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NEWSLETTER

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The RACE for Cures

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The Research to Accelerate Cures and Equity for Children (RACE) Act was signed into law in the United States in 2018 with the goal of addressing a frustrating problem in oncology: the paucity of treatments available for pediatric cancer. A recent report by the U.S. Government Accountability Office (GAO) suggests that the RACE Act may be starting to have its desired impact.

According to the National Cancer Institute (NCI), pediatric cancer is the leading cause of death by disease among children from birth to age 14 in the United States. NCI estimates that in 2022 alone, 10,470 new cases of cancer were diagnosed in children, of whom 10 percent would die from the disease. The news isn't all bad; after all, survival rates for pediatric cancers overall have been improving for several decades, the GAO noted in its report. However, survival rates for some pediatric cancers remain stubbornly low, in large measure because clinicians have few treatment options for many of these malignancies. As of December 2022, the GAO points out, there were just 54 drugs approved to treat pediatric cancer.

While cutting-edge new medicines have significantly improved survivorship in adult cancer patients, kids with cancer have not benefited nearly as much from these advances. The RACE Act, which took effect in August 2020, requires drug sponsors that intend to seek approval of a drug or biological product that is intended for treating an adult cancer to submit their planned approach for studying the drug in the pediatric population if the treatment is directed at a molecular target that the U.S. Food and Drug Administration (FDA) determines to be "substantially relevant to the growth or progression of a pediatric cancer."

As we approach three years since RACE took effect, the GAO wanted to know: Is it likely to result in more pediatric cancer drugs reaching

the clinic? Previous attempts to remedy the lack of medications available for childhood cancers have met with mixed success. For example, the Best Pharmaceuticals for Children Act (BPCA) of 2002 offered drug developers incentive to conduct voluntary studies in children by offering an additional six months of marketing exclusivity.

What's more, the Pediatric Research Equity Act (PREA) of 2003 required drug sponsors to consider seeking approval for pediatric indications when developing new drugs with relevance to childhood cancer. An FDA analysis found that BPCA and PREA and BPCA generated new or revised labeling for use in children for 658 drugs between 2007 and 2016. However, under BPCA, FDA has no authority to require pediatric studies. And PREA has a significant loophole, which is that many oncology drugs have orphan drug designation and are exempt from its requirements.

Prior to publication of the GAO report, other investigators had examined whether the RACE was having an impact. A 2022 paper in *Expert Review of Anticancer Therapy* assessed oncology drug approvals within the first year after the RACE Act took effect to evaluate its impact on the development of molecularly targeted oncology drugs for pediatric cancers and found "early evidence… that the RACE Act was effective at closing the loopholes of previous legislation and creating new opportunities for innovation in developing therapies for childhood cancers." In this analysis, researchers looked at drug approval data for 17 oncology drugs approved by the FDA over a one-year period starting on the day RACE went into effect, August 18, 2020. Of 12 drug approval requests that had been submitted prior to that date, none had pediatric requirements. Of the five submitted after that cutoff date, three included requirements for pediatric trials.

In its own analysis, the GAO studied FDA data and found that, since the RACE Act became law in 2020, 32 pediatric studies have been planned for adult cancer drugs. Prior to passage of RACE, none of these studies would have been required. While that's a promising shift, there are some important caveats to that news. For one, a significant number of these applicants have requested partial waivers, which allows the sponsor to exclude certain pediatric populations from the pediatric study. (GAO offered this example: If a drug is intended for patients who have failed all other existing treatment options, then a sponsor can justify requesting a partial waiver for children under one year of age, since they are unlikely to have exhausted available treatment options.)

Moreover, 30 applicants had requested deferrals, until after the adult version of a drug is approved, for example.

To be sure, the GAO noted that it is too soon to know if the RACE Act will increase the number of drugs approved for treating pediatric cancers. Yet, authors of the report interviewed FDA officials and other non-federal stakeholders (pediatric cancer advocacy groups, researchers, industry groups, and drug sponsors), and a majority said they believed that the RACE Act would positively influence pediatric cancer research and drug development. Simply shining a light on the problem, said several, was an important first step.

Research News

Pediatric Cancer Survivors Have 4-Fold Higher Risk of Death Decades After Diagnosis

People who survive pediatric cancer are four times more likely to die than age-matched peers in the general population 15 to 40 years after diagnosis, according to a recent study published in *The Lancet*. In the study, researchers looked at long-term health outcomes for 34,230 patients diagnosed with cancer before age 20 between 1970 and 1999. Cancer types included leukemia, lymphoma, central nervous system tumors, Wilms' tumor, neuroblastoma, and soft tissue or bone sarcoma. With a median follow-up from diagnosis of roughly 29 years, the researchers counted 5,916 deaths, of which about one third (34 percent) were attributed to a recurrence or progression of the original cancer. About half were attributed to new cancers or other health problems, such as cardiovascular disease and other diseases.

Comparing these patients to age-matched peers who didn't have pediatric cancer revealed a four-fold increased risk of death at 15 to 19 years through 40 years post-diagnosis. Pediatric cancer survivors had an increased risk of death from a long list of noncancerous conditions, such as influenza, kidney failure, heart attacks, strokes, and others. However, the *Lancet* study found that healthy behaviors on behalf of the survivors, as well as control of hypertension and diabetes, decreased mortality risk by 20 to 30 percent. The authors proposed that continued reductions in primary cancer therapy and promotion of healthy lifestyles could help extend the lifespans of survivors of pediatric cancer.

Study Identifies Genetic Variation in Therapeutic Response in ALL

Acute lymphoblastic leukemia (ALL) is the most

common childhood cancer. While the cure rate for childhood ALL exceeds 90 percent, more children die of this cancer than most solid tumors. Previous research indicated that both somatically acquired genomic alterations and inherited genetic variations are important determinants of not only susceptibility to ALL, but also to drug response and toxicities of ALL therapy. The current approach to risk stratification in pediatric ALL combines clinical features, leukemia somatic genomic aberrations, and early treatment response, as measured by minimal residual disease (MRD). However, because the pharmacological basis of inter-patient variability in MRD is not well understood and the relationships between somatic genomics and drug resistance is not clear, pediatric ALL patients generally receive uniform treatment with similar chemotherapy regimens.

A study published earlier this year in *Nature Medicine* could provide a "blueprint" for individualizing therapy in pediatric ALL patients. A team from St. Jude Research Hospital, in Memphis, Tennessee, analyzed primary leukemia cells from 805 newly diagnosed pediatric ALL patients to determine their sensitivity to 18 therapeutic agents. Samples included 23 molecular subtypes defined by leukemia genomics.

The analysis found wide variability in drug response. Favorable ALL subtypes showed the greatest sensitivity to L-asparaginase and glucocorticoids, which was highly associated with MRD, though only in B cell ALL. The analysis also identified six patient clusters associated with event-free survival based on ALL pharmacotypes, even after adjusting for MRD. Pharmacotyping identified a T cell ALL subset with a poor prognosis that was sensitive to targeted agents, suggesting that this patient population would benefit from alternative therapeutic approaches. Overall, the authors suggest that their findings could be used for more precise identification of therapies in pediatric ALL.

Exposure to CT Scans is Safe for Kids, But Only in Moderation

High doses of radiation therapy are a known risk factor for certain cancers, particularly leukemia. Children are more susceptible than adults to radiation-induced harm, but little is known about the risk of cancer after exposure to radiation during computed tomography (CT) among children at different ages. To learn more, a team from Taipei Medical University, Taipei, Taiwan, examined the risk of intracranial tumors, leukemia, and lymphoma among children and young adults under age 25 after radiation exposure from CT at or prior to age 18.

Using data from Taiwan's publicly funded healthcare system, the investigators identified 7807

cases of patients under 25 who were newly diagnosed with the cancers of interest. Data regarding CT scans received at or before the age of 18 and three or more years before the date of cancer diagnosis were compiled. The researchers assigned 10 control subjects who didn't have cancer for every cancer patient.

This study, published in *CMAJ* in April, found that a single exposure to CT did not increase the risk of intracranial tumors, leukemia, or lymphoma. However, exposure to four or more CT scans was associated with a 2.3-fold increased risk of one of the cancers of interest compared to controls. Notably, patients who received four or more CT scans at or before age six had the highest associated risk. The study authors note that their findings underscore the importance of following protective procedures for radiation exposure and avoiding unnecessary CT scans.

Novel Drug Combination May Benefit Pediatric Patients With Solid Tumors

Efforts to encourage drug developers to explore whether therapies approved for adults with cancer might benefit pediatric patients were discussed in the main story of this newsletter ("RACE for Cures," p. 2). The results of one such investigation were presented recently at the American Association of Cancer Research's Annual Meeting 2023, which was held in mid-April.

In the phase 1 portion of a phase 1/phase 2 trial, investigators from the University of Birmingham, in the United Kingdom, enrolled 18 pediatric and young adult patients who had relapsed or treatment-refractory solid tumors that were identified as having mutations associated with homologous recombination (HR), which can sensitize cells to PARP inhibitors. These patients were treated with a median of 3.5 28-day cycles of the PARP inhibitor olaparib (Lynparza), which is approved for several adult indications, and the experimental drug ceralasertib (on days one to 14).

At the AACR meeting, investigators reported that one patient with pineoblastoma experienced a confirmed partial response and received 11 cycles of treatment. Another patient with neuroblastoma experienced stable disease for nine cycles, then converted to a partial response. The response was confirmed after cycle 11, and the patient was still undergoing treatment in cycle 12 at the time of the presentation. Two other patients (cycles 8 and 15) also remained on treatment. The critical next step for this team is to use sequencing data to evaluate biomarkers to determine if there exist "molecular constellations" of response to the combination of olaparib and ceralasertib.

Patient Advocacy

The National Children's Cancer Society

The National Children's Cancer Society (NCCS) is a nonprofit organization that provides emotional, financial, and educational support to children with cancer, their families, and survivors of childhood cancer. The organization traces its roots to 1987, when bone marrow transplants became recognized as a viable treatment for cancers of the blood and bone marrow. However, most insurers considered the procedure experimental and refused to pay their costs. "It was for this reason the NCCS was started," states the organization's website, "because every child with cancer deserves every chance to live."

NCCS offers a variety of services to families and guardians of children with cancer. Key among them for many families is financial assistance, in the form of a transportation assistance fund, which helps pay for travel to receive treatment; and an emergency assistance fund, which can help offset expenses associated with cancer treatment. (Patients and their families must meet certain eligibility criteria to receive financial assistance.)

NCCS also provides another invaluable form of assistance through its support programs. Their Family Support Program offers trained case managers who provide practical and emotional support to parents and caregivers, who not only receive a shoulder to lean on, but also learn how best to advocate for their child. And patients themselves can receive much-needed emotional support through NCCS's Mentorship Program, which pairs patients aged 10 to 17 with recipients of NCCS college scholarships, who can offer a sympathetic ear and encouragement. (NCCS has awarded more than $2 million in college scholarships to 227 childhood cancer survivors.)

To help parents and caregivers understand and best manage a child's cancer, NCCS also offers a wealth of educational materials, including *The Other Side of the Mountain: A Parent's Guide to Surviving Childhood Cancer,* which addresses every aspect of a child's journey, from coping with difficult emotions to dealing with health insurance companies. NCCS also offers a Late Effects After Treatment Tool, which can help patients prepare for side effects that can emerge months and even years after treatment.