KPCRTF State Funded Projects Reporting Template

University of Kentucky – Project #2
Factors Associated with High Incidence of Pediatric Brain and Central Nervous System Tumors in Kentucky
Program Director: Eric Durbin

Reporting Period: April 1, 2021 – June 30, 2021

Below please provide a brief summary of the status of the Project listed as well as for each Aim listed below. Include any barriers, how and if they were overcome, and successes achieved.

This is the final report for the UK-Pediatric Brain and Central Nervous System Tumors project which completes the first phase of a population-based study of pediatric brain and central nervous system tumors (PBCNST) in Kentucky. The second phase continues with the ongoing KPCRTF Germline and Environmental Factors Associated with Pediatric Brain and Central Nervous System Tumors study. To our knowledge, this represents the first truly population-based genomic and environmental study of PBCNST ever conducted. In summary, this project has been highly successful despite challenging delays caused by the COVID-19 pandemic. All major study goals have been accomplished.

While significant findings regarding risks and molecular markers have emerged, the study has also generated a highly valuable dataset with tremendous potential to drive future research. In addition, the project received significant financial support from collaborators at the Children's Hospital of Philadelphia and has already served as a springboard that has delivered additional pediatric cancer research funding to Kentucky. The results of this study will likely facilitate future funding opportunities. The research team is grateful to the Kentucky PCRTF Board for the opportunity to advance the science of PBCNST and a greater understanding of the factors associated with these tumors among Kentucky's highly cancer burdened children. The report highlights several key accomplishments with detailed descriptions presented sections that follow.

Key Accomplishments

1) Aim 1: Detailed environmental and epidemiological analyses were successfully completed to characterize potential environment exposures and clustering of PBCNST in the state. The results demonstrate some clustering of high rates of PBCNST both temporally and spatially. Specifically, rates of all PBCNST were significantly higher primarily in the north central and Appalachian regions of the state, showing increased risks ranging from 1.74 to 1.80 during various time periods. Rates of gliomas demonstrated clusters of increased risk ranging from 1.93 to 2.04 in the central region of the state. Additional analyses of other sub-types did not reveal statistically significant clustering.
2) Aim 1: An examination of environmental exposure data and regional industry data did not reveal significant correlations with PBCNST clusters in the state. However, data related to residential pesticide use was not available for analysis but will be collected through household surveys in the phase 2 study.

3) Aim 2: The collection of cancer pathology specimens for 258 patients that were successfully retrieved from 11 different pathology labs and submitted to the Center for Data Driven Discovery in Biomedicine (D3b) at the Children's Hospital of Philadelphia (CHOP) for sequencing. This represents the entire census of available specimens and exceeded the study goal of 250 specimens.
4) Aim 2: Successful DNA and RNA extraction by D3b from 258 and 216 specimens, respectively. Extractions were followed by the generation of 180 tumor panel DNA sequences, 24 whole exome sequences, 140 tumor RNA fusion detection panel sequences and 230 tumor RNA gene expression panel sequences. Additional sequences will be generated at no additional cost to the study by September 2021.
5) Aim 2: Genomic analytic pipelines have been successfully developed and show unique molecular signatures of PCBNST in Kentucky. The frequency of somatic (cancer) mutations evident in targeted panel and whole exome sequencing results in the population are reported for the first time. RNA-seq gene expression data have demonstrated 4 major clusters related to histologic types for pilocytic astrocytoma, ependymoma, atypical teratoid/rhabdoid tumor and medulloblastoma. Unique gene fusions have also been identified. Additional somatic sequencing results and germline (normal) sequencing results from the Phase 2 study will significantly expand upon the current findings.
6) Aim 3: A data sharing infrastructure for hosting study generated genomic data was successfully established through the CAVATICA platform at D3b. The research team successfully utilized the platform to download and provide data access to study biostatisticians through the Kentucky Cancer Registry's Cancer Research Data Commons. Importantly, the research team was also able to access similar data from a large cohort of PBCNST cases from the Children's Brain Tumor Network, also made available through CAVATICA. These data were essential to identify data deficiencies from some of the study samples extracted from older and lower quality tissue blocks. Broader access to study-generated genomic data will be made available through cBioPortal.
7) All aims: This study has been presented at a variety of regional and national forums and has been well received. There is significant interest in the results of the study among the pediatric cancer research community. The study has also shown a solid return on investment with $263,815 in shared costs contributed by D3b at CHOP/ The study has also led to over $500,000 in subsequent funding from NCI with potential for additional $837,500 in NCI funding from a proposal that will be submitted in September.

Aim 1: Identify potential environmental exposures associated with Kentucky's high rate of brain and CNS tumors

On 03/25/2019, the final cohort of childhood brain and central nervous system cases was identified by the Kentucky Cancer Registry. A data file containing all PBCNST cases diagnosed in Kentucky from 1995 through 2017 (N=1252) was provided to the Aim 1 team. They have produced **Table 1**, showing the demographic characteristics of PBCNST patients. **Table 2** shows the distribution of PBCNST by ICCC Site Group. Geolocation data for each case have been analyzed using SaTScan™ software for spatial and spatio-temporal scan statistics. **Figure 1** shows the county level distribution of cases in Kentucky. An initial analysis has been performed using a Poisson-based spatio-temporal scan, with elliptical scan windows, and a maximum cluster size of 33.3% of the population at risk. In addition, a graduate student has been hired by Dr. Christian to assist with the identification of potential clusters. The team has also initiated mapping of Superfund, coal mining, and Toxics Release Inventory (TRI) data.

Table 1 shows basic demographic characteristics of all PBCNST patients in the data set. The overwhelming majority of cases were white (88.8%), followed by black (8.8%), and other (1.1%) Kentuckians. There was a similar distribution in cases between males and females and among the four five-year age groups (i.e., 0-4, 5-9, 10-14, 15-19).

Table 1. Demographic characteristics of PBCNST cases in Kentucky, 1995-2017

Gender	n	%
Female	637	50.9
Male	615	49.1
Total	1,252	100

Age Group	n	%
<5	328	26.2
5-9	299	23.9
10-14	301	24.0
15-19	324	25.9
Total	1,252	100

Race	n	%

White	1,112	88.8
Black	110	8.8
Other	14	1.1
Unknown	16	1.3
Total	1,252	100.0

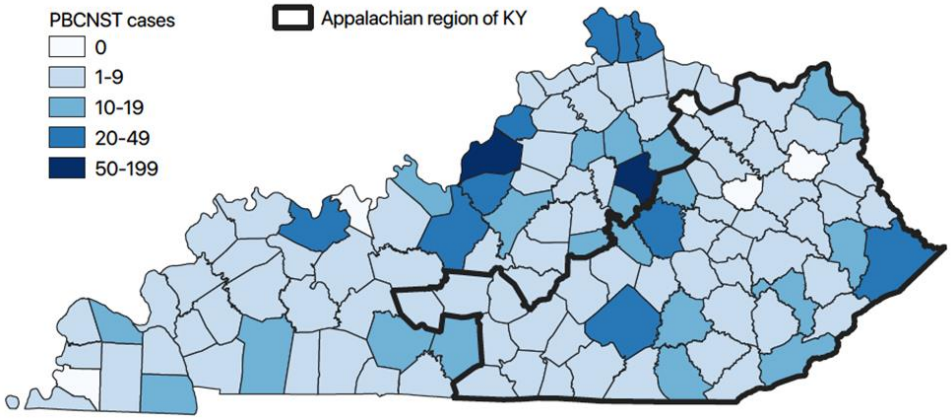
Table 2 shows the distribution of PBCNST by ICCC site. Astrocytomas were the most common (n=502, 40.1%), followed by other specified intracranial and intraspinal neoplasms (n=317, 25.3%). Together, these make up almost two-thirds of PBCNST during the study period.

Table 2. Distribution of PBCNST by ICCC site in Kentucky, 1995-2017

ICCC Site	n	%
Ependymomas and choroid plexus tumor	83	6.6
Astrocytomas	502	40.1
Intracranial and intraspinal embryonal tumors	151	12.1
Other gliomas	170	13.6
Other specified intracranial and intraspinal neoplasms	317	25.3
Unspecified intracranial and intraspinal neoplasms	29	2.3
Total	1,252	100

Figure 1 highlights the distribution of PBCNST by county. Jefferson County had the highest number of cases (n=199), representing 15.9% of all PBCNST during the 1995-2017 period; followed by Fayette (n=78, 6.2%), Boone (n=78, 6.2%), Kenton (n=78, 6.2%), and Campbell (n=78, 6.2%). Together, these urban counties comprised 31.7% (n=397) of all PBCNST in Kentucky during the study period. The Appalachian region accounted for 28.5% (n=357) of all cases.

Figure 1. Cases of PBCNST by county in Kentucky, 1995-2017



We conducted sub-analyses following site/histology categories that were published in Table 2B of the Central Brain Tumor Registry of the United States (CBTRUS) 2015 Neuro-Oncology manuscript entitled "*Alex's Lemonade Stand Foundation Infant and Childhood Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011*." We completed sex-specific analyses of the spatial and temporal distribution of PBCNST sub-types and created maps of TRI data by industry and agricultural pesticide use to guide further analysis.

Clustering of PBCNST Cases, 1995-2017

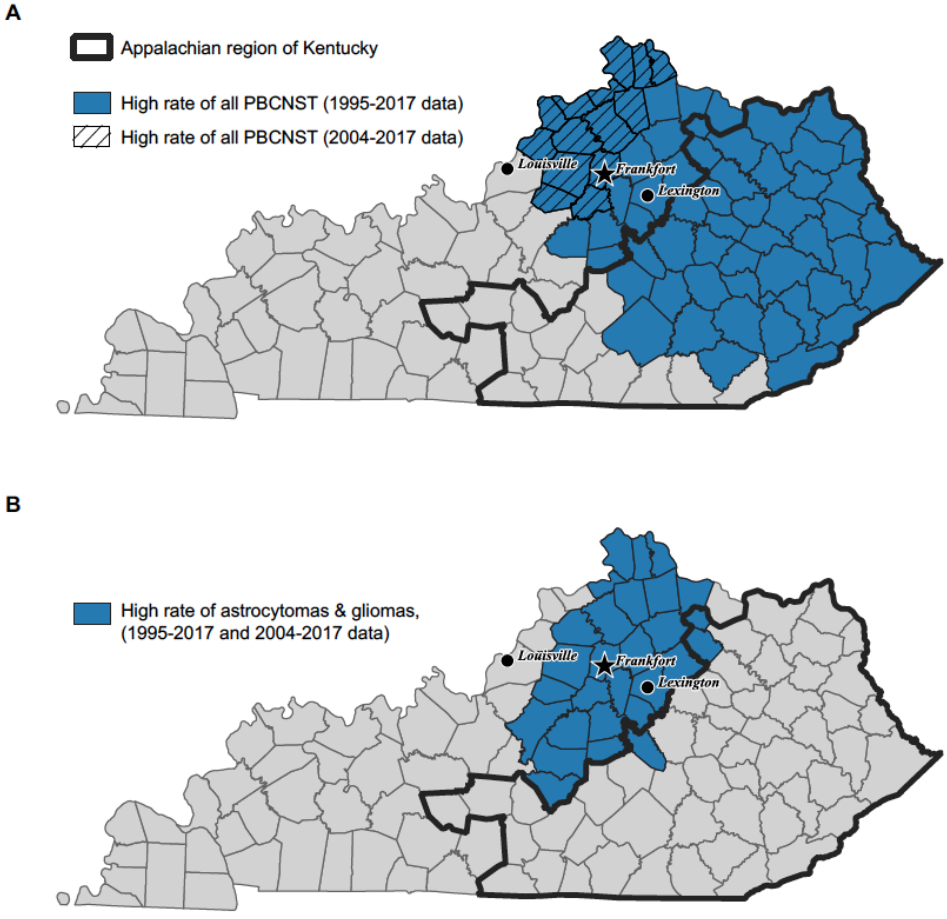
Spatio-temporal statistical analysis was limited to first primary cancers for all patients. The results demonstrated some clustering of high rates of PBCNST both temporally and spatially. When examining all primary cases of PBCNST diagnosed during the period 1995-2017 (N=1237), there was a significantly higher rate of PBCNST for the entire state during several latter years, 2007-2017. This cluster represented 771 cases of PBCNST, or 29% more than expected based on the overall rate during the time period under study, and a relative risk of 1.77 compared to the remainder of the state. ($p<0.001$). The same analysis also identified a statistically significant cluster covering a large swath of central and eastern Kentucky from 2007 through 2017 (blue in **Figure 2A**). That cluster represented 437 cases of PBCNST where only 295 were expected during this time period, or 48% more than expected given the population. This represents a relative risk of 1.74 compared to the rest of the state.

We also conducted similar analyses limited to the 2004-2017 period, since the reporting of benign and borderline cases to KCR began in 2004. When the analysis is limited to cases diagnosed during this period (N=935), the cluster appears much smaller, and is limited in scope to several counties in the north-central Kentucky region (cross-hatched in **Figure 2A**). Still, the number of cases (n=107) in this smaller cluster was 71% more than the number of expected cases (n=63), for a relative risk of 1.80 compared to the rest of the state.

We also reproduced the above analyses for gliomas only, which accounted for 750 (61%) of all 1237 PBCNST cases during 1995-2017, and 502 (54%) of 935 PBCNST cases during 2004-2017. The former analysis identified a cluster of 108 gliomas where only about 57 were expected, during the period 2012-2017 (**Figure 2B**). This is 89% more cases than expected in this area during that time period and equates to a relative risk of 2.04 compared to the rest of the state. In the latter glioma-specific analysis, for 2004-2017, we observed nearly identical results, with the same cluster of 108 cases—about 62 (73%) more than expected; slightly different than the previous analysis, due to the shorter time period. The relative risk for this cluster was also slightly different—1.93 compared to the rest of the state—for the same reason.

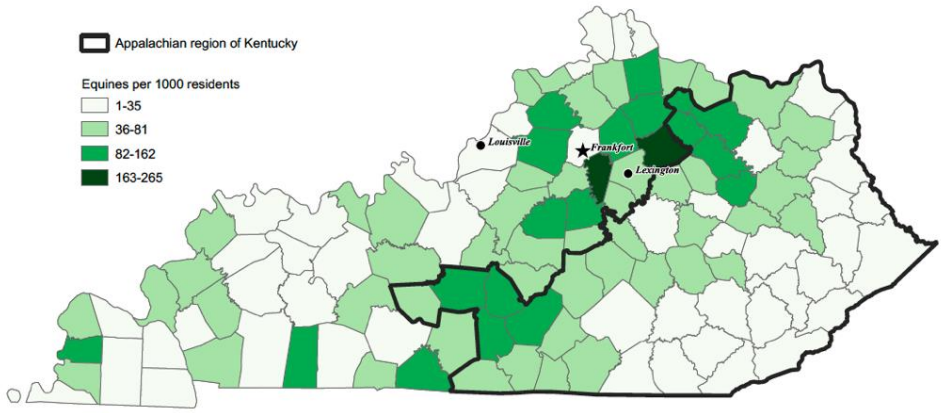
We conducted additional analyses for both time periods that included all other sub-types, but they did not reveal statistically significant clustering. For most sub-types other than gliomas, the very small number of cases was an impediment to meaningful statistical analysis. For example, an analysis of medulloblastomas included only 64 cases over 14 years (2004-2017) and 120 counties. The most likely candidate cluster in this analysis included seven cases (over 20 counties), which represented over eight times the expected number of cases, but the p-value was only 0.50.

Figure 2. Clustering of PBCNST cases in Kentucky



Taken together, the results of the most robust analyses suggest that gliomas, the most common type of PBCNST, as a group are likely the major contributor to elevated rates of PBCNST in Kentucky. Furthermore, the central Kentucky region, and—perhaps to a lesser extent—the Appalachian region seem to have the highest risk. It is important to note that the central Kentucky region—including counties near or adjacent to Cincinnati, Frankfort, Lexington, or Louisville—is also home to some important drivers of Kentucky's economy, including the equine and bourbon industries.

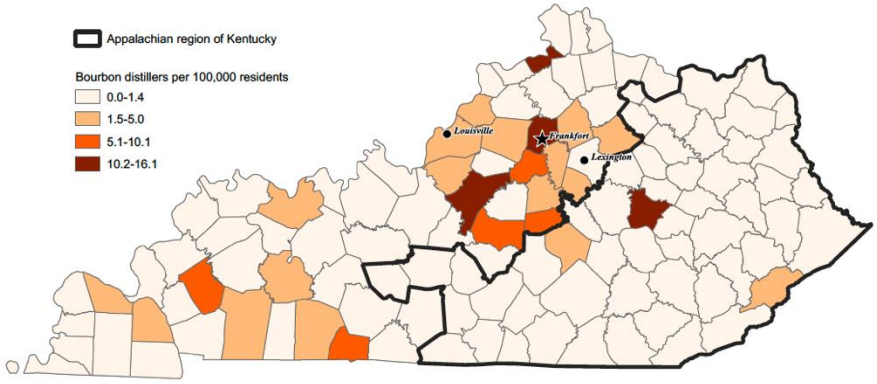
Figure 3. Equines by county in Kentucky, 2012



Potential Exposures

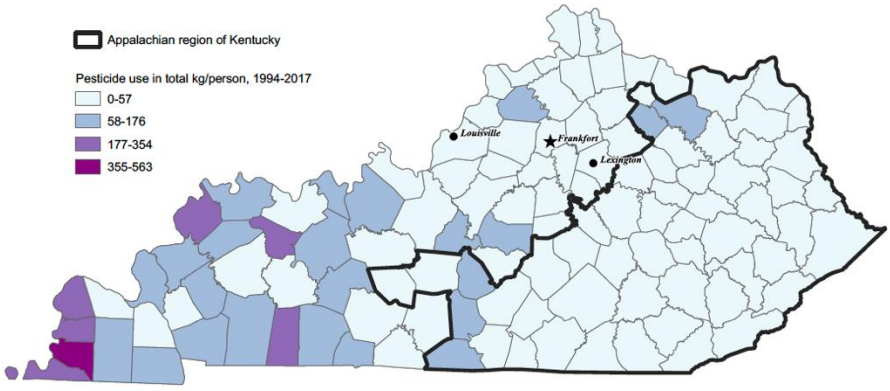
The map in **Figure 3** displays the number of equines per 100,000 residents by county in Kentucky in 2012,[1] and the map in **Figure 4** displays the number of bourbon distilleries per 1000 residents in 2019.[2]. Although these maps show some similarities with the maps of PBCNST clusters in Figure 2A-B, we did not observe any statistically significant correlations with county-level PBCNST rates over the study period. Still, further research at the case level should closely examine the exposures of the parents of PBCNST cases for occupational or other exposures potentially related to these industries.

Figure 4. Bourbon distilling by county in Kentucky, 2019



The map in **Figure 5** displays the total amount of pesticides, in kilograms (kg), applied within each county from 1994-2017,[3] divided by the population in 2005. This provides a rough estimate of per capita pesticide use by county during the study period. There was no statistically significant relationship between these median pesticide values and PBCNST rates during the study period. While no correlation with PBCNST clusters is apparent visually or statistically, it should be noted that this map does not depict use of any specific pesticides—some of which could be more common in central or eastern parts of the state—and the data are for agricultural pesticide use only. Pesticide use in homes is not included in this map, but could be very relevant for prenatal exposure, and should be examined in future studies at the case level.

Figure 5. Agricultural pesticide use by county in Kentucky, 1997-2014



The map in **Figure 6** displays median Risk Screening Environmental Indicator (RSEI) scores for each county in Kentucky during the period 2007-2018.[4] These unitless scores, derived from the EPA's Toxic Release Inventory, reflect the relative level of health risk posed by toxic releases after additional modeling for the fate, transport, and relative toxicity of agents.

Therefore, a two-fold difference in RSEI scores equates to about double the risk to health. Visual inspection and statistical analysis both suggest no correlation with PBCNST clusters noted in Figures 2A-B.

Figure 6. Median RSEI scores by county, 2007-2018

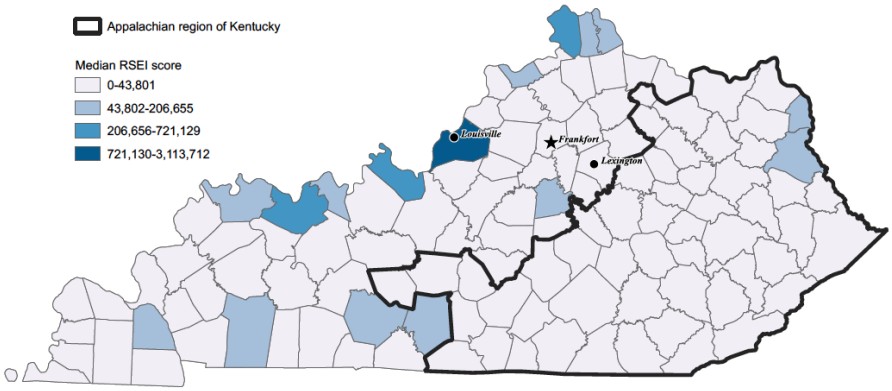
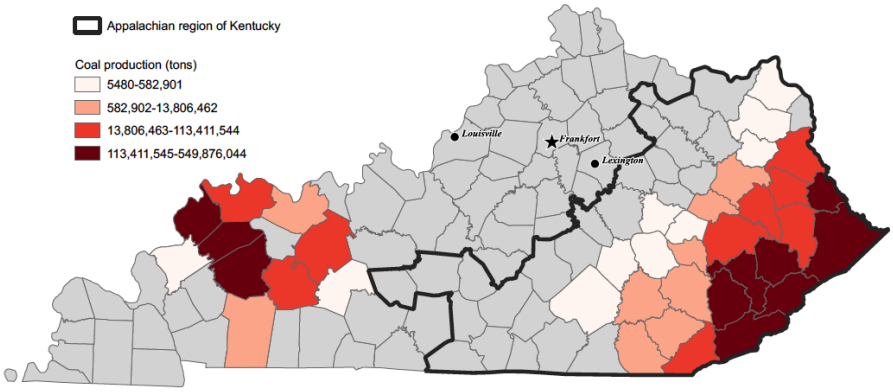


Figure 7 displays coal production, both underground and surface, by county for the period 1994-2017.[5] Although coal mining has previously been shown to be associated with higher rates of several diseases, including cancer, we observed no significant correlation with rates of PBCNST. Rather, the clusters of PBCNST we noted in Figure 1, above, are mostly located outside of the coal mining regions of Kentucky.

Figure 7. Coal production by county, 1994-2017



References

1. National Agricultural Statistics Service. 2019. USDA/NASS Quick Stats Ad-hoc query tool. https://quickstats.nass.usda.gov.

2. Kentucky Distillers' Association. 2019. *The Economic and Fiscal Impacts of the Distilling Industry in Kentucky*. Louisville, KY.
3. United States Geological Survey. 2020. USGS NAWQA Pesticide National Synthesis Project. https://water.usgs.gov/nawqa/pnsp/usage/maps/county-level/.
4. Environmental Protection Agency. 2020. Risk Screening Environmental Indicators Model. https://www.epa.gov/rsei.
5. Kentucky Geological Survey. 2021. Search the Coal Production Database. https://kgs.uky.edu/kgsweb/DataSearching/Coal/Production/prodsearch.asp.

Aim 2: Assess whether Kentucky-specific mutations and mutational signatures exist that may be related to brain and CNS tumors, and to determine whether known genetic risk factors for brain and CNS tumors are present among Kentucky children

- The standard operating procedure for determining biospecimen availability was established early on. A cohort of 379 subjects was initially identified and the availability of tissues was assessed. Of the 379, 9 subjects were found to be ineligible due to neoadjuvant therapy, 10 subjects were ineligible due to miscoding, 3 subjects were ineligible due to biopsy only and no resection, 50 subjects did not have any tissue blocks available, 14 subjects were ineligible due unavailable pathology reports, 27 subjects were ineligible due to insufficient quantity of tissue available and 8 subjects were ineligible due to passive refusal by pathology lab. The final cohort included 258 subjects. All 258 specimens were successfully retrieved from 11 facilities, processed and submitted to CHOP for sequencing.
- Accounts for study personnel were established on CHOP's CAVATICA platform, which holds the de-identified sequencing data for our patients.
- The data use agreement with the Children's Brain Tumor Tissue Consortium (CBTTC) that permits comparisons of the Kentucky mutational profiles with CBTTC cases was completed on December 2, 2020.

Data Generation at CHOP

Subjects/Specimens	Status
258	Completed DNA extraction
180	Tumor panel DNA sequencing completed
164	Tumor panel DNA sequencing data uploaded to CAVATICA
24	Whole exome sequencing completed, and data uploaded to CAVATICA
216	Completed RNA extraction
140	Tumor RNA fusion detection panel sequencing completed
99	Tumor RNA fusion detection panel sequencing data uploaded to CAVATICA
230	Tumor RNA gene expression panel (EdgeSeq) sequencing completed
92	Tumor RNA gene expression panel (EdgeSeq) sequencing data delivered

Analytic Results

- Somatic Mutation calling using Tumor Panel: 100 subjects were sequenced using CHOP Solid Tumor Panel (Division of Genomic Diagnostics at CHOP) targeting all coding exons of 238 genes and the flanking intronic regions. Sequencing data has been preprocessed standardly following GATK Best Practices. Somatic mutations have been identified using the Mutect2 mutation calling pipeline and the Cosmic Census hotspots mutation calling pipeline. In total, we identified 5340 non-coding mutations. The top 10 mutated genes are *PTCH1*, *TP53*, *KMT2C*, *SMARCB1*, *ATRX*, *PTEN*, *NF1*, *EGFR*, *SMARCA4* and SUFU (**Figure 7**).
- Somatic Mutation calling using Whole Exome Sequencing: 23 subjects were sequenced using Agilent SureSelect Human All Exon V6+COSMIC kit. Sequencing data has been preprocessed standardly following GATK Best Practices. Somatic mutations are identified using Mutect2 mutation calling pipeline and Cosmic Census hotspots mutation calling pipeline. In total, we identified 6654 non-coding mutations. The top 10 mutated genes are *PTCH1*, *SMARCB1*, *TP53*, *HLA-A*, *PTEN*, *ATRX*, *KMT2C*, *NF1*, *SMARCA4* and *FAT1* (**Figure 8**).

Figure 7. Summary of somatic mutation calling results using CHOP Solid Tumor Panel for 100 subjects.

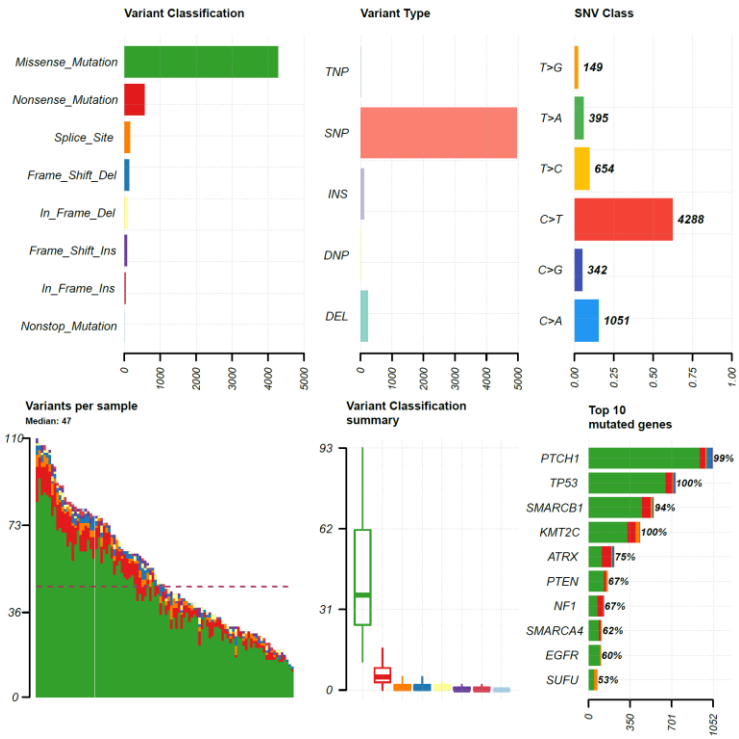
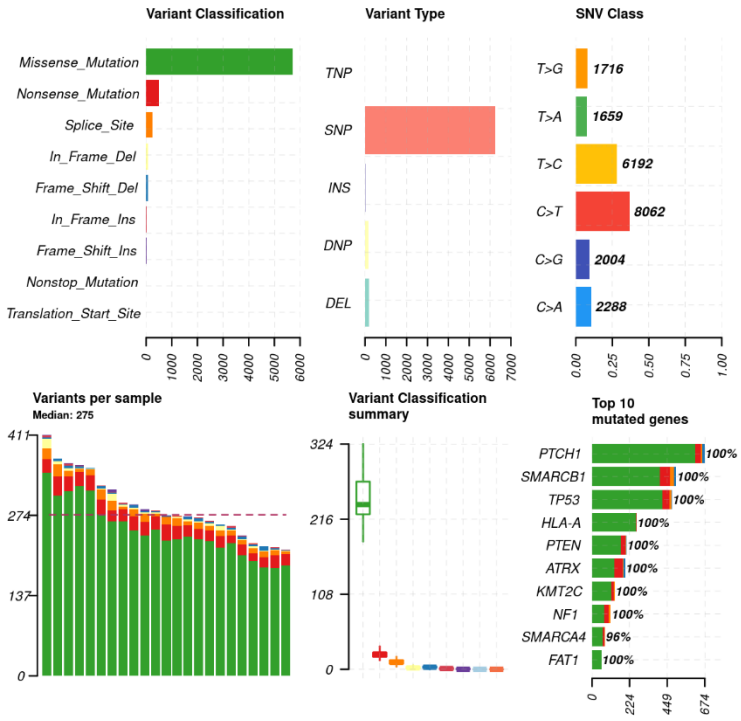


Figure 8. Summary of somatic mutation calling results using Whole Exome sequencing for 23 subjects.



- RNA-seq gene expression: 92 samples were sequenced using Gene expression panel (D3b Medical Diagnostic Unit) targeting 2,549 genes associated with tumor biology. Principle Component Analysis (PCA) from the normalized gene expression data shows that the gene expression profiles are associated with the tumor histological types (**Figure 9**). We identified 4 major clusters related to pilocytic astrocytoma, ependymoma, atypical teratoid/rhabdoid tumor and medulloblastoma. We further performed differential expression (DE) analysis comparing the pilocytic astrocytoma subjects with the others and identified 513 significant DE genes (**Figure 10**).
- Gene fusion: gene fusion of 28 subjects was detected using CHOP Gene Fusion Panel (Division of Genomic Diagnostics at CHOP) targeting 110 fusion genes for approximately 600 known fusions using anchored multiplex PCR technology followed by NGS. KIAA1549-BRAF fusions were identified in 9 of the samples (**Figure 10**) mainly in pilocytic astrocytoma histological type.

Figure 9. Principle Component Analysis using the RNA-seq gene expression panel data.

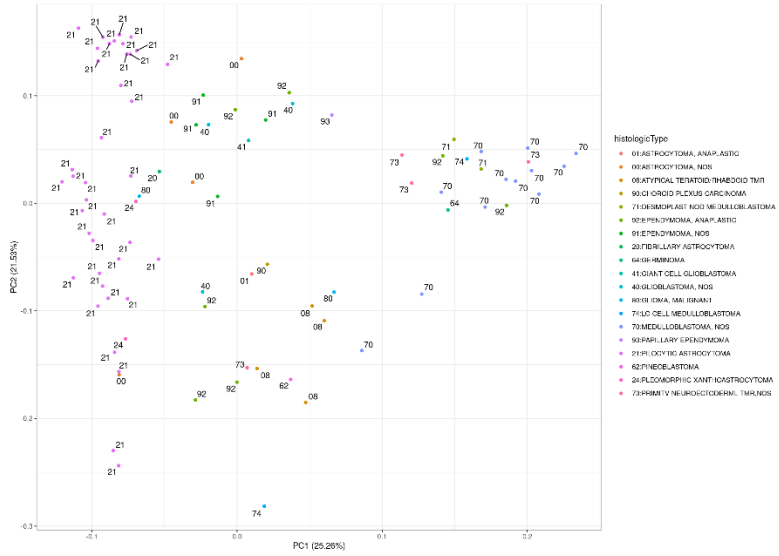
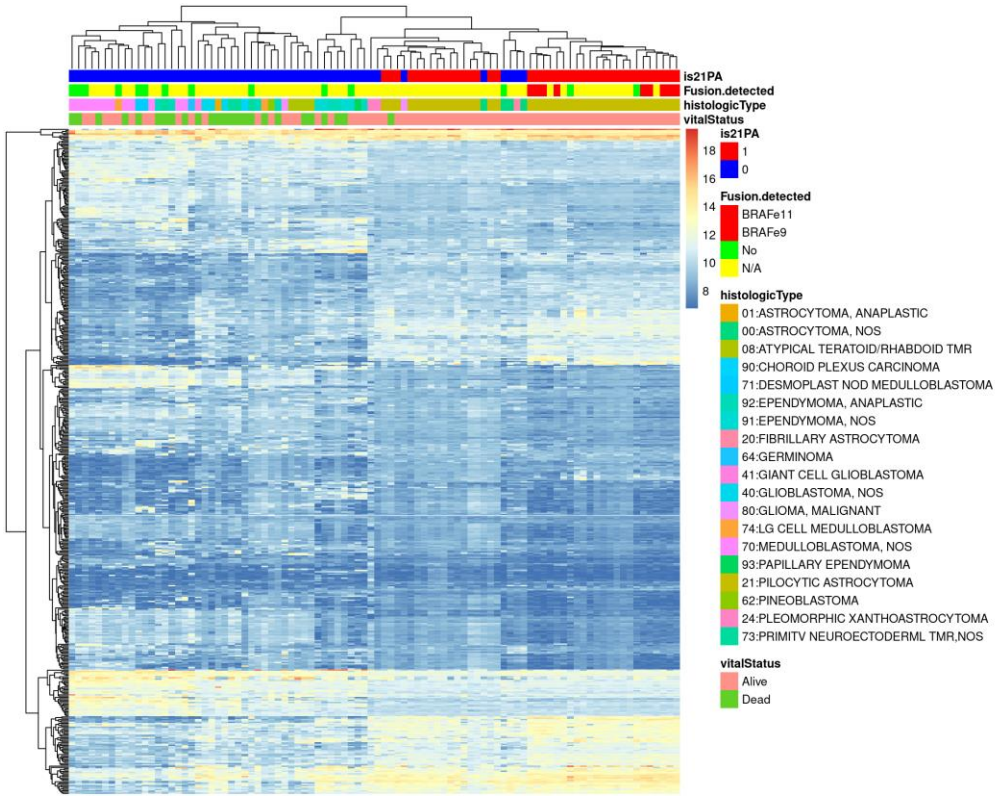


Figure 10. Differential gene expression analysis comparing pilocytic astrocytoma versus non pilocytic astrocytoma group with fusion and clinical information.



Aim 3: Enhance MCC informatics infrastructures for sustained and ongoing integration of our datasets and research with the consortia-based research efforts of CHOP, CBTTC, PNOC, and the DRC

- Clinical records for the remaining eligible cohort subjects have been uploaded to the Kids First Data Tracker for a total of 258 Kentucky Registry Records submitted.
- Successful sequencing on 49 subjects has been downloaded for analysis. Additional comparative analyses with non-Kentucky childhood PBCNST cases are planned. Additional sequencing results and analysis are anticipated in the next quarter.
- We are prepared to integrate molecular test data from CHOP into the Cancer Research Data Commons now that results are being returned to Kentucky. All data remain available in CAVATICA for research use as well. Data will be made available for other Kentucky investigators through KCR's cBioPortal.

Manuscript Preparation

A manuscript entitled *Informatics Methods and Infrastructure Needed to Study Factors Associated with High Incidence of Pediatric Brain and Central Nervous System Tumors in Kentucky* was published in the Journal of Registry Management in September 2020. (https://pubmed.ncbi.nlm.nih.gov/34128919/)

Presentations

This study has been widely disseminated and has garnered significant interest among the pediatric cancer research community.

	Alliance for Childhood Cancer
03/2019	Eric B. Durbin, DrPH, MS Invited Panelist/Childhood Cancer Action Days 2019 "From Evidence to Action: The Pediatric Early Case Capture Experience in Kentucky" Alexandria, VA
03/2020	Eric B. Durbin, DrPH, MS Invited Presentation "National and State Childhood Cancer Surveillance Initiatives"
	Cancer Informatics for Cancer Centers
10/2020	Eric B. Durbin, DrPH, MS Panelist/2020 Fall Conference: "Virtual Tissue Repository"
	University of Iowa **Carver College of Medicine**
10/2020	Eric B. Durbin, DrPH, MS

Invited Grand Rounds Presentation "National and State Childhood Cancer Surveillance Initiatives: Advancing the Research Data Ecosystem"

University of Missouri
Institute for Data Science & Informatics

01/2021 Eric B. Durbin, DrPH, MS
Invited Seminar "Building a Population-based Childhood Cancer Data Ecosystem: Challenges and Opportunities for Informatics and Data Science"

American Childhood Cancer Organization/Coalition Against Childhood Cancer

05/2021 Eric B. Durbin, DrPH, MS
Invited Panelist/Primer on State Cancer Action Plans
"Population-based Childhood Cancer Data to Support Evidence-based State Cancer Action Plans"

Children's Brain Tumor Network (CBTN)

05/2021 Eric B. Durbin, DrPH, MS
Invited Presentation/Children's Brain Tumor Network Investigator Meeting
"ACCELERATE Consortium and Pediatric Brain Tumors Across Appalachia"

Cost Share Contributions from CHOP

The Center for Data Driven Discovery in Biomedicine (D3b) at the Children's Hospital of Philadelphia has played a key role in the project by providing genomic sequencing services and a data management platform (CAVATICA). D3b generously contributed $389,115 in resources for the project and received $125,300 in funding under a subcontract, representing a greater than 3 to 1 return on investment.

	D3b Cost share - year 1	Subcontract - year 2	D3b Cost share - year 2	D3b -Cost share- estimated remaining	TOTAL
	7/1/19 - 6/30/20	7/1/20-6/30/21			
PERSONNEL	$ 92,965.53	$ 49,814.74	$ 33,630.00		$ 176,410.27
NON PERSONNEL	$ 45,874.00	$ 75,485.26	$ 6,108.10	$ 85,237.64	$ 212,705.00
TOTAL	**$ 138,839.53**	**$ 125,300.00**	**$ 39,738.10**	**$ 85,237.64**	**$ 389,115.27**

Additional Funding Opportunities

Three proposals directly related to the work of this project were submitted for funding to the National Cancer Institute. Two ongoing projects have been funded:

1) Administrative Supplement for the NCI P30 Cancer Center Support Grants to develop the National Childhood Cancer Registry (NCCR)

   Principal Investigator: B. Mark Evers, MD; Project Manager: Eric B. Durbin, DrPH, MS

   Award amount: $300,000 total; $196,000 in direct costs.

2) SEER Task Order: Pediatric Cancer Whole Slide Imaging (WSI)

   Principal Investigator: Thomas C. Tucker, PhD, MPH

   Award amount: $203,567; $153,969 in direct costs.

Dr. Durbin has also been invited to collaborate on an epidemiology study component as part of the Children's Brain Tumor Network SPORE proposal to be submitted in September of 2021 with an anticipated annual budget of $167,500 for five years, including indirect costs.

Timeline:

Aims (check appropriate time period when each Aim is completed)	**Month 1-6**	**Month 7-12**	**Month 13-18**	**Month 19-24**	**Month 25-30**	**Month 31-36**	√
Cohort Identification	√			√			√
Biospecimen Identification	√			√			√
Biospecimen Acquisition	√	√	√	√	√	√	√
Biospecimen Sequencing and Data Retrieval				√	√	√	√
Aim 1 Data Acquisitions	√			√			√
Aim 1 Data Analysis		√	√	√	√		√
Aim 2 Data Analysis		√	√	√	√		√
Aim 3 Data Sharing Agreements/Legal Review	√	√					√
Aim 3 Enhance CRDC (CAVATICA)	√	√	√	√	√	√	√
Aim 3 Implement Data Exchange Architecture			√	√	√	√	√
Manuscript Preparation						√	√

Deliverables:

Check when deliverable is completed	√
Obtain IRB clearance to proceed with objectives by June 30, 2019	√
Recruit and hire TBN staff position by June 30, 2019	√
Determine and document biospecimen availability of subject tissues from pathology laboratories and their willingness to share the specimens by June 30, 2019	√
Establish specimen and data sharing protocol and data sharing agreements (including legal review) with DRC by June 30, 2019	√
Develop specifications for data sharing with Kentucky researchers through the Markey Cancer Center Cancer Research Data Commons by June 30, 2019	√
Obtain and de-identify first cohort of pathology specimens for subjects by June 30, 2019	√
Send pathology specimens to DRC for sequencing by June 30, 2019	√
Obtain sequencing results and conduct initial analyses of genomic sequencing data by June 30, 2019	√
Map series displaying PBCNST incidence and mortality for major subtypes over time, including clustering of high rates, within KY by June 30, 2019	√
Conduct monthly meetings with Leadership Team to discuss progress and problem solve any potential barriers by June 30, 2019	√
Submit a report outlining progress and any preliminary findings through June 30, 2019	√
Obtain and de-identify second cohort of pathology specimens for subjects by December 31, 2019	√
Send specimens to DRC for sequencing by December 31, 2019	√
Obtain sequencing results and conduct analyses of genomic sequencing data by June 30, 2021 Note: Sequencing and analysis held up by COVID-19	√
Complete specifications for data sharing among KY researchers by December 31, 2019	√
Final report on spatial statistical analysis of PBCNST (and major subtypes) incidence in relation to possible environmental exposures by December 31, 2019	√
Conduct monthly meetings with Leadership team to discuss progress and problem-solve any potential barriers by December 31, 2019	√
Submit a report outlining progress and findings through December 31, 2019	√
Obtain final sequencing results and complete final analyses of genomic sequencing data by June 30, 2021 Note: Sequencing and analysis delayed by COVID-19; Completed for available results.	√
Complete implementation of data sharing infrastructures by June 30, 2020	√
Providing training materials for investigators to utilize the Cancer Research Data Commons to access data by June 30, 2021. Note: Delayed by COVID-19	√
Update “atlas” and environmental epidemiological analysis with updated incidence data from the KCR by June 30, 2020	√
Prepare manuscripts and new grant proposals for continuing PBCNST research by June 30, 2020 Note: Held up by COVID-19	√
Submit a report outlining progress and findings through June 30, 2021	√

Quarterly Reports are due:

- October 15, 2020
- January 15, 2021
- April 15, 2021
- July 15, 2021

Reports should be returned to:
Janet.luttrell@ky.gov
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