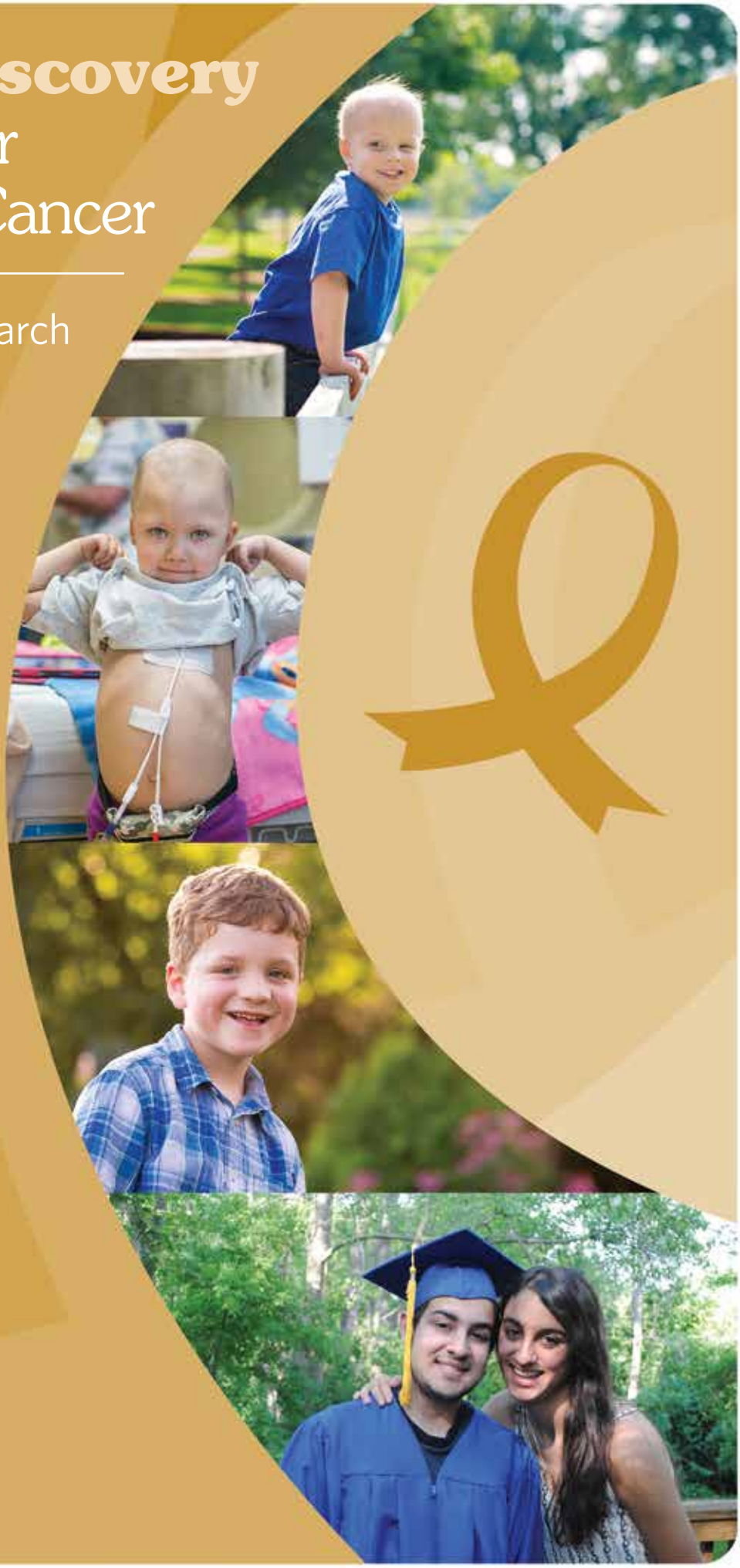
Translating **Discovery** into **Cures** for Children with Cancer

Childhood Cancer Research Landscape Report



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This report was created by a steering committee comprised of experts in the field of childhood cancer who served as primary editors and contributors to the report.

Steering Committee

Peter Adamson, MD
Chair, Children's Oncology Group (COG)
Chief, Division of Clinical Pharmacology and Therapeutics
Children's Hospital of Philadelphia

David Arons, JD
Chief Public Policy and Advocacy Officer
National Brain Tumor Society

James Baumberger, MPP
Assistant Director, Federal Affairs
American Academy of Pediatrics

Mark Fleury, PhD
Principal, Policy Development-Emerging Sciences
American Cancer Society Cancer Action Network (ACS CAN)

Ruth I. Hoffman, MPH
Executive Director
American Childhood Cancer Organization

Danielle Leach, MPA
Director of Advocacy and Government Relations
St. Baldrick's Foundation

Susan L. Weiner, PhD
President and Founder
Children's Cause for Cancer Advocacy

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Contributing authors providing content, data collection, and data analysis:

Catherine Alfano
Nancy Lenfestey
Kim D. Miller
Elizabeth Ward

Report contributors providing review, guidance and general support:

Rosalie Abbott
Rick Alteri
Rena Conti
Jill Courtney
George Dahlman
John Daniel
John DeCarlo
Sue Emmer
Ted Gansler
Jen Helfer
Ahmedin Jemal
Ethan Jorgensen-Earp
Kevin Mathis
Soheil Meshinchi
David Pugach
Katherine Sharpe
Becky Chapman Weaver

The following individuals provided their perspectives on the childhood cancer research landscape by participating in individual interviews that informed the report:

Jeff Allen
Scott Armstrong
Robin Boettcher
Christina Bucci-Rechtweg
Vickie Buenger
Renaud Capdeville
Giresh Dhall
Martha Donoghue
Chris Feudtner
Maryam Fouladi
Amar Gajjar
Richard Gorlick
Doug Hawkins
Charles Keller
Michael Link*
Donna Ludwinski
Crystal Mackall
Sabine Mueller
Gregory Reaman*
Carlos Rodriguez-Galindo
Raphael Rousseau
Malcolm Smith
Stacia Wagner

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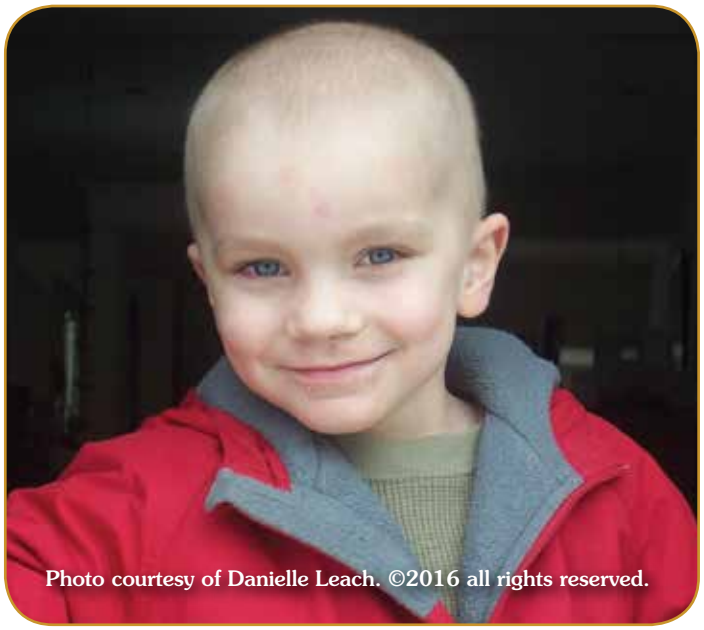
Executive Summary

Cancer is the leading disease-related cause of death for children aged 1-19. While cancer is much rarer in children compared to adults, the disease can take a tremendous toll because it strikes so early in life and survivors face extremely high rates of late effects that can last a lifetime. The American Cancer Society estimates that in 2016 there will be 10,380 new childhood cancer cases and 1250 cancer deaths among children (ages 0-14) in the US. Among adolescents (ages 15-19), there will be an estimated 4280 new childhood cancer diagnoses and 600 cancer deaths.

Outcomes for children diagnosed with cancer have greatly improved over the past 50 years for most types of cancer. However, some cancer types, such as diffuse intrinsic pontine glioma (DIPG), have seen limited improvements in treatments and outcomes and remain fatal types of childhood cancer. Developing drugs for childhood cancers that either have no effective treatments, or have treatments but with unacceptable toxicities, involves challenges unique to childhood cancer. While some cancers are seen in children and adults, other cancers are essentially only seen in children, and the four most common adult cancers (lung, breast, prostate, and colorectal) are essentially absent in children. Therefore, improving outcomes for children with cancer begins by recognizing the many fundamental differences between childhood cancers and adult cancers, and the landscape in which new drugs are developed. There are many key differences among childhood and adult cancers, including:

- Childhood cancers are often biologically different than the cancers that share the same name in adults, meaning that childhood-specific research is required, and children and adults ultimately may need different treatments.
- Side effects from treatment cause significant health impacts on children because the treatments occur during a vulnerable period of development and longer survival times mean more time for late effects to impact a childhood cancer survivor's health.
- Society has afforded special protective status for children involved in research, which changes the type of research generally considered to be ethical for children and also changes the process for approving such research.
- The rarity of childhood cancers can make recruiting children to participate in clinical research challenging, either due to a small number of diagnosed patients or due to competition between different research projects for the same children.
- The rarity of childhood cancers also means the financial incentives to develop and market drugs specifically for children with cancer are often not enough to entice industry to invest in this type of research.



Many of these differences discourage research and drug development for childhood cancers because they introduce added cost, complexity, and uncertainty to the research process, but there are also many efforts aimed at overcoming these barriers. The lack of financial incentives for research, for example, has led to additional incentives and requirements for adult drug developers to test their treatments in children. Likewise, philanthropic organizations augment research funding from federal and industry sources, and researchers and cancer centers have formed collaborative networks to optimize the ability to conduct research with limited patient populations.

This report provides important perspectives and data from the childhood cancer community on barriers to research and the current efforts to overcome those barriers. In creating this work, the goal is to provide anyone interested in improving the landscape for children who face cancer with reliable information and a comprehensive perspective on how the process currently works.

Introduction

Cancer ranks as the leading disease-related cause of death for children[1] aged 1-19 (see Figure A1). While cancer is much rarer in children than in adults, comprising approximately 1% of overall cancer diagnoses, it can have enormous effects because it strikes so early in life. In 2013, cancer deaths in children between 0-19 years of age resulted in an estimated 131,100 years of life lost (YLL), or an average of almost 69 years lost per death. The American Cancer Society estimates that in 2016 there will be 10,380 new cases and 1250 cancer deaths among children (ages 0-14) and 4280 new cases and 600 cancer deaths among adolescents (ages 15-19) in the US. Approximately one in 412 children will be diagnosed with cancer before age 15, and one in 285 children will be diagnosed with cancer before age 20 [1]. Mortality rates for childhood cancer are dropping, but many children who survive their cancer face a lifetime of side effects from their cancers and associated treatments. Nearly 40% of childhood cancer survivors aged 35 or older have experienced a severe or life-threatening health condition, or have died, which is a rate over five times higher than that of their siblings [2].

Between developing treatments for cancers that still have no effective treatment, and reducing the toxicities and side effects where treatments are successful, much work remains to be done in order to improve the pediatric cancer landscape. Improving outcomes for children with cancer begins by recognizing the many fundamental differences between childhood cancers and adult cancers. The cancers that occur in children are not the same as those experienced by adults. Furthermore, children are not simply small adults, but rather have important biological differences that mean that they respond to treatments in ways that differ from adults. Sometimes these differences may only require altered dosing or formulations of adult drugs, but in many cases childhood cancers are unique diseases.

Improving outcomes for kids with cancer will require optimization in how current treatments are administered, but that optimization will only go so far. In many cases, progress will only occur with the development of new drugs[2] for childhood cancer, and this report focuses on examining the pediatric cancer research and drug development landscape. While some aspects of research and drug

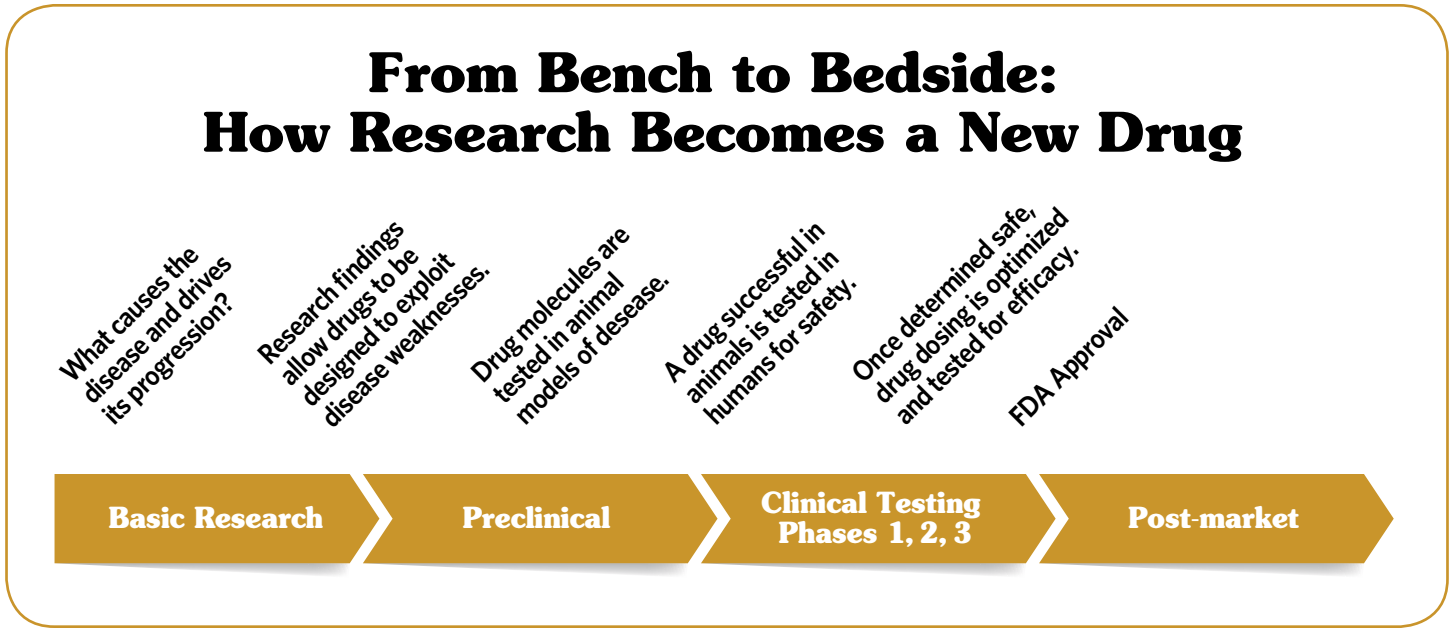
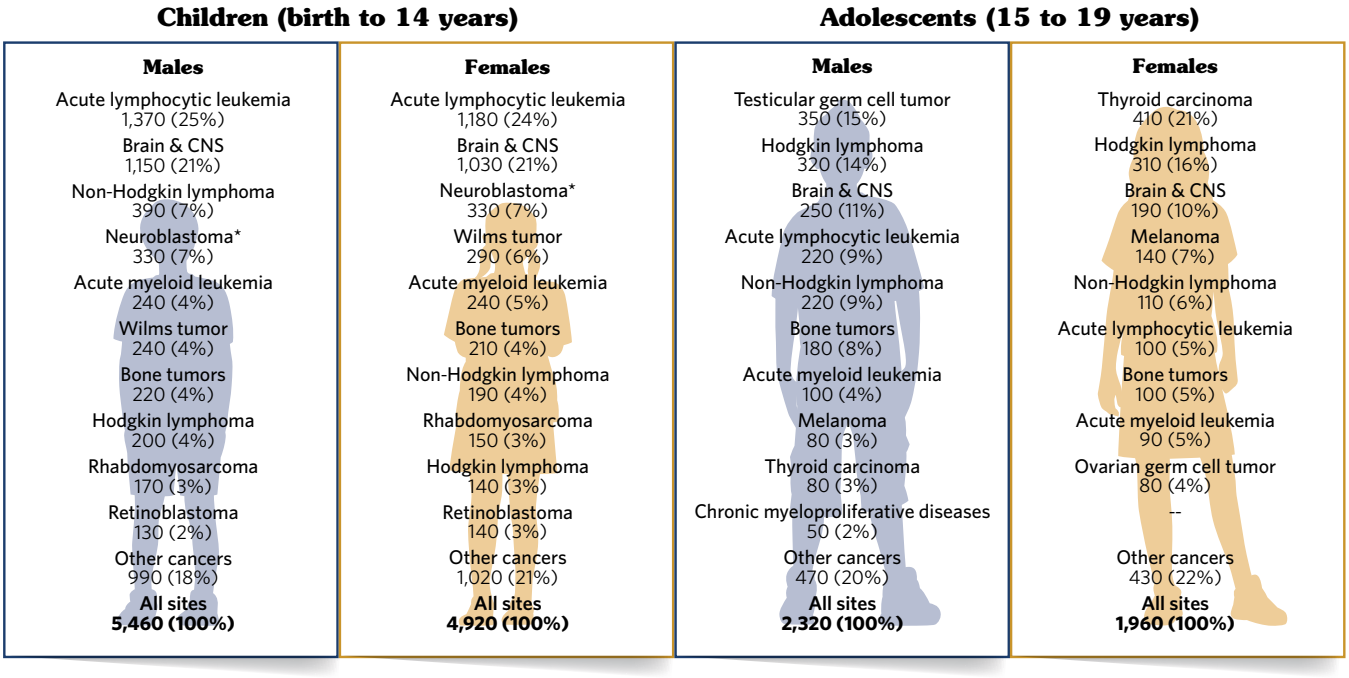


Figure 1: Drug development research starts with a basic understanding of a disease and then progresses to candidate drug molecules. These are tested in preclinical development using cell cultures and animal models to develop confidence that they will work in human disease. Clinical testing usually passes through three phases, which begins by testing basic safety in humans and progresses to determining safety and effectiveness. 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.

New Case Estimates for Leading Childhood and Adolescent Cancers by Sex, 2016



CNS indicates central nervous system. Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell carcinomas, in situ and borderline brain, and all other in situ carcinomas except urinary bladder. An estimate for the tenth most common cancer in female adolescents is unavailable due to estimate being <50 cases.

*Includes ganglioneuroblastoma.

Figure 2: In 2016 there will be an estimated 14,660 new cases of childhood cancer. The types of cancers that are common in younger children (0-14) differ from those in adolescents (15-19). The specific types of cancers also differ between boys and girls.

development are shared between children and adults, there are also significant differences. Developing therapies for pediatric cancers involves many unique scientific, logistical, economic and regulatory challenges. By understanding these unique aspects, efforts can be targeted to create better treatments for children with cancer.

Report Orientation

This report is divided into multiple chapters that detail various aspects of childhood cancer research and drug development. This introduction provides important statistics and context describing childhood cancer, while the remaining chapters focus more specifically on the research and drug development process that underlies the development of new drugs for children. As seen in Figure 1, by the time a drug is approved for use, it has progressed through multiple steps that include basic research, preclinical testing, clinical testing, and finally regulatory approval. The chapters of this report delve into the different challenges, organizations, and issues unique to each stage of the process. Vignettes featuring individuals and families who

1 Unless specified otherwise in this report, children refers to ages 0-19.

2 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.

Introduction

Childhood and Adolescent Cancer Incidence, 5-Year Observed Survival, and Survivors by Cancer Site

Cancer Type	Incidence Rate (0-19 Years) 2008-2012	5-year Observed Survival (%) (0-19 Years) 2005-2011	Estimated Number of Survivors by Age at Prevalence (as of January 1, 2012)		
			0-19 Years	20+ Years	All Ages
All sites	**179.0**	**83%**	**115,689**	**283,278**	**398,967**
Acute lymphocytic leukemia	34.4	87%	30,816	34,321	65,137
Brain & CNS	31.6	73%	21,183	40,881	62,064
Neuroblastoma	8.2	78%	9,642	10,751	20,393
Wilms tumor	6.3	91%	7,849	16,736	24,585
Soft tissue sarcomas	12.1	72%	6,987	25,776	32,763
Non-Hodgkin lymphoma	8.9	86%	6,848	18,964	25,812
Hodgkin lymphoma	12.3	97%	4,686	32,048	36,734
Acute myeloid leukemia	8.0	63%	3,991	4,897	8,888
Bone tumors	8.7	69%	3,642	13,815	17,457
Testicular germ cell tumors	10.0	95%	2,702	18,737	21,439
Ovarian germ cell tumors	4.5	97%	2,531	15,063	17,594

Incidence rates are per 1,000,000 and age-adjusted to the 2000 US standard population. CNS indicates central nervous system. Survival is for cases diagnosed from 2005 to 2011, all followed through 2012. Note: Data does not include benign and borderline brain. Non-Hodgkin lymphoma prevalence includes Burkitt lymphoma and other unspecified lymphoma subtypes. Wilms tumor prevalence includes other and unspecified renal carcinomas.

Sources: Incidence – North American Association of Central Cancer Registries (NAACCR), 2015. Survival – Surveillance, Epidemiology, and End Results (SEER) program 18 registries, National Cancer Institute, 2015. Cancer prevalence – Howleder et al, 2015.

Table 1: 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, rates range from 4.5 cases per 1,000,000 girls for ovarian germ cell tumors, to 34.4 cases per 1,000,000 population for ALL Five-year survival ranges from 63% to 97% for the cancers listed, and there were estimated to be nearly 400,000 survivors of childhood cancer in 2012.

have experienced childhood cancer are placed throughout the report, and provide personal perspectives on childhood cancer.

Childhood Cancer Incidence and Mortality

While cancers occurring in adults are 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) [3]. The distribution of the most common cancers in children and adolescents varies by age (Figure 2).

Excluding benign and borderline brain tumors, the cancers that are most common in children age 0–14 are acute lymphocytic leukemia (ALL) (25%), brain and CNS (21%), neuroblastoma (7%), and non-Hodgkin lymphoma (6%). The top four cancers in adolescents age 15–19 are Hodgkin lymphoma (15%), thyroid carcinoma (11%), brain and CNS (10%), and testicular germ cell tumors (8%).

Incidence rates for childhood and adolescent cancer are expressed as number of new cases per million individuals per year. The incidence rate per million population for all cancers combined, ages 0-19, in 2008-2012 was 179.0 (Table 1). Among the eleven most common cancers, the incidence rates ranged from 4.5 for ovarian germ cell tumors to 34.4 for

acute lymphocytic leukemia. Among children diagnosed with cancer in 2005–2011, the overall five-year survival rate was 83%, ranging from 63% for acute myeloid leukemia to 97% for Hodgkin lymphoma and ovarian germ cell tumors (Table 1). It is important to note that within many of the cancers listed here, there is a great deal of variation in prognosis depending on tumor subtypes and other factors. For example, while the five-year survival rate among children with neuroblastoma is 78% on average, children diagnosed with "high-risk" neuroblastoma have a 40–50% five-year survival rate. Further, less than 25% of children diagnosed with diffuse intrinsic pontine glioma (DIPG) will survive even two years [4]. Further statistics on individual types of cancer can be found in the Appendix.

Long-term Survival for Childhood and Adolescent Cancer

Although the incidence of childhood cancer has been increasing only slightly, at an average of 0.6% per year from 1975 to 2012 [5], the number of survivors of childhood cancers has increased substantially due to improving survival rates. An estimated 398,967 survivors of childhood and adolescent cancer (diagnosed at ages 0-19) were alive in the US as of January 1, 2012 (Table 1). The top three cancer sites among childhood cancer survivors are acute lymphocytic leukemia, brain and CNS tumors, and Hodgkin lymphoma. Most (71%) survivors of childhood and adolescent cancer are 20 years of age or older. Approximately one in 513 young adults between the ages of 20 and 39 is a survivor of childhood cancer [5].

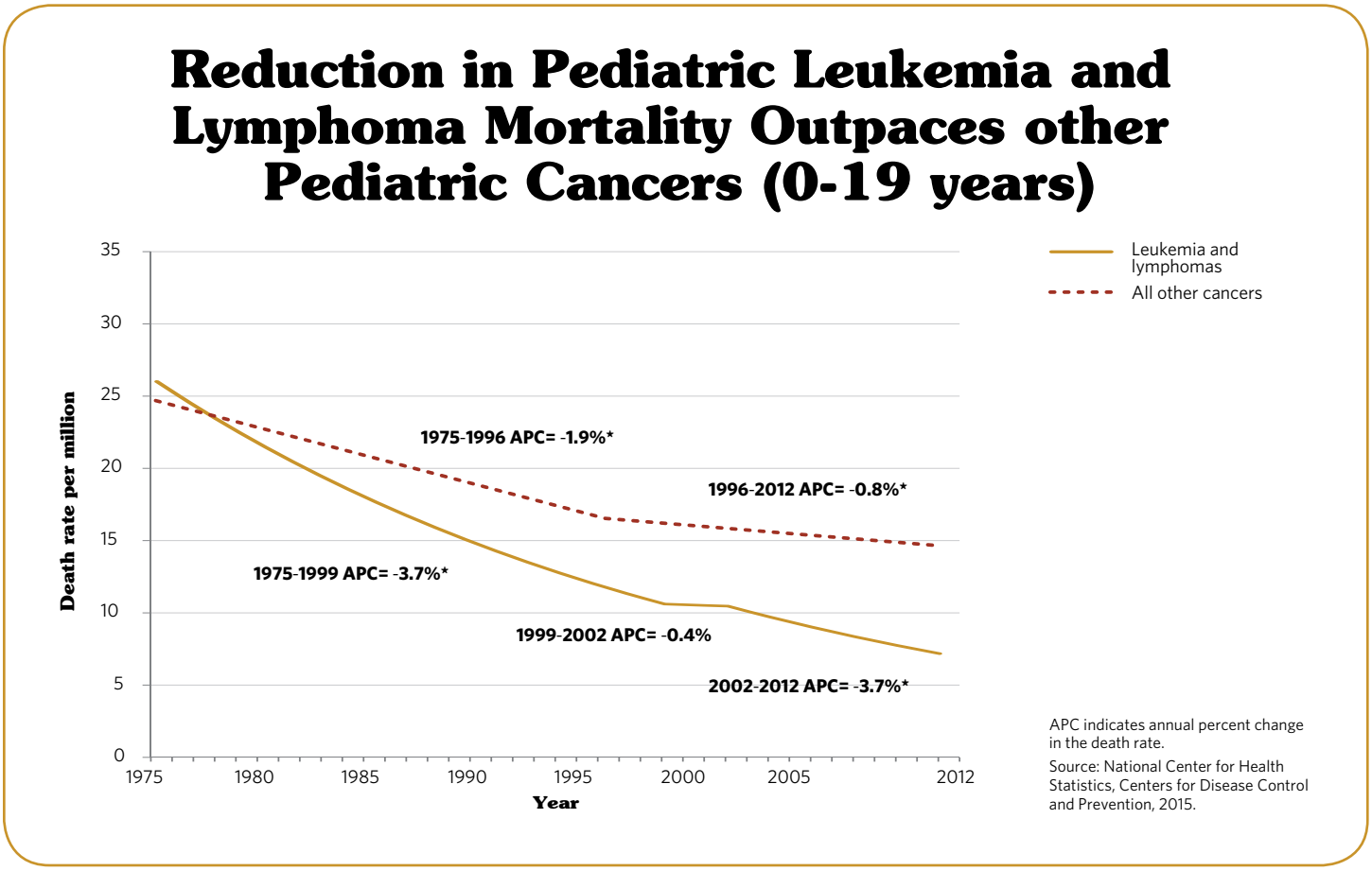
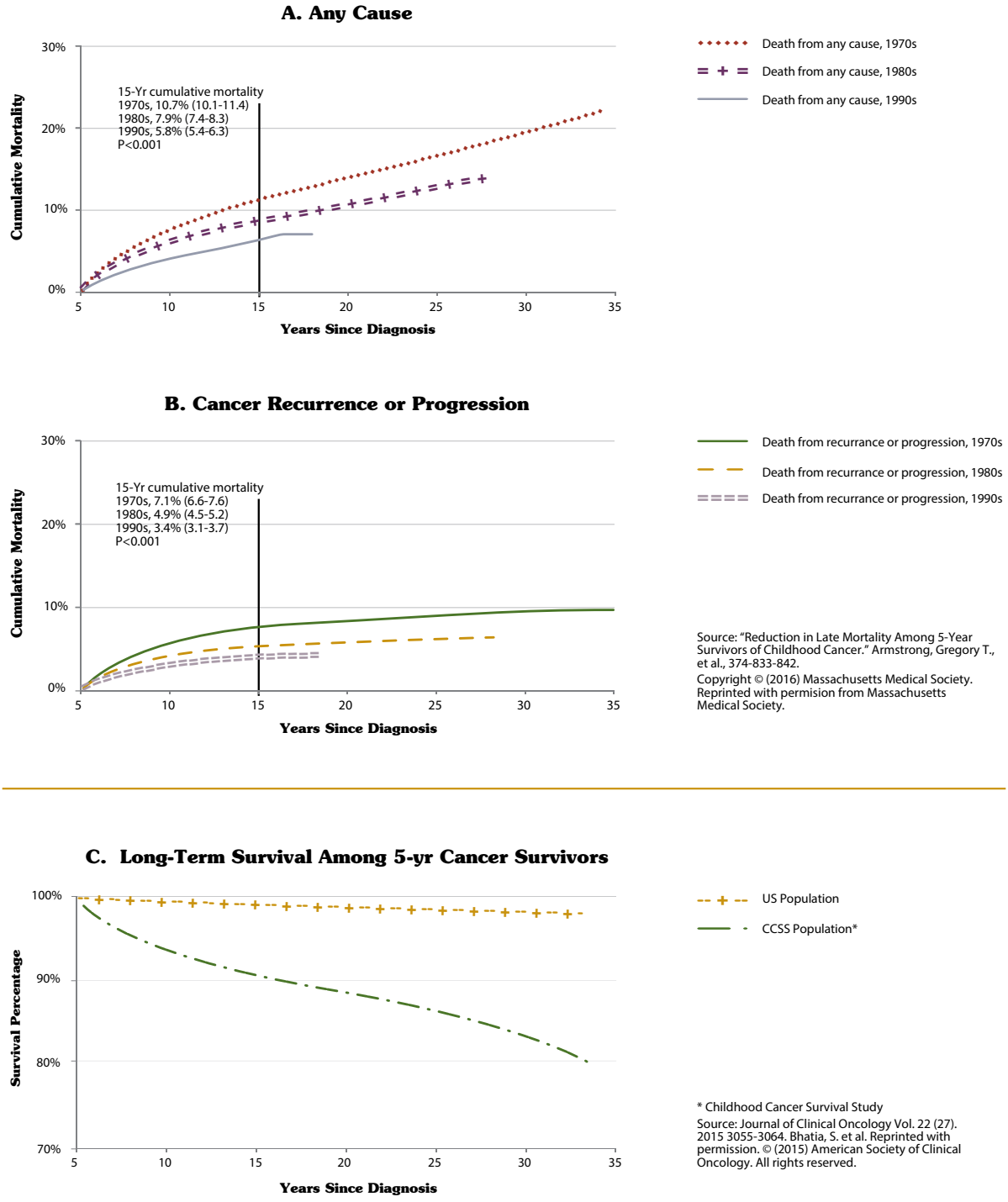


Figure 3: Progress in reducing mortality has been much more pronounced in leukemia and lymphomas, with recent mortality reductions of 3.7% annually during the decade from 2002-2012, while mortalitly for all other pediatric cancers has reduced at less than 1% annually during the same time period.

Introduction

Late Mortality Among 5-yr Cancer Survivors



Source: "Reduction in Late Mortality Among 5-Year Survivors of Childhood Cancer." Armstrong, Gregory T., et al., 374-833-842.

* Childhood Cancer Survival Study

Source: Journal of Clinical Oncology Vol. 22 (27). 2015 3055-3064. Bhatia, S. et al. Reprinted with permission. © (2015) American Society of Clinical Oncology. All rights reserved.

Figure 4. Cancer survivors continue to experience higher mortality even after reaching the five-year milestone, but trends have improved over time. Panel A displays mortality from any cause, while Panel B shows mortality from cancer recurrence. Death from recurrence or progression at the 15-year mark was reduced by half from the 1970s (7.1%) to the 1990s (3.4%), reflecting improvements in treatment. Panel C shows the excess mortality in cancer survivors compared to the general population.

The impact of any cancer diagnosis is one that is borne by an entire family, something that Raha can attest to. She was only 12 when her younger brother Roozie, then nine, was diagnosed with medulloblastoma, a type of brain cancer. She could not know it at the time, but it would mark the beginning of a protracted back-and-forth fight against cancer that would last for more than a decade and involve diagnoses with four different cancers.

Many of the tools used to fight cancer can also cause additional cancers at a later point, and Roozie's case was no exception. Five years after his first diagnosis he received his second cancer diagnosis, this time of lymphoma. A year after fighting lymphoma, Roozie developed myelodysplastic syndrome (MDS), a type of cancer affecting blood stem cells that required a stem cell transplant. He was told that if he made it five years from his bone marrow transplant that chances would be that he would have put his MDS behind, him, but just a few days shy of the fifth anniversary he got news that the MDS was back. Another transplant ensued, but this time his MDS morphed into acute myeloid leukemia (AML). The same doctors had been caring for him since his first diagnoses, but after successfully seeing him through so many prior cancers, the complications from his last diagnoses proved too much and Roozie passed away at the age of 21 with his family surrounding him.

Despite all his treatments, Roozie kept a relatively normal childhood and was always the life of the gatherings of his childhood friends at his parents' home. Photos show many happy times with Raha and Roozie, but cancer was never far from their minds. "People sometimes forget that with childhood cancer, it's not just done," reflected Raha. Even Roozie's college choice to major in engineering so that he could work as a research assistant on projects looking at bone marrow transplants was a reminder of how profoundly cancer had touched his life.

Raha and the rest of the family were devastated to lose Roozie, something that any family of a cancer patient can relate to. Several months later Raha had a rather unusual opportunity to share that grief with Vice President Joe Biden, who called her after the loss of his son as part of the launch of the National Cancer Moonshot Initiative. Raha has turned her brother's experience into her own passion and has become an active advocate for childhood cancer causes.

Introduction

Death rates for all childhood and adolescent cancers combined declined by more than 50% from 1975 (51.5 per million population) to 2012 (24.1 per million). Mortality declines were more pronounced for leukemia and lymphoma than for other types of cancer (Figure 3), and select cancers, such as adolescent ependymoma and neuroblastoma, have seen little or no declines in mortality (see Figure A4).

Although five-year survival rates are generally used to benchmark progress in cancer treatment and survival, for many cancers, mortality continues to be increased (compared to similar individuals who never had cancer) beyond the fifth year after their cancer diagnosis (Figure 4). This is true for many childhood and adolescent cancers as well as for adult cancers. Common causes of this "late mortality" among childhood and adolescent cancer survivors include recurrence or progression of the original cancer, development of subsequent cancers related to treatment, and other treatment-related toxicity. Research on the late effects of cancer and its treatment among survivors of childhood and adolescent cancers has been very important in identifying adverse effects, developing guidelines for prevention and medical surveillance for survivors, and improving treatments to reduce side effects [6]. In addition to the improvements in five-year survival for childhood and adolescent cancers since the 1970s, there have also been improvements in late mortality (Figure 4). Among children and adolescents diagnosed during the 1970s, 10.7% who survived five years after diagnosis died within the next 10 years; in the 1990s, the percent declined to 5.8% [7]. Children and adolescents treated for cancer in the 1970s and '80s have continued to have an elevated risk of mortality from long-term and late effects for the remainder of their lives. The Childhood Cancer Survivor Study (CCSS), a study of the mortality experience of 20,483 five-year childhood and adolescent cancer survivors who were diagnosed between 1970 and 1986, found an increased risk of all-cause mortality up to 30 years after diagnosis. In this long-term study of five-year cancer survivors, there was a 15-fold elevated risk of death from cancer, a seven-fold increased risk of death from heart disease, nearly nine-fold for pulmonary disease and 2.6-fold for other medical causes when compared to the general population [8]. The declines in 10-year and 15-year mortality for more recent cohorts likely portends lower long-term mortality compared to earlier cohorts as a result of more effective and less toxic cancer-directed therapy. Nonetheless, more recent cohorts of childhood and adolescent cancer patients must continue to be followed to determine how therapy modifications impact the prevalence and spectrum of late effects.

Between developing treatments for cancers that still have no effective treatment, and reducing the toxicities and side effects where treatments are successful, much work remains to be done in order to improve the pediatric cancer landscape.

Biological Understanding

The first step in developing better drugs for children with cancer is better understanding the cancers that children develop, along with how and why they are different from adult cancers. Childhood cancer is not one disease, but rather dozens of cancers that can often be further subdivided based on specific genetic or molecular features. While the list of common childhood cancers contains some cancers seen in adults, other cancers are essentially only seen in children, and the four most common adult cancers (lung, breast, prostate, and colorectal) are essentially absent in children. The differences between childhood and adult cancers can be explained in part by the types of tissue involved and the mechanisms that underlie each cancer. This section explores the differences between child and adult cancers, and highlights how understanding these differences is critical to the development of the most effective drugs for children.

Child-Adult Differences

A number of cancers are seen almost exclusively in children, and these childhood-specific cancers often arise from 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 of the different organs and parts of the human body according to complex biological control mechanisms. While much of the cellular differentiation of embryonal cells has stopped by birth, significant cellular reproduction continues through adolescence, at which point humans are essentially physically mature. Embryonal tumors come from embryonal cells whose control mechanisms fail to work properly, resulting in the cells continuing to reproduce 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), medulloblastoma (brain), and Wilms tumor (kidney) have the highest incidence in children between birth and four years of age, and occur progressively more rarely after that.

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

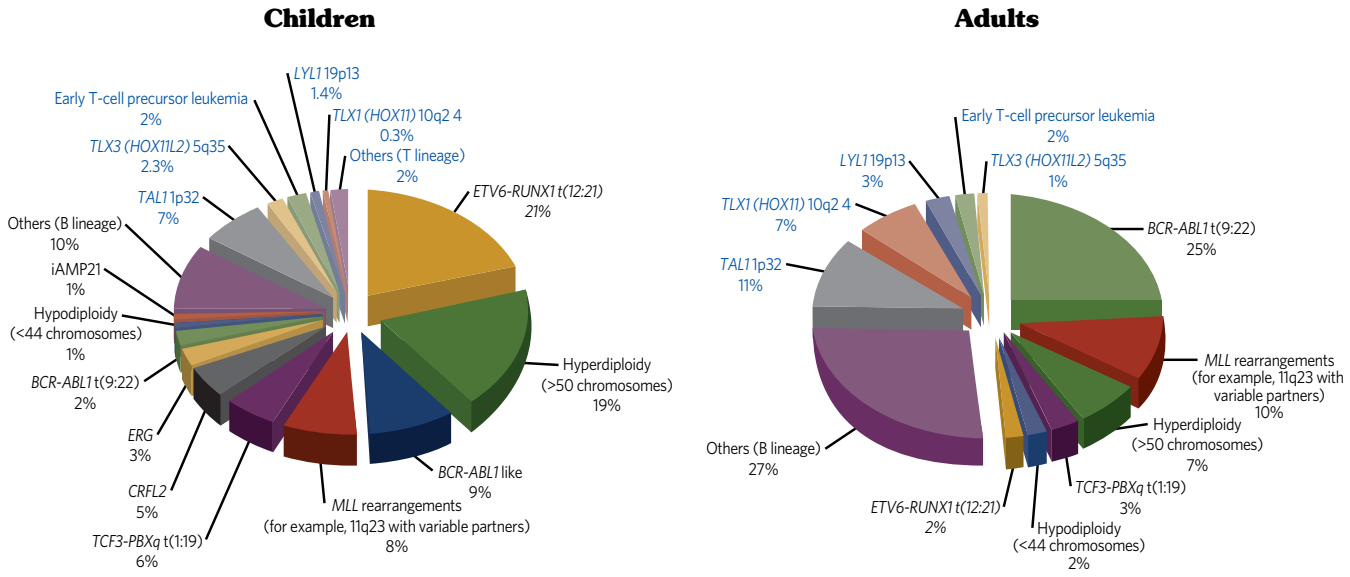
Among the cancers that are seen in both children and adults are acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), Hodgkin and non-Hodgkin lymphoma, thyroid cancer, melanoma, and glioblastoma (an aggressive type of brain tumor). While these cancers in children and adults share the same general names, the adult and child versions of the same cancer are often distinct biological subtypes. For example, genomic profiling of tumors shows that pediatric and adult B-cell non-Hodgkin lymphomas tend to have different genetic fingerprints [9, 10], as do glioblastomas [11] and acute lymphoblastic leukemia [12] (Figure 5). 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 (outlook) at different ages, partly due to different genetic subsets that tend to occur as a child develops [13]. (see below for more on genetics). Even where 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 fundamental biological differences between adults and children, including the greater potential for harm in children whose bodies are still developing.

Genetics

Cancer is a disease that results from mutations (changes) 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 result, in small or large part, from heritable genetic changes. Still, the majority (between 90 - 95%) of all adult cancers arise because of genetic changes that occur during a person's lifetime [14].

Our genes contain the instructions for how a cell should normally behave. Mutations in genes can affect these instructions. When a mutation occurs inside a cell 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

Acute Lymphoblastic Leukemia Subtypes Differ between Adults and Children



The frequency of T-cell lineage (blue text) and B-cell lineage (black text) subtypes of acute lymphoblastic leukemia (ALL) in children (left) and adults (right). Each chart is organized with ALL subtypes listed from the most common to the least common in a clockwise fashion. iAMP21, intrachromosomal amplification of chromosome 21.

Figure 5: Both children and adults are diagnosed with acute lymphoblastic leukemia (ALL), but the genetic subtypes, which often have different prognoses and responses, are not the same in children (left) and adults (right). This means that the therapies often must be tailored for each different subtype.

for other mutations to occur. Starting from a single damaged cell, eventually millions of abnormal clones can result in the condition we know as cancer. In this case, only the cancer cells will have the mutations that started the cancer, while all of the person's other cells would still have genes that were unchanged.

The cause of that original mutation to a single cell can be attributed to any number of factors. Some mutations are due to harmful exposures, like smoking or radiation, but often mutations happen by random chance during a normal cell division. One of the mutations implicated in certain cancers is in the ALK gene, and it was research into childhood anaplastic large cell lymphoma (ALCL) genetics that led to its discovery [15]. Subsequent to its discovery in ALCL, this mutation was also found in some cases of neuroblastoma [16] and non-small cell lung cancer [17].

Certain mutations tend to be associated with certain cancers, although any given cancer may have several different genes that are frequently mutated. The different mutations allow a given cancer type to be subdivided by its genetic characteristics. For example, medulloblastoma has been divided into four main subgroups based on the mutated genes driving the cancer [18]. Each of these different subtypes has a different prognosis, and different treatments might be used depending on the subtype, meaning that there are essentially four different types of cancers

that all belong to the medulloblastoma family. Neuroblastoma has similarly been subdivided into more than a dozen different risk classifications based partly on genetic and molecular abnormalities found in the tumor. These different risk subgroups have different prognoses and recommended treatments [19]. Other childhood cancers are similarly subdivided [11, 12, 20] (Figure 5). 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 [11, 21-24] (see Basic Research section).

Inherited Genes

While most cancers are the result of genetic mutations that occur during our lifetime, around 5–10% of adult cancers can be linked to mutations that are inherited from an individual's parents. In the case of inherited mutations, all the cells in the body would share the same problematic genes from birth. Inherited mutations in certain genes can substantially increase a person's lifetime risk of cancer.

The available evidence indicates that cancers in children due to inherited genetic mutations are no more common than cancers in adults due to inherited mutations. Overall between 1–10% of childhood cancers are due to inherited genetic mutations, which is a proportion very similar to that of adult cancers [25]. Select childhood cancers, however, are more frequently associated with inherited genetic mutations, notably retinoblastoma, where approximately 35–40% of cases can be traced to inherited mutations. In other childhood cancers, like those in the brain and spinal cord, the proportion that are due to inherited genes are thought to be extremely low, at around 2% [26].

Cancer Therapies Cause a Variety of Late Effects

System	Exposure	Effect
Cardiovascular	Radiation therapy Anthracyclines Platinums	Myocardial infarction or stroke Congestive heart failure Valvular disease Hypertension
Lungs	Radiation therapy Bleomycin Carmustine/Lomustine	Restrictive lung disease Pulmonary fibrosis Exercise intolerance
Kidney/urological	Radiation therapy Platinums Ifosfamide/cyclophosphamide	Renal insufficiency or failure Hemorrhagic cystitis
Endocrine	Radiation therapy Alkylating agents	Obesity Infertility and gonadal dysfunction Dyslipidemia Insulin resistance and diabetes
Central nervous system	Radiation therapy Intrathecal chemotherapy	Learning disabilities Cognitive dysfunction
Second cancers	Radiation therapy Alkylating agents Epipodophyllotoxins	Solid tumors Leukemia Lymphoma
Psychosocial	Cancer diagnosis	Affective disorders (anxiety, depression) Posttraumatic stress Sexual dysfunction Relationship problems Employment and educational problems Insurance discrimination Adaptation and problem solving

Table 2: A variety of treatments are used to treat children with cancer, and each treatment can lead to specific late effects ranging from second cancers to social disorders.

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 [22]. 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 being made incorrectly, or in 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 change a cell's general ability to translate genetic instructions into proteins. 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 pediatric high-grade gliomas, osteosarcomas, and T-cell ALL tumors harbor epigenetic mutations [22]. These differences are important, as they can sometimes dictate 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 evaluating tumor tissue from children. While biopsies taken as part of treatment often yield tumor tissue that can later be used for research, there has not always been a systematic and standardized collection of this tissue with an eye toward sharing with the broader research community. Not only is the tissue itself important, but to be optimally useful, the tissue should be accompanied by clinical information about the child, such as the treatment he or she received and what effects a treatment had. Sometimes additional healthy tissue from the same child or a healthy sibling is also placed into these collections to allow researchers to better understand how tumors differ from healthy tissue and whether any inherited mutations might be involved in the development of cancer. These collections of tissue and data are known as biorepositories, tumor banks, or biobanks.

> ***"The sample size is too small. We can't see a pattern with 80 samples because the cancer is too complex, perhaps we could see a pattern if our n was 1,000, but we can't get there with pediatric cancers."***
>
> — *Dr. Richard Gorlick, Division Chief, Pediatric Hematology/Oncology, The Children's Hospital at Montefiore*

Most childhood cancers are relatively rare, so if a researcher were to start collecting tissue after developing a research question, it could take years to obtain enough tissues from new cancer cases to answer the question. By banking tissue proactively 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 their own repositories, and even some collaborative groups organized around a specific cancer, such as the Children's Brain Tumor Tissue Consortium, have centralized collections of tissue and clinical data. 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) using private funding from Hyundai Hope on Wheels [27]. It began in 2015, and intends to collect 32,000 samples from children with cancer and link them to clinical records to provide researchers with access to a wealth of information about a variety of childhood cancers. Another study, the Childhood Cancer Survivor Study (CCSS), has collected normal tissue samples from nearly 7,000 children with cancer and their siblings in an attempt to better understand the biological factors that lead to long-term treatment effects on childhood cancer survivors (treatment effects discussed further in the next section).

Tissue can provide important information about a disease, but since there are only finite quantities, the tissue itself can only be shared a limited number of times. The genetic profile of a tumor is one of the most critical features for understanding a

disease, and the genetic profiles of tumor samples are being determined (in a process called genetic sequencing) in large numbers to generate more basic knowledge about pediatric cancers. Unlike the tissue itself, the genomic sequence data of a tumor can be shared without limit, allowing many researchers access to information that can help discover gene mutations responsible for the cancer, subdivide cancers based on their mutation patterns, identify potential targets within a cancer to direct drug development, and understand why therapies work for some children and not others. The Pediatric Cancer Genome Project is a sequencing project that was launched in 2012. Privately funded, and directed by St. Jude Children's Research Hospital and Washington University, it has sequenced over 1,000 pediatric tumors and made this information available to other researchers [12]. Findings from this project have included uncovering mutations that drive certain forms of childhood leukemia and brain cancer [20, 28]. A similar, publicly funded study is National Cancer Institute's (NCI's) Therapeutically Applicable Research to Generate Effective Treatments (TARGET) project. Through TARGET, over a thousand different tissues from five different types of cancers have been sequenced in an effort to find mutations within these cancers that could be targeted by drugs to fight the cancer. Findings from this study have led, for example, to the current testing of the drug ruxolitinib, which inhibits activity of a protein known as "JAK," in children with cancers harboring mutations in the JAK gene [29].

Tumor tissue is often taken at initial diagnosis as a normal part of clinical care, but 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 sometimes have significantly different genetic signatures than the originally diagnosed cancer [20]. Taking additional biopsies during the course of a child's cancer treatment solely for research studies can be difficult, as subjecting children to additional procedures that will not provide them 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 32 for further discussion of research ethics). However, as treatment choices are increasingly being based on a tumor's molecular characteristics, multiple biopsies are becoming a more frequent part of clinical care, and this offers more opportunities to store part of that tissue for further research.

"When a patient recurs, we used to say, "Is it ethical to take these kids back to surgery?" We are now starting to say, "Is it ethical not to take these kids back to surgery if the surgery can be conducted safely?"

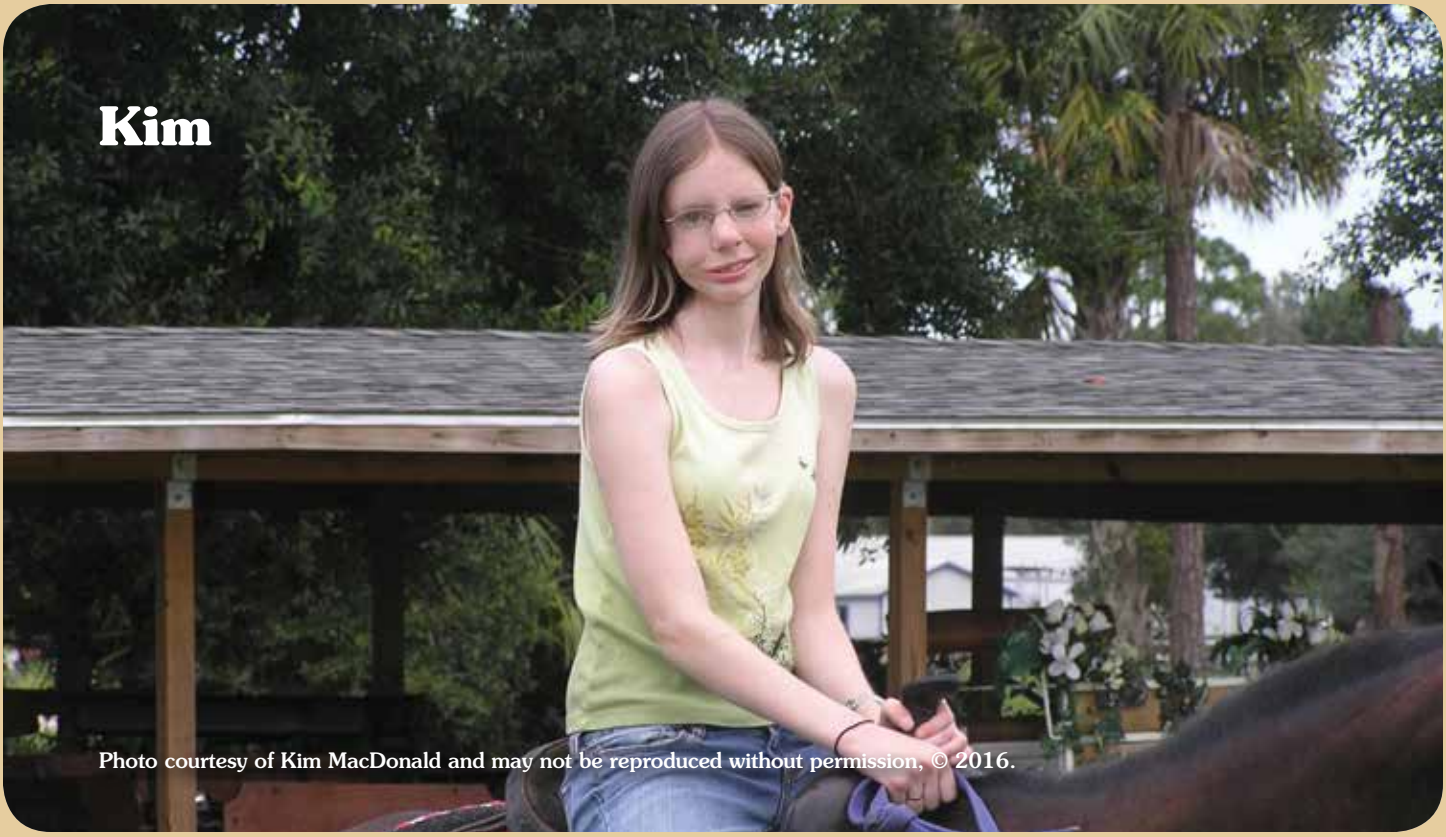
— *Dr. Maryam Fouladi, Medical Director, Brain Tumor Center, Cincinnati Children's Hospital*

While some tumors may be difficult to access without causing danger to a child, tissue can still be donated in the event that a child does not survive his or her cancer. Post-mortem tissue collection taken shortly after a child dies may still provide living tumor cells that are useful for research, and tissues 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 tissue collection from their children, pointing to another opportunity to contribute valuable tissue to research [30].

Biological Causes of Late Effects of Treatment

Research has documented the vulnerability pediatric cancer patients have to side effects over the long term, which are caused by multiple toxicities of cancer treatments (see Table 2). Prior research has shown that nearly 40% of childhood cancer survivors aged 35 or older have experienced a severe or life-threatening condition, or have died. This is a rate over five times higher than seen in the siblings of these survivors who were not treated for cancer but who presumably carry otherwise equivalent risk for severe health conditions due to genetics and environmental exposures [2]. 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. Even targeted therapies, which typically only interrupt select processes that tend to be overactive in cancer cells, can lead to long-term and late side 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 to whom they will apply.

Kim



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Shortly after her sixth birthday, Kim was diagnosed with rhabdomyosarcoma, a type of embryonal cancer that occurs in just over 300 children per year in the United States and affects muscles and soft tissue. The first clue that something was wrong occurred as Kim and her mother were whistling together in front of a mirror and Kim could not understand why her lips were not puckering the same way as her mother's. Her inability to pucker was the first stage of what became severe partial facial paralysis caused by the tumor exerting pressure on a nerve. Once diagnosed, Kim began therapy, which lasted over four years and included surgery, radiation, and chemotherapy, not only for the initial diagnoses but for two subsequent relapses as well.

"Despite these challenges, I managed to stay in school and have a relatively normal childhood. Kids can be very accepting, and my classmates never made me feel like I was different, even with facial paralysis and a bald head," said Kim.

By the time Kim started middle school she was finally cancer-free, thriving in the Gifted and Talented Center, playing the piano and singing in chorus. Nearly six years to the day after her first diagnosis, she was diagnosed with lymphoma after noticing a lump in her neck. It turned out that the chemotherapy that had saved her life before had caused a different type of cancer, and two more years of chemotherapy followed before being declared cancer-free for a second time in her relatively young life.

Kim has now been cancer-free for 18 years, and while she has left her cancer behind, she has been left with many late effects from her treatments. The list includes growth hormone deficiency, difficulty swallowing, speech issues, deafness in one ear and the need to use a hearing aid in the other, which makes it very it difficult to follow a conversation with multiple people or when there is any background noise. She was also diagnosed with hypersomnia, or excessive sleepiness, while in college, but fortunately was able to manage it through medication. After graduation she began a successful career in Virginia. Despite all she has been through, she is grateful for where she is today.

"Cancer has shaped me into the person I am today, and I cannot imagine who I might have been otherwise," said Kim.

Biological Understanding

Effects of cancer and cancer treatment take many forms. 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."

While many late effects of cancer treatment are common to both children and adults (e.g., cardiovascular disease), the effects of treatment on physical growth and development are particularly pronounced in pediatric cancer survivors treated during a time when their bodies are still growing and their organs are still developing [31, 32]. In particular, 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 matured organs in adults, and may only appear as the individual gets older. Recent research has also documented that 13.1% of women and 2.7% of men treated for cancer as children fulfilled criteria for frailty, a clinical syndrome usually associated with aging that is related to mortality [33]. In fact, frailty among childhood cancer survivors in this study currently in their 30s was on par with others without cancer who were 30 years older, representing a significantly accelerated aging process.

The age of the child during cancer treatment is an important factor in determining the burden of effects seen later in life [31, 32]. Infants who have received intensive treatment have higher risks of neurocognitive injury, growth delay, musculoskeletal defects, and organ dysfunction due to the increased toxicity to immature organ systems and tissues. Older children may have these same problems but also may be more vulnerable to emotional problems and deficits in social maturation or functioning, depending on their cognitive maturity and psychosocial support. Additionally, treatment during puberty carries further risks: pubescent girls treated for Hodgkin disease, especially those treated with higher cumulative radiation doses, have a 4–35% increased risk of subsequent breast cancer 20 years later [34].

"I think we must consider the long-term side effects of cancer therapies and cures. For example, if you cure a 75-year old and he dies five years later, you might not ever observe side effects with a long latency that might have arisen 20 years from the date of treatment. Young children cured of cancer have a lifetime ahead of them during which to manifest the long-term adverse effects of treatment."

— *Dr. Michael Link, Professor of Pediatrics, Stanford University School of Medicine*

Biomarkers of Late Effects

By definition, late effects of cancer and cancer treatment only become clinically apparent some time after treatment has been completed. This makes it more difficult to reduce late effects through modification of existing treatment strategies, or the development of altogether new treatments, 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 [35]. As the damage to the heart is occurring, the cells release certain proteins, including cardiac troponin-T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP), which can be measured at the time of treatment. Elevated levels of these proteins predict later cardiac effects and allow researchers to immediately understand how a therapy may cause late effects without having to wait years for the effects to become apparent [36]. These two proteins are examples of biomarkers, which are discussed further on page 26.

"Biomarkers are essential not only in working towards cure, but in predicting or eliminating late effects and/or understanding treatment effects. Many researchers are recognizing the value in these, which is promoting their development and utilization."

— *Ms. Stacia Wagner, Senior Director of Quality of Life Programs and Research at Children's Brain Tumor Foundation*

Even where 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 fundamental biological differences between adults and children, including the greater potential for harm in children whose bodies are still developing.

Preclinical Research

Research into the basic biology of cancer can provide an understanding of what may have led to the development of a given type of cancer and what makes a cancer grow and survive. Armed with the knowledge of what drives a given cancer, researchers can create drugs that can exploit weaknesses or attack biological processes that are critical to cancer growth. The first step of this translation of basic science to a usable treatment begins with preclinical research. Preclinical research is conducted in cell- or animal-model systems that are meant to mimic cancer in humans or that otherwise might provide insights into how a drug might work in a person without actually administering the drug to a human. This kind of research provides meaningful information about the impact of a drug on a particular cancer without exposing people to potential harm and the unknown benefit of an experimental drug candidate. Preclinical research can be thought of as a filtering step that determines whether a particular drug is able to kill targeted cancer cells in a test tube or in animal model (Figure 6). The US Food and Drug Administration (FDA) generally requires animal studies of a drug before introduction of a new drug into humans. Before new drugs are tested in children, in addition to preclinical data, in the majority of cases such new drugs undergo testing in adult human studies prior to exposing children to the unknown toxicities of novel agents. Studies of cancer drugs in adults also provide the best guess about the right dose to start testing a drug in children. In childhood cancer the preclinical phase of drug development is critical, as there are very few children on whom new therapies

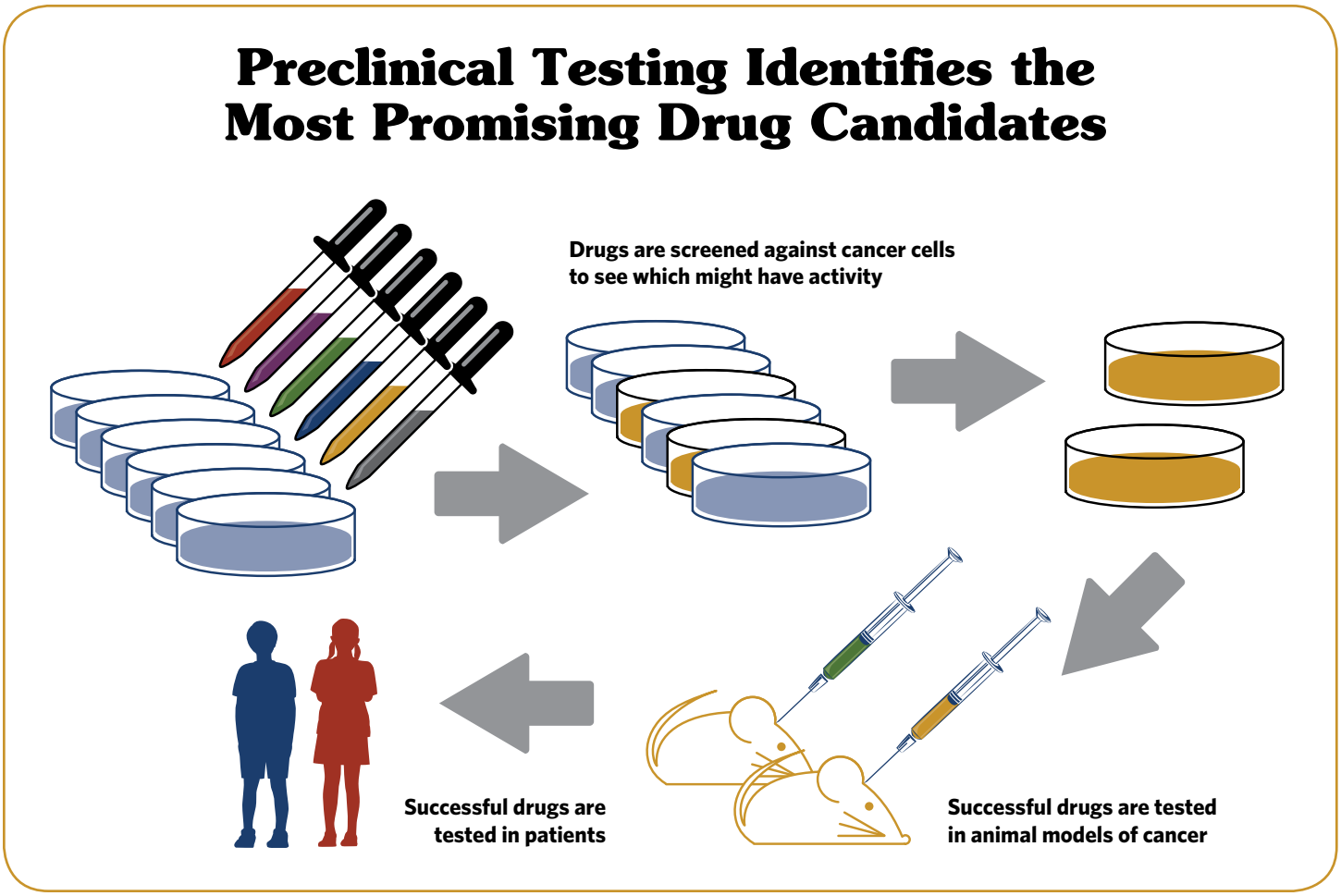


Figure 6: Preclinical testing involves initially testing drug compound in cell models of cancer. Drugs that show activity can then be further tested in animal models and those that perform well in animals can finally be tested in humans.

can be tested, and federal laws protect children from research that may be too risky (see Regulatory Requirements chapter, page 32). Therefore, the drugs that eventually move forward into pediatric clinical trials must be those with the highest probability of working [37].

Cell Models

One of the hallmarks of cancer is that it grows uncontrollably. This feature makes it possible to remove cancer cells from the body and continue to 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 [38]. Since that time, other types of tumors have been successfully grown in the laboratory, giving researchers access to cells from many different cancer types. Researchers can test drug candidates on these cancer cells in a petri dish to see whether cancer cells die without having to give drugs to patients directly.

Cell models can be an attractive way to conduct many types of research on cancers that are otherwise rare, but testing on cells has certain limitations. Not all cancer cells can grow and divide in culture, and in order for cancer cells to grow in culture indefinitely, they must acquire unique characteristics to allow such continuous growth. As a result, cell lines (a population of cloned cells grown from an original cell source like a tumor) 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 sub-clones that may have significantly different drug response profiles. As an example, there are as many as 30 rhabdomyosarcoma cell lines reported in the literature, but up to one-third of them have been found to be significantly different than the "parent" line originally generated [39]. Cell models also lack important features of tumors that naturally 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 models to drug concentrations that will effectively block cancer growth, but it might be impossible to achieve the same drug concentrations in a child without causing unacceptable toxicity.

"There is a lack of preclinical data to justify running some trials that are proposed."
— Dr. Gregory Reaman, Associate Director, Office of Hematology and Oncology Products, US FDA

Animal Models

While cell models may be able to identify which drug candidates have specific activity that might kill cancer cells, they are less likely to provide information about how a drug might behave in a human body, which is why animal models are important. 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, for example in 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 answer these questions, providing better predictions about drug success than is possible with cell cultures. Models vary, but the animals in which preclinical testing is performed are most often mice or rats, but may include rabbits, dogs or other animals.

The goal of animal models is to understand how well a drug candidate fights cancer in a live host. In animal studies, cancer is typically introduced into the animal 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 cancer that is being studied, for example sarcoma or melanoma [40]. These are known as genetically engineered models (GEM). A second type of animal model of cancer involves chemically induced models where known carcinogens are used to reproducibly create a specific type of cancer in an animal. Examples of this include colorectal cancer in rats [41]. The last type of animal model involves directly placing cancer cells into an animal, and is known as a xenograft model. In this case, often the same cancer cells that are used as part of a cell model of cancer described previously are injected into an animal which essentially leads to a human tumor growing within the animal's body [40].

Preclinical Research

Companion Animals in Cancer Research

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

Some researchers have realized that companion animals (pets) — and even more specifically, dogs — get certain types of cancer at roughly the same frequency of humans. Nearly a million dogs are diagnosed with cancer per year in the United States. Some of the cancers seen in dogs, like 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. Recognizing the potential of this type of research, NCI supports a comparative oncology trials consortium (COTC) of 20 academic veterinary centers to help advance this translational work. In 2015, the Institute of Medicine conducted a two-day workshop examining opportunities to advance this field [42].

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 xenograph, 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 xenograph models.

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 adult studies, so the scientific community has debated the value of juvenile models [43, 44]. FDA issued guidance in 2006 generally supporting the use of juvenile animal models in the context of pediatric drug development models [45]. More recently, however, they have suggested that juvenile animal studies for pediatric oncology drugs may not be necessary to initiate Phase 1 trials, but rather may be more useful at a later stage if a drug advances beyond Phase 1 testing [46].

Pediatric preclinical testing is a specialized form of research, and NCI has provided funding for six research centers that make up a Pediatric Preclinical Testing Consortium (PPTC), with each center focusing on a different category of pediatric cancers. The PPTC develops, characterizes and maintains tumor cell lines and animal models of cancer that are used to test between six and 10 drug candidates per year against pediatric cancers [37]. They also share these models with

Ian

Ian was 16 when he was hit particularly hard in his knee during a football game. In pain and worried that he had injured it, he saw his doctor and was surprised when the reason for his pain was not tendon damage, but instead from a tumor growing in his bone. His diagnosis was osteosarcoma, a type of bone cancer that develops in approximately 400 children and adolescents each year in the United States. After his somewhat accidental diagnosis he began a grueling series of treatments for his cancer, which included 19 rounds of chemotherapy and seven surgeries. While amputation used to be more common for osteosarcoma patients, advances in treatment meant that in Ian's case the tumor could be removed and his leg was spared with the use of cadaver bone and enough screws and rods that he sometimes sets off metal detectors. Not only did he keep his leg, but he went on to continue participating in athletics after recovering from treatment.

Ian has since graduated from high school, enrolling at Macalester College in Saint Paul, Minn., where he competes on the college's swim team and is studying public health. Determined to make a difference for other children with cancer, not only has he volunteered to take part in multiple research studies, but he is also working as a research intern on some of the very same studies in which he participated. The pediatric oncology laboratory that he is a part of is examining biomarkers that could help to identify those that are at higher risk for developing osteosarcoma, with hopes of identifying cancer earlier, or even one day being able to prevent it.

Now a towering young man well over six feet tall, he still returns back to the same children's clinic where he first got his care. While he may seem out of place with the cartoon-decorated walls and kid's toy boxes, he is cognizant of the added health risks that were caused by his previous cancer treatment. "If I stop going to the children's cancer center for my checkups, it would probably be because of a diagnosis of an adult cancer, so it makes me happy to keep going there," said Ian.

other researchers for drug development work. Since the drug candidates represent potential commercially marketable drugs and are typically patent-protected, the PPTC has developed model legal agreements which help spell out how intellectual property rights will be handled in the event that the use of shared preclinical models lead to drug development [47, 48]. Several drugs for children have moved from PPTC testing into clinical trials, including the MEK inhibitor selumetinib and the PARP inhibitor talazoparib [47]. Other organizations also 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 [49], and the Children's Oncology Group, which maintains a repository of cell lines that currently includes 75 lines covering five different types of pediatric cancers available for screening drugs [50].

Summary

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 molecule 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.

"Unless we can generate meaningful preclinical data, we won't be able to develop a treatment that is a home run. At present, people use weak rationales to justify taking a drug for adults and using it on kids without strong preclinical justification."

— *Dr. Girish Dhall, Director, Neuro-oncology program, Children's Hospital Los Angeles*

Before new drugs are tested in children, in addition to preclinical data, in the majority of cases such new drugs undergo testing in adult human studies prior to exposing children to the unknown toxicities of novel agents.

Clinical Research

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 safety and efficacy of a drug or drug combinations or other therapeutic interventions, and are among the most expensive and challenging phases of research.

Historically, cancer drugs have rarely been developed expressly for children. More commonly, drugs are tested in children only after they have been proven to be safe and effective in one or more types of adult cancer (see paths A, B, D in Figure 7). In the period from 2009 - 2015, there were 57 new cancer therapies approved, of which only two were developed initially for children (Table 5). Nonetheless, unlike for adults with cancer, participation of children in clinical trials is relatively common. High participation rates in clinical trials are frequently touted as the factor most responsible for the dramatic rise in survival rates for many childhood cancers. However, there are unique issues when conducting clinical research with children, and they are discussed below.

Anatomy of a Clinical Trial

Clinical trials for drug development are often divided into three phases. Phase 1 is focused on testing for safety; Phase 2 helps optimize dosage and determines initial efficacy, and Phase 3 is designed to confirm whether a drug works, especially as compared to the standard treatment in use at the time of the trial. While uncommon, Phase 0 trials also exist, which are very small trials conducted prior to Phase 1 trials. Each subsequent

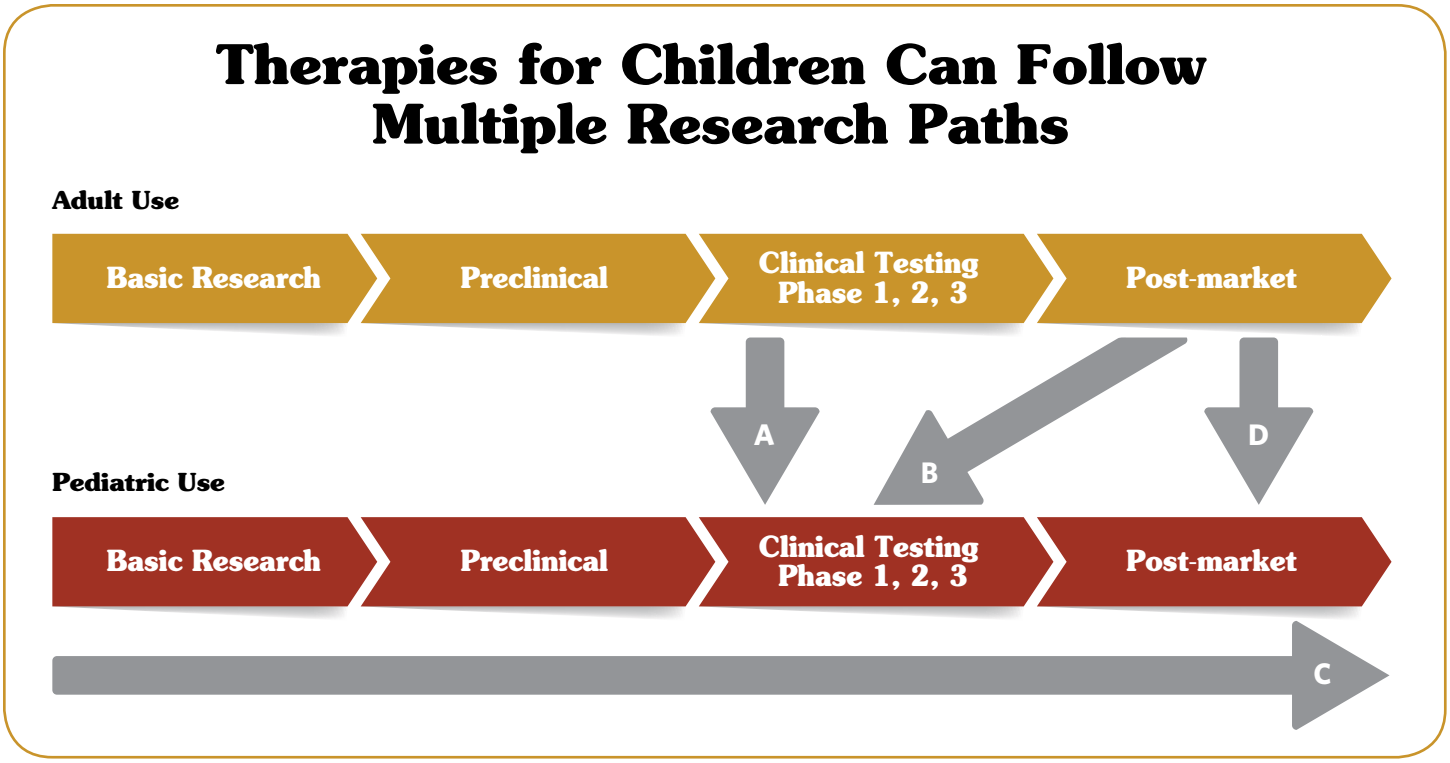


Figure 7: Drug development for children occurs in several different ways. A) Clinical testing in children can occur simultaneously with testing in adults. Research on a drug in children may lag behind research in adults - in this case by one or two phases, but nonetheless begins before the adult indication is approved. B) Testing in children sometimes only starts after a given drug has already been approved for use in adults. C) While it rarely occurs, drug development for childhood cancers can begin at the preclinical phase and continue through to 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 FDA review or inclusion of data into the label.

phase typically enrolls more participants than the previous one, and is sized only as large as necessary to answer the basic questions posed in each phase (safety, dosing, efficacy, etc.). Poor results in one phase means that a given drug typically does not progress to the next phase.

The classic paradigm for clinical research is often modified in cancer clinical trials. For example, when testing drugs for non-life-threatening diseases, Phase 1 trials are often done with healthy volunteers to find out how well a drug is tolerated and how fast it is cleared from the body. Many cancer drugs have significant side effects, so it is considered unethical to test them in healthy individuals. Instead, Phase 1 safety trials for cancer drugs are conducted in patients with cancer. In some cases, Phase 1 trials are focused solely on patients whose cancer the drug is designed to treat. If a drug successfully works against a particular cancer type, its efficacy can sometimes be observed at the same time as safety is being tested. In both adult and childhood cancers, it is sometimes possible to collect sufficient information about a drug's safety, dosing, and efficacy to satisfy FDA's approval criteria after Phase 2 studies. If a drug is particularly effective, it can even be approved after an expanded Phase 1 study. As a result, the classical paradigm of sequential and separate Phase 1, 2, and 3 studies may not always apply for cancer drug development.

In non-life-threatening diseases, drugs are sometimes tested in clinical trials against placebos, or "sugar pills," to make it easier to evaluate a drug's effect. However, cancer clinical trials rarely use placebos as the only treatment. When someone has a serious disease like cancer it is unethical to withhold treatment as part of an experiment, so in cancer clinical trials a new drug is usually tested against whatever treatment is considered standard at the time. In a randomized Phase 3 clinical trial, half of the patients typically get the standard treatment, while the other half get the new drug being tested. In some cases, the new drug is administered in addition to the standard therapy rather than in place of it. If the patients receiving the new drug fare better, then it is typically approved and becomes the new standard treatment for patients with that type of cancer.
Clinical trials do not necessarily stop once a drug has been approved by FDA. Once on the market, many drugs undergo additional testing through clinical trials to optimize dosing amounts, frequency, duration, or sequencing, and to detect uncommon side effects. Multiple approved drugs are also sometimes compared against each other, or compared against other treatment modalities like radiation or surgery. These post-market studies are sometimes referred to as Phase 4 studies, and they are intended to further refine and optimize the use of a treatment that has already been shown to be effective against a given cancer.

Measuring Outcomes

New cancer therapies are considered successful when they improve survival and/or reduce side effects over existing treatment options; however, determining how and when new cancer therapies are successful can be complex. Ten children with the same cancer could be given the same treatment and have very different outcomes because of differences in the children, such as age and underlying health, or their cancers, or because of random variation that occurs in any biological process. A standard way to rule out random variation is to repeat the same experiment enough times to be confident that the outcomes are very unlikely to be the result of chance, or in other words, to enroll more participants into a clinical trial or to repeat the trial on another occasion. Both of these strategies are hard to implement because of the small numbers of children with cancer.

The pace of disease progression for specific childhood cancers also affects the length of time needed to measure outcomes of trials in those cancers. diffuse intrinsic pontine glioma (DIPG), a rare cancer of the brain, has a median time to progression of six months and median time to death of a year or less, with fewer than a quarter of children diagnosed with this type of cancer still alive after two years [4]. The low survival rates and short progression time for DIPG means that determining whether a new drug results in improved overall survival in a clinical trial can happen quite quickly because changes within a year in the number of patients surviving would be obvious. Current treatments for ALL, however, provide a 90% five-year survival rate for children younger than 14. For ALL, a treatment that increased five-year survival from 90 to 95% would be more

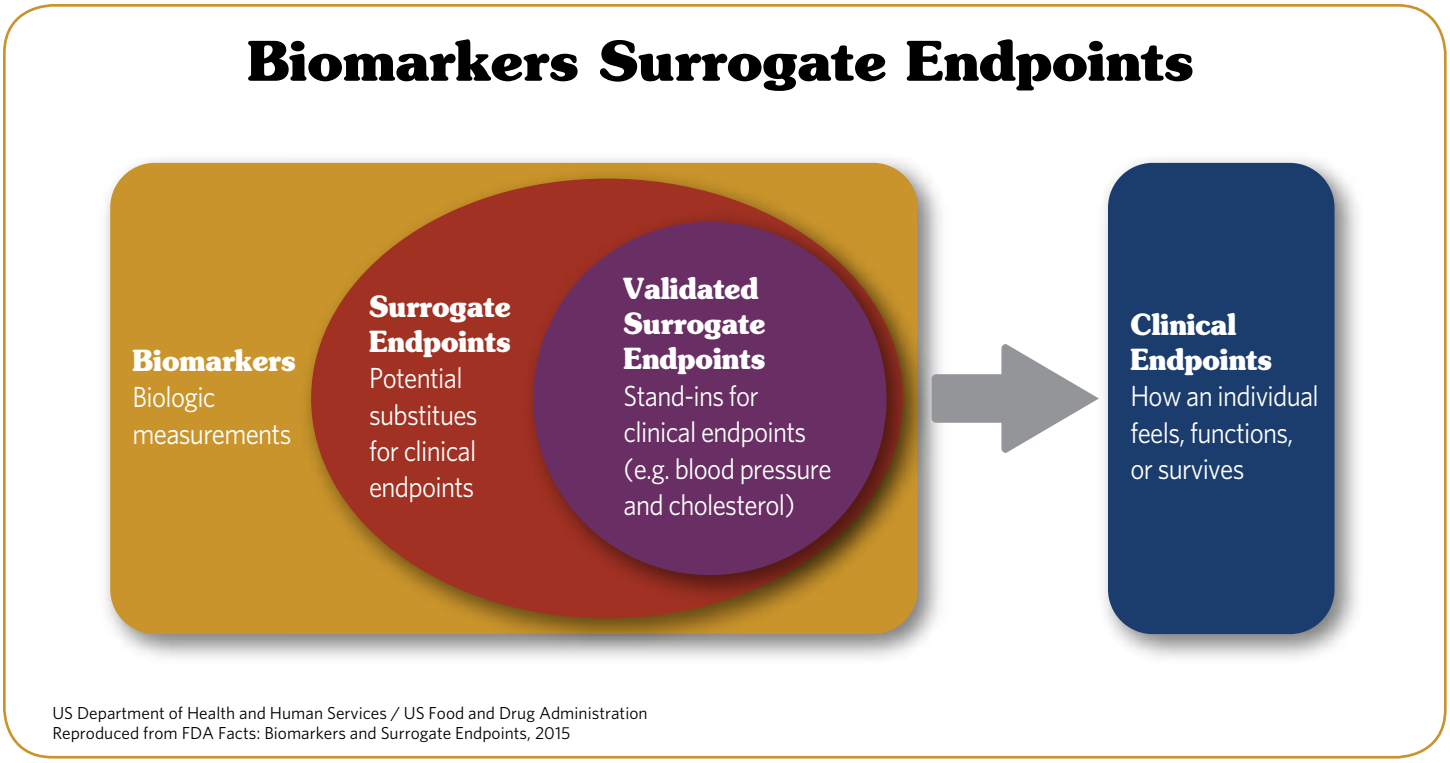
difficult to measure quickly because of the amount of time that would have to pass to observe a measurable difference in outcome. As cure rates increase and survival becomes longer, it takes longer and lengthier experiments—sometimes with more patients—to determine if a new drug works better than the previous one based on survival as the endpoint.

Biomarkers

With few children diagnosed with a specific cancer in any given year available to enroll in a clinical trial and a need to develop new treatments in a timely manner, efforts have been made to use advanced trial designs and outcome measures to minimize the number of children needed in clinical trials and the length of time needed to conduct them. 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 trial design, such as single-arm trials, Bayesian statistics, and measuring surrogate endpoints to make clinical research more efficient [51].

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 the time until a cancer progresses, tumor shrinkage as measured by imaging, the percentage of patients responding to a drug, or the change in some biological measurement, like white blood cell counts or a particular protein in the blood. These are considered "surrogate" endpoints because they do not directly measure the outcome of greatest interest, namely survival, but rather they are outcomes that typically correlate with survival that are easier and faster to measure.

Surrogate endpoints are members of 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



US Department of Health and Human Services / US Food and Drug Administration
Reproduced from FDA Facts: Biomarkers and Surrogate Endpoints, 2015

Figure 8: Biomarkers are biologic indicators that can provide information about the health or disease state of a person, and some of these biomarkers can stand in for clinical endpoints if they can be shown to reliably predict clinical outcomes like survival.

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 effects (e.g., cardiac troponin T (cTnT)—see page 16). The advantage of biomarkers is that they can yield vital information about the effect of a drug more rapidly than longer-term clinical outcomes like survival. Biomarkers must accurately predict later clinical effects (see Figure 8) 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 [52]. From 2010 - 2014 , more than 40% of all new drugs approved by FDA were approved based on a surrogate endpoint [53].

Innovative Trial Design

Newer treatments can work in ways that necessitate new clinical trial designs. For example, many targeted drugs only work on subsets of cancer that harbor a specific genetic mutation (see Biological Understanding chapter). Treatments that work in this way can make the pool of children potentially eligible for a targeted drug trial even smaller and rarer. To find and enroll appropriate participants in clinical trials for such targeted therapies, all patients must have their tumors genetically profiled. If the standard of care does not already include this profiling, it can add an extra step to the trial process. For example, around 10% of ALL cases harbor a mutation in one of the JAK genes [54], so testing a drug targeted to this mutation would mean that 90% of patients with ALL would be found unsuitable after genetic profiling to participate in a trial for a drug targeted to the JAK mutation.

Increasingly the idea of a "master protocol" is addressing the treatment of cancers that have different mutations. Master or umbrella protocols test multiple targeted agents within the same clinical trial against cancers with different mutations. In the ALL example above, if five different targeted drugs were being developed, instead of conducting five different clinical trials, a master protocol would consolidate all the trials into one large trial. A patient's tumor would be tested and then the trial participant would be placed in one of multiple arms, each of which has a different targeted drug designed for a different tumor mutation. Patients' tumors that do not match any of the targeted drugs might be put on a non- targeted experimental drug. In this way, a large proportion of patients attempting to enroll in a trial can be accommodated at the same time rather than turning many away because a lack of a matching genetic mutation. Recently, a large adult cancer master protocol began for lung cancer patients [55], and plans are underway for a pediatric subtrial in the larger NCI-sponsored Molecular Analysis for Therapy Choice (MATCH) trial. The pediatric MATCH trial will use genetic sequencing to identify genetic abnormalities for which there might be an available targeted drug [56].

Logistics

The relative rarity of childhood cancer has made collaboration among pediatric oncologists through clinical trials a key component of identifying new therapies. In contrast to adults with cancer, a substantial portion of children with cancer are cared for in children's hospitals and cancer centers, and the majority are entered on clinical trials. To enroll enough children into clinical trials often requires numerous locations throughout the US, and indeed throughout the world. Almost all centers treating children with cancer participate in networks and consortia in order to pool their research data to ensure there are enough children enrolled in clinical trials, and therefore, produce scientifically reliable results.

The largest of these networks is the Children's Oncology Group (COG). COG is supported through the NCI and consists of more than 200 pediatric centers in the US, Canada, Switzerland, Australia, the Netherlands, and New Zealand. It is estimated that somewhere between 90-95% of children diagnosed in the US under the age of 15 are seen at a COG institution [57].

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.

There are other groups and collaborations in addition to COG, which have a narrowed focus on a particular phase of a study. For example, some concentrate on early phase (Phase 1 or 2 trials) studies, including the Pediatric Brain Tumor Consortium (PBTC), Children's Brain Tumor Tissue Consortium, DIPG Consortium, and the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC). The Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC) is another cooperative network which emphasizes Phase 1 trials. While the membership, funding, and focus of each network varies, the intent of each is to make conducting trials and sharing of data, resources, and patients more efficient.

Children can participate in either therapeutic or non-therapeutic clinical trials. Non-therapeutic trials may include tissue or data collection for use in basic science (see page 13), while therapeutic clinical trials actively test new treatments or a modification of current treatment approaches. It is estimated that between 50-60% of children with cancer seen at COG institutions are enrolled in research studies of any kind (therapeutic and non-therapeutic), and between 20-30% of children are enrolled in a therapeutic clinical trial [57, 58]. Enrollment in research studies varies with age and may be as high as 90% for children under five. However, enrollment falls to under 20% for adolescents and young adults (generally aged 15 and older). The decline in participation with age is likely due in part because adolescents with cancer are often treated in community settings and at sites other than children's hospitals, where they may exceed age eligibility.

"There is some concern for some of us watching the Children's Oncology Group and other organizations that with the rise of industry trials, you might start to see these groups competing for patients."

— Dr. Vickie Buenger, President, Coalition Against Childhood Cancer

Snapshot of Currently Active Pediatric Cancer Clinical Trials

To provide a picture of current pediatric oncology clinical trials for this report, data on trials open to children with cancer were collected from www.clinicaltrials.gov in January 2016. Open clinical trials must be registered with ClinicalTrials.gov, a service from NIH, with information regarding the phase of the trial, intervention, sponsor, enrollment, and age requirements. Trials on this website that reported accepting children were further filtered to count only those trials for participants 21 years of age or younger, and included an active therapeutic intervention, as opposed to a nontherapeutic intervention. Many adult trials expand eligibility criteria to include physically mature adolescents, including those as young as 15 years of age, but these were excluded from this analysis to ensure that the data below were truly focused on children. Additionally, adult trials listed on ClinicalTrials.gov that included adolescents do not indicate the proportion of overall enrollment that is adolescent.

There were 166 trials listed as active that met the age and therapeutic criteria with a total potential enrollment of 17,543 participants. Potential enrollment is the reported overall trial enrollment goal noted in the record and did not reflect how much progress had been made toward that enrollment goal at the time of analysis. Phase 3 or combined Phase 2/3 made up only 17% (29) of the active trials, but because these late-phase trials tend to enroll more patients per trial, these trials accounted for more than half of the potential overall patient trial enrollment for children. Phase 3 trials averaged 339 participants per trial, but ranged from having 60-800 participants and included a wide variety of interventions beyond testing anti-cancer drugs, such as devices, radiation treatments, procedures, and some supportive medications. Phase 0, 1, and combination 1/2 trials made up a much greater proportion of the open trials at just under 50% (79 trials), but had openings for far fewer participants at 3695 openings (22% of total potential enrollment). This grouping of early phase trials ranged from 5 - 310 participants, with an average size of 47. If the combination phase 1/2 trials, which tend to be larger than phase 0 and 1 trials, are removed from this early phase grouping, the average size for the phase 0 and 1 trials shrinks to 34 participants, which is almost a tenth of the size of the average late-stage trial. Unlike Phase 3 trials, these early-stage trials almost exclusively test drugs, biologics, and devices.

Phineas

In spring 2013 Phineas had a cold and slight fever that wasn't going away. His mother, Tina, brought him to the doctor's office and noticed a rash that looked startlingly familiar to the petechiae she saw on her daughter, Althea, who died from acute myeloid leukemia at age two, two years before Phineas was born.

At four years old—six years after his sister's death from childhood cancer—Phineas was diagnosed with high-risk acute lymphoblastic leukemia (ALL). Phineas started treatment immediately, but it was apparent early on that the ALL Phineas had was chemo-resistant, leaving him with very few options.

A long-shot option was enrolling Phineas in an immunotherapy clinical trial. The luckiest of lucky breaks occurred when Phineas was accepted to an immunotherapy trial headed by Dr. Daniel Lee at the National Cancer Institute. Most of the other patients had gone through full treatment, went into remission and then relapsed, but Phineas was one of the first primary refractory patients—those who did not respond to the initial cycles of chemotherapy. "For those patients, yes, you can try more chemotherapy and more intensive chemotherapy," explained Dr. Lee. " But you really have a very, very, very low chance of curing a patient like that. For Phineas, there really was no other option."

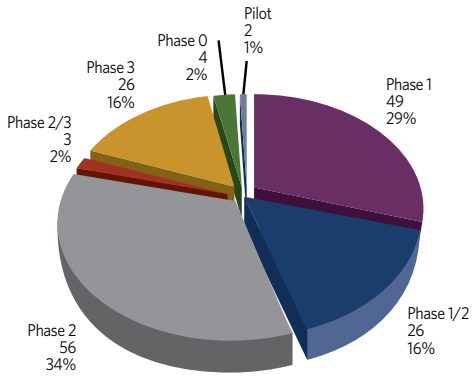
During the trial, some of Phineas' T cells were harvested from his blood, then grown and altered in the lab to lock onto cancer cells and destroy them.

Eleven days later, those cells were injected back into Phineas. For a few days, Phineas had a high fever and symptoms similar to a bad case of the flu. For a fleeting time he simply couldn't talk, which was a reaction seen in some other patients. Thankfully, the reaction, called cytokine release syndrome, was short-lived. More importantly, it actually indicated that the treatment was working.

Within a month of the treatment, Phineas was cancer-free and has subsequently gone through a bone marrow transplant to increase his chances of remaining in remission.

Three years later, Phineas is still cancer-free thanks to taking part in a clinical trial.

Active Trials by Phase



Potential Trial Enrollment by Phase

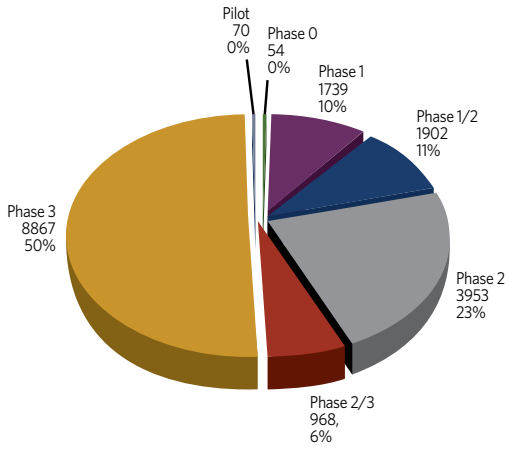


Figure 9: While Phase 3 trials make up a small proportion of active pediatric (<21 years) trials, they dominate the overall enrollment because they tend to enroll more subjects per trial than early phase trials. These late-phase trials test a wide variety of interventions beyond unapproved drugs, including radiation and other procedures. Phase 1 trials tend to focus on unapproved drugs and devices almost exclusively.

Prioritization of Trials Based on Available Patients

Despite the relatively high participation rate of children in clinical trials, the number of research trials for different types of cancers can be significantly limited by the number of eligible children. While 14,660 children are expected to be diagnosed with cancer in 2016, only 20-30% typically enroll in a therapeutic trial [57, 58]. The analysis presented here shows the overall potential enrollment by phase, but it does not reflect the potential enrollment to treat a specific cancer. Certain cancers may have few or no trials open, while others may have multiple trials open, creating competition for the same patients. This competition may be seen especially in cancers that may only have a few dozen to a hundred diagnoses per year. If competition for the trials is too strong, it can present recruitment challenges and lead to longer completion times for trials.

"Absolutely we compete for rare patients. This is why I think we need a prioritization forum to address this."

— Dr. Raphael Rousseau, Group Medical Director, Product Development Oncology, Global Franchise Head, Pediatrics, Genentech

Currently there is no central prioritization process for clinical trials to ensure that competition for patients does not slow down research, although several groups do provide guidance on research needs. The Pediatric Subcommittee of the Oncologics Drug 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 the Regulatory Requirements chapter). The Best Pharmaceuticals for Children Act (BPCA), also discussed in the Regulatory Requirements chapter charges the NIH, in consultation with FDA and pediatric experts, to develop and publish an annual list of priority needs in pediatric research. 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.

"I really think we need to develop a priority list or a hierarchy that will help us accelerate drugs that have the most promise."

— Ms. Donna Ludwinski, Director of Research Programs at Solving Kids' Cancer, Inc.

Dosing and Formulations

Most cancer drugs are initially designed for adult usage (paths A, B, D in Figure 7), which can pose unique challenges when attempting to test them in children. In the case of drugs that are already approved and sold, oftentimes 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, or in some cases, especially young children, they may not 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 to consume; however, issues of solubility and unpleasant taste can make this impractical. Therefore, prior to conducting pediatric trials, new formulations of drugs are sometimes required.

Summary

Low numbers of children with cancer can make recruitment for clinical trial participation challenging, but fortunately, children with cancer tend to be seen in very specialized institutions that participate in well-established collaborative networks, resulting in a relatively high proportion of children enrolling on clinical trials. Indeed, somewhere between 50-60% of children with cancer enroll into clinical trials (therapeutic and observational), and 20-30% enroll in therapeutic trials. The high proportion of children already in trials can limit attempts to expand clinical research, as trials risk competing for the same patients. Currently, no central process exists for prioritization of trials based on available patients, although several advisory committees are charged with setting research priorities. Challenges with small patient populations are magnified with targeted therapies that only apply to genetically selected subgroups within a given cancer. As trials get smaller and outcomes improve, more sophisticated clinical research designs will have to be used to ensure timely completion of trials and sound scientific evaluation of new therapies. Advanced techniques can streamline trials, but ultimately, sufficient numbers of children will be a limiting factor, reinforcing the importance of collaboration within the research community, both within the US and internationally, to ensure that the pediatric clinical trial enterprise is successful.

Regulatory Requirements

The purpose of conducting clinical trials is to gather evidence about whether a new treatment works and whether it is safe. The US Food and Drug Administration (FDA) is the federal agency that is tasked with protecting the public health by evaluating whether the evidence of a drug's safety and efficacy are such that its benefits outweigh its risks. FDA does not conduct the clinical trials leading to drug approval—that is the responsibility of the drug's sponsor (a biopharmaceutical company or research entity seeking the drug's approval). FDA does, however, 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 make a decision. In addition to protecting public health by deciding when a drug can be sold to the public, FDA is also tasked with protecting research participants during the investigational portion of drug development. Before a drug is taken by humans for the first time as part of a clinical trial, a drug sponsor must first apply to FDA for an investigational new drug (IND) application, which allows the sponsor to give unapproved drugs to patients in controlled research settings.

History of Regulation for Research and Drug Development

Drug development in the United States is governed by a number of laws, regulations and guidance documents that cover patient protection during the research phase. They also establish standards of evidence for drug approval, review 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 US 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. More than 100 people died after taking the formulation, including 30 children [59]. 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 animal and human studies (see Preclinical Research and Clinical Research chapters).

Regulations Governing Safety of Research Participants

Ethical considerations when designing research on 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). The job of an IRB is to ensure that the proposed research protocol is ethical, and to approve 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 that can 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 one centralized IRB that has the authority to review and approve a clinical trial protocol for all locations [60].

Pediatric-specific Requirements

Adults can vary in how much risk they are willing to take on 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 totally unwilling to participate in a Phase 1 trial where safety of a drug is largely

unknown. Participation in research is voluntary for adults, and a long history of ethical arguments confirm that no one can be forced to participate in research without his or her consent. Not everyone, however, is able to provide consent in the same way. Recognizing that certain segments of the population have a reduced ability to provide consent, federal regulations and standards have been developed for vulnerable groups which include prisoners, mentally handicapped, pregnant women and children [61].

Because children below age 18 are presumed not to comprehend fully the nature of a research study, parents technically "give permission" for their children to participate. Children and adolescents of mature mind also are expected to "assent" to participate in research studies, given sufficient explanation of its purpose and procedures. Federal law provides special protections for children when they participate in research studies [61]. Research in children cannot be conducted solely to answer scientific questions, regardless of how important they may be. At each phase in testing new cancer agents in children, law and ethics 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 10).

Phase 1 studies in pediatric oncology provide researchers other important opportunities for understanding how a child's body

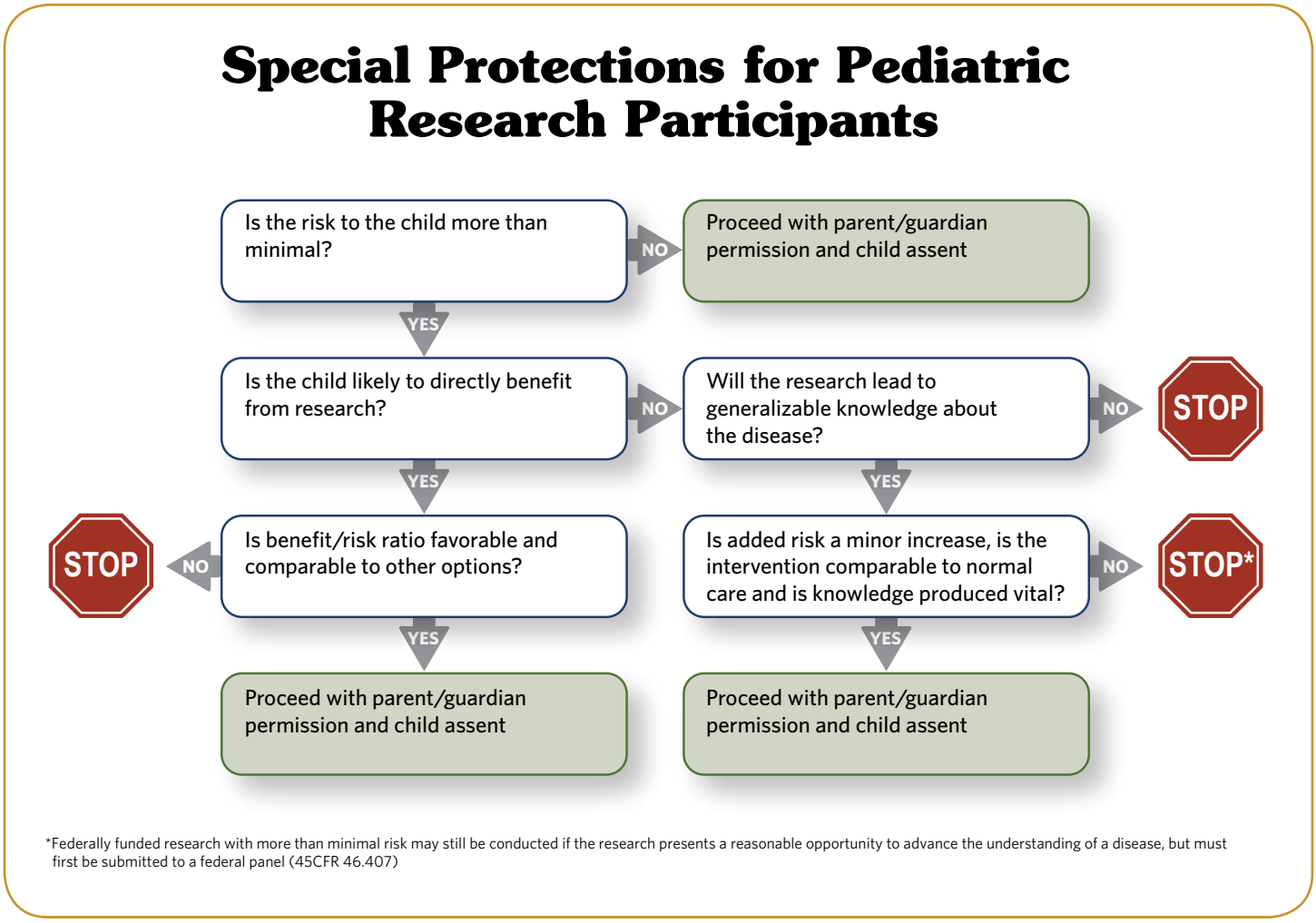


Figure 10: Federal regulations (21 CFR 50) provide special protections to children who participate in research. The ability to conduct pediatric research depends on the nature of the research and its anticipated risks and benefits for children.

processes a new drug, and whether the drug affects biological targets that can reduce or stop cancer growth. Answers to these critical scientific questions may require biopsies of a cancer or normal tissue to determine treatments for a particular child's cancer. However, if one or perhaps multiple biopsies are needed solely to answer scientific questions that may not benefit a particular patient, then they cannot be conducted if the procedures pose greater than minimal risk to a child (Figure 10). 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 in the scientific and family advocacy communities on ethics of non-therapeutic single or multiple biopsies in children [62].

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, page 10). 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 [63], and today all new drug labels include a dedicated "Pediatric Use" section. FDA has issued formal guidance about the language to be used to describe pediatric information, as well as where else in the labeling information about pediatric use must be included. 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 [63]. The pediatric labeling of drugs approved before pediatric labeling regulations were in place varies greatly. Tables 3 and 4 list cancer drugs that include some form of pediatric information within the drug label.

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 created two programs to promote pediatric research on drugs that are otherwise developed for adults. These two programs are often referred to as "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, as the Best Pharmaceuticals for Children Act (BPCA). BPCA provides an incentive for drug sponsors to conduct research using their drugs in childhood diseases. Originally only a temporary program, it has now been made permanent. 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.

The scope of the research needed to obtain the extra exclusivity is determined by FDA and is contained in 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 in a childhood cancer per the WR requirements and the drug is not found to work, the sponsor would still get the added exclusivity for adult uses of that drug. While the BPCA research requirements are

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: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm*

Few Cancer Drugs Have Formal Pediatric Labeling

FDA Actions on Submissions or Supplements for Pediatric Cancer Indications from 1953-2015

Drug	Date	Indication
Drugs approved prior to FDAMA where labeling includes pediatric indications		
Mercaptopurine	09/11/1953	ALL
Methotrexate	08/10/1959	ALL, meningeal leukemia, osteosarcoma, non-Hodgkins lymphoma
Cyclophosphamide	11/16/1959	Leukemia, lymphoma, NBL, retinoblastoma
Vincristine	07/10/1963	ALL, lymphomas, Wilms, rhabdomyosarcoma, NBL
Dactinomycin	12/10/1964	Ewing Sarcoma, sarcoma botyroides
Vinblastine	11/05/1965	Histiocytosis, testicular germ cell carcinoma, Hodgkins lymphoma
Thioguanine	01/18/1966	Acute non-lymphomatic leukemia
Cytarabine	06/17/1969	Acute non-lymphomatic leukemia
Procarbazine	07/22/1969	Hodgkins lymphoma
Doxorubicin	08/07/1974	Wilms tumor, NBL, soft tissue sarcoma, Hodgkins lymphoma, other lymphomas, ALL, AML
Lomustine	08/04/1976	Brian tumors, Hodgkins
Daunorubicin	12/19/1979	ALL
Drugs where labeling includes pediatric-specific indications		
Teniposide	07/14/1992	Refractory ALL
PEG-Asparaginase	02/01/1994	ALL
L-Asparaginase	02/09/1994	Leukemia
Arsenic trioxide	09/05/2000	APML
Clofarabine	12/28/2004	Refractory ALL
Nelarabine	10/28/2005	T-cell ALL
Imatinib	09/27/2006	Ph+ ALL and CML
Everolimus	10/29/2010	SEGA
Erwinia	11/18/2011	ALL
Denosumab	06/13/2013	Giant cell tumor of the bone
6-mercaptopurine	04/28/2014	(Liquid formulation approved)
Dinutuximab	03/10/2015	High-risk NBL
Drugs supporting safe administration of anticancer drugs		
Pegfilgrastim	01/31/2002	Decreases the incidence of infection, increases survival in patients acutely exposed to myelosuppresive doses of radiation
Aprepitant	03/27/2003	Prevent chemo-induced nausea
Palifermin	12/15/2004	Decreases the incidence and duration of severe oral mucositis
Levoleucovorin	03/07/2008	Rescue after HD-MTX

FDAMA-Food and Drug Administration Modernization Act (1997)
Source: Personal Communication G. Reaman, A. Barone, D. Casey, FDA

Table 3: Over the past 60 years, few cancer drugs have had pediatric indications listed in formal labeling. The 1997 FDA Modernization Act (FDAMA) added financial incentives to try to promote more pediatric research.

issued as a WR by FDA, the process can be initiated by either the drug sponsor or FDA (Figure 11). If 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. If FDA finds the PPSR insufficient, they can request that the sponsor amend their PPSR, or if they agree with the proposal, they can issue a WR. FDA does not need a PPSR, however, to issue a WR.

"You have some competing trials that slow one another down. The push for discovery is quick, which is great in some regards, but has the potential to make irrelevant other trials that were already underway."

— Dr. Jeff Allen, Executive Director, Friends of Cancer Research

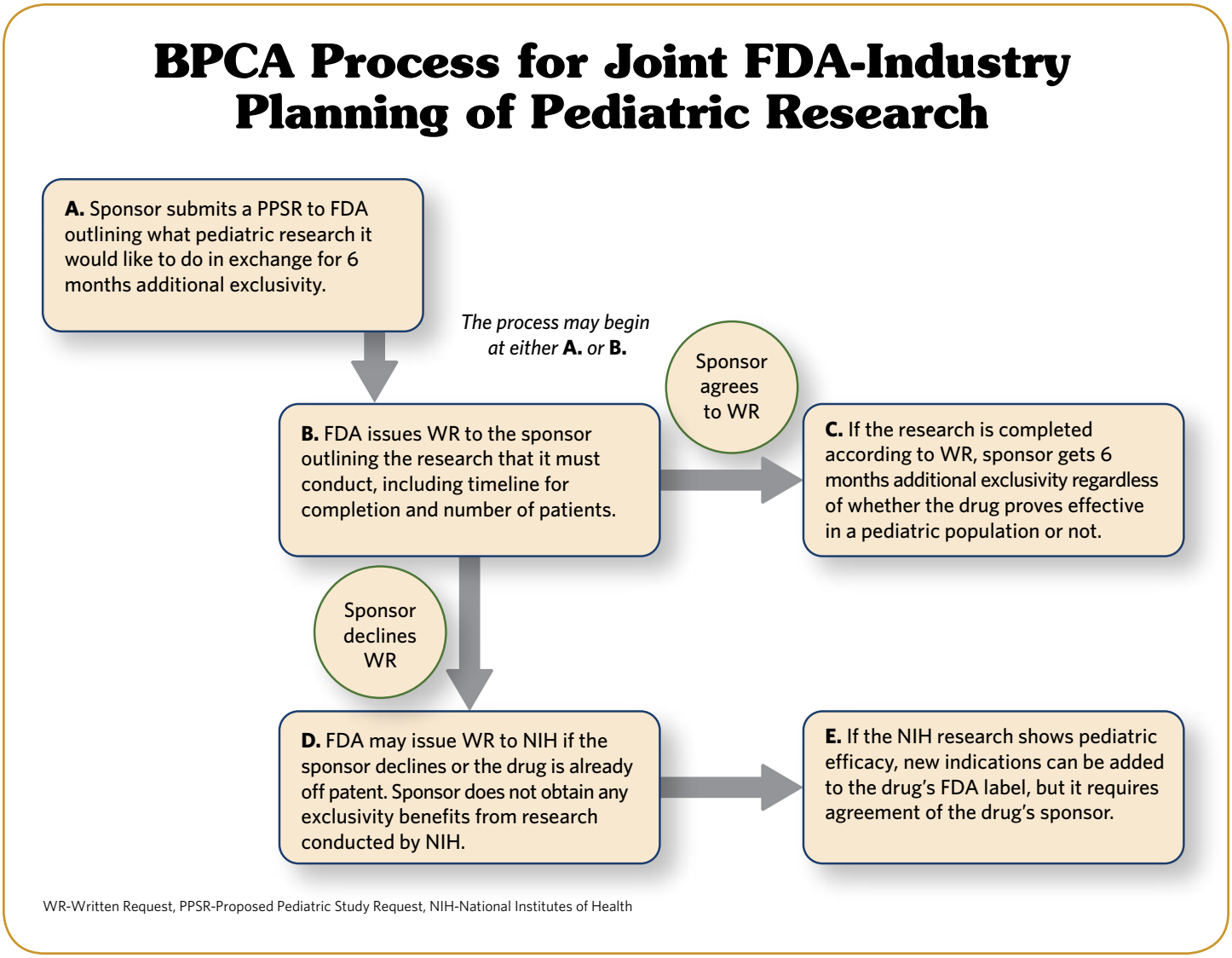


Figure 11: Pediatric research under BPCA involves interactions between FDA and industry. This process can be initiated either by the drug sponsor at A in the flowchart above, or by FDA at either B or D.

The voluntary nature of the program means that drug sponsors can choose whether to perform pediatric research, and to some extent, the timing of the research. The WR does contain 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, meaning that BPCA research can essentially be done at any time up to the expiration of a drug's exclusivity. Table 4 lists cancer drugs that have had pediatric information added to their labeling as a result of BPCA. Table 5 lists all new cancer drugs approved since 2009 and whether a WR was issued for that drug. BPCA and other market incentives are discussed further in the Research Funding and Economic Forces chapter beginning on page 42.

The Pediatric Research Equity Act (PREA) is the "stick" portion of the carrot-and-stick approach to promote pediatric drug research. It was first passed into law in 2003 and created a framework that requires sponsors who are developing a drug for adult indications to also test the drug in children when the same condition exists in children. PREA requires that drug

sponsors seeking approval for a new active ingredient, new indication, new dosage form, new dosing 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, it was originally a temporary program, but has since become permanent [64].

While PREA mandates pediatric research on drugs being developed for adults, there is an important exemption from these requirements for any drug being developed for a "rare" disease. Rare diseases are defined in US law as those that are diagnosed in fewer than 200,000 people per year in the US. Unfortunately, most cancers meet the definition of a rare disease (Figure 12). The three most common cancers in the US — lung, breast, and prostate cancers — do not meet the definition of a rare disease, and therefore would not receive a rare-disease exemption from PREA research requirements. However, there is a second limitation to PREA, which is that it only requires pediatric studies of a drug in the same disease ("indication") for which it is being studied in adults. Since children do not develop lung, breast or prostate cancer, drugs under development for these cancers do not have to be tested in kids. Between the rare-disease exemption and the indication-based exemption, PREA essentially has no impact on childhood cancer drug development. Since 2009, 58 new cancer drugs have been approved; PREA requirements have only been invoked on one drug, an anti-nausea drug (Table 5).

Cancer Drugs that Have Pediatric Information in Labeling as a Result of BPCA

Drug	Condition Studied Under WR
Bendamustine	Relapsed or refractory ALL and AML
Bortezomib	Relapsed ALL
Busulfan	Bone marrow transplant
Capecitabine	Newly diagnosed non-disseminated intrinsic diffuse brain stem glioma, HGG
Carboplatin	Refractory or relapsed malignancy
Docetaxel (confirm)	Refractory or relapsed solid tumors
Erlotinib	Refractory or relapsed ependymoma
Everolimus	Subependymal giant cell astrocytoma (SEGA)
Fludarabine	Refractory acute leukemia
Gemcitabine	Relapsed or refractory leukemia
Irinotecan	Refractory or relapsed solid tumors; newly diagnosed metastatic rhabdomyosarcoma
Ixabepilone	Advanced or refractory solid tumors
Oxaliplatin	Refractory or relapsed solid tumors
Pemetrexed	Refractory or relapsed solid tumors
Temsirolimus	Refractory or relapsed solid tumors; NBL, rhabdomyosarcoma, HGG
Topotecan	Relapsed or refractory solid tumors
Vinorelbine	Leukemia or refractory or relapsed solid tumors

BPCA-Best Pharmaceuticals for Children Act
Source: Personal Communication G.Reaman, A. Barone, D Casey, FDA

Table 4: The Best Pharmaceuticals for Children Act (BPCA) provides six months of additional exclusivity for adult drugs that are studied in children according to a formal written request (WR) issued by FDA. This research often leads to labeling changes that provide information about the drug's use in children.

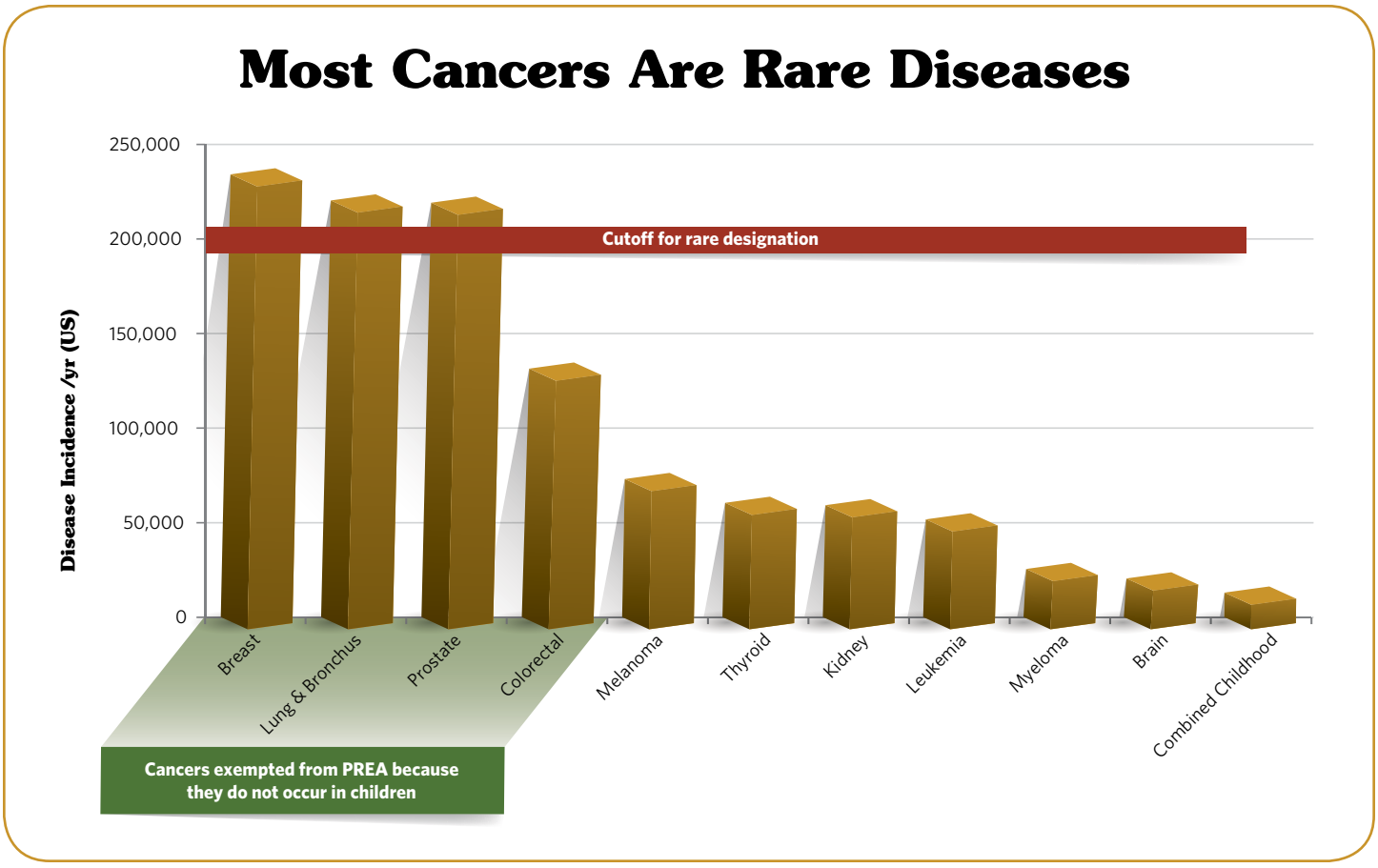


Figure 12: Any disease that affects fewer than 200,000 patients per year in the US is designated as a rare disease. Drugs for rare diseases are not subject to the same regulations as other drugs. All cancers except for lung, breast and prostate cancer are considered rare.

International Pediatric Requirements

While the focus of this report is the United States drug development landscape, drug development goes on outside of the US, and indeed, the majority of children with cancer who could benefit from new therapies live elsewhere [65]. Childhood cancers are rare, and in the US new diagnoses for any given cancer range from under 300 cases per year for retinoblastoma to almost 2,900 cases per year for 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, the trials often must take place simultaneously in multiple countries. This strategy can be challenging, as each country can have differing regulations regarding the participation of children in research, as well as differing requirements for drug approval.

> ***"Of course international cooperation has been necessary... With these small populations, we will not have success unless we collaborate internationally."***
>
> — *Dr. Carlos Rodriguez-Galindo, Chair, Department of Global Pediatric Medicine, St. Jude Children's Research Hospital*

Of all drugs approved in the US, an estimated 50% of trials supporting those approvals are done outside the US [66]. International clinical trials intended to support US drug approval may be conducted under FDA oversight as described previously, but not all are. FDA will still accept data from clinical trials held outside of the US that were not

New Cancer Drugs Approved 2009-2015 and Associated PREA and BPCA Activity

Year	Trade Name	Generic Name	Sponsor	PREA	WR Issued	Cancer
2009	Afinitor	everolimus	Novartis	Waived	X	renal cell carcinoma
	Folotyn	pralatrexate	Allos Therapeutics, Inc.	Orphan		peripheral T-cell lymphoma
	Votrient	pazopanib HCl	GlaxoSmithKline	Waived		renal cell carcinoma
	Istodax	romidepsin	Gloucester Pharmaceuticals, Inc.	Orphan		cutaneous T-cell lymphoma
	Arzerra	ofatumumab	GlaxoSmithKline	Orphan		chronic lymphocytic leukemia
2010	Jevtana	cabazitaxel	Sanofi Aventis US, Inc.	Waived	X	prostate cancer
	Halaven	eribulin mesylate	Eisai, Inc.	Waived		metastatic breast cancer
	Provenge	sipuleucel-T	Dendreon	Waived		prostate cancer
2011	Erwinaze	asparaginase Erwinia chrysanthemi	EUSA Pharma	Orphan		acute lymphoblastic leukemia
	Xalkori	crizotinib	Pfizer, Inc.	Orphan	X	non-small cell lung cancer
	Adcetris	brentuximab vedotin	Seattle Genetics	Orphan	X	Hodgkin lymphoma or anaplastic large cell lymphoma
	Zelboraf	vemurafenib	Hoffmann-La Roche, Inc.	Orphan	X	metastatic melanoma
	Zytiga	abiraterone acetate	Centocor Ortho Biotech	Waived		prostate cancer
	Caprelsa	vandetanib	IPR Pharmaceuticals	Orphan		medullary thyroid cancer
	Yervoy	ipilimumab	Bristol-Myers Squibb Co.	Orphan	X	unresectable or metastatic melanoma
2012	Bosulif	bosutinib	Wyeth Pharmaceuticals, Inc.	Orphan	X	chronic myeloid leukemia
	Cometriq	cabozantinib	Exelixis	Orphan	X	medullary thyroid cancer
	Erivedge	vismodegib	Genentech, Inc.	Waived		basal cell carcinoma
	Iclusig	ponatinib	ARIAD Pharmaceuticals, Inc.	Orphan	X	chronic myeloid leukemia
	Inlyta	axitinib	Pfizer, Inc.	Waived		renal cell carcinoma
	Kyprolis	carfilzomib	Onyx Pharmaceuticals	Orphan	X	multiple myeloma
	Perjeta	pertuzumab	Genentech, Inc.	Waived		HER2-positive breast cancer
	Stivarga	regorafenib	Bayer HealthCare	Waived		colorectal cancer
	Synribo	omacetaxine mepesuccinate	Teva Pharmaceuticals Industries	Orphan		chronic myeloid leukemia
	Xtandi	enzalutamide	Medivation Inc and Astellas Pharma US	Waived		prostate cancer
	Zaltrap	ziv-aflibercept	Sanofi US, Inc.	Waived		colorectal cancer
2013	Gazyva	obinutuzumab	Genentech	Orphan		chronic lymphocytic leukemia
	Gilotrif	afatinib	Boehringer Ingelheim	Orphan		non-small cell lung cancer, EGFR mutated
	Imbruvica	ibrutinib	Pharmacyclics	Orphan		mentle cell lymphoma
	Kadcyla	ado-trastuzumab emtansine	Genentech	Waived		HER2-positive breast cancer
	Mekinist	trametinib	GlaxoSmithKline	Orphan	X	BRAF mutant metastic melanoma
	Pomalyst	pomalidomide	Celgene Corporation	Orphan	X	multiple myeloma
	Tafinlar	dabrafenib	GlaxoSmithKline	Orphan	X	BRAF mutant metastic melanoma
	Xofigo	radium Ra 223 dichloride	Bayer HealthCare	Waived		prostate cancer
2014	Blincyto	blinatumomab	Amgen	Orphan	X	Philadelphia neg B-cell precursor acute lymphoblastic leukemia
	Cyramza	ramucirumab	Eli Lilly	Orphan		non-small cell lung cancer
	Keytruda	pembrolizumab	Merck	Orphan		metastatic melanoma
	Lynparza	olaparib	AstraZeneca	Orphan		gBRCAm ovarian cancer
	Opdivo	nivolumab	Bristol-Myers Squibb Co.	Orphan	X	metastatic melanoma
	Zydelig	idelalisib	GileadSciences	Orphan		chronic lymphocytic leukemia
	Zykadia	ceritinib	Novartis	Orphan		non-small cell lung cancer
	Beleodaq	belinostat	Spectrum	Orphan		peripheral T-cell lymphoma
2015	Unituxin	dinutuximab	United Therapeutics Corporation	Orphan		neuroblastoma
	Farydak	panobinostat	Novartis Pharmaceuticals	Orphan		multiple myeloma
	Lenvima	lenvatinib	Eisai, Inc.	Orphan	X	thyroid cancer
	Ibrance	palbociclib	Pfizer, Inc.	Waived		ER-positive, HER2-negative breast cancer
	Portrazza	necitumumab	Eli Lilly Co.	Orphan		squamous non-small cell lung cancer
	Empliciti	elotuzumab	Bristol-Myers Squibb Co.	Orphan		multiple myeloma
	Ninlaro	Ixazomib	Millenium Pharmaceuticals	Orphan		multiple myeloma
	Darzalex	daratumumab	Janssen Pharmaceuticals	Orphan		multiple myeloma
	Tagrisso	osimertinib	Astra Zeneca	Orphan		non-small cell lung cancer, EGFR mutated
	Cotellic	cobimetinib	Genentech	Orphan		metastatic melanoma with a BRAF V600E or V600K mutation
	Yondelis	trabectedin	Janssen Pharmaceuticals	Orphan	X	liposarcoma and leiomyosarcoma
	Lonsurf	trifluridine/tipiracil	Taiho Oncology	Waived		colorectal cancer
	Odomzo	sonidegib	Novartis Pharmaceuticals	Waived		basal cell carcinoma
	Iressa	gefitinib	Astra Zeneca	Orphan	X	non-small cell lung cancer, EGFR mutated
	Alecensa	alectinib	Hoffman La Roche/ Genentech	Orphan		ALK-positive non-small cell lung cancer
	Varubi	rolapitant	Tesaro, Inc.	Deferred		chemotherapy-induced nausea and vomiting prevention

Table 5: Therapeutic cancer drugs and biologics developed for adults since 2009 are listed along with any BPCA or PREA activity. WR-Written Request

performed under FDA oversight, so long as the trials conform to local laws and regulations, along with minimum ethical requirements regarding patient consent [67].

While international trial data may be used for US drug approval, and vice versa, the data format, review process, and standards for submission and approval may differ from country to country. Even if a drug is already approved in another country, it still must go through a full formal FDA application, as the US does not recognize reciprocal approval with any other countries. FDA does coordinate closely with the European Medicines Agency (EMA), which is the decentralized drug review body for the 28 member states of the European Union (EU), plus Iceland, Liechtenstein, and Norway [68]. FDA and EMA established a "Pediatric Cluster" in 2007, which consists of relevant staff from the two organizations that hold monthly conference calls to share information on pediatric clinical trials that the respective organizations are overseeing. Through this collaboration they 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 [69].

Much like the US has PREA and BPCA, the EMA has requirements for studying adult drugs in children that also involve awarding extended exclusivity for performing this research; however, the FDA and EMA programs differ. While drugs for rare diseases are exempted from PREA requirements in the US, they are not likewise exempted in the EU. The required study plans in the EU are referred to as Pediatric Investigation Plans (PIPs), and these must be submitted at the end of Phase 1 trials, much earlier than the corresponding FDA requirement for similar plans, which is 60 days after the completion of Phase 2 trials.

Summary

The process of developing effective pediatric drugs is an immense scientific challenge, which is made more difficult in the case of childhood cancer because of the relative rarity of the disease. The regulatory requirements that are imposed upon the scientific process are intended to ensure that drugs actually work and are safe before being sold to the public, and they also protect individuals who take part in research. Interestingly, research on children was once seen as unethical because of their vulnerable status; more recently it has been recognized that in order to make medical progress in treating childhood diseases, research with children is not only acceptable, but desired. This has led to certain regulatory requirements that are designed to push drug sponsors to conduct pediatric research that they might not otherwise do. Finally, while the scientific challenges to creating new treatments for children with cancer are inherent to the disease and are shared throughout the world, the regulatory requirements for research and drug approval may vary from country to country based on national laws, cultures and values.

Children often respond to a given drug differently from adults, resulting in different safety, efficacy, or dosing considerations. In recognition of these differences, beginning in 1994 federal requirements were instituted to explicitly include pediatric use information in drug labeling.

Research Funding and Economic Forces

The previous chapters of this report have detailed the lengthy process by which new drugs start as basic research and progress through preclinical and clinical research before becoming FDA-approved drugs available on the market. For any drug to advance through this process, whether for adults or children, it must be successful from a scientific standpoint, but sound science by itself is not sufficient to ensure that a drug makes it through clinical development. Research and drug development are expensive and require substantial financial resources to create the final drugs 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. This chapter examines the funding roles that each group assumes, the rationale for those roles, and the mechanisms by which that funding is provided.

Funding Sources Shift across the Spectrum of Drug Development

Ordinarily, in adult cancer drug development, private industry invests the largest share of overall research dollars required to turn basic scientific understanding into an approved drug [70]. This investment is typically in later stage drug development (Figure 13), and it is done in the hopes of creating a return on investment by marketing and selling an approved drug to patients over a period of years.

While private industry funds most of the later phases of research, the federal government funds most of the early basic research underpinning drug development (Figure 13). Basic research may reveal new biological understanding of diseases like cancer, but it is not always immediately clear how that understanding can be used to improve treatment. Sometimes it takes years or even decades of research to unravel mysteries of cancer sufficiently to finally understand how that knowledge can be applied to fight cancer in the form of a new drug. Private industry is able to support research that is closely linked to creating a new drug product, but because of the high cost and sometimes long time horizons involved in basic research, industry is not poised to make the significant investments needed to make scientific progress in the basic sciences.

By funding basic research, the federal government helps to create an ever-expanding basic scientific knowledge base that can then be used by private industry to create new drugs to treat cancer. The more basic knowledge about a disease that is generated, the easier it is for private industry to translate that knowledge into cancer drugs. As a society, the US has consistently confirmed that reducing the suffering from cancer is a priority worthy of public funding, so significant funds for basic cancer research have been provided by the federal government since NCI was created by the National Cancer Act of 1937. Not only does the federal government seek to make drug development easier by investing in basic science, it also funds clinical trial networks and regulatory initiatives (see Regulatory Requirements chapter) to help industry more easily conduct the clinical trials that are needed to bring a drug to market.

While private industry and federal funding are typically the largest funders of cancer research, philanthropies also play an important role in research funding, especially in the case of pediatric cancer. Philanthropies may fund along the spectrum of research in targeted fashion depending on the mission of the organization and the research needs in the disease area that they support.

Importantly, the distribution of funding previously described and depicted in Figure 13 represents typical adult cancer drug development. Pediatric cancer drug development differs in important ways, many of which are described elsewhere in this report. One of the major differences is that the market for pediatric-specific cancer drugs is small and does not provide the same kind of financial incentive for research into childhood cancers as exists for adult cancers. With less incentive for private industry to invest in pediatric research, the roles of philanthropies and the federal government become relatively more important for childhood drug development than is the case for adult drug development. The differences in these roles is discussed further in the sections that follow.

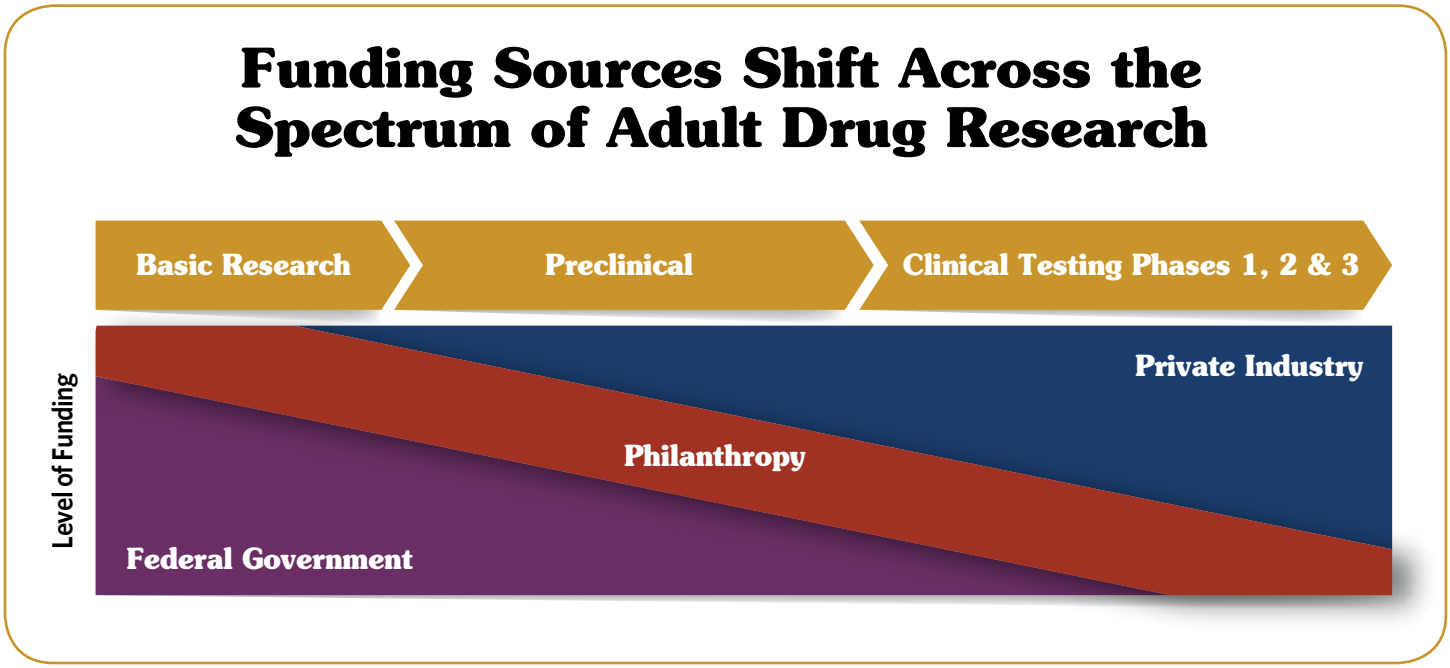


Figure 13: Funding for adult drug development is typically dominated by federal funding for early-stage basic research and by private industry for later-stage clinical research. Philanthropies contribute along the spectrum of drug development. In childhood cancer drug development, federal funding and philanthropies play larger roles overall and federal funding is more important in later phases of research.

Federal Funding of Childhood Cancer Research

National Cancer Institute (NCI)

The federal government is the largest single source of childhood cancer research funding in the US. The National Cancer Act of 1937 established NCI as the primary US government agency responsible for addressing the research and training needs required to discover the causes, diagnosis, and treatments for cancer. The Act also called for NCI to assist with and to 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, placing it as an operating division of the National Institutes of Health (NIH) and 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 [71]. NCI has a unique status among the other institutes and centers at NIH in that its director is appointed by the president of the United States, and it has the ability to produce its own budget proposal separate from the administration's official budget document. This separate document is sometimes known as the "bypass budget" and has no formal role in the appropriations process, but it does provide the NCI director with the opportunity to emphasize NCI's research priorities.

The NCI budget is funded through the Labor-Health and Human Services Education, and Related Agencies appropriations bill as part of the NIH and the US Department of Health and Human Services (DHHS). NCI's budget remained relatively flat from fiscal year (FY) 2005-2015, averaging $4.9 billion per year. At the same time, research costs increased and the NCI budget shrank in constant dollars. These factors have posed serious challenges for cancer research in recent years. However, the NCI FY 2016 budget allocation of $5.21 billion, an increase of $260.5 million from the previous year [72], is an encouraging upswing.

Research Funding and Economic Forces

NCI General Allocation of Funding

The annual congressional appropriation specifies the amount of funding provided to NCI but does not specify the amounts NCI should allocate to its various programs or to research on individual cancers. The NCI director is charged with making allocation decisions with counsel from the National Cancer Advisory Board, a panel of national experts, and internal NCI staff. The majority of the NCI's budget (~85%) funds grants and contracts awarded to universities, medical schools, cancer centers, research laboratories, and private companies in the US and approximately 60 other countries. The remaining funds (~15%) support intramural research, conducted by NCI on the NIH campus in Bethesda, Maryland [71].

NCI distributes funding through a variety of grant and contract mechanisms. Broadly speaking, these funding mechanisms are directed toward either specific projects, support of personnel, or infrastructure. 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. NCI intramural research programs are funded via the "Z" mechanism that encompasses research across the cancer continuum. Awards are also made to fund institutions that conduct research, including cancer centers and cooperative groups of institutions.

Grants to research networks and individual researchers are largely competitively determined by peer review of the proposals. This represents the major opportunity for individual researchers to seek research funding through the "R" category of grants. NCI advertises the availability of grants through a funding opportunity announcement, and researchers can propose projects along the spectrum of cancer types and scientific disciplines. Applications are then reviewed by other scientists in the field, and are scored according to scientific merit and impact irrespective of the cancer type or population being studied. There are always significantly more applications than available funding, so only a fraction of grant applications is funded in any given year. Based on score, the applications are ranked relative to each other, and most of the applications from the very best down to a certain rank are funded. Grants that are ranked below that cutoff must have some other attribute, such as fulfilling an unmet need, in order to be selected for funding. The cutoff line is often referred to as the "payline," which at NCI was at the 9th percentile from 2011 through 2013. Despite this cutoff, more than one-third of individual researcher grants that were awarded were ranked below the payline, and roughly one-fifth of exploratory grants awarded were similarly below the payline [73].

Under this method for reviewing and awarding grants, a variety of research proposals—including research on specific types of cancers along with research that is cross-cutting between cancers—compete against each other for available funding. Funding to individual cancer types is reflective of the number and quality of applications and the current scientific opportunities within each given field. With no specific funding allocations by cancer, one of the limited ways for NCI to exert any control on funding levels between cancer types is through the discretionary selection of projects that fall below the payline. One way that disease-specific philanthropy groups often try to direct more federal funding toward their disease of interest is by selectively supporting early-stage researchers within their disease in order to create a larger pool of experienced grant applicants and make them more competitive for federal grants.

"Nonprofit organizations can create grant programs to attract and maintain talented researchers into a specific field of discovery, which can then help them secure federal grants to ensure their work will continue to be supported."

— Ms. Robin Boettcher, President and CEO, Pediatric Brain Tumor Foundation

NCI Funding of Childhood Cancer

As noted previously, in adult cancer drug development NCI funding primarily targets basic research, with some funds directed toward clinical phase research. In the case of pediatric cancer research, NCI's role in later-phase clinical research

is more pronounced. In addition to conducting clinical trials directly, the NCI-funded Children's Oncology Group (COG), acts as infrastructure that can be used by industry sponsors of trials to conduct childhood cancer clinical trials more cheaply and efficiently than would be possible if such a network did not exist.

NCI tracks disease or focus-area spending retrospectively using what are known as "special interest categories" (SICs) which are "major scientific disciplines that are of stated or growing interest to the NIH, DHHS, Congress, and/or the public." [74] For each project, trained NCI scientific staff reviews the research proposals within already awarded grant applications, contracts, and intramural proposals to estimate the project's percent relevance to specific SICs. There is a childhood cancer SIC that allows tracking of spending by NCI on childhood cancer research. Spending is identified for projects with an apparent relevance to pediatric cancer research, and it is calculated by multiplying each project's total annual funding by its percent relevance to childhood cancer. As an example, if a $500,000 project is determined to be 50% related to childhood cancer, the amount counted toward the childhood SIC would be $250,000. The total NCI childhood spending is obtained by adding these amounts across all projects.

NCI's divisions, offices, and centers manage different types of pediatric research projects; however, the NCI's Division of Cancer Treatment, and Diagnosis, Division of Cancer Biology, Office of the Director, and Center for Cancer Research [74], are responsible for distributing the majority of pediatric cancer research funds. The extramural (R, P, and U) mechanisms account for the largest portion of funded research (Table 6), averaging over 80 % of childhood cancer funding (Figure 14). The R and P mechanisms support specific projects, while the cooperative agreements in the U category support collaborations like COG. The next largest investment in pediatric cancer research is through NCI intramural research programs via the Z mechanism. Career development (K), training (F and T) awards along with other funding mechanisms make up the remainder of the funding provided by NCI.

With the exception of FY2016, the flat NIH budget has meant that funding for research across a wide variety of diseases has been largely unchanged or has declined. While

NCI Childhood Cancer Research Funding by Funding Mechanism

Category	FY2011	FY2012	FY2013	FY2014
Extramural Research (R/P/U)	157.7	170	148.9	166.1
*Cooperative Agreements	52.6	60.4	53.8	69.6
Intramural Research (Z)	26.9	26.5	24.6	28.0
Career & Training (F/T/K)	7.5	7.9	7.1	7.7
Other (E/N/Unknown)	3.4	3.7	4.5	3.9
Total	**195.5**	**208.1**	**185.1**	**205.7**

*Cooperative agreements are part of Extramural Research
Funding in millions of dollars.

Table 6: NCI childhood cancer funding levels by category from FY2011 to FY2014. Cooperative agreements are counted in the total extramural research figure, but also listed separately.

How NCI Spends the Average Dollar on Childhood Research*

Extramural Research – $0.82
Research grants issued to universities and organizations across US and internationally

Other – $0.02
Contracted research and development and small business innovation awards

Intramural Research – $0.13
Research conducted at NCI campus in Bethesda, MD

Career Training – $0.03
Supports individuals rather than research projects

*Based off latest available fiscal year reporting data from 2011-2014. Values are expressed as the average percentage of total NCI pediatric budget for FY2011-2014.
See: http://fundedresearch.cancer.gov/nciportfolio/

Figure 14: The average allocation of research funding from 2011-2014 shows that most funding is directed to extramural research, composed of research and program grants along with cooperative agreements. Intramural is the next highest allocation, with career, training, and other support mechanisms accounting for the remainder.

NCI has remained at flat funding, inflation has increased the cost of conducting research. Consequently, when adjusted for inflation, NCI funding has declined by 24% between 2004 - 2015. Declines in the inflation-adjusted funding levels for pediatric cancer mirror the overall trend for NCI. Figure 15 shows funding for COG, a major cooperative group supporting clinical trials that is funded by NCI, in both absolute funding amounts as well as inflation-adjusted amounts. Factoring in inflation, COG's budget has shrunk by over 30% since 2004.

In addition to being classified by their relevance to SICs, NCI-funded projects are also classified by the Common Scientific Outline (CSO), a framework centered around seven broad scientific interest areas in cancer research (Figure 16): prevention; scientific model systems; early detection, diagnosis, and prognosis; etiology; cancer control, survivorship and outcomes research; biology; and treatment. In recent years, the largest percentage of NCI's estimated pediatric cancer research funding has supported projects pertaining to treatment (approximately 50%).

NCI's childhood cancer research funding can be further categorized by specific cancer types (Figure 17). Of the 440 NCI-funded research projects in 2012 with at least 25% relevance to the childhood cancers SIC, 30% involved childhood leukemias; approximately 21%, brain cancers; 16%, neuroblastoma; 15%, sarcomas, and 15%, lymphomas. It should be noted, however, that these estimates may not account for all relevant pediatric research supported by NCI, as important overlapping areas (e.g., shared molecular characteristics) may allow studies of one type of cancer to provide unanticipated insights and progress for other types of cancer. The proportion of cancer type/site-specific childhood cancer projects remained fairly constant throughout the period 2010 - 2012.

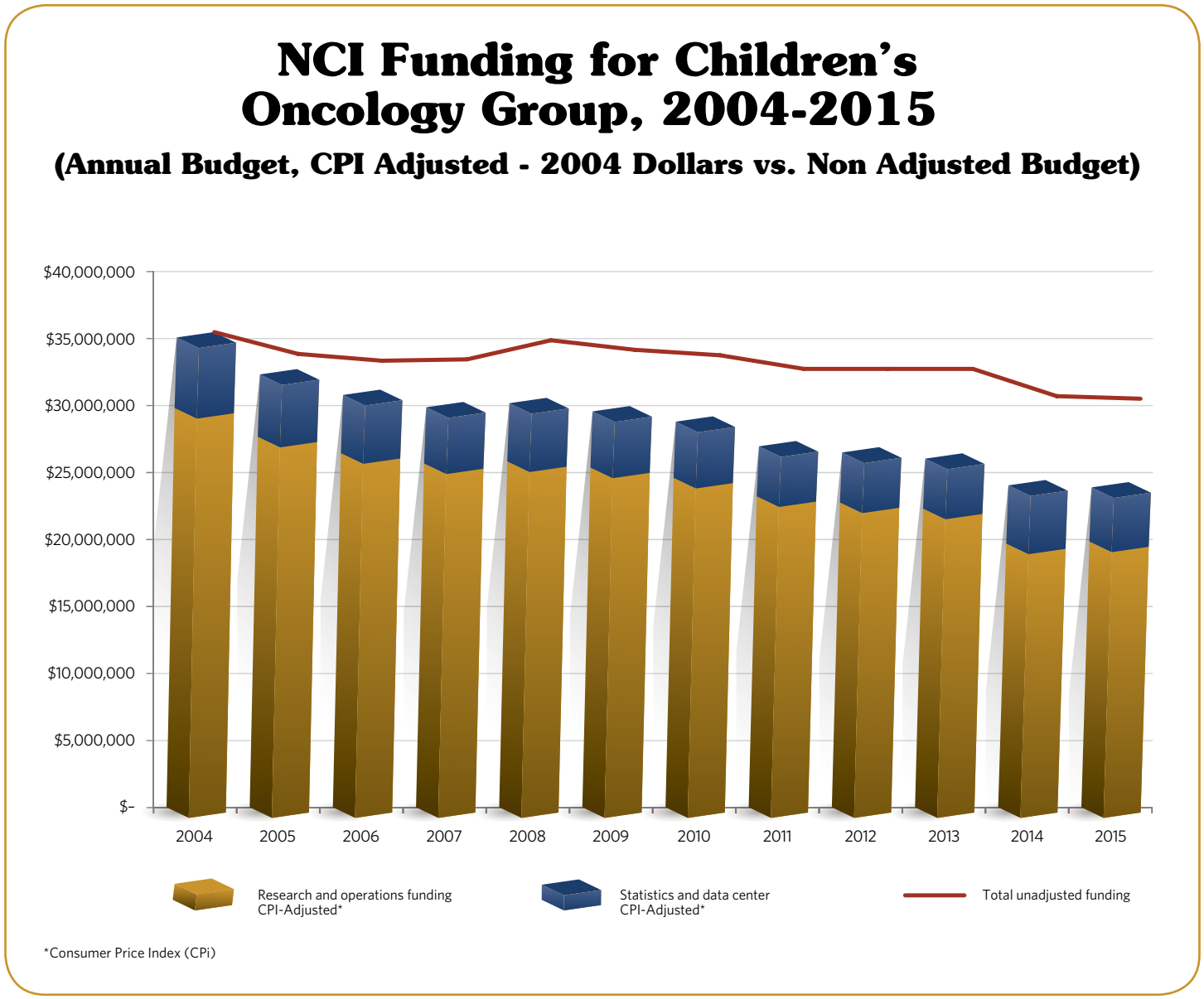


Figure 15: COG funding from 2004 to 2015 shows decline in actual funding (red line), which is made worse when inflation is factored in (bars).

Research Funding and Economic Forces

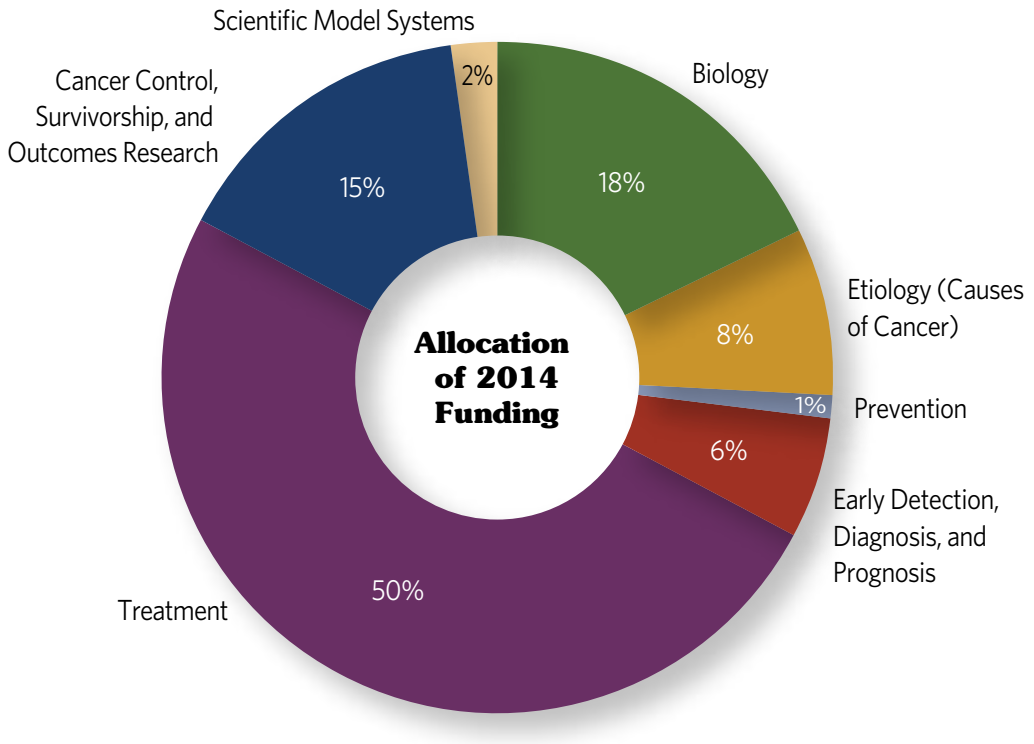
"There is a clear preclinical funding gap. Deprioritizing the thorough and expensive kind of preclinical studies that have depth of biological replicates and appropriate statistical power can leave many trials vulnerable to misinformed conclusions at their foundation. "

— Dr. Charles Keller, Scientific Director, Children's Cancer Therapy Development Institute

Department of Defense (DoD) Research Funding

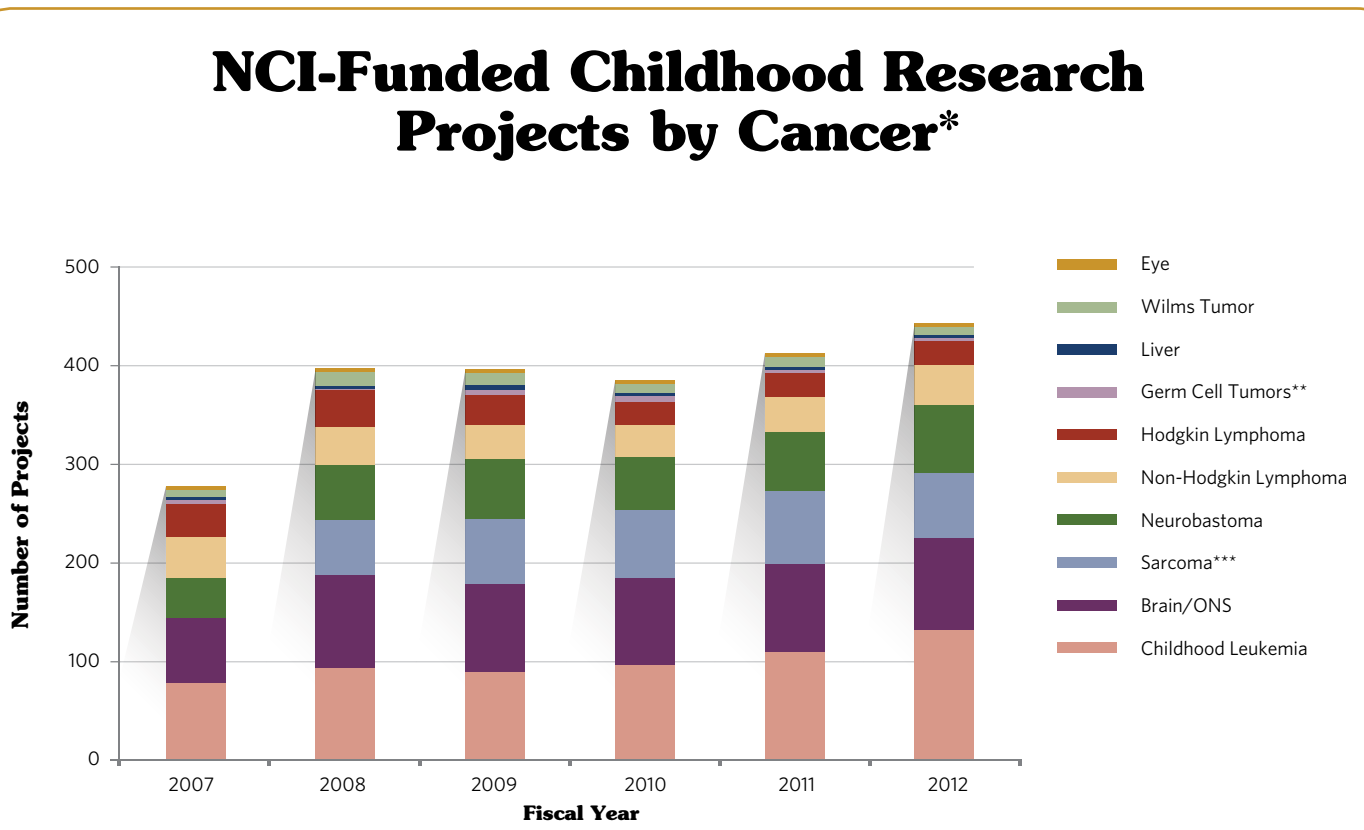
Other than NCI, the other major federal source of research funds for childhood cancer research is the Department of Defense (DoD). The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 as a result of a grassroots effort led by the breast cancer advocacy community to find new sources of federal research funding. This effort led to a congressional appropriation of breast cancer research funding within the DoD budget that facilitated a partnership among the public, Congress, and the military, and continues to fund valuable,

Types of Childhood Cancer Research Funded by NCI



Source: http://www.cancer.gov/research/progress/snapshots/pediatric

Figure 16: NCI funds a variety of research disciplines, ranging from treatment-related research, which received half of FY 2014 distributions, to prevention, which only amounted to 1% of funding.



Source: NCI, An Analysis of NCI's Investment in Pediatric Cancer Research, 2013

*Project list is limited to projects with at least 25% relevance to the "childhood cancers" SIC and at least 10% relevance to the specified cancer. Cancers are not mutually exclusive, and some projects are associated with multiple cancer sites.

**Includes testicular and ovarian cancer projects.

***Sarcoma data is not available for FY 2007.

Figure 17: The number of NCI-funded research projects grew between 2007 and 2012, with the largest gains in childhood leukemia. Numbers reflect project count rather than funding.

high-impact research today [75]. Funds for the CDMRP are added to the DoD budget to support programs such as the Peer Reviewed Cancer Research Program (PRCRP) with guidance from Congress. Established in fiscal year 2009, the PRCRP supports "innovative and impactful research in cancers specifically designated by Congress as relevant to military service members, their families, and other military beneficiaries [75]." Congressional language guides the research topics included in the PRCRP. The research topic areas change each fiscal year based on the current needs of the military, in response to an identified research gap or in response to a particular interest of a member of Congress. Over the years, pediatric cancers have been identified for directed funding at levels substantially lower than funding from NCI (Table 7). Funding for the CDMRP is much more variable, as programs must be actively authorized and appropriated every year. Further, some in Congress have also challenged the relevance of the CDMRP to military service members and their families, creating challenges to maintaining historical funding of medical research through this mechanism.

Philanthropic Funding for Childhood Cancer Research

Private philanthropy, typically given through 501 (c) (3) nonprofit organizations, is a significant source of funding for pediatric

Pediatric-Related CDMRP Funding

Topic Area	FY2009	FY2010	FY2011	FY2012	FY2013	FY2014
Neuroblastoma	$0	$0	$0	$0	$1,151,460	$1,065,601
Pediatric Brain Tumors	$1,786,229	$2,532,910	$0	$400,425	$1,647,150	$988,663
Pediatric Cancer	$0	$0	$770,586	$0	$0	$0

Table 7: Fiscal year 2009-2014 CDMRP funding of areas related to pediatric cancer. Federal funding through CDMRP is much lower than from NCI and is more highly variable [75].

cancer research. Based on data collected for this report, private philanthropy is estimated to amount in aggregate to 50% as much as provided annually by NCI for pediatric cancer research. This amount is considerably less than private philanthropy donated for adult cancer research, but plays a significant role given the lack of commercial incentives for investment by private industry. Pediatric cancer-directed 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 groups' capacity to allow more children to access to clinical trials.

"The federal funding model is inadequate and shrinking. We can't reverse that, so we should think of the alternatives that are available. Is it philanthropy?"

— Dr. Douglas S. Hawkins Associate Division Chief, Hematology/Oncology, Seattle Children's Hospital

For this report, a survey of childhood cancer funding nonprofits was conducted to generate a picture of the number and diversity of childhood cancer research funding groups. An online link to the survey was distributed to 160 organizations, identified by their websites and/or their IRS Form 990 as funding childhood cancer research. Of the 36 organizations that responded, the overwhelming majority reported that their entire cancer research budget was dedicated to childhood cancer. For other cancer research funding organizations, less than 10% was awarded to childhood cancer research. Almost all respondents indicated that they funded treatment-related research, followed in ranking by biology, cancer control, survivorship, and outcomes research. Many organizations reported that they fund a variety of other childhood cancer programs, for example, education and support services for patients and families.

Many of the responding groups that dedicated all of their funding to childhood cancer research were started in honor or in memory of a particular child with cancer. Other groups, allocating lower percentages to childhood cancer research, had missions that went beyond a focus on childhood cancer, such as adult cancers.

Groups varied widely in how much money they awarded for childhood cancer research. Roughly half reported issuing less than $200,000 in grants annually. Only seven groups responding to the survey funded over $1 million annually for childhood cancer research. While these latter organizations have large cancer research budgets, many did not focus solely on childhood

cancer, while the smaller philanthropic groups were more likely to dedicate their entire research budget to childhood cancer.
Childhood cancer charities, especially those dedicated in honor or memory of children affected by cancer, tend to fund research on one specific type of cancer. Many groups support research on neuroblastoma and pediatric brain tumor research, diseases where survival rates are poor. Some organizations indicated that they directed all of their research funding to cooperative research groups and consortia, such as the COG, in an attempt to maximize the utility of their relatively small grants. Other aggregates of small charitable nonprofits, such as the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), "... a national collaborative effort of researchers, oncologists and family advocates to bring forward new therapies for children with relapsed neuroblastoma and medulloblastoma..." [76], and the DIPG Collaborative [77] also pool funding to issue grants to research networks.

Economic Forces Affecting Industry Investment in Research

Basic biological findings and the identification of chemical compounds that might be effective against a cancer only lead to usable drugs for patients through the substantial investment of industry in clinical trials, formulation development and creation of manufacturing facilities. Industry and venture capitalists invest in drug development because they hope to have a marketable, profitable product once a drug is approved. When considering whether to pursue a particular drug development program, a drug sponsor can make a simple calculation of the amount of money that 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, ALL, has fewer than 3,000 new cases per year in children, and even this number is made up of different subtypes that would likely require different drugs. Some of the rarer pediatric cancers might only number in the dozens of patients per year. With such small populations, the only way to achieve financial returns from selling a rare cancer drug if it is solely used for childhood cancer (Path C in Figure 7, page 24) that would be commensurate with financial returns from drugs for more common cancers would be to charge unit prices many times higher than for other drugs—which is not likely to be achievable. However, when drugs are initially developed for adults before being developed for children (Paths A, B and D in Figure 7, page 24), the potential overall market size (children plus adults) for a drug is much larger. It is much more common that drugs treating childhood cancer are first developed to treat adults, but not all adult cancer drugs are developed for children. Several programs have been created to try to enhance the economic incentives to expand the number of drugs to treat childhood and rare diseases more generally. These are discussed below.

Exclusivity

When a company successfully tests its drug and receives FDA approval, it can sell it without competition for a specific period of time. The exclusive rights to a drug are critical economic incentives for companies to invest and develop drugs for patients. There are different forms of exclusive rights that a company can have for a molecule or a drug that include patent, data, and market exclusivity. Molecules created by a researcher can receive patent protection for 20 years, so competitors are not able to copy the same molecule until the remaining patent expires. Typically, considerable time elapses between when the drug molecule is patented and approved for sale, so the patent protection at the time of final FDA approval is typically much less than 20 years [78].

When patent life expires for a brand name drug, other companies can copy it and create a "generic" version of the drug. One reason that generic drugs can be sold more cheaply than brand name drugs is that generic manufacturers do not have to conduct all of the clinical research needed to prove the safety and efficacy of the drug, since it was already done 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 original 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. When a drug is approved, it is given five years of data exclusivity [78]. (Some drugs are

made using living organisms rather than chemical synthesis and are known as biologic drugs or biologics. Biologic drugs receive 12 years of data exclusivity.) 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 on to the market by using data from the original developer.

If a drug's patent has expired, but its data exclusivity has not, in theory another manufacturer could recreate all of the needed 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 orphan diseases (Figure 12), and drugs developed for these diseases can qualify for incentives under the Orphan Drug Act.

While orphan incentives depend on the size of the population affected by a disease, Congress also created a pediatric-specific exclusivity incentive through BPCA (see page 34). 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. Companies have primarily conducted pediatric studies under BPCA for drugs that have large associated adult markets. From 1997 to 2012 pediatric exclusivity awarded through BPCA was reported to have led to $71 billion in added revenue for pharmaceutical companies, most of which was reaped by the largest-selling quarter of drugs obtaining that pediatric exclusivity [79]. 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.

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. Orphan drugs are defined as drugs that treat conditions that affect 200,000 or fewer people per year in the US. This 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 per year, but a drug designed to treat people with epidermal growth factor receptor (EGFR) mutant lung cancer can still receive orphan designation because that subset falls below 200,000 patients per year.

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 resources at FDA, but orphan drugs are exempt from this fee, which can exceed $2 million. Developers of orphan drugs can also deduct 50% of their clinical trial costs from their tax burden [80]. Orphan-drug developers can also apply for a grant from FDA to help fund their clinical research, and FDA issues $14 million in these grants annually [81]. Lastly, as mentioned above, orphan drugs benefit from seven years of market exclusivity.

Orphan designation adds a number of incentives for researchers to develop drugs for rare diseases, but it can also work against childhood cancer drug development. As noted in the Regulatory Requirements chapter (page 32) orphan designation of a drug allows an exemption from otherwise mandatory requirements to study adult drugs in children.

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.

Chase was two-and-a-half years old when he was diagnosed with ATRT (Atypical Tetroid/Rhabdoid Tumor), a rare and deadly pediatric brain and spine cancer with only approximately 100 cases diagnosed in the United States each year. With limited treatment options available, Chase's family moved forward with what they believed to be their best shot.

Chase embarked on a rigorous plan that included 10 different chemotherapies and proton radiation. Over a 14-month period, this included 129 inpatient days, 37 bags of platelets, 29 bags of red blood cells, 33 days of radiation, 16 spinal taps, and 15 central line placements, removals or repairs. For 16 months, he remained on IV-nutrition as he lost the ability to sustain himself due to the intensity of his treatment.

Although Chase finished treatment, he continues to have echocardiograms to monitor his heart, as at least one of the adult chemo drugs given to him is known to cause heart damage.

He also deals with numerous late effects from his treatment including (but not limited to) hearing loss, cataracts, and other physical, neurological, and developmental challenges. His daily quality of life includes multiple therapies as well as constant threat of relapse and secondary cancers. At the time of this report, Chase was undergoing his second eye surgery in a three-week period to try and improve his sight so that he can better succeed at school.

Research Funding and Economic Forces

To create even further financial incentives to develop drugs for rare pediatric conditions, Congress passed the Creating Hope Act in 2011. Modeled on a program to stimulate drugs to treat tropical diseases, this law created a priority review voucher program. Vouchers are awarded to newly formulated drugs that treat any rare disease in children (not just childhood cancers) and do not have an associated adult use. A priority review voucher entitles a company to obtain a shorter FDA drug review time, 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 can use the voucher later for a subsequent drug application for another drug, or it can sell the voucher to another company. Priority review vouchers that shave four months off FDA's review time can mean significant financial benefits for a blockbuster drug, as evidenced by sales prices of vouchers that have been sold to date (Table 8). 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 7, page 24). The Creating Hope voucher program was created as a pilot program, and is scheduled to expire in 2016. Efforts have been made to extend the program, but at the time of publication the statute had still not been reauthorized by Congress.

Pediatric Vouchers Awarded

Awardee/date	Drug	Indication	Buyer	Sale Price ($ millions)	Sale Date
BioMarin 2/14/2014	Vimizim (elosulfase alpha)	Morquio A Syndrome	Sanofi/Regeneron	67.5	7/20/2014
Knight	Impavido (miltifosine)	Leishmaniaisis	Gilead	125	11/29/2014
United Therapeutics 3/10/2015	Unituxin (dinutuximab)	High-risk neuroblastoma	Abbvie	350	8/19/2015
Retrophin/ Asklepion 3/17/2015	Cholbam (cholic acid)	Rare bile-synthesis disorders	Sanofi	245	5/27/2015
Wellstat 9/4/2015	Xuriden (Uridine Triacetate)	Hereditary orotic aciduria	AstraZeneca	Not Disclosed	11/01/2015
Alexion Pharmaceuticals 10/23/2015	Strensiq (asfotase alfa)	Hypophosphatasia	**Held**	N/A	N/A

Table 8: Pediatric vouchers awarded since the inception of the Creating Hope Act of 2011, and sales price, if applicable. Only one of the vouchers to date, for Unituxin, has been for a pediatric cancer indication.

Photo courtesy of St. Baldrick's Foundation. ©2016 all rights reserved.

Pediatric Drug Prices in State Medicaid Programs

Medicaid is a joint state-federal insurance program for low and medium income families, and provides health care coverage to approximately one in four children in the US [82]. 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 [83]. 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. 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 will 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 clearly 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 [84]. 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 its associated benefits. This

Research Funding and Economic Forces

pathway to developing pediatric oncology agents is uncertain especially 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 industries that engage in large-scale drug development.

"Academic centers often do not have sufficient support or personnel to fulfill FDA or clinical study requirements in a timely fashion. This means that there are significant barriers to do clinical research in academic centers, and often means time is wasted getting things approved quickly."

— *Dr. Sabine Mueller, Pediatric neurologic cancer specialist, University of California, San Francisco Benioff Children's Hospital*

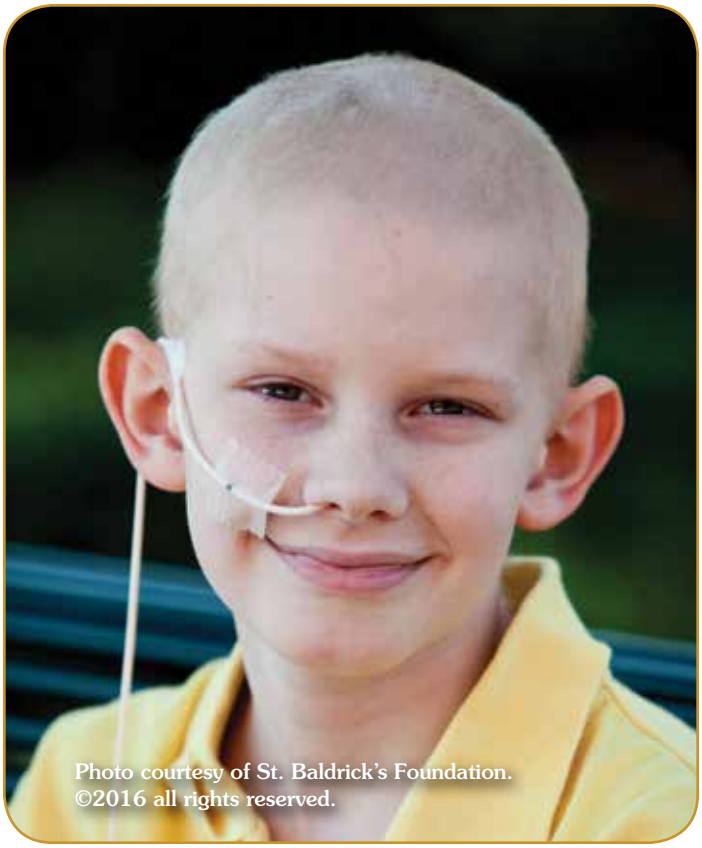


Photo courtesy of St. Baldrick's Foundation.

Summary

Increased understanding of the basic biology of pediatric cancers can lead to promising new drugs. In order to turn these promising ideas into safe, usable and effective drugs, however, a large investment in clinical research and drug development is critical. Private industry typically funds most of the later stages of drug development, largely driven by an expectation of eventual profits from the sale of an approved drug over a period of time. However, pediatric cancers are rare, meaning that the sales potential and incentive for developing pediatric cancer drugs is lower than for adult drugs. Federal funding for basic science and for some of the research infrastructure needed for clinical trials provides a launching point for private industry to carry out drug development, and in pediatric cancer the role of federal and philanthropic funding is more significant than in adult cancer. The overwhelming proportion of federal research funding is typically awarded under a system that does not allocate set amounts of funding for specific diseases, but rather tries to capitalize on scientific opportunity and ranks all research proposals against each other regardless of the cancer studied, funding those with the highest ranking. In addition to directly funding research and underwriting the costs of pediatric clinical trials, the federal government has created a number of incentive programs to augment the otherwise limited economic incentives inherent for any drug for a small patient population, like childhood cancer. All orphan drugs receive two extra years of exclusivity compared to non-orphan drugs, and the applications for approval have many of their application fees waived; drugs approved for adults that are tested in the pediatric population can receive six months of additional exclusivity for their adult indications through the BPCA program; lastly drugs developed exclusively for rare childhood diseases, including cancers, can obtain an expedited review voucher that can be sold for immediate financial gains. Despite these incentives, funding research and drug development for childhood cancer remains challenging.

Basic biological findings and the identification of chemical compounds that might be effective against a cancer only lead to usable drugs for patients through the substantial investment of industry in clinical trials, formulation development and creation of manufacturing facilities.

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. Consequently, developing effective drugs to treat children with cancer presents daunting challenges. It requires the collective engagement of research, advocacy, and regulatory communities in order 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 childhood cancers.

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 childhood cancers.

Appendix

Major Cancer Types

Childhood cancer is comprised of 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 childhood cancer, including specific statistics and where available information about subtypes, causes, and treatment.

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.

Acute lymphocytic leukemia (ALL)

An estimated 2550 children and 320 adolescents will be diagnosed with ALL in the US in 2016. ALL is the most common cancer in children, accounting for 25% of cancers diagnosed in ages 0-14. 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 US, 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 [85].

Improved treatment for ALL in childhood has increased the 5-year survival rate from 57% in 1975–1979 to 90% in 2005 - 2011. Treatment generally consists of 4–6 weeks of induction chemotherapy initially administered in the hospital, followed by several months of consolidation chemotherapy and 2–3 years of maintenance chemotherapy. The central nervous system (CNS) is a common site for relapse, so children receive specific treatment (CNS prophylaxis) to prevent this. Early forms of CNS prophylaxis that combined high doses of radiation and intrathecal (injected into the fluid surrounding the brain and spinal cord) chemotherapy had a high risk of damage to brain tissue resulting in neurocognitive defects; less toxic therapies that avoid the use of radiation have reduced but not eliminated these risks. Allogeneic (from another donor) bone marrow transplantation is recommended for some children whose leukemia has high-risk characteristics at diagnosis and for children who relapse after remission [86]. It may also be used if the leukemia does not go into remission after a successive course of induction chemotherapy. Successful treatment of ALL requires multidisciplinary teams to provide hematologic supportive care and careful monitoring for infection and adequate nutrition.

Long-term adverse health effects among children treated for ALL can include neurocognitive defects, growth deficiency, and increased risk of second cancers, including AML and CNS tumors [87]. Since radiation therapy is now used in only a small fraction of ALL patients at high risk of CNS relapse, much of the risk associated with high-dose radiation therapy has been reduced. Children treated with anthracyclines, among the most commonly used chemotherapeutic agents, are at risk for late cardiac effects [86].

Acute myeloid leukemia

An estimated 480 children and 190 adolescents will be diagnosed with AML in the US in 2016. 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). Many AML patients are prone to excessive bleeding and other blood clotting disorders. Death occurs during the first 2 weeks after diagnosis in 2–4% of children with AML due to bleeding or leukostasis [88]. Treatment for AML consists of induction chemotherapy, CNS prophylaxis, and post-remission therapy. Allogeneic stem cell transplant has been investigated in clinical trials and has been shown to improve survival rates for some children with AML. Treatment toxicity and long-term effects for AML are similar to those for ALL; however, AML less often requires treatment or prophylaxis of the CNS, so side effects related to radiation of the brain are not as common [88]. Five-year survival rates for AML have improved in recent decades but remain lower than for ALL (see Figure A4).

Hodgkin lymphoma

An estimated 340 children and 630 adolescents will be diagnosed with Hodgkin lymphoma (HL) in 2016. 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 [89].

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 15% of cancers diagnosed between ages 15 and 19. Incidence rates for HL are about 30% higher among white children and adolescents than among African American and Hispanic children. Asian/Pacific Islanders Alaska Natives have the lowest incidence rate for HL. Risk factors for HL include infection with the Epstein Barr virus (EBV) or a having a personal history of mononucleosis and human immunodeficiency virus (HIV) infection.

Survival rates for HL increased from 87% in 1975–1979 to 97% in 2005–2011. HL is highly sensitive to radiation, and cure can be achieved in some patients by radiation therapy alone, although this is seldom the preferred treatment in children and adolescents. The high dose of radiation used to treat HL in past decades was found to be damaging to organs such as the lungs and heart, so current therapies usually combine lower doses of chemotherapy and radiation to achieve a high cure rate with less toxicity [89]. 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 [90, 91]. The American Cancer Society recommends annual MRI in addition to mammographic screening for women who received radiation therapy to the chest for HL [92].

Non-Hodgkin lymphoma

An estimated 580 children and 330 adolescents will be diagnosed with NHL in 2016. The most common subtypes among children and adolescents in the US are Burkitt lymphoma (BL) (20%), diffuse large B-cell lymphoma (DLBCL) (24%), lymphoblastic lymphoma (17%), and anaplastic large cell lymphoma (8%) [93]. Both the incidence and distribution of NHL subtypes varies throughout the world. For example, in equatorial Africa, lymphomas account for nearly one-half of childhood cancers, reflecting the very high incidence of BL. The high incidence of BL in equatorial Africa is associated with high rates of co-infection with EBV and malaria [85]. 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 US, 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 [94]. Multiagent chemotherapy is the main form of treatment for most types of NHL. The dramatic improvement in survival rates for adults with DLBCL using rituximab (a monoclonal antibody) alongside multiagent chemotherapy has stimulated clinical trials to evaluate the role of monoclonal antibodies in treatment of

Appendix

pediatric DLBCL [94]. Survival rates for NHL in children and adolescents have increased dramatically in recent decades: from 47% in 1975–1979 to 86% in 2005–2011. 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 2180 children and 440 adolescents will be diagnosed with malignant CNS tumors in the US in 2016. Malignant CNS tumors are the second most common cancer in children, accounting for 21% of cases, and the third most common cancer type in adolescents, accounting for 10% of cases. 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. In 2016, an estimated 750 children and 560 adolescents will be diagnosed with benign and borderline malignant brain tumors. Three common types of brain and CNS tumors in children and adolescents are:

- **Astrocytoma**, the most common type of CNS tumor, accounts 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. 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 [95].
- **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 has a tendency to disseminate throughout the central nervous system early in its course [96].
- **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 [95].

Treatment of brain and other CNS tumors depends on the histology, grade, location, size, and other prognostic factors. Whenever possible, surgery is performed to remove as much of the tumor as possible while avoiding damage to healthy tissue. Subsequent chemotherapy and/or radiation therapy depends on the type of tumor, and optimal therapy requires coordinated efforts of pediatric specialists in fields such as neurosurgery, neuropathology, radiation oncology, and pediatric oncology who have special expertise in the care of patients with these diseases. Late effects can include impaired growth and neurologic development following radiation therapy, especially in younger children. For this reason, children under age 3 usually receive chemotherapy first with delayed and/or reduced radiation. Radiation is not always needed for low-grade tumors [95].

Five-year survival rates for brain and CNS tumors average vary depending on tumor type, location, and grade. For children age 0-14 diagnosed in 2005-2011, 5-year observed survival was 86% for astrocytoma, 74% for medulloblastoma, and 80% for ependymoma (Figure A3). However, less than 25% of children diagnosed with diffuse intrinsic pontine glioma (DIPG) will survive even two years [4].

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 690 cases of neuroblastoma will be diagnosed among children (ages 0-14) in 2016. It is the third most common childhood cancer, representing 7% of the total cases in this age group. 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 (system that controls heart rate and breathing) derived from a type of nerve cells 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. A family history of neuroblastoma is present in 1% to 2% of cases. Siblings of children with neuroblastoma are nearly 10 times more likely to also be diagnosed with the disease than children without affected siblings [97].

Neuroblastoma can metastasize through the lymph system and blood, and over half of children have regional or distant spread of their cancer at diagnosis [98]. 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 [99]. Depending on stage and other prognostic factors, children with neuroblastoma are most commonly treated with surgery and/or chemotherapy and radiation therapy; patients with high-risk disease may receive high-dose chemotherapy followed by stem cell transplant [98]. Ongoing clinical trials are investigating treatments for children with high-risk disease, for whom 5-year survival remains poor, although overall survival rates for neuroblastoma have increased from 54% in 1975 – 1979 to 77% in 2005 – 2011. 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 [98].

Wilms Tumor

An estimated 530 cases of Wilms tumor (WT) will be diagnosed among children (0 - 14) in the US in 2016. Also called nephroblastoma, WT is an embryonal tumor of the kidney that usually occurs in children under age 5 years. The vast majority (92%) of kidney tumors in this age group are WT [100]. 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 [101]. About 10% of cases are associated with a birth defect such as urogenital tract abnormalities [102].

The majority of children with WT are diagnosed with an asymptomatic abdominal mass that is incidentally noted while bathing or dressing the child [103]. WT may spread locally or through the bloodstream; distant metastases are uncommon at diagnosis. Treatment involves surgery and may include radiation and/or chemotherapy. In addition to stage, histology (anaplastic or favorable) and age at diagnosis are important prognostic factors [103]. Survival rates for WT increased from 75% in 1975 – 1979 to 93% in 2005 – 2011. 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 [103].

Retinoblastoma

An estimated 270 children 0–14 years will be diagnosed with retinoblastoma in 2016. 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 one-third of retinoblastomas are heritable [104]. Genetic counseling should be an integral part of the therapy for the family of a patient with retinoblastoma [104]. Patients who carry a germline RB1 mutation have an increased risk of second cancers, especially if they receive radiation therapy [105].

The type of treatment required for retinoblastoma depends largely on the extent of the disease within the eye and whether the disease has spread beyond the eye. Treatment options consider both cure and preservation of sight. Small tumors may sometimes be treated with cryotherapy (freezing), laser therapy, or thermotherapy (heat laser). Patients with more advanced disease involving only one eye without spread to nearby tissues are often treated with surgery to remove the eye (enucleation); this may be the only treatment needed. [104]. Children with bilateral disease and some children with unilateral disease may be treated with chemotherapy to shrink tumors to a size at which local treatment modalities are effective. Patients with more advanced disease are treated with chemotherapy, sometimes surgery, radiation, and/or chemotherapy [105]. Recent studies have investigated the efficacy of intra-arterial chemotherapy with promising results [106]. Five-year observed survival rates for retinoblastoma have increased from 92% in 1975 – 1979

to 97% in 2005 – 2011. Late effects of retinoblastoma include visual impairment and increased risks of second cancers, including bone and soft tissue sarcomas and melanoma [107].

Sarcomas of Bone and Soft Tissue

Sarcomas are tumors that develop from connective tissues in the body, such as muscles, fat, bones, membranes that line the joints, or blood vessels. An estimated 430 children and 280 adolescents will be diagnosed with bone tumors in 2016. 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, which will be diagnosed in an estimated 320 children (0 - 14) in 2014. 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 [85, 108].

Osteosarcoma

Osteosarcoma (OS) is the most common type of bone cancer in children and adolescents; an estimated 410 cases will be diagnosed in 2016. 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 [109].

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 [110]. Nearly all patients receive systemic therapy, since local therapy alone is associated with the development of distant metastases within several years in over half of cases treated this way. Current standard therapy consists of neoadjuvant (before the primary treatment) chemotherapy to shrink the tumor, followed by limb-sparing (or equivalent) surgery and adjuvant (after the primary treatment) chemotherapy [109]. Amputation is rarely needed. The 5-year survival rate for osteosarcoma was 71% in 2005 – 2011, up from 45% in 1975 – 79. 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 [109].

Ewing sarcoma

Ewing sarcoma (ES) is the second most common malignant bone tumor in children and adolescents; an estimated 230 cases will be diagnosed in 2016. It is more common among older children and adolescents than young children. Notably, incidence rates of ES are nearly 7.5 times higher in whites than African Americans, with smaller differences compared with Hispanics and Asian/Pacific Islanders. Similar differences in incidence are observed globally [85]. ES is a highly aggressive cancer, characterized by genetic translocations involving a specific genetic breakpoint region (EWSR1) [111]. It has been suggested that racial differences in the propensity for EWSR1 to undergo malignant transformation may contribute to this variation in incidence [112].

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 [113]. Treatment for ES typically involves induction (first-line) chemotherapy followed by local therapy (surgery and/or radiation) and adjuvant chemotherapy. There is continuing uncertainty about whether surgery or radiation therapy is preferred for local control, and sometimes radiation therapy is used both before and after surgery [114]. Survival rates for ES have increased from 42% in 1975 – 1979 to 77% in 2005 – 2011 (Figure A4). ES survivors are at increased risk for developing a second cancer, cardiac and pulmonary conditions, infertility, and musculoskeletal problems [114].

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a cancer made up of cells that normally develop into skeletal muscles; an estimated 320 cases will be diagnosed in 2016 among children under 14 years of age. 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 [115]. 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.

Patients with RMS receive several types of treatment, including chemotherapy in conjunction with surgery, radiation, or both [116]. Survival has improved for RMS (from 49% in 1975–1979 to 66% in 2005–2011), 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 and histology. Treatments for patients with intermediate and high-risk disease continue to be studied in clinical trials in hopes of achieving better outcomes [117]. 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. Incidence rates vary by race/ethnicity, with Hispanic children having the highest rates and African American children having the lowest.

Ovarian germ cell tumors

An estimated 170 girls ages 0 - 19 will be diagnosed with ovarian germ cell (OGC) tumors in 2016. 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 [118]. OGC tumors often cause abdominal pain and swelling and weight gain [119]. Surgery is the primary treatment; removal of only the affected ovary and fallopian tube (unilateral salpingo-oophorectomy) is an option for most patients who wish to preserve fertility. Patients with early-stage disease may be monitored after surgery, while those with more advanced disease receive chemotherapy. The 5-year observed survival rate is 97%. The chemotherapy regimens most commonly used for ovarian germ cell tumors may cause hearing loss and kidney damage [120].

Testicular germ cell tumors

An estimated 410 testicular germ cell tumors (TGCT) will be diagnosed in boys ages 0-19 in 2016. TGCT is the most common cancer in adolescent boys age 15–19. 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 [121]. A lump on the testicle is usually the first sign, and often leads to diagnosis at an early stage.

Risk factors for TGCT include a history of cryptorchidism (undescended testicle) and a family history of testicular cancer [120]. Orchiectomy (removal of the affected testicle) is the primary treatment for all TGCT; subsequent treatment varies by stage. Early-stage cancers (stages I and II) are observed closely after surgery; those with continued elevation of serum markers undergo radiation therapy. Later-stage cancer requires chemotherapy. Survival rates for testicular cancer have improved substantially since the mid-1970s (from 74% to 95% in 2005 - 2011), and most patients have a good prognosis.

Appendix

Supplemental Figures

Leading Causes of Death Among Children and Adolescents (1-19 years), United States, 2013

	1-14 years			15-19 years			1-19 years		
Rank		Count	Rate		Count	Rate		Count	Rate
1	Accidents (unintentional injuries)	2,837	49.5	Accidents (unintentional injuries)	3,652	172.3	Accidents (unintentional injuries)	6,489	81.9
2	Malignant neoplasms	1,223	21.4	Intentional self-harm (suicide)	1,748	82.5	Intentional self-harm (suicide)	2,143	26.9
3	Congenital anomalies	816	14.2	Assault (homicide)	1,407	66.4	Assault (homicide)	2,020	25.4
4	Assault (homicide)	613	10.7	Malignant neoplasms	627	29.6	Malignant neoplasms	1,850	23.6
5	Intentional self-harm (suicide)	395	7.0	Diseases of the heart	297	14.0	Congenital anomalies	982	12.5
6	Diseases of the heart	342	6.0	Congenital anomalies	166	7.8	Diseases of the heart	639	8.1
7	Influenza and pneumonia	230	4.0	Influenza and pneumonia	73	3.2	Influenza and pneumonia	303	3.9
8	Chronic lower respiratory diseases	219	3.8	Chronic lower respiratory diseases	60	2.8	Chronic lower respiratory diseases	279	3.6
9	Cerebrovascular disease	127	2.2	Cerebrovascular disease	56	2.6	Cerebrovascular disease	183	2.3
10	In situ and benign neoplasms and neoplasms of unknown behavior	112	2.0	Diabetes mellitus	52	2.5	Diabetes mellitus	150	1.9
	All causes	**9,408**	**164.2**	**All causes**	**9,480**	**447.3**	**All causes**	**18,888**	**239.0**

Rates are per 100,000 and age adjusted to the 2000 US standard population.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2015.

Figure A1: Cancer is the leading disease-related cause of death for younger children (1-14 years) as well as for adolescents (15-19 years) and the combined group.

Pediatric Case Estimates, 2016

Cancer Type	Birth-14 years			15- 19 years			Birth-19 years		
	Males	Females	Both	Males	Females	Both	Males	Females	Both
Acute lymphocytic leukemia	1,370	1,180	2,550	220	100	320	1,590	1,280	2,870
Brain & CNS[1]	1,150	1,030	2,180	250	190	440	1,400	1,220	2,620
Non-Hodgkin lymphoma	390	190	580	220	110	330	610	300	910
Neuroblastoma (including ganglioneuroblastoma)	360	330	690	*	*	--	--	--	--
Acute myeloid leukemia	240	240	480	100	90	190	340	330	670
Wilms tumor	240	290	530	*	*	--	--	--	--
Bone tumors	220	210	430	180	100	280	400	310	710
Hodgkin lymphoma	200	140	340	320	310	630	520	450	970
Rhabdomyosarcoma	170	150	320	*	*	--	--	--	--
Retinoblastoma	130	140	270	*	*	--	--	--	--
Testicular germ cell tumor	60	N/A	60	350	N/A	350	410	N/A	410
Thyroid carcinoma	50	140	190	80	410	490	130	550	680
Melanoma	60	70	130	80	140	220	140	210	350
Ovarian germ cell tumor	N/A	90	90	N/A	80	80	N/A	170	170
Hepatic tumors	110	70	180	*	*	--	--	--	--
All other[2]	650	590	1,240	470	390	860	1,120	980	2,100
Total	**5,460**	**4,920**	**10,380**	**2,320**	**1,960**	**4,280**	**7,780**	**6,880**	**14,660**

N/A indicates not applicable
[1] CNS indicates central nervous system.
[2] 'All other' includes all cancer types other than those listed in the table and excludes suppressed estimates.
* Estimate not provided due to fewer than 50 cases.
-- indicates that the estimate cannot be provided because it is the sum of a suppressed estimate.

Figure A2: Estimated number of pediatric cancer diagnoses in 2016 by cancer type and age range.

Changes in Pediatric Cancer 5-year Observed Survival Rates

	Children (0-14 years)				Adolescents (15-19 years)			
	Diagnosed 1975-1979	Diagnosed 2005-2011	Absolute Difference	Relative Improvement	Diagnosed 1975-1979	Diagnosed 2005-2011	Absolute Difference	Relative Improvement
All ICCC sites	60%	83%	24%	40%	68%	85%	17%	25%
Leukemia	53%	87%	34%	65%	26%	75%	50%	195%
Acute lymphocytic leukemia	60%	91%	31%	51%	31%	81%	50%	165%
Acute myeloid leukemia	21%	66%	45%	209%	20%	60%	40%	198%
Lymphomas and reticuloendothelial neoplasms	62%	92%	29%	47%	80%	91%	11%	14%
Hodgkin lymphoma	81%	98%	16%	20%	89%	97%	7%	8%
Non-Hodgkin lymphoma	48%	88%	40%	84%	46%	82%	36%	78%
Brain and CNS	58%	74%	16%	27%	60%	77%	17%	28%
Ependymoma	32%	80%	47%	148%	71%	69%	-3%	-4%
Astrocytoma	72%	86%	13%	18%	60%	80%	20%	33%
Medulloblastoma	48%	74%	26%	54%	36%	63%	26%	72%
Neuroblastoma and ganglioneuroblastoma	53%	78%	24%	46%	67%	60%	-7%	-10%
Retinoblastoma	92%	97%	5%	5%	*	*	--	--
Wilms tumor	75%	93%	18%	25%	50%	75%	25%	50%
Hepatic tumors	27%	73%	46%	171%	14%	52%	38%	262%
Bone tumors	49%	76%	27%	56%	48%	71%	23%	47%
Osteosarcoma	41%	70%	29%	73%	49%	72%	23%	46%
Ewing sarcoma	52%	84%	33%	64%	28%	68%	40%	141%
Rhabdomyosarcoma	55%	69%	14%	25%	30%	55%	25%	81%
Testicular germ cell tumors	91%	100%	9%	10%	70%	95%	24%	35%
Ovarian germ cell tumors	87%	98%	12%	13%	67%	90%	23%	34%
Thyroid carcinoma	>99%	>99%	0%	0%	99%	99%	0%	0%
Melanoma	83%	91%	8%	9%	82%	95%	13%	16%

CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers. Survival rates are based on cases diagnosed during 1975-1979 and 2005-2011, with all cases followed through 2012.

*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 2005-2011 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 9 registries, National Cancer Institute, 2015.

Figure A3: Current five-year survival rates have improved for nearly all cancers when compared to the five-year survival rates of children diagnosed in the late 1970s. Data are shown for younger children (0-14 years) and adolescents (15-19 years).

Appendix

Supplemental Figures

Changes in Pediatric Cancer 5-Year Observed Survival Rate, Ages Birth to 19 Years

	Year of Diagnosis			
	1975-1979	2005-2011	Absolute Difference	Relative Improvement
All ICCC sites	63%	84%	21%	33%
Leukemia	48%	85%	37%	77%
Acute lymphocytic leukemia	57%	90%	33%	58%
Acute myeloid leukemia	21%	64%	43%	205%
Lymphomas and reticuloendothelial neoplasms	72%	91%	19%	26%
Hodgkin lymphoma	87%	97%	10%	11%
Non-Hodgkin lymphoma	47%	86%	39%	83%
Brain and CNS	59%	75%	16%	27%
Ependymoma	37%	78%	41%	111%
Astrocytoma	69%	84%	15%	22%
Medulloblastoma	47%	72%	25%	53%
Neuroblastoma and ganglioneuroblastoma	54%	77%	23%	43%
Retinoblastoma	92%	97%	5%	5%
Wilms tumor	75%	93%	18%	24%
Hepatic tumors	25%	69%	44%	176%
Bone tumors	49%	74%	25%	51%
Osteosarcoma	45%	71%	26%	58%
Ewing sarcoma	42%	77%	35%	83%
Rhabdomyosarcoma	49%	66%	17%	35%
Testicular germ cell tumors	74%	95%	21%	28%
Ovarian germ cell tumors	75%	94%	19%	25%
Thyroid carcinoma	99%	99%	0%	0%
Melanoma	83%	94%	11%	13%

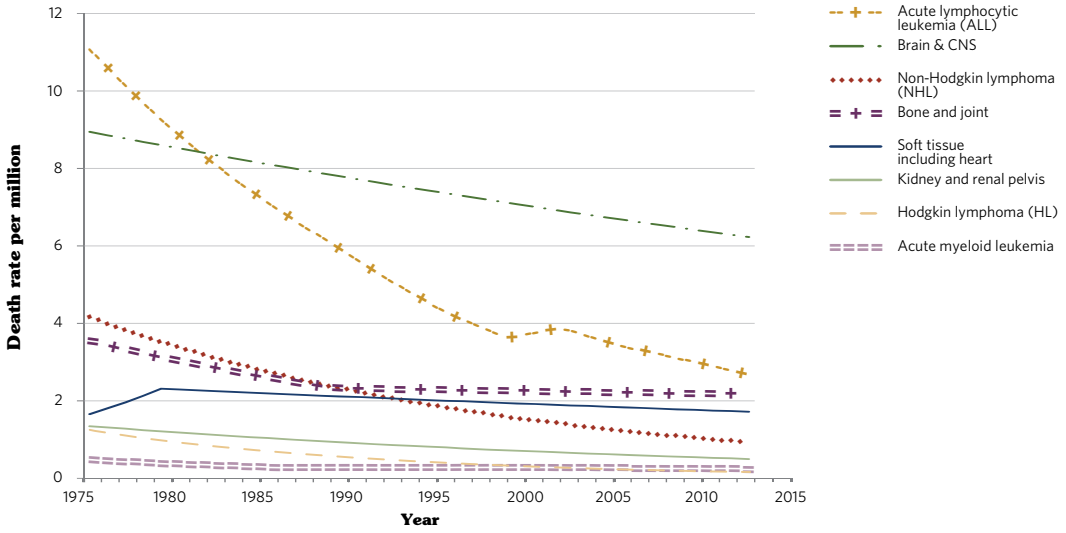
CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers. Survival rates are based on cases diagnosed during 1975-1979 and 2005-2011, with all cases followed through 2012.

Note: Survival rates not include benign or borderline brain tumors. Absolute difference is the difference between the observed survival during 1975-1979 and 2005-2011 in percentage points. Relative improvement is the absolute difference divided by the survival rate during 1975-1979.

Source: Surveillance, Epidemiology, and End Results (SEER) program 9 registries, National Cancer Institute, 2015.

Figure A4: Current five-year survival rates have improved for nearly all cancers when compared to the five-year survival rates of children diagnosed in the late 1970s. This chart shows the same data as Figure A3, combining the age range from 0-19.

Trends in Pediatric Cancer Mortality Rates by Site, Ages Birth to 19 Years, 1975 to 2012



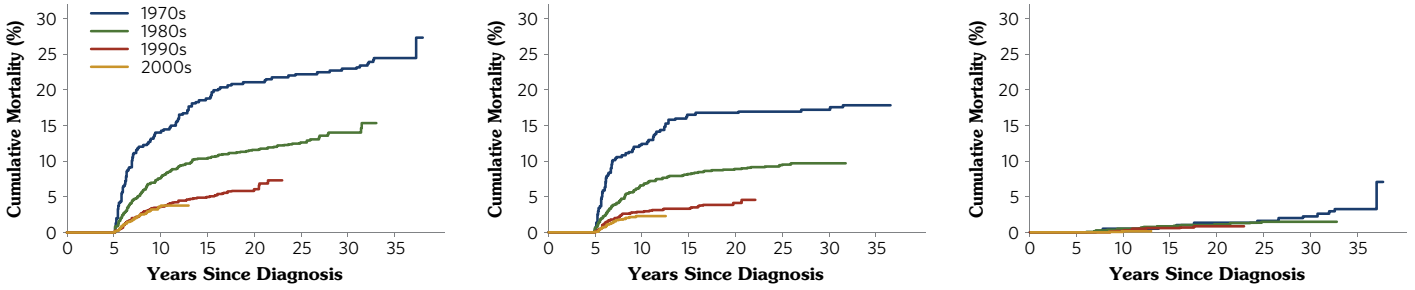
CNS indicates central nervous system.
Note: Lines represent joinpoint fitted trends.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2015.

Figure A5: Mortality for the most common cancers, ALL, Brain & CNS, and NHL, have all decreased considerably over the past 40 years, as has Hodgkin lymphoma on a relative basis, while mortality for other cancers has experienced more modest reductions.

Appendix

Late Mortality Among 5-year Pediatric Cancer Survivors by Decade of Diagnosis and Cancer Type, 1975-2005

Acute lymphocytic leukemia

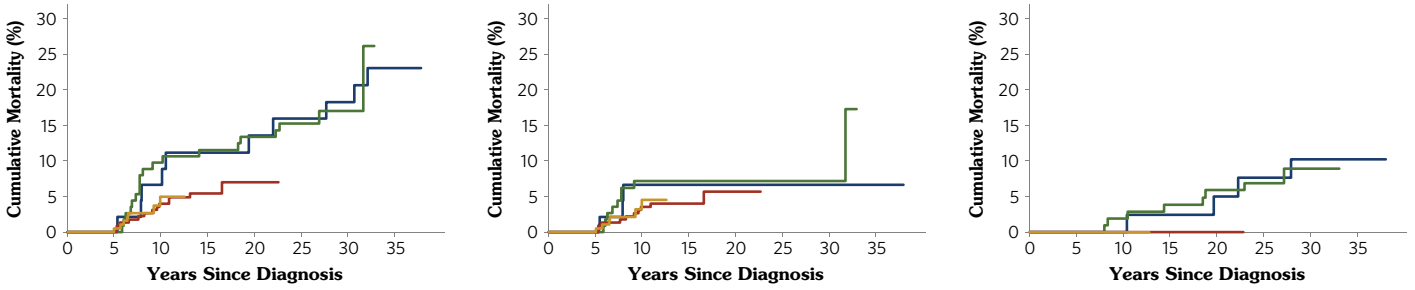


	10-year	15-year
1970s	14.9% (11.8%-18.4%)	19.6% (16.0%-23.4%)
1980s	8.2% (6.8%-9.8%)	11.0% (9.4%-12.8%)
1990s	4.0% (3.1%-5.0%)	5.3% (4.3%-6.5%)
2000s	4.0% (2.9%-5.4%)	N/A

	10-year	15-year
1970s	12.6% (9.7%-15.9%)	16.4% (13.1%-20.1%)
1980s	6.6% (5.3%-8.0%)	8.4% (7.0%-10.0%)
1990s	3.1% (2.3%-4.0%)	3.6% (2.8%-4.5%)
2000s	2.5% (1.7%-3.7%)	N/A

	10-year	15-year
1970s	0.7% (0.2%-2.0%)	1.0% (0.3%-2.5%)
1980s	0.6% (0.3%-1.2%)	1.1% (0.6%-1.8%)
1990s	0.5% (0.2%-0.9%)	0.8% (0.5%-1.4%)
2000s	0.4% (0.1%-1.1%)	N/A

Acute myeloid leukemia



	10-year	15-year
1970s	6.8% (1.7%-16.8%)	11.4% (4.1%-22.8%)
1980s	9.9% (5.2%-16.3%)	11.7% (6.6%-18.5%)
1990s	4.1% (2.0%-7.3%)	5.5% (3.0%-9.0%)
2000s	3.8% (1.5%-7.9%)	N/A

	10-year	15-year
1970s	6.9% (1.8%-17.1%)	6.9% (1.8%-17.1%)
1980s	5.6% (2.3%-11.1%)	5.6% (2.3%-11.1%)
1990s	3.2% (1.4%-6.2%)	3.7% (1.7%-6.8%)
2000s	3.3% (1.1%-7.2%)	N/A

	10-year	15-year
1970s	--	2.4% (0.2%-11.2%)
1980s	1.9% (0.4%-6.2%)	3.9% (1.3%-9.0%)
1990s	--	--
2000s	--	N/A

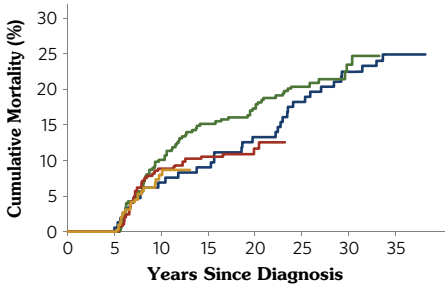
Figure A6: Even after surviving five years, childhood cancer survivors are subject to higher mortality than the general population. This late mortality has generally improved for most, but not all, types of cancers. These graphs show the cumulative mortality of five-year cancer survivors for specific cancer types from any cause (left), from the original cancer diagnosis (center), or from other health related cases (right), which includes secondary cancers, cardiopulmonary causes, and other conditions.

DEATH FROM ANY CAUSE

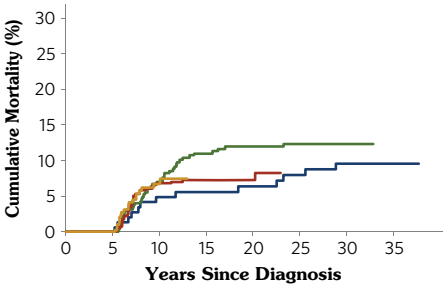
DEATH FROM ORIGINAL CANCER DIANOSIS

DEATH FROM OTHER HEALTH-RELATED CAUSE

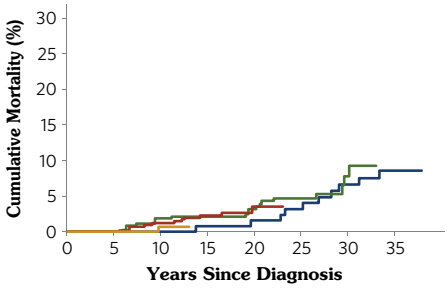
Bone tumors (including Ewing sarcoma)



	10-year	15-year
1970s	7.1% (3.6%-12.2%)	9.3% (5.2%-14.8%)
1980s	10.4% (7.4%-13.9%)	15.5% (11.2%-19.6%)
1990s	9.1% (6.6%-12.1%)	10.8% (8.1%-14.0%)
2000s	8.9% (5.6%-13.2%)	N/A

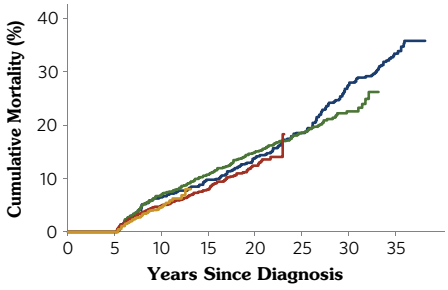


	10-year	15-year
1970s	5.1% (2.2%-9.7%)	5.8% (2.7%-10.6%)
1980s	7.2% (4.8%-10.4%)	11.0% (7.9%-14.7%)
1990s	6.6% (4.4%-9.2%)	7.1% (4.8%-9.8%)
2000s	7.7% (4.7%-11.6%)	N/A

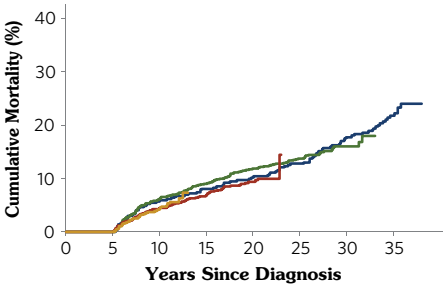


	10-year	15-year
1970s	--	0.8% (<0.1%-3.9%)
1980s	1.9% (0.8%-3.8%)	2.2% (1.0%-4.3%)
1990s	1.2% (0.5%-2.8%)	2.3% (1.2%-4.2%)
2000s	0.7% (<0.1%-3.6%)	N/A

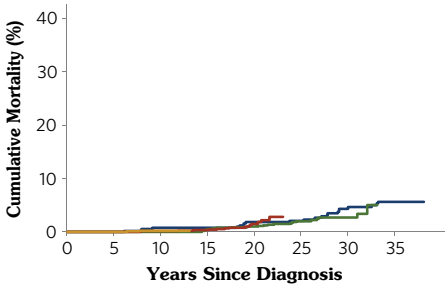
Brain & central nervous system



	10-year	15-year
1970s	6.9% (4.8%-9.4%)	9.9% (7.4%-12.9%)
1980s	7.3% (5.8%-8.9%)	11.2% (9.4%-13.1%)
1990s	5.2% (4.2%-6.4%)	8.5% (7.1%-10.0%)
2000s	5.1% (3.8%-6.8%)	N/A



	10-year	15-year
1970s	5.6% (3.7%-8.0%)	7.9% (5.6%-10.6%)
1980s	5.9% (4.6%-7.4%)	8.4% (6.8%-10.2%)
1990s	4.0% (3.1%-5.1%)	6.1% (5.0%-7.4%)
2000s	4.0% (2.8%-5.6%)	N/A



	10-year	15-year
1970s	0.9% (0.3%-2.2%)	0.9% (0.3%-2.2%)
1980s	<0.1% (<0.1%-0.5%)	0.7% (0.3%-1.4%)
1990s	0.1% (<0.1%-0.5%)	0.4% (0.2%-0.9%)
2000s	0.2% (<0.1%-0.7%)	N/A

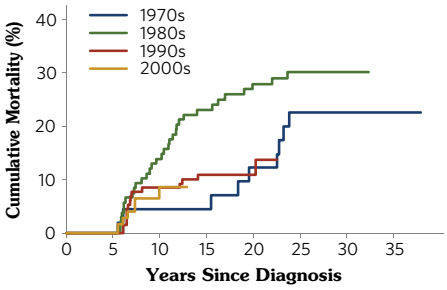
Patients were diagnosed from 1975 to 2005 and followed through 2012.
Source: Surveillance, Epidemiology, and End Results program 9 registries. – indicates estimate not available due to no deaths reported. N/A indicates not applicable.
Note: Figure A6 continued on following pages.

Appendix

Late Mortality Among 5-year Pediatric Cancer Survivors by Decade of Diagnosis and Cancer Type, 1975-2005

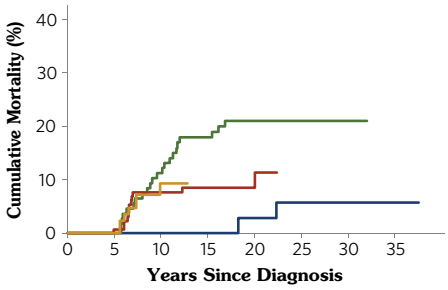
Ewing sarcoma

DEATH FROM ANY CAUSE



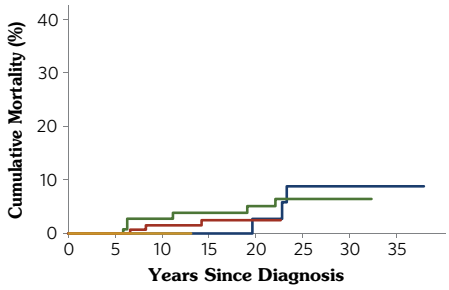
	10-year	15-year
1970s	5.3% (0.9%-15.7%)	5.3% (0.9%-15.7%)
1980s	14.8% (8.9%-22.2%)	24.2% (16.5%-32.6%)
1990s	9.3% (5.1%-15.1%)	11.8% (6.9%-18.1%)
2000s	9.5% (4.0%-18.0%)	N/A

DEATH FROM ORIGINAL CANCER DIANOSIS



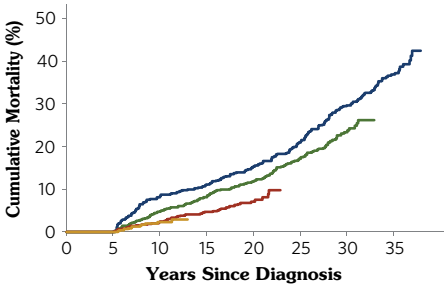
	10-year	15-year
1970s	--	--
1980s	11.4% (6.2%-18.3%)	18.2% (11.5%-26.2%)
1990s	7.8% (4.0%-13.3%)	8.6% (4.6%-14.3%)
2000s	9.5% (4.0%-18.0%)	N/A

DEATH FROM OTHER HEALTH-RELATED CAUSE

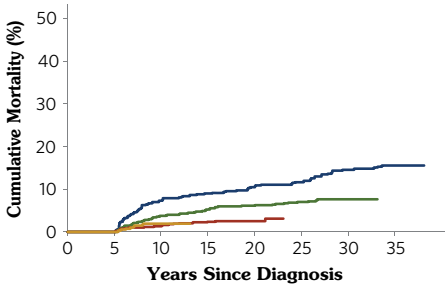


	10-year	15-year
1970s	--	--
1980s	2.8% (0.8%-7.5%)	3.9% (1.3%-9.1%)
1990s	1.6% (0.3%-5.3%)	2.6% (0.7%-6.8%)
2000s	--	N/A

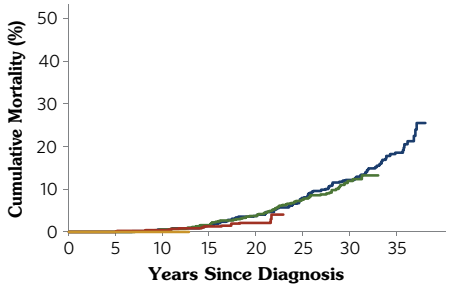
Hodgkin lymphoma



	10-year	15-year
1970s	8.5% (6.4%-11.0%)	11.2% (8.8%-14.0%)
1980s	5.0% (3.8%-6.5%)	8.3% (6.7%-10.2%)
1990s	2.6% (1.7%-3.8%)	4.8% (3.6%-6.3%)
2000s	2.5% (1.3%-4.2%)	N/A

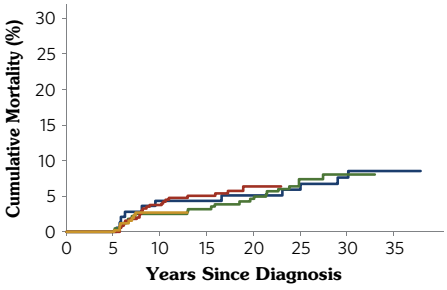


	10-year	15-year
1970s	7.3% (5.3%-9.6%)	8.7% (6.6%-11.3%)
1980s	3.5% (2.5%-4.8%)	5.0% (3.7%-6.5%)
1990s	1.4% (0.8%-2.3%)	2.1% (1.4%-3.2%)
2000s	1.7% (0.8%-3.1%)	N/A

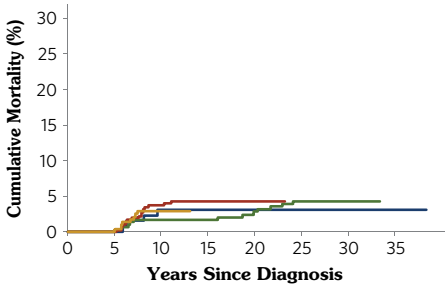


	10-year	15-year
1970s	0.6% (0.2%-1.6%)	1.6% (0.7%-3.0%)
1980s	0.6% (0.3%-1.3%)	1.7% (1.0%-2.7%)
1990s	0.5% (0.2%-1.2%)	1.4% (0.7%-2.3%)
2000s	--	N/A

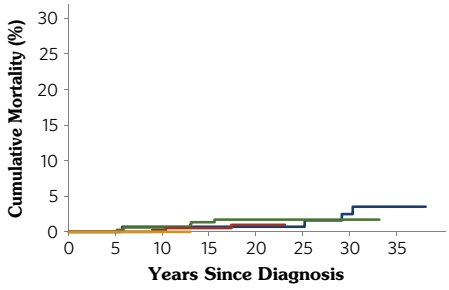
Neuroblastoma



	10-year	15-year
1970s	4.6% (1.9%-9.1%)	4.6% (1.9%-9.1%)
1980s	2.7% (1.3%-5.0%)	3.4% (1.7%-5.9%)
1990s	3.9% (2.4%-6.2%)	5.2% (3.3%-7.7%)
2000s	2.9% (1.4%-5.4%)	N/A



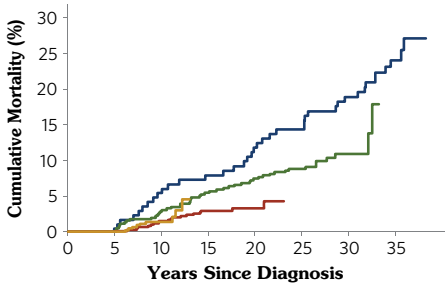
	10-year	15-year
1970s	3.1% (1.0%-7.3%)	3.1% (1.0%-7.3%)
1980s	1.7% (0.6%-3.7%)	1.7% (0.6%-3.7%)
1990s	3.5% (2.0%-5.6%)	4.0% (2.4%-6.2%)
2000s	2.9% (1.4%-5.4%)	N/A



	10-year	15-year
1970s	0.8% (<0.1%-3.8%)	0.8% (<0.1%-3.8%)
1980s	0.7% (0.1%-2.3%)	1.4% (0.5%-3.3%)
1990s	0.3% (<0.1%-1.4%)	0.5% (0.1%-1.8%)
2000s	--	N/A

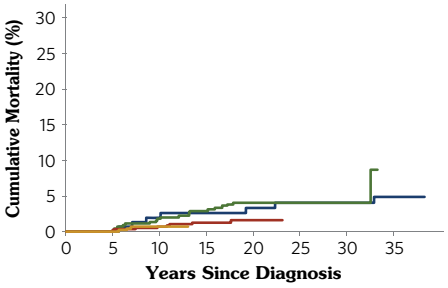
Non-Hodgkin lymphoma

DEATH FROM ANY CAUSE



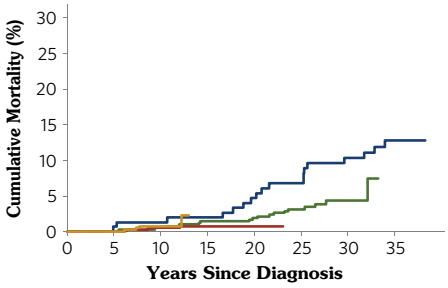
	10-year	15-year
1970s	5.6% (2.7%-9.8%)	8.1% (4.5%-12.9%)
1980s	3.0% (1.7%-4.8%)	5.6% (3.7%-7.9%)
1990s	1.7% (0.9%-3.0%)	3.1% (1.9%-4.7%)
2000s	1.6% (0.7%-3.1%)	N/A

DEATH FROM ORIGINAL CANCER DIANOSIS



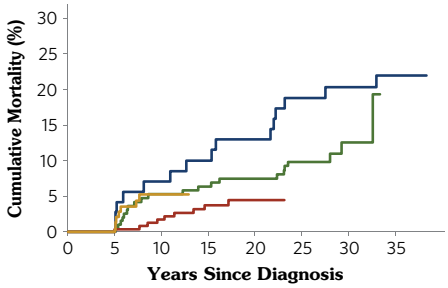
	10-year	15-year
1970s	1.9% (0.5%-5.0%)	2.5% (0.8%-6.0%)
1980s	1.5% (0.7%-3.0%)	2.6% (1.4%-4.4%)
1990s	0.7% (0.2%-1.6%)	1.2% (0.5%-2.4%)
2000s	0.6% (0.2%-1.7%)	N/A

DEATH FROM OTHER HEALTH-RELATED CAUSE

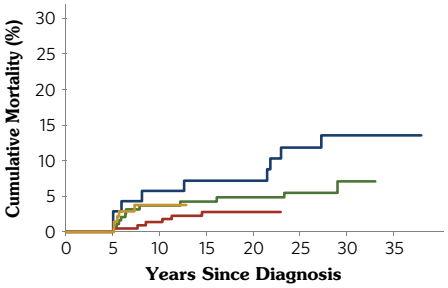


	10-year	15-year
1970s	1.2% (0.2%-4.0%)	1.9% (0.5%-5.0%)
1980s	0.4% (<0.1%-1.5%)	1.3% (0.6%-2.8%)
1990s	0.5% (0.1%-1.4%)	0.7% (0.2%-1.7%)
2000s	0.7% (0.2%-1.9%)	N/A

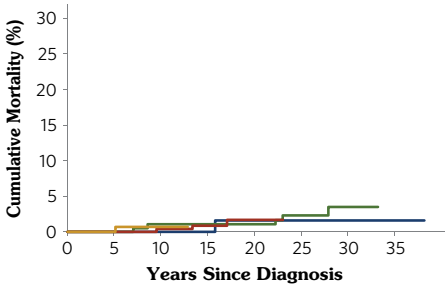
Rhabdomyosarcoma



	10-year	15-year
1970s	7.1% (2.6%-14.8%)	10.0% (4.4%-18.5%)
1980s	5.3% (2.7%-9.2%)	6.4% (3.5%-10.6%)
1990s	1.8% (0.6%-4.3%)	3.8% (1.8%-7.0%)
2000s	5.3% (2.3%-10.2%)	N/A

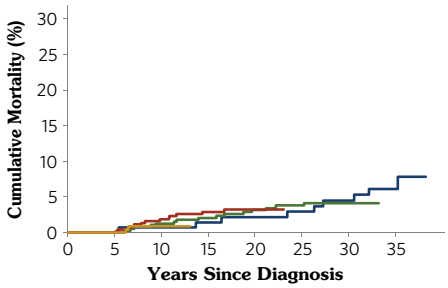


	10-year	15-year
1970s	5.8% (1.9%-13.2%)	7.4% (2.7%-15.2%)
1980s	3.7% (1.7%-7.2%)	4.3% (2.0%-7.9%)
1990s	1.4% (0.4%-3.7%)	2.8% (1.2%-5.8%)
2000s	3.8% (1.4%-8.1%)	N/A

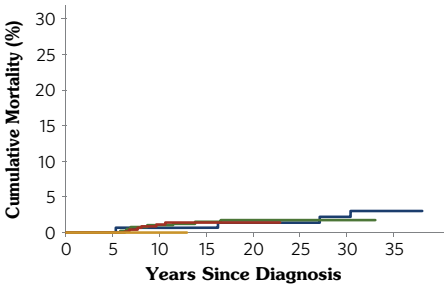


	10-year	15-year
1970s	--	--
1980s	1.1% (0.2%-3.7%)	1.1% (0.2%-3.7%)
1990s	0.5% (<0.1%-2.4%)	0.5% (<0.1%-2.4%)
2000s	0.7% (<0.1%-3.7%)	N/A

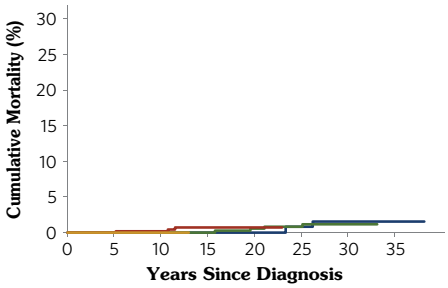
Wilms tumor



	10-year	15-year
1970s	0.7% (<0.1%-3.7%)	1.5% (0.3%-4.7%)
1980s	1.3% (0.5%-2.9%)	2.1% (1.0%-4.0%)
1990s	1.9% (0.9%-3.5%)	2.9% (1.6%-4.8%)
2000s	0.9% (0.2%-3.0%)	N/A



	10-year	15-year
1970s	0.7% (<0.1%-3.7%)	0.7% (<0.1%-3.7%)
1980s	1.1% (0.4%-2.5%)	1.6% (0.7%-3.3%)
1990s	0.9% (0.3%-2.3%)	1.2% (0.5%-2.6%)
2000s	--	N/A



	10-year	15-year
1970s	--	--
1980s	--	--
1990s	0.2% (<0.1%-1.2%)	0.7% (0.2%-2.0%)
2000s	--	N/A

Patients were diagnosed from 1975 to 2005 and followed through 2012.
Source: Surveillance, Epidemiology, and End Results program 9 registries. – indicates estimate not available due to no deaths reported. N/A indicates not applicable.

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Glossary

Unless indicated, all definitions are derived from: http://www.cancer.gov/publications/dictionaries/cancer-terms

Acute: Symptoms or signs that begin and worsen quickly; not chronic.

Adjuvant chemotherapy: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Allogenic: Taken from different individuals of the same species. Also called allogeneic.

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models.

Benign: Not cancerous. Benign tumors may grow larger but do not spread to other parts of the body. Also called nonmalignant.

Biologic drug: Sometimes also referred to as a biologic, a substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines.

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.

Biopsy: The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other test on the cells or tissue. There are many different types of biopsy procedures. The most common types include: (1) incisional biopsy, in which only a sample of tissue is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is sued, the procedure is called a fine-needle aspiration biopsy.

Biopsychosocial: In medicine, describes the biological, psychological (emotional), and social parts of a disease and its treatment. Some of the biopsychosocial parts of cancer are its effects on patients' feelings, moods, beliefs, the way they cope, and relationships with family, friends, and coworkers.

Biorepository: A facility that collects, catalogs, and stores samples of biological material, such as urine, blood, tissue, cells, DNA, RNA, and protein, from humans, animals, or plants for laboratory research. If the samples are from people, medical information may also be stored along with a written consent to use the samples in laboratory studies. Sometimes also called a tissue bank, or biobank.

Cell model: An experimental system using cells to study the development and progression of cancer, and to test new treatments before they are given to humans.

Chemotherapy: Treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. It may be given alone or with other treatments, such as surgery, radiation therapy, or biologic therapy.

Chronic: A disease or condition that persists or progresses over a long period of time.

Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Clinical trial phases are a part of the clinical research process that answer specific questions about whether treatments that are being studied work and are safe. Phase 1 trials test the best way to give a new treatment and the best

dose. Phase 2 trials test whether a new treatment has an effect on the disease. Phase 3 trials compare the results of people taking a new treatment with the results of people taking the standard treatment. Phase 4 trials are done using thousands of people after a treatment has been approved and marketed, to check for side effects that were not seen in the Phase 3 trial.

Clinical trial sponsor: A person, company, institution, group or organization that oversees or pays for a clinical trial and collects and analyzes the data. Also called a trial sponsor.

Cryotherapy: A procedure in which an extremely cold liquid or an instrument called a cryoprobe is used to freeze and destroy abnormal tissue. A cryoprobe is cooled with substances such as liquid nitrogen, liquid nitrous oxide, or compressed argon gas. Cryotherapy may be used to treat certain types of cancer and some conditions that may become cancer. Also called cryoablation and cryosurgery.

Drug sponsor: An applicant, or drug sponsor, is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations. The sponsor is usually an individual, partnership, corporation, government agency, manufacturer or scientific institution.[1]

Epigenetics: The study of how age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals, may cause changes in the way genes are switched on and off without changing the actual DNA sequence. These changes can affect a person's risk of disease and may be passed from parents to their children.

Exclusivity: Exclusive marketing rights granted by the FDA upon approval of a drug.[2]

Gene (genetic): The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. Humans have over 20,000 genes.

Genome (genomic): The complete set of DNA (genetic material) in an organism. In people, almost every cell in the body contains a complete copy of the genome. The genome contains all of the information needed for a person to develop and grow. Studying the genome may help researchers understand how different types of cancer form and respond to treatment. This may lead to new ways to diagnose, treat, and prevent cancer.

Histological (histology): The study of the tissues and cells under a microscope. In cancer diagnosis, histology tests usually refer to tumor samples that have been stained to identify specific proteins in the sample.

In vitro: In the laboratory or outside the body. The opposite of in vivo. This generally refers to tests done on cells grown in a petri dish.

In vivo: In the body. The opposite of in vitro. This generally refers to tests conducted within a living organism.

Induction therapy: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, induction therapy is the one accepted as the best treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead. Also called first-line therapy, primary therapy, and primary treatment.

Inherited: In medicine, describes the passing of genetic information from parent to child through the genes in sperm and egg cells. Also called hereditary.

Investigational New Drug Application (IND): A substance that has been tested in the laboratory and has been approved by the US Food and Drug Administration (FDA) for testing in people. Clinical trials test how well INDs work and whether they are safe to use. An IND may be approved by FDA for use in one disease or condition but still be considered investigational in other diseases or conditions. Also called an experimental drug, investigational agent, investigational drug, and investigational new drug.

[1] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm

Glossary

Late effect: A health problem that occurs months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental, and social problems and second cancers.

Leukostasis: A pathological diagnosis in which high numbers of leukemia cells in the blood cause problems with normal circulation.[3]

Malignancy: A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Malignant cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of malignancy. Carcinoma is a malignancy that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a malignancy that begins in bone, cartilage, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a malignancy that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are malignancies that begin in the cells of the immune system. Central nervous system cancers are malignancies in the tissues of the brain and spinal cord. Also called cancer.

Master protocol: Research process capable of testing multiple targeted agents or targeted therapeutic strategies in relatively small patient subpopulations. Patients' cancers are tested for targeted abnormalities and assigned to an arm of a clinical trial based on their abnormality.

Metastasize: To spread from one part of the body to another. When cancer cells metastasize and form secondary tumors, the cells in the metastatic tumor are like those in the original (primary) tumor.

Molecule: The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms. Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms.

Morbidity: Refers to having a disease or a symptom of a disease, or to the amount of disease within a population. Morbidity also refers to medical problems caused by a treatment.

Mutation: Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

Neoadjuvant chemotherapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. It is a type of induction therapy.

Neurocognitive: Having to do with the ability to think and reason. This includes the ability to concentrate, remember things, process information, learn, speak, and understand.

Phase 1, Phase 2, or Phase 3 clinical trial: See Clinical trial.

Placebo: An inactive substance or treatment that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or treatment are compared to the effects of the placebo.

Postmortem: After death. Often used to describe an autopsy.

Preclinical study: Research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing in humans is done.

Psychosocial: In medicine, describes the psychological (emotional) and social parts of a disease and its treatment. Some of the psychosocial parts of cancer are its effects on patients' feelings, moods, beliefs, the way they cope, and relationships with family, friends, and co-workers.

[3] www.cancer.org

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

Sequencing (genetic or genomic sequencing): A laboratory method that is used to determine the entire genetic makeup of a specific organism or cell type. This method can be used to find changes in areas of the genome that may be important in the development of specific diseases, such as cancer.

Surrogate endpoint: In clinical trials, an indicator or sign is used in place of another to tell if a treatment works. Surrogate endpoints include a shrinking tumor or lower biomarker levels. They may be used instead of stronger indicators, such as longer survival or improved quality of life, because the results of the trial can be measured sooner. The use of surrogate endpoints in clinical trials may allow earlier approval of new drugs to treat serious or life-threatening diseases, such as cancer. Surrogate endpoints are not always true indicators or signs of how well a treatment works.

Targeted therapy: A type of therapy that uses drugs or other substance to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cell and kill them. Targeted therapy may have fewer side effects than other types of cancer treatment. Most targeted therapies are either small molecule drugs or monoclonal antibodies.

Thermotherapy: Treatment of disease using heat.

Tissue: A group or layer of cells that work together to perform a specific function.

Xenograft: The transplant of an organ, tissue, or cells to an individual of another species.

Acronyms

ALL:	Acute Lymphoblastic Leukemia or Acute Lymphocytic Leukemia
AML:	Acute Myeloblastic Leukemia or Acute Myelogenous Leukemia
BPCA:	Best Pharmaceuticals for Children Act
CBER:	Center for Biologics Evaluation and Research (a division of the US FDA)
CDER:	Center for Drug Evaluation and Research (a division of the US FDA)
CDMRP:	Congressionally Directed Medical Research Programs
COG:	Children's Oncology Group
DIPG:	diffuse intrinsic pontine glioma
DNA:	Deoxyribonucleic acid
FDA:	US Food and Drug Administration
HL:	Hodgkin Lymphoma
IND:	Investigational New Drug Application
IRB:	Institutional Review Board
NCI:	National Cancer Institute
NHL:	Non-Hodgkin Lymphoma
NIH:	National Institutes of Health
PPSR:	Proposed Pediatric Study Request (part of BPCA)
PPTC:	Pediatric Preclinical Testing Consortium
PREA:	Pediatric Research Equity Act
WR:	Written request (part of BPCA)

Notes

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