Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018

Report to Congress on Biobanking Projects Supported through the National Cancer Institute's Implementation of Section 101
June 5, 2018 – March 31, 2022

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Executive Summary

The Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act (Public Law 115-180)[1] authorizes that the HHS Secretary, acting through the Director of the National Institutes of Health (NIH) may make awards to *"build upon existing research efforts to collect biospecimens and clinical and demographic information of children, adolescents, and young adults with selected cancer subtypes (and their recurrences) for which current treatments are least effective, in order to achieve a better understanding of the causes of such cancer subtypes (and their recurrences), and the effects and outcomes of treatments for such cancers."*

The Act requires the HHS Secretary to submit a report to Congress addressing the following information related to biobanking research efforts supported through the Act:

- The number of biospecimens and corresponding clinical demographic data collected through the biospecimen research efforts supported under [the Act];
- The number of biospecimens and corresponding clinical demographic data requested for use by researchers;
- Barriers to the collection of biospecimens and corresponding clinical demographic data;
- Barriers experienced by researchers or health care professionals in accessing the biospecimens and corresponding clinical demographic data necessary for use in research; and
- Recommendations with respect to improving the biospecimen and biorepository research efforts under [the Act].

This report, which includes relevant tables and appendices documenting the number of biospecimens and corresponding clinical demographic data requested, fulfills this requirement. The following report provides a thorough overview of the complementary biobanking research efforts the National Cancer Institute (NCI) supports through the STAR Act and through additional investments in childhood and adolescent and young adult (AYA) biospecimen collection and biobanking resources across the Institute's childhood and AYA research portfolio.

To fulfill the goals of the STAR Act, NCI provided supplemental funding to the Children's Oncology Group (COG) Biobank in 2019 to support immediate enhancements. NCI subsequently funded six supplemental projects starting in 2020 to bolster and expand the current programs. The supplements included projects to increase collection of diagnostic, relapse, and autopsy specimens, as well as specimens from childhood cancer survivors enrolled in NCI's Childhood Cancer Survivor Study (CCSS). Pediatric cancers are classified as rare cancers, and these efforts will increase sample availability to researchers and clinicians in an effort to advance research and improve patient outcomes, especially for children with the most rare cancer subtypes. Many of the STAR Act supplement projects are still collecting samples and will have biospecimens available for researchers in the coming years with continued support. Along with increasing the number of greatly needed samples, these projects also address other concerns and barriers to biobanking and provide opportunities to mitigate these challenges. Through implementation of the STAR Act biobanking provisions, NCI continues to support progress towards better understanding pediatric cancers.

[1] https://www.congress.gov/115/plaws/publ180/PLAW-115publ180.pdf

Introduction

The Childhood Cancer STAR Act, enacted in June 2018, aims to maximize "research through discovery" and delivery of "care, quality of life, survivorship, and caregiver support."[2] Through childhood and AYA cancer survivorship research, enhancing and expanding existing biorepositories, and improving tracking and reporting for childhood cancers, novel connections can be made to better understand pediatric cancers, improve treatment options and outcomes, and improve the quality of life for childhood cancer survivors.

Section 101 of the STAR Act authorizes NCI to expand current efforts supported by the NCI in pediatric cancer biobanking and research using biospecimens (see Table 1). NCI's efforts are especially aimed at cancer subtypes with the least promising current treatment options to gain a better understanding of the causes and progression of these cancers and any recurrences. This is especially important since childhood cancers are rare cancers, and there are fewer biospecimens available for research compared to adult cancers.

Table 1: STAR Act definitions for biospecimens and clinical and demographic information[3]

Biospecimens can include, but are not limited to:	Clinical and demographic information collected with biospecimens includes:
• solid tumor tissue or bone marrow • normal or control tissue • blood and plasma • DNA and RNA extractions • familial DNA • any other sample relevant to cancer research	• date of diagnosis • age at diagnosis • patient's sex, race, ethnicity, and environmental exposures • extent of disease at enrollment • site of metastases • coded location of primary tumor • histologic diagnosis • tumor marker data • treatment and outcome data • information related to specimen quality • any other applicable information

NCI is committed to making progress for children and AYAs with cancer, survivors, and their families. Biobanking efforts have long been a part of this mission, as well as a complement to other NCI pediatric cancer initiatives such as clinical trials, survivorship research, and the research efforts of the Pediatric Oncology Branch (POB),[4] located in the Center for Cancer Research, part of the NCI intramural research program (IRP). NCI supports nationwide clinical trials through the Children's Oncology Group (COG), the Pediatric Early Phase Clinical Trials Network (previously the COG Phase I/Pilot Consortium),[5] the

[2] https://www.congress.gov/115/plaws/publ180/PLAW-115publ180.pdf
[3] https://www.congress.gov/115/plaws/publ180/PLAW-115publ180.pdf
[4] https://ccr.cancer.gov/pediatric-oncology-branch#lab-about-tab-0
[5] https://ctep.cancer.gov/initiativesPrograms/pep-ctn.htm

Pediatric Cancer Immunotherapy Trials Network (Ped-CITN),[6] and the Pediatric Brain Tumor Consortium (PBTC).[7] The NCI IRP also conducts clinical trials at the NIH Clinical Center and internationally.

The POB focuses on improving treatment and survivorship outcomes for childhood and AYA cancer patients through basic science, translational research, and clinical trials, and is currently running over 30 clinical trials. A POB-led clinical trial led to Food and Drug Administration (FDA) approval of the first drug (selumetinib) to treat children with neurofibromatosis type 1 (NF1) with tumors growing along their nerves. The trial results showed not only tumor shrinkage, but decreased pain and improved quality of life for these pediatric patients.[8] POB is also engaged with subject matter experts across other parts of the NCI in special initiatives, including the My Pediatric and Adult Rare Tumor (MyPART) Network[9] and Pediatric and Wildtype GIST (Gastrointestinal Stromal Tumor) clinic.[10]

NCI conducts and supports research in childhood cancer survivorship through several ongoing efforts, including long-standing investments in the Childhood Cancer Survivor Study (CCSS),[11] which the Institute has supported continuously since establishing CCSS in 1994. This cohort of more than 38,000 childhood cancer survivors diagnosed between 1970 and 1999 (and 5,000 siblings of survivors who serve as the comparison group for the study) was created to gain new knowledge about the long-term effects of cancer and its treatment and serves as a foundational resource for the survivorship research community. Results from CCSS are used to help design treatment protocols and interventions to increase survival, while minimizing harmful late effects. This research is also used to develop and expand programs for early detection and prevention of late effects in children and adolescent cancer survivors. Two of the STAR Act biobanking projects that will be addressed in this report focus on collection of biospecimens from CCSS participants to support further research on the late effects of cancers and their treatment, including the development of subsequent cancers.

As authorized in Section 202 of the STAR Act, NCI continues to conduct and support research in childhood cancer survivorship, including new research opportunities. In addition to investments in the CCSS, NCI has issued two requests for applications since fiscal year (FY) 2019 that aim to improve care and health-related quality of life for childhood and AYA cancer survivors, and are directly aligned with survivorship research areas emphasized in Section 202 of the STAR Act.[12,13,14] NCI also supported several supplemental awards to NCI-designated Cancer Centers, to conduct research to understand and address organizational factors that contribute to disparities in outcomes among childhood cancer survivors. In addition, NCI continues to support research projects that investigators develop and submit independent of specific childhood and AYA cancer survivorship funding opportunities.

In 2019, the NCI launched the Childhood Cancer Data Initiative (CCDI) to improve use of childhood and AYA cancer data and make it easier for researchers to access and learn from pediatric cancer patients by building a community of researchers, care providers, advocates, families, and hospital networks committed to data sharing. There are multiple components of the CCDI, including a Molecular

[6] https://ctep.cancer.gov/MajorInitiatives/cancer_immunotherapy_trials_network.htm
[7] https://www.pbtc.org/
[8] https://www.cancer.gov/news-events/cancer-currents-blog/2020/selumetinib-nf1-fda-approval?cid=eb_govdel
[9] https://www.cancer.gov/pediatric-adult-rare-tumor/about/what-is-mypart
[10] https://ccr.cancer.gov/pediatric-oncology-branch/gist-clinic
[11] https://ccss.stjude.org/
[12] https://grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html
[13] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-027.html
[14] https://grants.nih.gov/grants/guide/rfa-files/rfa-ca-20-028.html

Characterization Initiative (MCI). Since pediatric cancers often have different genetic mutations that drive tumor formation and different physical presentation compared to adult cancers, it is important to better understand each type of childhood cancer to improve treatment and patient outcomes. Additionally, since the number of children and AYA diagnosed with cancer annually is much smaller than the number of adults, there is less data available. A goal of MCI is to develop and implement a national strategy to provide molecular characterization with clinical annotation to every pediatric and AYA cancer patient so that correct diagnoses are made and appropriate treatment options identified. Objectives include: creating comprehensive molecular and clinical datasets to push research and innovation forward; ensuring equitable access to this characterization for *all* pediatric cancer patients; identifying barriers (institutional and regulatory) to collecting and sharing clinical and molecular data and developing approaches to overcome those barriers; incorporating new data collection and management principles to best serve both patients and researchers; and making molecular characterization a standard-of-care appropriate for third-party reimbursement. The CCDI is complementary to other NCI initiatives working to advance the study of childhood cancer, including efforts aligned with the implementation of the STAR Act.

NCI remains committed to implementing the sections of the STAR Act, and to ensuring that these efforts continue to complement the Institute's broader portfolio of childhood and AYA cancer research and programs outlined above. This report will outline programs authorized by the STAR Act in regard to biobanking, their progress to date, challenges and opportunities facing the pediatric biobanking field, and future directions of NCI-supported pediatric biobanking activities.

Existing NCI Biobanking Efforts

The Children's Oncology Group (COG)

Before the STAR Act was enacted, there were already robust initiatives supported by NCI in pediatric cancer biobanking. COG,[15] with support primarily from the NCI over many years, has maintained the largest pediatric cancer biospecimen bank in the world for infants, children, and AYAs to aid current and future research efforts to improve treatment, prevention, and earlier disease detection.[16] The COG Biobank contains tissues from over 32,000 (and counting) childhood cancer patients. COG is the NCI National Cancer Trials Network (NCTN) pediatric group,[17] and it leads the NCI-COG Pediatric MATCH (Molecular Analysis for Therapy CHoice) trial[18] and is helping to develop the NCI-ComboMATCH precision medicine trial to follow the NCI-COG Pediatric MATCH trial. The COG infrastructure is also used by the Pediatric Early Phase Clinical Trials Network (PEP-CTN) to conduct early phase clinical trials of novel treatments for children with relapsed and recurrent cancers.[19] Additionally, the COG Biobank increases utilization of banked legacy biospecimens,[20] including tissue microarrays, by providing investigators access to these biospecimens through existing partnerships with the NCI-funded Pediatric

[15] https://childrensoncologygroup.org/aboutus
[16] https://childrensoncologygroup.org/biorespository-for-the-children-s-oncology-group
[17] https://www.cancer.gov/research/infrastructure/clinical-trials/nctn#network-groups-and-their-support-components
[18] https://childrensoncologygroup.org/index.php/pediatricmatch
[19] https://ctep.cancer.gov/initiativesPrograms/pep-ctn.htm
[20] Legacy specimens are specimens collected through a COG trial that are remaining once the trial is completed and available for use in additional research efforts.

Division of the Cooperative Human Tissue Network[21] (pCHTN), the NCTN Navigator, and other comprehensive database solutions and dynamic informatics tools.

COG is a clinical trials group primarily supported by NCI as the component of the NCI NCTN that conducts clinical trials for children with cancer and is the world's largest group focused exclusively on childhood cancer research. COG was created in 2000 by merging four NCI-funded pediatric research cooperative groups that had developed over the years beginning with a 1955 NCI-supported childhood cancer research consortium. In total, more than 10,000 pediatric cancer experts at over 200 hospitals, universities, and cancer centers across North America, Australia, and New Zealand are brought together through COG.[22] Over 90% of the children diagnosed with cancer annually are treated at a COG member institution and there are usually around 100 active COG clinical trials open at any given time, creating a huge collaborative clinical research network to improve all pediatric cancer outcomes. Ultimately, the goal of COG is to "cure all children and adolescents with cancer, reduce the short and long-term complications of cancer treatments, and determine the causes and find ways to prevent childhood cancer."[23]

Biospecimen Access

Once biospecimens have been collected and processed, the COG NCTN Biobank distributes them to COG investigators for integral and integrated studies. COG legacy specimens that are remaining once trials are completed are distributed to qualified investigators for secondary studies approved by the NCTN Central Correlative Studies Committee. NCI developed a pediatric expedited proposal review process for small, exploratory proposals requesting specimens solely from pediatric trials to facilitate access of researchers to childhood cancer specimens.[24] To search for and request specimens from completed COG Phase 2-3 trials, investigators can use the NCTN Navigator[25] resource, or the COG-NCTN Biobank website[26] for trials not yet available through Navigator.[27] There are currently 250 registered NCTN trials and over 1.4 million specimens from adult and pediatric cancer patients that can be requested through Navigator. Specimens can be searched by multiple characteristics including primary diagnosis, treatment agents, specimen type, and clinical time point, among others. Additionally, there is a special pediatric expedited review process to facilitate access to specimens when only a relatively small number of specimens are needed,[28] which was developed because of the scarcity of rare pediatric cancer samples.

To maximize the number of pediatric biospecimens accessible to investigators, legacy COG biospecimens are available to pCHTN basic and translational investigators and they can request these specimens through a separate mechanism via the CHTN website,[29] subject to application, scientific review, and approval by COG Disease Committees. The pCHTN is a component of one of NCI's longest running

[21] https://www.chtn.org/
[22] https://childrensoncologygroup.org/about
[23] https://childrensoncologygroup.org/about
[24] https://ctep.cancer.gov/initiativesPrograms/nctn_ccsc_pediatric_expedited_review.htm
[25] https://navigator.ctsu.org/navigator/login
[26] https://nctnbanks.cancer.gov/
[27] NCTN Navigator is limited to biospecimens collected from NCTN trials that were: phase 2/3, phase 3, or large biospecimen collection protocols with clinical data; activated 1995 or later (with some exceptions); and completed with the primary outcome reported. There may be other legacy biospecimens available on some COG trials not listed in Navigator that are smaller, activated before 1995, or COG banking only collections.
[28] https://ctep.cancer.gov/initiativesPrograms/nctn_ccsc_pediatric_expedited_review.htm
[29] https://www.chtn.org/

biospecimen programs, the Cooperative Human Tissue Network (CHTN).[30] The biggest difference between the CHTN and most other biospecimen resources is that it procures tissue prospectively, specifically at an investigator's request, allowing sample preparation to be customized to the investigator's needs, such as being fresh-frozen or fixed in special media. This longstanding relationship between pCHTN and the COG allows the pCHTN access to biospecimens submitted by over 200 national and international institutions participating in COG-sponsored pediatric clinical trials with biology components. The pediatric and AYA biospecimens linked to these clinical trials are often considered more valuable to pCHTN investigators because of their association with clinical data.

Specific Existing Biobanking Projects Supported and Expanded through STAR Act Implementation

Project:EveryChild: Expanding Collection of Rare and Under-represented Specimens

Project:EveryChild: A Registry, Eligibility Screening, Biology, and Outcome Study (COG protocol number APEC14B1) is a large biospecimen study led by COG. This effort is a registry, eligibility screening, biology and outcome study, [31] that opened in 2015 for patient biospecimen collection to all families of pediatric and AYA cancer patients at COG institutions, regardless of whether or not they were enrolled in a clinical trial.[32] This project aims to document the tumor biology and outcome data for every child with cancer. This protocol replaced most of the disease-specific biology protocols in an attempt to harmonize specimen submission across disease groups; the goal is to develop a well-annotated childhood cancer specimen bank for current and future research. Project:EveryChild collects demographic and epidemiologic information, plus extra tissue when a patient has a diagnostic procedure, such as surgery or a biopsy, and stores it in the COG Biorepository for current and future research. Additionally, the COG data center tracks and stores information on the patient's treatment outcomes, allowing scientists around the world to link disease characteristics to outcomes in order to advance treatments for all children with cancer. Patients have the option to consent to participate in future studies including survivorship studies and can also allow their tissues to be used for current and future research. So far, approximately 6,000 unique pediatric patients have donated biospecimens through this protocol, providing well-annotated specimens to be used by research laboratories around the world.[33] Project:EveryChild is ongoing and complements the STAR Act biobanking efforts.

The Project: EveryChild Protocol opened in phases starting in October 2015, with the first phase open to all, except those who were enrolled on disease classification studies. In August 2017, the Protocol was amended to support comparative biology studies. Several of the disease-specific biology studies closed to accrual in late 2017, including studies for rare tumors, brain tumors, Ewing sarcoma, Hodgkin disease, Non-Hodgkin Lymphoma, osteosarcoma, and soft tissue sarcoma. In July 2018, acute lymphoblastic leukemia was added to the Protocol, followed by the closure of the acute lymphoblastic leukemia protocols.

[30] https://www.chtn.org/
[31] http://projecteverychild.org/index.php
[32] https://childrensoncologygroup.org/cog-registry-project-everychild
[33] http://projecteverychild.org/discover.php#

Pediatric MATCH Trial: Expanding Collection of Diagnostic Specimens

The NCI-COG Pediatric MATCH trial[34] is a large clinical trial that has multiple objectives, including collecting biospecimens. This trial uses genomic sequencing of tumors to identify specific molecular changes that can be treated with experimental therapies in children and adolescents with refractory and/or recurrent cancers. A next-generation sequencing assay that identifies mutations, copy number differences, and gene fusions across a set of cancer genes, is coupled with a computer algorithm to match patients with actionable mutations to possible targeted therapies. To participate in this trial, refractory/recurrent tumor samples are required, except for in cases of patients with high-grade gliomas on or near the brain stem; in this case, a pre-treatment (diagnostic) tumor sample can be submitted. This novel approach assigns a treatment to patients based on the genetic makeup of their tumor, not by their cancer type or tumor site.

The Childhood Cancer Survivor Study (CCSS)

NCI has supported the CCSS continually since the study began in 1994, and the study includes biospecimen collection from this large cohort of childhood cancer survivors diagnosed between 1970 and 1999. Researchers often utilize CCSS data and biospecimens to conduct investigator-intiated survivorship research projects, and findings from CCSS are used to help design treatment protocols and interventions to increase survival, while minimizing harmful late effects. CCSS also informs development of programs for early detection and prevention of late effects in children and adolescent cancer survivors. Two STAR Act biobanking projects are supporting collection of biospecimens from CCSS participants to support additional research on chronic health conditions and the development of subsequent cancers.

Ongoing Biobanking Support: Specimens Collected Before and During the STAR Act

NCI support for the COG biobank, including support for processing and banking specimens from patients enrolled on Project:EveryChild and on COG clinical trials (e.g., the Pediatric MATCH trial), continues in addition to the specific STAR Act biobanking projects that will be explored in the next section. NCI also provides support to COG so that it can reimburse its member institutions for the costs of collecting and shipping specimens from patients enrolled on COG clinical trials. Table 2 highlights the number of solid tissues received for Project:EveryChild by year, and Table 3 illustrates the number of unique patients that contributed tumor specimens for Project:EveryChild.

Table 2: Solid Tissues Received on Project: EveryChild (APEC14B1) by Year

Note: It is likely that some of the specimen collection efforts performed at different submitting institutions were affected by pandemic-related issues, especially in 2020 and with lingering repercussions in 2021. The 2022 column represents reporting through March 31.

Specimen Category	2015	2016	2017	2018	2019	2020	2021	2022	Total
Frozen Tissue[1]	1	200	295	454	457	398	516	207	2,528
FFPE Tissue[2]	2	116	192	414	572	622	672	150	2,740
Slides[3]	21	6,560	10,576	16,463	18,689	17,225	24,294	6,136	99,964
Total Specimens	**24**	**6,876**	**11,063**	**17,331**	**19,718**	**18,245**	**25,482**	**6,493**	**105,232**

[1]Includes snap-frozen and OCT-embedded tissue; OCT is optimal cutting temperature compound used to embed fresh tissue specimens before frozen sectioning

[2]Includes formalin-fixed paraffin-embedded tissue blocks, scrolls, and cores; FFPE is Formalin Fixed Paraffin Embedded tissue to preserve the tissue proteins and structures

[34] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match

[3]Includes unstained, stained, and touch-preparation slides

Table 3: Number of Unique Patients that Contributed Solid Tumors on Project: EveryChild (APEC14B1) by Year

Note: It is likely that some of the specimen collection efforts performed at different submitting institutions were affected by pandemic-related issues, especially in 2020 and with lingering repercussions in 2021. The 2022 column represents reporting through March 31.

Specimen Category	2015	2016	2017	2018	2019	2020	2021	2022	Total
Frozen Tissue[1]	1	180	251	356	354	300	372	111	1,893
FFPE Tissue[2]	1	98	154	267	359	460	424	97	1,839
FFPE Tissue Slides[3]	1	298	481	715	880	775	1,227	256	4,433

[1]Includes snap-frozen and OCT-embedded tissue
[2]Includes formalin-fixed paraffin-embedded tissue blocks, scrolls, and cores
[3]Includes unstained, stained, and touch-preparation slides

Biospecimen Projects Implemented as Part of the STAR Act

Building upon existing NCI pediatric biobanking efforts, the first biospecimen projects implemented as part of the STAR Act began in FY 2019 (see Table 4 below). A scientific meeting, *Enhancing Biobanking for Childhood Cancers*,[35] was held at NCI in May 2019. Over 60 researchers and advocates came together to discuss pediatric specimen collection and biobanking challenges and opportunities. Discussions focused on issues with access to and sharing of specimens, standardization of specimen annotation, and specimen quality control. Opportunities to further enhance specimen collection, particularly with high-priority specimens collected outside of clinical trials and specimens from cancer types/subtypes for which treatments are least effective were also discussed. NCI also awarded the COG Biospecimen Core Resource at Nationwide Children's Hospital an additional $1.5 million in August 2019 for immediate enhancements to support specimen collection, analyses, and overall enhancements to the COG Biobank, the nation's largest pediatric biospecimen bank.[36] The STAR Act biobanking projects listed in Table 5, and described in additional detail following the table, are supported in addition to the longstanding support NCI has and continues to provide for the COG Biobank and other COG infrastructure over many years. For example, these investments include the COG Operations Center, Statistical and Data Management Center (SDMC), and Biorepository, each of which is supported by a different NCI grant. The NCI Division of Cancer Treatment and Diagnosis (DCTD), CCDI, and an additional cooperative grant are the funding sources for the multiple parts that make up the COG. For example, over the same time period of FY 2019 through FY 2021, the NCI provided nearly $125 million in support to the COG in addition to the STAR Act projects described in Table 4 and in the body of this report. This includes $82.8 million to the COG Operations Center, $30.4 million to the COG Statistical and Data Management Center, and $11.6 million to the COG Biobank for FY 2019-2021 in addition to the STAR Act biobanking projects highlighted below.

[35] https://www.cancer.gov/about-nci/legislative/recent-public-laws/biobanking-childhood-cancers-meeting.pdf
[36] https://www.childrensoncologygroup.org

Table 4. STAR Act biobanking projects by fiscal year

	Fiscal Year (FY) Funded		
Project Name	**FY 2019**	**FY 2020**	**FY 2021**
COG Biobank supplement for immediate enhancements	$1,500,000		
Childhood Cancer Survivor Study: Somatic & Germline Sequencing (CCSS)		$131,431	No cost extension
Banking of Blood on Childhood Cancer Survivors with Chronic Health Conditions (CCSS)		$1,256,999	No cost extension
NCI-COG Pediatric MATCH Diagnostic Tumor Specimens (COG)		$1,239,178	Completed
Postmortem Tumor Tissue Collection at Autopsy (COG)		$999,064	$912,159
Tumor Specimens from Patients at Relapse (COG)		$999,804	$807,919
Rare and Under-Represented Cancer Tissue Banking (COG), including CCDI Molecular Characterization Initiative Partnership		$2,399,989	$15,548,021*

**In addition to STAR Act funds supporting specimen collection, molecular characterization of specimens and subsequent data storage and data sharing will be supported through NCI's Childhood Cancer Data Initiative (CCDI). The CCDI investment is in addition to the STAR Act support noted here.*

FY 2019 STAR Act Supplement Projects

In FY 2019, supplements were provided for immediate enhancements to the COG Biobank; a brief overview and examples of biology projects are provided below.

Biospecimen Pathology Review and Nucleic Acid Extraction: To increase the utility of samples previously stored at the COG Biopathology Center (BPC), the COG solid tumor committees identified high-value specimens for which pathologic review and/or nucleic acid extraction had not been completed. The Solid Tumor Biobanking Supplements have been used to support several biology projects by providing pathology review of 1007 cases and nucleic acid extraction for 437 cases. Examples of biology projects include:

- ARST17B2-Q: The objective of ARST17B2-Q is to identify germline genetic variants associated with rhabdomyosarcoma susceptibility and survival. Additionally, recent work funded through the NIH Kids First Program has focused on the identification and sequencing of paired tumors, allowing for the first study to comprehensively evaluate the role of germline-somatic interactions in rhabdomyosarcoma risk.
- ARST1431: This is a Phase 3 study of patients with intermediate risk rhabdomyosarcoma. An embedded biology aim includes genomic profiling of DNA and RNA extracted from banked pre-treatment tumor samples to validate the prognostic value of somatic events in this disease, identify the presence of circulating tumor DNA (ctDNA) in blood samples collected from these same patients, and to study patterns of tumor evolution and treatment resistance.

- AOSTNV01-Q: The goal of this project is to evaluate the reported correlation of MYC gene amplification with poor clinical outcomes in osteosarcoma using OncoScan, a whole genome copy number microarray assay that is rapidly reported, clinically available, and inexpensive. Identification of MYC amplification as a prognostic marker would allow for its use as an integral biomarker in future clinical trial designs, with the goal of facilitating improvement in risk-stratification of osteosarcoma patients.

FY 2020 STAR Act Supplement Projects

In FY 2020, six new grant supplement awards were funded through the STAR Act to support new biobanking efforts. Each new project is outlined below.

CCSS Somatic & Germline Sequencing Project: The development of subsequent malignant neoplasms (SMN) is associated with significant morbidity and mortality for survivors of childhood cancer. The CCSS has prioritized collection of SMN somatic (tissues that do not produce reproductive cells) tissue specimens from childhood cancer survivors with confirmed cases of subsequent cancers. While a link between radiation and certain chemotherapies has been observed, the genetic and mutational profiles of these subsequent tumors is not well understood, nor is the process of how these tumors develop on a molecular level. The CCSS Biopathology Center at Nationwide Children's Hospital currently contains specimens for 645 distinct SMNs, which provide a unique opportunity for researchers to analyze how SMNs develop from a genomic perspective. Whole genome sequencing (WGS), whole exome sequencing (WES) of the DNA that codes for proteins, and RNA sequencing (RNAseq) will be used to investigate these samples. To complement this research, CCSS has already completed WES on 5,451 specimens that do not contain cancer (germline specimens) from survivors diagnosed between 1970 and 1986, and WGS and WES on 2,936 survivors who were diagnosed between 1987 to 1999. This equates to whole exome sequencing on 80% of the survivors that stored SMN tissue. Additionally, a separate CCSS pilot study that analyzed pairs of tumor and normal tissue by whole exome and genome sequencing indicated that SMNs result from a different mutational process than de novo cancer formation.

The two objectives of this project are:

1) Conduct whole genome sequencing, whole exome sequencing, and RNA sequencing on 645 SMN tumor specimens in the CCSS Biorepository to genomically understand SMN development
2) Conduct whole genome sequencing and whole exome sequencing on 161 matched germline (inheritable) specimens that haven't been sequenced yet, and carry out whole genome sequencing on 437 germline specimens that have only had whole exome sequencing

Banking of Blood on Childhood Cancer Survivors with Chronic Health Conditions: The CCSS research resource includes treatment annotation, ongoing post-disease follow up, and a database of genomic sequences from 8,000 survivors that will be available to researchers. This project proposes to collect a one-time blood sample from 1,350 survivors that have had a severe or life-threatening adverse event (unintended abnormal lab finding, symptom, or disease that requires treatment that may or may not be related to the treatment)[37] that is classified as a

[37] https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

grade 3 or 4 chronic condition according to the Common Terminology Criteria for Adverse Events (CTCAE). Having these extra blood samples will enhance the CCSS as a resource for future biologic and genetic evaluations to better understand the causes of chronic health conditions in survivors of childhood cancer. This study was originally planned for a 12-month time period, but is in a no-cost extension phase partially due to delays in biospecimen collection caused by the COVID-19 pandemic.

NCI-COG Pediatric MATCH Diagnostic Tumor Specimens: The MATCH screening protocol uses clinical and molecular data from patients to screen for a treatment match and measure the number of patients who have targetable genetic variations in their tumors. Most of the pediatric cancer data collected until the MATCH trial began was focused on samples collected at patient diagnosis and before treatment. However, there is a need for information about the evolving genetic landscape of recurrent and treatment-resistant tumors, but little data are available. The Pediatric MATCH trial genomically characterizes recurrent or resistant tumors and compares them to patient-matched, pre-treatment, diagnostic samples. Currently, only 25% of the patients enrolled in the trial have a diagnostic sample submitted so far. Increasing the number of patients for which diagnostic tumor is available represents an opportunity to increase the knowledge gained from this trial and aid future pediatric cancer research. This project aims to support COG member institutions to identify and submit diagnostic samples to the COG biorepository, with a goal of collecting and depositing 600 samples. Funding for this project included support for identification of diagnostic samples by individual institutions and submission to the COG Biorepository, and specimen processing at the COG Biorepository including pathologic review, specimen quality control, nucleic acid extraction, and preparation of nucleic acids for sequencing. Through CCDI, Pediatric MATCH tumor specimens from diagnosis and from relapse are being molecularly characterized to identify the changes in gene expression and evolution of gene mutations that occurred between diagnosis and relapse. This project will enable more in-depth understanding of the molecular changes that occur over time, which could better inform treatments.

Postmortem Tumor Tissue Collection at Autopsy: One reason that the development of new therapies for pediatric cancers with low survival rates has not progressed is that tissue samples from diagnosis, recurrence, and death are lacking. While evidence indicates parents are open to research-based autopsies, there is not sufficient coordination on this front with families. Project:EveryChild includes post-mortem tissue collection but has only been able to collect these specimens from 16 patients despite over 23,000 patients enrolled. The unique efforts that are required at the community level to collect post-mortem tissues are a major contributing factor to this low number. Through this supplement project, NCI and COG will work with patient organizations to support rapid autopsy collection of tumor samples from children and AYAs who have died of their disease. Foundations and families within the pediatric brain tumor community have been leaders in such programs, and NCI continues to learn from their experiences to expand this model to other childhood cancers. This project aims to increase the number of post-mortem tissues collected through three goals:

1) Create a network of COG institutions that have expertise in research-based autopsy collection coordination and select lead sites to coordinate this effort on the regional/community scale.
2) Incentivize COG institutions to submit post-mortem tissue from the primary tumor, metastatic sites, and a matched non-tumor sample, with a goal of 230 collections (all three types of tissue samples) within 12 months of project launch.

3) Partner with non-profits and philanthropic organizations, who may already have initiatives in this area, to increase awareness of the need for post-mortem tissues among medical providers and affected families.

Tumor Specimens from Patients at Relapse: There is a need for more information on the genetic and epigenetic (differences in gene activity without a change in DNA sequence) changes that occur when primary tumor cells metastasize and when a cancer recurs. An important impediment to understanding mechanisms of treatment failure for childhood solid tumors is the limited numbers of paired specimens from both diagnosis and relapse that are available for researchers to study. Specimens at relapse are critical for evaluating biological changes between diagnosis and relapse that can lead to the identification of mechanisms of treatment failure and to the development of strategies for circumventing these mechanisms. As part of this project, a plan is in place to improve the quality, characterization, storage, and utility of specimens already part of the COG Biorepository.

Rare and Under-Represented Cancer Tissue Banking: This project will enable tumor tissue and associated germline (e.g., blood) sample collection for specific groups of patients for which current tumor tissue collection is lacking or inadequate. The project will prioritize tumor types such as sarcomas and brain and central nervous system tumors, which have high risk of treatment failure. This supplement project will encourage institutions to submit rare tumor tissues to the COG Biorepository and consists of biospecimen collection for six subprojects:

1) Wilms tumor (AREN1921):[38] This subproject focuses on improving outcomes and treatment strategies for patients with types of high-risk Wilms tumor (a pediatric kidney cancer). The COG Renal Tumor Risk Classification and Biobanking Study will be used to help identify patients for the first year of this project.
2) Soft tissue sarcomas: Pediatric soft tissue tumors are varied, with over 50 different diagnoses based on tumor pathology, making each of these diagnoses a rare cancer. An average of only 100 tissue samples for soft tissue sarcomas are submitted to the COG Biorepository annually, making them underrepresented and presenting an opportunity for incentives to encourage institutions to submit more samples and corresponding clinical data.
3) Germ cell tumors: Samples and corresponding data are missing for adolescent populations because most germ cell tumor tissues are from adult males and young children. Besides this missing age group, there is under-representation in certain types of germ cell tumors including ovarian, mediastinal (the area that separates the lungs), and tailbone and sacrum. The addition of more of these tumor samples to the COG Biorepository would provide needed resources for the research community to understand these types of tumors.
4) Rare tumors: Treatment for many types of rarer tumors has not been studied in randomized clinical trials (pediatric cancers in general are considered rare diseases). Because of this, less than 10% of pediatric patients with these diseases have banked tissue and biospecimen collection remains a challenge. Over the last five years, only 227 patients with rare tumors have submitted samples through Project:EveryChild. Increased enrollment and biospecimen collection across COG institutions is essential to better understand the biology, genomics, and risk factors for rarer tumors and to improve survival rates and outcomes for the pediatric patients.

[38] https://clinicaltrials.gov/ct2/show/NCT04322318

5) Bone tumors: Tissue collection for bone cancers has been negatively affected by the limited numbers of clinical trials for these cancers and by the inherent challenges in collecting tumor tissue from bone. This has led to slow progress on prognostic risk factor and therapeutics identification. Additionally, a new World Health Organization (WHO) Classification of Tumors and Soft Tissue and Bone will break Ewing (a bone cancer primarily in children and AYAs) and Ewing-like sarcomas into four subcategories, instead of one, providing an opportunity for collection of new types of needed biospecimens. The COG Biorepository will be essential in getting these samples to better understand the rare bone tumor subtypes. This project has three goals:
    a) Incentivize specific types of biospecimen submission, especially longitudinal samples.
    b) Start specific collection of clinical data and biospecimens for two of the newly categorized rare Ewing/Ewing-like sarcomas.
    c) For existing biobanked samples, collect more information regarding pathology and clinical data.
6) Other solid tumors: The COG Central Nervous System and Liver Tumors Disease Committees would like to increase the number of biospecimens taken at initial diagnosis, including clinical annotation, to use for future research. They would also like to improve how currently banked biospecimens are used, characterized, and stored.

This supplement project also conducts tissue collection in support of the CCDI Molecular Characterization Initiative.[39] The funding for the tissue banking project supports specimen collection from COG member institutions and specimen processing and storage by the COG Biorepository. CCDI funds support the molecular characterization and all of the related data collection and storage, and data sharing supported as part of the protocol. The data generated will be returned to treating physicians to help guide the diagnosis and treatment of patients, and the data will additionally be stored and made available to the research community through CCDI data platforms. The CCDI Molecular Characterization Initiative is initially supporting characterization of tumors from children with central nervous system (CNS) tumors to be followed by children with soft tissue sarcomas. The Initiative aims to collect, store, and make available detailed clinical and molecular information for each child participating in the Initiative (with appropriate privacy protections), including data that will help a pediatric oncologist treat that patient, as well as data that will help researchers learn more about childhood cancers.

FY 2021 STAR Act Supplement Projects

In FY 2021, NCI supported several new and ongoing Childhood Cancer STAR Act research efforts, including continuation of several of the biobanking projects described above. By the end of FY 2021, the NCI-COG Pediatric MATCH Diagnostic Tumor Specimens collection had been completed and two of the COG supplemental projects continued (Postmortem Tumor Tissue Collection at Autopsy and Tumor Specimens from Patients at Relapse). Additionally, the two CCSS projects continued with no cost extensions into FY 2021 and FY 2022, partly due to delays in specimen collection because of the COVID-19 pandemic.

[39] https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/molecular-characterization

Number of Biospecimens and Corresponding Clinical Demographic Data for STAR Act Projects

COG STAR Act Supplement Projects

A status update on the collection and processing of biospecimens to date for the four COG STAR Act-supplement projects is provided in Tables 1-1 to 1-5, available in Appendix 1. Almost 1,500 patients have contributed specimens for the supplement projects since 2020, and 27,630 specimens have been processed through STAR Act projects since 2019, which includes frozen and formalin fixed tissues, glass slide samples, blood, bone marrow, plasma, DNA, and RNA. An important note is that the Molecular Characterization Initiative, for which COG received FY 2021 funds for specimen collection, launched on March 21, 2022, and only recently began to enroll patients, so it is too early to report specimens collected through this project. Specimen collection for this project is ongoing and planned for several years to come. Plans are underway for NCI to continue to support specimen collection as part of STAR Act efforts and in partnership with CCDI in FY 2022 and FY 2023, pending availability of appropriations.

Additional support for specimen collection through the various STAR Act supplement projects has led to notable increases in specimen collection for each effort. As a result of targeted requests and enhanced per case reimbursement to the COG institutions, the monthly rate of diagnostic tumor submission related to the Pediatric MATCH increased from 8.6 cases/month January 2020-October 2020 to 30.8 cases/month November 2020-February 2021. Between March 2021 and February 2022, 80 additional diagnostic tumor samples were received (despite a reduction in new enrollments on Pediatric MATCH in 2021), yielding tissue from 203 additional cases and resulting in diagnostic material available for 40% of patients enrolled on the Pediatric MATCH. The BPC completed extractions for 530 diagnostic samples, which are now undergoing whole genome, whole exome, and RNA sequencing paired along with tumor specimens obtained at relapse.

COG selected six lead institutions in November 2020 to facilitate post-mortem tissue collection throughout the COG network. Enhanced per case reimbursement was available to all COG institutions for tumor samples collected post-mortem. Educational sessions were included in the COG Fall 2021 meeting to promote the value of post-mortem tissue collection. It may be too early to determine the utility of the lead institution network or COG's efforts to increase tumor tissue collection at autopsy. However, there was a modest increase in the monthly rate of post-mortem tumor submission from 0.3 cases/month January 2020-October 2020 to 0.5 cases/month November 2020-February 2021 and 1.9 cases/month March 2021-February 2022.

As a result of targeted requests and enhanced per case reimbursement to the COG institutions, tumor tissue at relapse was obtained from 114 cases from November 2020 to February 2021, with an additional 104 cases received March 2021-Februrary 2022. In 2021, enhanced per case reimbursement was also provided for blood samples obtained at relapse to build a bank of sample for ctDNA analysis, resulting in 21 blood samples collected at relapse. The COG Biopathology Center completed pathology review to confirm appropriate tissue for 277 cases and nucleic acid extractions for 102 samples.

The following tables that focus on COG biospecimen collection and processing are available in Appendix 1:

- Table 1-1: Number of Unique Patients that Contributed Specimens (by Specimen Type) to COG STAR Act Supplement Projects from 2020-2022;

- Table 1-2: STAR Act Supplement Project Biospecimens Processed 8/1/2019 – 3/31/2022;
- Table 1-3: COG STAR Act Supplement Projects Specimen Glass Slide Pathology Reviews Completed from 8/1/2019 to 3/31/2022;
- Table 1-4: COG STAR Act Supplement Project Biospecimen Digital Pathology Reviews Completed from 8/1/2019 to 3/31/2022; and
- Table 1-5: COG STAR Act Supplement Project Specimen Slide Scanning Completed from 8/1/2019 to 3/31/2022.

CCSS STAR Act Supplement Projects

The CCSS supplements have made significant progress towards their goal. The Banking of Blood Among Survivors of Childhood Cancer project had a goal of 1,350 banked blood specimens. So far, they have already completed sample collection, processing, and biobank deposition for 1,216 survivors at the CCSS Biopathology Center and have another 449 survivors who have consented to sample collection and banking. Table 2-1, available in Appendix 2, shows the primary cancer diagnosis breakdown for collected samples. Additionally, the process has been cost effective, so collection has expanded to include a control cohort of 805 survivors, with plans to engage another 800 survivors for this control group.

The CCSS Somatic & Germline Sequencing supplement project seeks to understand the genetic profile of subsequent cancers (subsequent malignant neoplasms, or SMNs) that childhood cancer survivors develop. The methods used to identify the genetic basis of these SMNs are WGS, RNAseq, and WES. Before sequencing began, it was determined that deeper sequencing coverage than expected in order to confidently identify the genomic profile of each sample. Since deeper sequencing is more expensive, the researchers chose to focus on breast cancer, thyroid cancer, and a brain/central nervous system cancer (meningioma) specimens since these are three of the most common SMNs. To date, 71 matched (tumor sample and germline sample) pairs have been whole genome sequenced and 74 matched pairs have been whole exome sequenced for breast cancer, and 36 matched pairs have been whole genome sequenced and 62 matched pairs have been whole exome sequenced for thyroid cancer; central nervous system tumor sample sequencing has recently begun. Table 2-2, also available in Appendix 2, shows the project progression so far for each cancer type.

The following tables that focus on CCSS biospecimen collection and processing are available in Appendix 2:

- Table 2-1: CCSS Banking of Blood Among Survivors of Childhood Cancer Biospecimens by Primary Cancer Site for STAR Act Supplement project; and
- Table 2-2. Childhood Cancer Survivor Study: Somatic & Germline Sequencing STAR Act Supplement project biospecimen sequencing progress by cancer type.

Clinical Annotation

Table 3-1, found in Appendix 3, lists the annotation and collected clinical and demographic information for each supplement project. It is important to recognize that clinical annotation can vary widely. For example, if a specimen is from a child that enrolled on a clinical trial, then all of the clinical trial data for that child will be available. If the specimen is from a child enrolled on Project:EveryChild but not on a clinical trial, then much less clinical annotation data will be available. Additionally, the general CCSS clinical and demographic information collection from patients can be found in public access data

tables,[40] including tobacco use, education, symptoms, chronic conditions, treatment data, radiotherapy, and mortality outcomes.

Number of Biospecimens and Corresponding Clinical Demographic Data Requested for Use by Researchers

COG STAR Act Supplement Projects

Several STAR Act-funded COG supplemental projects have released samples to researchers. During the 2021 calendar year, the COG Biobank distributed over 39,400 total biospecimens and images, with over 19,500 distributed for protocol objectives (including testing for eligibility screening, which is funded separately) and over 19,900 legacy biospecimens were distributed to downstream investigators. These biospecimens were distributed to 48 investigators in the reporting period. Table 1-6 in Appendix 1 outlines the COG STAR Act samples from three of the supplement projects plus the 2019 supplement that were distributed to 11 researchers for 11 projects. Typically, the first investigator to request nucleic acids (DNA or RNA) must support the costs for the extraction, while future investigators only support the cost of preparing and distributing the aliquots. Finding funding that can support not only the analysis (e.g., genomic assays), but also the processing costs at the COG Biobank can be challenging. With the financial support for both pathology QC reviews and nucleic acid extractions, these investigators were able to receive the specimens needed for their research projects. For the specimens represented in Table 1-3 in Appendix 1 (glass slide pathology reviews), the pathology quality control (QC) assessment data will be readily available to potential investigators, reducing barriers to distributing these tissues for future research. Each disease group prioritized tissues (banked and/or newly received) to undergo pathology QC assessment. Future investigators may use this data to inform the list of cases to use for a research project; for example, only cases that meet minimum % tumor necrosis would be included in a case list. Additionally, the turnaround time from receiving the case list to specimen distribution will be reduced, since a major step in the tissue preparation process is already completed.

Since the CCDI Molecular Characterization Initiative has just started enrolling patients, there are no samples to share with researchers yet. Several projects are still in the collection and processing stage, which is why distribution numbers appear low (or are not available yet for researcher use). Additionally, a list of projects that requested and used specimens collected through the STAR Act supplement projects can be found in Appendix 1 as Table 1-7. While the STAR Act projects support specimen collection utilized by each of these projects, the projects represent new research projects proposed by investigators and funded by the NCI and by other funders of childhood cancer research; all but one of the projects listed are NCI funded. The STAR Act biobanking projects have helped to enable these studies, and NCI anticipates that investigators studying pediatric and AYA cancers – both through the COG and through individual proposals – will continue to request use of specimens collected through the STAR Act projects for further analyses.

The following tables related to COG supplement project specimen distribution are available in Appendix 1:

- Table 1-6: STAR Act Supplement Project Specimens Distributed 8/1/2019 – 3/31/2022; and
- Table 1-7: Projects that Requested and Used Biospecimens from STAR Act Funded Supplement Projects.

[40] https://ccss.stjude.org/public-access-data/public-access-data-tables.html

CCSS STAR Act Supplement Projects

Neither of the CCSS supplements are at a stage yet where data can be released for researcher use. Since sample collection and quality assessment is currently ongoing for the CCSS Somatic & Germline Sequencing supplement project, sequencing data is currently not available to researchers. Once quality control has been completed, CCSS will make sequenced data available through dbGaP[41] within six months, consistent with NIH data sharing policies. Similarly, sample collection for the Banking of Blood Among Survivors of Childhood Cancer supplement project is ongoing, so the samples have not been provided to researchers yet. However, researchers are currently submitting sample requests and CCSS leadership is working with investigators to develop grant applications for studies using this data.

Barriers to Biobanking, and Related Research Efforts to Address Barriers

The availability of biospecimens for cancer research is an ongoing challenge. Specific challenges include the sheer number of biospecimens that are needed for molecular research; the need for biospecimens to be collected under standardized and documented procedures to assure sufficient quality for analysis; the quantity of biospecimens needed for particular analysis techniques, particularly challenging in a time when small biopsy tissue is becoming the norm for clinical-use tissue collections; and specialized preservation methods, such as flash-freezing, that are needed for some advanced analysis technologies but are not standard practice in hospitals. Researchers' access to biospecimens to conduct research can also be challenging, as biospecimen collections can be distributed over many different research institutions, the informed consent of patient participants and the planned use of the biospecimens may differ depending on the original study objectives, and the extent of annotation of the biospecimens with regard to molecular quality and diagnosis may differ. Over the past 15 years, a better understanding of the barriers has emerged and best practices for biobanking including ethical, legal and policy, scientific, and operational best practices, have been developed by the NCI[42] and others;[43] a biobanking accreditation program[44] has been developed by the College of American Pathologists; and online compilations of research biospecimens have become available.[45] It is also critical that, to be useful for research, biospecimens be accompanied by robust clinical and demographic data. Generally, such data is manually extracted from electronic health records into study-specific forms and systems, after the informed consent of patient participants in research. With the hope of reducing the cost of data entry and increasing data accuracy, good progress is being made in the automatic extraction of such data for research studies, but the challenges of accessing electronic health records across large numbers of institutions and extracting data in ways that it can be facilely used for research purposes remain daunting. All these activities are conducted within the context of a robust set of federal privacy protections for individuals that include the Common Rule and the Health Insurance Portability and Accountability Act (HIPAA), as well as specific NIH policies such as Certificates of Confidentiality and NIH Data Management and Sharing Policy. Such regulations and policies aim to promote research that is conducted at the highest ethical levels while maximizing utility.

The issues outlined above are compounded in pediatric cancer research, where many pediatric cancers are essentially rare and collecting sufficient numbers of samples representing particular cancers can only

[41] https://www.ncbi.nlm.nih.gov/gap/
[42] https://biospecimens.cancer.gov/bestpractices/overview.asp
[43] https://www.isber.org/general/custom.asp?page=BPR
[44] https://www.cap.org/laboratory-improvement/accreditation/biorepository-accreditation-program
[45] https://navigator.ctsu.org/navigator/login

be achieved through collaborative networks that are sustained over time. Sample volumes may be lower than those from adult research participants. Ethical, legal and policy issues are complicated in that parents must provide informed consent of patient research participants until they reach the age of majority, when re-consent may be required. These challenges have been outlined in the recent literature.[46,47,48,49,50,51] New developments have been reported, for example, in biobanking of liquid biopsies (blood and other bodily fluids) and organoid development that may serve as important research models.[52,53,54] One example of a current critical unmet need for research biospecimens is for childhood brain tumors, which is being aided by the collaborative and multi-institutional Children's Brain Tumor Network[55] and Tissue Consortium,[56] and is also the focus of several of the STAR Act biobanking projects.

One of the first actions NCI took to address the biobanking section of the STAR Act was to hold the *Enhancing Biobanking for Childhood Cancers Meeting*[57] on May 13, 2019, to identify and discuss ongoing pediatric biobanking efforts and related biospecimen collection and biobanking challenges, which are outlined below. The NCI supplemental biobanking projects funded through the STAR Act, especially those led by COG, continue to serve as an opportunity to address several of the barriers and challenges that were identified at this meeting.

The italicized text below indicates the specific biobanking supplement projects underway to address such challenges, as well as additional NCI-supported efforts, including the CCDI, that are currently addressing challenges related to data sharing and access.

Barriers to the Collection of Biospecimens and Corresponding Clinical Data

Barriers to the collection of biospecimens and corresponding clinical data, as discussed at the May 2019 meeting:

- While less invasive biopsy procedures benefit the patient, these procedures remove less tissue and therefore provide less sample for biobanking. It's important to note that increased risks to patients resulting from more invasive biopsies for research purposes are considered. Additionally, it's a challenge to get relapse samples because the biopsy usually only takes a small amount of tissue.
    - Opportunity: Cancer registries can work with investigators on patient contact studies when re-contact is needed to gather samples.
    - Opportunity: Identifying high-priority tissues that will be used for important research that has the required clinical annotation and quality characteristics.
    - ***Several of the supplement awards focus on high-priority tissues, including the CCSS: Somatic & Germline Sequencing, Postmortem Tumor Tissue Collection at Autopsy,***

[46] https://curesearch.org/wp-content/uploads/Summit-White-Paper-September-14-2021.pdf
[47] https://pubmed.ncbi.nlm.nih.gov/33296265/
[48] https://pubmed.ncbi.nlm.nih.gov/33847522/
[49] https://pubmed.ncbi.nlm.nih.gov/33372833/
[50] https://pubmed.ncbi.nlm.nih.gov/32482235/
[51] https://pubmed.ncbi.nlm.nih.gov/29900801/
[52] https://pubmed.ncbi.nlm.nih.gov/33493007/
[53] https://pubmed.ncbi.nlm.nih.gov/34840249/
[54] https://pubmed.ncbi.nlm.nih.gov/32161258/
[55] https://cbtn.org/
[56] https://www.chop.edu/clinical-trial/cbttc-collection-protocol
[57] https://www.cancer.gov/about-nci/legislative/recent-public-laws/biobanking-childhood-cancers-meeting.pdf

Tumor Specimens from Patients at Relapse, and Rare and Under-represented Cancer Tissue Banking.

- There are already a limited number of children and AYAs with certain cancer types compared to adults, making pediatric specimen collection difficult for these cancers. Additionally, it's challenging to collect disease-specific specimens and establish common data elements across these diseases.
    - Opportunity: Creating a data bank linked to the biobank can help with standardization of tissue/data collections.
    - Opportunity: Focusing on patients for whom treatments have been inadequate. Tissues from these patients can help elucidate the reasons for treatment failure and provide insight into more effective treatments.
    - ***The Tumor Specimens from Patients at Relapse, the Postmortem Tumor Tissue Collection at Autopsy, and the NCI-COG Pediatric MATCH Diagnostic Tumor Specimens supplement awards address this challenge.***
- Due to ethical restrictions, the types and timing of biopsies that can be done on children are limited.
    - ***The Tumor Specimens from Patients at Relapse and the Postmortem Tumor Tissue Collection at Autopsy STAR Act supplement awards also aim to identify how to augment the numbers and timing of biopsies in a way that conforms to important ethical considerations for biopsy collections from children.***
- Biobanking efforts face competition with clinical trials and institutional needs for specimen and tissue availability.
    - Opportunity: Set realistic, achievable objectives that take into account the challenges for establishing biorepositories.
    - Opportunity: Emphasize specimens associated with clinical trials (consistent with the STAR Act) that already have clinical annotation associated with them and that offer the opportunity to define the conditions or patient populations in which certain treatments are successful.
    - ***All the NCI supplement awards supported through the STAR Act align with these suggestions.***

Data-related Biospecimen Challenges

The May 2019 meeting also addressed barriers experienced by researchers or health care professionals in accessing the biospecimens and corresponding clinical and demographic data necessary for use in research. Efforts are currently underway through NCI's CCDI to address the data-related challenges described below, as they are beyond the scope of biobanking alone.

Data-related challenges discussed at the May 2019 meeting included the following:

- It can be challenging when multiple funding sources are involved to determine who holds the data ownership for biospecimens. Some databases link the different biospecimen and clinical data ID numbers into a universal specimen identifier so that they can be identified and remain linked no matter where the data is sent, allowing for imperative long-term tracking of patient samples.
    - ***This is a challenge that NCI's CCDI is addressing.***
- Additionally, broad electronic consent is needed to maximize biospecimen use by researchers. If consent processes are centralized and/or coordinated, this can help patients and their families decide what the best research study is for them and can help prevent duplicative efforts.

    - *The Molecular Characterization Initiative, which builds upon the COG Project:EveryChild protocol (NCT02402244), utilizes a single informed consent, and the level of consent provided by patients nationwide is maintained centrally by COG so that acceptable uses of submitted tissues can be readily identified.*
- In general, coordination and communication are key for making the most of biobank specimens – communication with the cancer research community on how to best build out existing infrastructure and develop new projects, local communication and infrastructure to support patients and families, and coordination between researchers inside and outside of the institution(s) involved in biospecimen collection and research to define best practices and share models for collection and data sharing.
    - ***Maintaining trust through transparency and collaboration – across the STAR Act biobanking projects and throughout CCDI – also remains a top priority.***
- Consistent communication with parents and patients about how their tissues are being used, and the protections that apply to their data and biosamples, can strengthen trust and keep them aware of biobanking options and opportunities. A centralized system to navigate the available biospecimens along with a user guide would aid with database interoperability and could improve efficiency of biospecimen research use. The NCI's NCTN Navigator offers a searchable limited biospecimen inventory from "trials conducted by NCTN clinical trials Groups, Phase 3 or large biospecimen collection protocols with clinical data, and completed, with the primary outcome reported."[58] COG specimens are now included in this resource, which allows investigators to identify specimens to help test their hypotheses developed from exploratory correlative analysis.
    - ***Communication with parents and their children is a top priority across all STAR Act biobanking supplement projects and through the CCDI Molecular Characterization Protocol.***

While addressing these challenges are vital for maximizing the use and impact of biobanking, they are also applicable outside the scope of biobanking. Because of this, CCDI is taking on these data-related challenges through their working groups and mission.

Exploration of challenges and opportunities discussed at the 2019 meeting, along with barriers and challenges identified in the scientific literature, informed NCI's thinking and prioritization of projects for support through the STAR Act. This resulted in support for projects that directly address some of the most pressing barriers and challenges facing the field. These projects are aligned with the STAR Act's emphasis *"to build upon existing research efforts to collect biospecimens and clinical and demographic information of children, adolescents, and young adults with selected cancer subtypes (and their recurrences) for which current treatments are least effective, in order to achieve a better understanding of the causes of such cancer subtypes (and their recurrences), and the effects and outcomes of treatments for such cancers"* and to *"provide access to biospecimens and clinical and demographic data from children, adolescents, and young adults with cancer to researchers and qualified health care professionals for peer-reviewed research*."[59]

The six supplement awards NCI supported each address one or more of the barriers and challenges identified at the meeting. The NCI-COG Pediatric MATCH Diagnostic Tumor Specimens supplement aims to collect more longitudinal samples from relapsed patients, enroll more patients in the Pediatric

[58] https://navigator.ctsu.org/navigator/login
[59] https://www.congress.gov/115/plaws/publ180/PLAW-115publ180.pdf

MATCH trial since samples are lacking, and increase the number of rarer relapse tumor biospecimens and data available to researchers and clinicians, which is also addressed by the Tumor Specimens from Patients at Relapse and Somatic & Germline Sequencing supplements. Another supplement collecting rare biospecimens is the Rare and Under-Represented Cancer Tissue Banking project, which is prioritizing tumor types that have poor treatment response and those that have an inadequate number of samples, along with corresponding pathology and molecular data. The Postmortem Tumor Tissue Collection at Autopsy supplement addresses a lack of scare postmortem biospecimens, contributing to biospecimen collection over the lifespan of children and AYAs with pediatric cancer, and coordinating with families and community organizations and infrastructure to maximize biobanking efforts. The Banking of Blood on Childhood Cancer Survivors with Chronic Health Conditions supplement will continue to follow up with patients post-disease, providing important biospecimen annotation and specimens for future survivorship research. All of the STAR Act supplements are contributing to the identification of patient populations, in conjunction with clinical trials, that can be used to improve future pediatric cancer outcomes.

Additionally, several projects encountered unanticipated challenges during the COVID-19 pandemic, including delays and declines in anticipated specimen collection, particularly during calendar years 2020 and 2021. This appears to be temportary and participation is returning to anticipated levels. To address this challenge, certain projects have extended their time period for specimen collection beyond initial plans in order to meet their anticipated specimen collection.

Future Directions and Recommendations

In regard to the COG STAR Act supplement projects, there are plans to continue this vital work for multiple project areas. NCI recommends the following next steps to continue to improve and enhance the biospecimen and biorepository research efforts aligned with the STAR Act:

- **Continue collaboration with CCDI for the Molecular Characterization Initiative (MCI)**: STAR Act funding plays a critical role in allowing MCI to be successful in providing detailed molecular characterization for making the right diagnosis and identifying appropriate treatment options for participating patients and to be successful in making molecular data available to researchers, with proper privacy protections, to use in making new discoveries. STAR Act funding supports local institutions in consenting patients/families for MCI participation, in preparing specimens for submission to the COG Biopathology Center, and in submitting clinical data about the patient. STAR Act funds also support the COG Biopathology Center to ensure the quality of the submitted specimens and to process the tissue so that it can be used for molecular characterization. The actual testing of the specimens is performed by the Institute of Genomic Medicine at Nationwide Children's Hospital using CCDI funds, and testing includes whole exome sequencing of DNA from both tumor and blood, RNA sequencing to evaluate for gene fusions, and DNA methylation array analysis.

- **Continue supplemental funding for tissue collected at relapse**: Specimens collected at relapse are generally seen as even higher value than diagnostic specimens by investigators, since these specimens come from patients who have not been successfully treated with front-line therapy. Analysis of these samples can yield insights into the mechanisms of therapy resistance and alternative treatment approaches. However, specimens collected at relapse continue to be under-represented in the COG biorepository. Ongoing support to institutions to encourage

specimen submission is important. In addition, COG has recently initiated a process to contact institutions when a relapse event is reported on APEC14B1 for a patient with a solid tumor to remind them of the potential for specimen submission with enhanced per case reimbursement.

- **Expansion of supplemental funding for tissue collected at relapse to include leukemia and lymphoma:** Supplemental biobanking funding in 2020 and 2021 was restricted to solid tumors. This prioritization over leukemia and lymphoma reflects the relative under-representation of many solid tumors in the COG biorepository, as well as the generally inferior outcome for patients with solid tumors compared to leukemia and lymphoma. However, relapsed leukemia and lymphoma also have poor outcomes, and there is a relative paucity of specimens collected at relapse. The same scientific rationale to increase the banking of solid tumor specimens collected at relapse applies to leukemia and lymphoma.

- **Support serial blood sample collection for ctDNA during therapy and at relapse**: ctDNA is emerging as a powerful predictor of treatment failure in multiple tumor types. For example, two recent COG analyses in Wilms tumor and rhabdomyosarcoma showed that the presence of detectable ctDNA at diagnosis is strongly associated with inferior outcome. Many current and planned COG clinical trials include serial blood sampling during and after treatment in secondary or exploratory aims to determine if changes in ctDNA detection are predictive of outcome. ctDNA also has the potential to identify clonal molecular changes that are not seen in a limited biopsy specimen, since ctDNA in blood represents contributions from multiple tumor sites and sub-clones. Blood samples at relapse are also more easily obtained than tumor samples, despite the efforts outlined above to increase the number of tumor samples obtained at relapse. It is possible that building a bank of blood samples obtained at relapse will be more successful than building a bank of tumor samples obtained at relapse. The major barrier to including serial blood sampling for ctDNA analysis is the cost of Streck blood collection tubes (which are optimal to maximize ctDNA detection) and the cost of specimen processing at the COG Biopathology Center (BPC). The BPC covers the cost of processing for up to three samples on a clinical trial on its U24 grant, but not the cost of tubes or shipping. To cover the cost of Streck tubes, shipping, and processing beyond three samples, additional funding is needed. A dedicated fund available to clinical trials with embedded serial blood collection would build the bank of blood samples available for ctDNA analysis. Continued funding to support blood sample collection at relapse will also increase the availability of high-value blood samples.

The CCSS STAR Act supplement projects also plan to move ahead for funding into the future, in addition to other biobanking projects. CCSS plans to perform transcriptome analysis on over 1,350 CCSS participants (childhood cancer survivors) using specimens collected from the STAR Act supplements. Transcriptome analysis has not previously been performed on childhood cancer survivors and will provide information about all types of RNAs in survivors. Additionally, CCSS plans to increase the participation rate for the Banking of Blood Among Survivors of Childhood Cancer Biospecimens by Primary Cancer Site supplement project since the COVID-19 pandemic limited the participation rate. CCSS would like to collect additional samples from pediatric cancer survivors with the top 10 chronic health conditions observed. They will aim to increase participation by providing additional opportunities to obtain the blood samples that may be more appealing during the current COVID-19 pandemic as well as increasing the incentive for participation once people have resumed some of their normal routines. Lastly, CCSS has new germline specimens from 2,400 pediatric cancer survivors on which they would like to perform whole genome sequencing.

Conclusion

Researcher access to high-quality biospecimens plays a critical role for accelerating advances in improving outcomes for pediatric cancer patients, and NCI will continue to support this work through the STAR Act projects discussed in this report, and through longstanding and ongoing investments in key resources, such as the COG Biobank and pCHTN.

In alignment with the STAR Act, NCI has expanded its commitment to collecting specimens from children and AYAs with cancer from the time of diagnosis, recurrence, and into survivorship. These specimens and analyses, in parallel with additional NCI investments in childhood and AYA cancer research, hold potential for a deeper understanding of tumor evolution, risk, therapeutic options, and survivorship.

Appendix 1 – COG STAR Act Biobanking Supplement Projects

Table 1-1: Number of Unique Patients that Contributed Specimens (by Specimen Type) to COG STAR Act Supplement Projects from 2020-2022

Supplemental Project and Cancer Type	Frozen Tissue		FFPE Tissue [1]		Blood	Total
	Primary	Metastatic	Primary	Metastatic		
Postmortem Tumor Tissue Collection	**24**	**9**	**13**	**5**	**0**	**33**
Bone	1	2	0	2	0	2
Brain Tumors	20	2	10	0	0	24
Germ Cell Tumors (GCT)	0	0	1	0	0	1
Liver Tumors	1	1	1	0	0	1
Non-Hodgkin Lymphoma (NHL)	1	0	0	1	0	1
Soft Tissue Sarcomas (STS)	1	4	1	2	0	4
Rare and Under-Represented Cancer Tissue Banking	**248**	**7**	**971**	**46**	**18**	**1,101**
Bone	45	1	254	7	0	281
Brain Tumors	63	0	270	0	0	282
Germ Cell Tumors (GCT)	48	1	149	3	18	187
Rare Tumors	23	3	130	19	0	152
Soft Tissue Sarcomas (STS)	69	2	169	17	0	200
Tumor Specimens from Patients at Relapse	**13**	**31**	**51**	**87**	**30**	**167**
Bone	4	15	22	35	16	73
Brain Tumors	2	0	2	0	0	3
Germ Cell Tumors (GCT)	0	0	4	3	0	7
Neuroblastoma	3	11	7	34	14	51
Rare Tumors	0	1	0	3	0	3
Soft Tissue Sarcomas (STS)	4	4	16	12	0	30
Pediatric MATCH Diagnostic Specimen Banking			**191**	**12**		**203**
TOTAL	**285**	**46**	**1,214**	**146**	**48**	**1,462**

[1]Includes blocks, scrolls, and slides; FFPE is Formalin Fixed Paraffin Embedded tissue to preserve the tissue proteins and structures

Table 1-2: STAR Act Supplement Project Biospecimens Processed 8/1/2019 - 3/31/2022

	Frozen Tissue[1]	FFPE Tissue[2]	Glass Slide[3]	Blood[4]	Bone Marrow[4]	Plasma	DNA	RNA	Total
2019 Supplement	**2,111**	**619**	**2,457**	**0**	**0**	**0**	**2,116**	**8,363**	**15,666**
Bone Tumors	7	180	272	0	0	0	1,030	360	1,849
Renal Tumors	2,046	205	1,630	0	0	0	829	2,166	6,876
Soft Tissue Sarcomas (STS)	58	234	555	0	0	0	257	5,213	6,317
Neuroblastoma	0	0	0	0	0	0	0	589	589
Non-Hodgkin Lymphoma (NHL)	0	0	0	0	0	0	0	5	5
Rare Tumors	0	0	0	0	0	0	0	30	30
Rare and Under-Represented Cancer Tissue Banking	**917**	**1,367**	**2,377**	**3**	**4**	**39**	**1,970**	**4,139**	**10,816**
Bone Tumors	3	88	357	0	1	0	147	129	725
Brain Tumors	197	136	303	1	0	0	170	449	1,256
Germ Cell Tumors	306	291	453	2	0	0	421	1,133	2,606
Renal Tumors	3	6	3	0	0	0	7	19	38
Hodgkin Disease	5	1	15	0	0	0	1	3	25
Non-Hodgkin Lymphoma	4	5	15	0	1	0	5	11	41
Neuroblastoma	50	10	40	0	0	0	19	51	170
Rare Tumors	9	145	188	0	0	0	138	417	897
Soft Tissue Sarcomas (STS)	340	685	1,003	0	2	39	1,062	1,927	5,058
Tumor Specimens from Patients at Relapse	**136**	**91**	**261**	**15**	**0**	**36**	**180**	**429**	**1,148**
Bone Tumors	0	0	66	3	0	6	1	0	76
Brain Tumors	4	0	1	6	0	12	3	4	30
Germ Cell Tumors	2	3	11	0	0	0	5	12	33
Neuroblastoma	47	5	33	0	0	0	17	49	151
Rare Tumors	0	13	13	0	0	0	8	24	58
Soft Tissue Sarcomas (STS)	83	70	137	6	0	18	146	340	800
Pediatric MATCH Diagnostic Specimen Banking	**0**	**525**	**2,793**	**0**	**0**	**0**	**530**	**543**	**4,391**
Postmortem Tumor Tissue Collection	**61**	**0**	**21**	**0**	**0**	**0**	**0**	**0**	**82**
TOTAL	**3,164**	**2,077**	**5,095**	**18**	**4**	**75**	**4,266**	**12,931**	**27,630**

[1]Includes OCT-embedded tissue and snap-frozen tissue; OCT is optimal cutting temperature compound used to embed fresh tissue specimens before frozen sectioning
[2]Includes blocks, scrolls, tissue scrapings from unstained slides, and formalin fixed tissue; FFPE is Formalin Fixed Paraffin Embedded tissue and it preserves the tissue proteins and structures
[3]Includes stained and unstained tissues
[4]Includes cells, ficolled, and lysed cells

Table 1-3: COG STAR Act Supplement Projects Specimen Glass Slide Pathology Reviews Completed from 8/1/2019 to 3/31/2022
Notes on slide pathology review: Many solid tissues, especially tumors, are heterogeneous, and the tissue sections from tumors vary as to the extent of tumor cells, presence or absence of benign/normal tissue, scar tissue, and/or necrosis. Therefore, only knowing the surgical pathology diagnosis of a tissue section is not always adequate for tissues provided for research. Optimally, a pathology quality control (QC) assessment is made on a mirror image piece of tissue to that supplied for research. The majority of solid tissue specimens in the COG Biobank undergo this evaluation prior to distribution. Pathology review for tissues is based on microscopic evaluation of histologic (tissue) sections, from either FFPE or OCT-embedded frozen tissues stained with hematoxylin and eosin (H&E), one of the most common histological stains and used for disease diagnosis. Microscopic review by a COG Biobank-affiliated pathologist confirms the diagnosis, % tumor, % stroma (tissue connective tissue), % tumor necrosis, or other pertinent findings of the tissue and validates that the specimens provided to investigators meet the required quality metrics.

Supplement / Disease Group	Total Glass Slide Pathology Reviews
2019 Supplement	**2,825**
Bone Tumors	374
Renal Tumors	1,621
Soft Tissue Sarcomas (STS)	830
Rare and Under-Represented Cancer Tissue Banking	**2,762**
Bone Tumors	158
Brain Tumors	72
Germ Cell Tumor (GCT)	636
Hodgkin Disease	15
Neuroblastoma	85
Non-Hodgkin Lymphoma	9
Other[1]	4
Rare Tumors	294
Soft Tissue Sarcomas (STS)	1,489
Tumor Specimens from Patients at Relapse	**339**
Bone Tumors	5
Germ Cell Tumor (GCT)	13
Neuroblastoma	90
Rare Tumors	23
Soft Tissue Sarcomas (STS)	208

Pediatric MATCH Diagnostic Specimen Banking	**573**
Postmortem Tumor Tissue Collection	**42**
TOTAL	**5,926**

[1]Includes Liver tumors (2) and Langerhans cell histiocytosis (2)

Table 1-4: COG STAR Act Supplement Project Biospecimen Digital Pathology Reviews Completed from 8/1/2019 to 3/31/2022

Supplement / Disease Group	Total Digital Pathology Reviews
2019 Supplement	**651**
Bone Tumors	651
Rare and Under-Represented Cancer Tissue Banking	**648**
Bone Tumors	135
Brain Tumors	382
Germ Cell Tumors (GCT)	5
Hodgkin Disease	16
Non-Hodgkin Lymphoma	12
Other[1]	1
Soft Tissue Sarcomas (STS)	97
Tumor Specimens from Patients at Relapse	**64**
Bone Tumors	23
Brain Tumors	4
Soft Tissue Sarcomas (STS)	37
TOTAL	**1,363**

[1]Langerhans cell histiocytosis

Table 1-5: COG STAR Act Supplement Project Specimen Slide Scanning Completed from 8/1/2019 to 3/31/2022

Supplemental Group	Total Slides Scanned
2019 Supplement	**4,850**
Bone Tumors	2,559
Renal Tumors	1,543
Soft Tissue Sarcomas	748
Postmortem Tumor Tissue Collection	**2**
Bone Tumors	1
Brain Tumors	1
Rare and Under-Represented Cancer Tissue Banking	**3,343**
Bone Tumors	886
Brain Tumors	515
Germ Cell Tumor	619
Neuroblastoma	74
Rare Tumors	301
Soft Tissue Sarcomas	948
Tumor Specimens from Patients at Relapse	**358**
Bone Tumors	111
Brain Tumors	5
Germ Cell Tumor	14
Neuroblastoma	80
Rare Tumors	27
Soft Tissue Sarcomas	121
Pediatric MATCH Diagnostic Specimen Banking	**511**
TOTAL	**9,064**

Table 1-6: STAR Act Supplement Project Specimens Distributed 8/1/2019 – 3/31/2022

Supplemental Group	FFPE Tissue[1]		DNA	RNA	Total Specimens
	Primary	Metastatic			
2019 Supplement	1,024	9	1,390	16	2,682
Rare and Under-Represented Cancer Tissue Banking	0	0	195	158	825
Tumor Specimens from Patients at Relapse	0	0	7	8	15
Pediatric MATCH Diagnostic Specimen Banking	0	0	398	199	597
TOTAL	**1,024**	**9**	**1,990**	**381**	**4,119**

[1]Includes scrolls and slides; FFPE is Formalin Fixed Paraffin Embedded tissue to preserve the tissue proteins and structures

Table 1-7: Projects that Requested and Used Biospecimens from STAR Act Funded Supplement Projects

2019 Supplement		
Investigator	***Institution***	***Project Title***
Dr. Smita Bhatia	University of Alabama at Birmingham	Mitigating Long-Term Treatment-Related Morbidity in Childhood Cancer Survivors
Dr. Katherine Janeway	Dana-Farber Cancer Institute	Translocation Assessment of Ewing Sarcoma Cases Enrolled on Children's Oncology Group Clinical Trials
Dr. Elaine Mardis	Nationwide Children's Hospital	A Phase 3 Study of 131I-Metaiodobenzylguanidine (131I-MIBG) or Crizotinib Added to Intensive Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma (NBL)
Dr. Lisa Mirabello	National Cancer Institute	Germline Genomic Variation of Pediatric Osteosarcoma Cases Enrolled in the Children Oncology Group (COG)
Dr. Joshua Schiffman	University of Utah Huntsman Cancer Institute	Expanded Ewing Sarcoma Cohort for Tumor genomics and Association with DNA Repair Deficiencies, Clinical Presentation, and Outcome
Dr. Peter Schoettler	Western Michigan University	Clinical and Genomic Characterization of Renal Sarcomas
Pediatric MATCH Diagnostic Specimen Banking		
Dr. Donald Williams Parsons	Texas Children's Hospital	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)
Rare and Under-Represented Cancer Tissue Banking		
Dr. Frederic Barr[1]	National Cancer Institute	Genetic Analysis of Tumor Progression in Rhabdomyosarcoma
Dr. Brian Crompton	Dana-Farber Cancer Institute	A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)
Dr. Philip Lupo	Baylor College of Medicine	Germline and Somatic Genetic Landscape of Pediatric Rhabdomyosarcoma
Dr. Sarah Whittle	Texas Children's Hospital	Evaluation of MYC Amplification as a Prognostic Biomarker in Osteosarcoma
Tumor Specimens from Patients at Relapse		
Dr. Frederic Barr[1]	National Cancer Institute	Genetic Analysis of Tumor Progression in Rhabdomyosarcoma

[1]This project included specimens from both supplements

Appendix 2 – Childhood Cancer Survivor Study (CCSS) STAR Act Biobanking Supplement Projects

Table 2-1: CCSS Banking of Blood Among Survivors of Childhood Cancer Biospecimens by Primary Cancer Site for STAR Act Supplement project

Original Diagnosis	Number of samples collected
Acute lymphoblastic leukemia	215
Acute myeloid leukemia	41
Other leukemia	15
Astrocytomas (brain & spinal cord)	150
Medulloblastoma, PNET (brain)	52
Other central nervous sytem tumors	37
Hodgkins disease	120
Non-Hodgkins lymphoma	98
Kidney tumors	80
Neuroblastoma	66
Soft tissue sarcoma	109
Ewings sarcoma	48
Osteosarcoma	114
Other bone tumors	6
Total:	**1151**

Table 2-2. Childhood Cancer Survivor Study: Somatic & Germline Sequencing STAR Act Supplement project biospecimen sequencing progress by cancer type

	Cancer Type					
	Breast		**Thyroid**		**CNS**	
	New	Previously Sequenced	New	Previously Sequenced	New	Previously Sequenced
WGS Tumor	77	-	39	-	0	-
WGS Germline	98	9	71	8	74	4
WGS Matched Pairs	71		36		0	
WES Tumor	76	-	70	-	0	-
WES Germline	22	81	56	20	27	?
WES Matched Pairs	74		62		0	
RNASeq	34[1]	-	42[2]	-	31	-

[1]Could be up to 49 if some samples are recusable

[2]Could be up to 52 if some samples are recusable

Appendix 3 – Annotation of STAR Act Biobanking Supplement Project Biospecimens

Table 3-1. STAR Act Supplement project annotation and collected clinical and demographic information

Note: It's important to know that clinical annotation can vary widely. For example, if a specimen is from a child that enrolled on a clinical trial, then all the clinical trial data for that child will be available. If the specimen is from a child enrolled on Project:EveryChild but not on a clinical trial, then much less clinical annotation data will be available.

Project	Annotation	Clinical and demographic information
NCI-COG Pediatric MATCH Diagnostic Tumor Specimens	Specimen type (pre-treatment tumor biopsy) Diagnosis (solid tumors including non-Hodgkin lymphoma, brain tumor, histiocytosis) Actionable mutations Potential predictive biomarkers	Laboratory biomarker analysis (molecular analysis) Type of treatment received Response to treatment (response or no response) Number of adverse events Incidence of toxicity Progression free survival Pharmacokinetics (systemic treatment exposure, drug clearance, etc.) Changes in genomics Germline comparison to tumor Genomics of circulating tumor DNA
Postmortem Tumor Tissue Collection at Autopsy (COG)	Tumor type Digital image Nucleic acid extraction	
Tumor Specimens from Patients at Relapse (COG)	Tissue collection type (tissue, FFPE block, FFPE unstained slides) Digital slide Matched sample Diagnosis	Genomic analysis of paired samples of primary and metastatic Tumor or primary and recurrent tumor Anatomic and molecular pathology reports Tumor size and quantity Total RNA and DNA extraction Quality assessment
Rare and Under-Represented Cancer Tissue Banking (COG)	Tissue (complete set of recut H&E slides, frozen tissue, FFPE block, FFPE unstained slides) Malignant bone sarcoma samples (frozen or FFPE) Digital slide Total RNA and DNA (for future sequencing) Sample collection time (for longitudinal and spatial series of samples)	Anatomic and molecular pathology reports Tumor size and quantity Malignant behavior code Clinical trial enrolled in Quality assessment Pathology processing details

Childhood Cancer Survivor Study (CCSS): Somatic & Germline Sequencing	Tissue sample (FFPE tissue block, FFPE tissue scrolls, unstained FFPE tissue slides) Barcode Digital whole slide image Primary cancer diagnosis Vital status at collection (alive or dead)	Whole genome sequence Whole exome sequence RNA sequence Type of primary cancer DNA and RNA concentration and integrity Sex Race Ethnicity Age, age at cancer diagnosis, age at death Treatment exposure (chemotherapy, radiation fields, etc.) during first 5 years after diagnosis
CCSS Banking of blood among survivors of childhood cancer	Type of sample (blood) Tube number (1-3, each have different purpose) DNA extracted prior to storage Barcode CTCAE grade (3 or 4) and condition Primary cancer diagnosis	Sex Race Ethnicity Age, age at cancer diagnosis, age at death Vital status at baseline (alive or dead) Treatment exposure during first 5 years after diagnosis