

Enhancing Biobanking for Childhood Cancers

Meeting Minutes

National Cancer Institute (NCI)
National Institutes of Health (NIH)

NCI Shady Grove
Room TE 406 and by WebEx
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Speakers

A participant list is included in Appendix 1.

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Dr. Ira Dunkel, Pediatric Hematologist Oncologist, Memorial Sloan Kettering (MSK) Cancer Center
Dr. Julie Gastier- Foster, Senior Director, Institute for Genomic Medicine Clinical Laboratory, Vice Chair of Laboratory Genetics in the Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital
Ms. Holly Gibbons, Deputy Director, Office of Government and Congressional Relations, NCI
Dr. Andrew Kung, Chair, Department of Pediatrics, MSK Cancer Center
Dr. Irina Lubensky, Branch Chief, Pathology Investigation and Resource Branch, Cancer Diagnosis Program (CDP), Division of Cancer Treatment and Diagnosis (DCTD), NCI
Dr. John Maris, Giulio D'Angio Chair in Neuroblastoma Research, CHOP
Dr. Margaret Mooney, Acting Associate Director, Cancer Therapy Evaluation Program (CTEP), DCTD, NCI
Dr. Helen Moore, Branch Chief, Biorepositories and Biospecimen Research Branch, CDP, DCTD, NCI
Dr. Lynne Penberthy, Associate Director, Surveillance Research Program, Division of Cancer Control and Population Sciences (DCCPS), NCI
Dr. Nilsa Ramirez, Director of Autopsy Services, Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, and Director, Biopathology Center, Abigail Wexner Research Institute, Nationwide Children's Hospital
Dr. Karlyne Reilly, Senior Associate Scientist, Director, Pediatric Oncology Branch Rare Tumors Initiative, Center for Cancer Research, NCI
Dr. Adam Resnick, Research Scientist, Department of Biomedical and Health Informatics, CHOP
Dr. Nita Seibel, Head, CTEP, DCTD, NCI
Dr. Malcolm Smith, Associate Branch Chief for Pediatric Oncology, Clinical Investigations Branch, CTEP, DCTD, NCI
Dr. Samuel Volchenboum, Associate Chief Research Informatics Officer, Associate Director, Institute for Translational Medicine, The University of Chicago Medical Center
Dr. Brenda Weigel, Director, Division of Pediatric Hematology/Oncology, University of Minnesota
Dr. Peter White, Director, Division of Biomedical Informatics, CCHMC
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WELCOME AND MEETING GOALS

Ms. Holly Gibbons

Ms. Holly Gibbons, Office of Government and Congressional Relations, National Cancer Institute (NCI), opened the meeting and welcomed the participants, introducing those who attended by telephone. The goal of the meeting is to discuss the challenges and opportunities of childhood cancer biobanking. Ms. Gibbons also described the charge of the Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act of 2018 to the NCI. Two research focused sections of this bill are directed to the NCI. One section emphasizes childhood survivorship research, for which the NCI has published a request for applications (RFA) for 2019, “Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors”¹. The other section addresses biospecimen collection and research, and biobanking resources. The STAR Act specifically encourages the NCI to conduct specimen collection and biobanking and to focus resources on children, adolescents, and young adults with selected cancer subtypes (and their recurrences) for which current treatments are least effective. Specimen collection also is emphasized in the context of clinical trials. Ms. Gibbons thanked all of the participants and organizations their contributions to the STAR Act and efforts to ensure it is complementary to NCI’s existing biobanking efforts and current directions in biospecimen science. Ms. Gibbons also noted that NCI Acting Director, Dr. Douglas Lowy, is very supportive of NCI efforts to implement the STAR Act and regretted that he could not attend today’s meeting.

INTRODUCTION

Dr. Malcolm Smith

Dr. Malcolm Smith, Cancer Therapy Evaluation Program, NCI, described challenges to establishing biorepositories that go beyond funding, both those in common with adult-cancer biorepositories and those unique to childhood cancers.

- Less invasive biopsy procedures and more powerful diagnostic methods make obtaining tissue for clinical decision-making procedures less risky, but the amount of tissue collected is smaller, a condition to which biorepositories will have to adapt.
- Appropriate ethical restrictions apply when subjecting children to risk in the absence of any benefit. These considerations limit the types and timing of biopsies that can be performed on children.
- Limited numbers of children with any particular cancer type are seen at any particular institution, as compared to adult cancer patients.
- National Biobanking efforts compete with clinical decision making, required tissue samples for clinical trials, and institutional priorities for the availability of tissues specimens.

Dr. Smith noted, however, that opportunities do exist for biorepositories. Enhancing biobanking to support childhood cancer research should have four aims:

- Identifying high-priority tissues that will be used for important research, with the requisite clinical annotation and quality characteristics present.
- Setting realistic, achievable objectives that take into account the challenges for establishing biorepositories.

¹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html>

- Emphasizing 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.
- 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.

CHILDREN'S ONCOLOGY GROUP BIOBANKING ACTIVITIES

Drs. Peter Adamson and Nilsa Ramirez

Dr. Peter Adamson, Children's Hospital of Philadelphia (CHOP), introduced the Children's Oncology Group (COG), describing its unique features and activities.

- The COG is the world's largest organization devoted exclusively to childhood and adolescent cancer research. It is funded primarily by the NCI through the National Clinical Trials Network (NCTN) and has 200 research sites throughout the United States.
- More than 90 percent of the 14,000 children and adolescents diagnosed with cancer each year in the United States are cared for at COG member institutions.
- Participation rates in clinical trials vary from about 40 percent to 60 percent of potential patients, depending on the age groups being researched.
- COG has many sites in Canada, Australia, and New Zealand; a few sites in Europe; and one site in Saudi Arabia. It also collaborates with non-COG research sites that conduct childhood cancer research in Europe.
- Biospecimen studies are conducted with institutions throughout the world.

Dr. Nilsa Ramirez, Biopathology Center (BPC), Abigail Wexner Research Institute, Nationwide Children's Hospital, described the operation and specimens of the COG Biospecimen Bank (BB).

- The COG BB fits into a larger biobanking operation at the BPC, which is part of the Abigail Wexner Research Institute at Nationwide Children's Hospital.
- Two COG BB principal investigators share responsibility for leadership, implementation of biobanking regulations operations, and scientific aims:
 - Dr. Ramirez has primary responsibility for the Solid Tumors Bank.
 - Dr. Julie Gastier-Foster has primary responsibility for the Leukemia Bank.
- The leadership of the COG BB responds directly to the COG Chair, Dr. Adamson.
- The COG BB consistently works with the COG to harmonize protocols for biospecimen collection to optimize banking of biospecimens for testing and research.
- The biospecimens that the COG BB receives, banks, processes, and distributes are linked to demographic data, surgical-pathologic reports, treatment information, and follow-up data, including disease and survival status. These biospecimens, on review and approval, are prioritized for distribution to the specific COG investigators defined in the protocols.
- The BPC infrastructure is capable of supporting the collection of different types of biospecimens stored in a variety of modalities (e.g., frozen, ambient). Common biospecimens include tissue, nucleic acids, buffy coat, blood and its derivatives (e.g., plasma, serum), bone marrow, and other body fluids (e.g., urine, saliva).

- The biospecimens are prepared according the customized requests submitted by investigators, using a variety of methods (e.g., formalin-fixed paraffin-embedded [FFPE] tissue blocks, touch imprints of solid tumor surface).

Dr. Ramirez discussed some unique features of the COG BB:

- The BPC is experienced in—
 - Specific areas of biobanking.
 - Biorepository-related regulatory issues in the context of clinical trials.
 - Transferring biobanks/ biospecimen collections and data.
- Highly trained and experienced biorepository-based personnel are well versed in handling different pediatric, adolescent, young adult, and adult tumor types.
- Institutional support allows flexibility and ease of expansion, as well as new project acquisition.
- Economy of scale allows reduced operational costs and increased efficiency.
- Clinical laboratory professionals (including board-certified molecular geneticists and pathologists) offer expert advice regarding the quality of solid and liquid biospecimens.
- Three COG Molecular Reference Laboratories (for acute lymphoblastic leukemia, neuroblastoma, and medulloblastoma) also are housed at Nationwide Children's Hospital and affiliated with the BPC.
- The Pediatric Division of the Cooperative Human Tissue Network² (pCHTN) has a unique and long-standing relationship with the COG BB. This relationship allows the pCHTN to distribute COG-banked biospecimens after all clinical trial-specific correlative science studies are complete ("legacy biospecimens").

Dr. Adamson presented an overview of Project:EveryChild, in which an infrastructure would be devised to link cancer biology to outcomes.

- In 2015, the COG launched Project:EveryChild, a single protocol that provides for the collection of biospecimens and accompanying demographic, epidemiologic, therapeutic, and outcome data from all children diagnosed with cancer at participating COG institutions, independent of the patient's enrollment in a therapeutic clinical trial.
- The Project:EveryChild protocol has five major components:
 - Screening for eligibility.
 - Biobanking for future research.
 - Tracking outcomes.
 - Setting up a childhood cancer registry.
 - Contacting for future research.
- To date, more than 16,000 children have been enrolled into Project:EveryChild, which has been funded predominantly through philanthropic efforts, with some support from NCI's Cancer Therapy Evaluation Program.

² <https://www.chtn.org/about/>

- NCI currently supports the cost of specimen collection and banking of specimens for Project:EveryChild from children who also enroll in a COG treatment trial. It is anticipated that stable NCI funding will further enhance the productivity of this nationwide and groupwide effort.

Dr. Adamson discussed the QuadW Foundation's funding of a project to obtain clinical annotation of biospecimens.

- Eight sites varying in size, location, and sarcoma type were invited to be in this study.
- A 1-hour structured interview with the principal investigator and at least one clinical research associate (CRA) helped to identify challenges in obtaining biospecimens.
- Most larger institutions had mechanisms via CRAs to identify relapses for specimen collection. Smaller institutions did not have such a mechanism and missed the opportunity to obtain relapsed specimens.
- Needle biopsies often yielded little tissue.
- Tissue needs are protocol driven.
- In-house competition for tissue is a major problem.
- Parents often desire to keep tissue for studies that might specifically help their child.

Dr. Adamson described the quality control (QC) process used by the COG biorepository.

- Biobanking QC includes verifying that a tissue requested for withdrawal has the proper characteristics requested, identifying patients who possess this particular tissue, and ensuring that the requested tissue meets quality standards for specific research purposes. Biobanking QC involved in verification and fulfillment of requests is performed in addition to rigorous quality control standards and procedures that the COG BB follows throughout the process of specimen collection and initial storage.
- The COG biorepository does not control what specimens come into the repository, and the verification QC process occurs when requests are made for tissue specimen withdrawal.
- Tissue withdrawal requests are verified and reviewed before the request is approved,
- The amount of tissue distributed for a request depends on how many other requests there are for the same tissue. Usually, less tissue is given than is requested.
- Because biobanking QC is very resource intensive and expensive, it is performed only during sample withdrawal and not during sample deposit. Thus, tissues deposited into the bank are not well characterized, and their characteristics are examined in depth only when a withdrawal is requested.
- This system does not allow the COG to advise a site on quality improvement and affects planning for rare or ultra-rare tissue needs.
- Good stewardship of tissue deposits is a very high priority, and supporting sites to obtain high-quality specimens is very important.
- Providing productivity-linked support to sites could help sites obtain better quality specimens.
- Better molecular annotation of specimens is also vital.
- Biobanks should be encouraged to obtain tissue at the time of a patient's relapse.

Discussion

- Dr. Gastier-Foster clarified that certain exceptions to not performing verification QC on incoming specimens exist. Personnel prepare smears and cytospins of incoming leukemia specimens, for example, because obtaining these preparations on thawed specimens is difficult. Acute lymphoblastic leukemia, neuroblastoma, and renal tumors may be prospectively assessed for tumor content. Prospectively collecting some specific characteristics about incoming tissues would greatly assist in the annotation of these tissues.
- Dr. Ramirez stated that prospectively characterizing incoming tissues would be very helpful, but the resources to accomplish this are not available. Investigators occasionally will send results of their tissue experiments to the COG, but this practice is not uniform.
- Dr. Adamson mentioned that NCI support for Project:EveryChild has allowed the COG to have a robust infrastructure for incoming tissue samples. This single protocol is open at all 200 COG sites, and it provides the COG with broad permission to collect data, including outcome data, once the family gives permission for tissue donation.
- Dr. Nita Seibel, Cancer Therapy Evaluation Program, NCI, asked Dr. Ramirez about opportunities to link data from specimens collected through investigator-initiated research projects (that are NIH/NCI-funded), back to the COG BB bioinformatics infrastructure. Dr. Ramirez agreed that this would be an important opportunity, particularly when the slides/samples available for additional research are limited – if sequencing or other analysis has been performed already, a more robustly linked data infrastructure would allow for that data to be made available to inform future research projects. Such linkage could provide an opportunity to collect data prospectively on incoming tissue samples in cases where analysis had already been conducted.
- In response to a question from Dr. Smith about the financial and staffing practicalities of scaling up activities to conduct QC on all tissue specimens, Dr. Ramirez stated that pathology staff are available, but a QC scale up requires more funding than is currently available.
- In response to a question from Dr. Smith regarding the percentage of specimen slides that had been scanned, Dr. Ramirez stated that only a small percentage of slides had been scanned.
- Dr. Irina Lubensky, Cancer Diagnosis Program, NCI, concurred that financial obstacles prevent conducting QC on all incoming specimens to the biobank.
- Dr. Julie Gastier-Foster, Nationwide Children's Hospital, followed up on Dr. Smith's earlier question about scalability of nucleic acid extraction. She commented that the U-24 grant awards that support NCTN Biobanks (including COG) have traditionally only provided resources for equipment such as freezers and centrifuges, noting that this mechanism has not provided an investment into the infrastructure needed to conduct larger scale nucleic acid extraction. She indicated that efforts could be scaled up with the appropriate infrastructure. She also commented that COG, at a larger scale than adult networks, has collected many frozen tissue samples, which are incredibly valuable for future research use.
- A participant commented on the issue of sample depletion for relapse tumor specimens where the tissue sample is small. A targeted analysis should ensure that a small sample is placed into several aliquots for distribution to investigators.
- Dr. Peter White, Cincinnati Children's Hospital Medical Center (CCHMC), asked about distributing and incentivizing best practices to sites that contribute tissue samples to biorepositories. Dr. Adamson noted that the COG has been working toward that goal with solid and central nervous system tumors. Sites have difficulty dedicating staff to tissue collection and submission.

- Dr. Holcombe Grier, Harvard Medical School, stated that QuadW had been approached to incentivize sites to send in tissue samples. QuadW took the position that if sites were paid to send in tissue samples, the samples must be good quality. The COG has been considering writing management-oriented process documents outlining best practices. A challenge Dr. Grier acknowledged is that staff shipping the tissue samples may not read the process document before shipping the sample, and the committee is still working to identify how best to address and potentially incentivize this.
- Dr. Jason Jazembrowski, Children's Hospital of Wisconsin, commented that having resources to QC incoming samples for verification would be very useful. Digitized images with near real-time review would allow the scan to be read in a much shorter time frame than waiting for a pathologist. The difficulty of obtaining relapse samples is great because of the small amount of biopsy material taken, especially in needle biopsy samples, which contain only enough material for diagnosis. Relapse samples may be obtained more easily from autopsy samples.
- A participant commented that both genomic and QC information are very useful when matching patients for clinical trials.
- Ms. Amanda Haddock, Dragon Master Foundation, commented that having QC verification information on the front end lessens the burden when samples are requested. She asked how genetic data are being included and how this information can be used for cross-disease analysis. Dr. Adamson noted that the inclusion of genetic data is variable, both when samples are incoming and when they are distributed. Dr. Anders Kolb, Nemours/Alfred I. duPont Hospital for Children, observed that the COG Acute Myeloid Leukemia Committee has had difficulty obtaining genetic data to be integrated into the COG, but such efforts are ongoing. In the relapse setting, the COG Acute Myeloid Leukemia Committee is working with the Leukemia & Lymphoma Society to initiate biobanking for these samples.
- In response to a question from Ms. Haddock about the access that researchers have to digital information in the biorepository, Dr. Adamson explained that such access is limited, not routine. Linking accompanying data to the sample would represent a powerful way to access annotated information on the sample.
- Dr. Stephen Skapek, University of Texas Southwestern Medical Center, stated that a biospecimen repository with better annotation on incoming samples would allow better planning of clinical trials and moving forward with targeted therapy. He discussed the possibility that collecting only RNA and DNA from incoming tissue samples limits the types of research performed in the future.
- Dr. Vickie Buenger, Coalition Against Childhood Cancer, asked how common it is across COG sites, in the case of a relapse, to discuss with the parents the possibility of a biopsy that would obtain tissue for biobanking. Dr. Adamson replied that when a child can directly benefit from donating a tumor specimen, patient participation is very high. When there is no prospect of direct benefit to the child, parental consent is less likely.
- Dr. Karlyne Reilly, Center for Cancer Research, NCI, asked whether individual patient samples and information are linked to each other. Dr. Adamson replied that the data are linked in the database, and an identifier number allows access to sample data and patient demographic data. In response to a follow-up question from Dr. Reilly, Dr. Adamson explained that to protect patient privacy, biospecimen data have one unique identifier number, and clinical data have a separate identifier number in another database. All information is sent out using identifier numbers. Dr. Ramirez further clarified that the biorepository and the statistical unit have the key for the identifiers, but that key remains within the COG.

- Dr. Samuel Volchenboum, The University of Chicago Medical Center, complimented the COG on using the universal specimen identifier, which identifies that specimen wherever it goes and links the specimen to other data on the specimen. This approach could serve as a model for other groups.
- In response to a question from Dr. Smith regarding which samples have DNA extracted and which do not, Dr. Maryam Fouladi, CCHMC, explained that clinical testing has first priority, and the cancer committees have to prioritize which samples are treated a certain way.
- Dr. John Maris, CHOP, noted that samples can be preserved for other uses when they are prioritized.

PROGRAMS FOR SPECIMENS FROM RELAPSE

Consortia and Pediatric Molecular Analysis for Therapy Choice (MATCH) Study

Pediatric Early Phase Clinical Trials Network

Dr. Brenda Weigel

Dr. Brenda Weigel, University of Minnesota, outlined the Pediatric Early Phase Clinical Trials Network (PEP-CTN) and described its operations.

- During the last grant cycle, the COG Phase 1 and Pilot Consortium (a predecessor to PEP-CTN) protocols required blood samples for pharmacokinetics on all protocols, as well as archival tumor submission for any study that included biologic correlates in tumor tissue. These tissue and blood submissions were protocol specific; the Phase 1 and Pilot Consortium did not support a tissue-banking effort separate from Project:EveryChild.
- The COG PEP-CTN is developing a plan to standardize collection and banking of biospecimens in addition to specimen collection for protocol-specific aims.
- Because most children enrolled in PEP-CTN studies come from COG institutions, this annotated biospecimen collection effort will be carefully integrated with Project:EveryChild and other COG studies for which tumor samples are being collected (e.g., the Pediatric Molecular Analyst for Therapy Choice – MATCH – precision medicine clinical trial). This integration will maximize the scientific utility of the specimens for both disease-specific and longitudinal studies, while minimizing the burden on patients and families.

Pediatric Brain Tumor Consortium

Dr. Ira Dunkel

Dr. Ira Dunkel, Memorial Sloan Kettering (MSK) Cancer Center, described the operations of the Pediatric Brain Tumor Consortium (PBTC).

- The PBTC is an NCI-funded clinical research consortium that was established in April 2016. The PBTC biorepository is located in the Children's Hospital of Los Angeles Department of Pathology and Laboratory Medicine and run by Dr. Jennifer Cotter.
- The PBTC has 12 sites, with NCI's Pediatric Oncology Branch as the 12th site.
- The PBTC biorepository primarily serves as a site to receive, store, and distribute specimens for central pathology review and planned correlative studies that support the laboratory objectives of PBTC studies.

- PBTC protocols routinely allow subjects to consent for submission of specimens to be banked and used for unspecified research, but such samples represent a very small proportion of the inventory because PBTC sites also contribute samples to institutional banks, the COG, and/or the Children's Brain Tumor Tissue Consortium.

New Approaches to Neuroblastoma Therapy

Dr. John Maris

Dr. Maris provided an overview of the New Approaches to Neuroblastoma Therapy (NANT) program.

- Established in 2000, the NANT is an NCI-funded clinical trials consortium focused on relapsed neuroblastoma.
- NANT has 11 full-member institutions in the United States, and two other institutions participate in a subset of trials.
- NANT serves as a Core Resource within a multi-institutional Program Project Grant, with basic research focused on delivering new therapies to the NANT. A nontherapeutic biology study opened in 2005, with most specimen collection occurring in association with therapeutic trial enrollments.
- Approximately 2,200 specimens have been collected and banked from 317 unique patients through the NANT biology study and clinical trials.
- Future directions include maximizing opportunities to track genomics via cell-free DNA assays (currently in two ongoing protocols) and design trials in which fresh tumor tissue is an eligibility requirement.

NCI-COG Pediatric MATCH Study

Dr. Nita Seibel

Dr Nita Seibel discussed the Pediatric MATCH study and how it functions.

- Pediatric MATCH seeks to determine the objective response rate in pediatric patients who have advanced solid tumors and lymphomas harboring *a priori* specified genomic alterations treated with pathway-targeting agents.
- Pediatric MATCH also will determine the proportion of pediatric patients whose tumors have pathway alterations that can be targeted by existing anticancer drugs. Pediatric MATCH will compare the diagnostic yield of the relapse sample sequencing with the diagnostic yield of the pretreatment specimen (diagnostic sample, if available) sequencing.
- The frequency and spectrum of germline cancer susceptibility mutations in children, adolescents, and young adults with relapsed solid tumors and lymphomas will be assessed.
- A tissue sample for biobanking is not required, but a sample is necessary to be screened for a matching study agent treatment.

Discussion

- To answer a question from Dr. Smith about DNA and RNA extraction from tissue samples, Dr. Seibel explained that DNA and RNA remain after tissue analysis of the samples for the clinical trial.
- Dr. Smith highlighted the importance of collection specimens at relapse from Pediatric MATCH and having corresponding tumor tissue from diagnosis.

Programs for Post-Mortem Collection of Tumor Tissue

International Diffuse Intrinsic Pontine Glioma Registry

Dr. Maryam Fouladi

Dr. Maryam Fouladi, CCHMC, described the formation and programs of the International Diffuse Intrinsic Pontine Glioma (DIPG) Registry.

- The International DIPG Registry and Repository (IDIPGR), an observational cohort formed in 2012, comprises the largest and most comprehensive collection of linked clinical, radiologic, pathologic, molecular and genomics data from a diverse cohort of DIPG patients available to researchers throughout the world.
- IDIPGR now includes 110 collaborative sites in 15 different countries: the United States, Argentina, Australia, Brazil, Canada, Chile, China, Egypt, India, Israel, Japan, Lebanon, New Zealand, Saudi Arabia, and the United Arab Emirates. Earlier this year, the IDIPGR expanded to include patients with diffuse midline gliomas (DMG) and is now designated as the International DIPG/DMG Registry.
- The mission of the IDIPGR is to provide an integrated set of clinical, pathologic, radiologic, molecular, and genomics data to the clinical research community for promotion of hypothesis generation and analysis.
- The long-term goal of the Registry is to maintain a highly collaborative, international, hypothesis-driven research infrastructure to support a wide spectrum of interdisciplinary and translational projects in DIPGs/DMGs for all investigators.
- The specific objectives of the project are to—
 - Enroll DIPG/DMG patients from around the world.
 - Provide a repository of integrated data and establish collaborations among investigators for hypothesis-driven research studies that will lead to better diagnosis, classification, and treatment strategies.
 - Establish a national autopsy program with designated pathology centers around the United States (and eventually internationally) to facilitate conduct of autopsies, tissue sharing, and development of *in vitro* and *in vivo* models to be shared with investigators.
- The autopsy program for the IDIPGR has been modeled on the very successful Pediatric Brain Tumor Repository study at the CCHMC established by Drs. Fouladi and DeWire-Schotmiller and colleagues in 2013.
- Using this model, the IDIPGR operations team, under the leadership of Dr. Fouladi, has established an autopsy program with sites across the United States agreeing to act as regional

centers to facilitate the conduct of autopsies. Since 2013, 64 autopsies have been conducted on children with a variety of pediatric brain tumors.

- To develop an in-depth understanding of these rare diseases and improve outcomes for patients with DIPG and DMG, collaboration with other existing biorepositories, registries, pediatric consortia, and other research endeavors—such as the NIH Common Fund’s Gabriella Miller Kids First Pediatric Research Program—is critical.

Swifty Foundation and Children’s Brain Tumor Tissue Consortium

Dr. Adam Resnick

Dr. Adam Resnick, CHOP, provided an overview of the Children’s Brain Tumor Tissue Consortium (CBTTC) program and activities.

- The CBTTC was founded in 2011 with the driving mission to serve as a collaborative, publicly accessible, multi-institutional research platform dedicated to the study and treatment of childhood brain tumors. Its sole goal is addressing the critical unmet need of large-scale, biospecimen-driven pediatric brain tumor research.
- In addition to its centralized biospecimen collection efforts, the CBTTC and its member institutions spearheaded the development of a network of informatics and data application platforms that allow researchers around the world to work together to discover treatments via biospecimen-based research and data-driven discovery.
- In 2018, the CBTTC launched the Pediatric Brain Tumor Atlas, a large-scale data-generation effort that leverages collaborative, cloud-based data resources and computation environments, including the Gabriella Miller Kids First Data Resource, which is a pan-NIH research initiative on behalf of pediatric cancers and structural birth defects.

Programs for Tissue from Tumors Passaged in Mice (Xenografting)

Pediatric Preclinical Testing Consortium

John Maris

Dr. Maris described the Pediatric Preclinical Testing Consortium (PPTC) focus and research activities.

- The PPTC is an NCI-funded preclinical testing program designed to prioritize new cancer therapies for clinical development in children. It recently completed a comprehensive genomic profiling of 261 patient-derived xenograft (PDX) models derived from 29 unique pediatric cancers, with 33 percent of the models being derived from a sample at relapse or post-mortem.
- The major conclusion when comparing the PDX data to published sequencing data from diagnostic human tumor material is that PDXs faithfully recapitulate the genomic landscape of each histology, but the frequency of each genomic driver aberration is much higher, likely reflecting the large proportion of relapse specimens and the ultrahigh-risk nature of cancers from which PDX models are established.
- The 261 PDX models are being subjected to reverse-phase protein arrays and developed into tumor microarrays.

MSK Kids Pediatric Translational Medicine Program

Dr. Andrew Kung

Dr. Andrew Kung, MSK Cancer Center, described animal and cell-culture model development efforts and the biobanking of the MSK Kids Pediatric Translational Medicine Program (PTMP).

- Established in 2016, the PTMP is a horizontally integrated platform with a single portal of entry and automated workflow to access clinical sequencing, biobanking developmental therapeutics, translational sequencing, and post-clinical model development.
- Clinical molecular genomics includes MSK-IMPACT™ (which stands for integrated mutation profiling of actionable cancer targets and is a U.S. Food and Drug Administration [FDA]-authorized sequencing of 468 cancer-related genes), MSK-IMPACT Heme, and Archer FusionPlex (a gene panel that detects solid tumors or one that detects hematologic malignancies).
- The clinical trials portfolio includes 82 actively accruing clinical trials, including 67 early-phase trials and an additional 32 active FDA-approved single-patient use (SPU) protocols. MSK mandates that all adult Phase 1 trials be open to individuals ages 12 and above.
- Biobanking of solid tumor frozen samples utilizes the Pathology Precision Biobank Core, and viable frozen banking of hematologic malignancy samples utilizes the Hematologic Oncology Tumor Bank.

Discussion

- A participant mentioned being part of a decentralized group of PDX investigators that is assessing the possibilities of sharing these models. Dr. Kung suggested that working with a well-characterized NCI patient-derived mouse model for adult mouse models would be a better choice than a pediatric mouse model, and a patient-derived mouse model would be easier to share. Dr. Kung also suggested using a system like that of the Center for International Blood and Marrow Transplant Research tissue specimens for allogeneic transplant research.
- A participant asked Dr. Kung to further discuss the transitory nature of the PDX mouse models. Dr. Kung replied that although the murine PDX models are viable models, they lose the heterogeneity of their tumor cell populations after a few passages. Dr. Kung also explained that the tumor cell microenvironment that would be present at engraftment would be lost after tumor cell passage in the PDX mice.
- Dr. Maris commented that these models have limitations for research. Pediatric PDX models keep their heterogeneity in tumor cell populations for at least a few passages in PDX mice. One advantage of the PDX mice is that their engrafted tumor cells maintain their surface antigen profile, unlike tumor cells cultured in tissue culture.
- A participant was curious whether the drift Dr. Kung observed was related to the tumor type with which he was working. Dr. Kung doubted that this was the case and thought that drift of the tumor cells was driven by an underlying biological factor.

NCI PLANS FOR BIOBANKING AND CENTERS FOR DISEASE CONTROL AND PREVENTION PEDIATRIC CANCER REGISTRY EFFORTS

NCI National Clinical Trials Network Biorepository

Dr. Irina Lubensky

Dr. Lubensky described the activities and focus of the NCTN biorepository.

- The NCI supports the NCTN, which is a standing clinical trial infrastructure funded through the Cancer Therapy Evaluation Program U10 Cooperative Agreement grants. In 2017, five NCTN trial groups conducted 175 large-scale treatment and imaging trials, including definitive Phase 3 trials, randomized Phase 2 trials, across the United States, enrolling approximately 22,000 patients with adult and childhood cancers.
- The Cancer Diagnosis Program at NCI currently supports five NCTN biospecimen banks:
 - Alliance for Clinical Trials in Oncology
 - ECOG-ACRIN (Eastern Cooperative Oncology Group–American College of Radiology Imaging Network)
 - NRG Oncology
 - Southwest Oncology Group
 - COG
- The biobanking grants allow the biobanks to sustain operations, harmonize activities according to standard operating procedures, and establish a national inventory of samples held in central repositories with a clearly defined process for access by researchers.
- All NCTN biobanks maintain collections of solid tumors (i.e., brain, breast, gastrointestinal, genitourinary, gynecological, head and neck, melanoma-skin, central and peripheral nervous system, liver, lung/thoracic, and sarcoma). They collect FFPE blocks and histological slides from diagnostic biopsies and surgical resections. Frozen tissue specimens and macromolecules, such as nucleic acids, also are collected and prepared by the banks.
- Specimens are initially used by NCTN trial group investigators for integral and integrated biomarker studies/assays (prognosis/prediction).
- Specimens remaining in excess after clinical trial requirements have been met become “legacy” specimens and are available to investigators for secondary correlative studies following an NCTN biospecimen access process and approval by NCTN Core Correlative Science Committee (NCTN CCSC).
- NCTN “Legacy” Biospecimens are used for validation studies of predictive/ prognostic biomarkers based on the trial treatments and outcomes and assay development/validation.
- 572 publications, many with high impact, resulted from the use of NCTN trial specimens in 2013-2017.

NCTN Navigator

Dr. Margaret Mooney

Dr. Margaret Mooney, Cancer Therapy Evaluation Program, NCI, explained what the NCTN Navigator is and how it functions.

- The biospecimen collections developed from cancer clinical trials conducted by the NCTN are highly annotated with carefully collected clinical data, including outcome data.
- The NCTN Navigator Clinical Trials Specimen Resource fills a gap by providing the research community with high-quality, clinically annotated specimens and associated clinical data from a variety of cancer trials that can be used to test clinically important hypotheses.
- The Navigator inventory currently includes specimens from large adult treatment trials(Phase 3) that were conducted by the NCTN clinical trials groups and that have reported the primary outcome. Specimens from newly completed trials are added on a rolling basis, and Navigator will begin adding specimens from Phase 3 COG trials in the coming months.
- Investigators interested in conducting research using specimens from NCTN trials can visit the Navigator website and explore the available specimens. An investigator can search for specimens by building queries based on the trials from which the specimens were collected, the demographics of the patients, or the specific type of specimen.
- Investigator proposals that are submitted to the NCTN Core Correlative Sciences Committee are reviewed for scientific merit. This committee is made up of NCI and extramural experts in oncology, laboratory science, translational medicine, pathology, statistics, biobanking, and patient advocacy. The committee is charged with scientific review and prioritization of proposals to ensure optimal use of these irreplaceable clinical trial biospecimens.

Cancer Registries

Surveillance, Epidemiology, and End Results (SEER)

Dr. Lynne Penberthy

Dr. Lynne Penberthy, Surveillance Research Program (SRP), NCI, described the purpose of SEER and how it functions.

- Supported by the NCI and operated through the SRP, the NCI SEER cancer registry system has been ascertaining cancer cases and collecting data since 1973.
- Currently, SEER covers 35 percent of the U.S. population, with more than 500,000 incident cancer cases reported annually. SEER receives real-time pathology reports for approximately 85 percent of all cases. The availability of the pathology report identifies patients who might have samples available for research purposes either an initial FFPE tumor block or a block related to the recurrence.
- SEER has been supporting collection of specimens for research purposes since 2003, under the Residual Tissue Repository (RTR) initiative. In addition, the SEER program currently supports a large pilot study to inform the development of a SEER-wide biorepository infrastructure that will consist of both a residual (or discard) component and a virtual component, based on availability of diagnostic, archival FFPE tumor and nontumor blocks as indicated through linked pathology reports.
- These RTRs collect diagnostic archival FFPE diagnostic tissue blocks or slides from laboratories when they discard tissue after the requirement for retention has been met.
- The Virtual Tissue Repositories (VTR) system currently being piloted in six states will provide an infrastructure through which researchers can access deidentified, but linked, archival, diagnostic FFPE tissue; data; and digital slide images through the SEER registries, which will function as honest tissue and data brokers.

- It is estimated that the VTR system, which will be developed alongside expansion of the RTR system, will be scaled and available to researchers in approximately two years with the conclusion of the VTR Pilot.

Centers for Disease Control and Prevention National Program of Cancer Registries Pediatric and Young Adult Early-Case Capture

Ms. Toye Williams

Ms. Toye Williams, Centers for Disease Control and Prevention (CDC), provided an overview of the CDC's National Program of Cancer Registries (NPCR) and its activities.

- The CDC-funded NPCR is a population-based surveillance system of cancer registries established in 1992. NPCR supports the collection of high-quality data by central cancer registries in 46 states, the District of Columbia, Puerto Rico, the U.S.-affiliated Pacific Island jurisdictions, and the U.S. Virgin Islands. Registry data are critical for measuring progress and targeting cancer prevention and control actions.
- The Caroline Pryce Walker Conquer Childhood Cancer Act of 2008 authorized the CDC to expand and enhance the infrastructure of the central cancer registries to collect pediatric cancer cases within weeks of diagnosis.
- The STAR Act authorized the CDC to continue to enhance the infrastructure of cancer surveillance through electronic capture of pediatric and young adult cancer cases. The CDC will scale the lessons learned from the Pediatric and Young Adult Early Case Capture program to modernize the NPCR surveillance system for all cancers.
- The modernized NPCR program will focus on cancers in patients from birth to age 29 years.
- Electronically capturing pathology reports at a first occurrence of cancer and submitting them to a common, cloud-based platform to automate consolidation should result in much faster data availability.

NCI Rare Tumor Patient Engagement Network

Dr. Karlyne Reilly

Dr. Reilly discussed the activities of the My Pediatric and Adult Rare Tumor (MyPART) Network.

- The MyPART Network focuses on increasing collaboration among all stakeholders in rare tumor research and improving patient engagement in rare tumor research. MyPART fosters collaboration among patients and families, health care providers, investigators, and patient advocates.
- Developed in the Pediatric Oncology Branch of the NCI Center for Cancer Research, MyPART is part of the larger effort to act on the Cancer MoonshotSM Blue Ribbon Panel recommendation of creating a patient engagement network.
- The Direct Patient Engagement Network has the following aims:
 - Build a shared infrastructure across national and international sites to study selected rare pediatric and adult tumors, with specific attention to connecting patients and investigators through advocacy groups and other means.

- Collect and analyze all available data on selected rare tumors to be shared with patients and their families, as well as with researchers studying risk and disease trajectory with the goal of developing personalized therapies.
- To accomplish these aims, MyPART has begun to partner with patient advocacy groups and host clinics to bring rare cancer patients and their families to the NIH Clinical Center to meet with expert health care providers.
- The Natural History Study of Rare Solid Tumors will collect patient data, patient-reported outcomes, family history, and biospecimens at the NIH Clinical Center and at external sites.
- To promote the understanding of tumor biology and discovery of rare tumor therapies and cures, the MyPART Network will facilitate investigator access to the data collected from the Natural History Study of Rare Solid Tumors.

The Cancer MoonshotSM Biobank

Dr. Helen Moore

Dr. Helen Moore, Cancer Diagnosis Program, NCI, presented a discussion of the purpose and activities of the Cancer MoonshotSM Biobank.

- The Cancer MoonshotSM Biobank was started by the NCI to serve researchers who are working to better understand and treat cancer.
- The Cancer MoonshotSM Biobank will collect biospecimens longitudinally—that is, over the whole period of time that a person is receiving cancer treatment. The biospecimens and associated health information will be made available to qualified scientists to help those researchers learn how cancer grows and changes in people and find new cancer treatments.
- This 5-year effort will support cancer research by establishing an infrastructure for longitudinal biospecimen collections from a diverse patient population receiving standard-of-care cancer treatment at multiple medical institutions.
- Samples from 1,000–5,000 participants will be deposited into the biobank and made available to researchers.
- The Cancer MoonshotSM Biobank will work in collaboration with community hospitals to engage eligible patients and collect biospecimens and associated data. Electronic consent will be utilized for the project. Samples will be stored at a central biobank. The biobank will perform pathology QC and distribute biospecimens.
- A clinical laboratory will perform biomarker testing on participants' tumor tissue and return results to the participant and their health care provider.
- The tumor biomarker test results may provide more information for cancer treatment decisions for the participant and may help researchers better understand how genes within a tumor can affect cancer progression and treatment.

Discussion

- In response to a question from Dr. Smith, Dr. Reilly expanded on the definition of ultra-rare tumors within the MyPart program, adding that the program would like to enroll patients who have no other opportunities for research with other investigators.
- In response to a question about how biobanks avoid duplicating efforts, and a question about opportunities for integration among the networks, Dr. Reilly noted that biobank intramural programs should be coordinated with extramural efforts, similar models should be used, and best practices should be harmonized. Dr. Reilly also emphasized engaging patients and referring them to the most appropriate program. Dr. Penberthy also later commented to provide clarification that the future VTR and RTR programs through the SEER registry system collects clinical data elements and could serve as a complementary, yet not duplicative, source of additional data and potentially additional specimens.
- Dr. Resnick commented that in approaching rare tumor types, the young adult group has not been strategically addressed and presented opportunities for study.
- Dr. Smith asked about using tissue samples for research in the absence of consent and wondered about limitations on genomic data sharing affecting biorepositories. Dr. Penberthy stated that cancer registries, serving as an honest broker³, can allow use of tissue samples without consent. IRBs have accepted this practice as a method of using de-identified data and not requiring consent. At the NIH level, genomic data sharing could have restrictions if there is a risk of data re-identification. Dr. Petkov, Surveillance Research Program, NCI, added that institutions can share genetic data of specimens gathered before January 2015; for specimens obtained after January 2015, the NIH policy on genomic data sharing applies.
- In response to a question from Dr. Resnick about re-contacting patients for para-germline DNA data, Dr. Penberthy stated that cancer registries can work with investigators on patient contact studies.
- Participants discussed ways to obtain large quantities of high-quality data, noting that success in this area could come from working with advocacy groups or with cancer registries that collect complete sets of patient information and treatment information.
- Participants discussed the issue of future research and consents being used for biobanking. The consents may have to change to allow patients to consent to additional future research when signing the consent. Language for future research use is being revised by institutions to add more flexibility for the patient and researcher. Informing individual patients about what future unspecified research might be performed with their tissue samples is difficult. Participants discussed ways in which patients, as a group, could be notified of research results and future research on their samples.
- Dr. Moore commented that electronic health record (EHR) transfer pilot projects could be initiated.

³ **Honest broker.** An individual, organization, or system acting for, or on behalf of, a covered entity to collect and provide health information to research investigators in such a manner whereby it would not be reasonably possible for the investigators or others to identify the corresponding patients-subjects directly or indirectly. The honest broker cannot be one of the investigators. The information provided to the investigators by the honest broker may incorporate linkage codes to permit information collation and/or subsequent inquiries (i.e., a “re-identification code”); however, the information linking this reidentification code to the patient’s identity must be retained by the honest broker and subsequent inquiries are conducted through the honest broker (NCI Thesaurus).

DISCUSSION SESSION

Bioinformatics Issues

Drs. Volchenboum, Resnick, and White led a discussion about the influence of informatics research on pediatric cancer research with respect to biobanking. The discussion began with an overview of the NCI Cancer Research Data Commons (CRDC).

- A node is a repository in the NCI CRDC containing related data that have been harmonized and stored in a format that is ready for analysis by the research community.
- CRDC is a network of nodes that researchers, tool developers, clinicians, and patients can use to access and contribute tools and data across scientific domains.
- CRDC interaction with a pediatric biorepository is important to consider. Domain specificity is important, but building a large infrastructure ecosystem for domain-specific disease may not be practical. Integrating into an existing ecosystem should be considered.
- Government investment in large-scale infrastructure is needed for cross-disease ecosystems. The right balance between domain specificity and the ecosystem in which it resides must be made.
- A participant commented that harmonizing best practices would be helpful to limit over-specialization when staff work in this area. Dr. Resnick added that clinical data interoperability is important.
- Participants discussed a number of high-profile high-throughput initiatives that perform deep-data extraction from EHRs, speeding the collection of data. Public and private partnerships could be established to carry out these projects.
- Dr. Smith commented on the challenge of providing a focus on disease-specific collection and resources while at the same time establishing common data elements across disease types. Dr. Smith added that creation of a data bank biobank commons will recruit valuable specimens. A dictionary for each disease type will have to be created and must be harmonized with previously collected items. Specialty “spokes” of institutions—programs that excel in one type of research function—can be integrated into the commons, reducing competition among institutions and improving access to data.
- Ms. McLean also noted that additional communication with families is critical, citing surveys conducted within the pediatric brain tumor community finding that nearly 70% of families are never asked about tissue donation at diagnosis or post mortem, and 95% of these families wished they had known and they would have donated. She emphasized that the community cannot afford for parents not to be able to make an informed decision about what they want to do.
- Dr. Fouladi also shared data from her experience, noting that 3-4 years ago her team found that the approach rate among clinicians was only 60% and the consent rate was 50-60%. Now the approach rate is nearing 90% in the past year to year and a half, and the consent rate is nearing that same amount. She emphasized that education is very important, and sharing lessons learned from across disease communities, and families have been critical in moving this work forward and developing best practices.
- Dr. Resnick also emphasized the importance of continued communication with families regarding how specimens are used for research.
- Dr. Vickie Buenger shared comments from Dr. Susan Weiner from Children’s Cause, who participated remotely. Dr. Weiner commented on the earlier presentation regarding the NCTN

Navigator resource for investigators to explore availability of NCTN specimens for research projects. She and Dr. Buenger indicated that a streamlined Navigator-type tool specifically for pediatric and AYA samples that provides information on how to navigate through and use the available biospecimen resources and systems would be helpful.

- Dr. Fouladi also mentioned that investigators asked for this type of platform for the DIPG community, the LINKS program, that has been formed to allow investigators access to clinical images and hypothesis-generating data, based upon a set of 150 data elements identified by DIPG investigators. Dr. Buenger concurred that a resource similar to this program, for additional childhood and AYA cancer types, would be valuable.
- Dr. Volchenboum commented that good visualization data empowers people to consider how to utilize that data and engenders trust with researchers.
- In response to a question from Dr. Moore about how many biobank data elements from previous projects are in the Cancer Data Standards Registry and Repository (caDSR), Dr. Volchenboum stated that there has been successful engagement with the caDSR and that chances to augment data collection have increased by that collaboration.
- In response to a question about balancing the benefits of participating in a mini-commons without losing innovation, Dr. Volchenboum stated that the standards of the NCI dictionary and caDSR allow interoperability. Dr. Resnick added that a commons approach to standards allows utilizing common resources to accelerate research across disease groups
- Discussion also addressed maintaining trust among groups with collaborations as the biobanking community expands.
- Dr. Fouladi commented that the community does not want competition between biobanks and directs where it wants the autopsy samples to be sent. Dr. Resnick emphasized that small communities within a biobanking commons would operate with trust relationships and be able to discuss standards, rules, and practices with other commons.
- Dr. Resnick stated that data and transparency regarding the use of resources strengthens trust relationships across the cancer community.
- Dr. Resnick emphasized that because a proportion of data-driven research is funded by philanthropic organizations, researchers and biobanks need to inform these organizations about where the samples are going and who has data ownership.
- Mr. Keith Desserich commented that the DIPG community has established these resources out of necessity, given the nature of the disease. He emphasized the important role families have played as a driver of these efforts, and commented that programs established in the pediatric brain tumor community can serve as a model for other types of childhood cancers.

Biorepository Issues

Participants discussed issues related to biorepositories.

- Challenges for biorepositories include the following:
 - A broad, electronic computable consent is needed to maximize the ability of researchers to make use of biospecimens.
 - Tracking samples from a patient over time is important to understand the response to therapy of both the patient and the tumor. The ability to connect the clinical events (surgery,

radiation, chemotherapy, etc.) with the sample collection is critical and will depend on the quality of the associated data. Common identifiers are necessary.

- Pilot projects across repositories or initiatives could help to maximize use of resources.
- Consent processes should be harmonized and coordinated to allow parents to decide more easily in which research to have their child participate.
- Dr. Brenda Weigle commented that leveraging the infrastructure resources of Project:EveryChild allows the tracking of a single patient through his or her cancer trajectory. The infrastructure is growing from the bottom up. Very complete data are being collected, and patient privacy concerns need to be addressed.
- Dr. Adamson commented that the cancer community—including patient families and clinicians caring for children with cancer, especially at smaller institutions—must be included in discussions of new projects and infrastructure to encourage their participation in biobank research. Pediatric patients need to be supported in their local communities where they are being treated.
- Dr. Smith raised the question of whether biobanks are receiving circulating tumor DNA (ctDNA) from clinical trials. Biobanks are receiving ctDNA samples at the time of diagnosis and time of relapse. ctDNA is used to identify the evolution of tumor cells and subgroups of tumor cells. Participants agreed that ctDNA samples are being commonly received. COG members are freezing their samples with ctDNA because standards for detecting ctDNA are still being developed.

Institutional Issues

Participants discussed institutional issues related to biobanking.

- Dr. Smith asked whether tissue from Phase 3 clinical trials can be obtained for future research, despite other institutional priorities for that tissue. Dr. Adamson replied that a protocol may stipulate that tissue be sent to biobanks; however, IRBs do not usually agree to this. The major source of tissue may be smaller institutions, even though they lack the infrastructure to send large numbers of tissue samples into biobanks. Participants thought that larger institutions have a role as well, which must be balanced with that of small institutions. The DIPG registry is a good example of an initiative that shares tissue with many groups.
- Dr. Fouladi commented that the opportunity to share samples, with the assurance that investigators will have access to richer and more complete data on these samples as additional research is conducted, will serve as an incentive.
- Dr. Stephen Chanock commented that the community should consider identifying a standard set of tests and clinical elements for each sample, in addition to the prospective collection already underway through Project:EveryChild. Dr. Adamson mentioned that additional resources would need to be available to support such an effort.
- Dr. Fouladi commented on the need to harmonize beyond the U.S., including with European colleagues.

Approaches to Specimens Post-Relapse

- Dr. Fouladi commented that practices regarding resection and specimen collection at relapse are changing within the pediatric brain tumor field, and resection is occurring more often to inform

clinical decision making. She noted that infrastructure is needed to make sample collection possible.

- Dr. Smith asked about capacity for further collection of ctDNA, and whether additional collection at relapse is needed. Dr. Adamson indicated collection at relapse is underway and the community is supportive. A colleague also emphasized its role in monitoring tumor progression. Dr. Resnick also discussed bioinformatics challenges in this space and current efforts to identify standards.

Opportunities for Partnerships to Enhance Tissue Collection and Utilization

Participants discussed potential partnerships for biobanking throughout the closing discussion, spanning several areas as described above, particularly throughout the discussion of bioinformatics issues and opportunities.

ADJOURNMENT

Dr. Smith thanked the participants for their contributions, and the meeting was adjourned at 3:30 p.m.

APPENDIX 1. PARTICIPANT LIST

Enhancing Biobanking for Childhood Cancers

National Cancer Institute

NCI Shady Grove, Room TE 406 and by
WebEx May 13, 2019, 10:00 am – 3:30 pm

**Asterix indicates in-person participant*

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