Childhood Cancer Data Initiative Webinar Series

Impact of the Molecular Characterization Initiative on Pediatric CNS Tumors

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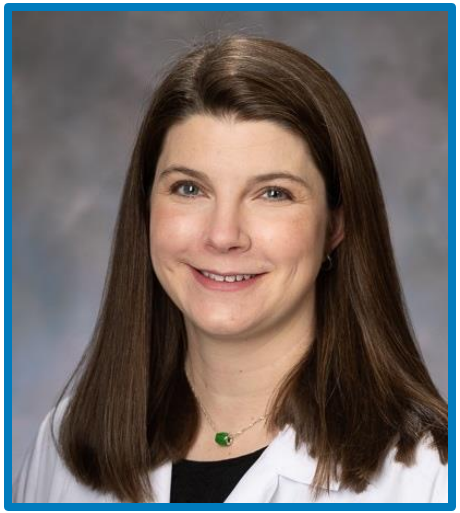
NIH NATIONAL CANCER INSTITUTE

September 10, 2024

Agenda

1. Molecular Characterization Initiative (MCI): Strategy
2. MCI Progress: Genomics and Clinical Data for CNS Subjects
3. MCI Data: Clinical Impact
4. MCI Data: Implications for Clinical Trials
5. Q&A

Today's Speakers



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Neuropathologist

- Pathology Operations Director, Biopathology Center
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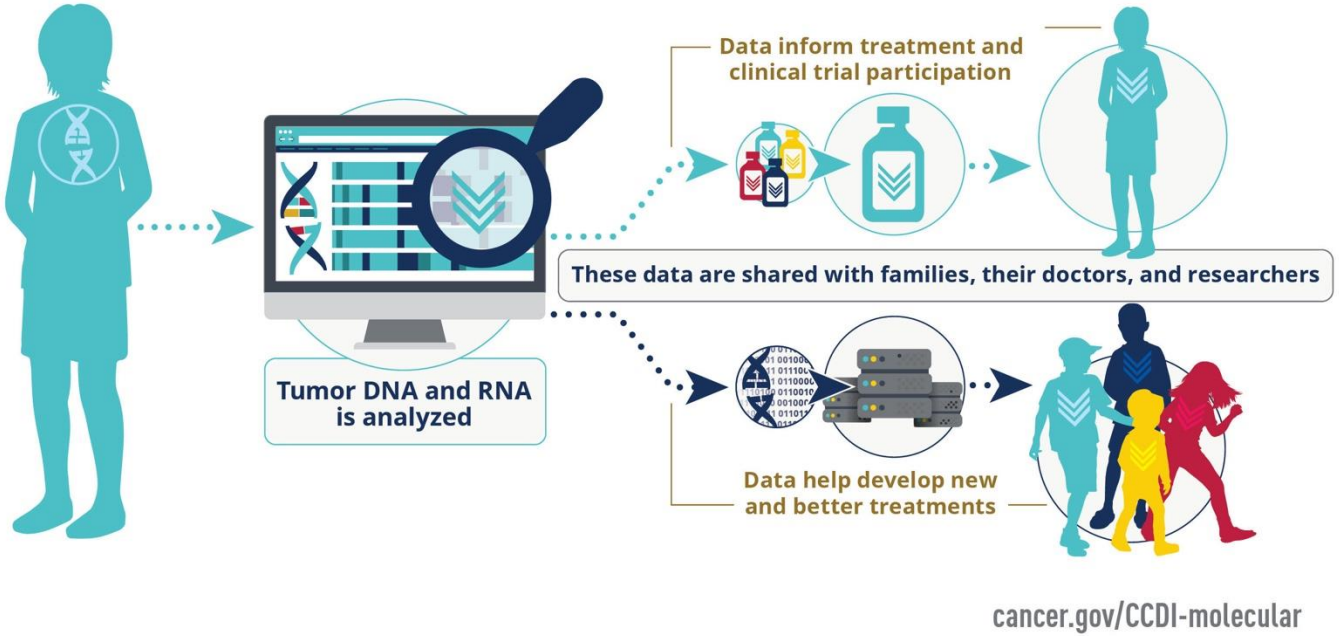
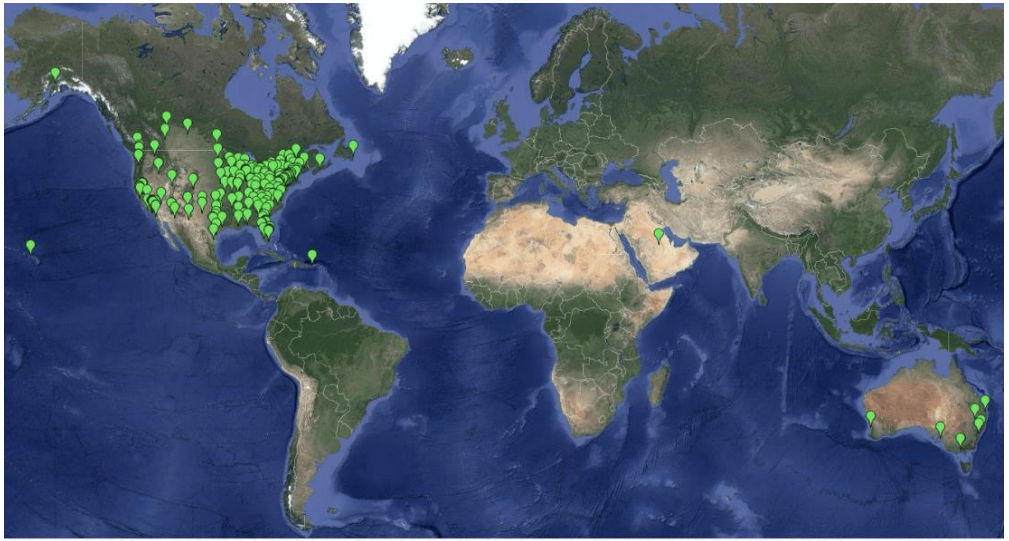
Molecular Characterization Initiative (MCI)

Strategy

WHAT IS THE CCDI Molecular Characterization Initiative?

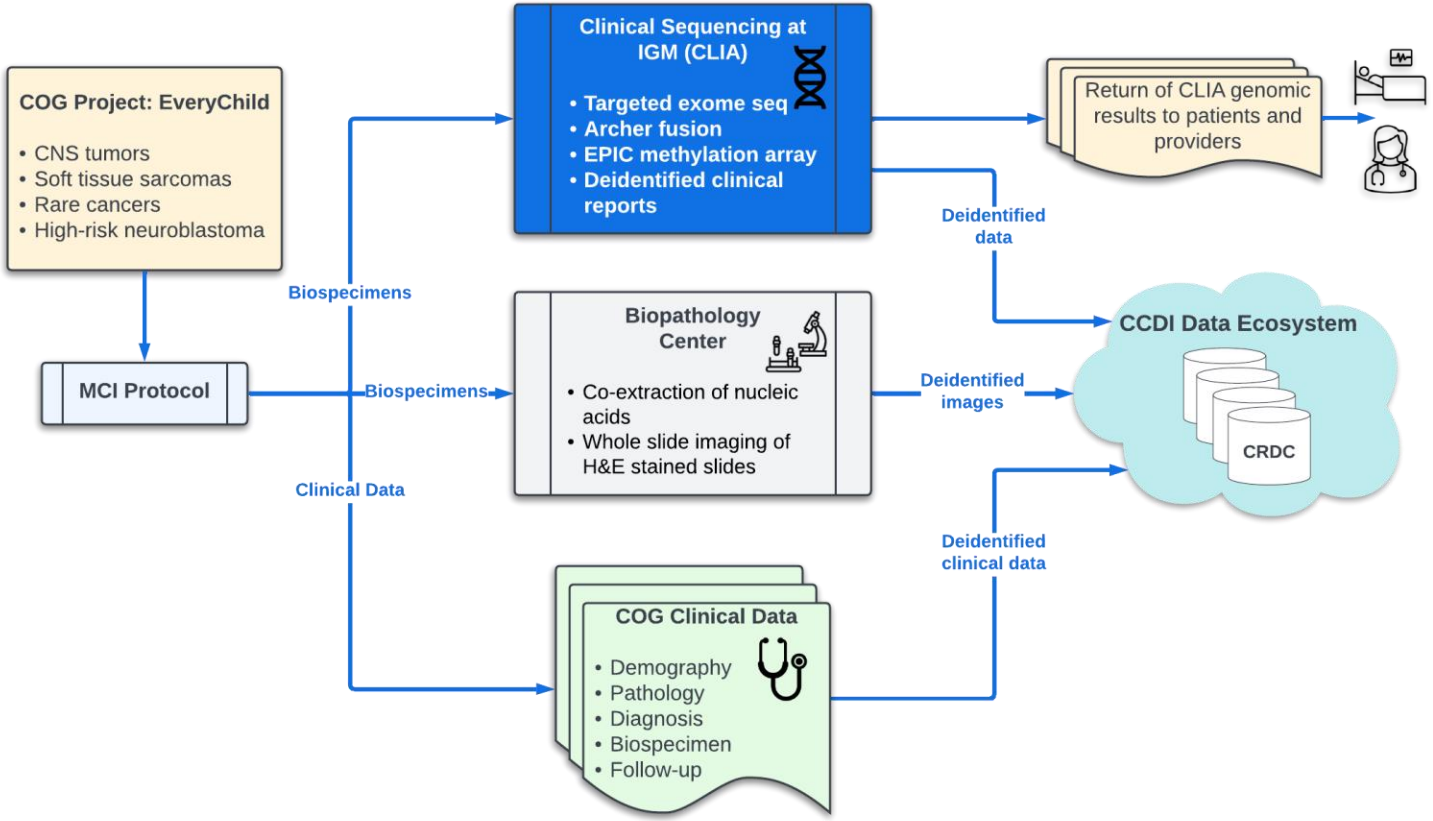


Children's Oncology Group (COG) Institutions



More than 90% of 16,000 children and adolescents diagnosed with cancer each year in the United States are cared for at Children's Oncology Group member institutions.

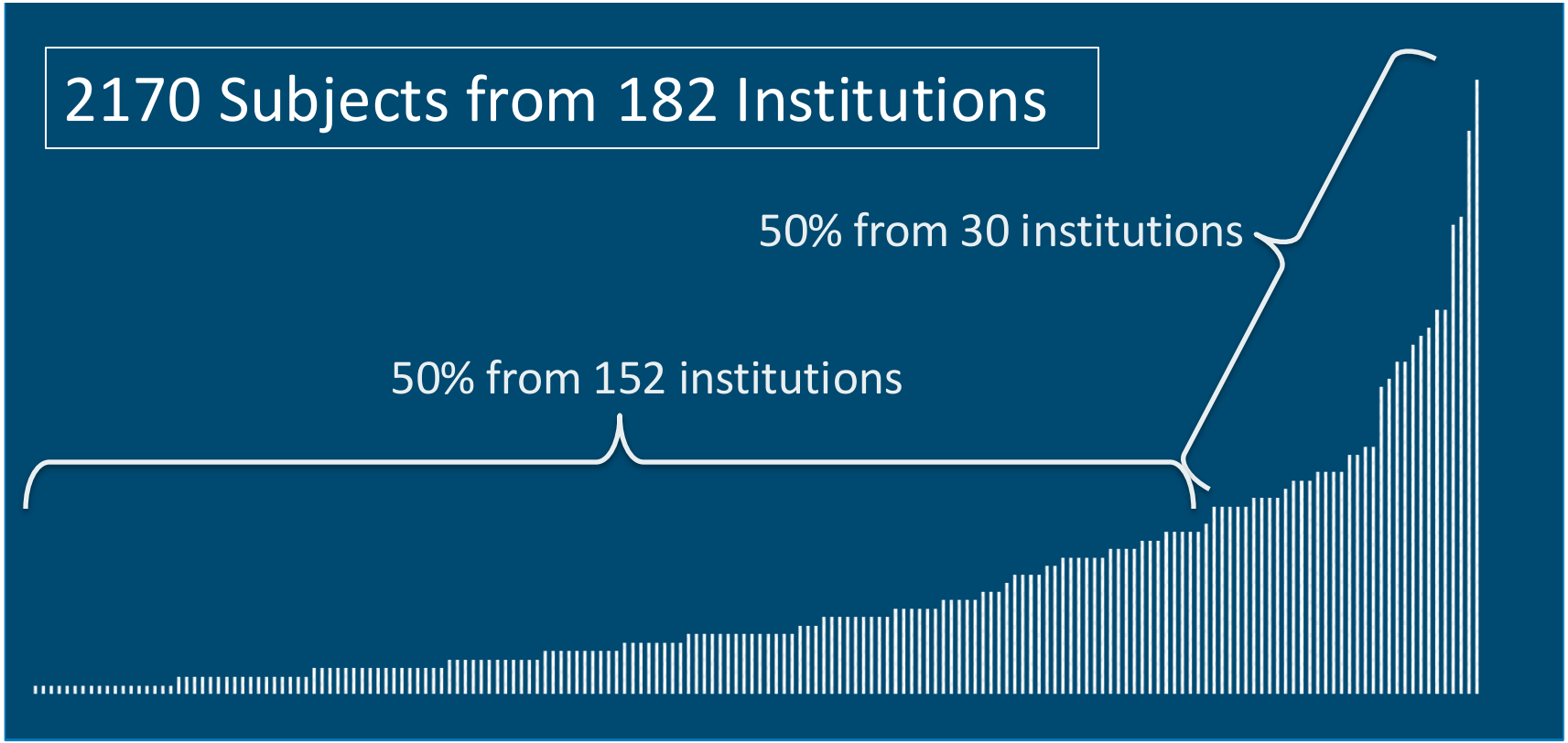
A Partnership Between NCI and COG Project: Every Child



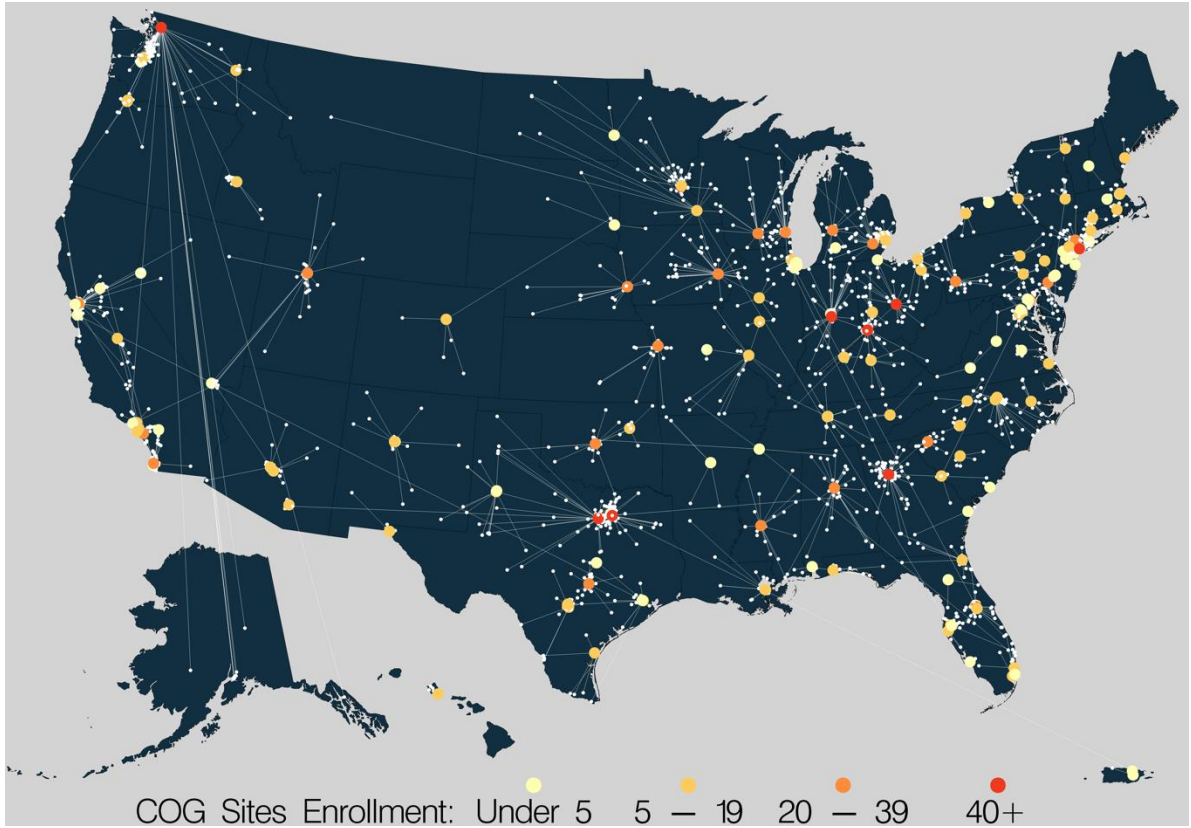
MCI Progress

Genomics and Clinical Data for CNS Subjects

MCI CNS Enrollment by Institution as of 12/31/2023

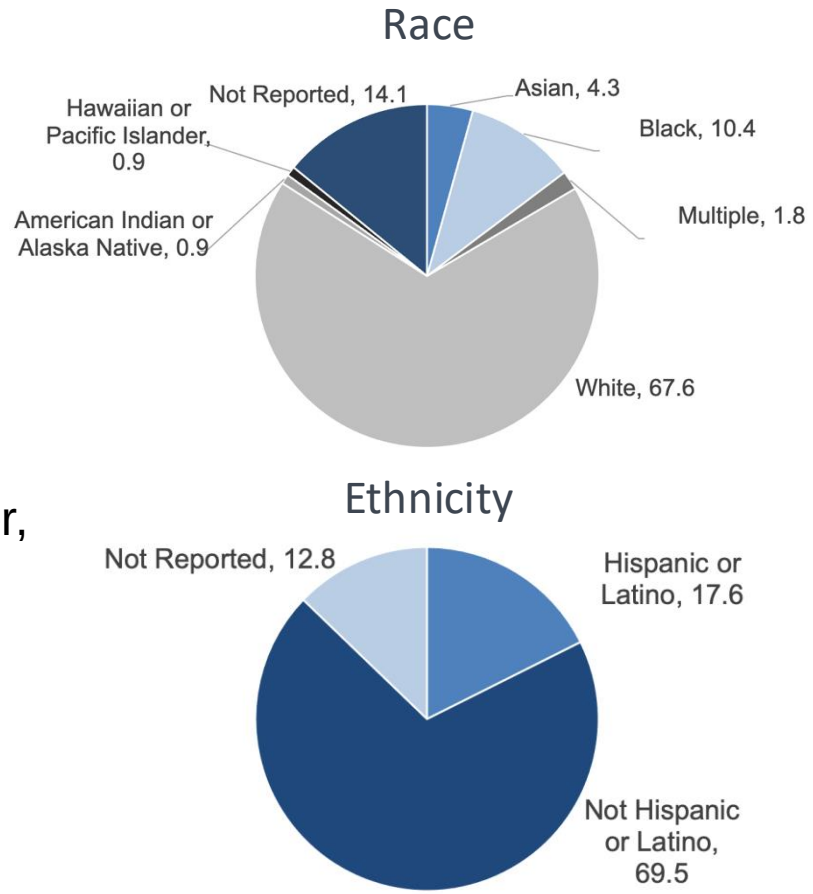


MCI CNS Enrollment (12/31/23) by Subject US Zip Code

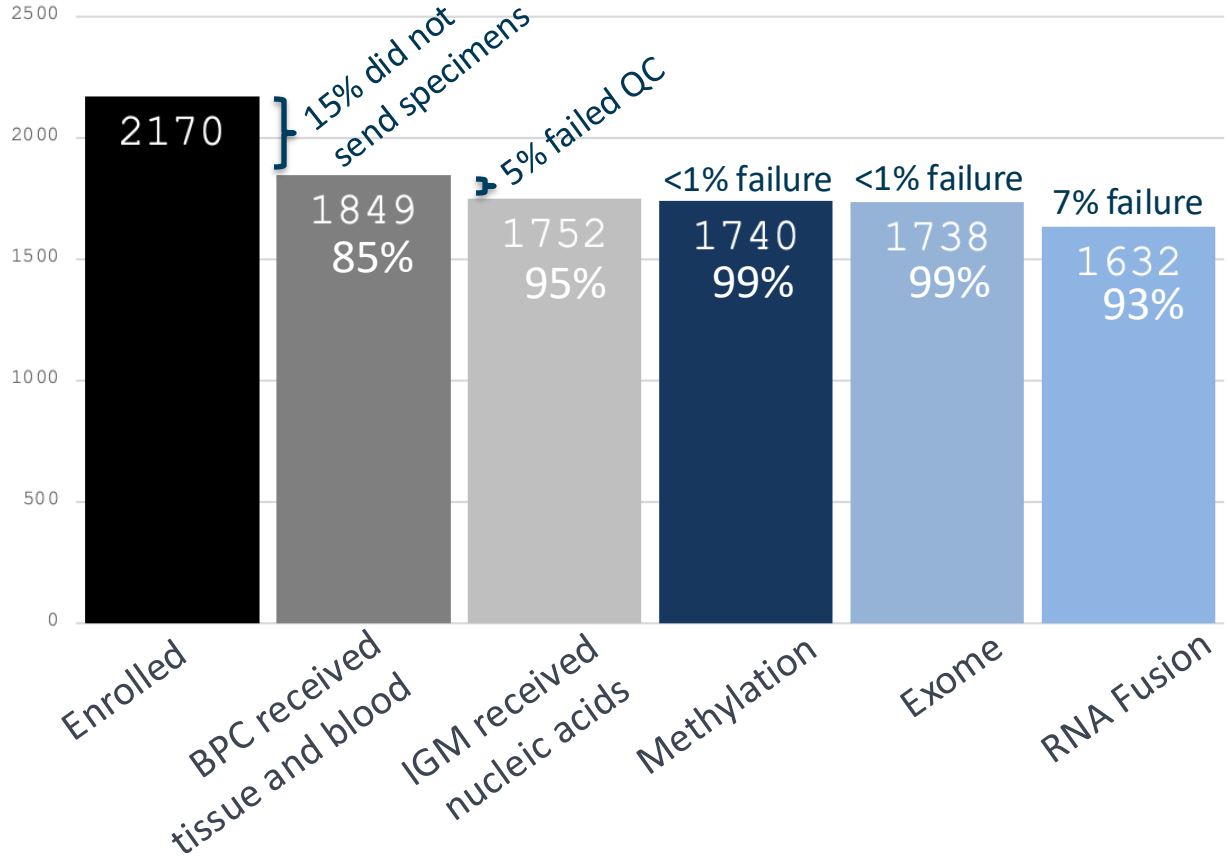


MCI CNS Patient Demographics

- Median Age: 8.9 years (range 0-25)
- Gender: 44% female, 56% male
- Country: 90% USA, 6% Canada, 1.6% Australia, 1.6% New Zealand
- Race: 4.3 % Asian, 10.4% Black, 1.8% multiple, 0.9% Hawaiian or Pacific Islander, 0.9% Native American
- Ethnicity: 17.6% Hispanic or Latino



MCI CNS Return of Results



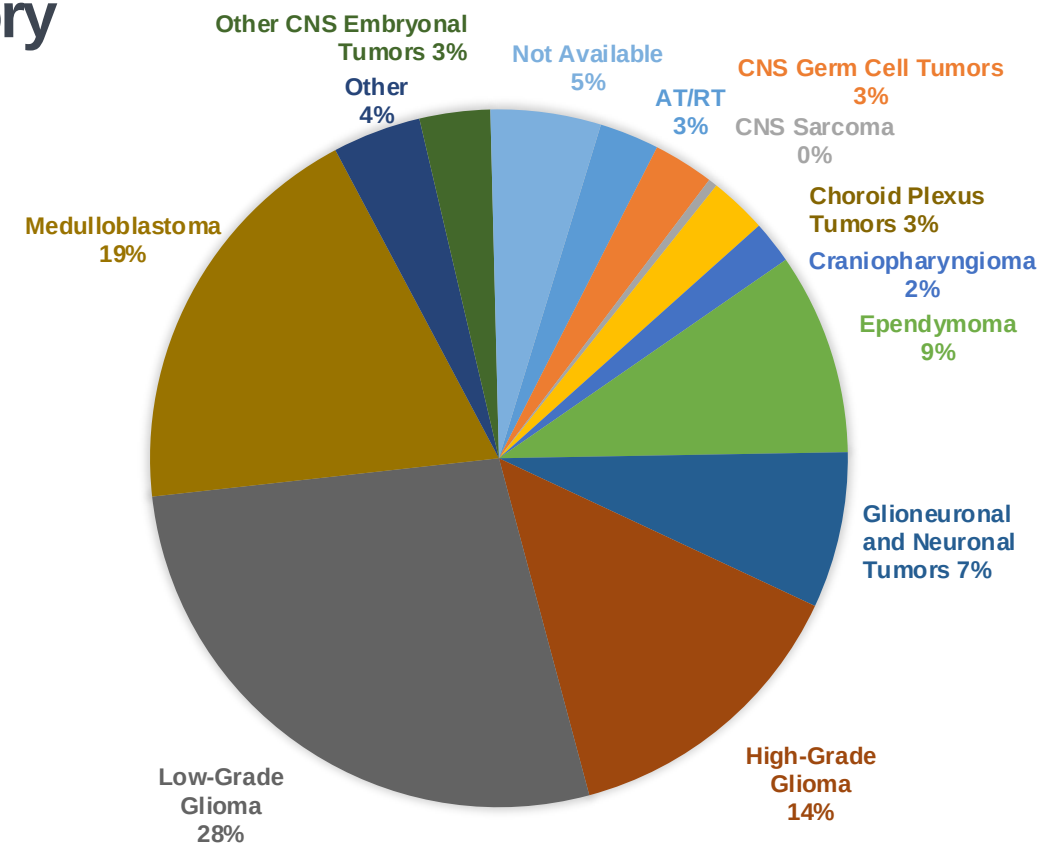
MCI Data

Clinical Impact

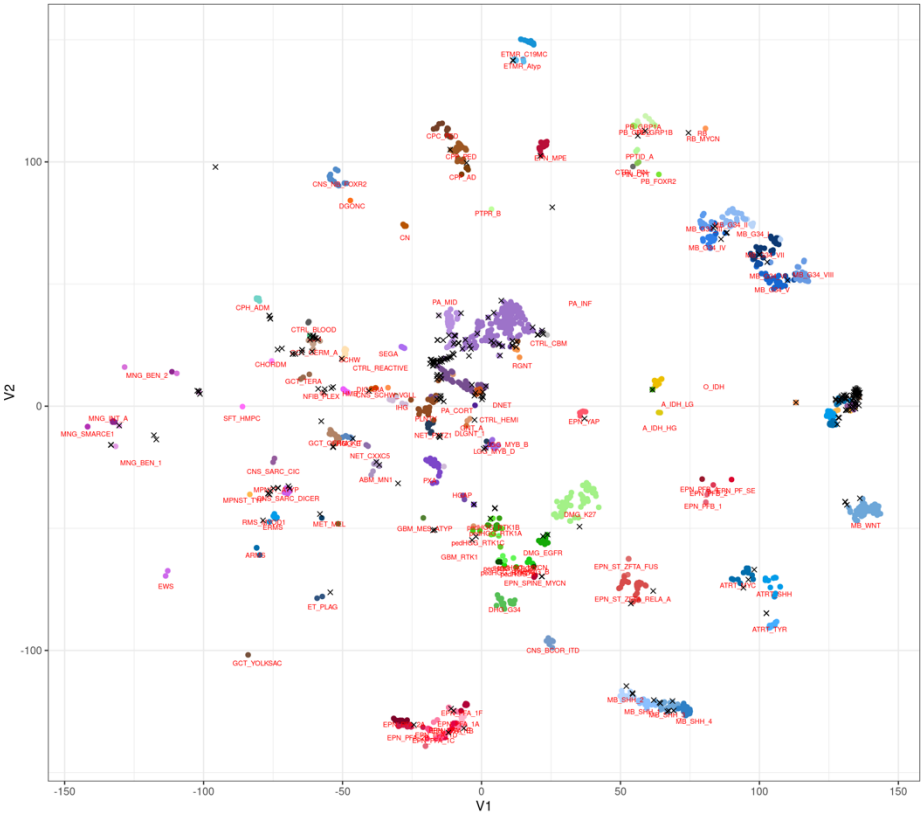
MCI CNS Diagnosis Category

	CNS Diagnosis Category	Frequency Count	Percent of Total (%)
*	Atypical teratoid/ rhabdoid tumor	60	2.8
*	CNS Germ Cell Tumors	61	2.8
	CNS Sarcoma	9	0.4
	Choroid Plexus tumors	58	2.7
	Craniopharyngioma	43	2.0
*	Ependymoma	203	9.4
	Glioneuronal and neuronal tumors	157	7.2
*	High-Grade Glioma	301	13.9
*	Low-Grade Glioma	595	27.4
*	Medulloblastoma	412	19.0
	Other	89	4.1
	Other CNS Embryonal tumors	71	3.3
	Not Available	111	5.1
		2170	***100.0***

* Current COG trial for selected patients
* Planned COG trial for selected patients



MCI CNS DNA Methylation Classification



- >100 Distinct CNS tumor classes identified

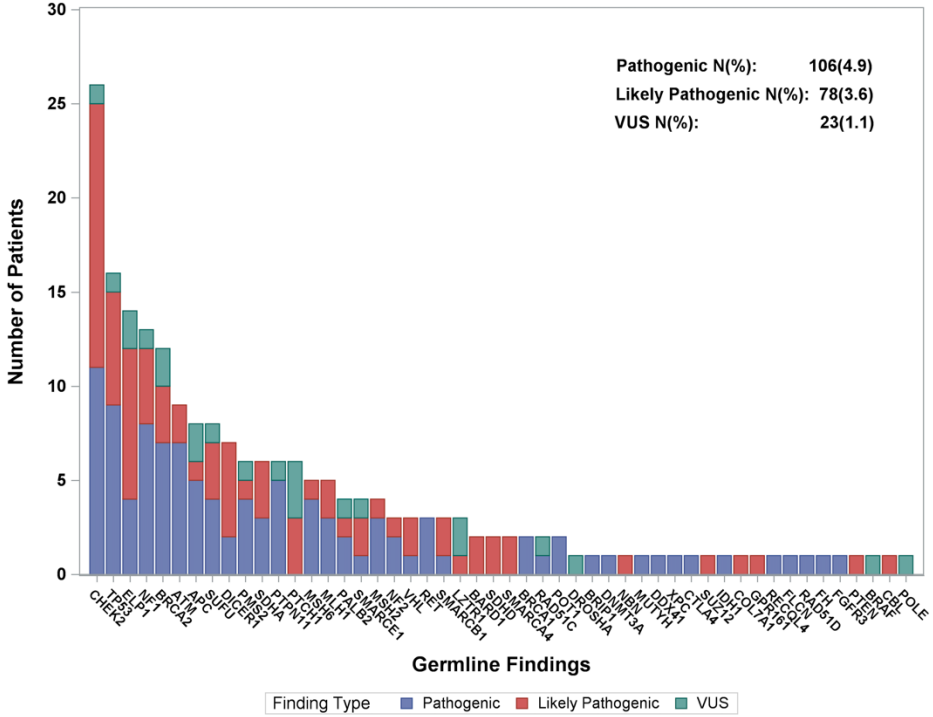
Methylation Classification	Frequency	Percent (%)
Match	1406	85%
Suggestive	100	6%
Not Determined	139	8%
Total Tested	1645	100%

Results: Somatic Alterations Detected in CNS Tumors

- Whole exome DNA sequencing:
  - Pathogenic variants detected in 43.2% of tumors (n=1829)
    - 111 *BRAF* V600
    - 28 *IDH1*
  - Medically-informative copy number variation (CNV) or loss of heterozygosity (LOH) in 76.3% of tumors
- Archer fusion panel: fusions detected in 28.5% of tumors (n=1683)
  - 289 *BRAF::KIAA*1549
  - 36 *NTRK/ROS/ALK* fusions

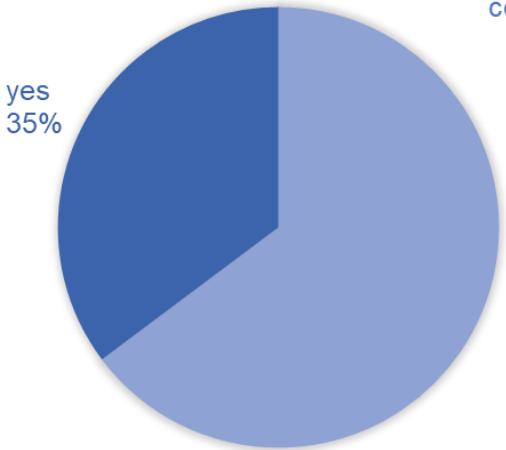
Results: 12% Germline Cancer Predisposition

- 207 of 1738 children tested found to have genetic cancer predisposition
- 49 different genes
  - CHEK2 (1.5%), TP53 (0.9%)
  - MMR defects (0.9%)
    - 12 high-grade glioma
    - 1 low-grade glioma
    - 2 medulloblastoma
  - ELP1 (0.8%), NF1 (0.7%)

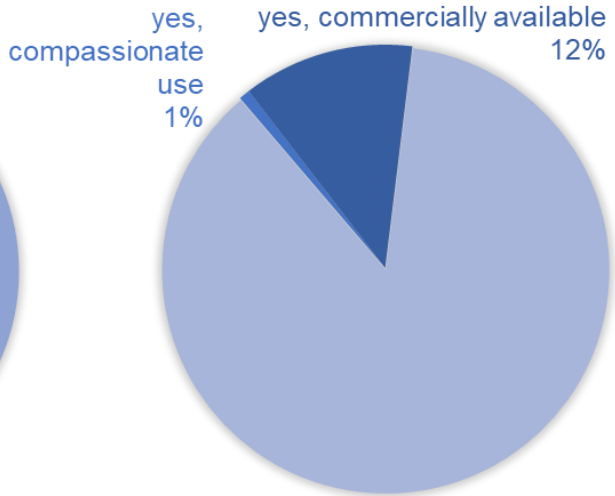


MCI CNS Follow-Up

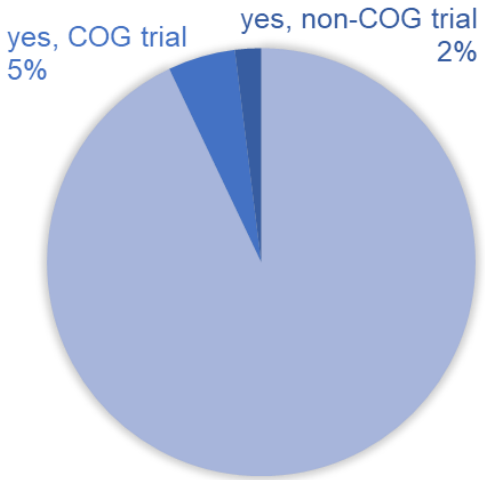
Diagnosis refined by testing?
N=965



Therapy matched by sequencing?
N=887

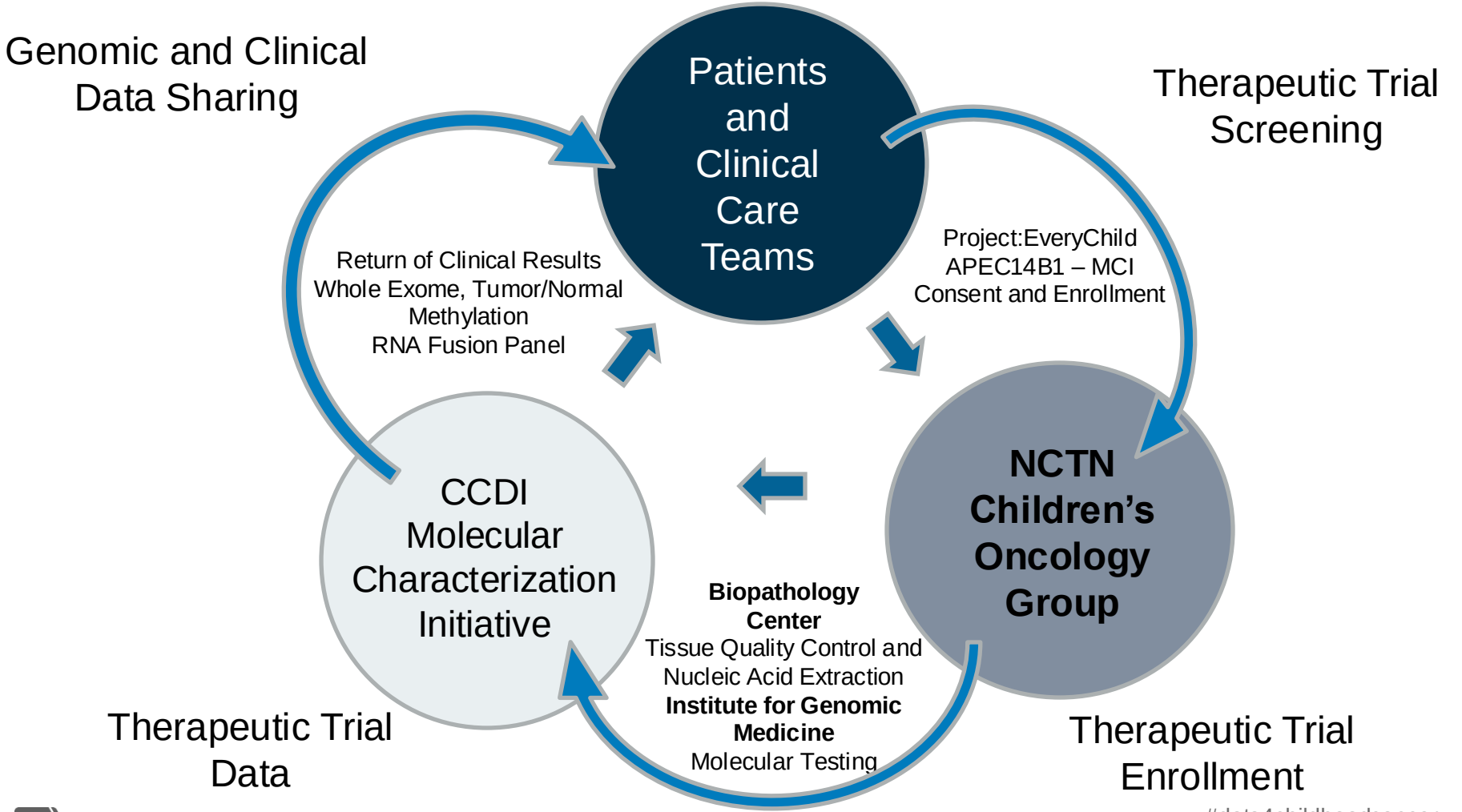


Trial enrolled using results?
N=964



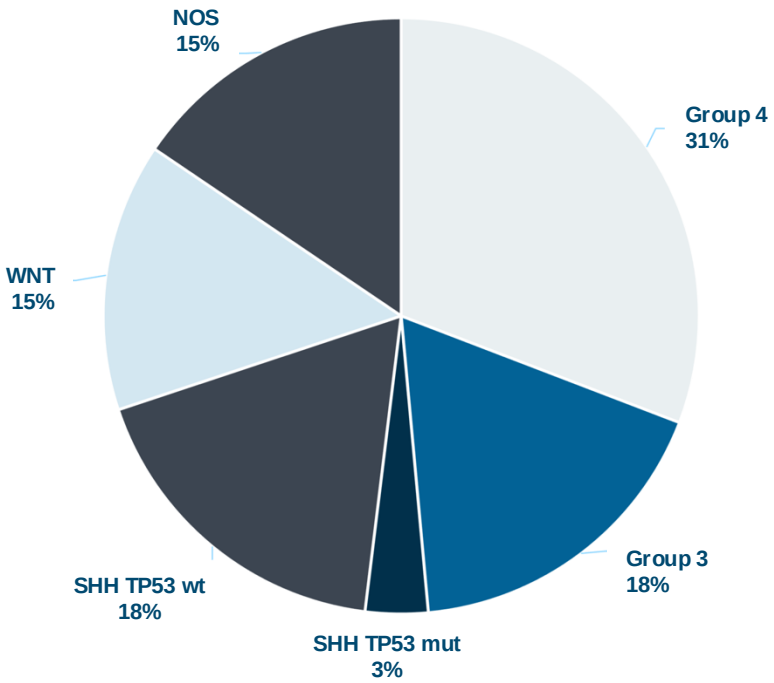
MCI Data

Implications for Clinical Trials


Genomic and Clinical Data Sharing
Patients and Clinical Care Teams
Therapeutic Trial Screening
Return of Clinical Results
Whole Exome, Tumor/Normal Methylation
RNA Fusion Panel
Project:EveryChild
APEC14B1 – MCI
Consent and Enrollment
CCDI Molecular Characterization Initiative
NCTN Children's Oncology Group
Biopathology Center
Tissue Quality Control and Nucleic Acid Extraction
Institute for Genomic Medicine
Molecular Testing
Therapeutic Trial Data
Therapeutic Trial Enrollment

MCI CNS Diagnosis: Medulloblastoma

MCI CNS Medulloblastoma (n=412 as of 12/31/2024)



Medulloblastoma Group	Frequency	Percent (%)
Group 4	127	31%
Group 3	73	18%
SHH TP53 wt	74	18%
SHH TP53 mut	14	3%
WNT	60	15%
NOS	64	15%
Total	412	100%

COG Clinical Trial Approach for Medulloblastoma Integrated Clinical and Molecular Risk Stratification

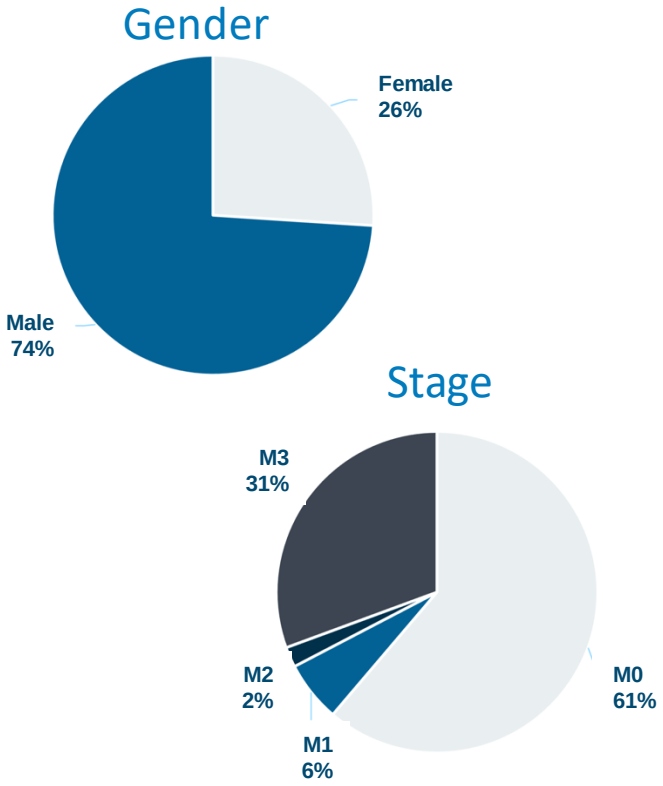
- Clinical Risk Factors
  - Metastatic Disease
  - Incomplete Resection
  - Anaplastic Histology
  - Age < 4*

    *radiation avoidance
- Molecular High-Risk
  - Group 3
    - MYC amplification
    - Isochromosome 17
  - SHH
    - TP53 mutation or deletion
    - NMYC or GLI amplification
    - Chromosome 14 loss
- Molecular Low-Risk
  - WNT
  - Group 4
    - Chromosome 11 loss

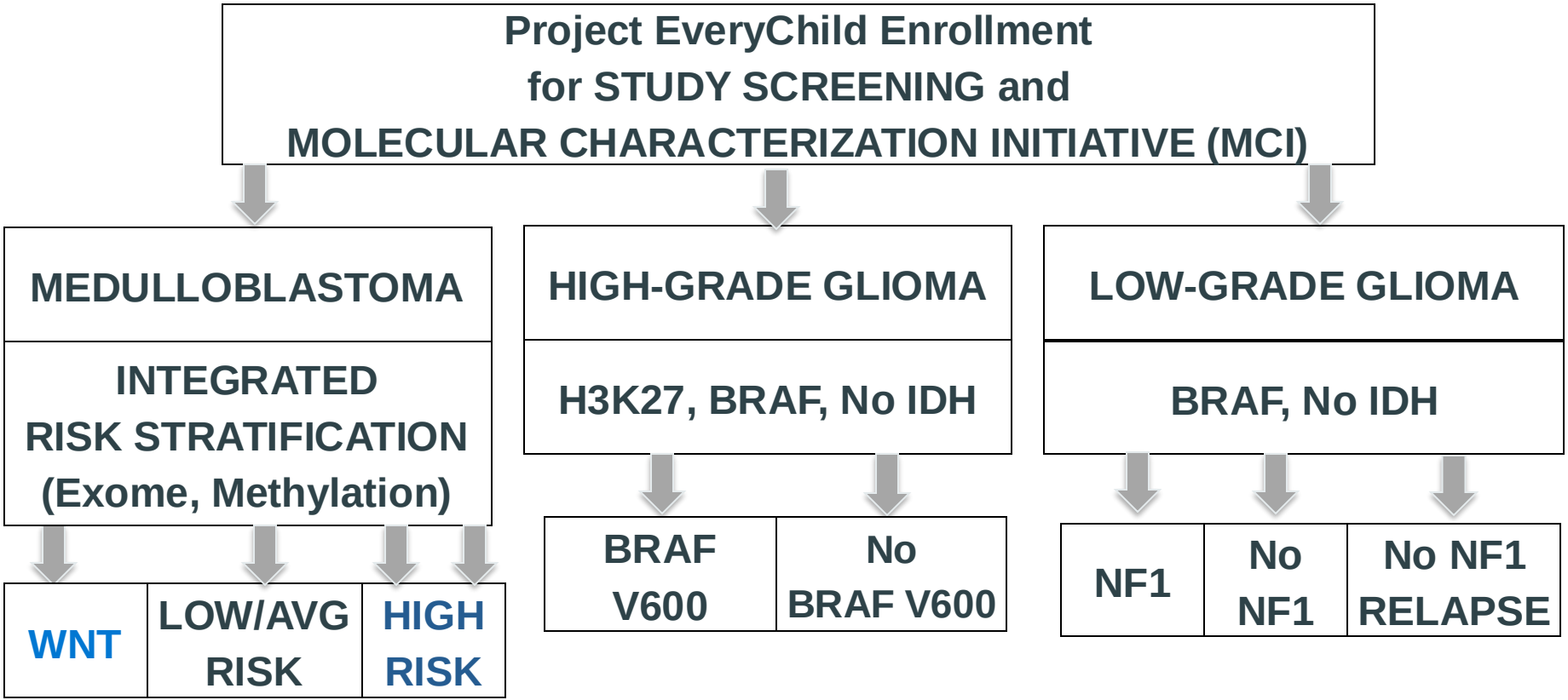
DNA Methylation | Exome Sequencing | Exome Copy Number

MCI CNS Diagnosis: Medulloblastoma Group 3 (n=73)

- Median Age: 5 years (range 1-23)
- >2:1 Male:Female
- Stage: 39% metastatic
- One Year Follow-Up (n=22)
  - Extent of Resection: 73% GTR
  - Radiation Therapy: 64% (all proton)
  - One Year Survival: 68%

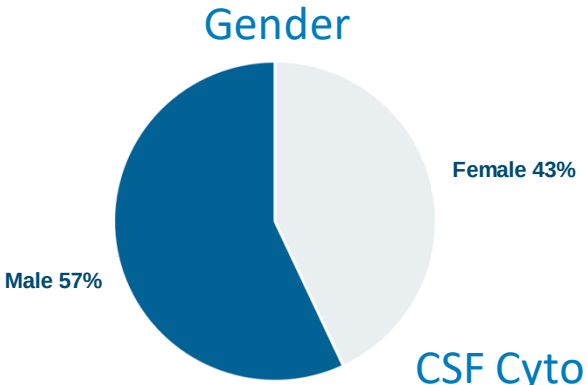


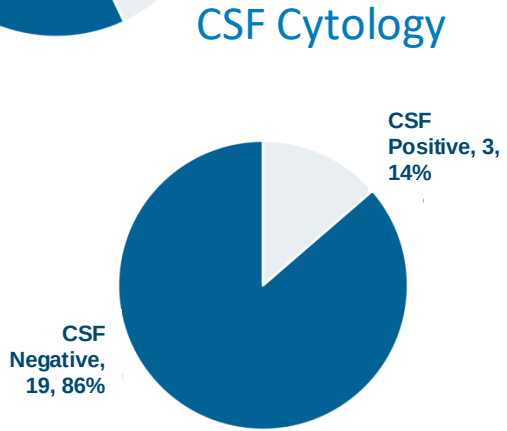
NCTN COG Clinical Trial Design



MCI CNS Diagnosis: Diffuse Midline Glioma, H3K27 Altered (n=86)

- Median Age: 9 years (range 3-20)
- Gender: 57% male:43% female
- Stage: 3/22 (14%) positive CSF cytology (most not tested)
- One Year Follow-Up available for first 14 patients: 43% survival
- All tumors with alterations in addition to H3K27



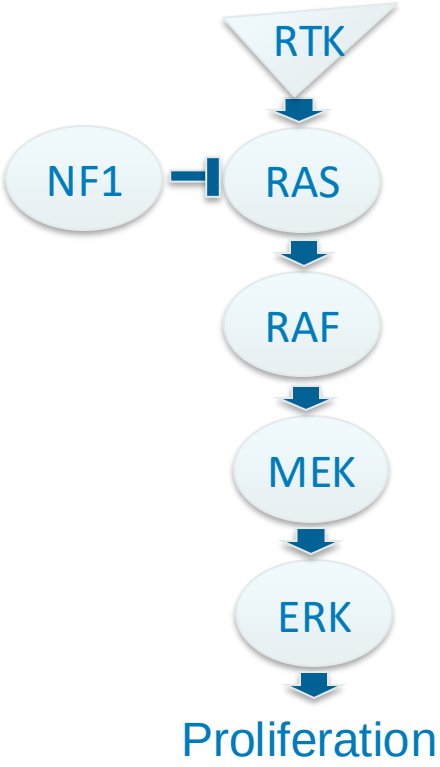


Potentially Targetable Pathway Alterations in Diffuse Midline Glioma, H3K27 Altered (n=86)

- MAPK pathway alterations
  - *BRAF*: 7 mutations

    (4 V600E, 4 other, 1 fusion)
  - RAS: 3 mutations

    (2 *NRAS*, 1 *KRAS*)
  - RAF: 1 mutation (*RAF1* germline)
  - *NF1*: 15 mutations (1 germline)



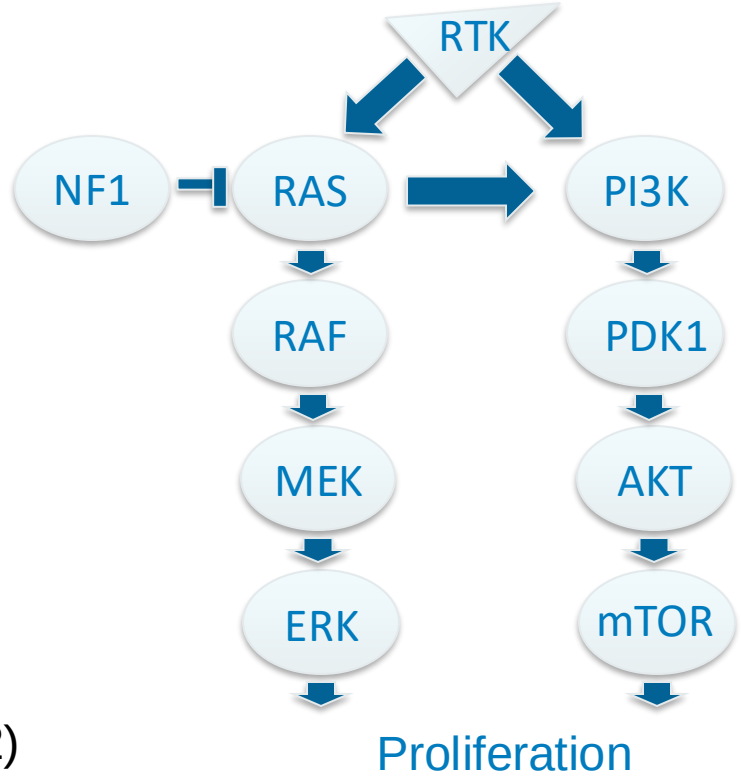
Potentially Targetable Pathway Alterations in Diffuse Midline Glioma, H3K27 Altered (n=86)

- Selected other targetable alterations
  - PGFR1: 9 mutations
  - PDGFRA: 11 mutations
  - PI3K: 15 mutations

    (10 *PIK3CA*, 5 *PIK3R1*)
  - 7 Fusions:

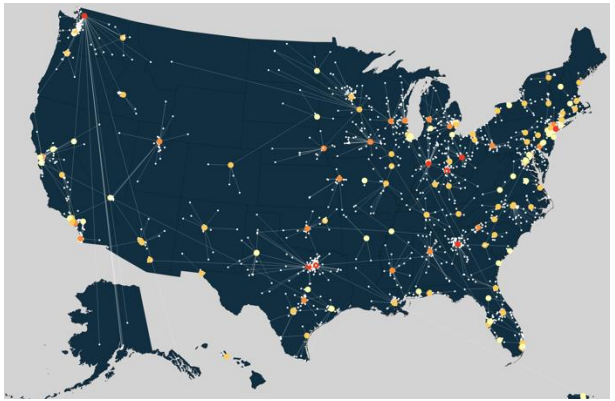
    (4 *MET*, 1 *BRAF*, 1 *NRG1, 1 NTRK*)
  - Germline: 5 alterations

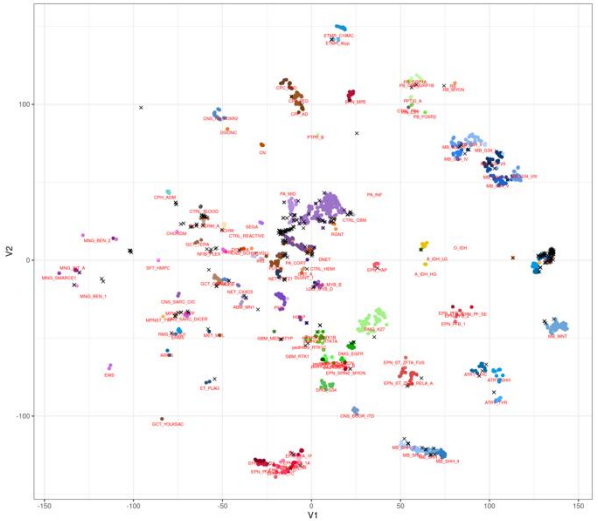
    (CHEK2, TP53, MUTYH, NF1, PMS2)



Building on the MCI

- Cancer predisposition
- Collection to other clinical data sources
- Genomic discovery
- Clinical research in ultra rare tumor populations





NCI/CCDI/COG/BPC/IGM Teams

COG Leadership/APEC14B1

- Doug Hawkins
- Mary Beth Sullivan
- Thalia Beeles
- Michael Thomas, Kelly Gissy

NIH CTEP

- Malcolm Smith

NCI CCDI

- Greg Reaman
- Subhashini Jagu
- Malcolm Smith
- Sean Burke
- Patrick Dunn

Biopathology Center

- Nilsa Ramirez
- Shountea Stover
- Natalie Bir
- Lisa Beaverson
- Yvonne Moyer

IGM

- Elaine Mardis
- Cathy Cottrell
- **Greg Wheeler**
- **Ke Qin**
- Katie Schieffer
- Grant Lammi

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- Dalia Ortega, Shu-Lin Shen

COG CNS Statisticians

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- Arzu Onar-Thomas

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- Maryam Fouladi (Columbus, Ohio)
- Nick Gottardo (Perth, Australia)
- Sarah Leary (Seattle, Washington)
- Diana Thomas (Columbus, Ohio)

Q&A

Join Us at Our Next Event

Comparing Proton and Photon Therapy: Insights from an NCI Pediatric Study

Tuesday, October 8, 2024, from 1:00–2:00 p.m. ET

Learn about a CCDI-supported study, the NCI Pediatric Proton and Photon Therapy Comparison Cohort. This webinar explores the study's design, current enrollment status, and state-of-the-art methods—developed specifically for this cohort—to determine a participant's amount of radiation exposure.

Learn more and register at **events.cancer.gov/ccdi/webinar**

How You Can Engage with CCDI

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Access CCDI data and resources:
ccdi.cancer.gov

Questions? Email us at:
NCIChildhoodCancerDataInitiative@mail.nih.gov

Thank you for attending!

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