

# Treatment Opportunities in Diffuse Intrinsic Pontine Glioma (DIPG)

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Children's Hospital Boston



**HARVARD MEDICAL  
SCHOOL**

DANA-FARBER/CHILDREN'S HOSPITAL CANCER CENTER

# Disclaimer

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I was the PI of the first US biopsy and targeted therapy clinical trial of newly diagnosed DIPG patients

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# Disclosures and Support

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- I have no stocks, patent rights or employment with any company
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Advantagene                      Merck GA                      Amersham  
Novartis                        AstraZeneca                      Transmolecular  
Celgene                        Wyeth

# Brainstem Tumors

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- 10% of pediatric brain tumors
  - 80% DIPG
    - 100% malignant
  - 20% not primarily of the pons
    - 80% low-grade, 20% malignant
- Median age 6-8y/o for DIPG

# DIPG Presenting Symptoms

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- Cranial nerve deficits
  - Long-track signs
  - Ataxia
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- Hydrocephalus is rare
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- Duration of symptoms is usually days to weeks, can be up to 3 (6) months.

# Classic MRI Findings

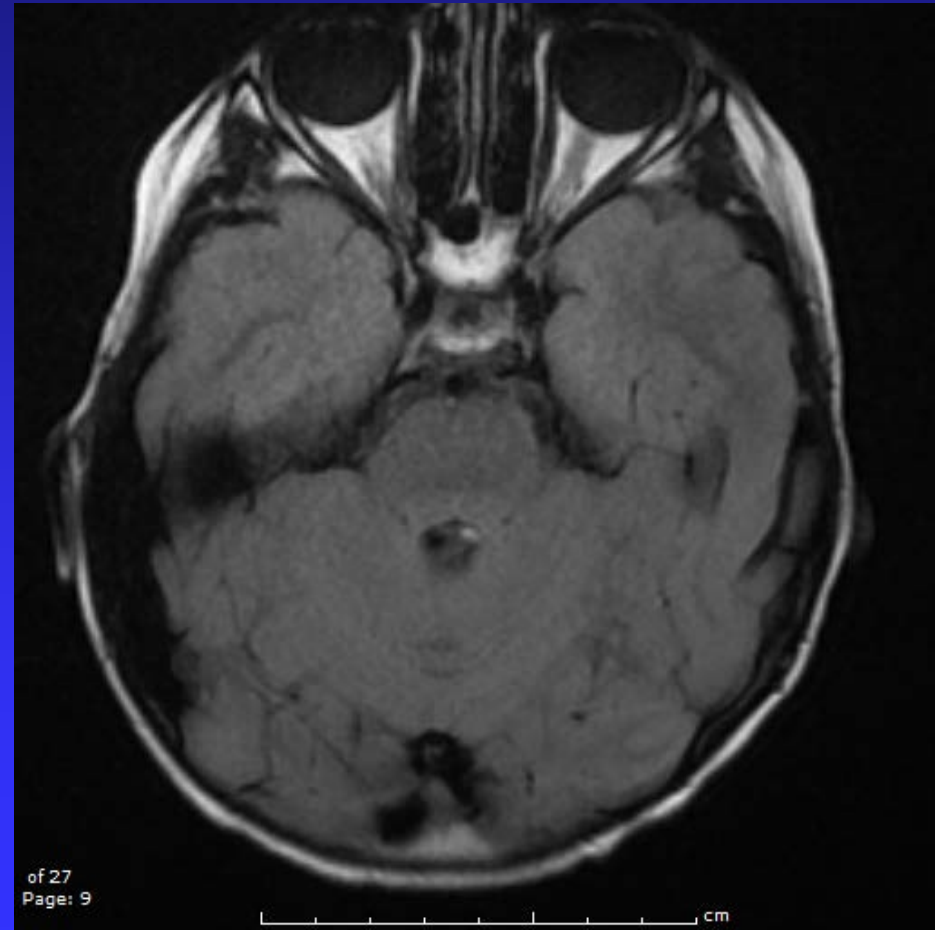
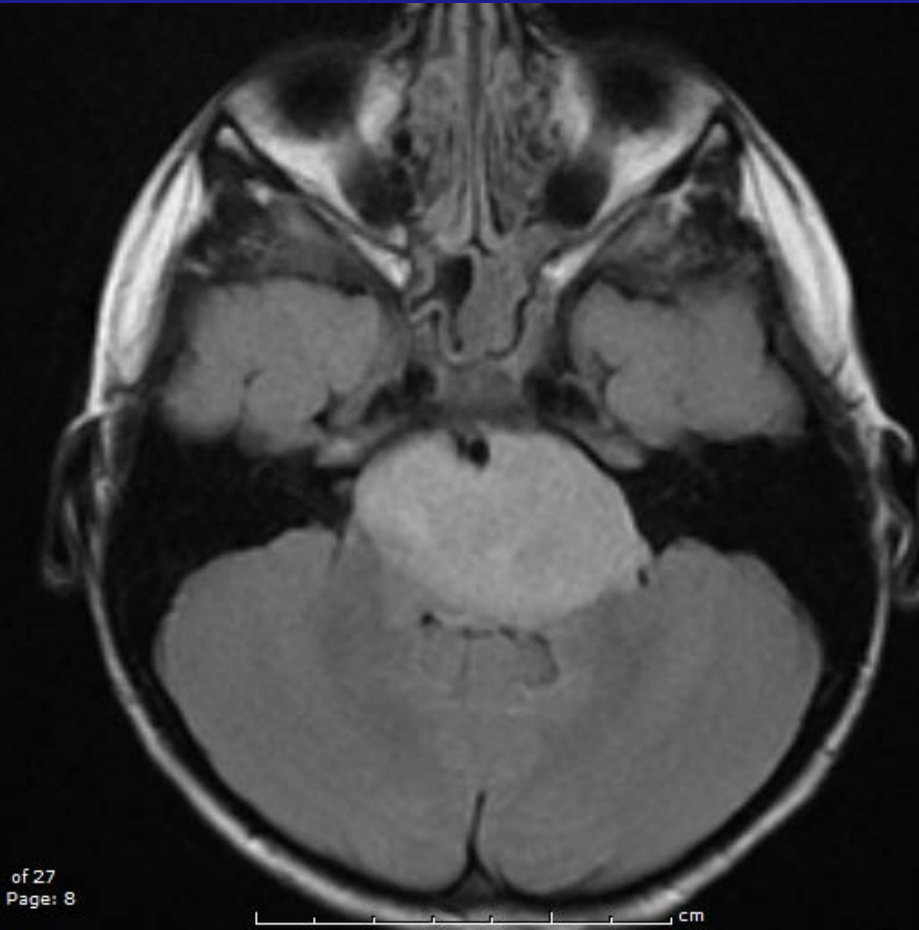
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- Dark on T1
- Bright on T2 or FLAIR
- Appear to have a border between pons and medulla
- Appears to envelope the basilar artery
- Not diffusely enhancing (can have an enhancing focus though)
- Should involve >50% (66%) of the pons
- Typically ventral pons > dorsal pons

# Diffuse Pontine Glioma Imaging

DIPG

Normal



# Treatment of DIPG

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- Surgical resection
- Chemotherapy
- Radiation
- Focal wide field photon radiation therapy
  - 5400-5940cGy given in 30-33 fractions at 180cGy/day
  - Proton therapy not indicated
- Radiation dose escalation
- Hypofractionation



# Outcome of DIPG

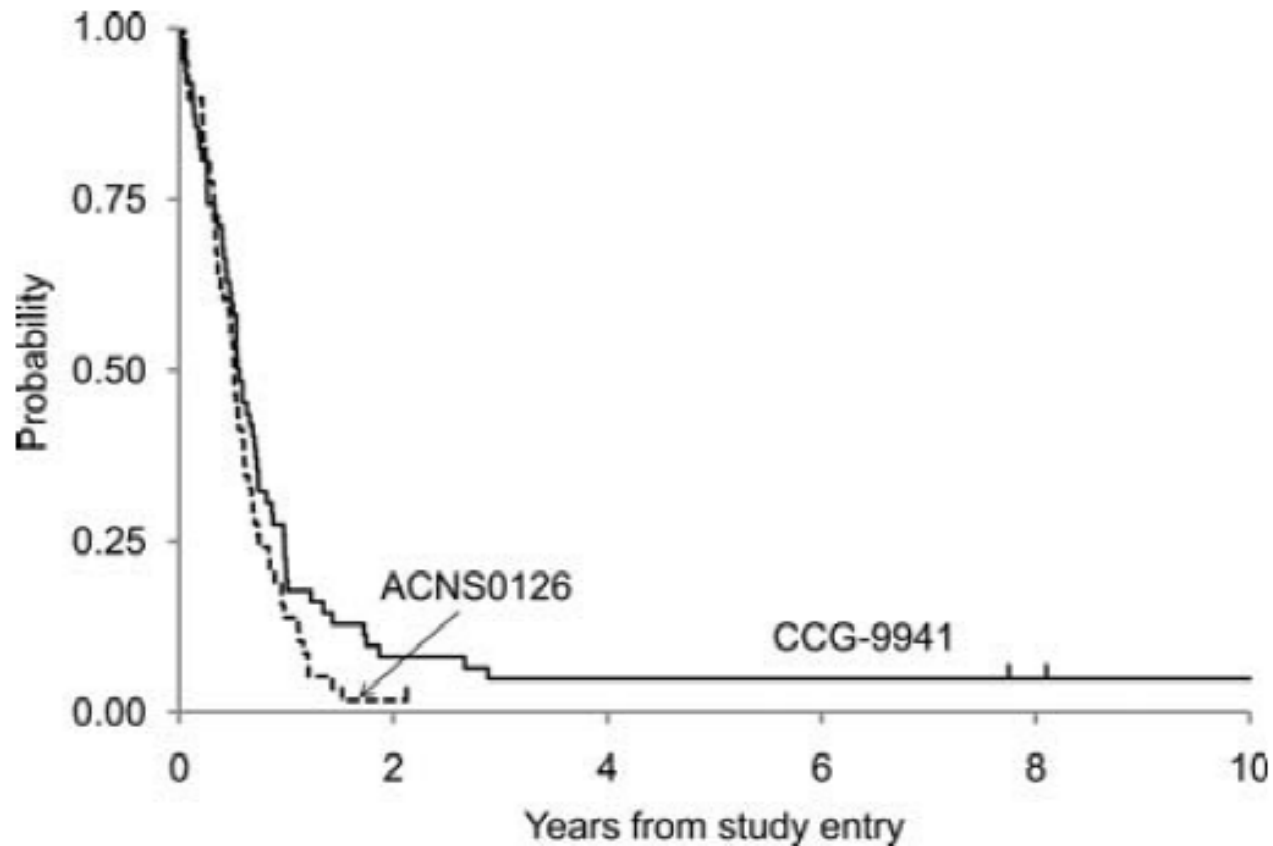


Fig. 2. Event-Free Survival Comparison of ACNS0126 and CCG-9941.

# Treatment of DIPG Over the Last 30 Years

- >250 clinical trials (based on MRI)
  - Pre-XRT chemotherapy
  - Post-XRT chemotherapy
  - Pre and Post-XRT chemotherapy
  - Immunotherapy
  - Biologic therapy
  - Radiation sensitizers
  - Anti-angiogenic therapies
- All of these patients died without benefit
- When we say a trial was negative, it was more than negative
  - Patients suffered toxicities with no benefit



Everything  
but the  
kitchen sink

# Discussion Points for On-Going Clinical Trials

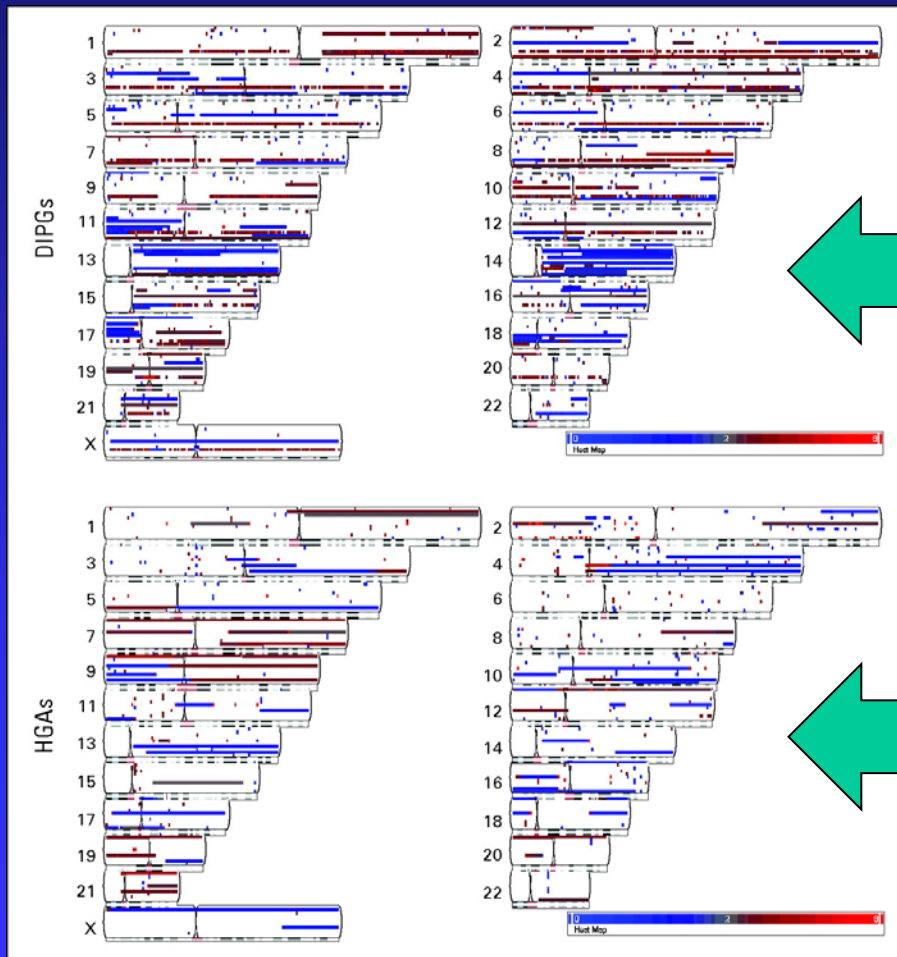
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- In many of these trials, combine HGG and DIPG patients.
  - In many ways, these are different diseases
- In many of these trials, combine DIPG with other brainstem tumors
  - These are usually different diseases

# Pre-Clinical Models of DIPG

- Derived from cells of glial origin, predominantly, supratentorial adult GBM
- Autopsy cases
- Upfront biopsy of atypical brain stem tumors
- Upfront biopsy of classic DIPG
  - New models now available
    - GEMM

# Whole Genome Copy Number Alterations in Pediatric DIPG vs Pediatric HGAs



9 autopsy and 2 up-front biopsy cases

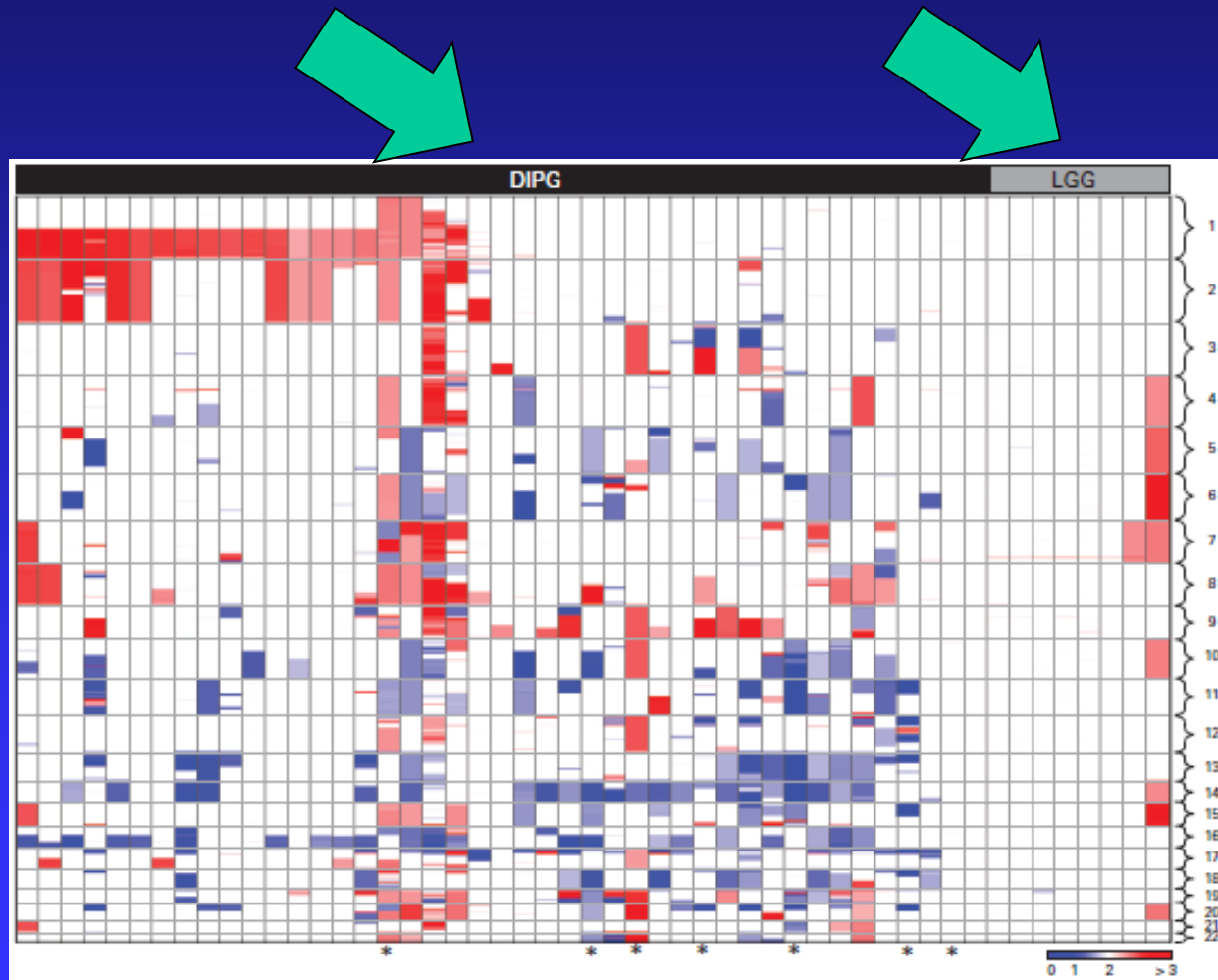
Whole genome view of copy number alterations for pediatric diffuse intrinsic pontine gliomas (DIPGs) versus pediatric supratentorial high-grade astrocytomas (HGAs) highlighting the distinct genetic characteristics of DIPGs. Patients are arranged sequentially with patient 1 at the top and patient 11 at the bottom. Red: copy number gain, blue: copy number loss.

Zarghooni M et al. JCO 2010;28:1337-1344 (Hawkins lab)

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# Whole Genome Copy Number Alterations in Pediatric DIPG vs Pediatric LGGs



37 autopsy and 7 up-front biopsy cases

Copy-number abnormalities in diffuse intrinsic pontine glioma (DIPG). (A) Heat map showing segmentation analysis of normalized data from Affymetrix SNP 6.0 arrays to identify copy-number gains (red) and losses (blue) in 43 DIPGs and eight brainstem low-grade gliomas (LGGs). Chromosome positions are indicated along y-axis and separated by dashed line. Histologic subtypes are indicated across top. Scale bar shows color gradient to indicate copy number. Comparison of frequencies of most common large-scale genomic

Paugh et al. JCO 2011;29:3999-4006 (Baker lab)

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# Histone H3 Mutations in DIPG

**Table 1** Frequency of recurrent somatic mutations in DIPG and GBM

Gene	Amino acid change	DIPG <sup>a</sup> (%)	non-BS-PG <sup>b</sup> (%)
<i>H3F3A</i>	p.Lys27Met	30 (60)	7 (19)
<i>H3F3A</i>	p.Gly34Arg	0	5 (14)
<i>HIST1H3B</i>	p.Lys27Met	9 (18)	1 (3)
All H3		39 (78)	13 (36)

<sup>a</sup>For DIPGs, total  $n = 50$ . <sup>b</sup>For non-BS-PGs, total  $n = 36$ .

# Clinical Trials for Histone Mutations

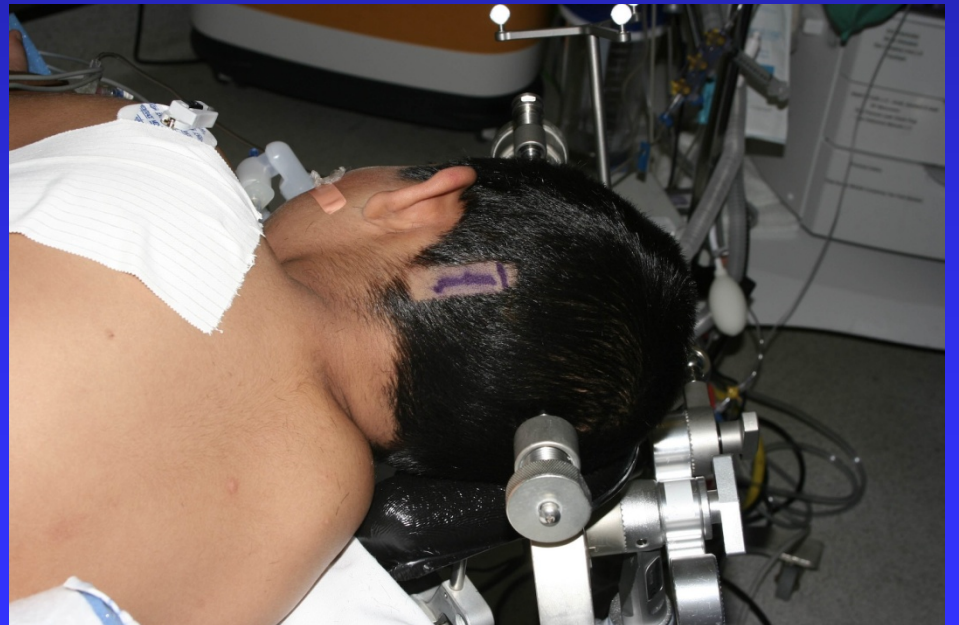
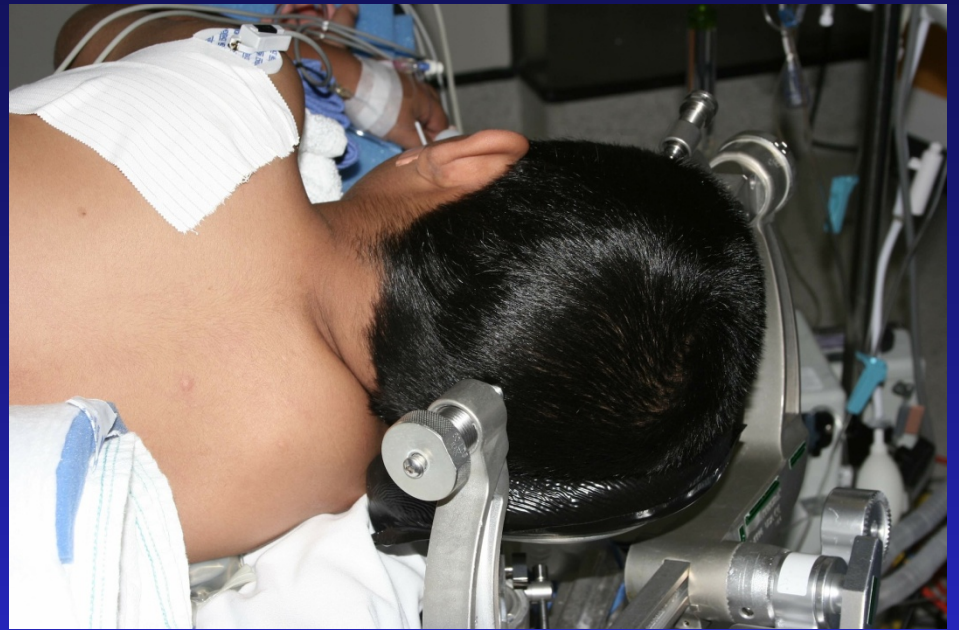
- Many epigenetic modifiers under study
- Histone deacetylase (HDAC) inhibitors
  - Valproic acid
  - SAHA (Vorinostat)
  - Panobinostat
- Histone demethylases
  - Jumanji 3 and 4 inhibitors

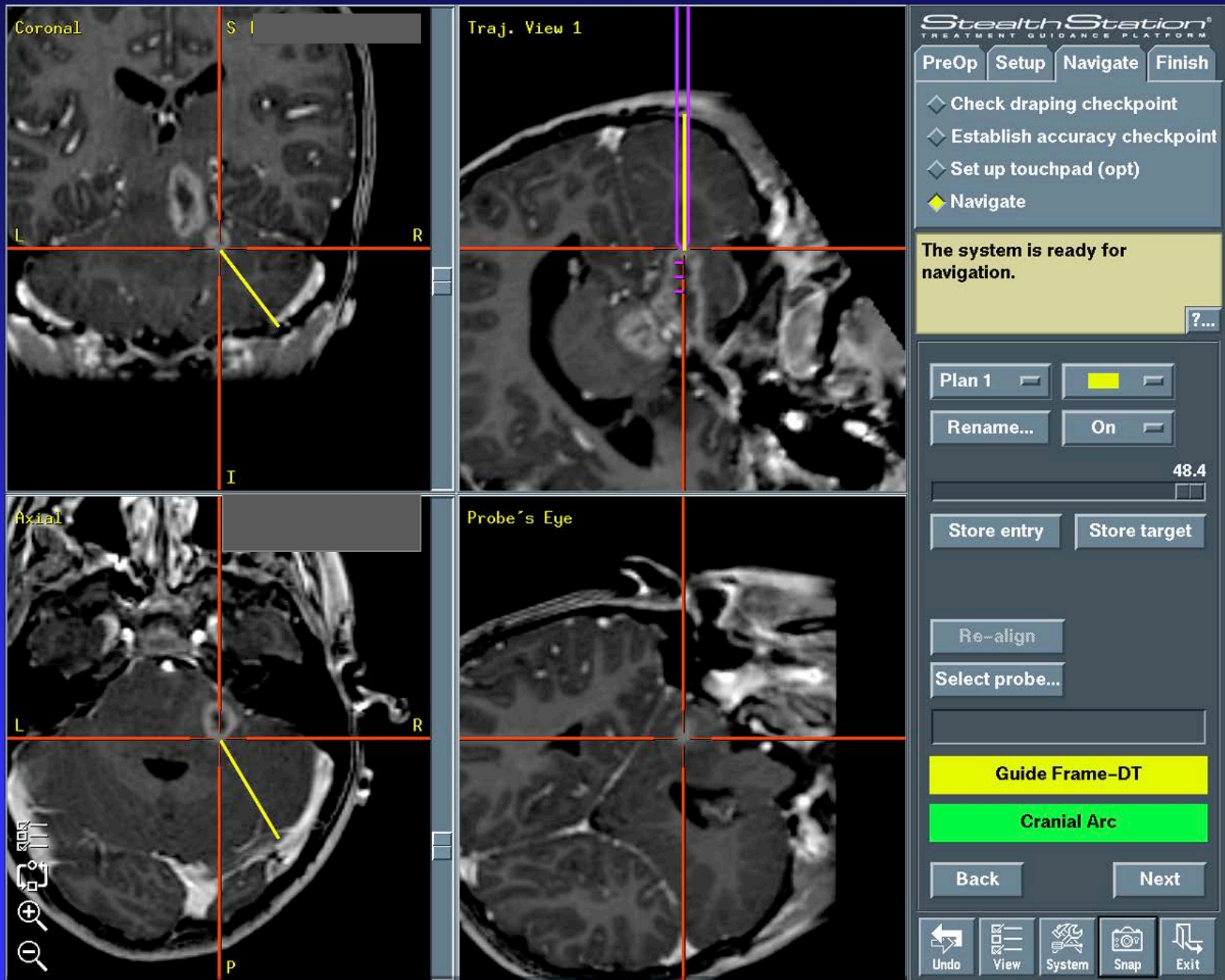


Entry point generally over midpoint of cerebellar hemisphere, at least 1 cm below transverse sinus

Single burr hole with coagulation of dura and cerebellar surface

Standard closure, with burr hole closure (plate, cement, or none) according to surgeon preference





# Have We Learned Anything?

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- Pilot assessment of biologic material to see if quality will support detailed analyses.

# Molecular Profile of Newly-Diagnosed DIPG

Pediatr Blood Cancer

## PRIORITY REPORTS

### Critical Oncogenic Mutations in Newly Diagnosed Pediatric Diffuse Intrinsic Pontine Glioma

Jacques Grill, MD, PhD,<sup>1\*†</sup> Stephanie Puget, MD, PhD,<sup>2</sup> Felipe Andreiuolo, MD,<sup>3,4</sup> Cathy Philippe,<sup>4</sup> Laura MacConaill, PhD,<sup>5‡</sup> and Mark W. Kieran, MD, PhD<sup>6§</sup>

20 up-front biopsy cases of DIPG

**TABLE I. Validated Mutations Detected in the 20 Diagnostic Samples Analyzed**

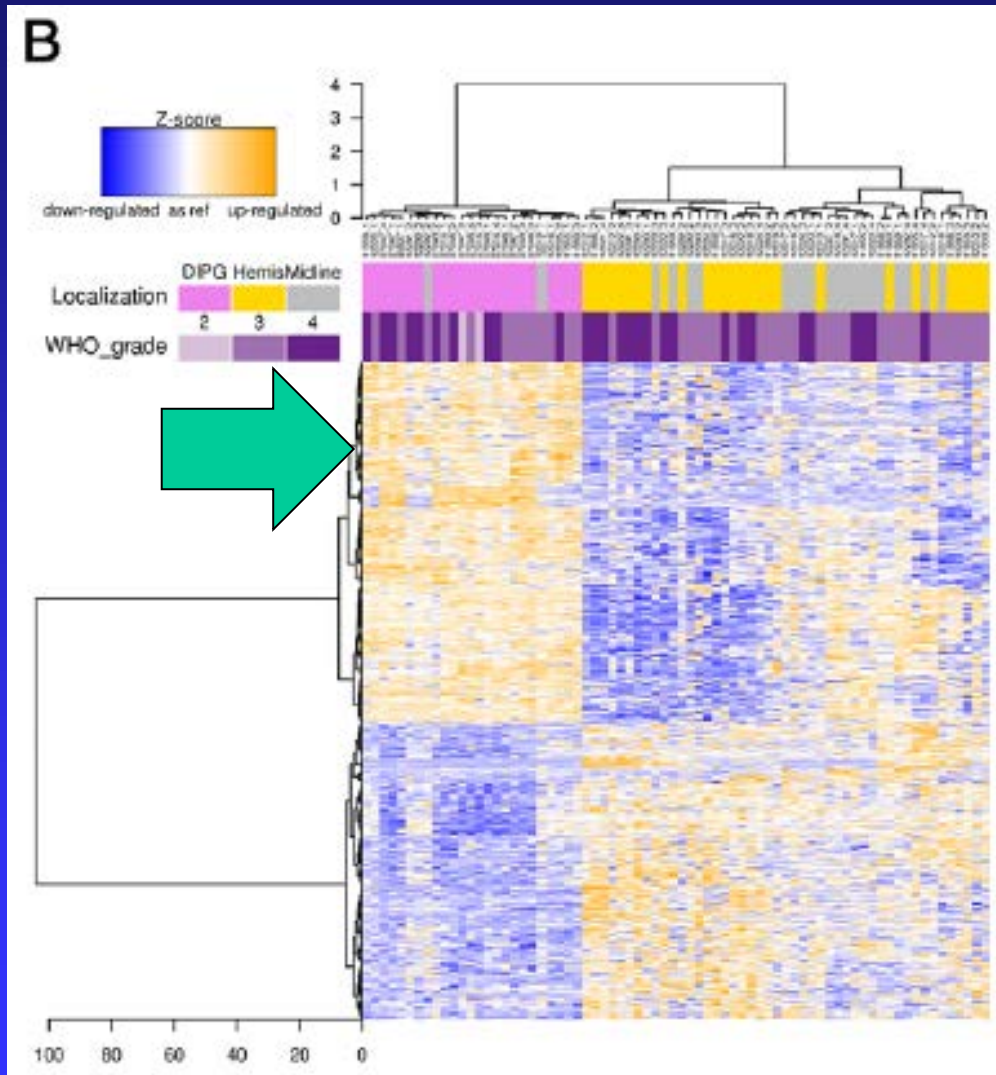
Patient	Gene	Mutation	p53 CNA	p53 IHC	PDGFRA CNA	PTEN CNA
1	ATM	P604S	-0.5292	—	-0.0375	-0.0224
1	MPL	W515L	-0.5292	—	-0.0375	-0.0224
2	PI3KCA	H1047R	0.0155	—	-0.0142	0.0002
3	PI3KCA	H1047L	0.0033	++	-0.0088	0.0010
4	PI3KCA	E542K	0.0421	+++	-0.0165	-0.0033
5	TP53	R248W	-0.4546	++	2.5200	-0.0153
6	TP53	R273H	-0.5166	++	-0.0386	-0.2063
7	TP53	V157F	-0.8058	+	-0.0076	-0.3552
8	TP53	R273*	-0.1597	NA	-0.0191	-0.2676
9	TP53	R273L	0.0011	+++	-0.0257	0.0006
10	TP53	R282W	0.0174	+++	2.2870	-0.3614
11	TP53	R273H	-0.3997	+++	1.7514	0.0019
12	TP53	R273L	0.0101	NA	-0.0079	-0.2159

Results of the CGHarray with Agilent 44K Whole Human Genome Array G4410B are indicated by the ratio of chromosomal imbalance; values above 1.5 were considered as amplifications and those below 0.3 were considered as losses. IHC for p53 (DO-7 antibody) was graded in a semi-quantitative way (cut-off 10%).

Grill et al. (Kieran) Pediatric Blood and Cancer58(4):489-91. Epub 2011 Dec 20



# DIPG is Different From GBM

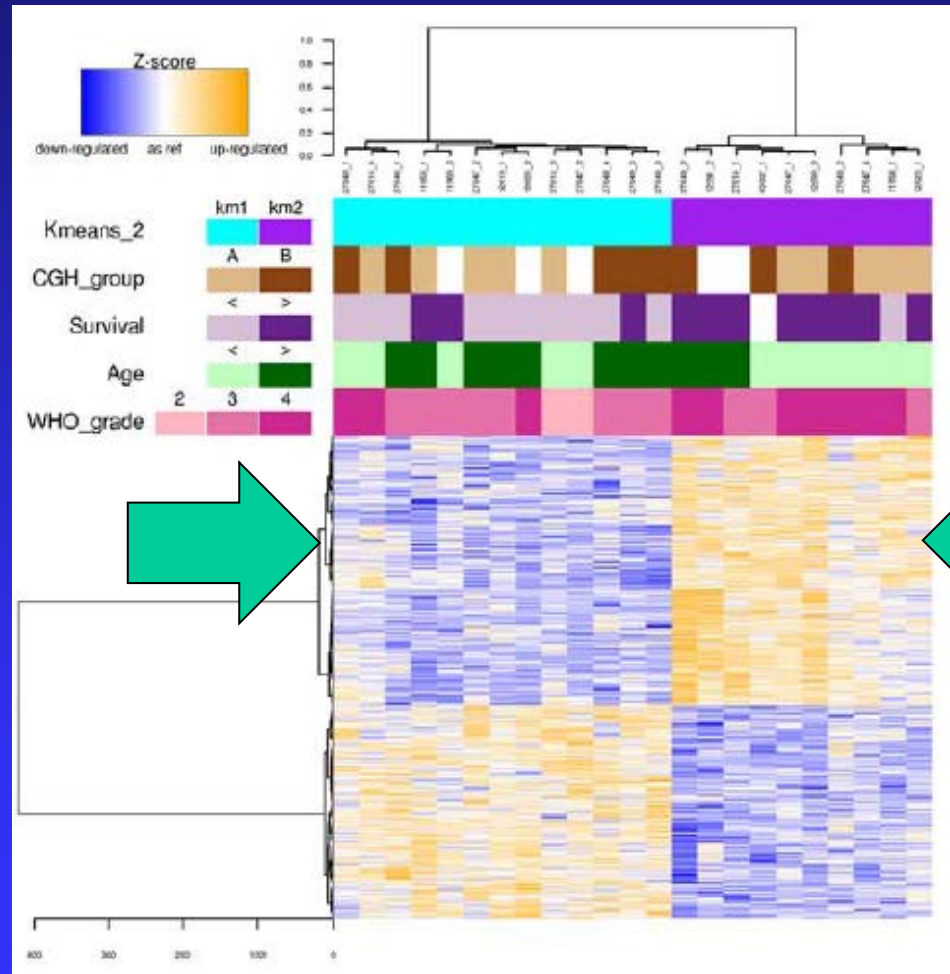


23 up-front biopsy cases of DIPG

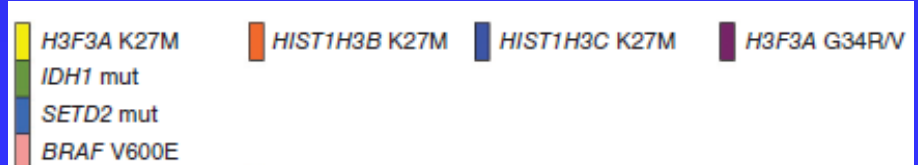
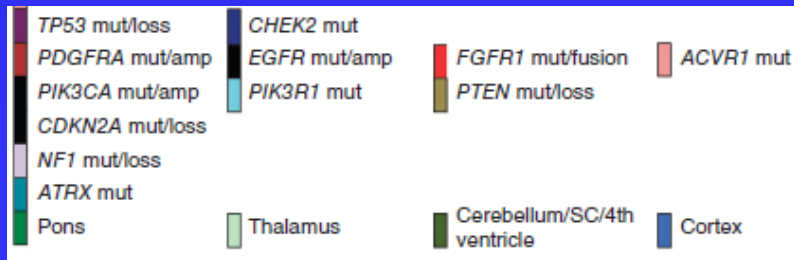
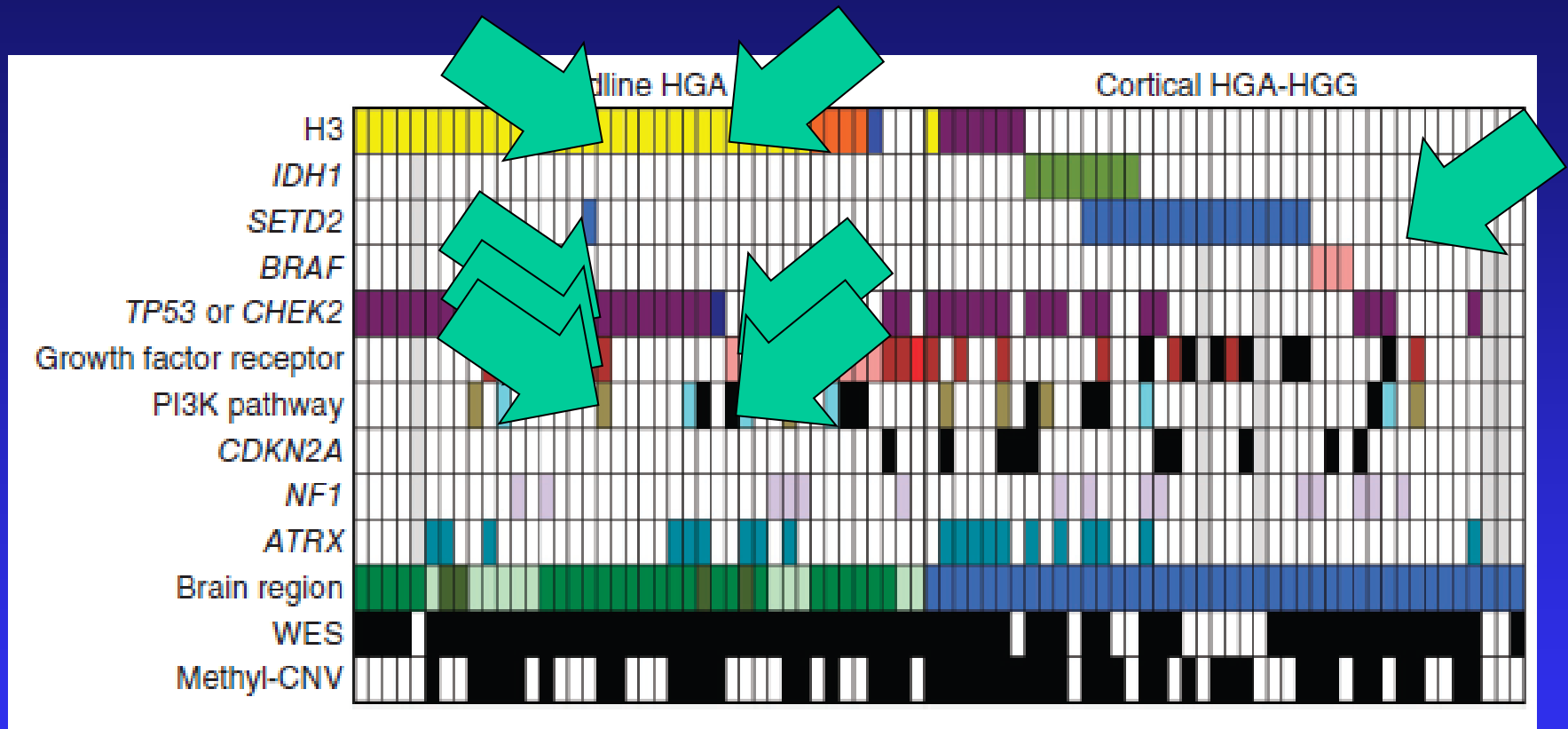
B: Heatmap of the 712 most differentially expressed genes between DIPG, midline and hemispheric tumors, selected using the moderated t-test of limma package of Bioconductor.

# Two Distinct Molecular Subgroups

- Mesenchymal/pro-angiogenic
- Oligodendroglial
  - PDGFR-A driven

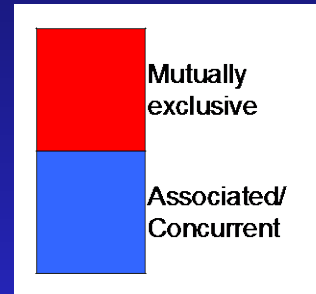


# New Targets in DIPG



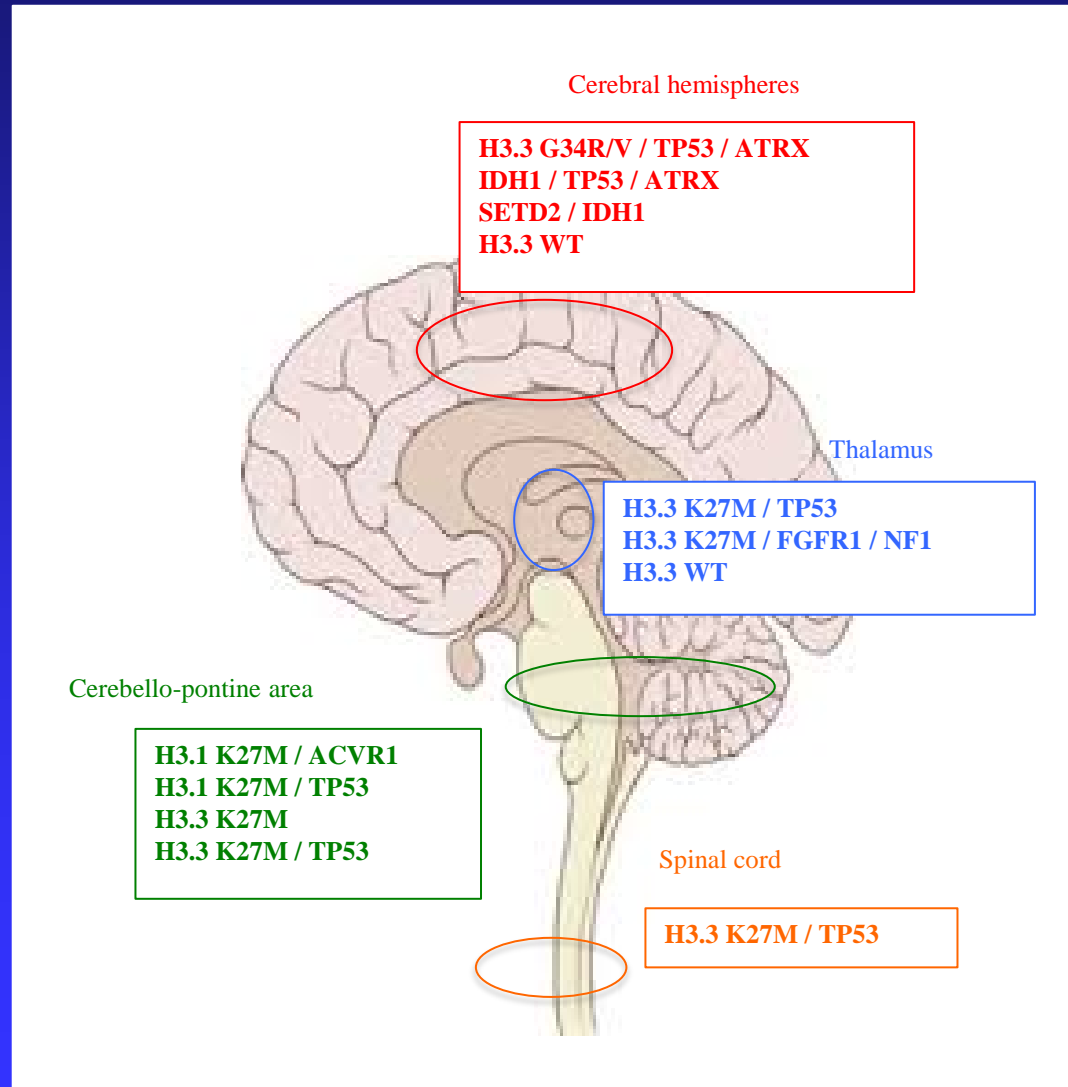
# Targets in Pediatric DIPG/HGG

	<i>H3F3A</i>	<i>HIST1H3B/ HIST1H3C</i>	<i>TP53</i>	<i>FGFR1</i>	<i>ACVR1</i>	<i>PDGFRA</i>	<i>PIK3CA/ PIK3R1/ PTEN</i>
<i>H3F3A</i>		0.0002	0.0331	0.5515	0.0015	0.5515	0.6488
<i>HIST1H3B/ HIST1H3C</i>	0.0002		0.0586	1.000	0.0002	1.000	0.1023
<i>TP53</i>	0.0331	0.0586		0.0154	0.0154	0.1445	0.2538
<i>FGFR1</i>	0.5515	1.000	0.0154		1.000	1.000	1.000
<i>ACVR1</i>	0.0015	0.0002	0.0154	1.000		1.000	0.048
<i>PDGFRA</i>	0.5515	1.000	0.1445	1.000	1.000		0.5536
<i>PIK3CA/ PIK3R1/ PTEN</i>	0.6488	0.1023	0.2538	1.000	0.048	0.5536	

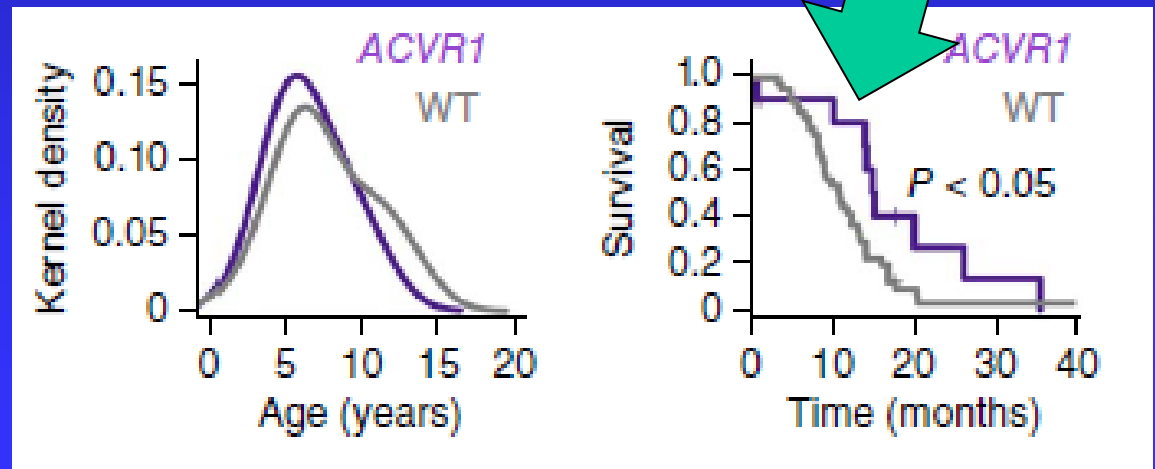
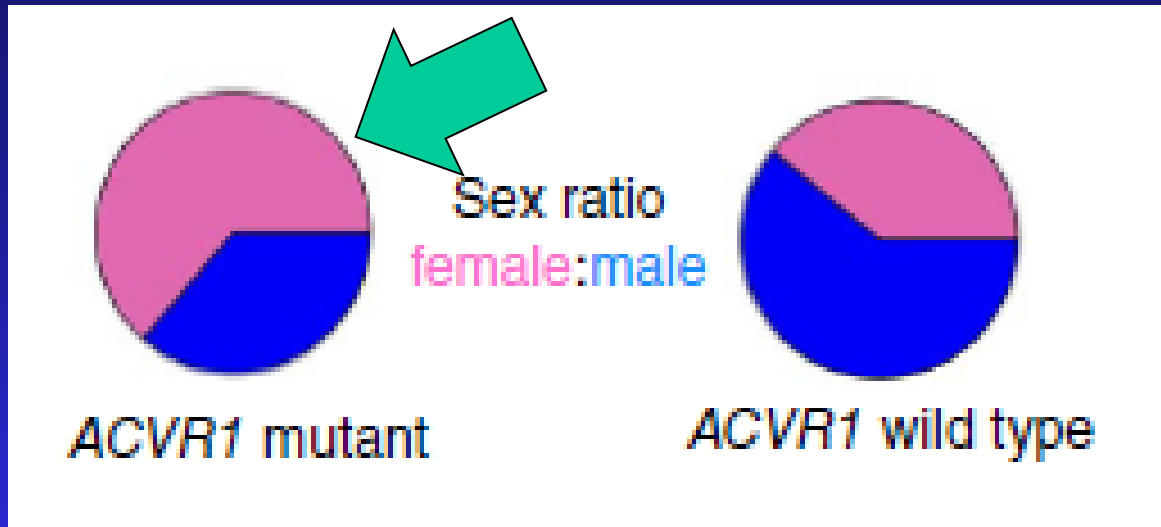




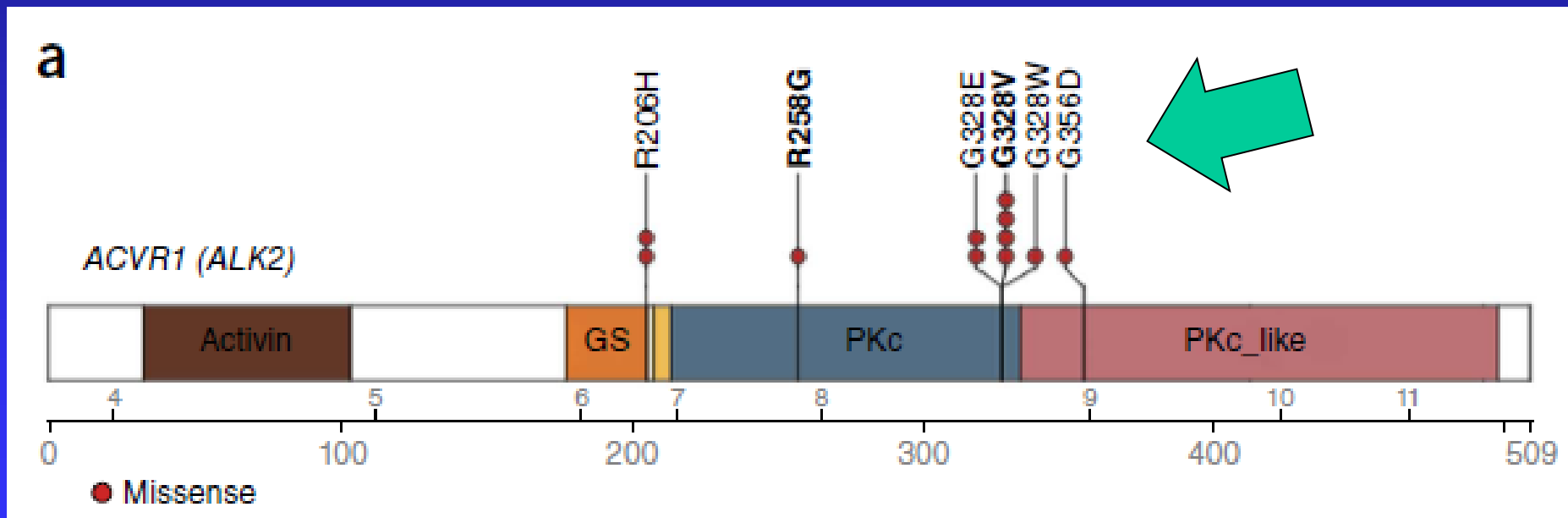
# New Targets in Pediatric DIPG



# ACVR1 and DIPG



# What Do We Know About ACVR1



# Fibrodysplasia Ossificans Progressiva

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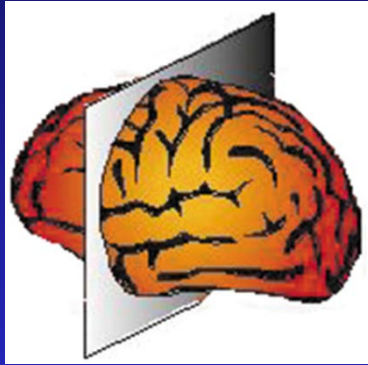
Fibrodysplasia ossificans progressiva

# Drug Distribution and CNS Penetration

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# Matrix Assisted Laser Desorption Ionization (MALDI) Mass Spectrometry Imaging

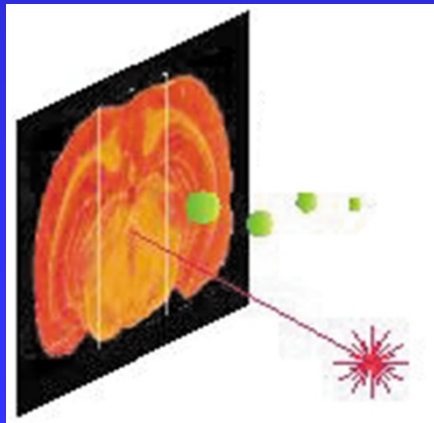
Frozen Section



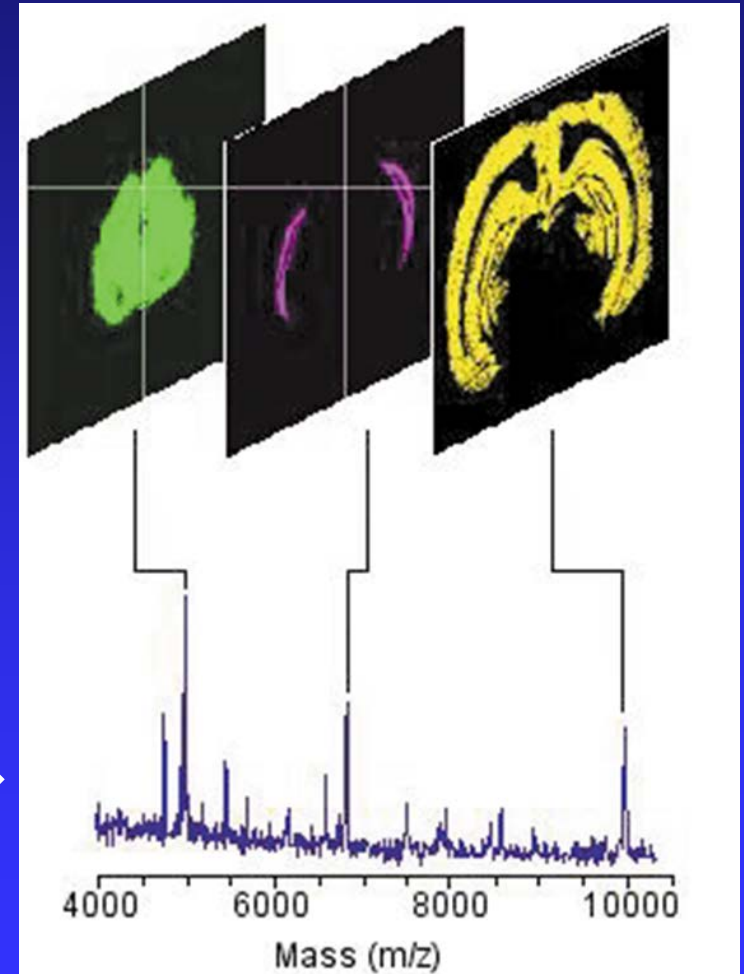
Matrix Application



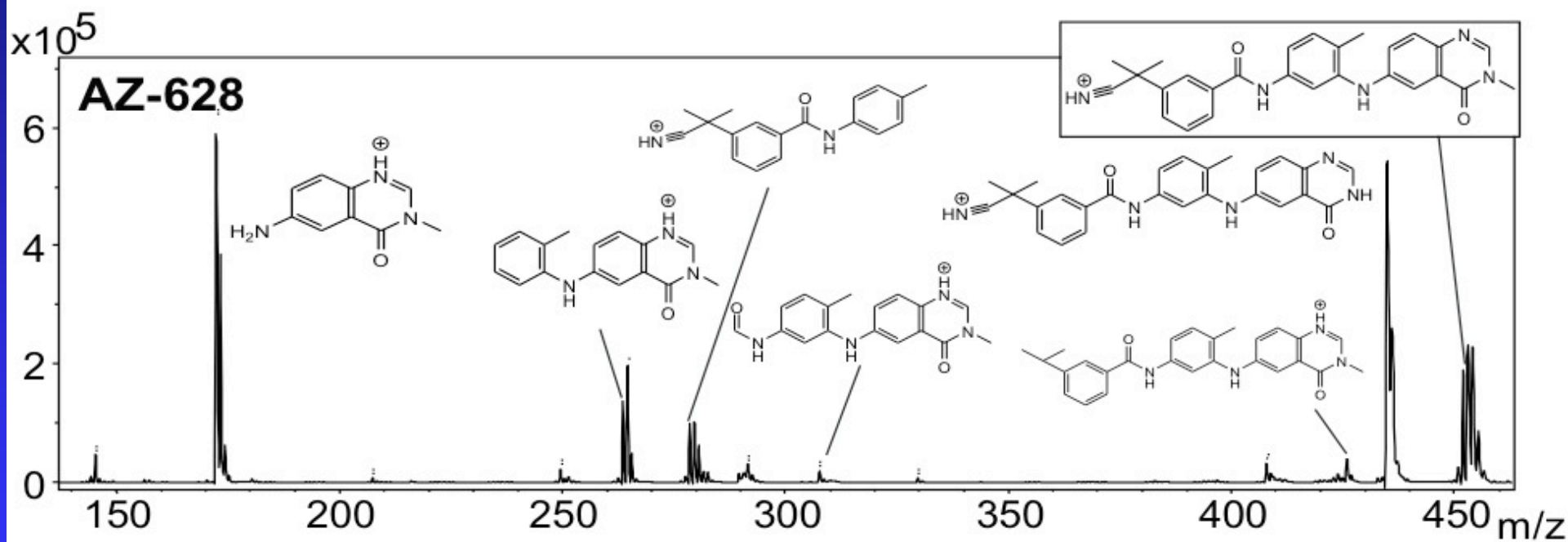
Nathalie  
Agar, PhD



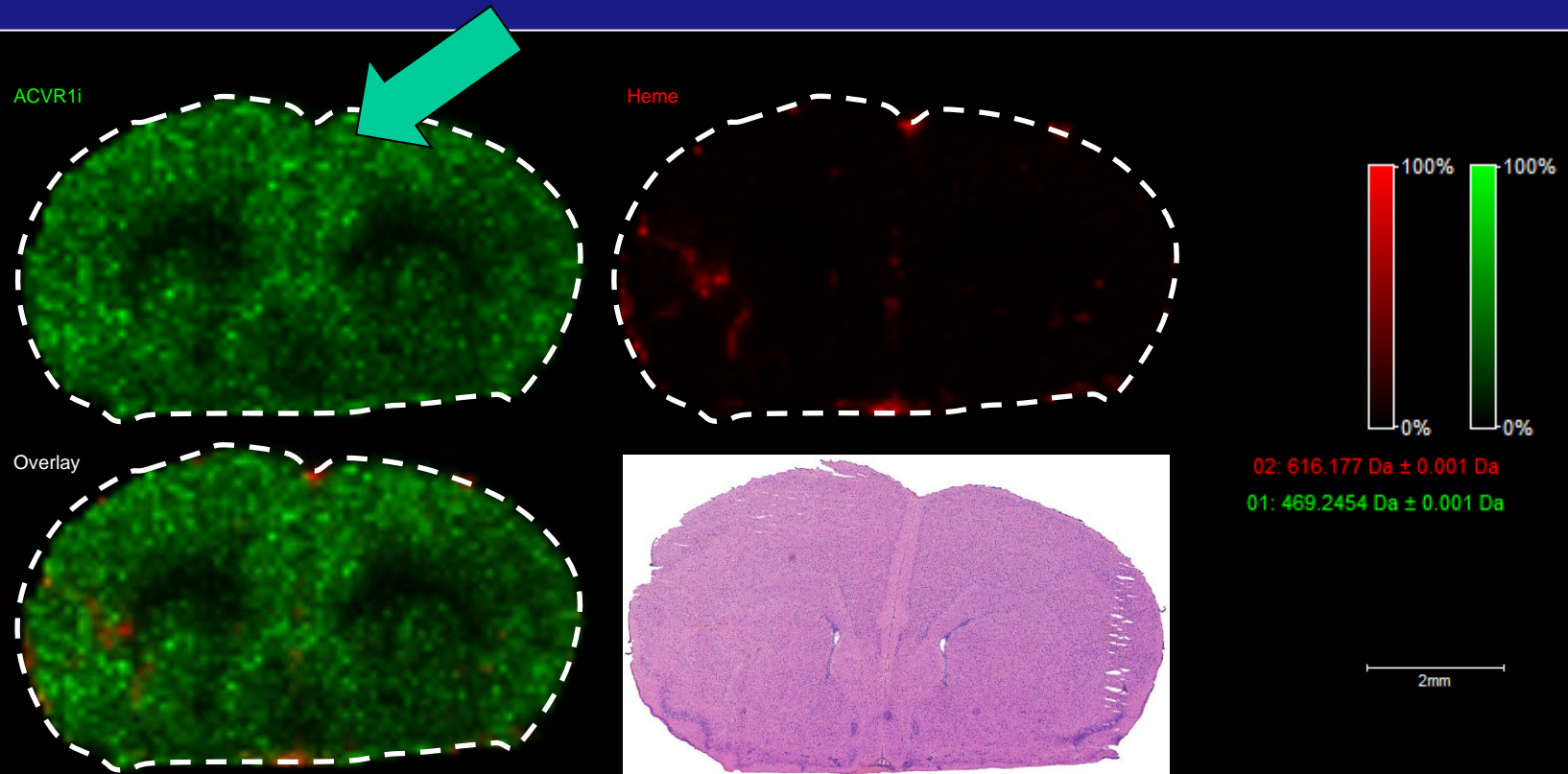
Mass  
Spectrometer



# Confirmation of Compound Identity by MS/MS with MALDI TOF/TOF



# ACVR1 Inhibitor CNS Penetration





# What Does This Mean for Patients with DIPG?

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- Histone demethylase and deacetylase inhibitors are being studied (BBB penetration)
- Targeting PI3k, PDGFR, ACVR1 mutations in newly diagnosed DIPG
  - New clinical trial

# Participating Institutions

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- DFCI, Boston
- UCSF, San Francisco
- Children's Memorial, Chicago
- CHLA, Los Angeles
- Jacksonville Children's, FL
- Seattle Children's, WA
- Denver Children's, CO
- Johns Hopkins, MD
- Miami Children's, FL
- Wayne State, MI
- Washington Univ, St Louis
- NYU Med Center, NY
- Doernbecher, OR
- CHOA, Atlanta
- Univ of MN, Minneapolis
- UT Southwestern, Dallas
- Louisville Children's, KY
- Univ South Carolina, SC
- Cook Children's, Fort Worth
- Duke University, NC

# Acknowledgments

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## McGill University

- Nada Jabado

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- Keith Ligon,
- Hayley Malkin, Lianne Greenspan

# Acknowledgments

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  - Ellie Kavalieros Foundation
  - Mikey Czech Foundation
  - Prayers From Maria Foundation
  - Hope for Caroline Foundation
  - Ryan Harvey DIPG Fund
  - DIPG Collaborative
  - The Cure Starts Now Cancer Foundation