular concern.

Nonetheless, Dr. Wheeler says, “there’s clearly an interest on the part of regulators in getting more [drug] development in children.”

Since the effectiveness of IGF-1 inhibitors is still unclear, and the experimental trial is closed for now, Callie’s family decided to try an alternate chemotherapy. Yet before the second round of chemo began, Callie asked her doctors to postpone treatment long enough for her to play in a weekend tennis tournament. The cancer would have to wait. At 17, she simply has too much life to live first.