Pediatric Cancer Landscape

2026

Pediatric Cancer Landscape 2026

Table of Contents

Issue Overview	1
Acknowledgments	4
1. Introduction	5
2. Biological Understanding	13
3. Preclinical Drug Development	20
4. Clinical Research	27
5. Regulatory Requirements	33
6. Data, Data Sharing, and Artificial Intelligence	44
7. Funding, Investment, and the Economics of Discovery	54
Conclusion	65
Appendix	66

This report is a product of the Alliance for Childhood Cancer and the American Cancer Society Cancer Action Network.

Copyright 2026. All rights reserved.

Pediatric Cancer Landscape 2026

Issue Overview

Cancer is the leading disease-related cause of death for children and adolescents aged 1-19. While cancer is much rarer in children than in adults, it has an enormous impact because it strikes so early in life. The high rate of late side effects in survivors of pediatric cancer can decrease life expectancy and impact quality of life for decades.[1] The American Cancer Society estimates that in 2026 in the U.S. there will be 9,680 new childhood cancer cases and 1,090 cancer deaths among children (ages 0-14). Among adolescents (ages 15-19), there will be an estimated 5,660 new cancer diagnoses and 730 cancer deaths.[2] By age 50, 96% of childhood cancer survivors had at least one grade 3-5 (severe, disabling, life-threatening, or fatal) chronic health condition.[1]

Despite substantial advances in pediatric cancer research and clinical care over the past decades, important challenges remain. Continued progress will require both the development of more effective therapies and the reduction of short- and long-term adverse effects of existing therapies. Improving outcomes for children with cancer begins by recognizing that cancers that occur in children are not biologically the same as those experienced by adults. Children's bodies are physiologically unique which means that they may respond to treatments in ways that differ from adults. Sometimes these differences may only require altered dosing or formulations of adult drugs, but in most cases, pediatric cancers require unique therapeutic regimens.

While optimization of current therapies can improve outcomes, for many children with cancer, meaningful progress will require new drugs developed specifically for pediatric cancer. It is important to understand current statistics and context surrounding pediatric cancer and examine the research process that underlies the development of new therapies for children. Creating therapies for pediatric cancers involves unique scientific, logistical, economic, and regulatory challenges.[3] By understanding these challenges, efforts to create better treatments for children with cancer will have more impact.

Key issues to consider in the pediatric cancer landscape include:

- **Pediatric cancer statistics:** Although cancer is much rarer in children and adolescents than in adults, the impact of pediatric cancer is substantial because it strikes so early in life. In 2024, cancer deaths in pediatric patients between 0-19 years of age resulted in an estimated 122,600 years of life lost, or a reduced lifespan of an average of about 68 years per death.[4] Among pediatric patients diagnosed with cancer in 2015–2021, the overall 5-year survival rate was 86%, up from less than 60% in the mid-1970s.[5] Further, prognoses vary considerably depending on tumor subtype and other factors. For example, while 5-year survival rates among children with low-risk neuroblastoma exceed 95%, children with higher-risk disease need much more intense treatments and have a much lower survival rate of nearly 60%.[6,7] Among the cancers with the poorest outcomes is diffuse intrinsic pontine glioma (DIPG), with fewer than 10% of children surviving even two years.[8]

- **Biology and preclinical research:** Pediatric cancer is unique biologically, and drugs developed to treat these cancers need to be tailored to the unique physiology of children and adolescents. Because children are still actively growing, treatments can cause side effects that may not occur in adults, or that may be more severe or debilitating in children. Examples of treatment-induced side effects include heart damage, deafness, infertility, or the development of subsequent cancers caused by treatments (e.g. radiation) for the initial cancer.[9,10] As a result, 96% of survivors will have a severe or life-threatening chronic condition by age 50.[1]

- **Clinical research:** Clinical trials are key to determining safety and efficacy of a drug or drug combinations, and often incorporate other treatment modalities such as surgery and radiation therapy. Although children's participation in cancer clinical trials is relatively common compared to adults with cancer, made possible in part through the National Cancer Institute's (NCI's) investment in the Children's Oncology Group network of trial sites, there are nonetheless unique issues when conducting clinical research with children. Trial designs and outcome measures need to be tailored to the specific biology of pediatric cancers and patients, as well as to the small population size of children with cancer.[11]

- **Research funding and economic forces:** Public policies have created pediatric-specific incentives and requirements to drive more development of drugs for pediatric cancers, yet progress still lags behind that of adult cancers.[12] Research and drug development are expensive and require substantial financial resources to create the final products that result in improved outcomes for children. Private industry, the federal government, and philanthropies all fund cancer research, but they tend to fund different aspects of cancer research. A primary incentive for private investment in drug development is the potential to profit from an approved drug; however, the relatively small number of pediatric cancers means limited incentives for industry investment in treatments for children and adolescents with cancer. With reduced industry funding, federal and philanthropic funding have increased relevance in driving clinical development in pediatric cancer, but these sources cannot fully replace industry funding.

- **Data, data sharing, and artificial intelligence:** While clinical trials are a formalized way to collect data about how a treatment works under very controlled conditions, huge volumes of data are generated every day outside of clinical trials during the normal course of care. Given the relative rarity of pediatric cancer, and the difficulty of running clinical trials, there is great opportunity to leverage a wide array of data to generate research insights. Every patient's medical record has the potential to transform fragmented clinical and research observations into a trustworthy data ecosystem, while maintaining essential patient privacy and data protections. Advances such as those enabled by the Childhood STAR Act, the NCI's investment into the Childhood Cancer Data Initiative (CCDI) and the Advanced Research Agency for Health's investment in the Pediatric Care eXpansion (PCX) program have created a foundation for a data ecosystem.[12,13,14] Built on that foundation, artificial intelligence (AI) can uncover meaningful patterns, reduce the burden of data-intensive research, test hypotheses, and return knowledge that benefits pediatric cancer patients and their families.

- **Regulatory landscape:** Before a drug can be approved in the U.S., the Food and Drug Administration (FDA) must review evidence submitted by the drug's manufacturer and conclude that the drug is safe and effective, and that its benefits outweigh its risks. While FDA does not conduct clinical trials leading to drug approval, the agency does work closely with drug sponsors, advising them as they design clinical trials so that the evidence collected during clinical trials is the right type, quality, and quantity for FDA to evaluate a drug. Further, FDA enforces regulatory requirements that require some adult cancer drugs to be tested for use as pediatric cancer treatments. These and other regulatory responsibilities are essential, but are time- and labor-intensive, so it is important to provide sufficient resources to researchers and regulators to regularly identify and adopt innovations in evidence generation and evaluation that can ensure that safe and effective therapies can reach pediatric patients in a timely manner.

Understanding the unique aspects of pediatric cancer and the associated research challenges can help guide efforts to overcome these barriers. The collective engagement of children, families, researchers, industry and government can make significant progress possible.

References

1 Bhakta, N., Liu, Q., Ness, K. K., et al. (2017). The cumulative burden of surviving childhood cancer: An initial report from the St Jude Lifetime Cohort Study. The Lancet, 390(10112), 2569–2582.

2 Siegel, R. L., Kratzer, T. B., Wagle, N. S., Sung, H., & Jemal, A. (2026). Cancer statistics, 2026. CA: A Cancer Journal for Clinicians, 76(1), Article e70043.

3 Barry, E., Walsh, J. A., Weinrich, S. L., et al. (2021). Navigating the regulatory landscape to develop pediatric oncology drugs: Expert opinion recommendations. Paediatric Drugs, 23(4), 381–394.

4 Arias, E., Xu, J. Q., & Kochanek, K. (2025). U.S. life tables, 2023. National Vital Statistics Reports, 74(6), 1–63.

5 National Cancer Institute (2026a). Surveillance, Epidemiology, and End Results Program. www.seer.cancer.gov

6 Coughlan, D., Gianferante, M., Lynch, C. F., et al. (2017). Treatment and survival of childhood neuroblastoma: Evidence from a population-based study in the United States. Pediatric Hematology and Oncology, 34(5), 320–330.

7 Liu, K. X., Naranjo, A., Zhang, F. F., et al. (2020). Prospective evaluation of radiation dose escalation in patients with high-risk neuroblastoma and gross residual disease after surgery: A report from the Children's Oncology Group ANBL0532 study. J. Clinical Oncology, 38(24), 2741–2752.

8 Hoffman, L. M., Veldhuijzen van Zanten, S. E. M., et al. (2018). Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma (DIPG): A collaborative report from the International and European Society for Pediatric Oncology DIPG Registries. J. Clinical Oncology, 36(19), 1963–1972.

9 National Cancer Institute (2024). Cancer in children and adolescents. www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet.

10 Tonorezos, E., Cohn, R. J., Glaser, A. W., et al. (2022). Long-term care for people treated for cancer during childhood and adolescence. Lancet 399(10334), 1561–1572.

11 Vassal G, Zwaan CM, Ashley D, et al. (2013). New drugs for children and adolescents with cancer: the need for novel development pathways. Lancet Oncol. 14(3):e117-24.

12 Flores-Toro, J. A., Jagu, S., Armstrong, G. T., et al. (2023). The Childhood Cancer Data Initiative: Using the power of data to learn from and improve outcomes for every child and young adult with pediatric cancer. Journal of Clinical Oncology, 41(24), 4045–4053.

13 National Cancer Institute (2025) About the Childhood Cancer Data Initiative (CCDI). www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/about

14 Advanced Research Projects Agency for Health (2026) ARPA-H announces $50M to expand pediatric care across the country. arpa-h.gov/news-and-events/arpa-h-announces-50m-expand-pediatric-care-across-country.

Acknowledgements

The content for this report was guided by, written, and edited by members of a cross-sector steering committee, without whose help this report would not have been possible.

Steering Committee

Stacey J. Adam
Foundation for the NIH

Rosalie Abbott
St. Baldrick's Foundation

Mackenzie Bloom
St. Jude Children's Research Hospital

Wendy Chill
American Society of Pediatric Hematology/Oncology

Robert Clark
St. Jude Children's Research Hospital

Martha Donoghue
U.S. Food and Drug Administration

Mark Fleury
American Cancer Society Cancer Action Network

Lawren Gaffey
Servier

Lia Gore
University of Colorado

Alice Kuaban
American Society of Hematology

Tyler B. Kratzer
American Cancer Society

Michael Link
Stanford University School of Medicine

Matt Mariani-Seltz
American Academy of Pediatrics

Matthew Marks
Blood Cancer United

Alex May
Genentech

Tyrone McClain
Pfizer

Linda McAllister-Lucas
Mayo Clinic

Erika Ninoyu
American Cancer Society Cancer Action Network

Namrata Pujara
American Academy of Pediatrics

Gregory Reaman
National Cancer Institute

Maggie Rogers
American Cancer Society

Jack Shern
National Cancer Institute

Sharon Shriver
American Cancer Society Cancer Action Network

Beth Siever
Children's National Hospital

Nikita Sandeep Wagle
American Cancer Society

Susan L. Weiner
Children's Cancer Cause

Additional Report Authors, Reviewers, and Contributors Include:

Maria Gonzalez Albuixech
American Cancer Society Cancer Action Network

Christina Annunziata
American Cancer Society

Elizabeth Darnall
American Cancer Society Cancer Action Network

Kayla Foster
American Cancer Society

Jen Fox
American Cancer Society Cancer Action Network

Anna Schwamlein Howard
American Cancer Society Cancer Action Network

Liora Sahar
American Cancer Society

Vanhvilai L Douangchai Wills
American Cancer Society

We extend our gratitude to the children, family and parents of the children featured in our vignettes and photos.

We also recognize all the children, the families and the researchers who have contributed to the research that has made improvements for childhood cancer possible.

Project management was provided by Danielle and Kirk Leach | Design work was provided by Amber Haynes

CHAPTER 1

Introduction

Summary

Cancer is the leading cause of disease-related death among children and adolescents. While progress has been made in understanding and treating pediatric cancer, many challenges remain. The types of cancer that occur, their response to treatment, and the broader health impacts of treatment differ between children and adults. Research and drug development should address the unique impact of treatment on children and drug effectiveness in pediatric cancers. This introduction summarizes the latest incidence and mortality statistics for pediatric cancers, and the chapters that follow describe current challenges, recent developments and major policies that impact progress in pediatric cancer research, drug development, and survivorship.

Introduction

Cancer is the leading cause of disease-related death among children aged 0-14 and adolescents aged 15-19 (see Figure A-1). While cancer is much rarer in children and adolescents than in adults, its impact is substantial because it strikes so early in life. In 2024, cancer deaths in pediatric patients between 0-19 years of age resulted in an estimated 122,600 years of life lost (YLL), or an average of about 68 years lost per death. (National Cancer Institute, 2026a; Arias, 2025) See Box for a discussion of categorization and terminology regarding childhood, pediatric, and adolescent cancer. The American Cancer Society estimates that in 2026 there will be 9,680 new cases and 1,090 cancer deaths among children (ages 0-14) and 5,660 new cases and 730 cancer deaths among adolescents (ages 15-19) in the U.S. (Siegel, 2026) Approximately 1 in 395 children will be diagnosed with cancer before age 15, and 1 in 265 children and adolescents will be diagnosed with cancer before age 20. (National Cancer Institute, 2026a; National Cancer Institute 2026b) Mortality rates for pediatric cancer are dropping, but many children who survive their cancer face a lifetime of side effects from their cancers and corresponding treatment. By age 50, 96% of childhood cancer survivors have at least one grade 3-5 (severe, disabling, life-threatening, or fatal) chronic health condition. (Bhakta, 2017)

TERMINOLOGY USED IN THIS REPORT

Definitions of "children," "adolescents," and "pediatric" vary between organizations and domains (e.g. legal versus research). A comprehensive overview of definitions used by different organizations is included in the *Appendix*; however, for the purposes of this report the following definitions will be generally used:

- Children/childhood cancer - ages 0-14
- Adolescents/adolescent cancer - ages 15-19
- Pediatric cancer - used in this report to include childhood and adolescent cancers (ages 0-19)

Note that some tools, studies, or other programs use "childhood cancer" in their formal name and apply to a broader age range than 0-14. For example, the Childhood Cancer Survivor Study (CCSS) comprises individuals diagnosed prior to the age of 21. Therefore, the use of "childhood" in these formal names within this report may not adhere to the general definitions otherwise used in this report.

Despite substantial advances in pediatric cancer research and clinical care, important challenges remain. Continued progress will require the development of more effective and less toxic therapies.

Improving outcomes for children with cancer begins by recognizing the many fundamental differences between pediatric and adult cancers. The cancers that occur in children are not biologically the same as those experienced by adults. Children may also respond differently to treatment. Sometimes these differences may only require a change in the dose or form of an adult cancer drug, but in many cases, pediatric cancer patients require unique treatment regimens.[1]

While optimization of current therapies can improve outcomes, for many children with cancer, progress requires new drugs specific to pediatric cancer biology. This report examines the pediatric cancer research and drug development landscape. While some aspects of research and drug development are shared between children and adults, there are also significant differences.

1 The general term "drug" is used throughout the report to represent small-molecule drugs, biological drugs, antibodies and other medicines or agents administered with the intent to treat cancer.

Developing therapies for pediatric cancers involves many unique scientific, logistical, economic, and regulatory challenges. By understanding these unique aspects, efforts can be focused on creating better treatments for children with cancer.

Report overview

This report is divided into multiple chapters that detail various aspects of pediatric cancer research and drug development. This introduction provides important statistics and context describing pediatric cancer, while the remaining chapters focus more specifically on the research and drug development process that underlies the development of new therapies for children. As seen in Figure 1-1, by the time a drug is approved for use, it has progressed through multiple steps that include basic science research to understand what drives cancer development, preclinical testing of new treatment ideas, clinical testing, and finally regulatory approval. This report is organized by the stages of the drug development process and outlines the unique challenges and opportunities associated with each stage. Vignettes featuring individuals and families who have experienced pediatric cancer are placed throughout the report and provide personal perspectives on pediatric cancer.

FIGURE 1-1

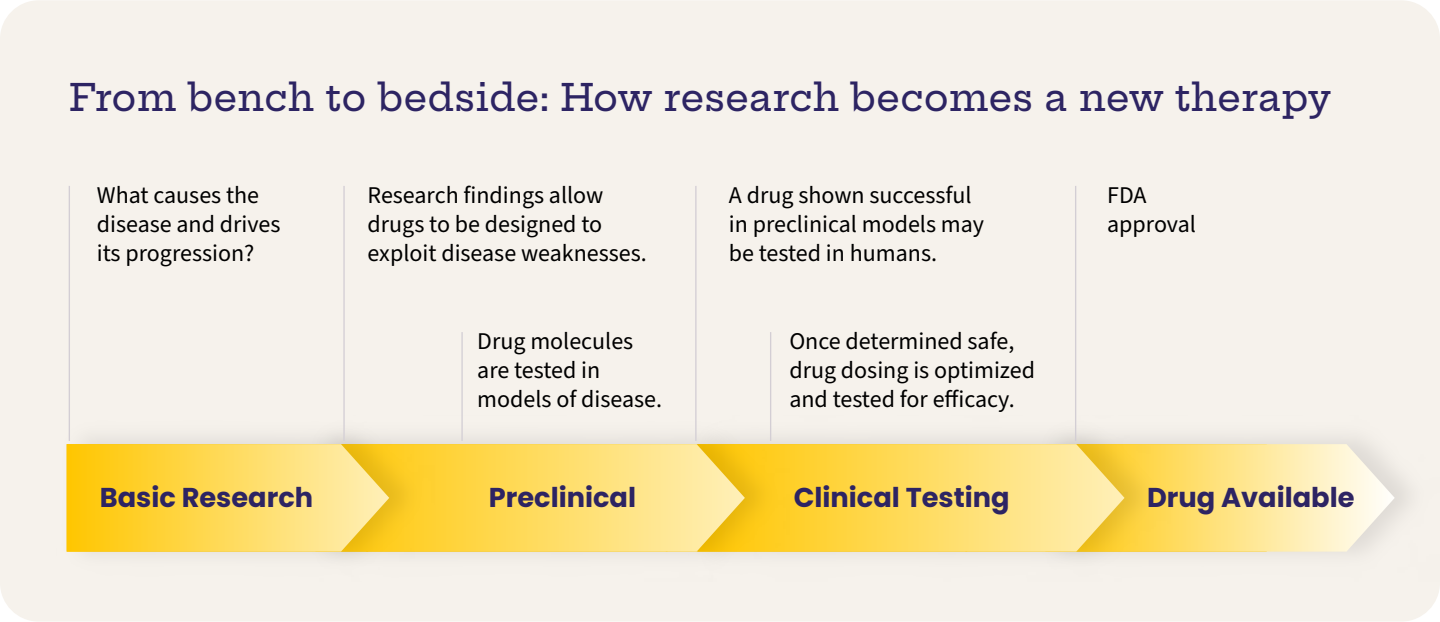


Figure 1-1: Drug development research starts with a basic understanding of a disease and then progresses to candidate drug molecules. These are tested in preclinical development using disease models to develop confidence that they will work in humans. Clinical testing usually passes through phases, which begin by testing basic safety in humans and progress to determining safety and effectiveness. The U.S. Food and Drug Administration (FDA) reviews data generated through clinical trials to determine if a candidate drug is both safe and effective for treating a disease before approving for widespread use.

Pediatric cancer incidence and mortality

While cancers that occur in adults are often classified by the anatomical site of the primary tumor, cancers in children and younger adolescents are classified by histology (tissue type) into 12 major groups using the International Classification of Childhood Cancers (ICCC). (Steliarova-Foucher, 2025) The distribution of the most common cancers in children and adolescents varies by age (Table 1-1).

The cancers that are most common in children age 0–14 are acute lymphocytic leukemia (24%), brain and CNS (19%), neuroblastoma (7%), and non-Hodgkin lymphoma (7%). The top four cancers in adolescents age 15–19 are thyroid carcinoma (14%), Hodgkin lymphoma (13%), brain and CNS (9%), and testicular/ovarian germ cell tumors (9%).

TABLE 1-1

Leading sites of new cancer cases for children and adolescents: 2026 estimates

CHILDREN (BIRTH TO 14 YEARS)

MALES	FEMALES	MALES	FEMALES
Acute lymphoctyic leukemia 1,340 (25%)	**Acute lymphoctyic leukemia** 1,020 (23%)	**Testicular germ cell tumor** 400 (13%)	**Thyroid tumors** 600 (23%)
Brain & CNS 1,020 (19%)	**Brain & CNS** 830 (19%)	**Hodgkin lymphoma** 380 (13%)	**Hodgkin lymphoma** 360 (14%)
Non-Hodgkin lymphoma 440 (8%)	**Neuroblastoma** 310 (7%)	**Acute lymphocytic leukemia** 320 (10%)	**Brain & CNS** 230 (9%)
Neuroblastoma 360 (7%)	**Wilms tumor** 240 (6%)	**Non-Hodgkin lymphoma** 300 (10%)	**Non-Hodgkin lymphoma** 150 (6%)
Bone tumors 240 (4%)	**Non-hodgkin lymphoma** 210 (5%)	**Brain & CNS** 270 (9%)	**Acute lymphocytic leukemia** 140 (5%)
Acute myeloid leukemia 230 (4%)	**Bone tumors** 200 (5%)	**Bone tumors** 140 (5%)	**Bone tumors** 120 (4%)
Wilms tumor 220 (4%)	**Acute myeloid leukemia** 200 (5%)	**Thyroid tumors** 140 (5%)	**Melanomas** 110 (4%)
Hodgkin lymphoma 210 (4%)	**Thyroid tumors** 150 (3%)	**Acute myeloid leukemia** 120 (4%)	**Ovarian germ cell tumors** 100 (4%)
Rhabdomyocarcoma 170 (3%)	**Hodgkin lymphoma** 130 (3%)	**Melanomas** 70 (2%)	**Acute myeloid leukemia** 100 (4%)
Hepatic tumors 130 (2%)	**Rhabdomyosarcomas** 120 (3%)	**Chronic myeloproliferative disease** 70 (2%)	**Chronic myeloproliferative disease** 50 (2%)
Other cancers 960 (18%)	**Other cancers** 960 (22%)	**Other cancers** 800 (26%)	**Other cancers** 690 (26%)
ALL SITES 5,320	**ALL SITES 4,360**	**ALL SITES 3,020**	**ALL SITES 2,640**

Table 1-1: The estimated 15,340 new cases of pediatric cancer in 2026 have different prevalence in children (0-14) than in adolescents (15-19). The specific types of cancers also differ in prevalence between females and males.

The incidence rate for malignant pediatric cancers, per million population for all cancers combined, age 0-19, in 2018-2022 was 184.4 (Table 1-2). Among the eleven most common cancers, the incidence rates ranged from 4.6 per million children and adolescents for ovarian germ cell tumors to 35.2 for acute lymphocytic leukemia. Among pediatric patients diagnosed with cancer in 2015–2021, the overall 5-year survival rate was 86%, ranging from 64% for rhabdomyosarcoma to 98% for Hodgkin lymphoma and ovarian germ cell tumors (Table 1-2). (National Cancer Institute, 2026a) It is important to note that within many of the cancer types listed here, prognosis varies considerably depending on cancer type and other factors, such as tumor genetics. For example, while 5-year survival rates among children with low-risk neuroblastoma exceed 95%, children with higher-risk disease need much more intense treatments and have a much lower survival rate near 60%. (Coughlan, 2017, Liu, 2020) Further, less than 10% of children diagnosed with diffuse intrinsic pontine glioma (DIPG) will survive even two years (Hoffman, 2018). Additional statistics on individual types of cancer can be found in the *Appendix*.

TABLE 1-2

Childhood and adolescent cancer incidence and 5-year observed survival

Cancer type	**Incidence rate** (0-19 years) 2018-2022	**5-year observed survival** (0-19 years) 2015-2021
All sites	184.4	86%
Acute lymphocytic leukemia	35.2	90%
Brain & CNS	29.3	75%
Neuroblastoma	9.1	83%
Wilms tumor	6.1	93%
Rhabdomyosarcoma	4.7	64%
Non-Hodgkin lymphoma	12.9	90%
Hodgkin lymphoma	12.1	98%
Acute myeloid leukemia	7.8	70%
Bone tumors	9.3	71%
Testicular germ cell tumors	9.3	97%
Ovarian germ cell tumors	4.6	98%

Source: North American Association of Central Cancer Registries, 2025; National Cancer Institute, 2026a
Incidence rates are per 1,000,000 and age-adjusted to the 2000 US standard population. CNS, central nervous system. Survival is for cases diagnosed from 2015 to 2021, all followed through 2022. Note: Data does not include benign and borderline brain.

Table 1-2: Childhood cancer is comprised of many individual types of cancer with varying incidence rates and survival. Among the 11 most common types of childhood cancer, the types of cancer range from the least common cancer, ovarian germ cell tumors, that occurs at a rate of 4.6 cases per million to the most common pediatric cancer, ALL, with an incidence over eight times higher at 35.2 per million. Five-year survival ranges from 64% to 98% for the cancers listed.

Long-term survival for pediatric cancer

The number of survivors of pediatric cancer has increased substantially over time; it has been estimated that the number of childhood cancer survivors in the U.S. will approach 580,000 by 2040. (Ehrhardt, 2023) Death rates for all pediatric cancers combined declined by 58% from 1975 (51.5 per million population) to 2024 (21.7 per million). Much of this progress has been reductions in leukemia and lymphoma mortality, for which death rates declined by 3%-4% per year from 1975 to 2020 before stabilizing, compared to declines of 1.9% per year from 1975 to 1996 and 0.5% per year thereafter for all other cancers (Figure 1-2). (National Cancer Institute, 2026a)

Five-year survival rates in pediatric cancers, used to benchmark progress in cancer survival, have greatly improved over time. Unfortunately, beyond 5 years, the mortality for many pediatric cancer survivors continues to outpace death rates of their same-age peers (Figure 1-3).

Investigators involved with the Childhood Cancer Survivor Study (CCSS) are studying the long-term health of childhood cancer survivors and the causes of increased mortality later in life. (National Cancer Institute, 2026c; St. Jude Children's Research Hospital, 2026) One study of 34,230 eligible 5-year pediatric cancer survivors who were diagnosed between 1970 and 1999 found a persistent, four-fold increased risk of death from any cause up to 40 years after diagnosis, attributable to health-related

FIGURE 1-2

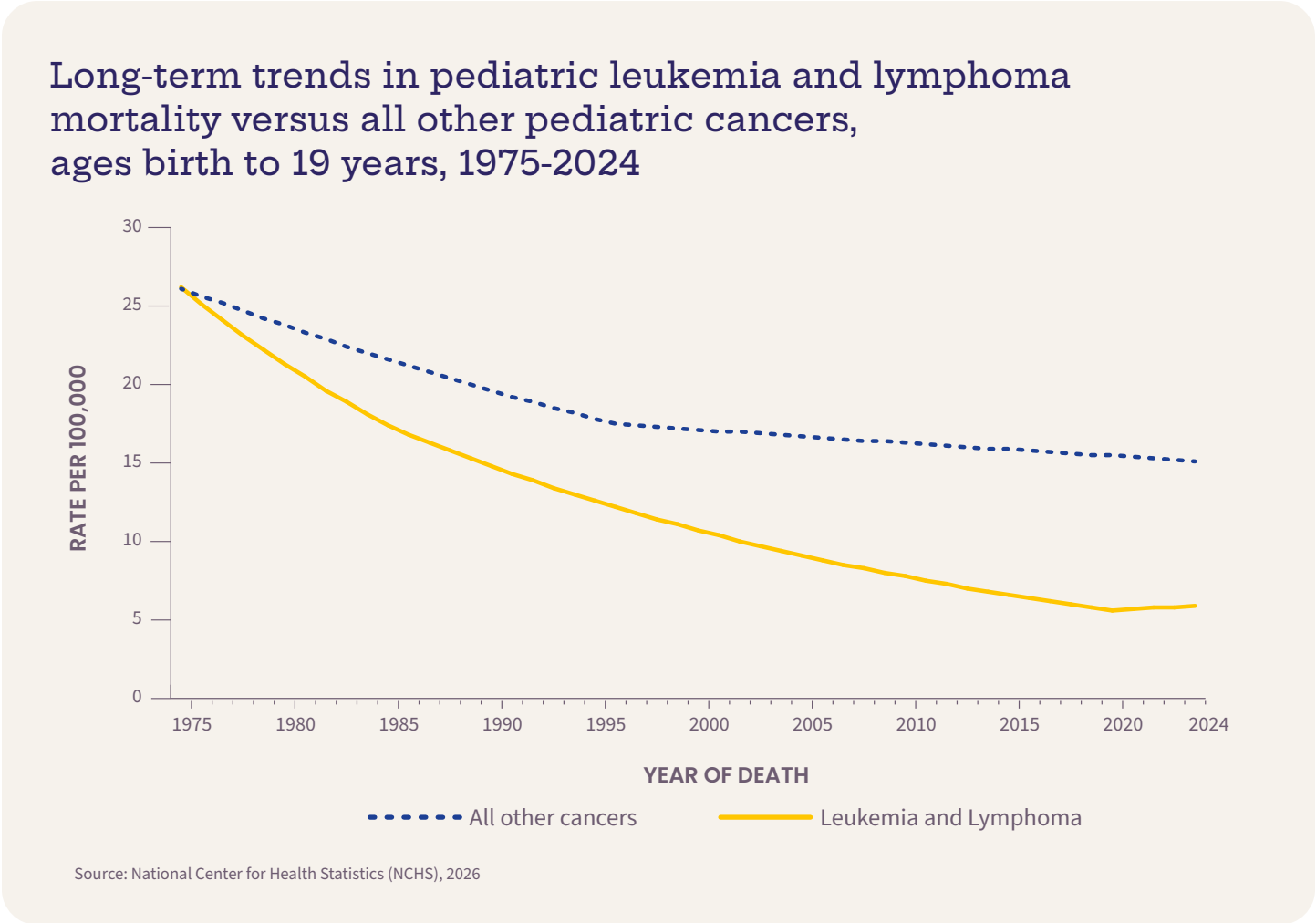
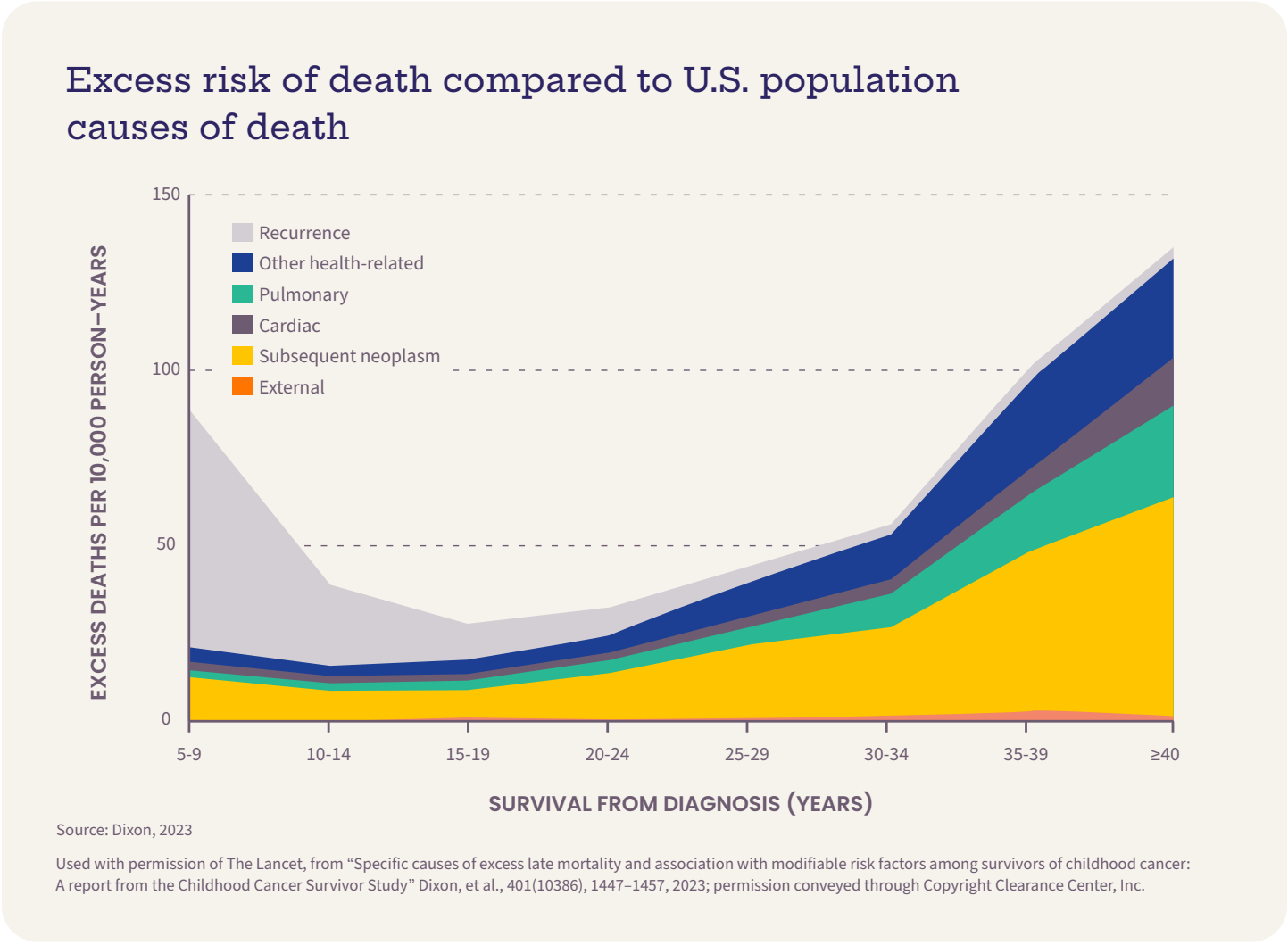


Figure 1-2: Progress in reducing mortality has been much more pronounced in leukemia and lymphomas, with mortality reductions of 3.2% annually from 1985 to 2020 before stabilizing, while mortality for all other pediatric cancers has reduced less than 1% annually since 1996.

causes. (Dixon, 2023) While the excess deaths from 5 to 9 years after diagnosis are primarily due to cancer recurrence, excess deaths after that period are largely due to other health-related causes. Common causes of mortality occurring more than 10 years after initial diagnosis among pediatric cancer survivors include development of subsequent cancers related to treatment, as well as cardiac, pulmonary, or other health-related causes. (Dixon, 2023; Yeh, 2025) Research on the late effects of cancer and its treatment among survivors of pediatric cancer has been very important in identifying adverse effects, developing guidelines for prevention and medical surveillance for survivors, and improving treatments to reduce side effects. (Ehrhardt, 2023)

Along with the improvements in 5-year survival for pediatric cancers since the 1970s, fewer childhood cancer survivors are dying from long-term health problems later in life. (Armstrong, 2016) Among children and adolescents diagnosed during the 1970s, 10.7% who survived 5 years after diagnosis died within the next 10 years; in the 1990s, the proportion declined to 5.8%. (Armstrong, 2016) The decline in 10-year and 15-year mortality for more recent cohorts likely reflects lower long-term mortality compared to earlier cohorts as a result of more effective and less toxic cancer-directed therapy. Researchers must continue following more recent cohorts of pediatric cancer patients to determine how therapy modifications impact the prevalence and spectrum of late effects.

FIGURE 1-3



Source: Dixon, 2023

Used with permission of The Lancet, from "Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study" Dixon, et al., 401(10386), 1447–1457, 2023; permission conveyed through Copyright Clearance Center, Inc.

Figure 1-3. At 40 years from diagnosis about half of deaths in pediatric cancer survivors were attributable to development of new cancers (not a recurrence of the original cancer) or causes related to heart or lung function.

References

Arias, E., Xu, J. Q., and Kochanek, K. (2025) United States life tables, 2023. National Vital Statistics Reports, 74(6), 1–63. doi.org/10.15620/cdc/174591

Armstrong, G. T., Chen, Y., Yasui, Y., et al. (2016) Reduction in late mortality among 5-year survivors of childhood cancer. The New England Journal of Medicine, 374(9), 833–842. doi.org/10.1056/NEJMoa1510795

Bhakta, N., Liu, Q., Ness, K. K., et al. (2017) Treatment and survival of childhood neuroblastoma: Evidence from a population-based study in the United States. Pediatric Hematology and Oncology, 34(5), 320–330. doi.org/10.1080/08880018.2017.1373315

Dixon, S. B., Liu, Q., Chow, E. J., et al. (2023) Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study cohort. The Lancet, 401(10386), 1447–1457. doi.org/10.1016/S0140-6736(22)02471-0

Ehrhardt, M. J., Krull, K. R., Bhakta, N., et al. (2023) Improving quality and quantity of life for childhood cancer survivors globally in the twenty-first century. Nature Reviews Clinical Oncology, 20(10), 678–696. doi.org/10.1038/s41571-023-00802-w

Hoffman, L. M., Veldhuijzen van Zanten, S. E. M., Colditz, N., et al. (2018) Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma (DIPG): A collaborative report from the International and European Society for Pediatric Oncology DIPG Registries. Journal of Clinical Oncology, 36(19), 1963–1972. doi.org/10.1200/JCO.2017.75.9308

Liu KX, Naranjo A, Zhang FF, et al. (2020) Prospective Evaluation of Radiation Dose Escalation in Patients With High-Risk Neuroblastoma and Gross Residual Disease After Surgery: A Report From the Children's Oncology Group ANBL0532 Study. J Clin Oncol. 38(24):2741-2752. doi:10.1200/JCO.19.03316

National Cancer Institute (2026a) Surveillance, Epidemiology, and End Results Program. www.seer.cancer.gov

National Cancer Institute (2026b) DevCan: Probability of developing or dying of cancer software (April 2026 release) [Software]. Surveillance Research Program, Statistical Methodology and Applications. surveillance.cancer.gov/devcan/

National Cancer Institute (2026c) Childhood Cancer Survivor Study: An overview. www.cancer.gov/types/childhood-cancers/ccss

Siegel, R. L., Kratzer, T. B., Wagle, N. S., et al. (2026) Cancer statistics, 2026. CA: A Cancer Journal for Clinicians, 76(1), Article e70043. doi.org/10.3322/caac.70043

St. Jude Children's Research Hospital (2026) Childhood Cancer Survivor Study. ccss.stjude.org/

Steliarova-Foucher, E., Colombet, M., Ries, L. A. G., et al. (Eds.), International incidence of childhood cancer, volume III (IARC Scientific Publication No. 170, pp. 31–36). International Agency for Research on Cancer. publications.iarc.who.int/658

Yeh, J. M., Ward, Z. J., Stratton, K. L., et al. (2025). Accelerated aging in survivors of childhood cancer—Early onset and excess risk of chronic conditions. JAMA Oncology, 11(5), 535–543. doi.org/10.1001/jamaoncol.2025.0236

Larkin

At six years old, I was diagnosed with anaplastic large cell lymphoma. I am now 16 years old, and 10 years in remission.

I underwent six months of chemotherapy, including roughly 15 different chemo medicines. I was very ill much of the time – I lost all my hair and had to be homeschooled because my immune system was suppressed. The cancer ate holes in my bones, and I suffered a compression fracture of my L1 vertebrae. I had to wear a brace through most of my treatment to stabilize the break.

I am one of the lucky ones because I survived my cancer and had really good health insurance. But after my battle with cancer, I was diagnosed with ADD and hypothyroidism, and I now suffer from depression and anxiety. These things could be due to what I've been through and the treatments I needed to save my life, but access to good care is why I'm still here at all.

Survivorship taught me things no one warned me about. After treatment, I had to learn how to adjust to life without cancer being the center of everything. Everyone around me was ready to move forward, but I was still figuring out what "normal" was supposed to look like. Finishing treatment doesn't mean everything goes back to the way it was before.

For me, survivorship was more than being told I was healthy. I had to figure out who I was outside of being a cancer patient. As I got older, I realized that cancer was a part of my story, but it didn't define my identity.

That's why, since 2018, I have traveled to Washington, DC, every year with the Alliance for Childhood Cancer and ACS CAN to advocate for better funding and research for childhood cancers.

I speak up for kids who can't yet fight for themselves. I want policymakers to understand that childhood cancer doesn't end when treatment ends. Survivors carry the effects of their experience for years, and support is needed for the challenges, often lifelong, that come later.

I am thriving in my life, and I overcame many obstacles along the way. I am grateful for the care and the opportunities I received and that we can continue this work — helping kids not only survive but thrive.

— Larkin

CHAPTER 2

Biological Understanding

Summary

Pediatric cancers differ from adult cancers, comprising distinct diseases arising in a unique physiological environment. Some pediatric cancers originate from embryonal cells that fail to properly differentiate and mature early in development. These cancers, such as neuroblastoma, retinoblastoma, and Wilms tumor, peak in the first few years of life. Older children might develop cancers with the same name as cancer that happens in adults, such as acute lymphoblastic leukemia or glioblastoma. However, the cancer's behavior, its genetics, and often the appropriate treatment, can be different. Because these diseases are rare in pediatric patients, collaborative programs are essential to bring together sufficient data and expertise for meaningful progress. These programs facilitate data sharing and molecular and genetic testing at scale, which can have multiple potential benefits including identifying predictors of cancer behavior and response to treatment; matching individualized, targeted treatments to cancers that might respond to them; and predicting who might need adjustments to standard treatment protocols to avoid side effects.

Introduction: Pursuing greater biological understanding

To develop better therapies for children and adolescents with cancer, understanding how those cancers develop, and how they differ from adult cancer, is critical. Pediatric cancer is not one disease, but rather dozens of cancers that occur in different tissues and are driven by specific gene changes. Some of the abnormalities known to be responsible for certain cancers in adults have also been identified in some pediatric cancers. However, in other cases, adult and pediatric tumors might look alike, but a child can respond to medicines differently or have cancer with a different underlying genetic cause and thus need a unique strategy for treatment.

While the list of common pediatric cancers contains some cancers also seen in adults, other cancers are only seen in children. Relying on treatments based on our understanding of adult cancers to treat children with cancer is not enough. This section explores the efforts to understand the unique biology of pediatric cancer and to develop better treatments specific to these cancers.

Child-adult differences

Children are not simply smaller adults; their bodies are uniquely growing and developing. This influences both the types of cancers that develop in children and adolescents, as well as the long-term health consequences of cancer treatment.

Several cancers are seen almost exclusively in children, and these childhood-specific cancers often arise from embryo-derived ("embryonal") cells. Beginning with egg fertilization, embryos start from a single cell and eventually become the billions of cells that make up a newborn child. Embryonal cells multiply rapidly and differentiate into all the different organs and parts of the human body according to complex biological pathways and control mechanisms. While much of the cellular differentiation of embryonal cells has stopped by birth, significant cellular growth continues through adolescence, at which point humans are essentially physically mature. Embryonal tumors come from these cells, whose control mechanisms fail to work properly, resulting in the cells continuing to grow and divide in an uncontrolled manner to become cancer.

These cancers often appear during the period not long after birth, as seen by the fact that embryonal cancers including neuroblastoma (nervous system), retinoblastoma (retina), rhabdomyosarcoma (muscle), hepatoblastoma (liver), and Wilms tumor (kidney) have the highest incidence in children between birth and four years of age.

The major cancers that are only found in adults most commonly arise from epithelial tissues, which line the inner and outer surfaces of the body, and are a result of multiple gene changes in cells and tissues that take a long time to occur. Some of these changes may be caused by combinations of exposures, such as tobacco smoke, certain infections, ionizing radiation, hormones produced by the body, or metabolites of some foods. Other changes in genes that contribute to cancer development can be inherited or occur randomly, without being caused by a specific exposure.

Some cancers are seen in both children and adults. These include acute leukemias, lymphomas, thyroid cancer, melanoma, glioblastoma, and even some sarcomas. While these cancers can share the same name in children and adults, they are often biologically different. For example, genomic profiling of tumors shows that pediatric and adult B-cell non-Hodgkin lymphomas (NHL) tend to have different genetic fingerprints as do glioblastomas and acute lymphoblastic leukemias (ALL). (Deffenbacher, 2012; Havelange, 2016; Sturm, 2014; Downing, 2012) The prevalence of certain genetic subtypes of these cancers varies at different ages, which impacts how effective a treatment might be and the overall prognosis.

The prevalence of these cancers overall can also vary in different age groups. For example, while sarcomas make up about 1% of adult cancers, they account for more than 20% of pediatric cancers and are responsible for significant mortality in children and young adults. (Damerell, 2021) Sometimes even within the childhood age group (birth–19 years) there are differences in the same cancer between younger children and older children. As an example, ALL can have a distinctly different prognosis at different ages, partly due to differing cancer genetics.

Even when adult and childhood cancers are very similar at the molecular level and have similar clinical behavior, different approaches to treatment may be necessary because of physiological differences between adults and children that are responsible for drug distribution, metabolism, and clearance, resulting in potential for harm in children whose bodies are still developing.

Genetics

Cancer is a disease that results from changes (mutations) in the genes inside cells. Genes are contained in each cell's DNA. A person's DNA is inherited from their parents, and some cancers can result from heritable genetic changes. Still, the majority (between 90% and 95%) of all cancers arise because of genetic changes that occur during a person's lifetime. (Zhang, 2015)

Our genes contain instructions that tell our cells what to do, allowing a cell to maintain its identity and perform its function. Changes (mutations) in genes can affect these instructions. When a mutation occurs in a gene that helps control a process such as cell division, the cell might start to reproduce uncontrollably. Each new cell division results in another chance for other mutations to occur. Starting from a single damaged cell, eventually millions of abnormal clones can result in cancer. In this case, only the cancer cells will have the mutations (somatic) that started the cancer, while all of the other cells in the body remain unchanged and healthy (germline). The cause of that original mutation to a single cell can be attributed to a number of factors. While certain environmental exposures increase the risk of adult cancers, these are thought to play less of a role in the development of pediatric cancers. Gene changes in pediatric cancers most often occurred by chance during normal cell division, or in a small percentage of cases were inherited from a parent. (Shakeel, 2022)

While some specific mutations are found in multiple types of cancer, most mutations are unique to a particular cancer type. Moreover, some genes are more likely to be affected in certain types of cancer. The different mutations allow a given cancer type to be subtyped by its genetic characteristics and better studied. Each subtype might have a unique treatment response and prognosis. For example, medulloblastoma has been divided into four main subgroups based on the mutated genes driving the cancer. (deSouza, 2014; Northcott, 2012) Gene changes in neuroblastoma have helped researchers better understand cancer

behavior to tailor treatments specific to patient factors and gene changes. (Irwin, 2021) The list of frequently mutated genes in childhood cancer is long and ever evolving as genetic sequencing of tumors becomes more common and additional mutated genes are discovered (see Basic Research discussion below). (Saletta, 2014; Huether, 2014; Sturm, 2014; Pizzo, 2015)

Heritable genes

While most cancers are the result of genetic mutations that occur during our lifetime, 5-10% of cancers can be linked to heritable mutations (those that are inherited from an individual's parents). In the case of heritable mutations, all the cells in the body would share the same problematic genes from birth. Heritable mutations in certain genes can substantially increase a person's lifetime risk of specific cancers. These gene changes can also affect family members and future children. Cancers in children due to heritable genetic mutations represent a slightly larger fraction (about 8-10%) of childhood cancer, compared to cancers in adults due to inherited mutations (about 5-10%). (Zhang, 2015; Grobnerr, 2018) This is likely because young people have had less time to accumulate mutations, either by chance or through exposure. Select childhood cancers are highly associated with heritable genetic mutations such as retinoblastoma, where 30–40% of cases can be traced to these mutations. (Abu-Amero, 2025)

Epigenetics

Research has shown that pediatric cancers overall tend to have fewer mutations than similar adult cancers, but the types of mutations can be different. (Huether, 2014) Many genes provide the building instructions for proteins that play important roles in normal cell function, and mutations in these genes can result in a protein made incorrectly, or too much or too little of it being made. There are also genes that control how the genetic instructions are read, and damage to these genes can impair the cell's ability to translate the genetic instructions properly. These are referred to as epigenetic changes. If your genes are like a how-to book with instructions for building a house, then mutations to protein-encoding genes would be like instructions for building windows that give the wrong dimensions resulting in windows that do not fit your house. Epigenetic changes, on the other hand, are more like changes that prevent the instructions from even being read or translated. In that case, even if the instructions for building windows are correct, because they cannot be read, for example, it would still result in the inability to correctly construct windows. Epigenetic changes are found at comparatively high rates in pediatric cancers compared to adult cancers. For example, one study found that over 50% of high-grade gliomas, osteosarcomas, and T-cell ALL tumors harbor epigenetic mutations. (Huether, 2014) These differences are important, as they can sometimes guide the types of treatment approaches likely to be successful.

Basic research

The current understanding of the role of genetics and molecular markers in pediatric cancer came from significant basic research efforts conducted by studying cancer cells collected from children. While biopsies taken as part of diagnosis and treatment often yield samples that can later be used for research, there has not until recently been a systematic and standardized collection of samples and related data with a focus on sharing those data with the broader research community. Other information must be collected to use tissue samples optimally. This might include information about the child, such as the treatment they received and what effects a treatment had, as well as normal tissue or cells from the child to allow researchers to better understand the changes that lead to the development of cancer. These collections of tissue samples and data are known as biorepositories, tumor banks, or biobanks.

Tumor samples are often collected at an initial diagnosis as a normal part of clinical care, and for banking for future research as described above. But in addition, sequential samples of the same child's cancer over time can prove valuable, as they can provide insight into how a cancer changes in response to treatment. Relapsed cancers, for example, can have different genetic signatures than the originally diagnosed cancer. (Andersson, 2015) Taking additional biopsies during a child's cancer treatment solely for research studies can be difficult, as subjecting children to additional procedures that will not provide them with any benefit may be considered unethical. This is especially true for tumors in difficult-to-access or sensitive areas such as brain tumors (see page 34 for further discussion

of research ethics). However, as treatment choices are increasingly based on a tumor's molecular characteristics, multiple biopsies are becoming a more frequent part of clinical care, and thus, when safe, offers more opportunities to bank part of that tissue for further research.

While some tumors are difficult to access without causing danger to a child, samples can still be donated if a child does not survive their cancer. Post-mortem samples collected shortly after a child dies may still provide living tumor cells that are useful for research, and samples can be taken even later for genetic or histological studies. Autopsies for patients who die in a hospital are not necessarily routine, but over 90% of parents surveyed whose children had died from cancer either did, or were willing to, allow post-mortem sample collection from their children, pointing to another opportunity to contribute valuable samples for research. (Alabran, 2013)

Most childhood cancers are relatively rare, so if a researcher were to start collecting samples from a rare tumor, it could take years or even be impossible to obtain enough samples from new cancer cases to answer the research question. By banking samples proactively and across sites for future research, biorepositories can provide researchers with access to large numbers of patient samples that have been collected over the course of many years. Many individual institutions have historically had their own repositories, and some collaborative groups organized around a specific cancer type, such as the Children's Brain Tumor Network, have centralized collections of tissue and clinical data. (Children's Brain Tumor Network, 2026) Recent efforts have been made to increase cooperation in tissue collection to create larger repositories open to more institutions and researchers, such as Project Every Child, a biorepository project developed by the Children's Oncology Group (COG). (COG, 2024) This project began in 2015 with a goal of collecting pediatric tumor samples and linking them to clinical records to provide researchers with access to a wealth of information about a variety of childhood cancers. In 2021, the National Cancer Institute's Childhood Cancer Data Initiative (CCDI), in collaboration with the COG, launched the Molecular Characterization Initiative, which provides standardized, state of the art molecular profiling of tumor and normal tissue without charge to patients and families. Tissue is submitted to the COG Biopathology Lab at Nationwide Children's Hospital, where it is processed, genetic material extracted, and remaining tissue stored for subsequent investigation. More than 9,000 patients have been enrolled, and an online database houses their information. Patient information and results are available to the patient and their doctor and then made available to researchers as deidentified/anonymous information for future study. The importance of these repositories and data sharing is discussed in more detail in the chapter "*Data, Data Sharing, And Artificial Intelligence*."

While these studies focus on collecting samples to guide research into cancer biology and the best treatments, other pediatric cancer biorepositories collect samples to understand how cancer and its treatment affect children as they age. The Childhood Cancer Survivor Study (CCSS) has collected noncancerous samples from children who survived cancer and their siblings to better understand the factors that lead to long-term treatment effects on childhood cancer survivors (see below for additional discussion of these treatment effects).

Late effects of treatment

Currently, over 85% of pediatric cancer patients survive for five years or longer. However, these survivors face a higher risk of late effects, including additional cancers and early mortality, compared to the general population. (Dixon, 2023) As late as 40 years following diagnosis, researchers still observed a higher mortality rate (from any cause) among pediatric cancer survivors (23%), compared to the expected mortality rate in the general population (<5%). (Dixon, 2023) About a third of deaths in pediatric cancer survivors were attributable to recurrence or progression of the primary cancer, and about half due to other causes, including new cancer development (not a recurrence of the original cancer) or causes related to heart or lung function (see Figure 1- 3 in *Introduction*). (Dixon, 2023) Treatments given as a part of cancer therapy during childhood likely have a significant impact on the increased rates of these health outcomes in survivors. Cytotoxic chemotherapy and radiation treatments typically kill or inhibit cancer cells by damaging their DNA and interrupting normal cellular reproduction processes. While such damage and disruption can kill cancer cells, it can similarly damage healthy cells. Short-term (acute) complications of chemotherapy and/or radiation are identified during

cancer therapy and typically resolve soon after treatment is over. Some effects, however, can persist long after treatment ends. These are known as "long-term (or chronic) effects." Other treatment toxicities or complications may not appear until months or even many years after treatment. These are deemed "late effects." (McCarthy, 2023) Even targeted therapies, which typically only interrupt select processes that tend to be overactive in cancer cells, can lead to long-term and late effects. In fact, a current concern is that it is difficult to predict or study the long-term effects of targeted therapies in children due to the newness of these therapies and the small number of children who will receive them during treatment. By age 50, 96% of childhood cancer survivors had at least one grade 3-5 (severe, disabling, life-threatening, or fatal) chronic health condition. (Bhakta 2017)

While many late effects of cancer treatment are common to both children and adults (e.g., cardiovascular disease), the effects of treatment are particularly pronounced in pediatric cancer survivors treated during a time when their bodies are still growing and their organs are still developing. (Hudson, 2005; National Cancer Policy Forum, 2014) Cancer treatment in children can have pronounced effects on linear growth, skeletal maturation, intellectual function, and emotional and sexual maturation. Damage to developing vital organs can be more severe than in fully mature organs and may only appear as the individual gets older. Frailty, a clinical syndrome usually associated with aging, is significantly increased in pediatric cancer survivors, affecting quality of life and increasing the risk of death threefold. (Guida, 2024)

The age of the child during cancer treatment is an important factor in determining the burden of effects seen later in life. (Hudson, 2005; National Cancer Policy Forum, 2014) Infants who have received intensive treatment have higher risks of neurocognitive injury, growth delay, musculoskeletal defects, and organ dysfunction due to the increased toxic effects of treatment on immature organ systems and tissues. Older children may have similar problems but also may be more vulnerable to impacts on fertility, mental health, and deficits in social maturation or functioning, depending on their cognitive maturity and psychosocial support.

Biomarkers of late effects

By definition, late effects of cancer and cancer treatment only become clinically apparent after treatment has been completed. This makes it more difficult to reduce late effects through modification of existing treatment strategies or the development of new treatments altogether, since the outcomes of any changes may not be known for decades. Some of the biological mechanisms of damage responsible for late effects, however, are well understood. For example, anthracyclines are a class of chemotherapy drugs used in over 50% of pediatric treatment protocols, but these drugs can damage the muscle cells in the heart, lead to myocardial fibrosis (stiffening of heart muscle) and heart disease in childhood cancer survivors. (Smith, 2010) As damage to the heart is occurring, the cells release certain proteins, which can be measured at the time of treatment. Elevated levels of these proteins are being studied as predictors of late cardiac effects. This type of research might provide opportunities for a better understanding of how to anticipate and potentially avoid late effects of cancer treatment. (Dixon, 2021)

References

Abu-Amero KK, Kondkar AA, Almontashiri NAM, et al. (2025) Genetics of Retinoblastoma: An Overview and Significance of Genetic Testing in Clinical Practice. Genes (Basel) 16(9):1031. doi: 10.3390/genes16091031. PMID: 41009976; PMCID: PMC12469762

Alabran JL, Hooper JE, Hill M, et al. (2013) Overcoming autopsy barriers in pediatric cancer research. Pediatr Blood Cancer 60(2):204-9. doi: 10.1002/pbc.24320. Epub 2012 Sep 26. PMID: 23015377; PMCID: PMC3522778

Andersson AK, Ma J, Wang J, et al. (2015) St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. The landscape of somatic mutations in infant MLL-rearranged acute lymphoblastic leukemias. Nat Genet. 47(4):330-7. doi: 10.1038/ng.3230. Epub 2015 Mar 2. PMID: 25730765; PMCID: PMC4553269

Bhakta N, Liu Q, Ness KK, et al. (2017) The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet 390(10112):2569-2582. doi: 10.1016/S0140-6736(17)31610-0. Epub 2017 Sep 8. PMID: 28890157; PMCID: PMC5798235

Children's Brain Tumor Network (2026). cbtn.org

Children's Oncology Group. (2024) Project: EveryChild. childrensoncologygroup.org/projecteverychild-a-game-changing-resource-in-the-fight-against-pediatric-cancer

Damerell, V., Pepper, M.S. & Prince, S. (2021) Molecular mechanisms underpinning sarcomas and implications for current and future therapy. Sig Transduct Target Ther 6, 246. doi.org/10.1038/s41392-021-00647-8

Deffenbacher KE, Iqbal J, Sanger W, et al. (2012) Molecular distinctions between pediatric and adult mature B-cell non-Hodgkin lymphomas identified through genomic profiling. Blood 119(16):3757-66. doi: 10.1182/blood-2011-05-349662. Epub 2012 Feb 28. PMID: 22374697; PMCID: PMC3335381

DeSouza RM, Jones BR, Lowis SP, Kurian KM. (2014) Pediatric medulloblastoma - update on molecular classification driving targeted therapies. Front Oncol. 4:176. doi: 10.3389/fonc.2014.00176. PMID: 25101241; PMCID: PMC4105823

Dixon SB, Howell CR, Lu L, et al. (2021) Cardiac biomarkers and association with subsequent cardiomyopathy and mortality among adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort. Cancer 127(3):458-466. doi: 10.1002/cncr.33292. Epub 2020 Oct 27. PMID: 33108003; PMCID: PMC7855049

Dixon SB, Liu Q, Chow EJ, et al. (2023) Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet 401(10386):1447-1457. doi: 10.1016/S0140-6736(22)02471-0

Downing JR, Wilson RK, Zhang J, et al. (2012) The Pediatric Cancer Genome Project. Nat Genet. 44(6):619-22. doi: 10.1038/ng.2287. Erratum in: Nat Genet. 44(9):1072. PMID: 22641210; PMCID: PMC3619412

Gröbner, S., Worst, B., Weischenfeldt, J. et al. (2018) The landscape of genomic alterations across childhood cancers. Nature 555, 321–327. doi.org/10.1038/nature25480

Guida JL, Hyun G, Belsky DW, et al. (2024) Associations of seven measures of biological age acceleration with frailty and all-cause mortality among adult survivors of childhood cancer in the St. Jude Lifetime Cohort. Nat Cancer. 5(5):731-741. doi:10.1038/s43018-024-00745-w

Havelange, V., Pepermans, X., Ameye, G., et al. (2016), Genetic differences between paediatric and adult Burkitt lymphomas. Br J Haematol, 173: 137-144. doi.org/10.1111/bjh.13925

Hudson, Melissa M. (2005) A model for care across the cancer continuum. Cancer 104.S11 (2005): 2638-2642

Huether R, Dong L, Chen X, et al. (2014) The landscape of somatic mutations in epigenetic regulators across 1,000 paediatric cancer genomes. Nat Commun. 8;5:3630. doi: 10.1038/ncomms4630. PMID: 24710217; PMCID: PMC4119022

Irwin MS, Naranjo A, Zhang FF, et al. (2021) Revised Neuroblastoma Risk Classification System: A Report From the Children's Oncology Group. J Clin Oncol. 39(29):3229-3241. doi:10.1200/JCO.21.00278

McCarthy E. (2023) A Review of Late Effects in Pediatric Cancer: Implications for Rehabilitation. Rehabil Oncol. 41(4):215-218. doi: 10.1097/01.reo.0000000000000351. Epub 2023 Oct 2. PMID: 38524881; PMCID: PMC10957136

National Cancer Policy Forum (2014) Board on Health Care Services; A Livestrong and Institute of Medicine Workshop; Institute of Medicine. Identifying and Addressing the Needs of Adolescents and Young Adults with Cancer: Workshop Summary. Washington (DC): National Academies Press (US)

Northcott PA, Dubuc AM, Pfister S, Taylor MD. (2012) Molecular subgroups of medulloblastoma. Expert Rev Neurother. 12(7):871-884. doi:10.1586/ern.12.66

O'Leary M, Krailo M, Anderson JR, Reaman GH (2008) Children's Oncology Group. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. Semin Oncol. 35(5):484-93. doi: 10.1053/j.seminoncol.2008.07.008. PMID: 18929147; PMCID: PMC2702720

Saletta F, Wadham C, Ziegler DS, Marshall GM, Haber M, McCowage G, Norris MD, Byrne JA. (2014) Molecular profiling of childhood cancer: Biomarkers and novel therapies. BBA Clin. 1:59-77. doi: 10.1016/j.bbacli.2014.06.003. PMID: 26675306; PMCID: PMC4633945

Shakeel O, Lupo PJ, Strong S, Arora M, Scheurer ME. (2022) A brief review of the current knowledge on environmental toxicants and risk of pediatric cancers. Pediatr Hematol Oncol. 39(3):193-202. doi:10.1080/08880018.2021.1979147

Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, Jones A. (2010) Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 10:337. doi: 10.1186/1471-2407-10-337. PMID: 20587042; PMCID: PMC2907344

Sturm D, Bender S, Jones DT, et al. (2014) Paediatric and adult glioblastoma: multiform (epi)genomic culprits emerge. Nat Rev Cancer. 14(2):92-107. doi: 10.1038/nrc3655. PMID: 24457416; PMCID: PMC4003223

Zhang J, Walsh MF, Wu G, et al. (2015) Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 373(24):2336-2346. doi:10.1056/NEJMoa1508054

Alique

I am a research scientist in cancer survivorship and supportive services. I am also a two-time survivor of Acute Myeloid Leukemia (AML). I was diagnosed with AML at the age of four in 1998.

At that time, AML was extremely difficult to treat in children, and I was given just a 13% chance of survival without a bone marrow transplant. I participated in one of the earliest pediatric biomarker studies, which helped lay the foundation for biomarker testing that guides treatment today. I achieved remission through an experimental chemotherapy regimen.

Less than a year after completing my PhD, at age 27, my AML relapsed. I became the first known person to experience an AML recurrence more than 22 years after an initial diagnosis. This time, advances in science worked in my favor. My biomarkers indicated a more favorable prognosis, and physicians were able to compare the characteristics of my leukemia to my previous cancer, showing how far precision medicine cancer treatment had advanced. I completed six months of intensive inpatient treatment followed by three years of maintenance chemotherapy, and this year I will celebrate five years in remission.

My case is proof of what precision medicine can do when the data exists to support it. But that data must be built, patient by patient, over decades, and pediatric cancers don't always get that investment. Pharmaceutical companies often have fewer financial incentives to conduct pediatric trials than adult trials, so new precision therapies often reach children years after they reach adults, and only a small proportion of new cancer drugs ultimately receive pediatric approval.

The biomarker study I took part in as a four-year-old in 1998 helped make my own treatment possible in 2021. That is what precision medicine promises every family: that today's data becomes tomorrow's better odds. Every child deserves access to the kind of individualized, biomarker-driven care that gave me a second chance — not decades from now, but as soon as the science allows.

— Alique

CHAPTER 3

Preclinical Drug Development

Summary

Preclinical research is a critical step in turning discoveries about cancer biology into safe and effective treatments for children. Through the use of tools such as cell cultures, organoids, computational models, and animal models, drug candidates can be tested to determine if they are effective at fighting cancer cells and whether they are safe enough to move into human trials. This stage is especially important in pediatric cancer because childhood cancers are rare; eligible patients are few; and children require added protections from unnecessary risk. Each model system offers value but also has limitations. While preclinical models have traditionally relied on cancer cell lines or animal models, new computing tools such as artificial intelligence are increasingly being used to simulate how drugs might behave in the body. As laws such as the RACE for Children Act expand pediatric testing requirements and new treatments such as immunotherapies emerge, strong preclinical systems will be increasingly important for identifying the most promising therapies before they reach children in clinical trials.

Introduction

Research into the basic biology of cancer can provide an understanding of what leads to the development of cancer and what makes cancer cells grow and survive. Armed with this knowledge, researchers can create therapies that exploit weaknesses or attack biological processes critical to cancer growth. The first step of this translation of basic science to a useable treatment begins with preclinical research. Preclinical research is conducted in non-human model systems that are meant to mimic cancer in humans to provide insights into how a drug might work within the human body. This step can determine whether a drug candidate is able to effectively target cancer cells in the model system before it may advance to additional testing in humans.

Preclinical research:
Laboratory, cell, and animal testing that is done before a drug is given to a human. It shows whether a drug candidate is safe enough and works well enough to move into human trials.

FDA generally requires safety and efficacy data on a drug candidate in a model system before introducing a new drug into humans. In addition to pre-clinical testing results, in many cases the results of clinical trials of new drugs in adults are considered when making decisions about clinical trials in children to avoid unnecessary risks of toxicity of novel agents in children. Previous trials in adults, however, are not a requirement to begin clinical trials of new drugs in children. Studies of cancer drugs in adults also provide an indication of a reasonable dose to start testing a drug in children.

In developing drugs to treat childhood cancer, the preclinical phase of drug development is critical, because pediatric cancer is rare and there are few children on whom new therapies can be tested. Therefore, researchers are increasingly using new tools to enhance the process of developing treatments for pediatric cancer. These tools include predictive computer models that forecast how a drug might work in children; molecular analysis indicating whether a drug effectively targets a specific child's cancer; and other laboratory-based research strategies. Together, this evidence can support starting pediatric drug development earlier, without waiting until a drug has been fully tested in adults. (Wen, 2026; Yates, 2025) Federal laws protect children from research that may be too risky (see chapter: *Regulatory Requirements*). Therefore, new drugs that eventually move into pediatric clinical trials must be those with the highest probability of working. (Smith, 2024)

Cellular and organoid models

One hallmark of cancer is that it grows uncontrollably. This feature has made it easier to remove cancer cells from the body and grow them in a laboratory. In fact, the first successful effort to grow human cells outside of the body came from cervical cancer tissue in 1951. (Skloot, 2010) Since then, cells from many different cancer types have been successfully grown in the laboratory, creating various model systems to isolate and study cancer growth and development (see Box on page 22 for a summary of main model systems). Importantly, these approaches allow researchers to access cells on which to test drug candidates prior to exposing patients directly to a new drug, a key part of preclinical research.

Cell cultures can be an attractive way to conduct many types of research on cancers that are otherwise rare, but this approach has certain limitations. Not all cancer cells can grow and divide in culture, and for some cancer cells to grow in culture indefinitely, they must undergo genetic transformation to allow such continuous growth. As a result, cell lines may not be fully representative of a cancer type and might not behave similarly to other tumor cells in the body. Further, as cell lines grow, they continue to acquire mutations and alterations that lead to generation of variants with significantly different response profiles. For example, for rhabdomyosarcoma, a type of cancer that develops in muscle tissue, there are as many as 30 cell lines reported in the literature, but up to one third of the lines have been found to be significantly different than the "parent" line originally generated. (Hinson, 2013) These models of rhabdomyosarcoma differ in how accurately they capture key features of the disease. Some models better represent certain cancer subtypes than others, how the cancer spreads through the body, the environment surrounding the tumor, and how the cancer responds to treatment. In other words, no single model captures every aspect of the disease equally well. (Martynov, 2024)

Cell cultures also lack important features of tumors that grow within the body. In cell culture, a drug can easily be added to the fluid the cells are grown in so that the cancer cells are evenly exposed to the drug being tested, but in the body, drugs are not distributed evenly. For example, drugs injected into a human intravenously might be found in high concentrations in the blood, but at lower concentrations in tissue. For some organs, such as the brain, a drug may not be able to reach its target. Further, it is possible to expose cell cultures to drug concentrations that will effectively block cancer growth, but it would be impossible to achieve the same drug concentrations in a child without causing unacceptable toxicity.

Cell cultures cannot provide information on how a drug candidate may impact a full body system. For example, it is important to understand how a drug is distributed within a body in order to determine whether it will reach the location of the cancer, and how quickly it is metabolized or removed from the body, such as in the urine. It is also important to understand if the drug might cause liver damage or otherwise cause toxicities that would limit the dosing or even make a drug altogether unsafe to give to humans. Animal models can be used to address many of these questions and have been created for many different types of cancers (primarily in rodents), so that new drug candidates can be tested.

A major goal of animal models is to understand how well a drug candidate fights cancer in a live host. Animal models for cancer are typically established in one of several ways. It is possible to breed or genetically manipulate animals so that they spontaneously develop tumors on their own that closely match the characteristics of the human cancer that is being studied (e.g. sarcoma, melanoma,

Cell cultures: Cancer cells isolated from tumor tissue and grown in a laboratory, most often as a flat, two-dimensional layer in a culture dish. They allow researchers to screen large numbers of drug candidates quickly and inexpensively, but they can change genetically over time and do not replicate how a drug is distributed and metabolized within a living body.

Animal models: Animal models of human cancer have been developed that carry mutations in the same cancer-causing genes as human cancer. These have been important sources of information to understand causes and development of cancer but have limitations due to the differences between animals and humans, such as size, lifespan, physiology, and exposures.

Xenografts: Animal models created by implanting human cancer cells or tumor tissue into a host animal, most often an immunocompromised mouse, so the cancer can grow within a living system. Standard xenografts use established cell lines, while patient-derived xenografts (PDX) use tissue taken directly from a patient's tumor, offering a closer match to the original cancer's biology.

In silico and computational models: Computer simulations use existing data to predict how a drug candidate might act before any lab testing starts. These models can quickly screen thousands of compounds and flag likely toxicity, but the results still need to be confirmed with cell, organoid, or animal studies.

Organoid models: Three-dimensional clusters of cancer cells grown in the lab that self-organize to mimic aspects of a tumor's natural structure and cell diversity. They provide a more realistic platform for drug screening than traditional two-dimensional cell cultures, though they still lack the blood vessels, immune cells, and systemic context of a living body.

etc.). (Ruggeri, 2014) These are known as genetically engineered models, or GEM for short. A second type of animal model is established when known carcinogens are used to reproducibly create a specific type of cancer in an animal. Examples of this include colorectal cancer in rats. (Kemp, 2015) Finally, xenograft models are created by introducing human cancer cells into an animal. (Li, 2021) In most xenografts, a standardized line of cancer cells is introduced into the animal. An alternate method used for solid tumors involves taking small pieces of tumor from a patient and surgically placing them into subject animals, allowing them to grow prior to drug testing. This process of directly growing patient cancer cells in animals is called patient-derived xenograft, or PDX. The PDX animal model is more representative of the patient's cancer and more closely matches human tumors than is usually the case for GEM-induced, or cell-line xenograft models. (Liu, 2025)

Of all the current approaches to treating cancer, immune-based therapies represent both the greatest promise and the toughest preclinical modeling challenges in pediatric oncology. Many of these therapies work by leveraging the body's own immune system to attack cancer cells. Most of this work in the pediatric field is still in the preclinical stage, and while a few cancer specific models have been created for Ewing sarcoma and pediatric diffuse midline glioma, (du Chatinier, 2022; Luo, 2023) there is still a shortage of animal models that can realistically represent how a human immune system interacts with a variety of cancer types. (Fløe, 2025; Park, 2024; Sousa, 2026)

Animal models meant to mimic pediatric cancers sometimes incorporate elements unique to children, for example by using juvenile, rather than adult, rodent models. Juvenile animals may reveal a drug's adverse effect on physical and mental development or drug metabolism, distribution and clearance. In many cases, however, potential side effects in children can be deduced from already completed adult studies, so the scientific community has debated the value of juvenile animal models. (Bailey & Mariën, 2011; Duarte, 2015) FDA issued guidance in 2006 which generally supports the use of juvenile animal models. (FDA, 2021; International Council for Harmonization, 2020) More recently, however, FDA has suggested that juvenile animal studies for pediatric oncology drugs may not be necessary to initiate the first stage of in-human testing (known as phase 1 trials) but rather may be more useful at a later stage if a drug advances beyond phase 1 testing. (Abulwerdi, 2025; Tavares, 2025)

Preclinical consortia

The Pediatric Preclinical In Vivo Testing (PIVOT) consortium comprises a coordinating center and seven academic research programs specializing in basic research and preclinical testing of treatments for the most common pediatric cancers. (NCI, 2026; Pediatric Preclinical In Vivo Testing Consortium, n.d.) PIVOT is a public-private partnership funded by NCI, replacing two earlier pediatric preclinical testing programs and incorporating years of research, experience, and partnerships. This work led to the creation of hundreds of PDX models of high-risk cancer and collaborations with more than 80 pharmaceutical companies to use these models to test new drugs. Genomic profiling of these PDX models provides key information for the PIVOT program to use molecular targeting to select model systems in which to test potential new treatments. (Pediatric Preclinical In Vivo Testing Consortium, n.d.; Smith, 2024) Genomic profiling of childhood tumor PDX models has helped enable more rational model selection and clinical trial design by linking drug targets to pediatric tumor biology (Rokita, 2019). More recent analyses reinforce that pediatric preclinical testing has been most useful when it is systematic, transparent, and tied to biologically relevant models, but they also show that negative preclinical results (when a drug appears ineffective) are important because they can prevent weak candidates from moving into scarce pediatric trial slots. (Smith, 2024)

Other organizations specialize in preclinical pediatric cancer models and resources, including the Children's Cancer Therapy Development Institute (CC-TDI), which is developing drugs for rhabdomyosarcoma and DIPG, and the Children's Oncology Group, who maintain a repository of cell lines that currently includes 75 lines covering five different types of pediatric cancers available for screening drugs. (CC-TDI, n.d.; Childhood Cancer Repository, n.d.)

USE OF COMPANION ANIMALS

At best, any animal cancer model is still only an approximation of a human cancer. In rodent models, for example, animals' genetic makeup and immune system are altered in order to create a permissive environment for the growth of human cells. As a result, in such an altered environment, cancer cells might behave differently than they would in patients. A common model involves mice without a functioning immune system, an important system that naturally occurs in the body for responding to cancer and infections. Further, artificial tumors are often made up of a homogeneous set of cells, while natural tumors tend to be heterogeneous.

Some researchers have realized that companion animals (pets) get certain types of cancer at roughly the same frequency as humans. Nearly a million dogs are diagnosed with cancer each year in the U.S. Some of the cancers seen in dogs, such as sarcomas, melanoma, lymphoma, osteosarcoma and glioma, are very similar to many pediatric cancers, and unlike artificial models, these cancers occur naturally and in animals with normal biological functions. For many of us, companion animals are like another member of the family, so when they develop cancer, there is a natural desire to treat them if possible, and indeed many cancer drugs are approved for both humans and dogs. This has led to a field known as comparative oncology, where pets who develop cancers can be enrolled in clinical trials for drugs to help advance drug development for humans as well. (Lenz, 2025; Oh, 2023) Recognizing the potential of this type of research, the National Cancer Institute (NCI) supports comparative oncology research through programs and resources that study naturally occurring cancers in companion dogs. NCI's Comparative Oncology Program works with the Comparative Oncology Trials Consortium (COTC), a network of academic veterinary centers in the U.S. and Canada that conducts clinical trials in dogs with cancer. NCI also supports canine immunotherapy studies, longitudinal studies, and the Integrated Canine Data Commons, which brings together genomic, imaging, clinical, and other data to facilitate comparisons between canine and human cancers. These efforts are designed to improve cancer treatment for companion animals while generating evidence that can inform human cancer research and drug development. (NCI, n.d.)

Preclinical testing is a powerful tool, but one with important limitations. Well-characterized cell lines and animal models do not exist for all pediatric cancers, leaving important gaps in the ability to develop drugs for some cancers. Preclinical testing in the academic setting is also often limited by a lack of access to commercial drug compound libraries. This lack of access, combined with constrained funding and resources, means that the rate at which drug candidates are tested in academic settings is much slower than is the case with pharmaceutical-sponsored preclinical screening programs. Drugs that do well preclinically do not always translate into drugs that work in humans; nonetheless, for pediatric cancers where patients are rare, preclinical research is an important part of drug development for pediatric cancer. (Smith, 2024)

Computational (in silico) modeling

Computer simulations, combined with existing scientific data, can be used to predict how a new drug candidate might behave — even before any laboratory testing begins. (Talkington, 2025; Wen, 2026; Yates, 2025) These computer-based, or "in silico," methods can quickly screen through thousands of chemical compounds and identify which ones are more likely to be toxic, helping prioritize which candidates merit the time and expense of lab testing. However, because these predictions are based on existing data rather than direct experiments, the results still need to be confirmed later through cell, organoid, or animal studies before they can be trusted. (Adefolaju, 2025; Talkington, 2025)

References

Abulwerdi, G., Nguyen, H., Samuels, S., (2025). Pediatric developmental drug toxicity: Description of juvenile animal studies in U.S. FDA prescribing information and reviews. The Journal of Clinical Pharmacology. doi.org/10.1002/jcph.70030

Adefolaju, A., Kram, D. E., Mann, B., Hingtgen, S., and Satterlee, A. (2025). Informing development of brain cancer therapies within "preclinical trials" using ex vivo patient tumors. Advanced Drug Delivery Reviews, 228, 115736. doi.org/10.1016/j.addr.2025.115736

Bailey, G. P., and Mariën, D. (2011). The value of juvenile animal studies. Birth Defects Research Part B: Developmental and Reproductive Toxicology, 92(4), 292-303. pubmed.ncbi.nlm.nih.gov/22623020

Childhood Cancer Repository. (n.d.). www.cccells.org

Children's Cancer Therapy Development Institute. (2024). www.cc-tdi.org

http://www.cogcell.org/Duarte, D. M. (2015). Use of juvenile animal studies to support oncology medicine development in children. Reproductive Toxicology, 56, 97–104. doi.org/10.1016/j.reprotox.2015.05.005

du Chatinier, A., Meel, M. H., Das, A. I., et al. (2022). Generation of immunocompetent syngeneic allograft mouse models for pediatric diffuse midline glioma. Neuro-Oncology Advances, 4(1), vdac079. doi.org/10.1093/noajnl/vdac079

Fløe, L. von B., Pedersen, M. G., and Møller, B. K. (2025). Animal models in preclinical evaluation of CAR-T cell therapy: Advantages and limitations. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1880(6), 189455. doi.org/10.1016/j.bbcan.2025.189455https://www.fda.gov/media/119658/download

Food and Drug Administration. (2021). S11 nonclinical safety testing in support of development of pediatric pharmaceuticals: International Council for Harmonisation; guidance for industry. www.fda.gov/regulatory-information/search-fda-guidance-documents/s11-nonclinical-safety-testing-support-development-pediatric-pharmaceuticals

https://www.gao.gov/products/gao-23-105947Hinson, A. R., Jones, R., Crose, L. E. S., et al. (2013). Human rhabdomyosarcoma cell lines for rhabdomyosarcoma research: Utility and pitfalls. Frontiers in Oncology, 3, 183. doi.org/10.3389/fonc.2013.00183

https://doi.org/10.1093/jnci/djz207International Council for Harmonisation. (2020). ICH guideline S11 on nonclinical safety testing in support of development of paediatric pharmaceuticals. www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s11-nonclinical-safety-testing-support-development-paediatric-pharmaceuticals-step-5_en.pdf

Kemp, C. J. (2015). Animal models of chemical carcinogenesis: Driving breakthroughs in cancer research for 100 years. Cold Spring Harbor Protocols, 2015(10), 865–874. doi.org/10.1101/pdb.top069906

Lenz, J. A., and Atherton, M. J. (2025). Maximizing the dual benefit of pet dogs in cancer trials. Nature Reviews Cancer, 25(3), 147–148. doi.org/10.1038/s41568-025-00792-0

Li, Z., Zheng, W., Wang, H., et al. (2021). Application of animal models in cancer research: Recent progress and future prospects. Cancer Management and Research, 13, 2455–2475. doi.org/10.2147/CMAR.S302565

https://doi.org/10.1542/peds.2024-066920Liu, M., and Yang, X. (2025). Patient-derived xenograft models: Current status, challenges, and innovations in cancer research. Genes & Diseases, 12(5), 101520. doi.org/10.1016/j.gendis.2025.101520

Luo W, Hoang H, Liao Y, et al. (2023). A humanized orthotopic mouse model for preclinical evaluation of immunotherapy in Ewing sarcoma. Front Immunol. 14:1277987. doi: 10.3389/fimmu.2023.1277987. PMID: 37868989; PMCID: PMC10587429.

Martynov, I., Dhaka, L., Wilke, B., et al. (2024). Contemporary preclinical mouse models for pediatric rhabdomyosarcoma: From bedside to bench to bedside. Frontiers in Oncology, 14, 1333129. doi.org/10.3389/fonc.2024.1333129https://doi.org/10.1056/NEJMoa1709866

National Cancer Institute. (n.d.). Comparative Oncology Program. ccr.cancer.gov/comparative-oncology-program

National Cancer Institute. (2026). NCI Pediatric Preclinical In Vivo Testing (PIVOT) Program. dctd.cancer.gov/research/networks/pediatric-pivothttps://doi.org/10.3389/fimmu.2024.1490911

Oh, J. H., & Cho, J. Y. (2023). Comparative oncology: Overcoming human cancer through companion animal studies. Experimental & Molecular Medicine, 55, 725–734. doi.org/10.1038/s12276-023-00977-3

Park, C.-K., Khalil, M., Pham, N.-A., et al. (2024). Humanized mouse models for immuno-oncology research: A review and implications in lung cancer research. JTO Clinical and Research Reports, 6(3), 100781. doi.org/10.1016/j.jtocrr.2024.100781

Pediatric Preclinical In Vivo Testing Consortium. (n.d.). preclinicalpivot.org

https://doi.org/10.1007/s12026-025-09687-6https://doi.org/10.3389/fmed.2025.1642279Rokita, J. L., Rathi, K. S., Cardenas, M. F., et al. (2019). Genomic profiling of childhood tumor patient-derived xenograft models to enable rational clinical trial design. Cell Reports, 29(6), 1675–1689. doi.org/10.1016/j.celrep.2019.09.071

Ruggeri, B. A., Camp, F., and Miknyoczki, S. (2014). Animal models of disease: Pre-clinical animal models of cancer and their applications and utility in drug discovery. Biochemical Pharmacology, 87(1), 150–161. doi.org/10.1016/j.bcp.2013.06.020

Skloot, R. (2010). The immortal life of Henrietta Lacks. Crown Publishers. pmc.ncbi.nlm.nih.gov/articles/PMC3516052

Smith, M. A., Houghton, P. J., Lock, R. B., et al. (2024). Lessons learned from 20 years of preclinical testing in pediatric cancers. Pharmacology & Therapeutics, 264, 108742. doi.org/10.1016/j.pharmthera.2024.108742

Sousa, F., Grau, A. M., Hameedat, F., et al. (2026). Are the current preclinical models adequate to evaluate CAR-T cell therapy in paediatric high-grade gliomas? Molecular Therapy. doi.org/10.1016/j.ymthe.2026.06.043

Talkington, A. M., Cao, Y., Kearsley, A. J., et al. (2025). Opportunities for machine learning and artificial intelligence in physiologically-based pharmacokinetic (PBPK) modeling. Advanced Drug Delivery Reviews, 227, 115716. doi.org/10.1016/j.addr.2025.115716

Tavares, D., Chien, H.-T., Sheean, M. E., et al. (2025). From guideline to practice: Three years of ICH S11 insights and recommendations. Frontiers in Medicine, 12, 1537001. doi.org/10.3389/fmed.2025.1537001

Wen, Y.-F., Wang, X., Boyanapalli, S., et al (2026). Accelerating pediatric oncology drug development: Advances in clinical pharmacology, trial design, non-clinical evidence, and regulatory science. The Journal of Clinical Pharmacology, 66(7), e70242. doi.org/10.1002/jcph.70242

Yates, J. W. T., Zientek, M., Taskar, K. S., et al (2025). Physiologically-based pharmacokinetic modeling to support pediatric clinical development: An IQ Working Group perspective on the current status and challenges. CPT: Pharmacometrics & Systems Pharmacology, 15(1), e70141. doi.org/10.1002/psp4.70141

August

When we were told August's diagnosis was terminal, we started thinking about legacy — about what his life could mean beyond the time we had left with him, and whether anything from our circumstances could make things easier for the families who would come after us.

Pediatric cancer research is chronically underfunded, and ependymoma remains one of the tumors we understand the least. Even among children who share the same pathology, every patient can feel like an n of 1, which means every family is making the hardest decisions of their lives on evidence that was never built from a child like theirs. So, when we learned that August's tumor could contribute to research, donating it became one of the few tangible things left for us to do. The possibility that our worst-case circumstances could one day contribute to another family's best-case scenario was the most meaningful thing we could do.

Statistics do not stay statistics. They become the stories families tell themselves at kitchen tables and hospital bedsides; the stories we tell our other children; the stories we carry into every consent form we sign. When your child has rare and aggressive cancer, the difference between an 80% chance of survival and a 20% chance is not a number; it is the story you are living inside. It shapes how treatment, acceptable risks, and length of your child's life vs. the quality of it. We donated August's tumor to change those stories.

Having an infant diagnosed with ependymoma put us in largely uncharted territory. August lived six and a half years after that diagnosis, with a quality of life that surprised nearly everyone who cared for him. He learned to talk, he learned to swim, he read, he played T-ball, and he became a big brother.

I hope what researchers learn from his tissue helps explain why, and the explanation gives the next family evidence for a decision, confidence in a path forward, or a clearer sense of what is possible for their child.

I hope his contribution helps move families out of being an n of 1. If his tissue adds one more piece to what we understand about ependymoma — improving treatment, changing expectations, or eventually contributing to a cure — then something meaningful from his life impacts future patients.

—shared by August's family

CHAPTER 4

Clinical Research

Summary

The relatively small number of children with cancer can make clinical research challenging, but fortunately children with cancer tend to be seen in very specialized institutions that participate in well-established cooperative research networks that collaborate internationally. This results in a relatively high proportion of children enrolling in clinical trials when compared to adults. Even with such infrastructure, small patient numbers often require innovative trial designs in order to reach valid conclusions. Many pediatric cancer studies follow adult studies with a given drug, but children may require different formulations or dosing, highlighting another challenge.

Introduction

When most people think of cancer research, they likely think of clinical trials where drugs are tested in patients. As explained in the previous chapters, clinical trials are the last of many steps in the research process but are essential to produce new drug therapies for children with cancer. Clinical trials are used to determine the safety and efficacy of a drug or a drug combination or other therapeutic interventions and are among the most expensive and challenging phases of research. While clinical trials frequently study new drugs, trials may also layer these new drugs onto older treatment regimes, or trials may also study already approved drugs in new diseases or under different dosing approaches.

Historically, cancer drugs have rarely been developed expressly for children. More commonly, drugs developed for adult cancers, but potentially applicable to one or more cancers in children, are tested in children only after they have been proven to be safe and effective in adults (see paths A, B, D in Figure 4-1). In the period from 2016 - 2025, there were 122 new cancer therapies approved, of which four were initially developed specifically for children (see Table A-5 in the *Appendix*). Unlike the situation for adults with cancer, participation of children in clinical trials is relatively common. High participation rates in clinical trials are likely the factor most responsible for the dramatic improvement in survival rates for many childhood cancers. However, there are unique issues when conducting clinical research with children, and they are discussed below.

Measuring outcomes

With limited numbers of children diagnosed with a specific cancer in any given year and a need to develop new treatments in a timely manner, efforts have been made to minimize the number of children needed to enroll on a trial and the length of time needed to conduct trials using advanced trial designs and outcome measures. From changes in the way a drug's safety profile is determined to the process for determining optimal dosage, new trial methods are reducing the number of children needed for these early-phase trials. Later-phase trials have also benefited from advances in study design, such as the use of historical control groups, single-arm trials, the use of adaptive Bayesian designs, use of real-world data, and measuring surrogate endpoints. (Vassal, 2013)

While survival is ultimately the most important endpoint when conducting a cancer clinical trial, often other outcomes besides survival are measured. These outcomes might be reduced toxicity, the time until a cancer

FIGURE 4–1

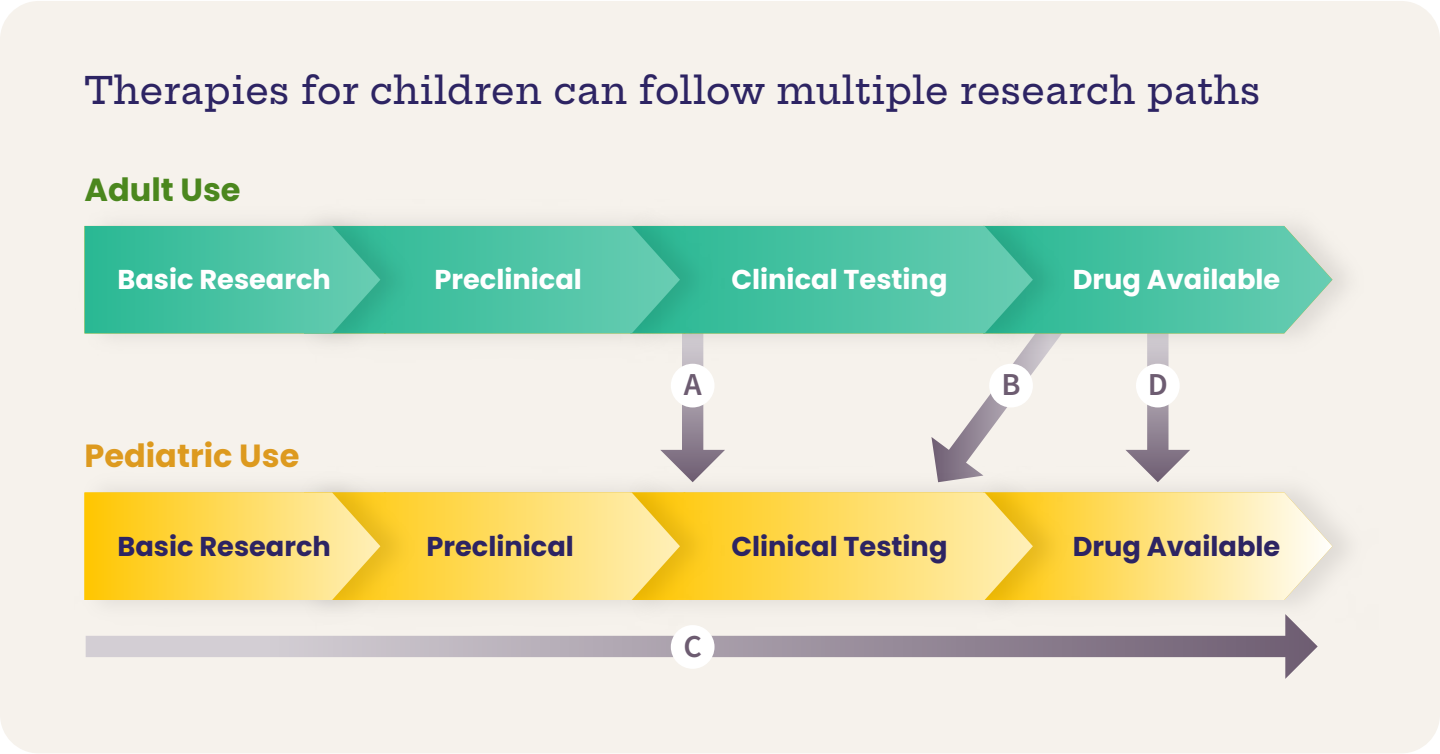


Figure 4-1: Drug development for children occurs in several different ways. A) clinical testing in children can occur simultaneously to testing in adults. Pediatric research on a drug may lag behind adult research but nonetheless may begin before the adult indication is approved. B) Testing in children sometimes only starts after a given drug has been approved for use in adults, either voluntarily or in response to postmarketing requirements imposed by FDA. C) Drug development for childhood cancers can begin at the preclinical phase and continue through drug approval completely in children and without parallel adult drug development. D) Some drugs approved for adult cancers may be tested in children and, if found successful, be used in childhood cancers without any formal inclusion of study results into the label.

progresses, disease response as assessed by tumor shrinkage as measured by imaging, the percent of patients responding to a drug, or change in some biological measurement like white blood cell counts or a particular protein in the blood. The latter are considered "surrogate" endpoints because they do not directly measure the outcome of interest, survival, but rather are outcomes that are typically correlated with the primary outcome measure that may be easier and faster to measure.

Surrogate endpoints may include a larger class of measurements known as biomarkers. Biomarkers are biologic indicators that can reflect the health or disease state of a person. Biomarkers can indicate not only what is happening with a cancer (e.g. tumor shrinkage), but they can also provide a window into safety of a drug (e.g. cardiac rhythm disruption), or even the likelihood of late side effects (e.g. cardiac troponin T (cTnT)). The advantage of biomarkers is that they can measure vital information about the effect of a drug more rapidly than longer-term clinical outcomes like survival. Biomarkers must accurately predict later clinical effects if they are to function as substitutes for clinical outcomes. For example, when a drug delays the time to tumor progression (TTP), it would seem to make sense that the patient would also live longer. It may be, however, that even though tumor progression may be delayed, when the cancer does grow again, it does so even more aggressively, and overall survival time can remain unchanged. In order for surrogate endpoints to be used for drug approval, biomarkers need to be thoroughly validated. FDA maintains a list of validated surrogate endpoints, but drug developers can also develop their own. (FDA, 2018) From 1992 to 2019, 194 oncology indications were approved for 132 drugs based on surrogate endpoints. (Chen, 2020) While select outcomes are rigorously collected as part of clinical trials, some effects of treatment may not be fully understood during the time window of a given clinical trial. Ongoing monitoring, especially for safety signals, continues using tools like the Sentinel system, which can detect adverse

effects by monitoring large volumes of electronic health data. (Sentinel, n.d.)

Logistics

The relative rarity of childhood cancer has made collaboration among pediatric oncologists through clinical trials a pivotal requirement for identifying new therapies. A substantial portion of children with cancer are cared for in children's hospitals and cancer centers rather than community care settings, and a significant portion are enrolled in clinical trials. To enroll enough children into clinical trials often requires numerous locations throughout the U.S., and indeed throughout the world. Almost all centers treating children with cancer participate in networks and consortia that enable them to pool their research data, ensuring clinical trials produce sufficient results within a reasonable timeframe to assess new therapies.

The largest of these networks is the Children's Oncology Group (COG). COG is supported by NCI and consists of over 220 pediatric centers in the U.S., Canada, Australia, and New Zealand. It is estimated approximately 80% of children diagnosed in the U.S. under the age of 19 are cared for at a COG institution. (Lupo, 2025) This concentration of children with cancer makes it easier to enroll children in clinical trials, and as a result, the clinical trial participation rate for children with cancer is very high. Indeed, for children, unlike adults, clinical trial participation is often considered the standard of care. Not only do NCI-sponsored trials use this network of institutions, but some industry trials also leverage this network**.** While distributed across the country, some less populated regions of the country have a lower concentration of institutions, meaning children may have to travel longer distances to be seen at a COG institution (Figure 4-2). Many established referral patterns are in place to ensure that children in more rural or remote areas can be cared for at a COG institution. In addition, the National Community Oncology Research Program (NCORP) has allowed the affiliation of some regional hospitals to participate in COG clinic trials as affiliate programs. To address the frequent need for pediatric patients to travel across state lines, in 2026 Congress passed the Accelerating Kids Access to Care Act (see *Appendix*), which streamlined the process for children on Medicaid to be seen at institutions in other states.

There are other groups and collaborations in addition to COG, which can encompass multiple institutions or single institution networks like those operated by St. Jude, Dana Farber Cancer Institute, or Memorial Sloan Kettering Cancer Center. Some groups have a narrowed focus on a particular phase of a study. For example, some concentrate on early phase (or phase 1 or 2 trials) studies, including the Children's Brain Tumor Tissue Consortium, the DIPG Consortium, the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), the New Agents in Neuroblastoma Therapy (NANT) consortium, Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) consortium, the Pediatric Neuro-Oncology Consortium (PNOC), and the Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC). The federally funded (NCI) cooperative network which conducts phase 1 trials and other early phase studies in children is the Pediatric Early Phase Clinical Trials Network (PEP-CTN). While the membership, funding, and focus of each network varies, the intent of each is to facilitate the efficient conduct of trials and sharing of data and resources.

Children can participate in either therapeutic or non-therapeutic studies. Non-therapeutic studies may include tissue or data collection for use in epidemiology research or basic science investigations, while therapeutic clinical trials actively test new treatments or a modification of current treatment approaches. Many trials combine clinical and non-clinical components, and children can enroll in clinical and non-clinical trials concurrently. It is estimated that approximately 38% of children with cancer seen at COG institutions between 2007 and 2018 were enrolled in COG research studies of any kind (therapeutic and non-therapeutic), and of those enrolled, 45.6% were enrolled in a therapeutic clinical trial. (Lupo, 2025) Enrollment in research studies varies with age and may be as high as 54% for children under five. However, enrollment falls to approximately 20% for adolescents and young adults (generally aged 15 and older). COG trial enrollment rates rose from 2007 to 2011, hitting a peak of nearly 43% before dropping to slightly less than 33% in 2018. (Lupo, 2025)

FIGURE 4–2

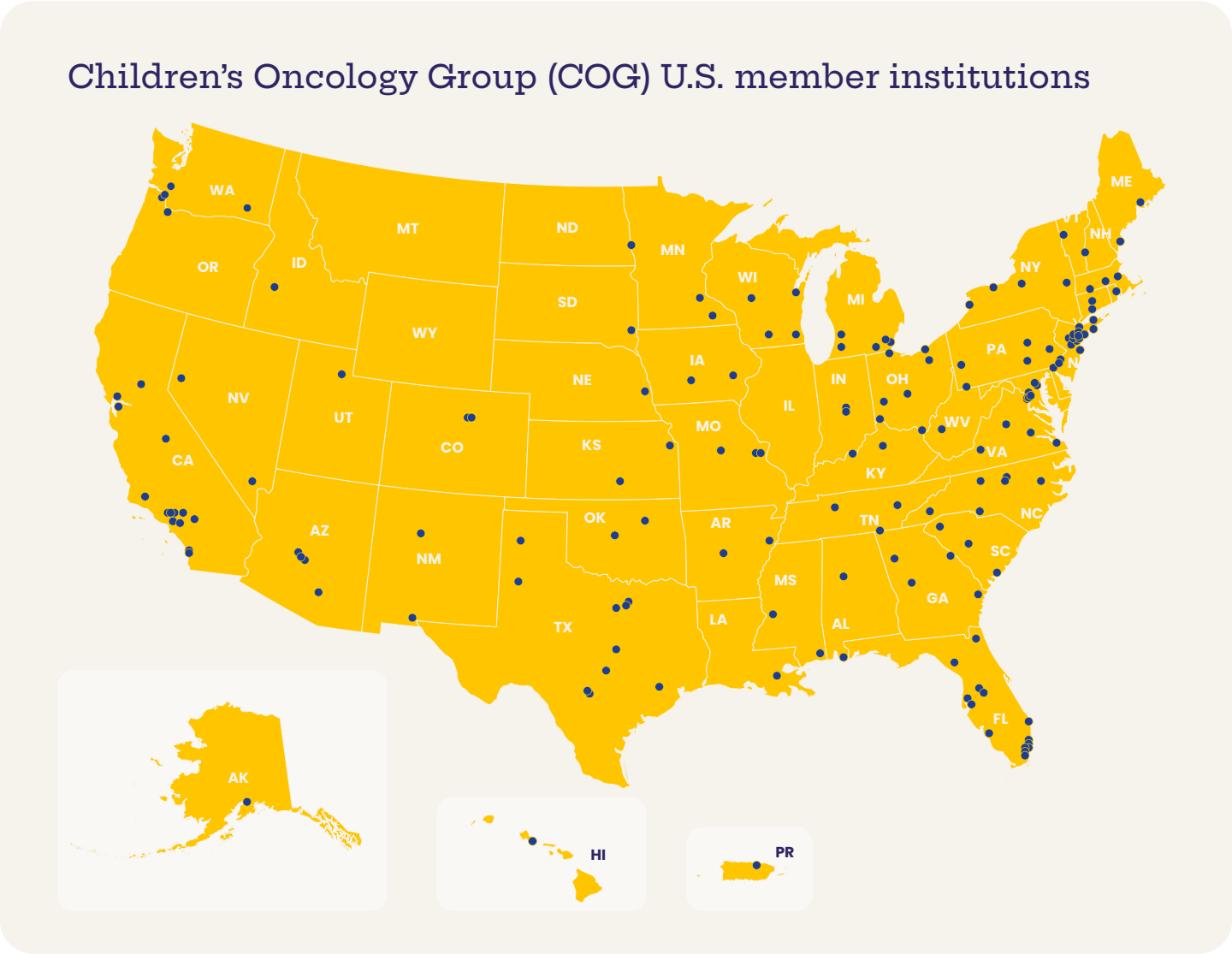


Figure 4-2: The 199 U.S. COG research sites are distributed throughout the country, but are concentrated in areas of higher population.

Prioritization

Despite children's relatively high participation rate in clinical trials, the number of research trials for different types of cancers can be significantly limited by the number of eligible children. While 15,340 children and adolescents are expected to be diagnosed with cancer in the U.S. in 2026, not all will enroll in a therapeutic trial. Because of their low incidence, certain cancers may have fewer trials open, while other cancer types may have multiple trials open, potentially creating competition for the same patients. If competition for the trials is too strong, it can present recruitment challenges and lead to longer completion times for trials or early closure of studies.

Prioritization of research needs can occur within some networks, with NCI's Cancer Therapy Evaluation Program (CTEP) providing oversight for all NCI-funded trials. The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) at FDA is charged with reviewing drugs for potential pediatric use and advising FDA on the issuance of written requests (discussed in *Regulations* chapter). The Best Pharmaceuticals for Children Act (BPCA) (also discussed in *Regulations* chapter) charges NIH, in consultation with FDA and pediatric experts, to develop and publish an annual list of priority drugs to be studied in children. These activities can provide important

signals and encouragement to the childhood cancer research community, but they do not represent active management of the entire portfolio of childhood cancer clinical trials.

Dosing and formulations

Most cancer drugs are initially designed for adult usage (paths A, B, D in Figure 4-1), which can pose unique challenges when attempting to test them in children. In the case of drugs that are already approved and sold, often the drug itself comes in dosages or forms that are inappropriate for use in children. Most drugs are dosed proportional to body size, and, in the case of drugs that come in a pill form, the available pill sizes may be too large for children, especially young children. Further, younger children may not even be able to swallow pills at all. If pills are the only available option, they are sometimes crushed and mixed with food or otherwise compounded into different formulations for children; however, issues of solubility and unpleasant taste can make this impractical. Therefore, prior to conducting pediatric trials, new formulations must sometimes be first developed or compounded when bioequivalence can be demonstrated.

Representation

Clinical trials are meant to test interventions in a small group of individuals, with the intention of extrapolating the results from that smaller group to the larger population with the given cancer. For that extrapolation to be valid, the trial participants must be representative of the larger group with the given cancer. This representation encompasses both clinical characteristics like medical history or disease severity, but also demographic factors like age, sex, race, and ethnicity. The dispersed network of pediatric trial sites, like COG (figure 4-2), allows diverse representation in trials. Importantly, drug development has increasingly become global, and frequently drug approval applications include patients from throughout the world. For adult oncology trials, the degree of international data collection has been raised as a challenge for representation of the U.S. cancer population, and for all oncology drugs newly approved in the U.S. in 2025, only 20% of the patients were from the U.S. (FDA, 2026) In contrast, two of the oncology drugs approved in 2025 included pediatric indications, and these drug trials were conducted wholly in the United States. (FDA, 2026)

References

Chen, E. Y., Haslam, A., & Prasad, V. (2020). FDA acceptance of surrogate end points for cancer drug approval: 1992-2019. JAMA Internal Medicine, 180(6), 912–914. doi:10.1001/jamainternmed.2020.1097.

Lupo, P. J., Siegel, D. A., Schussler, N. C., et al. (2025). Enrollment in Children's Oncology Group's clinical trials: Population-based linkage with the National Childhood Cancer Registry. Journal of the National Cancer Institute 117(9), 1868–1874. doi.org/10.1093/jnci/djaf134.

Sentinel (n.d.). Pediatrics. www.sentinelinitiative.org/featured-topics/pediatrics.

Food and Drug Administration (2018). Clinical trial endpoints for the approval of cancer drugs and biologics: Guidance for industry. www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics.

U.S. Food and Drug Administration (2026). Drug trials snapshots. www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots. Accessed September 7, 2026.

Vassal, G., Rousseau, R., Blanc, P., et al. (2013). New drugs for children and adolescents with cancer: The need for novel development pathways. The Lancet Oncology, 14(3), e117–e124. doi.org/10.1016/S1470-2045(13)70013-5.

Ailani

Six weeks before her third birthday, our daughter Ailani was diagnosed with pre-B cell acute lymphoblastic leukemia, complicated by a rare KMT2A-r mutation that made her disease high-risk with a poor prognosis. Over the seven years since, she has endured seven relapses yet has faced this relentless disease with extraordinary courage. She received her first bone marrow transplant with her father as her donor. In the years since, she has endured a second transplant, four different CAR T cell therapies, and trials at hospitals across the country, relapsing repeatedly despite it all.

Ailani is now 10 years old and loves singing, dancing, and playing with her friends. She has been a childhood cancer advocate since she was three, serving as an ambassador for the Childhood Cancer Caucus and speaking to Congress for the Kids vs. Cancer Act.

One decision stands out. In 2021, after Ailani's second relapse, we had almost no good options. A second transplant would be harsh on her body, and she hadn't recovered from the first, but our first choice of clinical trial had no spots available. That left only one option, at Stanford, with about a 50% chance of working and no one able to guarantee us anything. The hardest part wasn't the medicine

— it was leaving our home hospital with only hope on our side, not knowing if we would return home with her.

Ailani was too immunocompromised to fly commercially, so an organization called AeroAngel flew us across the country on a private plane, and we booked a hotel with little more than hope and a prayer. The moment that stands out most vividly is the flight home. It hadn't worked. After weeks of misery, with fevers hovering around 104, Ailani's disease returned before we ever departed California, and we left with a profound sense of sadness and failure.

Looking back, that experience shaped what we believe about clinical research access for pediatric cancer. Access sometimes means traveling thousands of miles at a tremendous cost, and it can be constrained by regulatory and enrollment timelines, so you may end up accepting a less promising therapy simply because it's the one available. Even great sacrifices to participate may still end in failure. But it can also give you more time — time to reach the one that finally provides long-term remission, and perhaps, someday, a forever cure. Why couldn't she have had the right therapy first, instead of the years of trial and error we went through to get here?

— shared by Ailani's family

CHAPTER 5

Regulatory Requirements

Summary

Developing effective pediatric drugs is an immense scientific challenge, made more difficult for childhood cancers by the relative rarity of those diseases. Regulatory requirements imposed on the drug development process serve dual purposes: ensuring that drugs work and are safe before being sold to the public and protecting the individuals who participate in research. Research involving children, once considered unethical due to their vulnerable status, is now recognized as not only acceptable but necessary for medical progress in treating childhood diseases. The U.S. Food and Drug Administration (FDA) is the federal agency responsible ensuring the safety, efficacy, and security of human drugs, biological products, and medical devices. FDA works closely with drug sponsors, advising them as they design clinical trials so that the evidence collected during clinical trials is the right type, quality, and quantity to inform the FDA decision-making process. FDA also administers regulatory requirements designed to require and incentivize drug sponsors to conduct pediatric research that they might not otherwise pursue; the most notable recent example is the 2017 Research to Accelerate Cures and Equity (RACE) Act, which for the first time gave FDA meaningful authority to require pediatric testing of adult cancer drugs based on shared molecular targets rather than disease sites. (Research to Accelerate Cures and Equity for Children Act, 2017) Finally, while the scientific challenges to creating new treatments for children with cancer are inherent to the disease and are shared throughout the world, regulatory requirements for research and drug approval may vary from country to country based on national laws, cultures, and values.

Introduction

Drug development in the United States is governed by several laws, regulations and guidance documents that cover patient protection during the research phase. They establish standards of evidence for drug approval, approval pathways, and the appropriate balance of risk versus benefit needed to secure product approval. Historically, drugs did not always have to undergo rigorous review before being sold to the public, nor were there always controls over the conduct of research on humans. Many of the current requirements for both research and drug approval can be traced back to either major ethical transgressions tied to research, or safety issues associated with the sale of dangerous medicines to the public. One particularly striking and tragic event in U.S. drug safety history occurred in 1937, when a drug manufacturer tried to create a liquid version of an antimicrobial called “elixir of sulfanilamide” that would be easier for children to take than the existing pill form. Chemists at the drug manufacturer found that the powdered drug could be dissolved in diethylene glycol, and with the addition of raspberry flavoring could be made into a liquid form that people would be willing to drink. The new formulation was never tested for safety before being shipped out for sale, and the chemists who created the formulation did not

realize that diethylene glycol was toxic. Over 100 people died after taking the formulation, including 30 children. (FDA, 2018a) This event helped usher in additional federal requirements to establish the safety of drugs. Later, in the 1960s, in response to birth defects caused by thalidomide, Congress passed additional drug laws that charged FDA with verifying the efficacy of drugs in addition to reviewing their safety. Today drugs must undergo much more scrutiny before being approved for sale to the public, including laboratory studies (in animals or using other methods) and human studies (see *Preclinical Drug Development* and *Clinical Research* chapters).

Ensuring safety of research subjects

Ethical considerations when designing research in humans dictate that risks be minimized, but with any research involving people, some risk will always remain. The risks posed by a clinical trial are reviewed prior to starting the trial by an oversight body known as an institutional Review Board (IRB). One task of an IRB is to ensure that the proposed research protocol is ethical. An IRB also approves informed consent documents that adequately educate research participants about the experiment for which they are volunteering, along with any potential risks that participation might entail. IRBs are made up of multiple stakeholders including researchers, ethicists and patient advocates. While most major research institutions have their own IRBs, independent and commercial IRBs also exist to review and approve research when a researcher does not have an IRB available at their institution. Many clinical trials are conducted at multiple sites, and while each site's IRB could review the same trial protocol, the inefficiencies of doing so have led to the increasing use of centralized IRBs that have the authority to review and approve a clinical trial protocol for all locations, (FDA, 2006)

Pediatric-specific requirements

Adults can vary in how much risk they are willing to assume by participating in research. For example, an individual may be willing to receive an experimental drug in a phase 3 trial after it has been shown to be safe in other patients and has shown some evidence of effectiveness, but that same person may be unwilling to participate in a phase 1 trial where safety of a drug is largely unknown. Participation in research is voluntary for adults, and no one can be forced to participate in research without their consent. Not everyone, however, is able to provide consent in the same way. Recognizing that certain segments of the population have limitations in their ability to provide consent, federal regulations and standards have been developed for vulnerable groups which include prisoners, mentally handicapped, pregnant women, and children. (FDA, 2015)

Because children below age 18 are presumed not to have the ability to fully comprehend the nature of a research study, parents technically "give permission" for their children to participate. When children and adolescents are sufficiently mature, researchers should explain the clinical trial's purposes and procedures in a way that is appropriate for their age and ask for their agreement to participate – this is called "assent." Federal law provides special protections for children when they participate in research studies. (FDA, 2015) At each phase in testing new cancer agents in children, federal laws and ethical standards require that an individual child participating in research must have the prospect of direct benefit from the study as compared to other available treatment alternatives (Figure 5-1). (FDA, 2022)

Phase 1 studies in pediatric oncology offer important opportunities to understand how children metabolize new drugs and whether those drugs affect biological targets that can reduce or stop cancer growth. These studies may require tumor or normal tissue biopsies to assess whether a child's cancer is susceptible to the therapy under investigation. However, biopsies performed solely to answer scientific questions – with no prospect of direct clinical benefit to the patient – cannot be conducted if they pose greater than minimal risk to the child (Figure 5-1). The balance between the need to advance the science of pediatric oncology treatment and the need to protect children from harm as research participants is at the heart of a current debate on the ethics of non-therapeutic single or multiple biopsies in children, and other research-only testing procedures. (Anderson, 2004) The development of minimally invasive alternatives such as blood-based liquid biopsy and circulating tumor DNA (ctDNA) assays have emerged as potential substitutes for tissue sampling in some contexts.

FIGURE 5-1

Figure 5-1: Federal regulations provide special protections to children who participate in research. The ability to conduct pediatric research depends on the nature of the research and its anticipated benefit for children.

Pediatric labeling requirements

Children often respond to a given drug differently from adults, resulting in different safety, efficacy, or dosing considerations (see *Biological Understanding* chapter). In recognition of these differences, beginning in 1994, federal requirements were instituted to explicitly include pediatric use information in drug labeling. Requirements were further refined with additional regulation in 2006, and today all new drug labels include a dedicated "Pediatric Use" section. (Code of Federal Regulations, 2026) FDA has issued formal guidance about the language to be used to describe pediatric information, as well as where else information about pediatric use must also be included in product labeling. (FDA, 2019) It should be noted that even if pediatric studies of a drug are inconclusive, or the only studies conducted in support of pediatric use were those on juvenile animals, this information can still be required within the label. (FDA, 2019) The pediatric labeling of drugs approved before pediatric labeling regulations were in place varied greatly. Table A-6 in the *Appendix* lists drugs with pediatric indications approved between 2016 and 2025.

DRUG LABELING

Drug labels are formal documents that go beyond the labels typically associated with over-the-counter medications and contain information learned from research studies. They may contain information regarding patient outcomes, adverse events, and special dosing information. A database of approved drugs and labeling information can be found at: www.accessdata.fda.gov/scripts/cder/daf/.

Laws to promote pediatric research

In cancer, as with many other diseases, most drugs are developed for adults in whom disease incidence tends to be higher— and therefore market incentives are greater— and drugs are easier to test. Lacking these inherent incentives, drugs under development for adult diseases are rarely studied in children, despite the possibility that they might prove effective for specific diseases. Recognizing the lack of pediatric research, Congress passed two laws to promote pediatric research on drugs that are otherwise developed for adults, the Best Pharmaceuticals for Children Act (BPCA), and The Pediatric Research Equity Act (PREA). (Best Pharmaceuticals for Children Act, 2002; Pediatric Research Equity Act, 2003) These two laws are often referred to as the "the carrot-and-stick" approach to promoting more research in children, as one provides voluntary incentives, and the other imposes requirements on developers of adult drugs.

The carrot portion of the approach comes in the form of "pediatric exclusivity" which was first enacted in 1997 (and later renewed in 2002 and 2007) as part of BPCA. BPCA provides an incentive for drug sponsors to conduct research using their drugs in childhood diseases (see chapter *Funding, Investment, and the Economics of Discovery*). Originally only a temporary program, it was made permanent in 2012. (Food and Drug Administration Safety and Innovation Act, 2012) The incentive provided by BPCA is in the form of an extra six months of market exclusivity for the drug being tested. This exclusivity is for all uses of the drug, including adult uses.

FDA determines the scope of the research needed to obtain additional exclusivity, providing a formal document known as the Written Request (WR). Importantly, the award of exclusivity does not depend on the outcome of the required research, only whether it was performed exactly as specified in the WR. In other words, if a sponsor tests a drug intended for a pediatric indication per the terms outlined in the WR and the drug is not found to work, the sponsor would still get the added six months of exclusivity for adult uses of that drug. Although WRs are issued by FDA, the process can be initiated by either the drug sponsor or FDA (Figure 5-2). When the drug sponsor starts the process, they do so by outlining suggested research in a Proposed Pediatric Study Request (PPSR), which is a formal method to request FDA to issue a WR. FDA reviews the PPSR to determine whether the studies outlined in the WR could provide information valuable to promote the public health of pediatric patients. During this review, FDA considers a variety of factors, including the scientific support of the study, the design and scope of the study and whether additional pediatric diseases should be included for the product. (FDA 2023a, FDA2023b) If FDA finds the PPSR insufficient, they can request that the sponsor submit a revised PPSR, or if FDA agrees with the PPSR, they can issue a WR. FDA does not need a PPSR, however, to issue a WR. If the sponsor declines to perform research outlined in a WR, FDA can issue the WR to the National Institutes of Health (NIH). If NIH performs the study, the sponsor does not obtain any exclusivity, but information may be added to the drug's label if the sponsor agrees.

In 2023, FDA issued draft guidance clarifying that WRs should generally be reserved for pediatric studies that go beyond what sponsors are already required to conduct under PREA, reflecting the agency's effort to sharpen the distinction between the voluntary BPCA incentive and mandatory PREA obligations. (FDA, 2023a)

The voluntary nature of the BCPA program means that drug sponsors can choose whether to perform pediatric research and to some extent the timing of the research. The WR contains timing requirements by which the agreed-upon research must be completed but the WR process can start years after a drug is approved in adults. Table 5-1 lists cancer drugs that have received pediatric exclusivity between 2016-2015 as a result of BPCA. *Appendix* Table A-5 lists all new cancer drugs approved between 2016 and 2025 and whether a WR was issued for that drug. BPCA and other market incentives are discussed further in the chapter *Funding, Investment, and the Economics of Discovery*.

The "stick" portion of the carrot-and-stick approach comes from PREA. First passed into law in 2003, it created a framework that requires sponsors developing a drug for adult indications to also study the drug in children when the same condition exists in pediatric populations. PREA requires sponsors seeking approval for a new active ingredient, new indication, new dosage form, new dosing

FIGURE 5-2

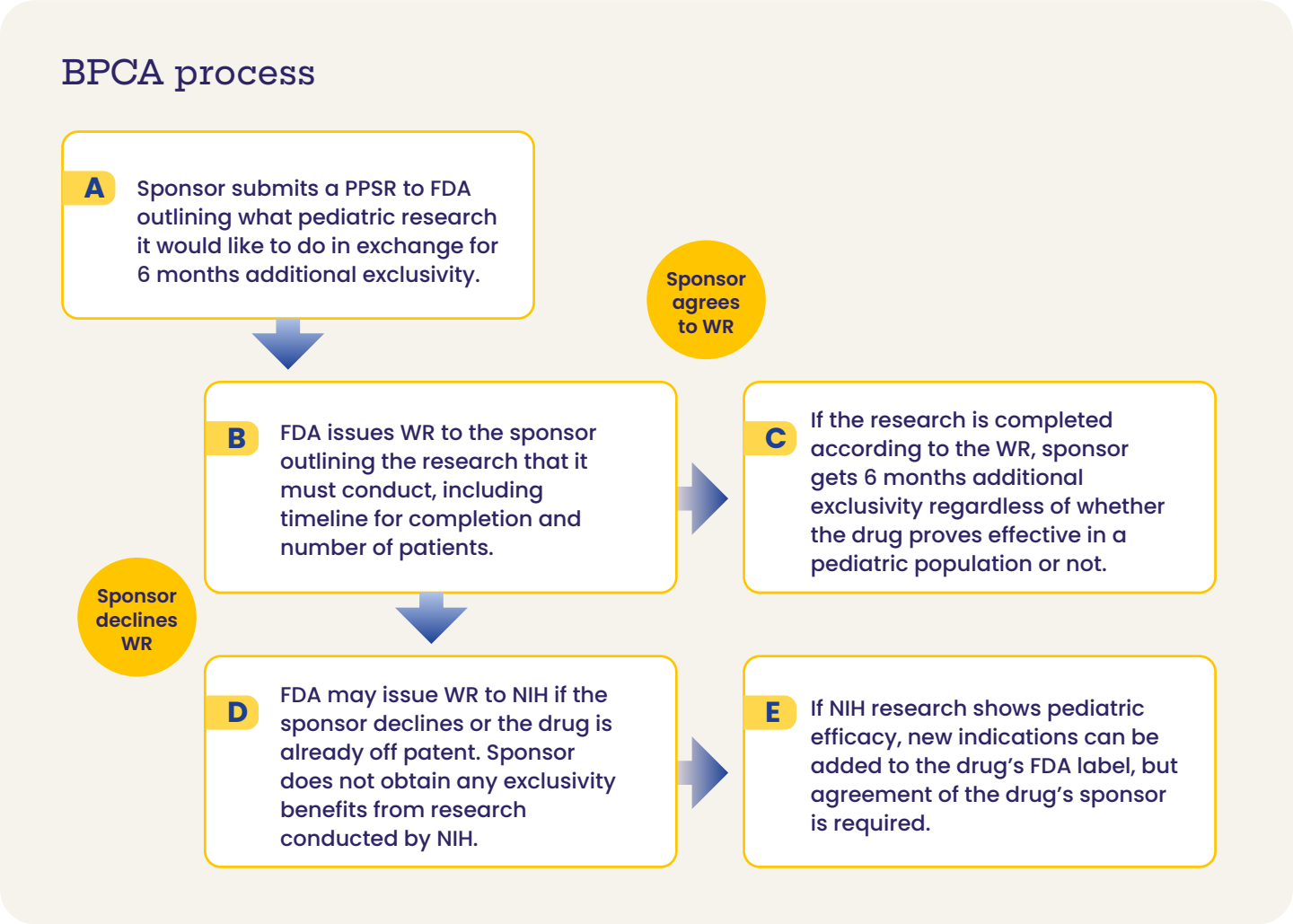


Figure 5-2: The BPCA process involves the sponsor, FDA, and potentially NIH and can be initiated by either the sponsor or FDA.

regimen, or new route of administration to conduct research in children (or have a plan to do so in place) before FDA will approve the drug for its adult indication. Like BPCA, PREA was originally a temporary program but has since become permanent. (FDA, 2026a)

Prior to 2020, there were important limitations to PREA that constrained its ability to spur pediatric oncology drug development. First, products to treat rare diseases were exempt from PREA requirements. Rare diseases are defined in U.S. law as those that are present in fewer than 200,000 people per year in the U.S. Because most cancers meet the definition of a rare disease many drugs developed for adult cancers were exempt from PREA requirements to conduct a pediatric assessment.

More common cancers— such as lung, breast, and prostate cancers—do not meet the U.S. definition of a rare disease, so drugs developed for those cancers were ineligible for orphan drug exemption from PREA research requirements. However, a second PREA limitation also prevented FDA from requiring pediatric assessments for these products: PREA only required pediatric studies in the same disease indication for which the drug was being developed in adults. FDA has maintained a list of adult indications that rarely or never occur in the pediatric population and historically drugs intended for these conditions received a pediatric study waiver, as pediatric studies for these indications would be impossible or highly impracticable. Between the orphan product exemption and the indication-based waivers of the pediatric study requirements, PREA had minimal impact on childhood cancer drug development.

TABLE 5–1

Oncology products with pediatric exclusivity, 2016-2025

Drug	Date of exclusivity determination	Condition(s) studied under the written request	WR resulted in a new pediatric indication	Currently approved pediatric indications
Cabazitaxel	5/18/17	Recurrent or refractory solid tumors, including high grade glioma or diffuse intrinsic pontine glioma	No	No
Tisagenlecleucel	6/12/17	Relapsed/refractory acute lymphoblastic leukemia	Yes	Yes
Ipilimumab	7/20/17	Unresectable or metastatic melanoma, solid tumors that are refractory to standard therapy	Yes	Yes
Nilotinib	3/20/18	Philadelphia chromosome positive (Ph+) hematologic malignancies	Yes	Yes
Trabectedin	6/12/18	Relapsed or refractory solid tumors	No	No
Dasatinib	9/27/18	Philadelphia chromosome positive (Ph+) leukemias, including acute lymphoblastic leukemia (ALL) & chronic myeloid leukemia (CML)	Yes	Yes
Sunitinib	2/7/19	Refractory solid & CNS tumors	No	No
Paclitaxel	11/8/19	Recurrent or refractory solid tumors, including neuroblastoma, rhabdomyosarcoma and Ewing sarcoma	No	No
Atezolizumab	9/22/20	Solid tumors with known or expected PD-L1 pathway involvement, including high-grade glioma, rhabdomyosarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, osteosarcoma, Ewing sarcoma, & Wilms tumor	No	Yes
Pomalidomide	10/16/20	Recurrent, progressive or refractory CNS or primary brain tumors, including high-grade glioma, medulloblastoma, ependymoma and diffuse intrinsic pontine glioma (DIPG)	No	No
Afatinib	3/8/22	Tumors with known ErbB deregulation	No	No
Cobimetinib	7/19/22	Relapsed or refractory pediatric solid tumors with known RAS/RAF/MEK/ERK pathway activation for whom standard therapy has proven to be ineffective or intolerable to standard therapy or for whom no curative standard-of-care treatment options exist	No	No
Ibrutinib	8/8/22	Chronic graft versus host disease (cGVHD) and non-Hodgkin lymphoma	Yes	Yes
Eribulin mesylate	8/9/22	Relapsed or refractory rhabdomyosarcoma, non-rhabdomyosarcoma, soft tissue sarcoma, and Ewing sarcoma	No	No
Brentuximab vedotin	11/18/22	Untreated and relapsed or refractory classical Hodgkin lymphoma (cHL) and systemic anaplastic large cell lymphoma (sALCL)	Yes	Yes
Ruxolitinib	12/1/22	Relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms (MPNs)	No	Yes
Nivolumab	2/2/23	Refractory or relapsed solid malignant tumors, Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, and melanoma	Yes	Yes
Dabrafenib	2/9/23	Relapsed or refractory solid tumors, including low- and high-grade gliomas, containing BRAF V600 activating mutations and in the treatment of adolescent patients with unresectable or metastatic melanoma containing BRAF V600 activating mutations	Yes	Yes
Trametinib	2/9/23	Advanced relapsed/refractory malignant solid tumors with activation of the RAS/RAF/MEK signaling pathway, including low- and high-grade gliomas, as well as adolescent patients with BRAF V600 mutant-positive malignant melanoma	Yes	Yes

TABLE 5–1, CONTINUED

Oncology products with pediatric exclusivity, 2016-2025

Drug	Date of exclusivity determination	Condition(s) studied under the written request	WR resulted in a new pediatric indication	Currently approved pediatric indications
Blinatumomab	6/13/23	Relapsed B-cell precursor acute lymphoblastic anemia (ALL)	No	Yes
Bosutinib	9/13/23	Chronic phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML), newly-diagnosed or resistant or intolerant to prior therapy	Yes	Yes
Lenvatinib mesylate	4/1/24	Ewing sarcoma (EWS)/peripheral primitive neuroectodermal tumor (pPNET), rhabdomyosarcoma (RMS), high-grade glioma (HGG), osteosarcoma, and other relapsed or refractory solid malignancies	No	No
Lutetium Lu 177 dotatate	4/18/24	Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	Yes	Yes
Axitinib	7/2/24	Recurrent or refractory solid tumors, including advanced translocation renal cell carcinoma	No	No
Ramucirumab	5/14/25	Relapsed or refractory solid tumors	No	No
Carfilzomib	5/19/25	Relapsed/refractory acute lymphoblastic leukemia (ALL)	No	No
Palbociclib	9/10/25	Recurrent/refractory pediatric solid tumors, including Ewing sarcoma (EWS)	No	No
Cemiplimab	10/24/25	Advanced solid tumors as well as pediatric patients with high grade central nervous system tumors, specifically high-grade gliomas and diffuse intrinsic pontine gliomas	No	No
Selpercatinib	12/4/25	RET-activated solid tumors	No	Yes

Source:https://www.fda.gov/drugs/development-resources/list-determinations-including-written-request

Table 5-1: Drugs receiving exclusivity as a result of a WR 2016-2025. Listed drugs may have received a WR prior to this period, but completion occurred during this time frame. Drugs receiving a WR during this time frame but not yet completing the required studies are not listed. Currently approved pediatric indications may not match the indications that were studied under the WR because they may have been approved prior to issuance of the WR or be unrelated to the WR studies.

In 2017, the Research to Accelerate Cures and Equity (RACE) for Children Act was passed as part of the broader FDA Reauthorization Act of 2017 (FDARA). (FDARA, 2017) It amended PREA to give FDA the authority to require sponsors of certain new molecularly targeted drugs to submit pediatric study reports with their original marketing application, unless the requirement is waived or deferred. The RACE Act provisions, which went into effect on August 18, 2020, apply to new oncology drugs directed at a molecular target determined to be substantially relevant to pediatric cancers, including drugs with an orphan designation. FDA publishes and periodically updates a list of targets considered substantially relevant to pediatric cancers (known as "The Relevant Molecular Target List") and a list of targets determined not to be substantially relevant to the growth or progression of pediatric cancers (known as "The Non-Relevant Molecular Target List"). (FDA, 2026c)

In practical terms, the RACE Act closes the rare-disease loophole specifically for oncology: it eliminates the automatic orphan-drug exemption for new molecularly targeted cancer therapies and gives FDA authority to require sponsors to conduct pediatric studies when a drug's molecular target is substantially relevant to the growth or progression of a pediatric cancer—even if the adult cancer for which the drug is being developed does not occur in children. (Chen, 2024; Research to Accelerate Cures and

Equity for Children Act, 2017) For example, a drug targeting a molecular pathway shared by an adult lung cancer and a pediatric brain tumor can now trigger a pediatric study requirement, something that was not possible under the original provisions of PREA. The rare-disease and indication-based exemptions described above therefore no longer apply in the same way to oncology drugs with a pediatric-relevant molecular target, even though they continue to apply, as before, to PREA generally for non-oncology indications.

Although experience with new provisions to PREA made via the RACE Act remains limited, the changes have fundamentally changed the landscape of pediatric oncology drug development. There is early evidence of favorable effects of RACE on sponsors' timely consideration and initiation of pediatric studies of targeted cancer drugs. Table 5-2 illustrates the impact of the RACE Act over the past five years by comparing the number of planned pediatric studies required under the RACE Act with what would have been required for these same products prior to RACE Act implementation. Of the 81 molecularly targeted products with agreed Initial Pediatric Study Plans (iPSPs) that included plans to conduct pediatric studies under the RACE Act, original applications for 30 (37%) of these products were subsequently approved by FDA during the reporting period and 51 (63%) remained under development at the end of this reporting period. As summarized in Table 5-2, of the 81 products, 65 (80%) would have qualified for a PREA exemption or waiver and only 16 (20%) could have been subject to the requirement to conduct a pediatric assessment under PREA prior to RACE Act implementation.

On February 3, 2026, the Mikaela Naylon Give Kids a Chance Act (GKAC Act) was signed into law, strengthening FDA's authority under PREA to require pediatric investigation of certain new molecularly targeted oncology drugs in combination with one or more other active ingredients, when warranted. (Consolidated Appropriations Act, 2026) This new authority is especially important because combining therapies is often key to achieving lasting cures for children with cancer. These changes to PREA will not come into effect until February 3, 2029, but are anticipated to help spur development of multi-drug approaches to pediatric cancer treatment.

The Creating Hope Act, enacted as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, established the Rare Pediatric Disease Priority Review Voucher (PRV) program to address a long-standing gap in drug development for pediatric patients

TABLE 5-2

Products with planned pediatric studies under the RACE Act versus pre-RACE Act (July 1, 2020, through June 30, 2025)

	Products with planned pediatric studies under RACE	Products with planned pediatric studies that would have been exempted or waived pre-RACE[a]	Products with planned pediatric studies that could have been required pre-RAC
TOTAL	**81**	**65[b]**	**16**

Table 5-2: Implementation of the RACE Act resulted in more required studies.
[a]Under the Pediatric Research Equity Act of 2003, which predates the RACE Act, requirements for pediatric studies do not apply to drugs for an indication for which orphan designation has been granted. See 21 U.S.C. § 355c(k)(1). These are commonly referred to as "orphan drugs." However, under the RACE Act, orphan drugs that are molecularly targeted cancer drugs are not exempt from pediatric study requirements. See 21 U.S.C. § 355c(k)(2).
[b]25 (31%) of the drugs that would have been exempted pre-RACE have orphan status, and 40 were for a condition that rarely or never occurs in the pediatric population, and for which a pediatric study would be impossible or highly impracticable.

suffering from serious and life- threatening rare diseases. (FDA Safety and Innovation Act, 2012)Unlike BPCA, the rare pediatric disease PRV program incentivizes development of new drugs specifically for rare pediatric diseases, rather than incentivizing pediatric studies of drugs already under development in adults. Further discussion of this Act can be found in the chapter *Funding, Investment, and the Economics of Discovery*.

International pediatric requirements

While the focus of this report is the U.S. drug development landscape, drug development occurs globally, and most children with cancer who could benefit from new therapies live outside of the U.S. (Sung, 2026) Childhood cancers are rare, and in the U.S. new diagnoses for any given cancer type range from only a few dozen cases per year for more rare cancer types to around 3000 cases per year for acute lymphoblastic leukemia (ALL), the most common childhood cancer. This rarity means that in order to collect enough data about a drug's safety and efficacy in a reasonable time frame, trials must often be conducted in multiple countries. This approach can be challenging, as countries can have differing regulations governing the participation of children in research, as well as differing requirements for drug approval.

International clinical trials intended to support U.S. drug approval may be conducted under FDA oversight as described above, but not all are. FDA will still accept data from clinical trials conducted outside of the U.S. that were not performed under FDA oversight, provided the trials conform to local laws and regulations and meet minimum ethical requirements regarding patient consent. (FDA, 2024)

While international trial data may be used for U.S. drug approval, and vice versa, the data format, review processes, and standards for submission and approval may differ from country to country. Even if a drug is already approved in another country, it must still undergo a full FDA application process, as the U.S. does not recognize reciprocal drug approvals with any other country. FDA coordinates closely with the European Medicines Agency (EMA), which is the decentralized drug review body for the 27 member states of the European Union (EU) plus Iceland, Liechtenstein, and Norway. (EMA, 2025)

FDA and EMA established a "Pediatric Cluster" in 2007, which consists of relevant staff from the FDA, EMA, and regulatory agencies from Canada (Health Canada), Japan (the Pharmaceuticals and Medical Devices Agency or PMDA), Australia (the Therapeutic Goods Administration or TGA), and Switzerland (Swissmedic). The Pediatric Cluster holds monthly conference calls to share information on pediatric clinical trials that the respective organizations are overseeing. Through this collaboration, the FDA and EMA have developed a tool known as the Common Commentary, with which the two groups share coordinated feedback to drug sponsors based on the cluster call discussions. (FDA, 2026b)

Much like the U.S. has PREA and BPCA, the EMA requires pediatric studies of drugs developed for adult indications and similarly awards extended market exclusivity as an incentive for conducting such research; however, the FDA and EMA programs differ in important ways. EMA's pediatric study requirements, referred to as Pediatric Investigation Plans (PIPs), are based on the adult indication for which a drug is being developed—similar to the U.S. PREA requirements prior to the molecular target-based provisions introduced under FDARA. PIPs must be submitted following completion of phase 1 trials in adults; this is considerably earlier than the corresponding FDA requirement for submission of iPSPs within 60 days after the completion of phase 2 trials. (Rho, 2025)

On December 11, 2025, the European Parliament and the Council of the European Union (EU) reached political agreement on the reform of the EU's pharmaceutical legislation. (EMA, 2026; EU, 2023) The final text of the new pharmaceutical legislation was published in 2026, with full implementation anticipated by 2028. Among its provisions, the new policy would require PIPs based upon the medicinal product's mechanism of action, rather than the adult indication under study, analogous to the U.S. PREA requirements based upon molecular target for oncology products. The policy also enables a more flexible, iterative approach to PIP development as adult development of a product proceeds.

References

Anderson BD, Adamson PC, Weiner SL, et al. (2004). Tissue collection for correlative studies in childhood cancer clinical trials: ethical considerations and special imperatives. J Clin Oncol. 22(23):4846-50. doi: 10.1200/JCO.2004.02.138. Erratum in: J Clin Oncol. 2005, 23(1):248. PMID: 15570088.

Best Pharmaceuticals for Children Act (2002). Pub. L. No. 107-109, 115 Stat. 1408. www.congress.gov/bill/107th-congress/senate-bill/1789.

Chen, E. Y., and Marcus, L. (2024). The RACE Act and pediatric trials of adult cancer drugs. Pediatrics, 154(4), Article e2024066920.

Code of Federal Regulations (2026). 21 CFR 201.56. https://www.ecfr.gov/current/title-21/part-201/section-201.56.

Consolidated Appropriations Act (2026). H.R. 7148, 119th Cong. https://www.congress.gov/bill/119th-congress/house-bill/7148.

European Medicines Agency (2025). Paediatric investigation plans. www.ema.europa.eu/en/human-regulatory-overview/research-development/paediatric-medicines-research-development/paediatric-investigation-plans.

European Medicines Agency (2026). Reform of the EU pharmaceutical legislation: Background. www.ema.europa.eu/en/about-us/what-we-do/reform-eu-pharmaceutical-legislation#background-81158.

European Union (2023). EUR-Lex. eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0193.

Food and Drug Administration (2006). Using a Centralized IRB Review Process in Multicenter Clinical Trials. www.fda.gov/regulatory-information/search-fda-guidance-documents/using-centralized-irb-review-process-multicenter-clinical-trials.

Food and Drug Administration (2015). FDA Policy for the Protection of Human Subjects. www.fda.gov/science-research/clinical-trials-and-human-subject-protection/fda-policy-protection-human-subjects.

Food and Drug Administration (2018a). Sulfanilamide Disaster. www.fda.gov/about-fda/histories-product-regulation/sulfanilamide-disaster.

Food and Drug Administration (2018b). Fact Sheet: Pediatric provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA). www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-pediatric-provisions-food-and-drug-administration-safety-and-innovation-act-fdasia.

Food and Drug Administration (2019). Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice. www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good.

Food and Drug Administration (2022). Ethical Considerations for Clinical Investigations of Medical Products Involving Children. www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children.

Food and Drug Administration (2023a). Pediatric drug development: Regulatory considerations—Complying with the Pediatric Research Equity Act and qualifying for pediatric exclusivity under the Best Pharmaceuticals for Children Act. www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-drug-development-regulatory-considerations-complying-pediatric-research-equity-act-and.

Food and Drug Administration (2023b) Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations. www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-drug-development-under-pediatric-research-equity-act-and-best-pharmaceuticals-children-act.

Food and Drug Administration (2024). Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-generating-clinical-evidence-oncology-multiregional-clinical-development-programs.

Food and Drug Administration (2026a). Pediatric Research Equity Act | PREA. www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea.

Food and Drug Administration (2026b). International Collaboration / Pediatric Cluster. www.fda.gov/science-research/pediatrics/international-collaboration-pediatric-cluster.

Food and Drug Administration (2026c). Pediatric Oncology: The Relevant Molecular Target List and The Non-Relevant Molecular Target Leading to Waiver List. www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology.

Food and Drug Administration Reauthorization Act (2017). Pub. L. No. 115-52, 131 Stat. 1005. https://www.congress.gov/bill/115th-congress/house-bill/2430.

Food and Drug Administration Safety and Innovation Act (2012). Pub. L. No. 112-144, 126 Stat. 993. www.congress.gov/bill/112th-congress/senate-bill/3187.

Pediatric Research Equity Act (2003). Pub. L. No. 108-155, 117 Stat. 1936. www.congress.gov/bill/108th-congress/senate-bill/650.

Research to Accelerate Cures and Equity for Children Act (2017). H.R. 1231, 115th Cong. www.congress.gov/bill/115th-congress/house-bill/1231.

Rho (2025). Successful Pediatric Investigation Plan (PIP) Application in the European Union – Part 1: Understanding the regulatory requirements. www.rhoworld.com/successful-pediatric-investigation-plan-pip-application-in-the-european-union-part-1-understanding-the-regulatory-requirements/.

Sung H, Filho AM, Laversanne M, et al. (2026). Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. CA Cancer J Clin. 76(4):e70090. doi: 10.3322/caac.70090. PMID: 42417444; PMCID: PMC13343830.

Ellie

On November 1, 2022, at age three, Ellie was diagnosed with Stage IV high-risk neuroblastoma. A tumor on her adrenal gland had already widely metastasized through her body. Her oncologist told us the goal was a cure, and we received a treatment plan that we were told needed to start immediately. The plan included chemotherapy, surgery, two stem cell transplants, and immunotherapy.

Ellie had a severe reaction to the first stem cell transplant, including septic shock. That meant four days in the PICU and additional surgeries for a bowel obstruction. It was too dangerous to attempt the second stem cell transplant, even though skipping it meant a reduced chance of survival. Nonetheless, after fifteen months of treatment, there was no evidence of disease. Because of chemo-induced hearing loss, Ellie now wears hearing aids in both ears.

Throughout her treatment, there were discussions about an experimental drug in clinical trials that Ellie would likely be eligible for once her original treatment plan ended. The drug, difluoromethylornithine (DFMO), was designed to help prevent relapse, specifically in high-risk neuroblastoma patients. Her oncologist told us it was our decision whether to enroll her in the trial. Participation would mean additional follow-up visits, additional bloodwork and medication, and potential side effects for two years.

We knew we would do whatever we could to help keep the cancer from coming back, so we decided we would do the trial. One month before Ellie was declared free of disease and would have been eligible to start the trial, DFMO received FDA approval. With the drug approved, she no longer needed the trial at all. Her oncologist could simply prescribe it, at an appropriate dose.

For two years, Ellie took four pills a day of DFMO, finishing her treatment in January 2026. She had minimal side effects, so the biggest challenge most days was just getting the pills down. As of August 2026, Ellie is still cancer-free.

Trials for pediatric cancer changed our lives and potentially saved our daughter's life. Ellie was able to access DFMO because of the many children before her who participated in clinical trials, because of the researchers and doctors who worked and continue to work to find cures and better treatments for childhood cancer, and because of the organizations and people who help fund that research. Access to trials gives people hope. It gave us hope throughout Ellie's treatment that work was being done, and that she might have access to something new.

— shared by Ellie's family

CHAPTER 6

Data, Data Sharing, and Artificial Intelligence

Summary

For pediatric cancer, data about every child's cancer, treatment, and outcomes matter. Because these diseases are rare, biologically diverse, and distinct from adult cancers, no single institution can generate enough information to answer many of the field's most important questions alone. Continued progress depends on responsibly connecting clinical records, molecular and genomic data, imaging, pathology reports, treatment exposures, outcomes, and long-term survivorship information across institutions and populations. The pediatric cancer community has long recognized the importance of collecting, standardizing, storing, and sharing data broadly, but isolated efforts and a lack of interconnectedness have been barriers to fully realizing the potential of collecting and analyzing data at scale. More recently, national collaborative efforts and new tools are helping build the infrastructure needed to turn scattered observations into a trustworthy learning ecosystem. New ways to mine data and link multiple datasets that were never designed with research in mind will allow new questions to be asked and answered. Within this learning ecosystem, artificial intelligence (AI) may help identify patterns, improve diagnosis, support clinical trial matching, reduce the burden of manual data review, and generate new research hypotheses. Realizing the potential of an interconnected system depends on data that are high quality, representative, interoperable, secure, and governed with transparency and trust. The goal is to ensure that each child's experience contributes to knowledge that can improve care not only for the child with cancer now but for the next child diagnosed.

Introduction

Pediatric cancer is a collection of many different diseases, including leukemias, brain tumors, sarcomas, embryonal tumors, and other rare cancers that occur only in a small number of children and adolescents each year. Even within these categories, cancers are further divided into molecular subtypes defined by differences in genetics, epigenetics, and the biology that drives tumor growth. Two children may appear to have the same diagnosis but have cancers that behave differently and require different approaches to treatment. This diversity creates a fundamental challenge for research: there are often too few patients within any individual pediatric cancer subtype to generate reliable answers through traditional approaches alone. A clinical trial or research study that is straightforward to conduct for a common adult cancer may take years or may not be feasible at all for a childhood cancer. The solution is not simply to study harder at individual institutions; it is to learn together by combining experiences and data across institutions, including hospitals, research centers, cancer centers, and children's hospitals, as well as across populations.

For pediatric cancer, sharing data is therefore not just an efficiency strategy. It is often the only way to assemble cohorts large enough to distinguish meaningful biological signals from random variation. By connecting patients with similar molecular features, treatment histories, and outcomes across institutions, researchers can uncover patterns that would remain invisible within smaller datasets. Pediatric oncology has long leveraged the power of collaboration. The remarkable improvement in childhood cancer survival over the past several decades is the result of both privately and federally funded cooperative research networks that bring together clinicians, scientists, patients, and families.

The future of pediatric cancer research will depend on the ability to transform individual experiences into collective knowledge. Every child's story, every diagnosis, every treatment, every response, and every outcome matters and has the potential to inform the next discovery.

Sharing data in a learning ecosystem

Creating a national pediatric cancer data ecosystem requires more than collecting large amounts of information. Data are valuable only when researchers can understand and use them responsibly. For data to generate knowledge, researchers must be able to find the right information, understand what each data element represents, evaluate how it was collected, connect records accurately across different sources, and access it under appropriate ethical and privacy protections. A dataset that exists but cannot be discovered, interpreted, linked, or responsibly analyzed is of limited scientific value.

A useful framework for thinking about this challenge is captured within the Findable, Accessible, Interoperable, and Reusable (FAIR) data principles. (Wilkinson, 2016) Importantly, "accessible" does not mean unrestricted public release of sensitive health information, especially when the data involve children. Rather, it means that appropriate researchers can access and use data through secure systems, transparent governance, and protections that preserve participant trust.

Interoperability is another essential concept. In simple terms, interoperability is the ability of different systems to communicate with one another. Today, hospitals and research programs often collect information in different formats and use different definitions for similar concepts. Common standards provide the shared "grammar" and "plumbing" that allow these systems to exchange information without requiring researchers to manually translate every data field.

Building this infrastructure is a scientific and policy challenge as much as a technical one. The goal is not merely to create larger databases. The goal is to create a trustworthy learning ecosystem where information from every child can contribute to discoveries that improve diagnosis, treatment, and survivorship.

Understanding pediatric cancer requires multimodal and longitudinal data

The complexity of pediatric cancer is reflected in the data required to understand it. Modern pediatric oncology does not rely on a single source of information. Instead, researchers and clinicians increasingly integrate multimodal data, which is information gathered from many different sources that together provide a more complete picture of a child's disease. This data may include clinical observations, laboratory results, genomic sequencing, radiology images, digital pathology slides, treatment exposures, patient-reported outcomes, and information about social and environmental factors that influence health. Each source provides a different perspective and informs the whole. A tumor's DNA may reveal a possible treatment target. An imaging study may show how a tumor changes over time. A patient's reported symptoms may reveal the impact of treatment on daily life. Together, these sources create a richer understanding than any single data type can provide.

Time is equally important. Pediatric cancer is not a single event, but rather it is a journey that unfolds across years and often decades. A meaningful pediatric cancer dataset should be longitudinal, connecting diagnosis, treatment, response, relapse, treatment-related toxicities, quality of life, and long-term survivorship. A one-time snapshot taken at diagnosis cannot answer critical questions about whether a treatment that improves survival also affects a child's ability to grow, learn, work, and live a healthy adult life.

This longitudinal perspective is especially important in pediatric oncology because children are still developing. Late effects from treatments that save a child's or teen's life may also impact growth, fertility, organ function, cognitive development, and future health. The NCI works to address longitudinal challenges through the Childhood Cancer Survivor Study (CCSS). (NCI, 2026a) CCSS is one of NCI's most successful and influential long-term research investments. Established in 1994 and continuously supported by NCI, CCSS is a unique multi-institutional resource of more than 25,000 childhood cancer survivors diagnosed between 1970 and 1999. It represents the world's largest and longest-followed cohort of childhood cancer survivors, with unparalleled longitudinal clinical, treatment, genomic, psychosocial, neurocognitive, and patient-reported outcome data. No comparable resources exist worldwide. Data from CCSS are available to researchers investigating cancer survivorship.

Importantly, the relationship between clinical care and research is not one-directional. Routine care generates observations: how children respond to treatments, which side effects occur, and what outcomes families experience. Research transforms these observations into evidence. That evidence should then return to clinical practice through improved guidelines, therapies, and care strategies. A learning health system depends on this continuous cycle.

A history of collective data and learning

The current focus on AI and large-scale data sharing can sometimes give the impression that data-driven medicine is a new development. In pediatric oncology, however, the opposite is true. The field has always advanced through collective learning. The tools have evolved from shared treatment protocols to national registries, to genomic and longitudinal datasets, but the underlying principle has remained the same: no single institution can learn enough alone. The work of the Children's Oncology Group (COG) has demonstrated the power of sharing clinical experience, data, and outcomes across institutions (see Box below). (COG, n.d.)

THE FIRST NATIONAL LEARNING NETWORK

Modern pediatric oncology was built on collaboration. Beginning in the 1950s, NCI-supported cooperative cancer research networks brought together institutions to study diseases that were too uncommon for individual centers to address independently. COG, which was formed in 2000 through the merger of four pediatric research organizations and is a member of NCI's National Clinical Trial Network, represents the evolution of this model into the largest pediatric cancer research network in North America (see Figure 4-2). (COG, n.d.) Today, COG connects more than 220 institutions and thousands of researchers, clinicians, and scientists. More than 80% of children and adolescents with cancer in the United States receive care at a COG member institution. Importantly, receiving care at a COG institution is not the same as enrolling in a clinical trial; rather, COG's strength comes from creating a shared infrastructure that combines clinical expertise, standardized approaches, research protocols, and outcomes data to provide the best possible care for children and adolescents with cancer. The remarkable improvement in outcomes for childhood acute lymphoblastic leukemia (ALL) demonstrates the power of cumulative learning. (Malczewska, 2022) Survival improvements did not result from a single breakthrough, but from decades of coordinated studies that progressively refined combination chemotherapy, risk classification, central nervous system treatment, supportive care, and strategies to reduce long-term toxicity. Each generation of patients contributed knowledge that improved care for the next generation. The lesson is fundamental: shared protocols that build upon the findings of previous studies, common definitions, statistical expertise, biospecimen resources, and sustained public and private investment are critical to making advances and improvements.

Population registries: Understanding cancer beyond the trial

Clinical trials answer important questions: Does a treatment work? For whom? Under what conditions? But trials alone cannot answer every question about cancer in society. To understand who develops cancer, how outcomes vary across populations, whether all groups have equal access to care, and where gaps remain, researchers need data representative of the broader population rather than just those taking part in research studies. The NCI Surveillance, Epidemiology, and End Results (SEER) Program, established in 1973, created one of the nation's most important resources for understanding cancer incidence, survival, and disparities over time. (NCI, 2026b) The SEER program provides grants to state or regional cancer registries throughout the U.S. to collect and centrally share standardized data on every patient diagnosed with cancer within specific geographic areas (often states). Building on this foundation, the National Childhood Cancer Registry (NCCR; see more below) brings together population-based data on children, adolescents, and young adults with cancer to support a more comprehensive understanding of incidence, outcomes, and survivorship. (NCI, 2020) Registries and clinical trials serve complementary purposes: trials provide rigorous evidence about specific interventions, while population datasets reveal how cancer affects communities in the real world.

The genomic era: More data, new opportunities, new challenges

The genomic revolution transformed pediatric cancer research by adding new layers of biological information. Launched in 2006, the NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program applied comprehensive molecular characterization to difficult-to-treat childhood cancers and made these data available to the research community, demonstrating the power of connecting tumor biology with clinical outcomes. (NCI, 2022) NCI's Childhood Cancer Data Initiative (CCDI) was launched in 2019 to collect, generate, and analyze comprehensive pediatric cancer data, including pooling de-identified patient data from hospitals and treatment centers nationwide. The CCDI's Molecular Characterization Initiative (MCI) provides eligible children and young adults treated at COG-affiliated hospitals with no-cost, state-of-the-art tumor characterization at diagnosis, returning clinically relevant results to participants and their clinicians while making de-identified data available for future research. (Flores-Toro, 2026; NCI, 2026c) By integrating molecular and clinical information across these efforts, researchers have identified new disease subtypes and potential therapeutic targets and gained insights into how pediatric cancers differ from adult cancers.

However, the genomic era also introduced a new challenge. As the scale of data became larger, the complexity of interpreting and managing data grew exponentially. Modern pediatric oncology now requires infrastructure capable of storing, harmonizing, securing, and responsibly sharing diverse information and long-term outcomes. The challenge shifted from simply collecting data to building systems that turn data into knowledge.

Making data sharing a national priority

The movement toward national pediatric cancer data infrastructure was accelerated by patients, families, and advocates who recognized that every child's experience could contribute to future discoveries. The Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act, signed into law in 2018 and later reauthorized, strengthened federal efforts in pediatric cancer surveillance, biospecimen collection, survivorship research, and data infrastructure. (Childhood Cancer STAR Act, 2018) The Gabriella Miller Kids First Pediatric Research Program, established in 2014 through the passage of the Gabriella Miller Kids First Research Act, expanded efforts to generate and share genomic and clinical data from children with cancer and structural birth defects, creating a collaborative data resource for pediatric research. (NIH, 2026)

Creating a national infrastructure

These efforts highlighted a persistent barrier: valuable information remained scattered across different institutions, systems, and databases. A substantial portion of clinically relevant data resides within individual healthcare systems and may not be readily accessible for research by the broader community. Clinical information is therefore often assembled retrospectively, creating

challenges related to data completeness, consistency, and quality assessment. Hence, the challenge is not only generating data; it is creating the infrastructure to transform existing and future data into knowledge.

One of the goals of CCDI, which has brought together researchers, clinicians, government leaders, industry partners, and advocacy organizations, has been to define the data needs, infrastructure requirements, and policy priorities needed for the next era of pediatric cancer research. (Jagu, 2025a; NCI, 2025) CCDI was conceived as a federal investment of $50 million per year for 10 years, organized around three foundational goals: gathering data from every child, adolescent, and young adult diagnosed with childhood cancer; developing a national strategy for clinical and molecular characterization; and creating platforms and tools that connect data generated through care and research (Figure 6-1). (NCI, 2025)

FIGURE 6-1

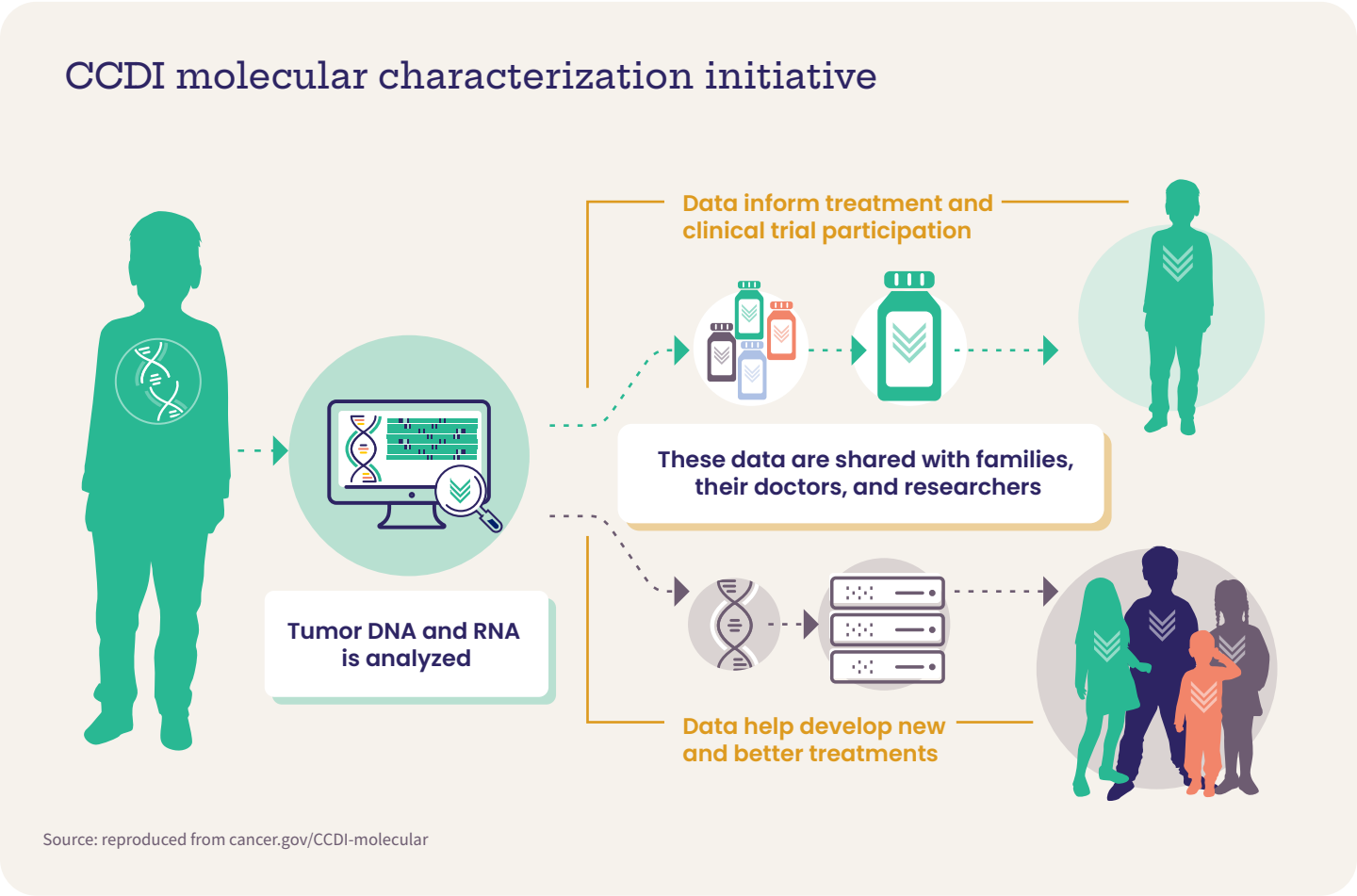
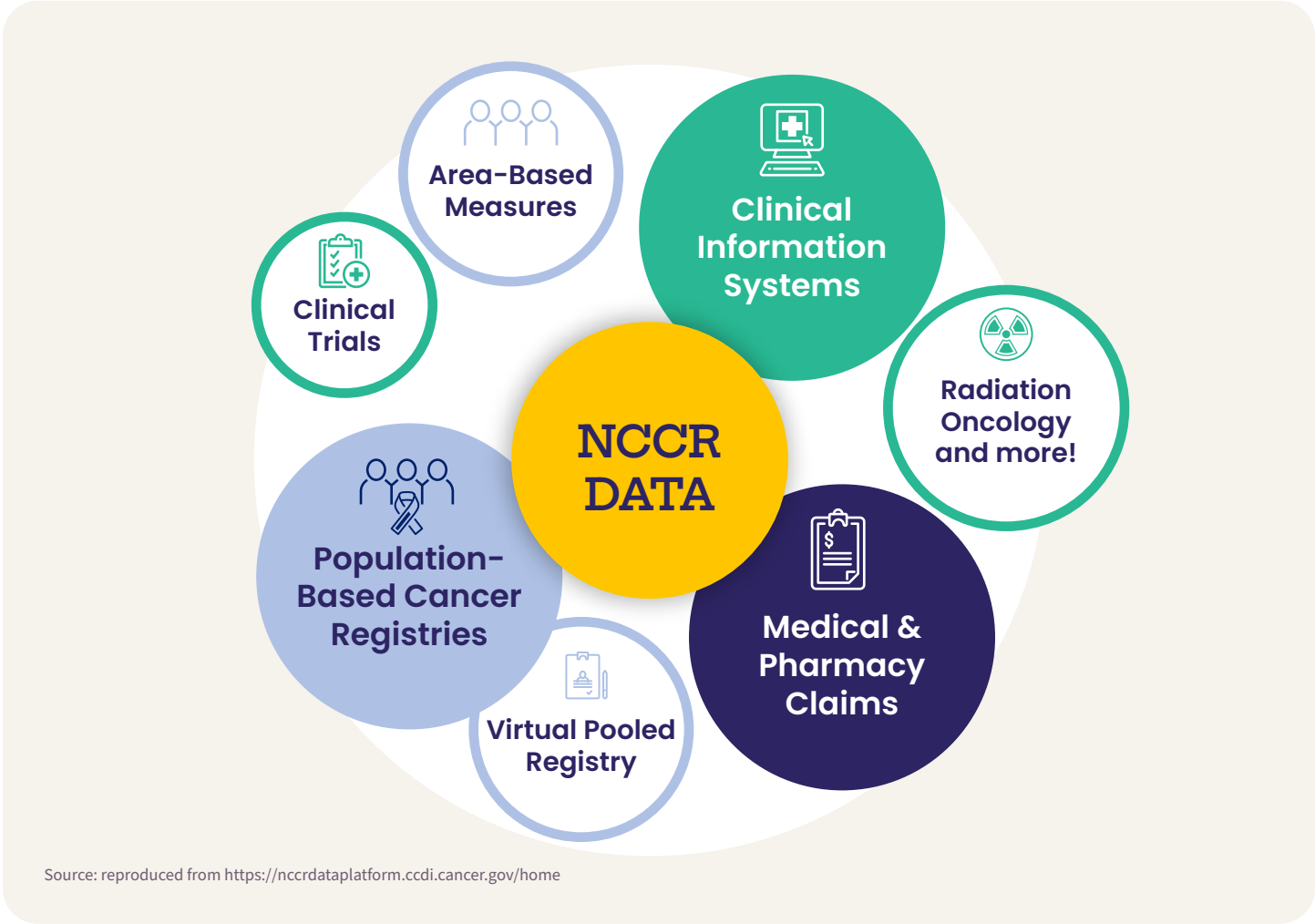


Figure 6-1: The CCDI molecular characterization initiative provides tumor testing that can both inform clinical care as well as drive research into new treatments.

Central to this vision is the CCDI Data Ecosystem, which provides infrastructure to make pediatric cancer data and resources more accessible and usable for research. (Flores-Toro, 2023; Jagu, 2024) The Data Ecosystem's interconnected resources support a variety of research functions (Figure 6-2). For example, the CCDI Hub provides an entry point for discovering studies, data, tools, and other resources available across the ecosystem. (Jagu, 2025b) The Childhood Cancer Clinical Data Commons (C3DC) and the NCCR support discovery across databases, while the CCDI cBioPortal enables data visualization. The CCDI Participant Index maps and cross-references research identifiers representing the same de-identified participant across studies, facilitating integrated analysis. (Jagu, 2026) CCDI continues to expand these capabilities through strategic collaborations across the federal research enterprise.

The power of CCDI tools depends on the ability to access shared data. To facilitate that sharing, CCDI collaborates with the Advanced Research Projects Agency for Health (ARPA-H) Pediatric Care eXpansion (PCX) program. ARPA-H's $50 million PCX effort, a national pediatric data and knowledge network, is being developed to connect more than 200 pediatric hospitals and care centers, beginning with pediatric brain cancer. (ARPA-H, 2026) It addresses challenges in accessing and using clinical data for research by enabling secure, interoperable exchange of clinical and research data across pediatric healthcare institutions, including longitudinal information from electronic health records (EHRs). (ARPA-H, 2026) The PCX program builds on ARPA-H's Biomedical Data Fabric Toolbox, which demonstrated interoperable exchange across two pediatric institutions, including harmonization and mapping of more than 90% of unstructured clinical, electronic

FIGURE 6-2



Source: reproduced from https://nccrdataplatform.ccdi.cancer.gov/home

Figure 6-2: The NCCR data platform enables automated deidentified linkages of individuals across multiple datasets, easing efforts to conduct research.

health records, and genetic data. PCX is intended to extend these capabilities across a much larger and more diverse network, including community and rural settings, while enabling secure data exchange and AI-ready analysis. Together, efforts such as CCDI and PCX illustrate how national research infrastructure and care-delivery infrastructure can become mutually reinforcing components of a learning pediatric cancer ecosystem.

Artificial intelligence (AI) brings new opportunities

This national data ecosystem creates an unprecedented opportunity for large-scale analysis that is not possible with data from single institutions alone. Advanced tools, such as AI, can be leveraged by researchers and clinicians to analyze complex combinations of information such as genomic profiles, pathology images, medical records, and treatment outcomes to identify patterns that may not be apparent through traditional approaches. However, analytical tools are only as powerful as the data on which they are built. In pediatric oncology, where patient populations are small and diverse, trustworthy data are essential. Incomplete or biased datasets risk creating tools that work well for some children but not for others. Building effective discovery workflows requires more than advanced algorithms; it requires investments in data quality, interoperability, privacy, security, and equitable participation. Issues and challenges related to transparency and consent are especially relevant in the pediatric cancer setting and come into sharper focus when AI tools are incorporated into care.

AI has generated tremendous excitement because it can analyze complex datasets at a scale and speed beyond human capacity. When properly developed and validated, AI has the potential to improve diagnostic accuracy, accelerate discovery, support clinical trials, reduce burdens on families, and identify new approaches for treating rare cancers. However, AI does not eliminate the fundamental challenges created by rare diseases. AI cannot transform a small, incomplete, or biased dataset into a representative one. Instead, AI systems depend on the quality of the information they are given. Reliable performance requires sufficient numbers of patients, accurate clinical annotation, consistent data collection, and validation in independent populations.

The role of AI therefore is not to replace the need for better data; it is to ensure that data is well sourced, appropriately curated, harmonized across uses and platforms, and accessible. When built on trustworthy datasets, AI can integrate many types of information, identify subtle patterns, generate new hypotheses, and support researchers and clinicians in making more informed decisions. But the foundation must come first: high-quality, representative, and responsibly shared data.

AI: What becomes possible?

AI is best understood here not as a single technology or an automated substitute for clinicians, but as an umbrella term for computer methods that recognize patterns, make predictions, generate or organize information, and automate components of complex tasks. In pediatric cancer research, these abilities are critical for evaluating large quantities of sometimes poorly structured data that reside in different locations. When clinical records, genomic information, treatment histories, outcomes, radiology, pathology, and other data can be linked using consistent standards, advanced computational methods may help researchers identify disease subgroups, candidate biomarkers, therapeutic targets, and patterns that would be difficult to detect in any one dataset alone.

Many of these tasks have traditionally been carried out by humans or less sophisticated tools, but the time involved, such as in manual data abstraction, often make some extraction and analysis efforts unfeasible. Less sophisticated technology requires very well-structured data, which can take large amounts of time and human effort to assemble. With the development of AI, not only is the speed of these activities greatly increased, but the minimum level of data structure and consolidation needed is also reduced. AI tools open the door to enhanced data generation (e.g. reading radiology images), data abstraction (e.g. finding unstructured data and structuring it), and data analysis (e.g. trial matching or causal connections between variables).

AI-ready infrastructure will also improve how information moves across the healthcare system. For families navigating complex pediatric cancer care, fragmented data systems can make parents and caregivers responsible for transporting records between institutions and

reconstructing a child's history for different specialists. Efforts such as PCX seek to shift that burden from families to the infrastructure itself, so that relevant clinical, imaging, pathology, laboratory, and genomic information can securely follow the child across participating care settings. Better-connected information can therefore improve patient experiences directly while also creating the longitudinal, computable data foundation needed for AI-assisted diagnosis, research, trial matching, and decision support.

The promise of AI is already becoming evident across pediatric cancer research and care. Because AI tools are able to overcome the current lack of standardization and integration of data, these applications are being explored to modernize clinical trials by streamlining protocol development, automating eligibility screening, supporting data abstraction, and identifying potential participants more effectively and efficiently. Researchers are also investigating AI-assisted external control cohorts that may complement traditional trial designs in selected settings where prospective enrollment is particularly challenging. Within healthcare systems, natural language processing and large language models are being evaluated to extract structured information from electronic health records, reducing the burden of manual chart abstraction while making longitudinal clinical data more accessible for research. AI is also advancing precision diagnostics. For example, machine learning methods that analyze DNA methylation profiles have transformed the classification of pediatric brain tumors, improving diagnostic accuracy and enabling more precise disease classification. Looking ahead, emerging approaches such as digital twins may integrate multimodal, longitudinal data to create computational models that simulate disease progression and treatment response, providing new opportunities to study therapies and personalize care.

In clinical care and trials, AI is often used as a decision support tool where it provides an initial analysis and supporting documentation to a human who ultimately engages in tumor classification, image segmentation, molecular interpretation, clinical trial matching, or the prioritization of unusually difficult cases. AI-based decision support tools must always be interpreted by qualified clinicians and validated in the pediatric population and care setting in which they will be used. Trial matching offers a practical example: Eligibility criteria can be lengthy, dispersed across protocol documents, and difficult to compare manually with information contained in a patient's record. Natural-language-processing systems can organize those criteria and flag potentially relevant studies. Similar methods might help predict toxicities, identify children who require closer monitoring, or connect survivors with risk-based follow-up. These applications require longitudinal data extending beyond initial diagnosis and treatment, as well as evidence that acting on the prediction improves care. A model that accurately identifies high-risk patients has limited clinical value if the health system cannot provide the recommended monitoring or if the intervention triggered by the model does not improve patient outcomes.

The growing capabilities of AI also underscore the importance of responsible implementation. Models trained on incomplete, biased, or poorly annotated data may produce inaccurate or inequitable results, particularly for rare pediatric cancer subtypes or historically underrepresented populations. Predictions that cannot be explained, reproduced, or linked to meaningful clinical action have limited value and may increase, rather than reduce, the burden on clinicians and families. The future of AI in pediatric oncology therefore depends not only on advances in algorithms, but also on trusted data ecosystems, rigorous validation, transparent governance, and sustained human oversight. With those foundations in place, AI has the potential to accelerate discovery, improve diagnostic accuracy and speed, modernize clinical research, and ultimately contribute to better outcomes for children and adolescents with cancer.

Federal policy has consistently signaled interest in advancing cancer research, including strategies raising the visibility of pediatric cancer data and AI on the national agenda. This support is important but does not by itself guarantee durable funding or implementation. Those outcomes still depend on congressional appropriations, transparent agency plans, meaningful participation by patients and families, independent evaluation, and continuity across administrations. The distinction is especially important in discussing the federal budget.

Ultimately, the promise of AI in pediatric cancer is that it will enable the generation of new insights from a broader array of data more quickly than human effort and traditional tools alone. It holds the promise of democratizing access to the latest research findings, ensuring that a patient seen in a remote rural setting has just as much opportunity to benefit from accumulated scientific knowledge as a patient seen in the largest academic medical center. An integrated data system that incorporates AI tools may help providers make better-informed decisions: recognizing a rare diagnosis, finding an appropriate trial, identifying a toxicity earlier, designing a more feasible study, or ensuring that a survivor receives the follow-up their treatment history warrants.

References

Advanced Research Projects Agency for Health (2026). Pediatric Care eXpansion (PCX): It takes a community to save a child. arpa-h.gov/news-and-events/pediatric-care-expansion-pcx-it-takes-community-save-child.

Childhood Cancer STAR Act (2018). S.292 - 115th Congress (2017-2018): Childhood Cancer STAR Act. www.congress.gov/bill/115th-congress/senate-bill/292.

Children's Oncology Group (n.d.) childrensoncologygroup.org.

Flores-Toro JA, Jagu S, Armstrong GT, et al. (2023). The Childhood Cancer Data Initiative: Using the Power of Data to Learn From and Improve Outcomes for Every Child and Young Adult With Pediatric Cancer. J Clin Oncol. 41(24):4045-4053. doi: 10.1200/JCO.22.02208. Epub 2023 Jun 2. PMID: 37267580; PMCID: PMC10461939.

Flores-Toro J, Jagu S, Smith M, et al. (2026). Childhood cancer data initiative: expanded access to tumor molecular profiling for children, adolescents, and young adults. J Natl Cancer Inst. 118(2):199-204. doi: 10.1093/jnci/djaf214. PMID: 40794906; PMCID: PMC12360469.

Jagu S, Mardis ER, Wedekind MF, et al. (2024). Childhood cancer data initiative: Status report. Pediatr Blood Cancer. 71(2):e30745. doi: 10.1002/pbc.30745. Epub 2023 Oct 27. PMID: 37889049.

Jagu S, Smith MA, Seibel NL, et al. (2025a). The impact of focused federal initiatives on pediatric cancer research. Cancer. 2025 Nov 15;131(22):e70172. doi: 10.1002/cncr.70172. PMID: 41237091; PMCID: PMC12617966.

Jagu S, Guidry Auvil JM, Reaman G. (2025b). The childhood cancer data initiative: enabling data sharing to drive research advances and transform pediatric cancer diagnosis and treatment. Curr Opin Pediatr. 37(1):42-47. doi: 10.1097/MOP.0000000000001422. Epub 2024 Nov 27. PMID: 39699099; PMCID: PMC11658014.

Jagu S, Guidry Auvil JM, Cunningham M, et al. (2025b). Building Pediatric Cancer Cohorts and Accessing Data Using Childhood Cancer Data Initiative Tools. JCO Clin Cancer Inform. 9:e2500217. doi: 10.1200/CCI-25-00217. Epub 2025 Dec 10. PMID: 41370779; PMCID: PMC12724070.

Jagu S, Guidry Auvil JM, Cunningham MD, et al. (2026). Childhood Cancer Data Initiative Participant Index: Mapping Pediatric Cancer Data to Facilitate Cross-Study Integrated Analysis. JCO Clin Cancer Inform. 10(2):e2500387. doi: 10.1200/CCI-25-00387. Epub 2026 Apr 8. PMID: 41950437; PMCID: PMC13068442.

Malczewska M, Kośmider K, Bednarz K, et al. (2022). Recent Advances in Treatment Options for Childhood Acute Lymphoblastic Leukemia. Cancers (Basel) 14(8):2021. doi: 10.3390/cancers14082021. PMID: 35454927; PMCID: PMC9032060.

National Cancer Institute (2020). National Childhood Cancer Registry. cancercontrol.cancer.gov/research-emphasis/supplement/childhood-cancer-registry.

National Cancer Institute (2022). Origins and Outcomes of the TARGET Childhood Cancer Program. www.cancer.gov/ccg/research/genome-sequencing/target/about.

National Cancer Institute (2025). Childhood Cancer Data Initiative (CCDI) www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/about.

National Cancer Institute (2026a). The Childhood Cancer Survivor Study. https://www.cancer.gov/types/childhood-cancers/ccss.

National Cancer Institute (2026). The Childhood Cancer Data Initiative Molecular Characterization Initiative. www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/programs/molecular-characterization.

National Cancer Institute (2026b). Surveillance, Epidemiology, and End Results (SEER) Program. seer.cancer.gov/.

National Cancer Institute (2026c). The Childhood Cancer Data Initiative Molecular Characterization Initiative. www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/programs/molecular-characterization.

National Institutes of Health (2026). Gabriella Miller Kids First Pediatric Research (Kids First). commonfund.nih.gov/KidsFirst.

Wilkinson, M., Dumontier, M., Aalbersberg, I. et al. (2016). The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 3, 160018. doi.org/10.1038/sdata.2016.18.

Neev

When Neev was diagnosed with diffuse intrinsic pontine glioma (DIPG) at four, we learned how little the world knew about this disease: limited research, few experts, and no approved treatment beyond radiation. Over fifteen months, Neev took part in five Phase 1 clinical trials, each one possible only because earlier families, in their own grief, had said yes to something that might help a child they'd never met. We already understood the debt before anyone asked us to repay it.

So, when Neev's neurosurgeon raised the idea of a research tissue donation, it aligned with everything we already knew: DIPG receives only a small share of pediatric cancer research funding, and if Neev's tumor tissue and its data live at UCSF and within the Children's Brain Tumor Network (CBTN), open to researchers doing exactly the work his neurosurgeon described, he could help contribute to future progress against the disease.

Here is the science we wish more families understood. Neev's data and tissue alone were never going to save anyone. DIPG is rare, so every dataset is small, and no single family's "yes" produces a breakthrough alone. The power is in the network, where patterns that are invisible in one sample can surface across many: shared mutations, common resistance, subtypes of a disease long treated as one. That is why, as a patient advocate now, I stay close to CBTN push for the Pediatric Care eXpansion, Advanced Research Projects Agency for Health's (ARPA-H) initiative to connect pediatric data nationally, so no child's contribution stays trapped in a system no one else can see.

Saying yes to tissue donation of Neev's tumor was hard. Very hard. We were already grieving, even as Neev kept fighting, holding the milestones we knew he might not reach alongside every day we still had with him.

Our son spent his whole short life making sure everyone around him got to win too. What we hope his tissue and data make possible is simple. We hope some family, years from now, sits in a hospital room with more options than we had. We hope a researcher touching CBTN data finds something in his cells, joined to hundreds of others, that shortens the distance between diagnosis and treatment for another child.

Neev's data is one thread in a system we are still building. Every family that says "yes" adds another. That is how we give every child with DIPG a fighting chance.

— Shared by Neev's family

CHAPTER 7

Funding, Investment, and the Economics of Discovery

Summary

Previous chapters of this report explored the lengthy process by which current therapies arise from basic research and progress through preclinical and clinical research before becoming FDA-approved and broadly available to children on the commercial market. To advance through this process, whether for adults or children, a therapy must have a scientific foundation. However, sound science by itself is not sufficient to ensure that a therapy is clinically successful. Research and drug development are expensive and require substantial financial resources to create the final products that result in improved outcomes for children. Private industry, the federal government, and philanthropies all fund cancer research, but they tend to fund different phases of cancer research. This chapter examines the funding roles that each group assumes, the rationale for those roles, and the mechanisms by which that funding is provided.

Introduction

By funding basic research, the federal government helps to create an ever-expanding scientific knowledge base that can then be used by private industry to create new therapies to treat cancer. As a society, the U.S. has consistently confirmed that reducing suffering from cancer is a national priority worthy of significant public funding. Federal funds for basic cancer research have been provided through the National Cancer Institute (NCI), which was created by the National Cancer Act of 1937. The more basic knowledge generated about a disease, the easier it is to translate that knowledge into tangible products that can improve patient outcomes. In addition to making drug development easier by investing in basic science, federal funding also supports clinical trial networks and regulatory initiatives (see chapter 5, *Regulatory Requirements*) that help industry conduct the clinical trials needed to bring new drugs to market.

In adult cancer drug development, basic scientific understanding is translated into approved drugs during later stages of drug development, and this is where private industry invests the largest share of research dollars (Figure 7-1). Industry now substantially outpaces the federal government in overall U.S. research and development spending, accounting for roughly three-quarters of the national total. (Dzau, 2025) Industry invests in late-stage drug development in order to create a return on investment by marketing and selling approved drugs to patients over a period of years. Given the reduced returns for developing drugs for small pediatric oncology indications, industry investment in pediatric cancer drug development is comparatively small. The impact and relevance, therefore, of federal and philanthropic funding is more pronounced in driving therapeutic insights and clinical development in pediatric cancer.

FIGURE 7-1

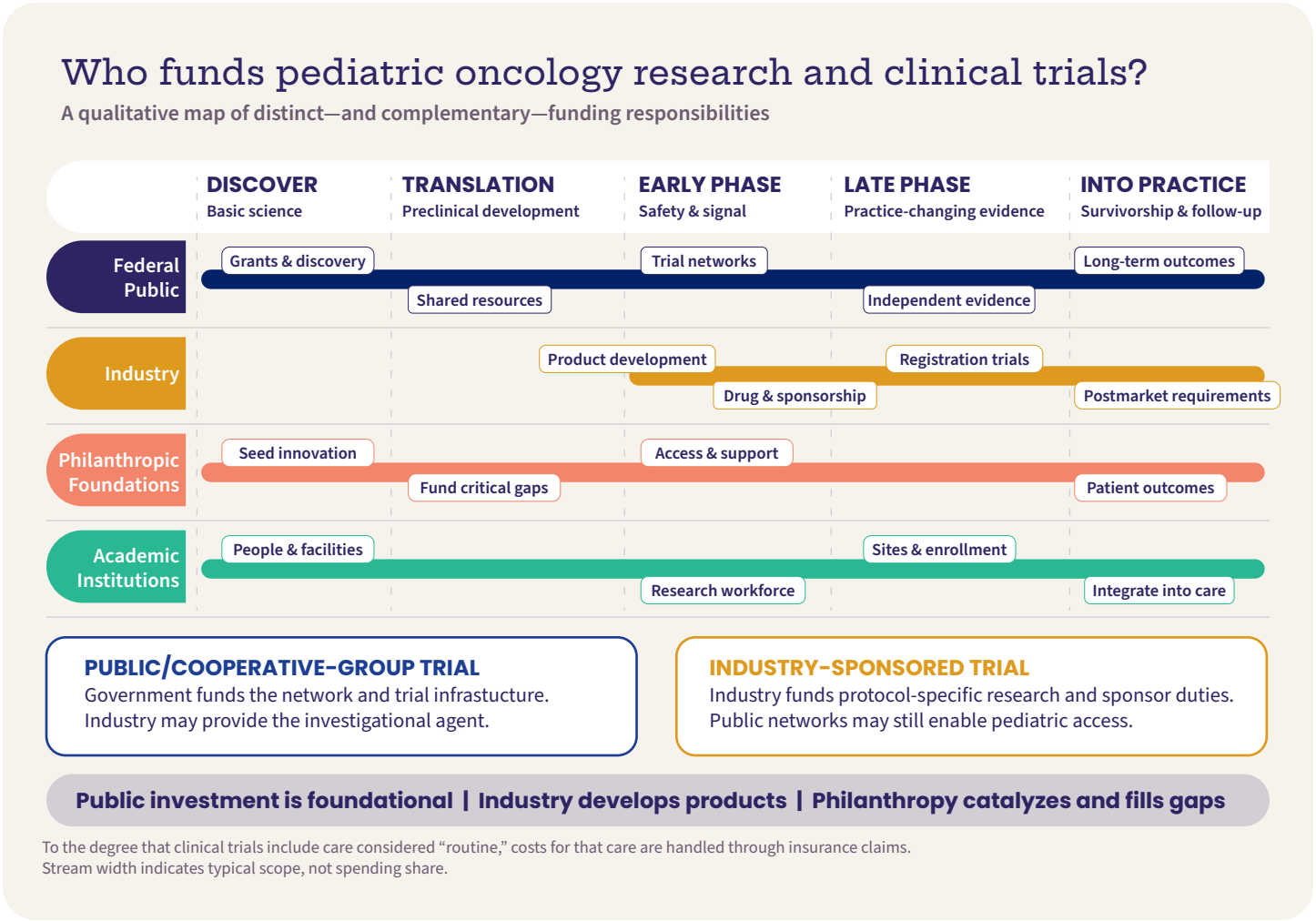


Figure 7-1: Federal, industry, and philanthropic funding all combine to fund the continuum of therapeutic development from discovery to development and application.

Federal funding of pediatric cancer research

NATIONAL CANCER INSTITUTE (NCI)

The federal government is the largest single source of childhood cancer research funding in the U.S. The National Cancer Act of 1937 established the NCI as the primary U.S. government agency responsible for addressing the research and training needs required to discover the causes, diagnosis, and treatments for cancer. The 1937 Act also called for NCI to assist with and promote similar research conducted at other public and private institutions. Passage of the Public Health Service Act of 1944, and later the National Cancer Act of 1971, further shaped NCI. These laws placed NCI as an operating division of the National Institutes of Health (NIH), charging it with awarding research grants and contracts, collaborating with other public agencies and private industry, conducting cancer control activities, and appointing advisory committees to explore new issues and opportunities. (NCI, n.d.) While NCI is the largest funder of pediatric cancer research, other NIH institutes may also fund research relevant to pediatric cancer, including the Eunice Shriver National Institute of Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Neurological Disorders and Stroke (NINDS). More recently, the Advanced Research Projects Agency for Health (ARPA-H), created in 2022, has begun investing in childhood research. (ARPA-H, 2026)

NIH funding of pediatric cancer research

An annual Congressional appropriation law specifies the amount of funding provided to NIH and NCI but, except for a few specific programs, does not specify the amounts NCI should allocate to individual programs or types of cancers such as pediatric cancer. The NCI director is charged with making allocation decisions between various funding categories with counsel from the National Cancer Advisory Board, a panel of national experts, and from internal NCI staff. The majority of the NCI's budget (~75%) funds grants and contracts that are awarded to universities, medical schools, cancer centers, research laboratories, and private companies in the U.S. and approximately 20 other countries. The remaining funds (~25%) support intramural research and overhead. (NCI, 2026a)

NCI distributes funds through a variety of grant and contract mechanisms. These funding mechanisms are directed toward specific research projects, support personnel, or infrastructure like biobanks or trial networks. Most funds are allocated to the cancer research community through extramural research and center (R) grants, program projects and center (P) grants, and cooperative agreement (U) mechanisms. Other grants focus on researchers' career development (K) and training (F and T) awards. For the most part, funding is not issued under cancer-specific funding programs (e.g. breast cancer, pediatric cancer, etc.), but rather through broad solicitations of research proposals. Under this method for reviewing and awarding grants, a variety of research proposals that may either focus on specific types of cancers, or address cross-cutting issues shared between cancers, compete against each other for available funding. Under this

FIGURE 7-2

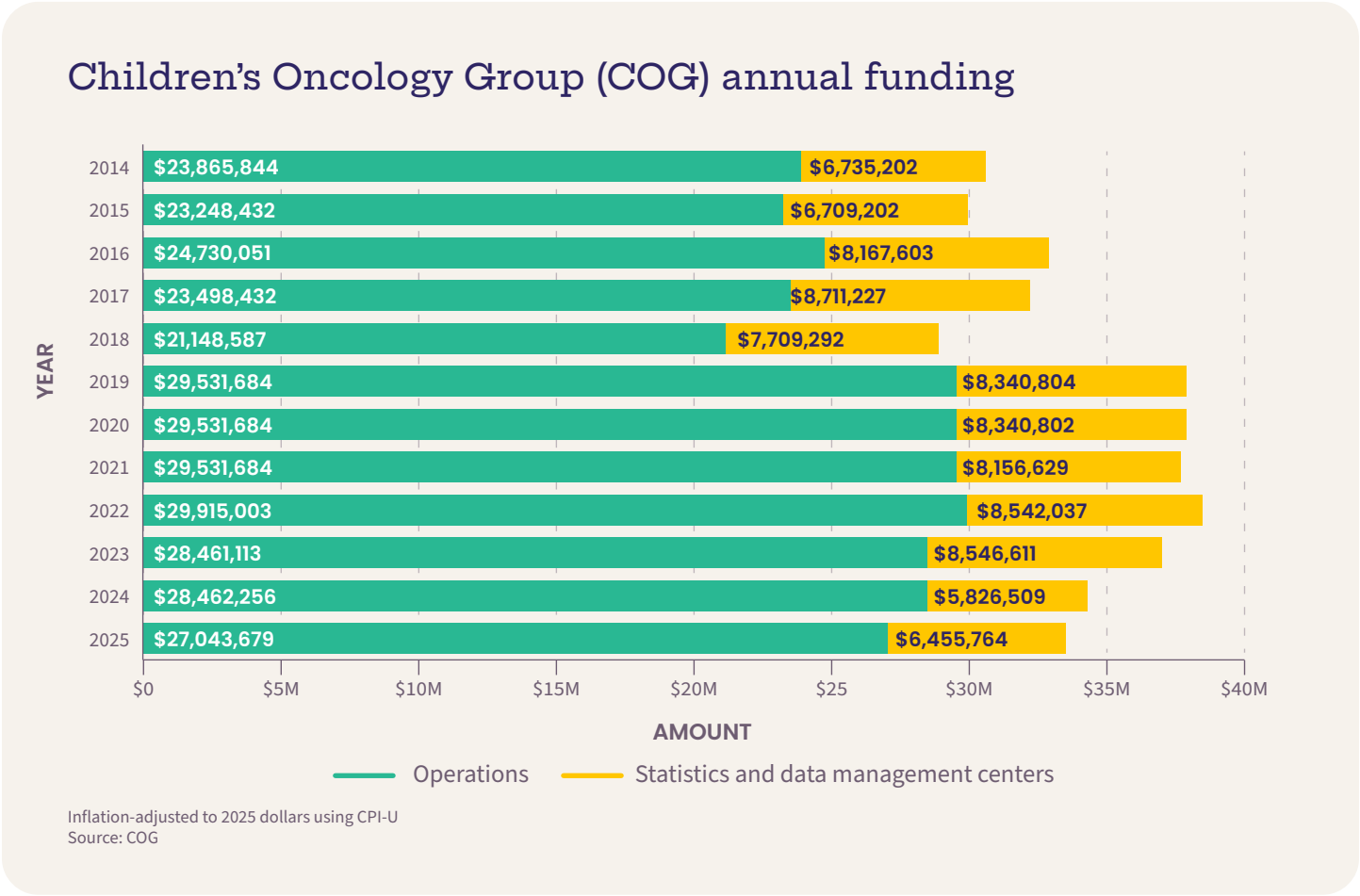


Figure 7-2: COG funding from 2014 to 2025 shows a slight overall increase in funding, factoring in inflation to adjust to 2025 dollars using: $Real_{2025}=Nominal_t \times CPI2025/CPI_t$ with CPIU annual averages from BLS. Source: Children's Oncology Group (n.d)

approach, the level of funding to individual cancer types is reflective of the number and quality of applications and the current scientific opportunities within each field rather than a prescribed proportion of the overall budget.

While much of NIH's funding is awarded through competition between research proposals representing a variety of types of cancer, NCI also has some dedicated funding specifically targeting pediatric cancer. Examples include funding for the Children's Oncology Group (COG) clinical trial network (Figure 7-2), the Childhood Cancer Survivorship Study, and programs under the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act, and the Childhood Cancer Data Initiative (CCDI) (see chapter 6, *Data, Data Sharing, and AI*).

While NIH does not proactively set up disease-specific funding allocations, it does attempt to track disease or focus-area spending through a variety of tools. Accurate accounting, however, is difficult since research that is not specific to pediatric cancer may lead to advances in caring for children. For example, broad research into blood cancers may benefit children with leukemia, basic research into the immune system may enable pediatric immunotherapies, or advances in genomic testing may lead to better targeting of therapies for children. With these overlapping research aims, determining an exact level of federal funding for pediatric cancer is difficult. One approach is to use research, condition, and disease categorization (RCDC) codes, which are a set of research categories maintained by NIH to track disease spending. There are over 300 such codes, and funding totals are

FIGURE 7-3

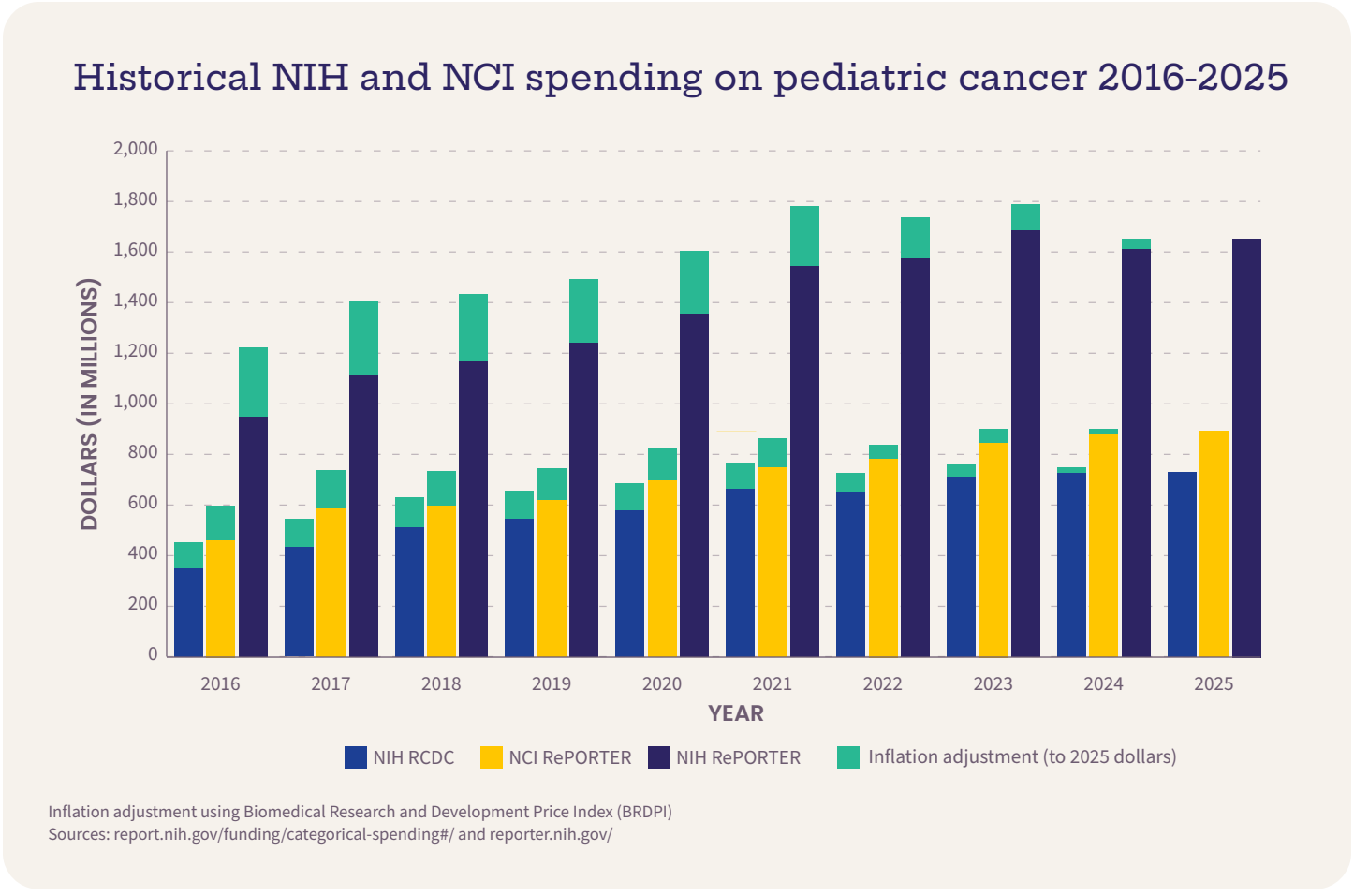


Figure 7-3: Trends in pediatric cancer funding at NIH and NCI. Different tools provide different estimates of annual funding, but all show general increases in spending on pediatric cancer. (RCDC, Research, condition, and disease categorization).

assigned to an RCDC through software that automatically categorizes research into non-exclusive categories. For example, a given research program on diffuse intrinsic pontine glioma (a deadly form of pediatric brain cancer) could be counted within the RCDCs of "Cancer," "Brain Cancer," and "Pediatric Cancer." NIH also maintains a database of all funded projects that can be accessed with the Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER) tool. This tool enables searches to identify funded research according to keywords in awarded grants. The methodologies of the RCDC and RePORTER tools differ, and they provide different numerical values for the amount of pediatric cancer research funded. However, they reveal similar trendlines of increased funding from 2016 to 2025 (Figure 7-3). Using the RePORTER tool searching for "pediatric cancer" funding at NCI, funding increased 93% during this time using unadjusted numbers, or 49% using an inflation adjustment, while the NCI's overall budget grew by approximately 39% using unadjusted numbers, or 7% factoring in inflation. (NCI, 2026b; NIH, 2026a, NIH, 2026b)

Department of Defense (DoD) cancer research funding

Outside of NIH, the other major federal source of research funds for childhood cancer research is the Department of Defense (DoD). The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 as a result of a grassroots effort led by breast cancer advocates to find new sources of federal research funding. (CDMRP, 2023) This effort led to congressional appropriations for cancer research funding within the DoD budget that facilitates a partnership among the public, Congress, and the military. Funds for the CDMRP are added to the DoD budget to support specific programs selected with guidance from Congress. Within the CDMRP, the Peer Reviewed Cancer Research Program (PRCRP) and the Rare Cancers Research Program (RCRP) play central roles in advancing childhood cancer research (Figure 7-4). The PRCRP supports innovative, impactful research in topic areas directed by Congress for cancer prevention, detection, treatment, and survivorship. (PRCRP 2026) The

FIGURE 7-4

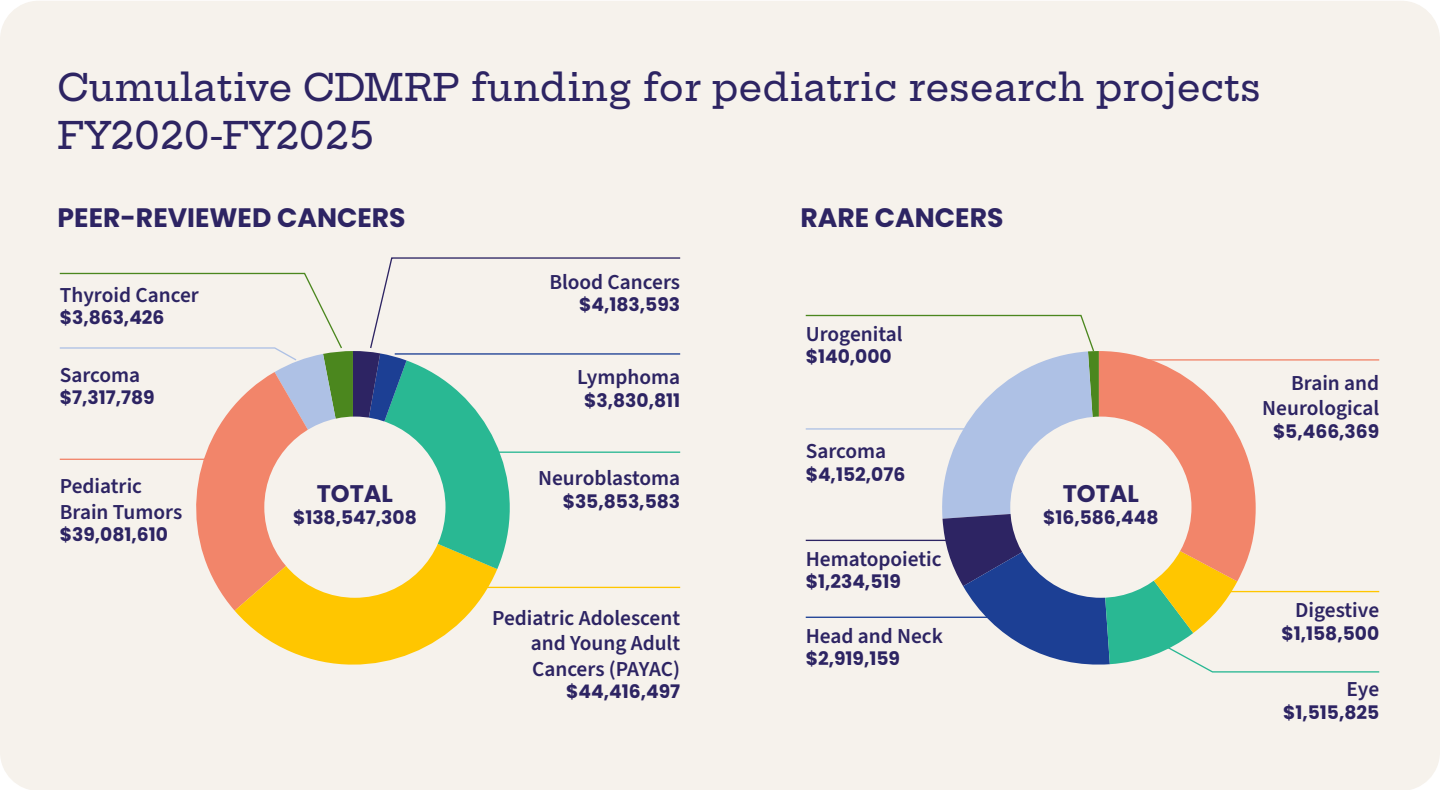


Figure 7-4: Cumulative childhood and adolescent cancer-related CDMRP research awards from FY2020-FY2025 for the Peer Reviewed Cancer Research Program (PRCRP, left) and the Rare Cancers Research Program (RCRP, right).

RCRP specifically supports research on rare cancers, including pediatric rare cancers, aiming to expand knowledge, enable discoveries, and catalyze advancements in cancers that only occur in six or fewer cases per 100,000 people annually in the U.S. (Figure 7-4).

State pediatric cancer funding

In addition to federal funding, at least 10 states also set aside funds dedicated to pediatric cancer research. Sources of the funding range from state general funds to tobacco settlement funds, targeted taxes or voluntary income tax refund donations. Some programs direct funding to specific in-state research institutions, while others create a competitive grant fund. (American Childhood Cancer Organization, n.d.)

International research funding

While the focus of this report is primarily on the pediatric research landscape in the U.S., pediatric cancer research occurs globally. Small numbers of patients in any given country for many rare pediatric cancers necessitate international collaboration. The Cancer UK/NCI Grand Challenges program offers specific research awards for pediatric cancer. (Cancer Grand Challenges, 2020) NCI's Children's Oncology Group (COG), a network of funded pediatric clinical research sites, includes 30 sites outside the U.S., and researchers frequently collaborate on research protocols and data collection and analysis. (COG (n.d.) The U.S. has historically been a global leader in pediatric cancer research funding. The U.S. has funded over 6.5 times the amount funded by the EU, UK, and Canada combined during the period from 2008-2016. (Loucaides, 2019)

Philanthropic funding for pediatric cancer research

Private philanthropy, typically given through 501 (c) (3) nonprofit organizations, is a significant source of funding for pediatric cancer research. While less than philanthropy support for adult cancer research and drug development, it nonetheless plays a significant role given the lack of commercial incentives for investment by private industry. Philanthropy supports basic, clinical, and translational research. It also provides funds for research infrastructure that can expand research opportunities, for example, for facilities, equipment, training, and support for professionals who coordinate trials at local institutions. Infrastructure grants can also expand research groups' capacity to allow more children to access clinical trials.

Industry funding of pediatric cancer research

Basic biological findings and the identification of chemical compounds that might be effective against a cancer only become usable drugs for patients through the substantial investment of industry in clinical trials, formulation development, and reliable manufacturing. Industry and venture capitalists invest in adult drug development because they hope to have an approved drug that can generate revenue through sales once a drug is approved. When considering whether to pursue a particular drug development program, a drug sponsor can calculate how much a company can earn from drug sales by multiplying the number of people that might take the drug by the price charged per patient minus the cost of developing the drug.

Pediatric cancers are rare, which means that the number of people that would eventually take any pediatric drug is small. The most common childhood cancer, acute lymphoblastic leukemia, has fewer than 3,000 cases per year in children, and this number is made up of different subtypes that would likely require different drugs. Some pediatric cancers are so rare that only a few dozen children are diagnosed annually in the U.S. With such small patient populations, it is difficult to achieve large financial returns from selling a cancer drug if it is solely used for childhood cancer (Path "C" in Figure 4-1). However, when drugs are initially developed for adults before being developed for children (Paths A, B and D in Figure 4-1), the potential overall market size (children plus adults) for a drug is much larger. Companies prioritize adult drug development prior to developing that drug for children in order to ensure successful investment. Several programs have been created to try to enhance the economic incentives for companies to increase the number of drugs to treat childhood and rare diseases. These are discussed below.

DRUG SHORTAGES

Shortages of cancer drugs have persistently occurred over the past decade, and the treatment for children has been especially affected. A large proportion of drugs in shortage are older, low-cost, generic, sterile injectable drugs. Because of their low reimbursement rates, there is little to no profit to be made, causing manufacturers to deprioritize their production, or in some cases to cease manufacturing them altogether. In 2019, a severe shortage of the childhood cancer drug vincristine occurred when one manufacture ceased production, and the remaining manufacturer was not immediately able to make up the shortfall. A few years later shortages in vinblastine, dacarbazine and methotrexate also emerged.

The lack of novel therapeutic agents for children with cancer means many treatment regimens rely on these older, yet often highly effective drugs, with no comparable products that could serve as a substitute during shortages. Such shortages lead to difficult decisions that include reducing or skipping doses or shortening treatment duration for kids with cancer. Not only do these shortages affect patients in active treatment, but these drugs are often part of the control arm of clinical trials or the backbone upon which new treatments are layered. Therefore, during shortages clinical trials must be paused, stalling research progress.

80%+

of surveyed institutions report an active shortage of a drug used to treat children with cancer

1 in 2

childhood cancer patients, survivors, and families report a life-saving drug that became unavailable during treatment

Source: Alliance for Childhood Cancer, Pediatric Cancer Drug Shortages survey of 184 health care providers, researchers, patients, survivors, caregivers, and family members (May–June 2023).

While the root cause of shortages of generic sterile injectable drugs is widely understood to be tied to a lack of sufficient incentives to manufacture these products, little has been done from a policy standpoint to address the issue other than enhancing notification requirements for sponsors to report planned changes in production.

Exclusivity

When a company successfully tests a drug and receives FDA approval, it can sell that drug without competition for a specific period. Exclusive rights to a drug are critical economic incentives for companies to invest in and develop drugs for patients. There are several forms of exclusive rights for a molecule or drug, including patent, data, and market exclusivity. Molecules created by a researcher can receive patent protection for 20 years, during which competitors may not copy the same molecule. Typically, a molecule is patented after discovery in the laboratory, and then considerable time often elapses during the preclinical and clinical development phases that follow. By the time a drug is approved as a therapy by the FDA for sale, roughly 13–15 years of the patent term has typically already elapsed, leaving a company with substantially less than 20 years—often only 5 to 7 years—of remaining exclusivity in which to realize a return on its investment. (Hickey, 2024)

When patent life expires for a brand name drug, other companies can copy it, and it becomes “generic.” One reason that generic drugs can be sold more cheaply than brand name drugs is that generic manufacturers do not have to conduct all the clinical research needed to prove the safety and efficacy of the drug, since this information was already gathered by the original drug developer. Data showing that the drug is safe and effective, however, are often not public but are held by FDA and the innovator company. While generic manufacturers can rely on these data for their products, they can only do so after a drug’s data exclusivity period has expired. The data exclusivity period is independent of the period of patent exclusivity. Even if a drug’s patent has expired, if the data exclusivity period is still in effect, no generic form of the drug can come onto the market by using data from the original developer. When a drug is approved, it is given five years of data exclusivity. Some therapies are made using living organisms rather than chemical synthesis and are known

PUBLIC–PRIVATE PARTNERSHIPS

Research funding does not always come exclusively from a single source. Public–private partnerships are a way to combine funding in a way that can make limited funding more effective and can drive commercial development that may not otherwise occur. These collaborations not only pool funds, but they leverage strength of each sector, such as regulatory expertise or academic trial networks. These models can distribute risk, reduce duplication, and fund critical translational work. In pediatric oncology, examples include *Break Through Cancer*, which supports coordinated, multi-center research in osteosarcoma; the Foundation for NIH (FNIH) *Ultra-Rare Cancer Treatment Advancement Program (ULTRA)*, which convenes public and private partners to address cancers for which conventional commercial models are inadequate; and the CRUK–LifeArc *C-Further* consortium, which combines pooled funding and industry-standard development expertise to create child-focused medicines. (Break Through Cancer, 2025; FNIH, 2026; C-Further, 2026)

as biologic drugs or biologics. Biologic drugs receive 12 years of data exclusivity. Even if a drug's patent has expired, if the data exclusivity period is still in effect, no generic form of the drug can come onto the market by using data from the original developer. (Hickey, 2024)

If a drug's patent has expired, but its data exclusivity has not, in theory another manufacturer could recreate all of the research needed for drug approval rather than relying on the original company's data. However, this would be expensive and time-consuming. Certain drugs for rare diseases, known as "orphan drugs," have a third type of exclusivity known as market exclusivity. For these drugs, not only does FDA not allow generic manufacturers to use data from the original approval for five years, but FDA will not allow approval for use of the same drug for seven years even if another manufacturer conducts their own research to obtain their own data for approval. All childhood cancers are rare diseases, and drugs developed for these diseases can qualify for incentives under the Orphan Drug Act.

While orphan incentives depend on the population affected by a disease being under the 200,000-person threshold, Congress also created a pediatric-specific exclusivity incentive through the Best Pharmaceuticals for Children Act (BPCA) (see chapter 5 *Regulatory Requirements*). (NIH, n.d.) Drug sponsors of adult drugs who conduct pediatric research according to a written request from FDA can earn an extra six months of marketing exclusivity for the drug being tested on all uses of the drug, including adult uses. This law was intended to generate much needed pediatric information on drugs developed for adult use but frequently used in children (Routes A and B in Figure 4-1). Companies have primarily conducted pediatric studies under BPCA for drugs that have large associated adult markets. From 2013 to 2023 pediatric exclusivity awarded through BPCA was reported to have led to $9 billion in added revenue for pharmaceutical companies, with individual drugs having a range of benefits from a $16.8 million to $1.34 billion. (Liu, 2025) However, FDA has also regularly used BPCA to encourage companies to determine whether or not drugs still in development for adult cancers can be useful in treating childhood cancers despite researchers' pushback that BPCA does not incentivize new drugs for children.

Incentives to develop orphan drugs

In order to promote the development of drugs for rare diseases like childhood cancers, Congress passed the Orphan Drug Act in 1983. (Congressional Research Service, 2024) Orphan drugs are defined as drugs that treat conditions that affect 200,000 or fewer people per year in the U.S. This law can include specialized subsets of diseases that otherwise affect more than 200,000 people per year, if the drug is designed solely to work for the subset. As an example,

lung cancer affects more than 200,000 Americans, but a drug designed to treat lung cancers with mutations in the ALK gene can still receive orphan designation because that subset numbers under 200,000 patients.

Orphan designation comes with a number of incentives. As part of an application to FDA for approval, drug manufacturers normally pay a "user fee" to enhance FDA resources needed for drug review, but orphan drugs are exempt from this fee, which can exceed $2 million. Developers of orphan drugs can also claim a federal tax credit currently equal to 25% of their qualified clinical testing expenses; this credit was reduced from 50% by the Tax Cuts and Jobs Act of 2017. (FDA, 2025; Legal Information Institute, n.d.) Orphan drug developers can also apply for a grant from the FDA to help fund their clinical research, and the FDA issued $9 million in these grants in FY2025. (FDA, 2026) Lastly, as mentioned above, orphan drugs benefit from seven years of market exclusivity. Drugs approved for only orphan indications are also exempt from price negotiations under the Inflation Reduction Act (IRA), a law which provides the federal government with the ability to negotiate for lower prices on certain drugs.

Additional economic incentives for pediatric drugs

Extra exclusivity can provide increased income over the lifetime of a drug, but some of the added benefits are realized in the future and can be uncertain. While exclusivity prevents the creation of competition from identical drugs, it does not prevent companies from developing completely different drugs for the same disease or condition. As a result, even the extra exclusivity is sometimes not enough to create sufficient potential revenue for companies to evaluate their drugs in children, since a drug may only be used by a few dozen or a few hundred children per year.

To create further financial incentives to develop drugs for rare pediatric conditions, Congress passed the Creating Hope Act in 2011. Modeled on a program to stimulate development of drugs to treat tropical diseases, this law created a priority review voucher program. Vouchers are awarded for newly approved drugs that receive FDA approval for a disease designated as a rare pediatric disease (not just childhood cancers). A priority review voucher entitles a company to obtain a shorter FDA drug application review time for a subsequent application, cutting it from 10 months to six months. A faster review allows a drug sponsor to begin selling its product and making money sooner. A drug company earning a voucher may use it for their own subsequent marketing application for another drug, or it can sell the voucher to another company. Priority review vouchers can shave four months off FDA's review timeline, which can provide significant financial benefits for a blockbuster drug, as evidenced by sales prices of vouchers that have been sold to date. Pediatric priority review vouchers that are sold have the advantage of providing immediate revenue to the original drug developer, and they provide incentives for companies to create new drugs specifically for rare diseases in children (Path C in Figure 4-1). After initial fluctuations in sales prices, vouchers now regularly sell for around $100 million.

Of the 75 pediatric vouchers awarded, six have been for cancer related therapies (Dinutuximab, Tisagenlecleucel, Naxitamab-gqgk, Tovorafenib, Dordaviprone, and Mirdametinib). Four of the six cancer-related vouchers have been sold, with one remaining unsold and one used by the company receiving it. Dinutuximab was one of the earliest vouchers and holds the record for sales price at $350 million. The other cancer-related vouchers sold for between $105 million and $200 million. Unlike BPCA and PREA, the Priority Review Voucher program is not permanently authorized and is created on a time-limited basis. The program has been renewed three times but also lapsed from late December 2024 to February 2026 (see *Appendix* for more detail). It is currently scheduled to expire on September 30, 2029. (FDA, 2026b)

Pediatric drug prices in state Medicaid programs

Medicaid is a joint state-federal insurance program for low-and medium-income families and provides healthcare coverage to approximately one in four children in the U.S. (Department of Health and Human Services, 2016) As a significant purchaser of drugs for children, prices paid by Medicaid for pediatric drugs have the potential to influence a drug company's incentives to develop drugs targeted toward children. Medicaid payments for drugs are based on a drug's average manufacturer price (AMP)

minus required and supplementary rebates. (Federal Register, 2016) Currently, name-brand drug manufacturers are required to offer a 23.1% rebate on AMP to state Medicaid programs as a precondition for participating in the Medicare and Medicaid programs. In an effort to improve incentives for pediatric drug development, an exception to this policy allows pediatric-only name-brand prescription outpatient drugs to rebate only 17.1% of their AMP to state Medicaid programs. (Legal Information Institute, n.d. b) The overwhelming majority of drugs used to treat pediatric cancer, however, are not pediatric-specific, so the drugs to which this policy exception apply are limited.

Non-industry pediatric clinical drug development

Academic researchers and philanthropic organizations sometimes bring basic research findings into the clinical phase of drug development for pediatric cancers, especially if promising early findings do not generate industry interest in carrying a specific drug's development forward. In fact, the development of one of the few pediatric-specific cancer drugs, Unituxin, was largely funded by NCI. These efforts, however, face their own challenges in the clinical phase of research. Funding is one challenge, but some specialized funding programs are in place to help investigators advance drug development beyond the laboratory. Specifically, NIH funds Small Business Innovation Research (SBIR) grants, and Small Business Technology Transfer (SBTT) grants geared toward helping commercialize research. (NIH, 2026c; NIH, n.d. b) Through these mechanisms, researchers can seek seed money to start a company; however, one barrier is that grant recipients must dedicate over half their time to the new company, effectively requiring them to leave their academic position and forgo associated benefits. This pathway to developing pediatric oncology agents is especially uncertain since, even if approved, pediatric-specific drugs are not likely to yield significant financial rewards. Further, drug development and the associated regulatory requirements are a complex undertaking, and academics attempting to seek approval of a drug often do not have access to the resources and specific regulatory expertise available to more established private biopharmaceutical companies that engage in large-scale drug development.

References

American Childhood Cancer Organization (n.d.). *What about kids?* www.acco.org/what-about-kids/.

ARPA-H (2026). *ARPA-H announces $50M to expand pediatric care across the country*. arpa-h.gov/news-and-events/arpa-h-announces-50m-expand-pediatric-care-across-country.

Break Through Cancer (2025). *Break Through Cancer launches largest-ever investment in pediatric osteosarcoma research*. breakthroughcancer.org/2025/09/largest-ever-investment-in-pediatric-osteosarcoma-research.

C-Further (2026) www.c-further.org/.

Cancer Grand Challenges (2020). *The challenges: Professor Crystal Mackall on the solid tumours in children challenge*. www.cancergrandchallenges.org/news/the-challenges-professor-crystal-mackall-on-the-solid-tumours-in-children-challenge.

Centers for Medicare & Medicaid Services (n.d.). *Unit rebate amount calculation*. Medicaid.gov. www.medicaid.gov/medicaid/prescription-drugs/medicaid-drug-rebate-program/unit-rebate-amount-calculation.

Federal Register (2016). Medicaid Program; Covered Outpatient Drugs www.federalregister.gov/documents/2016/02/01/2016-01274/medicaid-program-covered-outpatient-drugs.

Children's Oncology Group (n.d.). *COG member institutions*. childrensoncologygroup.org/patients-families/member-institutions/.

Congressionally Directed Medical Research Programs (2023). *Congressionally Directed Medical Research Programs*. U.S. Department of Defense. cdmrp.health.mil/.

Congressional Research Service (2024). *The Orphan Drug Act: Legal overview and policy considerations* (IF12605). www.congress.gov/crs-product/IF12605.

Department of Health and Human Services. (2016) *2015 annual report on the quality of care for children in Medicaid and CHIP*. www.medicaid.gov/medicaid/quality-of-care/downloads/2015-child-sec-rept.pdf.

Dzau, V. J., & Yamamoto, K. R. (2025). Government-funded health and biomedical research is irreplaceable [Commentary]. *NAM Perspectives*. doi.org/10.31478/202508b.

Food and Drug Administration (2025). *Prescription drug user fee rates for fiscal year 2026* (90 Fed. Reg. 35866). Federal Register. www.federalregister.gov/documents/2025/07/30/2025-14413/prescription-drug-user-fee-rates-for-fiscal-year-2026

Food and Drug Administration (2026). *Orphan products grants awarded*. www.fda.gov/industry/orphan-products-grants-program/orphan-products-grants-awarded.

Food and Drug Administration (2026b). *Rare Pediatric Disease Designation and Priority Review Voucher Programs*. www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-designation-and-priority-review-voucher-programs.

Foundation for the National Institutes of Health (2026). *Ultra-Rare Cancer Treatment Advancement Program design phase*. fnih.org/our-programs/ultra-rare-cancer-treatment-advancement/.

Hickey, K. J., & Ward, E. H. (2024). *The role of patents and regulatory exclusivities in drug pricing* (Report No. R46679). Congressional Research Service. www.congress.gov/crs-product/R46679.

Legal Information Institute (n.d.) Clinical Testing Expenses for Certain Drugs for Rare Diseases or Conditions, 26 U.S.C. § 45C. www.law.cornell.edu/uscode/text/26/45C.

Legal Information Institute (n.d. b) 42 CFR § 447.509 - Medicaid drug rebates www.law.cornell.edu/cfr/text/42/447.509.

Liu, I. T. T., Raymakers, A. J. N., Sarpatwari, A., & Kesselheim, A. S. (2025). Pediatric exclusivity-associated revenues and labeling changes, 2013–2023. *The Journal of Pediatrics, 284*, Article 114660. doi.org/10.1016/j.jpeds.2025.114660.

Loucaides, E. M., Fitchett, E. J. A., Sullivan, R., & Atun, R. (2019). Global public and philanthropic investment in childhood cancer research: Systematic analysis of research funding, 2008–16. *The Lancet Oncology, 20*(12), e672–e684. doi.org/10.1016/S1470-2045(19)30662-X.

Medicaid Drug Rebates (2024). 42 C.F.R. § 447.509. www.ecfr.gov/current/title-42/chapter-IV/subchapter-C/part-447/subpart-I/section-447.509.

National Cancer Institute (n.d.). *Comprehensive cancer information*. www.cancer.gov.

National Cancer Institute (2026a). *Obligations by budget mechanism and division*. www.cancer.gov/about-nci/budget/fact-book/data/obligations.

National Cancer Institute (2026b). *NCI budget and appropriations*. www.cancer.gov/about-nci/budget.

National Institutes of Health (n.d.). *Best Pharmaceuticals for Children Act*. www.nichd.nih.gov/research/supported/bpca.

National Institutes of Health (n.d.b). *Understanding SBIR and STTR*. seed.nih.gov/small-business-funding/small-business-program-basics/understanding-sbir-sttr.

National Institutes of Health (2026a). *Funding for various research, condition, and disease categories*. report.nih.gov/funding/categorical-spending#/.

National Institutes of Health (2026b). *NIH RePORTER*. reporter.nih.gov/.

National Institutes of Health (2026c). *Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR)*. www.nigms.nih.gov/Research/mechanisms/Pages/small-business-research.

Peer Reviewed Cancer Research Program (2026). *The Peer Reviewed Cancer Research Program vision video: Text version*. Congressionally Directed Medical Research Programs. cdmrp.health.mil/pubs/video/prc/prcrp_vision_video_text.

Conclusion

Children typically develop cancers that are quite different from cancers that occur in adults. Children also undergo treatment during a time of vital physical and mental development, leaving them vulnerable to a lifetime of side effects, even if their cancers have been cured. The smaller number of pediatric cancer cases also creates challenges with the conduct of trials and the economic returns associated with drug development to treat such cancers. Consequently, developing effective drugs to treat children with cancer presents unique challenges. It requires the collective engagement of research, advocacy, and regulatory communities to recognize and address the spectrum of hurdles described in this report. Challenges ranging from biological to logistical to ethical and economic require enhanced collaboration among stakeholders who share the common goal of advancing treatments to cure pediatric cancers.

Pediatric Cancer Landscape 2026

Appendix

Major Policy and Funding Changes 2016-2026	67
Pediatric Definitions	69
Major Cancer Types	74
Supplemental Figures	80

Major Policy and Funding Changes, 2016-2026

With incredible momentum, the childhood cancer community has helped secure a remarkable string of federal wins: the Creating Hope Act, the RACE for Children Act, the Childhood Cancer STAR Act and its reauthorization, sustained investment in the Childhood Cancer Data Initiative, and — most recently — the Give Kids a Chance Act and the Accelerating Kids' Access to Care Act. Each of these was the product of coordinated, persistent advocacy, met at every turn by Members of Congress on both sides of the aisle who chose to prioritize children with cancer, and by federal agency leadership who translated new authorities into real programs and real funding.

None of this is a one-time achievement. Authorizations expire. Appropriations must be renewed annually. That reality is precisely why sustained, disciplined advocacy matters as much as any single legislative victory — and why the consistent, bipartisan support of Congressional champions and the follow-through of federal agency leadership has been critical. It is why the pediatric cancer community returns to advocate every year and why continued collaboration with the lawmakers and public servants who choose, year after year, to stand with children with cancer and their families to create the cures and quality of life they so urgently need.

Creating Hope Act (2012, 2016, 2020, 2026) — Gives drug companies a financial incentive in the form of a fast-track review voucher they can use or sell to successfully bring a treatment for a rare pediatric disease to market. It exists because rare childhood diseases affect too few patients to be profitable to research on their own.

Gabriella Miller Kids First Research Act (2014, 2025) — Directs a dedicated stream of NIH funding toward genomic research into childhood cancer and structural birth defects. It is named for a 10-year-old advocate who died of a brain tumor and helped inspire the bill before her death. Original bill authorization was from 2014-2023, reauthorization from 2025-2028.

21st Century Cures Act / Cancer Moonshot (2016) — Provided a major, multi-year infusion of federal research funding aimed at accelerating progress against cancer broadly, with a specific focus on pediatric cancer drivers like fusion oncoproteins. It funded new research initiatives rather than creating new regulatory requirements.

RACE for Children Act (2017) — Requires drug companies developing new adult cancer drugs to also test them in children whenever the drug targets a biological pathway relevant to a childhood cancer. This closed a loophole that had let most cancer drugs to skip pediatric testing entirely.

Childhood Cancer STAR Act (2018, 2023) — Expands the collection of biological samples and data from children and young adults with cancer, and funds research and support programs for cancer survivors dealing with long-term effects of treatment. It also requires pediatric cancer expertise on federal cancer advisory boards. The reauthorization extends the original STAR Act's research and survivorship programs for several more years, adding new requirements for evaluating how survivorship care is delivered.

Childhood Cancer Data Initiative (2019) — Funds efforts to collect, share, and analyze data on childhood cancers across hospitals and research centers. Because pediatric cancers are individually rare, no single hospital sees enough cases to draw strong conclusions alone — this initiative pools that data nationally.

Executive Order 14355 (2025) — Directs federal health agencies to prioritize using artificial intelligence to analyze childhood cancer data and accelerate research and calls for increased federal investment in existing pediatric cancer data programs. It is a presidential directive to agencies, not new funding or law from Congress.

Mikaela Naylon Give Kids a Chance Act (2026) — Expands pediatric cancer drug testing requirements to cover combination therapies (not just single drugs), lets FDA penalize companies that skip required pediatric studies, and renews the rare pediatric disease voucher program through 2029. It closes gaps left by the original RACE Act, which only reliably covers single-drug applications.

Accelerating Kids Access to Care Act (2026) — Requires states to establish a process for out-of-state providers meeting specific qualifications to be able enroll as a provider for 5 years in Medicaid and the Children's Health Insurance Program (CHIP). This applies to treating individuals under 21, and the authorization lasts for five years. This facilitates cross-border travel to see specialists.

References

U.S. Congress. (2012). *Creating Hope Act, Section 908 of the FDA Safety and Innovation Act* (Pub. L. No. 112-144). U.S. Food and Drug Administration. www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-designation-and-priority-review-voucher-programs

U.S. Congress. (2014). *Gabriella Miller Kids First Research Act* (Pub. L. No. 113-233). National Institutes of Health, Common Fund. https://commonfund.nih.gov/kidsfirst

U.S. Congress. (2017). *RACE for Children Act*. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-resources/rare-pediatric-disease-priority-review-voucher-program-section-529

U.S. Congress. (2018). *Childhood Cancer STAR Act* (Pub. L. No. 115-180). National Cancer Institute. https://www.cancer.gov/about-nci/legislative/recent-public-laws/star-act

U.S. Congress. (2023). *Childhood Cancer STAR Reauthorization Act* (Pub. L. No. 117-350). National Cancer Institute. www.cancer.gov/about-nci/legislative/recent-public-laws/star-act

U.S. Congress. (2025). *Gabriella Miller Kids First Research Act 2.0* (Pub. L. No. 118-228). National Institutes of Health, Common Fund. commonfund.nih.gov/kidsfirst

National Cancer Institute. (n.d.-a). *Childhood Cancer Data Initiative (CCDI)*. U.S. Department of Health and Human Services. www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative

Executive Office of the President. (2025). *Unlocking cures for pediatric cancer with artificial intelligence* (Exec. Order No. 14355). Federal Register, 90 Fed. Reg. (Oct. 7, 2025). www.federalregister.gov/documents/2025/10/07/2025-19495/unlocking-cures-for-pediatric-cancer-with-artificial-intelligence

U.S. Congress. (2026a). *Mikaela Naylon Give Kids a Chance Act* (H.R. 1262, 119th Cong.). Congress.gov. www.congress.gov/bill/119th-congress/house-bill/1262

U.S. Congress. (2026b). *Accelerating Kids' Access to Care Act* (enacted as Section 6101 of the Consolidated Appropriations Act, 2026, H.R. 7148, 119th Cong.). Congress.gov. https://www.congress.gov/bill/119th-congress/house-bill/1509

Definitions & Language Differences: Pediatric, Children, Adolescent

Uses of the terms "pediatric", "children" or "childhood", and "adolescent" vary across epidemiological, cancer research, clinical trial, and consent/legal contexts; and definitions vary by agency and purpose. In the preceding report, the designation "pediatric cancer" includes childhood and adolescent cancers (ages 0-19), while "children/childhood cancer" refers to ages 0-14, and "adolescents/adolescent cancer" to ages 15-19. Other conventions are described below.

PEDIATRIC

General meaning: A regulatory/clinical umbrella term for the population under legal/developmental adulthood who require different drug dosing, trial design, and consent handling than adults. This term functions more as a *system/regulatory* category than a single fixed age band.

Source	Definition	Citation
FDA / ICH E11	Interprets "birth to 16 years" (per 21 CFR 201.57) as birth through age 16 (younger than 17), and separately references neonates, infants, children, and adolescents as sub-groups within the pediatric population; the upper boundary used in ICH E11(R1) varies by region, from 16 to 18	FDA, 2023a
ICH E11 (original guidance)	States the pediatric population spans neonates through adolescents, but notes "the upper age limit varies among regions"	FDA, 2000
EMA / EU Paediatric Regulation (EC) No 1901/2006	"'Paediatric population' means that part of the population aged between birth and 18 years"	EU, 2006
FDA medical device statute (21 U.S.C. § 360j(m))	Defines "pediatric patients" as age 21 years or younger at the time of diagnosis or treatment	FDA, 2014
45 CFR 46 Subpart D	Does not use the word "pediatric"; instead defines the operative research category as "children" (see below), making "pediatric" the informal umbrella and "children" the formal regulatory term	U.S. DHHS, n.d.(a)

Key distinguishing feature: "Pediatric" is the broadest umbrella term and is often used interchangeably with "children" in casual usage — but in most regulatory text it is the category name for the whole birth-to-adulthood span, while "children" and "adolescent" are sub-groups defined within it.

CHILDREN

General meaning: Used both colloquially (young people generally) and as a precise regulatory subgroup — notably, in U.S. federal research law, "children" is defined *functionally* by legal consent capacity rather than by a fixed number.

Source	Definition	Citation
45 CFR 46.402(a) (U.S. Common Rule, Subpart D)	"Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted"	U.S. DHHS, n.d.(b)
UN Convention on the Rights of the Child, Article 1	"A child means every human being below the age of eighteen years unless, under the law applicable to the child, majority is attained earlier"	U.N., 1989
ICH E11(R1) sub-classification	Places "children" as the 2–11 year age band, sitting between infants (1 month–23 months) and adolescents (12–18 years)	Lehmann, 2008
International Classification of Childhood Cancer (ICCC)	Uses ages 0–14 as the epidemiological cutoff for classifying "childhood cancer" specifically	NCI, n.d.

Key distinguishing feature: Unlike "pediatric" (regulatory umbrella) or "adolescent" (developmental stage), the U.S. federal research definition of "children" is functional — tied to legal consent capacity in a given jurisdiction — rather than numeric. This is why the same 16-year-old can be a "child" for research-consent purposes in one state while being classified as an "adolescent" in a clinical trial protocol's age stratification.

ADOLESCENT

General meaning: A developmental/biological stage term, more consistently tied to puberty and psychosocial development than to legal status — though trial protocols still impose numeric cutoffs on it.

Source	Definition	Citation
World Health Organization (WHO)	"Adolescence is the phase of life between childhood and adulthood, from ages 10 to 19"	WHO, 2022
WHO (regional/SRH programs)	Consistently defines adolescents as people aged 10–19, distinguishing this from "youth" (15–24) and "young people" (10–24)	WHO, 2022; WHO ROSEA, n.d.; WHO, n.d.
ICH E11(R1)	Places "adolescents" at 12 up to 18 years, with regional variation between 12–16 and 12–18 depending on jurisdiction	Lehmann, 2008
EU Paediatric Regulation guidance documents	References the same ICH-derived adolescent band (12–18) within the broader birth-to-18 paediatric population	EMA, 2026

Key distinguishing feature: "Adolescent" is the term most consistently grounded in developmental/biological criteria (WHO's ages 10–19 framing) rather than legal consent status — but regulatory/trial documents (ICH, EMA) narrow it further to ages 12–18 for drug development purposes, showing how the same word shifts range depending on whether the context is public health surveillance or pharmaceutical regulation.

Domain-specific differences: Cancer research, drug development, and epidemiological analysis

The same three terms take on different operative meanings depending on whether the context is *disease classification*, *regulatory drug development*, or *population-level epidemiological analysis*. These are not interchangeable uses — a person can be "pediatric" for FDA regulatory purposes, and a "child" for one epidemiological registry but not another, all at the same age.

In cancer research (classification & clinical trial design)

Term	How it's used in cancer research	Citation
Pediatric (cancer)	Refers to the overall population eligible for pediatric-designed cooperative group trials (e.g., Children's Oncology Group), which frequently enroll patients into their 20s or 30s for cancers that are biologically "pediatric-type" regardless of the patient's current age	FDA, 2026
Children (cancer)	Classified using the **International Classification of Childhood Cancer (ICCC)**, historically ages 0–14; cancer registries classify childhood tumors predominantly by **histology/morphology** rather than by primary site, unlike adult cancer classification	NCI, n.d
Adolescent (cancer)	The international successor classification, **ICCC-3**, extended the target age range to 0–19 specifically to better capture adolescent tumor types, while some registries still cap at 0–14 if they don't collect data on patients 15+	IARC, n.d.

Key difference from the general definitions: In cancer research, age cutoffs are driven by **tumor biology and trial-access patterns**, not legal or developmental criteria. A 25-year-old with a pediatric-type sarcoma may be enrolled on a "pediatric" cooperative group trial, while a 16-year-old with an adult-type cancer (e.g., colorectal) may be treated on an adult protocol — the disease type, not the age alone, often determines which classification applies.

In drug development (regulatory/legal definitions)

Term	How it's used in cancer research	Citation
Pediatric (drug development)	The formal regulatory category triggering **PREA** (Pediatric Research Equity Act) study requirements and **BPCA** (Best Pharmaceuticals for Children Act) exclusivity incentives; FDA's operative pediatric age band is generally birth through 16 years under 21 CFR 201.57, though ICH E11(R1) allows regional variation to 18	FDA, 2023
Children (drug development)	Distinct sub-band within FDA/ICH's pediatric classification (roughly 2–11 years), used to determine age-appropriate formulation, dosing, and pharmacokinetic study design separate from adolescents	Lehmann, 2008
Adolescent (drug development)	A distinct ICH E11(R1) sub-band (12–18) requiring its own PK/dosing consideration, since drug metabolism, growth, and puberty-related physiology differ meaningfully from younger children	Lehmann, 2008

Key difference from the general definitions: Drug development definitions are **statute-driven and often target-based rather than age-based** — the RACE Act specifically requires pediatric study of adult oncology drugs based on molecular target biology, meaning the regulatory trigger has nothing to do with whether the *cancer* is one that occurs in children, only whether the drug's *mechanism* is relevant to a pediatric cancer.

In epidemiological analysis (surveillance & population data)

Term	How it's used in cancer research	Citation
Pediatric (epidemiology)	Often operationalized simply as "ages 0–19" in population-based cancer surveillance (e.g., SEER historically studies "patients below the age of 20"), a broader working definition than the clinical/legal ones	Sultan, 2025
Children (epidemiology)	SEER and similar registries commonly stratify incidence into fine-grained bands (<1, 1–4, 5–9, 10–14 years) for children specifically, separate from the 15–19 "adolescent" stratum, allowing analysis of how incidence and survival differ even within the pediatric age range	Howlander, 2021
Adolescent (epidemiology)	Frequently isolated as its own 15–19 stratum in cancer surveillance because this group shows measurably different incidence and survival trends than younger children — historically the "neglected age group" whose cancers didn't fit neatly into either pediatric or adult surveillance systems	IARC, n.d.

Key difference from the general definitions: Epidemiological age bands are chosen to **maximize statistical and pattern-detection value**, not to reflect legal or developmental thresholds — registries often subdivide into narrow bands (single years or 5-year strata) specifically because incidence, survival, and tumor type shift meaningfully even within what clinical or legal definitions would treat as a single pediatric/adolescent category.

References:

European Medicines Agency. (2026, April 15). Procedural advice on paediatric applications: Guidance for applicants (EMA/672643/2017 Rev. 15). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-paediatric-applications_en.pdf

European Union. (2006). Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive No. 2001/20/EC, Directive No. 2001/83/EC and Regulation (EC) No. 726/2004. https://www.wipo.int/wipolex/en/legislation/details/5940

Food and Drug Administration. (2000). E11 clinical investigation of medicinal products in the pediatric population. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population

Food and Drug Administration. (2014). Premarket assessment of pediatric medical devices: Guidance for industry and FDA staff. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-assessment-pediatric-medical-devices

Food and Drug Administration. (2023a). Pediatric drug development: Regulatory considerations—Complying with the Pediatric Research Equity Act and qualifying for pediatric exclusivity under the Best Pharmaceuticals for Children Act. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-drug-development-regulatory-considerations-complying-pediatric-research-equity-act-and

Food and Drug Administration, Oncology Center of Excellence. (2026, February 18). Pediatric oncology program. https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

Howlader, N., Noone, A. M., Krapcho, M., et al. (2021). Childhood cancer by the ICCC. In SEER Cancer Statistics Review, 1975–2018. National Cancer Institute. https://seer.cancer.gov/archive/csr/1975_2018/results_merged/sect_02_childhood_cancer_iccc.pdf

International Agency for Research on Cancer. (n.d.). Highlights. In International Incidence of Childhood Cancer (IICC-3). https://iicc.iarc.fr/about-iicc-3/highlights/

Lehmann, B. (2008). Regulation (EC) No 1901/2006 on medicinal products for paediatric use & clinical research in vulnerable populations. Child and Adolescent Psychiatry and Mental Health, 2(1), 37. https://doi.org/10.1186/1753-2000-2-37

National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program. (n.d.). International Classification of Childhood Cancer (ICCC). https://seer.cancer.gov/iccc/

Sultan, I., Alfaar, A. S., Sultan, Y., et al. (2025). Trends in childhood cancer: Incidence and survival analysis over 45 years of SEER data. PLOS ONE, 20(1), e0314592. https://doi.org/10.1371/journal.pone.0314592

U.S. Department of Health and Human Services. (n.d.-a). 45 CFR Part 46, Subpart D: Additional protections for children involved as subjects in research. Electronic Code of Federal Regulations. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46/subpart-D

U.S. Department of Health and Human Services. (n.d.-b). 45 CFR § 46.402: Definitions. Electronic Code of Federal Regulations. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46/subpart-D/section-46.402

United Nations High Commissioner for Human Rights. (1989, November 20). Convention on the Rights of the Child. United Nations. https://www.ohchr.org/en/instruments-mechanisms/instruments/convention-rights-child

World Health Organization. (2022, June 23). Adolescent health. https://www.who.int/health-topics/adolescent-health/

World Health Organization. (n.d.). Adolescent sexual and reproductive health and rights. https://www.who.int/teams/sexual-and-reproductive-health-and-research-%28srh%29/areas-of-work/adolescent-and-sexual-and-reproductive-health-and-rights

World Health Organization Regional Office for South-East Asia. (n.d.). Adolescent health. https://www.who.int/southeastasia/health-topics/adolescent-health

Major Cancer Types

Pediatric cancer comprises dozens of different types of cancer, some with additional subtypes based on molecular characteristics. This appendix provides more detailed information about the major types of pediatric cancer, including specific statistics and, where available, information about subtypes and causes.

Leukemia and lymphoma

Leukemia is a cancer of blood-forming cells arising in the bone marrow. Lymphomas are cancers of a certain type of white blood cell (lymphocyte) that can arise anywhere lymphocytes can be found, including bone marrow, lymph nodes, the spleen, the intestines, and other areas of the lymphatic system. Leukemias and lymphomas are classified according to the type of cell that is exhibiting uncontrolled growth.

The two most common types of leukemia in children (0-14 years) and adolescents (15-19 years) are acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). Chronic leukemias are very rare in children and adolescents. ALL accounts for about 77% of leukemia cases in children and 50% of leukemia cases in adolescents. Acute myeloid leukemia (AML) is less common in children than ALL, comprising about 14% of leukemia cases in children and 29% in adolescents. There are two types of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL accounts for about 37% of lymphomas in children and about 65% in adolescents, while NHL accounts for 63% of lymphomas in children and 34% of lymphomas in adolescents. (Siegel, 2026)

Acute lymphocytic leukemia (ALL)

An estimated 2,820 children and adolescents combined will be diagnosed with ALL in the U.S. in 2026 (Table A-2). ALL is the most common cancer in children, accounting for 22% of cancers diagnosed in ages 0-14. (Siegel, 2026) ALL is a cancer of lymphocytes, a type of white blood cell. Most often ALL in children involves B lymphocytes, the type of lymphocyte that makes antibodies to infections, but ALL in children can also involve T lymphocytes, which help the body fight disease in other ways.

ALL occurs in children throughout the world, but it is more common in industrialized countries than in developing countries. In the U.S., ALL is more common in boys than in girls, and incidence rates are higher in Hispanic and White children than in African American children. In industrialized countries, there is a sharp peak in ALL incidence rates at ages 2-4, which is not apparent among children in developing countries. (Marcotte, 2022)

Improved treatment for ALL in childhood has increased the 5-year survival rate from 57% in 1975–1979 to 90% in 2015–2021 (Table A-4).

Acute myeloid leukemia

An estimated 660 children and adolescents combined will be diagnosed with AML in the U.S. in 2026 (Table A-2). AML arises from cells of the myeloid lineage, which includes all types of blood cells except lymphocytes. The incidence of AML is highest in the first year of life. Incidence rates for AML are slightly higher in Hispanic children and American Indians and Alaskan Natives compared to other racial/ethnic groups.

Children with AML and high white blood cell counts may develop symptoms due to impaired transit of cancer cells (blasts) through small blood vessels (leukostasis). (Karol, 2024) Many AML patients are prone to excessive bleeding and other blood clotting disorders. Five-year survival rates for AML have improved in recent decades, from roughly 20% in the 1970s to 70% today, but remain lower than for ALL (see Table A-4).

Hodgkin lymphoma

An estimated 1,090 children and adolescents combined will be diagnosed with Hodgkin lymphoma (HL) in 2026 (Table A-2). HL is a cancer of lymphocytes that often starts in the lymph nodes in the chest, neck, or abdomen. There are two major types of HL: classic, which is the most common and is characterized by the presence of multinucleated giant cells called Reed-Sternberg cells, and nodular lymphocyte predominant, which is characterized by so-called "popcorn cells," which are variants of Reed-Sternberg cells that have a popcorn-like appearance. This type is rare and tends to be slower growing than the classic form. (Kahn, 2024)

HL is rare among children younger than age 5; incidence rates increase slightly up to about age 10 and then rise rapidly through adolescence. HL is the most common cancer in adolescents, accounting for about 11% of cancers diagnosed between ages 15 and 19. (Siegel, 2026) Incidence rates for HL are about 30%-55% higher among White children and adolescents than for other racial and ethnic groups. Risk factors for HL include infection with the Epstein Barr virus (EBV) or having a personal history of mononucleosis and human immunodeficiency virus (HIV) infection.

Survival rates for HL increased from 87% in 1975–1979 to nearly 98% in 2015–2021 (Table A-4). Depending on the treatment received, long-term and late effects of treatment include pulmonary and cardiac diseases, thyroid abnormalities, infertility, and second cancers. Girls age 10 and older and young women treated with radiation to the chest for HL have an exceptionally high relative and absolute risk of developing breast cancer, with cumulative incidence reaching 10%–20% by age 40. (Moskowitz, 2020) The International Late Effects of Childhood Cancer Guideline Harmonization Group recommends annual mammography, breast MRI, or both beginning at age 25, or 8 years after chest radiotherapy, whichever occurs later, for women who received chest radiation doses of 20 Gy or higher. (Moskowitz, 2020)

Non-Hodgkin lymphoma

An estimated 1,100 children and adolescents combined will be diagnosed with NHL in 2026 (Table A-2). Both the incidence and distribution of NHL subtypes vary throughout the world. For example, in equatorial Africa, lymphomas account for nearly one-half of childhood cancers, reflecting the very high incidence of Burkitt's lymphoma (BL). The high incidence of BL in equatorial Africa is associated with high rates of co-infection with EBV and malaria. (El-Mallawany, 2018) BL in Africa, also known as endemic BL, is much more common in boys than in girls and often arises in the jaw or around the eyes. In the U.S., the incidence is also much higher in boys than in girls, but the abdomen is the most common site of origin, and African American children are at lower risk than non-Hispanic Whites.

EBV infection is also associated with many other types of NHL, although not as strongly as for BL in Africa. Immunosuppression from a variety of causes increases the risk of NHL, including inherited immunodeficiency disorders, human immunodeficiency virus (HIV) infection, and post-transplantation immune suppression. (Gross, 2010) Survival rates for NHL in children and adolescents have increased dramatically in recent decades: from 47% in 1975–1979 to 90% in 2015–2021 (Table A-4). Long-term and late effects of NHL include anthracycline-related heart damage, cognitive effects, infertility, and low bone density.

Brain and central nervous system tumors (CNS tumors)

An estimated 2,350 children and adolescents combined will be diagnosed with malignant CNS tumors in the U.S. in 2026 (Table A-2). Malignant CNS tumors are the second most common cancer in children, accounting for 17% of cases, and the fourth most common cancer type in adolescents, accounting for 8% of cases. (Siegel, 2026) CNS tumors are classified by histologic type and grade (according to features indicative of aggressiveness) ranging from I (low) to IV (high). Symptoms of benign tumors and side effects of treatment can be quite severe; therefore, since 2004 cancer registries have been collecting data for benign as well as malignant CNS tumors. Three common types of brain and CNS tumors in children and adolescents are:

- **Astrocytomas**, the most common type of CNS tumor, account for 35% of CNS tumors in ages 0-19. These tumors arise from brain cells called astrocytes, star-shaped glial cells that normally support the nerve cells in the brain. Astrocytomas range from low grade to high grade, and the current WHO classification divides

pediatric gliomas into pediatric-type diffuse low-grade gliomas, pediatric-type diffuse high-grade gliomas, and circumscribed astrocytic gliomas. (Chiang & Harreld, 2021) Pilocytic astrocytoma, the most common type of astrocytoma in children, is a low-grade tumor that typically arises in the cerebellum. **Fibrillary astrocytoma**, another type of astrocytoma common in children, is usually found in the mid-brain, has less well-defined borders, and can spread throughout both sides of the brain. (Chiang & Harreld, 2021)

- **Medulloblastoma** is more common in children under the age of 10 than in older children and adolescents. It is a highly invasive embryonal tumor that arises in the cerebellum and tends to disseminate throughout the central nervous system early in its course. It is now recognized as a biologically heterogeneous family of diseases defined by four principal molecular subgroups (WNT, SHH, Group 3, and Group 4) with distinct clinical outcomes. (Sabet, 2026)

- **Ependymoma** is a tumor that begins in the ependymal lining of the ventricular system (fluid-filled cavities in the brain) or the central canal of the spinal cord. Ependymomas range from low to high grade, and molecular classification has revealed this to be a complex diagnostic entity comprising multiple distinct biological subgroups rather than a single disease. (Hwang, 2023)

Five-year survival rates for brain and CNS tumors vary depending on tumor type, location, and grade. In more recent SEER data, 5-year survival is approximately 87% for astrocytoma overall, with low-grade subtypes such as pilocytic astrocytoma faring considerably better than higher-grade forms; 83% for neuroblastoma; and 82% for ependymoma (Table A-4). (Sultan, 2025) However, the prognosis for diffuse intrinsic pontine glioma (DIPG) remains dismal, with most children surviving less than 12 months from diagnosis. (Hoffman, 2018)

Embryonal tumors

Embryonal tumors arise from cells that are normally present in the developing embryo and originate in developing tissues and organ systems. These tumors are usually diagnosed in children before age 5. Three common types of embryonal tumors in children are neuroblastoma, Wilms tumor, and retinoblastoma. Other embryonal tumors, including medulloblastoma and rhabdomyosarcoma, are discussed in other sections of this report.

Neuroblastoma

An estimated 670 cases of neuroblastoma will be diagnosed among children and adolescents in the U.S. in 2026 (Table A-2). It is the third most common childhood cancer, representing 6% of the total cases in this age group. (Siegel, 2026) Neuroblastoma is the most common cancer diagnosed during the first year of life; it is very uncommon after age 10. Neuroblastoma is an embryonal malignancy of the sympathetic nervous system (the system that controls heart rate and breathing), derived from a type of nerve cell known as primitive neural crest cells. The incidence of neuroblastoma is slightly higher in boys than girls and substantially higher in non-Hispanic Whites than children of other races/ethnicities. Siblings of children with neuroblastoma are nearly 10 times more likely to be diagnosed with the disease than children without affected siblings. (Kamihara, 2024)

Neuroblastoma can metastasize through the lymph system and blood, and over half of children have regional or distant spread of their cancer at diagnosis. (Ross, 2025) A rare form of neuroblastoma (stage 4S) occurs in infants with a specific pattern of metastatic disease and often regresses with little or no treatment. Overall survival rates for neuroblastoma have increased from 54% in 1975-1979 to 83% in 2015–2021 (Table A-4). Children treated for high-risk disease have the greatest risk of treatment-related complications, including severe hearing loss, infertility, cardiac toxicity, and second cancers related to the use of high-dose chemotherapy. (Ross, 2025)

Wilms Tumor

An estimated 470 cases of Wilms tumor (WT) will be diagnosed among children in the U.S. in 2026 (Table A-2). Also called nephroblastoma, WT is an embryonal tumor of the kidney that usually occurs in children under age 5 years. The vast majority of kidney tumors in this age group are WT. The incidence rate of WT is slightly higher in girls than boys and in African American children compared to children of other races/ethnicities. WT is bilateral (occurring in both kidneys) in about 5%–10% of cases. About 10%

of cases are associated with a birth defect or congenital anomaly, such as urogenital tract abnormalities, aniridia, or overgrowth syndromes. (Smith, 2025)

The majority of children with WT are diagnosed with an asymptomatic abdominal mass that is incidentally noted while bathing or dressing the child. WT may spread locally or through the bloodstream; distant metastases are uncommon at diagnosis. Survival rates for WT increased from 75% in 1975–1979 to 93% in 2015–2021 (Table A-4). Late effects observed among survivors of WT include heart damage, diminished lung function, end-stage renal failure, reduced fertility and pregnancy complications among girls treated with radiation, and an increased risk of second cancers. (Smith, 2025)

Retinoblastoma

An estimated 220 children will be diagnosed with retinoblastoma in the US in 2026 (Table A-2). Retinoblastoma is a cancer that starts in the retina, the light-sensitive tissue lining the back of the eye. Retinoblastoma usually occurs in children under age 5 and accounts for 6% of cancers in this age group. The incidence of retinoblastoma is similar in boys and girls, does not vary substantially by race and ethnicity, and has been stable in the US population since 1975. Possible symptoms of retinoblastoma include "white pupil," in which the pupil of the eye appears white instead of red when light shines into it, eye pain or redness, and vision problems.

Retinoblastoma occurs in heritable and nonheritable forms; about 45% of retinoblastomas are heritable, caused by a germline pathogenic variant in the RB1 gene. Genetic counseling should be an integral part of the therapy for the family of a patient with retinoblastoma. Patients who carry a germline RB1 mutation have an increased risk of second cancers, especially if they receive radiation therapy. (Kamihara, 2025) Five-year observed survival rates for retinoblastoma have increased from 92% in 1975–1979 to 96% in 2015-2021 (Table A-4). Late effects of retinoblastoma include visual impairment and increased risks of second cancers, including bone and soft tissue sarcomas and melanoma. (Kamihara, 2025)

Sarcomas of bone and soft tissue

Sarcomas are tumors that develop from connective tissues in the body, such as muscles, fat, bones, and membranes that line the joints, or blood vessels. An estimated 700 children and adolescents combined will be diagnosed with malignant bone tumors in 2026 (Table A-2). The two most common types of bone tumors in children and adolescents are osteosarcoma and Ewing sarcoma. The most common type of soft tissue sarcoma is rhabdomyosarcoma; rhabdomyosarcoma and other soft tissue sarcomas together account for about 7% of childhood cancers (ages 0-19), or roughly 1,070 cases annually (Table A-2). Another type of soft tissue sarcoma, Kaposi sarcoma, while extremely rare among children in the US, is very common in children in Africa due in part to the high prevalence of HIV infection. (El-Mallawany, 2018; Reiner, 2022)

Osteosarcoma

Osteosarcoma (OS) is the most common type of bone cancer in children and adolescents. The incidence of osteosarcoma increases with age throughout childhood and adolescence; it is very rare among children under age 5. The incidence of OS is slightly higher in boys than girls and also higher in African American and Hispanic children than in white and Asian/Pacific Islander children. OS arises from primitive bone-forming stem cells and usually develops in areas where the bone is growing, such as near the ends of the long bones around the knee. OS commonly appears as sporadic pain in the affected bone that may worsen at night or with activity, with progression to local swelling.

Risk factors for osteosarcoma include prior radiation treatment for another tumor. Radiation-associated osteosarcomas usually occur 7 to 15 years after successful treatment of the primary tumor.

About 20% of patients have detectable metastases at diagnosis, most commonly in the lung. The 5-year survival rate for osteosarcoma is 66% and 62% for children and adolescents respectively (Table A-3). Therapy-related late effects can include heart damage, hearing loss, kidney dysfunction, second cancers, and infertility, especially in patients receiving alkylating agents. Patients treated for osteosarcoma may also have physical limitations resulting from surgery.

Ewing sarcoma

Ewing sarcoma (ES) is the second most common malignant bone tumor in children and adolescents. It is more common among older children and adolescents than young children. Notably, incidence rates of ES are markedly lower among children of African and East Asian ancestry than among children of European ancestry, with smaller differences compared with Hispanic children. (Spector, 2021) ES is a highly aggressive cancer, characterized by genetic translocations involving a specific genetic breakpoint region (*EWSR1*).

ES tumors arise about equally in bones of the extremities and those in other parts of the body and may also arise in soft tissues. The first symptom is usually pain at the tumor site, sometimes along with a mass or swelling. Metastases are present in about 25% of patients at diagnosis; the most common metastatic sites are the lungs, bone, and bone marrow. Survival rates for ES have increased from 42% to 76% (Table A-4). ES survivors are at increased risk for developing a second cancer, cardiac and pulmonary conditions, infertility, and musculoskeletal problems.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a cancer made up of cells that normally develop into skeletal muscles; an estimated 330 cases will be diagnosed in 2025 (Table A-2). This cancer accounts for 3% of childhood cancers and 2% of adolescent cancers. There are two major subtypes of RMS: embryonal RMS (about 75% of cases), whose incidence is highest in children under age 5, and alveolar RMS (about 16% of cases), whose incidence does not vary by age in children and adolescents. (Chen, 2025) Embryonal RMS most commonly occurs in the head and neck, whereas alveolar RMS is most common in the trunk and extremities. The first symptoms often include pain and/or a mass or swelling at the site of origin. RMS is associated with a number of genetic syndromes, including Li-Fraumeni syndrome and neurofibromatosis type 1.

Survival has improved for RMS, from 49% in 1975–1979 to 64% in 2015-2021 (Table A-4), yet it remains lower than many other pediatric cancers. RMS is classified as low-, intermediate-, and high-risk based on site, stage at diagnosis, presence of metastases, histology, and fusion status. Late effects of treatment for RMS depend on whether radiation therapy was given and the specific chemotherapy agents received, which have varied over time.

Gonadal germ cell tumors

Gonadal germ cell tumors are a diverse group of tumors that arise from either the ovaries in girls or the testicles in boys. These tumors are more common in adolescents than in young children and occur more frequently in boys than girls.

Ovarian germ cell tumors

An estimated 190 adolescent girls will be diagnosed with ovarian germ cell (OGC) tumors in 2026 (Table A-2). OGC tumors are more common in girls ages 10–14 and adolescents than in younger girls. The risk of ovarian tumors is increased among individuals with several genetic syndromes involving sex chromosomes, including Turner syndrome and Swyer syndrome (Travis, 2024). OGC tumors often cause abdominal pain and swelling and weight gain. The 5-year observed survival rate is 98% (Table A-4). Ovarian and testicular germ cell tumors show marked responsiveness to cisplatin-based chemotherapy, which may cause hearing loss and kidney damage as late effects. (Travis, 2024)

Testicular germ cell tumors

An estimated 450 testicular germ cell tumors (TGCT) will be diagnosed in boys ages 0-19 in 2026 (Table A-2). TGCT is the most common cancer in adolescent boys ages 15–19, and testicular cancer overall is the most common solid malignancy in young men in the U.S. The incidence of TGCT is higher among whites and Hispanics than among African Americans. There are two major types of TGCT: non-seminomas (accounting for the majority of TGCT in adolescents) and seminomas. (Singla, 2025) A lump on the testicle is usually the first sign and often leads to diagnosis at an early stage. Patients with testicular GCT have 5-year survival rates of 99%, 92%, and 85% for stages I, II, and III, respectively. (Singla, 2025)

Risk factors for TGCT include a history of cryptorchidism (undescended testicle) and a family history of testicular cancer. (Singla, 2025) Survival rates for adolescent testicular cancer have improved substantially since the mid-1970s (from 74% to 97% in 2015-2021, Table A-4), and most patients have a good prognosis.

References

Chen, S., Kelsey, A. M., & Rudzinski, E. R. (2025). Rhabdomyosarcoma in children and young adults. *Virchows Archiv, 486*(1), 101–116. doi.org/10.1007/s00428-024-03961-y

Chiang, J. C. H., & Harreld, J. H. (2021). Classification and treatment of pediatric gliomas in the molecular era. *Children, 8*(9), Article 739. doi.org/10.3390/children8090739

El-Mallawany, N. K., McAtee, C. L., Campbell, L. R., et al. (2018). Pediatric Kaposi sarcoma in context of the HIV epidemic in sub-Saharan Africa: Current perspectives. *Pediatric Health, Medicine and Therapeutics, 9*, 35–46. doi.org/10.2147/PHMT.S142816

Gross TG, Perkins SL. Malignant Non-Hodgkin Lymphomas in Children. (2010) In: Pizzo PA, Poplack DG, editors. Principles and Practise of Pediatric Oncology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2010:663-682.

Hoffman, L. M., Veldhuijzen van Zanten, S. E. M., Colditz, N., et al. (2018) Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma (DIPG): A collaborative report from the International and European Society for Pediatric Oncology DIPG Registries. Journal of Clinical Oncology, 36(19), 1963–1972. doi.org/10.1200/JCO.2017.75.9308

Hwang, E. I., Hanson, D., Filbin, M. G., & Mack, S. C. (2023). Why haven't we solved intracranial pediatric ependymoma? Current questions and barriers to treatment advances. *Neoplasia, 39*, Article 100895. doi.org/10.1016/j.neo.2023.100895

Kahn, J. M., Mauz-Korholz, C., Hernandez, T., et al. (2024). Pediatric and adolescent Hodgkin lymphoma: Paving the way for standards of care and shared decision making. *American Society of Clinical Oncology Educational Book, 44*, Article e432420. doi.org/10.1200/EDBK_432420

Kamihara, J., Diller, L. R., Foulkes, W. D., et al. (2024) Neuroblastoma predisposition and surveillance—An update from the 2023 AACR Childhood Cancer Predisposition Workshop. *Clinical Cancer Research, 30*(15), 3137–3143. doi.org/10.1158/1078-0432.CCR-24-0237

Kamihara, J., Schienda, J., & McGee, R. B. (2025). Update on retinoblastoma predisposition and surveillance recommendations for children. *Clinical Cancer Research, 31*(9), 1573–1579. doi.org/10.1158/1078-0432.CCR-24-3271

Karol, S. E. (2024). Pediatric acute myeloid leukemia—Novel approaches. *Current Opinion in Hematology, 31*(2), 47–52. doi.org/10.1097/MOH.0000000000000795

Marcotte, E. L., Domingues, A. M., Sample, J. M., et al. (2022). Racial and ethnic disparities in pediatric cancer incidence among children and young adults in the United States by single year of age. *Cancer, 128*(11), 2129–2138. doi.org/10.1002/cncr.34163

Moskowitz, C. S., Chou, J. F., Neglia, J. P., et al. (2020). Updated breast cancer surveillance recommendations for female survivors of childhood, adolescent, and young adult cancer from the International Guideline Harmonization Group. *Journal of Clinical Oncology, 38*(35), 4104–4112. doi.org/10.1200/JCO.20.00562

Reiner, A. S., Panageas, K. S. (2022). Kaposi sarcoma in the United States: Understanding disparate risk. *JNCI Cancer Spectrum, 6*(6), Article pkac079. doi.org/10.1093/jncics/pkac079

Ross, D. J., AlKhazal, A., Chohan, S., et al. (2025). Emerging clinical and research approaches in targeted therapies for high-risk neuroblastoma. *Frontiers in Oncology, 15*, Article 1553511. doi.org/10.3389/fonc.2025.1553511

Sabet, K., Lovell, H., & Fonseca, A. (2026). Pediatric medulloblastoma. *Child's Nervous System, 42*, Article 271. doi.org/10.1007/s00381-026-07376-9

Siegel, R. L., Kratzer, T. B., Wagle, N. S., Sung, H., & Jemal, A. (2026). Cancer statistics, 2026. *CA: A Cancer Journal for Clinicians, 76*(1), Article e70043. doi.org/10.3322/caac.70043

Singla, N., Bagrodia, A., Baraban, E., et al. (2025). Testicular germ cell tumors: A review. *JAMA, 333*(9), 793–803. doi.org/10.1001/jama.2024.27122

Smith, V., Wahba, A., Chintagumpala, M., & Mahajan, P. (2025). A review of Wilms tumor. *Pediatrics in Review, 46*(4), 206–212. doi.org/10.1542/pir.2024-006444

Spector, L. G., Hubbard, A. K., Diessner, B. J., et al. (2021). Comparative international incidence of Ewing sarcoma 1988 to 2012. *International Journal of Cancer, 149*(5), 1054–1066. doi.org/10.1002/ijc.33674

Sultan, I., Alfaar, A. S., Sultan, Y., Salman, Z., & Qaddoumi, I. (2025). Trends in childhood cancer: Incidence and survival analysis over 45 years of SEER data. *PLoS ONE, 20*(1), Article e0314592. doi.org/10.1371/journal.pone.0314592

Travis, L. B., Feldman, D. R., Fung, C., et al. (2024). Adolescent and young adult germ cell tumors: Epidemiology, genomics, treatment, and survivorship. *Journal of Clinical Oncology, 42*(6), 696–706. doi.org/10.1200/JCO.23.01099

Supplemental Figures

TABLE A-1

Leading causes of death among children and adolescents (1-19 years), United States, 2024

RANK	1–14 YEARS			15–19 YEARS			1–19 YEARS		
		Count	Rate*		Count	Rate*		Count	Rate*
1	Accidents (unintentional injuries)	2766	49.7	Accidents (unintentional injuries)	4235	189.3	Accidents (unintentional injuries)	7001	86.6
2	Malignant neoplasms	1124	20.0	Homicide and legal intervention	2213	98.9	Homicide and legal intervention	2852	35.5
3	Congenital anomalies	830	14.9	Intentional self-harm (suicide)	2106	94.1	Intentional self-harm (suicide)	2597	31.2
4	Homicide and legal intervention	704	12.7	Malignant neoplasms	633	28.3	Malignant neoplasms	1757	22.2
5	Intentional self-harm (suicide)	491	8.5	Diseases of heart	299	13.4	Congenital anomalies	1062	13.7
6	Diseases of heart	314	5.6	Congenital anomalies	232	10.4	Diseases of heart	613	7.7
7	Influenza and pneumonia	281	5.1	Chronic lower respiratory diseases	82	3.7	Influenza and pneumonia	355	4.6
8	Chronic lower respiratory diseases	171	3.0	Diabetes mellitus	75	3.4	Chronic lower respiratory diseases	253	3.2
9	Cerebrovascular diseases	170	3.0	Influenza and pneumonia	74	3.3	Cerebrovascular diseases	226	2.9
10	Septicemia	135	2.4	Cerebrovascular diseases	56	2.5	Septicemia	171	2.2

* Rates are per 1,000,000 and age adjusted to the 2000 US standard population.
Source: National Center for Health Statistics, 2026

TABLE A-2

Pediatric case estimates, United States, 2026

	BIRTH-14 YEARS			15-19 YEARS			BIRTH-19 YEARS		
CANCER TYPE	**Males**	**Females**	**Both**	**Males**	**Females**	**Both**	**Males**	**Females**	**Both**
Acute lymphocytic leukemia	1,340	1,020	2,360	320	140	460	1,660	1,160	2,820
Brain & CNS[1]	1020	830	1850	270	230	500	1,290	1,060	2,350
Non-Hodgkin lymphoma	440	210	650	300	150	450	740	360	1,100
Neuroblastoma (including ganglioneuroblastoma)	360	310	670	*	*	*	--	--	--
Acute myeloid leukemia	240	200	440	120	100	220	360	300	660
Wilms tumor	230	240	470	*	*	*	--	--	--
Bone tumors	240	200	440	140	120	260	380	320	700
Hodgkin lymphoma	220	130	350	380	360	740	600	490	1090
Rhabdomyosarcoma	210	120	330	60	*	*	--	--	--
Retinoblastoma	110	110	220	*	*	*	--	110	--
Testicular germ cell tumor	50	N/A	50	400	N/A	400	450	N/A	450
Thyroid carcinoma	50	180	230	140	600	740	190	780	970
Melanoma	40	40	80	70	110	180	110	150	260
Ovarian germ cell tumor	N/A	90	90	N/A	100	100	N/A	190	190
Hepatic tumors	130	80	210	*	*	*	--	--	--
All other[2]	640	600	1,240	770	680	1,510	1,410	1,280	2,750
TOTAL	**5,320**	**4,360**	**9,680**	**3,020**	**2,640**	**5,660**	**8,340**	**7,000**	**15,340**

TABLE A-3

Changes in pediatric cancer 5-year observed survival rates, United States

	CHILDREN (0–14 YEARS)				ADOLESCENTS (15–19 YEARS)			
	Diagnosed 1975-1979	Diagnosed 2015-2021	Absolute difference	Relative improvement	Diagnosed 1975-1979	Diagnosed 2015-2021	Absolute difference	Relative improvement
All ICCC sites	60%	85%	25%	42%	68%	88%	20%	29%
Leukemia	53%	89%	36%	68%	26%	78%	52%	200%
Acute lymphocytic leukemia	60%	92%	32%	53%	31%	77%	46%	148%
Acute myeloid leukemia	21%	70%	49%	233%	20%	70%	50%	250%
Lymphomas and reticuloendothelial neoplasms	62%	95%	33%	53%	80%	95%	15%	19%
Hodgkin lymphoma	81%	99%	18%	22%	89%	98%	9%	10%
Non-Hodgkin lymphoma	48%	91%	43%	90%	46%	90%	44%	96%
Brain and CNS	58%	74%	16%	28%	60%	78%	18%	30%
Ependymoma	32%	82%	50%	156%	71%	84%	13%	18%
Astrocytoma	72%	87%	15%	21%	60%	78%	18%	30%
Neuroblastoma and ganglioneuroblastoma	53%	83%	30%	57%	67%	89%	22%	33%
Retinoblastoma	92%	96%	4%	4%	*	*		
Wilms tumor	75%	93%	18%	24%	50%	89%	39%	78%
Hepatic tumors	27%	79%	52%	193%	14%	53%	39%	279%
Bone tumors	49%	73%	24%	49%	48%	68%	20%	42%
Osteosarcoma	41%	66%	25%	61%	49%	62%	13%	27%
Ewing Sarcoma	52%	80%	28%	54%	28%	68%	40%	143%
Rhabdomyosarcoma	55%	67%	12%	22%	30%	52%	22%	73%
Testicular germ cell tumors	91%	97%	6%	7%	70%	97%	27%	39%
Ovarian germ cell tumors	87%	97%	10%	11%	67%	98%	31%	46%
Thyroid carcinoma	>99%	>99%	0%	0%	99%	>99%	0%	0%
Melanoma	83%	94%	11%	13%	82%	98%	16%	20%

Source: NCHS, 2026
CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers. Survival rates are based on cases diagnosed during 1975-1979 and 2015-2021, with all cases followed through 2022. *Survival rate could not be calculated due to fewer than 25 cases. Note: Survival rates do not include benign or borderline brain tumors. Absolute difference is the difference between the unrounded observed survival during 1975-1979 and 2015-2021 in percentage points. Relative improvement is the unrounded absolute difference divided by the survival rate during 1975-1979. Source: Surveillance, Epidemiology, and End Results (SEER) program, National Cancer Institute, 2026.

TABLE A-4

Changes in pediatric cancer 5-year observed survival rate, ages birth to 19 years, United States

	YEAR OF DIAGNOSIS			
	1975–1979	2015–2021	Absolute difference	Relative improvement
All ICCC sites	63%	86%	23%	37%
Leukemia	48%	86%	38%	79%
Acute lymphocytic leukemia	57%	90%	33%	58%
Acute myeloid leukemia	21%	70%	49%	233%
Lymphomas and reticuloendothelial neoplasms	72%	95%	23%	32%
Hodgkin lymphoma	87%	98%	11%	13%
Non-Hodgkin lymphoma	47%	90%	43%	91%
Brain and CNS	59%	75%	16%	27%
Ependymoma	37%	82%	45%	122%
Astrocytoma	69%	85%	16%	23%
Neuroblastoma and ganglioneuroblastoma	54%	83%	29%	54%
Retinoblastoma	92%	96%	4%	4%
Wilms tumor	75%	93%	18%	24%
Hepatic tumors	25%	76%	51%	204%
Bone tumors	49%	71%	22%	45%
Osteosarcoma	45%	64%	19%	42%
Ewing Sarcoma	42%	76%	34%	81%
Rhabdomyosarcoma	49%	64%	15%	31%
Testicular germ cell tumors	74%	97%	23%	31%
Ovarian germ cell tumors	75%	98%	23%	31%
Thyroid carcinoma	99%	>99%	0%	0%
Melanoma	83%	96%	13%	16%

CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers. Survival rates are based on cases diagnosed during 1975-1979 and 2015-2021, with all cases followed through 2022. Note: Survival rates do not include benign or borderline brain tumors. Absolute difference is the difference between the unrounded observed survival during 1975-1979 and 2015-2021 in percentage points. Relative improvement is the unrounded absolute difference divided by the survival rate during 1975-1979. Source: Surveillance, Epidemiology, and End Results (SEER) program, National Cancer Institute, 2026.

TABLE A-5

New cancer drugs approved 2016 - 2025 and associated PREA and BPCA activity

Approval year	Proprietary name	Generic name	Sponsor	PREA	WR issued	Approved indication
2016	Tecentriq	atezolizumab	Genentech, Inc.	Waived	Yes	Urothelial carcinoma
	Defitelio	defibrotide sodium	Jazz Pharmaceuticals Inc.	Exempt		Hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome
	Rubraca	rucaparib	Pharmaand GmbH	Exempt		Deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer
	Venclexta	venetoclax	Abbvie Inc.	Exempt	Yes	Chronic lymphocytic leukemia with 17p deletion
2017	Verzenio	abemaciclib	Eli Lilly And Co	Waived	Yes	HR+, HER2- advanced or metastatic breast cancer
	Calquence	acalabrutinib	Astrazeneca Uk Ltd	Exempt		Mantle cell lymphoma
	Bavencio	avelumab	Emd Serono, Inc.	Exempt		Merkel cell carcinoma
	Alunbrig	brigatinib	Takeda Pharmaceuticals Usa Inc.	Exempt		ALK+ metastatic non-small cell lung cancer
	Imfinzi	durvalumab	Astrazeneca Uk Ltd	Waived		Urothelial carcinoma
	Idhifa	enasidenib	Bristol Myers Squibb Company	Exempt		Acute myeloid leukemia with an IDH2 mutation
	Besponsa	inotuzumab ozogamicin	Wyeth Pharmaceuticals LLC	Exempt		B-cell precursor acute lymphoblastic leukemia
	Rydapt	midostaurin, PKC412	Novartis Pharmaceuticals Corp	Exempt	Yes	Aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, mast cell leukemia, acute myeloid leukemia
	Nerlynx	neratinib maleate	Puma Biotechnology Inc.	Waived		HER2-overexpressed/amplified breast cancer
	ZEJULA	niraparib	Glaxosmithkline LLC	Exempt/ Waived		Epithelial ovarian, fallopian tube, or primary peritoneal cancer
	Kisqali	ribociclib	Novartis Pharmaceuticals Corp	Waived	Yes	HR+, HER2- advanced or metastatic breast cancer
2018	Erleada	apalutamide	Janssen Biotech Inc.	Waived		Non-metastatic castration-resistant prostate cancer
	Mektovi	binimetinib	Array Biopharma Inc.	Exempt		Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
	Asparlas	calaspargase pegol-mknl	Servier Pharmaceuticals LLC	Exempt		Acute lymphoblastic leukemia
	LIBTAYO	cemiplimab-rwlc	Regeneron Pharmaceuticals, Inc.	Waived	Yes	Cutaneous squamous cell carcinoma
	Vizimpro	dacomitinib	Pfizer Inc.	Exempt		Metastatic non-small-cell lung cancer with EGFR exon 19 deletion or exon 21 L858R substitution mutations
	COPIKTRA	duvelisib	Secura Bio Inc.	Exempt		Follicular lymphoma, chronic lymphocytic leukemia or small lymphocytic lymphoma
	Braftovi	encorafenib	Array Biopharma Inc.	Exempt		Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
	XOSPATA	gilteritinib	Astellas Pharma Us Inc.	Exempt	Yes	Acute myeloid leukemia with a FLT3 mutation
	Daurismo	glasdegib	Pfizer Inc.	Exempt		Acute myeloid leukemia
	Tibsovo	ivosidenib	Servier Pharmaceuticals LLC	Exempt		Acute myeloid leukemia with a susceptible IDH1 mutation
	Vitrakvi	larotrectinib	Bayer Healthcare Pharmaceuticals Inc.	Exempt	Yes	Solid tumors that have a NTRK gene fusion without a known acquired resistance mutation
	LORBRENA	lorlatinib	Pfizer Inc.	Exempt		ALK-positive metastatic non-small cell lung cancer
	Lutathera	lutetium lu 177 dotatate	Advanced Accelerator Applications Usa Inc.	Exempt	Yes	Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors including foregut, midgut, and hindgut neuroendocrine tumors
	Poteligeo	mogamulizumab-kpkc	Kyowa Kirin, Inc.	Exempt		Mycosis fungoides or Sezary syndrome
	Elzonris	tagraxofusp-erzs	Stemline Therapeutics, Inc.	Exempt		Blastic plasmacytoid dendritic cell neoplasm
	Talzenna	talazoparib	Pfizer Inc.	Waived	Yes	Deleterious or suspected deleterious gBRCAm HER2-negative locally advanced or metastatic breast cancer

TABLE A-5

New cancer drugs approved 2016 - 2025 and associated PREA and BPCA activity

Approval year	Proprietary name	Generic name	Sponsor	PREA	WR issued	Approved indication
2019	Piqray	alpelisib	Novartis Pharmaceuticals Corp	Waived	Yes	HR+, HER2-, PIK3CA-mutated, advanced or metastatic breast cancer
	Nubeqa	darolutamide	Bayer Healthcare Pharmaceuticals Inc.	Waived		Non-metastatic castration resistant prostate cancer
	PADCev	enfortumab vedotin-ejfv	Astellas Pharma Us, Inc.	Waived		Urothelial cancer
	Rozlytrek	entrectinib	Genentech Inc.	Exempt	Yes	Non-small cell lung cancer whose tumors are ROS1-positive
	Balversa	erdafitinib	Janssen Biotech Inc.	Waived		Urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations
	ENHERTU	fam-trastuzumab deruxtecan-nxki	Daiichi Sankyo, Inc.	Waived		HER2-positive breast cancer
	Turalio	pexidartinib	Daiichi Sankyo Inc.	Exempt		Tenosynovial giant cell tumor
	Polivy	polatuzumab vedotin	Genentech, Inc.	Exempt		Diffuse large B-cell lyphoma, not otherwise specified
	XPOVIO	selinexor	Karyopharm Therapeutics Inc.	Exempt		Multiple myeloma
	Brukinsa	zanubrutinib	Beone Medicines Usa Inc.	Exempt		Mantle cell lymphoma
	Inrebic	fedratinib	Impact Biomedicines, Inc.	Exempt		"Intermediate-2 or high-risk primary or secondary (postpolycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)"
2020	Ayvakit	avapritinib	Blueprint Medicines Corp	Exempt		Gastrointestinal stromal tumor harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations
	Tabrecta	capmatinib	Novartis Pharmaceutical Corp	Exempt		Non-small cell lung cancer whose tumors have a mutation that leads to MET exon 14 skipping
	INQOVI	decitabine and cedazuridine	Taiho Oncology Inc.	Exempt		Myelodysplastic syndromes
	Sarclisa	isatuximab-irfc	Sanofi-Aventis U.S. LLC	Exempt		Multiple myeloma
	Zepzelca	lurbinectedin	Jazz Pharmaceuticals Ireland Ltd	Exempt	Yes	Small cell lung cancer
	Pemazyre	pemigatinib	Incyte Corp	Exempt		Cholangiocarcinoma with a FGFR2 fusion or other rearrangement
	Qinlock	ripretinib	Deciphera Pharmaceuticals LLC	Exempt		Gastrointestinal stromal tumor
	Trodelvy	sacituzumab govitecan-hziy	Gilead Sciences, Inc.	Waived		Triple-negative breast cancer
	Retevmo	selpercatinib	Eli Lilly And Co	Exempt	Yes	RET fusion-positive non-small cell lung cancer, RET-mutant medullary thyroid cancer, RET fusion-positive thyroid cancer
	Koselugo	selumetinib	Astrazeneca Pharmaceuticals LP	Assessment		Neurofibromatosis type 1
	Monjuvi	tafasitamab-cxix	Incyte Corporation	Exempt		Diffuse large B-cell lymphoma, not otherwise specified
	Tukysa	tucatinib	Seagen Inc.	Waived		HER2-positive breast cancer, including patients with brain metastases
2020 FDARA IMPLEMENTATION						
2020	**Margenza**	**margetuximab-cmkb**	**Tersera Therapeutics LLC**	**Waived**		**HER2- positive breast cancer**
	DANYELZA	**naxitamab-gqgk**	**Btg International Inc.**	**Exempt**	**Yes**	**High-risk neuroblastoma in the bone or bone marrow**
	GAVRETO	**pralsetinib**	**Rigel Pharmaceuticals Inc.**	**Exempt**		**RET fusion-positive non-small cell lung cancer**
	Orgovyx	**relugolix**	**Sumitomo Pharma America Inc.**	**Waived**		**Prostate cancer**

TABLE A-5

New cancer drugs approved 2016 - 2025 and associated PREA and BPCA activity

Approval year	Proprietary name	Generic name	Sponsor	PREA	WR issued	Approved indication
2021	Rylaze	asparaginase erwinia chrysanthemi (recombinant)-rywn	Jazz Pharmaceuticals Ireland Limited	Deferred		Acute lymphoblastic leukemia and lymphoblastic lymphoma
	Welireg	belzutifan	Merck Sharp And Dohme Corp A Sub Of Merck And Co Inc.	Waived		von Hippel-Lindau disease-associated RCC, CNS hemangioblastoma, ePNET
	Jemperli	dostarlimab-gxly	Glaxosmithkline LLC	Waived		dMMR recurrent or advanced endometrial cancer
	Zynlonta	loncastuximab tesirine	ADC Therapeutics Sa	Partially Waived/ Deferred		Large B-cell lymphoma
	LUMAKRAS	sotorasib	Amgen Inc.	Waived		KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer
	Tepmetko	tepotinib	Emd Serono Inc.	Exempt		Non-small cell lung cancer harboring MET exon 14 skipping alterations
	Tivdak	tisotumab vedotin-tftv	Seagen Inc.	Deferred		Cervical cancer
	Fotivda	tivozanib	Aveo Pharmaceuticals Inc.	Waived		Renal cell carcinoma
	Rybrevant	amivantamab-vmjw	Janssen Biotech, Inc.	Waived		Non-small cell lung cancer with EGFR exon 20 insertion mutations
	Scemblix	asciminib	Novartis Pharmaceuticals Corp	Partially Waived/ Deferred	Yes	Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP); Ph+ CML in CP with the T315I mutation
	Besremi	ropeginterferon alfa-2b-njft	PharmaEssentia Corporation	Exempt		Polycythemia vera
2022	Krazati	adagrasib	Bristol Myers Squibb Company	Exempt		KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer
	Lytgobi	futibatinib	Taiho Oncology Inc.	Partially Waived/ Deferred		Intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements
	Pluvicto	lutetium (177Lu) vipivotide tetraxetan)	Novartis Pharmaceuticals Corp	Waived		PSMA-positive metastatic castration-resistant prostate cancer
	Elahere	mirvetuximab soravtansine-gynx	Abbvie Inc.	Waived		FRa-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
	Lunsumio	mosunetuzumab-axgb	Genentech, Inc.	Waived		Follicular lymphoma
	Opdualag	nivolumab and relatlimab-rmbw	Bristol-Myers Squibb Company	Partially Waived/ Deferred		Melanoma
	Rezlidhia	olutasidenib	Rigel Pharmaceuticals Inc.	Partially Waived/ Deferred		Acute myeloid leukemia with a susceptible IDH1 mutation
	Kimmtrak	tebentafusp-tebn	Immunocore Limited	Waived		Uveal melanoma
	Tecvayli	teclistamab-cqyv	Janssen Biotech, Inc.	Waived		Multiple myeloma
	Imjudo	tremelimumab	Astrazeneca Ab	Deferred		Hepatocelluar carcinoma
2023	Truqap	capivasertib	Astrazeneca Pharmaceuticals LP	Partially Waived/ Deferred		HR-positive, HER2-negative, locally advanced or metastatic breast cancer
	Orserdu	elacestrant	Stemline Therapeutics Inc.	Waived		ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer
	Elrexfio	elranatamab-bcmm	Pfizer Inc.	Exempt		Multiple myeloma

TABLE A-5

New cancer drugs approved 2016 - 2025 and associated PREA and BPCA activity

Approval year	Proprietary name	Generic name	Sponsor	PREA	WR issued	Approved indication
2023	Epkinly	epcoritamab-bysp	Genmab Us, Inc.	Partially Waived/ Deferred		Diffuse large B-cell lymphoma, not otherwise specified
	Fruzaqla	fruquintinib	Takeda Pharmaceuticals Usa Inc.	Waived		Colorectal cancer
	Columvi	glofitamab-gxbm	Genentech, Inc.	Partially Waived/ Deferred		Diffuse large B-cell lymphoma, not otherwise specified or large B-cell lymphoma arising from follicular lymphoma
	Jaypirca	pirtobrutinib	Loxo Oncology Inc.	Exempt		Mantle cell lymphoma
	Vanflyta	quizartinib	Daiichi Sankyo Inc.	Partially Waived/ Deferred	Yes	Acute myeloid leukemia that is FLT3 internal tandem duplication (ITD)-positive
	Augtyro	repotrectinib	Bristol Myers Squibb Company	Deferred		ROS1-positive non-small cell lung cancer
	Zynyz	retifanlimab-dlwr	Incyte Corporation	Waived		Merkel cell carcinoma
	Talvey	talquetamab-tgvs	Janssen Biotech, Inc.	Exempt		Multiple myeloma
	Loqtorzi	toripalimab-tpzi	Coherus Biosciences, Inc.	Waived		Nasopharyngeal carcinoma
	Ojjaara	momelotinib	GlaxoSmithKline LLC	Exempt		Intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)]
2024	Unloxcyt	cosibelimab-ipdl	Checkpoint Therapeutics, Inc.	Waived		Cutaneous squamous cell carcinoma
	Ensacove	ensartinib	Xcovery Holdings Inc.	Partially Waived/ Deferred		Non-small cell lung cancer
	Rytelo	imetelstat	Geron Corp	Partially Waived/ Deferred		Low- to intermediate-1 risk myelodysplastic syndromes with transfusion-dependent anemia
	Itovebi	inavolisib	Genentech Inc.	Waived		Endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer
	Lazcluze	lazertinib	Janssen Biotech Inc.	Waived		Non-small cell lung cancer with EGFR exon 19 deletions or exon 21 L858R substitution mutations
	Anktiva	nogapendekin alfa inbakicept-pmln	Altor Bioscience, LLC, An Indirect Wholly-Owned Subsidiary Of Immunitybio, Inc.	Waived		BCG-unresponsive nonmuscle invasive bladder cancer
	Revuforj	revumenib	Syndax Pharmaceuticals Inc.	Partially Waived/ Assessment		Acute leukemia with a KMT2A translocation
	IMDELLTRA	tarlatamab-dlle	Amgen Inc.	Exempt		Extensive stage small cell lung cancer
	Tevimbra	tislelizumab-jsgr	Beone Medicines Usa, Inc.	Waived		Esophageal squamous cell carcinoma
	Ojemda	tovorafenib	Day One Biopharmaceuticals Inc.	Exempt		Pediatric low-grade glioma harboring a BRAF fusion or rearrangement, or BRAF V600 mutation
	Voranigo	vorasidenib	Servier Pharmaceuticals LLC	Waived		Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation
	Ziihera	zanidatamab-hrii	Jazz Pharmaceuticals Ireland Limited	Waived		HER2-positive (IHC3+) biliary tract cancer
	Bizengri	zenocutuzumab-zbco	Partner Therapeutics Inc.	Waived		Non-small cell lung cancer harboring a NRG1 gene fusion; Pancreatic adenocarcinoma harboring an NRG1 gene fusion
	Vyloy	zolbetuximab-clzb	Astellas Pharma Us, Inc.	Exempt		HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are CLDN 18.2 positive

TABLE A-5

New cancer drugs approved 2016 - 2025 and associated PREA and BPCA activity

Approval year	Proprietary name	Generic name	Sponsor	PREA	WR issued	Approved indication
2025	Avmapki Fakzynja Co-Pack	avutometinib capsules, 0.8 mg; defactinib, 200 mg	Verastem Inc.	Partially Waived/ Deferred		KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC)
	Datroway	datopotamab deruxtecan-dlnk	Daiichi Sankyo, Inc.	Waived		HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer
	Modeyso	dordaviprone	Chimerix Inc.	Partially Waived/ Assessment		Diffuse midline glioma harboring an H3 K27M mutation
	Inluriyo	imlunestrant	Eli Lilly And Co	Waived		ER-positive, HER2 negative, ESR1-mutated advanced or metastatic breast cancer
	Lynozyfic	linvoseltamab-gcpt	Regeneron Pharmaceuticals, Inc.	Exempt		Multiple myeloma
	Gomekli	mirdametinib	Springworks Therapeutics Inc.	Exempt		NF1 who have symptomatic plexiform neurofibromas
2025	Keytruda Qlex	pembrolizumab and berahyaluronidase alfa-pmph	Merck Sharp & Dohme LLC	Partially Waived/ Assessment		Subcutaneous formulation of Keytruda (pembrolizumab) approved for all approved Keytruda solid tumor indications: melanoma, non-small cell lung cancer, malignant pleural mesothelioma, head and neck squamous cell cancer, urothelial cancer, MSI-H or dMMR, microsatellite instability-high or mismatch repair deficient colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocelluar carcinoma, biliary tract cancer, merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, cutaneous squamous cell carcinoma, triple-negative breast cancer,
	Hyrnuo	sevabertinib	Bayer Healthcare Pharmaceuticals Inc.	Waived		Non-squamous, non-small cell lung cancer whose tumors have HER2 (ERBB2) TKD activating mutations
	Zegfrovy	sunvozertinib	Dizal Pharmaceutical Co Ltd	Waived		Non-small cell lung cancer with EGFR exon 20 insertion mutations
	Ibtrozi	taletrectinib	Nuvation Bio Inc.	Deferred		ROS1-positive non-small cell lung cancer
	Emrelis	telisotuzumab vedotin-tllv	Abbvie Inc.	Waived		Non-squamous non-small cell lung cancer with high c-Met protein overexpression [=50% of tumor cells with strong (3+) staining]
	Grafapex	treosulfan	Medexus Pharma Inc.	Exempt		Preparative regimen for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia or myelodysplastic syndrome
	Romvimza	vimseltinib	Deciphera Pharmaceuticals LLC	Waived		Tenosynovial giant cell tumor
	Komzifti	ziftomenib	Kura Oncology Inc.	Partially Waived/ Deferred		Acute myeloid leukemia with a susceptible NPM1 mutation
	Hernexeos	zongertinib	Boehringer Ingelheim Pharmaceuticals Inc.	Waived		Non-squamous non-small cell lung cancer whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations
		penpulimab-kcqx	Akeso Biopharma Co., Ltd.	Waived		Non-keratinizing nasopharyngeal carcinoma

TABLE A-6

Pediatric oncology approvals 2016-2025

Drug	Date	Cancer Treated	Age Groups
Avelumab [Bavencio]	3/23/17	Merkel Cell Carcinoma (MCC)	12 years and older
Pembrolizumab [Keytruda]	5/23/17	Solid Tumors	All
Blinatumomab [Blincyto]	7/11/17	Acute lymphoblastic leukemia	1 month and older
Tisagenlecleucel [Kymriah]	8/30/17	Acute lymphoblastic leukemia	All
Gemtuzumab ozogamicin [Mylotarg]	9/1/17	AML	2 years and older
Dasatinib [Sprycel]	11/9/17	CML	1 year and older
Nilotinib [Tasigna]	3/22/18	CML resistant to TKI therapy	1 year and older
Nilotinib [Tasigna]	3/22/18	Newly diagnosed CML	1 year and older
Blinatumomab [Blincyto]	3/29/18	Acute lymphoblastic leukemia	1 month and older
Pembrolizumab [Keytruda]	6/13/18	Primary mediastinal large B-Cell lymphoma (PMBCL)	All
Iobenguane I-131 [Azedra]	7/30/18	Pheochromocytoma or paraganglioma	12 years and older
Emapalumab-lzsg [Gamifant]	11/20/18	Hemophagocytic lymphohistiocytosis (HLH)	All
Larotrectinib [Vitrakvi]	11/26/18	Solid Tumors	All
Pembrolizumab [Keytruda]	12/19/18	Merkel cell carcinoma	All
Tagraxofusp-erzs [Elzonris]	12/21/18	Blastic plasmacytoid dendritic cell neoplasm (BPDCN)	2 years and older
Dasatinib [Sprycel]	12/21/18	Acute lymphoblastic leukemia	1 year and older
Tazemetostat [Tazverik]	1/23/20	Sarcoma	16 years and older
Pembrolizumab [Keytruda]	6/16/20	Solid Tumors	All
Gemtuzumab ozogamicin [Mylotarg]	6/16/20	AML	1 month and older
Pembrolizumab [Keytruda]	10/14/20	cHL	All
Naxitamab-gqgk [Danyelza]	11/25/20	Neuroblastoma	1 year and older
Pralsetinib [Gavreto]	12/1/20	MTC	12 years and older
Pralsetinib [Gavreto]	12/1/20	Thyroid cancer	12 years and older
Crizotinib [Xalkori]	1/14/21	ALCL	1 year and older
Daunorubicin and cytarabine liposome [Vyxeos]	3/30/21	AML with myelodysplasia-related change	1 year and older
Asparaginase Erwinia chrysanthemi (recombinant)-rywn [Rylaze]	6/30/21	Acute lymphoblastic leukemia and LBL	1 month and older
Cabozantinib [Cabometyx]	9/17/21	DTC	12 years and older

ALL- Acute lymphoblastic leukemia, CML--Chronic myeloid leukemia, ALCL-Anaplastic large cell lymphoma, DTC-Differentiated thyroid cancer, LBL-Lymphoblastic lymphoma, cHL-Classical Hodgkin lymphoma, AML-Acute myeloid leukemia

TABLE A-6

Pediatric oncology approvals 2016-2025, continued.

Drug	Date	Cancer Treated	Age Groups
Rituximab [Rituxan]	12/2/21	DLBCL, BL BLL, or B-AL	6 months and older
Pembrolizumab [Keytruda]	12/3/21	Melanoma	12 years and older
Azacitidine [Vidaza]	5/20/22	Juvenile myelomonocytic leukemia	1 month and older
Crizotinib [Xalkori]	7/14/22	Inflammatory myofibroblastic tumor	1 year and older
Brentuximab vedotin [Adcetris]	11/10/22	cHL	2 years and older
Atezolizumab [Tecentriq]	12/9/22	Alveolar soft part sarcoma	2 years and older
Nivolumab [Opdivo]	2/15/23	Melanoma	12 years and older
Ipilimumab [Yervoy]	2/15/23	Melanoma	12 years and older
Trametinib [Mekinist]	3/16/23	Low-grade glioma	1 year and older
Dabrafenib [Tafinlar]	3/16/23	Low-grade glioma	1 year and older
Trametinib [Mekinist]	8/31/23	Solid Tumors	1 year and older
Dabrafenib [Tafinlar]	8/31/23	Solid Tumors	1 year and older
Bosutinib [Bosulif]	9/26/23	CML	1 year and older
Nivolumab [Opdivo]	10/13/23	Melanoma	12 years and older
Entrectinib [Rozlytrek]	10/20/23	Solid Tumors	1 month and older
Eflornithine [Iwilfin]	12/13/23	Neuroblastoma	All
Inotuzumab ozogamicin [Besponsa]	3/6/24	Acute lymphoblastic leukemia	1 year and older
Tovorafenib [Ojemda]	4/23/24	Glioma	6 months and older
Lutetium Lu 177 dotatate [Lutathera]	4/23/24	GEP-NETs	12 years and older
Selpercatinib [Retevmo]	5/29/24	Solid Tumors	2 years and older
Selpercatinib [Retevmo]	5/29/24	Thyroid cancer	2 years and older
Selpercatinib [Retevmo]	5/29/24	Medullary thyroid cancer, GEP-NET with gastroenteropancreatic neuroendocrine tumors	2 years and older
Repotrectinib [Augtyro]	6/13/24	Solid Tumors	12 years and older
Blinatumomab [Blincyto]	6/14/24	Acute lymphoblastic leukemia	1 month and older
Vorasidenib [Voranigo]	8/6/24	Astrocytoma or oligodendroglioma	12 years and older
Revumenib [Revuforj]	11/15/24	Leukemia	1 year and older

DLBCL-Diffuse large B-cell lymphoma, BL-Burkitt lymphoma, BLL-Burkitt-like lymphoma, B-AL-mature B-cell acute leukemia, cHL-Classical Hodgkin lymphoma, AML-Acute myeloid leukemia, CML--Chronic myeloid leukemia, ALCL-Anaplastic large cell lymphoma

TABLE A-6

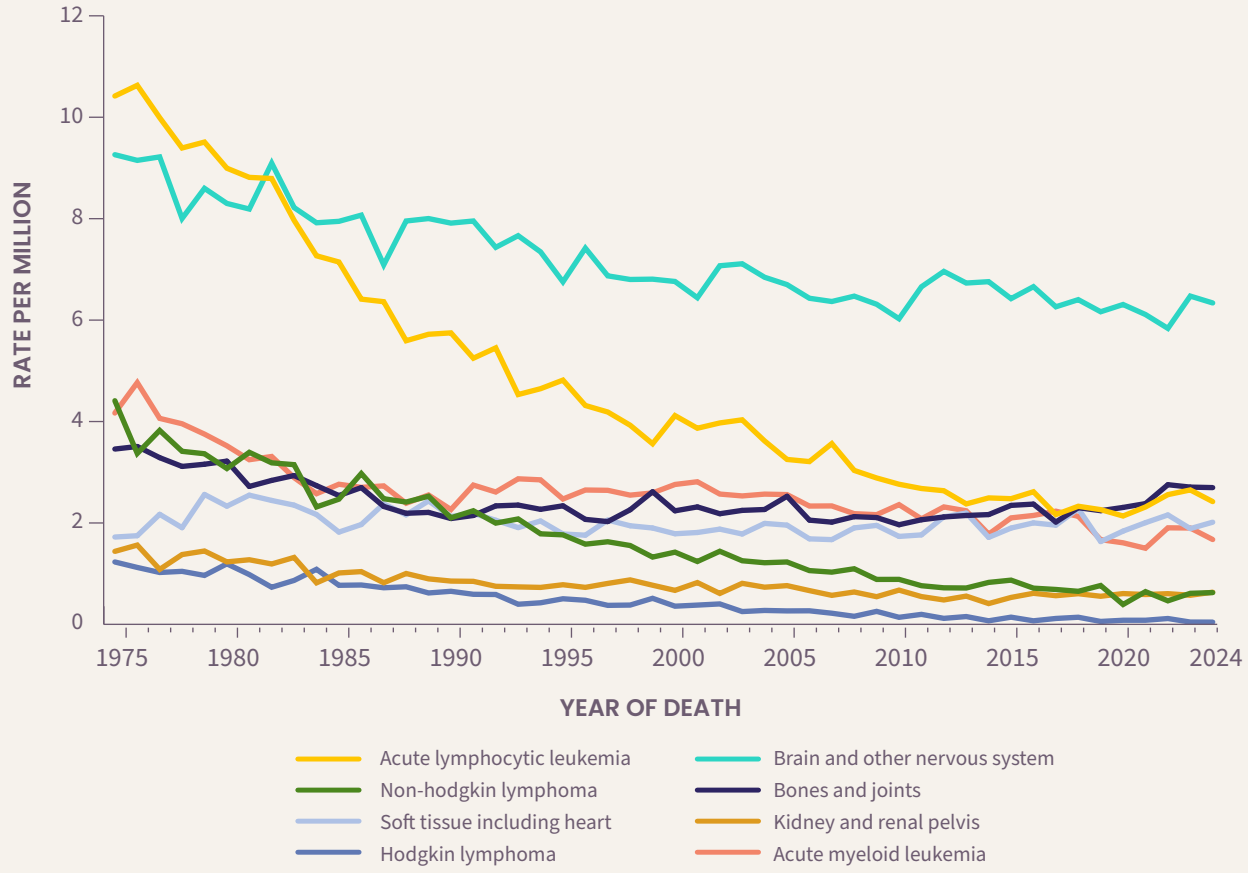
Pediatric oncology approvals 2016-2025, continued.

Drug	Date	Cancer Treated	Age Groups
Treosulfan [Grafapex]	1/21/25	AML	1 year and older
Treosulfan [Grafapex]	1/21/25	Myelodysplastic syndrome	1 year and older
Mirdametinib [Gomekli]	2/11/25	Plexiform neurofibromas (PN)	2 years and older
Cabozantinib [Cabometyx]	3/26/25	Extra-pancreatic neuroendocrine tumors	12 years and older
Cabozantinib [Cabometyx]	3/26/25	Pancreatic neuroendocrine tumors	12 years and older
Nivolumab [Opdivo]	4/8/25	Colorectal cancer	12 years and older
Nivolumab [Opdivo]	4/8/25	Colorectal cancer	12 years and older
Ipilimumab [Yervoy]	4/8/25	Colorectal cancer	12 years and older
Belzutifan [Welireg]	5/14/25	PPGL	12 years and older
Dordaviprone [Modeyso]	8/6/25	Glioma	1 year and older
Pembrolizumab and berahyaluronidase alfa-pmph [Keytruda Qlex]	9/19/25	Solid Tumors	12 years and older
Pembrolizumab and berahyaluronidase alfa-pmph [Keytruda Qlex]	9/19/25	Melanoma	12 years and older
Pembrolizumab and berahyaluronidase alfa-pmph [Keytruda Qlex]	9/19/25	Solid Tumors	12 years and older
Pembrolizumab and berahyaluronidase alfa-pmph [Keytruda Qlex]	9/19/25	Merkel Cell Carcinoma (MCC)	12 years and older
Revumenib [Revuforj]	10/24/25	AML	1 year and older
Selumetinib [Koselugo]	11/19/25	Plexiform neurofibromas	1 year and older
Atezolizumab and hyaluronidase-tqjs [Tecentriq Hybreza]	11/24/25	Alveolar soft part sarcoma	12 years and older
Nivolumab and hyaluronidase-nvhy [Opdivo Qvantig]	11/24/25	Colorectal cancer	12 years and older
Nivolumab and hyaluronidase-nvhy [Opdivo Qvantig]	11/24/25	Colorectal cancer	12 years and older
Nivolumab and hyaluronidase-nvhy [Opdivo Qvantig]	11/24/25	Melanoma	12 years and older
Nivolumab and hyaluronidase-nvhy [Opdivo Qvantig]	11/24/25	Melanoma	12 years and older
Nivolumab and hyaluronidase-nvhy [Opdivo Qvantig]	11/24/25	Melanoma	12 years and older

AML-Acute myeloid leukemia, (MTC- Medullary thyroid cancer

FIGURE A-1

Trends in pediatric cancer mortality rates by site, ages birth to 19 years, United States, 1975 to 2024



Source: National Center for Health Statistics, 2026
Underlying mortality data provided by NCHS (www.cdc.gov/nchs).
Rates are per 1,000,000 and age-adjusted to the 2000 U.S. Std Population (age <1 and 90+ - Census P25-1130) standard.

This report was made possible with support from the following:

SILVER SPONSORS

Pfizer

Genentech
A Member of the Roche Group

BRONZE SPONSOR

SERVIER