National Cancer Advisory Board

Childhood Cancer Data Initiative: Impact of the Molecular Characterization Initiative on Pediatric CNS Tumors

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NIH NATIONAL CANCER INSTITUTE

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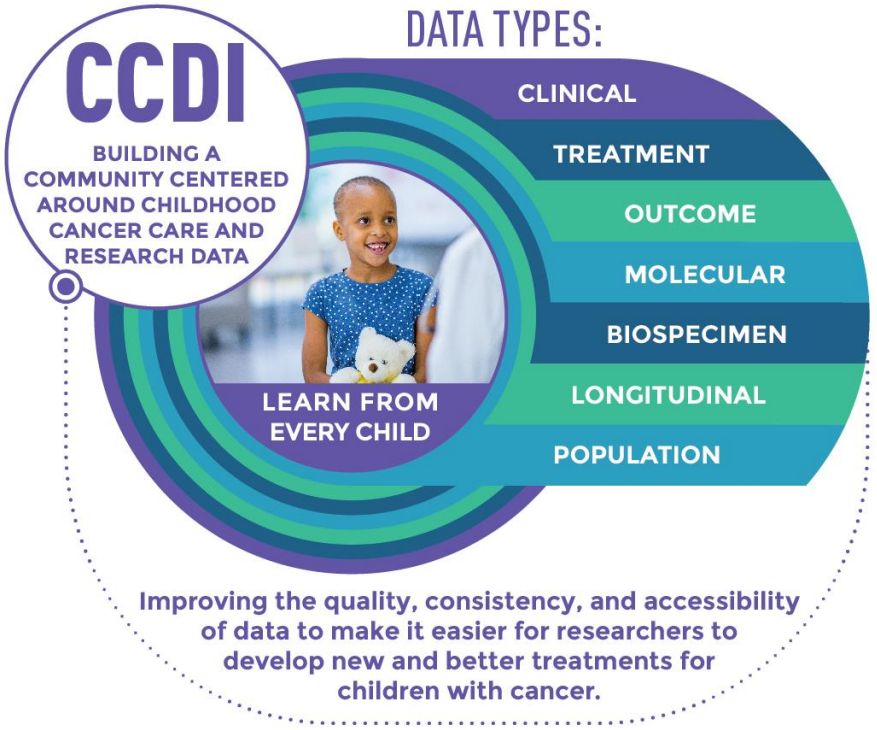
Agenda

1. *About CCDI*
2. *Molecular Characterization Initiative*
   - *Pediatric CNS Tumors*
3. *Rare Cancer Initiative*

About CCDI

CCDI's Key Goals

- Gather data from every child, adolescent, and young adult with childhood cancer
- Create a national strategy of molecular characterization to inform diagnosis and treatment
- Develop a platform and tools for clinical and research data to improve prevention, treatment, quality of life, and survivorship
- Engaging the entire childhood cancer care and research community



Flores-Toro JA et al., J Clin Oncol, 2023
Jagu S et al., Pediatr Blood Cancer, 2024

CCDI Hub

ccdi.cancer.gov

CCDI Stats At a Glance

317
Cataloged Datasets
Childhood Cancer Data Catalog >

2,990*
Participants with Available Genomic and Clinical Data
Molecular Characterization Initiative >

58,867
Potential Pediatric Molecular Targets
Molecular Targets Platform >

1,700,440
Reported Cases Under Age 40 (1995-2020)
National Childhood Cancer Registry Explorer >

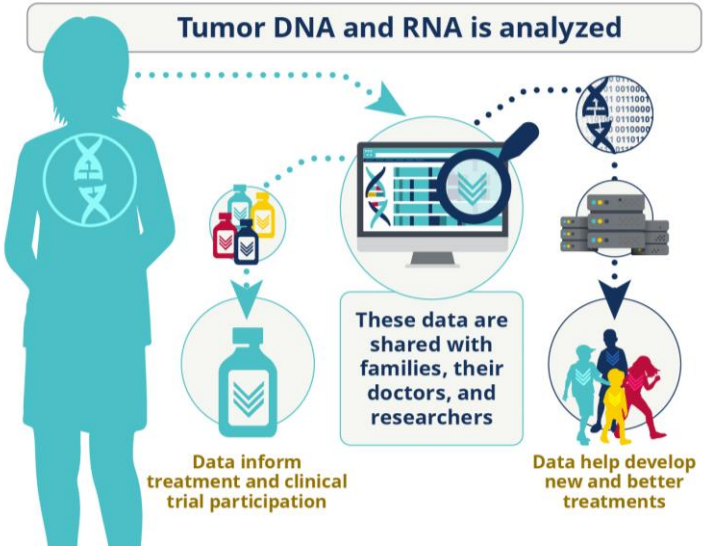
* Counts for MCI participants in CCDI Hub and total MCI participants consented may differ.

- Entry point for researchers, data scientists, and citizen scientists
- Information and direct links to CCDI platforms, tools and resources
- New discoveries that impact patient lives

CCDI Molecular Characterization Initiative

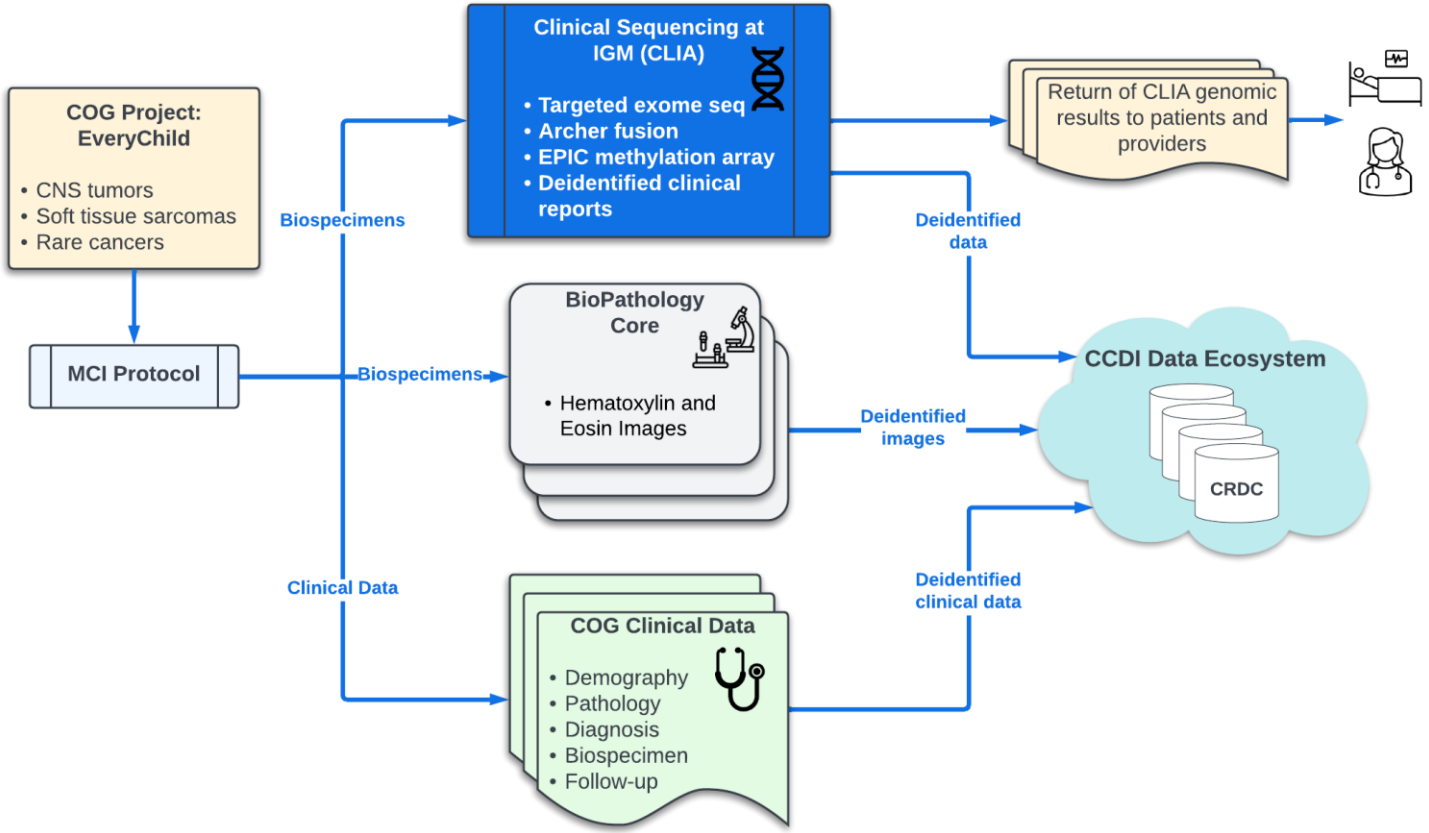
CCDI Molecular Characterization Initiative (MCI)

- National strategy for appropriate clinical and molecular characterization for every child with cancer:
  - Minimum set of molecular diagnostics
  - Standardized molecular profiling on up to 3,000 children annually
  - Enabling discoveries as clinical data are connected with other datasets
  - Building a clinically annotated biobank for future research from remaining tissues



cancer.gov/CCDI-molecular

A Partnership Between NCI and COG Project: Every Child



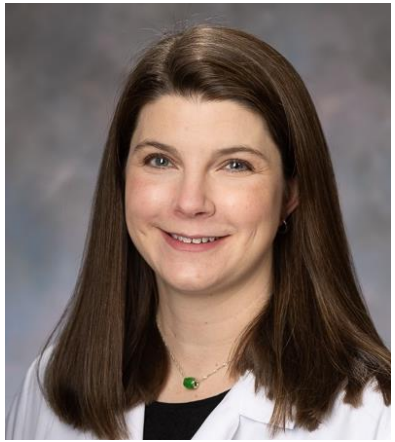
Rollout in Stages

Type	Introduced	Number
Newly diagnosed CNS tumors	March 2022	3095
Soft tissue sarcoma	May 2022	930
Rare tumors	September 2022	416
Neuroblastoma high risk	February 2024	174
Ewing sarcoma	2025	-
Relapsed tumors	Planned	-

Adding research molecular characterization (2025)

MCI Collaborators

- Diana L. Thomas, MD, PhD, Neuropathologist
  - Pathology Operations Director, Biopathology Center,
  - Nationwide Children's Hospital



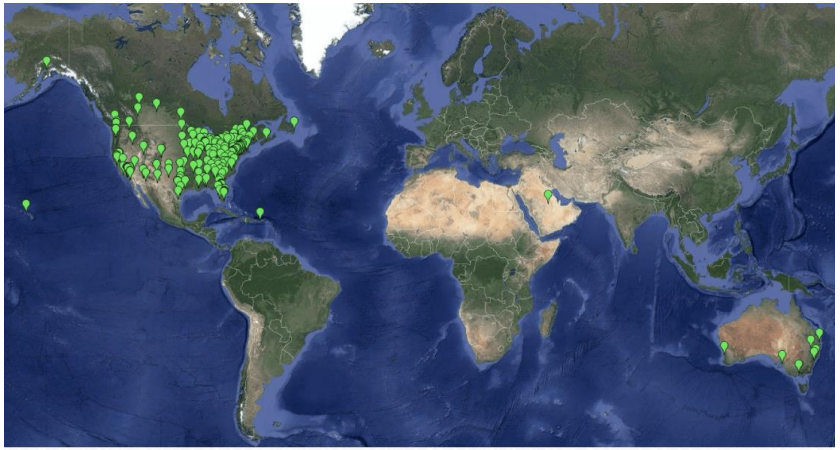
- Sarah E. S. Leary, MD, MS, Pediatric Oncologist
  - Medical Director, Pediatric Brain Tumor Program
  - Seattle Children's Hospital

MCI CNS COHORT

Genomics and Clinical Data for CNS Subjects

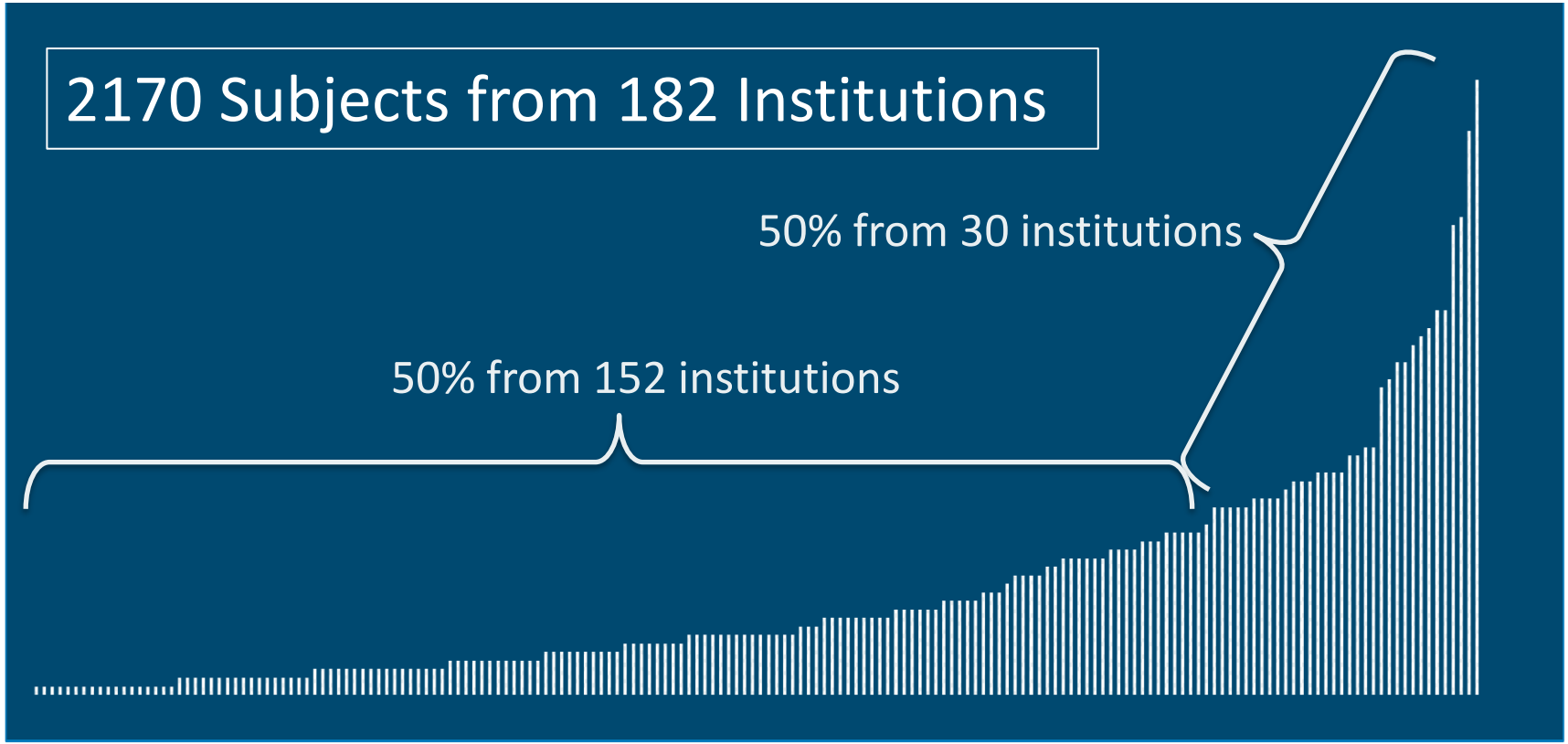
PROJECT:EVERYCHILD

Children's Oncology Group

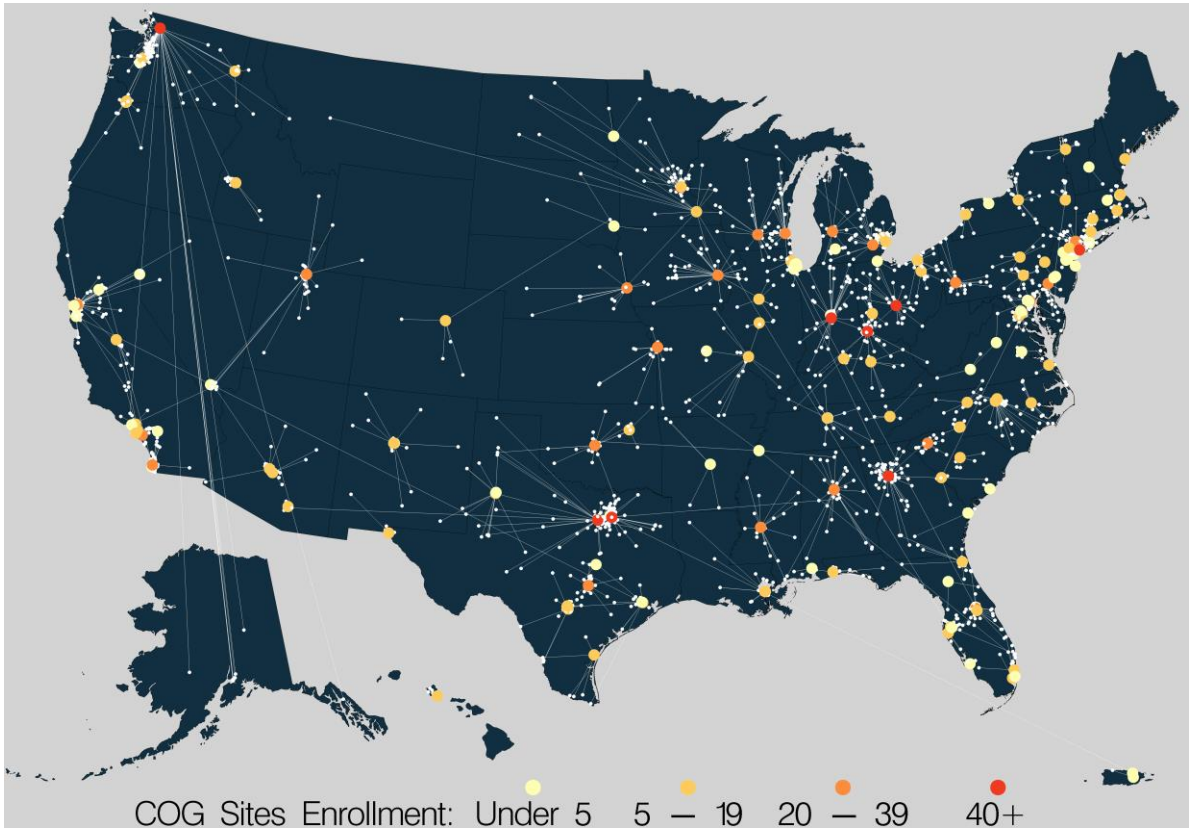


More than 90% of 16,000 children and adolescents diagnosed with cancer each year in the United States are cared for at Children's Oncology Group member institutions.

MCI CNS Enrollment (12/31/23) by Institution

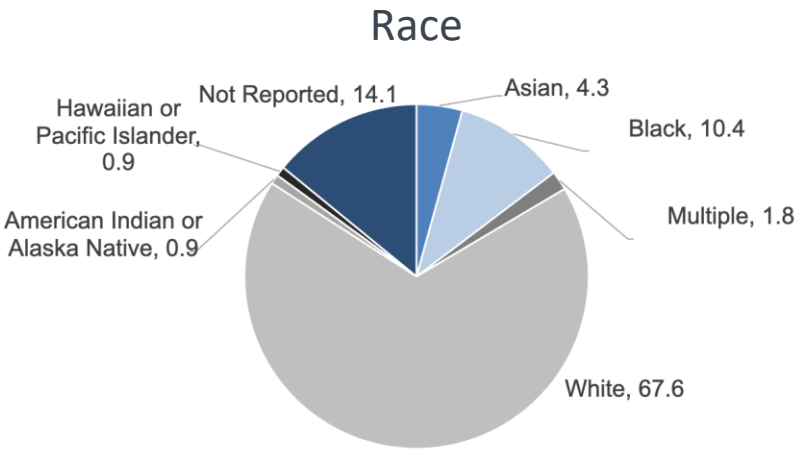


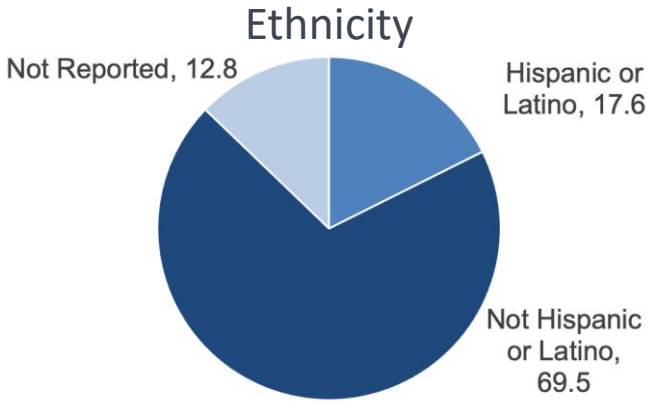
MCI CNS Enrollment (12/31/23) by Subject US Zipcode



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



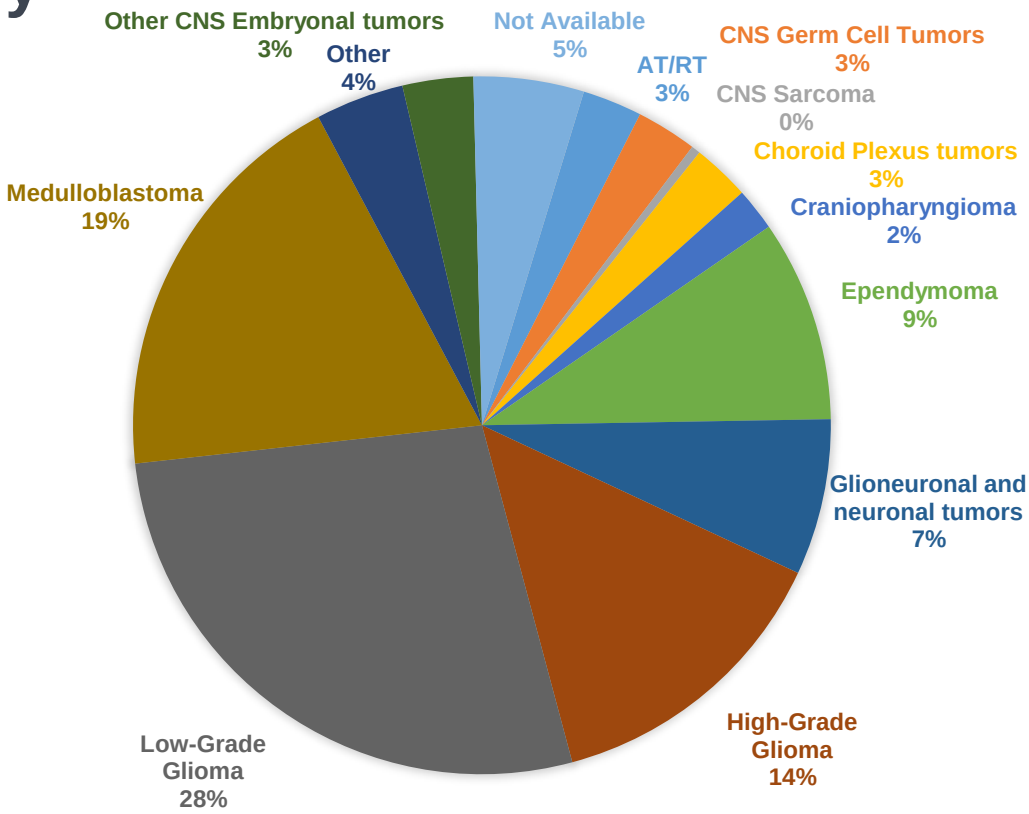


MCI CNS Diagnosis Category

	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***

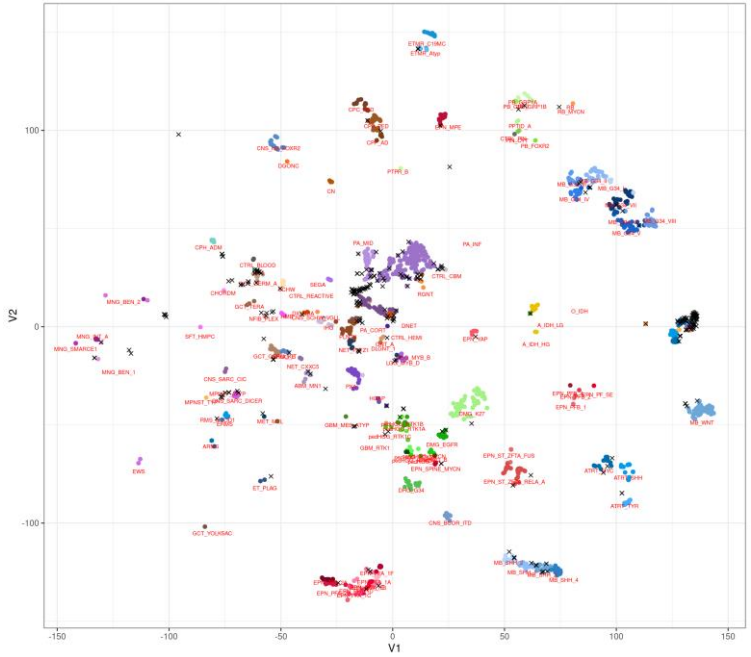
* Current COG trial for selected patients

* Planned COG trial for selected patients



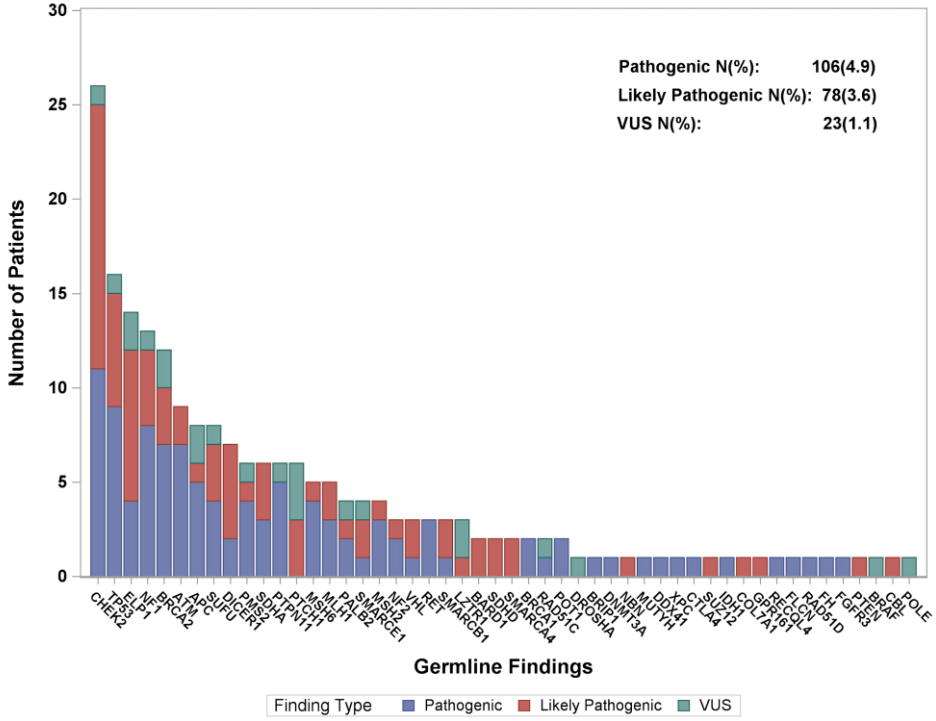
Return of Results: Molecular diversity of tumors with frequent clinically relevant molecular findings

- DNA Methylation (n=1645):
  - Match with high confidence in 85%
  - >100 distinct classes
- Whole exome DNA sequencing (n=1829):
  - Pathogenic variants detected in 43.2% of tumors
  - Copy number variation (CNV) or loss of heterozygosity (LOH) in 76.3% of tumors
- Archer fusion panel (n=1693):
  - Fusions detected in 28.5% of tumors (n=1683)



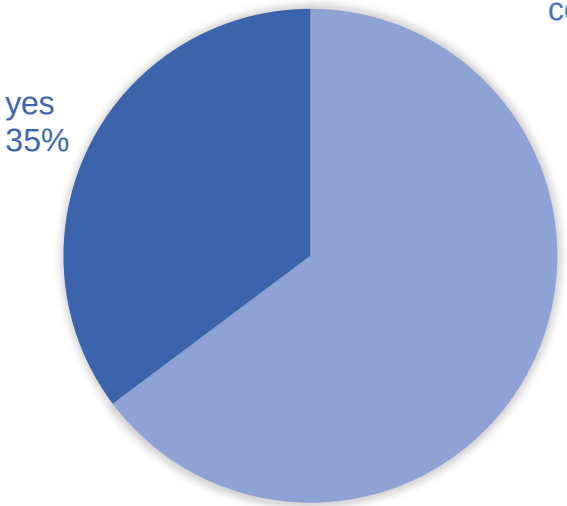
Results: 12% Germline Cancer Predisposition

- 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%)

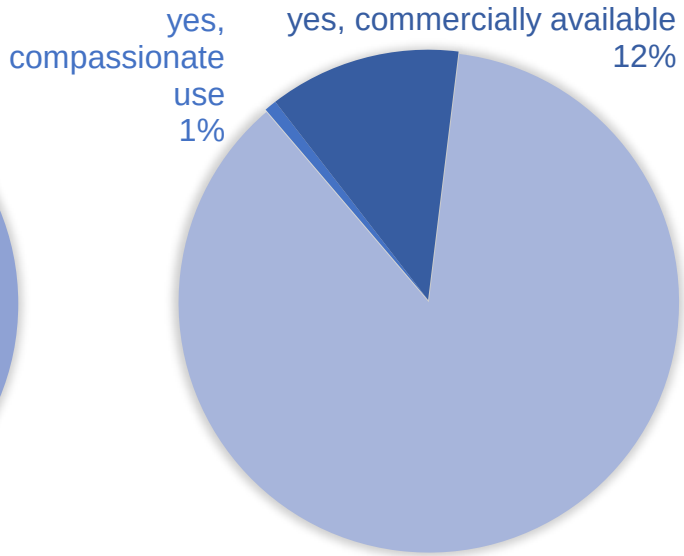


MCI CNS follow-up

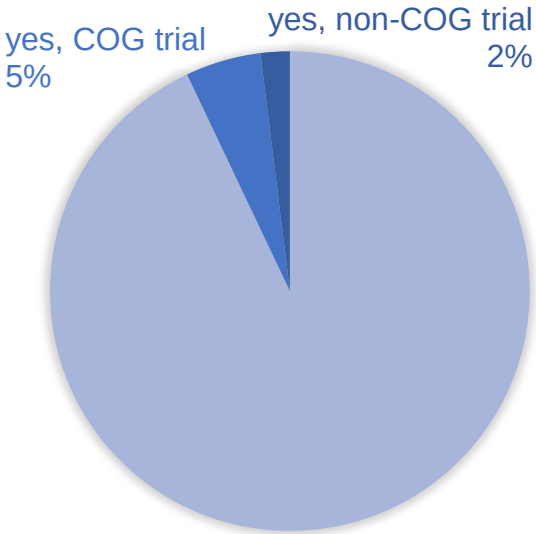
Diagnosis refined by testing?
N=965



Therapy matched by sequencing?
N=887

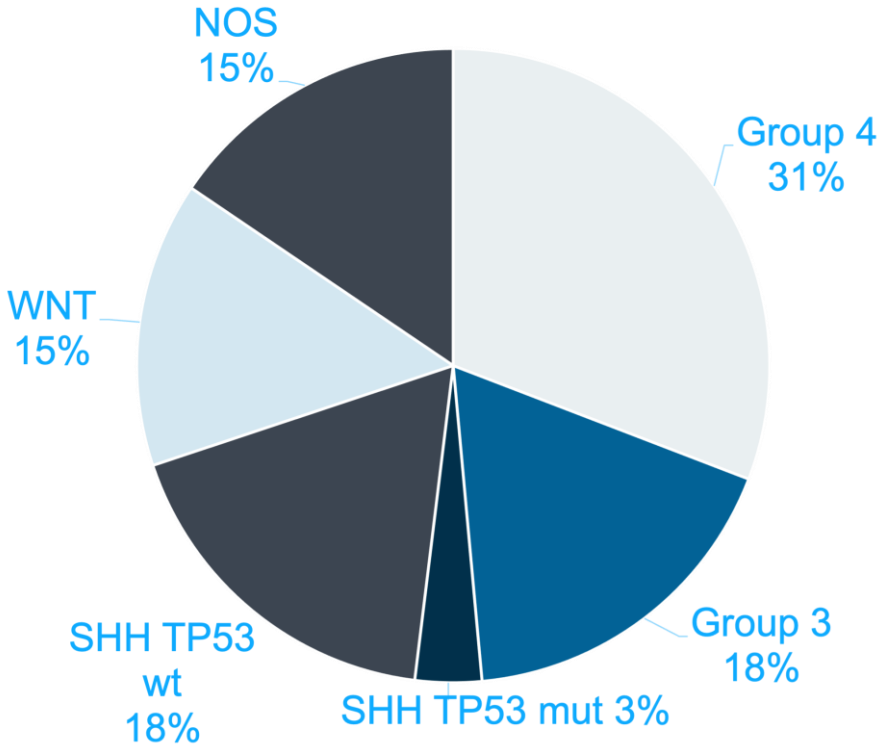


Trial enrolled using results?
N=964



MCI CNS Diagnosis: Medulloblastoma
(n=412 as of 12/31/23)

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

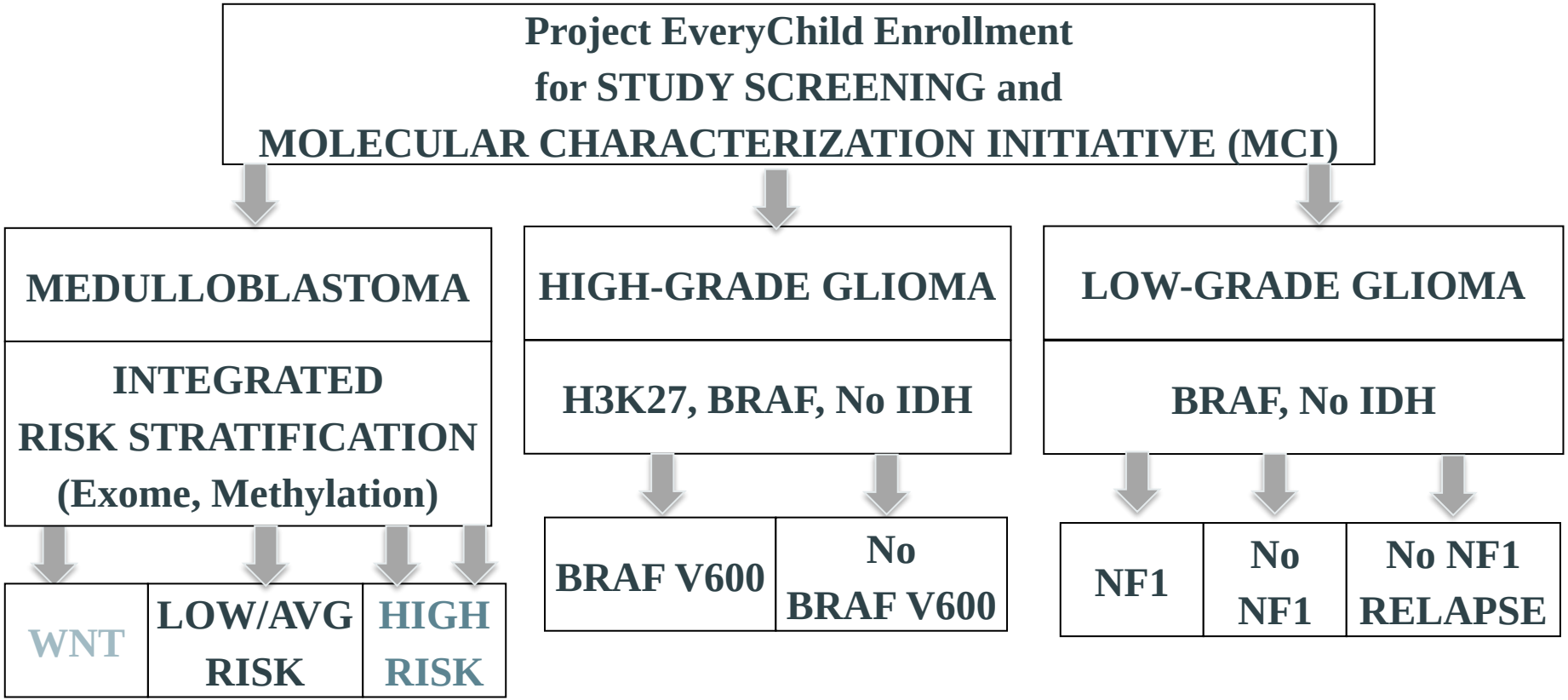
- Molecular Low-Risk
  - WNT
  - Group 4
    - Chromosome 11 loss

DNA Methylation

Exome sequencing

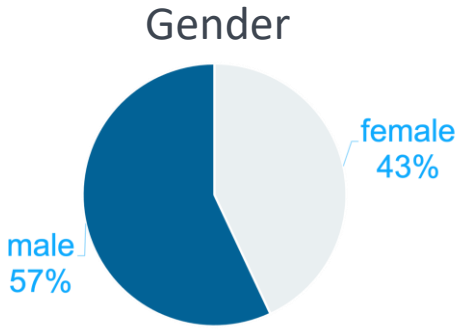
Exome copy number

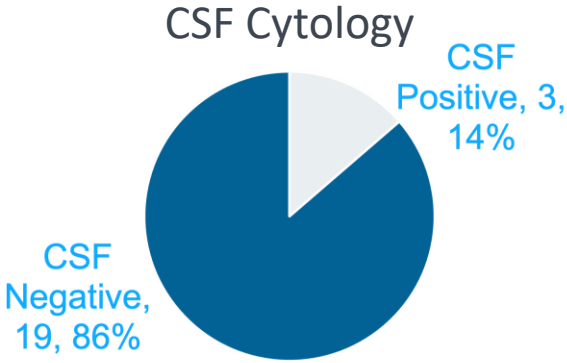
NCTN COG Clinical Trial Design



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



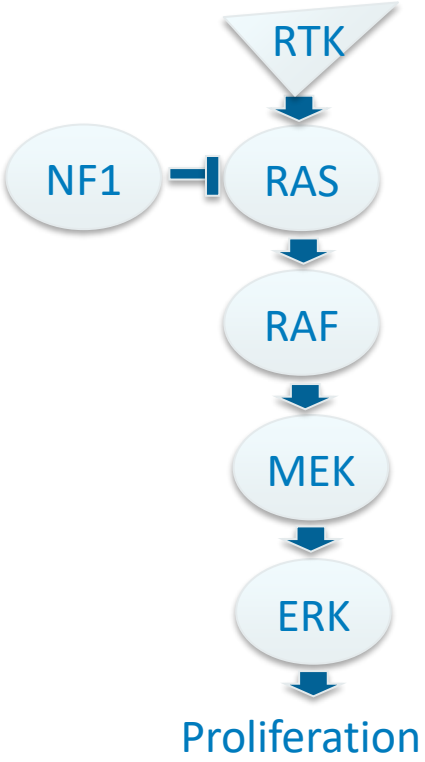


Potentially targetable pathway alterations in Diffuse Midline Glioma, H3K27 altered (n=86)

- 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)



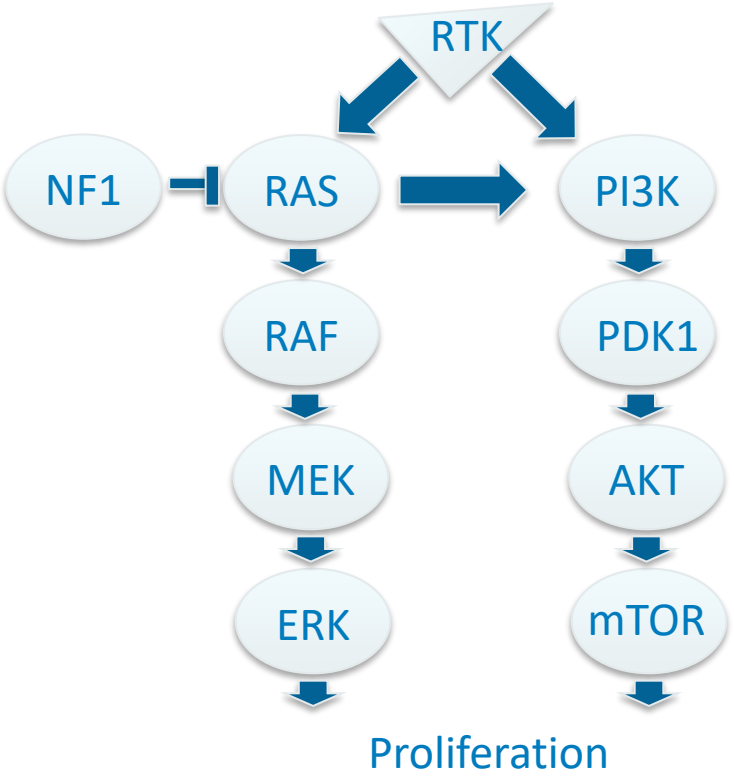
Potentially targetable pathway alterations in Diffuse Midline Glioma, H3K27 altered (n=86)

- Selected other targetable alterations
  - *FGFR1*: 9 mutations
  - *PDGFRA*: 11 mutations
  - PI3K: 15 mutations

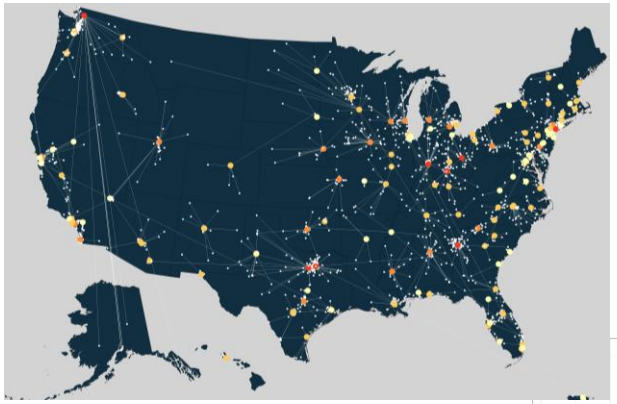
    (10 *PIK3CA*, 5 *PIK3R1*)
  - 7 Fusions:

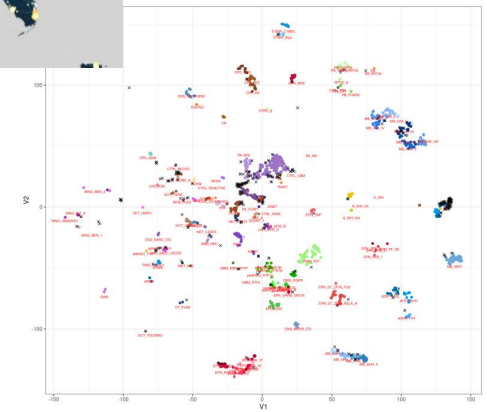
    (4 *MET*, 1 *BRAF*, 1 *NRG1, 1 NTRK*)
  - Germline: 5 alterations

    (*CHEK2, TP53, MUTYH, NF1, PMS2*)



Building on the MCI





- Cancer Predisposition
- Connection 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

NCI CTEP

- Malcolm Smith

NCI CCDI

- Greg Reaman
- Subhashini Jagu
- 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

COG/CNS Operations Team

- Linda Springer
- Natasha Mirt, Melina Chanthanouvong
- Dalia Ortega, Shu-Lin Shen

COG CNS Statisticians

- **Yu Wang**
- Arzu Onar-Thomas

MCICNS@childrensoncologygroup.org

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

CCDI Coordinated Pediatric, Adolescent, and Young Adult Rare Cancer Initiative

CCDI Coordinated Pediatric, Adolescent, and Young Adult Rare Cancer Initiative

Unmet need for rare pediatric and AYA cancers:

- A national effort will allow enrolling adequate numbers of participants to more rapidly, efficiently, and consistently study multiple rare cancers

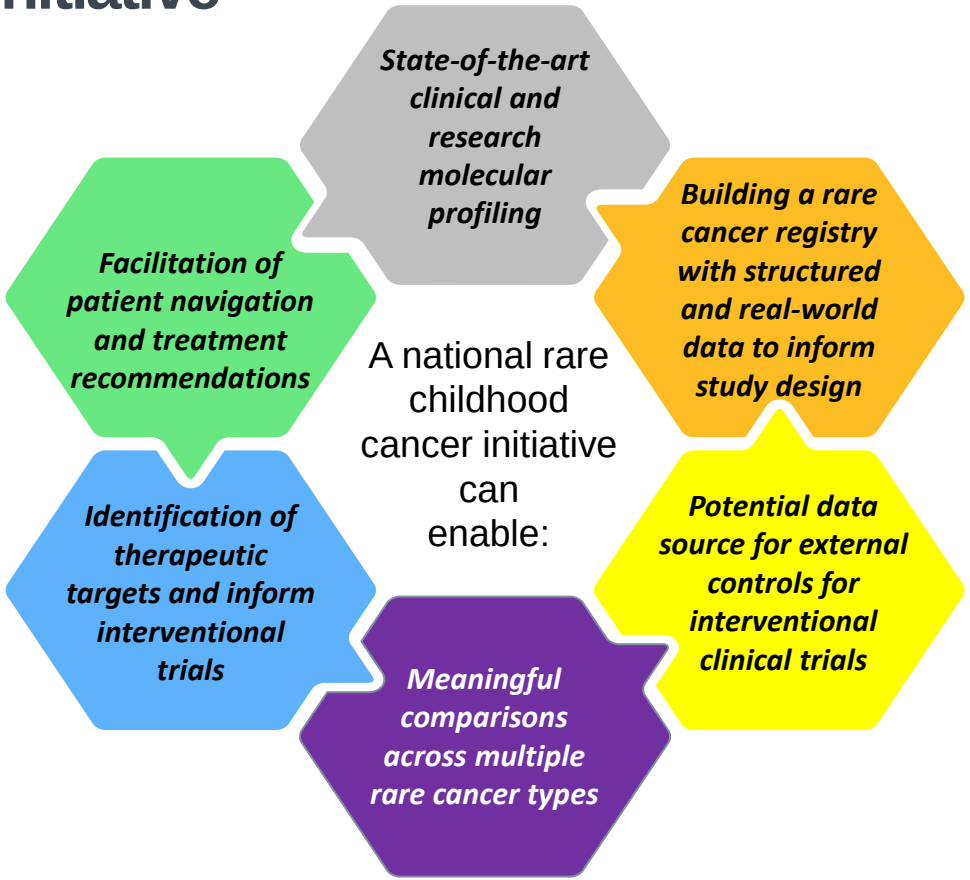
Objective:

- Feasibility of national observational study for children and AYA with rare cancers longitudinally evaluating disease course

Data Collection in all participants (baseline and longitudinally):

- Medical records, imaging, pathology
- Molecular characterization through MCI: Clinical and research
- Common data elements
- Patient reported outcomes

Rare Cancer Initiative



Common Data Elements Task Force

- Demographics
- Disease and treatment
- Tumor pathology and genomics
- Tumor response
- Family history
- Follow up

CDE Workshop July, 2024

Next Steps

- Finalize common data elements and PRO measures
- Finalize protocol
- Begin study enrollment in 2025
  - To join, a child or AYA must be diagnosed with a rare solid tumor.
  - All participants will be enrolled in the CCDI Molecular Characterization Initiative.
  - Study will expand to those with blood cancers in the future.

Learn more and sign up for monthly CCDI updates at:

cancer.gov/CCDI

Thank You

cancer.gov

cancer.gov/espanol