Pediatric Cancer Treatment Development

By Cynthia Jiles, R.Ph., BSPharm; and Eileen Wu, Pharm.D.

Reviewed by M. Brooke Bernhardt, Pharm.D., M.S., BCOP, BCPPS; and Salem Kamalay, Pharm.D., BCPS, BCPPS

LEARNING OBJECTIVES

1. Analyze the role of the Cancer Therapy Evaluation Program and the Pharmaceutical Management Branch in clinical trial development.
2. Evaluate the role of early pediatric cancer groups and current research organizations.
3. Analyze advances in pediatric cancer treatment.
4. Demonstrate the importance of advocacy and non-clinical research groups in cancer management.
5. Assess the impact of new initiatives on future pediatric oncology research.

ABBREVIATIONS IN THIS CHAPTER

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CCG	Children's Cancer Group
COG	Children's Oncology Group
CTEP	Cancer Therapy Evaluation Program
DCTD	Division of Cancer Treatment and Diagnosis
IRSG	Intergroup Rhabdomyosarcoma Study Group
NANT	New Approaches to Neuroblastoma Therapy
NCI	National Cancer Institute
NWTSG	National Wilms Tumor Study Group
OS	Overall survival
POETIC	Pediatric Oncology Experimental Therapeutics Investigators Consortium
POG	Pediatric Oncology Group
SIOP	International Society of Pediatric Oncologists
TRC	Treatment Referral Center

Table of other common abbreviations.

INTRODUCTION

Pediatric cancers are rare, representing only 1% of all new cancers diagnosed in the United States (Ward 2014); however, they are the second leading cause of death after accidents in children age 1 to 14 years (Siegel 2017). In 2017, an estimated 10,270 children (birth to 14 years) were diagnosed with cancer (excluding benign/borderline malignant brain tumors) and 1,190 died of the disease in the United States (Siegel 2017). Cancer occurs more commonly in adolescents and young adults age 15–39 years than in younger children.

Cancers occurring in adults are classified by the anatomical site of the primary tumor. Similarly, cancers in children and younger adolescents are classified by site but also according to histology. The six most common childhood cancers by International Classification of Childhood Cancers groups are listed in Table 1-1. Cancer affects children throughout the world, and there are many international cancer research groups. Unless otherwise indicated, the focus of this chapter will be limited to U.S.-based research groups.

Pediatric Oncology Research and Cooperative Groups

The effort to treat childhood cancers began with individual researchers at individual institutions. Early investigators were Sidney Farber at Children's Hospital Boston and Joseph H. Burchenal at Memorial Hospital Sloan-Kettering Institute, who both studied leukemia in the 1940s. As the most common type of pediatric cancer, leukemia naturally became a focus of early pediatric cancer research. At that time, children diagnosed with leukemia died within weeks of diagnosis. In 1947, Farber achieved the first partial remission of pediatric leukemia in a 4-year-old girl using the drug aminopterin (an analog of methotrexate). In a landmark scientific paper, Farber documented 10 cases of remission, although these were temporary (Farber 1948).

Burchenal reported the effects of nitrogen mustard compounds on mouse leukemia in 1948 and the activity of 6-mercaptopurine in children with acute leukemia (Burchenal 1948; 1953).

No institution was dedicated to fighting childhood cancer at the time, and no single institution had enough patients to conduct well-designed clinical trials. Eventually, investigators formed a consortium to combine research and patient resources into clinical trial groups.

Early Cooperative Groups

A U.S. *cooperative group* is a group of investigators who continuously develop new trials; conduct many multi-institution clinical trials to study promising treatment options; receive funding not linked to a particular trial; and accept substantial involvement of the National Cancer Institute (NCI) staff in these trials under the details of a cooperative agreement (Bleyer 1997). The organizational structure of each group includes the group chair's office, group operations office, statistics and data center and participating institutions that are organized to provide executive leadership, administrative, discipline, disease, and study committees. By the 1990s, 11 cooperative groups were part of the NCI cooperative group program. Among these, four were pediatric groups (Bleyer 1997).

Children's Cancer Group

Initially known as the Acute Leukemia Chemotherapy Cooperative Study Group A, Children's Cancer Group (CCG), was the first pediatric cooperative group formed in 1955 (Bleyer 1997). At the time, the Cancer Chemotherapy National Service Center encouraged cooperation of individual institutions to evaluate new anti-leukemic agents for children, but CCG did not limit their studies to leukemia. Dr. Burchenal was one of eight original members from major medical centers across the country.

Their first clinical trial was a comparison study of 6-mercaptopurine versus 6-mercaptopurine plus azaserine (O'Leary 2008). Phase I studies with other agents and combination studies were also being conducted. By 1959, the average annual accrual for the group was 200 to 250 patients with acute lymphoblastic lymphoma (ALL), and studies also included patients with metastatic solid tumors (O'Leary 2008). Cooperative groups founded during this time such as Cancer and Leukemia Group B in 1956 and Southwest Oncology Group in 1956 focused on adult cancers but also had pediatric components (Bleyer 1997). The first epidemiology study and the first pharmacology study were conducted in the early 1970s (O'Leary 2008). By 1996, CCG had conducted 160 studies, of which 45% were phase III studies (Bleyer 1997).

National Wilms Tumor Study Group

Wilms tumor is named after Dr. Max Wilms, a surgeon who described its pathology in 1899. It is the most common kidney tumor diagnosed in children younger than age 5 years (Ward 2014). At the time, operative mortality was about 62%. Early advances in Wilms tumor treatment (i.e., radiation, chemotherapy) were made in single institution studies involving only a few subjects. In order to test which agents were more effective and if they could be combined, more patients were needed than available in each individual cooperative group. This prompted the creation of the National Wilms Tumor Study Group (NWTSG) in 1968 (Nakayama 2016).

Table 1-1. Most Common Cancers in Children Ages 0–14 Years

International Classification of Childhood Cancers, 3rd Edition	Frequency
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	33.3%
CNS and miscellaneous intracranial and intraspinal neoplasms	27.9%
Lymphomas and reticuloendothelial neoplasms	10.1%
Soft tissue and other extra-osseous sarcomas	6.8%
Neuroblastoma and other peripheral nervous cell tumors	6.5%
Renal tumors	5.1%

Information from: National Cancer Institute Surveillance, Epidemiology, and End Results Program [homepage on the Internet]. 1975-2014. SEER Cancer Statistics Review, 1975-2014.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of terms associated with conducting clinical trials
- Basic knowledge of clinical trial design

Table of common pediatric laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Cancer Institute. NCI and the Precision Medicine Initiative [homepage on the Internet]
- National Cancer Institute. Cancer Moonshot Blue Ribbon Panel [homepage on the Internet]

Intergroup Rhabdomyosarcoma Study Group

After the creation of NWTSG, the cooperative model was repeated with other pediatric cancers in the United States. In 1970, a rhabdomyosarcoma task force was formed with representatives from CCG, Cancer and Leukemia Group B, and Southwest Oncology Group at the suggestion of NCI (O'Leary 2008). At the time, dactinomycin and vincristine were being studied with surgery and radiation therapy. The Intergroup Rhabdomyosarcoma Study Group (IRSG) was formed in 1972 with a focus on undifferentiated sarcoma and rhabdomyosarcoma, the most common soft tissue sarcoma encountered in the first two decades of life (Raney 2001). The first IRSG protocol activated the same year and included commercially available vincristine, cyclophosphamide, and dactinomycin. The National Institutes of Health was able to provide the doxorubicin for research purposes (O'Leary 2008). Since that time, five studies were conducted by IRSG involving 4,292 eligible patients (Raney 2001).

Pediatric Oncology Group

In 1980, the pediatric division of Cancer and Leukemia Group B joined the pediatricians of Southwest Oncology Group to become Pediatric Oncology Group (POG) (Bleyer 1997). This group was composed of large pediatric cancer centers such as St. Jude Children's Research Hospital, Stanford University Medical Center, Dana-Farber Cancer Institute, and a few international institutions and groups, and joined CCG as one of the two major pediatric cooperative groups. Like CCG, POG conducted studies in a wide range of diseases such as neuroblastoma, hepatoblastoma, risk-stratification of ALL, and infant CNS tumors (O'Leary 2008); many studies were jointly performed by POG and CCG. The POG Statistics and Data Center used remote data entry and the POG log, a precursor to the Children's Cancer Research Network, which later established a population-based pediatric cancer registry in North America (O'Leary 2008).

Creation of COG and the COG Phase 1/Pilot Consortium

The establishment of four pediatric groups—CCG, NWTSG, IRSG, and POG—created redundancies. Many investigators and institutions were members of multiple groups; each group also had duplicative systems (e.g., operations offices, statistics and data centers); and groups were competing for resources. Therefore, in 1998, these groups considered combining their efforts to accelerate progress and use resources more efficiently. Despite logistical challenges and no additional funding, the four pediatric groups merged to become Children's Oncology Group (COG) in 2000 (Reaman 2012). The sole organization among the five U.S. members of the National Clinical Trials Network focused on pediatric cancer is COG. Today, more than 90% of the 14,000 children and adolescents diagnosed with cancer each year in the United States are seen at a COG member institution. When a clinical trial is available, 50%–60% of eligible children are enrolled. In children age younger than 5 years, enrollment rates are closer to 90% (O'Leary 2008).

Because of the specialized and complex nature of early phase clinical trials, the COG Phase 1 and Pilot Consortium was formed in 2002. Although an independent entity with separate funding mechanisms and operational infrastructure, the consortium leverages the resources of the parent COG to develop and implement early phase clinical trials (COG website n.d.).

Other Current Pediatric Research Organizations

Table 1-2 summarizes the activities of the following six pediatric research organizations that are currently active: Pediatric Brain Tumor Consortium, New Approaches to Neuroblastoma Therapy (NANT) Consortium, Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC), Therapeutic Advances in Childhood Leukemia & Lymphoma, St. Jude Children's Research Hospital, and Pediatric Preclinical Testing Consortium.

NCI and the Role of CTEP and Pharmaceutical Management Branch

In 1937 NCI was established as the main federal agency for cancer research and training. The National Cancer Act of 1971 gave NCI unique financial autonomy that allows the NCI to acquire and identify new agents to test in cancer, to coordinate clinical trials, and to create designated cancer centers. The NCI Division of Cancer Treatment and Diagnosis (DCTD) is one of the divisions/offices/centers responsible for distributing pediatric cancer research funds. Within DCTD, the program that assesses new anticancer agents, radiation treatments, and surgical methods is the Cancer Therapy Evaluation Program (CTEP). Within CTEP, the Pharmaceutical Management Branch is the branch that delivers pharmaceutical support and registers investigators for NCI clinical trials.

In the United States, DCTD and pharmaceutical collaborators most commonly sponsor research with investigational agents in cancer. A sponsor is an individual or organization that assumes the legal responsibilities for overseeing clinical trials with investigational agents as defined by the FDA in Title 21 Code of Federal Regulations Part 312. The Investigator's Handbook is published by CTEP and outlines the policies and procedures for conducting all phases of clinical trials sponsored by the DCTD, including information on the protocol review process and how to become a CTEP investigator. The handbook is available on the CTEP website, which also includes helpful tools for the development of clinical trials including protocol and consent templates, condensed risk lists of commonly used oncology drugs and regimens, and biomarker study development resources (CTEP 2014). All investigators and study personnel should review the handbook.

Agent Management Policies and Guidelines

Table 1-2. Activities of Six Currently Active Pediatric Research Organizations

Organization (Year Founded)	Study Phase	Member Institutions	Focus	Funding
PBTC (1999)	I/II	11	• Correlative tumor biology • Novel therapies for primary CNS tumors of childhood • Improving support services and follow-up care	NCI; non-profit organizations; foundations
NANT (2000)	I/II	14	• Novel therapies for neuroblastoma • Identifying biomarkers	NCI; industry; foundations; donors
POETIC (2003)	I/II	10	• Biologic basis for anti-cancer therapy • Biologic correlative science studies • Novel therapies for pediatric cancer and related disorders	Foundations; non-profit organizations; industry; donors
TACL (2005)	I/II	35	• Novel therapies and combinations in recurrent childhood leukemia and lymphoma • Translational laboratory research	Anonymous donors; other sources
St. Jude Children's Research Hospital (1962)	All phases	1 with 8 domestic affiliate sites	• Cures for children with cancer and other catastrophic diseases • Molecular, genetic, and chemical bases of diseases	American Lebanese Syrian Associated Charities; NCI
PPTC (mid-2000s)	Pre-clinical	5 research programs with 1 coordinating center	• New drug candidates in pediatric cancers • Preclinical in vivo data using genomically characterized, patient-derived xenograft lines	NCI

NANT = New Approaches to Neuroblastoma Therapy; PBTC = Pediatric Brain Tumor Consortium; POETIC = Consortium, Pediatric Oncology Experimental Therapeutics Investigators' Consortium; PPTC = Pediatric Preclinical Testing Consortium; St. Jude Children's Research Hospital; TACL = Therapeutic Advances in Childhood Leukemia & Lymphoma.

Information from: Pediatric Brain Tumor Consortium [homepage on the Internet]; New Approaches to Neuroblastoma Therapy [homepage on the Internet]; Pediatric Oncology Experimental Therapeutics Investigators' Consortium [homepage on the Internet]; Therapeutic Advances in Childhood Leukemia & Lymphoma [homepage on the Internet]; St. Jude Children's Research Hospital [homepage on the Internet]; and Pediatric Preclinical Testing Consortium [homepage on the Internet].

Pharmacists and other individuals delegated by the clinical investigator to perform drug accountability are responsible for the agent from the time of receipt of the agent to the time of return or destruction. The agent management policies and guidelines and the investigational drug accountability training videos developed by Pharmaceutical Management Branch are available on the CTEP website (CTEP 2016). Box 1-1 summarizes these policies and guidelines.

NCI Audit Guidelines

The NCI audit guidelines are developed by the Clinical Trials Management Branch of CTEP to define the audit program. As specified by FDA regulations, to protect the human subjects of clinical trials and research data integrity, all DCTD sponsored trials are monitored routinely to ensure reliable and valid data, to ensure adherence to the protocol, and to prevent errors. On-site monitoring became a requirement in 1982. Because most cooperative groups had a quality assurance program in place, the groups were responsible for most of the on-site monitoring. As of 2017, all institutions are monitored at least once every 36 months.

Special Exception and Treatment Referral Center

The Treatment Referral Center (TRC) is a service provided by the Pharmaceutical Management Branch that was developed by the NCI to offer community oncologists and other health care professionals information on therapeutic options for cancer patients. For patients who have exhausted all standard therapies and cannot participate in a clinical trial, a non-research mechanism may be considered. Currently there are two options: TRC protocol and the Special Exceptions protocol. The TRC protocol is used when an agent has shown activity in a particular tumor type that can be used in a wide population but has limited availability. The Special Exception protocol differs from the TRC protocol because it is written for

Box 1-1. Cancer Therapy Evaluation Program Policy and Guidelines

- Agents supplied from PMB for NCI-sponsored or -funded clinical trials are shipped to the investigator's designated shipping address only.
- Agents cannot be re-shipped by mail or overnight delivery service to another institution, site, or study subject nor transferred to another institution or site without PMB approval.
- Agents are received by a Control Dispensing Area and then transported to a Satellite Dispensing Area if the following conditions are met: (1) the satellite is supported by the control area either within a single institution, within a medical center complex consisting of two or more institutions, or to local community-based investigators; (2) agents are transported to the satellite via staff or institutional courier using appropriate temperature controls and hazardous/infectious transportation procedures per institution policies; and (3) the control area is responsible for overall inventory control and must provide all accountability records during a CTEP audit.
- Record of receipt, use, and disposition of all investigational agents must be established per FDA regulations.
- Control NCI investigational agent accountability records must be maintained at the location that directly receives the agent from the NCI (Control Dispensing Area).
- Satellite NCI investigational agent accountability records must be maintained at each location that receives NCI supplied agent from a Control Dispensing Area and stores an agent for more than one day.
- Investigational agents supplied by the PMB may be transferred between eligible investigators within an institution or between DCTD-sponsored protocols if the protocol utilizes the same agent, strength, and formulation and a NCI Investigational Agent Transfer Form is submitted for approval.
- Transfer forms for urgent medical need should be submitted within 72 hours of the actual transfer.

CTEP = Cancer Therapy Evaluation Program; DCTD = Division of Cancer Treatment and Diagnosis; NCI = National Cancer Institute; PMB = Pharmaceutical Management Branch.

individual patients and is the most common type of protocol. In 2003, more than 708 Special Exception protocol requests were made for bevacizumab and 5-azacitidine alone (Johnson 2012). The number of requests for TRC has steadily decreased since 2003 likely because of increased industry development of novel agents, drug company development of early access programs, and off-label use (Johnson 2012). However, this decline could change as drug development paradigms shift and clinical pharmacists can play a large role in identifying patients who may benefit from this process as well as in preparing the protocols.

THERAPEUTIC ACHIEVEMENTS

Background

During the early part of the 20th century, cancer treatments were rare, consisting of surgery or radiation. Patients succumbed to their disease within weeks to months of diagnosis. In the 1950s and 1960s, as new drugs and treatment combinations were discovered or created, short remissions—followed by longer remissions and cures—became common in various cancers. By the end of the 20th century, the overall survival (OS) rate of pediatric cancers was 80%. These outcomes were the result of drug discoveries, innovation, and research trials.

These conceptual advances were presented by Paul Carbone at the National Conference on Advances in Cancer Management in 1988 as the Six Concepts Leading to Clinical Cures: (1) discovery of effective single agents; (2) treatment of sanctuary sites of disease; (3) use of combination chemotherapy; (4) integration of combined modality approaches; (5) development of biologic response modifiers; and (6) employment of clinical trial methodology (Carbone 1990).

An understanding of these concepts will help highlight the importance of the therapeutic achievements of individual investigators and research groups. Examples of achievements are in the sections that follow.

Accomplishments of the Early Research Groups

Acute Lymphoblastic Leukemia

The two most common types of leukemia in children and adolescents are ALL and acute myeloid leukemia (AML). Chronic leukemias are very rare in children and adolescents. The most common is ALL, accounting for about 80% of leukemia cases in children and more than 50% of leukemia cases in adolescents. Less common is AML, accounting for about 15% of leukemia cases in children and more than 30% in adolescents. The 5-year survival rate of children with ALL from 2006–2012 was about 90% from age birth to 14 years and 74% from age 15 to 19 years (Siegel 2017). At diagnosis, leukemic cells are found primarily in the bloodstream and bone marrow. They can also be found in sanctuary sites, such as the CNS, ovaries, and testes.

Between 1968 and 2000, CCG treated more than 16,000 children with ALL. In the 1970s, CCG adapted effective pre-symptomatic CNS therapy, pioneered by St. Jude Children's Research Hospital. It was demonstrated that cranial irradiation and intrathecal methotrexate might replace cranial spinal irradiation and that 18 Gy cranial irradiation might replace 24 Gy with similar efficacy. A widely adopted dosage schedule for intrathecal methotrexate was developed by CCG that improved efficacy and decreased neurotoxicity (Bleyer 1983). Post-induction intensification therapy was originally pioneered by Riehm, Henze, and colleagues at the Berlin-Frankfurt-Munster Group. In the 1980s, CCG adapted the strategy and demonstrated the value of longer augmented post-induction intensification regimen with additional agents for higher risk patients with a poor early marrow response.

During the first year of post-induction therapy, the augmented regimen included more vincristine, asparaginase, methotrexate, and dexamethasone than the standard regimen, although the standard regimen included more oral methotrexate, prednisone, and mercaptopurine. Therapy continued for 2 years for girls and for 3 years for boys, beginning with the first interim maintenance period (Nachman 1998). In addition, CCG demonstrated the superiority of dexamethasone over prednisone and observed that patients with suboptimal response may be rescued with changes in therapy (Gaynon 2000).

The next major accomplishment was by POG, which demonstrated that high dose L-asparaginase consolidation improved survival for patients with T-cell lymphoid malignancies when added to a backbone of effective rotating agents, as follows: vincristine, doxorubicin, cyclophosphamide, prednisone, teniposide, cytarabine, and mercaptopurine (Amylon 1999).

The POG 8035 Classification Study, conducted from 1981 to 1986, included the cytogenetic evaluation of leukemia cells of the newly diagnosed patients entered in this study. The investigators demonstrated that children with hyperdiploid ALL with an extra chromosome 6 fare better than those children with only hyperdiploid leukemic cells. This study was the first large randomized trial to confirm previous reports that hypodiploid or pseudodiploid karyotype confers a worse outlook for children with ALL and that patients with chromosomal translocations in their leukemic cells fare worse than those lacking translocations (Jackson 1990). Early large group studies of unselected patients failed to show a clinical significance of specific abnormalities and patterns, or the correlation between karyotype and treatment outcome that was seen in studies of patients with specific abnormalities in leukemic cells (Williams 1990).

St. Jude Children's Research Hospital conducted a series of "Total Therapy" studies (I-V) from 1962–1972. The studies evaluated drugs used during induction, post-induction, and maintenance phases, and the need for prophylactic craniospinal irradiation. Study V called for the maximum tolerated dose of chemotherapy, aggressive supportive care, and better CNS prophylaxis. This design changed the direction of the treatment of childhood ALL. A basic treatment plan follows this format:

- Remission induction – the goal is to eliminate leukemia cells from the body
- Consolidation/intensification - different drugs from induction
- Continuation/maintenance – using fewer and/or different drugs at lower doses over a 2-2.5 year period

Treatment of ALL can be summarized in the following categories:

- Diagnosis, classification and genetic alterations
- Determining the mechanisms of treatment resistance and relapse
- Factors influencing risk classifications
- Advances in treatment
- Modifying treatment to reduce/eliminate late complications of therapy (Pui 2010)

Acute Myelogenous Leukemia

Similar to treating ALL, treating AML follows the principle of eliminating the last leukemic cell present in the body. The presence of minimal residual disease is a prognostic indication of OS (Ribeiro 2005). Standard treatment consists of induction (with a goal of complete remission) and post-remission treatment. Post-remission treatment is chemotherapy with or without hematopoietic stem cell transplantation. Compared with ALL, OS rates for AML were lower, with a 64% 5-year survival rate for children diagnosed in 2003–2009.

Four AML trials were conducted by POG between 1981 and 2000. Observations were that cytarabine dose intensification improves results in childhood AML; cytogenetics are the best predictor of response and relapse risk; and children with Down syndrome and AML have a high cure rate. Studies done by CCG and St. Jude reached similar conclusions. In addition, CCG and St. Jude have conducted AML trials modifying drugs, doses, and frequencies, none of which have resulted in a significant change in OS.

Wilms Tumor

Wilms tumor treatment was the first to use a multimodality approach to treating cancer. Surgical techniques developed by Dr. Ladd, the Chief of Surgery at Boston Children's Hospital, improved outcomes and resulted in no operative deaths during the 1930s (Nakayama 2016). Post-surgical irradiation was added in the 1930s and 1940s (Evans 1976). The first randomized trial for non-metastatic Wilms tumor was completed by CCG in 1967. This study showed that 86% of those treated with multiple courses of the 5-day regimen of dactinomycin plus surgery and radiation had complete remission, whereas 48% achieved complete response after a single course (O'Leary 2008).

Tumors are classified by stage (I through V) and histology. In most cases, staging occurs after nephrectomy based on tumor location, penetration into other structures, the amount of tumor removed, and lymph node involvement.

After the formation of the NWTSG in 1968, five sequential trials were executed between 1969 and 2005. With each study, the treatment was modified to administer more or less chemotherapy of varying frequencies. Some of the important findings from these trials are the following:

- Postoperative flank radiotherapy was unnecessary for children with Stage I or II/favorable histology or Stage I/anaplastic tumors when treated with vincristine and dactinomycin after nephrectomy.
- The combination of dactinomycin and vincristine is more effective than either drug alone (Spreafico 2006).

- The addition of cyclophosphamide to vincristine-dactinomycin-doxorubicin did not improve the prognosis for patients with Stage IV/favorable histology tumors, but improved recurrence-free survival and OS in children with Stage II-IV anaplastic Wilms tumor.
- The loss of heterozygosity of 1p or 16q is associated with an increased risk of relapse and death. The risk is even greater for those with a loss of heterozygosity of both chromosomes (Spreafico 2006).
- Duration of therapy for 6 months was found to be as effective as 15 months for patients with stage III and IV disease and a favorable histology.
- The study of late effects of Wilms tumor treatment was initiated by NWTSG in 1969 as part of NWTS I, which paved the way for the more extensive follow-up programs integral to the care of every current pediatric oncology patient.

One of the primary objectives of COG AREN0533 was to improve the 4-year event-free survival to 75% for patients with Stage III or IV FH Wilms tumor with loss of heterozygosity for chromosomes 1p and 16q. In addition to standard treatment, patients received doxorubicin (stage I/II) or doxorubicin alternating with cyclophosphamide, etoposide and radiation (Stage III/IV). Improvement of event-free survival for Stage I/II patients was unclear; however, improvement was seen in Stage III/IV patients (Dix 2015).

During this same period, the International Society of Pediatric Oncologists (SIOP) began clinical trials for Wilms tumors in Europe. The approach of SIOP is to give preoperative chemotherapy and/or radiation before nephrectomy. The arguments for pre-nephrectomy chemotherapy (advocated by SIOP) are to reduce the chance of tumor spillage during nephrectomy and to provide the ability to study tumor changes induced by drugs, which could be a prognostic factor. The rationale for nephrectomy first (advocated by NWTSG) is the stage at presentation is an index of the tumor's inherent aggressiveness. For the approach of both groups, exceptions exist in which the order of surgery and chemotherapy are reversed. Although NWTS and SIOP have different philosophies on preoperative chemotherapy, the overriding message is that most patients with Wilms tumor survive long term, regardless of the sequence of therapeutic interventions (Bhatnagar 2009).

Improved risk stratification has divided the population of Wilms patients into small subgroups, challenging the designing and executing of clinical trials that are sufficiently powered to demonstrate the desired outcomes. For future clinical trials, COG, SIOP, and other Wilms Tumor groups intend to collaborate (Dome 2015).

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue tumor of childhood. However, these tumors are rare, representing only 3%–4% of pediatric cancers overall. There are two major subtypes of rhabdomyosarcoma: embryonal and alveolar. Embryonal rhabdomyosarcoma accounts for about 75% of cases and is most common in children younger than age 5 years. Alveolar rhabdomyosarcoma accounts for about 16% of cases, and the incidence does not vary by age in children and adolescents (American Cancer Society 2014).

The initial process of staging rhabdomyosarcoma was by the surgical/pathologic (or clinicopathologic) grouping system. Ranking occurred after surgery, before chemotherapy and radiation, based on tumor removal, lymph node involvement, residual disease, and the presence of metastases. The system relied on the surgeon, the surgeon's willingness to attempt tumor removal, and residual disease after removal. Although IRSG used the surgical/pathologic grouping system to stage disease, a preclinical staging system independent of surgical intervention and pathologic assessment of specimens was needed. Many research groups, both national and international use staging systems based on the International Union for Cancer Control TNM model. This TNM model is based on the site and size of the primary tumor (T), involvement of regional lymph nodes (N), and distant metastases (M) (Stanford Medicine website 2017).

One study compared the prognostic significance of staging factors of the International Union for Cancer Control system to data from IRS-II (Lawrence 1987). Lawrence concluded the study "indicates definite prognostic significance for all of the individual factors used on the International Union for Cancer Control system except clinical status of regional nodes" (p. 1). It was thought that histology should be included in the staging process because the presence of alveolar cells indicated an unfavorable prognosis.

Today, patients are classified into low-, intermediate-, and high-risk groups based on both a TNM staging system and a surgical/pathologic clinical grouping system previously described. Patient age and histology type are also considered when determining prognosis (Malempati 2012).

Throughout 30 years (1972–2005) IRSG conducted five studies. Important findings are listed in Box 1-2.

Accomplishments of Current Research Groups

COG and the COG Phase 1/Pilot Consortium

For both common and rare pediatric cancers, COG conducts trials with nearly 100 active clinical–translational trials open at any given time. Box 1-3 lists cancers studied by COG. In addition to disease specific research, COG conducts studies in developmental therapeutics (new cancer drug development), supportive care, epidemiology, stem cell transplantation, behavioral sciences, and survivorship (COG website n.d.).

For clinical trials of all phases in all disciplines of pediatric cancer, COG develops and executes studies ranging from pilot studies to Phase III studies. Table 1-3 provides a partial list of drugs tested in COG studies.

Changes and improvements in available treatments have led to an increase in the survivor rate in pediatric cancer. Unfortunately, current therapies remain unsuccessful for a

Box 1-2. Findings of Intergroup Rhabdomyosarcoma Research Group Studies

- Patients with localized, completely resected disease did not benefit from radiation added to VAC, if the histologic subtype is embryonal rhabdomyosarcoma.
- There is no benefit from adding doxorubicin to the combination of VAC in patients with group III and IV disease.
- Patients with tumor at or near the eye, vagina, or bladder have a good prognosis. Primary chemotherapy followed by radiation therapy is the recommended approach. Delayed excision of these tumors may improve prognosis by changing a partial response into a complete response after initial shrinkage of the tumor by chemotherapy, with or without radiation.
- Intensification of treatment correlated with improved outcome when a risk-based study design was used. The addition of doxorubicin and cisplatin with or without etoposide to the VAC regimen has not improved outcome for patients with advanced disease.
- The current standard combination of VAC, with cyclophosphamide at 2.2 g/m^2 per dose with granulocyte colony-stimulating factor, is equally efficacious with regard to failure-free and overall survival compared with VAI and VIE.

VAC = vincristine, dactinomycin, and cyclophosphamide; VAI = vincristine, actinomycin D, and ifosfamide; VIE = vincristine ifosfamide, and etoposide.

Information from Raney R, Maurer H, Anderson J. The Intergroup Rhabdomyosarcoma Study Group (IRSG): major lessons from the IRS-I through IRS-IV studies as background for the current IRS-V treatment protocols. Sarcoma 2001;5:9-15.

Box 1-3. Cancers Studied by Children's Oncology Group

Hematologic

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Myeloid leukemia
- Non-Hodgkin lymphoma
- Hodgkin lymphoma

CNS

- Medulloblastoma
- Ependymoma
- Brainstem gliomas
- Low- and high-grade gliomas
- Germ cell tumors

Solid tumors

- Neuroblastoma
- Ewing sarcoma
- Osteosarcoma
- Wilms tumor
- Rhabdomyosarcoma
- Other soft tissue sarcomas

Other tumors

- Retinoblastoma
- Hepatoblastoma

Information from: The Children's Oncology Group [homepage on the Internet].

Table 1-3. Sample of Drugs Evaluated in COG Trials

Drug	Indication	Protocol Number
Imatinib	Very high-risk ALL	AALL0031
Nelarabine	T-cell ALL	AALL0434
Pegaspargase	High-risk ALL	AALL07P4
Pegaspargase	High-risk ALL	AALL08P1
Azacitidine	Infants with ALL	AALL15P1
Gemtuzumab ozogamicin	Relapsed, refractory, or secondary AML	AAML0531
AZD1775	Diffuse intrinsic pontine glioma	ADVL1217
Entinostat	Recurrent/refractory solid tumors and lymphoma	ADVL1513
Temsirolimus Sirolimus	Recurrent/refractory solid tumors	ADVL0813
Oxaliplatin Irinotecan	Refractory solid tumors and lymphomas	ADVL0415
Dinutuximab	High-risk neuroblastoma	ANBL0032

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia.

Information from: IPAD System [Internet database]. Rockville, MD:NCI.

large percentage of children and adolescents. These individuals require treatment with novel therapies. Understanding the biology of cancers provides the opportunity to find, test, and possibly cure those not helped by conventional therapy. Elucidation of the molecular biology of tumors may lead to a reduction in the incidence and severity of late effects (Smith 2010).

As evident with research conducted by IRSG, NWTSG, and St. Jude Children's Research Hospital, research trials are developed based on knowledge learned or confirmed from past trials. Subsequent trials aim to improve survival and reduce toxicities by modifying doses, altering regimens, or substituting one drug or dosage form for another (e.g., substituting dexamethasone for prednisone, such as AALL0232 in high risk b-precursor ALL, or PEG-asparaginase for asparaginase, in Dana Farber Consortium Institution protocol DFCI 91-01). Treatment trials may focus on risk categories, such as AAML1531 in AML, or histology (AREN0532 in Wilms).

Pediatric Brain Tumor Consortium

The primary mission of the Pediatric Brain Tumor Consortium is to identify through laboratory and clinical science superior treatment strategies for children with brain cancers. Results of some completed studies are highlighted in Box 1-4.

Box 1-4. Select Pediatric Brain Tumor Consortium Studies

- Determined the maximum tolerated dose and recommended phase 2 dose (RP2D) of intrathecal mafosfamide in infants and children age 3 years or younger with newly diagnosed embryonal tumors (PBTC-001)
- Studied lenalidomide in pediatric patients with recurrent, refractory, or progressive primary CNS tumors. Antitumor activity, defined by both objective responses and long-term stable disease, was observed, primarily in patients with low-grade gliomas (PBTC-018)
- A Phase I trial of capecitabine and concomitant radiation therapy in newly diagnosed brainstem gliomas and high-grade gliomas, found the combination was generally well tolerated and the RP2D of capecitabine was determined (PBTC-021).
- Bevacizumab and irinotecan were tested in children with recurrent CNS tumors. The combination was fairly well tolerated, and most severe bevacizumab-related toxicities were rare, self-limiting, and manageable (PBTC-022)
- Determined the RP2D of selumetinib in recurrent or refractory low-grade glioma (Phase I of PBTC-029)
- A Phase II study to evaluate the efficacy of this regimen in children with intrinsic brainstem gliomas is in progress (PBTC-030)

Information from: Pediatric Brain Tumor Consortium [homepage on the Internet].

New Approaches to Neuroblastoma Therapy Consortium

The vision of NANT consortium is to "develop and test new therapies that will be targeted specifically to neuroblastoma cells, and therefore improve the outcome for children with advanced neuroblastoma with fewer side effects" (NANT website 2017). A brief description of two active trials follows:

- The Neuroblastoma Precision Trial aims to identify subgroups of refractory or relapsed neuroblastoma patients who have potentially targetable genetic and/or immunologic biomarkers. Additional potential novel biomarkers will also be evaluated (N2015-01).
- Lenalidomide added to the combination of ch14.18and 13-cis-retinoic acid to determine the maximum tolerated dose in the treatment of children with refractory or recurrent neuroblastoma (N2011-04).

Several trials by NANT have been conducted with metaiodobenzylguanidine, a norepinephrine analog. When labeled with iodine-123, metaiodobenzylguanidine has demonstrated activity for targeted therapy in both relapsed and newly diagnosed neuroblastoma (Matthay 2006). These studies provided the background for ANBL1531, a Phase III COG study in high-risk neuroblastoma.

Pediatric Oncology Experimental Therapeutics Investigators' Consortium

The mission of POETIC is to "promote the early clinical development of promising therapies for the treatment of children, adolescents and young adults with cancer and related disorders" (POETIC website 2017). In support of this mission, POETIC has completed research in cancer biology and clinical trials. Preclinical trials were designed to expand knowledge of cancer biology as follows:

- Performed drug sensitivity studies to identify agents with activity against the mixed-lineage-leukemia gene. Drugs not considered standard therapy for the leukemia were studied, with activity seen among some of the drugs.
- Conducted molecular profiling of teratoid/rhabdoid tumors to determine diagnostic, prognostic, and therapeutic value (Birks 2011).
- Used cells from a neurocutaneous melanocytosis biopsy samples and expanded them in xenografts to provide material for molecular and drug sensitivity studies (Ruan 2015).

This consortium has completed three First-in-Child trials, which tested 17AAG, cetuximab plus irinotecan, and deforolimus. The cetuximab plus irinotecan combination showed evidence of clinical benefit in CNS tumors and is now the target of a phase II trial (POETIC website 2017).

Therapeutic Advances in Childhood Leukemia and Lymphoma

At the time of this writing, Therapeutic Advances in Childhood Leukemia and Lymphoma has six active studies, listed in Box 1-5. One is a joint study with other research consortia.

Box 1-5. Select Therapeutic Advances in Childhood Leukemia and Lymphoma

Trials

- A Pilot Study of Decitabine and Vorinostat with Chemotherapy for Relapsed ALL (T2009-003)[a]
- A Phase I Dose Finding Study of Panobinostat in Children with Refractory Hematologic Malignancies (T2009-012)[a]
- A Pilot Study of Vincristine Sulfate Liposome Injection (Marqibo) in Combination with UK ALL R3 Induction Chemotherapy for Children, Adolescents, and Young Adults with Relapse of Acute Lymphoblastic Leukemia (T2012-002)[a]
- A Phase I Trial of Temsirolimus (CCI-779, Pfizer, Inc.) in Combination with Etoposide and Cyclophosphamide in Children with Relapsed Acute Lymphoblastic Leukemia and Non-Hodgkin Lymphoma (T2014-001)[a]
- A Phase I Trial of NECTAR (Nelarabine, Etoposide and Cyclophosphamide in T-ALL Relapse): A Joint Study of TACL, POETIC and ITCC (T2008-002)[a]
- Epigenetic Reprogramming in Relapse AML: A Phase 1 Study of Decitabine and Vorinostat Followed by Fludarabine, Cytarabine and G-CSF (FLAG) in Children and Young Adults with Relapsed/Refractory AML (T2016-003)[a]
- Bortezomib With Chemotherapy for Relapsed Pediatric Acute Lymphoblastic Leukemia (T2005-003)[b]
- Bortezomib given with vincristine, dexamethasone, pegylated asparaginase, and doxorubicin achieved a 73% response rate (Messinger 2012).
- EZN-3042 with intensive re-induction chemotherapy (T2009-007)[b]
- This combination was not tolerated and the trial was terminated. The manufacturer ended development of EZN-3042 (Raetz 2014).

[a]Active.

[b]Completed.

Information from: Messinger Y, Gaynon P, Sposto R, et al. Therapeutic advances in childhood leukemia & lymphoma (TACL) consortium: bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: therapeutic advances in childhood leukemia & lymphoma (TACL) study. Blood 2012;120:285-90; Raetz EA, Morrison D, Romanos-Sirakis E, et al. A phase I study of EZN-3042, a novel survivin messenger ribonucleic acid (mRNA) antagonist, administered in combination with chemotherapy in children with relapsed acute lymphoblastic leukemia (ALL): a report from the therapeutic advances in childhood leukemia and lymphoma (TACL) consortium J Pediatr Hematol Oncol 2014;36:458-63.

St. Jude Children's Research Hospital

St. Jude Children's Research Hospital opened its doors in 1962. By the end of the first year of operation, four studies were completed and more than 30 studies were ongoing. Like COG, the St. Jude Children's Research Hospital conducts all phases of clinical trials. In addition, organizational membership in COG enables researchers to participate in COG trials. An ALL treatment, called the "Total Therapy" regimen, developed in 1962 combined several anticancer drugs with radiation treatment, considered unconventional at the time. Total Therapy is a series of ALL trials conducted at St. Jude. Recruitment for Total Therapy protocol 17 is currently ongoing.

Total Therapy 17 includes newly diagnosed patients with ALL and lymphoma. Aims of the protocol include optimizing current therapy and reducing vincristine toxicity through dose minimization. Agents being investigated in this trial include blinatumomab, bortezomib, rituximab, and tyrosine kinase inhibitors.

Researchers developed the first immunologic method to diagnose solid tumors in children in 1965. Sustained remission in ALL was demonstrated in 1966, when several patients were taken off therapy. In the 1990s, an anaplastic lymphoma kinase gene was discovered and patented. The licensed gene and its product (a tyrosine kinase) were used to develop the targeted inhibitors crizotinib and ceritinib for the treatment of lung cancers. Currently, St. Jude is exploring the administration of natural killer cells in patients with relapsed/refractory leukemia.

Pediatric Preclinical Treatment Consortium

Pediatric Preclinical Treatment Consortium was created to develop reliable preclinical testing data for pediatric drug candidates. Working through the five member institutions, drug testing is focused on five cancer groups: sarcoma and renal, neuroblastoma, osteosarcoma, leukemia, and CNS.

Testing is performed on human cell lines that are diverse—there are multiple diagnoses within each cancer group, obtained at different points in therapy from different locations, from patients of varying ages. The cell lines are grouped into a panel of cell lines for in vitro testing and a panel of human tumor xenografts for in vivo testing.

The initial panel was composed of 27 cell lines; 23 are used as a primary panel for cytotoxicity assays, and four in a secondary panel for expanded testing. Six cell lines are common to both the in vivo and in vitro panels to enable comparisons between the in vivo and in vitro results.

As of May 2017, more than 80 agents have been tested, and seven are being evaluated in children in the clinical setting:

- Alisertib (MLN8237)
- NTX-010
- Selumetinib for BRAF-mutated low-grade astrocytoma
- Rapalog plus standard chemotherapy (for rhabdomyosarcoma)
- IGF-1R antibodies
- Eribulin
- Talazoparib (BMN 673) plus low-dose temozolomide

COMPLEMENTS TO CLINICAL RESEARCH

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study, also known as the Long-Term Follow-Up Study, is one of the largest epidemiological investigations of late effects outcomes of its kind. It is a collaborative, multi-institutional study initiated in 1994 and funded by the NCI. Eligible participants are cancer survivors 5 or more years after diagnosis, with a sibling cohort serving as controls.

This study was created to take advantage of the following: (1) the opportunity to gain new knowledge about the long-term effects of cancer and therapy, knowledge that can be used to help design treatment protocols and intervention strategies that will increase survival and minimize harmful health effects; and (2) the obligation to educate survivors about the potential impacts of cancer diagnosis and treatment on their health and to implement programs for the prevention and early detection of late effects.

To be eligible, cancer survivors must have received their initial diagnosis between January 1, 1970, and December 31, 1986. The protocol later added a second cohort of patients initially diagnosed between January 1, 1987, and December 31, 1999. Upon enrollment, participants completed a baseline survey to provide information about their original diagnosis, treatments received, adverse effects, second cancers and treatment as appropriate. Additional questionnaires are completed every 2–3 years. Investigators hope to gather information about behaviors and patterns of medical care use by survivors. Survey topics vary and have included insurance coverage, family life, fertility, and smoking.

The study enrolled about 35,923 childhood cancer survivors diagnosed between 1970 and 1999, and more than 5,000 siblings of survivors who serve as the comparison group for the study. An analysis of the data published in 2006 reported that adult survivors of pediatric cancer who were treated in the 1970s and 1980s are a high-risk population. Cancer survivors were eight times as likely as their siblings to have severe or life-threatening chronic health conditions (e.g., myocardial infarction, congestive heart failure, premature gonadal failure, second cancers, severe cognitive dysfunction) (Oeffinger 2006). The three groups that were at highest risk were survivors of bone tumors, CNS tumors, and Hodgkin disease and were also more likely to have multiple conditions.

Select observations from the Childhood Cancer Survivor Study are listed in Box 1-6.

In addition to managing the Childhood Cancer Survivor Study, St. Jude Children's Research Hospital manages its own long-term survivor study of former St. Jude patients, called the St. Jude Life Study (SJLIFE). Long-term follow-up guidelines for physicians of cancer survivors have been developed by COG. The guide is especially helpful for physicians unfamiliar with the potential long-term effects of childhood cancer survival (Bhatia 2015).

Box 1-6. Select Observations from the Childhood Cancer Survivor Study

- Of girls with Hodgkin lymphoma who received chest-directed radiation therapy, 30% will develop breast cancer by age 50 years. This finding led to the development of the EMPOWER study, which focused on increasing mammography screening rates among female survivors of childhood cancer who had chest-directed radiation therapy and, therefore, are at long-term risk for breast cancer. Further findings from the study showed that providing survivors with information and telephone counseling on their treatment exposure and risk for breast cancer doubled the rate of mammography screening among survivors (Oeffinger 2016).
- Behavioral, emotional, and social symptoms commonly co-occur in adolescent survivors of childhood cancer and are associated with treatment exposures and physical late effects. Assessment and consideration of symptom profiles are essential for directing appropriate mental health treatment for adolescent survivors (Brinkman 2016).
- The risk of subsequent malignancies at 15 years after initial cancer diagnosis remained increased for those diagnosed in the 1990s, although the risk was lower compared with those diagnosed in the 1970s. This lower risk was associated with reduction in therapeutic radiation dose. The cumulative incidence of subsequent neoplasms was 2.9% among individuals diagnosed in the 1970s, 2.4% among those diagnosed in the 1980s, and 1.5% among those diagnosed in the 1990s (Turcotte 2017).
- Diabetes mellitus, although an infrequent outcome, is more common in childhood cancer survivors than a sibling comparison group, particularly among those who were treated with either abdominal or total body irradiation. Respondents were classified as having diabetes if they had taken insulin or an oral medication for diabetes mellitus for more than 1 month in the preceding 2 years. Those taking insulin only (20.6%) were considered to have type 1 diabetes and the remainder (79.4%) to have type 2 diabetes. The pathogenesis of diabetes mellitus observed in these subjects remains unclear (Meacham 2009).

Information from: Brinkman T, Li C, Vannatta K, et al. Behavioral, social, and emotional symptom comorbidities and profiles in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2016;34:3417-25; Meacham R, Sklar C, Si S, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med 2009;169:1381-8; Oeffinger K, Ford J, Moskowitz C, et al. The EMPOWER Study: Promoting breast cancer screening: A randomized controlled trial in the Childhood Cancer Survivor Study. J Clin Oncol 2016;34(suppl 15):10506; Turcotte L, Liu Q, Yasui Y, et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015. JAMA 2017;317:814-24.

Role of Advocacy Groups/Other Major Stakeholders

Dealing with a diagnosis of cancer can be overwhelming. There is new language to learn, new routines for tests, drug administration, adverse effects to monitor, cost concerns, and mental anguish. Patients and family members have concerns about what to expect during and after the diagnosis, and how daily life will be affected (e.g., work, school, childcare, grocery shopping meal preparation). Health care providers and institutions do a remarkable job of providing and explaining information but are not available to the patient and family members on a continuous basis. Many organizations provide resources to help patients navigate the labyrinth of cancer treatment. A few broadly defined groups and the assistance they can provide to those dealing with a cancer diagnosis are noted here.

In addition to programs sponsored by health care organizations and institutions, a large number of groups and organizations are available to provide assistance to families and individuals affected by cancer. Some are large, national organizations whereas others are local. Whether they are identified as an advocacy group, support group, or "friends of" group, they each share the desire to provide support in many different areas. The following is a summary list of activities performed by various stakeholders. Any given organization may be involved with one, two, or more items listed.

- *Charities and nonprofit foundations* accept and raise funds to support individuals and families, the activities of a parent organization, and support research; they also raise awareness in the community about cancer.
- *Support groups* provide emotional support in peer setting; provide transportation, meals, and lodging for families traveling to appointments; provide hats and wigs to patients; sponsor camps for patients; provide emotional support to the bereaved; provide educational information; and raise awareness in the community about cancers.
- *Advocacy groups* provide peer support; provide educational information; raise funds; raise awareness (disease or patient specific); lobby the government for research funds; and provide financial assistance to researchers.

The high cost of cancer drugs is a burden to many. One contributing cause is the extended timeline of drug development. Product development may take 10 years or longer from initial testing to final approval. To offset the cost of chemotherapy medications, more than 200 drug companies have financial assistance programs. Organizations such as ChemoCare and the Partnership for Prescription Assistance guide patients through the process of applying for financial assistance.

The Federal Government as a Stakeholder in Cancer Research

The federal government has supported cancer research through the National Institutes of Health and NCI. The National Cancer Act of 1971 granted broad authority to develop a National Cancer Program and provided additional funding for NCI. About 41% of the 2016 NCI budget was allocated for research project grants.

Congress has passed legislation to provide funds for research and to encourage and sometimes mandate drug companies to conduct research directed at children. Several of these congressional Acts (not exclusive to cancer or cancer research) are listed in Box 1-7.

Box 1-7. Congressional Actions Related to Research

- Research to Accelerate "Cures and Equity for Children" Act or the "RACE for Children" Act H.R.1231/S. 456, signed into law August 18, 2017, as part of the FDA Reauthorization Act of 2017:
  - Updates the Pediatric Research Equity Act by providing that companies developing a cancer drug undertake the Pediatric Research Equity Act studies of their drug in children when the molecular target of their drug is relevant to a children's cancer.
- Gabriella Miller Kids First Research Act, P.L. 113-94 (H.R.2019, 113th Congress), signed into law April 4, 2014:
  - Amends the Internal Revenue Code eliminating taxpayer financing of political party conventions and reprograms savings to provide for a 10-year pediatric research initiative administered through the National Institutes of Health Common Fund.
- Best Pharmaceuticals for Children Act (2002, reauthorized in 2007 and 2012):
  - Encourages the pharmaceutical industry to perform pediatric studies to improve labeling for patented drug products used in children, by granting an additional 6 months patent exclusivity; supports the National Institutes of Health to prioritize therapeutic areas and sponsor clinical trials and other research about on- and off-patent drug products that need further study in children.
- Creating Hope Act of 2011
  - Provides market incentives to pharmaceutical companies to develop new drugs for children with rare pediatric diseases, such as childhood cancers and sickle cell.
- Pediatric Research Equity Act of 2003
  - Requires drug companies to develop their adult drugs in children as well.

At the time of this writing, the following legislation is under review by Congress:

- H.R. 820 / S. 929—The Childhood Cancer Survivorship, Treatment, Access, and Research Act of 2017 or the Childhood Cancer STAR Act.
  - The purpose of the bill is to maximize discovery and accelerate development and availability, of promising childhood cancer treatments.

NEW DIRECTIONS FOR PEDIATRIC ONCOLOGY RESEARCH

Since the first pediatric cooperative group was created in the 1950s, the improvement in 5-year survival rate of ALL from 4% in the 1960s to about 90% today shows how far the treatment of childhood cancer has come (Smith 2014). Not only has there been significant progress in prolonging survival rates, long-term quality of life has also improved. Between 1993 and 2009, 14 phase III COG studies were activated, but only four of these studies involved osteosarcoma or Ewing sarcoma. From 2000–2010, there was a significant decline in childhood and adolescent (age 15–19 years) cancer mortality overall (Smith 2014). From 2009–2013, the annual cancer incidence rate rose, mainly from ALL and non-Hodgkin lymphoma, but the known and suspected risk factors for ALL and non-Hodgkin lymphoma do not seem to have contributed to this increase (Jemal 2017). Of all drugs approved for adult cancers before 2002, only 15 of the 30 drugs used in the treatment of pediatric malignances had pediatric use information in their labeling (Hirschfeld 2003). Most of those drugs were approved between 1950s and 1970s. Despite new legislation designed to provide incentives for investigating pediatric disease and increasing the number of pediatric studies, few drugs have pediatric-specific indications on their labeling, including the following: clofarabine for refractory ALL; nelarabine for T-cell ALL; imatinib for Ph+ ALL and chronic myeloid leukemia; everolimus for subependymal giant cell astrocytoma; Erwinia for ALL; and denosumab for giant cell tumor of the bone. However, most recently, FDA has approved dinutuximab in high-risk neuroblastoma; avelumab in metastatic Merkel cell carcinoma; pembrolizumab in refractory classical Hodgkin lymphoma and unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumors; blinatumomab in relapsed/refractory B-cell precursor ALL; nivolumab in microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer; tisagenlecleucel for B-cell precursor ALL; and gemtuzumab ozogamicin in relapsed/refractory CD33+ AML.

Precision Medicine

Former President Barack Obama announced the launch of the Precision Medicine Initiative in 2015. This initiative will be a big step toward a new era of individualized medicine. Only recently have new technologies, such as massively parallel next-generation sequencing and the ability to analyze circulating free DNA, been developed to make precision medicine trials a reality (Coyne 2017). These trials will demonstrate if a specific molecular aberration can be modulated with a specific therapeutic agent that addresses or reverses this aberration to improve clinical outcomes.

The pediatric counterpart of the NCI Molecular Analysis for Therapy Choice (Pediatric MATCH) study opened in 2017. This study is designed as a basket trial in which a screening protocol directs patients using a computer algorithm to "match" targeted agents with specific molecular changes identified using a validated next-generation sequencing assay of more than 4000 mutations across more than 140 genes in refractory/recurrent tumors from children and adolescents with cancer. *Because c*hildhood cancers have fewer genetic alterations at diagnosis and lack the same targets that are present in adult cancers, there are fewer agents available with enough data to show activity at a particular genetic alteration (Mody 2017). Activity of a targeted agent for one histology does not necessarily mean that there will be activity in other histologies (Coyne 2017). The innovative design of these trials allows for a realistic sample size calculation to answer the primary objectives when incidence rates for certain mutations can be very low due to tumor heterogeneity. *The* Neuroblastoma Precision Study will identify targetable alterations in children with relapsed/refractory neuroblastoma by testing the feasibility of using a set of specific genetic and cellular biomarkers to guide the assignment of these children to future NANT trials more precisely based on the biology of their tumor.

Precision medicine could help identify early the patient populations that will likely benefit from a particular treatment option. One challenge of precision medicine includes not being able to differentiate between mutations that can be considered *passenger mutations* (those that do not contribute to tumor progression) and *driver mutations* (those that do influence proliferation or survival of cancer cells), dose-limiting toxicities, and drug resistance (Coyne 2017). Another limitation is the availability of and difficulty obtaining tumor samples due to the rarity of pediatric cancers. This limitation of tissue samples added to limitations in funding will require prioritization in future biomarker studies.

Correlative studies that identify and evaluate validated biomarkers are becoming increasingly important. There are two roles biomarkers can have in clinical trials: integral and integrated. *Integral biomarkers* are tests that must be performed on all subjects in real time for the trial to continue and are used to determine eligibility, assign treatment, or stratify patients for randomization (Dancey 2010). *Integrated biomarkers* are not used to determine treatment in a trial but are intended to identify or validate tests planned for use in future trials (Dancey 2010). Ancillary and/or exploratory biomarker data are used to develop biomarkers and/or assays or to better understand therapeutic agent potential. These data are not fundamental to the successful completion of a phase I or II trial.

Beau Biden Cancer Moonshot

In 2016, in his final State of the Union address, former President Barack Obama tasked former Vice President Joe Biden with heading up a new national effort to "end cancer as we know it," called the *White House Cancer Moonshot*. Congress has authorized $1.8 billion to fund Moonshot initiatives over 7 years. This initiative was renamed *The Beau Biden Cancer Moonshot* in honor of Joe Biden's son, Beau Biden, who died

of brain cancer. The funds available through this initiative will help augment the efforts of the Precision Medicine Initiative. The Cancer Moonshot™ Blue Ribbon Panel was established to advise the National Cancer Advisory Board on the scientific opportunities and directions for this initiative. One of the seven working groups established by the Blue Ribbon Panel is pediatric cancer. The panel also identified several policy issues, including coverage and reimbursement; privacy and consent with regard to patient data; fragmentation of the delivery of patient care in the community; the need to improve the clinical trials system; incentives to encourage pediatric drug development; new federal research funding models; barriers to data sharing; and ensuring that racial and ethnic minorities, as well as other underserved populations, are adequately represented when implementing policy-related recommendations (Blue Ribbon Panel Report 2016).

Of the 10 approved final recommendations of the Blue Ribbon Panel, two have a direct impact on pediatric cancer research: cancer immunotherapy translational science network, which includes a pediatric component, and fusion oncoproteins in pediatric cancer. They highlight two key new directions of pediatric research.

Pediatric Immunotherapy Discovery and Development Network

The Pediatric Immunotherapy Discovery and Development Network was created in response to the recommendation to create a cancer immunotherapy translational science network for pediatric cancers with a focus on accelerating development of novel immune therapies. This network would help coordinate efforts on collecting tumor samples and performing comprehensive profiling, including diverse populations and ultimately developing vaccines to prevent cancers.

Immunotherapy targets the host immune system and either stimulates its natural antitumor immune response (e.g., checkpoint inhibitors, checkpoint agonist antibodies, tumor vaccines, adoptive immunotherapy with tumor infiltrating lymphocytes) or creates new responses that target specific neoantigens (e.g., monoclonal antibodies, bispecific antibodies) (Majzner 2017). Neoantigens are antigens formed by peptides that are not present in the normal human genome. The experience of immunotherapies in children with cancer is currently limited. One phase I trial in pediatric patients with advanced solid tumors showed ipilimumab, an antibody targeting the T-cell checkpoint protein CTLA-4, had a similar toxicity and pharmacokinetic profile as seen in adult studies (Merchant 2016). This multicenter trial had 31 evaluable patients between age 28 months and 21 years with a variety of histologies. Objective responses were not observed during this trial, which was attributed to the small sample size, large tumor burden, and the fact that pediatric tumors have low levels of tumor-associated mutations (Merchant 2016; Alexandrov 2013). Other immunotherapies, such as dinutuximab , blinatumomab, and CD19-chimeric antigen receptors (CARs) have shown activity in specific histologies (Majzner 2017). However, it is likely that thoughtful combinations of the two categories of immunotherapeutics, such as synthetic immunotherapies with checkpoint inhibitors, other immune-modulating agents, or tumor vaccines, will be needed to achieve an effective response in childhood cancers (Merchant 2016; Majzner 2017).

Because immunotherapy combinations are evaluated more in clinical trials, there is a need to identify informative biomarker candidates through high-quality correlative studies. Early-phase clinical trials, such as those conducted by Pediatric Brain Tumor Consortium, will utilize the pediatric Cancer Immune Monitoring and Analysis Center and Cancer Immunologic Data Commons (CIMAC-CIDC), one of a four-center network supported by the NCI, to identify these biomarkers and optimize data collection methodologies.

Fusion Oncoproteins in Childhood Cancers

Although pediatric tumors lack the same targets that have been developed for adult cancers, they appear to be enriched for targetable gene fusions (Mody 2017). A fusion gene is created when chromosomal rearrangements lead to juxtaposition of two different genes (Dupain 2017). When these fusions result in proteins that are oncogenic, they are considered fusion oncoproteins. One example is the translocation of the Abelson murine leukemia viral oncogene homolog 1 (ABL1) and breakpoint cluster region (BCR) gene. Imatinib mesylate, which targets BCR-ABL and was approved in 2001 for chronic myeloid leukemia, showed that these fusions are potential therapeutic targets and driver mutations. Not only can they be potential therapeutic targets but also biomarkers. Fusions that are cancer specific are ideal for diagnostic purposes and for subgroup classifications (Mody 2017). This quality will be important because some of the challenges faced in the pediatric population are difficulty in obtaining biopsies and extracting DNA and RNA, detecting fusions from computer analysis artifacts, and the existence of passenger fusions that are not involved in the oncogenic process.

Very few agents have been developed to target these fusion oncoproteins, despite knowing that they can be reliable targets and are found in cancers with few other genetic aberrations (Blue Ribbon Panel Report 2016). The Blue Ribbon Panel recommends creating a network of collaborating investigators to conduct more research to better understand the mechanism of action of these fusion oncoproteins, and to develop pre-clinical models of fusion-driven pediatric cancers to accelerated development of specific gene and enzyme inhibiting medications.

CONCLUSION

There is much optimism about the potential to increase cancer survival rates, especially in advanced stage diseases, with the recent advances in precision medicine and immunotherapy in adult cancers (Jemal 2017). These advances inspire similar optimism with pediatric cancers, although special

Practice Points

- **Understanding the biology of tumor cells is an important role in determining the best treatment of a cancer.**
- **Pharmacists dispensing agents for NCI-sponsored trials should be familiar with pharmacy guidelines stated in the Investigator Handbook and the CTEP website.**
- **Due to limited resources in the pediatric population, sharing of knowledge from clinical trials is important to developing treatment regimens that lead to long-term remissions.**
- **Pharmacists can play a role in determining the best alternative treatment options when patients have exhausted all standard therapies and cannot participate in a clinical trial.**
- **Childhood cancers have fewer genetic alterations at diagnosis compared with cancers occurring in adults and often lack the molecular targets that are identified in adult cancers. New novel agents are needed to continue the progress made in curing childhood cancers.**
- **The use of biomarkers in drug evaluation is encouraged and can help streamline the drug development paradigm.**
- **Practitioners treating survivors of childhood cancer must be familiar with and monitor for potential late effects of cancer treatment.**
- **Cancer survivors should be encouraged to participate in long-term follow up studies, such as the Childhood Cancer Survivor Study.**

challenges apply in the pediatric setting. Improving survival may be the primary goal but it is not the only one. Reducing the long-term and late effects of cancer therapy is also an important effort. Progress in decreasing mortality rates must continue. The ability to rapidly identify effective novel targeted therapies or combination therapies as well as improvement in preventative measures and reducing long-term and late effects are needed in well-designed studies. However, challenges remain such as limited patient populations faced by the early pediatric research groups. International collaboration may now be necessary for future precision medicine trials but there are challenges in the exchange of information, funding, and harmonization of knowledge, methodologies, and technologies in other countries. Legislative initiatives may help to incentivize key stakeholders to prioritize development of childhood cancer specific agents. The collaborative efforts of researchers, patients and their families, advocacy groups, and the government will lead to significant progress in the fight to cure cancer.

REFERENCES

Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013; 500:415-21.

American Cancer Society [homepage on the Internet]. Cancer Statistics Center. Atlanta.

Amylon M. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. Leukemia 1999;13:335-42.

Bhatia S, Armenian S, Armstrong G, et al. Collaborative research in childhood cancer survivorship: the current landscape. J Clin Oncol 2015;33:3055-64.

Bhatnagar S. Management of Wilms tumor: NWTS vs SIOP. J Indian Assoc Pediatr Surg 2009;14:6-14.

Birks D, Donson A, Patel P, et al. High expression of BMP pathway genes distinguishes a subset of atypical teratoid/rhabdoid tumors associated with shorter survival. Neuro Oncol 2011;13:1296-307.

Bleyer W, Coccia P, Sather H, et al. Reduction in central nervous system leukemia with a pharmacokinetically derived intrathecal methotrexate dosage regimen. J Clin Oncol 1983:1;317-25.

Bleyer WA. The U.S. pediatric cancer clinical trials programmes: international implications and the way forward. Eur J Cancer 1997;33:1439-47.

Burchenal JH, Lester RA, Riley JB, et al. Studies on the chemotherapy of leukemia. Cancer 1948;1:399-412.

Burchenal JH, Murphy ML, Ellison RR, et al. Clinical evaluation of a new anti-metabolite, 6-mercapto purine in the treatment of leukemia and allied diseases. Blood 1953;8:965-99.

Cancer Moonshot Blue Ribbon Panel [homepage on the Internet]. Blue Ribbon Panel Report 2016.

Cancer Therapy Evaluation Program (CTEP) [homepage on the Internet]. Agent management, 2016.

Cancer Therapy Evaluation Program (CTEP) [homepage on the Internet]. Investigator's handbook: a handbook for clinical investigators conducting therapeutic clinical trials supported by CTEP, DCTD, NCI, 2014, version 1.2.

Carbone P. Progress in the systemic treatment of cancer, concepts, trials, drugs, and biologics. Cancer 1990;65:625-33.

childrensoncologygroup.org [homepage on the Internet]. The Children's Oncology Group.

Coyne GO, Takebe N, Chen AP. Defining precision: the precision medicine initiative trials NCI-MPACT and NCI-MATCH. Curr Probl Cancer 2017;41:182-93.

Dancey JE, Dobbin KK, Groshen S, et al. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. Clin Cancer Res 2010;16:1745-55.

Dix D, Fernandez C, Chi Y, et. al. Augmentation of therapy for favorable-histology Wilms Tumor with combined loss of heterozygosity of chromosomes 1p and 16q: a report from the Children's Oncology Group studies AREN0532 and AREN0533 [abstract]. J Clin Oncol 2015;33(suppl):10009.

Dome J, Graf N, Geller J. Advances in Wilms tumor treatment and biology: progress through international collaboration. J Clin Oncol 2015;33:2999-3007.

Dupain C, Harttrampf AC, Urbinati G, et al. Relevance of fusion genes in pediatric cancer: toward precision medicine. Mol Ther Nucleic Acids 2017;6:315–26.

Evans A. Pediatric cancer treatment: a model for oncology. Am J Roentgenol 1976;127:891-5.

Farber S, Diamond LK, Mercer RD, et. al. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N Engl J Med 1948;238:787-93.

Gaynon P, Trigg M, Heerema N, et al. Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983-1995. Leukemia 2000;14:2223-33.

Hirschfeld S, Ho PTC, Smith MA, et al. Regulatory approvals of pediatric oncology drugs: previous experience and new initiatives. J Clin Oncol 2003;21:1066-73.

Jackson J, Boyett J, Pullen J, et al. Favorable prognosis associated with hyperdiploidy in children with acute lymphocytic leukemia correlates with extra chromosome 6: a pediatric oncology group study. Cancer 1990;66:1183–9.

Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst 2017;109:1-22.

Johnson TM, Boron MJ. Early access to investigational agents through the National Cancer Institute's Treatment Referral Center. J Hematol Oncol Pharm 2012;2:120-7.

Lawrence W, Gehan E, Hays D, et al. Prognostic significance of staging factors of the UICC Staging System in childhood rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study (IRS-II). J Clin Oncol 1987;5:46-54.

Majzner RG, Heitzeneder S, Mackall CL. Harnessing the immunotherapy revolution for the treatement of childhood cancers. Cancer Cell 2017;31:476-85.

Malempati S, Hawkins D. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) soft-tissue sarcoma committee experience and rationale for current COG studies. Pediatr Blood Cancer 2012;59:5–10.

Matthay K, Tan J, Villablanca J, et al. Phase I dose escalation of iodine-131-metaiodobenzylguanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: a new approaches to Neuroblastoma Therapy Consortium Study. J Clin Oncol 2006;24:500-6.

Merchant MS, Wright M, Baird K, et al. Phase I clinical trial of ipilimumab in pediatric patients with advanced solid tumors. Clin Cancer Res 2016;22:1364-70.

Mody RJ, Prensner JR, Everett J, et al. Precision medicine in pediatric oncology: lessons learned and next steps. Pediatr Blood Cancer 2017;64:e26288.

Nachman J, Sather N, Sensel M, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N Engl J Med 1998;338:1663-71.

Nakayama DK, Bonasso PC. The history of multimodal treatment of Wilms tumor. Am Surg 2016;82:487-92.

nant.org [homepage on the Internet]. Los Angeles:Childrens Hospital Los Angeles.

Oeffinger K, Mertens A, Sklar C, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.

O'Leary M, Krailo M, Anderson JR, et al. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. Semin in Oncol 2008;35:484-93.

poeticphase1.org [homepage on the Internet]. New York: Emergingmed.

pbtc.org [homepage on the Internet]. Memphis: Pediatric Brain Tumor Consortium.

Pui C. Recent research advances in childhood acute lymphoblastic leukemia. J Formos Med Assoc 2010;109:777-87.

Raney R, Maurer H, Anderson J. The Intergroup Rhabdomyosarcoma Study Group (IRSG): major lessons from the IRS-I through IRS-IV studies as background for the current IRS-V treatment protocols. Sarcoma 2001;5:9-15.

Reaman GH. Successful integration of cooperative groups: the origin of the children's oncology group. Am Soc Clin Oncol Educ Book 2012:149-51.

Ribeiro RC, Razzouk BL. Successive clinical trials for childhood acute myeloid leukemia at St Jude Children's Research Hospital. Leukemia 2005; 19:22125-29.

Ruan Y, Kovalchuk A, Jayanthan A, et al. Druggable targets in pediatric neurocutaneous melanocytosis: molecular and drug sensitivity studies in xenograft and ex vivo tumor cell culture to identify agents for therapy. Neuro-Oncology 2015;27:822-31.

Siegel R, Miller K, Jemal A. Cancers statistics, 2017. CA Cancer J Clin 2017;67:7-30.

Smith MA, Altekruse SF, Adamson PC, et al. Declining childhood and adolescent cancer mortality. Cancer 2014;120:2497-506.

Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28:2625-34.

Spreafico F, Bellani F. Wilms tumor: past, present and (possibly) future. Expert Rev Anticancer Ther 2006;6:249-58.

Stanford Medicine [homepage on the Internet]. Stanford, CA.

Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83-103.

Williams D, Tsiatis A, Brodeur G, et al. Prognostic importance of chromosome number in 136 untreated children with acute lymphoblastic leukemia. Cancer 1990;66:1183-9.

Self-Assessment Questions

Questions 1–3 pertain to the following case.

COG1 and COG2 are two Division of Cancer Treatment and Diagnosis sponsored studies at your site involving the same investigational agent, formulation, and strength, and both are distributed by the Pharmaceutical Management Branch (PMB). A patient on COG1 will return to the satellite clinic on Monday to start cycle 4. On Friday morning you realize there is not sufficient inventory and your site cannot receive shipments on Saturday.

1. If COG2 has sufficient inventory, which one of the following is the next best step?

   A. Transfer the drug supply from COG2 and submit the transfer form later next week.
   B. Transfer the drug supply from COG2 after you receive approval from PMB to transfer the drug on Friday.
   C. Use commercial supply for the prescription and replace the supply once the new order is received.
   D. Use the drug supply from COG2 and replace the supply once a new order is received.

2. The study coordinator is not able to deliver the medication to the satellite clinic, and the patient on COG1 lives several hours from the main pharmacy site. What is the best action to take?

   A. Reschedule the patient visit to Tuesday.
   B. Make the patient travel to the main pharmacy site to receive the medication.
   C. Deliver the medication by the institutional courier service.
   D. Transfer the patient to another participating institution for the next cycle.

3. The satellite pharmacy does not document receipt of the medication from the control pharmacy for same day pick-up. However, the COG1 patient had to cancel the appointment on Monday and was rescheduled for Tuesday. Which one of the following is the most appropriate action?

   A. The medication can stay if a NCI Investigational Drug Accountability Record is completed.
   B. The medication must be returned to the main pharmacy and redispensed on Tuesday.
   C. The medication can stay in the satellite pharmacy and no documentation is needed.
   D. The medication must be returned to the main pharmacy and destroyed.

4. A 4-year-old girl presents with an asymptomatic abdominal mass originally discovered during a physical examination. A CT scan showed a large mass in the right kidney and involvement of abdominal lymph nodes. There was residual tumor following surgery, however, tumor cells were negative for anaplastic cells. Molecular studies showed loss of heterozygosity on chromosome 1p and 16q. Which one of the following is best to recommend for this patient?

   A. Dactinomycin plus vincristine plus doxorubicin
   B. Dactinomycin, vincristine, and doxorubicin plus 10 Gy flank radiation therapy
   C. Dactinomycin plus vincristine plus 20 Gy flank radiation therapy
   D. Dactinomycin, vincristine, doxorubicin, cyclophosphamide, and etoposide plus 10 Gy flank radiation therapy

5. A 10-year-old boy with a diagnosis of T cell ALL is transferred to your institution. He has already completed post-induction therapy and is now entering the maintenance phase with monthly cycles of the standard of care at your institution (i.e., intrathecal methotrexate, mercaptopurine, vincristine) over the next 2 to 3 years. This current stage of treatment best exemplifies which of the Six Concepts Leading to Clinical Cures?

   A. Integration of combined modality approaches
   B. Long-term therapy to prevent return of disease
   C. Treatment of sanctuary sites of disease
   D. Employment of clinical trial methodology

6. Each pediatric research group is given an equal quantity of a new compound. Based on their mission and research trials conducted, which research group is most likely to first see a positive response in osteosarcoma?

   A. Pediatric Brain Tumor Consortium (PBTC)
   B. New Approaches to Neuroblastoma Therapy (NANT)
   C. Pediatric Preclinical Testing Consortium (PPTC)
   D. Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL)

Questions 7 and 8 pertain to the following case.

K.T. has been receiving study agent Y for the past year on protocol ACME1234, and his disease is currently stable. K.T.'s oncologist has received a Dear Doctor letter from ACME Pharmaceuticals notifying him that they will no longer manufacture agent Y and the current lot expires in 12 months. You are asked to research alternative solutions for K.T.

7. What is the best next step to take for K.T.?

   A. Perform a search on clinicaltrials.gov to see if there is another clinical trial he is eligible for.
   B. Create a Special Exceptions protocol using agent Y.
   C. Create a Treatment Referral Center protocol for use of agent Y.
   D. Switch to a commercial supply.

8. All of the above options for K.T. are exhausted. Which one of the following groups is best for K.T.'s family and physician to approach first to petition the drug company?

    A. Advocacy group
    B. Support group
    C. Charities
    D. Foundation that supports a research group.

Questions 9 and 10 pertain to the following case.

INHIBIT is a new precision medicine trial studying three different agents in childhood neoplasms harboring B-raf mutations. Tumor specimens are collected at baseline and at progression. A 151-gene next-generation sequencing (NGS) panel will be used to assign the patients enrolled in INHIBIT to different arms and immunohistochemistry assays for protein expression to predict median progression-free survival (PFS).

9. Which of the following limitations of pediatric research group trial design in the 1960s and 1970s is also most likely to affect the INHIBIT trial?

    A. Limited pool of patients
    B. Inability to distinguish between "passenger mutations" and "driver mutations"
    C. Small number of drugs that can be used in the study
    D. Limited amount of tissue samples available for analysis

10. Which of the following roles best describes the NGS panel used to assign INHIBIT patients?

    A. Integral biomarker
    B. Integrated biomarker
    C. Exploratory biomarker
    D. Clinical end point

Questions 11 and 12 pertain to the following case.

G.A. is a 59-year old woman who received a diagnosis of ALL in 1963. After relapsing during initial treatment, G.A. enrolled in a CCG ALL protocol. Following the completion of treatment, she became a participant on the Childhood Cancer Survivor Study. In 2016, her granddaughter (D.D.) was diagnosed with B-cell precursor ALL. Before additional testing can be done, G.A. demands that D.D. be treated with the same protocol treatment she received.

11. Which one of the following is the most significant issue for G.A, based on decreased mortality rates after the formation of the early pediatric cooperative groups and development of combination therapies?

    A. Adverse pregnancy outcomes for female survivors treated with most chemotherapeutic agents was not observed.
    B. Long-term toxicities are now a big concern as children with cancer survive longer.
    C. Fewer treatment options are available to those who progress after combination therapies.
    D. It is unknown whether changes in the genetic profile decades after the end of therapy will occur or are significant.

12. Which of the following is the best argument to present to G.A. regarding treatment selection for D.D.?

    A. Cranial radiation will be added to chemotherapy during induction.
    B. More oncology drugs used in the pediatric population were approved in the 1960s than the 2000s.
    C. The increase in survival rates from the 1960s to 1990s increases the expectation for long term remission (cure).
    D. Genetic testing is available and can guide treatment selection.

13. Starpoint Pharmaceuticals recently completed a Phase 2 trial of Compound J in breast cancer. Due to poor efficacy results from the study, Starpoint decided to stop testing this agent. The PPTC testing found Compound J showed molecular activity in pediatric B-cell ALL. What legislation would most likely lead Starpoint to initiate pediatric testing of Compound J?

    A. Creating Hope Act of 2011
    B. Gabriella Miller Kids First Research
    C. Pediatric Research Equity Act of 2003
    D. RACE for Children Act

14. The newsletter for participants in the Childhood Cancer Survivors Study covers topics such as insurance coverage, family life, pregnancy, and smoking. In the upcoming anniversary issue, which topic should be emphasized?

    A. Participants should continue completing survey to increase knowledge of late outcomes
    B. Cancer survivors were 8 times as likely as their siblings to have severe or life threatening chronic health conditions
    C. Cancer survivors should maintain routine physical examinations with a practitioner familiar with their past history and knowledge of effects to monitor.
    D. Survivors of childhood cancer are at an increased risk of second primary neoplasms, influenced by both host and treatment characteristics of the initial cancer.

15. A 16-year-old adolescent female has enrolled in the master screening protocol for a pediatric precision medicine trial. The tumor biopsy assay results are available and did not match any of the actionable mutations of interest on the protocol. Which one of the following is best to recommend for this patient?

    A. She should be placed on palliative care until an actionable mutation of interest can be found.
    B. She should still be enrolled in a subarm of the protocol.
    C. A search should be performed to find another qualifying study or standard treatment regimen for her cancer.
    D. She should wait for a new arm to be added to the protocol that will allow her participation.