SPOTLIGHT ON THE GLOBAL LANDSCAPE OF PEDIATRIC CANCERS

AACR PEDIATRIC CANCER PROGRESS REPORT 2025

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About the American Association for Cancer Research®

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 58,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 141 countries and territories around the world. Presently, 34% of members live outside the United States and 20% of AACR's international members are located in countries building cancer research capacity. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting. The AACR publishes 10 prestigious, peer-reviewed scientific journals. Other AACR publications include *Cancer Today*, a magazine for cancer patients and caregivers; the annual *AACR Cancer Progress Report*; *AACR Cancer Disparities Progress Report*; *AACR Pediatric Cancer Progress Report; AACR Annual Impact Report*; *Leading Discoveries*, the AACR's awareness and donor magazine; and the blog, *Cancer Research Catalyst*. In addition, the AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit **AACR.org.**

A MESSAGE FROM THE AACR

We are witnessing a transformative era in cancer science and medicine. In the United States, overall cancer mortality has been declining consistently since the early 1990s, thanks to decades of sustained federal investment in scientific innovation and collaborations. Significant progress has also been made against pediatric cancers, with 5-year relative survival rate for all pediatric cancers combined now exceeding 85 percent.

The American Association for Cancer Research (AACR) has a longstanding and unwavering commitment to advancing pediatric cancer research. The inaugural *AACR Pediatric Cancer Progress Report 2025* represents a historic milestone as the first-of-its-kind report that is dedicated to educating the public, Congress, and the scientific community about the research-driven breakthroughs against pediatric cancers and the barriers to further progress that remain. We trust that this report will catalyze increased federal and private investments in pediatric cancer research, ensuring that children and adolescents benefit from the same advances transforming adult oncology.

Cancer is a devastating diagnosis for anyone, but it is especially tragic when cancer affects a child or an adolescent, as it endangers the prospect of a full life and deeply impacts patients and their families. Pediatric cancers are rare compared to adult cancers and biologically distinct in their cellular origins, genomic drivers, tumor types, and therapeutic vulnerabilities. Although highly effective therapies have been developed for certain pediatric cancers, treatments for many others have not fundamentally changed in more than four decades. Continued reliance on cytotoxic chemotherapy, surgery, and radiotherapy to treat pediatric cancers means that childhood and adolescent cancer survivors often face lifelong challenges, including risks of second primary cancers, chronic health conditions, and profound psychosocial and financial hardships that can shorten life expectancy and diminish quality of life. Many children and adolescents in high-income countries have access to cutting-edge medicine, but most pediatric patients in low-income and lower middle-income countries lack even the basic diagnostic and therapeutic resources. This report emphasizes the need for strengthening cross-sector collaborations, both nationally and internationally, that are proving to be the most effective approach in accelerating the pace of progress against pediatric cancers and addressing global inequities in pediatric cancer care.

Encouragingly, groundbreaking scientific and clinical advances are beginning to reshape the landscape of pediatric oncology. Comprehensive molecular profiling is enabling precise diagnoses, guiding risk-adapted therapy, and revealing inherited susceptibilities that can inform lifelong surveillance and care. In some high-income countries, such as Germany and Australia, the success of national molecular profiling programs has led governments of these countries to cover the cost of these tests for all newly diagnosed patients. Large-scale studies have revealed that 10–18 percent of pediatric patients develop cancer due to inherited genetic predisposition, underscoring the importance of early detection, surveillance, and genetic counseling. In parallel, cutting-edge technologies—such as liquid biopsies, functional genomics, and patient-derived model systems—are expanding our understanding of disease mechanisms and accelerating the development of safer and more effective therapies.

As highlighted in this report, several new therapies for pediatric cancers have been approved recently by the US Food and Drug Administration, leading to improved outcomes for certain cancer types. Many of these new treatments belong to the latest pillars of cancer medicine—molecularly targeted therapy and immunotherapy. Notable examples include the CAR T-cell therapy tisagenlecleucel and the bispecific T-cell engager blinatumomab for acute lymphoblastic leukemia, the monoclonal antibody dinutuximab for high-risk neuroblastoma, and the first menin-targeted therapy revumenib for leukemia carrying certain biomarkers. These therapeutics are offering hope to pediatric patients with cancer—some of whom are featured in this report—and helping save and extend lives, thus exemplifying the enormous return on investment from federal support for medical research. Therefore, it is concerning that pediatric cancer research currently represents only less than 5 percent of the National Cancer Institute's annual budget. A significant increase in federal investment is urgently needed to fuel new discoveries, develop effective drugs, improve survivorship care, and reduce the lifelong health and economic burden experienced by pediatric cancer survivors.

Despite major advances, many pediatric cancer patients, particularly those diagnosed with osteosarcoma, metastatic Ewing sarcoma, alveolar rhabdomyosarcoma, high-grade glioma, or acute myeloid leukemias, have experienced minimal to no improvements in treatment or outcomes. Progress against these rarer forms of pediatric cancer is constrained by the scarcity of experimental models and the lack of incentives to develop drugs for small patient populations. Eliminating these barriers and addressing the unmet needs in treating rarer forms of pediatric cancer require partnerships among government

agencies, academic institutes, biopharmaceutical companies, and professional organizations. These partnerships are also vital to increasing investments in basic and translational research, developing innovative model systems, implementing novel clinical trial designs, and accelerating drug development for rare and ultrarare pediatric cancers.

For many years, AACR has championed efforts to advance pediatric cancer research. Our organization has funded pediatric cancer research since 1999, driving innovations in diagnostics and therapeutics and fostering scientific careers. In 2011, AACR established the AACR Pediatric Cancer Working Group, which has become a focal point for the scientific community to identify research and policy priorities. The AACR Special Conferences on Pediatric Cancer Research, now in their third iteration, have emerged as a premier platform to disseminate the latest advances in the field. The AACR Childhood Cancer Predisposition Workshops, the most recent of which was held in 2023, have spearheaded the development of new evidence-based standards of clinical care for children and adolescents with cancer predisposition syndromes. Recognizing the importance of collaborative data-sharing to accelerating progress, the global pediatric cancer community is increasingly utilizing federated databases that allow analyses across institutions—an approach that can expand drug discovery and development. In this regard, the AACR Project GENIE®, whose consortium members include major children's hospitals and cancer centers, houses clinico-genomic data from nearly 10,000 pediatric patients and growing; these datasets are publicly available to researchers globally to accelerate the pace of discovery and precision oncology.

AACR is deeply committed to working with academic institutes, biopharmaceutical partners, policymakers, patient advocates, and all other stakeholders in the medical research community to catalyze the next generation of breakthroughs in pediatric cancer prevention, diagnosis, treatment, and survivorship. By increasing public and private partnerships and investments, expanding global collaborations, and ensuring equitable access to clinical trials and innovative therapies, we can transform the future for children and adolescents with cancer. The inaugural *AACR Pediatric Cancer Progress Report 2025* stands as both a celebration of scientific progress and an urgent call to action. With bold vision, unwavering dedication, and sustained support, together we can turn today's challenges into tomorrow's cures and bring new hope to children and adolescents affected by cancer.

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EXECUTIVE SUMMARY

Remarkable progress against pediatric cancers is driven by discoveries across the basic, translational, clinical, and population sciences. Fueled by technological innovations, knowledge gleaned from these discoveries is improving diagnosis and surveillance, enabling personalized treatments, and reducing long-term treatment-related harm. As the world's first and largest professional organization dedicated to preventing and curing all cancers, the American Association for Cancer Research (AACR) is committed to increasing public understanding of pediatric cancers, advocating for research funding, and supporting policies that accelerate the development and accessibility of effective treatments for our young patients.

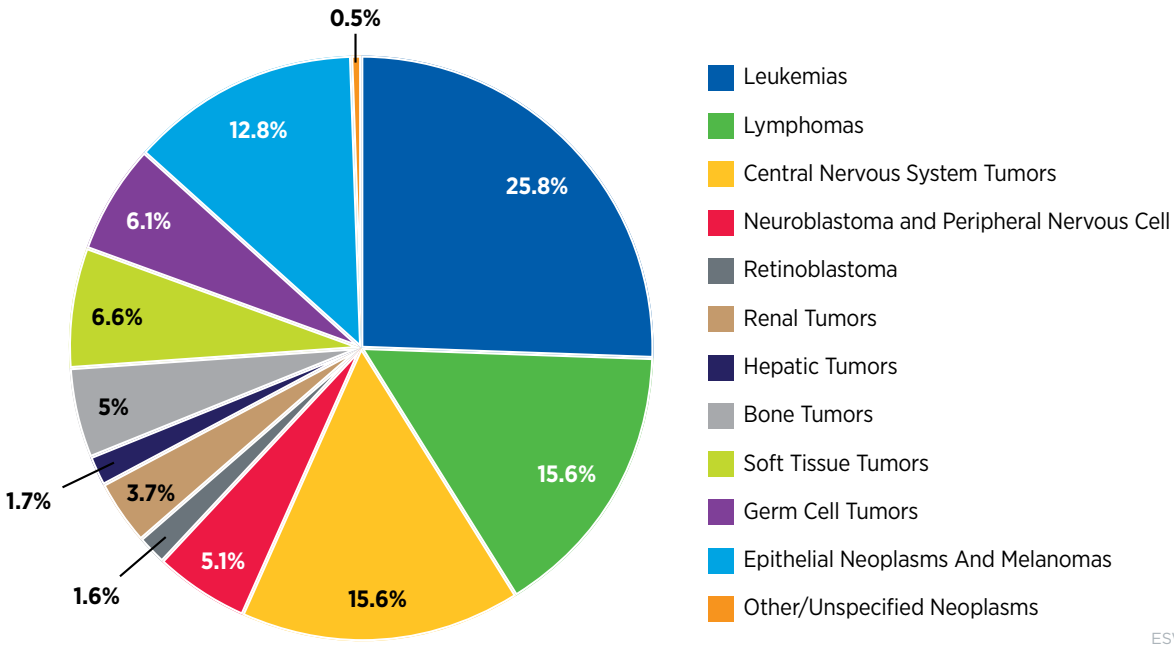
The inaugural *AACR Pediatric Cancer Progress Report 2025* highlights how research is transforming outcomes for children and adolescents, from molecularly targeted therapies and immunotherapies to genomic profiling that informs surveillance and treatment decisions. This first-of-its-kind report also underscores the gaps in our knowledge of pediatric cancers that are rare compared to most adult cancers, and are often understudied, and emphasizes the urgent need for increased federal investments, international collaborations, and innovative approaches to address these challenges.

Pediatric Cancer Trends in the United States

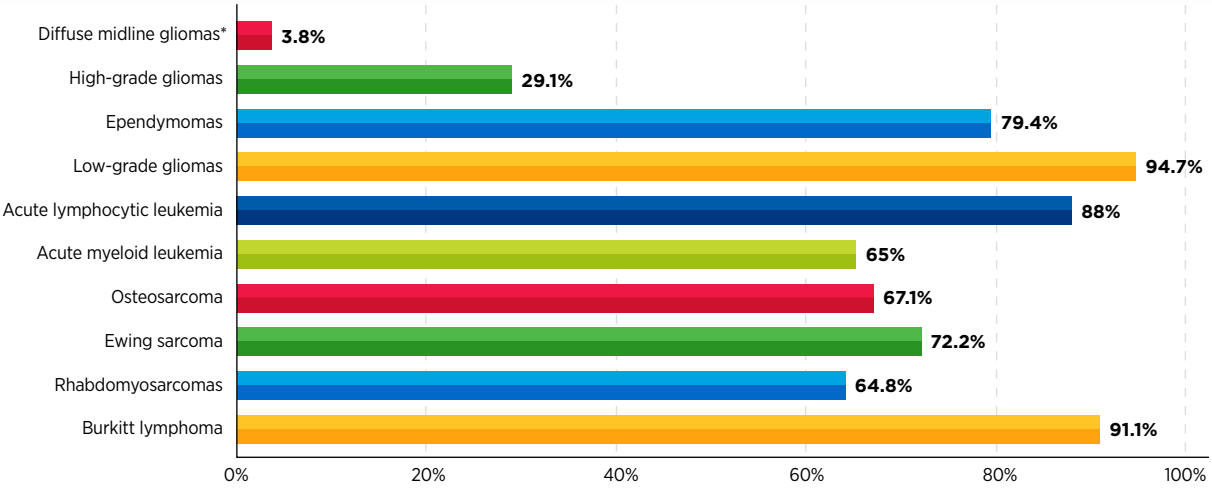
Decades of research and collaborations have transformed the outlook for cancers affecting children (ages 0 to 14) and adolescents (ages 15 to 19), collectively referred to as the pediatric cancers in this report. In the United States, the overall 5-year survival rate for pediatric cancers has risen from 63 percent in the mid-1970s to 87 percent in 2015–2021, although progress has slowed since 2000. Pediatric cancer mortality declined by 57 percent between 1970 and 2000 and by a further 19 percent from 2001 to 2023, reflecting continued progress driven by advances in risk-stratified therapy, precision medicine, and supportive care. Much of this progress stems from collaborative, multidisciplinary, international research initiatives supported by public and philanthropic funding sources.

Pediatric cancers are rare. In 2025, nearly 15,000 children and adolescents will be diagnosed with cancer in the United States. Commonly diagnosed cancers among children include leukemias, brain and central nervous system (CNS) tumors, and lymphomas, and those among adolescents include

Distribution of Pediatric Cancers in the United States



5-year Overall Survival at a Glance for Selected Pediatric Cancers: (2000–2022)



* 4-year overall survival.

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lymphomas, thyroid cancer, and germ cell tumors. Although survival exceeds 90 percent for some cancers, such as Hodgkin lymphoma, thyroid carcinoma, and retinoblastoma, others, including high-grade gliomas and certain sarcomas, remain among the deadliest, with survival rates below 20 percent. The uneven pace of progress underscores the need for new research models and greater investments in drug discovery and development to improve outcomes for patients affected by aggressive and rarer subtypes of pediatric cancers.

The rarity of pediatric cancers has catalyzed broad national and international collaborations and partnerships. National initiatives, such as Project:EveryChild of the Children's Oncology Group (COG) and Molecular Characterization Initiative (MCI) of the National Cancer Institute (NCI), are collecting comprehensive biospecimen and genomic data for common and rarer pediatric cancers. International partnerships like Cancer Grand Challenges and the COllaborative Network for NEuro-oncology Clinical Trials (CONNECT) are combining data and clinical expertise to develop novel therapeutics and expand access to innovative clinical trials. These collective efforts aim to ensure that all children and adolescents with cancer benefit from emerging therapies and precision medicine approaches.

Significant disparities in incidence and outcomes of pediatric cancers persist across racial, ethnic, geographic, and socioeconomic groups. For example, Hispanic children have the highest cancer incidence rates in the United States, while non-Hispanic Black children experience the lowest survival, with nearly a 30 percent higher likelihood of dying from select pediatric cancers than non-Hispanic Whites. Children and adolescents living in rural or economically disadvantaged areas also face higher mortality, often due to limited access to specialized centers, clinical trials, and supportive services.

The economic toll of pediatric cancers is substantial. The average cost of cancer care per child, including hospitalization and lost wages for parents, can approach $833,000 over the course of treatment and survivorship. Projections show that the cumulative cost of pediatric cancer care between 2020 and 2050 will exceed $594 billion globally, however, strategic investments can yield up to $2.6 trillion in lifetime productivity gains—a four-fold return on investment.

NCI allocated greater than $5 billion to pediatric cancer research between 2015 and 2024. Unfortunately, private-sector investments, which are pivotal to developing drugs and conducting clinical trials required for regulatory approvals, have lagged for pediatric cancers, making sustained federal and philanthropic support critical to continued progress. Philanthropic organizations focused on pediatric cancers have provided significant funding for basic research and clinical trials, bridging critical gaps left by the industry. Despite the public and philanthropic investments, the annual support for pediatric cancer research falls short. Sustaining the momentum of progress against pediatric cancers requires strengthening partnerships among federal agencies, industry, and philanthropic organizations so that every pediatric patient with cancer has the chance to survive and thrive.

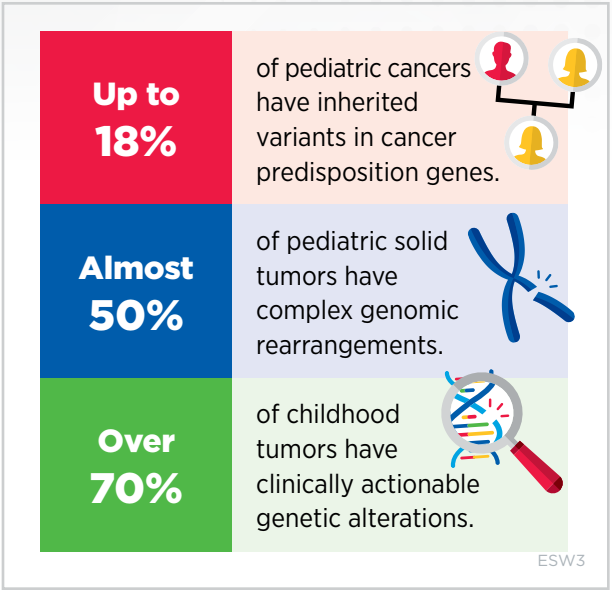
Unraveling the Genomics and Biology of Pediatric Cancers

Pediatric cancers are biologically distinct from adult cancers. Many of these cancers arise early in development and are driven by normal growth pathways in immature cells that can normally become multiple tissue types, but are hijacked by tumor cells to fuel uncontrolled growth. Large-scale DNA sequencing studies have shown that pediatric cancers are typically driven by specific genetic, epigenetic, or structural changes that influence how cells grow, mature, and communicate, leading to the disruption of normal developmental programs.

Advanced technologies, such as whole-genome and whole-exome sequencing, large-scale analyses of chemical changes in genes, and RNA sequencing, are offering insights into the molecular and cellular underpinnings of pediatric cancers. These approaches have revealed that both small mutations and large structural variants, such as gene fusions, chromosomal rearrangements, and amplifications, play critical roles in pediatric cancer development. While some gene fusions, for example those of *NTRK* and *ABL* genes, have become targets for precision therapies, many others are less well characterized or remain undruggable. Integrating tumor and germline sequencing has further revealed that over 70 percent of childhood tumors harbor clinically actionable alterations that can be used to make medical decisions, and up to 18 percent carry inherited mutations that predispose them to cancer. This knowledge has provided essential insights for improving diagnosis, guiding treatment, and identifying high-risk patients who may benefit from genetic counseling and surveillance.

Epigenetic alterations are another common driver of pediatric cancers, affecting how genes are switched on or off without changing the DNA sequence. Disruption of the proteins that regulate epigenetic changes can cause cells to lose identity and normal functions. A comprehensive understanding of the epigenetic landscape of normal and cancer cells is increasingly aiding tumor classification, diagnosis, and disease monitoring. As one example, profiling methylation, a common epigenetic alteration, has transformed tumor classification of brain tumors like medulloblastoma and glioma. Researchers are also exploring new therapeutics targeting epigenetic regulators to improve outcomes for pediatric patients with cancer.

The tumor microenvironment (TME)—the ecosystem of cancer cells and supportive non-cancer cells, blood vessels, signaling molecules, and structural components surrounding a tumor—plays a pivotal role in how pediatric cancers progress and respond to therapy. The pediatric TME differs markedly from that of adults and is shaped by the developmental stage, with unique interactions between the immune system and cancer cells. Advanced technologies that enable understanding of cancer cells at the individual level and within the context of their surroundings have shown how chemotherapy and radiotherapy modify the TME, sometimes creating resistance to subsequent immunotherapy. These insights are guiding strategies to reprogram TMEs and effectively treat cancers in pediatric patients.



Technological innovations are fueling progress against pediatric cancers. Single-cell and multi-omic profiling is mapping the diversity of cells within tumors, while CRISPR gene editing is enabling functional testing of genetic drivers of the disease. Artificial intelligence (AI) is accelerating the integration of genomic and imaging data to identify molecular subtypes of tumors and predict outcomes precisely.

Collaborations and data-sharing have become a cornerstone of progress in pediatric cancer research. Large-scale initiatives such as MCI, the Childhood Cancer Data Initiative (CCDI), and the Human Tumor Atlas Network (HTAN), are connecting genomic, clinical, and imaging data to accelerate discovery and guide precision medicine. These efforts are already improving diagnosis and therapy selection for thousands of pediatric patients. Global initiatives, such as the Cancer Grand Challenges, are bringing large-scale data analyses and clinical expertise together to unravel the mechanisms that drive pediatric cancers and develop innovative targeted treatments.

Pediatric Cancer Predisposition and Surveillance

Roughly 10 percent to 18 percent pediatric cancers arises from inherited genetic alterations that confer a predisposition to cancer. Advances in genomics have transformed how a child or adolescent with a cancer predisposition syndrome

(CPS) is diagnosed, enabling clinicians to identify risk of cancer development long before symptoms appear. Surveillance—the structured, ongoing monitoring through physical exams, imaging, or molecular tests—has become a cornerstone of pediatric cancer precision medicine, leading to the early detection of cancers in children with CPS, as well as monitoring children with CPS who have already been diagnosed with cancer for relapse or the development of second primary cancers.

Traditionally, clinicians have suspected a CPS when a child exhibits recognizable physical attributes, a strong family history, or a suggestive cancer pattern. Classic signs, such as light to dark brown flat birthmarks in neurofibromatosis type 1 or white pupils in heritable retinoblastoma, continue to guide early testing and surveillance, especially in health care settings where universal genetic screening is not available. However, many children with CPS lack outward features or family history, resulting in delayed diagnosis and missed opportunities for early intervention.

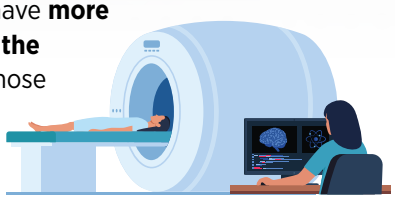
Modern approaches, such as single-gene tests, multigene panels, and whole-genome and whole-exome sequencing, can pinpoint inherited mutations responsible for CPS, for example those in the *TP53* gene in Li–Fraumeni syndrome. Although test results from these approaches are usually available within days or weeks, limited infrastructure, high costs, and shortages of trained professionals restrict access, especially for families in rural areas or low-resource settings. Psychosocial and ethical concerns, from anxiety and misunderstanding of results to questions about consent, further complicate uptake of genetic testing. Despite these challenges, integrating genetic testing into pediatric oncology has proven transformative. Identifying inherited genetic variants associated with cancers allows clinicians to implement syndrome-specific monitoring strategies, such as periodic whole-body magnetic resonance imaging (MRI) for children carrying *TP53* gene variants. Combined clinical and genetic assessments remain the most effective pathway for early and accurate risk detection in pediatric patients.

Genetic counseling is central to bridging scientific advances with coordinated care. Counselors guide families through testing decisions, explain results, and plan follow-up surveillance. They also help parents weigh the benefits and limitations of genetic testing, address ethical implications, and help manage a stressful situation for the patients and their families. Structured counseling paired with surveillance can substantially improve survival.

Dedicated cancer predisposition clinics, often a part of major cancer centers, provide multidisciplinary support to affected children and their parents. However, shortages of trained counselors and fragmented reimbursement continue to limit widespread availability of genetic counseling. Workforce expansion and licensure reform, among other interventions, can help mitigate these challenges.

Children with Li–Fraumeni syndrome who undergo whole-body and brain MRI monitoring have **more than double the survival** of those without surveillance.

Source: (5).



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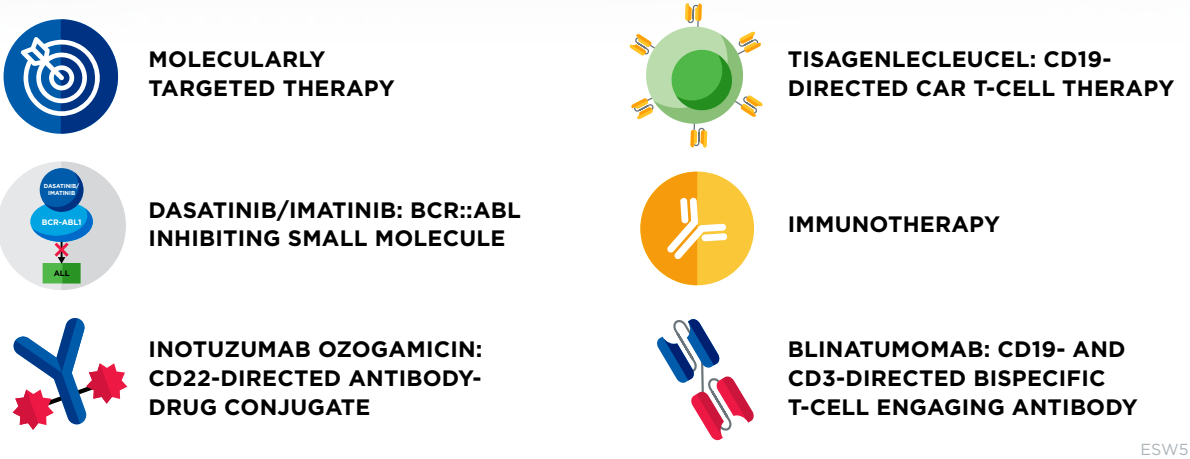
Standardized surveillance guidelines, historically available only for a few CPSs, are now available for many CPSs. In 2023, the American Association for Cancer Research Pediatric Cancer Working Group updated its landmark 2017 consensus surveillance guidelines, emphasizing radiation-sparing imaging—MRI and ultrasound—and recommending that surveillance for many CPSs begin at or soon after birth. The next frontier is the genomic newborn screening to identify infants at risk before disease develops. Modeling studies suggest that sequencing for a small set of cancer risk genes could reduce childhood cancer mortality by nearly half. While promising, these efforts raise complex issues surrounding consent, privacy, and security of children's health-related data. Experts are also concerned about findings of unknown significance that can cause unnecessary anxiety for the parents and/or medical procedures for the child.

New technologies are redefining early detection of cancers in children. Liquid biopsy—a minimally invasive technique that detects tumor DNA or cells in blood or cerebrospinal fluid—has been shown to detect cancer months before standard imaging in children with Li–Fraumeni syndrome. Multi-cancer early detection assays, an area of current intense research, could eventually enable broad, noninvasive screening across tumor types. Machine learning models that are trained using medical images or molecular data are showing promise in detecting patterns that can escape human observation. Smartphone-based applications, for example those capable of recognizing white pupils, a predictor of retinoblastoma, in family photographs offer a low-cost approach that is particularly useful in resource-limited settings. Similarly, other AI-driven tools, such as the McGill Interactive Pediatric OncoGenetic Guidelines application, are helping standardize evaluation for CPSs. Technological advances in imaging are improving safety and precision. As one example, standardized abdominal ultrasounds every 3 months during early childhood in children on the Beckwith–Wiedemann spectrum detect over 95 percent of Wilms tumors before metastasis, allowing organ-sparing surgery. Innovations, such as contrast-enhanced ultrasound, further enhance image resolution while minimizing radiation exposure.

Precision Medicine Driving Progress Against Pediatric ALL



Innovations in genomics, imaging, and artificial intelligence, together with equitable access and ethical oversight, can move pediatric oncology closer to a future in which cancer risk is detected early, monitored safely, and managed effectively, giving every child the best possible opportunity for surviving a cancer diagnosis and living a high-quality life.

Progress in Pediatric Cancer Treatment

Treatments for pediatric cancers have undergone a remarkable transformation over the past several decades, with 5-year survival from all cancers combined now exceeding 85 percent in the United States. These gains stem from advances in surgery, chemotherapy, and radiotherapy, coupled with a deeper understanding of cancer biology and the immune system that has enabled more personalized, less toxic therapies. Increasingly, clinicians are tailoring treatment intensity based on the molecular profile of a child's cancer, reducing therapy for children with a favorable disease profile and intensifying therapy for those at a higher risk of recurrence.

Innovations in chemotherapy, a cornerstone of pediatric oncology, have shifted toward safer regimens to reduce toxicities associated with the treatment. Precision radiotherapy approaches are helping to minimize damage to developing organs. Clinical trials in patients with Wilms tumors, Hodgkin lymphoma, and hepatoblastoma have demonstrated that omitting radiotherapy altogether, reducing the radiation dose, or minimizing chemotherapy can still successfully treat some children with these cancers while sparing them the severe long-term side effects of these treatments, without compromising survival or health-related quality of life. Similarly, advances in surgery, particularly minimally invasive techniques, are improving recovery and reducing complications for certain patients.

Precision medicine has been transformative for the treatment of certain pediatric cancers. Molecular profiling now routinely informs diagnosis, prognosis, and treatment selection for certain patients. For example, molecular testing in acute lymphoblastic leukemia (ALL), the most common childhood cancer, helps determine the level of risk based on genetic features, such as the presence of gene fusions *ETV6::RUNX1* or *BCR::ABL1*, thus allowing clinicians to tailor therapy for maximal benefit. Similarly, the molecular classification of medulloblastoma, the most common malignant brain tumor in children, and neuroblastoma, the most common solid tumor outside the brain, guides tailored treatments. National initiatives, such as MCI and international efforts like, Zero Childhood Cancer, MAPPYACTS, and AcSé-ESMART are expanding access to genomic testing to ensure that children and adolescents with cancer can benefit from precision medicine.

Molecularly targeted therapies are allowing successful treatments of some cancers that were once deemed intractable. Recent FDA approvals for childhood cancers, including revumenib for leukemia harboring *KMT2A* alterations; tovorafenib for low-grade glioma with *BRAF* alterations; and the first systemic therapy dordaviprone for H3K27M-mutated diffuse midline glioma, a fatal brain tumor, highlight how cancer genetics is driving clinical breakthroughs. Additional approvals, such as selumetinib and mirdametinib for neurofibromatosis type 1 and belzutifan for rare endocrine tumors, have increased treatment options for those with inherited CPSs. However, the pace of molecularly targeted drug development for childhood cancers lags far behind that for adult cancers, with very few new therapeutics specifically developed for and tested in pediatric patients.

Immunotherapy, which invokes a patient's own immune system to eliminate cancer and represents one of the most exciting approaches to cancer treatment, has added a powerful new dimension to pediatric cancer treatment. CAR T-cell therapy has revolutionized care for children with relapsed or refractory ALL, offering long-term remission. Other immunotherapeutics, including dinutuximab for neuroblastoma, rituximab for non-Hodgkin lymphoma, and blinatumomab for ALL, have become standard of treatment, reducing the need for more toxic regimens. However, one class of immunotherapeutics known as immune checkpoint inhibitors, which have transformed the treatment of many adult cancers, have not been successful thus far in pediatric cancers.

Treatment of pediatric cancers faces major challenges that are attributable to multilevel barriers. Current approaches are insufficient to develop effective drugs against fusion proteins or epigenetic alterations that drive many pediatric cancers. Low incidence rates of pediatric cancers and financial disincentives for the private sector limit patient recruitment for clinical trials, slowing discovery and regulatory approval. Racial and socioeconomic disparities persist, with Black and Hispanic children less likely to enroll in clinical trials and more likely to experience treatment-related complications. Evidence shows that expanding global clinical trial networks is critical to ensuring that progress against pediatric cancer benefits all children.

Although challenges remain, new technologies are poised to accelerate progress in pediatric cancer treatment. Innovative drugs, such as proteolysis-targeting chimeras, theranostics, and bispecific antibodies, are expanding treatment options by targeting historically intractable proteins that drive pediatric cancers. Liquid biopsy is showing promise for monitoring treatment response and detecting relapse in real time, especially in brain cancers and solid tumors for which the standard biopsy is highly invasive and carries significant risks. Artificial intelligence is accelerating diagnosis and trial design by analyzing imaging and molecular data to predict responses and simulate trial outcomes. Further, novel approaches in cellular engineering are rapidly extending the success of CAR T-cell therapies to additional subtypes of ALL, acute myeloid leukemia, and solid tumors, such as neuroblastoma and aggressive brain cancers.

Supporting Survivors of Pediatric Cancers

As of 2022, more than 521,000 pediatric cancer survivors were living in the United States, a number projected to exceed 580,000 by 2040. Yet, for many, survivorship is a lifelong journey shaped by the enduring physical, emotional, and financial consequences of cancer and its treatment. As more young people survive cancer, the focus of pediatric oncology has expanded to include promoting long-term health, improving quality of life, and delivering comprehensive survivorship care.

60% to more than 90% of pediatric cancer survivors develop one or more chronic health conditions in adulthood as a result of cancer or its treatments. **By age 50, these survivors experience an average of 17 chronic conditions, nearly double that of their peers without a history of cancer.**

ESW6

Pediatric cancer survivors are at higher risk for developing long-term health problems, known as late effects, that arise from cancer or from its treatments. These late effects may affect multiple organ systems and include heart disease, hormonal and growth disorders, infertility, hearing loss, neurocognitive impairment, and second primary cancers. Many survivors also experience accelerated aging—the premature onset of chronic, age-related diseases—driven by treatment-related DNA damage and inflammation.

Over the past several decades, reduced exposure to radiation and decreased use of anthracyclines (a class of chemotherapeutic drugs) has substantially decreased the risk of heart disease, hormonal and growth disorders, and second primary cancers among pediatric patients. The development of protective agents, such as dexrazoxane to prevent heart damage and sodium thiosulfate to reduce hearing loss, has further minimized chemotherapy-related toxicity. Moreover, advances in precision medicine are enabling tailored treatments based on molecular and genetic factors, thus improving outcomes and minimizing harm for certain patients.

Genetic predisposition plays an important role in determining which pediatric cancer survivors are most susceptible to late effects. Studies have identified inherited gene variants associated with DNA repair and cancer predisposition—for example, those of *TP53, RB1, BRCA2,* and *FANCM* genes—that can amplify the risk of second primary cancers or treatment-related heart disease. Integrating genetic information with treatment history helps identify survivors at a higher risk for late effects and develop targeted monitoring and prevention strategies.

The psychological and social toll of pediatric cancers can be profound. Survivors face an elevated risk of anxiety, depression, and posttraumatic stress, as well as learning and memory-related difficulties that can limit educational and employment opportunities. Young adult survivors (ages 20 to 39) of pediatric cancers are less likely to complete higher education, live

independently, or marry, compared to peers without a cancer history. These effects underscore the importance of providing psychosocial support throughout the survivorship continuum.

Pediatric cancer survivors and their families also face lasting economic strain due to high medical costs, missed work, and reduced earning potential. Nearly two-thirds of survivors report some form of financial hardship, and many experience difficulty maintaining health insurance coverage or paying for follow-up care. Legislative measures and state insurance mandates for fertility preservation have helped to alleviate some of these burdens, but disparities persist, particularly among survivors from low-income households, rural communities, or racial and ethnic minority populations.

Parents of children and adolescents with cancer bear significant emotional burdens, including higher rates of anxiety, depression, and posttraumatic stress, as well as long-term financial insecurity including job loss or reduced work hours during their child's treatment. These challenges highlight the need for care models that provide medical support, access to mental health services, financial counseling, and workplace protections for families of pediatric patients with cancer.

The complexity of pediatric cancer survivorship demands coordinated, multidisciplinary care across the lifespan. The COG Long-Term Follow-Up Guidelines provide a cornerstone for risk-based, lifelong surveillance. Updated in 2023, the guidelines include recommendations for genetic testing; monitoring after novel therapies, such as CAR T-cell treatment; and vaccination protocols. Tools, such as Passport for Care, help clinicians implement these guidelines through individualized, web-based survivorship care plans, ensuring that survivors receive consistent, evidence-based follow-up. Still, many pediatric cancer survivors forgo follow-up care or receive inconsistent care, particularly during the transition from adolescence to adulthood, which often complicates care continuity.

Collaborative models that integrate primary care providers, oncologists, and psychosocial specialists are emerging as best practices to improve coordination and address the full spectrum of survivorship needs. Patient-reported outcomes, digital health tools, and mobile applications are helping clinicians track symptoms, enhance communication, and promote engagement in care. These innovations, combined with improved coordination and training for primary care providers, are making survivorship care more accessible and effective.

Despite remarkable progress, many survivors continue to face lifelong health risks and social challenges. Holistic and equitable approaches that value both the years of life gained and the quality of those years, sustained investments in survivorship research and workforce development, and supportive health policies are essential to ensure that every pediatric cancer survivor can thrive in adulthood.

Understanding the Global Landscape of Pediatric Cancers

Pediatric cancer is a global health challenge, affecting nearly 400,000 children annually, with the vast majority of cases and deaths confined to low-income countries (LICs), lower middle-income countries (LMICs), and upper middle-income countries (UMICs). Despite tremendous advances in survival for certain pediatric cancers in high-income countries (HICs)—where 5-year survival for all cancers combined exceeds 85 percent—survival remains below 30 percent in LICs and LMICs, reflecting inequities in access to diagnostics, treatment, essential medicines, and a trained pediatric oncology workforce. The global burden is further compounded by the lack of population-based cancer registries in many low-resource settings, leading to incomplete data on incidence and outcomes and widespread underdiagnosis. Addressing these gaps requires strengthening health systems, building data infrastructure, and improving clinical capacity to ensure that every child, regardless of geography or income, can access timely and effective care.

The World Health Organization (WHO) Global Initiative for Childhood Cancer (GICC) with its Cure*All* framework represents the most ambitious effort to address global disparities in the burden of pediatric cancers. Launched in 2018 with the goal of achieving at least 60 percent survival for pediatric cancers globally by 2030, GICC provides a roadmap for integrating childhood cancer care into national cancer control plans through four pillars—centers of excellence, universal health coverage, standardized treatment regimens, and monitoring and evaluation—supported by advocacy, financing, and governance. More than 80 countries are already working with GICC to develop or strengthen national pediatric cancer care strategies.

Innovative partnerships are the driving force behind progress against pediatric cancers globally. The St. Jude–WHO Global Platform for Access to Childhood Cancer Medicines, launched in 2021, aims to deliver essential medicines to at least 120,000 children in LMICs over 7 years. This initiative, which is already operational across Asia, Africa, and Latin America, is expanding to include national programs, such as Ghana's plan to provide free essential medicines for children with cancer by 2026. Similarly, the Adapted Resource and Implementation Application (ARIA) Guide, developed through collaboration among several global organizations focused on pediatric cancers, provides clinicians with resource-adapted, evidence-based protocols to care for pediatric patients with cancer in regions with limited infrastructure.

Precision medicine and clinical research are offering molecularly guided treatment options that improve survival

INVESTMENTS IN EQUITABLE CHILDHOOD CANCER CARE
COULD AVERT 6.2 MILLION DEATHS
AND YIELD NEARLY **$2 BILLION**
IN LIFETIME PRODUCTIVITY GAINS BY 2050.
ESW7

and reduce toxicity. New multinational and adaptive trial platforms are expanding opportunities for children with relapsed or refractory cancers to access novel therapies matched to their tumor's molecular profile. Programs, such as the Netherlands' iTHER, Australia's Zero Childhood Cancer Program, and Europe's MAPPYACTS, have demonstrated the feasibility and clinical impact of integrating molecular profiling into pediatric cancer care. However, access to these technologies remains highly uneven. In some LMICs, resource-adapted approaches are helping to fill gaps in access to advanced technologies needed for molecular profiling.

Access to treatment remains the greatest challenge globally. The availability of WHO essential medicines for childhood cancers varies widely, and treatment abandonment rates in LICs and LMICs can exceed 30 percent due to high out-of-pocket costs, travel burdens, distrust in modern medicine, and lack of supportive services. Studies have shown dramatically improved treatment retention and survival through locally adapted protocols and social interventions, as seen in Guatemala and Malawi, where treatment abandonment rates have dropped below 1 percent and survival has doubled. Regional collaborations in Africa and Latin America promoting standardized protocols, shared expertise, and improved supportive care are aiming to close survival gaps for pediatric cancers, such as ALL, Burkitt lymphoma, and Wilms tumor.

The shortage of a skilled pediatric oncology workforce is another critical barrier. Across Africa, there is fewer than one clinician specialized in pediatric cancer for every one million children, and only four countries have the capacity to treat pediatric brain tumors. Expanding region-specific training programs, building multidisciplinary teams, and investing in infrastructure for radiotherapy and surgery are essential to achieve the GICC goal by 2030. Global partnerships, such as the Pediatric Oncology East and Mediterranean network and the Franco-African Pediatric Oncology Group, demonstrate that coordinated regional training and mentorship can increase workforce capacity and improve outcomes.

The global landscape of pediatric cancer reflects extraordinary progress in some regions and deep inequities in others. While HICs continue to benefit from advances in precision medicine, immunotherapy, and supportive care, most children worldwide lack access to standard of care treatment. Achieving the GICC goal requires sustained international collaboration and national policy commitments, as well as investments in health care infrastructure and workforce development.

Advancing Pediatric Cancer Research and Patient Care Through Evidence-based Policies

Federal government programs and policies are critical to catalyze progress against pediatric cancers. Robust and sustained investment in agencies, such as NIH and FDA, play key roles in driving progress, enabling scientific breakthroughs, supporting the next generation of researchers and physician-scientists, and improving patient care. Although NIH and NCI are global leaders in providing funding for pediatric cancer research, challenges persist, including workforce shortages, inadequate infrastructure for research and clinical trials, and inequities in support across cancer types and for survivorship research. Increased federal funding, more flexible grant models, and improved transparency in funding allocation are urgently needed to continue making significant progress and ensure equitable care for all children with cancer. Crucially, any cuts to federal agencies and their staffs or programs would drastically impact pediatric cancer research, stalling scientific discovery, reducing innovation, and harming patients and their families.

Bipartisan congressional support and key legislation have significantly advanced pediatric cancer research, data-sharing, and drug development over the past decade. Landmark legislations, such as the Creating Hope Act, RACE for Children Act, and the STAR Act, have incentivized pharmaceutical innovation, expanded clinical trials, and enhanced federal data infrastructure. However, ensuring that pediatric drug studies are completed and research is successfully translated into approved therapies for children with cancer continues to pose significant challenges. Reauthorization and continued funding of these initiatives, along with stronger enforcement, are essential to sustain momentum and improve outcomes for pediatric cancer patients.

Advances in regulatory science and specific regulatory reforms policy have further translated research into new treatments for children with cancer. FDA plays a critical role in advancing pediatric cancer treatment by ensuring that drug development processes account for the unique biological and clinical needs

of pediatric cancer patients, promoting early integration of pediatric considerations and innovative trial designs, and maintaining tools like the Pediatric Molecular Targets List to guide regulatory decisions.

However, and even despite these advances, pediatric cancer patients continue to face numerous challenges, including limited access to clinical trials (particularly for those in rural or underserved communities), financial burdens on families during and after treatment, and inadequate survivorship support. These challenges highlight the urgent need for continued legislative and policy action. A range of new and proposed legislation—such as the Innovation in Pediatric Drugs Act, Give Kids a Chance Act, EPIC Act, and Accelerating Kids' Access to Care Act—aims to strengthen drug development pipelines, enforce timely pediatric studies, enhance care access, and expand molecular diagnostics. Additionally, policies that promote comprehensive health insurance coverage, mitigate barriers to health care access, address health disparities, and enhance legislative implementation will be essential to sustain momentum, accelerate the development of innovative treatments, and ultimately improve care for pediatric patients. It is especially important for new evidence-based policies to prioritize research and drug discovery and development tailored to the unique biology of pediatric cancers and the needs of pediatric patients to ensure that all children can benefit equitably from scientific and medical progress.

AACR Call to Action

Congress plays a crucial role by funding vital research programs and advancing policies that improve the lives of children with cancer and pediatric cancer survivors. Unfortunately, the current political climate, budget cuts, and funding instability threaten to curtail scientific advancement, weaken America's biomedical enterprise, and stymie future progress. AACR calls on all stakeholders to engage with members of Congress and leaders at federal agencies to prioritize pediatric cancer research and patient care.

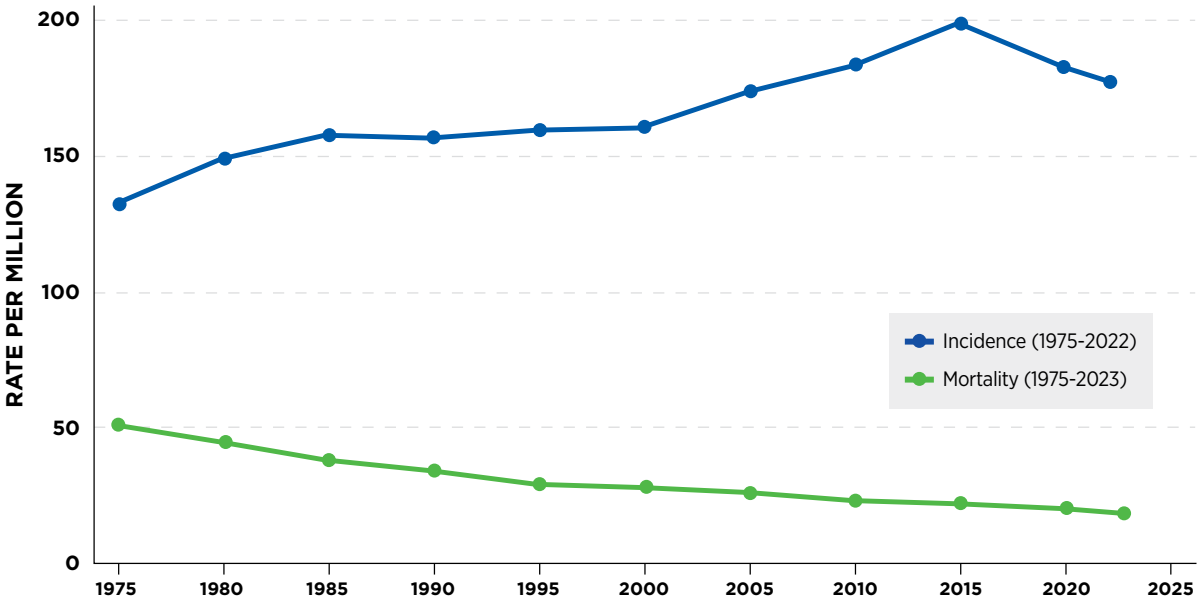
AACR recommends the following actions:

- Provide robust and sustained federal funding of no less than $51.303 billion for NIH and $7.934 billion for NCI in FY 2026 and increase support for the federal agencies and programs that are focused on pediatric cancer research and patient care.
- Expand access to clinical trials and promising therapies for children and adolescents with cancer through regulatory reform and policies to address barriers.
- Modernize and evaluate current pediatric cancer research programs and policies to better support the discovery and development of treatments as well as to improve patient care.
- Support efforts that leverage and harmonize all available data to aid pediatric cancer research including the objectives and proposals outlined in the Administration's recent Executive Order from September 30, 2025, to prioritize the harnessing of American artificial intelligence innovation to unlock cures for pediatric cancer.
- Foster global and public–private partnerships to accelerate pediatric cancer research and the development of innovative treatments for pediatric cancer patients.
- Strengthen survivorship and long-term care for pediatric cancer survivors by ensuring comprehensive, accessible, and reimbursable long-term care services.

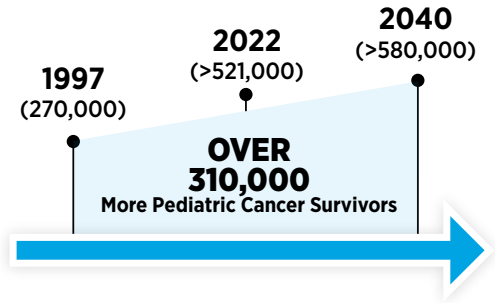
By following these recommendations, the United States will foster innovative research, accelerate scientific discovery, create groundbreaking cures, and remain the global leader in pediatric cancer research. Robust and sustained investment will improve our nation's health and deliver on the promise of a future without cancer. The progress against pediatric cancers is at a critical juncture, and now is the time for a renewed commitment to scientific research that can help save and improve the lives of millions of children and adolescents with cancer.

A SNAPSHOT OF PROGRESS AGAINST PEDIATRIC CANCERS IN 2025

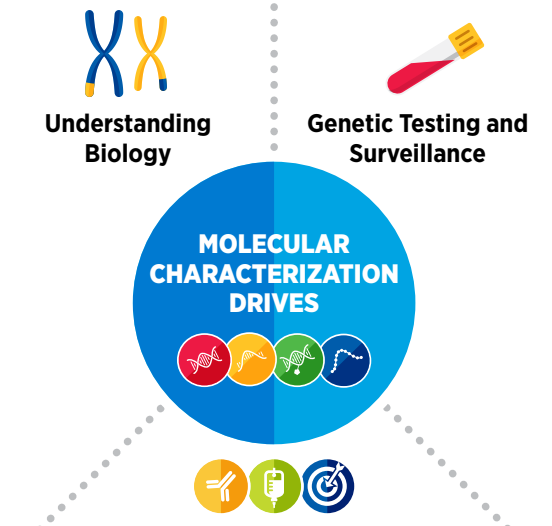
Pediatric Cancer Burden in the United States



The Rising Number of Pediatric Cancer Survivors



Although survival rates for pediatric cancers have improved dramatically, **many survivors continue to experience persistent physical, psychosocial, and financial challenges** resulting from the lasting effects of their disease and its treatment.



Global Precision Medicine Programs:
ZERO, MAPPYACTS, iTHER, NCI-COG Pediatric-MATCH, AcSé-ESMART, ITCC-Hopp, PROFYLE

Research is Advancing Personalized Treatments for Pediatric Cancers

Between 2015 and 2025, FDA approved **more than 20 molecularly targeted therapies** and **over 10 immunotherapies** for pediatric cancers. While these numbers remain much lower than approvals for adults, largely because many pediatric cancer drivers are hard to target with current approaches and pediatric tumors have fewer genetic alterations, the new treatments have been transformative for patients.

Basic research-driven clinical breakthroughs are creating personalized therapies for pediatric cancer patients. These advances are:

- **Putting patients with acute lymphoblastic leukemia into long-term remission with immunotherapeutics,** such as tisagenlecleucel or blinatumomab;
- **Allowing patients with high-risk neuroblastoma** treated with the immunotherapeutic dinutuximab to live with no evidence of disease;
- **Providing molecularly targeted options,** such as revumenib, for relapsed leukemias with specific genetic alterations;
- **Improving outcomes for patients with brain tumors** harboring certain mutations through molecularly targeted therapeutics, such as vorasidenib and dordaviprone;
- **Shrinking inoperable plexiform neurofibromas** in patients with a cancer predisposing syndrome using mirdametinib; and
- **Allowing patients to avoid serious treatment-related side effects** such as heart muscle damage and hearing loss through the use of protective agents like dexrazoxane and sodium thiosulfate.

Global Landscape of Pediatric Cancers

- Between **2020 and 2050, nearly 14 million children** are projected to **develop cancer worldwide,** with **nearly 6.1 million** expected to go undiagnosed.
- **Nearly 90% of pediatric cancers** occur in low-income, lower middle-income, and upper middle-income countries, but only 28% of pediatric cancer clinical trials are conducted there.
- **The WHO Global Initiative for Childhood Cancer** aims to achieve at least 60% survival for children with cancer in all countries by 2030 through its Cure*All* framework.

Call to Action

For Fiscal Year 2026, AACR urges Congress to support robust and sustained funding for the federal agencies and initiatives vital to progress against pediatric cancer. Congress and the federal government must prioritize pediatric cancer research and patient care and enact critical legislation and policies to address key challenges.

AACR is deeply committed to working with academic institutes, biopharmaceutical partners, policymakers, patient advocates, and all other stakeholders in the medical research community **to catalyze the next generation of breakthroughs in pediatric cancer prevention, diagnosis, treatment, and survivorship**.

PEDIATRIC CANCER TRENDS IN THE UNITED STATES

IN THIS SECTION, YOU WILL LEARN:

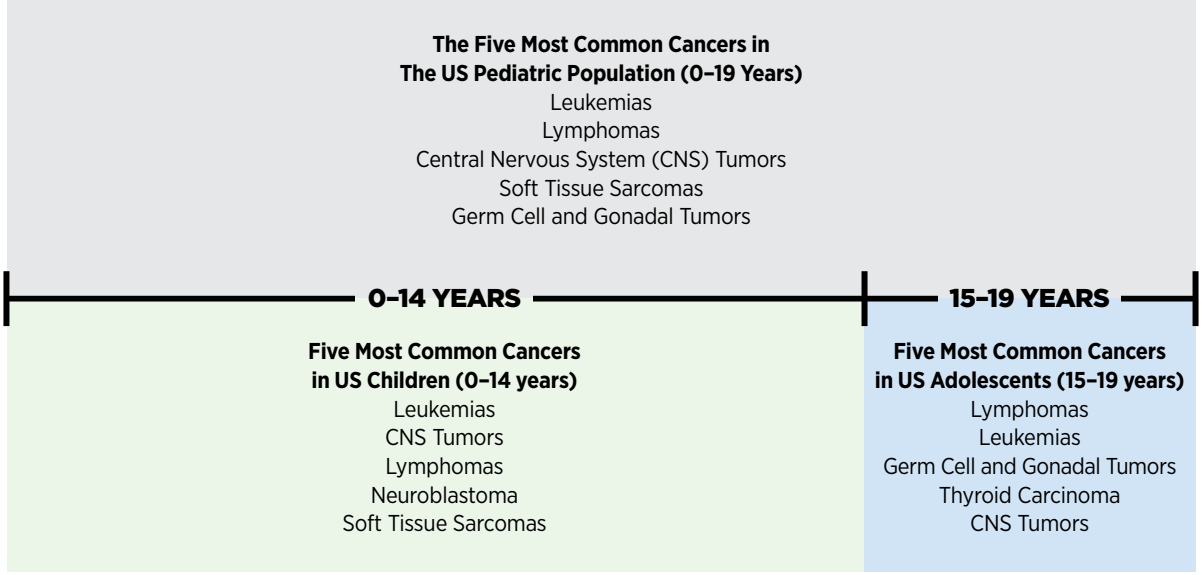
- The 5-year survival for all pediatric cancers combined has increased from 63 percent in the mid-1970s to 87 percent in 2015–2021.
- Between 2000 and 2020, mortality rates for pediatric acute lymphoblastic leukemia (ALL) declined by an average of 3.3 percent per year, thanks to improved risk stratification and availability of new FDA approved targeted therapies and immunotherapies. However, comparable progress has not been observed across all pediatric cancers.
- A majority (60% to more than 90%) of pediatric cancer survivors develop one or more chronic, treatment-related health conditions affecting multiple organ systems, including cardiac, pulmonary, endocrine, reproductive, and neurocognitive disorders, as well as second cancers and impaired growth and development.
- Pediatric cancers are rare, biologically distinct, and unevenly studied when compared to adult cancers. Survival gains are concentrated in the more common pediatric cancers, while rare or more aggressive tumors—characterized by metastases at diagnosis or poor response to therapy—continue to have dismal outcomes.
- Pediatric cancer incidence and survival vary by race, ethnicity, geography, and social drivers of health; underserved populations experience higher mortality and more barriers to care.
- Progress against pediatric cancers depends on robust public funding, committed advocacy on behalf of pediatric patients, continued national and international collaborations, private–public partnerships, philanthropic investment, and policy incentives to close gaps in funding, research infrastructure, and access to innovative therapies to accelerate pediatric drug discovery and development.

Research is the foundation of progress against the diverse diseases that make up pediatric cancers. Research drives improvements in survival and quality of life for children (ages 0 to 14) and adolescents (ages 15 to 19) worldwide by fueling clinical breakthroughs and informing public policies that promote health. Decades of discoveries across basic, clinical, translational, and population sciences have enhanced our understanding of pediatric cancers, which in turn has laid the groundwork for advances in early detection, diagnosis, treatment, and long-term survivorship.

Saving Lives Through Research

Early progress in pediatric cancers dates to the mid-20th century, when several drugs were introduced for the treatment of children with leukemia (1-3). Use of these drugs improved median survival from 8 months for patients diagnosed between 1948 and 1952 to 22 months for those diagnosed in the mid-1950s (4). These treatment advances spurred the creation of the first collaborative

The National Cancer Institute (NCI) defines pediatric cancer as cancers that occur from birth through 14 years of age. The age range covered in our inaugural Pediatric Cancer Progress Report is 0 to 19 years, encompassing both children (0–14 years) and adolescents (15–19 years); throughout the report, we refer to this entire group as pediatric. Of note, certain cancers, such as osteosarcoma and Ewing sarcoma, are predominantly pediatric but can also occur in individuals over 19 years of age. Conversely, other diagnoses such as colon carcinoma and melanoma, are primarily adult cancers that are being increasingly diagnosed in the pediatric population.



Sources: (5,17).

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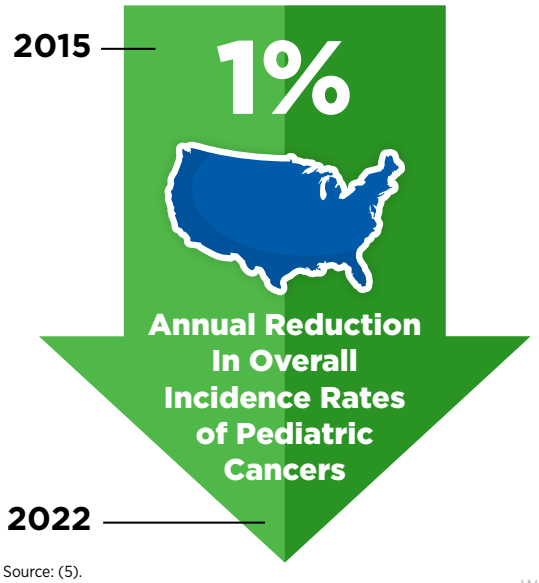
group dedicated to pediatric cancer care—the Acute Leukemia Chemotherapy Cooperative Study Group A—which brought together scientists from major research institutions across the United States (US) to investigate pediatric leukemia.

Collaborative efforts (i.e., multicenter and multidisciplinary clinical trials to overcome the challenge of smaller patient populations) have emerged as the cornerstone of progress against pediatric cancers (see **Sidebar 1**, p. 16). Clinical research led by pediatric cancer–focused cooperative groups has driven major breakthroughs in pediatric oncology. These advances include improved methods for staging tumors, assessing tumor size and spread, optimizing treatment approaches, and understanding the long-term effects of childhood cancer therapies (6). As a result, the overall 5-year survival rates for pediatric cancers have risen from 63 percent in the mid-1970s to 87 percent between 2015 and 2021 (5,7).

Advances in pediatric cancer highlight the necessity of the ongoing, multidisciplinary collaborations that span both research and patient care as well as the robust, predictable, and sustained public funding, as exemplified by the Children's Oncology Group (COG) and the support of its research activities by the National Cancer Institute (NCI) (see **Figure 1**, p. 17) (6). In the United States (US), 9 out of 10 children



Source: (5).

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and adolescents diagnosed with cancer are treated at a COG member institution, where they receive the most promising therapies available (8).

SIDEBAR 1

Advancing Pediatric Cancer Research Through Global Collaboration

The Children's Oncology Group (COG) is the only group within the National Cancer Institute's National Clinical Trials Network (NCI-NCTN) and the largest organization focused on pediatric cancer. Through international collaboration, more than 12,000 researchers across over 220 institutions in the United States, Canada, Australia, New Zealand, and Saudi Arabia are a part of COG. Research performed by COG institutions spans the full spectrum of pediatric cancers, including blood cancers, cancers of the central nervous system (CNS), and solid tumors outside the CNS.

Eighty-seven percent of COG institutions are located throughout the United States with at least one facility in each state, with the exception of Kansas, Montana, and Wyoming. Of these, 38 sites are NCI Community Oncology Research Program participants, with 14 categorized as serving underserved/minority populations. COG currently has more than 100 active studies, with nearly 40 percent of children treated at a COG institution enrolled in at least one study.

COG's work is made possible through critical support by publicly funded grants from NCI. **Two major grants provide core funding:**

- **NCTN Operations Center Grant**—supports day-to-day research operations and staff at member institutions.
- **NCTN Statistics and Data Center Grant**—supports data collection and analysis for clinical trials.

Other key public funding initiatives include the Pediatric Early Phase Clinical Trial Network Grant, which supports early testing of promising new therapies, and the NCI Community Oncology Research Program Grant, which helps bring clinical trials to local community hospitals.

Sources: (8,9).

Research-driven advances across the clinical cancer care continuum have led to a considerable decrease in pediatric cancer mortality. Over the past 50 years, overall cancer death rates among US children and adolescents have declined by 70 percent (6.3 per 100,000 to 1.9 per 100,000) and 63 percent (7.2 per 100,000 to 2.7 per 100,000), respectively. These improvements reflect the identification and therapeutic targeting of cellular and molecular drivers of cancer, complemented by a greater understanding of biology and advances in precision medicine including immunotherapy, surgical techniques, refinements in radiotherapy and chemotherapy dosing, and improvements in supportive care (see **Figure 2**, p. 18). Despite these tremendous gains, survival rates have only increased, on average, by only about 0.5 percent annually since 2000 (5). The minimal improvements observed in more recent years underscore the urgent need to accelerate progress in pediatric drug discovery and development.

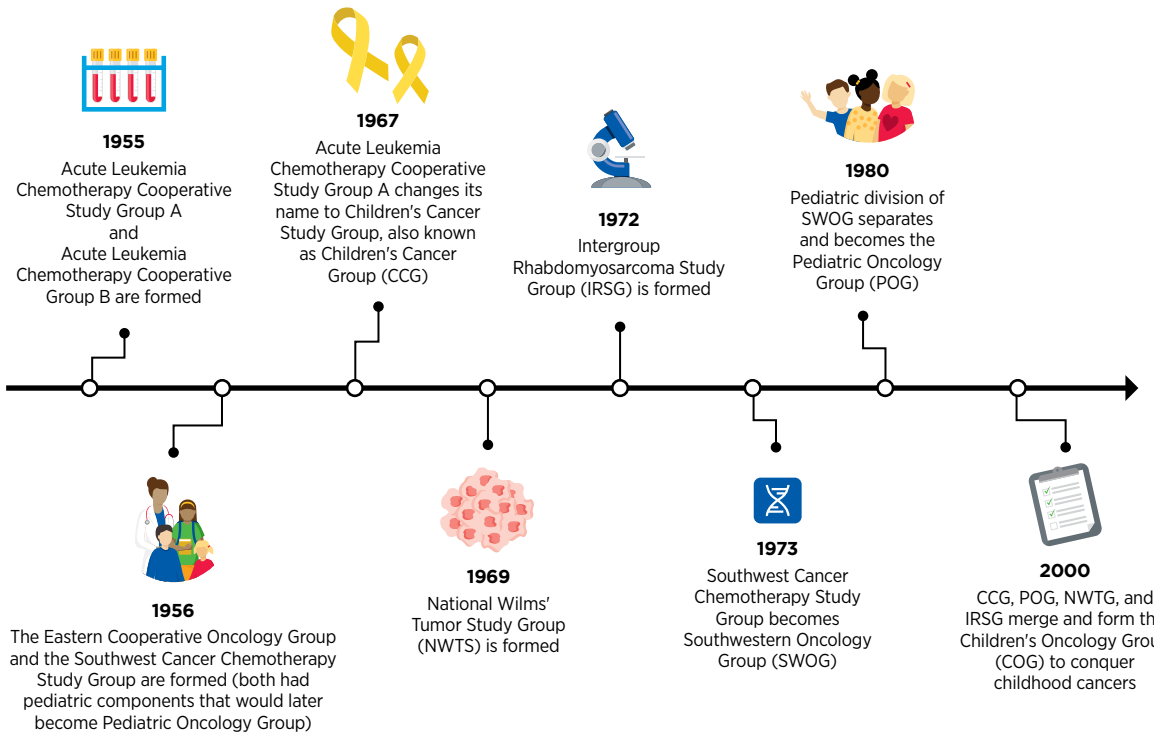
Advances in identifying prognostic markers and clinical care over the past several decades have led to marked improvements across specific pediatric cancer types. Acute lymphoblastic leukemia (ALL), the most common cancer among children and adolescents, has seen substantial improvements in survival. Between 2000 and 2020, mortality rates among children and adolescents declined by an average of 3.3 percent per year, reflecting the impact of advances in risk stratification, targeted therapy, and other treatment innovations (11). Risk stratification allows patients with specific genetic features to receive tailored treatment plans and disease monitoring. Minimal residual disease (MRD) monitoring—which detects a very small number of cancer cells in the body and is now a standard practice—guides treatment intensity by identifying patients at higher risk of relapse and can detect disease weeks to months earlier than conventional imaging or blood tests, contributing significantly to improved survival (12).

Genetic characteristics also influence ALL prognosis and outcomes. Specifically, high hyperdiploidy and *ETV6::RUNX1* rearrangements are associated with favorable prognosis, whereas a range of alterations such as hypodiploidy (fewer than 44 chromosomes), *MLL* rearrangements, or *BCR::ABL1* is linked to high-risk clinical features or poor outcomes (see **Somatic Mutations**, p. 35, and **Molecular Insights Driving Risk Stratification and Treatment**, p. 71) (13).

Advances in molecularly targeted therapy and immunotherapy have improved outcomes for nearly all ALL subtypes (see **Progress in Pediatric Cancer Treatment**, p. 63). For example, 3-year survival has nearly doubled for individuals with Philadelphia chromosome–positive ALL treated with the molecularly targeted tyrosine kinase inhibitor imatinib (Gleevec). Precision medicine has improved outcomes in high-risk neuroblastoma, with anti-GD2 antibodies (e.g., dinutuximab and naxitamab)

FIGURE 1

Establishment of the Children's Oncology Group



The rare nature of pediatric cancers makes it challenging to study without broad national and international collaboration among institutions dedicated to investigating these diseases. The Children's Oncology Group (COG) emerged from decades of pioneering work by four collaborative, site-specific clinical trial groups that laid the foundation for modern advances in treatment and outcomes. Since its formation, COG has driven progress to help improve survival and quality of life for children, adolescents, and young adults afflicted by cancer. Although additional federally and privately funded collaborative research groups are complimenting COG-led trials, sustained funding for COG is essential to continue its international leadership and advance the mission of curing and preventing pediatric cancers.

Source: (6).

approved over the past decade (14). Newly FDA-approved targeted treatments and immunotherapies continue to enhance survival and reduce mortality across a range of pediatric cancers.

The cumulative impact of these advances is reflected in significant declines in all-cause mortality among pediatric cancer survivors diagnosed between the 1970s and 1990s, dropping from 10.7 percent to 5.8 percent (15), indicating improved long-term health and quality of life. Subsequently, more than 521,000 pediatric cancer survivors were living in the United States in 2022, with the majority living at least 5 years or more after diagnosis (5). Despite these gains, important challenges remain in understanding and addressing the unique burden of pediatric cancers in the United States.

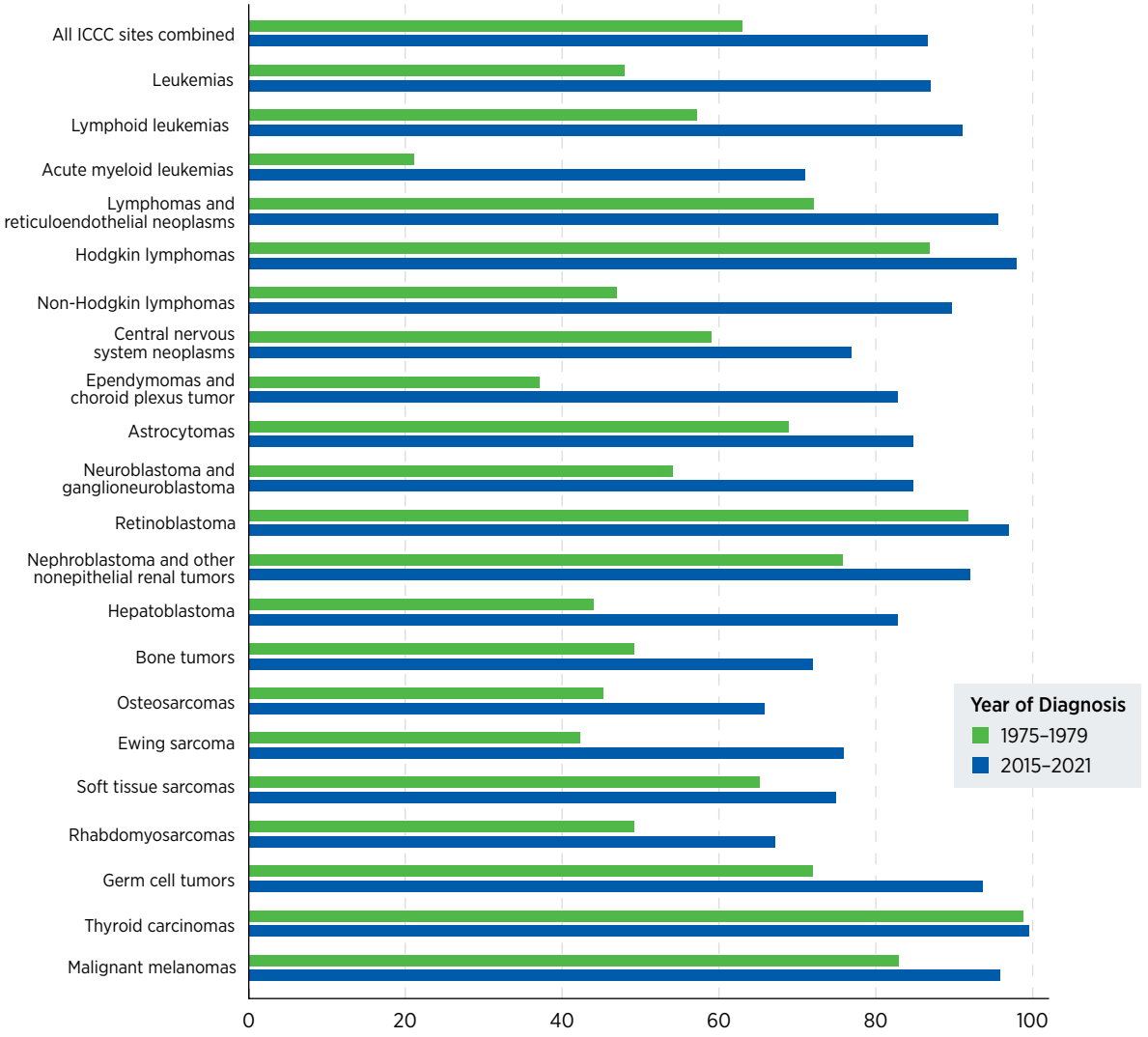
Ongoing Challenges in Pediatric Cancers

In 2025, an estimated 14,690 children and adolescents will be diagnosed with cancer, compared to roughly two million cases in adults (16). Overall, the most common cancers in children and adolescents (ages 0 to 19) are leukemias, CNS tumors, and lymphomas (see **Table 1**, p. 19, and **Supplementary Table 1**, p. 175) (16). When examining cancers by age group, the five most common cancers among children ages 0 to 14 are leukemia, CNS tumors, lymphomas, neuroblastoma and related tumors, nephroblastoma and other nonepithelial kidney tumors. For adolescents ages 15 to 19, the five most common cancers are lymphomas, leukemias, thyroid cancer, germ cell and gonadal tumors, and CNS tumors.

FIGURE 2

Progress Against Pediatric Cancer

FIVE-YEAR SURVIVAL RATES (%) FOR CERTAIN PEDIATRIC CANCERS (0–19 YRS): IN 1975–1979 AND 2015–2021



Five-year relative survival rates for US children and adolescents (ages 0 to 19) who were diagnosed with cancer between 2015 and 2021 were substantially higher compared to rates for those diagnosed between 1975 and 1979. Pediatric cancers are classified using the International Classification of Childhood Cancer (ICCC). An improvement in the 5-year relative survival rate was observed for all cancers combined, as well as for most individual cancer types.

Data reflect 5-year relative survival rates for main ICCC diagnostic groupings and selected subgroups within these categories.

Sources: (5,10).

Over several decades, sustained progress in cancer research and treatment—driven by advances in identifying and therapeutically targeting cellular and molecular drivers of cancer—has contributed to steady improvements in outcomes for children and adolescents (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29, and **Progress in Pediatric Cancer Treatment**, p. 63).

In the United States, 5-year relative survival rates for pediatric cancers have increased substantially over the past five decades. However, progress has slowed in recent years, with survival improving by only 0.5 percent per year since 2000 (5). Survival outcomes also vary considerably by cancer type and age group (see **Supplementary Table 1**, p. 175). As one example, adolescents and young adults (AYAs) experience notably lower

TABLE 1

Pediatric Cancers (0–19 years) in the United States: Incidence Rates and 5-year Relative Survival Rates

	INCIDENCE RATES* (%)†	5-YEAR SURVIVAL‡ (%)
All ICCC groups (malignant only)	**186.2 (100)**	**87**
Leukemias	48.0 (26)	87
Acute lymphoid leukemia	35.5 (19)	91
Acute myeloid leukemia	8.0 (4)	71
Lymphomas and reticuloendothelial neoplasms	29.0 (16)	95
Hodgkin lymphoma	12.3 (7)	98
Non-Hodgkin lymphoma	10.5 (6)	90
Central nervous system neoplasms	29.0 (16)	77
Neuroblastoma and other peripheral nervous cell tumors	9.5 (5)	85
Retinoblastoma	3.0 (2)	97
Nephroblastoma and other nonepithelial renal tumors	6.0 (3)	92
Hepatic tumors	3.2 (2)	77
Hepatoblastoma	2.4 (1)	83
Bone tumors	9.3 (5)	72
Osteosarcoma	5.3 (3)	66
Ewing tumor and related bone sarcomas	2.9 (2)	76
Soft tissue sarcomas	12.3 (7)	75
Rhabdomyosarcoma	4.8 (3)	67
Fibrosarcomas/ Peripheral nerve sheath tumors	1.1 (1)	85
Other specified soft tissue sarcomas	4.7 (3)	81
Unspecified soft tissue sarcomas	1.7 (1)	76
Germ cell and gonadal tumors	11.4 (6)	94
Thyroid carcinomas	10.8 (6)	>99
Malignant melanomas	2.9 (2)	96

* Incidence rates are per 1,000,000 population, based on diagnoses during 2018–2022, and age-adjusted to the 2000 US standard population.

† Percent of total cases.

‡ Survival rates are based on diagnoses during 2015–2021, all followed through 2022.

Sources: (5,17).

5-year survival rates compared with children diagnosed with the same cancers. Specifically, survival for AYAs with ALL is 63.2 percent compared with 91.6 percent in children; for Ewing sarcoma of the bone, 55.3 percent versus 76.9 percent; and for Ewing sarcoma of the soft tissue, 60.8 percent versus 84.7 percent (18). While survival disparities remain, attention has increasingly turned to the lasting health effects faced by those who survive pediatric cancer.

Pediatric cancers constitute a major public health challenge, as they are the leading cause of disease-related mortality in children and a substantial contributor to long-term morbidity in survivors. While survival has improved, many pediatric cancer survivors live with chronic and often serious health conditions related to their cancer or its therapy (see **Challenges Faced by Pediatric Cancer Survivors**, p. 105). Studies show that 60 percent to more than 90 percent of pediatric cancer survivors develop one or more chronic health conditions following their cancer diagnosis (19,20). These treatment-related adverse effects can involve multiple organ systems and include heart and lung problems, second cancers, impaired growth and development, endocrine and reproductive disorders, and neurocognitive impairments (21).

However, as pediatric cancer survivors continue to live longer, mortality related to late recurrence, second primary cancers and other treatment-related toxicities (i.e., cardiac events

Incidence and 5-Year Overall Survival Rate of Select Pediatric Central Nervous System Neoplasms: 2000–2022

TUMOR TYPE	NUMBER OF NEW CASES	INCIDENCE RATE*	SURVIVAL RATE
Diffuse midline gliomas†	240	2.2	3.80%
Ependymomas	1,202	2.3	79.4%
Low-grade gliomas	2,468	4.8	94.7%
High-grade gliomas	1,385	2.7	29.1%
Medulloblastoma	2,009	3.9	74.1%

* Incidence rates are per 1,000,000 population and age-adjusted to the 2000 US standard population.
† Data only available from 2018 to 2022; 4-year overall survival.
Source: (17).

W3

or pulmonary conditions) has declined, while there was a simultaneous increase in mortality from external causes, including accidents and suicide (22). Survivors and their families often face psychosocial challenges, difficulties with social relationships and educational attainment, as well as financial hardships related to the costs of medical care (22). Continued research to address the complex survivorship needs of the growing number of pediatric cancer survivors must remain a public health priority (see **Supporting Survivors of Pediatric Cancers**, p. 104).

Challenges of Rare Disease Research

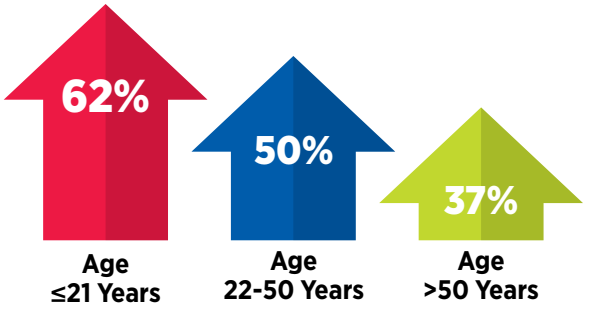
NCI defines rare cancer as a cancer that occurs in fewer than 15 out of 100,000 people each year in the United States, placing all pediatric cancers within this category. The Joint Action on Rare Cancers, in cooperation with the European Cooperative Study Group for Pediatric Rare Tumors, classifies very rare cancers as tumors that occur in less than 2 children per 1 million annually (23). Within this already rare group, some cancer types occur even less frequently, making them especially difficult to study.

Due to unique biological and histologic characteristics, pediatric cancers are classified primarily by tumor morphology—the appearance of cells and their organization—rather than by anatomic site, which is the convention for adult cancers (24). This approach reflects the fact that many pediatric cancers arise from undifferentiated cells with distinct histologic features and can develop in multiple sites throughout the body, such as neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma (see **Molecular and Cellular Influences Driving Pediatric Cancers**, p. 30) (25). Because of these biological and histologic differences from adult tumors, specialized classification of pediatric cancers is required for diagnosis.

To standardize reporting, the International Classification of Childhood Cancer (ICCC) groups pediatric cancers into 12 categories (see **Supplementary Table 2**, p. 176). Although this classification has enabled easier interpretation and dissemination of incidence and mortality data, ICCC's aggregation of diverse cancer types can obscure the true burden of cancers with lower incidence but disproportionately high mortality. This, in turn, may hinder efforts to identify priorities for research, determine allocation of resources, and improve outcomes for the children most at risk. Pediatric CNS tumors illustrate this limitation, as the overall 5-year survival rate for this group is 77 percent, yet certain subtypes have extremely poor prognoses. For instance, children diagnosed with diffuse midline gliomas have a survival rate of only 4 percent (17).

Major challenges in pediatric cancer research, specifically rare tumor research, include the small number of patients available to participate in clinical trials and observational studies; clinical heterogeneity—differences in patient characteristics, disease severity and outcomes, and treatments used; limited understanding of the biology of rare tumors; lack of preclinical models; lack of new therapies; less interest from pharmaceutical companies; and constrained funding and limited infrastructure (26). The consequences of these challenges are evident by the heterogeneity of outcomes. For example, the overall 5-year survival rates are only 60.7 percent for adrenocortical carcinoma—a rare cancer of the adrenal glands—22.6 percent for desmoplastic small round cell tumor (DSCRT)—an aggressive soft tissue sarcoma—and just 2.2 percent for diffuse intrinsic pontine glioma (DIPG), an aggressive form of brain cancer (5,27,28). In contrast, the overall 5-year survival rates for children and adolescents diagnosed with leukemia and Hodgkin lymphoma are 87 percent and nearly 100 percent, respectively (5,29).

Variation in Colorectal Cancer Diagnosed at Advanced Stage in the United States: Data from the National Cancer Database, 1998–2011.



Source: (31).

W4

In the United States, COG engages its Rare Tumor Committee to study cancers that are ultra-rare or understudied in children and adolescents (30). These include tumors classified within group XI of ICCC—other malignant epithelial neoplasms and melanomas—such as adrenocortical, nasopharyngeal, colorectal (CRC), and thyroid cancers; melanoma; pleuropulmonary blastoma; retinoblastoma; gonadal stromal, pancreatoblastoma, and gastrointestinal stromal tumors; non-melanoma skin cancers; neuroendocrine tumors; and desmoplastic small round cell tumors (26,30). Collectively, these tumors account for less than 10 percent of all pediatric cancers (30).

Within the pediatric population, some cancers (i.e., thyroid and CRC) are more common in adolescents than children. As one example, although only about 5 in 1 million children in the United States are diagnosed with CRC annually (5,11,16), they are often diagnosed at an advanced stage with poor outcomes (31). Despite presenting with disease that resembles early-onset CRC in adults, children are 22 percent more likely to die from the disease than adults diagnosed between ages 22 and 50 (31). The difference observed in outcomes for individuals younger than 21 diagnosed with CRC has been attributed to the biology of the tumor rather than disparate treatment modalities (31). This example underscores the need for pediatric-specific molecular profiling, development of tailored therapies, and more robust outcome data collection for meaningful improvements in survival for children with CRC.

To overcome the lack of data needed to accelerate progress against rare pediatric cancers, such as detailed information on tumor biology, COG collects patient samples (e.g., blood, tumor tissues, and urine) to advance the development of targeted therapies. Through its biospecimen collection initiative, Project:EveryChild, partially supported by NCI, COG gathers samples from patients with all types of pediatric cancer. In 2022, NCI further expanded efforts with the Molecular

The National Cancer Institute's Initiatives to Increase Data Availability for Pediatric Cancers

Childhood Cancer Data Initiative (CCDI)

LAUNCHED IN 2019, CCDI AIMS TO:

- **Gather data** from every child, adolescent, and young adult (AYA) diagnosed with cancer, regardless of where they receive their care;
- **Create a national strategy** of appropriate clinical and molecular characterization to speed diagnosis and inform treatment for all types of pediatric cancers; and
- **Develop a platform and tools** to bring together clinical care and research data that will improve prevention, treatment, quality of life, and survivorship for pediatric cancers.

Molecular Characterization Initiative (MCI)

LAUNCHED IN 2022 AS A PART OF THE CCDI, MCI AIMS TO:

- **Collaborate with** the pediatric cancer community, including advocates, pediatric oncologists, molecular pathologists, researchers, data scientists, children and AYAs with cancer, and their families;
- **Provide state-of-the-art** clinical molecular characterization at the time of primary diagnosis that helps participants and doctors select the best and most appropriate treatment; and
- **Deposit de-identified data** into the Childhood Cancer Database, providing publicly available data to enable new discoveries about pediatric cancers, including rare cancer types.

W5

Characterization Initiative—part of the NCI's Childhood Cancer Data Initiative (see **Shared Data and Collaborations Advancing Pediatric Cancer Research**, p. 44)—to provide comprehensive clinical sequencing of pediatric tumors, including rare types. Together, these strategies are increasing the representation of rare childhood cancers in the NCI-sponsored COG biobank and allowing for precision diagnosis, treatment, and determining clinical trial eligibility (26,32). To address the needs of patients with very rare cancers, CCDI is also launching the Coordinated Pediatric, Adolescent and Young Adult Rare Cancer Initiative, which provides comprehensive molecular profiling through the MCI in addition to collection and extraction of clinical data (32,33).

NCI-funded initiatives underscore the need for sustained funding in pediatric cancer research, particularly to improve outcomes for children and adolescents affected by rare cancers (see **Policies Advancing Pediatric Cancer Research and Care**, p. 147). Equally important, meaningful progress will require cross-disciplinary international collaborations to assemble sufficiently large patient cohorts for impactful research. NCI, in partnership with Cancer Research UK, founded Cancer Grand Challenges (CGC), a global research initiative to overcome the most difficult challenges in cancer research, which includes developing targeted therapies in pediatric oncology (34). Currently, CGC sponsors three collaborative teams (NexTGen, KOODAC, and PROTECT) to tackle challenges centered on developing therapeutics for children and adolescents with cancer (see **Shared Data and Collaborations Advancing Pediatric Cancer Research**, p. 44).

Uneven Progress Against Pediatric Cancers

In the United States, 1,050 children and 600 adolescents are estimated to die from cancer in 2025 (16). However, the impact of the pediatric cancer burden extends far beyond mortality, encompassing the significant years of life lost, long-term health complications among survivors, profound emotional and financial strain on families, and broader societal costs.

Over the past several decades, major advances in cancer prevention, early detection, and treatment have contributed to substantial improvements in survival for many adult cancers (35). However, pediatric cancers have not seen comparable progress. As one example, lung cancer, the leading cause of cancer deaths in adults, has benefited enormously from advances in precision medicine over the past 15 years. More than 45 new therapies, including molecularly targeted therapies and immunotherapies, have been approved by FDA for patients with advanced lung cancer. Thanks to these advances, lung cancer mortality rates have declined by 38 percent since 2010 (11). In sharp contrast, pediatric CNS tumors, which are the leading cause of cancer-related death in children, have seen only four new FDA-approved treatments over the same time frame. Alarmingly, mortality from pediatric CNS tumors has increased by nearly 8 percent since 2010, reflecting the lack of meaningful progress despite ongoing research (11). Advances in precision medicine have also transformed outcomes in other previously intractable cancers in adults, such as metastatic melanoma, yet similar breakthroughs have not been realized for aggressive pediatric cancers such as rhabdomyosarcoma.

Although 40 percent of adult cancers are attributable to modifiable risk factors, the relationship between pediatric cancers and modifiable exposures remains poorly understood. Moreover, although tumor sequencing has advanced the understanding of inherited genetic alterations driving pediatric tumors, only 10 to 18 percent of cases can be explained by genetic predisposition syndromes (see **Pediatric Cancer Predisposition and Surveillance**, p. 47) (36,37). In many cases, this lack of information is due to our limited understanding of the normal development of the tissues and organs in which pediatric cancers arise, as well as the lack of suitable experimental models that reflect the inherited genetic drivers of these cancers. Without strong investment in research on cancer predisposition genes and the causes of pediatric cancers, opportunities for prevention and early detection will be missed, survival gains will plateau, and the gap with adult outcomes will widen.

While significant progress has been made against pediatric ALL, individuals diagnosed with less common cancers, such as high-grade gliomas (i.e., DIPG and glioblastoma multiforme) and certain sarcomas, continue to face dismal prognoses, with the overall survival often around 20 percent or less (38). Specifically, children with DIPG only survive about 12 months after diagnosis (39). The poor prognosis is largely attributed to the lack of progress in advancing treatments for this disease despite a strong understanding of the biological underpinnings of DIPG (see **Personalizing the Treatment of Brain Tumors**, p. 80).

The majority of new cancer drugs are first developed for, tested, and approved in adult populations, even when they are evaluated in cancers relevant to pediatric patients (40), leaving pediatric applications years behind. Specifically, after a new cancer drug receives FDA approval for adults, it can take as long as 10 years before it becomes available for pediatric use (41). Notably, research has shown that there is a very small overlap in the genomic alterations in adult cancers when compared to pediatric cancers. Pediatric cancers that share molecular features with adult malignancies (e.g., melanoma) are often treated with adult regimens that are not tailored to pediatric patient's developmental stage, raising concerns about efficacy, toxicity, and long-term adverse effects (31,42).

Limited funding remains a significant barrier to developing new and effective treatments for pediatric cancers (see **Investing in Pediatric Cancer Research to Secure a Healthier Future**, p. 146). Currently, the majority of funding for therapy development to treat pediatric cancers is provided by NCI and philanthropic organizations, while pharmaceutical companies have little incentive to invest, given the small patient population.

Restricted access to experimental therapies, regulatory and drug approval complexities, and the difficulty of conducting early-phase international trials for rare tumors further hinder progress. In this context, international collaborations are critical to accelerate progress against pediatric cancers. For example, COG uses its international research network in Canada, Europe, and Australia to enroll more patients in clinical trials, ensuring that children and adolescents with very rare cancers can also access promising new investigational therapies. Other international pediatric trial consortia, such as the COllaborative Network for NEuro-oncology Clinical Trials (CONNECT), play a critical role in expanding access to clinical trials and advancing new therapies (see **Global State of Pediatric Cancer Clinical Trials**, p. 131). Pooling patients and resources across institutions around the globe, makes it possible to accelerate discoveries and improve outcomes for children and adolescents worldwide.

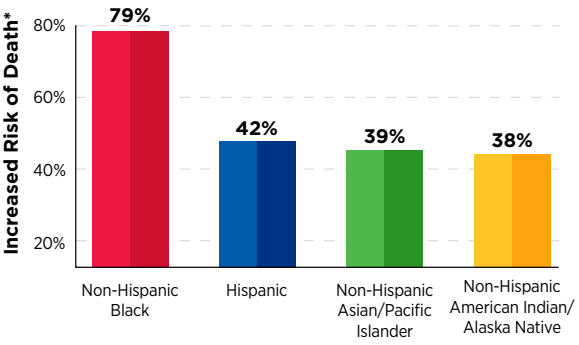
Pediatric Cancer Disparities

Disparities in incidence and outcomes remain a critical challenge, attributable to a lack of equitable access to treatment for children and adolescents with cancer and affecting their quality of life after therapy. NCI defines cancer disparities as adverse differences in cancer-related measures, such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and cancer stage at diagnosis, that exist among certain population groups. Children and adolescents with cancer face these inequities, underscoring the need to better understand and address the social, biological, and systemic factors that drive cancer disparities.

In general, cancers are more frequently diagnosed in boys, who also have a slightly lower 5-year survival rate than girls (86.4 percent vs. 87.7 percent, respectively) (5,11). Beyond these sex-based differences, disparities in cancer incidence and outcomes are more pronounced across US racial and ethnic minority groups and other medically underserved populations, both overall and for specific cancer types. For example, while overall pediatric cancer incidence was historically the highest among non-Hispanic White (NHW) individuals, this shifted in 2012 with American Indian/Alaska Native (AI/AN) individuals having the highest incidence rates (5). Since then, incidence rates have alternated between these two groups, with the most recent data from 2022 indicating that Hispanic individuals have the highest rate (200.1 [Hispanic] vs. 185.1 [NHW] vs. 136.5 [AI/AN] per 1 million) (5,11).

Considerable disparities in mortality are also observed in pediatric cancers. A national study of over 132,000 children diagnosed with leukemia, lymphoma, CNS tumors, and non-CNS solid tumors between 2004 and 2020 found that non-Hispanic Black (NHB) individuals were 28 percent more likely to die from their cancer than NHW children and adolescents (43). Five-year relative survival is generally higher among NHW and Asian/

Pediatric patients from racial and ethnic minority groups are at an increased risk of early mortality from cancer



* Relative to non-Hispanic White children.

Source: (46).

W6

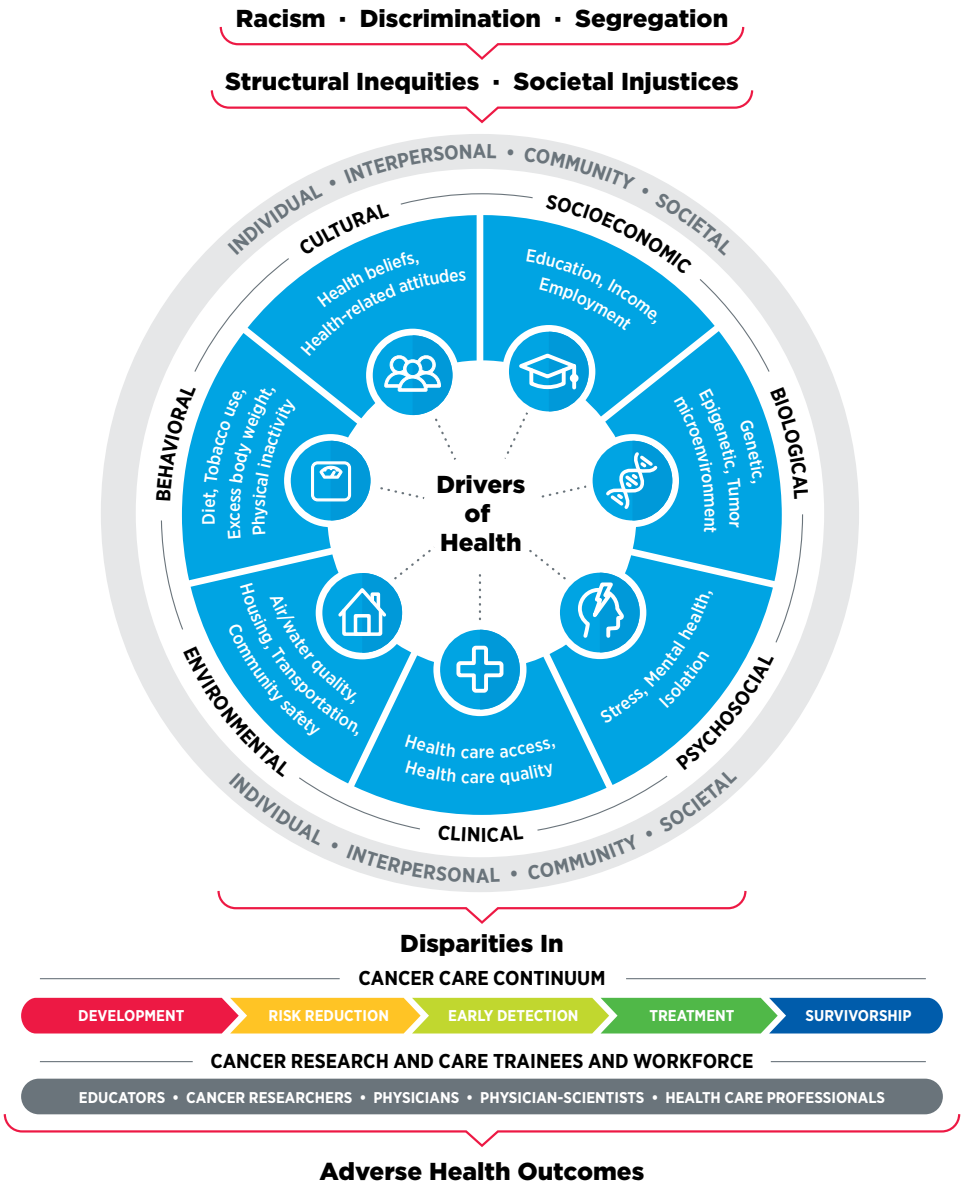
Pacific Islander AYAs than among NHB, Hispanic, and AI/AN AYAs (18). A smaller study of more than 2,000 children with ALL found that those with higher proportions of Native American or African genetic ancestry had poorer outcomes compared to children with majority European, Asian, or Southeast Asian ancestry (44). Differences in outcomes within subgroups of certain racial minorities have also been reported. Specifically, among US children diagnosed with ALL, the risk of death was 42 percent higher in East Asian patients and 50 percent higher in Southeast Asian patients compared to NHW patients (45).

Disparities in pediatric cancer outcomes are not limited to race and ethnicity; they also extend to geography and other social drivers of health (SDOH)—including household income, parental education, access to quality health care, housing stability, food security, and neighborhood environment (see **Figure 3**, p. 24). Children and adolescents residing in rural areas without close access to urban medical centers are nearly 20 percent more likely to die from their cancer than those living in urban areas (47). Furthermore, the excess risk of death can vary considerably based on cancer type. Children and adolescents with neuroblastoma, retinoblastoma, and renal tumors who reside in rural areas face at least a 35 percent higher risk of mortality compared to those living in urban areas (47).

In addition to biological and clinical factors, SDOH can also shape outcomes for children and adolescents with cancer (48,49). Children are not in direct control of these circumstances, but they are deeply affected by the conditions experienced by their parents or guardians. Limited access to reliable transportation, time off from work, or childcare for unaffected siblings may prevent families from reaching specialized cancer centers for timely diagnosis and/or treatment (46). Similarly, financial strains can affect a family's

FIGURE 3

Why Do US Cancer Disparities Exist?



Complex and interrelated structural and social factors, stemming from a long history of racism and discrimination, drive cancer disparities. These factors include social drivers of health (SDOH) as well as biological factors, mental health, and modifiable risk factors. The National Cancer Institute defines SDOH, also known as social determinants of health, as the social, economic, and physical conditions in the places where people are born and where they live, learn, work, play, and age that can affect their physical and mental health, well-being, and quality of life. In the United States, historical racism and contemporary injustices have perpetuated and exacerbated systemic inequities, resulting in adverse differences in SDOH for racial and ethnic minority groups and medically underserved populations. The circle in the figure depicts key drivers of health and how they interconnect at societal, communal, and individual levels. Selected examples of the multilevel factors that make up drivers of health are highlighted. Collectively, these factors impact every stage of the cancer continuum, leading to worse health outcomes for affected individuals.

ability to afford extensive hospitalization, obtain supportive care, participate in clinical trials, or manage the long-term health needs that often accompany pediatric cancer.

Although research on the impact of SDOH on pediatric cancer burden is still emerging, the current evidence is compelling. One study found that pediatric patients from households with a median income below $63,000, those covered by public insurance or those with no insurance, and those living more than 60 miles from a treatment facility had an increased risk of death of 11 percent, 16 percent, 36 percent, and 20 percent, respectively (43). Pediatric patients living in disadvantaged neighborhoods also experience worse outcomes (50-53). A recent study developed an area-level socioeconomic composite score—based on median household income and the percentage of residents without a high school degree—to capture neighborhood disadvantage and its relation to outcomes in children with Wilms tumor, neuroblastoma, and hepatoblastoma. Pediatric patients who resided in areas with higher neighborhood disadvantage scores were significantly more likely to die from these cancers (54).

NCI-designated Comprehensive Cancer Centers (CCC) and COG-affiliated sites meet rigorous standards for transdisciplinary, state-of-the-art research aimed at advancing cancer prevention, diagnosis, and treatment of pediatric cancers. Children and adolescents treated at these sites often experience better outcomes than those treated elsewhere (55-58). For instance, pediatric patients with acute myeloid leukemia (AML) who were treated at non–CCC-COG sites were nearly twice as likely to die as pediatric patients treated at CCC-COG sites (56). These disparities likely reflect the comprehensive care model of CCC-COG institutions—which includes enhanced supportive and psychosocial services—combined with greater access to clinical trials and the expertise of clinicians engaged in cutting-edge research (58).

Collectively, this evidence underscores how non-biological factors such as income, education, area of residence, and access to care play a critical role in shaping outcomes for children and adolescents with cancer. These social drivers may also influence biological processes. As an example, chronic stress associated with economic hardship can alter immune function and physiological responses to therapy, potentially contributing to poorer outcomes even among pediatric patients receiving equivalent inpatient treatment.

While some disparities in the incidence and mortality of pediatric cancers among racial and ethnic minority groups are because of SDOH, not all differences are explained by these factors, suggesting genetic or biological mechanisms may also contribute to differences in survival. This is exemplified by findings from a recent review demonstrating that individuals with high-risk neuroblastoma treated at COG institutions and enrolled in clinical trials still faced disparities in outcomes, despite access to high-quality care and novel therapies (53).

Continued investment in research is, therefore, critical to uncover these mechanisms, advance our understanding of pediatric cancer disparities, and develop therapies that can improve outcomes for all children and adolescents.

Funding Pediatric Cancer Research: A Vital Investment

Significant progress in pediatric cancer survival has been driven by decades of collaborative research that has transformed the standard of care for many pediatric cancers in addition to improvements in survivorship care (see **Supporting Survivors of Pediatric Cancers**, p. 104). In particular, clinical advances made during the late 20th century greatly improved outcomes for many of the most commonly diagnosed pediatric cancers (6). These breakthroughs have been made possible through sustained investment from the federal government as well as critical support from philanthropic initiatives (see **Investing in Pediatric Cancer Research to Secure a Healthier Future**, p. 146). Continued robust, predictable, and sustained funding is essential to maintain the pace of progress, especially for rare and aggressive cancers, to develop new model systems including patient-derived models that can accelerate discoveries in pediatric cancer biology, to ensure every child and adolescent has equal access to cutting-edge treatments, and to address long-term physical and mental health effects experienced by pediatric cancer survivors. Ultimately, more effective and less toxic therapy will be needed to cure the currently uncurable, and to reduce the short- and long-term toxicities that affect many survivors.

Economic Toll of Pediatric Cancers

Although survival outcomes for children and adolescents with cancer have improved markedly, the economic toll of these diseases remains profound (see **Challenges Faced by Pediatric Cancer Survivors**, p. 105). In the context of adult cancer, financial toxicity—defined as the financial problems a patient experiences related to the cost of medical care—is typically centered on the individual patient. In pediatric cancers, however, the financial and social impact reverberates across the entire family unit and society.

Parents often experience lost wages or jobs due to the need for extended caregiving, while simultaneously shouldering new expenses, such as travel to specialized cancer centers, temporary housing near treatment facilities, and childcare for siblings (see **Supporting Parents and Other Caregivers**, p. 121) (59,60). Out-of-pocket costs for medications, rehabilitation, and long-term follow-up visits further compound the financial strain, persisting well beyond the active treatment phase, particularly for survivors managing

A review of over **389,000 pediatric cancer survivors** found that, compared to individuals without a history of cancer, survivors were:

30 percent less likely to complete higher education (college or beyond)

Nearly three times more likely to experience health-related unemployment

Approximately 30 percent less likely to be married

Had a 40 percent lower likelihood of having children

Source: (68).

W7

late effects (59-61). An estimate from 2017, combining both hospital costs and parental loss of wages, placed the total economic cost of childhood cancer in the United States at approximately $833,000 per patient (62).

At the population level, the societal burden of pediatric cancers is substantial. Because childhood cancers occur early in life, each premature death represents decades of potential life, and societal contributions lost. One way to measure this is through disability-adjusted life years (DALYs), a measure of health outcomes that combines years of life lost due to premature mortality with years lived with disability or impaired health (63,64). For survivors, long-term health complications—such as chronic physical and mental conditions or late effects of treatment that can reduce educational attainment, limit workforce participation, and necessitate ongoing medical care—collectively diminish productivity and quality of life (21). In the United States, the estimated DALYs associated with pediatric cancers were over 158,000 in 2021, which is equivalent to 158,000 years of healthy life lost due to premature death and long-term disability in a single year (65).

Globally, between 2020 and 2050, pediatric cancer treatment is projected to cost over $594 billion. However, interventions that reduce the burden of these cancers could save over 318 million life years and generate nearly $2.6 trillion in productivity gains, more than four times the cost of treatment (66). This equates to a return of $3 for every $1 invested in pediatric cancer research (66,67).

Taken together, the dual burden on families and society, both in the United States and globally, underscores the importance of continued investment in pediatric cancer research, treatment innovation, and survivorship care. Sustained and equitable funding is essential not only to alleviate the economic consequences borne by families but also to reduce the broader societal impact of pediatric cancers across the life course.

Framework for Funding Pediatric Cancer Research

In the United States, breakthroughs in pediatric cancer care have been driven largely by sustained funding from the National Institutes of Health (NIH) (see **Investing in Pediatric Cancer Research to Secure a Healthier Future**, p. 146). In 2024, $729 million was allocated across 1,280 pediatric cancer research projects (69). Yet, the cost of bringing a single cancer drug to market can exceed $1.2 billion, with the majority of expenses concentrated in preclinical and clinical development (70). This stark imbalance between the resources required for drug development and the federal funds dedicated to pediatric cancer research underscores the urgent need to reimagine the current funding framework and identify innovative approaches to accelerate the discovery and delivery of effective therapies for children and adolescents with cancer.

The pharmaceutical industry plays a significant role in the development of drugs to treat adults with cancer. Of over 26,000 clinical trials conducted in adult cancer drug discovery from 2008 to 2022, nearly 32 percent were industry-sponsored compared to just under 7 percent funded by the federal government (72). However, in pediatric drug development, the pharmaceutical industry has had limited involvement because of financial disincentives (73,74). As an example, refractory pediatric cancers, cancers that don't respond to treatment, often require combination therapies. Conducting these studies is particularly challenging, as it requires coordination and data-sharing among multiple drug companies, which can be difficult to negotiate and implement.

Further compounding these challenges, pediatric cancers encompass a distinct spectrum of diseases, many of which are genetically and biologically different from adult cancers and may not benefit from therapies developed for adult

Phase I clinical trial → FDA New Drug Application or Biologics License Application submission can take more than a decade and cost over $1 billion.

Sources: (70,71).

W8

SIDEBAR 2

Philanthropic Organizations Accelerating Pediatric Cancer Research

Philanthropic organizations have played a crucial role in driving progress against pediatric cancers, supporting a wide range of activities. These include direct financial support of research for pediatric cancer; identifying research questions rooted in lived experience; building collaboratives to tackle complex scientific challenges; educating the public on research and policy; providing financial assistance to families for expenses such as travel, housing, food, and uncovered medical costs; and offering psychosocial services like counseling, support groups, and sibling programs. Many also play a vital advocacy role, working to educate policymakers about the needs of children and adolescents with cancer and the impact of legislation on pediatric research and care.

Pediatric cancer advocacy networks have organized into two complementary coalitions – **the Alliance for Childhood Cancer (Alliance)** and **Coalition Against Childhood Cancer (CAC2)**. The Alliance focuses on national advocacy and includes professional societies as members. CAC2 with hundreds of philanthropic and individual members host an array of programs for families and survivors. These have been instrumental in advancing research, collectively raising funds to support the Children's Oncology Group, National Cancer Institute (NCI) disease-specific consortia, and pediatric oncology programs at academic centers.

Philanthropic organizations within these networks also fund pediatric cancer research and support clinical trials, biobanking, and translational research aimed at developing safer, more effective therapies. Among the largest funders are **Alex's Lemonade Stand Foundation** and the **St. Baldrick's Foundation,** raising close to **$670 million,** combined, since 2005.

Many groups support research on specific pediatric cancers, such as brain tumors where outcomes remain poor. **The Cure Starts Now Foundation** has aggregated dozens of parent groups to form the diffuse intrinsic pontine glioma (DIPG)/diffuse midline glioma (DMG) Collaborative, which has funded an international registry of DIPG/DMG tumors available for research. Advocacy groups have played a pivotal role in driving research and translation into new therapies, directly influencing clinical care for children and adolescents with cancer. As one example, collaborative efforts between **ChadTough,** in conjunction with NCI's Small Business Innovation research program and the private sector, supported development of an investigational therapeutic dordaviprone **(Modeyso)** to treat DIPG and DMG, resulting in FDA approval in 2025. Similarly, the **Children's Tumor Foundation (CTF),** the Department of Defense's **Congressionally Directed Medical Research Programs (CDMRP),** and the **Neurofibromatosis Therapeutic Acceleration Program (NTAP)** have focused on children with neurofibromatosis (NF) type 1 and 2, contributing to FDA approval of two drugs: selumetinib **(Koselugo)**, with clinical trials led by **NCI's Pediatric Oncology Branch,** and mirdametinib **(Gomekli)**, for children and adults with NF1 related plexiform neurofibromas.

Through coordinated advocacy efforts such as **CureFest** each September, as well as the annual **Childhood Cancer Action Days** in Washington, DC, the Alliance and CAC2 bring together families, survivors, and advocates to elevate pediatric cancer as a national priority. These initiatives have had a measurable impact on shaping research priorities, advancing drug development, and contributing to the passage of key federal legislation:

The RACE (Research to Accelerate Cures and Equity) for Children Act requires companies to evaluate their cancer drugs for adults, if in children if the molecular target is the relevant to a pediatric cancer.

Gabriella Miller Kids First Research Act allocates $12.6 million each year in genetic sequencing services to pediatric cancers and birth defects.

The STAR Act expands NCI biospecimen collection and repository pediatric programs, provides support for survivorship studies, funds state-level cancer registries through the Centers for Disease Control and Prevention (CDC) to identify and track incidences of pediatric cancer and support the collection of cases into national cancer registries and funded the NCI Childhood Cancer Data Initiative.

The ORPHAN Cures Act of 2025 extends orphan drug marketing exclusivity, including cancer, from 7 to 9 months.

Pediatric Rare Disease Priority Review Vouchers (expired December 2024) incentivized drug development for rare pediatric diseases by providing a redeemable voucher to sponsors who received approval for a drug or biological product. The sponsor could use this voucher for priority review for a different product or transfer or sell it to another sponsor. This program is under consideration for renewal.

These examples illustrate how philanthropic organizations not only provide critical support for patients and families but also drive innovation in pediatric cancer research. Yet, the scale of their contributions is eclipsed by the resources required to transform outcomes. Continued and expanded federal investment is vital for eliminating the burden of pediatric cancer.

indications. Unlike drug development for adults, drug development for children must account for the rapid biological and developmental changes that occur throughout childhood and adolescence (see **Progress in Pediatric Cancer Treatment**, p. 63) (74). Children and adolescents have unique physiology, organ function, immune system, and metabolism, all of which change substantially from infancy to adolescence to adulthood, influencing how drugs are absorbed, distributed, and metabolized in the body (75,76). The rarity of these cancers further complicates trial design, requiring multicenter or international collaborations to recruit adequate numbers of patients.

To bridge the funding gap, a reimagined framework for pediatric cancer research is needed and will require leveraging multiple strategies. One such initiative, the Pediatric Advanced Medicines Biotech, would help increase the number of cell and gene therapies for pediatric cancers by partnering with the academic ecosystem, manufacturing products in academic facilities, and working closely with regulatory bodies to ensure new therapies reach the children and adolescents who need them most (77).

Partnerships between public and private funding sources can help distribute the costs of drug development while accelerating the translation of promising discoveries into clinical trials. Policy and regulatory incentives, such as extended market exclusivity, tax credits, or streamlined approval pathways for pediatric indications, can encourage greater investment from industry (see **Policies Advancing Pediatric Cancer Research and Care**, p. 147). Philanthropic organizations, which have helped filled critical gaps in pediatric cancer funding, remain essential for supporting high-risk, high-reward projects that might otherwise be overlooked (see **Sidebar 2**, p. 27).

Incorporating health economic evaluations that consider the long-term benefits of molecularly targeted therapies in pediatric patients, such as sustained remission and reduced side effects, can provide critical insight into the overall value of these treatments. Such analyses account for the greater lifetime productivity of survivors and can further strengthen the case for increased investment in developing, testing, and approving pediatric cancer therapies.

Despite remarkable gains in pediatric cancer survival over the past five decades, the pace of therapeutic advances for pediatric patients continues to lag behind that of adults, leaving critical gaps in personalized treatments. A renewed emphasis on collaborative innovation—highlighted in emerging research—underscores the transformative potential of cross-sector partnerships in bridging this divide. By prioritizing joint efforts in cancer characterization, target identification, drug discovery, and novel approaches to previously "undruggable" targets, stakeholders can accelerate the development of next-generation therapies tailored to pediatric needs.

Collaborative frameworks not only foster scientific breakthroughs but also lay the groundwork for a more sustainable model of therapeutic advances. Yet, a viable economic infrastructure within the private sector remains elusive. Strengthening partnerships among federal agencies, industry, and philanthropic organizations will be essential to ensure that children and adolescents with cancer benefit equitably from the next generation of lifesaving therapies (73). Continued and expanded federal investment is essential not only for maintaining US leadership in medical research but also, more urgently, for eliminating the burden of pediatric cancer. Greater investment in pediatric cancer research is essential to securing the long-term survival, health, and productivity of the nation's youngest patients.

UNRAVELING THE GENOMICS AND BIOLOGY OF PEDIATRIC CANCERS

IN THIS SECTION, YOU WILL LEARN:

- Pediatric cancers usually arise during early development and exhibit biological features that are distinct from those of adult cancers.
- Compared to adult cancers, pediatric cancers harbor fewer mutations overall and are more often driven by specific mutations or structural changes in DNA that modify the epigenome.
- Changes in the genome, epigenome, developmental pathways, and tumor microenvironment contribute to how pediatric cancers originate, progress, and respond to treatment.
- Innovative technologies, including single-cell and spatial profiling, multi-omics, and CRISPR gene editing, are revealing the hidden complexities of pediatric cancers.
- Large-scale global collaborations and data-sharing initiatives are accelerating discoveries and translating them into safer, more effective therapies that are tailored for pediatric cancers.
- Despite advances in pediatric cancers, scientific and clinical challenges remain, including limited research models and datasets for pediatric cancers, a lack of targeted therapies against most proteins driving pediatric cancers, and treatment-related toxicities that can impact growth, development, and quality of life for children and adolescents.

Cancer is a collection of diseases in which some of the body's cells acquire changes that allow them to grow uncontrollably and spread to other parts of the body. Throughout the course of cancer development, abnormal or damaged cells acquire distinct traits—known as the "hallmarks of cancer"—that set them apart from normal cells. Research in the past few decades has uncovered the unique biological underpinnings of pediatric cancers in children (ages 0 to 14) and adolescents (ages 15 to 19) and the features that distinguish them from adult cancers (see **Sidebar 3**, p. 30). Unlike adult cancers, which often result from accumulated genetic damage attributable to normal aging as well as modifiable risk factors, pediatric cancers typically have fewer overall mutations and fewer known links to environmental exposures.

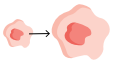
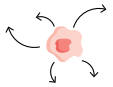
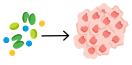
Many pediatric cancers originate during early stages of development, sometimes even before birth, when cells are rapidly dividing and acquiring traits to play specific roles in the body. The alterations that drive pediatric cancers frequently lead to normal developmental pathways being hijacked by cancer cells to drive tumor growth, resulting in tumors that can progress quickly and behave differently from their adult counterparts. Understanding these distinct genomic and biological features is essential for developing therapies that are safe and effective for pediatric cancers.

Large-scale, multidisciplinary pediatric-focused collaborations are generating shared data resources and accelerating the clinical integration of new discoveries, paving the way for

SIDEBAR 3

Key Differences in the Hallmarks of Cancer Between Pediatric and Adult Cancers

Large-scale genomic discovery research has revealed key differences between pediatric and adult cancers. Some of these differences in the hallmarks of cancer are highlighted below:

Hallmark of Cancer	Pediatric Cancers	Adult Cancers
 **SOMATIC MUTATIONS***	Fewer cancer-specific mutations, frequently in genes involved in normal embryonic development, such as transcription factors and epigenetic regulators	More cancer-specific mutations, frequently in genes involved in key cellular signaling pathways
 **UNRESTRICTED GROWTH**	Driven by signals that control normal development being expressed at the wrong time in development	Driven by signals that control cell division and growth
 **EVADING CELL DEATH**	Often depends on activation of survival pathways involved in embryonic development	Often depends on inactivation of pathways that direct cell death
 **METASTASIS**	Often occurs through pathways involved in embryonic development	Often occurs through epithelial-to-mesenchymal transition
 **ALTERED METABOLISM**	Metabolic changes resemble embryonic developmental states of rapid multiplication	Metabolic changes include altered lipid, sugar, and amino acid metabolism

* Somatic mutations are genetic alterations that arise in individual cells during a person's lifetime.

Sources: (78-81).

more precise diagnoses and tailored treatments for young patients. Advances in pediatric cancer research continue to reveal molecular and cellular changes that shape the initiation and progression of childhood and adolescent cancers. Many of these advances are made possible by innovative technologies that provide new insights into the complex changes in the genome, epigenome, developmental pathways, and tumor microenvironment that drive pediatric cancers.

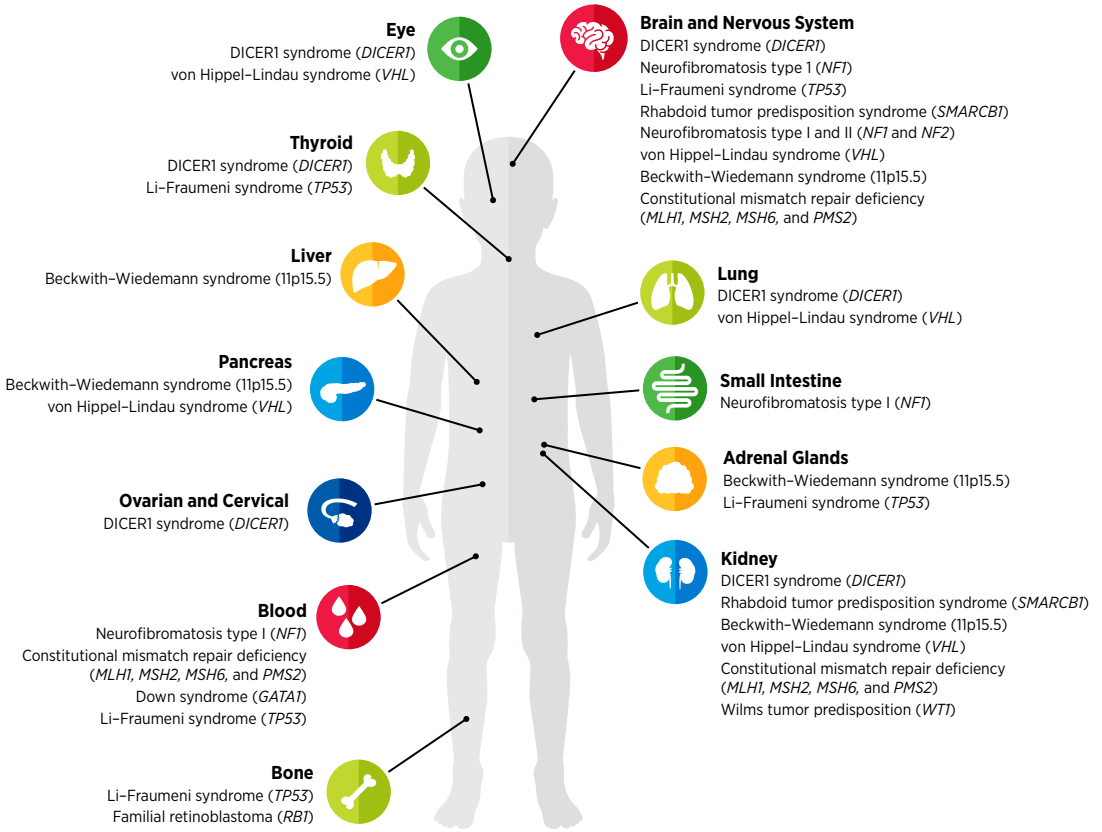
Molecular and Cellular Influences Driving Pediatric Cancers

Cells store their genetic information in deoxyribonucleic acid (DNA), a molecule comprising a double helix made of paired chemical bases—adenine (A), thymine (T), cytosine (C), and guanine (G)—arranged in repeating units called nucleotides. The entirety of a person's DNA is called the genome. In human cells, DNA is packaged with proteins called histones into structures known as chromatin, which are further compacted into chromosomes. Each chromosome contains hundreds to thousands of genes, which are segments of DNA that contain the directions for making proteins. Through a process called transcription, these directions are used to make messenger ribonucleic acid (mRNA), which is then translated to make specific proteins that carry out essential functions in the body.

When the genetic instructions or the processes that interpret them to make protein are altered, the finely tuned molecular and cellular programs that guide normal growth and development can be disrupted, leading to cancer development. These disruptions can stem from changes in the DNA sequence (genetic alterations) or its chemical modifications that control when and how genes are expressed (epigenetic modifications). These changes result in altered proteins or amounts of proteins, which in turn interfere with biological processes that guide cell growth and tissue formation (developmental pathways) as well as interactions with the surrounding tissue environment (tumor microenvironment).

FIGURE 4

Inherited Cancer Risk in Children and Adolescents



Depicted here are selected childhood and adolescent cancer types associated with inherited cancer predisposition syndromes. Also shown are the genes and variants linked with these syndromes, which increase the risk of developing specific cancer types.

Sources: (87,88).

Genetic Alterations

Understanding the genetic alterations that drive pediatric cancers is essential to unraveling cancer development and guiding the discovery of new, more effective therapies. Genetic alterations, also called mutations or variants, can be passed down through the germline or acquired throughout a person's life. Germline mutations are typically present in every cell in the body and can be inherited from parents or occur *de novo*—arising at conception or during early embryo development without being inherited—while somatic mutations, which are acquired over an individual's lifetime, are restricted to selected cells. Whether germline or somatic, pathogenic genetic mutations are those changes in DNA sequence that disrupt normal cellular functions, leading to cancer. For example, pathogenic mutations can activate oncogenes (genes that promote cell growth) or inactivate tumor suppressor genes (genes that restrict cell growth), both of which can contribute to cancer development.

These alterations are classified based on whether they are present in the DNA of germline and/or cancer cells, as well as based on their potential impact on gene and protein function, which can influence disease risk (see **Sidebar 4**, p. 32). As researchers continue to uncover the full spectrum of genetic changes in pediatric cancers, their discoveries are reshaping how these diseases are diagnosed, classified, and treated.

Research has revealed that integrating genomic data generated from both somatic alterations in a child's tumor and germline alterations in the child's normal tissue can provide powerful insights into pediatric cancer biology. Large-scale sequencing studies have found that over 70 percent of childhood tumors have diagnostic or actionable genetic alterations, including inherited mutations in cancer predisposition genes and somatic changes in developmental pathways, which could help clinicians either diagnose the cancer or identify appropriate treatments (82,83). Similarly,

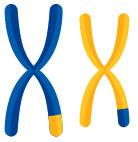
SIDEBAR 4

Genetic Alterations Driving Pediatric Cancers

Genetic alterations in pediatric cancers often differ from those in adults. These alterations disrupt normal growth and development pathways, drive tumor formation, and/or affect response to treatment. Pediatric cancers typically harbor fewer mutations overall, but they often involve structural changes in DNA that result in altered proteins, such as fusion genes, or lead to epigenetic dysregulation of cellular pathways.

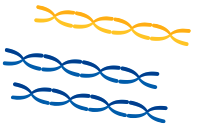
Types of Genetic Alterations That Contribute to Pediatric Cancer Development

TRANSLOCATION OR REARRANGEMENT: Occurs when two separate genes or pieces of chromosomes join to produce a new protein or different amount of protein. These changes often generate gene fusions.



EPIGENETIC VARIATION: Changes in methylation or chromatin packaging that either make genes available or unavailable for transcription at the wrong developmental time point.

GENE AMPLIFICATION: Reflects extra copies of genes in the genome, which may lead to higher quantities of certain proteins that can enhance cell survival and growth.



SINGLE BASE CHANGE: Refers to deletion, insertion, or substitution of a single nucleotide in DNA that can result in new proteins, altered versions of normal proteins, loss of protein function, or changes in the amount of protein produced.

LARGE DELETION: Indicates loss of larger sections of genes or regions of chromosomes, which can eliminate genes encoding key regulators of normal cell growth and survival.

How Genetic Alterations are Classified and Interpreted in Pediatric Cancer

Genetic alterations, also called variants, can be classified and interpreted in different ways. These classifications can guide how clinicians interpret whether a variant is likely to cause disease.

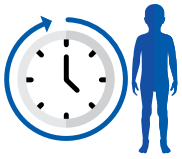
Based on their origin and distribution in the body

GERMLINE: Present in egg or sperm cells; typically present in all cells of the body. These mutations are either:

- **Inherited:** Passed from parents to child through the germline; or
- ***De novo:*** Arise for the first time in the egg or sperm cell of a parent, or in the fertilized egg itself, but not inherited from either parent.

SOMATIC: Acquired during a person's life; present in only certain cells in the body, such as those that give rise to tumors.

MOSAIC: In some cases, mutations can be present in only a subset of cells, a state known as mosaicism, which can be germline or somatic.



Variants are often classified based on their clinical effect*

PATHOGENIC (P): Variants are expected to affect gene function and are disease-associated.

LIKELY PATHOGENIC (LP): Variants are likely to affect gene function and are disease-associated, but this is not definitive or is not definitive for that specific disease.

BENIGN (B): Variants are not expected to affect gene function and are not disease-associated.

LIKELY BENIGN (LB): Variants are likely not expected to affect gene function and are likely not disease-associated, but this is not definitive.

VARIANT OF UNKNOWN SIGNIFICANCE (VUS): Variants for which there is not enough information to support a definitive classification as benign or pathogenic. Also called variant of uncertain significance.

* This is a rapidly evolving field. As more data become available, variants may be reclassified into more definitive groups.

SIDEBAR 5

Technologies Accelerating Discovery in Pediatric Cancers

Innovative technologies are driving progress in pediatric cancer research by enabling the generation and analysis of diverse types of biological data, each offering unique insights into the molecular and cellular underpinnings of pediatric cancers.

Types of Technological Approaches*

TECHNOLOGY	IMPACT ON PEDIATRIC CANCER RESEARCH
Whole-genome sequencing (WGS): Provides the entire sequence of the human genome from normal and cancer cells.	Reveals both common and rare variants of small and large sizes across the entire genome, including variants in coding and non-coding regions, providing a comprehensive view of alterations that contribute to cancer development.
Whole-exome sequencing (WES): Provides the sequence of the "exome," the protein-coding regions of the genome.	Identifies variation in genes that may affect protein function and contribute to cancer development, providing a focused and cost-effective view of clinically relevant alterations in coding regions of the germline and cancer exomes.
DNA methylation profiling: Detects chemical modifications to DNA that define the cell type of origin, providing more definitive diagnosis.	Enables tumor classification, identifies methylation patterns driving cancer, and provides biomarkers for prognosis, capturing signatures that genetic data alone cannot.
RNA sequencing: Reads RNA molecules and measures gene expression.	Quantifies gene expression levels, detects fusion genes and tandem duplications, and identifies transcript variants, providing insight into dysregulated pathways driving cancer and can be used to refine diagnosis.
Single-cell analysis: Examines genomic, epigenomic, transcriptomic, or proteomic information in individual cells.	Captures differences between tumor and healthy cells or between individual cells within a tumor, revealing tumor heterogeneity and detecting cell-specific signals that could be missed in bulk cell analysis.
Spatial omics (e.g., spatial transcriptomics, spatial proteomics): Maps molecular information, such as gene and protein expression, across regions of a tissue.	Provides context to how cancer and immune cells are positioned in a tissue and how they interact within a spatial context, revealing heterogeneity and region-specific interactions and microenvironments.
Computational analysis and modeling tools: Use algorithms to integrate omic datasets and model the biology of cancers.	Predict cancer biology, therapy-driven evolution and treatment responses, progression from primary to metastatic disease, identify new therapeutic strategies, and integrate complex datasets into testable hypotheses.
Open-access platforms and big data portals: Provide access to public databases sharing cancer data.	Facilitate collaborations by making large datasets available, promoting transparency, democratizing data access, and accelerating innovation in pediatric cancer research.

Types of Biological Data*

GENOMICS: Data that details the sequence of genomic DNA in a biological sample, including altered sequences that drive cancer predisposition, development, or progression.

TRANSCRIPTOMICS: Data that details all RNA molecules in a biological sample, including which genes are being expressed or silenced and which exons are used.

PROTEOMICS: Data that details all proteins in a biological sample, including quantities, structures, and interactions used to identify disease markers and therapeutic targets in cancer.

EPIGENOMICS: Data that details epigenetic changes in cells of the body, such as DNA methylation and histone modification, to understand how gene regulation is altered in cancer.

MULTI-OMICS: Integrated data from multiple "omic" measures of a biological sample that can be used to provide a comprehensive view of the molecular changes underpinning cancer biology. For example, proteogenomics combines genomic, transcriptomic, and proteomic data to link DNA and RNA alterations to protein expression.

* This list presents a selected set of technologies and biological data that are accelerating discovery in cancer research and is not intended to be comprehensive.

pan-cancer studies analyzing tumors from children and from adolescents and young adults (AYAs) showed that over half of them carried potentially druggable mutations, and up to 18 percent of pediatric patients had an inherited germline variant predisposing them to cancer (84,85).

Emerging technologies are expanding our ability to detect a wide spectrum of genetic alterations (see **Sidebar 5**, p. 33). For example, researchers using an approach that combines whole-genome sequencing (WGS), whole-exome sequencing (WES), and RNA sequencing to analyze paired tumor and normal tissue samples uncovered both large and small genetic alterations in 86 percent of the pediatric cancers sequenced, including clinically relevant variants that would have been missed or not effectively detected using any one sequencing approach alone (85). Similarly, a study integrating WGS, RNA sequencing, and DNA methylation profiling of paired tumor and normal samples in high-risk pediatric cancer patients identified actionable variants and refined diagnoses (83). These studies demonstrate the value of combining these technological approaches for comprehensive molecular characterization.

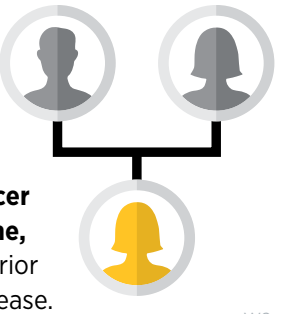
The following sections describe how different genetic alterations contribute to pediatric cancer risk, development, and treatment outcomes.

Germline Variants in Cancer Predisposition Genes

Germline variants in cancer predisposition genes play a critical role in determining the risk of developing pediatric cancer (see **Sidebar 4**, p. 32). A recognizable pattern of cancer within families that stems from pathogenic germline variants in cancer predisposition genes is often classified as a cancer predisposition syndrome (CPS) (see **Figure 4**, p. 31). For example, at least 13 CPSs are now known to increase the risk of developing pediatric acute lymphoblastic leukemia (ALL), including both overt syndromes with recognizable features and covert syndromes lacking clear clinical features (see **Pediatric Cancer Predisposition and Surveillance**, p. 47) (86).

Up to 18 percent of all pediatric cancer cases are attributed to pathogenic or likely pathogenic germline variants in cancer predisposition genes, including those in the *TP53, BRCA2, NF1,* and *RB1* genes (87,89). Genome-wide association studies and sequencing efforts have identified recurrent germline mutations that increase risk for specific pediatric cancers. For example, alterations in the *IKZF1, PAX5,* and *ETV6* genes increase risk for ALL, the most common childhood cancer; alterations in the *ALK* and *PHOX2B* genes are linked to neuroblastoma, the most common solid tumor in children arising outside the brain; and alterations in DNA damage repair genes—such as *FANCA, FANCC,* or *ATM*—increase the risk for Ewing sarcoma and leukemias (90-92).

Although ***de novo* germline mutations** are not inherited, they can still predispose the affected child to cancer and **may result in a cancer predisposition syndrome,** even when there is no prior family history of the disease.



W9

These inherited alterations can shape the biology of pediatric cancers and influence clinical outcomes. For example, children with Down syndrome—a genetic condition caused by having an extra copy of chromosome 21 in some or all of the body's cells—who are diagnosed with a rare subtype of acute myeloid leukemia have vastly better outcomes than children without Down syndrome with the same subtype of leukemia (93). This is due to the unique biology of Down syndrome–associated myeloid leukemia, which is more sensitive to chemotherapy.

Pediatric colorectal cancer is extremely rare, and children often experience delayed diagnosis and poor clinical outcomes due to nonspecific clinical symptoms and limited awareness among clinicians. Findings from a small clinical study showed that CPSs caused by inherited mismatch repair deficiency—a condition resulting from mutations in genes responsible for correcting mistakes made when a cell makes copies of its DNA—underlie a subset of pediatric colorectal cancer cases, underscoring the need for earlier detection and diagnosis to improve outcomes in children with this rare disease (94).

Recent research has also demonstrated that an understudied class of rare germline variants, germline structural variants—which are large genomic rearrangements that involve 50 or more nucleotides—can increase the risk of developing pediatric solid tumors like neuroblastoma, Ewing sarcoma, and osteosarcoma (95). These structural variants disrupted critical genes, including those involved in DNA repair and normal tissue development, and many occurred *de novo* or were inherited from unaffected parents. Although germline structural variants contribute to only a minority of pediatric cancer cases, they represent an important and previously underrecognized form of inherited cancer risk.

These examples highlight how germline mutations can influence cancer risk, disease progression, and response to treatment, emphasizing the importance of integrating germline testing into routine pediatric cancer care. Importantly, identifying a germline mutation can guide ongoing follow-up for the child and adolescents, and inform genetic counseling and testing for family members (see **Pediatric Cancer Predisposition and Surveillance**, p. 47).

Somatic Mutations

Somatic mutations are genetic alterations that arise in individual cells during a person's lifetime (see **Sidebar 4**, p. 32). In pediatric cancers, these mutations typically occur early in development and drive tumor formation by disrupting genes that control cell growth, differentiation, or DNA repair. Somatic alterations range from small single-nucleotide variants (SNVs) and insertions or deletions (indels) to large structural variants (SVs), including chromosomal translocations, inversions, and complex genomic rearrangements. Both large and small alterations may contribute to the genetic complexity of pediatric tumors and influence cancer development.

Somatic mutations can also play a role in the development of cancer in children and adolescents with inherited CPS (see **Figure 4**, p. 31), as described by the "two-hit hypothesis." This model suggests that even when a mutation is present from birth (first hit), some malignancies develop only after a second pathogenic mutation (second hit) is acquired in the remaining healthy copy of that gene. Recently, a study in children with the neurofibromatosis type I (NF1) predisposition syndrome found that second hits in the NF1 gene can occur in normal tissues, not just in tumors. These second hits were found in normal tissues throughout the body, showing that cells can acquire cancer-related mutations without immediately progressing to tumors, underscoring the complexity of tumor initiation (96).

Somatic mutations in pediatric tumors often show unique features compared to those in adults. A large-scale WGS analysis of 785 pediatric tumors across 27 cancer types revealed that fewer SNVs and indels drive cancers in children than in adults, but when they do act as drivers of pediatric cancers, they often disrupt biological processes that are distinct from those in adults (see **Sidebar 3**, p. 30) (97).

Age-based genomic comparisons further underscore how pediatric and adult cancers are driven by distinct mutational profiles. A study in hematologic malignancies in children, young adults, and older adults reinforced a general feature of pediatric cancers—children and young adults tend to have lower tumor mutational burdens but more frequent oncogenic gene fusions and copy number alterations compared to older adults. Several mutations, such as those in the *NRAS, KRAS,* and *WT1* genes, were more prevalent in children and young adults, whereas *TP53* and *DNMT3A* mutations were more common in older adults (98). These findings emphasize the need for tailoring genomic profiling and treatment strategies to distinct age-related genomic features.

Large-scale genomics studies of pediatric B-cell ALL (B-ALL) have defined more than 20 molecular subtypes, each with specific germline and somatic alterations that shape disease biology and influence clinical outcomes (99). T-cell ALL (T-ALL) has historically been less well characterized, but recent research has identified biologically distinct subtypes of pediatric T-ALL based on alterations in segments of DNA that encode proteins (coding regions) as well as the parts that do not encode proteins but may control how certain genes are turned on and off (non-coding regulatory regions). In a study of over 1,300 pediatric T-ALL cases, researchers identified 15 molecular subtypes, each with distinct genomic drivers, gene expression patterns, and clinical outcomes. Notably, 60 percent of alterations driving leukemia development were in non-coding regions, many of which hijacked mechanisms that control normal gene activity (100). These advances are enabling new ways to assess and classify the risk of pediatric cancers and help clinicians personalize therapies using such classification (see **Progress in Pediatric Cancer Treatment**, p. 63).

Large SVs—such as chromosomal rearrangements, gene fusions, and complex rearrangements—represent a distinct category of genomic alterations that drive pediatric tumor development. These large-scale events can rewire gene regulation, create fusion proteins with abnormal activity, and disrupt tumor suppressor genes. Advances in DNA and RNA sequencing technologies and structural variant detection have uncovered the influence of SVs across many pediatric cancer types.

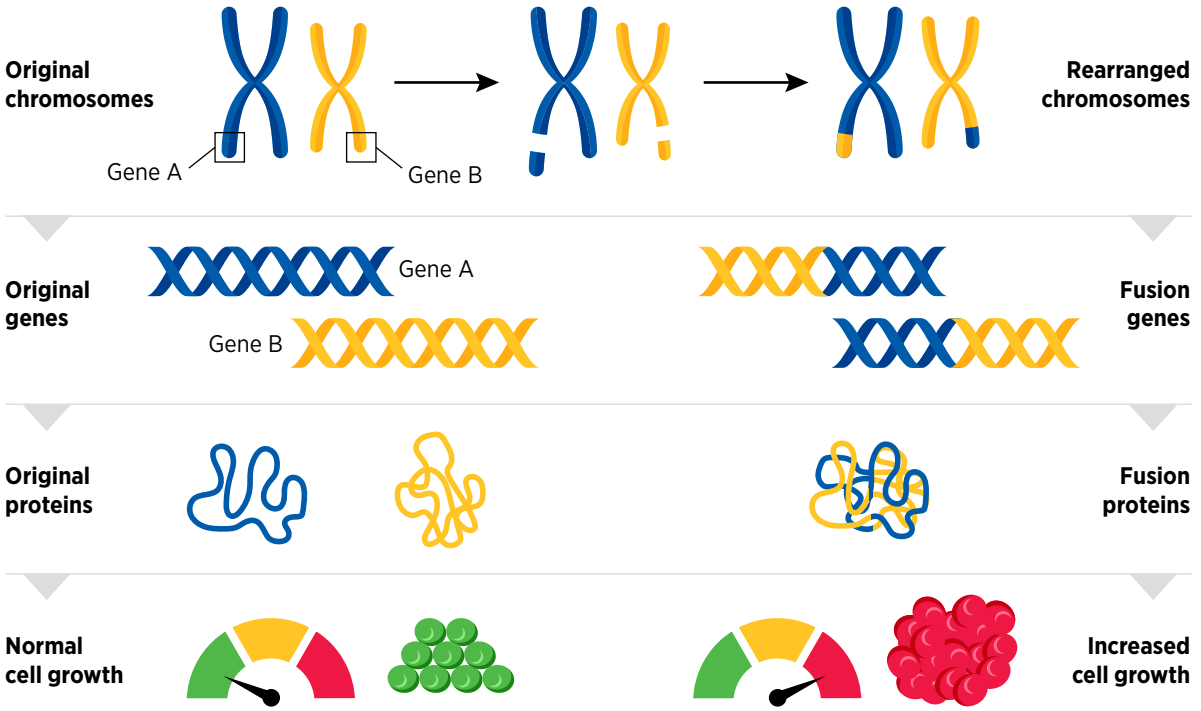
Cancer-causing gene fusions result from chromosomal rearrangements and constitute a class of genetic alterations in which two genes, present on two different chromosomes (more common) or on the same chromosome (less common), fuse to make a gene that is not present in normal cells and, in turn, a unique protein with altered function known as a fusion oncoprotein. These fusions occur across a wide range of pediatric cancers and are known drivers of cancer development (see **Figure 5**, p. 36).

Chromosomal rearrangements frequently involve genes encoding either specialized enzymes that are present on the surface of the cell and regulate cell growth, migration, and survival, or specialized proteins called transcription factors that bind to DNA and turn genes on or off. The resultant fusion oncoproteins act as potent cancer drivers. Cancers driven by some fusions, such as those involving ABL or NTRK, can be effectively targeted with matched therapies, but other fusions, such as EWSR1::FLI1 in Ewing sarcoma or PAX3::FOXO1 in rhabdomyosarcoma, remain difficult to target directly (101).

Specific SVs can also be used to assess risk and predict treatment responses in pediatric cancer. The *IKZF1* gene encodes a protein that plays a critical role in normal blood cell development, including guiding B-cell maturation. A recent study of over 680 children with B-ALL indicated that certain large deletions in the *IKZF1* gene are strongly associated with relapse. These deletions were most common in B-ALL

FIGURE 5

Generation of Fusion Proteins Through Chromosomal Rearrangements



Chromosomal rearrangements, including chromosomal translocations, deletions, inversions, and duplications, occur due to errors in cell division and can bring genes into proximity or fuse them to create abnormal proteins. For example, chromosomal translocations happen when genes present on different chromosomes (depicted as Gene A and Gene B) fuse to give rise to fusion genes that are not present in normal cells (shown as multicolor genes). Proteins made from the fusion genes (fusion oncoproteins) often have novel properties that hijack normal cellular mechanisms, such as cell growth, to drive cancer development.

cases with *BCR::ABL1* gene fusions and in *BCR::ABL1*–like (or Philadelphia chromosome–like) subtypes, two high-risk genetic forms of the disease, often with available drugs targeting the gene fusion (102).

Large SVs that involve oncogene amplifications can drive uncontrolled cell proliferation and tumor development. The *MYCN* gene encodes a member of the MYC protein family that plays a critical role in both normal development and tumor growth. In neuroblastoma, the most common type of extracranial solid tumor in children, amplification and overexpression of the *MYCN* gene have emerged as an indicator of high-risk disease (103). Indeed, amplification and overexpression of *MYCN, ALK,* and other genes have also been shown to be predictive of a poor outcome in pediatric brain tumors, retinoblastoma, sarcomas, and other solid tumors. Although it remains difficult to target the MYCN protein directly, emerging strategies, such as destabilizing the protein or interfering with the regulatory networks and molecular partners that control its function, offer promising therapeutic opportunities (see **Evaluating Novel Targets and Innovative Therapeutic Strategies**, p. 101) (104).

Complex genomic rearrangements are large structural changes in DNA that can disrupt normal genome organization and drive cancer development. Examples include chromothripsis—a phenomenon in which a chromosome shatters and is pieced back together in the wrong order—and amplification of extrachromosomal DNA, which are circular DNA fragments that exist outside chromosomes and can drive high oncogene expression and genomic instability. In a recent study, researchers using WGS from 120 primary tumors showed that 47 percent of pediatric solid tumors harbor complex genomic rearrangements that are linked to worse clinical outcomes (105).

Both small and large somatic alterations shape the biology and, in turn, the clinical landscape of pediatric cancers. This knowledge also emphasizes the need for more comprehensive

characterization of pediatric cancer genomes to improve diagnostic precision and guide therapeutic care for each patient. Emerging technologies and advances in molecular profiling will be essential to guide the development of more precise, age-tailored treatment strategies for children and adolescents with cancer.

Epigenetic Modifications

Epigenetic modifications are chemical changes that regulate how genes are expressed without altering the underlying DNA sequence. These modifications involve the addition or removal of chemical marks on DNA and modifications to the sequences of histones—the proteins that package chromosomal DNA into chromatin. In healthy cells, both epigenetic modifications and chromatin packaging tightly regulate gene expression, but in cancer this regulation is disrupted. Unlike adult tumors, which tend to harbor high mutational burdens, pediatric cancers are often driven by disruptions in the epigenetic machinery that controls gene activity.

One common type of epigenetic modification is DNA methylation, in which methyl groups are added to specific regions of the genome to regulate whether nearby genes are turned on or off. Recently, researchers studying how germline SVs influence tumor DNA methylation across more than 1,200 pediatric brain tumors have demonstrated that these alterations can significantly influence the epigenetic landscapes in important parts of the DNA that regulate gene activity, altering the expression of cancer-related genes and affecting clinical outcomes (106).

Characterization of DNA methylation patterns has emerged as an important biomarker for diagnosis and risk stratification in pediatric cancers (see **Sidebar 5**, p. 33). The World Health Organization's 2021 guidelines established DNA methylation arrays as an important diagnostic tool for pediatric brain tumors, providing more precise tumor classification than traditional tissue analysis and reducing unclear diagnoses (107). Methylation profiles are increasingly being coupled with artificial intelligence (AI), shifting the diagnostic standard for brain tumors, such as medulloblastoma and gliomas, and illustrating how AI is being integrated into pediatric oncology to enhance diagnostic accuracy (see **Artificial Intelligence**, p. 43).

In pediatric leukemias, DNA methylation-based classifiers use patterns of DNA methylation to group patients into biologically or clinically meaningful subtypes (108,109) and has entered routine clinical practice for juvenile myelomonocytic leukemia, a rare forms of childhood leukemia (110). For T-ALL, which had defied genomic classifiers, methylation profiling significantly improved prognosis when combined with an assessment of minimal residual disease (MRD), which detects a very small number of cancer cells in the body. Subtypes determined by this classifier were associated with distinct transcriptomic, genomic, and cellular features, suggesting different pathways that contribute to leukemia and offering opportunities to refine treatment decisions (108).

Epigenetic regulators are being explored as therapeutic targets, given their importance in driving pediatric cancers, including fusion protein–driven cancers. For example, in January 2020, the US Food and Drug Administration (FDA) approved the molecularly targeted therapeutic tazemetostat for the treatment of pediatric patients age 16 years and older with a certain type of sarcoma. Tazemetostat works by targeting the epigenetic regulator EZH2 and preventing it from adding methyl groups to histones (see **Expanding Treatment Options for Patients with Solid Tumors**, p. 84). Additionally, in November 2024, FDA approved the small molecule revumenib for pediatric patients 1 year and older with acute leukemia that has relapsed or stopped responding to standard treatments. Revumenib disrupts the binding of a protein encoded by the *KMT2A* gene, which plays a role in normal blood cell development through epigenetic regulation of gene expression (see **Adding Precision to the Treatment of Leukemia**, p. 74). Additional epigenetic drug classes, such as DNA hypomethylating agents and histone deacetylase inhibitors, are also under investigation in pediatric settings and may further expand therapeutic strategies that modulate the epigenome.

As the field advances, integrating epigenomic profiling into clinical workflows may allow for earlier detection, refined prognosis, and personalized therapies targeting the epigenetic underpinnings of pediatric cancers.

Developmental Pathways Gone Awry

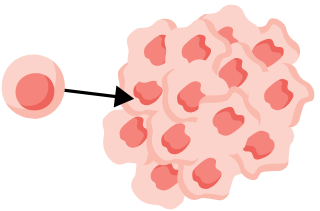
Genetic and epigenetic alterations often drive pediatric cancers by functionally rewiring or arresting normal developmental pathways. Pediatric cancers often arise from cells at specific embryonic or fetal developmental stages in which key pathways controlling tissue growth and differentiation have been disrupted (see **Sidebar 6**, p. 38) (25).

In the developing body, immature stem-like cells normally keep dividing until they develop into fully mature cells with specialized roles. Recent research has revealed that some cancers take control of and block the processes that normally guide cells into their final, specialized roles. In diffuse midline gliomas (DMGs), a fast-growing, highly aggressive brain cancer, a mutation in the histone protein known as H3K27M changes the way DNA is packaged, whether genes are turned on or off, and how much they are expressed. A recent study showed that this mutation locks cells in an immature, proliferative state that fuels cancer growth, highlighting a potential therapeutic opportunity for this pediatric brain cancer (117).

SIDEBAR 6

Key Developmental Pathways Disrupted in Pediatric Cancers

Many pediatric cancers arise from disruptions in the cell-signaling pathways that guide normal growth and development. These pathways—which help shape tissues and organs during early life—can be hijacked by cancer cells when mutations or other changes occur. Mutations can occur in different genes within the same pathway and lead to disruption of normal signaling. Highlighted below are several key developmental pathways often altered in pediatric cancers.



Developmental Pathway*	Normal Role in Childhood Development	How Cancer Disrupts the Pathway	Cancer Types
SONIC HEDGEHOG	Regulates cell growth and organ formation, especially in the brain and limbs.	Persistent activation through mutations drives uncontrolled proliferation, making brain and muscle cells grow unchecked.	Medulloblastoma and rhabdomyosarcoma.
WNT/β-CATENIN	Controls cell fate and location during organ formation, especially in the nervous system and skeletal development.	Aberrant activation leads to accumulation of signals that keep cells multiplying instead of maturing.	Hepatoblastoma, medulloblastoma, Wilms tumors, desmoid tumors, and colorectal cancer.
NOTCH	Directs cell–cell communication to regulate growth and tissue boundary formation.	Dysregulated signaling keeps cells in an immature state and promotes survival of malignant cells.	T-ALL, certain brain tumors, and sarcomas.
HIPPO	Restrains organ size by inhibiting growth when the appropriate size is reached.	Loss of regulation drives uncontrolled cell growth and survival.	Rhabdomyosarcoma, hepatoblastoma, and sarcomas.
RAS/MAPK	Regulates cell growth, survival, metabolism, and differentiation, and guides organ development and cell fate decisions.	Persistent activation through mutations drives uncontrolled cell growth and survival.	Gliomas, neuroblastoma, rhabdomyosarcoma, and leukemia.
PI3K/AKT/MTOR	Controls cell growth, protein synthesis, metabolism, and survival signals during organ development and neuronal growth.	Persistent activation through *PTEN* loss, growth factor receptor overexpression, or mutations leads to uncontrolled cell growth and survival.	Leukemias, neuroblastoma, rhabdomyosarcoma, and brain tumors.

* This list presents only a selected set of developmental pathways disrupted in pediatric cancers and is not intended to be comprehensive.

PI3K/AKT/mTOR, phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin pathway; *PTEN,* phosphatase and tensin homolog (deleted on chromosome 10); RAS/MAPK, rat sarcoma/mitogen-activated protein kinase; T-ALL, T-cell acute lymphoblastic leukemia; Wnt/β-catenin, wingless/integrated–β-catenin signaling pathway.

Sources: (111-116).

Disrupted developmental pathways can also intersect with the nervous system to fuel tumor growth. During normal brain development, nerve cells called GABAergic neurons signal to immature brain cells to support their growth. In DMGs, the same signals are hijacked by tumors to accelerate growth and progression. This effect is further accelerated in the presence of lorazepam (Ativan)—a common sedative that works by enhancing GABA signaling. These findings underscore the importance of understanding the unique tumor–nervous system interactions that drive DMG progression to enable the development of effective and safe therapeutic strategies (118).

New therapeutic advances have emerged that target neuronal signaling. In August 2025, FDA approved dordaviprone for children age 1 year and older with DMG harboring an H3K27M mutation. Dordaviprone works by blocking dopamine receptors,

components of a normal neuronal signaling pathway essential for brain development and function, that tumor cells can hijack to promote their growth and survival (see **Personalizing the Treatment of Brain Tumors**, p. 80). Because pediatric cancers often hijack normal developmental pathways to promote growth, understanding these mechanisms provides critical opportunities to develop additional therapies that disrupt tumor-supportive signaling and restore developmental programs.

Importantly, our ability to discern these mechanisms often requires investigating specific cancer drivers in model systems or using patient-derived models. However, few models exist for studying pediatric cancers because of their rare nature, which hinders our ability to mechanistically evaluate the cancer driving events and devise approaches to address the dysregulated pathways.

Tumor Microenvironment

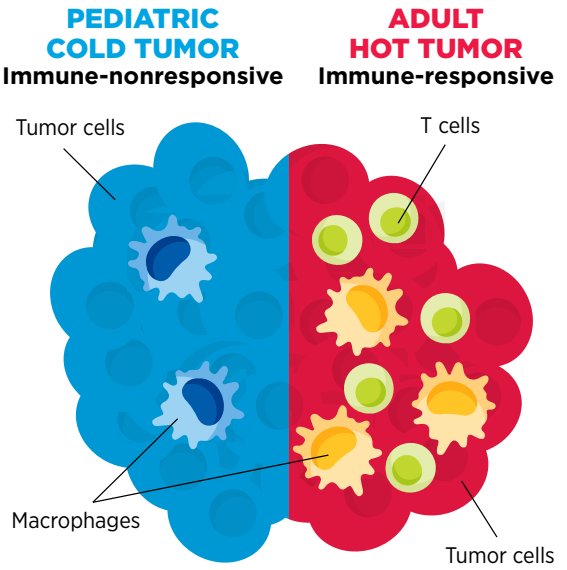
Complex interactions between cancer cells and their surrounding environment, known as the tumor microenvironment (TME), contribute to disease progression. The TME—composed of cancer and supportive, non-cancer (immune, stromal) cells, blood vessels, signaling molecules, and structural components—plays a critical role in all cancers, including pediatric cancer, by influencing tumor initiation, growth, and response to treatment. Pediatric TMEs are shaped by developmental stage, unique immune system characteristics, and tumor-intrinsic features, such as specific mutations, epigenetic changes, altered signaling, and metabolic rewiring.

Research comparing pediatric cancers with adult cancers has demonstrated that the TME is greatly influenced by a patient's age. For example, the TME in children and AYAs with classical Hodgkin lymphoma often exhibits patterns that are distinct from those in older adults, including differences in cellular composition and cell–cell signaling networks that support malignant cell growth and influence treatment response (119). These differences underscore why diagnostic, prognostic, and treatment approaches designed for adults may not always work in children, and those designed for children may not be effective in adults, highlighting the need for age-tailored strategies to target the unique TME in pediatric patients.

Within the TME, the tumor immune microenvironment (TIME) refers to the network of immune cells and immune-modulating factors that interact with the tumor. The TIME can shape how pediatric cancers develop and respond to treatments, and a deeper understanding of these processes is essential for advancing effective immunotherapies for young patients.

In a recent study, immune profiling in 191 children with diverse solid tumors showed that certain tumor types—such as neuroblastoma, Wilms tumors, liver tumors, lymphomas, and retinoblastomas—share systemic immune characteristics, suggesting that immune markers and treatment approaches could be applied across certain cancer types (120).

Tumor Immune Microenvironment



Advanced technologies that allow analyses of single cells in their normal spatial context inside tissues and tumors are revealing how cancer treatments reshape the TIME. In high-risk neuroblastoma, 22 patients analyzed before and after chemotherapy showed significant shifts in tumor and immune cell subpopulations, with a reduction of certain fast-growing tumor cells but an increase in certain immune cells that weaken the immune response (121). In pediatric high-grade gliomas, chemotherapy and radiation reduced certain pro-inflammatory immune cells, reshaping the TIME. When patients received subsequent immunotherapy, the altered TIME had a disproportionate number of immune-suppressing T cells, which may limit long-term success of the treatment (122). These findings emphasize that an initial therapy can rewire the TME in ways that may influence the success of subsequent treatments.

The pediatric TME/TIME can act as both a barrier to and an opportunity for successful cancer treatment. By uncovering how these environments develop, support tumor growth, and evolve with treatment, researchers can design more precise interventions. Integrating emerging single-cell, spatial, and multi-omic technologies will deepen our understanding of pediatric biology and accelerate the translation of these insights into more effective, tailored therapies for pediatric cancers.

Innovative Technologies Decoding Pediatric Cancer Complexities

Innovative technologies are transforming the way researchers study pediatric cancer. WGS and WES are expanding our ability to uncover genomic features that provide information on likely outcomes, therapeutic targets, and germline predisposition in children and adolescents (85). In addition, scientific breakthroughs like AlphaFold—which earned David Baker, PhD, John M. Jumper, PhD, and Demis Hassabis, PhD, the 2024 Nobel Prize in Chemistry for leveraging AI to predict the three-dimensional (3D) structure of proteins—are helping researchers better understand the altered structures of proteins resulting from pathogenic variants that are associated with pediatric cancers, opening new paths to drug development (123).

Tumor heterogeneity describes the differences that can exist between tumors arising in the same tissue type across different individuals as well as among multiple tumors or cells in the same tumor within an individual patient when the cancer evolved or spread. Single-cell, multi-omic, and spatial profiling technologies are uncovering previously underappreciated tumor heterogeneity, including differences in cell types and their expression of gene variants, deepening insights into pediatric cancer development.

Gene editing tools such as CRISPR are clarifying how specific genetic changes drive disease, knowledge that can reveal new therapeutic targets. Advanced model systems are capturing the unique genetic, epigenetic, and microenvironmental characteristics of pediatric cancers. AI-based tools are integrating complex imaging, genomic, and clinical data to enable earlier diagnosis and more accurate tumor classifications. Liquid biopsy, which analyzes cancer-derived material circulating in blood, urine, or other body fluid, is offering a minimally invasive way to monitor cancers in real time, enabling earlier detection, treatment response monitoring, and timely relapse intervention.

The knowledge gained from these technologies is reshaping both the research landscape and the future of pediatric cancer care, paving the way for more personalized, less toxic therapies.

Single-cell, Multi-omic, and Spatial Technologies

Single-cell, multi-omic, and spatial technologies (see **Sidebar 5**, p. 33) are allowing researchers to better understand the biology of pediatric cancers. These cutting-edge tools can trace cancer development to its earliest stages by capturing the diversity of cell types and states within tumors and their microenvironments (see **Tumor Microenvironment**, p. 39), offering insights into how pediatric cancers evolve, recur or metastasize, and respond to treatment.

Using these technologies, researchers analyzed over 540,000 individual cells from 159 pediatric leukemia cases and healthy bone marrow samples to build a comprehensive single-cell atlas—a detailed map indicating what types of cells are present and how they behave. This effort identified a nine-gene–signature that may reflect common features of malignant transformation across diverse genetic subtypes of pediatric leukemia (124). The resulting *Pediatric Single-cell Cancer Atlas* is an open-access resource enabling researchers to investigate gene expression, cell types, and potential biomarkers in pediatric leukemias. In a similar study, researchers used single-cell transcriptomic technologies to identify gene signatures that reflect shared mechanisms of malignant transformation and predict poor outcomes and resistance to standard chemotherapy across diverse pediatric leukemia subtypes (125).

Multi-omic technologies are also helping researchers uncover how developmental lineages shape disease progression and the mechanisms that influence treatment response in pediatric leukemia. Single-cell transcriptomics and epigenomic studies are revealing the developmental trajectories cells take as they mature and identifying small populations of cells that display characteristics similar to stem cells—cells from which other types of cells develop—across multiple leukemia subtypes (126-129). Integration of transcriptomic, proteomic, and drug sensitivity data resulted in a better understanding of subtype-specific differences in cancer biology and treatment response. These studies revealed distinct molecular features across subtypes and identified potential therapeutic candidates through drug sensitivity profiling.

By combining single-cell and spatial technologies, researchers are also gaining new insights into pediatric solid tumors. For example, researchers identified a transient cell state that is unique to high-risk neuroblastoma and associated with poor outcomes. This state is shaped by epigenetic changes and the resulting cell signaling that influences the ability of cells to change their identity or function over time to help them survive, grow, or resist treatment (130). In another study, researchers traced the timing of genetic events in an aggressive subtype of medulloblastoma to identify when and how key alterations emerge during tumor growth. The findings show that large-scale chromosomal changes initiate tumor growth early in fetal development, while single-gene alterations arise later, contributing to disease progression and resistance to therapy (131). These discoveries reveal how advanced molecular tools can uncover features of tumor development, shedding light on why some pediatric cancers become more aggressive.

CRISPR Gene Editing

CRISPR is a powerful and versatile gene editing tool that allows researchers to precisely modify DNA. Researchers have harnessed CRISPR to deepen our understanding of mechanisms that drive human diseases and explore new ways to treat them. For example, CRISPR can be used in model systems to re-create genetic mutations to understand how they affect the body, fix or replace faulty genes, add tags to track how genes behave, turn genes on or off without changing the DNA itself, or engineer immune cells to fight disease.

Traditional CRISPR editing tools are made up of two parts, a programmable RNA guide that can find a specific site in the DNA and a Cas protein that acts like molecular scissors to cut both strands of DNA at that site. After DNA has been cut, the cell's natural DNA repair processes can be harnessed to make changes with high precision and accuracy. These innovative tools are supporting a new era of discovery in pediatric cancer research. While pediatric cancers often harbor fewer mutations than adult tumors, they remain genetically complex and biologically distinct.

High-throughput CRISPR functional genomic assays are being applied to address one of pediatric oncology's most persistent challenges: how to interpret variants of unknown significance, variants whose role in the disease is unclear and therefore cannot be understood in terms of their clinical impact (see **Sidebar 4**, p. 32). In many cases, comprehensive DNA sequencing, such as WGS or WES, reveals rare or novel somatic or germline variants in cancer-relevant genes with unclear clinical significance. These are typically variants that change one amino acid for another, but without an obvious impact on the resulting protein.

Using CRISPR-based screening to functionally test all possible variants of unknown significance in known cancer predisposition genes can improve how genetic findings can be interpreted, guide clinical decision-making, and help determine which children or adolescents may benefit from enhanced surveillance or targeted interventions (132). In a recent study, researchers used CRISPR to investigate germline variants in the *BARD1* gene, which is associated with increased risk of neuroblastoma, and identified a subset that exhibited compromised DNA repair, widespread genomic instability, and heightened sensitivity to DNA-damaging therapies. These findings help clarify how inherited genetic variants contribute to pediatric cancer and may lead to their inclusion in clinical reporting of cancer predisposition, resulting in enhanced surveillance (133).

In cancer, gene dependencies occur when cancer cells rely on specific genes for their survival and growth, making those genes potential therapeutic targets. Researchers using large-scale CRISPR screening have enabled the development of a pediatric cancer dependency map, revealing that pediatric cancers exhibit distinct gene dependencies from those in adult cancers (134). These results reveal new therapeutic vulnerabilities unique to childhood and adolescent cancers and emphasize the need for leveraging these vulnerabilities to develop drugs specifically against pediatric cancers.

CRISPR has also been used to find effective drug combinations for high-risk subtypes of neuroblastoma, for which standard therapies often fail. By mapping how the loss of a specific gene changes the way cells respond to drugs across more than 94,000 gene–drug–cell line combinations, researchers identified new drug combinations, including inhibition of the DNA repair gene *PRKDC,* that dramatically improved sensitivity to doxorubicin, a commonly used chemotherapy drug (135).

Research Model Systems

Model systems enable researchers to investigate how pediatric tumors develop, test new therapies, and explore resistance mechanisms before moving into clinical trials (see **Sidebar 7**, p. 42). By capturing the genetic, epigenetic, and microenvironmental characteristics of pediatric cancers, model systems accelerate the translation of laboratory discoveries into safer, more effective treatments (136).

Traditional cell line cultures, in which cancer cells grow as flat monolayers on plastic, offer a simple and accessible way to study cancer biology but often fail to replicate the complex architecture and microenvironment of patient tumors. To address these limitations, researchers are increasingly using 3D culture models to more closely re-create the architecture, cell–cell interactions, and microenvironmental cues of the original tumor.

In preclinical pediatric cancer research, organoids—miniature organ-like structures grown from a patient's own cells—are enabling studies of patient-derived tissues in 3D systems that retain genetic, histologic, and molecular features. These models can also capture cellular diversity and tumor heterogeneity. For example, by co-culturing 3D models with immune or stromal cells, the TIME can be more closely replicated (137). Tumoroids, sometimes referred to as cancer organoids, are 3D models derived from patient tumor cells that self-organize into multicellular structures that retain multi-omic characteristics of the original tumor (138). Pediatric cancer organoids are a valuable tool for modeling tumor biology and studying how these cancers respond to treatment.

Patient-derived xenografts (PDXs) are widely used for experimentally modeling human tumors and evaluating new therapies in mice. Some models incorporate human immune components to create "humanized" PDXs. These models

SIDEBAR 7

Commonly Used Models in Pediatric Cancer Research

To understand the biology of a disease, researchers use a variety of models that mimic what happens in healthy and disease conditions. Below are some of the most commonly used models in pediatric cancer research.

CELL LINES are cancer cells originally derived from tumors or tissues that have acquired, either naturally or through manipulation, the ability to grow indefinitely.

ORGANOIDS are three-dimensional, mini-organ-like structures generated from a patient's healthy or diseased cells that can resemble the structure, organization, and some of the functions of human tissues and organs. Organoids grown using a patient's tumor cells are called tumoroids.

GENETICALLY ENGINEERED MOUSE MODELS (GEMMS) are mice in which specific genes are intentionally altered to mimic cancer-driving variants. They retain their natural immune system and are ideal for studying tumor development and immune interactions.

PATIENT-DERIVED XENOGRAFTS (PDXS) are created by transplanting a patient's tumor into immunodeficient mice. They preserve the genetic and intratumoral cellular diversity of the tumor, though they do not retain the human immune microenvironment. They are widely used for testing drug responses and studying drug resistance mechanisms.

CELL LINE–DERIVED XENOGRAFTS (CDXS) are created by implanting cancer cell lines into immunodeficient mice. They are cost-effective to create and widely used for testing drug responses.

HUMANIZED XENOGRAFTS are models that incorporate human immune components to create "humanized" PDXs or CDXs, making them ideal for immunotherapy research.

ZEBRAFISH are small vertebrates that develop tumors that are histologically and genetically similar to human tumors and have transparent bodies that allow researchers to visualize tumor development in real time. They are widely used for studying tumor biology and testing drug responses.

FRUIT FLIES, also called *Drosophila melanogaster,* are easily genetically modifiable organisms that share similarities to human signaling pathways and regulatory systems. They are widely used for studying mechanisms of tumor initiation and progression and for modeling specific cancer gene alterations.

can better reflect pediatric TIME interactions and provide a powerful platform for evaluating immunotherapeutics. The Individualized Therapy for Relapsed Malignancies in Childhood program, led by the Hopp Children's Cancer Center and the German Cancer Research Center, shows how such models are being integrated into precision oncology. Within this effort, a multinational phase I/II clinical trial is evaluating novel immunotherapy combinations in children with high-risk cancers, using PDXs in parallel to understand how well these models predict drug response (139).

Genetically engineered mouse models (GEMMs) allow for investigations into the molecular underpinnings of pediatric cancers by introducing specific cancer-driving mutations in mice to study the effect of a single mutation or the impact of an altered signaling pathway. GEMMs carrying germline mutations that mirror predisposition syndromes have been used to understand how inherited genetic changes drive tumor initiation, why they arise in specific tissues, and how these cancers progress in children (140). Additionally, researchers have used GEMMs to recapitulate the histologic, epigenetic, and transcriptomic features of certain pediatric cancers while revealing profound variations within the same tumor as well as maturation patterns specific to cell lineage (141).

Some of the most powerful applications of model systems emerge when multiple research models are integrated to study disease mechanisms and treatment vulnerabilities. For example, researchers used organoids, PDXs, and GEMMs to investigate a key tumor-driving pathway in medulloblastoma and tested a novel treatment strategy targeting therapeutic vulnerabilities (142). This multi-model strategy shows how

integrating different research tools can accelerate discovery and translation into targeted treatments for children with aggressive cancers.

Collectively, these model systems form the foundation for translating discoveries in pediatric cancer biology into effective treatments. Initiatives such as the Pediatric Preclinical In Vivo Testing (PIVOT) Program of the National Cancer Institute (NCI) are building on this foundation. The PIVOT Program is systematically evaluating promising agents using rigorously characterized preclinical models to accelerate the development of effective therapies for pediatric cancers (143). By combining innovative model systems with coordinated testing efforts, the pediatric cancer research community can continue to accelerate the development of safer, more effective therapies.

Artificial Intelligence

AI is rapidly emerging as a transformative technology across the cancer care continuum, offering unprecedented opportunities to integrate complex imaging, genomic, and clinical data for improved patient care. In pediatric cancer, progress is restricted by the rarity of these diseases. As a result, datasets available to train robust AI models are much smaller, limiting performance, generalizability, and speed of translation into the clinic. Still, by leveraging machine learning (ML) and deep learning (DL) algorithms, AI can identify subtle patterns that may be imperceptible by traditional approaches, enabling earlier diagnosis, more accurate tumor classification, and better-informed treatment selection (144,145).

In diagnostics, AI is already demonstrating its potential to enhance the interpretation of histology and imaging data. For example, DL models trained on harmonized, multi-institutional libraries of pediatric sarcoma histology images achieved high accuracy in classifying tumor subtypes, including rare cases that can be difficult to identify using conventional methods (146). Similarly, DL approaches applied to serial magnetic resonance imaging (MRI) scans of children with gliomas predicted tumor recurrence up to a year in advance, enabling more tailored surveillance and potentially reducing unnecessary imaging (see **New Frontiers in Surveillance for Children With Cancer Predisposing Syndromes**, p. 58) (147).

AI has also advanced molecular profiling, particularly through ML-driven DNA methylation–based classification of certain pediatric tumors. In pediatric central nervous system (CNS) tumors, such tools have improved diagnostic accuracy, particularly for difficult-to-classify brain tumors like medulloblastoma and high-grade gliomas, and in some cases could improve prognosis and influence treatment decisions compared to conventional histopathology-based grading alone (148,149). Models that enable rapid molecular profiling are also emerging, making it possible to classify brain tumors based on sequencing and methylation signatures in less than an hour, or to provide tumor classification with detailed genetic and epigenetic information within 1 day. Similar ML approaches have been developed for cancers such as soft tissue and bone sarcomas, aiding diagnosis even when typical genetic markers are absent (150). These applications can potentially offer broad accessibility to tumor profiling, even in settings with limited resources, and can guide surgical decisions and enable faster, more personalized treatment planning (151,152).

Beyond tumor classification, AI-enabled integration of structural and functional genomics is revealing new biological insights into pediatric cancers. In a recent study, ML was used to merge large-scale protein interaction data with high-resolution cell imaging, creating detailed maps of the human cell. Researchers applied these maps to genomic data from 772 pediatric tumors across 18 cancer types, which assigned unexpected functions to 975 proteins and identified numerous proteins not previously recognized as pediatric cancer drivers (153). These multilayered maps provide a valuable tool for understanding pediatric cancer genomes and demonstrate how AI can connect basic molecular discoveries to new therapeutic targets.

AI applications in pediatric cancer research and care have the potential to enable early detection, deliver more accurate diagnoses, and provide deeper insights into tumor biology. However, the impact of these applications will depend on overcoming challenges such as limited pediatric datasets, model generalizability, and ethical considerations, as well as demonstrating their effectiveness through large clinical trials to determine if they improve outcomes before they can be integrated into practice.

Liquid Biopsy

Liquid biopsy analyzes cancer-derived material circulating in the body and has the potential to transform pediatric oncology, offering a minimally invasive way to capture real-time molecular information about a child's cancer. By detecting and analyzing tumor-derived materials—including circulating tumor cells and cell-free DNA (cfDNA) such as circulating tumor DNA (ctDNA)—in blood, urine, or cerebrospinal fluid (CSF), liquid biopsies can overcome many limitations of traditional tissue biopsies, including limited tissue availability, heightened risks from invasive procedures, and challenges associated with repeated sampling over the course of therapy. Thus, liquid biopsies could enable earlier diagnosis, more precise risk stratification, dynamic monitoring of treatment response, MRD detection, and relapse prediction. While applications for this technology are more advanced in adult cancers, continuing to develop approaches specific to pediatric cancers is essential to ensure

that children and adolescents equally benefit from these innovations.

Researchers have recently developed a method that could perform genomic characterization at diagnosis using cfDNA in children with hematologic malignancies and certain solid tumors. The new method offers several advantages over existing detection methods, which include needing only a limited sample amount and demonstrating robust detection of a diverse set of genomic aberrations (154). Similarly, for pediatric patients with advanced Wilms tumors, ctDNA profiling identified key chromosomal alterations and suggested potential prognostic value, with detectable ctDNA at diagnosis linked to poorer event-free survival (155). These findings highlight the value of ctDNA as a critical tool for both genetic characterization and risk assessment.

For CNS tumors, for which surgical access is limited, liquid biopsy of CSF is especially promising. In medulloblastoma, CSF ctDNA profiling accurately captured molecular characteristics of the tumor and detected MRD with greater sensitivity than standard methods, identifying relapse earlier than MRI in many cases (156,157). Additionally, liquid biopsy in pediatric CNS tumors could help distinguish true progression from pseudo-progression—a phenomenon in which new lesions develop or a tumor first appears to grow based on therapy response but not because the cancer is progressing—and monitor molecular changes during therapy to guide treatment decisions without the need for repeated invasive procedures (158).

In solid tumors, liquid biopsy is enabling insights into tumor evolution and therapeutic resistance. In high-risk neuroblastoma, serial ctDNA profiling uncovered clinically actionable mutations, revealed resistance mechanisms in response to targeted therapy, and detected progression before standard imaging or biomarkers (159). A recent review of over 340 research studies investigating the utility of liquid biopsy in pediatric solid tumors emphasized that these benefits extend to multiple tumor types with applications across diagnosis, monitoring, and relapse detection (160).

Taken together, these studies underscore the versatility of liquid biopsy in pediatric oncology, with demonstrated potential for refining risk assessment, guiding therapy, and detecting relapse across cancer types. Beyond these applications, liquid biopsy holds promise for surveillance of children and adolescents with inherited CPSs, where it could help detect primary or secondary cancers at the earliest stages (see **New Frontiers in Surveillance for Children With Cancer Predisposing Syndromes**, p. 58).

Yet routine clinical use of liquid biopsy remains limited in pediatric cancers compared to adult cancers, and a significant amount of research is still needed to improve assay sensitivity and standardize methods. Overcoming these hurdles will require continued investments in early detection, interception, and surveillance research to accelerate progress and ensure that the promise of liquid biopsy in pediatric cancer care matches advances already seen in adult oncology.

What Is Cell-free DNA?

Cell-free DNA (cfDNA) consists of tiny **DNA fragments** released into the blood when cells die. Tumor-derived cfDNA—including circulating tumor DNA—**can be analyzed through liquid biopsy assays to detect cancer, monitor treatment response, and track relapse,** offering a safer, less invasive alternative to surgery or repeated imaging.

W11

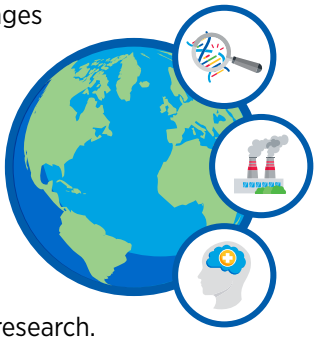
Shared Data and Collaborations Advancing Pediatric Cancer Research

Because pediatric cancers are rare and biologically distinct from adult cancers, progress depends on large-scale, interdisciplinary collaborations that facilitate sharing of patient samples, genomic data, research expertise, and clinical insights across institutions and around the globe. By sharing data and resources, these collaborations can accelerate our understanding of pediatric cancer biology and transform patient care. Building large-scale data resources that connect researchers worldwide, applying deep molecular profiling to personalize treatments for even the rarest tumor types, and harnessing cutting-edge technologies will drive the next generation of discoveries.

One of the most powerful strategies for advancing our knowledge of pediatric cancer biology has been the generation of shared data resources that give researchers and clinicians access to large, high-quality datasets linking genetic, clinical, and research information in ways that accelerate basic research discoveries and guide more personalized care.

For example, the Human Tumor Atlas Network (HTAN), launched as part of the Cancer Moonshot, is a collaborative, data-intensive research initiative supporting projects that apply advanced technologies to study individual cells and their

Cancer Grand Challenges



Cancer Grand Challenges is a global initiative launched in 2020 by the **National Cancer Institute** and **Cancer Research UK** to address some of the most complex and pressing scientific challenges in cancer research.

Scope: Challenges focus on critical unmet needs and are designed to tackle questions that no single team or institution could solve alone, spanning cancer biology, environmental exposures, and social drivers of health.

Funding: Each funded team receives up to $25 million to pursue high-risk, high-reward research. Funding rounds occur approximately every 2 years, with teams selected through a competitive, expert-reviewed process.

Currently, three funded teams are tackling two active challenges developing new strategies to target oncogenic drivers and unique features of childhood solid and brain tumors, with the goal of delivering innovative therapeutics.

W12

molecular features within the structure of tumors. HTAN projects use single-cell and spatial multi-omic technologies (see **Sidebar 5**, p. 33)—including transcriptomics, proteomics, epigenomics, and advanced imaging—to map the cellular and molecular architecture of tumors throughout the course of disease progression and treatment (161). Shortly after its launch in 2018, the Center for Pediatric Tumor Cell Atlas was established as an HTAN center, which has developed foundational atlases of high-risk pediatric cancers, including high-grade glioma, neuroblastoma, and very high-risk ALL (121,162). Another HTAN project is now leading the development of the Pediatric Solid Tumor Microenvironment Atlas, aimed at mapping the unique cellular and spatial features of the tumor microenvironment (see **Tumor Microenvironment**, p. 39) in pediatric solid tumors, including rhabdomyosarcoma, neuroblastoma, and Wilms tumor, to uncover mechanisms of acquired therapy resistance and identify targetable vulnerabilities.

Building and Connecting Data Networks

NCI initiatives are laying the foundation for precision medicine in childhood and adolescent cancers by creating integrated data and molecular characterization programs. For example, the NCI Childhood Cancer Data Initiative (CCDI) aims to gather data from every child and AYA diagnosed with cancer and build a pediatric cancer data network that integrates genomic, clinical, imaging, and laboratory data. Under this initiative, the National Childhood Cancer Registry (NCCR) was launched in 2024. NCCR expanded upon the limited epidemiologic data (e.g., cancer incidence and survival data) previously available through the NCI Surveillance, Epidemiology, and End Results (SEER) Program. By integrating epidemiologic, molecular, and clinical data, NCCR provides a more comprehensive resource than SEER for understanding cancer trends in children and AYAs. Developing platforms and tools to bring together research and clinical care data will improve treatment outcomes, quality of life, and survivorship for pediatric cancers.

The CCDI Molecular Characterization Initiative (MCI) was launched in collaboration with the Children's Oncology Group (COG) (see **Figure 1**, p. 17) to provide comprehensive clinical molecular characterization for children and AYAs with newly diagnosed solid tissue malignancies. MCI is leveraging molecular data from clinical assays of paired tumor and germline testing, which can distinguish inherited gene alterations from tumor-specific gene alterations. Furthermore, it can also identify fusion genes based on RNA as well as classify CNS cancer based on methylation. Additional efforts to produce research-based data from assays such as WGS, RNA sequencing, proteomics, and emerging technologies such as spatial transcriptomics, to inform clinical trials and tailor therapeutic treatment strategies, are planned or underway.

Data gathered from MCI is being integrated alongside existing genomic and clinical datasets from initiatives such as the NIH Gabriella Miller Kids First Pediatric Research Program (see **Advancing Pediatric Cancer Research and Patient Care Through Evidence-Based Policies**, p. 146) for open-access sharing available to researchers and clinicians through the CCDI Data Ecosystem—a platform of tools and resources for storing, harmonizing, and sharing pediatric cancer data from separate repositories.

Other foundational resources include the Pediatric Cancer Data Commons, which harmonizes clinical datasets from disease-specific consortia and facilitates global data-sharing, and the St. Jude Cloud, which houses the largest publicly available pediatric cancer genomic dataset alongside an advanced suite of analysis tools. These platforms make rare tumor datasets accessible to a broad research community and provide critical clinical genomic data that could inform patient

care. International efforts to harmonize data across national precision medicine programs are also ensuring that data can be shared broadly through internationally accessible data portals. For example, a joint initiative between Innovative Therapies for Children with Cancer and Hopp Children's Cancer Center is working to create a platform for real-time federated archiving of data collected from international molecular tumor profiling platforms across seven countries (see **Molecular Profiling Driving Precision Medicine**, p. 131).

Another example of how collaborative resources are advancing biological discovery is the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium. This initiative brought together experts in cancer biology, genomics, proteomics, chemistry, structural biology, and computational science to investigate fusion oncoproteins—molecular drivers that are a hallmark of many pediatric cancers (see **Somatic Mutations**, p. 35). By pooling technologies, model systems, and expertise, FusOnC2 uncovered the mechanisms by which certain fusion proteins fuel tumor development.

Integrating Molecular Insights Into Clinical Care

Comprehensive molecular profiling has become one of the most powerful tools for advancing precision medicine. When combined with large-scale collaborations, these approaches can reveal disease mechanisms, uncover new therapeutic targets, and match children and adolescents to precision therapies. For example, through MCI, comprehensive molecular testing for over 6,000 patients with newly diagnosed cancers resulted in a refined diagnosis for nearly 34 percent of patients, directly informed initial treatment with targeted therapy for 15 percent of patients, and facilitated clinical trial enrollment for 8.5 percent of patients (32).

The NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program is another effort demonstrating how molecular characterization can directly inform patient care. By applying comprehensive genomic analyses across childhood cancers, TARGET has identified key alterations driving diseases such as leukemias, neuroblastomas, Wilms tumor, and osteosarcomas (164). For ALL, TARGET researchers defined the Philadelphia chromosome–like subtype, and uncovered that many of the patients harbored activated signaling, often driven by the BCR::ABL1 or other fusions involving key kinase proteins (see **Somatic Mutations**, p. 35). Importantly, adding the tyrosine kinase inhibitor imatinib to chemotherapy dramatically improved outcomes for these children without a need for hematopoietic stem cell transplant.

Collaborative, multi-institutional molecular profiling efforts are revealing the unique genetic drivers of childhood and adolescent cancers and creating the infrastructure to act on these insights to advance precision medicine in pediatric cancer care. Similar global initiatives are advancing precision medicine programs, expanding access to matched therapies, and establishing nationwide frameworks to bring precision medicine into routine pediatric cancer care (see **Global State of Pediatric Cancer Clinical Trials**, p. 131).

NCI–COG Pediatric Molecular Analysis for Therapy Choice (Pediatric MATCH) was a precision medicine clinical trial that took place at about 200 hospitals, university medical centers, and cancer centers in the United States, Canada, New Zealand, and Australia.

Pediatric MATCH screened young patients, whose cancer had worsened during treatment or had come back after treatment, for actionable genetic alterations and assigned them to matched targeted therapies.

In the first 1,000 children and young adults screened, 31% of tumors carried genetic changes targetable with available drugs and 28% of patients were assigned to a trial treatment arm, with 13% enrolled in a matched therapy.

Source: (163).

W13

PEDIATRIC CANCER PREDISPOSITION AND SURVEILLANCE

IN THIS SECTION, YOU WILL LEARN:

- Surveillance for early detection in pediatric cancers means structured monitoring of physical traits and/or clinical signs in children who are at higher risk of developing cancer.
- Physical traits and personal or family history as well as genetic testing are routinely used to identify individuals with a cancer predisposition syndromes and to identify early signs of cancers in at-risk children.
- Genetic counseling helps families of at-risk children navigate through genetic testing–related decision-making and surveillance.
- Multi-disciplinary panels of experts in pediatric cancers and cancer genetics periodically issue guidelines for surveillance and screening in at-risk children.
- New frontiers in early detection of cancer predisposition syndromes and/or early signs of cancer in at-risk children include minimally invasive tests like liquid biopsies, artificial intelligence–based tools, and enhanced imaging strategies.
- Psychosocial and financial issues associated with surveillance and genetic testing pose a significant burden for children and their parents.

Pediatric or childhood cancers, although significantly less common than adult cancers, are the leading cause of disease-related deaths in children (ages 0 to 14) and adolescents (ages 15 to 19) (see **Pediatric Cancer Trends in the United States**, p. 14). Over the past several decade, understanding of pediatric cancer biology has undergone a tectonic shift with advances in genomics and epigenomics, as well as in novel laboratory models that closely resemble pediatric cancers including brain tumors such as organoids and neurospheres. Although most childhood cancers are attributed to somatic alterations, available evidence shows that at least 10 percent to 18 percent arise from pathogenic germline alterations in cancer predisposition genes, although experts think this number will increase with refinements in, and access to, gene sequencing technologies, as well as increased awareness of cancer predisposition by clinical practitioners (36,37). Germline alterations are often inherited from parents but may also occur de novo in germ cells (egg and sperm) (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29). The knowledge of molecular underpinnings of childhood cancers has enabled precise detection of a number of germline alterations that may increase the risk of cancer in children and adolescents (132). The sections below describe the role of surveillance for early detection of these cancers, the current state of the field, and what the future holds.

Identifying Children With Cancer Predisposition Syndromes

Early detection of cancer in children means closely monitoring a child for physical and/or clinical signs of a cancer predisposition syndrome (CPS) that can increase their

TABLE 2

Selected Examples of Distinctive and Recognizable Signs or Symptoms That May Warrant Genetic or Epigenetic Testing and Initiate Surveillance for Early Detection of Cancer in Children

Signs or Symptoms	Relevance to Cancer Risk	Associated CPS
Large tongue, one side of the body larger than the other, belly button or abdominal wall opening at birth	Increases risk for Wilms tumor (kidney) and hepatoblastoma (liver), especially in the first 7–8 years of life	Beckwith–Wiedemann spectrum (BWSp)
Born without the colored part of the eye	High risk of Wilms tumor (kidney)	WAGR (11p13 deletion)
Six or more light-brown skin spots and/or freckles in the armpit or groin area	Earliest sign of NF1, which raises the risk of certain brain and nerve tumors in childhood	Neurofibromatosis type 1 (NF1)
Multiple jaw cysts in childhood	Greatly increases the risk for skin cancers and certain brain tumors	Gorlin syndrome (nevoid basal cell carcinoma syndrome)
White glow in the pupil or a turned eye or crossed or wandering eye in a baby or toddler	Early signs of retinoblastoma, an eye cancer	Heritable retinoblastoma (RB1)
Bumpy lips or tongue, tall/slender build with long limbs, or nerve-related growths in the intestines	Causes aggressive thyroid cancer very early in life	MEN2B (RET)

MEN2B, multiple endocrine neoplasia type 2B; NF1, neurofibromatosis type 1; RB1, retinoblastoma gene 1; RET, rearranged during transfection proto-oncogene; WAGR, Wilms tumor–aniridia–genitourinary anomalies–range of developmental delays syndrome (11p13 deletion).

risk of developing cancer (see **Figure 4**, p. 31). If diagnosed with a CPS, the child is evaluated periodically by routine monitoring, or surveillance, for early signs of cancer using specific approaches. Conversely, a child may have a suspected CPS if diagnosed with more than one primary tumor throughout the body; a primary tumor in both organs of the paired set (e.g., in both kidneys) or multiple independent sites; more than one type of cancer; a cancer diagnosis at an earlier age than typically occurs in the population, such as colon cancer during adolescence; or specific types of tumors during childhood, such as choroid plexus carcinoma. Surveillance strategies are also used to find early signs that the cancer has come back and/or for early detection of second primary cancers (see **Supporting Survivors of Pediatric Cancers**, p. 104). This approach contrasts with cancer screening for early detection in adults, which, for most common cancer types, is carried out at the population level in individuals with no signs or symptoms of the disease.

The Role of Distinctive Signs or Symptoms

Traditionally, the clinical approach to genetic testing and surveillance begins after a child has been identified to have a strong or suggestive family history of a CPS, shows specific signs or symptoms associated with the syndrome, or has been diagnosed with specific cancers (see **Table 2**, p. 48). The recently updated surveillance recommendations issued by the American Association for Cancer Research (AACR) Pediatric Cancer Working Group (PCWG), a multidisciplinary group of experts in pediatric cancers and cancer genetics provide detailed, evidence-based guidance regarding the distinctive and recognizable signs or symptoms that may warrant surveillance (see **Screening and Surveillance Recommendations**, p. 56).

Using signs or symptoms to inform whether a child should undergo surveillance and genetic testing can be highly efficient. This initial approach in settings where broad genetic screening is not yet feasible would allow health care providers to focus resources on children who have the highest likelihood of a CPS (see **New Frontiers in Surveillance for Children With Cancer Predisposing Syndromes**, p. 58) (165). Because recognizable and distinctive signs and symptoms, such as skin lesions and morphologic features, are often incorporated into established criteria for the diagnosis of certain CPSs (e.g., the diagnostic criteria for neurofibromatosis type 1 by the International Consensus Group on Neurofibromatosis Diagnostic Criteria) (166), the approach benefits from decades of clinical validation. It also minimizes unnecessary testing in children at lower risk, reducing the potential for uncertain findings that could lead to over-surveillance or psychological burden. When

implemented systematically, the approach of using signs or symptoms can identify many children with a high-risk of CPS and facilitate the initiation of syndrome-specific, evidence-based surveillance recommendations in a timely manner (see **Screening and Surveillance Recommendations**, p. 56).

The primary limitation of initiating surveillance based on signs or symptoms is its dependency on visible or otherwise recognizable indicators, which may may be absent entirely in some children carrying harmful genetic alterations or may appear only after disease has advanced. Studies have consistently demonstrated that the majority of children with a CPS lack recognizable or distinct features or family history that would suggest a need for surveillance or genetic testing or both (89,167,168). The current approach also relies heavily on the expertise of the health care professional, often a pediatrician, because subtle features may be overlooked or misattributed to benign conditions. Collectively, this approach can cause delays in early detection of cancer in at-risk children, thus leading to missed opportunities for potentially less invasive interventions.

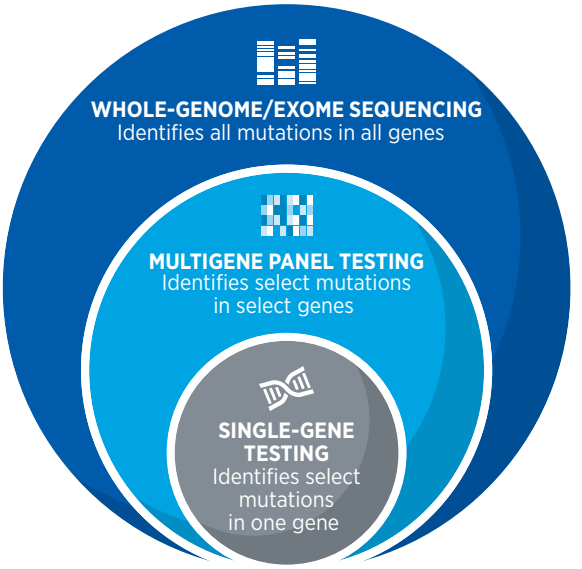
The Role of Genetic Testing

Genetic testing, also called genetic analysis, refers to a laboratory method that looks for changes in the germline chromosomes and genes that could alter the expression or function of specific genes or corresponding proteins in a person's cells or tissues. Genetic tests are typically conducted on readily accessible biological samples, such as blood or saliva, with results generally becoming available within a time frame of 2 to 3 weeks (see **Figure 6**, p. 49). In clinical practice, genetic testing may be performed for several reasons, including assessing risk for medical conditions such as cancer. Germline testing for cancer is a type of genetic testing that looks for inherited or *de novo* genetic changes that may increase the risk of developing cancer. For example, gene testing is performed if someone's children, siblings, or other close family members have cancer or if there is an indication that a person may have a CPS (169). By contrast, somatic testing for cancer is done to search for genetic changes that occur during a person's lifetime. Somatic testing is conducted using cancer tissue or other biospecimen from patients and can be used to diagnose the cancer, plan treatment, or determine how well the treatment is working (in samples taken after treatment has started).

Studies have shown that distinctive physical traits, a strong family history of certain cancers, germline genetic testing, or a combination thereof, is the most effective way to identify children with CPS (170). Genetic testing also helps determine whether specific conditions, such as retinoblastoma or Wilms tumor, are heritable or sporadic by identifying specific genetic alterations associated with these cancers. However, it is important to note that genetic testing and counseling is not readily available for many because it requires state-of-the-art infrastructure and trained health care professionals (see **Sidebar 8**, p. 50). Another issue is the lack of education and understanding of the tests, their findings, and how they are used to inform clinical management among health care providers, patients, and family members (171). Research has

FIGURE 6

Ways to Perform Genetic Testing for Cancer Predisposition Syndromes in Children



Different methods are used for clinical genetic testing. In recent years, these methodologies have evolved significantly and offer varying degrees of information, depending on the purpose. Single-gene testing detects specific gene mutations, allowing for targeted screening. Multigene panel tests simultaneously screen for variants across multiple cancer predisposition genes, and are particularly useful when a person is diagnosed with cancer predisposition syndrome (CPS) but the underlying specific variant is unknown. Whole-exome or whole-genome sequencing provides a comprehensive examination of nearly all genes or DNA content. Information gleaned from these advanced sequencing techniques is used for a variety of purposes, including confirmation that the child is carrying a pathogenic cancer predisposition gene variant and is at a higher risk of developing cancer.

SIDEBAR 8

Barriers to Access in Genetic Testing and Genetic Counseling

Despite clear benefits in improving the likelihood of finding early signs of cancer predisposition syndromes (CPS) and/or cancers in children, genetic testing and genetic counseling remain out of reach for many. The barriers to accessing these options are multiple and multilevel (174), as underscored below by examples from recent studies:

37% and 54%	About 37 percent of parents of children with CPS surveyed rated cost and genetic testing as not being helpful, while ~54 percent rated distress to their child or family as an important/most important concern for forgoing genetic testing. These concerns were significantly higher in families with lower income, Medicaid coverage, or Spanish as their home language (175).
More than 50%	Over half of health care providers surveyed indicated that many families struggle to understand genetic risk, limiting follow-through on testing even when referrals are made (176).
Fewer than HALF	Over 80 percent of families surveyed shared with at least one first-degree relative that their child has a cancer predisposing genetic variant, yet fewer than half (42 percent) reported that relatives pursued testing (177).
Only 61%	More than one third of children with brain and spinal cord tumors (35 percent) had tumor profiling results suggesting an inherited cancer risk, yet only 61 percent of those went on to receive confirmatory genetic testing (178).
4.5X more likely	Families of Black children with cancer were 4.5 times more likely to decline enrolling their child on a next-generation sequencing study than families of White children with cancer. The most common reasons for declining included feeling overwhelmed and fear that their children will face discrimination from insurance companies (179).
About 66%	Two out of three childhood cancer specialists reported that immediate treatment needs often take priority, delaying or sidelining referrals for genetic testing or counseling or both (176).
Almost HALF	Almost half of families (45 percent) surveyed lived in medically underserved areas and indicated long travel times, insurance hurdles, and fragmented referrals as significant barriers to cascade testing and surveillance (180).

also found that pediatric patients and their siblings face higher rates of insurance denials for genetic testing (172).

The use of genetic testing of children for a CPS also raises ethical concerns about a child's autonomy over health-related decisions. The lifelong psychosocial impact on children, including anxiety, guilt, and changes in family dynamics, presents yet another concern (173). These considerations underscore the need for all stakeholders working together to increase patient education to mitigate these risks and to ensure ethical, equitable access to childhood genetic testing.

Despite implementation challenges and ethical concerns associated with genetic testing, the identification of inherited mutations is a critical step for accurate cancer risk assessment, comprehensive genetic counseling, and the initiation of specific surveillance protocols. Recognizing the importance of genetic testing in developing a comprehensive surveillance and treatment plan, many pediatric oncology

SIDEBAR 9

Genomic Newborn Screening

Genomic newborn screening uses DNA sequencing soon after birth to look for inherited changes that raise a child's risk of certain cancers. Unlike traditional screening (which looks for abnormal signals in the blood), it examines genes directly so care teams decide if and start targeted surveillance early.

Approaches

TARGETED GENE PANEL: Tests a short list of well-known cancer risk genes; used for broad screening or when there is a family history; detects harmful changes in those specific genes.

WHOLE-EXOME SEQUENCING: Reads all protein-coding genes; used when a panel may miss something; detects changes across many relevant genes at once.

WHOLE-GENOME SEQUENCING: Reads nearly all of a baby's DNA; used for the most complete screen; detects small genetic changes as well as larger missing/extra pieces or rearrangements.

IMPRINTING/METHYLATION TESTS: Checks for epigenetic changes associated with certain syndromes (e.g., Beckwith–Wiedemann); detects abnormal gene regulation.

Benefits of Genomic Screening in Newborns

- Enables earlier, targeted surveillance when tumors are most treatable.
- Shortens the diagnostic process and guides personalized care plans.
- Supports family counseling and testing for at-risk relatives.
- Can focus imaging and follow-up on infants with cancer risk.

Drawbacks of Genomic Screening in Newborns

- Uncertain results can create ambiguity and anxiety, such as finding a variant of unknown significance (VUS).
- Ethical and privacy concerns (e.g., consent, data storage, and secondary findings).
- Although the incidence of false positive test results is extremely low, they can lead to unnecessary medical procedures.
- Although the incidence of false negative test results is extremely low, they can cause missed early detection of cancer and potentially curative interventions.

Genomic newborn screening will not replace clinical judgment, but it can identify infants who benefit from early, syndrome-specific surveillance and counseling. Clear consent, validated tests, confirmatory tests, and equitable access are key to turning early genetic insights into better outcomes.

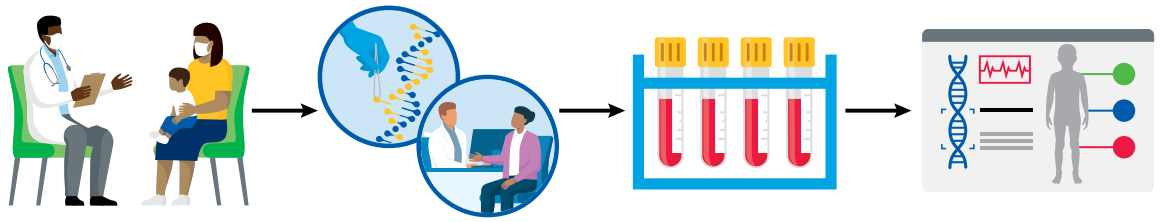
Source: (183).

centers in the United States, some as part of the National Cancer Institute–designated Comprehensive Cancer Centers (NCI CCC), and some embedded in hospitals affiliated with an NCI CCC, have established dedicated cancer predisposition clinics staffed by genetic counselors, medical geneticists, and oncologists, who systematically evaluate and advise affected children and their families. These clinics often handle the unique issues of testing minors, coordinating follow-up screening, and providing counseling. Although identifying the balance of benefit and harm in genetically testing a child is an active area of research, such proactive measures are aimed not only to significantly improve health outcomes for children, but also to extend benefits to at-risk siblings and first-degree relatives.

The idea of offering genetic screening at birth is gaining attention as a means to identify children at risk for serious conditions, including certain cancers, before symptoms appear. Traditional newborn screening already checks for a small set of metabolic and genetic diseases using blood tests. Advances in genetic sequencing now raise the possibility of expanding that window dramatically by flagging certain CPS that lead to cancer early in

FIGURE 7

The Early Detection, Diagnosis, and Surveillance Continuum for Individuals with Cancer Predisposition Syndromes



Early Recognition of Distinctive Attributes	Genetic Testing and Genetic Counseling	Surveillance	Better Outcome

Children are typically referred for genetic counseling when presenting with early-onset cancer, multiple primary cancers, tumor types strongly associated with a cancer predisposition syndrome (CPS), physical features of a CPS, or a suggestive family history. The counselor explains potential benefits (e.g., surveillance opportunities), limitations (e.g., variants of uncertain significance), possible secondary findings, and psychosocial considerations. Parents or guardians provide consent, while children are engaged through age-appropriate assent to respect emerging autonomy. Counselors help determine whether to pursue targeted single-gene tests, multigene panels, or broader approaches such as whole-exome/genome sequencing with or without RNA sequencing, and they manage insurance authorizations. Results are contextualized in terms of the likelihood of whether a person would develop cancer, at what age, and of what type. Counselors then facilitate the development of tailored surveillance plans, such as whole-body magnetic resonance imaging (MRI) to detect tumors in children with *TP53* mutations and Li–Fraumeni syndrome, or constitutional mismatch repair deficiency (CMMRD) syndrome/Lynch syndrome coordinate cascade testing for first-degree relatives, and provide ongoing psychosocial support.

Source: (168).

life, when careful monitoring or preventive steps might make the greatest difference. This approach can be especially impactful in newborns who are, effectively, born with cancer.

Across the globe, researchers are testing whether newborn genetic screening could spot cancer risks before the disease develops. Modeling studies suggest that sequencing panels for a handful of cancer predisposition genes could reduce childhood cancer deaths by nearly half and may become cost-effective as sequencing prices fall (181). Real-world studies demonstrate feasibility of the approach across families (182,183), while population-based studies show clinical benefits and cost-effectiveness of *TP53* gene testing for Li–Fraumeni syndrome (LFS) in newborns (184). Additional studies, such as the Generation Study in the United Kingdom, which aims to sequence the genomes of 100,000 newborn babies to identify rare conditions, including CPSs, are ongoing (185). Key questions that remain, and require additional research, include which genes to evaluate, how to balance benefits against potential harms such as false positives, cost-effectiveness, and how families and health care systems will manage the ethical and practical challenges of sequencing every newborn (see **Sidebar 9**, p. 51).

The Role of Genetic Counseling

Although the benefits of early surveillance are well proven in some CPSs, the evidence is limited in others, and screening may lead to unnecessary tests, false alarms, or anxiety for families. In addition, uncertainty may arise in interpreting some genetic findings, especially when the link between a genetic alteration and cancer risk is not fully understood. This means careful genetic counseling is essential to explain the results, outline the benefits and risks of surveillance, and avoid overtreatment (see **Figure 7**, p. 52).

Genetic counseling combines multiple specialties, such as clinical genetics, cancer care, and psychosocial care, to guide families through the evaluation of inherited cancer risk in children (186). It is a communication process in

which a genetic counselor—a health professional who has specialized training in clinical genetics and counseling—helps the parents or guardians understand their child's risk of developing cancer, as well as options for genetic testing, including its risks and benefits. After genetic testing is done, genetic counselors help parents or guardians understand genetic test results, including how the results can affect other family members, and provide counseling and support for next steps that may include surveillance planning and cascade testing. Recent pediatric oncology frameworks and guidelines emphasize that timely identification of a CPS can alter the course of care and improve outcomes by enabling early, targeted surveillance and risk-reduction strategies (see **Screening and Surveillance Recommendations**, p. 56) (186). In addition, there is emerging evidence that patients with constitutional mismatch repair deficiency (CMMRD)-related cancers can benefit from treatment with immune checkpoint blockade immunotherapies (187-189).

For children with inherited cancer risk and their families, genetic counseling is critical both for making informed decisions about the next steps and for considering the ethical implications of those decisions. Genetic counselors are trained to help families navigate complex results of genetic tests and support informed decision-making under stressful and often emotionally charged circumstances. Protocol-based surveillance—a planned schedule of medical checkups, imaging, and lab tests—for certain CPSs, notably LFS, has been shown to improve overall survival, underscoring the value of early counseling and structured monitoring (190), as is reflected by the experience of **Chenia Lloyd-Gascho** (see p. 55), an adolescent with LFS. As one example, in a long-term study with an 11-year follow-up, researchers evaluated the impact of a surveillance protocol—consisting of frequent physical examinations, biochemical and imaging studies, including whole-body MRI, brain MRI, breast MRI and mammography (adult women), abdominal and pelvic ultrasound, and colonoscopy (for adults)—for individuals with LFS (190). Findings revealed that 84 percent of individuals who underwent surveillance and developed cancer were alive at a 4-year follow-up, compared to 49 percent of those not on surveillance (190).

Several recent studies have shown similarly improved survival outcomes for individuals who carry germline mutations with or without an LFS diagnosis and undergo surveillance protocols. In one study, 92 percent of the children undergoing surveillance with screening MRI were diagnosed with low-grade brain tumors before symptoms appeared. In contrast, 85 percent of children who were not undergoing routine surveillance and were diagnosed after symptoms appeared had high-grade tumors. All children with low-grade tumors whose tumors were surgically removed after they were diagnosed during screening MRI were alive at 30 months, compared to only half of those who were not undergoing routine surveillance and were diagnosed with high-grade tumors after the symptoms appeared (191). Another study of 31 children with LFS revealed that whole-body and brain MRI with ultrasound was accurate and feasible for early detection of cancer (192). Updated guidelines confirm that standardized surveillance enables early detection of cancer in LFS patients without symptoms, and guides treatment decisions that improve outcomes (see **Screening and Surveillance Recommendations**, p. 56) (193,194).

Evidence shows that counseling prior to genetic testing improves knowledge retention and decision confidence while helping families prepare for uncertain or unexpected results (175). If a pathogenic variant is identified (see **Sidebar 4**, p. 32), counselors coordinate testing of at-risk relatives, enabling risk reduction or early detection in additional family members. Pediatric cases carry unique ethical challenges. Genetic counselors are trained to balance immediate medical benefits against preserving the child's right to make decisions later in life. Most approaches re-consent patients as they turn 18 years of age, to preserve ongoing surveillance in an adult setting.

Evidence shows that using telehealth for genetic counseling can provide knowledge and satisfaction comparable to that achieved with in-person visits, with the added benefit of reduced travel and wait times (195,196). Demand for pediatric cancer genetic counseling currently exceeds the available number of trained counselors, especially outside large academic centers (197). Even with advanced sequencing, variants of uncertain significance remain common, requiring nuanced interpretation and long-term follow-up. Although the federal Genetic Information Nondiscrimination Act (GINA) prohibits discrimination based on genetic information in health insurance and employment, adolescents with cancer and their parents often report heightened anxiety and concern about future insurability after receiving genetic test results (198). Several additional barriers to access to genetic testing and counseling may further affect the uptake of these services (see **Sidebar 8**, p. 50).

Expanding the reach of genetic counseling and testing is becoming an urgent priority, especially because technological advances are enabling diagnoses of more children and adults carrying inherited risks for cancer and other serious conditions (197). Several recent studies and reviews highlight both the promise of telehealth genetic counseling and the challenges that remain for its broader adoption (195,199). Evidence from more than 13,000 patients needing genetic counseling across dozens of studies indicates that telehealth, whether by phone or video, delivers counseling outcomes comparable to those achieved with in-person care (195). Patients and parents report high levels of satisfaction, reduced travel costs, and improved

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SURVIVOR STORY

CHENIA LLOYD-GASCHO

AGE: 18 | DIAGNOSIS: BRAIN CANCER (GLIOMA) | TORONTO, ONTARIO, CANADA

Living Fully, Thanks to a Breakthrough in Targeted Therapy

At 18 years old, Chenia Lloyd-Gascho is thriving as a first-year civil engineering student at the University of Toronto, with plans to one day design cities and improve public transportation systems. But behind Chenia's bright future lies a journey shaped by rare genetics, remarkable science, and resilience.

When Chenia was 8, he and his older sister were diagnosed with Li–Fraumeni syndrome (LFS)—a hereditary condition that dramatically increases the risk of developing cancer. The diagnosis came after the family had already endured several losses to cancer, including Chenia's aunt and grandmother. "It was pretty confusing, and I didn't fully grasp what was happening at the time," Chenia said. "I got pulled out of school every 3 months for scans and tests, but I didn't fully understand why."

For several years, blood tests and MRIs were regular parts of life for their family. Then, in late 2021, the phone rang. Chenia's mother, Denise, immediately recognized the number—it was The Hospital for Sick Children (SickKids) in Toronto where Chenia is being treated.

"The doctor said, 'We found something,'" she remembered. "It's surreal to hear that news over the phone. Your life has just been turned upside down, and you don't know what the other side of this looks like."

A biopsy confirmed a genetic mutation in the *IDH1* gene, and the diagnosis became official: a grade 2 astrocytoma, a type of slow-growing glioma (brain tumor). "I was 14, at my dad's family cottage when my mom called and told me that they had found some sort of mutation," Chenia said. "At first, I didn't process it. Days later, I realized—this means I have cancer."

Because the tumor was slow-growing and caught early through LFS surveillance, Chenia's doctors recommended laser ablation, a procedure that uses focused heat to destroy tumor tissue. The surgery, performed in April 2022, was successful—but recovery was grueling. "I couldn't tell where my hands or feet were in space," Chenia said. "I kept bumping into walls. It was funny for like an hour, then it wasn't."

For Denise, watching this unfold was heartbreaking. "There are ways in which brain surgery changes your personality and confidence," she explained. "The hope of new treatment options meant maybe no one would ever have to cut into my child's head again."

That hope became a reality in the form of an emerging targeted therapy called vorasidenib, an oral IDH inhibitor designed to slow tumor growth in patients with the same genetic mutation driving Chenia's cancer. "We were on vacation in Jamaica for Chenia's 17th birthday," Denise said. "Our oncologist called to say you've been approved for vorasidenib. I said, this is the best birthday present ever, the best of all worlds."

Starting the drug was not easy; fatigue and neck pain made school difficult at first. "Sometimes I would have to come home early because of how tired I was. I would fall asleep at 4 p.m. and sleep through the entire night," Chenia recalled. "But compared to the alternative, it was definitely better."

The drug has allowed Chenia to regain a sense of normalcy—balancing coursework, friends, and hobbies while managing ongoing monitoring. For Denise, the change has been transformative. "This treatment gave me my child back," she said. "It means Chenia can go to school, see friends, live life—and not face another surgery."

This journey shaped Chenia's deep appreciation for the importance of continued research and mental health support. Now, they speak openly about living with LFS and cancer, hoping to reduce the stigma and highlight the power of science. "I used to hide it," Chenia said. "Now I'm honest about being tired, about what I'm going through. This medication didn't just change my health—it changed how I think about my future."

To policymakers, Chenia's message is clear: "Cancer research changes everything. It turns what used to be a death sentence into something you can live with. Every discovery gives people like me a future. That's why funding this research matters—it's what keeps hope alive."

Scan the QR code to watch Chenia's video interview.

access, and many now prefer hybrid models that combine virtual and in-person visits (195,199).

Professional guidelines, such as those from the National Society of Genetic Counselors, cautiously recommend telehealth as a safe and effective alternative, noting its potential to increase health equity by reaching rural or underserved families (200). The AACR PCWG recently updated its guidelines for genetic counselor practice and surveillance of childhood CPS, emphasizing the need for universal access to genetic testing, early referral (within 1 to 2 months of diagnosis), and ongoing surveillance throughout survivorship care. The guidelines, among other recommendations, include incorporating the education of families through web-based tools, videos, and chatbots; banking DNA for children for whom genetic counseling and/or testing cannot be completed; and psychosocial care. Nevertheless, barriers persist (186), such as provider licensure rules that vary from state to state, and access to reliable Internet or devices to support web-based care (180).

In pediatric cancer care, additional challenges surface. Children with suspected CPS often face delays in diagnosis, with some studies showing that nearly 40 percent are recognized only after their first cancer develops (201). Dedicated pediatric CPS programs that include access to oncologists, genetic counselors, psychologists, and social workers all in one place can improve detection and offer structured surveillance (202). However, limited workforce capacity, high demand, and gaps in psychosocial support remain pressing problems (203).

Taken together, these findings argue for sustained investment in telehealth infrastructure and educational initiatives for providers, patients, and families. Only then can the benefits of genomic medicine be delivered equitably, ensuring that lifesaving diagnoses, surveillance protocols, and therapies reach children and families when they are needed most.

Screening and Surveillance Recommendations

Genetic testing is uncovering CPS at an increasingly rapid pace (84,204,205). For these children and families, structured surveillance, such as whole-body MRI in LFS or renal imaging in Wilms tumor predisposition, have already shown to improve care and outcomes (193,206,207). Advances in the identification of novel biomarkers for CPSs, as well as artificial intelligence (AI)–based solutions for streamlining surveillance strategies, offer the potential to expand predictive tools, creating time windows for earlier detection or targeted treatment (see **Artificial Intelligence–based Solutions**, p. 59) (208).

Surveillance for children with CPS aims to find tumors early, ideally before symptoms appear so that treatment can be less intensive and outcomes are better. Recent evidence demonstrates clear benefits of surveillance for children with CPS. In a 2024 study at a major pediatric cancer center, 274 children and adolescents on protocol-based surveillance were followed for a median of 3 years (207). Thirty-five tumors without any prior symptoms were identified in 27 patients, or about 10 percent of the cohort, and nearly one-third of these were discovered on the very first scan after the diagnosis of the CPS. Importantly, 83 percent of solid tumors, including brain tumors, found through surveillance were confined to one site at diagnosis, compared with roughly 57 percent of comparable tumors that were detected before CPS diagnosis, a difference that strongly favors a structured early detection or surveillance approach (207).

Historically, standardized surveillance protocols existed for only a few CPSs, and there are only a handful of cancer-focused organizations that issue and/or incorporate surveillance guidance for children with CPS. For example, some groups have had long-standing guidance on genetic testing for children with CPS, such as the National Comprehensive Cancer Network in the United States (209) and the National Institute for Health and Care Excellence in the United Kingdom (210). The National Society of Genetic Counselors issues guidance on genetic counseling standards (211), ensuring families understand results and implications for relatives. For surveillance, the Children's Oncology Group integrates monitoring into treatment protocols, while the European Society for Paediatric Oncology sets continent-wide standards (212). Several syndrome-specific groups, such as those focused on LFS or Beckwith–Wiedemann spectrum, issue their own recommendations (213,214).

To standardize surveillance protocols for children with CPS, AACR convened a workshop in 2016 to develop consensus recommendations for early cancer detection in affected children (215). A follow-up workshop in 2023 expanded and updated these guidelines to reflect new data and include newly identified syndromes, while also exploring emerging surveillance technologies and potential prevention strategies for high-risk pediatric populations (36,91,186,193,194,206,216-231). The updated guidelines for certain CPSs now recommend that surveillance begin at birth or during early childhood, depending on the syndrome, with blood tests and with ultrasound or MRI imaging prioritized over computed tomography (CT) to reduce radiation exposure. These protocols aim to catch tumors early when cure rates exceed 90 percent, such as for Wilms tumor or hereditary retinoblastoma (see **Table 3**, p. 57).

While structured surveillance protocols are beneficial for children with CPS, one of the key remaining concerns is radiation exposure of children as a result of surveillance protocols, many of which require imaging approaches involving radiation. The 2023 AACR PCWG update emphasizes the use of MRI (especially whole-body MRI) and ultrasound whenever possible, with the sparing use of CT for specific indications

TABLE 3

A Brief Overview of Surveillance Guidelines From the American Association for Cancer Research® Pediatric Cancer Working Group's 2023 Workshop

Syndrome	When to Test	Who Should Be Tested	Gene(s) Tested	Recommended Surveillance/Test
Beckwith–Wiedemann and Wilms tumors/ Hepatoblastoma	At birth or diagnosis	Every child clinically diagnosed with the syndrome	11p15, *WT1*	Abdominal ultrasound q3mo until age 8; AFP until age 4*
DICER1 syndrome	At birth or diagnosis	Every child clinically diagnosed with the syndrome or with strong family history	*DICER1*	Chest X-ray, q6mo until age 8, thyroid US age 8+, renal and pelvic US every 6mo until age 8, then annual until age 12
Li–Fraumeni syndrome	At birth or diagnosis	Every child genetically diagnosed to have germline pathogenic/likely pathogenic *TP53* variant	*TP53*	Annual WB-MRI, brain MRI, q3mo abdominal ultrasound, annual dermatologic exam, organ-specific imaging, q3–4mo adrenocortical profile bloodwork
GI cancer syndromes (FAP, JPS, PJS, etc.)	Ages 2–5 (APC); Age 10 (JPS)	Children with family history† or clinical signs of polyposis	*APC, MUTYH, SMAD4, BMPR1A, STK11*	Colonoscopy/sigmoidoscopy, endoscopy, gene-specific schedules
Hereditary PHEO and PGL	By ages 6–21 (variant-dependent)	Children with known germline pathogenic variants or suggestive family history*	*SDHA, SDHAF2, SDHB,SDHD, SDHC, MAX, NF1, RET, TMEM127, VHL*	Annual biochemical screening, MRI neck-to-pelvis (some do q6mo)
Retinoblastoma	At diagnosis	Every child clinically diagnosed with the syndrome or with strong family history	*RB1*	MRI brain/orbits q6mo for 5 years, second cancer education
Von Hippel–Lindau (VHL) syndrome	At diagnosis or infancy	Every child clinically diagnosed with the syndrome	*VHL*	Eye exam (infancy), abdominal US (age 8+), brain/spine MRI (11–15)
MPNST in NF1 and related syndromes	At diagnosis or ages 8–10	Every child clinically diagnosed with the syndrome or with strong family history	*NF1, SUZ12, EED*	Whole-body MRI annually, symptom-directed neuroimaging
Wilms tumor and hepatoblastoma in BWS	At diagnosis	Children with family history of hepatoblastoma or associated syndromes	*APC, TP53, BWS*-related	Genetic evaluation; and US and AFP in at-risk families
Pediatric pancreatic tumors	At diagnosis	Children with known germline mutation or strong family history*	*BRCA2, PALB2, STK11*	Genetic counseling; no standardized surveillance
SMARCB1/SMARCA4 deficiency	At diagnosis	Every child clinically diagnosed with the syndrome or with strong family history	*SMARCB1, SMARCA4*	Brain MRI q3mo (SMARCB1), limited data for SMARCA4
Supratentorial embryonal tumors	At diagnosis	Every child clinically diagnosed with the syndrome or with strong family history	*DICER1, LIN28A*	Gene testing; MRI surveillance if mutation present
Wilms tumor predisposition (new genes)	At diagnosis	Every child clinically diagnosed with the syndrome or with strong family history	*REST, TRIM28, CTR9*	Broader testing for all Wilms cases; surveillance guidance varies
Schwannomatosis (NF2/SMARCB1/LZTR1)	At diagnosis or suspicion	Children with multiple schwannomas or suggestive imaging/clinical history	*NF2, SMARCB1, LZTR1*	Baseline brain/spine MRI, annual neuro exams, symptom-directed imaging
Pediatric hematologic malignancy predisposition	At diagnosis or suspicion	Children with family history, chronic cytopenias, or MDS-like features	*GATA2, RUNX1, ETV6,* others	Genetic testing if family has cytopenias, or MDS features present
Pediatric adrenocortical tumors	At diagnosis	Every child clinically diagnosed with the syndrome or with strong family history	*TP53* (Brazil founder variant)	Genetic testing; cascade testing
DNA repair deficiency (CMMRD, Lynch, etc.)	At diagnosis or family history	Children with high-grade gliomas, polyposis, or affected siblings	*PMS2, MSH6, MSH2, MLH1, POLE, POLD1*	Brain MRI q6mo, WB-MRI, GI endoscopy from age 6, skin/genitourinary screening
Rare syndromes (incl. HLRCC)	Varies	Children with FH-deficient histology or family history of HLRCC	*FH,* others	Annual renal MRI for FH, targeted testing based on histology

Syndrome: BWS, Beckwith–Wiedemann spectrum; CMMRD, constitutional mismatch repair deficiency; FAP, familial adenomatous polyposis; GI, gastrointestinal; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; JPS, juvenile polyposis syndrome; LFS, Li–Fraumeni syndrome; MPNST, malignant peripheral nerve sheath tumor; PGL, paraganglioma; PHEO, pheochromocytoma; VHL, von Hippel–Lindau syndrome.

Gene(s) Tested: *APC,* adenomatous polyposis coli; *BMPR1A,* bone morphogenetic protein receptor type 1A; *BRCA2,* breast cancer 2 susceptibility protein; *DICER1,* double-stranded RNA-specific endoribonuclease; *ETV6,* ETS variant transcription factor 6; *FH,* fumarate hydratase; *GATA2,* GATA binding protein 2; *LIN28A,* Lin-28 homolog A; *LZTR1,* leucine zipper-like transcriptional regulator 1; *MLH1,* MutL homolog 1; *MSH2,* MutS homolog 2; *MSH6,* MutS homolog 6; *MUTYH,* MutY DNA glycosylase; *NF1,* neurofibromin 1; *NF2,* neurofibromin 2; *PALB2,* partner and localizer of BRCA2; *POLE,* DNA polymerase epsilon; *POLD1,* DNA polymerase delta 1; *PMS2,* postmeiotic segregation increased 2; *RB1,* retinoblastoma 1; *RET,* rearranged during transfection; *REST,* RE1 silencing transcription factor; *RUNX1,* runt-related transcription factor 1; *SDHB,* succinate dehydrogenase complex iron sulfur subunit B; *SDHC,* succinate dehydrogenase complex subunit C; *SDHD,* succinate dehydrogenase complex subunit D; *SMAD4,* SMAD family member 4; *SMARCA4,* SWI/SNF-related matrix associated actin dependent regulator of chromatin subfamily A member 4; *SMARCB1,* SWI/SNF-related matrix associated actin dependent regulator of chromatin subfamily B member 1; *STK11,* serine/threonine kinase 11; *TP53,* tumor protein p53; *VHL,* von Hippel–Lindau.

Recommended Surveillance/Test: AFP, alpha-fetoprotein; CT, computed tomography; DNA, deoxyribonucleic acid; MRI, magnetic resonance imaging; q3mo, every 3 months; q6mo, every 6 months; WB-MRI, whole-body magnetic resonance imaging.

* Surveillance guidelines and recommendations included in this table have been significantly shortened and simplified. Information in this table is not meant to replace professional advice from a trained health care provider.

† Family history: Any cancer in close relatives; suggestive family history: multiple relatives with early onset and/or rare cancers; strong family history: several generations with same/syndrome-related cancers.

A recent study showed that children **exposed to radiation** during medical imaging, especially from computed tomography, had a **1.41 fold higher risk of developing blood cancers** compared to those with no radiation exposure; the risk was 3.59 fold higher at the highest dose of radiation used.

Source: (233).

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and syndromes. Recent studies have provided strong evidence to spare the use of CT when possible. In a study of nearly one million children, adolescents, and young adults who received computed tomography, those who received very high exposure to radiation had a 2.66-fold higher risk of blood cancers later in life, compared to those with very low exposure (232). These principles should also be considered when imaging these patients for indications unrelated to cancer (218).

Another concern pertains to children's risk of developing second primary cancers, either due to treatment of the primary cancer or because of a CPS. Although this risk is known, continued research can further help identify and refine surveillance strategies that will be most effective for this population (231).

New Frontiers in Surveillance for Children With Cancer Predisposing Syndromes

Major strides have been made in genome sequencing and in understanding the role of genetic alterations in CPS in childhood cancer causation. However, the window in which a child's risk for developing cancer can be detected and a care plan can be developed to mitigate the risk remains very brief, posing a serious challenge. Researchers are developing innovative new approaches and improving established methods that are noninvasive or minimally invasive and can detect children who may be at higher risk of developing cancer accurately and in a timely manner. In this section, we highlight some of the approaches that are either being implemented in the clinic now or are on the horizon to accelerate the pace of progress in early detection of childhood cancers.

Minimally Invasive Approaches

Liquid biopsies are emerging as a powerful, minimally invasive alternative to traditional, invasive tissue biopsies, with potential application across the continuum of care for children with cancer (see **Liquid Biopsy**, p. 43) (234,235). Two recent studies point to a promising role for liquid biopsy in early detection among children with a CPS (236,237). In a cohort of 89 people with LFS, including 26 children, researchers analyzed 193 blood samples using an approach that detects DNA alterations, variations in the size of the circulating tumor DNA (ctDNA) fragments, and epigenetic marks. In some cases, cancer-related signals appeared when the child had no clinical symptoms, and in several cases, these signals emerged months before standard surveillance detected any lesions. Among clinically cancer-free carriers, just over half of positive results (54 percent) reflected a true cancer signal, and a negative result was 95 percent accurate (237). In individual samples, epigenetic marks were detectable about 20 months before traditional detection methods for osteosarcoma, a type of bone cancer, and combined DNA fragment and

Collaborative Approaches Investigating the Utility of Liquid Biopsy in Identifying Cancer Predisposition Syndromes

- **CHARM** (cfDNA in Hereditary and High-Risk Malignancies, Canada), established in 2017, unites eight Canadian genetics centers with the goal to test cell-free DNA (cfDNA) in serial plasma and tumor samples for somatic gene alterations and methylation changes as early biomarkers in hereditary cancer syndromes. Preliminary findings show that cfDNA alterations are detectable in some Li–Fraumeni patients before clinical diagnosis of a cancer, though sensitivity remains variable (238-240).
- **EDISYN** (Early Detection In Syndromic Cancers), established in 2022, is an international collaboration of clinicians, researchers, genetic counselors, and patient advocates with the goal of using liquid biopsy assays, particularly circulating tumor DNA detection, for early diagnosis in children and adults with cancer predisposition syndromes. EDISYN aims to develop liquid biopsy tests that are highly sensitive and specific, and are broadly accessible for surveillance (241).

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epigenetic signals preceded clinical diagnosis of leukemia or melanoma by about 6 to 18 months (237).

The second study evaluated plasma from 101 patients with neurofibromatosis type 1 and 21 controls for size variations in cell-free DNA (cfDNA) fragments—tiny DNA pieces released into the blood when cells die—and compared the findings with those from the tumor fraction test, which measures how much tumor DNA is present compared to normal DNA in a sample (236). The tumor fraction test detected many cancerous nerve tumors, but it could not detect the difference between benign and early-stage malignant tumors. In contrast, the accuracy of using cfDNA fragments was much better and detected 91.4 percent of malignant samples compared with 74.3 percent using tumor fraction alone. It also resolved several clinically ambiguous cases (236). Together, these results suggest that liquid biopsy can help detect cancers early in children with a CPS and inform surveillance decisions, while minimizing harm to children.

Multi-cancer early detection (MCED) tests, a variation of liquid biopsy, broadly aim to detect cancer-related signals from emergent cancers in the same assay. These tests typically detect molecular features of cfDNA, such as epigenetic marks it carries, known cancer predisposing mutations and somatic alterations in children, and/or size variations in DNA fragments. For the detection of cancer predisposing gene variants, MCED tests are carried out in specialized clinical settings designed for the detection of CPSs due to the complexity of the tests. The information gathered from these tests is integrated together to evaluate whether an individual should be screened for an emergent cancer and, if so, what type of cancer, including which area of the body should be imaged for further evaluation.

MCED tests carry enormous potential to revolutionize cancer screening in adults, although no MCED test has been approved for routine screening (242-244). Although studies evaluating the utility of MCED tests in children with a CPS or cancer are rare, those discussed above provide important groundwork for the utility of MCED tests in children who are at higher risk of developing cancer due to genetic predisposition. More research is needed to establish the utility of MCED tests in children with CPS. If these tests can detect very small amounts of tumor signal with very high accuracy, they could serve as a minimally invasive way to prompt urgent, targeted imaging in children who have other symptoms of a CPS or are already in well-defined high-risk groups, based on an earlier cancer diagnosis and clinical testing result indicating at CPS. With sufficient data to support the clinical utility of MCED surveillance, the time to diagnosis of an emergent cancer would be shortened as would the potential for improved outcome.

Numerous studies have shown that liquid biopsies are also a superior choice for monitoring disease progression and the patient's response to treatment following a cancer diagnosis.

A powerful example of the benefits of liquid biopsy is its application in brain cancers, one of the most common cancers among children (see **Pediatric Cancer Trends in the United States**, p. 14). Detecting brain cancers in children often relies on procedures that are invasive and potentially harmful. MRI scans, while essential, usually require sedation or anesthesia in young patients, which carries risks when repeated over time. In many cases, diagnosis also involves surgical biopsy of brain tissue, a procedure that may have significant potential complications, depending upon the location of the cancer. Even the collection of cerebrospinal fluid (CSF), though less invasive than surgery, is still uncomfortable and carries its own, albeit minimal, risks.

Liquid biopsy offers a promising new approach by analyzing tumor DNA or cells in blood or CSF samples. A simple blood draw, in particular, could provide critical diagnostic and monitoring information without exposing children to the potential harms of surgery or repeated anesthesia, marking a major step forward in safer care (235,245). Research has demonstrated that the detection of tumor DNA in CSF or in plasma can identify subtypes of brain tumors and help track disease over time, often earlier than MRI and cytology (157,246). More recent studies have shown further promise of liquid biopsy in childhood cancer care. For example, in children with embryonal brain tumors, testing tumor DNA fragments in CSF found cancer signals in 92 percent of samples versus 17 percent with the tissue biopsy (247). In neuroblastoma, a personalized blood test was negative for tumor DNA in every follow-up sample from children who remained well, but was positive for tumor DNA in all four cases of relapse, including one detected 78 days earlier than with the standard testing. This approach also outperformed five routinely surveyed markers in detecting relapse (248). In another recent study in which researchers evaluated samples collected at diagnosis from 233 children with hematologic, solid and brain tumors, ctDNA was detectable in all 177 children with hematologic malignancy; in 19 of 38 solid tumor patients and in 1 of 18 brain tumor patients. The assay also detected DNA sequence alterations, copy number variations, and structural variations responsible for oncogenic gene fusions (154).

Artificial Intelligence–based Solutions

Artificial Intelligence (AI) is a general term that applies to training a computational model to perform tasks commonly associated with human intelligence, such as how to reason, and learn. The use of AI carries enormous potential across the continuum of cancer care for adults, including in early detection of cancer, as is increasingly evident from US Food and Drug Administration (FDA) approvals and the integration in the clinic of AI-based software and devices. However, the field remains nascent for surveillance and screening in children with CPSs (see **Sidebar 10**, p. 60) (249-252).

SIDEBAR 10

Artificial Intelligence: A New Frontier in Surveillance for Early Detection in Pediatric Cancers

Artificial intelligence (AI) refers to the ability of a computer program to perform tasks commonly associated with human intelligence, such as learning, reasoning, and problem-solving. AI is a large field of study, with numerous branches, specialties, and applications, with relevance to many aspects of life, including cancer science and medicine. Some of the most common types of AI are described below:

MACHINE LEARNING (ML) is a type of AI that trains a computational program to learn and perform certain functions without being specifically programmed to perform those functions based on a previously characterized data set.

DEEP LEARNING (DL) is a type of ML that learns from vast amounts of data using complex processes called artificial neural networks, which are modeled after how the human brain works.

GENERATIVE AI (GENAI) is an ML method, usually powered by DL, that uses patterns from the data with which it was trained to generate new content.

LARGE LANGUAGE MODEL (LLM) is a type of GenAI that is trained on large text-based data to understand and produce human-like language. ChatGPT is a well-known LLM application.

AGENTIC AI is a type of AI capable of autonomously setting goals, planning multistep actions, interacting with tools or environments, and adapting to feedback.

The use of AI in cancer science and medicine is an active area of research, with enormous potential in early detection for surveillance and screening in children and adolescents with cancer. However, the rare nature of pediatric cancer limits the use of AI to machine learning-based approaches:

The use of AI in pediatric oncology can help:

- Detect subtle patterns in medical images and lab data, improving early cancer detection;
- Identify early signs of relapse or minimal residual disease in biospecimens, allowing closer post-treatment surveillance;
- Classify tumor types and molecular subgroups noninvasively through radiomic and genomic analysis, supporting precision diagnosis; and
- Integrate diverse data sources, from imaging to electronic health records, to guide more personalized and evidence-based surveillance decisions.

The use of AI in pediatric oncology may:

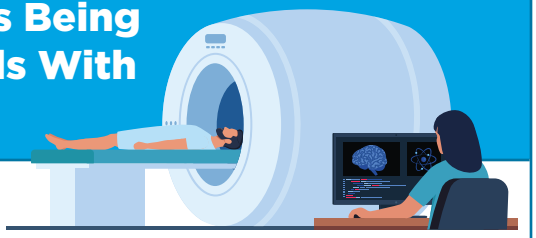
- Face limits in reliability because pediatric cancers are rare and datasets are often too small;
- Overrely on small or biased datasets, reducing accuracy when applied to broader patient populations;
- Struggle with variability in imaging protocols, clinical data, and patient characteristics, limiting consistency across hospitals; and
- Raise ethical risks around protecting the privacy of children and adolescents because of opaque regulations surrounding AI use, and reinforcing inequities if safeguards are not in place.

Recent studies, although investigating small patient cohorts and often in a single institute, are underscoring the immense potential of AI-enabled tools for surveillance in childhood cancers.

Leukocoria, or white pupil, is an eye condition in which the pupil reflects light in a way that makes it appear white instead of the usual red (253). Leukocoria is one of the most common signs leading to the diagnosis of retinoblastoma (254), which accounts for about 2 to 3 percent of all childhood cancers around the globe (255). Easy-to-perform approaches, such as CRADLE—a smartphone app that uses computer vision to scan photos and identify leukocoria as a way to screen for early detection of retinoblastoma—have been effective in real-world settings (256).

SIDEBAR 11

Innovations in Imaging Techniques Being Used for Surveillance of Individuals With Cancer Predisposition Syndromes



More than 100 pediatric cancer predisposition syndromes are now recognized, each with distinct cancer risks and sometimes other health issues. Identifying children at higher genetic risk allows health care providers to tailor care, including surveillance that aims to find tumors early, when treatment is most effective. Imaging is central to these programs, and the specific tests are chosen based on the child's syndrome, the typical age when tumors arise, and what each technique does best. Examples of some of these imaging techniques, their uses in surveillance for early detection of cancer, and recent innovations are described below:

Technique	Use	Innovation
CONTRAST-ENHANCED ULTRASOUND (CEUS)	Secondary characterization of liver lesions flagged on surveillance ultrasound.	Adds real-time image enhancement without radiation, improves lesion triage at the point of care.
RAPID, MOTION-ROBUST MRI SEQUENCES	High-quality anatomic views for tumor surveillance in young children.	Short, motion-tolerant scans that reduce or avoid the need for anesthesia.
PHOTON-COUNTING DETECTOR CT (PCD-CT)	Pulmonary tumor surveillance, with potential extension to other regions as protocols evolve.	Higher-resolution imaging at equal or lower doses of radiation than with conventional CT.
LONG-AXIAL FIELD-OF-VIEW PET/CT	Small, metabolically active lesions across the whole body.	Far higher sensitivity enables shorter scans or lower exposure to radiation for children.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.
Source: (260).

Researchers are now leveraging AI to further improve detection of leukocoria in family photos. In this regard, a research team recently developed EyeScreen, a smartphone app designed to detect leukocoria through a combination of low-cost hardware and machine learning. The study involved smartphone-taken eye photos from 1,500 children who participated in the study (257). Eighty percent of the participant images were used to train a machine learning model. When tested for accuracy using images from 291 participants, the model showed 87 percent sensitivity (meaning detected true positive results) and 73 percent specificity (meaning avoided false positive results). It is important to note that the study was performed in Ethiopia and required only Android smartphones, which are less costly and readily available in the country (257), indicating an easy-to-perform approach to flagging potential early signs of retinoblastoma, especially in resource-limited settings.

Beyond smartphone photos, researchers tested a deep learning model trained on clinical-grade images of the eye that can distinguish between normal eye images and those showing signs of retinoblastoma (258). On a test dataset containing images from children with or without retinoblastoma, the model distinguished between the two groups with 97 percent accuracy and 99 percent precision, indicating that it could reliably detect cases while minimizing missed diagnoses (258). While results are promising, the model needs to be validated in real-world clinical settings with larger and more diverse datasets.

Two recent studies highlight how AI and digital tools can improve early tumor detection in children with *TP53* variants. In one study, a machine-learning model, trained and validated using DNA methylation profiles from blood draws of 301 *TP53* variant carriers, reached about 93 percent accuracy in a test group of 79 children with *TP53* variants, correctly flagging most cancers before age six while sparing many low-risk children from extra scans (259). In the second study, the McGill Interactive Pediatric OncoGenetic Guidelines (MIPOGG) app standardized evaluation for CPSs, identifying 99.5 percent of 412 children with cancer, and when compared directly with genetic testing, showed high sensitivity (90.7 percent), a very strong ability to rule out disease (negative predictive value 98.6 percent), but only a modest ability to confirm cases (positive predictive value 17.6 percent) (165).

AI based tools are an emerging frontier in early detection of cancer, but their use in surveillance and treatment decisions

in pediatric oncology remains sparse. Additionally, large-scale studies will be critical to realize the general applicability and integration of AI-based solutions into clinical decision-making.

Innovative Imaging Enhancements

Imaging is the backbone for finding tumors early and tailoring tests according to specific risks associated with different CPSs, as well as with children's ages of onset (260). In recent years, many advances and innovations in imaging techniques have significantly improved the surveillance of children with CPS (see **Sidebar 11**, p. 61).

Over the past decade, whole-body MRI has become a backbone of cancer surveillance for children with certain CPSs, such as LFS and constitutional mismatch repair deficiency (261). Unlike CT or positron emission tomography (PET) scans, whole-body MRI avoids radiation, making it safer for repeated use in children, with studies confirming that it can detect asymptomatic but treatable tumors during follow-up scans (193). Importantly, evidence indicates that interventions based on whole-body MRI scans improve outcomes for children with LFS who have central nervous system (CNS) tumors. One study showed that whole-body MRI detected low-grade CNS lesions in 92 percent of children with LFS on the surveillance protocol. Importantly, early surgical interventions led to a significant survival advantage in children with low-grade lesions, with an overall survival of 100 percent at 30 months (191). The consensus among experts is that whole-body MRI works best when integrated into syndrome-specific protocols rather than as a general screening tool (193,261).

For syndromes such as the Beckwith–Wiedemann spectrum, in which errors in growth regulation lead to larger-than-expected growth in children and increase their risk of developing certain tumors, ultrasound-based surveillance has proven equally transformative. In Beckwith–Wiedemann spectrum, standardized abdominal ultrasound scans every 3 months during early childhood detect more than 95 percent of Wilms tumors, usually before cancer spreads, enabling surgery that spares the kidney (262,263). In retinoblastoma, imaging of the eye with handheld spectral domain optical coherence tomography (HH-SD-OCT) has revolutionized clinical care. Enhancements in HH-SD-OCT—higher-speed scanning, wider field of view to the periphery, and optimization for use for children (264)—can also enable earlier and more eye-sparing therapies by helping to detect microscopic retinal tumors invisible on fundus exam, a test in which an eye doctor uses a special instrument to examine the back part of the eye (the fundus), which includes the retina, optic nerve, and blood vessels (265). Together, these imaging innovations are shifting care toward earlier, safer, and less invasive interventions.

Despite advances in imaging for surveillance of children with CPS, major gaps remain. Evidence linking survival outcomes with detection of tumors during surveillance remains scarce, since randomized trials are not feasible or considered ethical. Operational barriers, such as the need for anesthesia in very young children, limited pediatric MRI availability, and false positives leading to unnecessary biopsies, further complicate implementation (266). Equally concerning is the uneven access: Many high-risk children still lack routine surveillance because of geographic differences in the availability of resources and expertise (266). Addressing these gaps will be essential to ensure that these advances translate equitably into real-world improvements in survival and quality of life for children with cancer.

PROGRESS IN PEDIATRIC CANCER TREATMENT

IN THIS SECTION, YOU WILL LEARN:

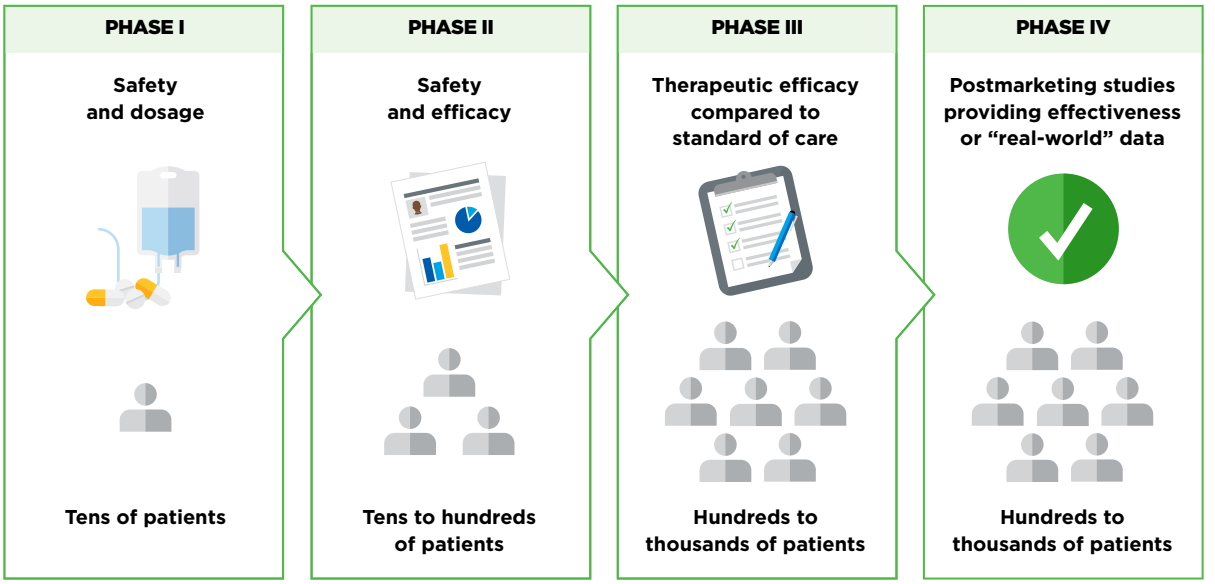
- Advances in the treatment of pediatric cancers are reflected in the greater than 85 percent 5-year relative survival rates for all cancers combined among children and adolescents. Despite the remarkable progress, cancer remains the leading cause of disease related death in children, and more than 60 percent of survivors experience significant long-term effects of treatment.
- The use of surgery, radiotherapy, and chemotherapy continues to evolve as more advanced forms of these treatments are developed and as better ways to apply them are discovered to improve survival and quality of life for pediatric cancer patients.
- With greater understanding of the biology of pediatric cancers, comes an increasing focus on utilizing personalized approaches to target cancers more precisely as well as on reducing treatment intensities among patients who have a favorable prognosis, to improve their quality of life.
- Molecular characterization of cancers and the use of targeted therapies, cellular therapies, and other immunotherapies have improved the care of certain pediatric cancers. However, progress still lags behind what has been achieved in adults, as most molecular drivers of pediatric cancers remain difficult to target and these tumors typically carry far fewer mutations, making them less responsive to immunotherapies.
- A new wave of pediatric cancer treatments is on the horizon, from innovative small molecules that target tumor-driving fusion proteins to next-generation CAR T-cell therapies designed to tackle brain cancer and other hard-to-treat solid tumors.
- Increased investments in pediatric cancer drug discovery and in global clinical trial collaborations are needed to accelerate the development of safer and more effective treatments for children and adolescents with cancer.

In the United States (US), an estimated 9,550 children (ages 0 to 14 years) and 5,140 adolescents (ages 15 to 19 years) will be diagnosed with cancer in 2025. Enormous progress has been made in the treatment of pediatric cancers over the past several decades, as reflected in the greater than 85 percent 5-year relative survival rates for all cancers combined. However, survival rates for children vary considerably depending on cancer type and patient age, among other factors, with some cancers, such as bone sarcomas and certain brain tumors, being difficult to treat and continuing to have poor survival.

Many of the initial advances in treating pediatric cancers were made through intensification of cytotoxic chemotherapeutics, which, while effective, were associated with significant toxicities, including short- and long-term adverse effects (267). With greater understanding of the biology of childhood and adolescent cancers and innovations in technology, has come an increasing focus on identifying therapeutic vulnerabilities and utilizing personalized approaches to target these diseases. Research has shown that cutting-edge technologies such as molecular profiling can improve the clinical care of children with

FIGURE 8

Phases of Clinical Trials



Clinical trials evaluating potential new therapeutics for treating patients with cancer have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how the human body metabolizes it, and potential toxicities. Phase II studies are designed to determine the initial efficacy of investigational therapy, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy as compared to standard of care; when successful, the results of these trials can be used by the US Food and Drug Administration (FDA) to approve new therapeutics or new indications for existing therapeutics. Phase IV studies are conducted after a therapy is provisionally approved by FDA and provide additional effectiveness or "real-world" data on the therapy. In some cases, researchers combine different phases into one clinical trial (labeling depends on the phases combined, e.g., phase I/II or phase III/IV clinical trials), which allows research questions to be answered more quickly or with fewer patients.

cancer by informing personalized treatment options (268). In addition, efforts to reduce treatment intensities among patients with curable cancers who have a favorable prognosis have been equally impactful by improving their quality of life (269).

Modernizing Clinical Research

Clinical trials, a central part of the medical research cycle, ensure scientific discoveries ultimately reach the patients who need them the most as quickly and safely as possible. Before most new diagnostic, preventive, or therapeutic products can be approved by the US Food and Drug Administration (FDA) and used as part of patient care, their safety and efficacy must be rigorously tested through clinical trials. All clinical trials are reviewed and approved by institutional review boards before they can begin and are monitored throughout their duration. Federal funding is vital for pediatric cancer clinical research, as it provides the essential support needed to launch and sustain clinical trials that would otherwise not be possible, given the limited private sector investment because of the rarity and smaller patient populations of pediatric cancers compared to adult cancers (270).

There are several types of cancer clinical trials, including treatment trials, prevention trials, screening trials, and supportive or palliative care trials, each designed to answer important research questions. In general, clinical studies in which participants are randomly assigned to receive an investigational treatment or the standard treatment (randomized clinical trials) are considered the most rigorous but can be challenging to conduct in rare diseases.

Cancer clinical trials have historically been conducted in three successive phases (see **Figure 8**, p. 64). This approach has yielded numerous advances in patient care. However, the multiphase clinical testing process requires a large number of patients and takes many years to complete, making it extremely costly and one of the biggest barriers to rapid translation of scientific knowledge into clinical advances. Pediatric cancers are rare, with only about 15,000 cases annually in the United States, and some subtypes are diagnosed in fewer than 100 children each year. This limited patient population adds to the challenge of enrolling enough participants in pediatric cancer clinical trials in a timely manner. Studies evaluating overall survival as a primary endpoint can take more than one decade to complete, and by the time results are available, they may be outdated or inconclusive, delaying the development of new, effective treatments.

A higher proportion of childhood and adolescent patients with cancer, ranging from 20 percent to over 30 percent, depending on cancer type, participate in clinical trials in the United States, compared to approximately 7 percent of adult patients (9,271). Enrollment of pediatric patients from racial and ethnic minority groups is also higher than that of adult patients (272,273). However, a lack of diversity still exists among clinical trial participants (274). For example, a retrospective analysis of clinical trial participation among children and adolescents with blood cancer showed that Black patients were 60 percent less likely than White patients to enroll in a trial (275).

Conducting pediatric cancer clinical trials globally can potentially help speed up drug development and approval by increasing the pool of eligible patients. This broader participation may allow trials to enroll faster, gather more diverse data, and generate results sooner, ultimately accelerating the availability of new treatments for children worldwide. Expanding global access to cancer clinical trials must become a strategic priority for all stakeholders committed to accelerating breakthroughs in pediatric cancer care (see **Global State of Pediatric Cancer Clinical Trials**, p. 131).

US lawmakers and FDA have also been working on legislation and guidelines intended to increase the diversity of clinical trial participants. FDA has taken actions to improve the availability of anticancer therapeutics for pediatric patients. In 2020, the agency provided guidance that included recommendations regarding the inclusion of children and adolescents, when appropriate, in clinical studies, and initiated enforcement of key provisions in the Research to Accelerate Cures and Equity (RACE) for Children Act requiring certain targeted cancer therapies developed for adult patients to be studied in pediatric patients (see **Advancing Pediatric Cancer Research and Patient Care Through Evidence-Based Policies**, p. 146).

On average, it takes about **6.5 years** from the first human trial of a cancer treatment in adult patients to the start of clinical trials evaluating that treatment in children, highlighting a **significant lag** in drug development for pediatric cancers.

Source: (276).

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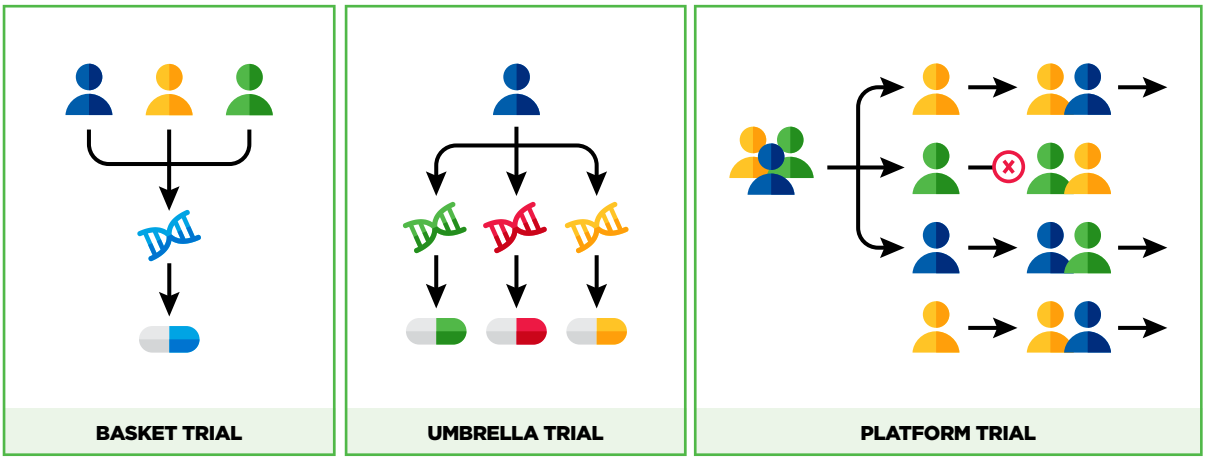
Research-driven advances in our understanding of cancer biology, in particular the genetic mutations that underpin cancer initiation and growth (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29), are enabling researchers and regulators to develop new ways of designing and conducting pediatric cancer clinical trials, including the emergence of adaptive and seamless clinical trial designs (277). These new approaches aim to streamline clinical trials of new anticancer therapeutics by using biomarkers—molecular features that help identify which patients are most likely to benefit—to match the right treatments with the right patients earlier in the process. Such strategies can reduce the number of patients who need to be enrolled in clinical trials; combine separate phases of trials into a single, continuous study; and decrease the length of time it takes for a new anticancer therapeutic to be tested and made available to patients.

In some clinical trials, cancer-driving genomic alterations, rather than the anatomic site of diagnosis of the original cancer, are being used to identify patients most likely to benefit from an investigational anticancer therapeutic (see **Figure 9**, p. 66). If successful, these clinical trials, which are called "basket" trials, have the potential to lead to FDA approvals that are agnostic of the site of cancer origin. One example of a basket trial is the NCI Pediatric MATCH study that was launched in 2017 (see **Integrating Molecular Insights Into Clinical Care**, p. 46). The trial aimed to systematically test therapeutics that target specific genetic changes in children, adolescents, and young adults (AYAs) between 1 and 21 years old who are diagnosed with advanced cancers that have gotten worse while on treatment or have relapsed after treatment. Results from the study indicated that about one-third of patients who had their tumors tested had targetable genetic changes, highlighting the potential of precision medicine in pediatric cancer care (163). Another genomics-informed clinical trial that yielded promising results involved the testing of a molecularly targeted therapeutic called larotrectinib in adult and pediatric patients who have any type of cancer characterized by the presence of genetic alterations called TRK fusions (see **Advances in Biomarker-based Treatments**, p. 85) (278).

FIGURE 9

Genomically Informed Clinical Trials



A major use of genomics in clinical research is in the design and execution of novel types of clinical trials. Two such types of trials are called basket and umbrella trials. In basket trials, one drug is tested against a particular genetic mutation across different cancer types. For example, the National Cancer Institute (NCI) Pediatric MATCH study explored targeted therapies in pediatric patients with advanced solid tumors, non-Hodgkin lymphomas, and histiocytic disorders which are ultrarare cancers of the immune system. In umbrella trials, different drugs are tested against multiple genetic mutations within the same cancer (279). In addition, platform designs are used to assess multiple interventions against a cancer type and modify aspects of the clinical trial design, if needed, by leveraging the accumulating data, thereby increasing the efficiency of the clinical research process. This design allows researchers to terminate ineffective interventions or add new interventions during the study. One example is the OPTIMISE platform trial that matches children with targeted therapies based on their tumor's genetic profile, using multiple basket trial arms focused on the most common altered pathways.

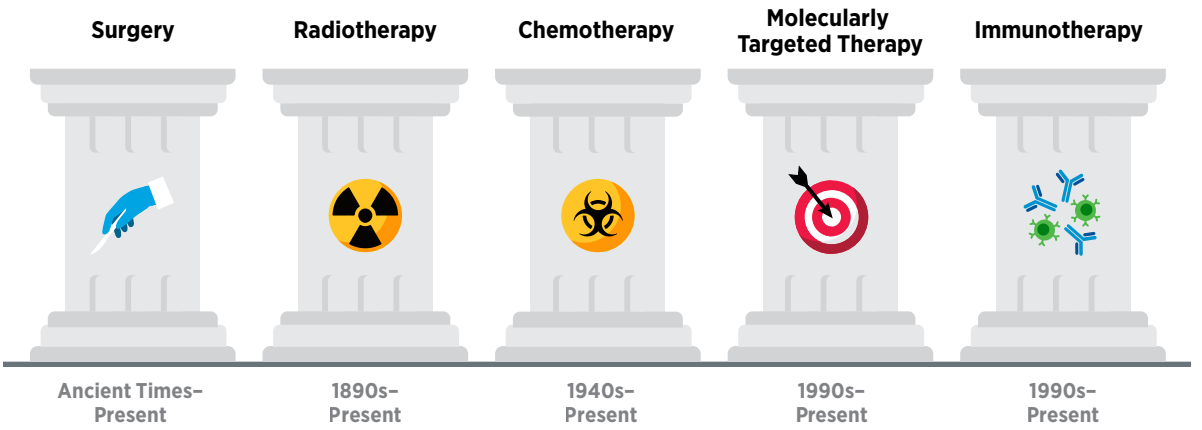
Future progress in pediatric cancer treatment necessitates further embracing innovative, biologically driven research frameworks. Designing biologically driven protocols and utilizing collaborative global networks may address the unique challenges in childhood cancer, such as small patient populations and diverse cancer subtypes (280). According to an encouraging recent report, pediatric cancer trials over the past 20 years have shifted toward more efficient designs, greater use of biomarkers, and combination therapies, reflecting advances in understanding the molecular complexity of cancer and evolving regulatory needs (see **Applying Regulatory Science to Advance Pediatric Cancer Research and Care**, p. 151) (281).

As trial designs evolve, it will be equally important to integrate patient-reported outcomes (PROs) to ensure that children's own experiences and quality of life are central to evaluating new therapies. Incorporating PROs into pediatric cancer clinical trials is critical for capturing the full impact of treatment beyond traditional clinical measures (282,283). Direct reports from children and adolescents about their symptoms, side effects, and quality of life offer unique insights that may be missed by physician assessments or laboratory tests (see **Care Coordination Across the Pediatric Cancer Survivorship Continuum**, p. 118). Recent work highlights validated, age-appropriate tools as well as the growing role of electronic PROs, which allow for timely and efficient symptom monitoring. Embedding these measures in trial design not only elevates the patient's voice but also supports more responsive, patient-centered care, ultimately leading to therapies that improve both survival and quality of life.

Harnessing emerging technologies such as artificial intelligence (AI) and machine learning may further improve clinical research by helping to identify patients eligible for trials, predicting which patients are most likely to benefit from experimental treatments, simulating how new therapeutics work, and creating virtual patient cohorts using past data and assessing how well trial results apply to real-world patient populations (252,284). However, current limitations of AI, including a lack of data diversity, standardized benchmarks, and proper regulatory oversight, must be overcome before these tools can become part of regular clinical practice.

FIGURE 10

The Pillars of Cancer Treatment



The cancer treatment paradigm is built upon what physicians often refer to as the "pillars" of cancer treatment. For centuries, surgery was the only treatment for cancer (285). In 1896, treatment of a patient with breast cancer with X-rays added radiotherapy as the second pillar (286). The foundations for the third treatment pillar—chemotherapy—were established in the early 1940s, with the use of a derivative of nitrogen mustard to treat lymphoma (287). These three pillars—surgery, radiotherapy, and chemotherapy—continue to be critical components of cancer treatment. Introduction of the first molecularly targeted agent in the late 1990s led to the establishment of the fourth pillar, molecularly targeted therapeutics (288). Also, in the late 1990s, decades of discovery science laid the groundwork for the fifth treatment pillar, immunotherapy (289). Continued evolution of new approaches, such as analysis of tumors aided by artificial intelligence, enhanced molecular imaging, and validation of new biomarkers, plays a critical role in advances in each of these therapeutic areas.

Advances in Pediatric Cancer Treatment With Surgery, Radiation, and Chemotherapy

Surgery, radiotherapy, and chemotherapy are the three long-standing pillars of cancer treatment and continue to be the mainstays of clinical care for most pediatric patients. However, in the past two decades, we have witnessed the emergence of two new pillars of cancer care—molecularly targeted therapy and immunotherapy, including cellular therapy (see **Figure 10**, p. 67). The therapeutics that form these pillars of cancer care can be remarkably effective and often less toxic than radiotherapy and chemotherapy. However, only a minority of pediatric patients with cancer are treated with molecularly targeted therapy or immunotherapy. Often this is because there are no effective molecularly targeted therapeutic or immunotherapeutic approaches available. It may also be that surgery, radiotherapy, and/or chemotherapy result in excellent outcomes.

Importantly, the use of surgery, radiotherapy, and chemotherapy is constantly evolving as we develop new forms of these treatments and identify new ways to use existing treatments to improve survival and quality of life for children and adolescents. Additionally, even though surgery, radiotherapy, and chemotherapy are mainstays of cancer treatment, they can have long-term adverse effects, which are particularly debilitating for pediatric patients (see **Supporting Survivors of Pediatric Cancers**, p. 104). For example, while chemotherapy has transformed outcomes for many children with cancer, recent studies have found that these treatments can also leave lasting marks on healthy tissues. By studying children who developed a second primary cancer, researchers showed that chemotherapy, especially platinum-based drugs, can accelerate DNA damage far beyond what happens through natural aging, helping to explain how some second cancers arise (290). These findings have led many researchers to investigate whether less aggressive treatment can allow some patients the chance of an improved quality of life without an adverse effect on long-term survival. In the past decade, a deeper understanding of pediatric cancer biology has driven the implementation of risk stratification and treatment de-escalation approaches in the clinic (see **Molecular Insights Driving Risk Stratification and Treatment**, p. 71).

Less Is Sometimes More

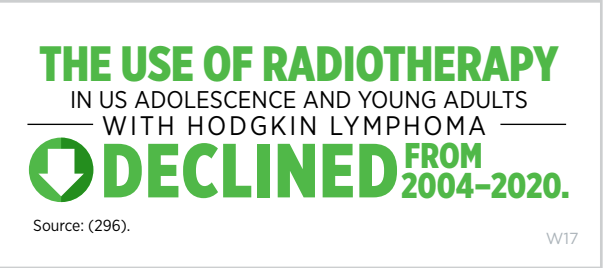
Long-term effects of radiation therapy can negatively impact a child's quality of life. Researchers continue to evaluate approaches to making radiotherapy safer and more effective,

including the use of biomarkers to identify patients who are unlikely to benefit from radiation or those who may be more vulnerable to its toxic effects, allowing radiotherapy to be reduced or even avoided without affecting patient outcomes.

For example, a number of studies have now demonstrated that in children with acute lymphoblastic leukemia (ALL), irradiation of the brain to prevent relapses is likely unnecessary in most cases (291,292). Instead, researchers found that administering chemotherapy into the spinal fluid lowered the risk of ALL relapses in the brain and spinal cord with reduced side effects, compared to irradiation. These findings are vital, considering that brain irradiation in children, especially young children, can cause devastating health problems, including a higher chance of developing a second primary cancer in the brain, difficulties with memory and thinking, hormone problems, and dementia later in life.

A major clinical trial found that some patients with Wilms tumor, the most common type of kidney cancer in children, can safely skip radiation therapy, helping to reduce its long-term adverse effects (293). Traditionally, the treatment for patients with stage IV Wilms tumors that have spread to the lungs has been chemotherapy and surgery, followed by radiation therapy to the lungs. Data from the trial suggest that nearly half of children with advanced Wilms tumor can avoid lung radiation therapy if they respond well to initial chemotherapy (293). Children whose lung nodules disappeared after 6 weeks of standard chemotherapy and continued treatment without radiation had a 4-year survival rate of over 96 percent, which was similar to the survival in those who received radiation. Omission of radiation can reduce serious long-term side effects, such as heart and lung damage or second primary cancers (see **Supporting Survivors of Pediatric Cancers**, p. 104).

Another example of reducing treatment intensity comes from children with intermediate-risk Hodgkin lymphoma. Researchers have shown that children with intermediate-risk Hodgkin lymphoma who receive intense chemotherapy, and those whose disease responds quickly, could skip radiation without affecting remission rates (294). Similar results were seen in another large study conducted in Europe, in which researchers evaluated a more precise approach to treating intermediate and advanced pediatric Hodgkin lymphoma (295). All children in the study received two cycles of chemotherapy, after which their response was assessed with imaging. Those whose cancer had responded well did not receive radiotherapy and still had excellent outcomes, similar to those who received radiotherapy. These data demonstrate that radiotherapy can be eliminated for these patients and underscore the power of tailoring treatment based on early responses, thus helping to minimize long-term side effects without compromising effectiveness.



In another study, researchers evaluated whether two cycles of chemotherapy could be just as effective as the usual four, while also reducing the harmful side effects in children who had a rare liver cancer called hepatoblastoma, and whose tumors could be completely removed by surgery (297). The phase III trial demonstrated that giving less chemotherapy after surgery led to equally excellent outcomes: Over 90 percent of children remained free from cancer recurrence, and 95 percent were alive after 5 years, with far fewer side effects like hearing loss.

This finding supports a broader goal of ensuring children have the highest chance of cure that restores them to full health and well-being. Importantly, the reduced-chemotherapy approach is currently being tested in a much larger international clinical trial so that physicians worldwide can confirm these data.

Researchers are also evaluating the optimal sequence of surgery, radiation, and chemotherapy to maximize benefits for patients. As an example, a study aimed to assess the best strategy for the use of chemotherapy, radiation, and surgery in patients with embryonal sarcoma of the liver (ESL), a rare and aggressive liver cancer that primarily affects children and young adults (298). The findings demonstrated that even though most patients with ESL are diagnosed with advanced disease, treatment with several cycles of chemotherapy followed by a complete tumor removal can lead to good outcomes, reduce surgical risks, and sometimes avoid the need for radiotherapy altogether.

To lower the adverse effects and morbidity associated with surgery, minimally invasive procedures—driven by technological advances and surgeon expertise—are being used more often in pediatric cancer care (299,300). Less invasive surgeries can offer benefits, such as smaller incisions and improved precision, though their appropriate use in pediatric cancer still needs to be defined through randomized clinical trials to ensure treatment standards and optimal outcomes are upheld.

A New Era for Radiotherapy

Over the past few decades, childhood cancer survival rates have greatly improved, but long-term side effects from treatment remain a concern. Radiation therapy, while vital

for treating certain childhood cancers, can cause significant long-term problems. Research has focused on reducing or even eliminating radiation in children who respond very well to chemotherapy, as seen in patients with Hodgkin lymphoma, certain Wilms tumors with lung metastasis, intracranial germinoma, and pediatric nasopharyngeal carcinoma. In medulloblastoma, the most common malignant brain tumor in children, genetic testing can identify subgroups of patients for whom lower doses of radiation are being studied to limit long-term harm (301).

At the same time, new strategies such as stereotactic ablative body radiotherapy, which can precisely deliver radiation to tumors, are being explored for children with limited metastasis, to deliver very high, precise doses over fewer sessions (see **Sidebar 12**, p. 70). This approach can help control tumors in difficult-to-treat cancers like rhabdomyosarcoma and Ewing sarcoma (302). Advances in modern radiation techniques, including proton therapy and highly targeted photon therapy, are also allowing health care providers to spare more healthy tissue and reduce long-term side effects, making it possible to tailor radiation more safely and effectively to the needs of each child.

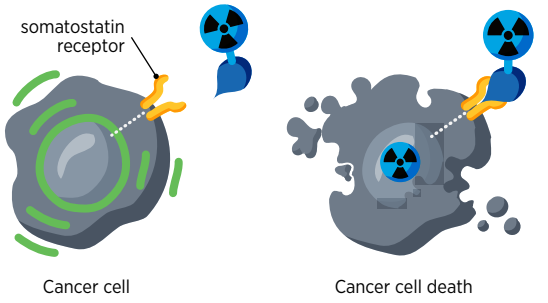
One of the most exciting and fastest-growing areas in radiotherapy is the use of radiopharmaceuticals or molecularly targeted radiotherapeutics—radiation-emitting molecules that are linked to targeting molecules, which steer the radiation specifically to cancer cells. A particularly promising innovation is theranostics, which combines diagnostic imaging and molecularly targeted radiotherapy to deliver personalized treatment based on a patient's unique tumor characteristics. A few such diagnostic therapeutic pairs have already been approved by FDA in recent years for adult patients and many more are at various stages of preclinical and clinical testing.

In April 2024, FDA approved the molecularly targeted radiotherapeutic lutetium Lu 177 dotatate (Lutathera) for children age 12 and older with gastroenteropancreatic neuroendocrine tumors that express proteins known as somatostatin receptors, including tumors originating in the foregut, midgut, and hindgut. This was the first FDA approval of a radiopharmaceutical for this condition in children. Gastroenteropancreatic neuroendocrine tumors are extremely rare in children and have few available treatment options, highlighting the importance of this approval.

Evolving Chemotherapy Strategies

As with surgery and radiotherapy, chemotherapy is more commonly used to treat cancer in combination with one or more additional types of treatments. Newer and more effective chemotherapeutics continue to be evaluated in clinical research. In addition, researchers are investigating optimal dosage, novel formulations, treatment combinations, and optimal timing of chemotherapy delivery to improve patient outcomes. For example, the chemotherapeutic nelarabine was first approved in 2005 for children whose T-cell leukemia had come back or had not responded to treatment, but it is now part of the initial treatment after studies showed it helps more children survive when added to standard initial chemotherapy (303). T-cell acute lymphoblastic leukemia (T-ALL) is less common than the B-cell form of the disease but historically it had been more difficult to treat requiring more intensive chemotherapy regimens.

How Lutetium Lu 177 Dotatate Works



Lutetium Lu 177 dotate
for treatment of neuroendocrine tumors.

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Transforming Pediatric Cancer Outcomes Through Precision Diagnostics

Remarkable advances in our understanding of cancer biology, including the discovery of numerous cellular and molecular alterations that drive tumor growth, have ushered in a new era of precision medicine. As a result, the standard of care is shifting away from a one-size-fits-all approach toward treatments tailored to the patient and the unique characteristics of their cancer. Therapeutics directed to molecules that influence cancer cell multiplication and survival target tumor cells more precisely, thereby limiting damage to healthy tissues, compared to chemotherapeutics, which generally target all rapidly dividing cells. As a result, molecularly targeted therapies are not only saving lives but also enabling patients with cancer to have a higher quality of life.

Unfortunately, our understanding of pediatric cancer biology does not consistently match the depth of knowledge we have

SIDEBAR 12

Using Radiation in Pediatric Cancer Treatment

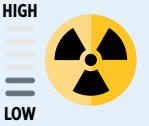
Ionizing radiation has **two major applications** in cancer care:

Treatment of cancer

Radiotherapy, or radiation therapy, uses high-energy radiation to control and eliminate the disease.

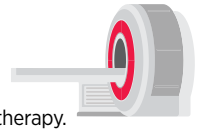
Detection of cancer

Radiology largely uses low-energy radiation to image tissues to diagnose the disease.



Types of Radiotherapy

EXTERNAL BEAM RADIOTHERAPY
delivers radiation, usually photons (X-rays) or electrons, to the tumor from outside the body; it is the most common form of radiotherapy.



There are several types of external beam radiotherapy:

- **Conventional external beam radiation therapy** delivers a high-energy X-ray beam from one or more directions and is primarily used when high precision is not required.
- **Three-dimensional conformal radiotherapy (3D-CRT)** delivers high-energy X-rays via multiple beams that, with the help of computed tomography and/or magnetic resonance imaging, enable more precise planning to best target the shape and size of the tumor.
- **Intensity-modulated radiotherapy (IMRT)**—a refinement of 3D-CRT—delivers radiation by dividing each beam into many "beamlets," each of which can have a different intensity, to achieve improved conformality.
- **Intraoperative radiation therapy** delivers electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures, or to the tumor cavity immediately after cancer removal.
- **Stereotactic radiotherapy** delivers radiation to very well-defined smaller tumors, typically using sophisticated immobilization and imaging system. It is used in both stereotactic radiosurgery (to treat tumors of the brain and central nervous system) and stereotactic body radiotherapy (SBRT) (to treat small tumors within the rest of the body).

PARTICLE THERAPY
using protons or carbon ions instead of X-rays, delivers radiation more precisely to tumors, sparing surrounding healthy tissue because these particles deposit most of their energy directly in the target. Proton therapy is increasingly used in pediatric cancers, such as brain tumors and others where it can reduce long-term side effects. Although proton facilities are more expensive than conventional radiation centers, evidence supports their benefit in these selected pediatric populations, though ongoing studies continue to define the full scope of clinical advantage.

BRACHYTHERAPY
delivers radiation by placing small radioactive sources in or next to the tumor either temporarily or permanently.

RADIOISOTOPE THERAPY
delivers radiation to the tumors via systemic ingestion or infusion of radioisotopes.

HYPOFRACTIONATED RADIOTHERAPY
delivers fewer but higher doses of radiotherapy compared to the traditional regimen. As a result, patients complete their radiotherapy over a shorter period and in fewer treatment sessions.

Uses of Radiotherapy

CURATIVE RADIOTHERAPY
Used to eliminate cancers, often in combination with systemic therapy.

NEOADJUVANT RADIOTHERAPY
Used to shrink a tumor so that it can be subsequently treated by a different method, such as surgery.

ADJUVANT RADIOTHERAPY
Used to eliminate any remaining cancer, often directed to the tumor cavity following prior surgical removal.

PALLIATIVE RADIOTHERAPY
Used to reduce or control symptoms of disease when cancer is considered incurable.

SALVAGE RADIOTHERAPY
Used to treat cancer after the cancer has not responded to other treatments but could be successfully controlled by radiotherapy.

for common adult cancers, largely due to the rarity of these diseases and historical gaps in research investment. In addition, the known molecular drivers in pediatric cancers often make for difficult drug targets. As a result, progress in implementing precision medicine approaches to pediatric cancers has not kept pace with advances seen in adult cancers. Despite these challenges, considerable progress has been made in recent years. Large-scale tumor profiling, genomic sequencing, epigenetic characterization, and collaborative research initiatives from the United States and around the globe have already identified actionable targets in some pediatric cancers, leading to changes in treatment for selected patients (see **Integrating Molecular Insights Into Clinical Care**, p. 46, and **Sidebar 13**, p. 72). In many others, the molecular drivers have been identified but they are not yet pharmacologically actionable. Ongoing studies continue to expand our understanding, offering hope that precision medicine will increasingly benefit more children with cancer.

In the United States, the Childhood Cancer Data Initiative (CCDI), launched in 2019, is a national effort to collect information from every child, adolescent, and young adult diagnosed with cancer, no matter where they receive care. The goal of CCDI is to use clinical and genetic data to speed diagnosis, guide treatment, and improve prevention, quality of life, and long-term outcomes for all pediatric cancers (see **Policies Advancing Pediatric Cancer Research and Care**, p. 147). Building on this, the Molecular Characterization Initiative (MCI), launched in 2022, and Children's Oncology Group's Project:EveryChild, provide advanced molecular testing at diagnosis, helping health care providers and families choose the most effective treatment while linking clinical care and research to further accelerate discoveries (see **Shared Data and Collaborations Advancing Pediatric Cancer Research**, p. 44) (309).

As of July 2025, MCI has analyzed samples from over 6,000 children and adolescents, encompassing a wide range of cancers, most of them solid tumors (32). Most cases are central nervous system (CNS) tumors, followed by soft tissue sarcomas, rare tumors, neuroblastomas, and Ewing sarcomas. Molecular testing helped refine the diagnosis for about one-third of participating children with cancer. Although MCI is ongoing, early indications are that this complex clinical testing led to 15 percent of those tested receiving treatments targeting specific molecular changes, and 8.5 percent being enrolled in clinical trials based on their test results, demonstrating how comprehensive molecular profiling can directly guide care and improve access to cutting-edge therapies. Additionally, the analysis revealed that about 14 percent of patients carried inherited or de novo mutations linked to cancer (see **Genetic Alterations**, p. 31), which may guide clinical care for their family members.

European precision oncology studies—MAPPYACTS, which demonstrated the real-world feasibility and impact of tumor molecular profiling in relapsed pediatric cancers, and AcSé-ESMART, a proof-of-concept platform trial aimed at genetically matching childhood cancer patients to targeted therapies under a single adaptive protocol—together underline some of the global efforts in generating molecularly driven treatment strategies for childhood cancer (see **Molecular Profiling Driving Precision Medicine**, p. 131) (310,311).

Molecular Insights Driving Risk Stratification and Treatment

Advances in molecular profiling of childhood cancers have significantly improved clinical care. By identifying genetic features that help predict how likely it is for a child's cancer to return, health care providers can tailor the modality or intensity of treatment to each patient's specific needs.

For example, by analyzing the molecular features of B-cell ALL (B-ALL) cells, clinicians can more accurately assess each patient's risk of relapse and tailor therapy accordingly (312). Research has indicated that children with genetic alterations such as the *ETV6::RUNX1* fusion or hyperdiploidy, a condition in which leukemia cells have more chromosomes than normal, tend to have favorable outcomes and may be treated with less intensive chemotherapy to help reduce long-term side effects. In contrast, children with high-risk alterations such as *BCR::ABL1* fusion or *KMT2A* gene rearrangements often require more intensive chemotherapy or targeted treatment approaches. Moreover, recent studies show that even within favorable or high-risk subtypes, additional genetic changes, such as alterations in *IKZF1* or *CREBBP,* or certain chromosomal gains and losses, can further influence the chance of relapse (313).

Although T-ALL is much less common than B-ALL in children, it is often more aggressive. In a recent study, scientists analyzed genomic, transcriptomic, and epigenomic data from over 1,300 uniformly treated pediatric patients and uncovered 15 distinct subtypes of T-ALL (100). Each subtype was shown to have distinct molecular characteristics linked to how aggressive the cancer was and how patients responded to treatment. These discoveries could lead to more precise diagnosis, better ways to predict outcomes, and ultimately more personalized therapies tailored to each child's cancer.

Comprehensive molecular testing has become indispensable for accurately diagnosing, grading, and predicting outcomes in CNS tumors for which these tests are no longer optional, but the standard diagnostic criteria as established by the World Health Organization (WHO) (314). In fact, many CNS tumor types cannot be reliably diagnosed under the current WHO criteria without molecular data, which means that routine molecular profiling is now fundamental for correct patient classification and subsequent treatment planning. Despite cost concerns, these tests account for less than 5

SIDEBAR 13

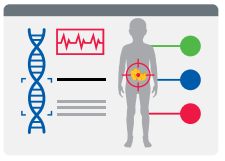
Molecular Characterization Driving Clinical Advances Against Pediatric Cancers

Many studies have shown that molecular characterization of pediatric cancers can accelerate research and inform patient care. Such efforts can identify actionable mutations, inform the design of future clinical trials, and help clinicians make personalized treatment decisions (304). These actions could be critical for rarer pediatric cancers where standard therapies are limited.

Selected examples from recent years are highlighted below:

A study that explored whether analyzing genetic makeup of tumors using DNA and RNA sequencing could guide effective, personalized treatments found that among children and young adults with rare or difficult-to-treat cancers, sequencing uncovered actionable genetic information in about 46 percent of patients, leading to changes in clinical care for some (305).

A study that analyzed the genomes of 309 children with various cancers using three types of sequencing to examine both DNA and RNA found that 86 percent of children had genetic changes that could help diagnose the cancer, predict outcomes, suggest treatments, or indicate inherited cancer risk. Specifically, 25 percent of patients had alterations that could directly guide therapy (85).



A study that analyzed tumor DNA from 888 children with a wide range of solid tumors over 6.5 years found that 33 percent of patients had genetic alterations that matched them to an ongoing precision oncology trial, and 14 percent of those children were treated with therapies specifically targeting those alterations (306).

A study in Canada analyzed the DNA and RNA of 300 children and young adults with rare or high-risk cancers and found that 56 percent of patients had genetic changes that could inform clinical care, and 54 percent had alterations that could potentially be targeted with therapies. Importantly, genetic alterations often changed over time, with one-third of patients, for whom multiple samples from different time points were available, showing new targetable mutations at relapse (307).

A multinational study of 519 children with relapsed, progressive, or high-risk cancers, showed that about 8 percent of patients had genetic changes that could be targeted with therapy. Those who received matched treatments experienced longer periods without disease progression (308).

A study in Australia used detailed DNA and RNA sequencing to evaluate 252 children with rare, relapsed, or high-risk cancers. Almost all patients had at least one genetic change, with 71 percent having alterations that could be targeted with therapy and 16 percent carrying inherited cancer predisposing variants. Molecular testing also helped refine or change diagnoses in some cases (83).

While these efforts underscore the vital role of molecular characterization of pediatric cancers in advancing precision diagnostics and medicine, it should be noted that even when a targetable genetic change is found, access to appropriate therapies can be limited by drug availability, clinical trial eligibility, and safety concerns. Moreover, many of the genetic alterations identified in cancers in children and adolescents are highly specific to pediatric disease and currently lack corresponding targeted therapies, leaving significant gaps in treatment options. Additional research is also needed to confirm whether matched treatments can improve overall survival.

percent of the average overall cost of treating CNS tumors but still deliver major benefits in patient management, including more precise prognoses, better therapeutic matching, and clearer clinical trial eligibility.

One CNS tumor in which molecular classification is driving diagnosis and clinical care is medulloblastoma. Advances in genetic testing now allow clinicians to classify patients with medulloblastoma based on their underlying biological drivers into four distinct subgroups. Referred to as WNT, SHH, Group 3, and Group 4 medulloblastoma, these subtypes differ in how aggressive they are and how likely they are to respond to treatment. These subtypes can be further divided based on epigenetic patterns that help predict how the cancer will behave (315). Research has identified that children in the WNT subgroup have an excellent prognosis. Studies are evaluating whether radiation and chemotherapy doses can be safely reduced among these patients to limit long-term side effects, with early results showing prolonged survival and fewer complications (301). At the same time, researchers are identifying high-risk subgroups, such as patients within Group 3 or Group 4 with certain mutations, that are resistant to treatments (316), and exploring stronger, targeted approaches to improve outcomes.

In neuroblastoma, the most common pediatric solid tumor outside the CNS, rigorous molecular and clinical risk stratification (using age, stage, spread, and specific genetic and chromosomal aberrations) has enabled reduction of therapy intensity in low-risk cases while enabling intensified multi-modal treatment for high-risk patients, resulting in significantly improved cure rates (317).

Molecular profiling has also allowed researchers to precisely monitor minimal residual disease (MRD), which occurs when a very small number of cancer cells remain in the body during or after treatment, helping clinicians adjust therapy in real time based on how well the cancer is responding. This approach is significantly improving outcomes while minimizing unnecessary toxicity, marking a major advance in the personalized treatment of pediatric cancers. For example, a large international study found that combining MRD status with genetic alterations enables more refined risk classification in pediatric ALL, allowing low-risk patients to receive less intensive therapy to reduce long-term side effects, while directing more intensive treatment to high-risk patients, thereby improving overall outcomes (318).

Recent research is demonstrating the growing promise of liquid biopsies in MRD testing (see **Liquid Biopsy**, p. 43). These innovative techniques allow doctors to detect small amounts of cancer DNA in bodily fluids such as blood or cerebrospinal fluid (CSF), offering a less invasive way to monitor disease, guide treatment, and predict outcomes. As one example, in children with solid tumors, including sarcomas and neuroblastoma, liquid biopsies along with innovative new technologies to analyze DNA and RNA have made it possible to detect gene fusions, a common driver in many childhood cancers, directly from blood samples and help track how tumors respond to treatment and identify early signs of recurrence (319). In children and adolescents with newly diagnosed Ewing sarcoma or osteosarcoma, circulating tumor DNA in the blood was linked to a significantly poorer outcome (320).

In childhood brain tumors, including medulloblastoma and diffuse midline glioma, researchers have demonstrated that analyzing tumor DNA in CSF can provide critical insights into whether cancer remains after surgery or how tumors respond to radiotherapy (157,321). Another study was able to correlate genetic alterations in circulating tumor DNA to MRD levels in nearly every child with leukemia, showing how liquid biopsies could provide a powerful new tool for monitoring childhood cancers (154). Liquid biopsy and MRD tools have immense potential in pediatric oncology, offering safer and more precise ways to track disease, personalize therapy, and ultimately improve outcomes for children with cancer.

Advances in Pediatric Cancer Treatment With Molecularly Targeted Therapeutics

Remarkable advances in our understanding of the biology of cancer, including the identification of numerous cellular and molecular alterations that fuel tumor growth, have set the stage for a new era of precision medicine (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29). Molecularly targeted cancer treatments, which form the foundation of precision medicine, work by homing in on the molecules such as mutated proteins that drive a tumor's growth, which makes them more precise and often less toxic than traditional chemotherapy that indiscriminately attacks both cancerous and rapidly dividing healthy cells. As a result, these treatments are saving and improving the lives of some children with cancer. However, progress in developing such targeted therapies for pediatric cancers has been limited. Many of the key genetic drivers in childhood cancers such as *MYC* and *MYCN* (in medulloblastoma and neuroblastoma), *PAX* fusions (in rhabdomyosarcoma), and *EWSR1* fusions (in Ewing sarcoma) have long been considered undruggable. Emerging therapeutic approaches, including targeted protein degradation, RNA-based, and epigenetic strategies, are beginning to offer new ways to tackle these challenging targets and may ultimately expand the benefits of precision medicine to more children with cancer.

Since 2015, FDA has approved and expanded the use of many molecularly targeted therapeutics for treating children with

Compared to 5.9% during the 2012–2016 period, **the proportion of drugs approved specifically for pediatric use during the 2017–2021 period rose to 13.8%.**

Source: (322).

W19

cancers (see **Table 4**, p. 75). However, these numbers remain far short of the approvals seen in adult cancers, and very few of these drugs have been developed specifically for pediatric patients. For instance, between 1997 and 2017, just six out of 117 FDA approved cancer therapeutics had an initial approval that included children (276). The following sections highlight the molecularly targeted therapies that have been approved by FDA for pediatric cancers over the past 10 years.

Adding Precision to the Treatment of Leukemia

Leukemias are the most common cancer among US children and adolescents. Among children ages 0 to 14, ALL is the most common cancer diagnosis. The 5-year survival for children and adolescents is greater than 90 percent, attributable to spectacular advances in risk stratification at diagnosis, with treatment escalation for those with high risk of relapse as well as to the new and improved treatment options that are now available in the clinic. Decades of basic, translational, and clinical research have enhanced our knowledge of the underpinnings of leukemia as well as knowledge of the immune system. Researchers are harnessing this knowledge to develop personalized treatments including molecularly targeted therapeutics and immunotherapeutics that target ALL.

Antibody–drug conjugates are an emerging class of molecularly targeted therapeutics that use an antibody to deliver an attached cytotoxic chemotherapeutic directly to the cancer cells that have the antibody's target on their surfaces. Once the antibody attaches to its target on the surface of a cancer cell, the antibody–drug conjugate is internalized by the cells. This leads to the chemotherapeutic being released from the antibody and killing the cancer cell. The precision of antibody targeting reduces the side effects of the chemotherapeutic compared with traditional systemic delivery.

In most children, ALL arises in immune cells called B cells, which have a protein called CD22 on the surface. Inotuzumab ozogamicin (Besponsa) is an antibody–drug conjugate comprising a CD22-targeted antibody linked to the chemotherapeutic calicheamicin. It was approved for treating adults with B-ALL in August 2017. Subsequent studies have shown that inotuzumab ozogamicin is also effective in children and adolescents. In March 2024, FDA approved the therapeutic for pediatric patients 1 year and older with CD22-positive B-ALL that has relapsed or stopped responding to standard treatments. The approval was based on findings from a clinical trial in which about 40 percent of patients who received inotuzumab ozogamicin achieved a complete remission, which means they had no evidence of cancer (323).

Patients who receive inotuzumab ozogamicin may need a stem cell transplant to ensure durable cancer remission. While treatment with inotuzumab ozogamicin increases the risk of developing serious liver toxicities in certain patients, its approval has increased treatment options for a group of ALL patients who may be ineligible for chimeric antigen receptor (CAR) T-cell therapy (see **Boosting the Cancer-killing Power of Immune Cells**, p. 90) and have no remaining options.

Philadelphia chromosome–positive (Ph+) ALL is a rare but aggressive form of ALL in children caused by a genetic mutation that leads to the formation of the *BCR::ABL* fusion gene, the same structural variation (see **Sidebar 4**, p. 32) that drives most cases of chronic myeloid leukemia (CML), a slow-growing blood cancer. Decades of research led to the discovery of the *BCR::ABL1* fusion gene that produces an abnormal BCR::ABL protein which drives uncontrolled growth of CML cells. These findings spurred the development and FDA approval of molecularly targeted therapeutics, such as imatinib and dasatinib, which specifically block BCR-ABL protein function, and have transformed the treatment of CML.

Based on positive data from clinical trials, imatinib and dasatinib have since received expanded approval by FDA for treatment of children with Ph+ ALL and are significantly improving outcomes for patients (324,325). When used in combination with chemotherapy, these treatments have reduced the need for more aggressive therapy like stem cell transplantation and have led to better survival rates for pediatric patients.

CML is rare in children, accounting for only 2 percent to 3 percent of leukemias diagnosed in those under 15 years

CHILDHOOD LEUKEMIA REPRESENTS

MORE THAN 25%

OF ALL NEW CHILDHOOD CANCER CASES.

Source: (11).

W20

TABLE 4

FDA-approved Molecularly Targeted Therapies to Treat Pediatric Cancers (2015–2025)

Generic Name (Nonproprietary)	Trade Name (Proprietary)	Approved For	Mechanism of Action	Year(s) Approved
Dordaviprone	Modeyso	Patients 1 year and older with diffuse midline glioma harboring an H3K27M mutation with progressive disease following therapy	Cell death promoting agent	2025
Belzutifan	Welireg	Patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma	Gene transcription modifier	2025
Mirdametinib	Gomekli	Patients 2 years and older with neurofibromatosis type 1 who have unresectable symptomatic plexiform neurofibromas	Cell-signaling inhibitor	2025
Revumenib	Revuforj	Patients 1 year and older with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene translocation	Gene transcription modifier	2024
Vorasidenib	Voranigo	Patients 12 years and older with grade 2 astrocytoma or oligodendroglioma with an *IDH1* or *IDH2* mutation	Epigenome-modifying agent	2024
Repotrectinib	Augtyro	Patients 12 years and older with solid tumors that have a *NTRK* gene fusion	Cell-signaling inhibitor	2024
Selpercatinib	Retevmo	Patients 2 years and older with advanced or metastatic medullary thyroid cancer with a *RET* mutation; patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion	Cell-signaling inhibitor	2024; 2024*
Tovorafenib	Ojemda	Patients 6 months and older with relapsed or refractory pediatric low-grade glioma harboring a *BRAF* fusion or rearrangement, or *BRAF* V600 mutation	Cell-signaling inhibitor	2024
Inotuzumab ozogamicin	Besponsa	Patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL	DNA damaging agent	2024
Eflornithine	Iwilfin	Patients with high-risk neuroblastoma	Cancer metabolism inhibitor	2023
Entrectinib	Rozlytrek	Patients older than 1 month with solid tumors that have a *NTRK* gene fusion	Cell-signaling inhibitor	2023
Bosutinib	Bosulif	Patients 1 year and older with Philadelphia chromosome-positive CML	Cell-signaling inhibitor	2023
Dabrafenib plus trametinib	Taflinar plus Mekinist	Patients 1 year and older with low-grade glioma with a *BRAF* V600E mutation; patients 1 year and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation	Cell-signaling inhibitor	2023; 2023*
Brentuximab vedotin	Adcetris	Patients 2 years and older with high risk classical Hodgkin lymphoma	Cell-lysis mediator	2022
Cabozantinib	Cabometyx	Patients 12 years and older with locally advanced or metastatic differentiated thyroid cancer; patients 12 years and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic and extra-pancreatic neuroendocrine tumors	Angiogenesis inhibitor	2021; 2025
Crizotinib	Xalkori	Patients 1 year and older with relapsed or refractory, systemic anaplastic large cell lymphoma that is ALK-positive; patients 1 year and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor that is ALK-positive	Cell-signaling inhibitor	2021; 2022
Pralsetinib	Gavreto	Patients 12 years and older with advanced or metastatic thyroid cancer with *RET* alterations	Cell-signaling inhibitor	2020
Selumetinib†	Koselugo	Patients 2 years and older with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas	Cell-signaling inhibitor	2020
Tazemetostat	Tazverik	Patients 16 years and older with metastatic or locally advanced epithelioid sarcoma	Epigenome-modifying agent	2020
Tagraxofusp-erzs	Elzonris	Patients 2 years and older with blastic plasmacytoid dendritic cell neoplasm	Cell-lysis mediator	2018
Larotrectinib	Vitrakvi	Pediatric patients with solid tumors that have a *NTRK* gene fusion	Cell-signaling inhibitor	2018
Nilotinib	Tasigna	Patients 1 year or older with Philadelphia chromosome positive CML	Cell-signaling inhibitor	2018
Dasatinib	Sprycel	Patients 1 year and older with Philadelphia chromosome-positive CML; Pediatric patients 1 year and older with Philadelphia chromosome-positive ALL	Cell-signaling inhibitor	2017; 2018
Gemtuzumab ozogamicin	Mylotarg	Patients 2 years and older with relapsed or refractory CD33-positive AML	DNA damaging agent	2015

* Duplicate years indicate multiple approvals in that year.

† FDA expanded the use by approving selumetinib granule formulation for pediatric patients 1 year and older in September 2025.

For complete information on pediatric cancer drug approvals visit: https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology-drug-approvals.

old, and about 9 percent of cases among adolescents ages 15 to 19 (326). BCR::ABL targeted therapeutics such as dasatinib, nilotinib, and bosutinib, which are approved for adult patients, have also been approved by FDA for pediatric patients with CML driven by the *BCR::ABL1* fusion gene. However, because these drugs also interfere with pathways important for growth, metabolism, and hormone function, their long-term effects in children, who are still developing, remain unclear. As newer and safer treatments are explored, defining the safety and effectiveness of existing therapies in pediatric patients is critical.

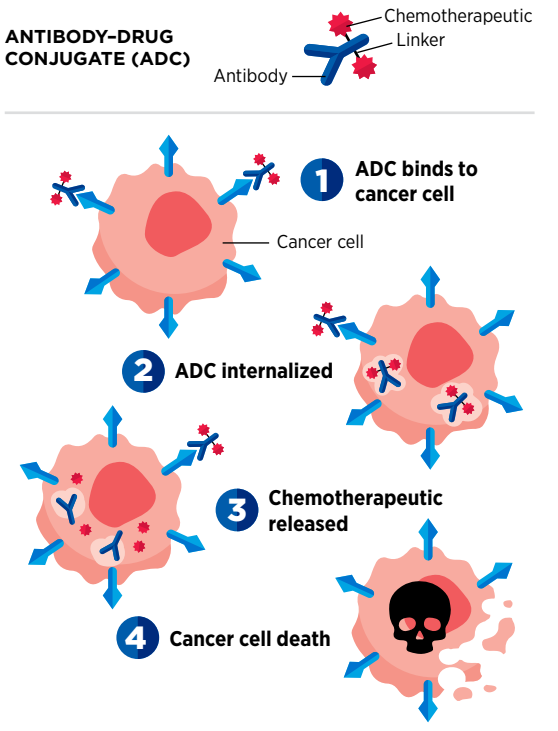
Structural variations, also known as rearrangements, in the *KMT2A* gene are observed in up to 80 percent of infant ALL and in 5 percent to 15 percent of children and adults with acute leukemia, including those that originate in myeloid or lymphoid cells, or a mix of both (327). The *KMT2A* gene encodes a protein called MLL1, which plays a critical role in normal blood cell development by regulating gene expression through epigenetic mechanisms.

KMT2A rearrangements disrupt normal cell development by causing blood cells to revert to an immature state, preventing them from forming functional blood cells. The result is the formation of leukemia cells instead of mature blood cells. This disruptive process is driven by the interaction of MLL1 with another protein called menin (328). Together, menin and MLL1 form a complex that binds to DNA in the cell's nucleus and triggers harmful genetic programs that lead to leukemia. Acute leukemia with *KMT2A* rearrangements is associated with treatment resistance and poor prognosis (329). In addition to *KMT2A* rearrangements, mutations in the *NPM1* gene—detected in up to 30 percent of adult acute myeloid leukemia (AML) cases—also depend on menin to promote leukemia development (330,331).

These discoveries led to the development of menin-targeted therapies (see **Figure 11**, p. 77) (332,333), culminating in the November 2024 FDA approval of revumenib (Revuforj), the first menin inhibitor, for adult and pediatric patients (1 year and older) with acute leukemia harboring *KMT2A* rearrangements who never responded to or experienced relapse after initial treatments. Revumenib works by blocking the interaction between menin and MLL1. By binding to menin, it prevents the menin–MLL1 complex from attaching to DNA, thereby halting the abnormal genetic programs that fuel leukemia. As a result, leukemia cells are either driven to mature into healthy blood cells or are eliminated.

FDA approval of revumenib was based on a phase I/II clinical trial in which more than 21 percent of patients experienced complete remission (cancer no longer detectable in the bone marrow, and the number of healthy blood cells returned to normal levels) or complete remission with partial recovery of their blood counts (cancer is no longer detectable in the bone marrow, with partial recovery of the number of healthy blood cells). The benefits lasted a median of over 6 months. Revumenib has provided patients such as **Tyler Peryea** (see p. 79) with a personalized treatment option that is much less aggressive than traditional chemotherapeutics.

How Antibody-drug Conjugates Work

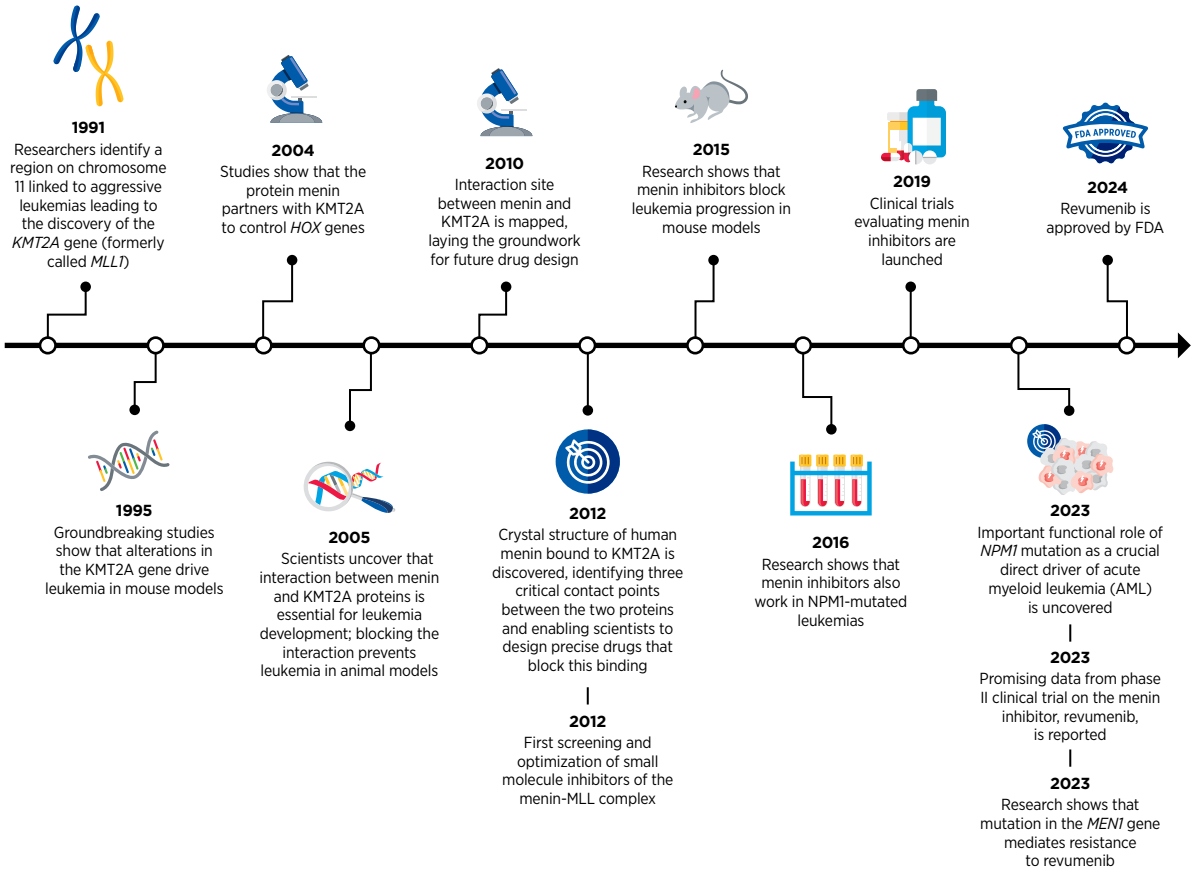


Ongoing studies are looking to identify mechanisms of resistance to revumenib treatment and evaluating revumenib as the initial treatment as well as in combination with other molecularly targeted therapeutics or chemotherapeutics to improve outcomes for more patients.

AML is the second most common leukemia in children, accounting for 25 percent of childhood leukemia cases. Traditionally, most children were treated with chemotherapy followed by stem cell transplants (267). Molecularly targeted therapeutics, such as revumenib and others, are now becoming the standard treatment for many children. As one example, in September 2017, FDA approved gemtuzumab ozogamicin (Mylotarg) for the treatment of adults and pediatric patients 2 years and older whose AML has relapsed or has stopped responding to other treatments and whose leukemia cells have the protein CD33.

FIGURE 11

Milestones in the Development of Menin-targeted Therapy for Leukemia



This timeline illustrates key scientific breakthroughs that led to the development and eventual US Food and Drug Administration (FDA) approval of revumenib, a molecularly targeted treatment for aggressive leukemias involving alterations in the *KMT2A* or *NPM1* genes. In 1991 scientists discovered the critical leukemia-linked region on chromosome 11, and in 2004 researchers uncovered how a protein called menin interacts with MLL1, the protein encoded by the *KMT2A* gene to drive leukemia growth. Over the next two decades, scientists mapped this interaction, solved its three-dimensional structure, and designed drugs to block it. In 2023, promising clinical trial results showed that revumenib could help patients with difficult-to-treat leukemias, leading to its approval by FDA in 2024.

Sources: (327,328,330,332,334-351).

Gemtuzumab ozogamicin is an antibody–drug conjugate comprising the chemotherapeutic calicheamicin attached to a CD33-targeted antibody. In most patients, AML cells have the molecule CD33 on the surface, and FDA approval was specifically for this precisely defined patient population. The approval was based on clinical trials that indicated adding gemtuzumab ozogamicin to standard chemotherapy lowered the chance of relapse and improved outcomes for children and adolescents with AML, especially for those whose cancer cells had high levels of the protein CD33 (352,353).

In June 2020, FDA expanded the use of gemtuzumab ozogamicin for children 1 month and older with newly

continued on page 80

“Research is very important because childhood cancer is very rough and being in the hospital and being sick is not fun.”

SURVIVOR STORY

TYLER PERYEA

AGE: 15 | DIAGNOSIS: ACUTE MYELOID LYMPHOMA | CUMBERLAND, RI

A Second Chance, Thanks to Research and Hope

At 15 years old, Tyler Peryea is focused on the same things as most teenagers—watching movies, playing video games with his friends, and dreaming of becoming an actor. His easy smile and quick humor belie an extraordinary journey that has tested his strength, his family's resolve, and showed the power of research to save lives.

Tyler's health challenges began when he was just 16 months old. A healthy, thriving toddler, he suddenly became gravely ill with complete organ failure. Doctors at Hasbro Children's in Providence, Rhode Island suspected a rare immune disorder called hemophagocytic lymphohistiocytosis (HLH)—a life-threatening condition treated with chemotherapy and steroids, much like cancer. "The doctor told us he had heard of HLH only once before," recalled his mother, Jamie. "Thank goodness he recognized it—because that saved Tyler's life."

After months on life support, Tyler was transferred to Cincinnati Children's Hospital, where one of the world's experts in HLH was on staff. There, at just shy of 2 years old, Tyler received a bone marrow transplant. Complications followed, including a rare autoimmune anemia that left him dependent on blood transfusions for about 2 years. "He had every complication imaginable," Jamie said. "But he pulled through."

Balancing Tyler's medical care with caring for his newborn younger brother, Cameron, also became a significant challenge for their parents Jamie and Brad. Jamie had to quit her job to stay by Tyler's side during the weekdays, and Brad would join them over the weekends. They are both thankful for all the support they received. "I don't think we could have done it without family, friends, and the community," Jamie said.

Tyler thrived for the next 7 years. He went to school, played with his brother, and enjoyed his childhood without major hospital stays. Then, in September 2024 at age 14, everything changed again. After just 9 days of high school, Tyler came down with what seemed like pneumonia caused by COVID-19. His family was actually relieved—COVID was something treatable. But within days, doctors spotted atypical cells in his blood. A bone marrow biopsy confirmed their worst fear: Tyler was diagnosed with a very rare form of acute myeloid leukemia (AML).

"It was very difficult to hear, and I don't think we were ready for it," said Brad. "We'd already been through this once. Hearing it again—it just broke us."

Because of a rare genetic mutation found in Tyler's cancer his doctors referred him to the Dana-Farber/Boston Children's Cancer and Blood Disorders Center for a clinical trial for a menin inhibitor called revumenib. "We didn't know if it would work, but we had no other options," said Jamie. "When you're out of options, research is all you have left."

Tyler began chemotherapy combined with investigational therapeutic, which was designed specifically for patients with AML that has a mutation in the *NPM1* gene. Despite the long list of potential side effects, he tolerated revumenib well. Then, in a remarkable stroke of timing, revumenib received FDA approval as his clinical trial was ending. "It meant he could stay on the medicine," Jamie explained. "And it worked—his leukemia dropped low enough for a second transplant."

In January 2025, Tyler underwent another stem cell transplant at Dana-Farber/Boston Children's. Recovery was difficult—he spent 9 weeks in intensive care and required 24-hour dialysis for kidney failure. "There were moments he asked, 'Why me? Why again?'" said Brad. "All we could tell him was to hold on—that we'd get through it together." Slowly, Tyler's strength returned. Within months, he was home, with his positive and happy personality coming back.

Today, Tyler continues taking revumenib to prevent a relapse. He's regaining weight, catching up on schoolwork, and planning to return to 10th grade this fall. "He's doing amazing," Jamie said. "You'd never know what he's been through."

The Peryeas remain steadfast advocates for research funding, knowing firsthand that each new discovery can mean the difference between life and loss. "Clinical trials gave Tyler his future," Jamie said. "There's not enough funding for pediatric cancer, and that has to change. Every child deserves a chance."

Brad agreed. "Funding cancer research is so important. Without clinical trials and new medicine, so many cancers wouldn't be cured. Research gives patients a chance to live longer."

Scan the QR code to watch Tyler's video interview.

diagnosed CD33-positive AML based on findings from a large clinical trial that showed that adding gemtuzumab ozogamicin to standard chemotherapy helped more children stay in remission without the cancer returning (354).

New Hope for Patients With Lymphoma

Classical Hodgkin lymphoma (cHL) is a blood cancer that accounts for approximately 6 percent of all childhood cancers. The disease is most common in adolescents. Historically, pediatric cHL has been treated with intensive chemotherapy combinations. While these treatments have been successful in curing many patients, they carry long-term risks, including damage to the heart and lungs or the risk of second primary cancer later in life.

In a significant advance, in November 2022, FDA approved the antibody conjugate brentuximab vedotin (Adcetris) for the treatment of children ages 2 and older with untreated cHL who are more likely to experience relapse or be resistant to treatment. This was the first approval of the therapeutic for pediatric patients, being already used in adults. Brentuximab vedotin delivers a cytotoxic chemotherapeutic known as monomethyl auristatin E directly to cancer cells expressing a protein called CD30, which is found on the surface of Hodgkin lymphoma cells. This targeted approach aims to kill cancer cells more precisely, potentially reducing side effects.

The approval was based on results from a phase III clinical trial in which children and adolescents treated with brentuximab vedotin in combination with chemotherapy were 59 percent less likely to experience relapse, disease progression, or death compared to those receiving standard chemotherapy (355). This approval marks a major step toward safer, more effective, and potentially less toxic treatment for children with high-risk HL. More than half of the children in both treatment groups received carefully tailored, lower-dose radiation after chemotherapy because their tumors were slow to shrink as evidenced from interim positron emission tomography (PET) scans. This approach highlights how response-based imaging can guide radiotherapy and help reduce side effects of radiation and preserve long-term health while still achieving high cure rates.

Non-Hodgkin lymphoma (NHL) is a group of blood cancers that originate from different kinds of immune cells such as B cells, T cells, or natural killer cells. Common NHLs in children include Burkitt lymphoma (BL), lymphoblastic lymphoma, diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL). Of these, ALCL is a rare but fast-growing cancer that originates from T cells and makes up 10 percent to 15 percent of pediatric NHL cases.

Research has demonstrated that 90 percent of children with ALCL have alterations in the ALK gene. A key therapeutic advance in treating ALCL in children was the expanded use of the ALK-targeted therapeutic crizotinib (Xalkori)—originally approved in 2011 to treat certain patients with lung cancer—for treatment of children and adolescents who have experienced relapse or who have refractory ALCL expressing aberrant forms of the *ALK* gene. The approval of crizotinib to treat ALK-positive ALCL was based on findings from a phase II clinical trial. Eighty-one percent of patients who participated in the trial no longer showed any signs of cancer. Of the patients who responded to the treatment, 39 percent maintained a response for at least 6 months, and 22 percent maintained a response for at least a year following treatment (478). Researchers are now evaluating whether crizotinib in combination with chemotherapy could be used as the initial treatment for children with newly diagnosed ALCL (356).

Personalizing the Treatment of Brain Tumors

Brain and other nervous system tumors are the second most diagnosed cancer in children. Low-grade glioma is the most common type of brain tumor in children. These are slow-growing tumors that can often be cured with surgery alone. However, depending on their location in the brain, some low-grade gliomas cannot be fully removed, for example, if they are adjacent to vital structures in the brain. Additionally, in some cases low-grade gliomas may grow back even after complete surgical removal. Traditionally, most children whose tumors are not surgically removable or have come back after surgery receive chemotherapy. While often effective, chemotherapy is associated with substantial side effects. Therefore, alternative treatments for these children are an urgent need.

Alterations in the *BRAF* gene leading to aberrant activation of the BRAF protein signaling pathway are common in pediatric low-grade gliomas. The BRAF protein has a critical role in controlling cell growth. The *BRAF* gene is altered in approximately 6 percent of all human cancers (402). Most cancer-related changes in the *BRAF* gene cause the protein to continuously stay active, thus helping cancer cells grow faster than normal cells. Common cancer-related changes in the BRAF gene include structural variations such as BRAF gene fusions or rearrangements and/or single base changes such as the *BRAF* V600E mutation. *BRAF* structural variations are more common than *BRAF* V600E mutations in children and adolescents with low-grade gliomas (357).

A combination of two molecularly targeted therapeutics that target BRAF and MEK—another protein that is part of the BRAF signaling pathway—dabrafenib (Tafinlar) and trametinib (Mekinist), was approved by FDA in March 2023 for children with low-grade glioma that has a BRAF V600E mutation. The approval was based on data from a clinical trial of children with BRAF V600–mutant low-grade glioma, in which the combination significantly outperformed chemotherapy, shrinking tumors more often, keeping the cancer from growing nearly three times longer, and causing fewer serious side effects (358). Emerging evidence

suggests that the combination treatment may also be effective in children with more advanced gliomas (359).

The dabrafenib and trametinib combination, however, does not work in patients who have *BRAF* gene fusions or rearrangements. Therefore, FDA approval of tovorafenib (Ojemda) in April 2024 for patients 6 months and older with relapsed or treatment-unresponsive low-grade glioma that has a *BRAF* fusion or rearrangement, or the V600 mutation, brings hope to many more parents and families whose children are diagnosed with glioma. The approval was based on a clinical trial in which tumors shrank or disappeared entirely in almost 70 percent of children treated with tovorafenib (360).

Researchers are now investigating whether tovorafenib in combination with chemotherapy could be used as the initial therapy to treat children with low-grade gliomas that have fusions, rearrangements, or other mutations in the *BRAF* gene (361). Additionally, researchers are evaluating a separate molecularly targeted therapy, selumetinib (Koselugo), as the initial treatment after surgery for children with low-grade glioma regardless of their *BRAF* status. Selumetinib blocks the function of MEK and was approved by FDA in 2020 for the treatment of a different childhood tumor known as neurofibromatosis type 1 (NF1)–related plexiform neurofibroma.

While rare in children, low-grade gliomas with mutation in the *IDH1* or *IDH2* genes are common malignant primary brain tumors diagnosed in young adults. Patients with *IDH*-mutated astrocytoma have a median age at diagnosis of 36 years (362). Patients with *IDH*-mutant gliomas often receive a combination of radiation and chemotherapy after surgery, especially if they are at high risk of disease progression. While this regimen can keep the cancer in check for years, it is not curative and can lead to serious long-term side effects.

Research has shown that mutations in the *IDH1* or *IDH2* genes result in abnormal IDH1 and IDH2 proteins, leading to the production of an abnormal molecule, 2-hydroxyglutarate, which causes widespread epigenetic changes that disrupt normal cell function and drive brain tumor development (363-366). These findings led to the investigation of therapeutic approaches for treating *IDH1*- and *IDH2*-mutant brain tumors by blocking the production or effects of 2-hydroxyglutarate. Building on this work, scientists developed vorasidenib (Voranigo), a molecularly targeted therapeutic that blocks the altered IDH1 and IDH2 proteins and substantially reduces levels of 2-hydroxyglutarate and the associated epigenetic changes related to *IDH1* or *IDH2* gene mutations (367).

In August 2024, vorasidenib was approved by FDA for patients 12 years and older with certain slow-growing gliomas, known as grade 2 astrocytoma or oligodendroglioma, that have *IDH1* or *IDH2* mutation, after patients have undergone surgery, whether a full removal, partial removal, or just a biopsy of the tumor. FDA approval was based on results from a clinical trial demonstrating vorasidenib significantly delayed tumor progression. Patients who received vorasidenib had a 61 percent lower risk of tumor progression compared to those who received a placebo (367,368). Ongoing research is evaluating potential mechanisms of resistance to vorasidenib as well as its effectiveness in combination with immunotherapy.

Researchers are also exploring new and improved therapeutic options for children with high-grade brain tumors such as diffuse midline glioma (DMG), a fast-growing, highly aggressive cancer arising in the brain or spinal cord. DMGs with an H3K27M mutation are rare but aggressive cancers that mostly affect pediatric population and young adults. The H3K27M mutation is a change in a protein called histone H3, which helps package DNA and control how genes are switched on and off (see **Epigenetic Modifications**, p. 37). DMGs with the H3K27M mutation typically occur in critical areas such as the brainstem or thalamus, where surgery is not possible, and standard treatment with radiation has limited benefit.

Despite many clinical trials, no treatments have improved survival until recently, and most patients live only 11 to 15 months after diagnosis (369). Therefore, FDA approval of dordaviprone (Modeyso) in August 2025 offers new hope for patients such as **Kaley Ihlenfeldt** (see p. 83) and their families facing this devastating disease. Dordaviprone works by targeting two important proteins involved in certain brain tumors. First, it blocks dopamine receptors, which are proteins on the surface of brain cells that normally respond to the chemical messenger dopamine in the brain. In some aggressive brain cancers, these receptors are overactive and help tumors grow. Second, dordaviprone activates the protein caseinolytic protease P inside mitochondria, the organelles that provide energy to cells. By activating this protein, dordaviprone disrupts the mitochondrial function, causing stress that leads to cancer cell death. This combined effect helps slow tumor growth.

FDA granted approval to dordaviprone for adults and children age 1 year and older with DMG that has an H3K27M mutation and has worsened after earlier treatment. This is the first approval of a systemic therapy for DMG, marking an important milestone for patients who previously had no effective options. The approval was based on data from five clinical studies showing that about 20 percent of patients responded to the treatment (369,370). Among those who responded, 73 percent experienced benefits lasting at least 6 months, and 27 percent had benefits lasting a year or longer.

Researchers are also examining CAR T-cell therapy, a form of cellular immunotherapy, in some children and young adults with a highly aggressive form of DMG, called diffuse intrinsic

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“We wouldn’t be here today if it wasn’t for cancer research—it sounds cliché, but it literally saves lives.”

—Chris Ihlenfeldt, Kaley’s Father

SURVIVOR STORY

KALEY IHLENFELDT

AGE: 14 | DIAGNOSIS: BRAIN CANCER (GLIOMA) | KENOSHA, WI

Defying the Odds Through a Clinical Trial

At 14, Kaley Ihlenfeldt radiates confidence and joy. A high school freshman, she loves theater, drawing, and spending time with her younger sister, Aubrey. To anyone who meets her, Kaley looks like any other teenager-full of energy with countless plans for the future. But 5 years ago, her parents were told she wouldn't live long enough to reach high school.

In May 2020, at 8 years old, Kaley began complaining of persistent headaches and nausea. After a visit to her pediatrician, COVID was ruled out and her parents, Jenny and Chris, assumed it was the flu. After a week without improvement, they rushed her to the emergency room where an MRI revealed a mass on her brain. Kaley then received a CT scan. "I'm an accountant," Jenny recalled. "They showed us the CT scan, and I just thought, that doesn't look normal." Kaley was immediately admitted to the ICU, where doctors discovered a mass in her brain. A biopsy confirmed the diagnosis: diffuse midline glioma (DMG), an aggressive pediatric brain cancer.

The prognosis was devastating. "They told us she will not survive this," Jenny said. "Only 5 percent of kids live beyond 2 years... As parents, that's not an acceptable answer."

Kaley underwent surgery at Children's Wisconsin to remove as much of the tumor as possible, followed by 6 weeks of radiation therapy. Those treatments would give Kaley more time, but they weren't curative. Determined to find another option, Jenny and Chris began contacting hospitals across the country while researching online and connecting with other families. "We just refused to stop looking," Chris said. "We're math people. There's always a solution to the problem; you just have to keep working at it."

Through social media, they learned about an experimental therapy called ONC201, now known as dordaviprone, being tested at the University of Michigan Health Rogel Cancer Center and C.S. Mott Children's Hospital in Ann Arbor, Michigan. Led by pediatric neuro-oncologist Dr. Carl Koschmann, the trial was evaluating a first-of-its-kind drug designed to target tumors carrying the *H3K27M* genetic mutation which is the alteration driving Kaley's tumor. The drug, taken orally, "crosses the blood–brain barrier and acts on dopamine receptors to slow tumor growth," said Dr. Koschmann.

"We had just moved to Wisconsin," Jenny said. "The trial is out of Michigan. It's about a 6-hour drive through Chicago traffic. It's been tough, but you'll do anything for your child."

Kaley began the ONC201 clinical trial in late 2020. She takes the drug twice a week and has experienced almost no side effects. "It hasn't really interrupted her life," Chris said. "She's in the drama club at school, she plays softball, she gets to hang out with her sister and her friends, and it's kind of just business as usual for her." Every 9 weeks, Kaley returns to Michigan for an MRI. "With brain cancer, the only way we can really monitor it is through MRIs." Jenny explained. "We would anxiously await results to see if the drug was working, to see if anything was growing. ONC201 has kept this demon at bay for us."

Dr. Koschmann says Kaley's story reflects what many families are now experiencing thanks to research breakthroughs. "Diffuse midline glioma is a very difficult tumor to manage. We don't have effective therapies," he explained. "Radiation does help slow the tumor, but it doesn't get rid of the tumor. Dordaviprone changed that." His research helped uncover how the drug works–by reprogramming cancer cell metabolism and partially restoring the molecular markers of normal brain cells. These discoveries are possible partially due to funding and advocacy from patient families and philanthropic foundations, like the ChadTough Defeat DIPG Foundation. These efforts led to the FDA approval of dordaviprone in 2025 for recurrent DMG, marking the first-ever approved therapy for this cancer.

Today, Kaley continues to take the medication while balancing the routines of teenage life. "She's living a normal 9th grader's life," Chris said proudly. "And she's really enjoying high school."

The Ihlenfeldts remain deeply committed to advocacy and research. "We wouldn't be here today if it wasn't for cancer research–it sounds cliche, but it literally saves lives," Chris said. Jenny added, "These kids deserve to live a full life, to go to high school and college, to get married and have kids of their own. We need to support cancer research."

Scan the QR code to watch Kaley's video interview.

pontine glioma (DIPG) (see **A New Age of Cell Therapies**, p. 102) (371,372). The CAR T cells—which in this case target the tumor-associated GD2 glycolipid (a lipid molecule attached to a carbohydrate molecule) on the surface of DIPG cells—are administered in small doses and infused directly into the brain. Initial findings from the study reported positive responses in terms of reductions in tumor size as well as improvements in cancer-related symptoms.

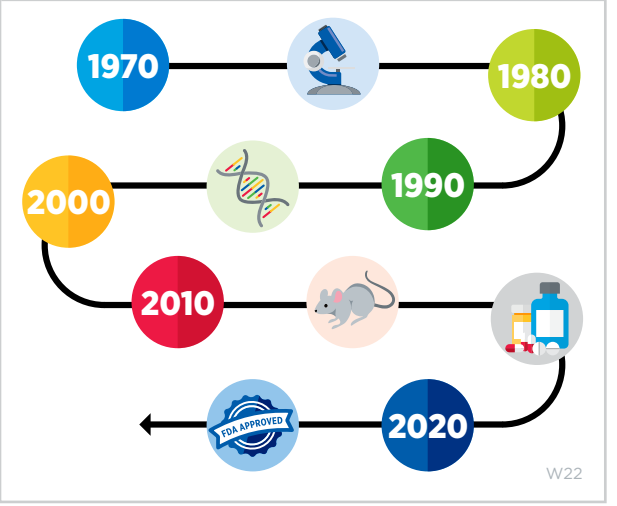
Expanding Treatment Options for Patients with Solid Tumors

Neuroblastoma is the most common solid tumor outside the brain in children. Despite recent advances, only around 50 percent of children with high-risk neuroblastoma survive 5 years or longer. Patients whose cancer has come back have a poor outcome, with a 5-year overall survival of less than 10 percent (373). Therefore, additional treatment options are urgently needed. In this regard, in December 2023, FDA approved the first therapeutic with the potential to reduce the risk of relapse in children with high-risk neuroblastoma. The treatment, eflornithine (Iwilfin), was approved for adult and pediatric patients with high-risk neuroblastoma with at least a partial response to prior therapies, including anti-GD2 immunotherapy. Eflornithine blocks the function of a protein, ornithine decarboxylase, which has a high activity in tumor cells and promotes tumor cell proliferation.

NF1 is an inherited genetic disorder that causes severe symptoms and complications including a significantly increased risk for developing various types of tumors (see **Figure 4**, p. 31). Although the tumors that develop in individuals with NF1 are usually benign, some patients develop malignant tumors, usually in adolescence or adulthood. Plexiform neurofibromas (PN) are tumors arising in cells that form the covering of peripheral nerves. These benign tumors occur in up to 50 percent of patients with NF1 and can cause pain, disability, and disfigurement. They can also go on to become cancerous.

Research has demonstrated that the growth of PN in patients with NF1 is fueled by a signaling pathway that includes MEK proteins, a large family of proteins that helps control cell division, cell maturation, and cell death (374). In 2020, FDA approved a MEK-targeted therapeutic, selumetinib (Koselugo), for treating pediatric patients age 2 years and older who have NF1-related PN that cannot be safely removed surgically. FDA approval was expanded in September 2025 to include patients 1 year and older. The 2020 approval was based on results from a phase II clinical trial showing that 66 percent of pediatric patients who received selumetinib had partial tumor shrinkage (375). In addition, many of the children reported experiencing reduced pain, which is one of the most common neurofibroma-related symptoms. More recently, researchers have demonstrated that with up to 5 years of additional selumetinib treatment, most children with PN have durable tumor shrinkage and sustained improvement in pain (376).

Decades of basic, translational, and clinical research led to the development of tazemetostat.



In February 2025, FDA approved a second MEK-targeted therapeutic, mirdametinib (Gomekli), for both adult and pediatric patients 2 years of age and older with NF1 who have symptomatic PN not amenable to complete resection. The approval was based on results from a phase II clinical trial indicating that 52 percent of pediatric patients who received mirdametinib had tumor shrinkage (374). Mirdametinib and selumetinib have been approved by FDA as suspension or granule formulation, which do not require swallowing of whole capsules making it easier for children who may have difficulty swallowing capsules, such as younger children. The approval of mirdametinib is bringing new hope to patients such as **Alexander Owens** (see p. 87) and their family.

Childhood gastrointestinal neuroendocrine tumors are rare cancers in hormone-producing cells, most often found in the appendix, where they usually grow slowly. Tumors in other digestive organs, including the pancreas, are less common and may behave more aggressively. In March 2025, FDA approved the molecularly targeted therapeutic cabozantinib (Cabometyx) for treating children 12 years and older with pancreatic or non-pancreatic neuroendocrine tumors that have spread or are not surgically removable and have not responded to earlier treatments. Blood vessel growth helps neuroendocrine tumors develop. Cabozantinib blocks several key signals including VEGF, which stimulates blood vessel growth and was previously approved for the treatment of differentiated thyroid cancer in children 12 years and older.

How and when genes are turned "on" or "off" is regulated by special factors called epigenetic modifications (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29). The sum of these modifications across the entire genome is called

the epigenome. Genetic mutations that disrupt the epigenome can lead to cancer development. For example, mutations in the SMARCB1 gene that lead to loss of the corresponding BAF47 protein, which helps regulate cell growth by controlling epigenetics, drive more than 90 percent of cases of epithelioid sarcoma, a rare type of slow-growing cancer that develops in deep soft tissue or the skin of a finger, hand, forearm, lower leg, or foot (377).

Researchers found that the multiplication and survival of cancer cells lacking BAF47 depend on EZH2, a protein that adds epigenetic modifications called methyl groups to histones (378). The molecularly targeted therapeutic tazemetostat (Tazverick) targets EZH2, preventing it from adding methyl groups to histones. It was approved by FDA in January 2020, for treating patients age 16 or older with metastatic or locally advanced epithelioid sarcoma that cannot be completely removed with surgery.

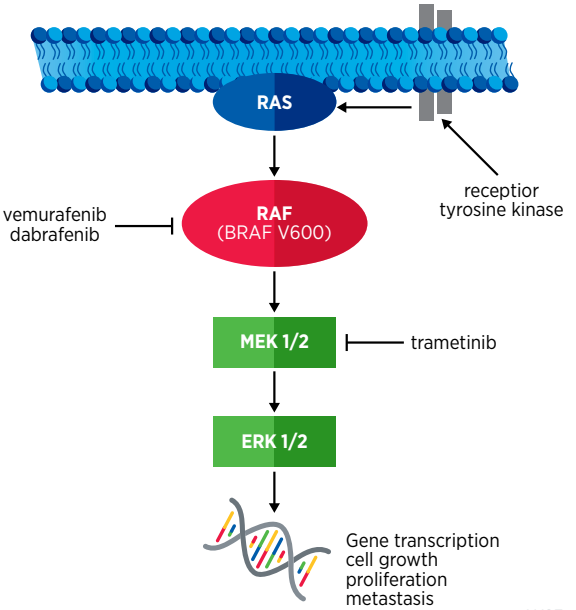
Von Hippel–Lindau syndrome (VHL) is an inherited disorder characterized by the formation of tumors (e.g., kidney cancer and pancreatic cancer) and benign cysts in different parts of the body (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29). Individuals with VHL develop tumors most frequently during young adulthood. Belzutifan (Welireg), the first drug for the treatment of VHL-associated tumors, was approved by FDA in August 2021. In May 2025, FDA expanded the use of belzutifan as the first oral therapy for the treatment of children 12 years and older and adults with pheochromocytoma or paraganglioma—rare tumors that develop in the adrenal glands or nearby nerves—that have spread or are not surgically removable.

Advances in Biomarker-based Treatments

The characterization of genetic alterations that drive tumor growth has been instrumental in understanding tumor biology and conducting genetically informed clinical trials such as basket, umbrella, and platform clinical trials (see **Figure 9**, p. 66). These advances have accelerated the pace of development and FDA approvals of molecularly targeted therapeutics and immunotherapeutics that are effective against cancers that originate at different sites in the body but share biological underpinnings. In fact, one of the most notable achievements in precision medicine was the first FDA approval of a molecularly targeted therapeutic to treat cancer based on the presence of a specific genetic biomarker in the tumor irrespective of the site at which the tumor originated. This therapeutic, larotrectinib (Vitrakvi), was approved by FDA in 2018 for treating children and adults who have solid tumors with *NTRK* gene fusions.

Larotrectinib works by targeting three related proteins called *TRKA, TRKB,* and *TRKC.* The genes *NTRK1, NTRK2,* and *NTRK3* provide the code that cells use to make these proteins. Genetic alterations known as structural variations that involve the three *NTRK* genes and lead to the production of *NTRK* gene fusions, and subsequently to TRK fusion proteins, drive the growth of several cancer types that occur in children and AYAs, including rare sarcomas such as infantile fibrosarcoma and certain types of brain tumors. *NTRK* gene fusions fuel the growth of less than 1 percent of all solid tumors overall but the frequency is higher in pediatric cancers (379,380).

A combination of two molecularly targeted therapeutics that target the BRAF pathway, dabrafenib and trametinib, was approved by FDA in June 2022 for the treatment of children with any solid tumor that has a *BRAF* V600E mutation.



Larotrectinib was approved based on findings from three basket trials (see **Figure 8**, p. 64) showing that 75 percent of patients treated with the molecularly targeted therapeutic had complete or partial tumor shrinkage (278). Since the approval of larotrectinib, two additional molecularly targeted therapeutics, entrectinib and repotrectinib, have been approved by FDA for treating children with solid tumors based on the same *NTRK* gene fusion biomarker (see **Figure 12**, p. 88). The approvals of larotrectinib, entrectinib, and repotrectinib for use in a tissue-agnostic way followed several decades of research in cancer science and medicine.

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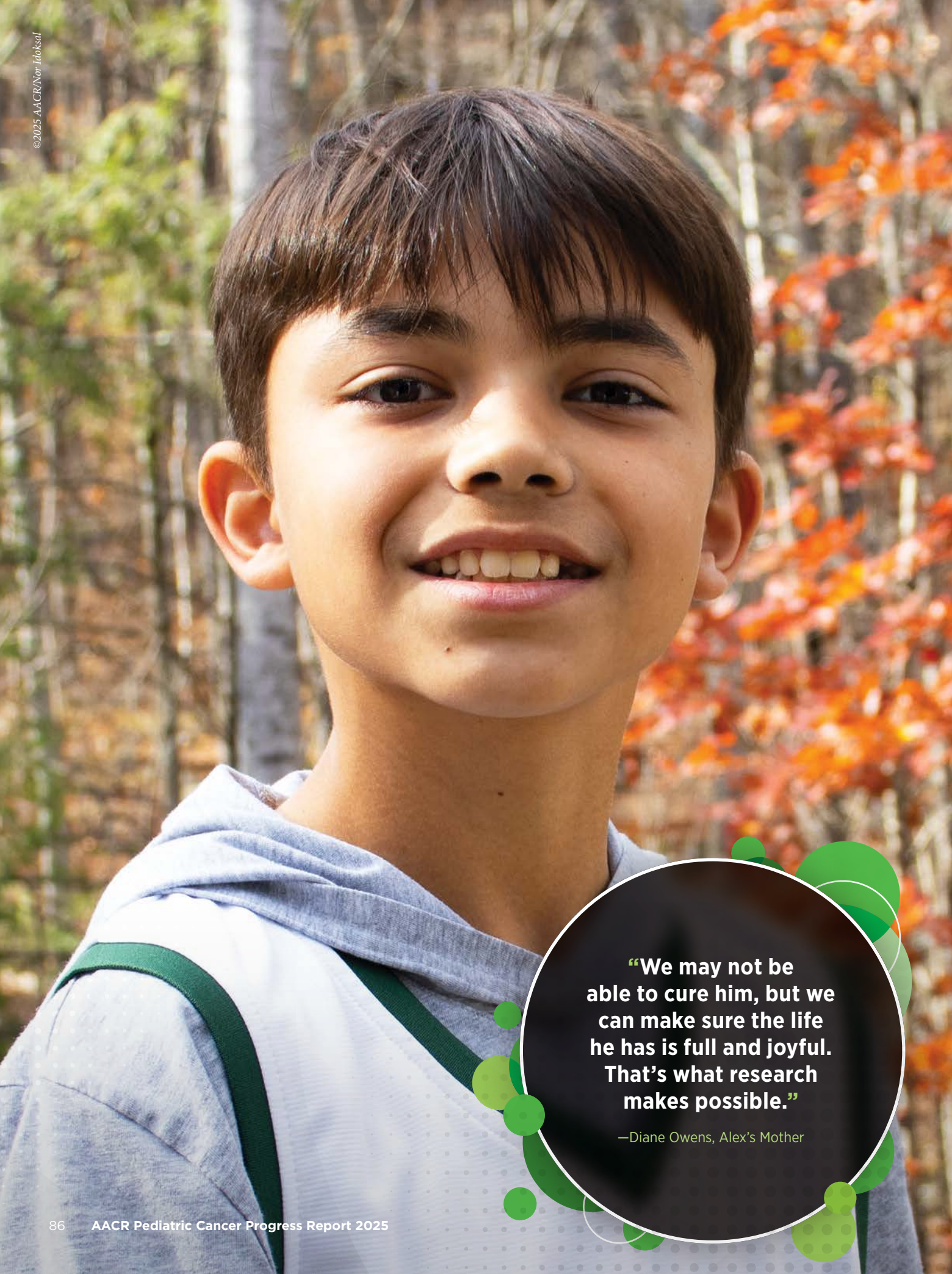


"We may not be able to cure him, but we can make sure the life he has is full and joyful. That's what research makes possible."

—Diane Owens, Alex's Mother

SURVIVOR STORY

ALEXANDER OWENS

AGE: 13 | DIAGNOSIS: NEUROFIBROMATOSIS TYPE 1 | SOUTHBURY, CT

Decades of Research Brings a Breakthrough Therapy and a Bright Future

In 2012 when Diane Owens took her 2-month-old son Alex for a routine checkup, she never imagined that visit would change their lives forever. She had noticed what looked like birthmarks near his groin and pointed them out to the pediatrician. Those marks turned out to be café-au-lait spots, a common sign of neurofibromatosis type 1 (NF1), a rare genetic disorder that can cause tumors to grow along nerves in the body.

At 4 months old, Alex was officially diagnosed. "It felt like we got hit by a freight train," Diane recalled. "We were told there was no cure, no treatment, and no way to predict what would happen. All we could do was watch and wait."

For years, that's exactly what they did. Regular MRIs tracked the growth of tumors, including a plexiform neurofibroma on Alex's back and several others near his brain stem. While not cancerous, plexiform neurofibromas can cause many clinical problems including pain and functional deficits, and they can transform to aggressive cancers. Surgery was an option to remove some of the tumors, but others were too large. "We tried everything we could think of, diet changes, eliminating sugar and dairy, but nothing stopped the tumors from growing," Diane said.

The emotional toll on the family was heavy. At 5 years old, Alex's older brother, Justinian, struggled to understand the disease. When doctors found a tumor on Alex's brain, Justy asked if his little brother was going to die. "That was crushing," Diane said. "We reassured him, but the fear was real."

For years, Diane's hope was channeled into advocacy and working with the Children's Tumor Foundation. She threw herself into fundraising for research, running races, and rallying family and friends. "When you're told there's nothing you can do, you hit your 'no way' button," she said. "There's always something you can do. If there's no treatment, then research has to happen, and research needs funding."

When the FDA approved the MEK inhibitor selumetinib (Koselugo) as the first drug for NF1 tumors in 2020, the family decided the time wasn't right to start Alex on treatment. Alex's tumors were mostly cosmetic—easily covered with a shirt—and they didn't want to risk anything that could potentially compromise his immune system during the pandemic.

But the tumors continued to grow and started to limit what Alex could do. "The one on his back became so large he couldn't lie flat or do simple things like sit-ups in gym class," Diane said. By then, the FDA had approved another MEK inhibitor, mirdametinib (Gomekli), in February 2025 that showed promise in shrinking NF1 tumors and improving quality of life.

Alex began treatment in July 2025. The regimen required 3 pills twice a day for 3 weeks, followed by a week off, which he tolerated remarkably well. "We were warned about side effects like skin infections, nausea, and hair color changes," Diane said. "But Alex has had only mild stomach upset. Nothing that makes us think twice."

The results were stunning. "We were told not to expect measurable changes for 6 to 12 months," Diane said. "After one cycle, his tumor had already shrunk by a centimeter. That's huge." Today, Alex's tumors continue to shrink, and the pain that once plagued him daily has all but disappeared. He still travels to New York every 3 months for scans, but life feels different now—lighter, more hopeful.

The biggest change is in Alex himself. "He's more confident," Diane said. "He's running cross-country, something he couldn't do before. He signed up for basketball for the first time in years. He doesn't feel like the kid with tumors anymore."

Alex is thriving. He loves music, teaching himself guitar and trombone, and playing in the school jazz band. He's passionate about cooking, whipping up fried chicken, kale slaw, and Harry Potter-inspired butterbeer from his growing collection of cookbooks. "He's fearless in the kitchen," Diane laughed. "He'll try anything."

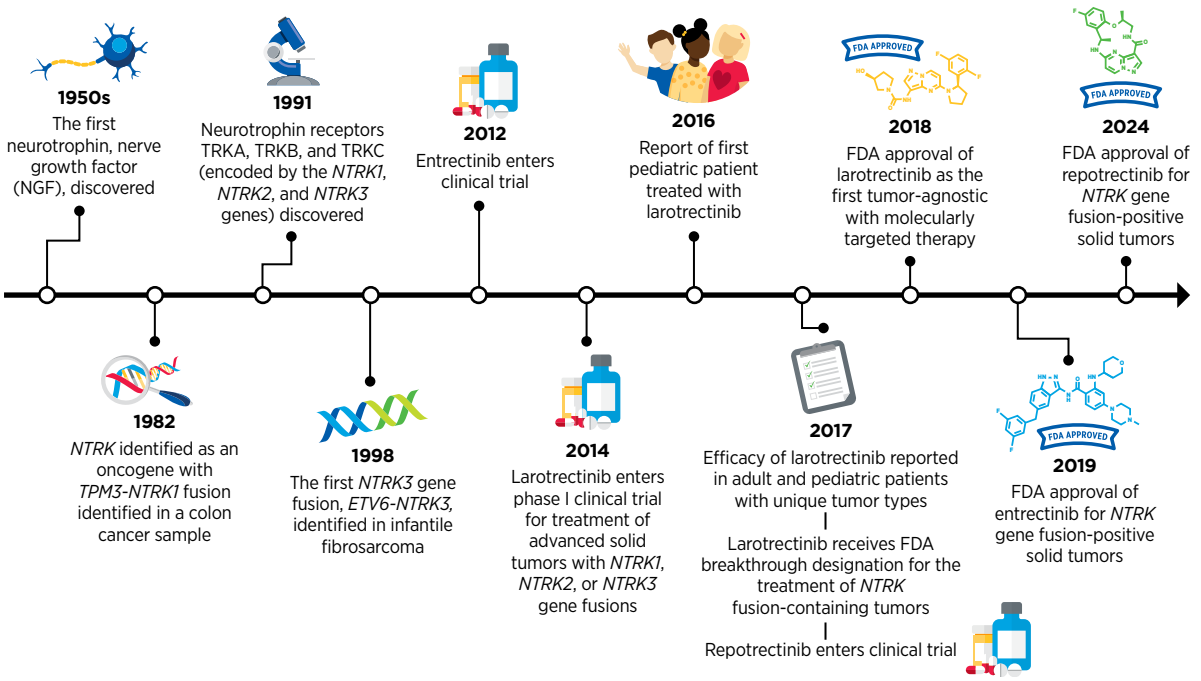
For Diane, advocacy remains central. Her family has raised close to a million dollars for research, and she urges policymakers to keep funding science. "When you fund cancer research, you're giving life," she said. "You're not just helping kids survive, you're giving them back their childhood. You're giving families hope."

Alex's journey is far from over, but thanks to decades of research and a breakthrough therapy, his future looks brighter than ever. "We may not be able to cure him," Diane said. "But we can make sure the life he has is full and joyful. That's what research makes possible."

Scan the QR code to watch Alexander's video interview.

FIGURE 12

Research Milestones on the Road to Developing TRK-targeted Therapeutics



Decades of basic, translational, and clinical research paved the way for the landmark approval of larotrectinib followed by entrectinib and repotrectinib, starting with the seminal identification of the first neurotrophin, nerve growth factor, in the 1950s. Other basic research milestones on the way to FDA approval are the identification of the neurotrophin receptor proteins, TRKA, TRKB, and TRKC, and the genes that encode these proteins, *NTRK1, NTRK2,* and *NTRK3,* and the discovery that *NTRK* fusion genes and proteins fuel the growth of a wide array of cancer types that occur in adults and children. Together, this body of research led to the development of the three TRK-targeted therapeutics, which target TRKA, TRKB, and TRKC, and their testing in basket clinical trials involving patients who have cancers driven by an *NTRK* gene fusion.

The approval of repotrectinib in June 2024 for children 12 years and older and adults was based on findings from a clinical trial that evaluated the therapeutic in patients who had or had not received a prior TRK-targeted therapy. The study showed that tumors shrank in nearly 60 percent of patients who had not received a prior TRK-targeted therapy and in half of patients who had received a prior TRK-targeted therapy (381). Ongoing research is evaluating the efficacy of NTRK inhibitors as the initial treatment for several types of pediatric cancer (382-384).

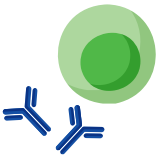
Mutations in the *RET* gene, including single base changes, fusions, and deletions that lead to abnormal activation of the RET protein, are rare alterations observed mostly in patients with certain types of thyroid cancer and lung cancer (385). In children and AYA patients, *RET* mutations are frequently reported in papillary thyroid carcinomas and medullary thyroid cancers and less frequently in glioma, lipofibromatosis, inflammatory myofibroblastic tumor, and infantile myofibromatosis (386).

A RET-targeted therapeutic, selpercatinib, was approved by FDA first in 2020, for children 12 years and older with certain types of advanced thyroid cancer caused by changes in the *RET* gene. In May 2024, FDA approved selpercatinib for the treatment of pediatric patients 2 years and older with metastatic thyroid cancer or any solid tumor with a *RET* gene alteration, as detected by an FDA-approved test. The approval was based on the findings of a clinical trial in which nearly 50 percent of patients treated with selpercatinib saw their tumors shrink. In addition to selpercatinib, FDA has also approved another RET-targeted therapeutic, pralsetinib (Gavreto), for children with thyroid cancer with *RET* alterations.

SIDEBAR 14

Key Cells of the Immune System

Cells of the immune system are made in the bone marrow and are called white blood cells. White blood cells work together to protect the body from external (such as pathogens) and internal (such as cancer cells) threats. Here, we briefly describe the unique functions of the white blood cells that have a central role in eliminating cancer.

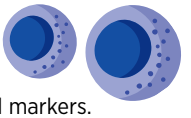


B cells make antibodies (e.g., against pathogens such as viruses and bacteria) that help eliminate pathogens as well as help other components of the immune system to function. Some remain as memory B cells to make the same antibody again later, if needed. Understanding of the role of B cells in eliminating cancer is growing, but the ability of these cells to make antibodies that can be used to treat patients has been harnessed for several decades.

T cells help protect the body from infection and can also help fight cancer. Some remain as memory T cells to fight again later. There are different types of T cells:

- **CD4+ T cells** help orchestrate the immune response.
- **Regulatory T cells** are a subset of T cells that keep the immune system from becoming over-active; tumors can exploit these cells to suppress immune attack.

- **CD8+ T cells** kill infected, damaged, and abnormal cells, including cancer cells, in part by recognizing abnormal markers that appear only on cancer cells.
- **Gamma delta T cells** are rare immune cells that can quickly detect and kill cancer cells; researchers are studying how to use them to develop cancer immunotherapies.



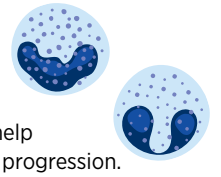
Natural killer cells kill infected, damaged, and abnormal cells, including cancer cells, by sensing stress signals or the absence of normal markers.

Dendritic cells educate T cells about what kinds of cells they should and should not attack.

Macrophages eat foreign materials and can ingest and fight against cancer progression, but they can also make molecules that help cancers grow.

Neutrophils are among the first immune cells to respond to external and internal threats, releasing chemicals that fight pathogens and stimulate the immune system. The effects of these cells can either fight against cancer progression or potentially help cancers grow.

Mast cells release chemicals against pathogens and stimulate the immune system but can also provide factors that aid tumor growth and spread.



Basophils and eosinophils release chemicals against pathogens and stimulate the immune system. The effects of these cells can either help cancers grow or fight against cancer progression.

Source: (387).

Advances in Pediatric Cancer Treatment With Immunotherapy

The immune system is a complex network of cells (called white blood cells; see **Sidebar 14**, p. 89), tissues (e.g., bone marrow), organs (e.g., thymus), and the substances they make that help the body fight infections and other diseases, including cancer. The immune system actively monitors threats from external sources (such as viruses and bacteria) and internal sources (such as abnormal or damaged cells) and works to eliminate them from the body.

The immune system is highly effective in detecting and eliminating cancer cells, a process also known as cancer immune surveillance (388). During the course of cancer development (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29), some cells find ways to "hide" from the immune system, such as by decreasing or eliminating the numbers and/or amounts of proteins on the surface of tumor cells that are used by the immune system to recognize cancer cells. This acquired property of cancer cells triggers certain brakes on immune cells that prevent them from eradicating cancer cells, and releases molecules that weaken the ability of immune cells to detect and destroy cancer cells (389). The field of cancer immunology is focused on better understanding how tumor cells evade the immune system and leveraging this knowledge to develop novel cancer treatments.

Cancer immunotherapy refers to any treatment that works by using the immune system to eliminate cancer. Unprecedented

advances in cancer immunology have firmly established immunotherapy as the fifth pillar of cancer medicine, with transformative impact in certain childhood cancers such as B-ALL and neuroblastoma (see **Table 5**, p. 91) (390). However, the benefits of immunotherapy have not yet been as widespread in children as they have been in adult cancers, for which these therapies have transformed outcomes in previously intractable diseases such as advanced lung cancer and metastatic melanoma.

Different immunotherapeutics unleash the immune system in various ways to fight cancer (see **Sidebar 15**, p. 90). The following sections highlight the immunotherapeutics that have been approved by FDA for childhood cancers over the past 10 years.

Boosting the Cancer-killing Power of Immune Cells

Research has demonstrated that immune cells, such as T cells, are naturally capable of destroying cancer cells. It has also shown that in patients with cancer, often the numbers of cancer-killing T cells are insufficient, and that the cancer-killing T cells that are present are unable to find or destroy the cancer cells for one of several reasons. This knowledge has led researchers to identify several ways to boost the ability of T cells to eliminate cancer cells.

Adoptive cell therapy, also called cellular immunotherapy, is designed to dramatically increase the number of cancer-killing immune cells a patient has, thereby boosting the immune system's ability to seek and destroy cancer cells (391). CAR T-cell therapy is one type of cellular immunotherapy that has generated enormous excitement in pediatric oncology in recent years because this treatment has demonstrated unprecedented efficacy in some children with advanced leukemia.

CAR T-cell therapy is the culmination of decades of research utilizing knowledge of the cellular and molecular components of the immune system, genetic engineering, and the biological underpinnings of blood cancers. It works by collecting a patient's own immune cells (T cells) and genetically modifying them to produce a special receptor, called a chimeric antigen receptor (CAR), on their surface. This receptor enables the T cells to recognize and attack cancer cells. After being expanded in numbers in the laboratory, these engineered cells are infused back into the patient to target and destroy the cancer.

The first CAR T-cell therapy tisagenlecleucel (Kymriah) was approved by FDA in 2017 and as of September 30, 2025, is the only approved cellular immunotherapy for pediatric cancers. It was approved for the treatment of children and young adults with B-ALL that had not responded to standard treatments or had relapsed at least twice. Tisagenlecleucel is developed by genetically modifying a patient's T cells to have a CAR that targets the molecule CD19, a protein found on the surface of immune cells called B cells, as well as on the surface of several types of leukemia and lymphoma cells that arise in B cells, including most cases of ALL. The approval was based on results from a phase II clinical trial indicating that more than 80 percent of the children and young adults with multiply relapsed leukemia who were treated with tisagenlecleucel had remission within 3 months of receiving the CAR T-cell therapy (392).

This revolutionary immunotherapeutic has been transformative for children with ALL, such as **Lianna Munir** (see p. 93). CAR T-cell therapy has led to complete remission for some patients whose leukemia has returned or stopped responding to other treatments. A long-term follow-up of patients treated with tisagenlecleucel showed that more than 60 percent were living 3 years or longer after their first infusion of CAR T cells (393). Additionally, more than 50 percent of patients were living without their disease coming back 3 years after treatment completion, suggesting that CAR T cells can lead to durable cancer control.

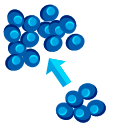
SIDEBAR 15

How Immunotherapeutics Work

The way in which different immunotherapeutics unleash a patient's immune system to fight cancer varies. Immunotherapies that have been approved by FDA for the treatment of pediatric cancers work in one of four ways:

Some **release the brakes** on the natural cancer-fighting power of immune cells called T cells, for example, nivolumab (Opdivo) and pembrolizumab (Keytruda). These therapeutics are commonly known as immune checkpoint inhibitors.

Some **amplify the killing power of the immune system** by direct infusion of immune cells called T cells engineered to target cancer cells, for example, chimeric antigen receptor (CAR) T-cell therapies such as tisagenlecleucel (Kymriah).



Some **flag cancer cells for destruction** by the immune system, for example, therapeutic antibodies such as dinutuximab (Unituxin).

Some **bring cancer cells in close proximity to T cells** so that the immune cells can eradicate them, for example, bispecific T-cell engagers such as blinatumomab (Blincyto).

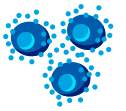


TABLE 5

FDA-approved Immunotherapeutics to Treat Pediatric Cancers (2015–2025)

Generic Name (Nonproprietary)	Trade Name (Proprietary)	Approved For	Mechanism of Action	Year(s) Approved
IMMUNE CHECKPOINT INHIBITORS				
Ipilimumab plus nivolumab	Yervoy plus Opdivo	Patients 12 years and older with unresectable or metastatic MSI-H or dMMR colorectal cancer	CTLA-4 and PD-1 blocking antibodies	2025
Nivolumab	Opdivo	Patients 12 years and older with completely resected advanced melanoma; patients 12 years and older with MSI-H or dMMR metastatic colorectal cancer	PD-1 blocking antibody	2023; 2025
Ipilimumab and nivolumab	Yervoy and Opdivo	Patients 12 years and older with unresectable or metastatic melanoma as single agents or in combination	CTLA-4 and PD-1 blocking antibodies	2023
Atezolizumab	Tecentriq	Patients 2 years and older with unresectable or metastatic alveolar soft part sarcoma	PD-L1 blocking antibody	2022
Nivolumab plus relatlimab-rmbw	Opdualag	Patients 12 years or older with unresectable or metastatic melanoma	PD-1 and LAG-3 blocking antibodies	2022
Pembrolizumab	Keytruda	Patients with unresectable or metastatic, MSI-H or dMMR solid tumors; patients with refractory primary mediastinal large B-Cell lymphoma; patients with recurrent locally advanced or metastatic Merkel cell carcinoma; patients with refractory, unresectable or metastatic, TMB-H solid tumors; patients with relapsed or refractory classical Hodgkin lymphoma; patients 12 and older with completely resected advanced melanoma	PD-1 blocking antibody	2017; 2018; 2018; 2020*; 2020; 2021
Avelumab	Bavencio	Patients 12 years and older with metastatic Merkel cell carcinoma	PD-L1 blocking antibody	2017
MONOCLONAL ANTIBODIES				
Rituximab	Rituxan	Patients 6 months and older with CD20-positive DLBCL, BL, BLL, or mature B-ALL	CD20-targeted antibody	2021
Naxitamab-gqgk	Danyelza	Patients 1 year and older with relapsed or refractory high-risk neuroblastoma	GD2-targeted antibody	2020
Emapalumab-lzsg	Gamifant	Pediatric patients (newborn and older) with primary hemophagocytic lymphohistiocytosis	Interferon gamma blocking antibody	2018
Blinatumomab	Blincyto	Patients one month and older with relapsed or refractory CD19-positive B-cell precursor ALL	CD19- and CD3-targeted bispecific T-cell engager	2017
Dinutuximab	Unituxin	Patients with high-risk neuroblastoma	GD2-targeted antibody	2015
CAR T-CELL THERAPY				
Tisagenlecleucel	Kymriah	Patients up to 25 years with relapsed or refractory B-cell precursor ALL	CD19-targeted CAR T-cell therapy	2017

* Duplicate years indicate multiple approvals in that year.

For complete information on pediatric cancer drug approvals visit: https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology-drug-approvals.

CAR T-cell therapies can cause significant side effects, such as cytokine release syndrome, a condition characterized by excessive immune activation. The hyperactive immune system can lead to organ toxicity, and immune effector cell-associated neurotoxicity syndrome, a neurologic condition that causes confusion, speech difficulties, and seizure, all of which can be potentially life-threatening. Research has shown that in patients affected by cytokine release syndrome, there is an overwhelming release of immune molecules called cytokines into the bloodstream, which can cause high fevers, flu-like symptoms, and a dramatic drop in blood pressure. For many patients, treatment with steroids can relieve the cytokine release syndrome. However, others require treatment with tocilizumab (Actemra), which blocks a cytokine called IL-6.

continued on page 94

"We need the funding to keep moving forward, to get to a place where you don't only have that one option, you have more than one option, and you're not as afraid."

—Adrian Horn, Lianna's Mother

SURVIVOR STORY

LIANNA MUNIR

AGE: 8 | DIAGNOSIS: ACUTE LYMPHOBLASTIC LEUKEMIA | BELLMAWR, NJ

A Bright Future, Thanks to CAR T-Cell Therapy

Eight-year-old Lianna Munir is bursting with energy again—running, laughing, and learning her way through 2nd grade. But just 2 years ago, her family's world was turned upside down when what seemed like repeated colds and fatigue led to a diagnosis of a rare and aggressive form of Philadelphia chromosome (Ph)–like acute lymphoblastic leukemia (ALL).

Lianna had always been an active child who loved swimming, soccer, and cooking with her mimom and pop-pop. "I couldn't force her to come in the house after school or sit down," recalled her mom, Adrian Horn. "Then, she just started slowing down a lot and it was not like her. So that's how we knew something was wrong." At first, doctors thought she had strep throat or tonsil issues. But one night, Lianna, then 6, fainted at home, prompting an emergency trip to the hospital. After several visits and a series of tests, she was medically transferred to Children's Hospital of Philadelphia (CHOP), where doctors would eventually confirm the unthinkable—Lianna had leukemia.

After a 2-week stay at CHOP, where Lianna received multiple blood transfusions, she seemed to be getting better and was sent home without a definitive diagnosis. However, after just 3 days at home, Lianna's symptoms returned, and the family headed back to CHOP. The news came around 1:30 a.m. that night. "Five doctors walked in and said: 'We believe it's leukemia,'" Adrian recalled. "I was in shock. I just wanted information. I was like, 'What's our next step?'"

Lianna began intensive chemotherapy immediately. Initially, her care team expected good results. But genetic testing revealed her Ph-like ALL had a *PAX5::JAK2* fusion marker which is known to resist standard treatments. After 3 months of chemotherapy, her bone marrow still showed more than 70 percent leukemia cells. Lianna's care team, including pediatric oncologist Dr. Susan Rheingold, advised harvesting her T cells to prepare her for a form of immunotherapy. "CAR T-cell therapy, which is an immunotherapy whereby we take T cells, one of the body's own immune cells, out of the patient," Dr. Rheingold explained. "We then genetically manipulate them so that instead of going back in and attacking things like viruses, they attack the child's leukemia cells."

Adrian said they explained it in a way Lianna could understand. "They told her, 'We're taking your cells from kindergarten and sending them off to college, and eventually you will get them back,'" adding that those cells would then fight her cancer.

Before reaching that point, Lianna experienced a multitude of treatment-related side effects, including a new diagnosis of supraventricular tachycardia (SVT)—an irregularly fast or erratic heartbeat—severe allergic reactions, temporary whole-body paralysis, and three cardiac emergencies within 8 days. "There were 50 doctors in the room around our baby, and I couldn't do anything," Adrian said. "You're kind of helpless."

On November 28, 2024, Lianna finally received her re-engineered T cells through an infusion of tisagenlecleucel (Kymriah), the first and, so far, only FDA-approved CAR T-cell therapy for pediatric leukemia. Within weeks, her cancer began to disappear. "Out of everything that we've done, CAR T was the easiest on her body," Adrian said. "It used her own cells, and her body absorbed them. It has been so much easier on her bones, her joints, no nausea, she didn't lose all her hair."

Today, Lianna shows almost no evidence of leukemia. Her CAR T cells remain active in her body, continuing to patrol for any lingering cancer cells. She visits CHOP once a month for infusions and blood tests, but the Munir-Horn family's life has slowly returned to normal. She's back in school, catching up on lessons she missed, and once again playing and cooking with her family.

Reflecting on the journey, Adrian calls research the difference between despair and hope. "Ten years ago, CAR T therapy didn't exist," she said. "Without it, Lianna's next step would've been a bone marrow transplant."

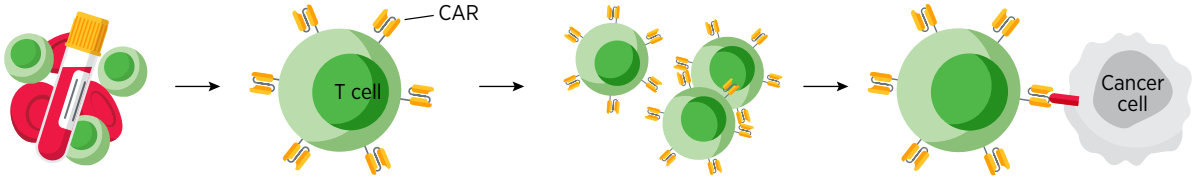
When asked what she'd tell policymakers, Adrian didn't hesitate: "I believe that it's vital. We need continued funding for cancer research. Not only is it giving us hope that there's something else [another treatment option], but it lets parents know that researchers are never going to stop trying."

Scan the QR code to watch Lianna's video interview.

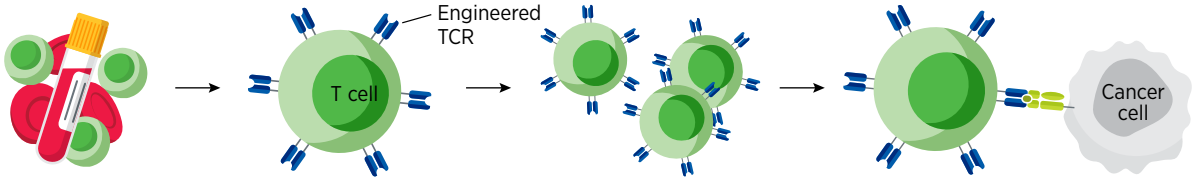
Types of Adoptive T-cell Therapy

There are three main types of adoptive T-cell therapy:

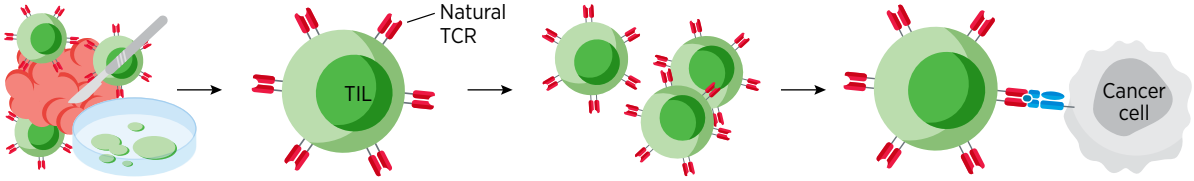
CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY



T-CELL RECEPTOR (TCR) T-CELL THERAPY



TUMOR-INFILTRATING LYMPHOCYTE (TIL) THERAPY



As of September 30, 2025, FDA has approved nine adoptive T-cell therapies. However, only one, a CAR T-cell therapy, is available for pediatric cancer patients. The first-ever TCR T-cell therapy, afamitresgene autoleucel, was recently approved for adults with synovial sarcoma, but remains unavailable for pediatric patients, highlighting the urgent need for research to determine how to safely and effectively make this therapy accessible to children and adolescents.

W24

Tocilizumab had previously been approved by FDA for treating several forms of arthritis but was approved to treat severe or life-threatening cytokine release syndrome caused by CAR T-cell therapy in August 2017.

Because of serious or life-threatening immune-related adverse reactions, FDA initially required CAR T cells to be administered only at specially certified large academic hospitals by qualified health care professionals with appropriate medical support. However, health care teams and institutions have since gathered greater experience in identifying and managing toxicities with the currently approved CAR T products. Therefore, in June 2025, FDA removed the safety requirements, a decision that may expand and expedite access to these lifesaving treatments by allowing more treatment centers—including those in community settings and rural areas—to administer these therapies without additional regulatory steps (394). Researchers are also actively working to identify biomarkers that can predict side effects and to mitigate the significant immune-related toxicities associated with CAR T-cell therapy (395).

Releasing the Brakes on the Immune System

Decades of research have revealed that some tumor cells have increased levels of certain proteins on their surface that attach to and activate "brakes" on T cells, thus stopping them from attacking cancer cells. These brakes are proteins on the surface of T cells and are called immune checkpoint proteins. Immune

checkpoint inhibitors (ICIs) are a class of transformative new therapeutics that block the checkpoint proteins and can thereby release the brakes on T cells that trigger previously restrained T cells to attack and destroy cancer cells (396). These immunotherapeutics have become the foundation of treatment for a wide range of solid tumors in adults, including previously intractable cancers such as advanced kidney cancer, lung cancer, and melanoma, for which they have transformed patient outcomes.

ICIs have had limited success in treating childhood cancers thus far with a few exceptions (see **Table 5**, p. 91) (397). ICIs have shown the most success in treating children with classic Hodgkin lymphoma. This is so because these cancer cells often have specific genetic changes that make them more responsive to ICIs. In fact, pembrolizumab, an ICI that targets the checkpoint protein PD-1, is approved by FDA to treat children with relapsed Hodgkin lymphoma, in which it has improved outcomes for 30 percent to 60 percent of patients.

Unfortunately, ICIs have been far less effective for other childhood cancers. In studies involving solid tumors and NHL, response rates were very low: Only about 3 percent of patients with solid tumors showed any improvement (397). Drugs like nivolumab, atezolizumab, and ipilimumab have shown limited benefit in these cancers, and combination treatments have not been significantly better either. Researchers believe this is partly because most childhood cancers do not have the same immune characteristics as adult cancers—they tend to have fewer mutations and fewer immune cells around them, making them harder for immunotherapy to target (see **Tumor Microenvironment**, p. 39). Still, some rare types of pediatric cancer, as well as those with certain genetic features, may respond better. For example, children whose tumors cannot repair DNA damage properly or have many mutations can benefit from ICIs, and several of these immunotherapeutics have been approved by FDA for use in such settings (see **Table 5**, p. 91). For instance, recent studies have found that children and young adults with inherited mismatch repair–deficient brain tumors and other solid cancers showed remarkable and durable responses to nivolumab, demonstrating that immunotherapy can be highly effective in this rare, genetically driven subset of cancers (398,399).

Another example is highlighted by the December 2022 FDA approval of the ICI atezolizumab (Tecentriq) for the treatment of patients 2 years and older with the extremely rare cancer alveolar soft part sarcoma (ASPS) that has spread to other parts of the body or cannot be removed by surgery. ASPS is a slow-growing cancer that forms in soft tissues such as muscle, fat, or nerves and mainly affects AYAs. Although the disease grows slowly, once metastatic, ASPS has poor outcomes. Chemotherapeutics have limited benefit and molecularly targeted therapeutics do not have lasting effectiveness against ASPS. Atezolizumab was approved by FDA based on data from a phase II clinical trial showing that 37 percent of patients with ASPS responded with some tumor shrinkage (400).

Flagging Cancer Cells for Destruction by Immune System

An immune cell must find a cancer cell before it can destroy it. Many therapeutic antibodies that have been approved by FDA for the treatment of various types of cancer work, at least in part, by helping immune cells find cancer cells. One example is the immunotherapeutic dinutuximab (Unituxin), which was approved by FDA in March 2015 for treating children with high-risk neuroblastoma such as **Ayden Newman** (see p. 97) whose disease had progressed after responding to prior treatments.

Neuroblastoma is a rare childhood cancer of immature nerve cells, affecting about 700 US children annually, mostly under age 5. Around half of cases are classified as high-risk, which means that the cancer has certain features that indicate it is aggressive and often has spread beyond its original site. Researchers use patient characteristics (e.g., age at diagnosis, disease stage) and tumor genetics to predict the likelihood that a child with neuroblastoma will be cured and then decide treatments accordingly. While children with high-risk disease have had poorer outcomes historically, research-driven clinical breakthroughs in recent years have made major strides in clinical care for these patients.

Discoveries across basic, translational, and clinical research, starting from the recognition of the molecule GD2 as a tumor-associated glycolipid in 1984, led to the development of dinutuximab. Dinutuximab works by attaching to GD2 on neuroblastoma cells and flagging them for destruction by immune cells using a natural process called antibody-dependent cellular cytotoxicity. The 2015 FDA approval was based on clinical trial results showing that adding dinutuximab and two immune system–boosting agents, granulocyte macrophage colony-stimulating factor and IL-2, to the standard 13-cis-retinoic acid (RA) treatment at the time significantly extended overall survival (401).

Data from a more recent follow-up clinical study of nearly 1,200 children with high-risk neuroblastoma demonstrated that dinutuximab is extending lives for many patients (402). Five years after being treated with dinutuximab, more than 70 percent of children in the study were still alive, and more than 60 percent of children had no evidence that their cancer had come back, or their tumors had grown. Since the approval of dinutuximab in 2015, FDA has approved a second therapeutic, naxitamab-gqgk (Danyelza), which works similarly to dinutuximab, for the treatment of patients with neuroblastoma.

continued on page 98

“To the researchers, they’re in the trenches. I would honestly thank them. You really saved my child’s life.”

—Ashley Moore, Ayden’s Mother

SURVIVOR STORY

AYDEN NEWMAN

AGE: 6 | DIAGNOSIS: NEUROBLASTOMA | MUNSTER, IN

Thriving After High-Risk Neuroblastoma, Thanks to Research

When 6-year-old Ayden Newman bounds through his 1st-grade classroom in Munster, Indiana, it's hard to imagine the journey he and his family have already endured. Bright, curious, and full of energy, Ayden loves science, video games, and playing soccer. To his parents, Ashley and Nate, every ordinary day now feels extraordinary.

In the fall of 2023, life suddenly changed. While out trick-or-treating, then 4-year-old Ayden—normally the most energetic child in the group—grew tired and wanted to go home early, complaining of stomach, leg, and arm pain. After making a trip to the emergency department of a community hospital in Lafayette, where tests didn't identify a cause, his parents were told that Ayden was probably just experiencing "growing pains." Ashley recalled, "We gave him Tylenol at home to just try to ease the pain. It never got better. It just honestly got worse."

A week after Halloween, while the family was visiting relatives in northwestern Indiana, Ayden became disoriented and collapsed. "He's literally just not talking. He's not moving," Ashley said. "He was drooling. So at this point we think it's a seizure." Nate snatched him up and they went to the local hospital.

From there, Ayden was sent to the University of Chicago Medicine Comer Children's Hospital, where a battery of tests revealed the cause of this event: a tumor pressing on his kidney. On November 16, 2023, a biopsy confirmed high-risk neuroblastoma, an aggressive cancer that most often affects children under 5. After receiving Ayden's cancer diagnosis, Nate remembers being devastated. "It's going to break any parent," he said. "It shook the whole household."

Ayden's doctors moved quickly. He began four rounds of high-dose chemotherapy, each requiring a week-long hospital stay. Surgery followed, removing about 70 percent of the tumor. Then came combination chemoimmunotherapy, two stem cell transplants, and radiation, each requiring up to a full month in the hospital. During much of this time, Ashley was also caring for their newborn, and the family relied on support from Ayden's grandmother, aunts, and other family members. In addition, the family received financial, lodging, and other essential assistance through grants from Comer Children's and philanthropic organizations, like the Ronald McDonald House, to stay afloat as Ashley left her job to care for Ayden during his treatment. "It takes a village," Nate said. "Everybody pitched in where it was needed."

Throughout treatment, Ayden faced enormous challenges—hearing loss, nausea, fatigue, and the temporary inability to eat or walk. "We had to learn how to care for him at home with a feeding tube," Ashley said. A major turning point came when Ayden's oncologist recommended adding immunotherapy to his chemotherapy regimen. "His Curie score went from a 22 to a 2. Ayden responded very well to the immunotherapy. Almost wiped it completely out," Ashley said.

After nearly 2 years of intensive therapy, Ayden completed treatment in early 2025 and now takes difluoromethylornithine (Iwilfin), a maintenance medication designed to reduce the risk of relapse. His energy has returned, and he's back in school, playing sports, and spending time with his brothers. The family recently celebrated with a "cancer-free" party—complete with a bouncy house, swimming, and much more. It was a joyous day and the first time Ayden could just be a kid again.

The family also took a Make-A-Wish trip to Disney World, a long-awaited milestone after 18 months of hospital stays. "Ayden's exact words: 'a magical trip,'" Ashley and Nate said with a smile. "Just seeing him be able to play like that … we literally prayed for those days."

Ashley and Nate are deeply grateful to Ayden's care team and to the researchers developing new therapies. "Without research, our son wouldn't be here," Nate said.

"They really saved my child's life," Ashley added. "Funding for cancer research means giving families and their children a fighting chance, not just for survival though, for living a full and healthy life."

Scan the QR code to watch Ayden's video interview.

Another immunotherapeutic that works in the same way to trigger immune attacks against cancer cells is rituximab (Rituxan). Rituximab binds to the protein CD20, which is found in abundance on the surface of cancerous B cells and directs other immune cells to the tumor, where they kill the target cancer cells utilizing antibody-dependent cellular toxicity. Rituximab was first approved by FDA in 1997 to treat NHL in adults and has become a main treatment option for a broad variety of B-cell cancers.

In December 2021, FDA expanded the use of rituximab in combination with chemotherapy for children who are between 6 months and 18 years of age; have not been previously treated; and are at an advanced stage of one of the following rare forms of B-cell cancers—DLBCL; BL; Burkitt-like lymphoma (BLL); or mature B-cell acute leukemia (BAL)—that have the CD20 protein on their surface.

The clinical study that led to FDA approval showed that those who received rituximab along with chemotherapy had much better outcomes than those who received chemotherapy alone. After 3 years, about 94 percent of patients in the rituximab group were alive without the cancer getting worse or coming back, compared with about 82 percent of patients in the chemotherapy-only group (403). While rituximab has greatly improved cure rates for children with aggressive B-cell lymphomas, many patients in low- and middle-income countries still lack access to this treatment or to the supportive care needed to tolerate intensive therapy, leaving cure rates far lower than in high-income countries and underscoring the need for greater global efforts to change this picture (see **Understanding the Global Landscape of Pediatric Cancers**, p. 123).

Redirecting T Cells to Attack Cancer Cells

Bispecific T-cell engagers are antibodies that function as a connector, bringing T cells into close proximity with cancer cells, which are then eliminated by the T cells. The first of these therapeutics, blinatumomab (Blincyto), was approved by FDA in December 2014 for treating adult patients with B-ALL. Blinatumomab attaches to a molecule called CD3 on normal T cells and to CD19, a molecule found on the surface of most B-ALL cells. By attaching to these two molecules on different cells, blinatumomab brings the two cell types together, directing T cells to home in on the B-ALL cells. Since its first approval in 2014, FDA has approved blinatumomab to be used in more groups of people with B-ALL, including those who still have some cancer left after treatment, and even those who are in remission and have no trace of their disease.

One example is the expanded approval of blinatumomab in 2017 for treating children whose ALL has returned following at least one course of treatment. The FDA decision was based on clinical studies showing that in children, AYAs, and adults with B-ALL that had relapsed or was not responding to therapy, treatment with blinatumomab led to better outcomes and fewer side effects compared to chemotherapy alone (404-406). Moreover, research has indicated that even patients who have responded extremely well to chemotherapy and have no trace of ALL, live longer when blinatumomab is added to their maintenance treatment (407).

Another key finding was that the addition of blinatumomab to chemotherapy was highly effective for infants with newly diagnosed ALL carrying the *KMT2A* rearrangement, a disease historically associated with poor outcomes (408).

Ongoing research is exploring the effectiveness of blinatumomab in combination with other therapeutics as well as in earlier stages of the disease, and even as the initial treatment for certain patients with B-ALL. In this regard, a large NCI-supported study of more than 1,400 children newly diagnosed with B-ALL, who were considered at lower risk for cancer coming back, showed that those who received blinatumomab along with standard chemotherapy had better outcomes. After about two and a half years, 96 percent of children who received the combination treatment remained cancer-free, compared to 88 percent who received only chemotherapy (409). Therefore, blinatumomab combined with chemotherapy is now considered the standard of care treatment in industrialized countries.

Bispecific T cell engagers are one of the most rapidly growing therapeutic areas in cancer and are providing new hope for many patients who have few other choices remaining. Of the nine bispecific T-cell engagers approved by FDA to date, only blinatumomab is approved in pediatric cancer.

Critical Gaps in Pediatric Cancer Clinical Care

Despite significant progress in the treatment of pediatric cancers, they remain one of the leading causes of death in children and adolescents in the United States. Treatments for childhood cancers still lag behind those for adult cancers, attributable to several barriers (410). There is a shortage of drugs designed specifically for pediatric cancers rather than adult agents repurposed in children. Out of more than 140 cancer drugs that have received approval from FDA since 2015, very few have been developed specifically for children. A lack of robust preclinical and clinical research is another reason why drug development for pediatric cancers has not kept pace with that for adults. Additionally, some cancers such as sarcomas, AML, and high-grade gliomas occur across the adolescent and young adult (AYA) age spectrum, making clinical trial enrollment challenging because these patients are split between

pediatric and adult oncology, and AYA participation in trials has historically been low.

Barriers to Turning Research Into Practice

Although a few molecularly targeted therapies and immunotherapies are approved for children, many pediatric cancers, especially rarer subtypes, do not have suitable preclinical research models (see **Sidebar 7**, p. 42) (136). Most childhood cancers are biologically unique and behave differently than adult cancers. Therefore, there is a vital need for research that focuses specifically on identifying the underpinnings of cancer in children. More preclinical investment in creating pediatric tumor banks and specialized research models and getting them integrated across research sectors for testing new treatments is vital to bringing a broader range of investigational agents to childhood cancer clinical trials.

Unlike adult cancers, pediatric cancers often lack a high burden of genetic mutations, especially single base changes in cell signaling proteins known as kinases. Instead, they commonly rely on epigenetic or transcription factor–driven mechanisms, for which there are currently far fewer drugs. Many childhood cancers are driven by gene fusions, which can produce altered proteins that are difficult to target with small molecules. In addition, pediatric cancers have a low number of mutations compared to cancers in adults, which contributes to poor responses to immunotherapies such as ICIs. This constraint limits the effectiveness of a strategy that has helped in many adult cancers.

Most current understanding of pediatric cancers comes from tumor tissue samples collected at diagnosis. Collecting longitudinal biopsies from children is especially challenging because the procedures are invasive, can pose medical risks, and may require anesthesia, making it difficult to obtain repeated tissue samples over time. Yet, tumors evolve, especially in response to treatment or when a disease relapses or recurs. Therefore, we lack crucial insights into how treatment resistance develops over time. This understanding is essential for designing effective sequential and precision therapies.

A major barrier in childhood cancer research is that each pediatric cancer subtype is rare, meaning there are far fewer patients per disease compared to adult cancers. This creates huge challenges in enrolling enough patients and running statistically meaningful clinical studies and fast-tracking new treatments for even less common cancer types. When clinical trials are conducted in parallel for therapeutics that act through the same mechanism, especially in rare pediatric cancers, they can end up competing for the same small patient pools. This fragmentation slows progress and reduces the chance that any one trial will successfully enroll enough participants. Notably, clinical trials that match therapies to molecular features in pediatric tumors significantly outperform one-size-fits-all approaches (280).

Advanced diagnostic tests, including DNA sequencing and protein analysis, are used to match patients with the most effective targeted therapies, with companion diagnostics required for certain FDA-approved treatments. While childhood cancer genomic testing has enormous potential, it faces regulatory hurdles, such as inconsistent insurance coverage and limited clinical trial data in pediatric populations. Additionally, the scope of precision medicine is rapidly expanding to include proteomics, liquid biopsies, and tumor microenvironment characterization for biomarker identification. Therefore, any framework for standard-of-care use must be flexible and adaptive to evolving scientific evidence and regulatory policies.

Traditional phase I trials in children usually begin with doses that are based on those first defined in adult studies. Given developmental differences and a growing body, optimal dosing in pediatric oncology needs more refinement. Recent efforts are focusing on using pharmacologic modeling to identify safer and more effective pediatric doses. Children are still developing, and long-term or unexpected toxicities are a major concern. Even targeted therapies can cause lifelong harm—such as developmental, hormonal, cognitive, or cardiac effects—so balancing effectiveness with safety is particularly critical.

Both in the United States and globally, regulatory programs intend to spur pediatric drug research (e.g., FDA mandates and the European Medicines Agency (EMA)'s equivalent), but automatic waivers for orphan or rare disease designations often exempt drug developers from requiring evaluation in children and limit the effectiveness of regulatory mandates (411). The inconsistency in requirements and exemptions across agencies undermines efforts to bring new therapies to children. To address these gaps, researchers and lawmakers are increasingly collaborating to create more consistent and effective regulatory frameworks that ensure children have timely access to new therapies (see **Potential Policy Actions to Advance Pediatric Cancer Research and Care**, p. 155).

Due to the smaller number of patients, the financial incentives for developing childhood cancer treatments are much lower than for adult cancers, so the private sector is less likely to invest, leaving much of the funding responsibility to government agencies and nonprofit organizations (see **Investing in Pediatric Cancer Research to Secure a Healthier Future**, p. 146). Strong involvement from patient advocates, academic groups, and pharmaceutical partners is vital for prioritizing pediatric-specific targets and harmonizing trial designs. Advocacy efforts help align stakeholders and drive research forward despite the economic challenges of rare diseases. Increased communication and intentional collaboration among funders from all sectors offer the greatest

opportunity to initiate and complete research that truly addresses patients' needs, while ensuring that limited resources are used responsibly and efficiently (412).

Another major challenge in pediatric cancer drug discovery is that childhood cancers are often deprioritized when drug development decisions are based on results from adult trials. Setback in adult trials may lead to discontinued production of the therapeutic, ultimately blocking access for children. Addressing these challenges will require regulatory incentives from FDA, increased funding support, and advocacy from philanthropic organizations to ensure that investigational agents with strong biological rationale for pediatric cancers are advanced even if they falter in adult settings. Researchers have outlined strategies and incentives to repurpose oncology drugs discontinued in adult development for use in children and adolescents, addressing key scientific, regulatory, and commercial barriers (413).

Disparities in Cancer Care

Recent studies highlight that children with cancer face persistent inequities across diagnosis, treatment, and survival. For example, according to a recent report, children with thyroid cancer face differences in presentation, treatments, and outcomes attributable to race, ethnicity, language proficiency, socioeconomic status, and access to care (414). Similarly, a study evaluating outcomes after pediatric brain tumor resections showed that children from racial minority groups and underserved populations faced worse outcomes after brain tumor surgery, including more complications and higher readmission rates, while White children and those treated at larger hospitals had better survival and surgical results (415).

Evidence from Children's Oncology Group (COG) trials further demonstrated that children with neuroblastoma from racial and ethnic minority groups have worse survival compared to non-Hispanic White children, despite receiving the same standard treatment in clinical trials (53). These findings indicate that multilevel factors, including systemic and structural inequities as well as biological differences, may drive outcome gaps. Future research focused on treatment-related side effects and clinical care beyond trial participation, such as after disease relapse, is needed to help improve equity.

Access to timely treatment can be hindered by distance to health care facilities. A study of more than 90 million US children and AYAs showed that while over 80 percent of this population lived within an hour of the nearest pediatric oncologist, there are disparities among population groups (417). Median travel times were longest for American Indian or Alaska Native children and those living in the US South and Midwest, in areas with a high deprivation index, and in rural areas. Disparities in childhood cancer care also emerge from structural challenges in clinical trial participation and drug development. Pediatric cancer trials often underrepresent racially and ethnically diverse patients, limiting generalizability and perpetuating inequities in access to novel therapies (275).

Among 370 children with high-risk neuroblastoma treated on standardized Children's Oncology Group trials, about **one in four needed intensive-care support,** a proxy for treatment-associated toxicity, during therapy. Hispanic children were three times more likely than non-Hispanic White children to require ICU care, often for heart and blood vessel issues.

Source: (416).

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Together, these studies reveal that disparities in pediatric oncology are multifactorial, arising from socioeconomic conditions, unequal trial access, lack of culturally tailored care, treatment non-adherence, language barriers, implicit racial bias, and systemic barriers in drug development, all of which must be addressed to ensure equitable progress.

Accelerating Advances in Pediatric Cancer Medicine

Advancing the frontier of childhood cancer treatment requires the discovery of molecular targets unique to pediatric cancers through basic research, followed by careful validation of their therapeutic potential in translational and clinical studies. A new wave of innovative therapies, including novel molecularly targeted drugs and immunotherapies, is already moving from the laboratory into the clinic, while emerging technologies such as AI and liquid biopsy are accelerating these advances by improving target discovery, patient stratification, and real-time monitoring of treatment response (see **Innovative Technologies Decoding Pediatric Cancer Complexities**, p. 40).

As one example, a new AI-driven model has shown high accuracy in distinguishing among different subtypes of pediatric sarcoma using only routine pathology images (146,418). Diagnosing pediatric sarcomas is currently challenging because different subtypes can appear very similar under the microscope but require distinct treatment approaches. The AI tool has the potential to deliver faster, accurate, and more consistent diagnoses to guide treatment decisions, particularly in low-resource or remote settings without access to an expert sarcoma pathologist.

Another recent study showed that childhood cancers evolve in specific ways between diagnosis and relapse, revealing both tumor-specific and shared genetic drivers of relapse (419). It also demonstrated that analyzing cell-free DNA (cfDNA) from the blood can uncover these key genetic and epigenetic factors, including the cancer's cell of origin, using standard, clinically available sequencing tools. By providing a minimally invasive way to track tumor genetics over time, liquid biopsy has the potential to guide more precise treatment decisions for children with cancer.

Accelerating the pace of progress in pediatric cancer treatments will require concerted efforts from all stakeholders across the medical research ecosystem, along with regulatory policies from FDA and legislative actions from Congress that incentivize the development of pediatric cancer treatments (see **Advancing Pediatric Cancer Research and Patient Care Through Evidence-Based Policies**, p. 146). A recent consensus from an international multistakeholder pediatric cancer group examined the potential of repurposing cancer drugs that were discontinued or shelved in adults for pediatric use (413). The experts outlined strategies to identify new applications for these medications in children and AYAs, aiming to expand treatment options for pediatric cancers. The statement recommended creating structured pathways and incentives to systematically evaluate these drugs for pediatric indications, ensuring that promising therapies reach children who could benefit the most.

The US Food and Drug Administration (FDA) began enforcing the RACE Act in 2020 to ensure more cancer drug trials included pediatric populations. Between 2017 and 2024, FDA approved 61 adult cancer drugs with molecular targets relevant to pediatric cancer; **none of the 40 drugs approved before the RACE Act carried pediatric testing requirements, while 15 such requirements were attached to the 21 drugs approved afterward.**

Source: (420).

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Evaluating Novel Targets and Innovative Therapeutic Strategies

Researchers are making progress in finding new ways to treat pediatric cancers by identifying and validating unique targets that drive these diseases (421-423). For instance, studies are exploring new strategies against high-risk neuroblastoma, a childhood cancer often fueled by alterations in the difficult-to-target *MYCN* gene. Research has shown that MYCN protein drives cancer growth by activating a protein complex called FACT. Blocking FACT with an investigational therapeutic slowed tumor growth and made chemotherapy more effective in preclinical models of neuroblastoma (424). When combined with another molecularly targeted treatment, panobinostat, the investigational drug worked even better, eliminating tumors in animal models (425). These promising findings have led to a phase I clinical trial now testing the therapeutic in children and young adults with additional cancer types (426).

Just as blocking the FACT complex can indirectly turn off MYCN activity in neuroblastoma, researchers have uncovered a similar weakness in some childhood rhabdomyosarcoma tumors. These tumors are driven by a fusion protein (see **Sidebar 4**, p. 32) called PAX3::FOXO1, which is difficult to target directly, but the evidence indicates that it depends on another protein, KDM4B, to fuel tumor growth. Using an experimental drug to block KDM4B, and combining it with chemotherapy, nearly eradicated rhabdomyosarcoma tumors in mice (427).

In many pediatric cancers driven by fusion oncoproteins, emerging therapies are focusing not on the fusion protein itself, but on the partner proteins that help carry out its cellular functions. For example, in NUP98-rearranged AML in children, researchers have identified the histone-modifying proteins KAT6A and KAT7 as critical collaborators of the NUP98 fusion protein that drives cancer (428). These two proteins help maintain the cancer-promoting gene activity of the NUP98 fusion protein. Inhibiting KAT6A and KAT7 disrupts this process, leading to reduced leukemia cell growth, and lower disease burden. This strategy highlights the therapeutic potential of targeting fusion-associated epigenetic regulators to improve outcomes in pediatric leukemia.

Ewing sarcomas are rare but aggressive cancers that typically arise in the bones or soft tissues of children and adolescents. Similar to many pediatric cancers, they are driven by fusion proteins, most frequently by one known as EWS::FLI1. The EWS::FLI1 fusion protein has proven extremely difficult to target directly with therapeutics. Researchers are evaluating various approaches to interfere with EWS::FLI1 activity. One strategy includes targeting the protein TRIM8 which is responsible for tagging EWS::FLI1 for degradation (429). Researchers have demonstrated that targeting TRIM8 can cause cancer cells to "overdose" on EWSR1::FLI1 and die. Other studies have shown that Ewing sarcoma cells depend on proteins called p300/CBP to grow (430). Blocking these proteins shuts down the cancer's main driver and forces the tumor cells into a weakened state where they can be more easily destroyed with other drugs, pointing to a promising new treatment approach (431). Researchers are also evaluating trabectedin, a chemotherapeutic that targets the EWS::FLI1 fusion protein, and changes gene activity in cancer cells to slow tumor growth (432)

A recent clinical trial has shown promising results for a new targeted approach to treating advanced soft tissue sarcomas. Researchers tested the addition of the molecularly targeted therapeutic pazopanib (Votrient) to standard chemotherapy and radiation. This combination helped shrink tumors more effectively before surgery (433). Pazopanib works by blocking the growth of blood vessels that supply nutrients to tumors. By cutting off this supply, the drug helps starve the cancer and slow its spread. While pazopanib is already used in adults, this trial marks a new and innovative step toward using targeted therapies in children, who often have fewer treatment options for rare cancers like sarcoma.

Researchers are urgently searching for new targets to treat DIPG, a rare and aggressive childhood brain tumor that is nearly impossible to remove surgically and resists standard therapies. A key discovery in recent years was that many DIPGs carry a mutation in histone proteins—molecules that help package DNA (see **Sidebar 4**, p. 32)—which changes how genes are turned on and off. Building on this insight, early studies demonstrated that molecularly targeting two proteins, BET and PRC2, that mediate the effects of mutated histone proteins, could shrink tumors and extend survival in preclinical models (434). Continued research is needed to identify the most effective therapeutics to target these pathways in DIPG and other cancers driven by similar mechanisms.

One of the challenges in advancing pediatric cancer treatments has been the fact that many of the childhood cancer-driving proteins are difficult to target using traditional small molecule drugs attributable to their structure or location in the cell. Unprecedented progress in the fields of medicinal chemistry and structural biology has led to an emerging area of active investigation whereby cancer-causing proteins, especially ones that have been difficult to target by conventional methods, are selectively degraded using a cellular machinery known as the proteasome. The proteasome is naturally found in cells and breaks down proteins the cell no longer needs. The process helps control multiple functions, including cell division and survival.

Proteolysis-targeting chimeras (PROTACs) are a class of therapeutics that can induce targeted degradation of disease-causing proteins. These bifunctional small molecules consist of two protein binding elements that are attached by a linker; one binds to the protein of interest (target) and another recruits the protein, E3 ubiquitin ligase, a key component of the proteasomal machinery. By bringing the target close to the E3 ligase, PROTACs initiate breakdown and elimination of the target proteins. Researchers are hopeful that this could be a promising approach for childhood solid tumors that have long lacked targeted therapies (435).

One major focus is on neuroblastoma, for which researchers are developing PROTACs to degrade MYCN, a protein previously considered "undruggable" due to its lack of binding pockets, or its binding partner proteins (436). In T-ALL, a highly aggressive blood cancer, researchers demonstrated the efficacy of a PROTAC-based approach to target a protein that is highly expressed in cancer cells (437). Additionally, international cross-disciplinary collaborations are ongoing to evaluate PROTACs in targeting fusion proteins that drive aggressive pediatric cancers, including Ewing sarcoma, rhabdomyosarcoma, and liver cancer (438,439). These fusion proteins persist as tumors evolve, making them ideal candidates for degradation. With several PROTACs already in clinical trials for adult cancers, pediatric cancer investigations will soon follow. If successful, these therapies could offer more effective treatments for some of the most challenging childhood cancers.

Researchers are continuously refining the use of cytotoxic chemotherapeutics to make them more effective, less toxic, easier to administer, and more capable of overcoming treatment resistance. In many high-risk childhood cancers, including neuroblastoma, medulloblastoma, and rhabdomyosarcoma, patients often receive a class of chemotherapeutics called camptothecins. Unfortunately, tumors can develop resistance to these drugs, limiting their effectiveness. To address this challenge, researchers have engineered a new version of camptothecin, called a prodrug, that is optimized to enter tumors more efficiently and remain active longer. In preclinical studies, this redesigned drug overcame resistance and effectively killed cancer cells, restoring the treatment's ability to shrink tumors (440).

A New Age of Cell Therapies

The past decade has witnessed a remarkable transformation in the treatment of childhood cancers through the introduction of CAR T-cell therapies. By engineering a patient's own immune cells into "living drugs," researchers are changing the outlook for children with the most difficult-to-treat forms of blood cancer. Nowhere is this more evident than in relapsed or refractory B-ALL, in which CD19-directed CAR T cells have induced deep remissions in children who have exhausted conventional options, often within weeks of the initial infusion (441). Although many patients achieve lasting responses, relapses remain a challenge, underscoring the need to build on this remarkable foundation.

For children with B-ALL that has relapsed after CD19 CAR T-cell therapy, researchers are developing multiple new strategies. One of these includes the generation of CAR T cells targeting the protein, CD22 (442). This approach has provided benefits in some children with B-ALL who have received multiple prior therapies, though responses are often short-lived without stem cell transplantation. Although a few patients have experienced prolonged remission with CD22 CAR T cells alone, most require additional therapy (443).

To reduce the risk of relapse, dual-targeted CARs, typically against CD19 and CD22, have also been developed (444). Early data demonstrate strong initial responses, but relapses still occur, arising both from reduction in the levels of CD19 or CD22 by cancer cells and from inadequate CAR T-cell persistence. Current evidence suggests that insufficient persistence is often the dominant barrier, but both mechanisms remain important challenges (444). Innovative engineering approaches, including trispecific CARs, tuning of cancer cell CAR binding affinity, optimizing CAR T-cell fitness, and sequential infusion strategies, are now in development to address these challenges.

Pediatric T-ALL presents a tougher challenge, as malignant and healthy T cells share most surface markers (445,446). CD7-directed CAR T cells, both patient-derived (autologous) (447) and donor-derived (allogeneic) (445), have shown the ability to induce rapid, deep remissions, though a stem cell transplant is usually needed for long-term control. Risks associated with T-cell depletion, infection, and graft-versus-host disease remain substantial. Other targets, such as CD5, are being explored to expand options, particularly for children with T-ALL that has relapsed after CD7-directed therapy (446). These efforts highlight both the risks and the potential of CAR T cells for this difficult disease.

AML in children presents unique challenges because the disease lacks a single, universal target (448). To circumvent this, researchers are pursuing several candidate targets, most notably CLL1 and CD33, and early pediatric studies of CLL1- and CD33-directed CAR T cells have shown that deep remissions are possible, though toxicities and relapse remain obstacles (448-451). To address these issues, new approaches are under development, including dual-target CARs that can recognize both antigens (448) and "safety switch" mechanisms that allow rapid deactivation in the event of severe side effects (449-451). In nearly all cases, stem cell transplantation remains an important strategy to further bolster remissions achieved with CAR T cells. Although in their early days, CAR T-cell therapies for AML are advancing with creative solutions to the barriers that have long limited progress.

One of the most ambitious frontiers for CAR T-cell therapy is in childhood cancers of the brain and CNS, including DMGs such as DIPG where conventional treatments are limited and outcomes remain poor (452). Researchers are now adapting CAR T cells to tackle these solid tumors, with early evidence of feasibility and antitumor activity.

A central obstacle in brain and CNS cancers is the blood–brain barrier (BBB), which may restrict circulating CAR T cells from reaching tumor sites. To overcome this, investigators are testing localized delivery approaches, including intracerebroventricular delivery into the cerebrospinal fluid and intratumoral infusions directly into lesions (372,452). Tumor heterogeneity poses another challenge. Pediatric brain and CNS cancers often express a patchwork of different surface proteins, making single-target approaches less effective. CAR T cells targeting several antigens are under consideration, including GD2, B7-H3, HER2, IL-13Rα2, and EGFRvIII, each with distinct promise and pitfalls. The first four targets are normal proteins that are found on healthy cells and also frequently expressed in pediatric CNS tumors, whereas EGFRvIII is a mutated, tumor-specific protein that provides precision-targeting opportunities but is present in narrower subsets of patients.

The tumor microenvironment adds a third barrier. Pediatric brain tumors, like their adult counterparts, are surrounded by an immunosuppressive milieu that can blunt the activity of CAR T cells. Efforts to engineer cells that resist exhaustion, modulate responses through immune molecules, or can be combined with ICIs are underway (372,452,453).

The layered challenges of tumor heterogeneity, the BBB, and an inhospitable tumor microenvironment make the task formidable. Yet the ingenuity of approaches now being tested has opened the door to a future where CAR T-cell therapies may provide meaningful new options for children with lethal brain and CNS cancers.

CAR T-cell therapy innovation has also occurred in neuroblastoma, a solid cancer of the peripheral nervous system that is often diagnosed at advanced stages and remains challenging to treat with conventional therapies (454). CAR T cells directed against GD2, a molecule often found at high levels on neuroblastoma cells, have now demonstrated that durable remissions are possible (454,455). In recent clinical trials using both autologous (454) and allogeneic (455) approaches, GD2 CAR T cells induced long-lasting responses in subsets of patients.

Researchers are also extending GD2-directed strategies to retinoblastoma, a rare childhood eye cancer. Here, CAR T cells are being combined with innovative delivery systems such as hydrogels that allow localized release near the tumor in preclinical models (456).

The new wave of CAR T-cell therapies for childhood cancers is more than a scientific achievement. It is a testament to what can be accomplished when basic research, clinical innovation, and patient-centered care converge. From innovation in B-ALL, T-ALL, and AML, to novel approaches in brain cancers, neuroblastoma, and retinoblastoma, each advance represents a step toward a future in which more children can be cured with therapies that are not only effective but also safe. Challenges remain, such as ensuring persistence, reducing toxicities, and broadening applicability, but the trajectory of progress provides hope.

SUPPORTING SURVIVORS OF PEDIATRIC CANCERS

IN THIS SECTION, YOU WILL LEARN:

- As of 2022 (the most recent year for which data are available), more than 521,000 pediatric cancer survivors were living in the United States (US), and this number is projected to exceed 580,000 by 2040.
- Thanks to advances in treatment, the 5-year relative survival rate for US children and adolescents diagnosed with cancer now exceeds 85 percent for all cancers combined.
- Pediatric cancer survivors face a multitude of long-term physical, psychosocial, and financial challenges because of their cancer and treatment.
- Evidence-based frameworks for survivorship care, including the Children's Oncology Group Long-Term Follow-Up Guidelines, are essential to monitoring, preventing, and managing late effects across the lifespan.
- Parents and caregivers of children with cancer often experience significant psychological and financial strain, highlighting the need for comprehensive, family-centered support throughout the cancer journey.

According to the National Cancer Institute (NCI), a person is considered a cancer survivor from the time of cancer diagnosis through the balance of the person's life (457,458). Pediatric cancer survivors include individuals of any age who were diagnosed with cancer between the ages of 0 and 19.

As of 2022, which is the most recent year for which such data are available, more than 521,000 pediatric cancer survivors were living in the United States (US), and this number is projected to grow to over 580,000 by 2040 (459). In addition, an estimated 9,550 US children (ages 0 to 14 years) and 5,140 adolescents (ages 15 to 19 years) are expected to be diagnosed with cancer in 2025 (460).

Thanks to remarkable advances in treatment, children and adolescents diagnosed with cancer today are living longer and healthier lives. Among US children, the 5-year relative survival rate for all cancers combined has improved from just 58 percent in the mid-1970s to more than 85 percent for those diagnosed between 2015 and 2021 (see **Pediatric Cancer Trends in the United States**, p. 14). Similar progress has been observed among US adolescents, whose 5-year relative

As of January 1, 2025, it is estimated that **more than 84,500 children and adolescents** (ages 0 to 19) are **living with a previous cancer diagnosis** in the United States.

Source: (460).

W27

survival rate increased from 68 percent in the mid-1970s to 88 percent between 2015 and 2021 (5,16).

As more children and adolescents survive cancer and reach adulthood, it is increasingly important to understand their unique survivorship experiences. Therapies used to treat cancer can damage organs, tissues, or bones, putting survivors at risk of adverse health outcomes known as late effects. These late effects include physical, neurocognitive, psychosocial, and financial problems that can emerge months or years after diagnosis or treatment. Because children with cancer are treated while their bodies are still growing and developing, they are particularly susceptible to late effects and therefore require long-term follow-up care to monitor and manage these late effects.

A cancer diagnosis in childhood or adolescence also deeply affects families, caregivers, and peers, who often serve as the primary support network. The emotional, financial, and logistical burdens on these individuals can be profound and long-lasting. Therefore, research, services, and care strategies must extend beyond survivors to include their broader support system.

The following sections underscore the challenges faced by pediatric cancer survivors and their families, highlight advances in pediatric cancer survivorship, and present evidence-based approaches to delivering effective, age-appropriate survivorship care.

Challenges Faced by Pediatric Cancer Survivors

While advances in pediatric oncology have markedly improved survival rates, pediatric cancer survivors remain at risk for long-term physical, psychosocial, and financial difficulties resulting from the cancer itself or the therapies used to treat it. The type and severity of these late effects depend on several factors, including the cancer type and stage at diagnosis, the specific type of treatment and doses received, as well as the survivor's age and overall health at the time of treatment. These long-term challenges can adversely affect survivors' quality of life and place additional emotional and financial strain on families and caregivers. Although research is ongoing, a greater understanding of these challenges and strategies to address them is essential to better support this vulnerable population.

Physical Challenges

Pediatric cancer survivors are at risk for a broad spectrum of short- and long-term health effects resulting from their disease and its treatments. Short-term effects, which typically arise during therapy or shortly thereafter, may include hair loss, nausea, vomiting, fatigue, pain, and changes in appetite or taste. Some survivors of pediatric cancer, such as **Martin Townsend** (see p. 107), continue to experience lasting effects—for example, fatigue and low energy—long after completing therapy. As survival rates improve and many children live decades beyond their initial diagnosis, the burden of long-term and late effects has become a central focus of survivorship care. Late effects can involve multiple organ systems and include heart and lung problems, impaired growth and development, endocrine and reproductive disorders, neurocognitive impairments, reduced sex hormone production (hypogonadism), bone damage (osteonecrosis), and second primary cancers (see **Table 6**, p. 108).

Endocrine disorders

Endocrine dysfunction refers to problems with the body's hormone system, which regulates essential functions such as growth, sexual development, reproduction, sleep, hunger, and metabolism. Endocrine dysfunction is a common late effect of pediatric cancer treatment, affecting up to 50 percent of childhood cancer survivors (461). The risk of endocrine dysfunction varies depending on factors, such as age at treatment, sex, tumor location, and the type and intensity of therapy received. For example, radiation to the brain can impair growth hormone production, leading to short stature and/or delayed puberty; radiation to the neck can result in thyroid disease; and pelvic radiation or certain chemotherapy drugs can affect fertility (i.e., the ability to conceive children) (462,463). Endocrine-related dysfunction can also lead to obesity, metabolic syndrome, diabetes, and impaired bone health, all of which may contribute to long-term cardiovascular and skeletal complications (461-464). Many endocrine-related late effects can be effectively managed with appropriate medical care, underscoring the importance of lifelong, risk-based follow-up care.

Cardiotoxicity

Cardiotoxicity, or heart damage, is a common late effect of childhood cancer therapy. Certain cancer treatments can damage the heart and blood vessels, leading to long-term heart problems such as cardiomyopathy (weakening of the heart muscle), coronary artery disease (narrowing of the heart's blood vessels), congestive heart failure, arrhythmia (abnormal heart rhythms), and pericardial disease (inflammation around the heart). Cardiovascular disease (CVD) is the leading cause of non–cancer-related mortality in pediatric cancer survivors, who have a four-fold increased risk of CVD-related mortality compared with the general population (465,466).

continued on page 108

"Without cancer research, my son wouldn't have had another chance.

We would ask our legislatures to continue to fund research—just to save a life is worth it."

—Virgie Townsend, Martin's Mother

SURVIVOR STORY

MARTIN TOWNSEND

AGE: 34 | DIAGNOSIS: BIPHENOTYPIC LEUKEMIA | BIRMINGHAM, AL

Surviving Leukemia and Finding Purpose Through Research

When 34-year-old Martin Townsend of Birmingham, Alabama, looks back on his journey with leukemia, he sees a story of science, perseverance, and faith. Today, Martin works in information technology and spends his free time immersed in photography, gaming, and playing guitar—creative outlets that remind him how far he's come.

Martin's story began in March 2011, during his sophomore year at the University of Alabama. After weeks of feeling unusually fatigued, he visited the student health center, where blood tests revealed abnormal results. He was referred to Druid City Hospital in Tuscaloosa and then to the University of Alabama at Birmingham (UAB) Hospital, where further testing confirmed the diagnosis—biphenotypic acute leukemia, a rare and aggressive form that shares characteristics of both acute lymphoblastic leukemia and acute myeloid leukemia.

At just 19 years old, Martin faced an uncertain future. "Getting the confirmation at UAB, that's when I really got emotional about it because it started to hit home that I was in the hospital," he recalled. "Initially [the doctors] said that they thought it was going to just be acute lymphoblastic leukemia, but it ended up being a bit more complex than that."

Martin's mother, Virgie, drove from Birmingham to be by his side. "When he told me, 'Mom, I have cancer,' I knew I had to be strong for him," she said. "I just went into mama bear mode and told myself, it's going to be all right—whatever it is, we are going to get through it." Martin was hospitalized for about 40 days for induction therapy and followed a pediatric chemotherapy protocol, which offered a better chance of remission. By day 39, he was in remission. Given the high risk of recurrence, Martin remained on chemotherapy for the next three and a half years, often spending long hours at the clinic. "It became like a full-time job," he said.

After completing treatment, Martin enjoyed about 9 months of normalcy before learning in March 2015 that the leukemia had returned. The relapse was devastating for both mother and son. "It took me about 2 weeks to really get in that state of mind where I said, 'Okay, we've got this again. We are going to get through it again,'" Virgie recalled.

"Things seemed hopeless for a short period after four weeks of conventional chemotherapy failed to get Martin back in remission. Then Martin's oncologist recommended we turn to Blincyto," recalled Virgie. Blinatumomab (Blincyto), is an immunotherapeutic that had been approved by the FDA just a few months earlier. The first infusion was difficult, but after doctors adjusted his medications, he tolerated the treatment well. "It was a brand-new drug—they were just beginning to use it, and Martin was one of the first patients they gave it to. They didn't know how well it would work, but it worked for him," Virgie recalled.

Martin achieved remission again, paving the way for a bone marrow transplant using cells from his father. Recovery brought new challenges, including a serious complication called graft-versus-host disease in which the transplanted immune cells attacked his body, causing severe itching and skin irritation. Doctors treated it successfully with photopheresis, a process that uses light to modify immune cells and reduce inflammation.

Nearly a decade later, Martin remains cancer-free and now sees his oncologists once a year. "I'm doing really well," he said. "The visits are pretty boring now—and that's a good thing." His experience deepened his appreciation for research: "Funding for cancer research is really integral to why I'm still here," he said. "It's about giving people a second chance at life."

Scan the QR code to watch Martin's video interview.

TABLE 6

Common Late Effects of Treatment for Pediatric Cancer

	Therapy-related Exposures	Potential Late Effect
Cardiovascular System	Anthracycline chemotherapy, chest radiation, total body irradiation	Cardiomyopathy
	Chest radiation	Cardiovascular disease (valvular disease, pericardial disease, coronary artery disease, atherosclerosis)
Central Nervous System	Cranial radiation and high-dose or intrathecal methotrexate	Neurocognitive impairment
Endocrine System	Cranial radiation, total body irradiation	Growth hormone deficiency
	Cranial radiation (involving the pituitary region)	Central adrenal insufficiency, hypopituitarism, gonadotropin deficiency
	Neck radiation, total body irradiation	Hypothyroidism
	Abdominal radiation, total body irradiation	Diabetes
Musculoskeletal System	Corticosteroids, allogeneic hematopoietic stem cell transplant	Reduced bone mineral density, osteonecrosis
	Radiation (especially to the abdomen, chest, extremities, total body)	Muscular atrophy, skeletal hypoplasia, scoliosis, kyphosis
Pulmonary System	Chest radiation, pulmonary surgery, alkylating agent chemotherapy, anti-tumor antibiotics (bleomycin)	Restrictive pulmonary disease (reduced lung capacity)
	Alkylating agent chemotherapy	Pulmonary fibrosis (scarring of the lung)
	Chest radiation, total body irradiation, anti-tumor antibiotics (bleomycin)	Lung damage
Reproductive System	Pelvic radiation, alkylating agent chemotherapy (especially in higher doses), total body irradiation	Primary gonadal insufficiency, testicular or ovarian hormone deficiency, premature ovarian failure
	Pelvic radiation, testicular radiation, alkylating agent chemotherapy (especially in higher doses), total body irradiation	Reduced fertility, infertility, shortened lifetime period of fertility
Sensory System	Radiation to the eye, corticosteroids, alkylating agent chemotherapy	Cataracts, vision problems
	Platinum-based chemotherapy, high-dose cranial radiation	Hearing loss
Second Primary Cancers	Any radiation, allogeneic hematopoietic stem cell transplant	Basal cell carcinoma
	Chest radiation, total body irradiation, anthracycline and alkylating agent chemotherapies	Breast cancer
	Abdominal radiation, pelvic radiation, total body irradiation	Colorectal cancer
	Cranial radiation, total body irradiation	Glioma
	Anthracycline and alkylating agent chemotherapies, autologous hematopoietic stem cell transplant, topoisomerase inhibitors (etoposide)	Leukemia
	Cranial radiation, total body irradiation	Meningioma
	Anthracycline chemotherapy, radiation involving bones or soft tissue	Sarcoma
	Cranial radiation, neck radiation, total body irradiation	Thyroid cancer

Source: (21).

A substantial proportion of cardiovascular conditions are attributable to prior exposure to anthracycline chemotherapeutics—a type of antibiotics that damage the DNA in cancer cells—and/or irradiation as part of childhood cancer treatment (see **Less Is Sometimes More**, p. 67). Numerous studies have demonstrated a clear dose–response relationship, whereby higher cumulative doses of anthracyclines or radiotherapy are associated with a proportionally greater risk of subsequent heart problems, particularly cardiomyopathy (467-469). In the case of radiotherapy, cardiotoxicity risk is determined not only by the total radiation dose, but also by the volume of cardiac tissue exposed to radiation (470).

Because cardiovascular complications may develop decades after treatment and often without early warning signs, experts recommend lifelong cardiac monitoring for anyone exposed to anthracyclines or radiation near the heart. Regular follow-up care, heart imaging, and reducing other heart disease risk factors—such as smoking, high blood pressure, or obesity—can help detect problems early and improve long-term health.

Second Primary Cancers

Second primary cancers (SPCs) are a leading cause of morbidity and mortality among survivors of pediatric cancers (465,471). Unlike recurrence of the original cancer, SPCs represent a new, biologically distinct cancer that can emerge months or years after the original cancer was diagnosed and treated. Research shows that people who survive childhood cancer are two to six times more likely to develop SPC in their lifetime compared to the general population (466,472-474). The most common SPCs in this population include breast cancer, thyroid cancer, central nervous system (CNS) tumors (notably meningiomas and gliomas), soft-tissue sarcomas, and certain skin cancers such as basal cell carcinoma (21,474-476).

Among pediatric cancer survivors, the development of SPCs is primarily attributable to prior treatment exposures. Radiation therapy is a well-established, dose-dependent SPC risk factor, especially for tumors that arise in or near areas of the body directly exposed to the radiation (21,474,477). For example, radiation to the neck increases the risk of developing thyroid cancer, while radiation to the abdomen and pelvis increases the risk of colorectal cancer (21). Additionally, certain chemotherapy agents (e.g., alkylating agents, anthracyclines, and platinum-based compounds) have been associated with increased risk of SPCs, including breast cancer, sarcoma, and certain blood cancers (459,472,474,478).

The reduced use and lower dosing of radiotherapy in recent decades have led to meaningful declines in the SPC incidence (15,22,474). Despite these improvements, the absolute lifetime risk of SPCs among pediatric cancer

SIDEBAR 16

Fertility Preservation in Children and Adolescents with Cancer

A common adverse effect of cancer treatments is infertility, or the inability to conceive children. This may result from surgery on reproductive organs, radiation, or effects of cancer medications on reproductive cells and can affect both male and female survivors. Experts recommend that clinicians discuss methods of fertility preservation with patients and guardians as early as possible, ideally before treatment begins, with referrals to fertility specialists as needed. Fertility preservation for minors requires parental or guardian consent and, whenever possible, assent from the child or adolescent. The options for fertility preservation depend on whether a child has gone through puberty, and include:

Prepubertal Patients

- **Girls:** Banking of ovarian tissue
- **Boys:** Banking of testicular tissue*

Postpubertal Patients

Girls and young women:

- Banking of ovarian tissue
- Banking of eggs
- Banking of embryos
- Surgically moving ovaries away from areas of radiotherapy
- Fertility-sparing surgery (surgery that treats the cancer while leaving the uterus or ovaries in place, so pregnancy may still be possible)

Boys and young men:

- Sperm banking
- Testicular sperm extraction

Currently, cancer-focused organizations have guidelines that recommend discussions of fertility preservation and sexual health as part of comprehensive cancer care and long-term follow-up (462). Furthermore, as of September 2025, 21 states and the District of Columbia have enacted mandates requiring insurance coverage of fertility preservation for patients at risk of infertility from treatments such as chemotherapy or radiation (468). This reflects considerable progress since 2015, when no states had such mandates.

* For prepubertal males, testicular tissue banking remains experimental and is currently available only in clinical trial settings.

Source: (484).

survivors remains elevated compared to the general population, underscoring the need for lifelong, risk-based follow-up care to support early detection and improve long-term outcomes. Although treatment-related exposures have long been recognized as the primary drivers of SPC risk in childhood cancer survivors, emerging evidence suggests that inherited genetic factors also play a significant role and are an area of active study.

Reproductive Health and Fertility

Survivors of pediatric cancers often face lasting reproductive health challenges as a result of their treatment. Certain therapies, including alkylating chemotherapy agents and radiation to the pelvis or abdomen can damage the ovaries or testes (479,480). This damage may occur during treatment or may develop years afterward, leading to early menopause or premature ovarian failure in women, and reduced or absent sperm production in men (481).

Female survivors are less likely to achieve pregnancy compared with peers or siblings without a history of cancer. Those who become pregnant have an increased risk of complications, such as preterm birth and low birth weight, especially after pelvic radiation (482,483). Male survivors are similarly less likely to father children, particularly after treatment with high-dose alkylating agents or radiation affecting the testes (479).

Because cancer treatment can affect fertility, parents/guardians of children and adolescents diagnosed with cancer should talk with their child's health care providers about whether infertility is a risk and, if so, which fertility preservation options may be appropriate (see **Sidebar 16**, p. 109) (481). Experts recommend discussing fertility and sexual health at the time of cancer diagnosis, before starting therapy, and revisiting these topics during follow-up care (481,484). However, many survivors report receiving inadequate information about the potential reproductive or sexual health effects of cancer treatment. In a recent study of pediatric and young adult cancer survivors, nearly 70 percent expressed concerns about their sexual health and function, and 36 percent reported concerns about fertility. However, only about half of these survivors reported having received any communication from a health care professional about sexual health issues and reproductive concerns (485).

Integrating fertility preservation programs into cancer care may help address these gaps. A recent study found that implementing a multidisciplinary program at a large pediatric cancer center resulted in nearly all eligible patients receiving fertility counseling or consultation and increased use of fertility preservation methods (486).

Adult survivors of childhood cancer who engaged in consistent physical activity over time had fewer neurocognitive problems, including **fewer difficulties with task efficiency, regulation of emotions, organization, and memory.** They also experienced larger neurocognitive improvements over time, compared to survivors with inconsistent activity levels.

Source: (496).

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Neurocognitive Impairment

An estimated one-third of pediatric cancer survivors experience long-term neurocognitive impairments attributable to their cancer and its treatment (19,488,489). Frequently observed impairments include deficits in attention, processing speed, memory, learning, planning, and organizational skills, often accompanied by difficulties with regulation of emotions. These impairments are strongly associated with adverse educational, social, and occupational outcomes in adulthood (490). For example, in a large study of more than 1,500 survivors of childhood acute lymphoblastic leukemia (ALL), survivors demonstrated higher rates of inattention, hyperactivity, learning problems, and were more likely to require special education services than siblings without a cancer history (491,492). Survivors with neurocognitive deficits are less likely to complete higher levels of education, and are more likely to be unemployed, compared to survivors without such difficulties (68,493,494).

Importantly, for pediatric cancer survivors, neurocognitive impairment is not limited to the early post-treatment years. Longitudinal studies show that survivors who initially exhibit no cognitive deficits can develop cognitive problems decades after treatment (495). These late-onset impairments are associated with prior treatment exposures (e.g., cranial radiation therapy and high-dose alkylating agents), chronic health conditions, as well as potentially modifiable risk factors including smoking and physical inactivity. Collectively, these findings underscore the need for lifelong, risk-adapted neurocognitive surveillance and timely interventions, beginning during treatment and extending well into adulthood (21).

Accelerated Aging and Chronic Health Conditions

Survivors of pediatric cancers are also at an increased risk of developing chronic, age-related health conditions earlier in life (see **Sidebar 17**, p. 111). These include CVD, stroke, and

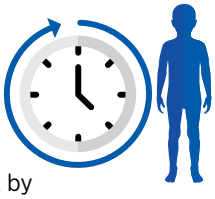
SIDEBAR 17

What is Accelerated Aging?

Children and adolescents diagnosed with cancer often receive intensive treatments while their bodies are still developing. This early exposure may set survivors on a faster aging trajectory, leading to health problems in young adulthood that typically emerge much later in life.

Chronological age refers to the number of years a person has lived.

Biological age reflects how well (or poorly) the body's cells, tissues, and organs are functioning compared to what is typical for someone of the same chronological age.



Accelerated aging occurs when the body ages faster biologically than expected for a person's chronological age. Accelerated aging not only increases cancer risk by impairing cellular repair and immune function, but it can also arise as a consequence of cancer and its treatment, resulting in long-term health challenges for survivors.

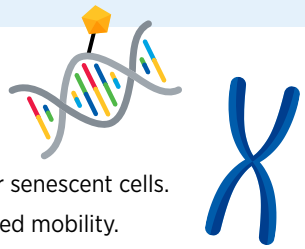
What Causes It?

Risk factors linked to both cancer and accelerated aging include:

- **Genetics and epigenetics** – Some individuals are biologically more prone to aging-related changes.
- **Chronic inflammation** – Fuels both tumor growth and biological aging.
- **Lifestyle factors** – Smoking, obesity, poor diet, inactivity, and stress.
- **Cancer therapies in childhood** – Treatments such as chemotherapy, radiation, and immunotherapy can damage DNA and healthy cells.

How Is It Measured?

Scientists assess accelerated aging using:



- **Epigenetic clocks** – Track biological age based on DNA methylation patterns.
- **Telomere length** – Shortened telomeres signal cellular aging.
- **Markers of inflammation and senescence** – Elevated inflammatory markers or senescent cells.
- **Frailty and functional decline** – Clinical signs like weakness, fatigue, and slowed mobility.

How Does It Manifest?

- Early-onset of age-related chronic diseases (e.g., cancer, heart disease, diabetes, and osteoporosis).
- Fatigue, muscle loss, and limited physical function.
- Cognitive decline and memory issues.
- Increased vulnerability to infections or injuries.
- Premature death.

Sources: (502-504).

SPCs. Reports indicate that 60 percent to more than 90 percent of childhood survivors develop one or more chronic health conditions following their cancer diagnosis (19,20). By age 50, adult survivors of childhood cancer have an average of 17 chronic health conditions—which is nearly double the burden of disease, compared to the general population at that age (20).

Research measuring biological age has shown that pediatric cancer survivors age about 5 percent faster per year and can appear up to 16 years older biologically than their cancer-free peers, with faster aging linked to increased risk of premature mortality (497). Other studies report that by age 30, many survivors have health profiles similar to healthy individuals in their 60s (498).

This earlier onset and higher frequency of chronic conditions in survivors is often referred to as accelerated aging. Among survivors, accelerated aging arises, in part, from damage caused by cancer treatments, such as radiation therapy, chemotherapy, and stem cell transplantation. These therapies can harm DNA, shorten telomeres (the ends of chromosomes), alter epigenetic patterns, and trigger chronic inflammation, all of which speed up the deterioration of organs and tissues (499).

Treatment-related injuries activate many of the same biological pathways that underlie normal aging, reducing organ reserve (e.g., the capacity of an organ to perform functions beyond baseline daily needs) and increasing vulnerability to chronic diseases. However, the mechanisms behind accelerated aging are likely multifactorial and remain partially understood. Accelerated aging can be quantified using clinical tools, such as cumulative burden scores that summarize the total impact of chronic health conditions, as well as molecular measures like DNA methylation–based "epigenetic clocks," which may help identify survivors most in need of early interventions (497,500,501).

Because survivors are at risk for developing age-associated diseases decades earlier than the general population, lifelong, risk-adapted follow-up care is essential. This includes earlier and more frequent screening for conditions such as CVD and SPCs, along with preventive strategies aimed at slowing biological aging.

Late Effects of Precision Medicine

In recent years, improved understanding of the biology of pediatric cancers has led to the development of novel therapies that promise more effective and less toxic treatment. However, these new therapies are not without risk for late effects. Molecularly targeted treatments, such as tyrosine kinase inhibitors, have been associated with growth impairment, thyroid dysfunction (most commonly hypothyroidism), and other endocrine abnormalities that may persist long after therapy completion (505-507). Other targeted agents, such as vascular endothelial growth factor inhibitors, have been linked to cardiovascular complications, such as hypertension and/or blood clots, however the long-term cardiac effects for pediatric survivors remain incompletely understood (508,509).

Certain immunotherapies, including rituximab, have been linked to prolonged immune complications. Among the most notable are B-cell aplasia, a depletion of antibody-producing white blood cells, and hypogammaglobulinemia, an immune system disorder that heightens the risk of recurrent infections (403,510). The late effects of other novel therapies, including biologic agents and antibody-based immune therapies, remain poorly understood in the pediatric population, underscoring the importance of continued research.

Psychosocial Challenges

A cancer diagnosis during childhood or adolescence coincides with stages of rapid development of essential psychological, cognitive, and social skills. Children with cancer often face disruptions in their psychosocial development as a result of their diagnosis, treatment, and subsequent late effects. In the short term, these challenges may manifest as emotional distress, adjustment difficulties, maladaptive coping, reduced social engagement with peers, missed educational and employment opportunities, and financial toxicity.

The emotional toll of a cancer diagnosis during childhood can be profound. In fact, survivors of pediatric cancers are more likely to have symptoms of anxiety and depression compared to siblings and the general public (511-513). This population is also more susceptible to major psychiatric conditions, including autism, attention-deficit disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and posttraumatic stress disorder, with the greatest number of mental health illnesses experienced by survivors of brain cancers and blood cancers (514).

Fear of cancer recurrence is also common among pediatric cancer survivors. According to a recent study, approximately one-third of adult survivors of childhood cancer reported heightened fear that their cancer might return or that they could develop SPCs. These fears were strongly associated with elevated symptoms of anxiety and depression (515). Mental health challenges in this population also extend to suicidal ideation, or thoughts of suicide. Reports indicate that approximately 10 percent of childhood cancer survivors report experiencing suicidal ideation, particularly during active treatment. While childhood cancer survivors are more likely to report suicidal ideation, their risk of suicide death is comparable to that of the general population (516).

The psychological burden of pediatric cancer often extends into daily life, influencing coping strategies and risky health behaviors. When compared to healthy siblings, young adult survivors of childhood cancers reported increased loneliness that subsequently increased anxiety, depression, and the likelihood of smoking. Long-term follow-up with these patients found higher levels of suicidal ideation, as well as heavy/risky alcohol consumption (517).

Survivors of pediatric cancers also face unique social and educational challenges, including difficulties with peer relationships, academic performance, and establishing independence from parents and caregivers (see **Sidebar 18**, p. 114). Compared to their siblings, survivors are more likely to experience social withdrawal and antisocial behaviors, which can hinder healthy social development (492,518). According to a recent analysis, individuals diagnosed with CNS tumors in early childhood experienced slower development of academic

The annual productivity loss for adult survivors of childhood cancer is $8,169 due to factors like missed workdays, lower wages, or reduced ability to work full-time due to chronic illness or other late effects. **By comparison, the annual productivity loss for adults without a cancer history is $3,083,** often due to common reasons like short-term illness or other minor health issues.

Source: (530).

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readiness skills, particularly in reading and math, which was associated with poorer academic outcomes later in life (519). These challenges often persist into adulthood, as survivors are less likely to complete higher levels of education, live independently, or marry and have children compared to those without a cancer history (68,491,520).

Financial Challenges

The economic burden of a cancer diagnosis and treatment, known as financial toxicity, is a significant challenge for survivors of pediatric cancer and their families, especially those from disadvantaged backgrounds. Evidence from large cohort studies demonstrates that adult survivors of childhood cancer are more likely than siblings or peers to report many forms of financial hardship, including material (e.g., difficulty paying bills or medical expenses), psychological (e.g., worry or distress about finances), and behavioral (e.g., delaying or forgoing medical care due to cost) (525). In one study, nearly two-thirds (63 percent) of adult survivors of childhood cancer reported some type of financial hardship, including being reported to debt collection, facing problems paying medical bills, and worrying about paying rent or affording nutritious food (526).

Financial hardship in this population is also associated with difficulties in acquiring health insurance, life insurance, and planning for retirement. These financial challenges can have profound effects on survivors' mental health and quality of life. For example, survivors experiencing financial hardship are more likely to report anxiety, depression, and lower quality of life compared to those without financial hardship (527).

Many survivors face long-term health issues and functional limitations that affect their ability to work, leading to employment instability and health-related unemployment (68). Long-term studies show that a substantial proportion of survivors who initially achieved full-time employment later transitioned to part-time work or unemployment over time (528). Pediatric cancer survivors are less likely than peers without a cancer history to graduate from college, a disadvantage that often translates into lower-paying jobs, reduced lifetime earning potential, and an increased risk of financial toxicity (68,529,530).

The combination of elevated health care needs, reduced earning potential, and persistent financial hardship among pediatric cancer survivors underscores the critical importance of access to affordable, comprehensive health insurance coverage for this population. Survivors who lack stable employment or who face gaps in employer-sponsored insurance are particularly vulnerable to being uninsured or underinsured, which can lead to delayed or forgone treatment, poorer long-term health outcomes, and increased financial distress.

Key provisions of the Patient Protection and Affordable Care Act (ACA)—including the establishment of Marketplace coverage, protections against coverage denial or increased premiums due to preexisting conditions, removal of lifetime and annual coverage limits, Medicaid expansion in participating states, and extension of dependent coverage to age 26—play a critical role in increasing access to insurance and health care for adult survivors of childhood cancer (531). However, ongoing efforts to roll back or repeal parts of the ACA threaten to undo these important protections, making it harder for adult survivors of pediatric cancer to get and keep health insurance. Such changes would likely exacerbate existing disparities in survivorship care and outcomes, particularly among survivors from low-income, rural, and racial/ethnic minority populations who already face barriers to accessing consistent, high-quality care (see **Sidebar 19**, p. 115).

Advances in Pediatric Cancer Survivorship

Over the past several decades, progress in pediatric oncology has shifted from improving survival to also enhancing long-term quality of life. Historically, pediatric cancer treatment often relied on high doses of chemotherapy and radiation, which saved lives but left many survivors with serious late effects, including CVD, SPCs, and premature mortality. Today, therapies are increasingly tailored to each child's clinical and biological features, helping to reduce toxicities without compromising survival (see **Progress in Pediatric Cancer Treatment**, p. 63). At the same time, advances in genomics are revealing why some survivors are more vulnerable than others to treatment-related complications. These advances are transforming pediatric cancer survivorship care, paving the way for safer treatments today and more personalized care in the years ahead.

SIDEBAR 18

Support for Childhood and Adolescent Cancer Patients and Survivors

Children and adolescents with cancer face unique challenges in school due to treatment side effects, frequent absences, and changes in physical or cognitive functioning. Several federal laws provide critical protection and support to help students access education and thrive during and after treatment.

The Rehabilitation Act of 1973 – Section 504

Section 504 is a federal civil rights law that prohibits disability-based discrimination in schools receiving federal funding. Cancer qualifies as a disability under Section 504 because it substantially limits major bodily functions, such as normal cell growth and immune system function, which are considered major life activities under the law.

Students with cancer are entitled to reasonable accommodations, such as:

- Extra time for tests and assignments.
- Preferred seating and help with concentration challenges.
- Modified schedules or rest breaks.
- Distance learning or virtual instruction during intensive treatment.

Schools are also required to respond to bullying or harassment related to cancer or its treatment.

The Individuals with Disabilities Education Act (IDEA)

IDEA ensures that public schools provide a free and appropriate education to students with qualifying disabilities from ages 3 to 21. For cancer survivors, common qualifying categories include specific learning disability, traumatic brain injury, or other health impairment. Parents can request an evaluation to create an Individualized Education Plan (IEP), which specifies the child's educational supports.

Services may include:

- Specialized instruction or tutoring.
- Psychological services.
- Occupational, physical, or speech therapy.
- Transportation services.

The Americans with Disabilities Act (ADA)

The ADA protects individuals with disabilities from discrimination in employment, higher education, transportation, and access to public spaces. For survivors, the ADA can be especially important when transitioning to higher education or entering the workforce.

Under the ADA:

- Schools, colleges and universities must provide reasonable accommodations (e.g., extended testing time, housing modifications, or flexible course loads).
- Employers must ensure equal opportunities and make workplace accommodations (e.g., flexible schedules and modified duties during treatment or recovery).

Why These Protections Matter

Pediatric cancers and their treatment can disrupt learning, attention, energy, and emotional well-being. These federal protections help level the playing field, ensuring that pediatric cancer patients and survivors have the same opportunities as their peers to learn, grow, and thrive in supportive environments.

Sources: (521-524).

SIDEBAR 19

Disparities in Pediatric Cancer Survivorship in the United States

Pediatric cancer survivors face distinct health challenges compared to their cancer-free siblings and peers. These differences reflect the lasting impact of cancer and its treatment on long-term health. In addition, not all survivors experience survivorship equally. Significant disparities also exist within survivor groups, shaped by race, ethnicity, socioeconomic status, geography, and insurance status.

COMPARED TO CANCER-FREE PEERS AND SIBLINGS, PEDIATRIC CANCER SURVIVORS EXPERIENCE THE FOLLOWING DISPARITIES:

4X increased risk	Cardiovascular disease (CVD) is the leading cause of non-cancer mortality in pediatric cancer survivors, who have a four-fold increased risk of CVD-related death compared to the general population (465).
SIGNIFICANTLY higher rates	Survivors of childhood acute lymphoblastic leukemia who received chemotherapy had significantly higher rates of inattention, hyperactivity, social withdrawal, and learning problems relative to siblings (491).
2-6X more likely	Survivors of pediatric cancer are two to six times more likely to develop a subsequent neoplasm in their lifetime compared to the general population (472-474).
SIGNIFICANTLY more likely	Pediatric cancer survivors are significantly more likely than their siblings to forgo needed medical care due to financial challenges (526).

WITHIN THE SURVIVOR POPULATION, DISPARITIES ALSO EXIST:

6-9X higher risk	Compared to childhood cancer survivors living in the least economically disadvantaged neighborhoods, those in the most economically disadvantaged neighborhoods had approximately a 6- to 9-fold higher risk of death occurring 5 or more years after diagnosis (532).
1.4- to 1.8-fold MORE LIKELY	Compared to non-Hispanic (NH) White survivors, childhood cancer survivors who identified as NH Black or Hispanic were 1.4- to 1.8-fold more likely to have comorbid conditions, including diabetes or obesity (533).
4X greater risk	Survivors of childhood cancer residing in rural areas had a 4 times greater risk of CVD compared to survivors from urban areas (534).
2.5- to 3.6-fold INCREASED RISK	Among 5-year survivors of pediatric cancer, those identifying as NH American Indian/Alaska Native or NH Black had a 2.5- to 3.6-fold increased risk of mental health–related hospitalization compared with NH White survivors (535).
53% less likely	NH Black survivors of childhood cancer were about 53 percent less likely to adhere to survivorship care guidelines than survivors of other racial and ethnic groups (536).
4X more likely	Uninsured survivors were more than 4 times as likely to have no regular provider for cancer follow-up care compared to those with private coverage (537).

Reducing Treatment-related Toxicities

Growing awareness of late effects, together with advances in pediatric cancer biology, imaging, and supportive care, has altered both the prevalence and nature of treatment-related morbidity and mortality. In recent decades, advances in pediatric oncology have focused not only on treating childhood cancers, but also on reducing the long-term toxicities of therapy. Evidence of the long-term harms of intensive therapies prompted therapeutic modifications that reduced harmful exposures while maintaining efficacy.

The benefits of these therapeutic modifications to reduce harmful exposures have been documented in long-term survivor studies. In an analysis of more than 23,000 survivors, the 20-year cumulative incidence of severe or life-threatening chronic conditions declined from 33 percent among those diagnosed in the 1970s to 27 percent among those diagnosed in the 1990s, largely due to reductions in endocrine-related disorders and SPCs (538). Similarly, a landmark study of more than 34,000 survivors diagnosed between 1970 and 1999 found that survivors treated in the 1990s experienced nearly a 50 percent lower risk of treatment-related mortality compared to those treated in the 1970s—a trend that paralleled declines in the use of cranial radiation for ALL, chest radiation for Hodgkin lymphoma, abdominal radiation for Wilms tumor, and reductions in cumulative anthracycline exposure (15). These improvements in morbidity and mortality have also translated into longer life expectancy (22).

A key advancement underpinning these improvements is risk-stratified therapy, or the tailoring of treatment intensity to the clinical and biological features of each child's cancer. For example, in a study of more than 6,000 pediatric ALL survivors, those classified as standard-risk and treated with contemporary regimens in the 1990s had lower rates of health-related mortality, SCPs, and chronic health conditions compared with survivors treated in the 1970s. Notably, the risk of late mortality and SPCs among survivors treated with 1990s standard-risk regimens were comparable to those of the general population, demonstrating that reductions in treatment intensity over recent decades have not compromised long-term survival (539).

New strategies are being tested to prevent late effects among survivors who remain at high risk. For example, women who received chest radiation during childhood or young adulthood face breast cancer risks that are comparable to those of *BRCA* gene mutation carriers. A randomized phase II clinical trial tested whether low-dose tamoxifen (Nolvadex), a drug that blocks estrogen, could reduce breast cancer risk in this population (540). The study found that women taking low-dose tamoxifen showed a reduction in dense breast tissue visible on mammograms and circulating insulin-like growth factor levels, both established markers of breast cancer risk, without causing serious side effects. These results suggest that low-dose tamoxifen may represent a safe and effective preventive option for certain high-risk groups.

Certain chemotherapy drugs, known as anthracyclines, used to treat pediatric cancers can increase the risk of developing heart problems later in life. This treatment-related heart damage may not appear until years after treatment completion and can lead to long-term complications such as cardiomyopathy (weakening of the heart muscle) or heart failure. Multiple studies show that cumulative anthracycline doses above a certain level can increase the risk of cardiotoxicity, though more recent research suggests that no dose is entirely safe (470,541). Consequently, many contemporary pediatric chemotherapy regimens restrict cumulative anthracycline doses to reduce the likelihood of long-term cardiac complications.

To further reduce risk, a cardioprotective medication called dexrazoxane (Zinecard) was first approved by the US Food and Drug Administration (FDA) in 1991 to prevent chemotherapy-related heart damage in adults with certain cancers. Since then, studies in pediatric patients have shown that dexrazoxane significantly lowers the long-term risk of cardiac complications without reducing the effectiveness of cancer treatment (542,543). In 2014, FDA granted orphan drug designation to dexrazoxane for the prevention of cardiomyopathy in pediatric and adolescent patients receiving anthracycline-based chemotherapy.

Pediatric patients who receive chemotherapy are also at an increased risk of developing hearing loss, also called ototoxicity. One study found that 75 percent of children under the age of five and 48 percent of children over the age of five who were treated with cisplatin had hearing loss related to their treatment (544). In September 2022, FDA approved sodium thiosulfate (Pedmark) to reduce the risk of hearing loss associated with the chemotherapeutic cisplatin in pediatric patients. Sodium thiosulfate reduced the risk of cisplatin-associated hearing loss by almost 60 percent compared to those who did not receive the drug (545). A recent analysis of clinical trial data found that sodium thiosulfate provided the greatest protection in the groups most vulnerable to hearing loss from cisplatin—children under five and those with hepatoblastoma, medulloblastoma, or neuroblastoma—reducing their risk by up to 80-90 percent (546). Additional research has also shown that the drug is safe and effective in everyday clinical use, further supporting its role in protecting young patients from the long-term effects of treatment (547).

TABLE 7

Selected Genetic Factors Associated with Treatment-Related Late Effects in Pediatric Cancer Survivors

Genetic Factor(s)	Potential Late Effect(s)	Treatment Exposure(s)
Cancer predisposition genes (*TP53, RB1, NF1,* and others)	Second primary cancers and related mortality	Radiation and chemotherapy
Certain DNA repair genes (*BRCA1, BRCA2, PALB2, FANCM, EXO1, ATM,* and others)	Second primary cancers	Radiation and chemotherapy
HTR2A	Subsequent basal cell carcinoma	Radiation
1q41, 11q23, and 1q32.3	Subsequent breast cancer	Chest irradiation
CELF4, RARG, and *ROBO2*	Cardiomyopathy	Anthracycline chemotherapy

Source: (501).

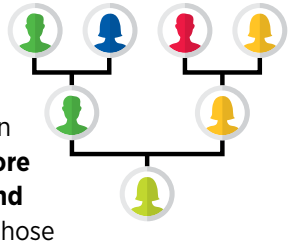
Genetic Susceptibility to Late Effects of Cancer Treatment

Although treatment exposures are the predominant drivers of late effects, researchers have found that not all survivors are equally affected. Over the past decade, rapid advances in molecular profiling have enabled researchers to identify genetic factors that influence survivors' risk of late effects (see **Table 7**, p. 117).

Large survivorship studies have shown that rare germline mutations—inherited changes in cancer predisposition genes that strongly increase cancer risk— such as TP53 and RB1, are more common among survivors than in the general population (475,501,548,549). A growing body of research indicates that these germline mutations not only drive the development of certain pediatric cancers but also appear to increase survivors' chances of developing SPCs later in life (see **Germline Variants in Cancer Predisposition Genes**, p. 34) (501). Importantly, carriers of these mutations face both a higher likelihood of SPC occurrence and increased SPC-related mortality.

Mutations in genes involved in DNA repair pathways (e.g., *BRCA1/2, FANCM,* and *EXO1*) can further magnify risks of SPCs, particularly when combined with treatment exposures (501,550,551). Mutations in DNA repair genes can impair the body's ability to correctly repair DNA damage caused by therapies such as radiation and/or chemotherapy, increasing the likelihood of developing SPCs. For example, female survivors with such mutations who also received chest radiation or cytotoxic chemotherapy had more than a four-fold higher risk of developing breast cancer in adulthood compared to women without these mutations

Childhood cancer survivors carrying germline mutations in cancer predisposition genes were **4 times more likely to develop second primary cancers** than those without such mutations.



Source: (548).

W30

(550). In addition to rare germline mutations, genome-wide association studies have also identified more common genetic variants or inherited differences in DNA sequence, predisposing pediatric survivors to SPCs, including radiation-induced breast cancer (1q41) and basal cell carcinoma (HTR2A) (552,553).

Inherited susceptibility also contributes to a broad spectrum of other late effects. For example, genetic variants in genes regulating cardiac muscle contraction and drug metabolism (e.g., *CELF4, GSTM1,* and *ROBO2*) have been associated with an increased risk of chemotherapy-induced cardiomyopathy (554-556). Additional genetic associations have been identified for neurocognitive dysfunction, gonadal impairment, stroke, diabetes, and obesity, underscoring the broad influence of genetic background on survivorship outcomes (501). Together, these findings highlight the importance of integrating genetic information with treatment history to more accurately identify survivors at highest risk for late effects and to inform precision survivorship care.

TABLE 8

Recommended Screening for Second Cancers in Childhood, Adolescent, and Young Adult Cancer Survivors

Cancer Type	Treatment Exposure	Screening Recommendation
BREAST	• Chest/axillary radiation • Total body irradiation	• Clinical breast examination yearly until age 25, then every 6 months. • Mammogram with adjunct breast MRI yearly beginning 8 years after radiation or age 25 (whichever occurs last).

COLORECTAL	• Abdominal, pelvic, or spinal radiation
	• Total body irradiation
		• Regular screening from the options below* beginning at age 30 years or 5 years after radiation (whichever occurs last):
		  • Colonoscopy every 5 years.
		  • Stool DNA test every 3 years.

SKIN (INCLUDING BASAL CELL CARCINOMA)	• Any prior radiation	• Monthly skin self-exam. • Full-body skin exam (by clinician) yearly.
THYROID	• Neck, head, or spinal radiation • Total body irradiation	• Thyroid exam yearly.
ACUTE MYELOID LEUKEMIA	• Anthracycline and alkylating agent chemotherapies, autologous hematopoietic stem cell transplant	• Full-body skin exam (by clinician) yearly up to 10 years after treatment/transplant.

* Based on informed decision-making between patient and provider.

Source: (521).

Care Coordination Across the Pediatric Cancer Survivorship Continuum

The multifaceted nature of pediatric cancer treatment necessitates comprehensive survivorship care that addresses the wide range of needs survivors face as they grow and age. These needs include support during the transition from pediatric to adult health services, coordination of routine and specialty appointments, monitoring for late effects, and assistance with psychosocial challenges. However, children and AYAs with cancer are often ill-equipped to navigate a complex health care system on their own, leaving critical survivorship needs unmet.

In recognition of these challenges, the Children's Oncology Group (COG) developed the Long-Term Follow-Up (LTFU) Guidelines to provide a standardized, evidence-based framework for survivorship care for children and AYAs (557). Organized by the organ system and therapeutic exposure, the guidelines provide detailed recommendations for clinical evaluations, screening intervals, diagnostic testing, and preventive health counseling. Importantly, the guidelines also include recommendations for the early detection of SPCs in survivors at elevated risk based on their prior treatments (see **Table 8**, p. 118). First released in 2003, the COG LTFU Guidelines have been regularly updated to reflect new evidence and evolving treatment practices, with the most recent version published in 2023 (558).

The COG LTFU Guidelines are designed with three primary aims: to provide evidence-based recommendations for the screening and management of treatment-related late effects; to increase awareness of potential complications among health care providers and survivors; and to standardize and improve the quality of survivorship care across clinical settings. By offering a structured, risk-based framework, the COG LTFU Guidelines enable clinicians to anticipate, identify, and manage a wide spectrum of late effects in a proactive manner (559). The guidelines also serve as a critical resource for educating survivors and their families, empowering them to engage in their care by improving awareness of risks and preventive strategies.

The most recent update reflects the evolving landscape of pediatric cancer care, introducing recommendations for genetic predisposition surveillance, monitoring after exposure to novel therapies, and updated vaccination practices (see **Sidebar 20**, p. 119) (558). Collectively, the COG LTFU

SIDEBAR 20

New Guidance for Long-Term Follow-Up Care for Pediatric Cancer Survivors

In 2023, the **Children's Oncology Group** released the latest version (v 6.0) of its Long-Term Follow-Up Guidelines, providing updated recommendations to guide survivorship care and promote long-term health for pediatric cancer survivors. Key additions include:

Genetic Risk Assessment

Genetic testing is now recommended for survivors with bilateral cancers (e.g., cancers in both of the same organ, such as lungs or kidneys), >1 primary cancer, adult-type cancers in children (e.g., breast, colon, or ovarian cancers), concerning family history (e.g., multiple relatives with early-onset or rare cancers), or relatives with known predisposition syndromes.

Late Effects from Novel Treatments

New sections provide surveillance guidance for survivors treated with novel agents such as **immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy,** including monitoring for late effects like endocrinopathies, cardiotoxicity, and neurotoxicity.

Vaccination and Revaccination

- Survivors **may lose protective immunity** to childhood vaccinations, increasing infection risk.
- Recommends a **3-dose human papillomavirus (HPV) vaccination** series for survivors.
- Supports **shared decision-making** between provider and patient on revaccination for other childhood vaccines when immunity has diminished.

Source: (558).

Guidelines have advanced both the science and practice of survivorship care and remain the most widely adopted framework for addressing the complex, lifelong health needs of childhood and AYA cancer survivors.

Although many survivorship resources exist, access to high-quality survivorship care remains a challenge for pediatric survivors. For example, a 2017 survey of COG institutions found that while nearly all centers (96 percent) offered pediatric survivorship care, fewer than three-quarters of eligible survivors utilized these services (560). Similarly, in a study of more than 900 childhood cancer survivors, over half had not attended a cancer-related follow-up visit within the past two years and did not plan to have one within the next two years (561). Adherence to guideline-recommended surveillance among pediatric cancer survivors is also poor. A recent study found that only about one-third of survivors received recommended screening for late effects, such as cardiomyopathy, thyroid dysfunction, or breast cancer (562).

As pediatric cancer survivors age, coordinated care is often complicated by care transitions, including the transition from oncology to long-term survivorship care, as well as the transition from pediatric to adult health care. Differences in the structure of pediatric versus adult-oriented health care can place survivors at risk for disengagement and loss to follow-up. Furthermore, many pediatric cancer centers do not have formal plans or systems in place to guide survivors as they transition from pediatric to adult care. A national survey of COG institutions found that while most programs eventually transfer survivors to another institution for adult cancer-related follow-up, few provide comprehensive resources to aid in successful health care transition (563,564). Barriers to transitioning from pediatric to adult survivorship care included a perceived lack of knowledge about late effects among clinicians and survivor reluctance to transfer care (563). Structural barriers, such as insufficient funding for survivorship program development and oncology workforce shortages, further limit the delivery of high-quality care (560,565). These challenges are compounded by adversities

related to social drivers of health, such as poverty, inadequate insurance coverage, and living long distances from survivorship clinics, all of which are associated with a lower likelihood of receiving recommended follow-up care (566).

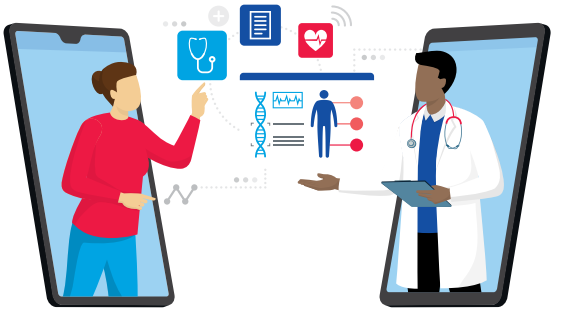
Recognition of the critical role that primary care providers (PCPs) play in survivorship is growing, because they are well-positioned to manage comorbidities, deliver preventive care, and support long-term health and well-being. However, research shows persistent challenges in fully integrating PCPs into survivorship care. In one survey, fewer than half of pediatric PCPs reported feeling comfortable independently providing health maintenance to pediatric cancer survivors (567). Evidence shows that PCPs frequently report limited knowledge of survivorship care and a need for additional training before they feel confident providing care to survivors (568).

However, PCPs report that their comfort level providing survivorship care increased substantially when care was provided in collaboration with pediatric oncologists. Comfort levels were highest when PCPs worked as a part of a multidisciplinary team, underscoring the value of shared care models—an approach in which oncologists and PCPs actively collaborate with oncologists to deliver comprehensive survivorship care (569). Beyond provider knowledge, systemic barriers such as inadequate reimbursement incentives, poor communication between oncology and primary care, and lack of accessible survivorship guidelines also hinder integration. Experts have suggested new strategies, such as training PCPs with added survivorship expertise, and testing payment incentives that reward coordinated, comprehensive care (568). However, these strategies remain underdeveloped and inconsistently applied.

Survivors themselves report similar concerns. In a large survey of adult survivors of childhood cancer, 87 percent reported having a PCP, yet only 33 percent had ever seen that provider for a cancer-related concern (561). Confidence in PCP cancer expertise was low, with only about one-third of survivors believing their provider could adequately manage cancer-related issues.

Survivorship care plans (SCPs) are one effective tool for improving care coordination among pediatric cancer survivors. SCPs typically include a summary of the patient's diagnosis and treatment, follow-up care recommendations, and guidance on managing long-term effects. SCPs serve as a critical bridge between pediatric oncology and primary care settings, promoting coordinated, continuous care as patients transition out of active treatment and into long-term survivorship care. Recent studies have shown that survivors who receive SCPs are more likely to adhere to recommended late effects screening (570). Unfortunately, SCPs are often underutilized by PCPs, who cite lack of clarity, insufficient training, and competing demands as barriers to their utility (571).

Passport for Care (PFC) is a free, web-based tool that transforms the COG Long-Term Follow-Up Guidelines into personalized survivorship care plans. Based on a survivor's treatment history, **PFC provides tailored screening recommendations and educational resources.** Used by more than 150 clinics and supporting over 60,000 care plans worldwide, **PFC helps ensure consistent, evidence-based follow-up care.**



Source: (572).

W31

The Passport for Care (PFC), a web-based clinical decision support tool developed in collaboration with COG, has demonstrated effectiveness in helping PCPs generate and deliver SCPs to pediatric cancer survivors (572). Launched in 2007, PFC integrates patient diagnosis and treatment histories with the latest COG LTFU Guidelines to create individualized SCPs. Beyond SCP generation, PFC also serves as a secure platform that enables both clinicians and survivors to access, update, and share health information to support care coordination.

In a survey of clinicians, PFC was most commonly used to create individualized SCPs and guide surveillance, with nearly 70 percent of clinicians reporting that PFC substantially improved adherence to the COG LTFU guidelines (573). As of May 2022, 54 percent of COG-affiliated survivorship clinics providing late effects services to childhood cancer survivors were enrolled in the PFC program. Ongoing efforts to expand PFC adoption focus on reducing implementation barriers by streamlining data entry through integration with electronic health records and by enhancing educational content delivery through technological innovations, including the development of a mobile health application to strengthen survivor engagement.

In addition to SCPs, patient-reported outcomes (PROs) offer another valuable tool for enhancing coordination and

ensuring that the survivor's perspective remains central to care. PROs are reports provided directly by patients about their health status without interpretation by clinicians or caregivers (574,575). PROs provide critical insights into patient symptoms, functional status, and quality of life, enabling a more comprehensive understanding of treatment tolerability and overall well-being.

In pediatric oncology, PROs are typically collected through age-appropriate questionnaires or electronic platforms that ask children and adolescents about their symptoms, daily functioning, and psychosocial well-being during and after treatment (576). Increasingly, PROs are administered electronically, offering advantages such as real-time data capture, integration with clinical records, and automated alerts to care teams (575,577). Such tools allow clinicians to track changes in symptoms over time, enabling them to tailor care to the child's evolving needs. Research demonstrates that many children can reliably self-report their experiences beginning around age eight (578,579). When self-report is not feasible, such as in case of very young children or those too ill to complete questionnaires, parents or other caregivers may provide proxy reports to complement or substitute for the child's perspective (576,580).

A growing body of research highlights the value of incorporating PROs into pediatric oncology care. Two large-scale randomized controlled trials in pediatric cancer patients demonstrated that electronic PRO monitoring improved recognition and management of symptoms (581,582). PROs are also increasingly being used in pediatric palliative and supportive care, where they empower children to share their experiences directly with providers. Families and clinicians report that PROs strengthen communication and foster a greater sense of partnership in care (583,584). Use of PROs are particularly valuable in sensitive contexts such as end-of-life care, where monitoring and responding to the child's symptoms and quality of life are especially critical.

Despite clear benefits, PROs remain underutilized in pediatric oncology research and practice . An analysis of FDA approvals for pediatric oncology products between 1997 and 2020 found PRO data in only 4 of 17 submissions (24 percent) (585). Similarly, another study reported that fewer than half (44 percent) of registered clinical trials evaluating supportive care interventions for children with cancer incorporated PROs, underscoring their limited use across both drug development and supportive-care research (586).

Barriers contributing to underuse of PROs in pediatric oncology include limited clinician training, technological constraints, and disparities in digital access and literacy across families (576,587). Addressing these gaps will require investment in infrastructure, clinician training, and ongoing validation of PRO tools for diverse populations. Incorporating PROs into standard pediatric oncology care represents a meaningful step toward more patient- and family-centered cancer care. As the evidence continues to grow, prioritizing PRO integration will help ensure that the voices of pediatric patients remain central to guiding treatment decisions and improving care.

Beyond PROs, digital health interventions—including virtual reality, mobile applications, computer programs, video games, and other interactive platforms—have emerged as effective tools by supporting symptom management, promoting health education, and expanding access to resources and services. A recent analysis showed that these tools eased pain, nausea, anxiety, distress, and fear, while also improving quality of life for pediatric cancer survivors (588).

Models of care coordination offer promising approaches to further improve care continuity for pediatric cancer survivors. Researchers emphasize that effective models incorporate multidisciplinary collaboration, patient navigators, and family-centered services tailored to survivor needs (589). Programs that integrate psychosocial support, health education, PROs, and financial assistance within long-term follow-up frameworks may improve the quality and continuity of care for pediatric cancer survivors.

Supporting Parents and Other Caregivers

A diagnosis of pediatric cancer profoundly affects the parents and caregivers who take on the primary responsibility for the child's medical and psychosocial care throughout treatment and survivorship. These responsibilities include managing medications, attending medical visits, providing emotional support, and navigating complex health care systems. As a result, parents and caregivers often experience heightened psychological strain and disruptions to their overall well-being.

Research shows that parents of children with cancer are more likely to experience anxiety, depression, and posttraumatic stress than the general parent population, with prevalence estimates of 21 percent, 28 percent, and 26 percent, respectively (590). Parents are also more likely to utilize mental health services for anxiety and depression following their child's diagnosis than parents of children without cancer (591).

Unmanaged caregiver distress has consequences that extend beyond the individual. High levels of distress not only affect the well-being of caregivers, including parents, but are also linked to poorer outcomes for children. Studies indicate that caregiver distress is closely tied to children's health-related quality of life, with higher caregiver distress predicting poorer physical and psychosocial outcomes in pediatric patients (592).

Beyond the psychological toll, caring for a child with cancer places immense strain on parents' economic and professional lives. Following a pediatric cancer diagnosis, many parents face job loss, reduced work hours, or other disruptions to employment, often leading to long-term financial insecurity (593). Studies reveal that approximately 60 percent of parents and/or caregivers experience financial hardships following a pediatric cancer diagnosis (594,595). Material hardships, such as food, housing, and energy insecurity (i.e., the inability to adequately meet basic household energy needs) are common and disproportionately affect families from disadvantaged backgrounds (595). In response, parents often adopt coping strategies such as incurring debt or reducing spending, while barriers to assistance programs leave vulnerable groups at heightened risk for financial hardship (596). Together, these findings highlight the interconnected psychological and financial pressures facing parents and caregivers of children with cancer, reinforcing the need for comprehensive psychosocial and economic support throughout the cancer care continuum.

In recognition of these challenges, the pediatric oncology field has advanced efforts to define and improve psychosocial services for pediatric cancer patients and their families and caregivers. In 2015, an interdisciplinary group of clinicians, researchers, and parent advocates established *Psychosocial Care for Children with Cancer and Their Families,* which outlined 15 evidence-based Standards to ensure consistent, high-quality psychosocial care (597). *These Standards* address a wide range of psychosocial needs, including assessment of distress, parental mental health, school reintegration, adherence to treatment, and bereavement support. The overarching goal was to provide a framework to ensure that all families, regardless of treatment setting, receive high-quality psychosocial services alongside medical care (597).

Despite the endorsement of these *Standards* by numerous professional organizations, implementation into routine clinical practice has been slow. A 2016 survey of pediatric oncology programs found that while most programs offered some psychosocial services, many lacked the full range of specialized providers needed to deliver comprehensive care (598). While more than 90 percent of pediatric oncology programs employed social workers and child life specialists (i.e., professionals who help children and families cope with the stress of cancer and treatment), fewer had psychologists (60 percent), neuropsychologists (31 percent), or psychiatrists (19 percent). Psychosocial care was also frequently provided reactively after problems were identified rather than systematically across all patients (598). Notably, only about half of pediatric oncologists described the care at their centers as comprehensive and state-of-the-art (599).

A follow-up assessment in 2023 showed modest improvements. Nearly all programs reported access to social workers (97.2 percent) and child life specialists (92.5 percent), but psychologists (69.2 percent), neuropsychologists (39.3 percent), and psychiatrists (15.0 percent) were still far less common (600). The median staffing ratios remained concerning, with one full-time equivalent (FTE) psychologist per 100 patients and one FTE psychiatrist per 200 patients. Although progress has been made, many centers continue to lack the breadth and depth of staffing necessary to fully implement the *Standards*. Persistent barriers include limited funding, inadequate institutional resources, and workforce shortages.

To support wider adoption, implementation tools have been developed to help programs evaluate and strengthen their psychosocial services. These resources include structured frameworks for assessing a program's level of implementation, rating quality of care, and identifying specific action steps and resources for improvement (601). Together, these initiatives reflect ongoing progress in aligning psychosocial services with the published *Standards*. Continued investment in staffing, resources, and implementation strategies are essential to ensure that all children with cancer, along with their families and caregivers, receive the comprehensive psychosocial support needed to promote resilience, enhance quality of life, and improve long-term outcomes.

UNDERSTANDING THE GLOBAL LANDSCAPE OF PEDIATRIC CANCERS

IN THIS SECTION, YOU WILL LEARN:

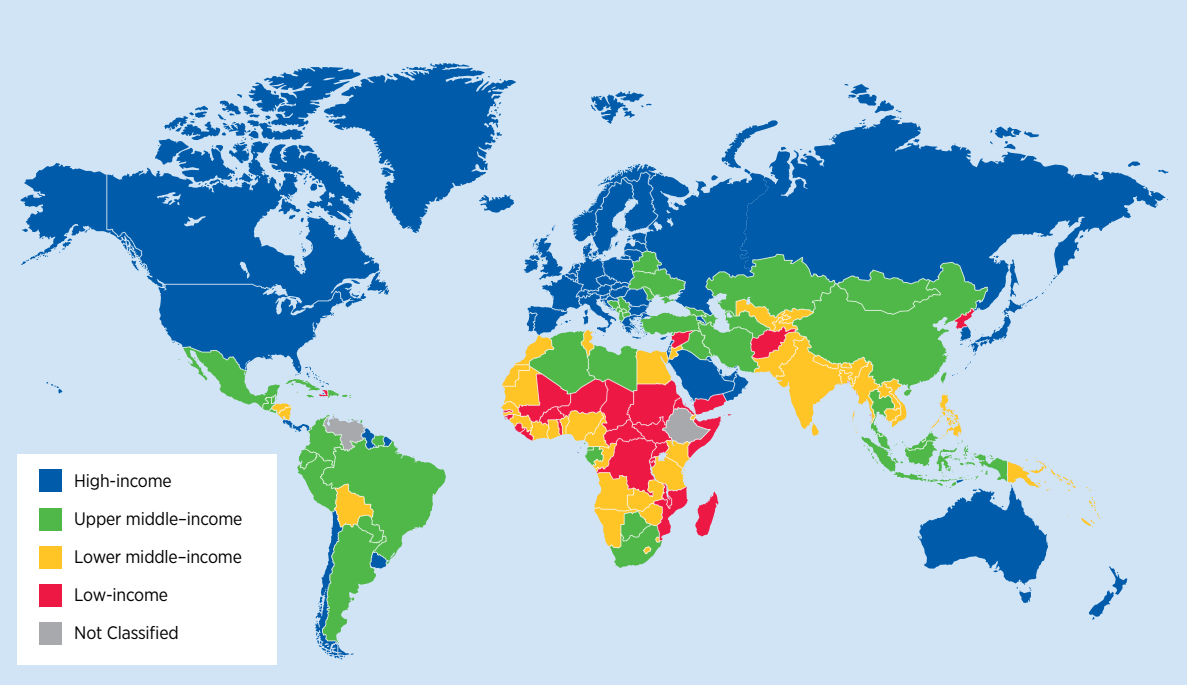
- Childhood cancer is a major global health challenge affecting hundreds of thousands of children annually. Global projections put the incidence of childhood cancers at close to 400,000 a year, with most cases and deaths occurring in low-income countries (LICs), lower middle-income countries (LMICs), and upper middle-income countries (UMICs), where survival remains far below that of high-income countries (HICs).
- Major inequities in access to timely and accurate diagnoses, essential medicines, treatments, supportive care, and trained health care providers across regions around the world result in children dying not because their disease is untreatable but because they do not have access to optimal clinical care.
- Precision medicine, molecular profiling, and multinational clinical trial platforms are expanding access to novel targeted therapies, though their benefits are concentrated in high-resource settings. International and regional collaborations between HICs and countries that are not high income are helping to strengthen health systems, improve trial participation, generate high-quality data, and broaden access to care.
- Sustainable progress against pediatric cancer depends on implementing solutions that are adapted to regional resources, strengthening local data systems and trial infrastructure, and ensuring that breakthroughs in treatment and supportive care reach every child worldwide.
- Pediatric cancer survivorship research remains disproportionately concentrated in HICs. Expanding research capacity in LICs, LMICs, and UMICs is essential to ensure that survivorship programs and care models reflect the realities and needs of children and families across diverse cultural and economic contexts.
- Addressing global workforce shortages through education, mentorship, and regional partnerships is key to ensuring that every child with cancer has access to skilled care providers, timely treatment, and quality survivorship care

Pediatric cancer is a significant global health challenge, extending far beyond the United States (US) and other high-income countries (HICs), which together account for only an estimated 10 percent to 20 percent of the total pediatric cancer burden (66,602). In contrast, between 80 percent and 90 percent of pediatric cancers occur in low-income and middle-income countries (see **Figure 13**, p. 124) (602,603).

The absence of standardized, population-based cancer registries in many low-income and lower middle-income countries (LIC and LMIC, respectively) makes it difficult to capture the true burden of disease. A simulation study estimating the global burden of pediatric cancers in 2015 projected nearly 400,000 incident cancers in children 0 to 14 years, compared with only 224,000 cases diagnosed, a more

FIGURE 13

World Bank Classification of Countries



The 189 member countries of the World Bank, along with 28 territories that have a population greater than 30,000, are classified by income level and geographic region for cross-country comparisons and monitoring of countries' development progress. In cancer research, the World Bank classification of countries is used to group nations based on these income levels. This framework helps researchers identify geographic areas that may benefit most from tailored interventions, while also considering differences in health care infrastructure, resource availability, and access to treatment.

Based on a country's gross national income per capita in US dollars, the World Bank classifies a country's economy into four income groupings: Low-income countries (LICs; ≤$1,135); Lower middle-income countries (LMICs; $1,136-$4,495); Upper middle-income countries (UMICs; $4,496-$13,935); High-income countries (HICs; >$13,935).

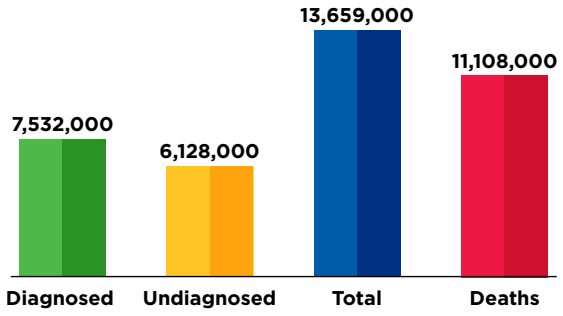
Source: (609).

than 40 percent difference (602). Although these estimates of actual cases diagnosed align with those from the International Agency for Research on Cancer (IARC), an agency within the World Health Organization (WHO), and the Institute for Health Metrics and Evaluation (IHME) for similar time periods, health system barriers to access, referrals, and data collection contribute substantially to underdiagnosis (604,605).

In addition, discrepancies in global cancer estimates from IARC and IHME arise from methodological differences, including the number of registries included (375 vs. 562, with 7 percent vs. 12 percent representing LICs and LMICs coverage, respectively) and the number of countries and territories analyzed (184 vs. 195, respectively) (605,606). Together, these challenges underscore the urgent need to strengthen global cancer surveillance, improve diagnostic capacity, and ensure that all children and adolescents, regardless of where they live, are counted and have access to timely, effective care.

In 2025, IARC estimated more than 280,000 new pediatric cancer cases and nearly 108,000 deaths worldwide (606). However, as outlined above (i.e., differences in data collection methods, the number of registries included, underdiagnosis), these figures must be interpreted with caution, as they are likely underestimated by more than 40 percent and at least 5 percent, respectively (602,605). Adjusting for these discrepancies suggests the true burden of pediatric cancers in 2025 may be closer to 470,000 new cases and 113,000 deaths. Despite the

Projected Global Burden of Pediatric Cancer: 2020–2050



Source: (66).

W32

Overall, it is estimated that more than **70 percent** of all pediatric cancer cases worldwide are concentrated in **Asia** and **Africa.**

Source: (608).

W33

challenges in data collection and reporting, current estimates still provide important insight into the expected global burden of pediatric cancers.

Beyond the total burden, the types of cancers affecting children and adolescents worldwide mirror those seen in the United States. Globally, the most frequently diagnosed pediatric cancers are leukemias, central nervous system (CNS) tumors, and lymphomas (607).

Global pediatric cancer patterns reveal substantial disparities in incidence and outcomes, largely influenced by differences in demographics, health care infrastructure, socioeconomic development, and timely access to diagnosis, treatment, and supportive care. For example, although treatment advances in the United States and other HICs have dramatically improved survival, these gains have not been realized uniformly around the globe. Although 5-year survival rates for pediatric cancers approach 80 percent in HICs, survival rates for these cancers in LICs and LMICs remain below 30 percent (610).

Several system-level factors contribute to these disparities. In many low-resource settings, the availability of WHO's essential medicines for childhood cancer as well as supportive care is limited (see **Access to Clinical Care: Disparities and Solutions**, p. 138). A global survey of LICs and LMICs revealed that 60 percent of pediatric cancer patients had limited or no access to standard-of-care drugs needed to treat their disease (611). In addition, insufficient pediatric oncology infrastructure and workforce capacity often result in underdiagnosis, misdiagnosis, and delays in care. Retinoblastoma (RB)—a rare but aggressive eye tumor—offers a clear example of this disparity, whereby 30 percent to 40 percent of cases in developing countries are diagnosed at an advanced stage, compared to only 2 percent to 5 percent in developed countries(612). The lack of diagnostic infrastructure and trained personnel in LICs and LMICs leads to delayed diagnosis, resulting in more advanced disease at presentation and, consequently, markedly lower survival. As a result, survival rates for RB reach up to 98 percent in HICs but fall to just 57 percent in LICs (613).

The economic burden on families is also profound. Bangladesh illustrates a challenge common to many LICs and LMICs. An estimated 9,000 pediatric cancer cases occur annually in Bangladesh; however, only about 5 percent of children receive care in a hospital setting (617). This gap is driven by limited infrastructure—only two cancer centers serve the entire country—as well as by the overwhelming out-of-pocket costs faced by families. In many LMICs, families spend more than their total monthly income on cancer treatment, often without financial assistance (e.g., subsidized health insurance) (614,617). Even when treatment costs are subsidized, the additional expense of traveling long distances to access care results in another unaffordable burden on families (618). These financial pressures not only limit access and delay the start of treatment but also increase the likelihood of treatment abandonment (see **Access to Clinical Care: Disparities and Solutions**, p. 138) (619).

Treatment refusal and suboptimal quality of care further exacerbate disparities. For example, RB in LMICs is usually treated by enucleation—a surgical procedure that involves the removal of the eye from the socket (620). However, the

INVESTMENTS IN CHILDHOOD CANCER
TO INCREASE ACCESS TO AND QUALITY OF CARE COULD
AVERT 6.2 MILLION DEATHS
IN CHILDREN WITH CANCER
AND GENERATE LIFETIME GAINS IN GLOBAL PRODUCTIVITY
OF NEARLY $2 BILLION BETWEEN 2020 AND 2050.

Source: (66).

W35

Cancer Care in Nigeria Compared to the United States

	NIGERIA:	UNITED STATES:
Median duration from onset of symptoms to diagnosis	4 months	4 months
Diagnosis to remission or death cost	$13,876	$300,000
Average monthly family earnings	$316	$7,350

Sources: (59,614-616).

W34

treatment is often refused due to lack of support for the visually impaired after the procedure, cultural beliefs in alternative treatments, and social stigma (621-624).

Together, these factors highlight critical inequities in global health, wherein a child's chance of surviving cancer is shaped less by biology, and more by geography, family income, and access to basic medicines.

Global Epidemiology of Pediatric Cancers

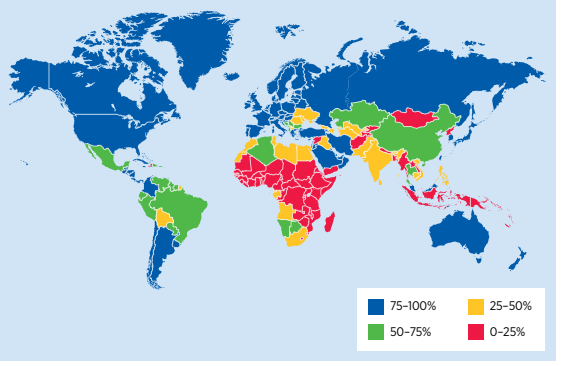
Epidemiologic studies provide important insights into the incidence, outcomes, and burden distribution of pediatric cancers across different regions of the globe.

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and represents a major public health burden worldwide (626). From 1990 to 2021, the incidence of pediatric ALL increased globally by nearly 60 percent, reaching 168,879 cases in 2021 (627). Over the same period, however, deaths from ALL and the associated disability-adjusted life years (DALYs)—a measure of overall disease burden that combines years of life lost due to premature death and years lived with disability—declined by approximately two-thirds, reflecting significant progress in treatment and early detection (627).

However, these improvements were concentrated in regions with a high and high-middle sociodemographic index (SDI)—a composite measure of income per capita, average years of education, and total fertility rate for citizens younger than 25—where access to health care infrastructure and diagnostic capacity have advanced markedly (627). In contrast, low SDI regions continue to face substantial barriers, with increasing ALL death rates and DALYs between 1990 and 2021 (627). High SDI regions, such as East Asia, achieved the greatest reductions in mortality and DALYs, while low SDI regions, including sub-Saharan Africa and the Caribbean, continue to experience disproportionately high burdens of pediatric ALL. These disparities highlight the urgent need to strengthen health care infrastructure and improve resource allocation to support earlier detection and effective treatment and survivorship care of ALL in lower SDI regions (627).

The WHO Cure*All* framework aims to achieve at least 60% survival for pediatric cancer globally by 2030.

High-income countries report survival rates of **80% or higher,** whereas low-income and lower middle–income countries report substantially lower rates, ranging from **below 10% to 30%.**



Sources: (610,625).

W36

Many pediatric cancers remain asymptomatic in their early stages and can mimic common conditions such as malaria or tuberculosis, leading to delayed and often inaccurate diagnoses (610,629,630). These delays stem from both patient- and health care provider–related factors. Cultural beliefs and stigma compound these challenges. For families, limited awareness of pediatric cancer, low health literacy, and reliance on traditional healers often postpone medical evaluation (629,631,632). For example, a study in Rwanda reported some pediatric patients were treated by traditional healers for up to 8 months before ultimately being diagnosed

THE GLOBAL INCIDENCE OF THYROID CANCER IN CHILDREN (AGES 0 TO 14) AND ADOLESCENTS (AGES 15 TO 19) **INCREASED 1.17%** EVERY YEAR BETWEEN 1990 AND 2021.

Source: (628). W37

with leukemia in a health center (633). In some cultures, there is no word for pediatric cancer, and families may avoid medical care due to fear, social stigma, or preference for alternative treatments (617,623,634-636).

Health care providers frequently misdiagnose pediatric cancers due to limited training and minimal exposure to pediatric cancer cases (637). A study of 123 newly diagnosed Kenyan children with cancer noted that nearly 70 percent of participants were initially misdiagnosed and treated for malaria, infection, pain, or anemia (631). When cancer is suspected, referral to specialized oncology centers is often difficult due to their scarcity and the long travel required, which many families with limited resources cannot manage (634).

Delays in diagnosis and referral to equipped health care facilities are particularly consequential for certain cancers. One pediatric cancer for which delayed diagnosis can have particularly severe consequences is RB, which is often first detected by the appearance of visible signs such as leukocoria (a white or gray reflection from the pupil of the eye) or strabismus (misaligned eyes that point in different directions).

A global cohort of 4,351 RB patients from 153 countries found nearly 85 percent of RB cases diagnosed in 2017 were from LICs and LMICs. The most common presenting sign was leukocoria (62.8 percent), followed by strabismus (10.2 percent) and proptosis (bulging of the eye; 7.4 percent). In patients living in HICs, RB was diagnosed earlier, with disease overwhelmingly confined to the eye and with very few cases of metastasis (638). By contrast, patients in LICs and LMICs presented later and had higher rates of metastasis and extraocular disease, which is disease that affects the muscles and tissues around the eye (638).

Pediatric CNS tumors represent a significant global health concern, accounting for more than 20 percent of all pediatric cancers and serving as a leading cause of cancer-related mortality among children and adolescents (639). Over the past two decades, both incidence and mortality rates have been declining in HICs, and this decline is attributable to advances in early diagnosis and treatment for low-grade disease (640). Conversely, persistent challenges experienced in LICs and LMICs result in higher mortality and lower 5-year survival rates (641).

TABLE 9

Estimated Childhood Cancer (0–14 years) 5-year Net Survival for All Cancers Combined (2015–2019)

Region	5-year Net Survival (%)
Global	**37.4**
World Bank Income Group	
Low-income countries	7.4
Lower middle-income countries	24.0
Upper middle-income countries	55.5
High-income countries	79.8

Source: (625).

Low-grade gliomas (LGG), which are often slow growing and under diagnosed because of their anatomic location and non-specific symptoms, account for 30 to 40 percent of pediatric CNS tumors, globally (642,643). Differences in data reporting, healthcare infrastructure, and access to high-quality, targeted treatment interventions affect the accuracy of the true burden of this disease, particularly in low-resource settings (644).

A recent study, analyzing data between 2008 and 2018 across 15 pediatric oncology units in 6 African countries, illustrates this (645). More than half of pediatric patients with LGG did not undergo surgery, nearly 77 percent did not receive radiation, over 45 percent did not undergo chemotherapy, and only 3 percent had access to molecularly targeted therapy. Patients who received complete or partial resection, radiation therapy, chemotherapy, or targeted therapy were mainly from pediatric oncology units in upper middle-income countries (UMICs). Despite these gaps, the overall 5-year survival rate for LGG across the study cohort exceeded 90 percent, reflecting the potential for cure when effective treatment is available. However, this figure largely represents outcomes from higher-resource centers, and must be interpreted with caution, as long-term follow-up was limited in LICs. Specifically, 5-year survival reached 100% in Tunisia, an LIC with comparatively greater resources but limited follow-up, and was nearly 90 percent in South Africa (UMIC), compared with just 67 percent in Uganda, a limited-resource LIC (645). These findings illustrate that while LGG can be highly curable, even in LICs, survival depends heavily on access to surgery and adjuvant therapies, which remain unevenly

Pediatric cancer burden in areas with armed conflict:

In 2019, an estimated **46%** of new pediatric cancer cases and 58% of pediatric cancer deaths worldwide **occurred in countries with armed conflict**.

Source: (646).

W38

Multisectoral collaboration has advanced the implementation of the Cure*All* pillars across Africa, the Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific Regions—supported by the GICC's enablers of advocacy, financing, and governance—and led to greater prioritization of childhood cancer, resulting in:

- **Increasing prioritization of childhood cancers in national policies,** with inclusion in 20 cancer control policies in 2022.
- **Incorporating childhood cancers into universal health coverage packages** through new legislation in countries such as El Salvador, Ghana, Mongolia, the Philippines, and Zimbabwe.

Source: (648).

W39

distributed across Africa (see **Access to Clinical Care: Disparities and Solutions**, p. 138).

In addition, variations in SDI and political unrest—areas with armed conflict, tht is, use of force that results in at least 25 battle-related deaths per year in a specific country—contribute to the pronounced regional differences observed in pediatric cancer incidence, mortality, and survival. Together, these factors reveal that pediatric cancer is not only a medical challenge but also a reflection of broader social, economic, and political inequities that demand global attention.

The global burden of pediatric cancer highlights a profound inequity, where survival is determined less by biology than by geography and resources (see **Table 9**, p. 127). Addressing these disparities requires urgent investment in pediatric oncology services, workforce training, and health system infrastructure, particularly in LICs and LMICs, if the WHO's Cure*All* goal of at least 60 percent survival by 2030 is to be achieved.

Global Policies and Partnerships to Improve Care

Improving childhood cancer outcomes worldwide, particularly in LICs and LMICs where survival gaps are the greatest, relies on the global pediatric cancer research community (see **Sidebar 21**, p. 129) to join forces in expanding access, promoting equity, and strengthening health care systems to improve care. In 2018, WHO, in partnership with St. Jude Children's Research Hospital (St. Jude), the International Society of Paediatric Oncology (SIOP), the patient advocacy and support organization Childhood Cancer International, and other global organizations, launched the Global Initiative for Childhood Cancer (GICC), with the goal of achieving at least 60 percent survival for children with cancer in all countries by 2030. The GICC works with governments to incorporate childhood cancer into broader cancer control and universal health coverage plans and to accelerate long-term policy and funding commitments. Since its launch, the initiative has engaged with over 80 countries, working to develop or strengthen national childhood cancer care strategies. Early efforts have focused on strengthening care systems for six cancers that together account for 50 percent to 60 percent of childhood cancers—ALL, Burkitt lymphoma, Wilms tumor, non-Hodgkin lymphoma, low-grade glioma, and RB (647).

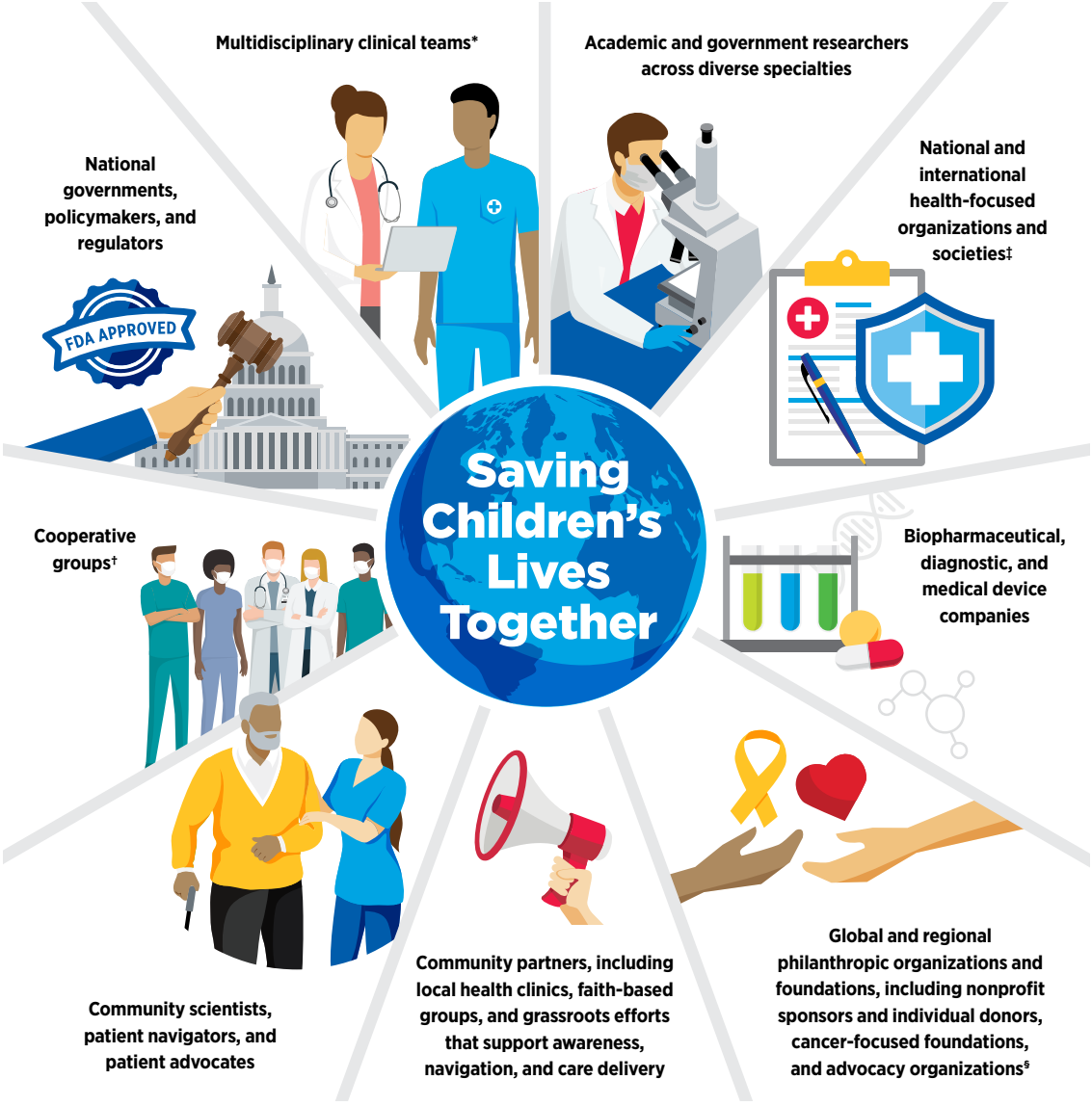
Cure*All* is the operational framework of the GICC that provides a structured approach to strengthening health care systems (610). Its four pillars—centers of excellence, universal health coverage, standardized treatment regimens, and evaluation and monitoring—are supported by three enablers—advocacy, financing, and governance. Together, they guide countries in adapting evidence-based strategies to local contexts, ensuring that improvements in childhood cancer care are systematic, sustainable, and scalable.

In Latin America and the Caribbean, the Pan American Health Organization (PAHO), in collaboration with St. Jude and regional partners, has advanced the GICC using the Cure*All* framework. In 2021, regional working groups involving over 200 experts from 21 countries produced 14 regional resources, including technical guidelines, virtual training courses, parent/caregiver educational series, and awareness campaigns developed to address early detection, nursing, psychosocial support, nutrition, supportive care, treatment abandonment, and palliative care at the local level (649). As of 2023, these resources had already been widely disseminated and utilized across regions. For example, over 77,000 and nearly 9,000 participants enrolled in early diagnostic and palliative care courses, respectively, and

SIDEBAR 21

Stronger Together: The Global Pediatric Cancer Research Community

Coordinated efforts across diverse stakeholders, institutions, and countries are necessary to generate knowledge, improve care, reduce global survival disparities, and address the unique challenges faced by children and adolescents with cancer. Further increasing collaborations will amplify future breakthroughs. The key stakeholders in global pediatric cancer medical research include: children and adolescents with cancer, their caregivers, families, and friends.



* Multidisciplinary clinical teams: May include pediatric oncologists, surgeons, radiation oncologists, nurses, primary care providers, social workers, psychologists, nutritionists, and palliative care specialists.

† Cooperative groups: Formal research collaborations that bring together institutions to conduct clinical trials and research (e.g., Children's Oncology Group [COG] and regional consortia).

‡ Health-focused organizations: National and international bodies that provide leadership, data, and guidance for cancer control worldwide, such as St. Jude Global, World Health Organization (WHO), International Agency for Research on Cancer (IARC), and the International Society of Paediatric Oncology (SIOP).

§ Global and regional philanthropic organizations and foundations: Entities that raise funds, provide support services, and advocate for children with cancer at local, national, and international levels, such as Childhood Cancer International (CCI), Alex's Lemonade Stand Foundation, and other nonprofit and advocacy organizations.

technical documents, regional snapshots, and caregiver modules had more than 10,000 downloads. In addition, videos produced for an awareness campaign on childhood cancer symptoms and signs to improve early detection were viewed more than 11,000 times during the first month after its launch. This collaboration demonstrates the power of combining the Cure*All* framework with international and regional expertise, laying the groundwork for governments to integrate addressing childhood cancers into broader health agendas and to strengthen care across resource levels.

Global implementation networks, such as the St. Jude Global Alliance (St. Jude Global), also play an important role in addressing the needs of children with cancer. For example, St. Jude Global unites institutions and health care providers in more than 90 countries to create a network that focuses on improving access to quality pediatric cancer care and outcomes through strengthening workforce training and development of educational and clinical research infrastructures. For example, Targeting Childhood Cancer through the Global Initiative for Cancer Registry Development (ChildGICR) is a collaboration, established in 2020, between St. Jude Global and the International Agency for Research on Cancer. Through its educational programs, ChildGICR aims to address the unique challenges of childhood cancer by strengthening global cancer registration and improving high-quality population-data collection on cancer incidence and survival.

One such program was the ChildGICR Masterclass to improve capacity for population-based cancer registries on childhood cancer. This 12-week online program trained participants from 18 countries to create standard teaching materials for pediatric cancer registration, which have since been implemented in follow-up courses across 16 countries (650). The ChildGICR Masterclass can serve as a model for designing, planning, and implementing educational programs for health care professionals supporting better data collection for childhood cancer worldwide.

SIOP brings together more than 3,500 members from 130 countries, including oncologists, nurses, researchers, and patient advocates (651). Through regional branches in Africa, Asia, Latin America, and Europe, SIOP works to build pediatric oncology capacity by training health care providers, supporting regionally adapted treatment protocols, and advocating for pediatric oncology to be prioritized within national health plans. Its emphasis on creating sustainable, locally driven solutions ensures that progress is not dependent solely on external aid.

Developed through a partnership among St. Jude Global, SIOP, the International Society of Paediatric Surgical Oncology, the Paediatric Radiation Oncology Society, and other global organizations, the Adapted Resource and Implementation Application (ARIA) Guide provides consensus-driven, evidence-based treatment recommendations that can be adapted to local resource levels By offering context-specific guidance, ARIA empowers clinicians to deliver effective care despite systemic constraints (see **Sidebar 22**, p. 130).

These partnerships exemplify what can be achieved when governments, health organizations, and regional groups work together, creating sustainable frameworks that strengthen health systems, expand access, and ultimately improve childhood cancer care. However, significant challenges remain, and continued commitment will be essential to ensure that every child, everywhere, has access to timely diagnosis and effective treatment.

SIDEBAR 22

ARIA Guide: A Global Compass for Childhood and Adolescent Cancer Care

The Adapted Resource and Implementation Application (ARIA) Guide is a free, web- and mobile-based clinical decision tool designed to provide resource-stratified treatment and management guidance for childhood and adolescent cancers.

- Developed through a collaboration between St. Jude Global, the International Society of Paediatric Oncology, and partner organizations, the ARIA Guide offers evidence-based, consensus-driven recommendations that can be adapted to diverse health care settings.
- The development process has engaged more than 600 health care professionals from 90 countries to ensure relevance across a range of resource environments.
- Accessible both online and offline, the ARIA Guide is particularly valuable in low-resource settings, where reliable Internet access may be limited.

By providing practical, adaptable protocols, ARIA supports the goals of the World Health Organization's Global Initiative for Childhood Cancer to improve 5-year survival to at least 60 percent for all children with cancer worldwide by 2030, while enhancing the capacity of health systems to deliver timely and effective pediatric oncology care.

Source: (652).

Global State of Pediatric Cancer Clinical Trials

Nearly 90 percent of pediatric cancers occur in LICs, LMICs, and UMICs—yet only 28 percent of pediatric cancer clinical trials are conducted in these regions (653). Although advances in molecular profiling and adaptive clinical trial designs are reshaping childhood and adolescent cancer care, the benefits of these cutting-edge approaches have been felt primarily in HICs. Just 8.7 percent of pediatric clinical trials between 2010 and 2020 were international, and only 5.4 percent were intercontinental (654).

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have increasingly collaborated to align pediatric drug development requirements. These efforts aim to reduce duplication of studies, shorten drug development timelines, and provide consistency in evaluating safety and efficacy of treatments. For example, greater coordination of pediatric study plans has made it more feasible for sponsors to design global trials that include sites across both high- and low-resource regions, expanding access for patients while generating more robust data.

Clinical trials vary widely in their timing of data collection, study approach, design structure, and geographic scope—factors that influence where and how they are conducted (see **Sidebar 23**, p. 132). A major milestone in streamlining regulations across regions came in December 2024 with the finalization of the International Council for Harmonization (ICH) E11A Pediatric Extrapolation Guideline (655). This guidance builds on earlier frameworks by encouraging the use of existing data, whether from adult or pediatric populations, to inform study design for childhood cancers. By carefully applying lessons learned from one setting to another, regulators can reduce the need for unnecessary trials, focus research efforts where evidence gaps are greatest, and bring promising therapies to children with cancer quicker.

Molecular Profiling Driving Precision Medicine

Precision medicine programs aim to match a child or adolescent with cancer to the most effective therapy based on their cancer's unique molecular features. By pairing molecular profiling with targeted treatments, precision medicine is reshaping pediatric cancer care across the globe, particularly in high-resource settings.

An observational study in the United Kingdom (UK) evaluated whether routine whole-genome sequencing (WGS) (see **Sidebar 5**, p. 33) for all children with suspected cancer, not just for high-risk patients, could provide clinical benefit beyond standard of care molecular testing. The study found that across two childhood cancer centers, WGS reproduced all standard tests, modified treatment decisions in 7 percent of cases, and delivered additional diagnostic, risk, therapeutic, or germline genomic findings in 29 percent of cases (268).

As our knowledge of how tumors evolve over the course of disease deepens, it is becoming clear that profiling a patient's tumor repeatedly over time is as important as the initial profile. The Stratified Medicine Paediatrics program, the UK's national precision medicine program for children and adolescents, offers clinical-grade sequencing to patients at the time of relapse or for treatment-refractory disease. In a retrospective study, tumor profiles at the time of diagnosis and at relapse were compared to understand how pediatric cancers evolve under therapy. The study found mutations that were only present at relapse, discovered patterns of relapse-associated mutations that were tumor type specific, and identified those common across cancer types. In addition, analysis of cell-free DNA (cfDNA), collected from liquid biopsy in patients with solid tumors that have returned after treatment or continued to worsen despite therapy, demonstrated that this approach not only assesses genetic heterogeneity better than a single tissue biopsy in certain patients, but can also identify genomic and epigenomic drivers of pediatric cancer relapse and therapy resistance (see **Liquid Biopsy**, p. 43) (419).

In the Netherlands, the individual Therapies (iTHER) program demonstrated the feasibility of using molecular profiling across the pediatric patient age groups and tumor types to inform diagnostic, prognostic, and targetable genetic alterations—including both somatic and germline cancer predisposing variants (see **Genetic Alterations**, p. 31). In a prospective observational study, molecular profiling of tumors identified somatic alterations in 90 percent of patients, 82 percent of which were targetable, and germline cancer predisposing variants in 10 percent of patients. In addition, these findings helped refine diagnoses of 3.5 percent of patients and led to 13.9 percent of patients receiving molecularly matched treatments. This study demonstrates the feasibility of comprehensive molecular profiling in pediatric cancers, and as a result has made whole-exome sequencing (WES) and RNA sequencing, as well as DNA methylation profiling for CNS tumors and sarcoma, standard of care for all children and adolescents with cancer at a national pediatric center in the Netherlands (656).

Australia's Zero Childhood Cancer Program (ZERO) has similarly implemented a national multi-omic profiling framework advancing precision medicine for children with cancers. In an initial cohort of 247 high-risk pediatric patients, tumor and germline WGS and RNA sequencing identified targetable molecular alterations in over 70 percent of patients, and 5 percent of patients had changed diagnoses based on their tumor's genomic profile. Among patients who were treated with therapies informed by molecular profiling,

SIDEBAR 23

Types of Clinical Trials

Clinical trials are research studies that test new methods for screening, prevention, diagnosis, or treatment of a disease. There are many types of clinical trials, categorized based on the timing of data collection, the study approach, the design structure, and its geographic scope.

By the timing of data collection*

RETROSPECTIVE: A study that uses previously collected data.

PROSPECTIVE: A study that follows participants over time after enrollment.

By the type of study approach*

OBSERVATIONAL: A study in which participants are observed or certain outcomes are measured without receiving any intervention or treatment.

INTERVENTIONAL: A study in which participants receive a specific intervention, such as a treatment or procedure.

By the trial design*

MULTI-ARM: A study that evaluates multiple treatment options simultaneously.

ADAPTIVE: A study that allows pre-specified modifications to be made to the trial design based on the interim data.

PLATFORM: A study designed to test multiple interventions against a disease and modify aspects of the trial if needed.

By the geographic scope*

MULTICENTER: A study conducted at more than one institution.

INTERNATIONAL: A study conducted at institutions in more than one country.

INTERCONTINENTAL: A study conducted across institutions located on more than one continent.

* This list presents selected examples of clinical trial types and is not intended to be comprehensive.

more than 30 percent experienced measurable clinical benefit (83). In an expanded cohort of 384 high-risk pediatric patients with more than 18 months of clinical follow-up data, where 43 percent of patients given a precision guided-treatment recommendation received that treatment, the 2-year progression-free survival was more than double that of patients receiving standard therapy and five times higher than that in patients receiving new or targeted therapies not guided by molecular findings (26 percent vs. 12 percent vs. 5.2 percent, respectively) (657). Importantly, children who received their recommended therapy early on in their treatment journey did significantly better than those who received it after their disease had progressed, with overall 2-year survival of greater than 50 percent among these children, all of whom had highest-risk cancers and a less than 30 percent likelihood of survival at enrollment.

Following the success of its national clinical trial focused on high-risk cancers, ZERO has expanded to include all children and adolescents (ages 0–18) diagnosed with cancer in Australia, regardless of cancer type or risk profile, enrolling more than 2,800 children and adolescents to date. In 2025, the Australian Government announced AUD 112.6 million investment over 3 years for ZERO, enabling it to continue delivering precision medicine for all children and adolescents, and to expand access to those ages 19 to 25 with pediatric-type cancers or relapsed childhood cancers. This pioneering nationwide effort can serve as a model for integrating precision medicine into routine pediatric cancer care worldwide.

Global collaboration and data-sharing are critical to advancing pediatric cancer research and care. Because pediatric cancers are both rare and highly diverse, breakthroughs in treatment are seldom achieved by any institution or country on its own. By connecting researchers, harmonizing data, and building shared platforms, international initiatives make it possible for discoveries in one part of the world to accelerate progress for all children and adolescents.

One example is the Pediatric Cancer Data Commons (PCDC) platform, which has worked with the international research community to standardize and federate, or link across institutions, oncology datasets for childhood cancers (659). By uniting clinical, genomic, and imaging data under shared governance and harmonized platforms, PCDC aims to remove barriers to research worldwide and provide more opportunities for developing treatments and improving outcomes for children. Likewise, the European Union (EU) has launched initiatives such as the UNCAN.eu platform, a federated data hub aiming to consolidate cancer research data and accelerate innovation, including for pediatric cancers (660).

Data-sharing initiatives, such as the joint initiative between Innovative Therapies for Children with Cancer (ITCC) and Hopp Children's Cancer Center (Hopp), are aiming to

As part of **Australia's Zero Childhood Cancer Program,** researchers worked with families and experts in pediatric oncology, genetics, bioethics, and law to develop a model framework supporting and guiding parents in **accessing their child's unprocessed genomic data** (data without filtering, annotation, or interpretation)—offering a **potential roadmap** for ethical data-sharing in other pediatric precision medicine programs.

Source: (658).

W40

integrate pediatric precision medicine data across national programs. The ITCC Hopp initiative is working to create a platform for real-time federated archiving of data collected from international platforms for molecular tumor profiling around the globe, including Germany, France, the Netherlands, Denmark, Canada, Australia, and the UK.

For children and adolescents with recurrent or high-risk cancers, studies integrating multi-omic profiling can identify actionable alterations that enable matched therapies with clinical benefit in some cases. MAPPYACTS is one such international prospective trial of pediatric patients across France, Italy, Ireland, and Spain that aims at characterizing molecular features of recurrent or refractory cancers to suggest targeted therapies and referring patients into early-phase trials (e.g., AcSé-ESMART). The study identified at least one genetic alteration suggestive of a targeted therapy in 69 percent of patients. Of the patients with follow-up beyond 12 months, 30 percent received one or more matched targeted therapies; 56 percent of these treatments were in early clinical trials. Additionally, MAPPYACTS was the first study that used liquid biopsy and cfDNA analysis as a noninvasive approach to identify 76 percent of actionable genomic alterations in tumors of pediatric and young adult patients with non-CNS solid tumors (310).

MSK-IMPACT is a specialized tumor-sequencing test used to detect large and small genetic alterations across more than 500 cancer-related genes. The Make-an-IMPACT program aimed to overcome financial and geographic barriers to molecular profiling by offering MSK-IMPACT testing at no cost to children and adolescents with rarer cancers across 11 countries. The program identified clinically relevant diagnostic or prognostic information in nearly 40 percent of pediatric patients with solid tumors including CNS cancers.

Targetable alterations were identified in 44 percent of solid tumors and 21 percent of cerebrospinal fluid (CSF)–derived cfDNA samples. Serial CSF sampling also uncovered mutations that confer treatment resistance, underscoring the potential of cfDNA as a minimally invasive approach for monitoring disease (661).

These studies highlight the feasibility of providing global access to advanced molecular profiling and its value in informing diagnosis, prognosis, and treatment for pediatric cancer worldwide.

Multinational Platform Trials

A persistent gap remains between drug approvals for adult and pediatric cancers. This gap stems from scientific challenges such as the rarity of pediatric cancers, regulatory complexities, and practical barriers including limited trial enrollment and scarce resources, all of which delay access of children and adolescents with cancer to promising new therapies that are often available to adults years earlier. In 2020, a cross-region analysis of approvals in the United States, the European Union, and Japan found that, compared to 103 targeted anticancer drugs labeled for adults, only 19 are approved for pediatric cancers, and just three have pediatric indications in all three regions (662). Policies around the world are beginning to shift the drug development landscape for pediatric cancers by requiring and incentivizing the inclusion of children and adolescents in clinical studies. Continued progress will depend on the outcomes of innovative trials (see **Sidebar 23**, p. 132), which are essential to demonstrate safety and efficacy of new therapies in pediatric populations.

In pediatric patients with advanced solid tumors, the expected response rate in traditional phase I trials is between 10 percent and 12 percent, whereas response rates in trials testing molecularly matched therapies have been shown to be 40 percent or higher (311). AcSé-ESMART, a pan-Europe multi-arm adaptive interventional platform trial (see **Sidebar 23**, p. 132), is using targeted treatment strategies to advance precision medicine for children, adolescents, and young adults (AYAs) with relapsed or refractory cancers. Since the AcSé-ESMART trial opened, over 250 patients have enrolled, and the trial has provided access to 13 new drugs or drug combinations, incorporating 16 adaptive arms for patients across six countries in Europe. Importantly, molecular profiling programs like MAPPYACTS (see **Molecular Profiling Driving Precision Medicine**, p. 131) serve as a gateway to such trials. For example, 72 percent of patients who received matched treatment in a clinical trial after participating in MAPPYACTS did so within AcSé-ESMART, highlighting how profiling programs can facilitate therapeutic access for children and adolescents (311,663).

The United States–led international Pediatric Molecular Analysis for Therapy Choice (MATCH) trial has also tested the use of precision medicine for pediatric cancers. This trial took place at about 200 children's hospitals, university medical centers, and cancer centers in the United States, Canada, New Zealand and Australia. Pediatric MATCH has proven to be a feasible, tumor-agnostic framework matching children and AYAs who have refractory cancers with molecularly targeted therapy trials (see **Integrating Molecular Insights Into Clinical Care**, p. 46).

The Optimal Precision Therapies to CustoMISE Care in Childhood and Adolescent Cancer (OPTIMISE) trial is a multi-arm adaptive platform trial jointly led by Australia's ZERO and Canada's PRecision Oncology For Young peopLE (PROFYLE) initiative. This trial is a companion to the ZERO and PROFYLE precision oncology programs that will link patients to therapies based on their unique tumor profiles. OPTIMISE aims to evaluate molecularly targeted and immune-based therapies for children and adolescents with relapsed or refractory cancers and improve the outcomes for patients with advanced solid tumors, brain tumors, or lymphomas.

By bridging molecular findings with pediatric trial enrollment and aligning regulatory, industry, and academia partners around pediatric-focused drug development pathways, multinational platforms can accelerate the delivery of timely, evidence-based targeted treatments to the children and adolescents who need them.

Challenges and Opportunities in Trials Globally

Access to and enrollment in pediatric cancer clinical trials is uneven worldwide, influenced by barriers such as limited research infrastructure and staffing, inconsistent insurance coverage and financing, complex regulatory pathways, fragmented data systems, and practical barriers to accessing studies beyond national borders. While regions such as North America, Australia, and Europe have established strong clinical trial frameworks, many regions—including Latin America, Africa, and parts of Asia—lack robust infrastructure or connections to global networks (664). Improving childhood and adolescent cancer outcomes will require a deeper understanding of local stakeholders and resources necessary to establish effective clinical trial infrastructures, as well as increasing collaboration between international pediatric cancer clinical trial groups.

For example, collaborative clinical trial groups in pediatric oncology are unequally developed across Asia. The Asian Pediatric Hematology and Oncology Group (APHOG) was established to identify barriers and overcome hurdles in running collaborative clinical trials in Asia. Some of the key challenges the group reported included lack of insurance coverage, fragmented regulatory processes, limited data-sharing infrastructure, and a shortage of trained clinical trial staff (666). In response, organizations across Asia are working to expand clinical trial opportunities for pediatric patients with cancer. As one example, the Korean Society of Pediatric Hematology-Oncology in South Korea has initiated a number of multicenter clinical trials, including studies in ALL and acute myeloid leukemia (AML); however, challenges remain in performing nationwide studies—including limited workforce, resources, and institutional participation (666). APHOG recommended strengthening insurance frameworks to ensure that the cost of new treatments will be reimbursed and investing in expanding the health care workforce—including clinical investigators and nurses, data managers, and project coordinators—to support clinical trial operations.

BETWEEN 2008 AND 2016
LESS THAN 0.1%
OF GLOBAL CHILDHOOD CANCER RESEARCH FUNDING WAS AWARDED DIRECTLY TO INSTITUTIONS IN COUNTRIES THAT ARE
NOT HIGH INCOME
WHERE **90%** OF CHILDREN WITH CANCER ARE DIAGNOSED.

Source: (665).

W41

In India, systemic, socioeconomic, and cultural barriers hinder early cancer diagnosis and sustained access to quality care, with many children presenting at advanced stages of disease. Regulatory bodies and regional initiatives are working to address these challenges. For example, the Indian Pediatric Oncology Group (InPOG) aims to accelerate the development of prospective multicenter clinical trials in the region, with the goal of improving the outcomes of childhood cancer in India through collaborative research. Since its launch in 2015, InPOG has initiated 31 studies—covering both observational (69.3 percent) and interventional (30.7 percent) trials—and has enrolled over 10,000 children across 114 institutions (667). While challenges remain, including limited financial resources and the need for dedicated infrastructure, efforts are underway to train clinicians and standardize research protocols to continue improving survival, quality of life, and treatment options for children across the country.

In Africa, the overall survival for childhood cancers is poor, ranging from 30.3 percent in North Africa to 8.1 percent in East Africa (668). A systematic assessment of pediatric oncology clinical trials across 54 African countries found that only 12 percent of trials included children and adolescents,

only 50 percent of pediatric trials were interventional, and sub-Saharan countries accounted for only 10.6 percent of pediatric trial activity. Additionally, 14 counties reported having no full-time pediatric oncologists and only two countries had pathology research capabilities, including WGS and molecular pathology for all diseases (668). Africa-focused collaboratives and investments in improving access to diagnostic tools and health care infrastructure will be essential to respond to these challenges and improve outcomes for children in the continent.

Expanding access to pediatric cancer trials will require sustained global collaboration and innovative approaches to overcome regulatory and resource barriers. Leveraging collaborations between institutions in HICs and countries that are not high income can help transfer expertise, mentorship, and trial infrastructure. Additionally, sustained investment in training clinical personnel and strengthening data infrastructure will be pivotal to support these efforts and improve clinical trial participation, high-quality data generation, and equitable access to innovative therapies for children and adolescents everywhere.

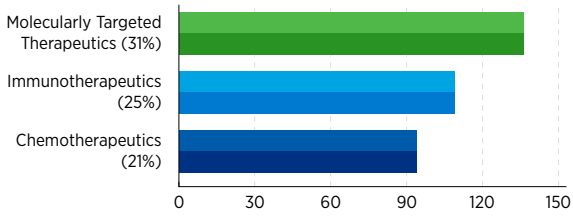
Global State of Pediatric Cancer Treatment

Childhood cancer treatment has advanced dramatically over the past few decades. Once nearly fatal diseases, childhood cancers are increasingly treatable, with an overall 5-year net survival rate of nearly 80 percent in HICs (see **Pediatric Cancer Trends in the United States**, p. 14) (625). Breakthroughs in childhood cancer treatment, once confined to HICs, are slowly making a tangible impact in countries that are not high-income or upper middle-income, although implementation and access remain substantially uneven within these countries as well as when compared to HICs (669,670). Gains against childhood cancers in non-HICs thus far stem from cooperative clinical trials (see **Access to Clinical Care: Disparities and Solutions**, p. 138), refinements in surgery and radiotherapy, safer chemotherapy regimens, and the systematic integration of supportive care that includes essential services, such as infection control, nutrition, and pain relief (see **Sidebar 24**, p. 136).

Around the globe, treatment options for children with cancer have expanded well beyond conventional chemotherapy in recent decades, although uneven access remains a major challenge (see **Access to Clinical Care: Disparities and Solutions**, p. 138). In a recent study, researchers conducted a large-scale review of more than 5,000 clinical trials registered worldwide between 2007 and 2022, focusing on medicines tested in children with cancer. The analysis showed that there are 440 unique cancer medicines under study, excluding cell therapies (41). Furthermore, targeted therapies and immunotherapies made up more than half of all medicines tested in children (55 percent), reflecting a shift from traditional chemotherapy (see **Figure 14**, p. 135) (41).

FIGURE 14

A Global Snapshot of Pediatric Cancer Drugs: Current Landscape and Pipeline



According to a recently published analysis of global drugs pipelined for treating childhood cancers, 440 unique cancer medicines, excluding cellular therapies, have been studied in children between January 2007 and August 2022. Fifty-five percent of these were precision drugs, and 85 (19 percent) and 37 (8 percent) had been approved for children by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), respectively. Out of the 440 drugs identified, drugs were divided into 9 general drug categories. The three most common drug categories were molecularly targeted therapies (135; 31 percent), followed by immunotherapy (108; 25 percent) and then cytotoxic chemotherapy (93; 21 percent).

Source: (41).

Pediatric oncology has pioneered risk-stratified therapy, which tailors treatment intensity according to a child's prognosis and helps reduce overtreatment in low-risk cases while escalating treatment in high-risk ones (673). These improvements mean more children not only survive cancer but do so with fewer permanent side effects.

Pediatric ALL as a Model of Global Progress

A few decades ago, an ALL diagnosis was considered fatal for most children around the globe (see **Table 10**, p. 137). In the 1960s, survival rates in HICs were below 10 percent, while in many LICs and LMICs, children with ALL had little chance of cure well into the 1990s (669,674). Today, thanks

SIDEBAR 24

A Global Timeline of Progress in Pediatric Cancer Treatment

Over the past few decades, treatments for pediatric cancer have evolved from chemotherapy to highly targeted therapies and cutting-edge immunotherapies. Each milestone along the way reflects not only scientific discovery but also the growing ability to translate breakthroughs into treatments for children and adolescents. The following timeline illustrates advances that have reshaped pediatric oncology, leading to improved survival, reduced toxicities, and the introduction of novel therapies such as CAR T cells that are redefining what is possible in pediatric cancer care.

1960s — Chemotherapy Era Begins

- **HICs (1960s–1980s):** Chemotherapy involving multiple drugs is established as the backbone of pediatric oncology through cooperative group trials.
- **NON-HICs (1980s–1990s):** Basic chemotherapy is introduced, but access is limited by resource constraints.

1970s — Maintenance Therapy Proven Essential

- **HICs (1970s):** Randomized trials demonstrate the necessity of oral maintenance therapy—given to help keep cancer from coming back after it has disappeared following the initial therapy; duration and scheduling are shown to be critical for cure.
- **NON-HICs (1970s–1980s):** Maintenance therapy is implemented but has limited impact because of drug shortages and poor monitoring.

1980s — Delayed Intensification Strategies Introduced

- **HICs (1980s):** Delaying intensification therapy—given after there are no signs of cancer that can be detected by clinical tests following the initial therapy—improves 5-year survival toward 60 percent to 70 percent.
- **NON-HICs (1980s–1990s):** Intensification therapy proves feasible but is rarely implemented outside a few large centers (e.g., in India, Brazil).

1990s — Risk-Adapted Approaches Established

- **HICs (1990s):** Risk-adapted protocols—treatment regimens tailored based on risk assessment (i.e., the lower the risk, the less intense the treatment) become standard of care in pediatric ALL, reducing cranial irradiation.
- **NON-HICs (2000s–2010s):** Uptake is gradual as diagnostic capabilities mature.

2000s — Molecularly Targeted Treatments Introduced

- **HICs (2001):** Imatinib (Gleevec) is approved for Ph+ leukemia.
- **NON-HICs (2002 ONWARD):** GIPAP is launched to deliver imatinib access across more than 80 countries.

2010s — First Pediatric-Specific Molecularly Targeted Drug Approved

- **HICs (2010–2015):** Clinical efficacy of dinutuximab (Unituxin; an anti-GD2 antibody)—the first molecularly targeted therapeutic tested and approved specifically for children—against high-risk neuroblastoma is demonstrated in 2010, with FDA approval granted by 2015.
- **NON-HICs (2018 ONWARD):** Although an alternative drug, dinutuximab beta (Qarizba), is available in some UMICs, such as China and Brazil, wider uptake in LICs and LMICs remains limited because of the lack of good generic alternatives and prohibitive drug prices.

2010s — CAR T-cell Therapies Implemented

- **HICs (2017):** FDA approves of tisagenlecleucel for pediatric ALL.
- **NON-HICs (2018 ONWARD):** China and India begin domestic CAR T-cell therapy trials.

2020s — Pipeline Expansion Underway

- **HICs (2020s):** The Childhood Cancer Drug Current Landscape and Pipeline Characteristics dashboard enlists 440 medicines, approved or being studied at various stages of clinical trials, including 48 CAR T-cell therapeutics.
- **NON-HICs (2025 ONWARD):** WHO–St. Jude platform begins delivering essential drugs to LMICs.

ALL, acute lymphoblastic leukemia; CAR T, chimeric antigen receptor T cell; CML, chronic myeloid leukemia; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GIPAP, Glivec International Patient Assistance Program; HIC(s), high-income country or countries; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

Note: Non-HICs include countries that are not high income, covering low-income countries (LICs), lower middle-income countries (LMICs), and in some cases, upper middle-income countries (UMICs).

Sources: (80,671,672).

TABLE 10

Decline in Acute Lymphoblastic Leukemia Deaths Around the Globe Among Children Ages 0–5 Years from 1990 to 2021

SDI*	Death Rate†		Annual Decrease in Death Rate‡
	1990	2021	
High	0.73	0.24	3.1%
High-middle	4.45	0.75	5.7%
Middle	4.38	0.94	4.7%
Low-middle	1.89	0.89	2.2%
Low	2.47	1.37	1.8%
Global	**3.05**	**0.96**	**3.6%**

* Sociodemographic index, a composite measure of income per capita, average years of education, and total fertility rate for citizens younger than 25.
† Per 100,000 population.
‡ Estimate annual percentage change; rounded to nearest integer.
Source: (627).

to decades of research, 5-year survival for children with ALL exceeds 90 percent in most HICs, but survival remains much lower in non-HICs, where resources and access to therapies are limited (675,676).

The first major shift in treatment and management of pediatric ALL occurred in HICs, when risk-stratified therapy based on clinical and biological features such as age, white cell count, and cytogenetic markers, became routine. This approach, developed in the 1980s and 1990s, allowed lower-risk children to avoid overly harsh treatment and higher-risk children to receive more aggressive, targeted regimens. The result was a safer, smarter way of curing leukemia that steadily increased survival and quality of life (676).

With advances and innovations in understanding the genetic underpinnings of the disease, molecular classification of ALL became more precise (677,678). Discoveries such as the Philadelphia chromosome—a genetic mutation that leads to the formation of the oncogenic *BCR::ABL* fusion gene—enabled targeted therapies like tyrosine kinase inhibitors to be combined with chemotherapy, dramatically improving outcomes for children with ALL carrying the Philadelphia chromosome (679). Genomic profiling also guided more personalized approaches, reducing toxicity while improving survival (680). These scientific advances created a template for precision medicine in childhood cancer (677,681).

Countries like Brazil, India, and South Africa adapted these advances by tailoring HIC protocols to their regional needs. Simplifying risk stratification, enhancing regional drug supply, and modifying supportive care strategies helped increase survival rates to 60 percent to 80 percent in some centers (see **Global State of Pediatric Cancer Survivorship**, p. 143).

India provides a striking example of how locally adapted approaches can improve childhood cancer survival. Indian pediatric oncology centers adopting modern risk-stratified protocols have reported survival rates approaching 70 percent, demonstrating sustained progress from decades of local adaptation. In a recent study involving nearly 2,700 patients ages 1 to 18 at centers across India, the Indian Childhood Collaborative Leukaemia (ICiCLe) group used genetic testing and minimal residual disease (MRD) to categorize B-cell ALL into standard, intermediate, and high-risk groups to deliver progressively intensified therapy (682). Children identified as standard risk and treated with lower-intensity regimens had better survival than high-risk patients who required more intensive therapy (disease-free and overall survival of 61 percent and 73 percent, respectively) (682). This is the first collaborative clinical study in children with ALL in India using genetic testing and MRD risk stratification to decrease the intensity of treatment in standard-risk ALL and streamlining treatment across all participating pediatric oncology centers (683). Through cooperative protocol adherence, risk stratification, data collection, and approaches to overcome regulatory hurdles, the ICiCLe group demonstrates that even with fewer resources, these strategies can yield survival outcomes approaching those in HICs (682,683).

In Latin America, the Pediatric Oncology Latin America (POLA) network launched resource-adapted ALL protocols in 2018. By addressing challenges, such as controlling infections and obtaining drugs, POLA rapidly improved access to

TABLE 11

Innovations Against Pediatric ALL in Low-resource Settings

Country/Region (HDI category)	Implementation/ Innovation	Barrier Addressed	Outcomes Reported
China (UMIC)	Domestic CAR T-cell therapy program; local manufacturing	Local CAR T manufacturing cuts costs/logistics of imported products.	MRD-neg CR 96.5%; 4-year OS ~70% (687)
India (LMIC)	Domestic CAR T-cell therapy manufacturing and delivery	Local CAR T manufacturing cuts costs/logistics of imported products.	Durable responses, management of side effects (multicenter cohort) (688)
Mexico (UMIC)	Centralized resource serving public hospitals; rapid turnaround for MRD risk stratification	Cutting-edge MRD was brought to resource-limited region.	Decreased early mortality (10.8% vs. 24.8%); increased 1-year OS (89.6% vs. 75.2%) (689)

CAR T, chimeric antigen receptor T cell; CR, complete response; HDI, human development index; LMIC, lower middle-income country; MRD, minimal residual disease; OS, overall survival; UMIC, upper middle-income country.

care and ALL survival across multiple centers (684). South American centers have also documented major gains against pediatric ALL. An analysis across multiple countries in Latin American showed 5-year overall survival improvements for pediatric ALL ranging from 52 percent in low-resource areas to more than 86 percent where standardized protocols were implemented with adequate supportive care (684). The wide survival gap in pediatric ALL is in part explained by the findings of a recent survey of Latin American countries, which indicated that countries with the highest human development index (HDI)—a composite measure of health, education, and income—generally showed dramatic advances in survivorship, access to treatment, and availability of national pediatric cancer control programs (685).

Researchers across the globe are continually working to implement regionally tailored strategies that are helping to further close the gaps in survival outcomes for pediatric ALL between HICs and LMICs (see **Table 11**, p. 138). Despite challenges, pediatric ALL has become a model of progress against childhood cancers, with survival gains that are no longer confined to HIC nations but are increasingly, albeit unevenly, achievable across diverse settings (686).

Still, persistent challenges remain. Many non-HICs continue to struggle with late diagnosis, limited laboratory infrastructure, and high treatment abandonment rates (see **Table 12**, p. 140) (690,691). Without reliable access to essential medicines, even the best protocols cannot succeed. Moving forward, success depends on building stronger health systems and improving access to diagnostics and affordable chemotherapy drugs.

Access to Clinical Care: Disparities and Solutions

Over the past decade, advances in pediatric oncology have transformed survival for many children in HICs. At the same time, the gap between HICs and non-HICs in access to cutting-edge therapies has widened; the reasons for this disparity are multifactorial reasons and include the failure of advances made in HICs to reach countries that are not high income and the inequality of health systems and resources in non-HICs. Children in LMICs and LICs often face delayed diagnoses; shortages of trained specialists; limited access to chemotherapy, surgery, and radiation; and challenges such as malnutrition, treatment complications, and families abandoning care due to cost (see **Global State of Pediatric Cancer Survivorship**, p. 143; **Sidebar 25**, p. 139; and **Table 12**, p. 140) (637).

The inequities in cancer outcomes illustrate one of the most urgent global health challenges—children dying not because their disease is untreatable, but because effective therapies fail to reach them. The most impactful progress against pediatric cancers will not necessarily be the most cutting-edge treatments, but rather access to care that is affordable, scalable, and sensitive to the realities of health care systems worldwide. Recognizing this challenge, WHO and St. Jude launched the Global Platform for Access to Childhood Cancer Medicines (Global Platform) in 2021 with $200 million in funding from St. Jude to provide uninterrupted access to essential medicines to 120,000 children with cancer in up to 30 to 40 LICs and LMICs within the next 5 to 7 years. Supported by the United Nations International Children's

SIDEBAR 25

Global Disparities and Barriers in Access to Clinical Care for Children With Cancer

Every year, approximately 400,000 children are diagnosed with cancer, but their chance of survival depends greatly on where they live. In HICs, nearly 80 percent survive at least 5 years, while in many LICs and LMICs survival is less than 30 percent. This gap reflects weaker health systems, limited access to medicines and specialists, and economic and structural barriers that delay or prevent access to cutting-edge diagnostics and treatment.

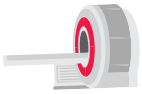
Below are examples from recent studies highlighting global disparities in access to clinical care for children with cancer.

HIGH TREATMENT-RELATED DEATHS:

Compared to HICs, treatment-related deaths among children with cancer are nearly double in LMICs (about 9 percent) and triple in LICs (about 14 percent) (670).

LACK OF CURATIVE RADIOTHERAPY:

The percentage of children treated with curative radiotherapy decreases sequentially with country's income level from, on average, 82 percent of children with cancer in HICs to, on average, 53 percent of children with cancer in LICs (692).



LACK OF RADIATION FACILITIES:

As of 2020, 14 of 48 countries surveyed in Africa did not have any radiotherapy facilities for treatment of children with cancer (693).

DELAYED REFERRAL:

Among children with ALL registered at an oncology center in Pakistan, an LMIC, mean referral time to the pediatric oncologist was nearly 2 months, adversely affecting overall survival (690), compared to typical referral time of 2 to 3 weeks in many HICs.

SHORTAGE OF ESSENTIAL MEDICINES:

LMICs in the Americas, Africa, Europe, the Eastern Mediterranean Region, the Southeast Asian Region, and the Western Pacific Region reported less than 50 percent stocks of essential medicine for childhood cancer, well below the WHO-recommended target of 80 percent (611).

SUBSTANDARD QUALITY OF ANTICANCER DRUGS:

In a recent analysis of 251 samples of chemotherapy drugs in two LICs and two LMICs in sub-Saharan Africa between 2023 and 2024, 24 percent of the tested drugs were expired, and active pharmaceutical ingredient contents ranged from 28 percent to 120 percent of the stated contents (694).

LACK OF ACCESS TO PRECISION MEDICINE:

As of 2025, LMICs accounted for only 1.5 percent of all pediatric CAR T-cell therapy trials. UMICs accounted for 56.9 percent and HICs accounted for 41.6 percent of these trials (695).

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; HICs, high-income countries; LICs, low-income countries; LMICs, lower middle-income countries; UMICs, upper middle-income countries; WHO, World Health Organization.

Emergency Fund (UNICEF) and PAHO for procurement and distribution, the Global Platform aims to address long-standing weaknesses in fragmented medicine markets that often leave LICs and LMICs vulnerable to supply shortages, high costs, and substandard or falsified drugs.

In February 2025, the first medicines were delivered to countries across Asia, Africa, and Latin America, providing an example of how a unified system can ensure safe, affordable access to childhood cancer medicines (696,697). In September 2025, as a part of the Global Platform, health

TABLE 12

Treatment Abandonment and Refusal in Low-income and Lower Middle-income Countries: Drivers and Interventions

Country	WB Income Group	Cancer Type	Treatment Abandonment	Drivers/Interventions Noted in the Study
Bangladesh; Pakistan	LMICs	Retinoblastoma	11% overall	Female sex and advanced stage increased risk
Ethiopia	LIC	All childhood cancers	39%	Lack of belief that cancer can be cured; treatment toxicities and/or cancer progression or relapse
Gambia	LIC	All childhood cancers	21% overall	Late-stage diagnosis; limited in-country radiotherapy capacity; financial/transport barriers noted
Central America	LMICs	High-risk Hodgkin lymphoma	17%	Weekly chemotherapy increased travel burden; inconsistent RT delivery
Kenya	LMIC	Mixed childhood cancers	28%	Health insurance coverage associated with reduced abandonment; many late-stage diagnoses
Malawi	LIC	Mixed childhood cancers	9% (2022), 10% (2023), 3% (2024)	Cash-transfer support and social interventions improved retention and reduced TA over time
Malawi	LIC	Wilms tumor	26.5%	Socioeconomic constraints; delays in diagnosis; limited access to RT
Nigeria	LMIC	Childhood solid tumors	51.2% for malignant tumors	Financial constraints; distance to care; treatment complexity
Philippines	LMIC	Retinoblastoma	13%	Access and non-medical costs; regional disparities in specialists/equipment (e.g., RT, MRI)
Tanzania	LMIC	Burkitt lymphoma	34%	TA contributed to poorer survival; need for supportive care and timely diagnosis

LIC, low-income country; LMICs, lower middle-income countries; MRI, magnetic resonance imaging; RT, radiotherapy; TA, treatment abandonment; WB, World Bank.
Sources: (691,699-707)

officials in Ghana announced a program that will provide free essential medicines to children from low-income families beginning in early 2026 through nine treatment centers nationwide. Through this program, developed in partnership with the St. Jude Global Platform, Ghanaian government officials hope to narrow the survival gaps for children with cancer, in line with the Cure*All* framework (698).

Global cooperation can help address formulation and dosing challenges that remain significant barriers to equitable access. Child-friendly liquid formulations or dispersible tablets, for example, are often unavailable in low-resource settings, making safe administration for younger children difficult (708). Coordinated regulatory action and public–private partnerships will be critical to accelerating the development and distribution of appropriate formulations worldwide.

Chimeric antigen receptor (CAR) T-cell therapy is one of the most significant breakthroughs in pediatric oncology (see **Progress in Pediatric Cancer Treatment**, p. 63). In children with ALL, this treatment can induce deep, durable remissions where other therapies fail. Early trials demonstrated the dramatic efficacy of the treatment in pediatric ALL and showed how transformative this could be for young patients, but access remained clustered in HICs (709). In 2025, large follow-up studies confirmed that CAR T-cell therapy is a lifesaving therapy for children, yet LICs and LMICs remain almost entirely excluded because of the cost of production,

infrastructure demands, and reimbursement barriers (710). Although some CAR T-cell therapies can be produced from T cells that have been frozen and shipped across borders, others require fresh cells and local manufacturing facilities and expertise, limiting availability by geography (711,712).

Additional barriers—including high costs, limited clinical infrastructure, and shortages of trained personnel—further restrict access to these lifesaving therapies for pediatric patients in many regions. However, researchers are beginning to find innovative solutions to address these barriers. In India, the CAR T-cell therapy NexCAR19 is being manufactured at roughly one-tenth the cost of comparable commercial therapies, with early-stage clinical trials showing encouraging safety and efficacy profiles (713). This achievement demonstrates the potential of regionally developed, lower-cost CAR T-cell therapies to expand access in LMICs and bridge the gap in delivering transformative treatments worldwide.

Research has shown that the success of treatment depends on accurate diagnosis and risk stratification. MRD testing has rapidly become a cornerstone of modern leukemia care, but such capacity is rare in many LIC and LMIC settings. A recent study from Mexico demonstrated the impact of bringing standardized MRD diagnostics into public hospitals. By centralizing testing in a reference laboratory and ensuring timely turnaround, researchers showed that early mortality dropped from nearly 1 in 4 to just over 1 in 10. One-year overall survival improved from 75 percent to almost 90 percent (714). This is a clear example of how diagnostic innovation can close survival gaps when thoughtfully implemented in constrained settings.

Next-generation sequencing (NGS) has also expanded dramatically over the past decade, enabling precision approaches that can guide targeted therapy decisions. Consortia such as INFORM (Individualized Therapy For Relapsed Malignancies in Childhood) in Europe, ZERO in Australia, and PG4KDS (Pharmacogenetics for Kids) in the United States have shown that genomic profiling identifies actionable findings in a majority of pediatric cancers (see **Global State of Pediatric Cancer Treatment**, p. 135). Yet, uptake of matched therapies remains low in many places, largely because LIC and LMIC health systems lack the infrastructure, trained workforce, and financial resources to support NGS integration in routine care for children (715).

Researchers are taking innovative, locally developed and resourced approaches to overcome some of these challenges. As one example, in India, resource-adapted molecular profiling—using fluorescently labeled probes to visualize genetic changes and antibody-based assays to detect protein expression and localization within tumor cells—has been used for pediatric CNS tumors, including medulloblastomas and gliomas. These low-cost imaging methods can substitute for advanced platforms when methylation profiling or next-generation sequencing is not feasible and have improved diagnostic precision and risk-based treatment planning in resource-limited settings (716,717).

Several molecularly targeted therapies and immunotherapies have become standard in HICs but remain out of reach elsewhere. Dinutuximab, an anti-GD2 antibody, improves survival for children with high-risk neuroblastoma and is a standard component of therapy in HICs. However, access is constrained in LICs and LMICs by cost and procurement challenges, limiting its uptake despite strong evidence of benefit (718-720). Similarly, brentuximab vedotin combined with chemotherapy improves event-free survival for children with Hodgkin lymphoma, yet adoption has been variable (see **New Hope for Patients With Lymphoma**, p. 80). Even in health systems that recognize its value, high cost remains a barrier to widespread use (355,721,722).

The same story holds true for NTRK inhibitors, which are highly effective molecularly targeted therapies for rare pediatric CNS tumors driven by NTRK fusions and represent

Global Disparities in Regulatory Approvals of Precision Medicine Drugs for Pediatric Cancers

As of 2025, **only 21%** of the globally available molecularly targeted therapies and immunotherapies are formally approved for pediatric use, and **very few are formulated in ways suitable for children,** such as liquid preparations.

On average, there was a **lag of 2 to 3 years** between adult and pediatric approvals by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA).

Low-income countries and lower middle-income countries often **lack regulatory approval processes** for precision medicine drugs and rely on approvals by EMA and FDA, **further delaying children's access to promising treatments.**

Source: (41).

W42

a new frontier. But global access to these therapeutics remains a barrier, with high drug cost limiting their use and leaving children in most countries without a potentially lifesaving option (723). Researchers are working to mitigate some of these issues. For example, a new study GLOBOTRK, launched with a partnership between academia and industry, is recruiting children with brain tumors from the US as well as from several LMICs, including Egypt, India, Jordan, Brazil, and Peru. The study, a phase II trial, aims to give entrectinib as a first treatment to young children with brain cancers whose tumors have the *NTRK* or *ROS1* fusions. Importantly, entrectinib is formulated to be administered orally, which makes it ideal to help treat children in low-resource settings, where access to dedicated infusion centers is not always possible (724).

Another source of disparities in access to precision medicine drugs is the lack of rigorous drug approval processes in LICs and LMICs, which largely rely on approvals by EMA and FDA, further delaying access to cutting-edge treatment for children with cancer (41,725).

Radiotherapy, or radiation therapy, remains an essential part of treatment for many childhood cancers, yet it is one of the most unevenly distributed resources globally, including in HICs (726). Expert panels have issued guidance about how to deliver safe and effective radiotherapy for children in resource-limited settings (727). The guidance emphasizes adapting treatment protocols, ensuring basic quality assurance, and prioritizing training as essential steps in settings where sophisticated equipment and staffing are lacking (727). Furthermore, the Rays of Hope initiative of the International Atomic Energy Agency (IAEA) aims to improve access to and quality of radiation therapy in LMICs through training the workforce and procuring equipment, among other approaches (728). In a partnership with St. Jude's, the initiative also focuses on delivering technical resources, curricula and guidance documents for radiation oncologists, radiotherapy technicians and medical physicists, and supporting their implementation in selected LMICs (729). Even in HICs, advanced radiotherapy approaches, such as proton therapy, are unequally distributed. Children with cancer face additional, disproportionate barriers to accessing cutting-edge radiotherapy, with geography and socioeconomic status strongly influencing whether children with cancer can benefit from proton therapy (726). These disparities underscore that access challenges not only are an issue in countries that are not high income but also persist within HICs.

Beyond access to specific drugs, treatment types, and technologies, broader socioeconomic factors continue to drive survival differences. Multiple studies have shown that outcomes for several pediatric cancers are directly correlated with HDI: The higher the HDI, better the outcomes (see **Global Epidemiology of Pediatric Cancers**, p. 126) (730,731). At the same time, examples from Latin America and Asia show that strategies tailored to regional needs can make a real difference. The challenge now is to scale these models globally. Ensuring access to diagnostics such as MRD and NGS would allow clinicians everywhere to tailor therapy. Developing strategies for purchasing immunotherapies and targeted drugs in bulk and pricing them for different countries based on income level could reduce cost barriers. Expanding radiotherapy infrastructure, including adapted protocols for non-HICs, would address one of the longest-standing inequities in access to these treatments. And creating international frameworks to accelerate pediatric approvals could shorten the lag that leaves children waiting years for therapies already available to adults. Without deliberate efforts to extend access to the full continuum of care, from diagnosis and supportive care to advanced therapeutics, these survival gaps will persist.

Partnerships between institutions in HICs and non-HICs have demonstrated that sustainable pediatric cancer care programs can also be built even in resource-limited settings. In Latin America, a partnership between St. Jude, Guatemalan medical, political, and community leaders, and the Guatemalan government Ministry of Health and Social Welfare enabled the establishment of the National Pediatric Cancer Unit, which provides cancer care to all Guatemalan children regardless of ability to pay. As a result, treatment abandonment dropped from 42 percent to less than 1 percent and survival rates more than doubled (732). In Brazil, collaboration between St. Jude, a local grassroots advocacy group, and a regional hospital resulted in increased training and education of health care providers and implementation of adjusted ALL treatment protocols, increasing 5-year survival in pediatric ALL from 25 percent to 63 percent (732).

Across Africa, regional collaboration has been equally transformative. Through strengthening workforce development and regionally adapted treatment protocols, efforts led by the Franco-African Pediatric Oncology Group have improved the outcomes of Burkitt lymphoma from 50 percent to 60 percent (668). Similarly, the Collaborative Wilms Tumour Africa Project was established to improve Wilms tumor outcomes by implementing consensus-adapted treatment protocols–developed by the SIOP Committee for Paediatric Oncology in Developing Countries–across eight centers in sub-Saharan Africa. Protocol adaptation led to improved survival without evidence of disease from 52 percent to 69 percent, reduced treatment abandonment from 23 percent to 12 percent, and decreased treatment-related deaths from 21 percent to 13 percent. The Collaborative Wilms Tumour Africa Project is now just one initiative under the Collaborative African Network of Clinical Care and Research for Childhood Cancer network, which also includes the Supportive Care for Children With Cancer in Africa initiative to improve supportive care and the Toward Zero Percent Abandonment initiative to eliminating treatment abandonment (733).

Taken together, the global landscape of pediatric cancer reveals both remarkable progress and stark inequities. Advances in diagnosis, treatment, and supportive care have transformed outcomes for many children in HICs, yet survival remains unacceptably low in parts of the world where most cases occur. Sustained progress will depend on closing these gaps by expanding access to essential medicines and technologies, strengthening health systems and clinical trial capacity, and ensuring that breakthroughs in precision medicine and supportive care reach every child, everywhere.

Global State of Pediatric Cancer Survivorship

Globally, survival after a childhood cancer diagnosis remains marked by profound inequities. The 5-year net survival for childhood cancer is estimated at 37 percent for 2015 to 2019, with wide variation between regions (625). In recognition of this disparity, the WHO GICC aims to increase pediatric cancer survival rates to 60 percent worldwide by 2030 (see **Global Policies and Partnerships to Improve Care**, p. 128). Achieving this goal requires not only access to timely diagnosis and curative therapy but also increased attention to supportive and survivorship care.

In HICs, advances in supportive care, such as infection prevention, transfusion support, and symptom management, have been central to survival gains, making intensive treatments more tolerable (734-737). Efforts to safeguard long-term quality of life, such as fertility preservation, have also expanded (484,738). However, both access to these services and research evaluating their impact remain largely confined to HICs, leaving children in less developed countries with few supportive care options and little evidence to guide survivorship care.

Within the framework of the WHO GICC and the Cure*All* approach, survivorship care in non-HICs remains a critical area in need of immediate attention. Despite this need, investment in pediatric cancer survivorship research remains inadequate. Between 2008 and 2016, only 11.6 percent of the $2 billion invested globally in childhood cancer research supported survivorship studies (including research into patient care and pain management, supportive and end-of-life care, quality of health care delivery, and long-term side-effects of cancer treatment), while the majority of funds enabled research into pediatric cancer biology and drug development (665). Even more concerning, only 5.5 percent of global pediatric cancer research funding supported health care delivery, an area essential for establishing sustainable survivorship programs, underscoring the lack of investment in interventions to improve long-term outcomes in resource-limited settings. This chronic underfunding has left major gaps in knowledge about childhood cancer survivorship in non-HICs.

A recent assessment of the global landscape of childhood cancer survivorship research from 1980 to 2021 found that 95 percent of pediatric cancer survivorship research originated from HICs, with a disproportionately large proportion of studies originating from the United States (739). By contrast, only 5 percent of survivorship studies were conducted in UMICs and LMICs, and no survivorship studies emerged from LICs. Moreover, when survivorship research is conducted in UMICs and/or LMICs, it is almost exclusively limited to physical late effects, with little attention to mental health, psychosocial challenges, or health promotion (739,740). Studies conducted in low-resource settings also tend to be smaller and limited to single institutions, reducing generalizability. This imbalance raises concerns that existing survivorship guidelines and models of care are poorly aligned with the realities of survivors in resource-limited settings.

While comprehensive long-term follow-up guidelines developed in North America and Europe provide valuable frameworks for survivorship care, they are based on treatment exposures and resources specific to high-income settings. However, children in non-HICs often receive modified treatment regimens that alter their risk for late effects (603). For example, in some LICs and LMICs, regional treatment guidelines that omit radiotherapy and lower anthracycline doses have been implemented in response to limited resources and constrained health infrastructure (670,741). By contrast, in HICs, irradiation and anthracycline exposure have been consistently identified as risk factors for second primary cancers, cardiotoxicity, infertility, endocrine disorders, and other late effects (21). The less intensive regimens used in some non-HICs may therefore alter both the prevalence and spectrum of late effects. As such, long-term follow-up guidelines must be adapted to reflect local treatment patterns and health system capacities.

Although knowledge of physical late effects has expanded considerably, research addressing mental health, psychosocial well-being, and health promotion in pediatric cancer survivorship remains limited (740). The lack of focus on these areas is especially concerning for patients in non-HICs, where stigma surrounding mental health, shortages of trained mental health professionals, and the high cost of services limit access to psychosocial care (740,742-744). As a result, many children and families in non-HICs remain without the support needed to address anxiety, depression, fear of recurrence, and the broader social challenges that persist long after treatment ends.

Supportive care and palliative care are essential components of survivorship, designed to relieve pain and other symptoms, improve quality of life, and support families of children with cancer and other serious illness (745). Yet in most non-HICs, these services remain underdeveloped. A global survey found that fewer than half of pediatric oncology units in non-HICs provide specialized palliative care, and fewer than 15 percent

report consistent access to high-potency opioids or adjuvant medicines for neuropathic pain (746). Limited provider awareness, restricted drug availability, and fragile health system infrastructure contribute to these gaps (747,748). Malnutrition compounds these challenges, affecting up to 80 percent of children with cancer in some non-HICs (749). Poor nutrition exacerbates treatment-related toxicity, increases the risk of severe infections, and undermines recovery, making it a key determinant of both survival and long-term outcomes (750). Together, these deficits in supportive, nutritional, and palliative care weaken children's ability to complete treatment and prevent survivors from realizing their full potential after therapy.

Reliable data systems are also central to effective survivorship care, yet many non-HICs lack population-based cancer registries (751). The absence of accurate data limits the ability to estimate disease burden, identify survivor populations, anticipate late effects, and design evidence-based long-term follow-up programs (602). Without robust registries, governments cannot document survivor outcomes, allocate resources effectively, or integrate survivorship into national cancer control plans.

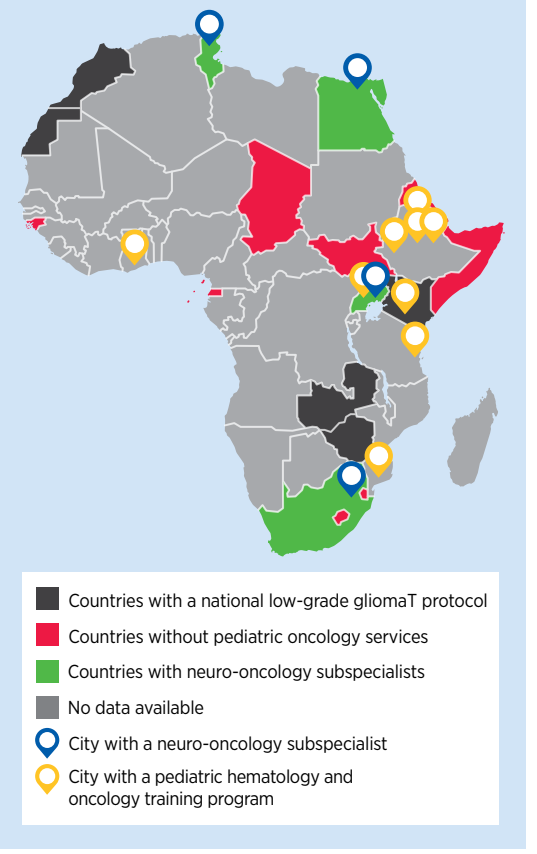
Looking ahead, survivorship must be embedded within national and global cancer control strategies. The WHO Cure*All* framework emphasizes that survivorship is an integral part of the cancer care continuum and calls on governments to provide lifelong, equitable services for survivors of pediatric cancer. Achieving this vision requires investments in supportive and survivorship care infrastructure, integration of psychosocial services, adaptation of long-term follow-up guidelines to local contexts, and the strengthening of cancer registries to guide resource allocation. It also demands greater international collaboration to ensure that survivorship research and care models reflect the needs of pediatric cancer survivors worldwide, not only those in HICs.

Global State of the Pediatric Oncology Workforce

A strong pediatric oncology workforce is critical to deliver timely diagnosis, coordinated treatment, and supportive care that improves health outcomes for children with cancer. Examples from HICs show how organized and coordinate care for children with cancer makes a positive impact. One such example is dedicated pediatric radiotherapy departments and trained expert teams in HICs that raise the quality and consistency of care and serve as a useful reference point for other countries that are still struggling to increase the capacity for radiotherapy (752). Having dedicated experts specifically trained to perform a range of tasks—such as diagnosis, surgery, and radiation, among others—can determine whether complex

FIGURE 15

Pediatric Cancer Workforce Across Continental Africa



The availability of pediatric oncology services varies greatly across Africa, with just one radiotherapy center available for every 2.24 million children under the age of 15, one neurosurgeon for every 304,685 children, and only one pediatric neuro-oncology specialist for more than 150 million children. By comparison, in the United States, there is one radiotherapy center per 28,000 children, one neurosurgeon per 15,468 children, and one pediatric neuro-oncology specialist per 373,330 children. Moreover, only 4 of Africa's 54 countries have the capacity to treat pediatric CNS tumors, with neurosurgeons and trained radiotherapy staff who are primarily focused on adult patients. This places an immense burden on the few facilities able to provide care for children with CNS tumors. There were 236 trained pediatric hematologists/oncologists in 37 of 54 countries in Africa. This translates to 0.35 pediatric hematologists/oncologists for every 1,000,000 children <17 years in Africa.

Sources: (645,759).

treatments can be delivered safely and on time (692,753). Assessing the pediatric oncology workforce in HICs also helps determine the optimal approaches for training the workforce and delivering the best possible care for children with cancer that other countries can adapt as targets to plan for and invest in necessary resources (754).

Across countries that are not high income, the pediatric oncology workforce falls behind in numbers, specialization, and organization. An International Atomic Energy Agency survey found a stepwise drop in the proportion of children treated with curative radiotherapy, from 82 percent in HICs to 53 percent in LICs, alongside gaps in radiotherapy technology, imaging, supportive care, and multidisciplinary teams, which were reported by 92.3 percent of HICs but only 65.5 percent of centers in lower-income settings (692). Similarly, a global assessment of pediatric neurosurgical capacity for childhood brain tumors found that resources vary by country income level, with respondents in LICs reporting needs in basic neurosurgical instrumentation and program support, a signal that staffing and equipment constraints together often limit care (753).

Regional and cancer type–specific studies show how these gaps in the pediatric oncology workforce shape care. In the Pediatric Oncology East and Mediterranean (POEM) network, 50 centers reported 12,496 new cases per year managed by 299 pediatric oncologists and 1,176 nurses, with workforce availability and subspecialty access rising with country income level. The survey identified 25 physician fellowships and 13 nurse training programs, yet capacity clustered in higher-income parts of the region, leaving many centers under-resourced (755). A focused comparison between a pediatric oncology center in Brazil, a UMIC, and one in the United States, an HIC, highlighted tangible differences, including two part-time neuroradiologists and one neuropathologist , as well as longer time to start radiotherapy in the former versus eight full-time neuroradiologists and two neuropathologists in the latter, illustrating how staffing and workflow constraints delay treatment even in places in UMICs with strong pediatric oncology infrastructure (756). Even in predominantly high-income Europe, a multicenter survey documented uneven organization of pediatric radiotherapy, with limited involvement and integration of multidisciplinary teams. (752).

The COVID-19 pandemic further stress-tested pediatric cancer services around the globe and highlighted the need for adequately staffed teams. In a 79-country mixed-methods study, more than half of institutions reported decreased clinical staff availability, and two-thirds reported provider reassignment or reduced availability, with role changes disproportionately affecting nurses. Physical illness, psychological distress, and financial strain on health care providers were common, and the effects tended to be more severe in settings with fewer resources (757). These findings further reinforce how disruptions caused by unforeseen circumstance can widen existing workforce gaps in LICs and LMICs.

Assessment of pediatric oncology services in Africa makes the depth of shortage in the region clear, but also helps set measurable targets (see **Figure 15**, p. 144) (693,758). A recent regional analysis identified 236 fellowship-trained pediatric hematology-oncology specialists across 37 countries, with 17 countries having none. Countries who did have pediatric hematology-oncology specialists had an average burden of about 205 new pediatric cancer cases per specialist. Program evaluations identified interventions that can help mitigate this shortage, including standardized curricula and leadership development to increase training as well as retain trainees (759). These data align with the POEM network's catalog of physician and nurse training programs and its observation that training capacity and access to specialists is linked with national income, indicating that coordinated regional networks may help overcome uneven distribution of the pediatric oncology workforce (755). Together, these findings underscore that workforce shortfalls are systemic across countries that are not high-income, with serious consequences for children with cancer, including timeliness of treatments and use of standardized treatment protocols, as well as survival outcomes (692,753).

Studies have consistently shown that closing the gap between HICs and non-HICs regarding the pediatric oncology workforce requires action on several levels. First, it is critical to expand accredited, region-specific training for pediatric oncology and nursing, and use standard curricula, mentors, and exchange programs to build staff where they are needed the most (755,759). Second, it is vital to invest in dedicated pediatric teams and essential equipment for complex care, such as radiotherapy and neuro-oncology, and use treatment protocols that fit local resources (692,752,753). Third, it is important to learn from HICs when deciding how many people to train, how to divide patient care, and how to build teams within the limits of available local resources (754,760). If governments, regional networks, and global partners align around these workforce priorities, the path to reliable, timely, multidisciplinary care for children with cancer outside high-income settings can become much more attainable (692,755,759).

ADVANCING PEDIATRIC CANCER RESEARCH AND PATIENT CARE THROUGH EVIDENCE-BASED POLICIES

IN THIS SECTION, YOU WILL LEARN:

- Sustained and robust investment in federal agencies and programs is vital to advancing pediatric cancer research and training the future workforce.
- Targeted legislative and policy efforts are helping pediatric cancer patients live longer, healthier lives.
- Global collaboration and partnerships are essential for accelerating the development of safe and effective therapies for pediatric cancer patients, including through innovative clinical trials that deliver meaningful impact.

Pediatric cancers pose unique challenges compared to adult cancers, but scientific advances continue to improve overall life expectancy, with marked increases in 5-year survival rates for pediatric cancers from 63.1 percent in the 1970s to 85.2 percent in the 2010s (see **Pediatric Cancer Trends in the United States**, p. 14). This remarkable progress against pediatric cancer has been facilitated by beneficial legislation and federal policies. Additionally, Department of Health and Human Services agencies including the National Institutes of Health (NIH), the National Cancer Institute (NCI), and the US Food and Drug Administration (FDA) are playing key roles in furthering pediatric cancer research and continuing to improve patient outcomes.

Unfortunately, the burden of pediatric cancer remains high, as about 15,000 individuals under age 20 are diagnosed with cancer in the United States every year and cancer remains the leading cause of death by disease for children (16). Moreover, advances in treatment and improved survival are not uniform across pediatric cancer types, and survival rates remain low for certain diagnoses (see **Uneven Progress Against Pediatric Cancers**, p. 22). As more children continue to live longer after a cancer diagnosis, addressing the specific needs of long-term survivors will require increased research. NCI-sponsored programs like the *Childhood Cancer Survivor Study* are also critical for identifying and combating the long-term effects of cancer diagnosis and treatment experienced by pediatric cancer survivors (761).

Investing in Pediatric Cancer Research to Secure a Healthier Future

Robust and sustained federal investments in pediatric cancer research and patient care infrastructure are required to translate scientific advances into improved outcomes for children with cancer. NIH and NCI are global leaders for pediatric cancer research and support numerous grants, programs, and initiatives. For example, NIH and NCI provide federal grants for investigator-initiated research, and NCI also supports critical collaborations such as the Children's Oncology Group and the Pediatric Early Phase Clinical Trials Network. At NCI, pediatric oncologists and scientists across disciplines also conduct pediatric cancer research through NCI's intramural research program, including the NCI Center for Cancer Research Pediatric Oncology Branch and the Division of Cancer

Epidemiology and Genetics. In addition, NIH and NCI manage $28 million for Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act initiatives and $50 million for the Childhood Cancer Data Initiative (CCDI) each fiscal year (FY) (762). The STAR Act is authorized through FY 2028, and both STAR Act and CCDI funds must be appropriated by the US Congress each year. The CCDI was launched in FY 2020 as a special 10-year initiative proposed in the President's Budget Request, and Congress has appropriated the proposed funds each fiscal year since (309, 763). In recognition of CCDI's impact, the Trump administration recently proposed that CCDI annual funding be doubled from $50 million to $100 million to support an expansion and increased focus on integrating artificial intelligence tools and approaches to advance pediatric cancer research (764).

Federal funding for pediatric cancer research is critical for obtaining and maintaining necessary laboratory facilities and equipment as well as supporting the scientific workforce and the staffing needed for clinical trials conducted in the spectrum of rare diseases that comprise childhood cancers. Universities and academic medical centers at the forefront of cutting-edge pediatric cancer research rely on federal funding to fuel their efforts and train the next generation of researchers and clinicians. Indirect cost support is essential for covering the infrastructure and administrative expenses that make scientific discoveries possible. Indirect costs include maintaining laboratory equipment, ensuring compliance with safety and ethical standards, and supporting essential research staff. Without adequate reimbursement for indirect costs, research institutions will struggle to sustain the environment needed for groundbreaking pediatric cancer studies. Challenges to the pediatric physician–scientist workforce include the lack of structured and robust mentorship, significant personal financial opportunity cost, and inadequate research funding (765). One survey of pediatric cancer physicians found that a lack of institutional funding was considered the top barrier facing the workforce (754). Moreover, developing a sustainable pediatric cancer research workforce also requires building a diverse workforce equipped to address health disparities and the needs of a diverse patient population (766). Importantly, pediatric cancer research output over the past decade, as measured by publications, has not kept pace with other pediatric diseases or cancer research overall and accounts for less than 5 percent of all cancer research output (767). Pediatric cancer research requires innovative and sometimes high-risk approaches that do not always fit traditional funding models. Employing more flexible grant structures would allow researchers to pivot as the field rapidly evolves, foster collaboration across disciplines, and accelerate discovery.

There are also inequities in the distribution of research funding for pediatric cancers. While pediatric cancer survival rates have significantly increased over time, these improvements have not been even across all disease areas, with the greatest advances occurring in hematologic malignancies (768). For example, the 5-year survival rate for diffuse intrinsic pontine glioma (DIPG), an aggressive form of brain cancer, remains below 3 percent (28). Research dedicated to some rare pediatric cancers was found to receive less funding than expected based on their disease burden (769). In addition, there remains an urgent need for more funding for research related to survivorship and quality of life care, health disparities, infrastructure, and technology. A recent analysis found that while nearly one-third of all survivorship research focuses on pediatric cancer, very few studies focus on long-term survivors, adolescent and young adult (AYA) survivors, or adult survivors of pediatric cancers (770).

Overall, it is difficult to accurately estimate federal pediatric cancer research investment. NIH funding and NCI funding are reported for pediatric cancer broadly but do not include detailed breakdowns or fully capture investments in basic research and other cross-cutting efforts, and many other federal agencies such as the Department of Defense do not release specific funding information. Likewise, it is difficult to characterize the pediatric cancer research workforce due to limited data and coordination between funding entities and employers. Increased study and tracking of pediatric cancer research funding and workforce trends would help reveal challenges and better inform policy solutions. One historical analysis found that only 4 percent of federal cancer research funding goes to studying cancer in children and AYAs (763). Furthermore, pharmaceutical companies are less likely to invest in pediatric cancer drug development and clinical trials due to the smaller patient population, limited market potential, and strict regulatory requirements (771). Therefore, any cuts to federal agencies and their programs would disproportionately impact pediatric cancer research, as combined public and philanthropic funding commitments to pediatric cancer are already considered inadequate and have been in decline (665). The consequences of recent disruptions to NIH and NCI funding are already being felt by pediatric cancer patients (772,773).

Policies Advancing Pediatric Cancer Research and Care

Past investments, support, and legislative actions from the US government have played a crucial role in accelerating progress against pediatric cancer. Bipartisan congressional efforts in both the House and Senate, including champions within the Congressional Childhood Cancer Caucus, have been key to many of the past decade's achievements, especially in expanding pediatric cancer data collection, building research infrastructure, and accelerating drug development (see **Sidebar 26**, p. 148).

SIDEBAR 26

Legislative Achievements Driving Progress Against Pediatric Cancer (2010–2025): 15 Years of Milestones

Looking back over the past 15 years, bipartisan congressional efforts have transformed pediatric cancer research and care. This timeline highlights key milestones that have helped accelerate progress, bringing new hope to patients and their families.

2010 The Patient Protection and Affordable Care Act is signed into law, improving insurance coverage and survival outcomes for children, adolescents, and young adults with cancer. Provisions include prohibiting insurance companies from denying coverage or increasing premiums for children who develop cancer; allowing young adults to remain on their caregivers insurance plans until age 26, thereby ensuring continuity of care for childhood cancer survivors into adulthood, and expanding Medicaid and Children's Health Insurance Program coverage.

2012 The Creating Hope Act is first passed as part of the US Food and Drug Administration (FDA) Safety and Innovation Act of 2012 as a 4-year program incentivizing the development of drugs for rare pediatric diseases, including cancer, by offering priority review vouchers.

2014 The Gabriella Miller Kids First Act is signed into law, authorizing $12.6 million each year for 10 years to support pediatric research within the National Institutes of Health (NIH) Common Fund.

2016 The Creating Hope Act is reauthorized for 4 more years.

2017 Congress passes the Research to Accelerate Cures and Equity (RACE) for Children Act to accelerate the development of new treatments for pediatric cancers by requiring that new adult cancer drugs be studied in children, when molecularly relevant to childhood cancer and studies are feasible.

2018 The comprehensive Childhood Cancer Survivorship, Treatment, Access, and Research Act of 2018 (STAR Act) is passed. It focuses on expanding research opportunities, enhancing survivorship care, and improving childhood cancer surveillance.

2019 The Childhood Cancer Data Initiative (CCDI) is established by the National Cancer Institute (NCI) to improve data collection, sharing, and analysis for childhood cancer research. CCDI is supported by a $50 million annual federal investment, subject to continued appropriation by Congress.

2020 The RACE for Children Act goes into effect.

The Creating Hope Act is reauthorized a second time for another 4 years.

2023 The Childhood Cancer STAR Reauthorization Act is signed into law and reauthorizes funding for pediatric cancer research and related programs through 2028.

2024 The Gabriella Miller Kids First Research Act 2.0 is passed, which reauthorizes federal funding for the NIH Gabriella Miller Kids First Pediatric Research Program (Kids First).

2025 The Optimizing Research Progress Hope And New (ORPHAN) Cures Act is passed to amend the Inflation Reduction Act's orphan drug provisions to encourage continued research and innovation for rare disease treatments, including pediatric cancer.

Pediatric cancers are rare, which poses significant challenges for drug development, compared to other diseases. FDA has only issued roughly 100 pediatric cancer drug approvals ever, while there have been over 300 approvals in oncology overall since 2020 (774,775). Moreover, although studies have shown that approximately 30 percent of children with high-risk cancers have molecularly targetable findings, only 13.1 percent were receiving matched targeted therapies (163).

Legislation encouraging and facilitating pediatric cancer drug development has been one crucial way the US federal government has sought to bridge these gaps.

The landmark Creating Hope Act of 2011 incentivized pharmaceutical companies to develop drugs for rare pediatric diseases by expanding FDA's Priority Review Voucher (PRV) program. Specifically, the updated PRV program allowed pharmaceutical companies to expedite FDA review of more profitable drugs in return for the development of treatments that combat rare pediatric diseases, including cancer. Between 2012 and 2024, four PRVs were granted for drugs that treat pediatric cancer (776). A reauthorization of this essential piece of legislation, H.R.7384 Creating Hope Reauthorization Act of 2024 (777), would incentivize the continued development of new medications and treatments for pediatric cancer patients.

In 2003, the Pediatric Research Equity Act (PREA) passed, requiring sponsors of new drug applications or biologics license applications to submit assessments to FDA regarding potential applications for pediatric patients. However, the original law exempted therapeutics with orphan designations, which excluded almost all pediatric cancer studies since 75 percent (103 out of 137) of new drug and biologics applications for oncology received an orphan designation since 2013 (778). Introduced by Congressional Childhood Cancer Caucus Founder and Chair **Representative Michael McCaul (R-TX)** (see p. 150), the Research to Accelerate Cures and Equity (RACE) for Children Act, signed into law in 2017 and first implemented in 2020, amended PREA and authorized FDA to direct companies developing cancer drugs in adult settings to study the effects of those drugs in pediatric patients when the molecular targets of the drug are relevant to pediatric cancers (779). Furthermore, the recently passed ORPHAN Cures Act encourages drug sponsors to investigate the utility of existing FDA-approved treatments in additional pediatric cancer settings. The RACE for Children Act has been credited for greater numbers of post-approval pediatric testing requirements and the earlier initiation of pediatric trials for new therapies (420). No drugs approved between 2017 and 2020 had post-approval pediatric testing requirements. After enactment of the RACE for Children Act, from 2020 to 2024, 15 of 21 new adult drugs had required pediatric testing. However, while the RACE Act strengthened the requirements to conduct pediatric testing, it does not guarantee that the studies will be completed. Since there are limited enforcement mechanisms to ensure study completion and no mandate to develop these drugs further, it remains an open question whether there will be any notable increase in new drug approvals for pediatric populations.

Legislative actions have also promoted pediatric cancer research by enhancing the storing, harmonizing, and sharing of genomic and clinical data. The Gabriella Miller Kids First Research Act 2.0, a reauthorization of the 2014 act, ensures that research of pediatric cancer and structural birth defects remains an NIH priority. Named after Gabriella Miller, who died from an aggressive, deadly brain cancer (DIPG, mentioned above) in October 2013, this bill continues support for the Gabriella Miller Kids First Pediatric Research Program, including initiatives to perform sequencing on patients with pediatric cancer and structural birth defects and the comprehensive Kids First Data Resource Center (see **Building and Connecting Data Networks**, p. 45) (780). The Kids First Data Resource Center has enabled large-scale collaborative research that accelerates the translation of data into clinical insights (781). Initiatives like the Data for Pediatric Brain Cancer Act of 2023, introduced by Representative Mike Kelly (R-PA) and **Representative Ami Bera, MD (D-CA)** (see p. 152), aim to further these efforts for pediatric brain cancer by creating a new registry to systematically collect and manage real-world data on pediatric brain tumors.

The STAR Act and the STAR Reauthorization Act furthered these efforts to facilitate pediatric cancer research by creating various new data collection and sharing initiatives (782). This multi-pronged act includes the expansion of NCI biospecimen collection and repository programs for pediatric cancers and additional support for studies related to pediatric cancer survivorship. It also funds state-level cancer registries through the Centers for Disease Control and Prevention (CDC) to identify and track incidences of pediatric cancer and support the collection of cases into national cancer registries. Additionally, it requires that at least one pediatric oncologist be present on the National Cancer Advisory Board, a federal committee that advises the NCI Director on grants and policy to ensure that a focus on pediatric cancer remains at the forefront of NCI-supported research. The STAR Act has been credited for significantly expanding pediatric cancer research efforts, improving survivorship care, and enhancing data collection initiatives (783). Through authorization of $30 million annually for pediatric cancer research programs, the STAR Act has also helped support many projects through the Children's Oncology Group (COG) to collect data on rarer and understudied childhood cancers (784,785).

Following the STAR Act, the Childhood Cancer Data Initiative was established by NCI to increase data collection and sharing efforts across the pediatric cancer research community. Its goals include gathering data from every child and AYA regardless of where they receive care, creating a national strategy to accelerate molecular insights for diagnosis and treatment, and developing a platform and tools for researchers to utilize the data (309). The CCDI has expanded molecular profiling of pediatric cancers to better understand their unique tumor biology, driven therapeutic development, and built a critical data ecosystem that enables comprehensive data collection, sharing, and analysis (33). Through the CCDI Data Ecosystem, cancer researchers can further our understanding of pediatric cancers and investigate novel research questions.

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THE HONORABLE

MICHAEL MCCAUL

US REPRESENTATIVE FOR TEXAS'S 10TH DISTRICT

Pediatric cancer has profound effects on children and their families. Could you share how it has impacted you personally, or someone close to you?

"I first learned about cancer in fourth grade, when I noticed my best friend's hair falling out, and he told me he was really sick. I attended his funeral one month later. While it's impossible for a nine-year-old to really make sense of that, I knew I wanted to keep it from happening to other kids."

How has that experience influenced your work in Congress?

"I founded the Childhood Cancer Caucus as soon as I joined Congress because I noticed kids with cancer didn't have a voice in Washington. That's why I don't just work to pass legislation, but I also hold summits and opportunities for children fighting this brutal disease to visit D.C., make their voices heard, and show the world their incredible strength. Members of Congress may be able to say no to me, but they can't say no to these precious kids, who need us to fight on their behalf."

Which legislative or policy accomplishments are you most proud of that help address the needs of pediatric cancer patients and their families?

"I'm proud to have authored and passed several bills that are currently saving thousands of young lives. My Creating Hope Act, for example, established the Priority Review Voucher program, which was used by a dear friend of mine — Dr. Allison from MD Anderson in my home state of Texas — to obtain FDA approval for a groundbreaking treatment called CAR-T immunotherapy. Sixty-three vouchers have so far been awarded for rare pediatric diseases treatments since the bill's enactment. "

"This Congress, I'm working to reauthorize this crucial voucher program through my Give Kids A Chance Act. This bill would also authorize the FDA to direct companies to study combination drugs and therapies in pediatric trials — giving children the same chance as adults to beat cancer."

How has the tremendous bipartisan support for pediatric cancer research helped make an impact?

"It's truly inspiring to see congressmembers from both sides of the aisle come together to work on such an important topic. Without bipartisan support, none of our caucus' achievements would have been possible. My Give Kids A Chance Act currently has nearly 270 cosponsors, making it one of the most bipartisan bills in Congress, and it recently passed the House Energy and Commerce Committee with a rare, unanimous vote of 47-0. I'm hopeful this bipartisan momentum will help bring it to the House floor for a vote in the coming weeks."

Over the next five years, what do you see as the best opportunities for further improving outcomes for children with cancer in the U.S., particularly in rural or underserved communities?

"Telehealth will be vital in reaching our rural and underserved communities, allowing them to visit and keep up with doctors from afar. The Health Resources and Services Administration has been working to expand and improve broadband connections, so specialists can use technology like artificial intelligence to provide care without being in the same room. Additionally, President Trump recently issued an Executive Order that doubles the funding for the Childhood Cancer Data Initiative, which uses AI to advance research and treatments. My current bill, the Give Kids A Chance Act, would also help drug companies test developing combination drug therapies for children, and AI could play a large role in creating those future treatments."

What message would you like to share with the scientists, clinicians, and patient advocates working every day to make progress against pediatric cancer?

"Keep up the good work! Each year at my Childhood Cancer Summit, I bring in top scientists and researchers to share the exciting work being done in the childhood cancer space, and I'm never disappointed. From new cancer vaccines to natural killer cell therapy, significant breakthroughs are being made, and I am confident we are not far away from beating this heartbreaking disease — once and for all."

These legislative and policy achievements, the result of extensive coordination between advocacy groups, health professionals, and policymakers, continue to make significant, tangible steps forward in pediatric cancer research and help accelerate the development of new and more effective treatments (420).

Applying Regulatory Science to Advance Pediatric Cancer Research and Care

FDA plays a central role in safeguarding public health by evaluating the safety and efficacy of medical products, including cancer therapies. In pediatric oncology, this responsibility is heightened by the urgent need to address rare, biologically distinct, and often aggressive cancers that occur in young patient populations, requiring tailored scientific and regulatory approaches to ensure that children benefit from advances in cancer research as quickly and safely as possible.

Within FDA's Oncology Center of Excellence (OCE), the Pediatric Oncology Program leads efforts to integrate pediatric considerations early in oncology drug development. The program engages industry sponsors, academic investigators, and patient advocates to evaluate the relevance of molecular targets to pediatric cancers; encourages inclusion of children and AYAs in clinical trials when appropriate; and supports innovative trial designs such as basket and platform studies (see **Figure 9**, p. 66) (786,787). A chief responsibility of the program is to maintain the Pediatric Molecular Targets List, which was required by the RACE Act to guide FDA in determining whether drug development programs will be subject to additional pediatric clinical studies required under PREA. These approaches help maximize the efficiency of pediatric trials and aim to reduce the lag time between approval of adult and pediatric indications.

The Pediatric Oncology Program also holds meetings with various stakeholders, including the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (786). The Pediatric Subcommittee was created in recognition of the unique scientific, clinical, and ethical considerations involved in pediatric oncology to provide a formal mechanism to bring pediatric expertise into the regulatory process. Composed of pediatric oncologists, biostatisticians, and patient advocates, among others, the subcommittee serves as a forum for reviewing pediatric study plans, assessing trial design feasibility, developing strategies to overcome enrollment challenges, and considering age-appropriate endpoints and dosing.

Through the agency's coordinated efforts, FDA is working towards a regulatory framework that is scientifically rigorous, responsive to the unique needs of children and AYAs with cancer, and addresses the distinct challenges of rare pediatric cancers. By fostering collaboration among academic researchers, industry, and patient advocates, applying innovative trial designs, and ensuring that expert pediatric perspectives inform decision-making, the agency can help bring promising therapies to young patients faster, without compromising safety or efficacy.

The Next Decade: Challenges and Opportunities in Pediatric Cancer Research and Care

In the past decade, significant bipartisan US policymaking efforts have advanced pediatric cancer research and care. Scientific advances have dramatically increased survival for many patients, of even once incurable cancers. As pediatric cancers are rare, streamlined infrastructure, public–private partnerships, and international collaborations to support large multicenter clinical trials, biorepositories, and data-sharing projects have been crucial components underlying these successes (80). Despite notable progress, many challenges remain, including funding gaps, regulatory hurdles, and disparities in access and outcomes.

Pediatric cancer clinical trials face a multitude of barriers, including limited trial availability and eligibility, difficulties with enrollment, lack of adequately trained investigators and staff, financial constraints, and regulatory complexity (788,789). It is estimated that only one in five pediatric cancer patients is able to enroll in a clinical trial (273). Despite the push for incentivizing pediatric cancer research, pediatric clinical trials have not significantly increased. Moreover, pediatric tumors differ greatly from adult tumors, and more research is needed to understand their unique biological underpinnings (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29) (790). Fully funded and nationally coordinated pediatric cancer screening and surveillance programs are also critical for the early detection of childhood cancers, which helps inform epidemiologic studies, increases our understanding of their unique biology, and improves treatment outcomes (see **Pediatric Cancer Predisposition and Surveillance**, p. 47) (36).

Cancer care for pediatric patients also faces persistent challenges. Pediatric cancer patients and their families experience substantial negative financial impacts, which follow them into survivorship (see **Financial Challenges**, p. 113) (791,792). Financial support for patients and their families during and after treatment is critical for ensuring that children and adolescents with cancer have access to necessary care and specialized services such as psychosocial support (600). Another common barrier to care is the

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THE HONORABLE

AMI BERA, MD

US REPRESENTATIVE FOR CALIFORNIA'S 6TH DISTRICT

Pediatric cancer has profound effects on children and their families. Could you share how it has impacted you personally, or someone close to you?

"As a young medical student, I initially thought I would become a pediatrician. During my pediatric rotation, I cared for children—sometimes infants—battling cancer. That experience left a lasting impression on me. I know it takes a resilient person to care for young patients whose lives are often cut tragically short. That's one of the reasons I serve as co-chair of the Pediatric Cancer Caucus—because we must do everything we can not only to support children diagnosed with cancer, but also to ease the anguish on their parents' faces. That sense of purpose has stayed with me throughout my medical career and continues to guide me in Congress."

How has that experience influenced your work in Congress?

"One of the reasons I agreed to co-chair the Pediatric Cancer Caucus is because I strongly believe we can cure cancer. With major advances in gene therapy, biologics, and cutting-edge research, we're not only slowing the disease—we're helping more patients achieve remission and live longer, healthier lives. But the majority of that research is focused on adult cancers, and I want to make sure we're making the same level of effort and investment to address pediatric cancer."

How has the tremendous bipartisan support for pediatric cancer research helped make an impact?

"I'm extremely proud of the bipartisan effort to drive progress toward finding a cure for pediatric cancer. Through legislation like the Childhood STAR Act, we have provided critical federal support to advance research, improve treatments, and give more children the chance to grow up healthy and strong. We must maintain and expand these investments to ensure our doctors and researchers can continue building on this vital work and ultimately cure pediatric cancer."

Over the next five years, what do you see as the best opportunities for further improving outcomes for children with cancer in the U.S., particularly in rural or underserved communities?

"In the immediate term, we must preserve a health care system that provides coverage for folks in rural and underserved communities. That means pushing back against Medicaid cuts, which disproportionately harm these areas. We've also seen reductions to the NIH budget that threaten our ability to advance cancer research. I'm committed to working with my Republican colleagues to prevent further cuts and to reverse those that have already been made."

What message would you like to share with the scientists, clinicians, and patient advocates working every day to make progress against pediatric cancer?

"***To the parents:*** Don't lose hope."

"***To the children:*** You are some of the most courageous individuals I've ever met—bravely enduring incredibly difficult treatments."

"***To the scientists, clinicians, and advocates:*** Let's keep working together to find a cure and ease the suffering. The breakthroughs we achieve in pediatric cancer research will not only save young lives—they'll also help us better understand and treat cancer in adults."

lack of hospitals or clinical trial sites that are equipped to serve pediatric patients within accessible travel distance. Such geographic limitations exacerbate disparities among underserved and rural populations and will require expanding the capabilities of local health care facilities or building new centers (417). Moreover, understanding and mitigating the late effects of cancer treatment in children is an area in which further research is needed to improve the health and quality of life of the growing population of childhood cancer survivors (see **Supporting Survivors of Pediatric Cancers**, p. 104) (476). It is increasingly important for researchers and oncologists to consider the long-term and late effects of existing cytotoxic chemotherapy and radiotherapy, as well as newer cancer treatments, including novel targeted therapies, immunotherapies, cell and gene therapies, and combination regimens as they are developed to improve outcomes.

These challenges highlight the urgent need for continued action. Although past legislation and policies have stimulated industry productivity and the clinical development of new potential therapies for children, there is an opportunity for additional efforts to produce tangible advances in care and outcomes. Novel approaches to studying pediatric cancer that provide financial incentives for biotechnology and pharmaceutical companies to invest in childhood cancer therapies is a clear need. Additionally, simplifying the regulatory environment for drug development would be immensely beneficial. A meaningful opportunity exists over the next decade for stakeholders, including policymakers and the public, to further accelerate progress in pediatric cancer research and care.

Current Legislation Under Consideration

To address areas of unmet need in pediatric cancer, Congress has introduced several bills for consideration to spur increases in drug development and access to care. One potential legislation that would benefit pediatric cancer drug development is the Innovation in Pediatric Drugs Act of 2025 (793). This bill would modify existing pediatric drug laws like PREA and the Best Pharmaceuticals for Children Act to ensure timely completion of pediatric studies. Currently, under these laws, pediatric studies are required for certain new drugs designed for adult populations, but exemptions exist for rare diseases—which encompass indications for most new pediatric drugs. Enactment of the newly proposed legislation would enable FDA to close this loophole, penalize companies who fail to complete required pediatric studies in a timely manner, and provide funding for the study of older drugs approved for adults in children.

The Give Kids a Chance Act of 2025, introduced in the House by Representative McCaul (R-TX) and cosponsored in the Senate by Senator Mullin (R-OK) and **Senator Michael Bennet (D-CO)** (see p. 154), contains provisions from four bills previously proposed but not yet passed, including the Innovation in Pediatric Drugs Act, Give Kids a Chance Act of 2024, the Creating Hope Reauthorization Act, and the Retaining Access and Restoring Exclusivity Act (794). Together, this multi-part bill would remove multiple barriers in pediatric drug development. In addition to requiring pharmaceutical manufacturers to invest in drugs with potential indications for rare pediatric diseases by granting FDA greater authority to enforce pediatric study requirements, it also may require pharmaceutical companies to study drug combinations in children to help address the need for timely development of combinatorial trials. Moreover, this bill would reauthorize and strengthen the pediatric rare disease PRV program. Reauthorizing the PRV program for an additional 6 years would ensure that pharmaceutical companies developing drugs to treat pediatric cancers can expedite FDA review of more profitable drugs in their pipeline, powerfully incentivizing their development. Since the original Creating Hope Act was first passed into law in 2012, 53 PRVs have been awarded for 39 rare pediatric diseases (776).

Similarly, the Ensuring Pathways to Innovative Cures (EPIC) Act would modify the Inflation Reduction Act to enhance drug development for rare diseases in ways that could benefit pediatric cancer. Under the Inflation Reduction Act, small molecule drugs are exempt from Medicare price negotiations for only 9 years, compared with 13 years for biologics. This discrepancy could disincentivize the development of small molecule drugs in favor of biologics, an important consideration because small molecules are more accessible to patients than biologics (795). The EPIC Act would equalize this discrepancy, with both receiving 13 years of exclusion. This could lead to the development of more small molecule drugs and improve access to lifesaving medications for pediatric patients.

The impact of novel, transformative therapeutics for pediatric cancer would be greatly diminished without ensuring patients have widespread access to them. As such, many pieces of legislation are under consideration that can facilitate clinical care access for patients with pediatric cancer. For example, the Knock Out Cancer Act of 2025 calls for significant funding increases for NCI each year for the next 5 years—based on FY 2022 funding—to both address the dire need for increased research funding and to address the national crisis of cancer drug shortages (796).

Crucially, in addition to the inadequate availability of therapeutics, access to care for many patients is hindered by a lack of access to highly specialized providers. Treatments for children on Medicaid needing care outside their home state are often limited by restrictive provider screening and enrollment processes. Streamlining the process of accessing these experts is essential for timely and quality care. The Accelerating Kids'

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THE HONORABLE

MICHAEL BENNET

US SENATOR FOR COLORADO

Which legislative or policy accomplishments are you most proud of that help address the needs of pediatric cancer patients and their families?

"Families in Colorado and across the country face barriers in accessing innovative pediatric cancer treatments and lifesaving care. Researchers and clinicians are battling bureaucratic red tape and inadequate funding in their search for the next cure. In 2017, when Congress passed my legislation, the *RACE for Children Act,* we took a tremendous step forward in the fight to expand access to cutting-edge treatments by requiring drug companies to study the potential of promising adult cancer treatments for children. I continue to work across the aisle to champion the Accelerating Kids' Access to Care Act, which simplifies out-of-state Medicaid screening and enrollment for pediatric doctors so that kids don't have to wait to get the treatment they need. Additionally, I have introduced the Give Kids a Chance Act to give children with cancer access to combination therapy trials and incentivize pharmaceutical companies to develop treatments for rare pediatric diseases. Kids battling cancer deserve bright futures. If we do our job, we can help them realize those futures and end pediatric cancer as we know it."

How has the tremendous bipartisan support for pediatric cancer research helped make an impact?

"Advancing cures and expanding access to the best possible care for children with cancer shouldn't be a partisan issue. I have worked closely with my Republican colleagues to champion bipartisan legislation accelerating research and expanding access to care. The bipartisan support for the *RACE for Children Act* was critical to passing the bill into law. I have also partnered with Senator Markwayne Mullin to introduce the Give Kids a Chance Act. I am hopeful that, despite divisions in Congress, Democrats and Republicans will continue to work together to advance lifesaving legislation that meets the scale of the challenge that children with pediatric cancer face across our country."

Over the next five years, what do you see as the best opportunities for further improving outcomes for children with cancer in the U.S., particularly in rural or underserved communities?

"Our health care system repeatedly falls short of giving working families the care they need, especially in rural communities. Across our state, I hear from Coloradans forced to drive hours to receive specialized care. We must refocus Congress's attention on expanding health care access, not cutting it. Extending the Enhanced Premium Tax Credits is critical to ensure all families, including those facing a pediatric cancer diagnosis, have affordable insurance and can get the care they deserve. My legislation, the Medicare-X Choice Act, would create a public health insurance option. It would offer families, individuals, and small businesses affordable health insurance. This would decrease the number of uninsured Americans, help to control the cost of health care, and increase competition in the health insurance market. Every American deserves access to affordable health care."

What message would you like to share with the scientists, clinicians, and patient advocates working every day to make progress against pediatric cancer?

"Your dedication gives kids across the country hope and a chance to beat cancer and reclaim their lives. In Colorado, we are proud of our world-class hospitals and research institutions that serve as models in pioneering next-generation discoveries. Children's Hospital Colorado and the University of Colorado continue to transform the standard of pediatric cancer care and lead groundbreaking clinical trials. We have made great strides in recent years, and we cannot slow down the pace. Further cuts to research funding will only set us back and hinder lifesaving discoveries. I will continue to be a partner at the federal level to restore health research funding and provide the necessary support in the race to save children's lives."

Access to Care Act of 2025 would create a pathway for pediatric providers to enroll in multiple state Medicaid programs, reducing overall administrative burden, bureaucratic hurdles, and therefore delays in accessing specialized care for children with cancer (797).

Furthermore, molecularly targeted therapeutics frequently require the use of companion diagnostics to select patients who are most likely to benefit from therapy. The Finn Sawyer Access to Cancer Testing Act would provide Medicare, Medicaid, and Children's Health Insurance Program coverage for cancer patients to receive molecular diagnostics during their cancer diagnosis (798). It would also provide increased resources for genomic testing and genetic counseling. The bill is named after Finn Sawyer, who died from rhabdomyosarcoma before his fourth birthday following years of chemotherapy. The act would ensure that children with cancer, like Finn Sawyer, receive molecular testing at initial diagnosis and can benefit from lifesaving personalized treatments right away rather than waiting for when cancer recurs.

For the pediatric patient community, the cancer journey does not end once treatment is completed. Often, lifelong support is needed, given the significant health concerns experienced due to the potential long-term and late side effects of cancer treatment. The Comprehensive Cancer Survivorship Act (CCSA) would provide coverage for care-planning to address the transition from oncology to primary care, develop helpful patient navigation for survivorship services, establish employment assistance grants, increase education on survivorship needs, ensure coverage for fertility preservation services, and examine existing payment models and ways they can be improved (see **Supporting Survivors of Pediatric Cancers**, p. 104). The CCSA aims to address known gaps in survivorship care for pediatric cancer patients and will also require additional research on the long-term and late effects of cancer diagnosis and treatment in these populations (799).

Potential Policy Actions to Advance Pediatric Cancer Research and Care

While legislation currently under consideration has the potential to bring hope to the pediatric cancer community, additional opportunities exist that can catalyze further progress. Last reauthorized in January 2023, the STAR Act has been imperative to the expansion of pediatric cancer research funding, and lawmakers would be forward-thinking to reauthorize it again before the law expires at the conclusion of FY 2028. However, annual federal appropriations are still required to ensure funding for the STAR Act. Importantly, to achieve equitable outcomes for all children and adolescents with cancer, research to understand health disparities and the development of policies to address those disparities must be supported (800). Policies that promote comprehensive insurance coverage for all populations, mitigate barriers to health care access, and incorporate social drivers of health would ensure access to high-quality cancer care and state-of-the-art treatments.

Additional policy opportunities can improve pediatric drug development. First, pediatric studies mandated by the RACE Act face the same issues around delays and noncompletion that are seen in overall pediatric research. Given the limited authority FDA has to address delays in study completion, policymakers could consider updating the RACE Act with new provisions that set timelines for initiating clinical trials and making pediatric data available. Second, FDA could reconsider how it determines whether a pediatric study is required under the RACE Act. The Pediatric Molecular Target List currently has more than 200 relevant targets, and more regular updates that adopt innovative, data-driven approaches to identify new molecular targets could increase the number of adult cancer drugs that go on to receive pediatric approval. Finally, FDA could consider ways to maximize the impact of pediatric cancer studies by streamlining the process to accept amendments to clinical trials, prioritizing enrollment based on anticipated level of benefit (especially for patients with molecular profiling data, where applicable), allowing trials that evaluate multiple therapies at once (see **Figure 9**, p. 66), incentivizing combined trials in pediatric and adult populations when the target is present in both, and coordinating regulatory requirements and timelines with the European Medicines Agency and other international regulators to reduce duplication and conflicting requirements (801).

Finally, policies that financially incentivize biotechnology and pharmaceutical companies to invest in therapies that specifically target pediatric cancer are critical. Over half of pediatric tumors are driven by genetic mutations not found in adult cancers (see **Unraveling the Genomics and Biology of Pediatric Cancers**, p. 29) (164). Consequently, the current model of developing drugs for adult cancers and then studying them in pediatric patients will not lead to mutation-targeted therapies for a majority of childhood cancers. Instead, strategies must be employed to increase drug development that is specific to pediatric cancer targets.

AACR CALL TO ACTION

Tremendous progress has been made against pediatric cancer over the past several decades, and many achievements are detailed in this inaugural report. Remarkable advances across the continuum of pediatric cancer science and patient care have translated to a measurable impact, with cancer death rates among youth (age 19 and younger) in the United States declining by 24 percent between 2001 and 2021. As a result, today more than 85 percent of children diagnosed with cancer are alive at least 5 years after diagnosis. These scientific achievements are attributable in large part to bipartisan support in Congress, innovative public and private initiatives, and the commitment of patient advocates.

Continued progress requires robust and sustained federal investments, as well as enacting critical legislation to address key challenges. Pediatric cancer patients and their families rely on federally supported health care services and infrastructure. Without federal support, future breakthroughs as well as ongoing care for pediatric cancer patients are at risk. The bottom line is that decisions made today by Congress and the federal government will shape the fight against pediatric cancer for decades to come.

Therefore, we call on all stakeholders to engage with members of Congress and leaders at federal agencies to prioritize pediatric cancer research and patient care. More specifically, AACR recommends the following actions:

- **Congress needs to provide robust and sustained funding for the federal agencies and programs that are focused on supporting pediatric cancer research and patient care.** To maintain American global leadership in medical research, Congress should provide at least $51.303 billion for the National Institutes of Health (NIH) in fiscal year (FY) 2026. Congress should also provide at least $7.934 billion for the National Cancer Institute (NCI) in FY 2026, while also prioritizing pediatric cancer research.
- **Expand access to clinical trials and promising therapies for children and adolescents with cancer.** Introducing targeted regulatory incentives, such as tax credits or extended market exclusivity, to encourage greater industry participation in pediatric cancer trials would very likely increase the number of available clinical trials and eventually accelerate drug approvals to benefit pediatric cancer patients. Beyond the amount of ongoing clinical pediatric cancer research, additional barriers to access exist that must be addressed. Most clinical trials are offered only at academic medical centers, which may be logistically or economically difficult for patients and their caregivers to reach. Moreover, patient and provider awareness of the clinical trial landscape also greatly varies. Increased and targeted outreach efforts to rural and socially disadvantaged areas, Medicare reimbursement models that support the costs involved with clinical trial participation, and increased use of decentralized trials will be required to increase the number and diversity of pediatric patients receiving state-of-the-art care in clinical trials.
- **Modernize and evaluate current pediatric cancer research programs and policies to better support the discovery and development of treatments as well as to improve patient care.** Lawmakers must update the RACE Act and ORPHAN Cures Act to improve those policies and provide additional incentives to companies to develop pediatric oncology drugs and ensure that pediatric studies beyond their initial evaluation are carried out. Renewing and expanding the Rare Pediatric Disease Priority Review Voucher program will accelerate pediatric oncology drug development and increase the number of available treatment options.
- **Support efforts that leverage and harmonize all available data to aid pediatric cancer research.** The rarity of pediatric cancers is further compounded by the rarity of individual cancer subtypes that fall under the umbrella of pediatric cancer. The NCI Childhood Cancer Data Initiative (CCDI) is essential to maximizing the quantity and quality of all data collected on pediatric cancer to enhance research capabilities and identify and address potential disparities. The Administration's recent Executive Order from September 30, 2025, to "prioritize the harnessing of American artificial intelligence innovation to unlock cures for pediatric cancer" includes important objectives and proposals that must be fully supported. In addition, continued STAR Act support for the CCDI will be crucial to efforts to create an environment in which pediatric cancer researchers will have enough data available for studies to uncover and understand drivers of disease, disparities, and outcomes. These programs should be further leveraged to develop a national pediatric data infrastructure that allows for improved data collection and sharing, and informs pediatric cancer diagnostic testing.
- **Foster global and public–private partnerships to accelerate pediatric cancer research and the development of innovative treatments for pediatric cancer patients.** Pediatric cancer research efforts are often fragmented across different institutions and countries, limiting the ability to pool resources,

data, and expertise. Clinical trials for especially rare pediatric cancers require international collaboration and support. Streamlining data-sharing through federated databases and harmonizing regulatory processes across the globe will accelerate research and facilitate the conduct of meaningful clinical trials by providing access to statistically powered patient populations. The United States must build on successful models and prioritize global and public–private partnerships to increase survival rates and improve quality of life for pediatric cancer patients.

- **Strengthen survivorship and long-term care for pediatric cancer survivors by ensuring comprehensive, accessible, and reimbursable long-term care services.** After enduring pediatric cancer treatment, survivors often face a lifetime of potential late-onset effects, including heart disease, second primary cancers, infertility, and cognitive impairments. These long-term health challenges significantly impact their quality of life, educational attainment, vocational opportunities, and financial well-being. Strengthening survivorship research and care services is an investment in the future of these patients and in society as a whole. Such strengthening includes supporting dedicated and comprehensive survivorship programs at treatment centers, streamlining transitions to adult care, and mitigating financial costs. Oncology professional societies (physicians, nurses, and social workers) should develop standards for transitions of survivors from oncology care to primary care and for appropriate follow-up programs for survivors of different cancer types.

Fulfilling the recommendations of this Call to Action will build on past achievements and further accelerate progress against pediatric cancer. Now is the time for a renewed commitment from stakeholders, including the biopharmaceutical industry, academic and medical institutions, patient-centric organizations, and the federal government, to scientific research with the potential to save and improve the lives of millions of children and adolescents who have or have had cancer. Congress holds tremendous power to continue to advance the progress that has already been made and sustain it for future generations. AACR urges everyone to come together at this critical moment in the fight against pediatric cancer to provide hope to children, adolescents, and their families.

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APPENDIX

SUPPLEMENTARY TABLE 1

Pediatric Cancers in the United States: Age-Specific Incidence Rates and 5-year Survival Rates

	Children (0-14 years)		Adolescents (15-19 years)	
	INCIDENCE RATES* (%)‡	5-YEAR SURVIVAL† (%)	INCIDENCE RATES (%)	5-YEAR SURVIVAL (%)
All ICCC groups (malignant only)	**167.0 (100)**	**86**	**243.6 (100)**	**88**
Leukemias	52.2 (31)	89	36.5 (15)	79
Lymphoid leukemia	41.1 (25)	93	19.6 (8)	79
Acute myeloid leukemia	7.6 (5)	71	9.3 (4)	72
Lymphomas and reticuloendothelial neoplasms	20.8 (12)	95	53.3 (22)	95
Hodgkin lymphoma	5.6 (3)	98	32.3 (13)	98
Non-Hodgkin lymphoma	8.2 (5)	91	17.0 (7)	89
Central nervous system neoplasms	31.3 (19)	76	21.2 (9)	80
Neuroblastoma and other peripheral nervous cell tumors	12.1 (7)	85	1.3 (1)	84
Retinoblastoma	4.0 (2)	97	-	-
Nephroblastoma and other nonepithelial renal tumors	7.9 (5)	93	0.3 (<1)	-
Hepatic tumors	3.7 (2)	81	1.6 (1)	53
Hepatoblastoma	3.2 (2)	82	0.1 (<1)	-
Bone tumors	7.3 (4)	74	15 (6)	69
Osteosarcoma	4.2 (3)	67	8.5 (3)	64
Ewing tumor and related bone sarcomas	2.5 (1)	82	4.3 (2)	68
Soft tissue sarcomas	10.9 (7)	76	16.3 (7)	74
Rhabdomyosarcoma	5.0 (3)	69	4.0 (2)	55
Fibrosarcomas/Peripheral nerve sheath tumors	0.9 (<1)	90	1.6 (<1)	77
Other specified soft tissue sarcomas	3.5 (2)	81	8.2 (3)	80
Unspecified soft tissue sarcomas	1.5 (<1)	75	2.3 (<1)	76
Germ cell and gonadal tumors	5.7 (3)	93	28.7 (12)	95
Thyroid carcinomas	3.4 (2)	>99	32.8 (13)	>99
Malignant melanomas	1.3 (1)	94	7.5 (3)	97

ICCC, International Classification of Childhood Cancer.

* Incidence rates are per 1,000,000, based on diagnoses during 2018–2022, and age-adjusted to the US standard population.

† Survival rates are based on diagnoses during 2015–2021, all followed through 2022.

‡ Percent of total cases.

Sources: (5,17).

SUPPLEMENTARY TABLE 2

International Classification of Childhood Cancer

Site Group	Types
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	Lymphoid leukemias; acute myeloid leukemias; chronic myeloproliferative diseases; unspecified and other specified leukemias
II. Lymphomas and reticuloendothelial neoplasms	Hodgkin lymphomas; non-Hodgkin lymphomas (except Burkitt lymphoma); Burkitt lymphoma; miscellaneous lymphoreticular neoplasms; unspecified lymphomas
III. CNS and miscellaneous intracranial and intraspinal neoplasms	Ependymomas and choroid plexus tumor; astrocytomas; intracranial and intraspinal embryonal tumors; other gliomas; other specified intracranial and intraspinal neoplasms; unspecified intracranial and intraspinal neoplasms
IV. Neuroblastoma and other peripheral nervous cell tumors	Neuroblastoma and ganglioneuroblastoma; other peripheral nervous cell tumors
V. Retinoblastoma	
VI. Renal tumors	Nephroblastoma and other nonepithelial renal tumors; renal carcinomas; unspecified malignant renal tumors
VII. Hepatic tumors	Hepatoblastoma ; hepatic carcinomas; unspecified malignant hepatic tumors
VIII. Malignant bone tumors	Osteosarcomas; chondrosarcomas; Ewing tumor and related sarcomas of bone; other specified malignant bone tumors; unspecified malignant bone tumors
IX. Soft tissue and other extraosseous sarcomas	Rhabdomyosarcomas; fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms; Kaposi sarcoma; other specified soft tissue sarcomas; unspecified soft tissue sarcomas
X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	Intracranial and intraspinal germ cell tumors; malignant extracranial and extragonadal germ cell tumors; malignant gonadal germ cell tumors; gonadal carcinomas; other and unspecified malignant gonadal tumors
XI. Other malignant epithelial neoplasms and malignant melanomas	Adrenocortical carcinomas; thyroid carcinomas; nasopharyngeal carcinomas; malignant melanomas; skin carcinomas; other and unspecified carcinomas
XII. Other and unspecified malignant neoplasms	Other specified malignant tumors; other unspecified malignant tumors

Source: (803).

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