The Children's Brain Tumor Network (CBTN) - Accelerating Research in Pediatric Central Nervous System Tumors through Collaboration and Open Science

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Running title: CBTN Facilitates Pediatric CNS Tumor Research

Keywords: Collaborative international research infrastructure, pediatric brain tumors, multi-omic data, longitudinal clinical data, biospecimens, molecular clinical trials

Abstract

Pediatric brain tumors are the leading cause of cancer-related death in children in the United States and contribute a disproportionate number of potential years of life lost compared to adult cancers. Moreover, survivors frequently suffer long-term side effects, including secondary cancers. The Children's Brain Tumor Network (CBTN) is a multi-institutional international clinical research consortium created to advance therapeutic development through the collection and rapid distribution of biospecimens and data via open-science research platforms for real-time access and use by the global research community. The CBTN's 32 member institutions utilize a shared regulatory governance architecture at the Children's Hospital of Philadelphia to accelerate and maximize the use of biospecimens and data. As of August 2022, CBTN has enrolled over 4,700 subjects, over 1,500 parents, and collected over 65,000 biospecimen aliquots for research. Additionally, over 80 preclinical models have been developed from collected tumors. Multi-omic data for over 1,000 tumors and germline material is

currently available with data generation for > 5,000 samples underway. To our knowledge, CBTN provides the largest open-access pediatric brain tumor multi-omic dataset annotated with longitudinal clinical and outcome data, imaging, associated biospecimens, child-parent genomic pedigrees, and *in vivo* and *in vitro* preclinical models. Empowered by NIH-supported platforms such as the Kids First Data Resource and the Childhood Cancer Data Initiative, the CBTN continues to expand the resources needed for scientists to accelerate translational impact for improved outcomes and quality of life for children with brain and spinal cord tumors.

Introduction

Brain and other central nervous system (CNS) tumors are the leading cause of cancer-related death in children and frequently result in substantial long-term morbidity and disability (1). Despite scientific advances in brain tumor biology across a large number of tumor types and histologies, improvements in long-term survival and quality of life for CNS tumors have remained elusive compared to other childhood cancers. Barriers to therapeutic advancement include lack of clinically-annotated biospecimens, insufficient preclinical models, and siloed, disconnected datasets (2).

The mission of the Children's Brain Tumor Network (CBTN, https://cbtn.org/), launched in 2011 as the Children's Brain Tumor Tissue Consortium (CBTTC), is to serve as a collaborative multi-institutional research consortium with a publicly-accessible biosample and data repository dedicated to the study and treatment of childhood brain tumors. CBTN seeks to address critical unmet needs for integrated, large-scale biospecimen, multi-omic, and longitudinally clinically-annotated resources. As of 2022, the CBTN comprises 32 member institutions within the United States, Italy, Switzerland, and Australia. To overcome the challenges of global, collaborative research and siloed resources, CBTN spearheaded the development of cloud-based informatics and data applications that allow researchers to access

and collaboratively analyze datasets. As such, CBTN's foundation of "Innovation through Collaboration" is being realized through its creation of a state-of-the-art biorepository, innovative analytics platforms, and real-time sharing of data and specimens. By design, CBTN initiatives build upon the success of The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research To Generate Effective Treatments (TARGET) consortia by further developing standards for the collection of specimens and comprehensive longitudinal clinical data while addressing gaps in pediatric brain tumor representation in such resources. Recently, CBTN resources have contributed to the development of cross-disease resources such as the Gabriella Miller Kids First (GMKF) Data Resource and the NCI's Childhood Cancer Data Initiative (CCDI).

Collaborative biobanking with the CBTN

Patients are consented by one of 32 participating sites and enrolled on a local IRB-approved protocol which includes key language to enable prospective collection of, future research on, and sharing of, de-identified surgical specimens, patient demographics, medical history, diagnoses, treatments, and clinical imaging. CHOP reviews each site's regulatory documents prior to submission and maintains copies along with annual approvals. When possible, site-enabled workflows support the generation of cell lines, organoids, and/or patient-derived orthotopic xenografts from available tissue (**Figure 1A**).

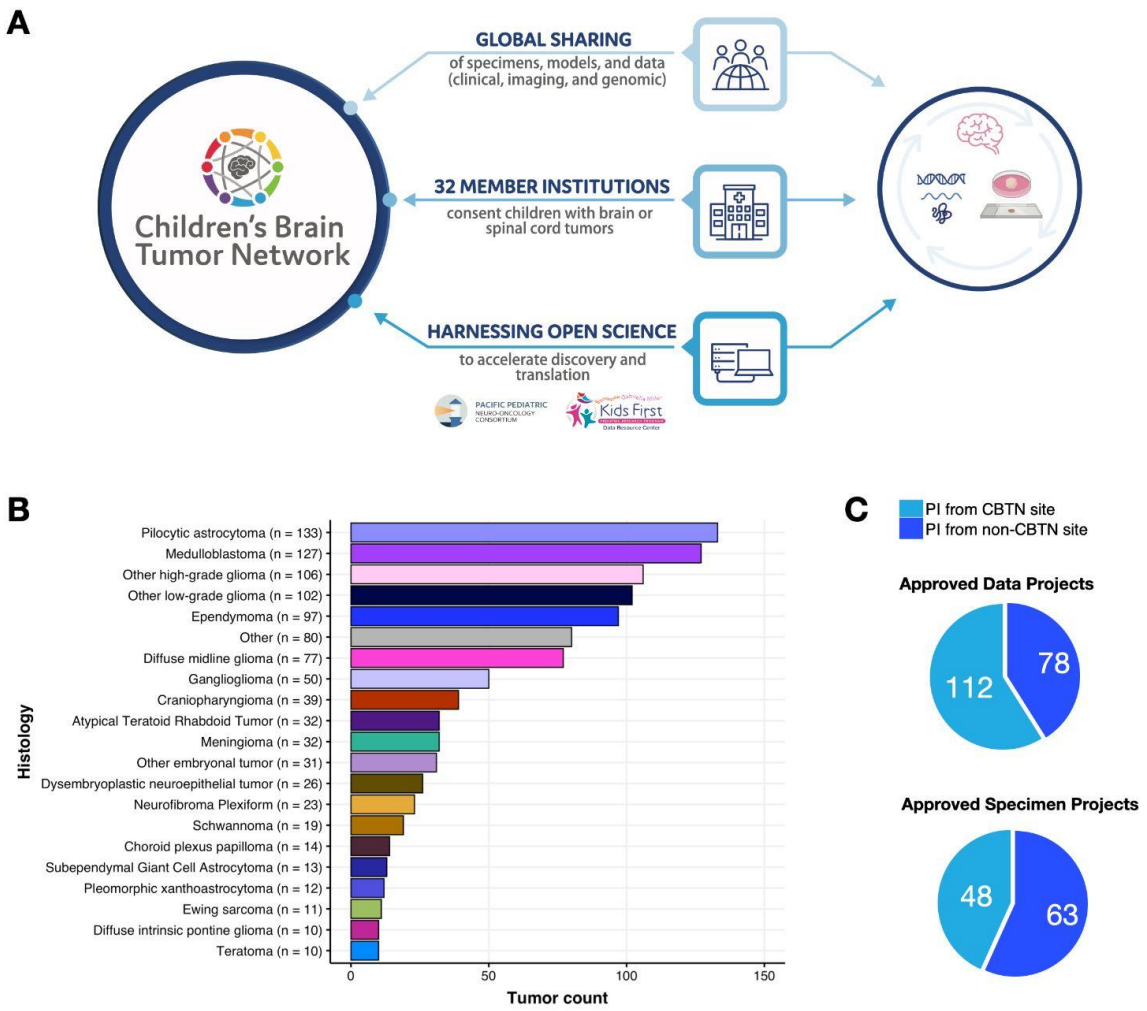

Figure 1. The Children's Brain Tumor Network enables collaborative biospecimen, model, and data sharing Shown in **A** is the CBTN ecosystem, consisting of patient enrollment at one of 32 institutions to sample and clinical data collection, biobanking, preclinical model generation, and genomic data generation to collaborative open science to accelerate discovery and clinical translation through ongoing trials such as PNOC. **B**, histologic distribution of unique tumors from the OpenPBTA (non-cancerous samples collected such as benign tumors and/or cysts are not plotted). **C-D,** number of approved data and biospecimen projects, respectively, by PI site membership. (Biorender.com used for selected images in Panel A).

In addition, CBTN's cross-disease research platform supports the integration and management of partnered, disease-specific biospecimen and data resources including NF2 Biosolutions (https://nf2biosolutions.org/), the Embryonal Tumor with Multilayered Rosettes One Registry (https://hmh-cdi.org/etmr/), the Chordoma Foundation (https://www.chordomafoundation.org/), and OligoNation (https://www.oligonation.org/). These

collaborative efforts advance disease-specific research while harnessing CBTN's operational and research infrastructure.

Creation of the Pediatric Brain Tumor Atlas

Created as a multi-center, multi-omic effort, the CBTN's Pediatric Brain Tumor Atlas (PBTA) includes matched tumor-normal whole genome sequencing (WGS), tumor RNA-Seq, methylation, and proteomics, as well as longitudinal clinical data, images (MRIs, histology slides images, radiology reports), and pathology reports (3). The first PBTA dataset release of nearly 3,000 specimens from 1,074 tumors and germline sources occurred in 2018 (**Figure 1B**). A second dataset of nearly 5,000 samples including tumor/normal WGS and RNA-seq, as well as parental germline WGS, jointly sponsored by GMKF and CCDI (4), along with methylation data for > 1,700 tumors, will be released with no embargo. Additionally, building upon an initial proteogenomic PBTA dataset generated in partnership with the NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC) (5), a large > 400 sample proteogenomic cohort is underway.

In partnership with CHOP's Center for Data Driven Discovery and Biomedicine (D3b) and the NIH GMKF Data Resource Center, the PBTA data has been integrated into cloud-based resources within the GMKF portal (http://kidsfirstdrc.org/) enabling cross-disease analysis with other GMKF datasets or those hosted by NCI's cloud resources, such as TCGA and TARGET. In 2019, Researchers at D3b and Alex's Lemonade Stand Foundation's Childhood Cancer Data Lab launched the Open Pediatric Brain Tumor Atlas (OpenPBTA). OpenPBTA is a first-in-kind, open-science, collaborative analysis and manuscript-writing effort to comprehensively analyze PBTA tumors (6). OpenPBTA openly provides reproducible workflows and processed data on GitHub, PedcBioportal, and CAVATICA supporting multiple research publications as well as informing clinical trial decision-making in molecular tumor boards (7). OpenPBTA's success has paved the way for additional efforts such as OpenPedCan (8) currently informing the new pediatric Molecular Targets Platform (https://moleculartargets.ccdi.cancer.gov/) developed with

the CCDI in support of the Research to Accelerate Cures and Equity (RACE) for Children Act (9) and the Schwannomatosis Open Research Collaborative led by SAGE Bionetworks (10). CBTN promotes releasing data without embargo periods, allowing near real-time integration, dissemination, processing, and sharing of associated petabyte-scale harmonized data.

As of 2022, CBTN has supported 190 data projects and 111 biospecimen projects (**Figure 1C-D**) spanning > 25,000 biosamples. CBTN-collected biospecimens are available for request via a common approval process by both members and non-members. Such common workflows have led to the publication of >100 scientific articles and 25 abstracts in >30 peer-reviewed journals.

CBTN partners across the globe

Embedded in the mission and vision of CBTN is the notion that collaboration is key for accelerated discoveries required to improve clinical outcomes. CBTN has benefitted from many academic, commercial, government, and advocacy partnerships (**Table 1**), empowering both molecularly-based therapeutic development and decision support as part of drug-repurposing initiatives (7) through institutional initiatives and clinical trials, such as the Pacific Pediatric Neuro-Oncology Consortium (PNOC, https://pnoc.us/).

Table 1. Key CBTN Strategic Partnerships Listed below are major national and international partners, their websites, and our collaborative goals.

Key Strategic Partner	Website	Collaborative Mission
Alex's Lemonade Stand Foundation Childhood Cancer Data Lab (CCDL)	https://www.ccdatalab.org/	Accelerate research through reproducible analysis of big data
Appalachian and Inner-city Pediatric, Adolescent, and Young Adult Cancer Data Ecosystem (ACCELERATE) consortium	https://cbtn.org/news/accelerate-consortium-and-pediatric-brain-tumors-across-appalachia	Expand cancer research across the Appalachia, focusing on underserved regions with increased cancer burden
Australia's Zero Childhood Cancer	https://www.zerochildhoodcancer.org.au/	Collaborate and innovate around multi-omic data to personalize treatment for Australian children with cancer
Australian BioCommons	https://www.biocommons.org.au/	Collaboratively create a

		cloud-based computing infrastructure using CAVATICA
Chordoma Foundation	https://www.chordomafoundation.org/	Invest in research to find better treatments, in patient services to create better services, and in healthcare improvement to drive better care
Childhood Cancer Data Initiative (CCDI)	https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative	Harmonize pediatric cancer data and develop platform(s) which will help accelerate cures
Clinical Proteomic Tumor Analysis Consortium (CPTAC)	https://proteomics.cancer.gov/programs/cptac	Layer proteogenomics into multi-omics analyses of pediatric brain tumors
Common Fund Data Ecosystem (CFDE)	https://www.nih-cfde.org/	Enable broad use of common fund funded data
European Union's Horizon 2020 Individualized Pediatric Cure (iPC) program	https://ipc-project.eu/	Collaborate and innovate around multi-omic data to personalize treatment for European children with cancer
Gift From a Child	https://giftfromachild.org/	Support families to empower research through end-of-life tissue donation from their child
Global Alliance for Genomics and Health (GA4GH)	https://www.ga4gh.org/	Develop standards for responsible sharing of genomic and health data
Human Tumor Atlas Network (HTAN)	https://humantumoratlas.org/	Create a pediatric tumor atlas characterizing cells from pre-cancer through various stages of tumor evolution
NF2 Biosolutions	https://nf2biosolutions.org/	Accelerating gene therapy research for Neurofibromatosis Type 2
International Cancer Genome Consortium Accelerating Research in Genomic Oncology (ICGC-ARGO)	https://dcc.icgc.org/	Develop cloud computing solutions to harness cross-study sample integration
International Central Nervous System Pediatric Research Consortium (INSPiRE)	https://commons.cri.uchicago.edu/inspire/	Collaboratively centralize data resources from pediatric CNS tumor consortia worldwide in the Pediatric Cancer Data Commons (PCDC)
Oligo Nation	https://www.oligonation.org/	Develop new treatments for oligodendroglioma
International DIPG/DMG Registry	https://www.dipgregistry.org/	Centralize and standardize the collection of clinical data and tumor samples from DIPG and DMG patients
INvestigation of Co-occurring conditions across the Lifespan to	https://includedcc.org/	Enable cross-cohort study between Down syndrome and

Understand Down syndromE (INCLUDE)		cancer patients
NIH Cloud Platform Interoperability effort (NCPI)	https://anvilproject.org/ncpi	Establish and implement cloud-based interoperability across NIH and other platforms
NIH Gabriella Miller Kids First Pediatric Research Program (Kids First)	http://kidsfirstdrc.org/	Integrate PBTA data within Kids First without embargo
Pacific Pediatric Neuro-Oncology Consortium (PNOC)	https://pnoc.us/	Develop new trials and inform clinical translation
Project HOPE (Pediatric and AYA High-grade glioma Omics ProjEct)	https://braintumor.org/research/workshops-meetings/projects-hope-gbm-care/	Study evolutionary dynamics of high-grade gliomas with single-cell resolution
UCSC Treehouse Childhood Cancer Initiative	https://treehousegenomics.ucsc.edu/	Integrate UCSC as an official data satellite site to enhance data integration

Discussion

CBTN's successes to date are empowered by its commitment to partnering with families and advocates supporting the sharing of biospecimens and data on behalf of accelerating clinical translation. CBTN, together with its partners, has developed a combination of open-science governance and platform resources that support the largest, accessible genomic and proteomic pediatric brain tumor data repository annotated with longitudinal clinical data, pathology reports and histologic images, MRI reports and images, and available biospecimens and preclinical models.

CBTN's support of > 300 research projects generated reagents, models, data, and publications that have, in turn, enriched the CBTN's offerings. Likewise, consortium-wide efforts towards foundational data generation like the PBTA, in combination with cloud-based platforms, support a dynamic research ecosystem that continually increases the volume and rate of brain tumor research, accelerates the development of clinical trials, and provides decision support resources to improve the outcomes of children diagnosed with CNS tumors. Importantly, CBTN is also poised to help support enforcement of the RACE Act (9), which requires companies to test cancer drugs in children that are used in adults when there is a shared molecular target.

The CBTN collaborative framework of governance and paired technology advances rapid data sharing and clinical translation, defining a new model for research that breaks the traditional mold of siloed, individual achievement. Together with the many institutions, patient families, foundations, and community stakeholders, CBTN will improve the outcomes for children affected with brain cancer.

Conflicts of interest

David S. Ziegler is a consultant, or on the advisory board, of Bayer, AstraZeneca, Accendatech, Novartis, Day One, FivePhusion, Amgen, Alexion, and Norgine. Angela J. Waanders is on the advisory board of Alexion and Day One.

Acknowledgments

We would like to thank the patients and families participating in CBTN. CBTN is in large part philanthropically-funded, and we thank each donor for their dedication and support in making the CBTN possible. The following donors have provided leadership level support: Children's Brain Tumor Foundation, Eaise Family Foundation, Kortney Rose Foundation, Lilabean Foundation, Minnick Family Charitable Fund, Perricelli Family, Psalm 103 Foundation, and Swifty Foundation. CBTN's leadership would like to recognize and thank the early leadership and foundational contributions of Drs. Tom Curran, Ph.D., FRS (currently at Children's Mercy Kansas City) and Peter Phillips, M.D. (formerly at CHOP, retired) to the creation of Children's Brain Tumor Tissue Consortium (CBTTC) which has evolved into the Children's Brain Tumor Network (CBTN).

Children's Brain Tumor Network Members

Past and present members of CBTN's Executive Council and CHOP's 's Brain Tumor Board of Visitors who inspired the creation and ensured the sustainability of CBTN are Alan

Stalling, Jr., Al Gustafson, Al Musella, Amanda Haddock, Ammar S. Naqvi, Amy Summy, Amy Weinstein, Amy Wood, Andrea Gorsegner, Anita Nirenberg, Ann Friedholm, Bob Budlow, Caroline Court, Carrie Ann Stallings, Charles Genaurdi, Jr., Daniel Hare, Daniel Lipka, David Bovard, Dean Crowe, Deborah Eaise, Eliza Greenbaum, Gerald Kilhefner, Geralyn Ryerson, Ginny McLean, Graham Cox, Heather Ward, Hank Summy, James Blauvelt, James Minnick, James Ryerson, Jeannine Norris, Jessica Kilhefner, John Nilon, Kevin Eaise, Kim Hare, Kim MacNeill, Kim Wark, Kristen Gillette, Laura Cooke, Leigh Anna Lang, Lisa Ward, Liz Dawes, Mario Lichtenstein, Mark Mosier, Meghan Gleeson, Meghan Gould, Nancy Minnick, Nicole Giroux, Patti Gustafson, Patricia Genuardi, Paula Olson, Paul Touhey, Peter Norris, Richard Haddock, Robert Martin, Sarah Lilly, Scott Perricelli, Stacia Wagner, Stephanie Strotbeck, Stephanie Marvel, Stephan Ward, Sue Perricelli, Susan Funck, Timothy Court, Toni HeadTrisha Danze, W. Craig Marvel, and Wendy Payton.

Past and present members of CBTN who contributed to the generation of biospecimens and clinical and/or genomic data are Adam C. Resnick, Alexa Plisiewicz, Allison M. Morgan, Allison P. Heath, Avi Kelman, Alex Felmeister, Alex Gonzalez, Alyssa Paul, Amanda Saratsis, Amy Smith, Ana Aguilar, Ana Guerreiro Stücklin, Anastasia Arynchyna, Andrea Franson, Angela J. Waanders, Angela N. Viaene, Anita Nirenberg, Anna Maria Buccoliero, Anna Yaffe, Anny Shai, Anthony Bet, Antoinette Price, Arlene Luther, Ashley Plant, Augustine Eze, Bailey K. Farrow, Baoli Hu, Beth Frenkel, Bo Zhang, Bonnie Cole, Brian M. Ennis, Brian R. Rood, Brittany Lebert, Carina A. Larouci, Carl Koschmann, Caroline Caudill, Caroline Drinkwater, Cassie N. Kline, Catherine Sullivan, Chanel Keoni, Chiara Caporalini, Christine Bobick-Butcher, Christopher Mason, Chunde Li, Claire L. Carter, Claudia MaduroCoronado, Clayton Wiley, Cynthia Wong, Dan Kolbman, David E. Kram, David Haussler, David Pisapia, David S. Ziegler, Denise Morinigo, Derek Hanson, Donald W. Parsons, Elizabeth Appert, Emily Drake, Emily Golbeck, Ena Agbodza, Eric H. Raabe, Eric M. Jackson, Erin Alexander, Esteban Uceda, Eugene Hwang, Fausto Rodriquez, Gabrielle S. Stone, Gary Kohanbash, Gavriella Silverman,

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