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# CHILDHOOD BRAIN CANCER: A GIVING SMARTER GUIDE

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## FOREWORD

In my years as a pediatric neurologist, I have cared for thousands of children with brain tumors and have likely designed more than 100 therapeutic studies. I have seen many of my patients survive and thrive but, all too many times, have seen children lose their battles or suffer long-term, devastating aftereffects. However, there is now a palpable excitement in the field because of all the new insights, the burgeoning field of immunotherapy, and availability of amazing, novel technologies.

Current federal funding for childhood brain tumor research is falling woefully short of what is needed to advance progress. Industry partners are hesitant because they consider pediatric studies as financially riskier and a poor return on investment, especially for application in newly recognized, even rarer primary brain tumors. For all these reasons, philanthropy has become critical to promote and expedite more effective therapeutic approaches.

Philanthropists, many of them with first-hand experience of how devastating brain cancer can be, have been stepping in to fill the funding gap, but much more is desperately needed. New funding avenues are, of course, needed to support procurement and operation of new (expensive) technologies, and the time needed for investigators to focus efforts on these challenges. But most essential of all is the role that philanthropy can play in promoting the incorporation of novel approaches, expediting more high-reward investigations, opening up new avenues to work with industry, and enabling focus on rarer poorly understudied and treated tumor types.

If used appropriately and creatively, philanthropy can help break down institutional silos, facilitate collaboration across sites nationally and internationally, increase the critical mass of researchers focusing on brain tumors, and avoid unnecessary duplication of efforts. Philanthropy can be the stimulus to focus research on neglected tumor types, research that often has generalizable benefit, while promoting and expediting novel transformational approaches without sacrificing scientific validity.

If philanthropic investments are used appropriately, outcomes should be tangible and measurable. The gains made through these investments should be sustainable, generalized to others battling the disease, and, most importantly, meaningful for children affected and their families. As a researcher who has had an opportunity to shape the field, I truly see amazing new opportunities to quickly change how childhood brain tumors are managed and positively impact the quality of life of survivors. Although I remain haunted by the system's failures, I am energized by the growing cadre of dedicated scientists who have entered the field motivated to make outcomes better, not only incrementally but exponentially, and the opportunity for philanthropy to make this possible.

### **Roger Packer, MD**

Director and Chief, Brain Tumor Institute

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## EXECUTIVE SUMMARY

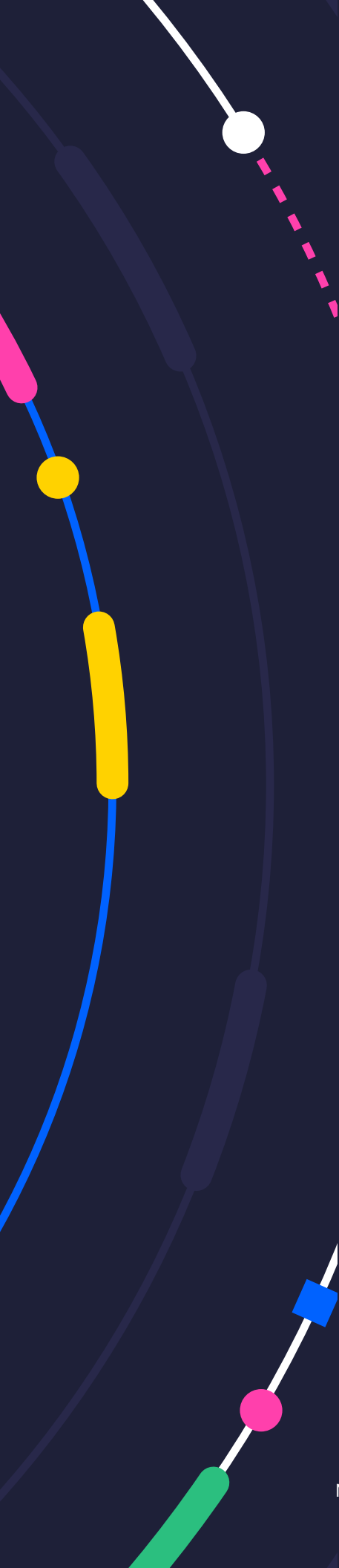
Pediatric brain cancer accounts for 16 percent of all new childhood cancer diagnoses, making it one of the most common cancer diagnoses in children and adolescents. Brain cancer is also the leading cause of cancer death within this age group. Because brain cancer is further subdivided into more than 12 types and more than 100 subtypes, it is complex and rare, requiring additional research and patient samples to understand each diagnosis fully. The five-year relative survival rate is approximately 75 percent, but outcomes vary widely. Some slow-growing tumors have survival rates of around 95 percent, while for some brain cancer types, such as diffuse midline glioma, the median duration of survival from diagnosis is nine months, and only 10 percent of patients live longer than two years.

Unlike adult bodies, children's bodies continue to develop while in treatment. Because many current treatment strategies impact dividing cells, therapeutic intervention can uniquely damage children and lead to significant long-term morbidity. Greater than 95 percent of childhood cancer survivors will have a significant health-related issue by the age of 45, and one-third of survivors experience cognitive impairment. Families bear the enormous financial burden of initial treatment and long-term management of pediatric cancer patients, an extraordinary hardship, especially when one in five children in the US diagnosed with cancer already lives in poverty. One in four families loses more than 40 percent of their household income due to treatment-related work disruption, and parents of long-term childhood cancer survivors report lower household income and higher risk of poverty.

Pediatric brain cancers have been historically treated similarly to adult brain cancers, but assessment of the genetic underpinnings of childhood brain tumors has revealed significant differences from those diagnosed in adults. As researchers better define pediatric brain cancers, opportunities for pediatric cancer-specific therapy development are increasing. Unfortunately, the field still lacks cancer-appropriate tools to assess promising therapies.

Additionally, significant systemic challenges must be overcome in terms of research and drug development for ultra-rare cancers. Federal funding of pediatric brain cancer is 20 percent of total brain cancer research funding, and because of the small population size, market potential is low. Thus, pharmaceutical interest in drug development for pediatric brain cancers is limited. Philanthropy has and will continue to play a significant role in pushing research in this field forward.

This Giving Smarter Guide describes the primary scientific and infrastructure needs and opportunities for philanthropists considering entering the pediatric brain cancer research field. Philanthropic capital is critical in addressing gaps not covered by federal or commercial funders. Particularly in rare diseases, philanthropy can (1) seed



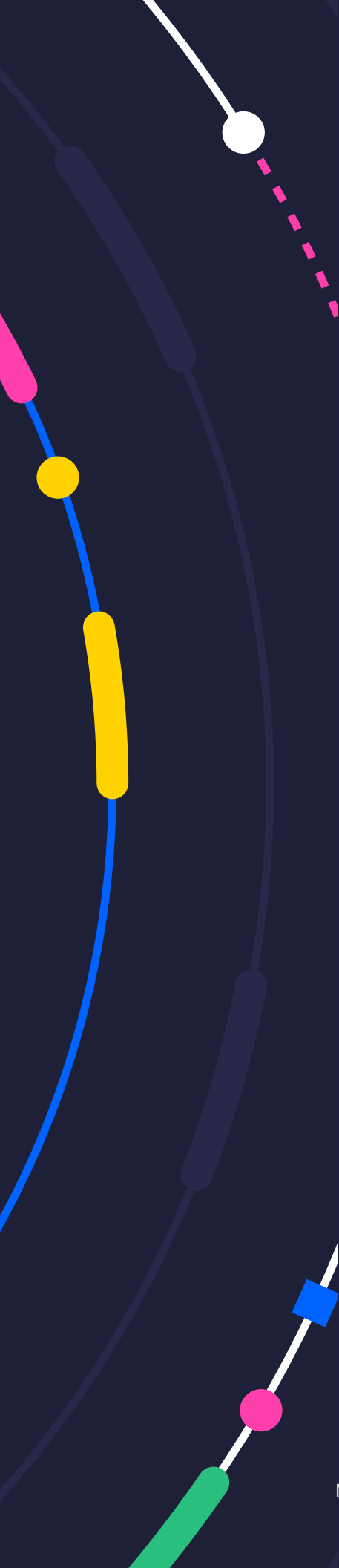
research efforts with high promise, providing researchers with the initial data and tools they need to pursue additional funding, (2) de-risk novel therapeutics to garner commercial interest, (3) establish and support a collaborative research infrastructure, and (4) foster the next generation of pediatric brain cancer-focused experts.

## Philanthropic Opportunities to Address Scientific and Systemic Needs

The opportunities outlined in this Giving Smarter Guide were informed by a thorough review of the scientific literature, an examination of public and private funding patterns, an in-depth analysis of the therapeutic pipeline, and conversations with stakeholders across the pediatric brain cancer and rare disease ecosystems. These stakeholders include foundations, advocates, researchers, clinicians, data scientists, and industry members representing biotechnology and pharmaceutical companies and clinical research organizations. Through this deep due diligence effort, the MI Philanthropy identified seven areas for philanthropic investment that, if realized, will build on the meaningful strides made so far and catalyze further progress in pediatric brain cancer, especially within the constantly evolving field of rare and less well-understood subtypes.

### SCIENTIFIC OPPORTUNITIES

1. **Enhance knowledge of molecular subtypes and etiology**, especially for rare pediatric brain tumors. Advocating for tissue donation and insisting on collaborative data collection and sharing are critical roles for philanthropy, which can support large-scale, collaborative initiatives.
2. **Develop a research toolkit that enables discovery and translational research**. The field needs models that effectively recapitulate the tumor in its native environment and incorporate models into efficient screening platforms. Philanthropy can bridge the gap by funding resource development.
3. **Identify therapeutics that cross the blood-brain barrier and technologies that can enhance drug delivery to the brain**. Philanthropists can address challenges to therapy delivery to the brain by supporting projects that aim to develop brain penetrant therapies or resources that promote and confirm delivery of the therapeutic to the tumor.

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4. **Expand and improve the safety and efficacy of the therapeutics toolbox.** Philanthropic capital is risk capital that can fund promising research that develops targeted therapies, explores a rational selection of combinations to reduce recurrence, and leverages immunotherapy in a way that overcomes the suppressive immune microenvironment that is unique to the brain.

## SYSTEMIC OPPORTUNITIES

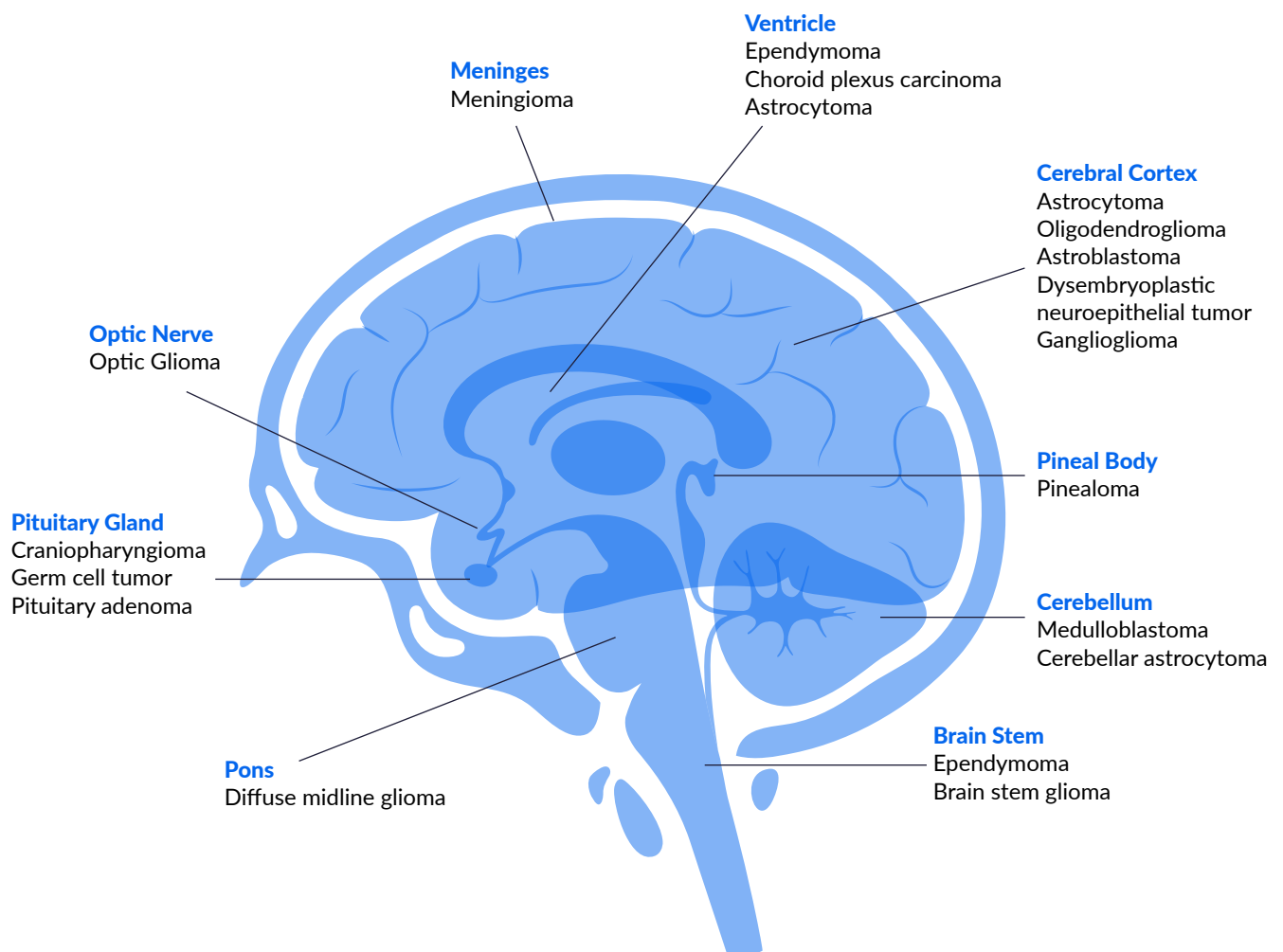
5. **Facilitate the development of innovative clinical trial protocols and platforms.** Philanthropists are uniquely positioned to require the implementation of novel protocols by investigators seeking funding and advocate for regulatory consideration of disease-appropriate protocols and endpoints.
6. **Drive collaboration between academia and industry and incentivize drug development for pediatric brain cancer.** There is an opportunity to convene stakeholders in the drug development space and to strategically support collaborative research, which has had marked success in other research fields.
7. **Incentivize collaboration and foster the development of early-stage investigators who have diverse and multidisciplinary backgrounds.** Philanthropists should promote mentoring relationships within and outside of investigators' fields, provide seed funding for innovative, cross-departmental and -institutional work, and be risk-tolerant in identifying and funding young, investigator-driven, collaborative research.

# OVERVIEW OF PEDIATRIC BRAIN CANCER

## Characteristics and Epidemiology

Despite the fact that brain cancer is the greatest contributor to cancer mortality in children and teens, science is only beginning to understand the molecular drivers of childhood brain cancer, and very little is known about the factors that contribute to risk. There is a wide range of pediatric brain cancers, each named according to several factors, including the type of cell from which they develop, the area of the brain where they are found, and their genetic features (Figure 1).

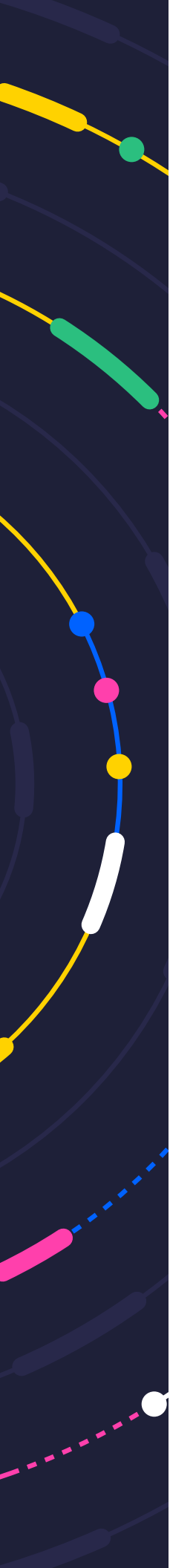
**Figure 1: Childhood Brain Tumor Types and Locations**



*Note: This is a non-exhaustive overview of types of pediatric brain tumors that highlights the predominant tumor locations within the brain.*

*Source: Goldman (2017), Albright (1993), Borgenvic (2021)*





Brain cancers are broadly classified as either (1) benign, or nonmalignant, or (2) malignant. Among the major pediatric brain tumor types are gliomas, embryonal tumors, choroid plexus tumors, and mixed glial and neuronal tumors.

Pediatric brain cancers can be difficult to identify and diagnose in children because their symptoms can be confused with those of other conditions. Because the brain functions differently by region, symptoms depend on the location of the tumor. Some of the most common symptoms include headaches; unexplained nausea or vomiting; abrupt and unexpected onset of vision problems, such as double vision; seizures; abnormal eye movement; difficulties with swallowing, walking, or balance; confusion; memory issues; or personality and/or behavior changes.

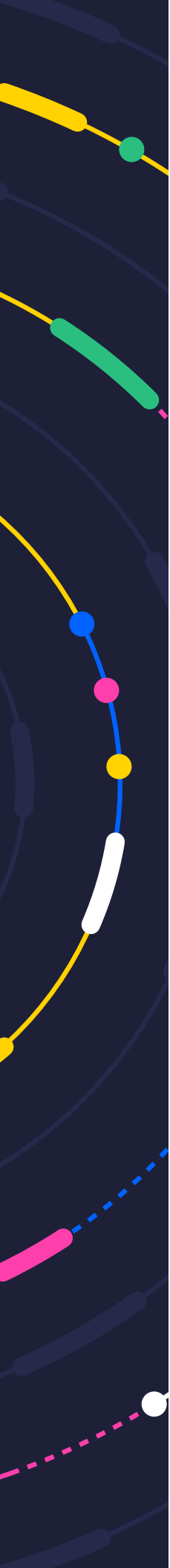
Young children tend to be diagnosed with tumors in the cerebellum, which can block the flow of fluid to the brain, resulting in a condition called hydrocephalus, a buildup of fluid in the ventricles of the brain. Hydrocephalus can lead to elevated pressure and symptoms like headaches, vomiting, and difficulty with balance. Tumors that grow in the brainstem, the lower part of the brain that is connected to the spinal cord and responsible for the body's automatic functions, tend to result in difficulty swallowing, balance and coordination issues, and facial weakness.

The outlook for children diagnosed with brain tumors can vary dependent on tumor location, age at diagnosis, race, ethnicity, and gender. Childhood brain tumors are most frequently diagnosed in children ages five to nine and are more common in non-Hispanic White populations than non-Hispanic Black, Asian/Pacific Islander, American/Indian Alaska Native, or Hispanic populations. Despite higher incidence in non-Hispanic White populations, the death rate for pediatric brain tumors is highest in non-Hispanic American/Indian Alaska Native populations. Although brain cancer-related mortality decreased by 2.5 percent from 1969 to 1978 and 0.9 percent from 1978 to 2007, survival improvements have stagnated since 2007.

## Etiology

The established risk factors for childhood brain cancer are few. Although several genetic studies have been performed in adults, far fewer have been conducted in children with cancer, limiting understanding of factors that contribute to genetic predisposition. Approximately 4 percent of childhood gliomas are attributable to single-gene disorders or inherited genetic cancer syndromes. Approximately 5–10 percent of children and adolescents diagnosed with brain and other central nervous system (CNS) tumors have a family history.

Nonhereditary risk factors may also contribute to the development of certain childhood brain tumors. Despite many being assessed, only two are consistently validated: (1) ionizing radiation and (2) structural congenital disabilities. Ionizing radiation can lead to DNA damage and is known to have cancer-causing effects in adults and children. Children are more radiosensitive than adults; their cells divide at an increased rate during development and are more likely to be



impacted by the mutagenic effects of radiation. Treatment of early-onset cancers with radiation that includes brain exposure, such as acute lymphoblastic leukemia or medulloblastoma, correlates with an increased risk of brain cancer.

Studies have also linked prenatal exposure to radiation from maternal diagnostic tests during pregnancy to an increased risk of brain cancer in the child. Approximately 7 percent of pediatric brain tumors are associated with structural birth defects, for example, cleft palate, heart defects, and missing limbs. There is an even higher risk associated with birth defects specifically seen within the CNS or with neurological anomalies. Notably, children with birth defects tend to be diagnosed with astrocytoma, medulloblastoma, and ependymoma earlier than those without structural birth defects.

Further large-scale, collaborative genetic studies will be required to understand better the etiology of pediatric brain cancers, especially those that are rare. Because this is a heterogeneous disease type, it will be challenging to identify risk factors without a concerted, systematic analysis of high-quality genetic and environmental data as well as data available from cancer and birth defect registries, which must all be publicly available.

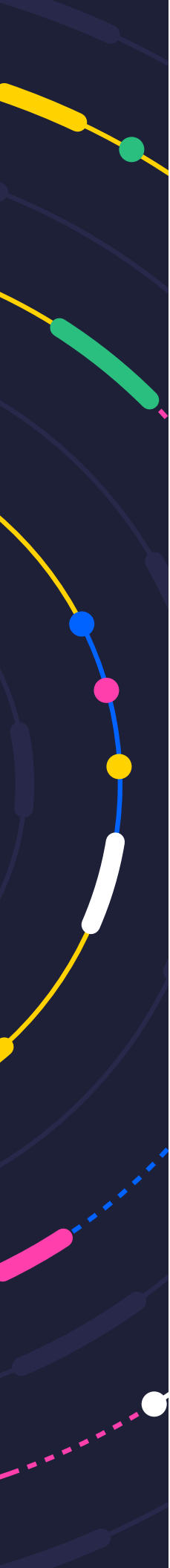
## Disease Pathways

### BIOLOGY REFRESHER: GENES AND PROTEINS

*Deoxyribonucleic acid (DNA)* is a molecule that contains the instructions (genetic information) required for producing the machinery that drives the development, functioning, growth, and reproduction of organisms. *Ribonucleic acid (RNA)* carries the instructions from the DNA to the site where proteins are made within the cell. Proteins are the machinery that is encoded by the DNA and performs the functions of the cell, ultimately contributing to the development and activity of an organism.

When DNA is altered or the amount of RNA produced or its ability to deliver the instructions from the DNA changes, proteins may be made incorrectly so that they either overperform or underperform, or too few or too many are produced. This “aberrant” activity can lead to changes in how the cell performs its function. If changes occur in proteins that manage cell growth, death, and development pathways, then cell division can become uncontrolled, appropriate cell function can be lost, and a tumor can develop.





Unlike adult tumors, which are characterized by point mutations, pediatric cancers are more commonly the result of rearrangements of large segments of DNA, known as somatic structural variants, which may include deletions, insertions, and translocations. Translocations are often seen in childhood brain cancers. These occur when a large section of DNA breaks off and then attaches to another section of DNA. This mixing of genetic material can result in proteins that do not perform their normal functions, which can lead to improper cell growth, death, and differentiation.

Dozens of somatic structural variants can be found in a given pediatric brain tumor, and the number and type of variants differ according to tumor type. The impact of all of the changes that have been identified in many brain cancers is not fully understood, and they warrant further exploration to establish novel pediatric brain cancer drivers.

## Diagnosis

The path to a pediatric brain cancer diagnosis begins with the identification of initial symptoms and then the integration of a range of procedures, which include the following:

- **Neurological exam.** This set of tests may involve checking vision, hearing, balance, coordination, strength, and reflexes. Different symptoms revealed by such assessments can help the doctor identify the part of the brain in which the tumor is growing.
- **Imaging.** The use of sophisticated imaging techniques enables doctors to visualize the location and size of the brain tumor. Technologies such as magnetic resonance imaging (MRI), computerized tomography (CT), and positron emission tomography (PET) rely on structural and functional differences between normal tissue and tumor tissue in the brain to view the tumor.
- **Lumbar puncture/spinal tap.** Cerebral spinal fluid (CSF) surrounds the brain, and spinal cord and brain cancer cells can slough off of the primary tumor and travel to the CSF. Additionally, brain tumors release molecules into the CSF that can be identified with specialized technologies such as genetic sequencing. A needle inserted into the spinal canal can collect CSF for identification of cancer markers. This is a form of liquid biopsy.
- **Biopsy.** With the variety of brain tumors, each characterized by different cellular and molecular features that can contribute to differences in prognosis and treatment strategy, this is the most accurate diagnosis based on analysis of the tumor tissue itself. The removal of tumor tissue for pathological assessment is called a biopsy.

Pathologists study tissue to diagnose tumors, using resources such as the World Health Organization (WHO) Classification of Tumors to support their determination of a diagnosis. The most recent (fifth edition) of the WHO classification of tumors, produced in 2021, is the first to address pediatric tumors in a volume separate from adult tumors. Table 1 reflects the range of diagnoses presented in the WHO classification of pediatric brain tumors.

**Table 1: Classification of Pediatric Brain Tumors**

Tumor Category	Tumor Family	Tumor Type
Gliomas, glioneuronal, and neuronal tumors	Pediatric-type diffuse low-grade gliomas	Diffuse astrocytoma, MYB or MYB1-altered
		Angiocentric glioma
		Polymorphuous low-grade neuroepithelial tumor of the young
		Diffuse low-grade glioma, MAPK pathway-altered
	Pediatric-type diffuse high-grade gliomas defined by H3 status	Diffuse midline glioma, H3K27-altered
		Diffuse hemispheric glioma, H3G34-mutant
		Diffuse pediatric-type high-grade glioma, H3-wild-type and IDH-wild-type
		Infant-type hemispheric glioma
	Circumscribed astrocytic gliomas	Pilocytic astrocytoma
		High-grade astrocytoma with piloid features
		Pleomorphic xanthoastrocytoma
		Subependymal giant cell astrocytoma
		Astroblastoma, MN1-altered
	Glioneuronal and neuronal tumors	Ganglioglioma
		Desmoplastic infantile ganglioglioma/Desmoplastic infantile astrocytoma
		Dysembryoplastic neuroepithelial tumor
		Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
		Diffuse leptomeningeal glioneuronal tumor
		Multinodular and vacuolating neuronal tumor
	Ependymal tumors	Supratentorial ependymoma
		Supratentorial ependymoma, ZFTA fusion-positive
		Supratentorial ependymoma, YAP1 fusion-positive
		Posterior fossa ependymoma
Posterior fossa ependymoma, Group PFA		
Posterior fossa ependymoma, Group PFB		
Spinal ependymoma, MYCN-amplified		
Myxopapillary ependymoma		
Choroid plexus tumors	Choroid plexus papilloma	
	Atypical choroid plexus papilloma	
	Choroid plexus carcinoma	

**Table 1: Classification of Pediatric Brain Tumors (continued)**

Tumor Category	Tumor Family	Tumor Type
Central nervous system (CNS) embryonal tumors	Medulloblastomas, molecularly defined	Medulloblastoma, WNT activated
		Medulloblastoma, SHH-activated & TP53 wild-type
		Medulloblastoma, SHH-activated & TP53-mutant
		Medulloblastoma, non-WNT/non-SHH
	Medulloblastomas, histologically defined	Medulloblastomas, histologically defined
	Other CNS embryonal tumors	Atypical teratoid/rhabdoid tumor
		Cribiform neuroepithelial tumor
		Embryonal tumor with multilayered rosettes
		CNS neuroblastoma, FOXR2-activated
		CNS tumor with BCOR internal tandem duplication
CNS embryonal tumor not otherwise specified		
Pineal region tumors		Pineoblastoma
Melanocytic tumors		Meningeal melanocytosis and melanomatosis
Tumors of the sellar region	Pituitary endocrine tumors	Pituitary adenoma/PitNET
		Pituitary blastoma
	Craniopharyngiomas	Adamantinomatous craniopharyngioma

Source: Pfister (2022)



## Treatment

Pediatric brain tumor treatment has relied on surgery, chemotherapy, and radiation therapy for decades, often based on treatment paradigms used in adult brain cancers. Although these general techniques have been utilized for a long time, considerable advances within these techniques have occurred during the past decades. Additionally, engagement of a multidisciplinary team of specialized clinicians ensures that appropriate expertise is incorporated into the planning and implementation of an overall treatment strategy. Consideration of the tumor location, grade, and histology is integrated into decisions about the combination of techniques to be integrated into the therapeutic plan for a given patient.

### TRADITIONAL CHILDHOOD BRAIN CANCER TREATMENT STRATEGIES

**Surgery.** The pediatric neurosurgeon on the team provides insight into the possible surgical procedures based on the size and location of the brain tumor. If the tumor is located in a region of the brain accessible to the neurosurgeon, there is a significant benefit to removing as much tumor as possible because remaining cells can reestablish the tumor. In areas where separating the tumor from surrounding tissue is more challenging, or where the tumor is located near sensitive areas of the brain, technological innovations are enabling removal of as much tumor as possible while minimizing damage to normal brain tissue. The use of imaging technology such as MRI during surgery enables neurosurgeons to perform safer and more precise resection of the tumor. Special dyes that light up the tumor can also be used in conjunction with imaging to improve visualization of the tumor. Neurosurgeons can also be assisted by robotic systems that provide increased control and precision. Surgical techniques that do not require a knife are becoming more commonplace as neurosurgeons engage MRI-guided, high-intensity laser probes to precisely target laser-generated heat into a tumor, killing cancer cells and sparing surrounding brain tissue.

**Chemotherapy.** Chemotherapy is the use of drugs to kill tumor cells. These drugs target features of cancer cells that make them unique from most normal cells, such as their high rate of replication and increased mutations. The selection of chemotherapeutic or combination of chemotherapeutics depends on the tumor and overall treatment strategy.

**Radiation Therapy.** Radiation uses beams of high energy, such as X-rays or protons, to damage the DNA of cancer cells. Because cancer cells already have a high burden of DNA damage and are less efficient at repairing damage than normal cells, they are more significantly impacted by this damage, which leads to cell death. Fractionated radiotherapy, that is, dividing the dose of radiotherapy over the course of several days or weeks, is most commonly used in pediatric brain tumors because it produces a lower dose of radiation while increasing the probability of specifically hitting tumor cells during cell division and sparing normal tissue. Radiation therapy is usually avoided in patients younger than three years to limit damage that might affect brain development.

## THE EVOLVING TREATMENT LANDSCAPE

As reflected in prior sections of this report, a deeper understanding of the molecular characteristics of different childhood brain tumors opens the doors for new treatment modalities that more precisely target the mechanisms that make these cancers malignant. Such therapies, called targeted therapies, aim to reduce side effects and long-term effects resulting from chemotherapy and address tumors that have limited therapeutic options and poor prognosis.

Two molecular-targeted therapy options are approved for treatment of childhood brain tumors:

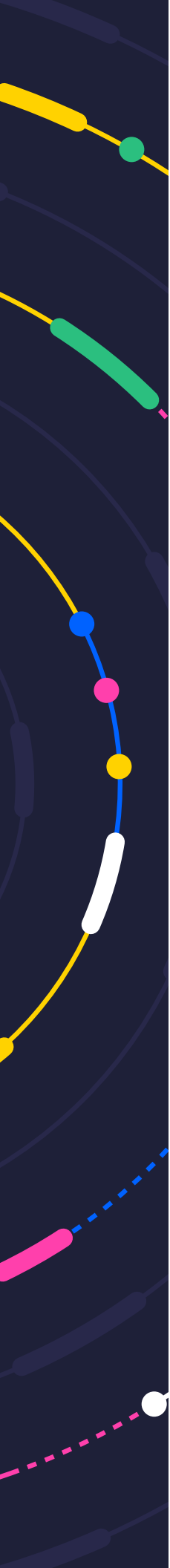
- Everolimus (Afinitor) was approved in 2012 to treat a rare low-grade glioma called subependymal giant cell astrocytoma. A form of everolimus, sold under the brand name Afinitor Disperz, was the first approved pediatric-specific dosage form developed for the treatment of a pediatric tumor. Everolimus blocks the mammalian target of the rapamycin (mTOR) pathway that is overactivated in the setting of altered MAPK signaling. Everolimus reduces cell growth, proliferation, and survival in cancers with mTOR activation.
- Dabrafenib (Tafinlar) and trametinib (Mekinist) combination therapy was approved in 2023 for the treatment of children with low-grade glioma (LGG) with BRAF V600E mutation. These drugs impact proteins within the pathway that are disrupted when BRAF is mutated. This combination is approved as a first-line treatment, meaning that children with BRAF V600E LGG can take this combination therapy without first undergoing other treatments with potentially higher toxicity, such as chemotherapy. Additionally, the liquid formulation of this combination enables its use in children as young as one year.

## CLINICAL TRIALS IN PEDIATRIC BRAIN CANCER

Pediatric brain cancer survival rates have improved minimally over the past 20 years. To move out of the lab and into patients, promising treatment strategies must be assessed through a set of human safety and efficacy studies called clinical trials. As one indicator of the need for new therapeutic options in pediatric cancers, in the US, more than half of pediatric cancer patients are estimated to receive treatment on a therapeutic clinical trial compared to only 6 percent of adults with cancer. This difference can be attributed to the suboptimal nature of standard therapies for pediatric cancer, especially if the cancer has returned after initial treatment. Enrollment is even higher for many brain tumor patients with limited treatment options, such as those with high-grade gliomas or ultra-rare tumors.

Traditionally, clinical trials are divided into four phases where the primary information learned from one phase determines whether the therapy will continue into the next phase. Because pediatric brain tumors are rare, the format of clinical trials, which has traditionally required hundreds of patients, must be flexible and employ innovative approaches to ensure that safety and efficacy of new therapies are established with fewer patients.





The pediatric brain cancer clinical trial landscape presented in this guide is informed by an assessment of the brain cancer clinical trials on [clinicaltrials.gov](https://clinicaltrials.gov) for which children are eligible. It reveals mixed phases and smaller patient numbers than are traditionally seen in adult cancer clinical trials (**Figure 3**). Phase I/II clinical trials not only incorporate safety assessment and determination of the best dose of a new treatment but also test how well the cancer responds to the new treatment. Although currently implemented in only 1 percent of pediatric clinical trials, likely because very few late-stage clinical trials are being conducted in pediatric brain cancer, Phase II/III clinical trials require fewer patients and may accelerate the time to approval of the new therapy by assessing the efficacy of a therapy, comparing it with the standard of care, and gathering additional information on safety and side effects all in a single phase.

Additional clinical trial design innovations will be required to enable the efficient and effective conduct of trials in pediatric brain cancer, as it is a rare childhood disease. There are some examples of such designs in current clinical trials. Still, they will need to become more mainstream, and additional updates will be required as our understanding of these cancers better defines personalized therapeutic strategies. Innovative designs that are being implemented in clinical trials now include:

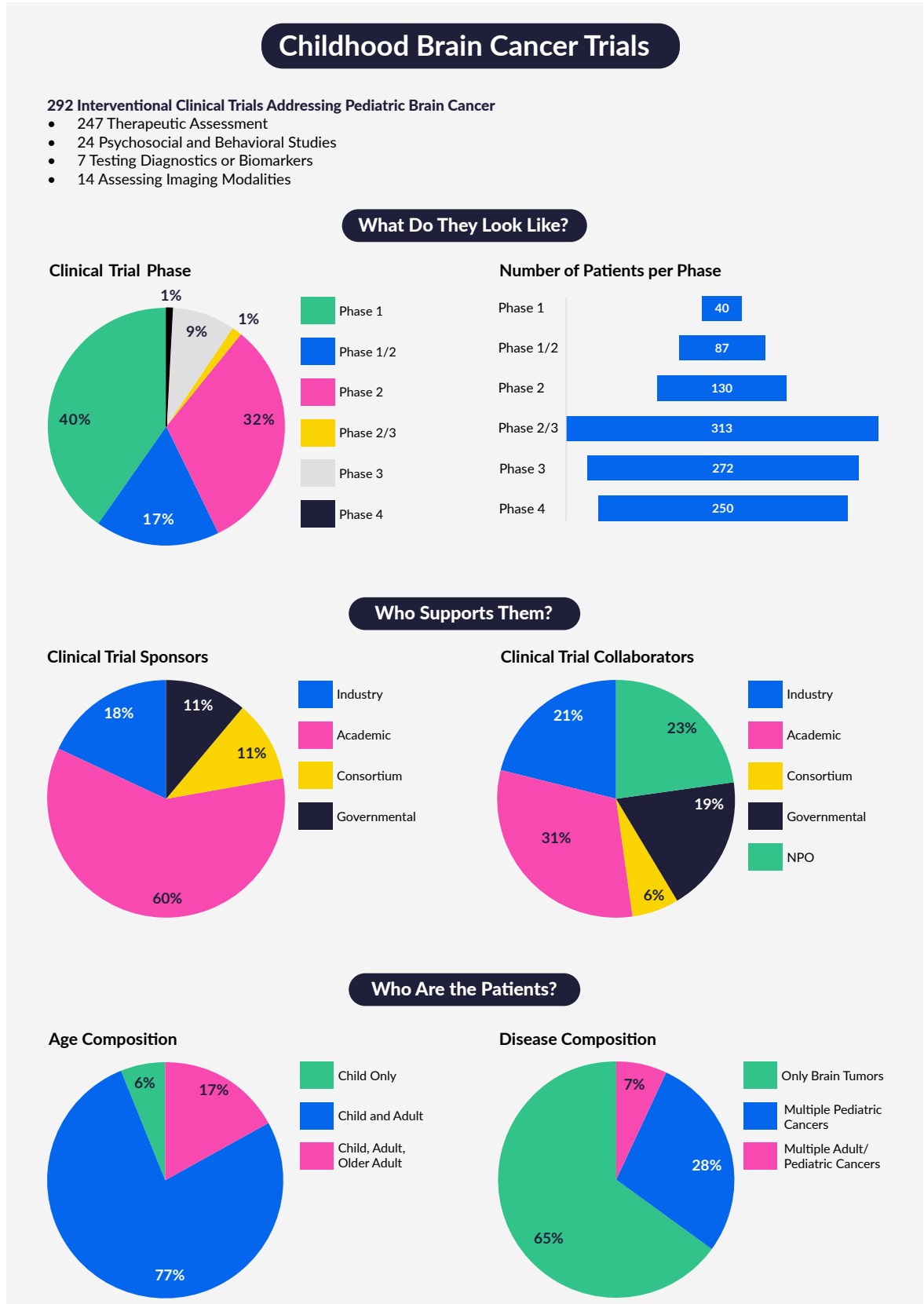
**Risk-Adapted Clinical Trial Approaches.** Not all patients or tumors require the same amount or duration of therapies. Especially when considering therapeutic toxicities, there are times when “less means more” in terms of therapeutic administration. Risk-adapted therapy administration strategies assess adaptations that can be made to treatment based on prognostic risk.

**Adaptive Trials.** Clinical trials that implement adaptive designs enable modifications to the clinical trial or statistical analysis of the trial either as the result of external information or a review of data from the ongoing trial.

**Basket Trials.** A basket trial tests a therapy in different cancers with the same mutation/target. Because these trials require fewer patients with a specific diagnosis, they can assess rare tumor types more efficiently.

**Umbrella Trials.** An umbrella trial assesses a therapy’s effectiveness in patients with the same type of cancer but different mutations/targets. Here, patients are stratified into subgroups based on the molecular alterations in their tumors. Because they enable simultaneous evaluation of several treatment options, umbrella trials may facilitate testing and approval of new drugs. Additionally, because the provision of multiple therapy options is inherently flexible, umbrella trials offer a better risk/benefit ratio for trial participants.

Figure 3: The Pediatric Brain Cancer Clinical Trial Landscape



Note: NPO=nonprofit organization

Source: Milken Institute analysis, Clinicaltrials.gov (2023)

Analysis of the clinical trial landscape answers important questions about pediatric brain cancer clinical trials. Understanding the landscape enables researchers to identify trends and opportunities for improvement in therapeutic development.

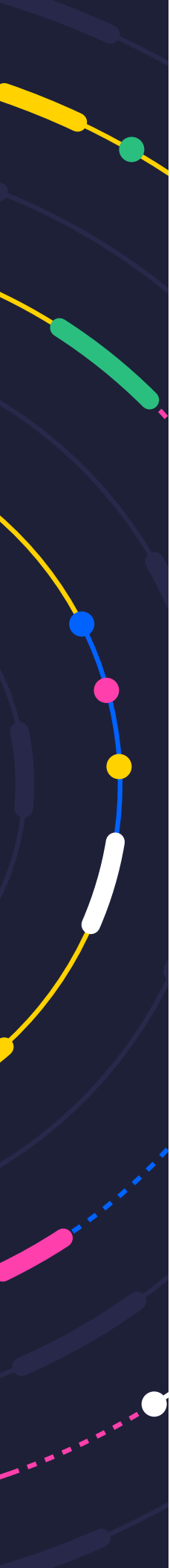
## WHAT IS BEING ASSESSED IN PEDIATRIC BRAIN CANCER CLINICAL TRIALS?

The clinical trial landscape presented in this report focuses on interventional clinical trials that include childhood brain cancer patients; the clinical trial search was performed in January 2023. In an interventional clinical trial, participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on health-related outcomes. Of the 292 interventional clinical trials for which brain tumor patients aged 0–17 are eligible, 85 percent (245) are testing therapies. The therapeutic settings are broadly classified into seven groups (Table 2), with the most prevalent therapeutic trials assessing combination therapies (38 percent) and new agents (27 percent).

**Table 2: Pediatric Brain Cancer Therapy Settings**

Therapy Setting	Percent of Total Therapeutic Clinical Trials	Description
Combination Therapy	38%	A therapy that combines more than one medication or modality. For example, use of therapies that target different pathways to reduce therapeutic resistance and recurrence.
New Agent	27%	Assessment of a single therapeutic agent that is not FDA-approved. For example, a novel anti-cancer vaccine.
Repurposing of Approved Drug	21%	Testing an agent in a disease other than the one for which it is FDA approved. For example, testing a therapy that is approved for treatment of leukemia in glioma.
New Device	2%	Use of a device that is intended to directly treat a disease. For example, MRI-guided laser ablation to kill cancer cells.
New Therapeutic Delivery Method	4%	Assessment of a drug or device that assists in the delivery of a therapeutic across the blood-brain barrier or to the tumor site. For example, the use of focused ultrasound to open the blood-brain barrier for delivery of a drug that is not brain penetrant.
New Radiation Therapy	6%	Testing a new or improved radiation therapy regimen, type, or delivery method. For example, peptide receptor nucleotide therapy.
Molecularly-Directed Targeted Therapy	2%	Identification and administration of one of a set of targeted agents based on the molecular characterization of a tumor. For example, a trial with several therapeutic options available, one of which is selected based on the driver of the patient's specific cancer.

Source: Milken Institute analysis of [clinicaltrials.gov](https://clinicaltrials.gov) (2023)



There are two primary drivers of combination therapies in pediatric brain cancer. The first centers on the idea that, because cancers are heterogeneous and individual cancer cells can rely on multiple protein or pathway alterations, combining drugs that target more than one mechanism of malignancy will increase the probability that all of the cells within the tumor are killed. Further, this treatment paradigm may use lower doses of each drug than would be required as a single agent.

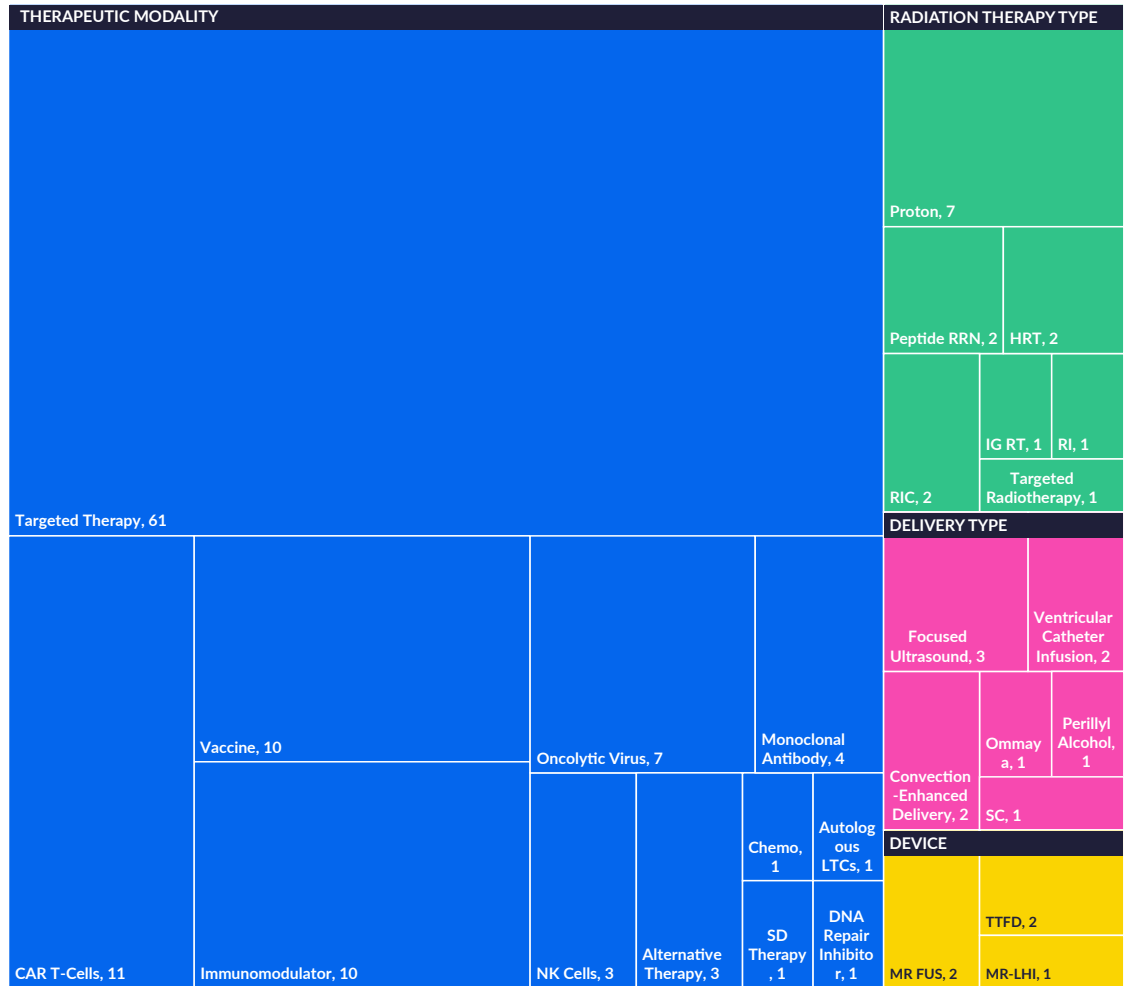
The second addresses the cancer cell's ability to develop resistance to a therapy over time. When a cancer stops responding to a therapy, it is because a survival response in cancer cells allows them to adapt and escape the cancer-destroying effects of the drug. Administration of a combination therapy that increases tumor cell killing can minimize the likelihood of drug resistance by hitting two different mechanisms at once. With each new rationally selected therapy used, the cancer cell would have to develop a new resistance mechanism to break through growth inhibitory effects.

Among the non-combination therapeutic modalities in clinical trials for pediatric brain cancer (Figure 4), some of the most prevalent are targeted therapies and immunotherapies. Targeted therapies are administered according to our understanding of the patient's specific tumor and aim to reverse molecular changes that drive malignancy. Immunotherapy is a treatment that activates the patient's immune system to fight cancer. Human immune systems are designed to identify and destroy foreign molecules and abnormal cells. In fact, human immune systems destroy precancerous cells regularly when they begin to express abnormal proteins.

When a cancer cell is able to evade immune detection, it grows into a tumor. Tumors produce factors that deaden the antitumor immune response and enhance the activation of immune cells that can promote tumor growth. Immunotherapy can boost or alter how the immune system works to specifically enhance its ability to identify and destroy cancer cells. An immunotherapy can be produced that either stimulates the natural defenses of a patient's immune system or replicates immune system components so that it better finds and attacks cancer cells.

Although the growing number of clinical trials addressing pediatric brain cancer is exciting, the vast majority of these clinical trials are early-phase trials (89 percent, Phase I, I/II, II), many of which will not progress into Phase III. In fact, generally 70 percent of drugs in Phase I move on to Phase II, 33 percent of drugs in Phase II move on to Phase III, and 25 percent of drugs in Phase III are approved, translating to a 6 percent success rate. To increase the number of therapeutics that move into late-phase clinical trials, thoughtful research must occur before a therapeutic even moves into clinical trials. This research will require models that appropriately recapitulate the range of pediatric brain tumors within their normal immune environment, drug screening platforms that enable the assessment of a wide range of therapies in combination, feedback of clinical trial data back into the preclinical research system, and continued improvements in the understanding of the molecular characteristics of brain cancer subtypes that enable the integration of some of the exciting big data approaches, such as machine learning, into therapy identification and development.

**Figure 4: Therapeutic Modalities in Clinical Trials**



Notes: Acronyms—autologous lymphocyte transfer cells (autologous LTCs), sonodynamic therapy (SD therapy), peptide receptor radionucleotide (peptide RRN), hypofractionated radiotherapy (HRT), radioimmunoconjugate (RIC), image-guided radiotherapy (IG RT), re-irradiation (RI), SonoCloud (SC), magnetic resonance focused ultrasound (MR FUS), tumor treating field device (TTFD), MRI-guided laser heat ablation (MR-LHA)

Source: Milken Institute analysis of clinicaltrials.gov (2023)



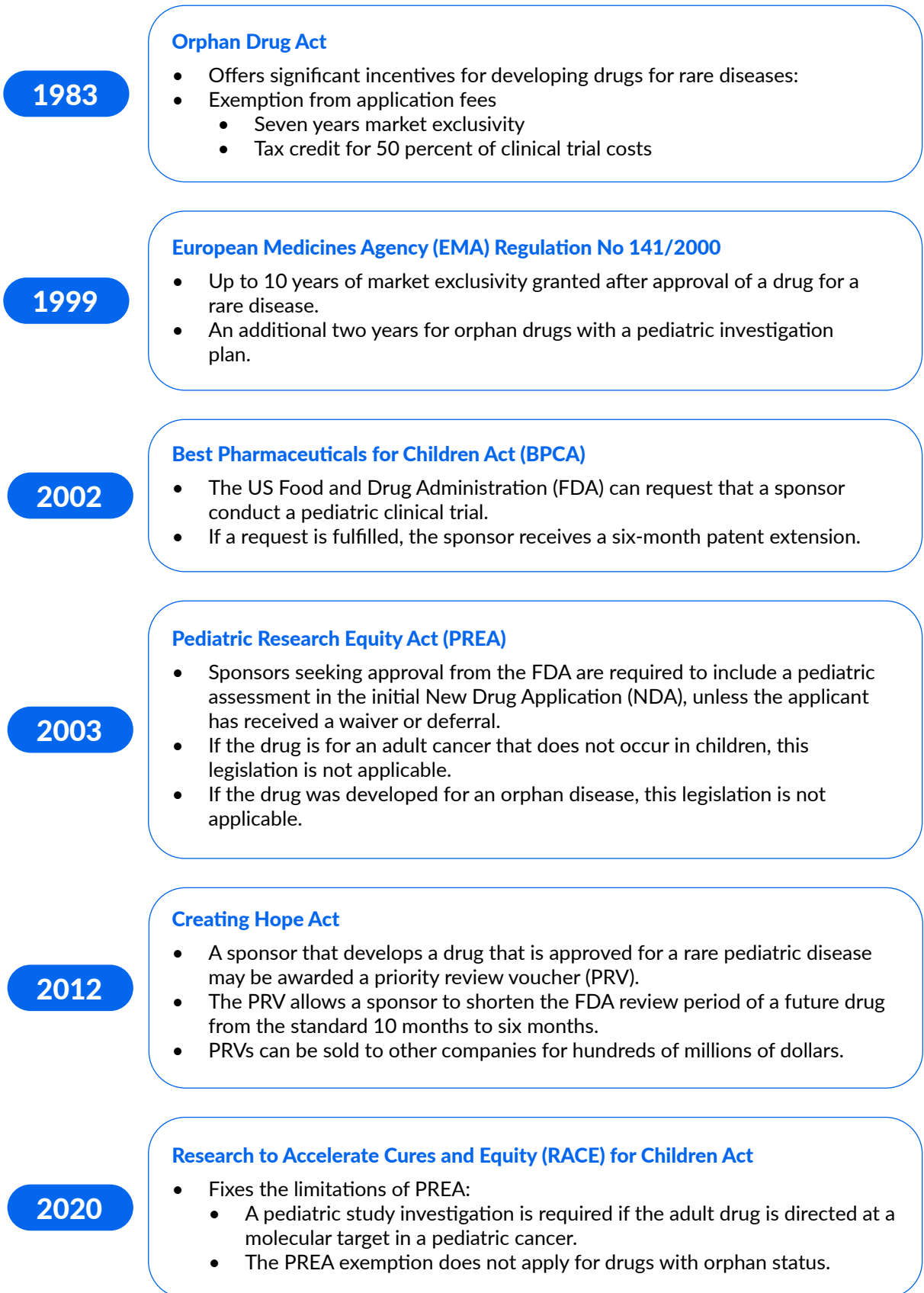
## WHO SUPPORTS PEDIATRIC BRAIN CANCER CLINICAL TRIALS?

Pediatric brain cancer clinical trials are unique in that the small number of patients requires collaborative infrastructure and concerted funding efforts. Because drugs that are approved for diseases with fewer patients have a smaller market and make less money, the high cost of research and development for a cancer drug—\$648 million on average—is difficult for industry to justify. Although the US Food and Drug Administration (FDA), spurred by patient advocates, has developed regulatory incentives to promote drug development in pediatric and rare diseases (Figure 5), industry involvement in pediatric cancer clinical trials is still low.

Overall, industry sponsors 33 percent of adult oncology trials and only 17 percent of pediatric oncology trials. Pediatric brain cancer clinical trials track well with overall pediatric cancer trials, with 18 percent industry sponsorship. A clinical trial sponsor is the organization that oversees or pays for a clinical trial and collects and analyzes the resulting trial data. Notably, for pediatric brain cancer clinical trials, when industry is the trial sponsor, greater than 60 percent of the time, other entities also contribute to funding. These collaborating entities include nonprofit organizations, academic institutions, governmental entities, and clinical trial consortia.

**Nearly a fourth of pediatric brain cancer clinical trials receive funding from nonprofit organizations, indicating the impact of philanthropy on pediatric brain cancer drug development.**

**Figure 5: Pediatric Oncology Regulatory Landscape**



Source: Barry (2021), Wang (2021)

## WHAT ARE THE CHARACTERISTICS OF PATIENTS PEDIATRIC BRAIN CANCER CLINICAL TRIAL PARTICIPANTS?

In addition to the innovations in clinical trial design that have been reviewed in this document, sponsors can broaden clinical trial eligibility to expand the clinical trial patient population. A review of the age composition of pediatric brain cancer clinical trials reveals that only 6 percent of clinical trials for which children, defined as birth to age 17 years, are eligible *only* recruit children. In 77 percent of trials, children and adults (age 18–64) are eligible; even a trial with a maximum age of eligibility of 18 will still include adults on [clinicaltrials.gov](https://clinicaltrials.gov), so the number of truly pediatric cancer-specific clinical trials may be higher than noted in this assessment. In 17 percent of trials, older adults (age 65+) are also eligible for participation. These trials are likely focused less on childhood-specific cancer and more on a target that is shared by adult and childhood cancers or brain cancers in children and adults that are more similar histologically.

Clinical trials for which children with brain cancer are eligible also demonstrate a range of disease eligibility. Although a significant proportion of clinical trials address only brain tumors (65 percent and could include children and adults), over one-fourth are trials that address non-CNS pediatric cancers (e.g., osteosarcoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma), and 7 percent include a mixture of non-CNS adult (e.g., lung, colorectal, cervical) and pediatric cancers.

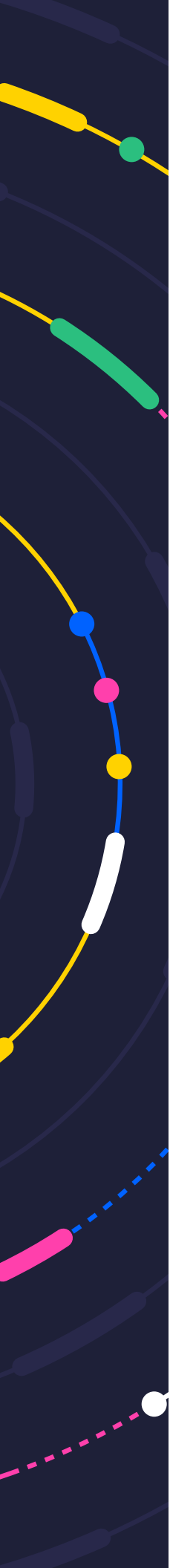
## The Impact of Brain Tumor and Treatment on Psychological Well-Being

All cancer patients and their families experience distress as the result of a cancer diagnosis, the cancer itself, and treatment. Brain cancer patients feel these more acutely. As a result of the growth of the tumor within the brain and the impact of the treatment on the brain, a childhood brain tumor diagnosis means that the cancer itself results in psychological and neurocognitive effects. Without intervention, many of these effects will not resolve when the cancer is gone. Survivors are more susceptible to long-term effects on cognition, mood, and personality. Patients with brain tumors suffer from a high rate of psychiatric and psychological disorders in addition to challenges with memory, attention, and concentration.

Tumor growth itself leads to changes in mood and cognition, but so do the most common brain cancer treatments: surgery, radiotherapy, and chemotherapy. Notably, pediatric brain tumor patients have higher rates of psychological distress, depression, fatigue, insomnia, and daytime sleepiness than other cancer patients. Therefore, the need for psycho-oncological care is high in these patients. Fortunately, intervention and even prevention are possible when identified early and treated properly.

Routine assessment of the psychological and neurocognitive well-being of pediatric cancer patients—especially adolescents—throughout treatment, as well as the incorporation of complementary therapies into treatment, can assist the physician’s ability to look after the





patient's physical and mental well-being. Complementary therapies such as music and art therapy, massage, physical activity, and nutrition guidance can help reduce the side effects of cancer treatment, improve physical and emotional well-being, and enhance recovery. Child life specialists provide therapeutic play opportunities to children, enabling them to express their feelings creatively during treatment. Psychologists can offer children and families the opportunity to discuss their feelings in association with the diagnosis. All of these elements are critical to the patient experience, especially for a child undergoing such a life-altering diagnosis.

Many of these resources, though, are not reimbursed by insurance. Hospitals that provide these services often raise philanthropic funds to offset the cost. Philanthropic support ensures uninterrupted care and long-term programs that treat children and build an evidence base of the critical nature of these resources for cancer outcomes. Every children's hospital should strive to offer these programs to patients. Evidence to support their necessity to payers will promote equity for all children diagnosed with pediatric brain cancer.

Long-term cognitive problems, called cognitive late effects, must also be managed after the patient has completed treatment and throughout the rest of their life. Risk factors associated with progressive cognitive decline in childhood cancer survivors include complications during surgery, high radiation dose, large volume radiation, and methotrexate chemotherapy. Many of these factors will become less impactful as innovations in neurosurgery and radiation techniques and supplementation of chemotherapy for more targeted therapies are integrated into treatment. However, more than 115,000 survivors of pediatric brain cancer in North America live with cognitive late effects. Until treatment paradigms change, more survivors will need support navigating the impact of brain cancer therapy.

Fortunately, in addition to efforts to reduce exposure to therapies that can lead to cognitive late effects, significant efforts are being made to address prevention currently in clinical trials. Of the 24 psychosocial and behavioral clinical trials addressed in the childhood brain tumor clinical trial analysis, 14 are assessing interventions aiming to improve cognitive function.

# PEDIATRIC BRAIN CANCER RESEARCH FUNDING

## Federal Funding

The world's largest public funder of biomedical research is the National Institutes of Health (NIH), contributing more than \$32 billion each year to scientists in the US and internationally. The National Cancer Institute (NCI), established under the National Cancer Institute Act of 1937, is the federal government's principal cancer research funding agency within the NIH and the largest funder of cancer research in the world. NCI-funded research projects are publicly available and searchable through the NCI Funded Research Portfolio. Assessment of projects funded by the NCI in the most recent fiscal year with data (2018) that address *only* brain cancer reveals 384 research projects amounting to nearly \$147 million in funding. Of these projects, only 17 percent address childhood brain cancer, accounting for 20 percent of total extramural brain cancer-specific research funding (\$30,287,841).

The Cancer Moonshot, initially funded through the 21st Century Cures Act passed in 2016, engaged experts within the cancer research field to develop a report on future priorities for cancer research. Among the 10 research recommendations presented, one focused specifically on childhood cancers: *Intensify research on the major drivers of childhood cancers*. Based on the recommendations, 12 research initiatives were developed. Among those, two specifically focus on pediatric cancer: (1) improve our understanding of fusion oncoproteins in pediatric cancer and use new preclinical models to develop inhibitors that target them and (2) generate a cancer immunotherapy research network to overcome challenges in the development of immunotherapies for childhood cancers.

Moreover, the fiscal year 2022 spending bill provides funding for critical childhood cancer initiatives focused on sample and data collection and analysis (Figure 6). These large-scale investments can be attributed, in large part, to committed and sustained advocacy for increased federal funding led by parent-led groups and pediatric cancer-focused advocacy organizations.

Notably, the efforts listed here primarily focus on sample and data acquisition. These are essential to an understanding of the basic biology of pediatric cancers and align with the NIH mission to seek fundamental knowledge about health and disease. This type of research forms the foundation for therapeutic development in childhood cancer, but efforts to address pediatric cancers are divided among 12 major types of pediatric cancer, only one of which is brain cancer. Moreover, these initiatives do not address the higher-risk, costly research associated with drug discovery and preclinical testing.

**Figure 6: Childhood Cancer Initiatives Funded in Fiscal Year 2022 Childhood Cancer**

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

- Funding: \$30M
- Expand existing efforts to collect biospecimens, relevant clinical, biological, and demographic information for childhood cancer patients enrolled in NCI-sponsored clinical trials
- Authorize grants to state cancer registries to identify and track childhood, adolescent, and young adult cancer incidence
- Enhance research on the late effects of childhood cancers

**Childhood Cancer Data Initiative (CCDI)**

- Funding: \$50M
- Gather data from every child, adolescent, and young adult diagnosed with a childhood cancer
- Create a national strategy of appropriate clinical and molecular characterization to speed diagnosis and inform treatment for all types of childhood cancers
- Develop a platform and tools to bring together clinical care and research data that will improve preventive measures, treatment, quality of life, and survivorship for childhood cancers

**Gabriella Miller Kids First Research Act (Kids First)**

- Funding: \$12.6M
- Support childhood disease research with a focus on childhood cancer and structural birth defects
- Identify children with childhood cancer and structural birth defects and their families for whole genome sequencing performed by the Kids First sequencing centers
- Develop the Gabriella Miller Kids First Data Resource, a large-scale database of clinical and genetic data from patients with childhood cancers and structural birth defects and their families

Source: *Children's Cancer Cause* (2022)



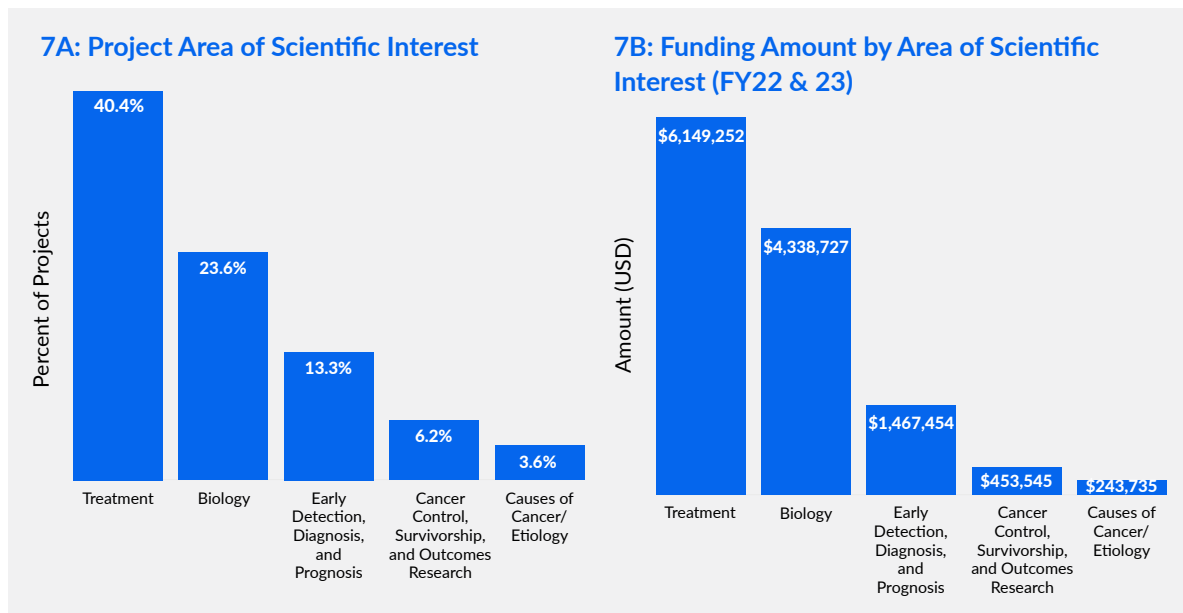
## Nonprofit Funding

Because pediatric brain cancer is an orphan disease, many children within the patient community and their families have experienced inefficiencies in the pediatric brain cancer funding and research landscapes. Responding to significant needs for improving diagnosis, treatment, and lifelong health for childhood brain cancer patients, a multitude of pediatric cancer foundations support brain cancer research as well as pediatric brain cancer-specific nonprofit organizations.

The most comprehensive understanding of the landscape is derived from childhood cancer collaboratives that unite the efforts of pediatric cancer foundations. The Coalition Against Childhood Cancer (CAC2) is a collaborative network of childhood cancer-focused nonprofits, corporations, and individuals from 39 states and nine countries. As a reflection of the breadth of this community, CAC2 comprises 131 member organizations that drive efforts in one or more of five pillars: Advocacy, Awareness, Research & Treatment, Family Support, and Survivorship. Thirteen of these organizations focus specifically on pediatric brain cancer. However, many organizations not specifically focused on brain cancer do, in fact, fund pediatric brain cancer research. Eighty-four of the CAC2 member organizations fund research efforts.

Another resource for assessing nonfederal cancer research funding is the International Cancer Research Partnership (ICRP), an alliance of cancer research organizations from Australia, Canada, France, Japan, the Netherlands, the United Kingdom, and the United States. These organizations share funding information to enhance global collaboration and strategic coordination of research between individual researchers and organizations. In 2018, the ICRP made a concerted effort to differentiate childhood and adult cancer research funding and expand membership and data collection from pediatric cancer research funders. Although the data collected by the ICRP do not reflect all pediatric brain cancer funding by nonprofit entities, they provide a representative cross-section of 19 nonprofit organizations funding 87 total pediatric brain cancer research projects in 2022 and 2023. Notably, greater than 40 percent of supported projects are focused on treatment development, toward which approximately half of funding is dedicated (Figure 7), and nearly 22 percent are clinical trials. These values indicate that the philanthropic space recognizes the need for therapeutic development for patients with pediatric brain cancer.

**Figure 7: Pediatric Brain Cancer Nonprofit Funding Priorities**



Source: Milken Institute analysis of ICRP database (2023)

Nearly a quarter of clinical trials in pediatric brain cancer are receiving nonprofit funding. Forty-five nonprofit organizations (Appendix) are supporters of current pediatric brain cancer clinical trials compared to 11 foundations supporting adult brain cancer clinical trials. Among some of the most well-known funders focused specifically on pediatric brain cancer, the average grant size per year is \$105,000, with an average grant duration of two years, based on publicly available data. Generally, these grants are focused on seed funding of promising research and investigators as well as translational research, ensuring that the best ideas have the initial funding needed to demonstrate feasibility and apply for more substantial and long-term federal funding.

This dynamic and varied funding environment offers benefits for pediatric brain cancer research. Benefits include diverse thought, the ability to address the many needs of the field, and the infusion of family and patient experience into funding strategy. However, the funding ecosystem will lack cohesion and efficiency until the funding landscape is clarified and foundations delineate and share their priority research areas and funding levels. Continued collection and sharing of funding data from players in this ecosystem will benefit both funders and researchers, fostering collaboration and reducing duplicative efforts.

# SCIENTIFIC AND SYSTEMIC NEEDS AND OPPORTUNITIES

MI Philanthropy identified three scientific and three systemic barriers hindering scientific and therapeutic research progress in pediatric brain cancer. An infusion of focused and sustained financial support will have a significant impact.

## Scientific Needs

### **I. An in-depth understanding of the molecular characterization of all pediatric brain tumors is required for biomarker and therapy development as well as identification of risk factors.**

The range of pediatric brain cancer types, subtypes, and molecular mechanisms is wide, which means that an already rare diagnosis is being further subdivided and that more work will be required to understand the biology of these cancers fully.

Data are key. There is a need to collect diverse, longitudinal patient tumor samples. As appropriate and applicable, samples (e.g., tumor, blood, CSF) should be collected at diagnosis, after each treatment, after each recurrence, and post-mortem. Samples should be immediately analyzed based on the most up-to-date technology, and data—including deidentified clinical data—should be included in databases that are openly accessible by the wider research community.

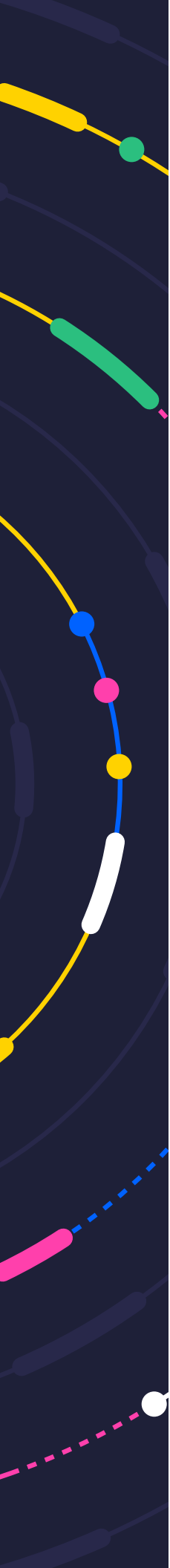
The remaining samples should be saved in the event of subsequent molecular characterization advancements. Iterative and integrated analysis of complementary and complex data streams should be performed. International collaborative initiatives should be prioritized for data collection, analysis, and sharing to reduce duplication of efforts and better harmonize data.

Representative models and preclinical platforms are needed to assess therapies. Patient tumor samples should be developed into cell models, including next-generation models such as organoids, and patient-derived xenograft animal models. Given the unique microenvironment of the brain, models should approximate the tumor microenvironment as closely as possible. Preclinical screening platforms should integrate systems biology approaches to better leverage data obtained as the result of drug screens.

#### **PHILANTHROPIC OPPORTUNITY #1**

*Enhance knowledge of molecular subtypes and etiology, especially for rare pediatric brain tumors.*

Advocating for tissue donation and insisting on collaborative data collection and sharing are critical roles for philanthropy, which can support large-scale collaborative initiatives. The collection and analysis of sufficient numbers of samples to provide a thorough understanding of pediatric brain cancer requires significant and long-term collaboration among research



and medical institutions. Inherent in that collaboration are open data and resource sharing. An effective model for collaborative biorepository networks is the “hub and spoke” model, whereby a central repository (hub) collects and compiles samples and data from institutional collaborators (spokes). This model ensures standardized processing of samples and harmonization of data so that data provided by different institutions can be directly compared. This is especially important when international institutions contribute data.

One challenge of the hub and spoke model relates to the ability of the hub to maintain sustained funding sources. Lulls in funding can result in a backlog of sample analysis, which delays access to datasets critical to research. Although the federal government awards grants to these central core facilities, the funds are not sufficient to maintain all activities of the center and to spur innovation and scope expansion. External sustained funding that enables flexibility can fill gaps in federal funding, ensuring the continued activity of collaborative initiatives.

Within institutions, securing funding for sample and data collection beyond that necessary for diagnosis can also be challenging. Samples must be collected expediently and processed for submission to the central hub. These additional steps require coordination at the collection site as well as dedication to standard operating procedures. Philanthropy can advance tissue collection at the institutional level by providing the funding needed for clinical research coordinators and resources dedicated to facilitating tissue donation and processing and drive institutional interest in collaborating within a tissue network.

An additional benefit of philanthropy is its ability to leverage funding terms to ensure that data sharing is a priority, supplying support to activities that promote collaboration, and making funding contingent upon open data sharing.

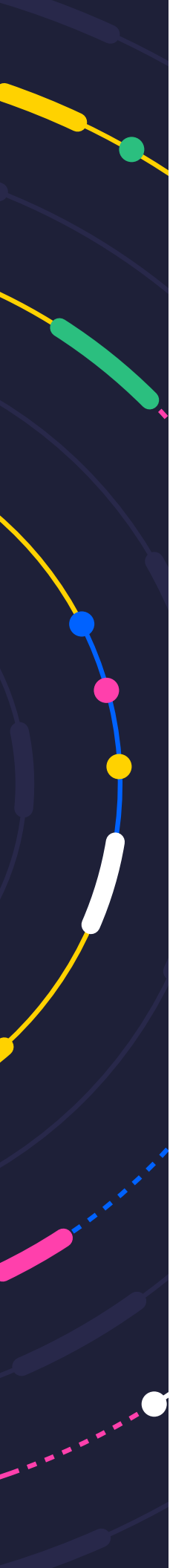
## PHILANTHROPIC OPPORTUNITY #2

*Develop a research toolkit that enables discovery and translational research.*

The field needs models that effectively recapitulate the tumor in its native environment and the incorporation of models into efficient screening platforms. Philanthropy can bridge the gap by funding resource development.

Within this challenge and building on the successes of Philanthropic Opportunity #1 is the development of accurate models that can be employed for discovery and preclinical research. The next generation of cell and animal models is being derived from patient tumor samples, so sample collection and analysis are key to a researcher’s ability to develop these research tools. Even models that are not directly developed from patient tumor samples require a detailed understanding of the basic biology of tumors that is acquired through the compilation of pediatric brain cancer data.

Moving beyond sample collection and analysis, model development and characterization require significant researcher time and effort. Next-generation cell models such as organoids, spheroids, and cocultures can more accurately reflect the cellular composition of tumors.



Protocols for developing these models are not one-size-fits-all and can require significant time and effort to optimize depending on the tumor type.

Animal models include patient-derived xenografts (animals with patient cancer cell implants) and genetically engineered mouse models (animals with pro-cancer mutations and pathway alterations that can model tumorigenesis). These tools play a critical role in the assessment of therapeutics prior to clinical trials in human patients; therefore, these models must replicate the disease condition and microenvironment as closely as possible.

Moreover, because a single model will never perfectly represent the human condition, a combination of models is needed to ensure a more fulsome view of the clinical situation. Therefore, more models that are highly characterized to improve understanding of results are especially needed in a disease represented by such heterogeneity. Large-scale model development centers integrate specialized tools and reagents, expertise, and samples and biological information to create models that the broader community can use. Centralization of all of these resources requires significant funding that can be provided in a more strategic and unencumbered manner by philanthropy.

## **II. Tactical treatment planning and a range of options are required to address a heterogeneous disease located within a particularly delicate organ.**

The brain is an extraordinarily difficult organ to treat because it is delicate and performs complex activities.

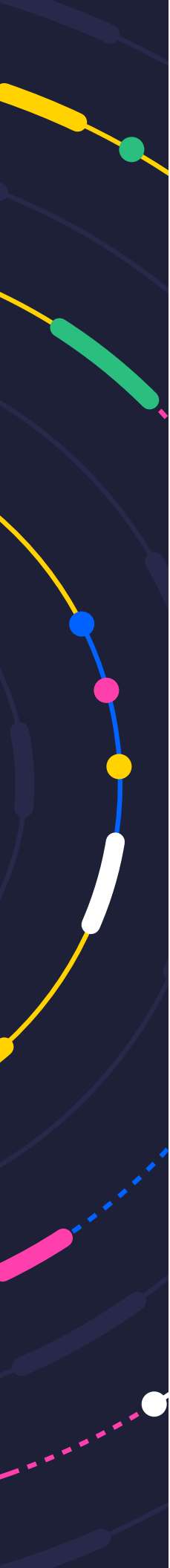
There are significant challenges to surgical removal and radiotherapy within a delicate and indispensable organ. Innovations in neurosurgical methods and a better understanding of the negative impacts and mitigation factors related to radiotherapy are essential.

This field requires continual innovation to ensure the maximal removal of cancer while sparing normal tissue. Integration of imaging technologies will continue to benefit the field, as will the use of robotics in surgery. Critically, process and outcome data collection and analysis will contribute to the field's evolution as new procedures are tested. Successful innovations should be published immediately to share progress across the field.

The blood-brain barrier complicates therapeutic delivery. Biopsy has improved the understanding of drug access to the brain, and researchers are careful in the design and selection of therapeutics for brain cancer. However, highly effective drugs cannot be used if they cannot pass the blood-brain barrier.

Needed are additional efforts to design brain-permeable therapies. Because they are larger in size, immunotherapies are especially excluded by the blood-brain barrier. The development of safe and effective methods for the delivery of therapies across the blood-brain barrier will expand the therapeutic options available for use in brain cancer.





The brain has its own immune system, separated from that of the rest of the body by the blood-brain barrier. This neuro-immune system functions differently from the immune system throughout the rest of the body. The brain decreases inflammatory responses to protect itself, but this limits the response of immune cells to brain tumors. Moreover, tumors further deaden the immune response. CAR T-cell therapies and other immunotherapies have been extensively studied in cancers outside of the brain, both in children and adults. Still, we need to understand better the unique response of the brain and brain tumor to immunotherapies and how that response can be boosted against the cancer while maintaining the safety of the brain.

### PHILANTHROPIC OPPORTUNITY #3

*Identify therapeutics that cross the blood-brain barrier and technologies that can enhance drug delivery to the brain.*

Philanthropists can address challenges to therapy delivery to the brain by supporting projects that aim to develop brain penetrant therapies or resources that promote and confirm delivery of the therapeutic to the tumor.

Innovation will be a key element for quick movement beyond the status quo in terms of neurosurgical innovation and drug delivery. Innovations that will accelerate the field to a point where the long-term cognitive effects of brain tumor treatment are reduced, both through improving surgical techniques and delivering therapies directly to the tumor where they will be more effective, urgently need more funding. This type of research spans a gap between federal funding and implementation within clinical trials.

Without philanthropic seed funding, researchers in academia and start-ups and biotechs find it difficult to develop the evidence base needed to achieve interest from investors. Being more risk-tolerant, philanthropy provides an important bridge toward device and procedural development.

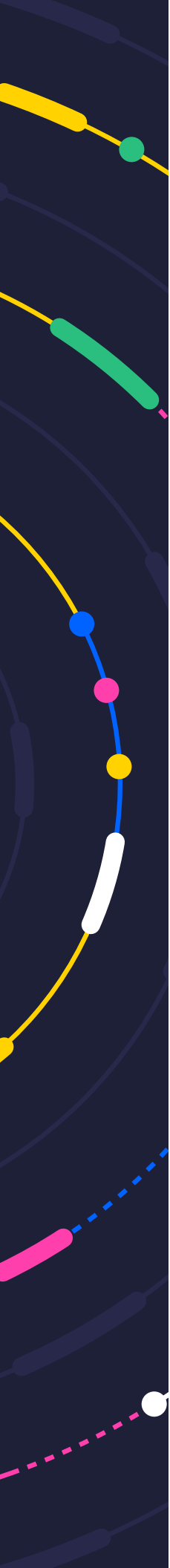
### III. Therapeutic safety, not just efficacy, is paramount in this population.

The brains and bodies of pediatric patients are developing, and they will live with the impacts of their treatments later in life. Therapies must be not only effective but also assessed for long-term toxicity.

The development of therapies that address pathways unique and specific to the cancer will be key for enhancing safety and improving outcomes by enabling appropriate dosing and combination of therapies. Also needed is a better understanding of the long-term impacts of immunotherapy on pediatric cancer survivors. Patients who have received immunotherapy—a relatively new field—will need to be monitored across decades to understand better how immunotherapy treatment impacts the body over the long term.

### PHILANTHROPIC OPPORTUNITY #4

*Expand and improve the safety and efficacy of the therapeutics toolbox.*



Philanthropic capital is risk capital that can fund promising research that develops targeted therapies, explores a rational selection of combinations to reduce recurrence, and leverages immunotherapy in a way that overcomes the suppressive immune microenvironment that is unique to the brain.

When a translational funding gap exists, promising treatments fail to move from the lab into clinical trials. If a therapeutic has limited market potential, this gap becomes nearly insurmountable, which is often the case for rare diseases such as pediatric brain cancer. Funding is required to support preclinical and early-phase clinical research to determine proof of concept.

This de-risking process is one for which flexible, patient, risk-tolerant philanthropic capital is uniquely positioned to address. When deployed strategically to address gaps in the therapeutic development pipeline, such capital enables promising research to generate evidence of a return on investment if pursued by industry. Targeted therapies, immunotherapies, and devices could redefine pediatric brain cancer research but will require strategic and sustained funding. Not all avenues will be successful, but all will build the knowledge base contributing to the advancement of the pediatric brain cancer therapeutic landscape. Philanthropic support should be provided with the implicit understanding that these discoveries must be open access for the betterment of the field.

## Systemic Needs

### IV. An antiquated clinical trial structure does not suit rare disease populations.

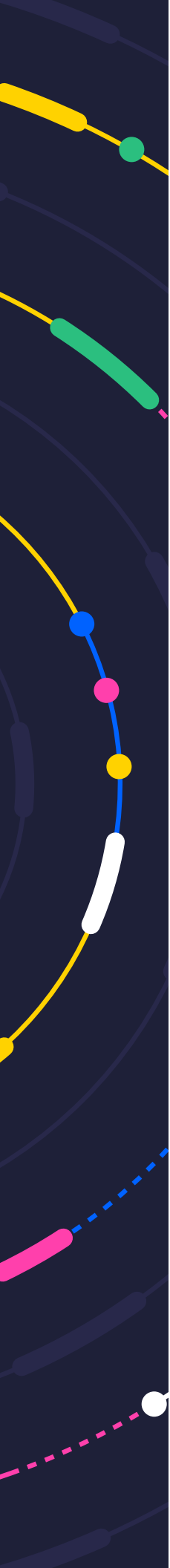
Innovations in clinical trial design are essential to ensuring proper therapeutic selection earlier and in a smaller population.

The system used to assess therapies in patients, the clinical trial, was developed to test treatment strategies for large populations of patients with common diseases. The public became more aware of this system during COVID when millions of patients had the same infectious disease. A single trial requires hundreds of patients, yet, only a few hundred children are diagnosed with a disease in a year. Needed is innovation in trial design to reduce the number of patients required and hasten the speed of the trial so that promising drugs can reach more children faster.

#### PHILANTHROPIC OPPORTUNITY #5

*Facilitate the development of innovative clinical trial protocols and platforms.*

Philanthropists are uniquely positioned to require the integration of novel protocols by investigators seeking funding and to advocate for regulatory consideration of disease-appropriate protocols and endpoints.



Innovative designs, such as adaptive platform clinical trials, as well as integration of a tumor board (i.e., a group of doctors and other health-care providers who meet regularly to discuss cancer cases and share knowledge) into the clinical trial selection process would greatly benefit patients with individualized therapeutic needs. The optimal trial design would feed preclinical and prior clinical data into a tumor board, whose members would use those data to identify the most appropriate treatment within a platform trial. Biomarker integration that enables rapid understanding of the tumor's response to a therapy, and the subsequent ability to shift patients to new treatment options when one fails to work, would greatly benefit the trial. The collection of correlative data (i.e., markers associated with clinical activity and/or therapeutic bioactivity and mechanism of action) is important to improve further clinical development and help researchers understand why therapeutics do or do not work in certain patient populations. The collection of this type of secondary data during a clinical trial is often underfunded but significantly influences the speed and efficiency with which a therapy can move into later-stage trials and the marketplace as it provides evidence of the activity and mechanism of a therapeutic in patients.

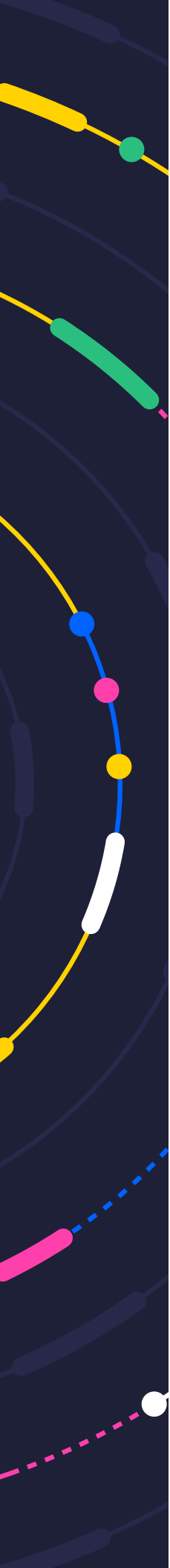
Finally, the ability to feed back the clinical trial data to inform the next set of patients would form a learning network within the trial, ensuring constant improvement over time. Philanthropists are uniquely positioned to require the clinical trials they fund to utilize platforms appropriate for the size and needs of the patient population.

Philanthropists and foundations within this space are often deeply embedded within the patient community, whether through personal experience or relationships built with supporters and stakeholders. From this position, they not only have the perspective of patients but also can integrate families into important conversations regarding community and research needs and advocate for change. Patient inclusion in the development of clinical trial protocols provides researchers with the opportunity to understand the patient perspective and the patients with the knowledge necessary to drive advocacy where it is most needed as clinical trial innovations meet barriers.

## **V. There is an absence of commercial interest in drugs for rare diseases, especially those in children.**

Drug development is an expensive proposition, even more so for rare diseases, because potential treatments lack the market potential to garner industry interest. Additionally, children are a vulnerable population, and there is concern that attempts to repurpose an approved adult drug for pediatric cancer will jeopardize adult approval.

As noted in prior sections of this report and reviewed in **Figure 5**, some regulatory initiatives are aimed at expanding the development of therapeutics for pediatric patients. Unfortunately, many of these initiatives do not address the need to develop therapeutics specific to pediatric cancer; rather, they focus on expanding adult therapies to pediatric patients. For cancers that are driven by fusions or pathways less common in adult cancers, the need for therapeutics that are not created through an adult pipeline will be likely. The development of therapeutics



for rare populations such as pediatric brain cancer is driven by two key forces: (1) a promising therapeutic target and a convincing preclinical package for a therapeutic that addresses that target and (2) an industry entity with a business model prepared to take that therapeutic to market. Important factors to success are:

- infrastructure and support to drive discovery and preclinical research that is de-risked to the point that industry will pursue the therapy,
- collaboration between academia and industry as the therapeutic transitions from preclinical and early-stage clinical trials to a for-profit entity that can move the therapeutic into later-stage clinical trials and the marketplace, and
- a for-profit entity with leadership passionate about the disease area and an innovative business model that paves the way for the development of a drug for a smaller patient community.

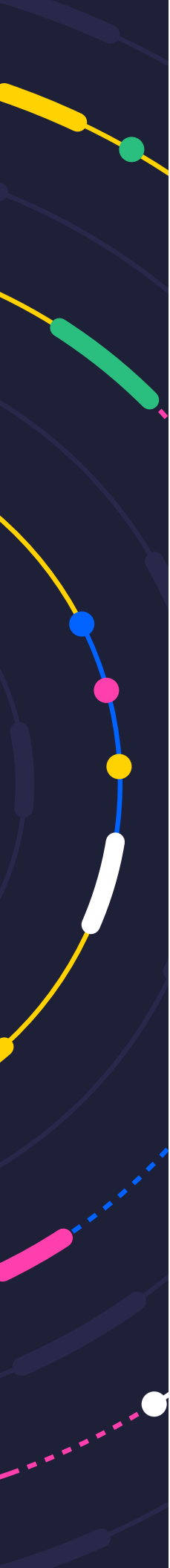
The ability to leverage philanthropic funds and regulatory incentives appropriately may support a company's progress toward success. This model requires thoughtfulness and collaboration with academics for preclinical studies, consortia for clinical studies, and regulatory authorities to ensure the development of a robust and efficient clinical trial. The earlier these entities interact in the process, the greater the potential for success.

#### PHILANTHROPIC OPPORTUNITY #6

*Drive collaboration between academia and industry and incentivize drug development for pediatric brain cancer. Convene stakeholders in the drug development space and strategically support collaborative research that has been successful in other research fields.*

With the passing of the RACE for Children Act, industry is increasingly responsible for developing clinical study plans that address childhood cancers. This is, however, not a space in which many large pharmaceutical companies are necessarily adept. Academic institutions and clinical trial networks within the childhood cancer space have expertise that industry can leverage, and industry has the drugs, finances, and regulatory expertise that clinical trialists could benefit from. The time has come for these groups to work together and for biotech companies to play an important role in bridging some of this experience to benefit patient communities. Biomedical research funders are in a position to provide a safe space for important conversations to align stakeholders along the drug development pipeline and drive promising collaborations forward with philanthropic support.

A well-validated preclinical finding may wither on the vine when the significant funding required to initiate an early-phase clinical trial cannot be identified. Even when early-phase clinical trials are successful, the risk exists for a therapeutic taken up by industry either being shifted to a more profitable disease or remaining on the "shelf," undeveloped, because of a change in a company's business model. Development of a therapeutic for a rare disease has the greatest



potential for success when champions from academia, industry, and the nonprofit/philanthropic space regularly interact and when:

- stakeholders are vested in the success of a therapy for the indication,
- funding is committed to support de-risking and the stages needed to generate proof-of-concept, and
- all parties are willing to contribute their expertise and connections to design a program that considers and mitigates potential pitfalls.

Treatments for spinal muscular atrophy, cystic fibrosis, amyotrophic lateral sclerosis, and neuroblastoma were made possible through collaborations synthesized by patients, families, foundations, and philanthropy.

## VI. Incentives are incompatible with collaboration and innovation.

Metrics for success focus on competitive activities that can hinder the development of the deeper levels of collaborative activity needed.

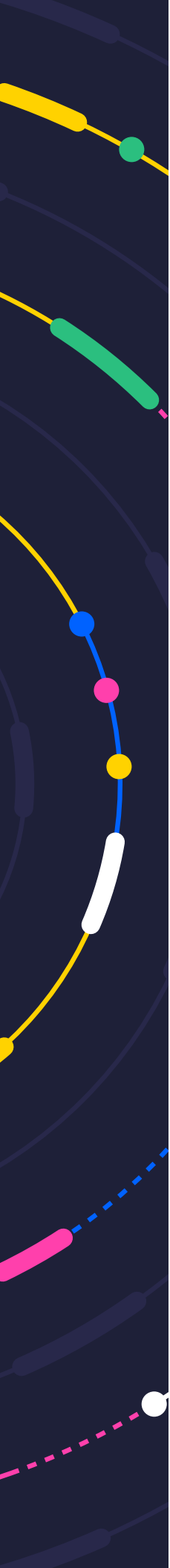
As researchers continue to appreciate the complexity of pediatric cancer, collaboration becomes increasingly important in terms of resource development and idea sharing. Although new federal funding mechanisms encourage interdisciplinary research within universities, there is a continued need for universities to revise internal incentives to promote collaboration and to apply funding to cross-institutional and academic-industry collaborations. Challenges can arise in the allocation of platform resources, the division of labor, and choices about scientific output and academic careers (e.g., publications, grants). Institutions attempt to address these tensions by modifying policies to encourage interdisciplinary research and providing seed money for interdisciplinary projects. However, expanding collaboration beyond a single institution requires not only that the investigators seek and establish collaboration but also that the institution encourages—or at least allows—resource and information sharing among institutions.

### PHILANTHROPIC OPPORTUNITY #7

*Incentivize collaboration and foster the development of early-stage investigators who have diverse and multidisciplinary backgrounds.*

Philanthropists should promote mentoring relationships within and outside of investigators' fields; provide seed funding for innovative, cross-departmental and -institutional work; and be risk-tolerant in identifying and funding young, investigator-driven, collaborative research.

To drive cross-institutional collaboration, parties external to the institution must provide incentives that benefit the individual investigators and the research institutions. Significant and sustained funding for collaboratives provides institutions with the freedom to allow scientists to work on collaborative projects without concern for financial liabilities for the institution. Moreover, this funding enables the philanthropist to prioritize and support collaboration,



including requiring and implementing yearly collaborative meetings, prioritizing data sharing, and creating relationships among players within and outside the field.

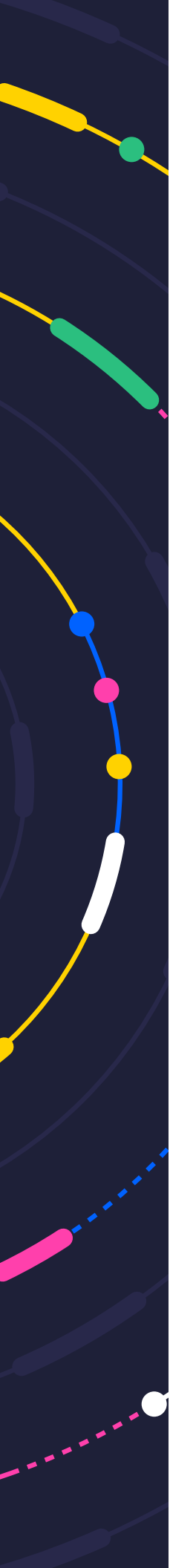
As the scientific research field evolves, the new generation of investigators is addressing more complex challenges that require a broader level of expertise. They are being trained in an environment that requires collaboration. These early-stage investigators need funding support to establish themselves within this new framework.

Identification and significant, sustained support of investigators who have diverse and multidisciplinary backgrounds and prioritize partnerships that help them answer tough questions will drive systemic change.

## CONCLUSION

A childhood brain cancer diagnosis causes a ripple effect that impacts the child and every member of their family. Financial, psychological, and social upheaval amplifies the stress of an already devastating diagnosis. Identification of risk factors, improved biomarkers to assess progress throughout the therapy journey, and development of safer and more effective therapeutics would enhance the treatment experience and outcomes—resulting in a family less burdened by the diagnosis and more confident in the outcome. There are still rare subtypes of brain cancer with survival at less than 50 percent that require innovative approaches to therapy, and all new drug development should consider factors such as the brain immune environment and the blood-brain barrier.

Fortunately, the research ecosystem has been coalescing around the challenges associated with brain cancer diagnosis in a manner that should serve as a model for the broader cancer and rare disease fields. Beginning with an improved understanding of the molecular characteristics of childhood brain tumors and their differentiation from adult tumors, continuing through collecting and curating samples from the majority of patients who are diagnosed with brain cancers, and culminating with a recognition of a system that is not built for pediatric or rare diseases and addressing necessary infrastructure changes, a global shift in how pediatric brain cancers are managed has been taking shape over the past 10 years. With additional time, resources, and talent, there is promise on the horizon for children diagnosed with brain tumors. Regardless, every parent shares the conviction that the horizon is not close enough. Existing systems have the potential to accelerate discovery with an infusion of dedicated and strategic funding in some of the highest-need areas as well as integration of the patient and parent voice into the regulatory and industry landscapes.



Strategic philanthropic investments will push research forward by addressing the most immediate needs in the pediatric brain cancer field. Philanthropic capital is agile, able to be deployed to the areas of highest need to catalyze immediate change. Philanthropy can also provide stability to a research system that is currently highly dependent on the federal budget and priorities and has little to no support from for-profit entities for paradigm-shifting work. The opportunities provided in this guide represent needs revealed by the investigators performing the research and nonprofits currently bolstering work in the field. Providing resources to address these needs could further incentivize collaboration and transform how we manage and treat the disease and its long-term effects for all children diagnosed with brain cancer.

## GLOSSARY

Unless otherwise noted, definitions have been acquired or modified from the [NCI Dictionary of Cancer Terms](#).

**Cellular signaling pathway:** A series of chemical reactions in which a group of molecules in a cell work together to control a cell function, such as cell division or cell death. A cell receives signals from its environment when a molecule, such as a hormone or growth factor, binds to a specific protein receptor on or in the cell. After the first molecule in the pathway receives a signal, it activates another molecule. This process is repeated through the entire signaling pathway until the last molecule is activated and the cell function is carried out.

**Choroid plexus tumors:** A rare tumor that forms in the choroid plexus (a network of blood vessels and cells in the fluid-filled spaces of the brain). These tumors are most common in children younger than two years. Choroid plexus tumors may be benign (not cancer) or malignant (cancer).

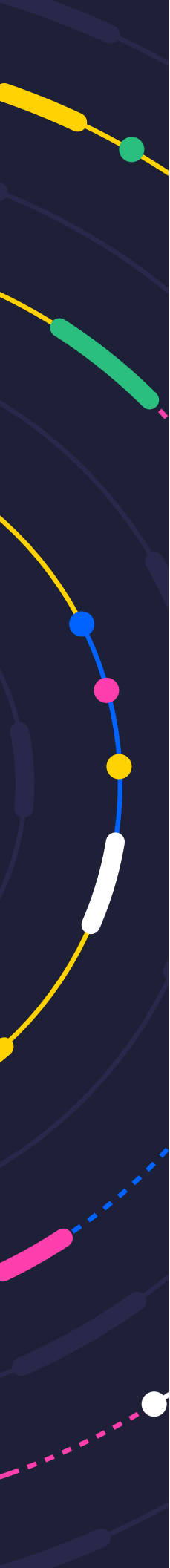
**Coculture:** A mixture of two or more different kinds of cells that are grown together in a laboratory setting.

**Deidentification:** The process by which identifiers are removed from health information to mitigate privacy risks to individuals and thereby support the secondary use of data for comparative effectiveness studies, policy assessment, life sciences research, and other endeavors. ([hhs.gov](https://www.hhs.gov))

**Embryonal tumors:** Embryonal tumors develop from the early forms of neurons and are most common in younger children. The most prevalent type of embryonal tumor is medulloblastoma.

**Genetic predisposition:** An inherited increase in the risk of developing a disease. Also called genetic susceptibility, hereditary predisposition, and inherited predisposition.

**Genetic study:** Sequencing and analysis of the DNA in germ cells (egg and sperm cells that join to form an embryo). This is the process of evaluating genetic information of non-tumor origin as opposed to tumor sequencing.



**Glioma:** The most common type of brain tumor. Gliomas are named after the cells from which they arise, the glial cells, which form the supportive tissue of the brain.

**Harmonize (in relation to data harmonization):** Efforts to combine data from different sources and provide users with a comparable view of data from different studies. ([University of Michigan](#))

**Histology:** The study of tissues and cells under a microscope.

**Ionizing radiation:** A type of high-energy radiation that has enough energy to remove an electron (negative particle) from an atom or molecule, causing it to become ionized. Ionizing radiation can cause chemical changes in cells and damage DNA. This may increase the risk of developing certain health conditions, such as cancer. Ionizing radiation can come from natural sources, such as radon and cosmic rays (which enter Earth's atmosphere from outer space). It may also come from medical imaging equipment, such as X-ray, CT scan, or PET scan machines.

**Liquid biopsy:** A laboratory test done on a sample of blood, urine, or other body fluid to look for cancer cells from a tumor or small pieces of DNA, RNA, or other molecules released by tumor cells into a person's body fluids. Liquid biopsy allows multiple samples to be taken over time, which may help doctors understand what kind of genetic or molecular changes are taking place in a tumor. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or whether cancer has come back.

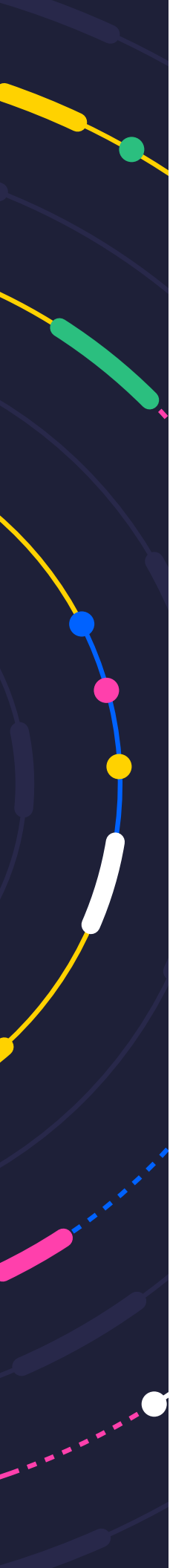
**Longitudinal (as in tissue collection):** A type of research study that collects tissue from groups of people over a period of time. Samples can be compared among the different people as well as over time from the same person.

**Malignancy:** A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Malignant cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of malignancy. Carcinoma is a malignancy that begins in the skin or tissues that line or cover internal organs. Sarcoma is a malignancy that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a malignancy that begins in blood-forming tissue, such as the bone marrow, and causes too many abnormal blood cells to be made. Lymphoma and multiple myeloma are malignancies that begin in the cells of the immune system. Central nervous system cancers are malignancies that begin in the tissues of the brain and spinal cord. Also called cancer.

**Mixed glial and neuronal tumors:** These tumors are composed of both neuronal and glial cells and tend to develop in children and young adults.

**Molecular driver (or driver mutation):** A term used to describe changes in the DNA sequence of genes that cause cells to become cancer cells and grow and spread in the body. Checking tumor tissue for driver mutations may help plan treatment to stop cancer cells from growing, including drugs that target a specific mutation.





**Organoid:** A tiny, three-dimensional mass of tissue that is made from a person's tumor cells or by growing stem cells (cells from which other types of cells develop) in the laboratory. Organoids contain many different types of cells and are designed to closely mimic the structure, organization, and some of the functions of human tissues and organs. Organoids made from a person's tumor cells have features, including genomic and molecular features, that are similar to those found in the original tumor. Organoids are used in the laboratory to study how normal tissues or diseases, such as cancer, form and to test new drugs and other types of treatment before they are given to people.

**Pathological assessment (or pathologic diagnosis):** Identifying a disease or condition by examining cells and tissues under a microscope. In cancer, a pathologic diagnosis usually includes information about the cancer type, grade (how abnormal the cancer cells look under a microscope and how quickly the cancer cells are likely to grow and spread), and stage (the extent of cancer in the body). It may also include information about any special features of the cancer, such as the presence of hormone receptors or other tumor markers.

**Point mutation:** When a single base pair of a genome is added, deleted, or changed. ([National Human Genome Research Institute](#))

**Spheroids:** Three-dimensional cell aggregates that can mimic tissues and microtumors. ([Molecular Devices](#))

**Structural birth defects:** Structural birth defects are related to a problem with the structure of body parts. ([National Institute of Child Health and Human Development](#))

# APPENDIX:

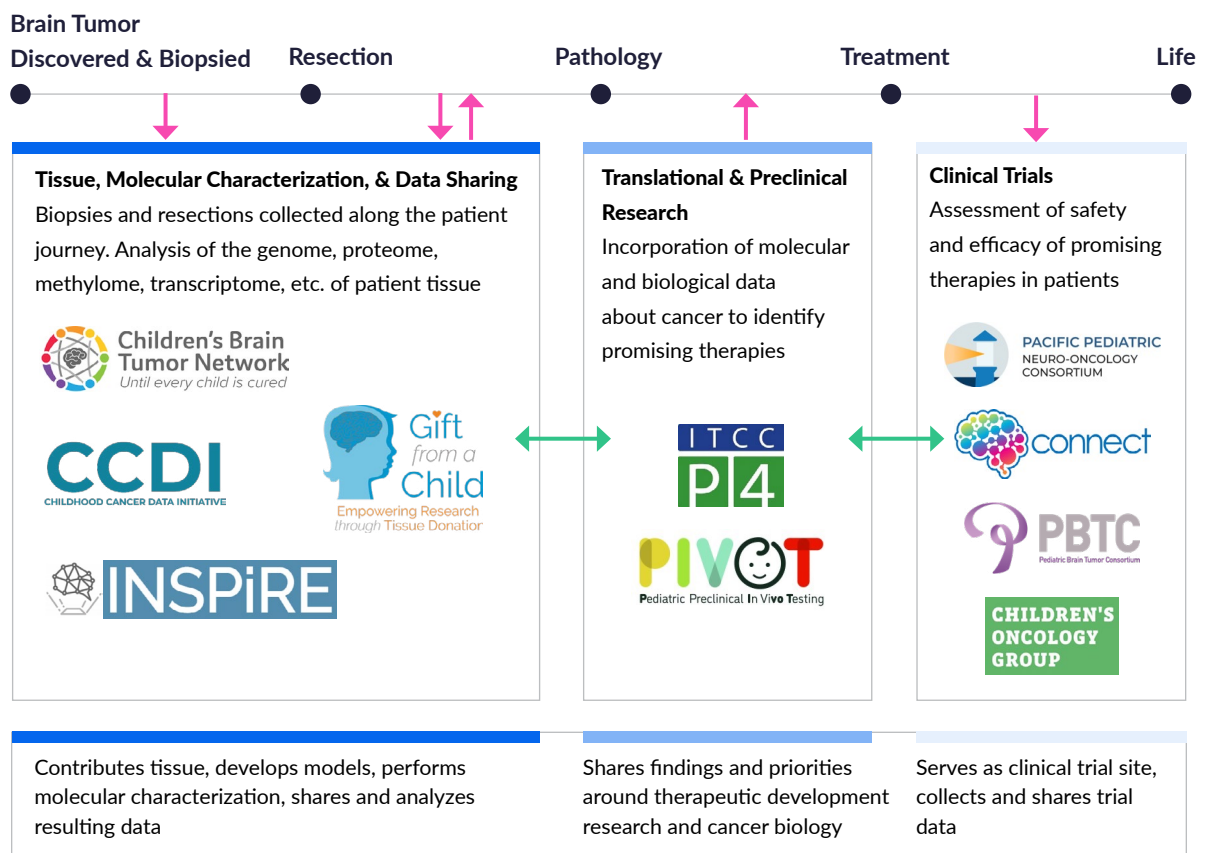
## SNAPSHOT OF PEDIATRIC BRAIN CANCER NONPROFIT ORGANIZATIONS, RESOURCES, AND COLLABORATIVES

The following section provides information about selected collaboratives and nonprofit organizations in pediatric brain cancer research. We also highlight research resources that provide investigators with a broader view of these very rare tumors. This summary is intended as a snapshot and is not an exhaustive accounting of all organizations and activities within the pediatric brain tumor space.

### Pediatric Brain Cancer Collaboratives

The rarity and unmet need in pediatric brain cancer have driven significant collaboration. Collaboratives addressing the range of needs in the field not only are incredibly active and continually growing but also interact with one another in meaningful ways, feeding data and resources among one another to progress the field (**Figure A**). Not all of the collaboratives highlighted below are pediatric brain cancer-specific, but they address pediatric cancers, and their efforts are significant contributors to pediatric brain cancer research.

**Figure A: Collaboratives and Their Contributions to Research and Clinical Care along the Patient Journey**



Source: Milken Institute analysis of childhood cancer collaboratives (2023)

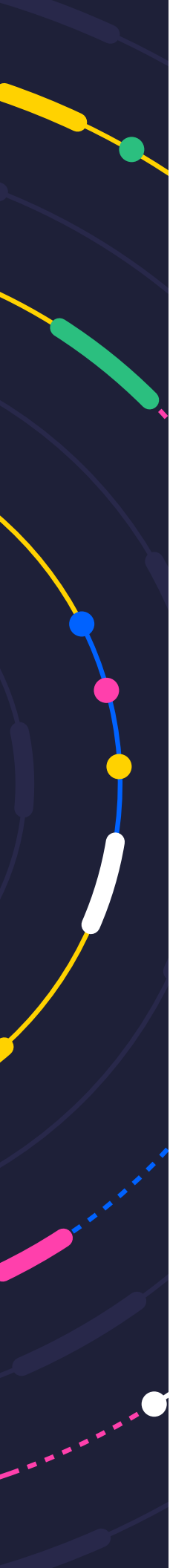
## PRECLINICAL RESEARCH PLATFORMS

Because of limitations on patient samples and resulting pediatric cancer models, retaining cell and animal models within a central repository and running preclinical assessment of potential therapies through a clinical research organization broaden the accessibility of models to both institutions and pharmaceutical companies. Preclinical drug testing to identify promising treatment options that match the molecular make-up of the tumor is hampered by the facts that (1) molecular genetic data on pediatric tumors from relapsed patients and, thus, our understanding of tumor evolution and therapy resistance are very limited to date and (2) for many of the high-risk entities, no appropriate and molecularly well-characterized patient-derived models and/or genetic mouse models are currently available. Thus, quality-assured upfront preclinical testing of novel molecularly targeted compounds in a repertoire of well-characterized models will establish the basis to increase therapeutic success of these drugs in children with malignancies. Importantly, preclinical research consortia lower the activation energy for pharmaceutical companies to pursue therapeutic development for pediatric cancer because accessibility to testing resources is a major barrier to establishing the feasibility of therapeutic success in pediatric cancer.

Innovative Therapies for Children with Cancer Paediatric Preclinical Proof-of-concept Platform (ITCC-P4) is a European-based pediatric preclinical proof-of-concept platform aiming to allow pharmaceutical companies to assess the applicability of therapeutics under development in pediatric cancer models. To address this high but as yet unmet clinical need, the main objectives for this preclinical platform project are the following:

- Establish a representative collection of patient-derived models as well as genetic mouse models of the most common pediatric high-risk entities, including a significant proportion of models from relapses.
- Molecularly characterize and quality-assess the models as well as the matching primary tumor samples and germline controls with state-of-the-art molecular diagnostic tools.
- Enable regulatory filings in the EU by developing comprehensive preclinical data packages necessary to move drugs into clinical trials for children with tumors.
- Prioritize pediatric drug development using existing collections of molecular data for systematic target reports, followed by drug testing in faithful disease models.
- Identify suitable biomarkers for future clinical stratification of patients across entities.

Ultimately, the ITCC-P4 platform will overcome a long-standing gap by performing thorough molecular characterization of high-risk pediatric malignancies coupled with standardized preclinical testing procedures and will thus greatly expedite the development of more precise and efficacious drugs for this patient group.



The NCI-supported Pediatric Preclinical in Vivo Testing (PIVOT) program systematically evaluates novel agents against genomically characterized childhood cancer solid tumor and leukemia in vivo models. The primary goal of the PIVOT program is to develop high-quality preclinical data to help pediatric oncology researchers identify new agents that will show significant activity when clinically evaluated against selected childhood cancers. By supporting a more reliable agent prioritization process, the PIVOT program contributes to the goal of accelerating the discovery of more effective treatments for children with cancer.

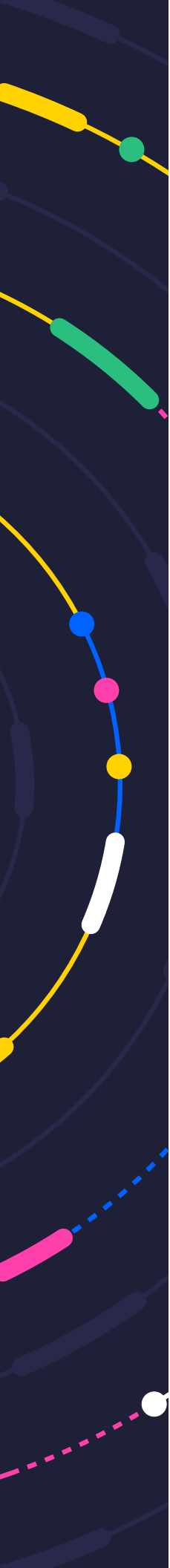
The PIVOT consortium collaborates with industry partners on preclinical testing of molecularly targeted agents developed for adult cancers to evaluate their applicability to the treatment of pediatric cancer. The program builds upon more than 15 years of experience with the Pediatric Preclinical Testing Program (PPTP) and the Pediatric Preclinical Testing Consortium (PPTC), which collaborated with more than 80 pharmaceutical companies to test novel agents against the programs' pediatric preclinical models. The PPTP and PPTC found that many agents that are effective for adult cancers have limited activity against pediatric preclinical models. The PIVOT program testing strategy is based upon research showing that preclinical testing using genomically characterized models, when combined with knowledge about the relative drug exposures tolerated in mice and in humans, provides powerful insight into the likely clinical utility of investigational agents.

## **CLINICAL TRIAL CONSORTIA**

Clinical trial consortia organize, plan, and implement strategies and initiatives designed to grow the clinical research community, provide increased access to cutting-edge medicine, and engage local physicians in research. Clinical trial consortia align protocols across the landscape and integrate a wide range of institutions to ensure that trials can complete enrollment and that patients are offered the most appropriate clinical trial options for their tumors.

The Pacific Pediatric Neuro-oncology Consortium (PNOC) is an international consortium with centers within the United States, Europe, Asia, and Australia. PNOC is dedicated to bringing new therapies to children and young adults with brain tumors. Its goal is to improve outcomes by translating the latest findings in brain tumor biology into better treatments for children with brain cancer. PNOC is currently running 24 pediatric brain cancer clinical trials at institutions around the world.

Investigators within or beyond the more than 30 institutions composing PNOC and the Children's Brain Tumor Network (CBTN) participate and meet to bring forward their best ideas and strategies for research. Consensus decisions for clinical trial development based on high-quality preclinical investigations are prioritized. Collaborating teams share data monthly or bimonthly, analyze their findings, and share resources to hasten progress. The key goal is to develop the best trials possible through extensive preclinical testing and investigations using imaging, body fluids, tumor tissue, and functional studies, including quality of life and cognitive outcomes collected as part of ongoing PNOC trials.



The Children's Oncology Group (COG), a National Cancer Institute-supported clinical trials group, is the world's largest organization devoted exclusively to childhood and adolescent cancer research. The COG unites more than 10,000 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers across North America, Australia, New Zealand, and Europe in the fight against childhood cancer.

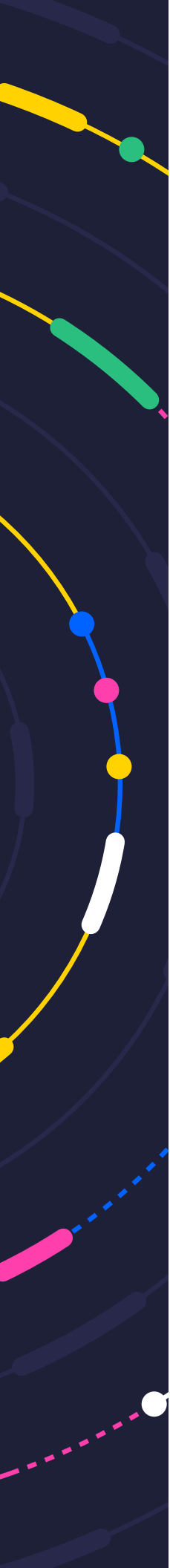
In addition to disease-specific research, COG conducts studies in developmental therapeutics (new cancer drug development), supportive care, epidemiology, stem cell transplantation, behavioral sciences, and survivorship. Additional collaborative initiatives that take place under the umbrella of the COG include:

- The Project:EveryChild initiative aims to find better cures for every type of childhood cancer, no matter how rare. All children with cancer cared for at COG's pediatric cancer programs can submit tumor tissue to be molecularly characterized through Project:EveryChild.
- The Pediatric Early Phase Clinical Trial Network (PEP-CTN) comprises 21 premier COG pediatric core member sites in the US and 21 noncore member sites in the US, Canada, and Australia selected through peer review. The PEP-CTN leverages collaborative interaction with COG disease committees, COG leadership, NCI leadership, and the pharmaceutical industry to prioritize and streamline the development of new, targeted therapies for children with cancer. Innovative trial design and endpoints, genomic biomarkers, and other correlative studies augment the impact of PEP-CTN trials on individual patients and drug development for childhood cancer.

The Pediatric Brain Tumor Consortium (PBTC) was formed by the National Cancer Institute in 1999 to improve the treatment of primary brain tumors in children. The participating academic centers and children's hospitals are responsible for the diagnosis and treatment of a large percentage of children with primary brain tumors in the US and Canada.

To accomplish its objectives, the PBTC has an Operations, Biostatistics and Data Management Core based at St. Jude Children's Research Hospital in Memphis, Tennessee. The PBTC also aims to develop and coordinate innovative neuro-imaging techniques through its Neuro-Imaging Center (NIC) led by Tina Young Poussaint, MD, at Harvard Medical School. The NIC's research focuses on evaluating new treatment response criteria and neuro-imaging methods to understand regional brain effects. Pharmacokinetic (PK) studies are overseen by the PBTC PK Core, which is led by Clinton Stewart, PharmD, at St. Jude Children's Research Hospital. They are an integral component of new agent clinical trials within the PBTC and help develop a better understanding of the disposition of the new agents.

The PBTC Pathology Central Review and Biorepository (CRB) is located at Children's Hospital Los Angeles and is led by Jennifer Cotter, MD. The CRB's function is to collect, store, and distribute specimens for central pathology review and planned correlative studies, which



support the laboratory objectives of PBTC studies. The CRB also serves as a central repository for specimens collected for future research from patients who consent to long-term storage.

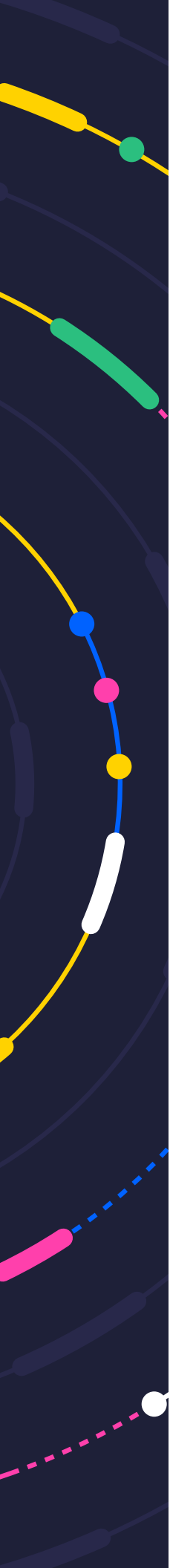
The Collaborative Network for Neuro-oncology Clinical Trials (CONNECT) Consortium conducts clinical trials in high-risk pediatric brain tumors (such as diffuse intrinsic pontine glioma [DIPG]) to investigate combinations of novel drugs with traditional therapies. CONNECT is an international collaborative network of pediatric cancer centers with the objective of improving outcomes for children with newly diagnosed, high-risk brain tumors (including DIPG, high-grade gliomas, atypical teratoid rhabdoid tumors, and high-risk medulloblastoma). CONNECT conducts small, scientifically rational, pilot studies to assess the feasibility and early efficacy of incorporating promising new therapies into established frontline therapeutic regimens.

## **TISSUE, ANALYSIS, AND DATA SHARING**

Because of the limited number of patients and increasing complexity of pediatric brain cancer diagnoses, there is a substantial need for tissue repositories and data-coordinating centers that store, analyze, and share samples and data with the wider research community. Consortia and initiatives focused on tissue and data sharing require substantial infrastructure and technological knowledge to ensure data harmonization and appropriate storage and processing of patient samples. Biobanks collect, analyze, and store tissue and data. Networks such as those highlighted in this section collect this information from a range of institutions, harmonize it so that data from different institutions can be directly compared, and share the tissue, data, and analysis tools with the wider community so that the entire research community can benefit from patient donations and leverage cross-institutional information to increase the numbers of samples that can be analyzed.

The Children's Brain Tumor Network (CBTN) is dedicated to driving innovative discovery, pioneering new treatments, and accelerating open science to improve health for all children and young adults diagnosed with a brain tumor. Researchers use samples of brain tumors to learn more about their biology to develop new and more effective treatments for children. Donations of brain tumor tissue and other biosamples from patients allow scientists to understand better how to target and treat these conditions. Samples collected from CBTN member institutions are processed and stored in the CBTN's operations center at Children's Hospital of Philadelphia. These preserved specimens may then be requested by researchers and investigators who can use the samples to learn more about each of the more than 100 unique childhood brain tumor histologies. Each collected sample is paired with different types of data, including clinical data from patient visits, imaging data from MRI scans, histology data from stained slides of tissue, genomic data extracted from whole genome sequencing (WGS) with paired RNAseq data, and proteomic data that reveal the properties of a patient's proteins.

The CBTN has co-developed a suite of cloud-based data platforms that allow researchers to access these rich collections of brain tumor data from anywhere in the world. These platforms include CAVACTICA, PedcBioPortal, and the Kids First Data Resource Portal. In 2019, the



CBTN launched the Pediatric Brain Tumor Atlas, which now comprises the largest collection of childhood brain tumor data in the world. This resource is not only helping to accelerate brain tumor research but also empowering discovery for other rare childhood conditions.

Gift from a Child (GFAC) is a national initiative supported by families who have lost children to brain cancer, private foundations, researchers, and medical professionals. It currently receives its funding from the Swifty Foundation. Gift from a Child's mission is to increase post-mortem pediatric brain tissue donations through advocacy as well as the education of families. GFAC has formed partnerships with researchers and medical providers who value information and data sharing. These strategic partnerships will accelerate breakthrough cancer research, improve treatments, and ultimately cure childhood brain cancer.

The International Central Nervous System Pediatric Research (INSPIRE) consortium was established in 2021 to compile and harmonize data from large-scale brain tumor biorepositories into an interoperable format that all researchers can access. While the other data repositories analyze and collect institution-level data, INSPIRE compiles large-scale, consortium-level pediatric brain cancer data from international sources and makes it interoperable, providing a comprehensive data resource.

NCI's Childhood Cancer Data Initiative (CCDI) is building a community centered around childhood cancer care and research data. Through enhanced data sharing, it aims to improve understanding of cancer biology to improve preventive measures, treatment, quality of life, and survivorship, as well as ensure that researchers learn from every child with cancer. CCDI represents an ambitious effort in data collection, sharing, analysis, and access.

In addition to currently available platforms and tools, the ecosystem will also include data from the CCDI Molecular Characterization Initiative, a national collaboration of the childhood cancer community that is providing free, state-of-the-art molecular testing to children and adolescents and young adults (AYAs) with certain rare or hard-to-treat cancers, with plans to expand further.

## **INTEGRATIVE COLLABORATIVES**

The Defeat Pediatric Brain Tumors Research Collaborative, a subsidiary of the National Brain Tumor Society, is a global research and drug discovery program. The program is designed to accelerate research through a platform that fosters collaboration as well as research data, information, and materials sharing. The platform consists of four cores that work on critical areas of research simultaneously and in concert with one another to encourage sharing of findings and discoveries in real time. Through research collaboration, four synergistic research cores focused on discovery, drug development, predictive biomarkers, and innovative clinical trials have been combined. They are being driven by world-class teams with proven track records of research accomplishments to accelerate the pace of therapeutic discovery and improve patient survival. By design, the individual project cores within the overall Defeat Pediatric Brain Tumors initiative provide strategic data-sharing opportunities to inform the



overall effort and advance potential therapies through the drug discovery development process much more quickly.

## Nonprofit Organizations

### NONPROFITS CONTRIBUTING FUNDING TO CURRENT PEDIATRIC BRAIN CANCER CLINICAL TRIALS

- Accelerate Brain Cancer Cure funds the development of new treatments and also offers information about patient care, clinical trials, and research advances for brain cancer patients.
- American Lebanese Syrian Associated Charities was founded by Danny Thomas in 1957 to be the fundraising and awareness organization for St. Jude Children's Research Hospital, and its sole mission is to raise the funds and awareness necessary to operate and maintain the hospital.
- Battle for a Cure Foundation's mission is to enrich the lives of children fighting cancer by offering various outreach programs to them and their families, and by funding the most promising research specifically targeted toward childhood cancers.
- Cannonball Kids' Cancer Foundation was founded in 2014 to fund innovative, accessible research for children fighting cancer to provide better treatments and quality of life and educate for change.
- Connor's Cure, in partnership with The V Foundation for Cancer Research, raises awareness and funds that support cutting-edge research at pediatric cancer facilities around the world while advocating for increased public funding for pediatric cancer research in the US.
- Cookies for Kids' Cancer funds early research that has the strongest science behind it and the best chance of getting from a research lab to a child's bedside in the shortest timeframe possible.
- CURE Childhood Cancer is dedicated to conquering childhood cancer through funding targeted research while supporting patients and their families.
- CureSearch for Children's Cancer's mission is to end childhood cancer by driving targeted and innovative research with measurable results in an accelerated timeframe.
- Eli Jackson Foundation is dedicated to conquering pediatric brain cancer through funding targeted research and supporting children and their families.
- Eli's Block Party Childhood Cancer Foundation directly applies the funds it raises to the root of research by putting it in the hand that holds the microscope. It seeks out doctors whose innovative research shows promise toward more effective treatments and whose compassion for the patients and passion for the cause set them apart.



- Ellie Kavalieros Fund is dedicated to changing the landscape of cancer treatment to significantly impact the outcome of diffuse intrinsic pontine glioma.
- Faris Foundation focuses on three key areas: childhood cancer research, creative arts programs at children's cancer centers, and public engagement and awareness around childhood cancer.
- Focused Ultrasound Foundation's vision is that focused ultrasound will be used worldwide to improve the quality of life and longevity of millions of patients with serious medical conditions in the shortest time possible. In that aim, the foundation's mission is to accelerate the development of new applications of focused ultrasound and its widespread adoption as a standard of care.
- Gateway for Cancer Research accelerates practice-changing discoveries in cancer care by harnessing the unrelenting passion of the research community and empowering patients to triumph over their disease.
- Hyundai Hope On Wheels is dedicated to supporting pediatric cancer research that finds innovative approaches, creates discovery, and improves care for children to fight cancer.
- Jaxon's F.R.O.G. Foundation serves as the hands and feet of Jesus to bring smiles to children battling cancer, support ongoing research to find a cure for our young heroes, and be a light in the darkness to encourage the impacted families to Fully Rely On God.
- Kelsie's Crew raises funds to support research in the lab of Gregory Friedman, MD at the University of Alabama at Birmingham.
- Kom Op Tegen Kanker helps avoid, fight, and mitigate the disease and advocate for better cancer policies until there is a world without cancer. To do this, it mobilizes as many people as possible to fight cancer: as care volunteers, activists, or donors.
- Ligue contre le cancer, France has been fighting against cancer since 1918 by being the first independent funder of research.
- Lyla Nsouli Foundation aims to improve the prognosis and eventually find a cure for the worst forms of brain cancer. It hopes to achieve this by awarding brain cancer research grants.
- Mithil Prasad Foundation's mission is to support DIPG researchers and patients.
- National Pediatric Cancer Foundation is dedicated to funding research to eliminate childhood cancer. Its focus is to find less toxic, more effective treatments through a unique collaborative research initiative called the Sunshine Project.
- No More Kids With Cancer is uniquely focused only on funding groundbreaking childhood cancer research, such as genetic sequencing, precision medicine, and clinical trials, that leverages an understanding of cancer biology.

- Parker Institute for Cancer Immunotherapy has built a bespoke infrastructure to quickly mobilize discoveries and fortify the process from idea to outcome.
- Peach Bowl LegACy Fund is hyper-focused on funding the most promising clinical drug trials. The overall goal of the Peach Bowl LegACy Fund is to ensure that high-priority novel agents, devices, and treatment strategies can be tested in patients at an accelerated pace, eventually leading to additional treatment options for patients.
- Pediatric Brain Tumor Foundation, the largest patient advocacy funder of pediatric brain tumor research, also funds and advocates for innovative projects that lead to vital discoveries, new clinical trials, and better treatments—all bringing us closer to a cure.
- Rally Foundation for Childhood Cancer Research empowers volunteers across the country to raise awareness and funds for childhood cancer research to find better treatments with fewer long-term side effects and, ultimately, cures.
- Sandcastle Kids provides children who have endured a challenging battle with cancer a week's vacation with their families on the beaches of Destin and South Walton, Florida.
- Solving Kids' Cancer focuses on aggressive childhood cancers with low survival rates because Every Kid Deserves to Grow Up. Solving Kids' Cancer helps accelerate new, next-generation treatments, including immunotherapy, cancer vaccines, and new drugs, by applying an understanding of the entire childhood cancer research landscape to invest in innovative projects wisely.
- St. Baldrick's Foundation's mission is to find cures for childhood cancers and to give survivors long and healthy lives.
- Stand Up To Cancer (SU2C) funds and develops the newest and most promising cancer treatments to help patients today. SU2C dramatically accelerates the rate of discoveries by connecting top scientists in unprecedented collaborations to create breakthroughs.
- Stichting Semmy aims to increase the life expectancy and, ultimately, the chances of survival of children affected by brain stem cancer.
- Storm the Heavens Fund is committed to spreading awareness and funding desperately needed research for diffuse intrinsic pontine glioma.
- Team Jack Foundation's mission is to raise money to fund impactful pediatric brain cancer research and work to create national awareness for the disease.
- TeamConnor Childhood Cancer Foundation raises awareness about childhood cancer, supports families, and funds treatments to help find a cure.
- Andrew McDonough B+ Foundation's mission focuses on four areas: financial assistance, childhood cancer research, awareness, and spreading positivity.

- Brain Tumour Charity is committed to improving life for everyone affected and to defending the most incredible part of the human body. Its goals are to double survival in the UK and halve the harm that brain tumors have on the quality of life in the UK.
- ChadTough Defeat DIPG Foundation funds the most innovative, promising research on DIPG, which is underfunded compared to most cancers.
- Children’s Tumor Foundation’s mission is to drive research, expand knowledge, and advance care for the neurofibromatosis community.
- Lilabeen Foundation (LBF) for Pediatric Brain Cancer Research seeks to fund critical childhood brain cancer research and to help raise awareness of the severity of this fatal disease.
- Matthew Larson Foundation for Pediatric Brain Tumors aims to build a network committed to providing assistance to reduce family hardship, fund pediatric brain tumor research, and advance patient care.
- Pediatric Low-Grade Astrocytoma (PLGA) Foundation Fund at the Pediatric Brain Tumor Foundation fuels the most promising pediatric low-grade glioma and astrocytoma research in addition to equipping, educating, and empowering PLGG/PLGA families with resources and a community so that they can thrive.
- Pew Charitable Trusts, founded in 1948, uses data to make a difference. Pew addresses the challenges of a changing world by illuminating issues, creating common ground, and advancing ambitious strategies that lead to tangible progress.
- V Foundation for Cancer Research was founded by ESPN and legendary basketball coach Jim Valvano with one goal: to achieve Victory Over Cancer.
- Ty Louis Campbell Foundation is a nonprofit organization that funds innovative research and clinical trials specifically geared toward treating the most aggressive childhood cancers with a strong focus on brain tumors. Its mission is to help fund the intelligence and technology that will improve long-term survival rates and minimize side effects for children diagnosed with the deadliest cancers while helping to care for families when their child is in treatment by providing financial assistance and uplifting experiences.

## PEDIATRIC BRAIN CANCER ORGANIZATIONS

The pediatric brain cancer nonprofit ecosystem comprises dozens of organizations with priorities that span advocacy, family support, experiences, research, and more. The figure below provides a snapshot of the range of organizations primarily focusing on pediatric brain cancer research support in the US. This figure does not represent an exhaustive list but is intended to demonstrate the range of funding priorities in the space (**Figure B**).

**Figure B: Nonprofit Funders of Pediatric Brain Cancer Research and Funding Priority Areas**

Organization	Pediatric Brain Cancer Focus	Priority Areas			
		Basic	Translational	Clinical	Infrastructure
Pediatric Brain Tumor Foundation	Pan Brain Cancer	●	●	●	●
Children's Brain Tumor Foundation	Pan Brain Cancer	●			●
Team Jack Foundation	Pan Brain Cancer		●		
Aiden Snyder Pediatric Brain Cancer Foundation	Pan Brain Cancer	●			
Pediatric Brain Tumor Research Fund	Pan Brain Cancer	●	●	●	
Ross K. MacNeill Foundation	Pan Brain Cancer		●	●	●
Hope4ATRT	Atypical Teratoid Rhabdoid Tumor	●	●		
Swiftly Foundation	Recurrent Medulloblastoma		●	●	●
ChadTough	Diffuse Intrinsic Pontine Glioma		●	●	
The Rory David Deutsch Foundation	Pan Brain Cancer				●
Kamen Brain Tumor Foundation	Pan Brain Cancer		●	●	
Mithil Prasad Foundation	Diffuse Intrinsic Pontine Glioma			●	●
Lilabeau Foundation	Pan Brain Cancer		●	●	

Source: Milken Institute analysis of nonprofit pediatric brain cancer funders (2023)

### PAN-PEDIATRIC CANCER ORGANIZATIONS

The broader pediatric cancer funding space includes what is now estimated to be more than 100 nonprofit organizations. Many of these organizations prioritize areas of unmet need in the pediatric cancer research and treatment space resulting in a focus on pediatric brain tumors, among other pediatric cancers with low survival or fewer treatment options. Therefore, the pan-pediatric cancer nonprofit ecosystem also contributes significantly to the support of

pediatric brain cancer research. The following US organizations were most commonly identified during the landscaping process as contributing to the pediatric brain cancer funding landscape (Figure C).

**Figure C: Nonprofit Funders of Pediatric Cancer Research and Funding Priority Areas**

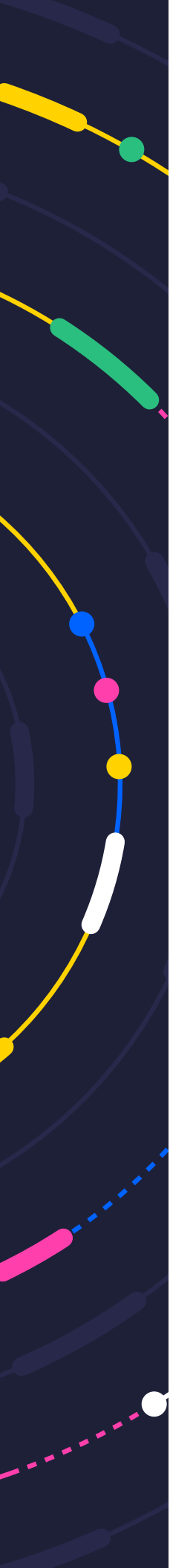
Organization	Priority Areas				
	Data	Basic	Translational	Clinical	Infrastructure
Alex's Lemonade Stand Foundation	●	●	●		
CureSearch for Children's Cancer			●	●	
Cannonball Kids' Cancer Foundation			●	●	●
Dragon Master Foundation	●				
CURE Childhood Cancer			●	●	
Rally Foundation for Childhood Cancer Research			●	●	
Solving Kids' Cancer			●	●	
St. Baldrick's Foundation		●	●	●	●
The Andrew McDonough B+ Foundation			●	●	
Ty Louis Campbell Foundation			●	●	
Pediatric Cancer Research Foundation		●	●	●	
Pediatric Cancer Research Foundation			●	●	
Children's Cancer Research Fund		●	●	●	

*Note: Although these funders do not specifically focus on funding pediatric brain cancer research, they contribute significant funds to pediatric brain cancer across a broad portfolio.*

*Source: Milken Institute analysis of nonprofit pediatric cancer funders (2023)*

## Resources for Researchers

Rare diseases, including pediatric cancer and the subtypes that fall within pediatric brain cancers, rely on collaborative initiatives to provide the tools and resources required to perform research. Data, animal and cell models, tissue, and analysis platforms are all important factors for accelerating research, especially in a rare disease area. One goal of the NCI-sponsored Childhood Cancer Data Initiative (CCDI) is to develop a catalog of available data resources.



The Childhood Cancer Data Catalog is a searchable database of NCI and other pediatric cancer resources. Resources include repositories, registries, programs, knowledge bases, analytic tools, and catalogs that either manage or refer to data. Users can browse and filter the list of data resources or enter search terms to identify data of interest.

## **BIOREPOSITORIES**

The Children's Brain Tumor Network (CBTN) houses more than 30 types of pediatric brain and spinal cord tumor clinical and molecular data, biospecimens, and cell lines that are free to academic researchers. Samples collected from CBTN member institutions are processed and carefully stored in the CBTN's operations center at Children's Hospital of Philadelphia. Researchers and investigators may then request these preserved specimens. Each collected sample is paired with different types of data, including clinical data from patient visits, imaging data from MRI scans, histology data from stained slides of tissue, genomic data extracted from WGS with paired RNAseq data, and proteomic data that reveals the properties of a patient's proteins. These datasets are reviewed for accuracy, and any identifying information is removed to protect the privacy of each research subject.

The CBTN has co-developed a suite of cloud-based data platforms that allow researchers to access these rich collections of brain tumor data from anywhere in the world. These platforms, including Cavatica, PedcBioPortal, and the Kids First Data Resource Portal (see Datasets below for more information), are accelerating the research process and enabling members of the scientific and patient communities to partner and make discoveries faster than ever.

The Biorepository for the Children's Oncology Group is at The Research Institute of Nationwide Children's Hospital (NCH) in Columbus, Ohio. The biorepository maintains the largest pediatric cancer biospecimen bank in the nation. The biorepository contains tissue from more than 32,000 children with childhood cancer and related diseases. The Biopathology Center (BPC) offers a wide range of services related to the procurement, processing, banking, and distribution of biospecimens in support of research, including access to specialized BPC-based services (e.g., biomedical imaging [virtual microscopy/digital pathology], informatics, and kit management) and centralized shared NCH-based research resources (Biopathology Center Core, Morphology Core).

The Ian's Friends Foundation (IFF) Brain Tumor Biorepository at Children's Health Care of Atlanta (CHOA) has been established to collect, culture, and distribute pediatric brain tumor biospecimen for research studies with CHOA Institutional Review Board approval and patient consent. IFF aims to make these biospecimens available free of charge except for shipping to research investigators working on advancing the molecular understanding and treatment of pediatric brain tumors. Currently, the biorepository has several pediatric brain tumor neurosphere cultures available. Also available are viable brain tumor tissue and early-growth neurospheres that have not undergone quality control and have not proliferated or thrived after passaging in the lab but may be used for xenograft, cell sorting, or other research.

## DATASETS AND ANALYSIS PLATFORMS

CAVATICA is a cloud-based portal environment developed to securely store, share, and analyze large volumes of pediatric brain tumor genomic data to accelerate collaboration in research. Named for the popular children's story *Charlotte's Web*, CAVATICA allows researchers and investigators to access and share a network of data, pipelines, algorithms, visualizations, and hypotheses about specific types of tumors. CAVATICA includes data from a number of sources, including CBTN, Pacific Neuro-oncology Consortium (PNOC), Stand Up To Cancer, Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and The Cancer Genome Atlas Program (TCGA). CAVATICA is improving collaboration between data scientists, statisticians, data engineers, programmers, application developers, bioinformaticians, and scientists. Following its launch in October 2016, CAVATICA has become the largest clinically annotated pediatric cancer database.

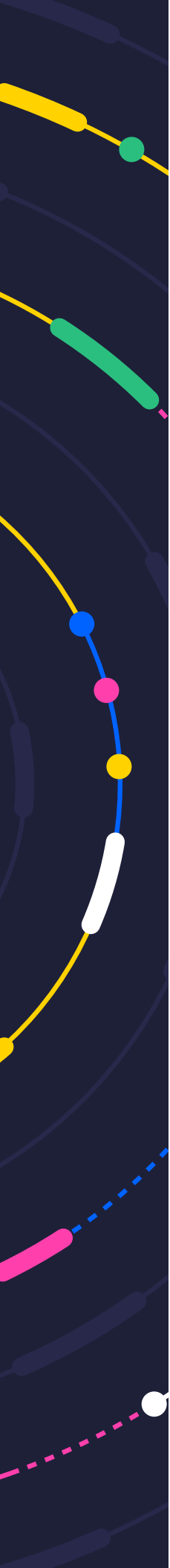
The PedcBioPortal is an open-access resource for childhood cancer genomics that enables users to visualize, analyze, and download large-scale cancer genomics datasets. These data help researchers to investigate the molecular mechanisms of cancer and design therapies based on a patient's unique profile. PedcBioPortal is a variation of the original cBioPortal (developed at Memorial Sloan Kettering), which enables investigators and researchers to rapidly explore data stored in the adult-focused TCGA database. Although these adult data are accessible through PedcBioPortal, the platform analyzes high-quality childhood cancer datasets. This platform works uniquely within the CBTN applications ecosystem to empower research and the translation of genomics data into biological insights and improved clinical therapies.

The Gabriella Miller Kids First Data Resource Portal provides access to more than 8,000 samples of childhood cancer and structural birth defects genomic data. The Kids First Data Resource Portal stores the CBTN's Pediatric Brain Tumor Atlas data and allows cross-analysis of different disease types to uncover the potential links between genetic diseases occurring in children.

The Childhood Cancer Data Lab was established by Alex's Lemonade Stand Foundation (ALSF) in 2017. ALSF introduced the Data Lab to empower researchers and scientists across the globe by removing roadblocks, supporting opportunities for collaboration and sharing, and developing resources to accelerate new treatment and cure discovery. The Childhood Cancer Data Lab constructs tools that make vast amounts of data widely available, easily mineable, and broadly reusable. They also train researchers and scientists to understand their data better and advance their work more quickly.

## PRECLINICAL MODELS

The Seattle Children's Brain Tumor Resource Lab generates and distributes patient-derived xenograft models and cell lines with a focus on pediatric brain tumors. Similar to American Type Culture Collection (ATCC), the only way to obtain these lines is to place an order through the Brain Tumor Resource Lab site.



The Broad Institute Cancer Cell Line Factory (CCLF) is committed to five goals: (1) convert any patient tumor sample into a perturbable cell model, (2) fill cancer cell model collection gaps to cover as many tumor types and genotypes as possible, (3) share new patient models broadly, (4) increase the representation of underrepresented ethnicities in patient models available for cancer researchers, and (5) integrate ex vivo functional testing into cancer precision medicine workflows. The CCLF has developed 476 verified models from unique patients and acquired 2,900+ samples. Of the models made and distributed by the CCLF, 36 percent are from rare or pediatric cancers.



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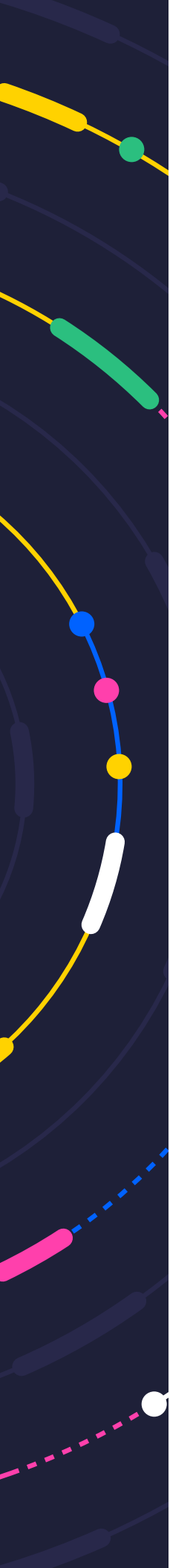
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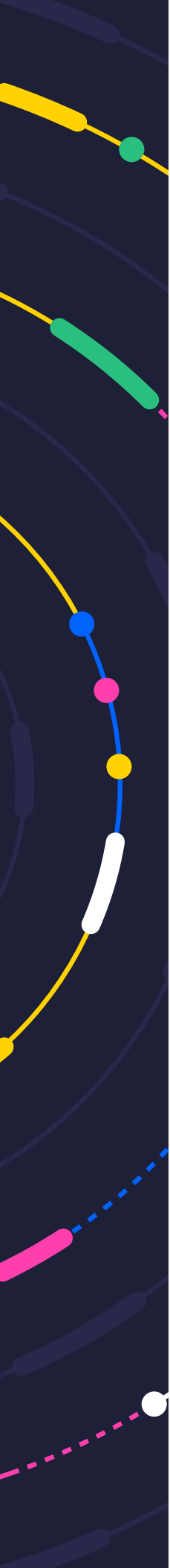
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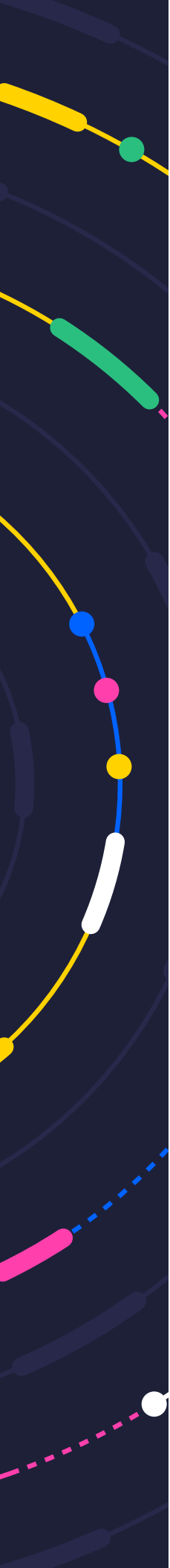
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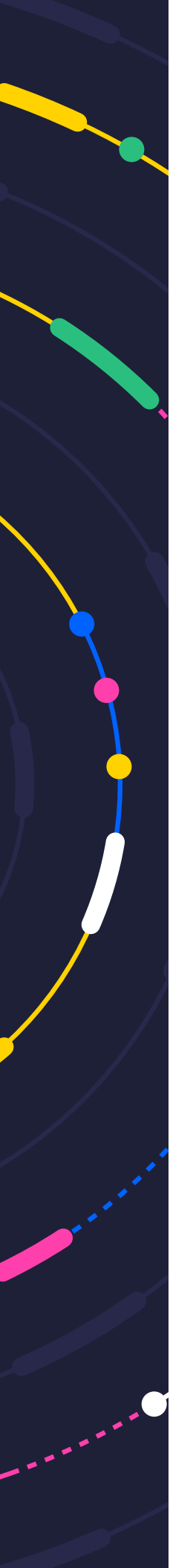
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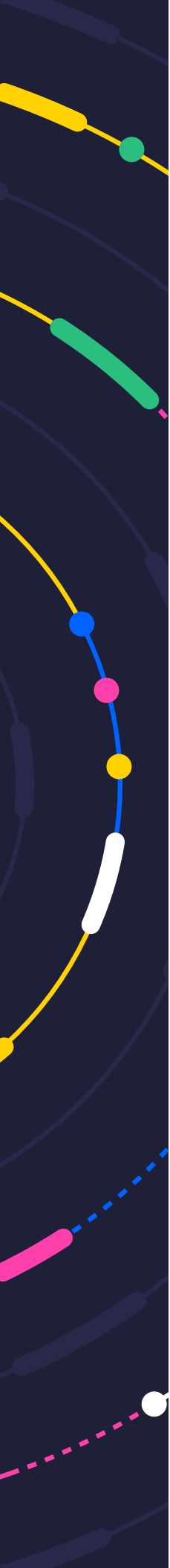
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