



Fighting Childhood Cancer: The National Children's Cancer Society Calls Attention to New Report Outlining Pediatric Drug Research and the Needs of Long-Term Survivors

We at The National Children's Cancer Society ([NCCS](#)) recognize that despite better childhood cancer survival rates than ever before in the United States, there are many families who are grieving the loss of a child. A new report about the development of treatment drugs for pediatric cancer is the focus of this paper, with our hopes and prayers that the information included here will inform and educate parents who have faced, or are facing, a battle against cancer with a child.

More than 14,500 American children ages 1 to 19 will face a cancer diagnosis this year in the U.S. Cancer is still the leading cause of death among this age group. Although cancer in children is less common than in adults, the effects can be worse since it occurs so early in life and the late effects from the disease and treatments can last a lifetime.

Recognizing that progress is still needed in treating childhood cancer, the American Cancer Society and Alliance for Childhood Cancer developed the *Childhood Cancer Research Landscape Report*. The report, "[Translating Discovery into Cures for Children with Cancer](#)," describes the process in which childhood cancer drugs are developed. The report is the first time that comprehensive information about childhood cancers has been brought together with a critical analysis of challenges along with opportunities for prevention and treatment. The report includes statistics, trends, a current list of treatment drugs, and details about ongoing pediatric cancer clinical trials and research. It also outlines challenges facing survivors.

This paper attempts to distill the information from the report into a more palatable form. Below are the highlights:

Incidence and mortality

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. However with many cancers there is a great deal of variation in prognosis depending on tumor subtypes and other factors. For example, the five-year survival rate among children with neuroblastoma is 78% on average, but the survival rate for those children diagnosed with "high-risk" neuroblastoma drops to 40–50%.

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). The decline in death rates was more pronounced for leukemia and lymphoma than for other types of cancer. Unfortunately, select cancers such as adolescent ependymoma and neuroblastoma have seen little or no declines in mortality.

Although five-year survival rates are generally used to benchmark progress in cancer treatment and survival, for many cancers mortality increases beyond the fifth year, as compared to similar individuals who never had cancer. 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.

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

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. Combinations of external exposures such as tobacco smoke, infections or radiation may cause some of these changes; or internal exposures such as hormones produced by the body. 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 pediatric versions of the same cancer are often distinct biological subtypes. Sometimes even within the childhood age group (birth to 19 years) there are differences in the same cancer between younger children and older ones. As an example, ALL can have a distinctly different outlook at different ages, partly due to varying genetic subsets that tend to occur as a child develops.

Even where adult and childhood cancers are very similar at the molecular level, 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.

Long-term Survival for Childhood and Adolescent Cancer

Although the incidence of childhood cancer has been slightly increasing, at an average of 0.6% per year from 1975 to 2012, the number of childhood cancer survivors has also increased. An estimated 398,967 survivors of childhood and adolescent cancer (diagnosed at ages 0-19) were alive in the U.S. as of January 1, 2012. The top three types of cancer among childhood cancer survivors are Acute Lymphocytic Leukemia, brain and CNS tumors, and Hodgkin's lymphoma. Most survivors of childhood and adolescent cancer (71%) are 20 years of age or older. Approximately one in 513 young adults between the ages of 20 and 39 is a childhood cancer survivor.

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. Prior research has shown that nearly 40% of childhood cancer survivors aged 35 or older have experienced a severe illness, 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. 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 side effects that appear later in a survivor's life. In fact, a current concern is that it is difficult to predict or study the long-term effects of targeted therapies in children due to the newness of these therapies and the small number of children who have received a specific treatment.

Organizations like The National Children's Cancer Society now provide wide-ranging support and education for survivors facing late effects. The NCCS even created an [online assessment tool](#) to help survivors determine possible physical, cognitive and emotional late effects from their cancer or treatment. The organization's Beyond the Cure program also provides help to survivors with issues related to education, relationships, medical care, employment, insurance and healthy living. "Families are often unprepared for dealing with late effects," explained Mark Stolze, president and CEO of the NCCS. "Many don't even realize the problems their child is having several years after ending treatment are directly related to the treatment they received.

"Because the NCCS offers resources to families dealing with late effects, we continually seek new information about treatment drugs and challenges that survivors face so that we can better help them identify, treat and ultimately overcome those challenges," Stolze added. Additional information about late effects can be found [here](#).

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

Source: The National Academies Press, *“Identifying and addressing the needs of adolescents and young adults with cancer: Workshop summary,”* Copyright 2013, National Academy of Sciences.

Drug Research, Preclinical

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 being 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 animal model. In childhood cancer the preclinical phase of drug development is critical, as there are very few children on whom new therapies can be tested, and federal laws protect children from research that may be too risky. Therefore, the drugs that eventually move forward into pediatric clinical trials must be those with the highest probability of working.

Before new drugs are tested in children, most undergo testing in adult human studies prior to exposing children to the unknown toxicities of novel agents.

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. Additionally, 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.

Clinical Research

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. Each subsequent 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 mean that a given drug typically does not progress to the next phase.

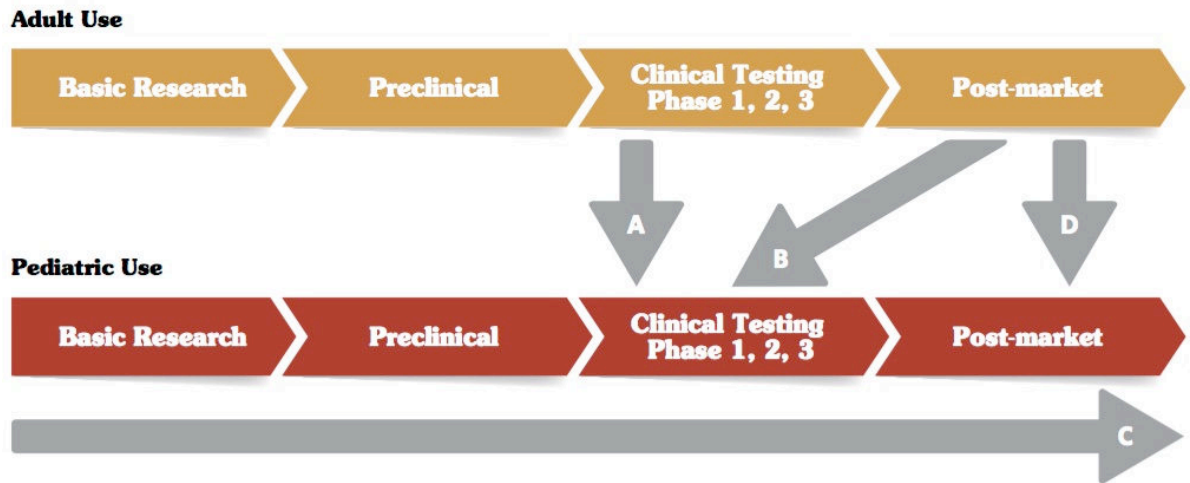
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The classic paradigm for clinical research is often modified in cancer clinical trials. For example, when testing drugs for non- life-threatening diseases, Phase 1 trials are often done with healthy volunteers to find out how well a drug is tolerated 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.

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 the FDA has approved a drug. Once on the market, many drugs undergo additional testing to determine optimum 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.

Therapies for Children Can Follow Multiple Research Paths



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.

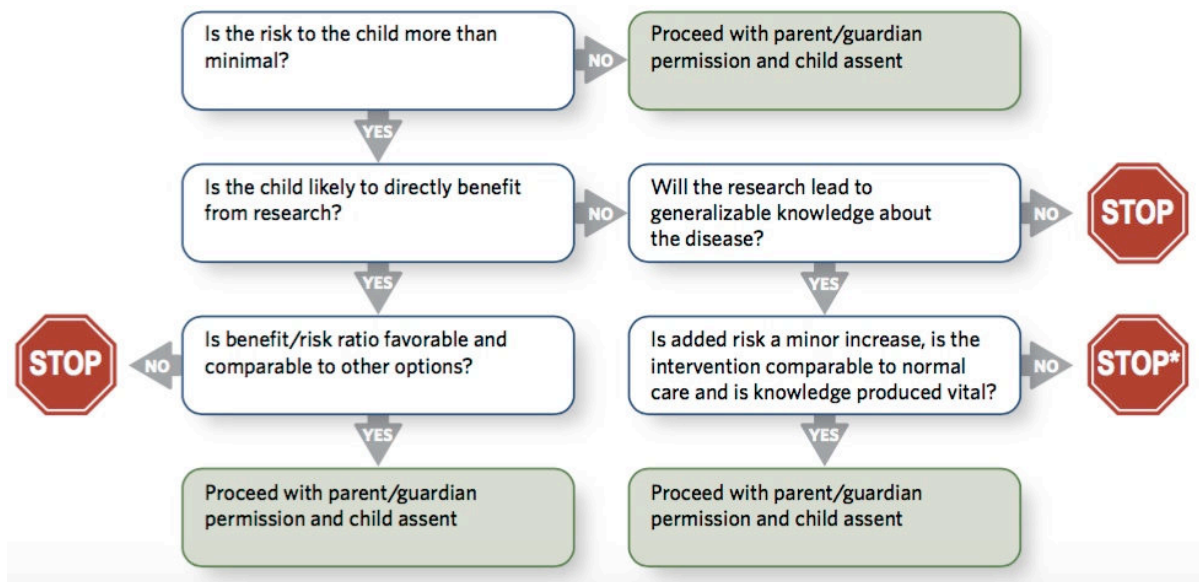
Source: Childhood Cancer Research Landscape Report

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 adults and children.

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. 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.

Special Protections for Pediatric Research Participants



Federal regulations provide special protections to children who participate in research. The ability to conduct pediatric research depends on the nature of the research and its anticipated risks and benefits for children.

Source: Childhood Cancer Research Landscape Report

Federal Funding of Childhood Cancer Research

The federal government is the largest single source of childhood cancer research funding in the U.S. The National Cancer Act of 1937 established [The National Cancer Institute \(NCI\)](#) as the primary U.S. government agency responsible for addressing the research and training needs required to discover the causes, diagnosis and treatments for cancer. The Act also called for NCI to assist with and promote similar research conducted at other public and private institutions. Passage of the Public Health Service Act of 1944, and later the National Cancer Act of 1971, further shaped NCI, placing it as an operating division of the National Institutes of Health (NIH). Among the NIH's many duties, it was charged with distributing research grants and contracts, collaborating with other public agencies and private industry, conducting cancer control activities, as well as appointing advisory committees to explore new issues and opportunities.

NCI has a unique status among the other institutes and centers at NIH because its director is appointed by the president of the United States. The NCI has the ability to produce its own budget proposal separate from the administration's official budget. This separate document has no formal role in the appropriations process, but it does provide the NCI director with the opportunity to emphasize NCI's research priorities. 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. These factors have posed serious challenges for cancer research in recent years. However, the NCI FY 2016 budget increased over last year by \$250.5 million to \$5.21 billion, an encouraging upswing.

Research Funding and Economic Forces

Creating even further financial incentives for drug companies 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 cancers). 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 sooner.

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.

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.

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 (those that remain undeveloped because they have limited potential for profitability) receive two extra years of exclusivity compared to non-orphan drugs, and the applications for approval have many of their application fees waived. Despite these incentives, funding research and drug development for childhood cancer remains challenging.

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.

Conclusion

Children typically develop cancers that are quite different from cancers that occur in adults. They 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.

About The National Children's Cancer Society

The mission of The National Children's Cancer Society is to provide emotional, financial and educational support to children with cancer, their families and survivors. To learn more about the NCCS and its support services, visit thenccs.org. The National Children's Cancer Society is a 501C(3) organization that has provided over \$63 million in direct financial assistance to more than 40,000 children with cancer. To contact the NCCS, call (314) 241-1600. You can also find the NCCS on [Facebook](#) and [Twitter](#).