NYU Langone Health

Department of Pathology

DNA methylation

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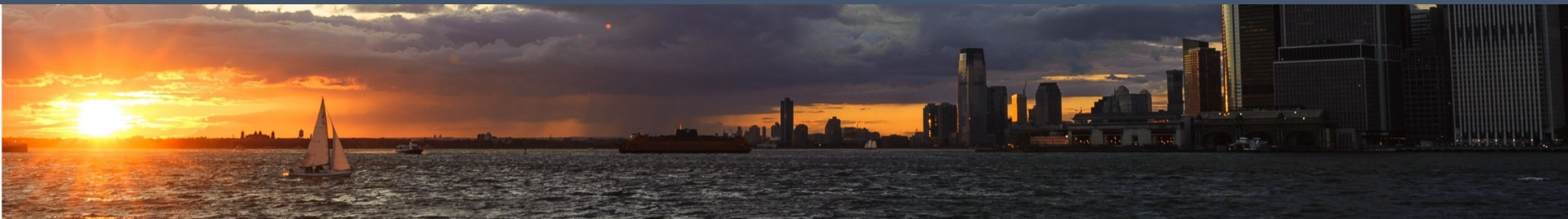


Financial disclosures

- I have nothing to disclose

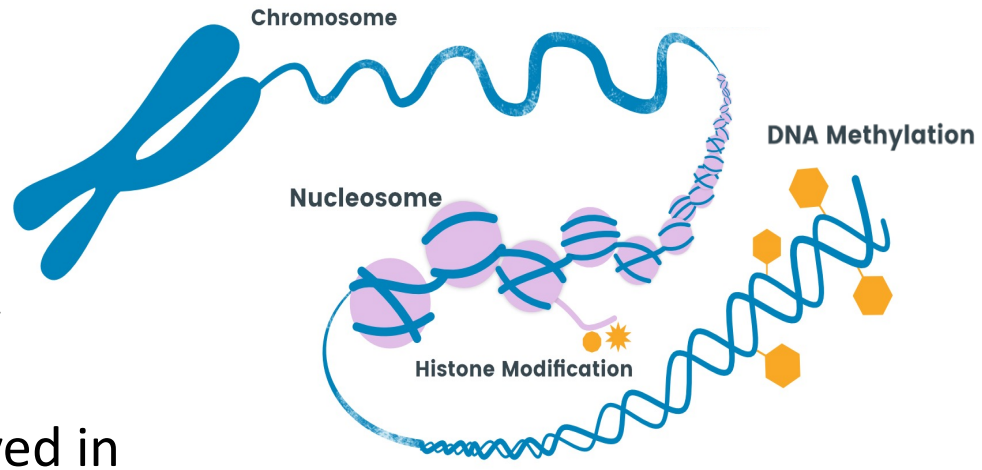
Learning Objectives

- Describe the development and workflow of the DNA methylation classifier
- Determine the utility of the DNA methylation classifier in routine tumor diagnostics
- Recognize the pitfalls of the DNA methylation classifier and ways to overcome them

Outline

- What is DNA methylation?
- How was the classifier developed?
- How has the classifier been used in tumor diagnostics?
- When should we use the classifier?
- How has DNA methylation been included in the WHO?
- Diagnostic challenges when using DNA methylation
- Future uses of DNA methylation in tumor diagnostics
- Billing for the DNA methylation classifier

DNA methylation



- DNA methylation is the addition of a methyl group to DNA
- DNA is methylated at CpG sites throughout the genome
- It is an ancient evolutionary epigenetic modification involved in
  - Chromatin structure
  - Gene silencing
  - Genetic stability
- This methyl mark is maintained throughout cell divisions establishing an epigenetic mark of the genome
- The genome-wide DNA methylation pattern is a composite of methylation patterns of the cell of origin and changes due to aging, environment, or mutations
- Methylation patterns of tumors remain preserved and accurately reflect the cell of origin, remaining stable throughout the course of disease
- Serves as an epigenetic fingerprint that can be utilized for tumor classification

Technical aspects of DNA methylation

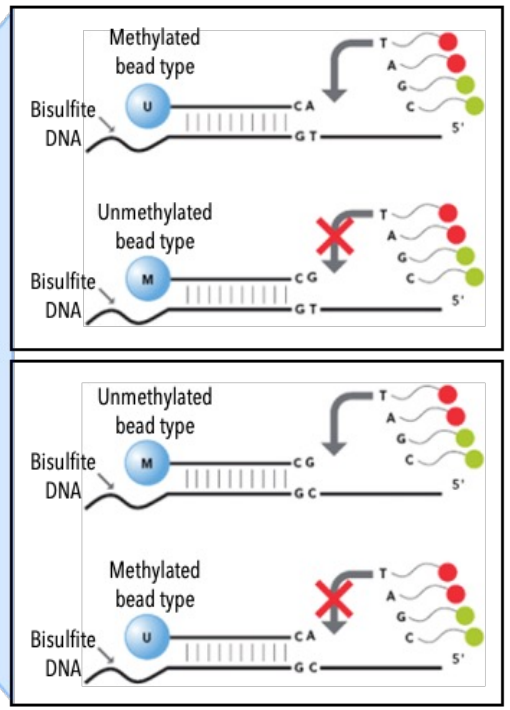
- DNA methylation analysis scan be performed using
  - Whole genome bisulfite sequencing
    - Most comprehensive
    - Requires high quality DNA
    - Costly
    - Not suitable for FFPE tissue
  - Target bisulfite sequencing
    - Not compatible with FFPE
  - DNA methylation array
    - FFPE compatible
    - Requires a relatively low starting DNA input
    - Lower cost than other methods

DNA methylation array

- DNA is extracted using any method of DNA isolation
- DNA undergoes bisulfite conversion
  - Any C that is methylated stays a C
  - Any C that is unmethylated is converted to a U
- Array hybridized DNA is scanned
  - DNA from the tumor is added to the BeadChip (8 cases per chip)
  - Individual beads hold oligos that identify the physical location on the BeadChip and a 50 base probe (beads for methylated and unmethylated)
  - Probes are designed to be complementary to specific 50 base regions of bisulfite converted DNA
  - After hybridization of probes, a single base extension of the probe incorporates a fluorescently labeled ddNTP
- The fluorescent signal is then measured
- Raw data files with intensity data for each probe are produced by the iScan system for analysis (idat file)
- This idat file is then processed through customized bioinformatics pipelines
- The proportion of DNA methylation at a CpG site is known as the beta-value which is the ratio of methylated signal to unmethylated signal

Patients with CNS Tumors

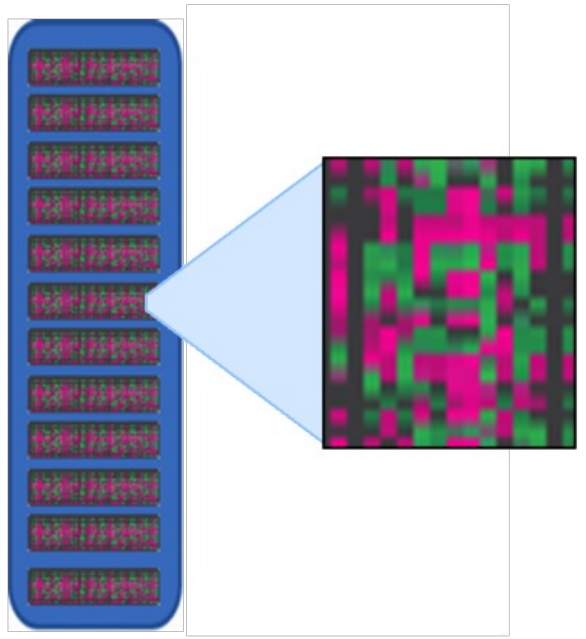
High-throughput DNA Methylation Bead Chip



Methylated Locus

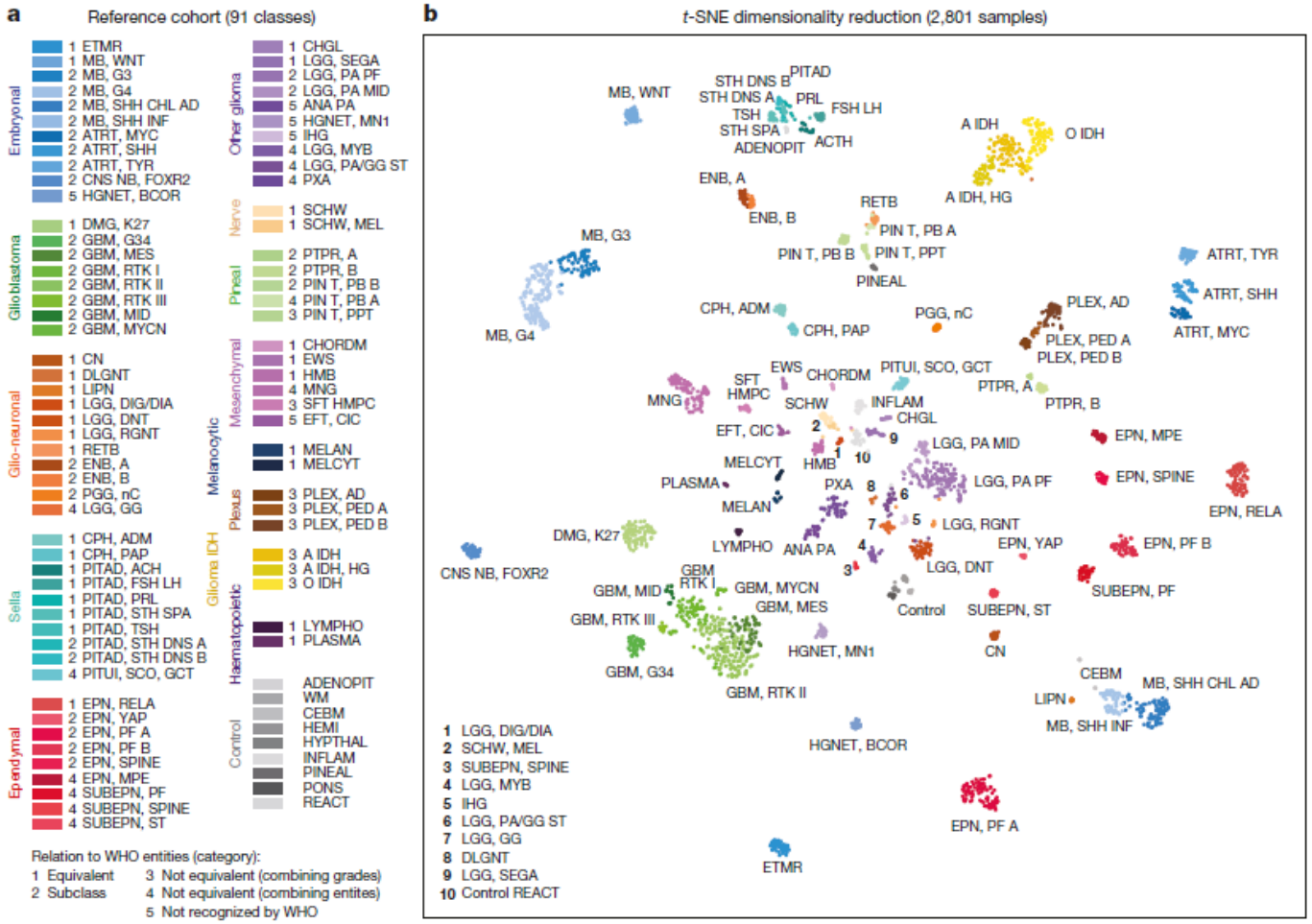
Unmethylated Locus

>850K methyl-sites



Development of the classifier

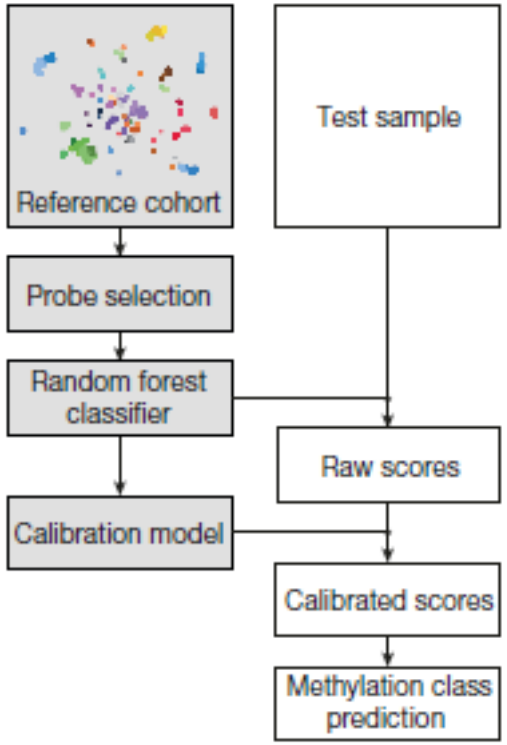
- Established a reference cohort of CNS tumors
  - Genome-wide DNA methylation
    - WHO-defined CNS tumors
    - Mesenchymal tumors
    - Melanoma
    - DLBCL and plasmacytomas
- Unsupervised clustering performed within each entity and across histologically similar tumor entities
  - 29 classes match a single WHO entity
  - 29 classes were subclasses within a WHO entity
  - 11 classes were not identical to a WHO entity
  - 5 classes were not defined by the WHO



Capper et al. 2018. *Nature*

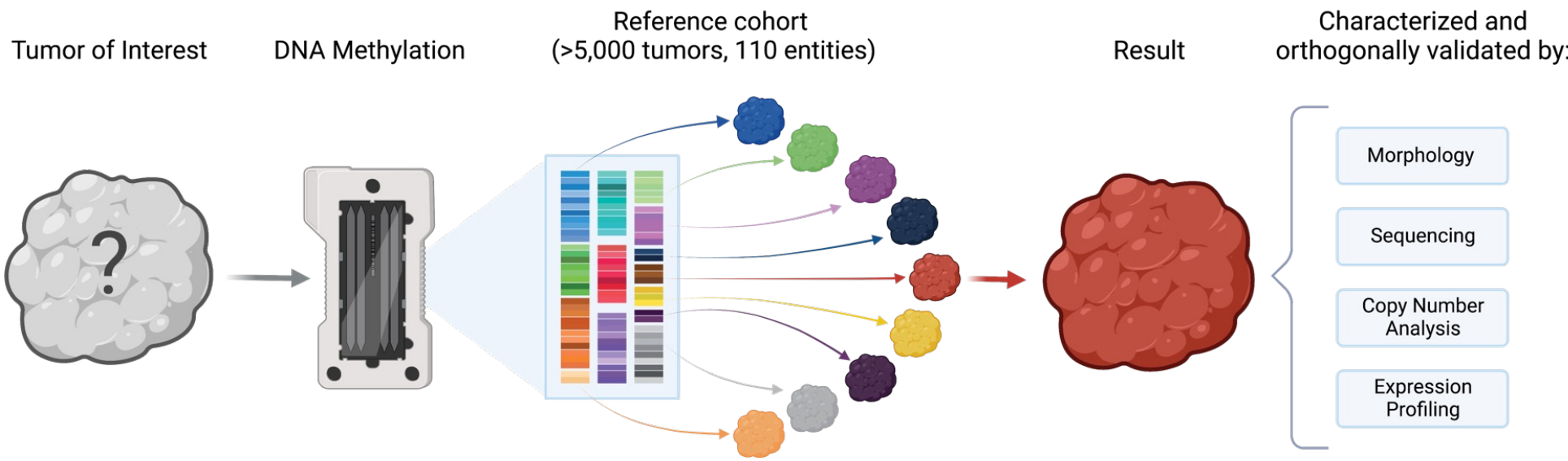
Classifier development

- Machine learning random forest algorithm
- Generated 10,000 binary decision trees with data from all 2,801 reference samples
- Each tree assigns a given tumor sample to one of the 91 classes resulting in an aggregate raw score
- Raw score transformed into a probability that measures the confidence of the class assignment
  - AKA: calibrated score



Capper et al. 2018. *Nature*

How it works

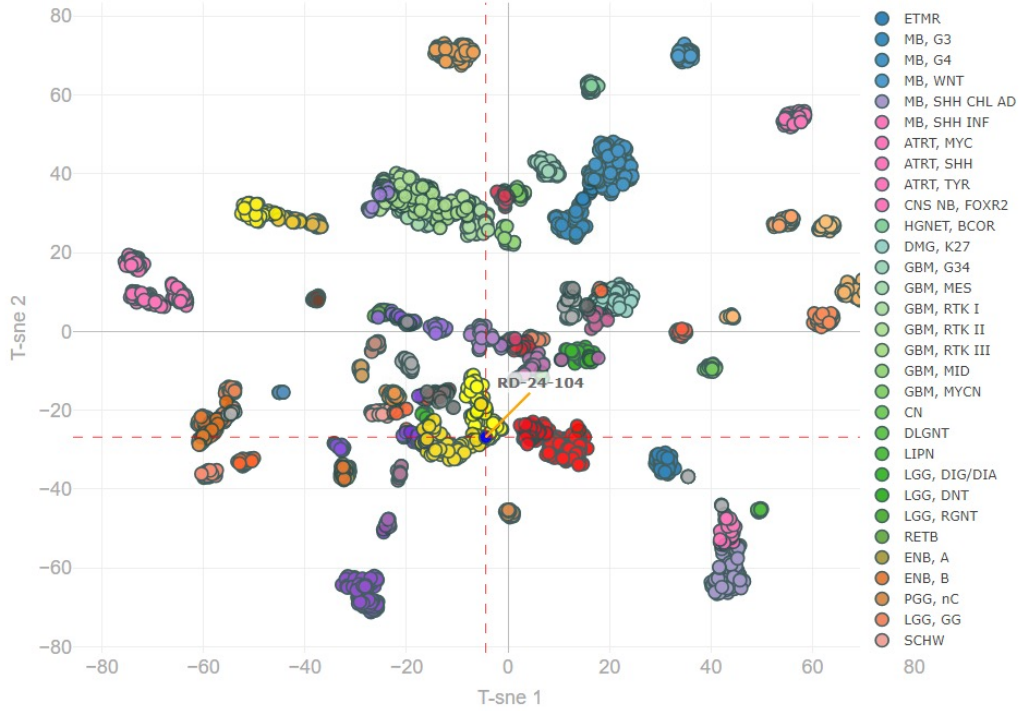

Tumor of Interest
DNA Methylation
Reference cohort
(>5,000 tumors, 110 entities)
Result
Characterized and
orthogonally validated by:
?
Morphology
Sequencing
Copy Number
Analysis
Expression
Profiling

Classifier result

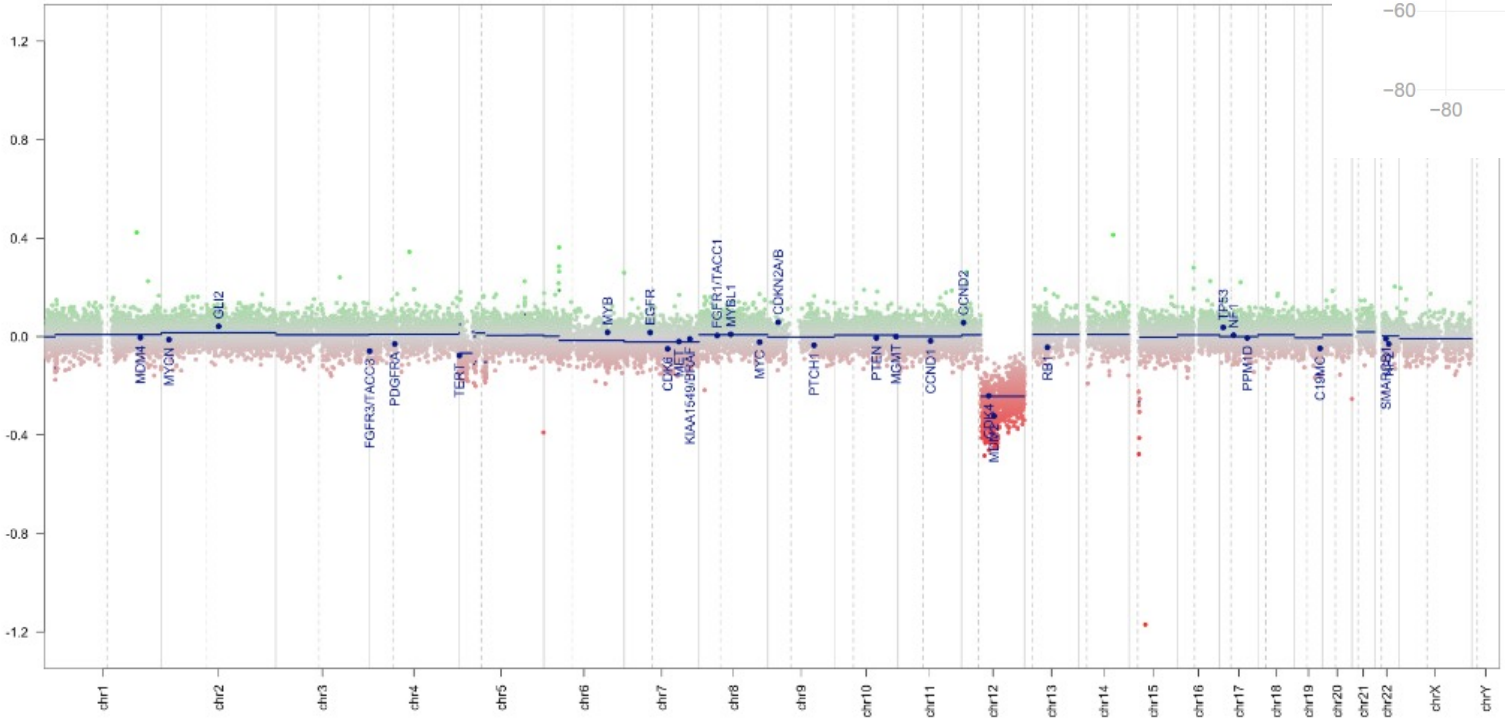
Brain Tumor Methylation Classifier Version 12

	predicted	Calibrated score
Super Family	Adult-type diffuse gliomas	0.9814
Family	diffuse glioma, IDH mutant	0.9805
Class	diffuse glioma, IDH-mutant and 1p19q retained [astroglial type]	0.8787
Subclass	Astrocytoma, IDH-mutant; lower grade	0.8787

T-sne



Copy number plot



Calibrated score	Result
>0.9	Positive
0.3-0.9	indeterminant
<0.3	Negative

Practical implementation of DNA methylation and copy-number-based CNS tumor diagnostics: the Heidelberg experience

David Capper[1,2,3,4] · Damian Stichel[1,2] · Felix Sahm[1,2] · David T. W. Jones[5,6] · Daniel Schrimpf[1,2] · Martin Sill[5,7] · Simone Schmid[3] · Volker Hovestadt[8,9] · David E. Reuss[1,2] · Christian Koelsche[1,2,17] · Annekathrin Reinhardt[1,2] · Annika K. Wefers[1,2] · Kristin Huang[1,2] · Philipp Sievers[1,2] · Azadeh Ebrahimi[1,2] · Anne Schöler[3,4] · Daniel Teichmann[3] · Arend Koch[3] · Daniel Hänggi[10] · Andreas Unterberg[11] · Michael Platten[12,13] · Wolfgang Wick[14,18] · Olaf Witt[5,15,16] · Till Milde[5,15,16] · Andrey Korshunov[1,2] · Stefan M. Pfister[5,7,15] · Andreas von Deimling[1,2]

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- Studies have been published showing that DNA methylation accurately reclassifies 14% of tumors
- These studies are biased towards difficult to diagnose cases

Neuro-Oncology

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Impact of the methylation classifier and ancillary methods on CNS tumor diagnostics

Zhichao Wu,[†] Zied Abdullaev,[†] Drew Pratt, Hye-Jung Chung, Shannon Skarshaug, Valerie Zgonc, Candice Perry, Svetlana Pack, Lola Saidkhodjaeva, Sushma Nagaraj, Manoj Tyagi, Vineela Gangalapudi, Kristin Valdez, Rust Turakulov, Liqiang Xi, Mark Raffeld, Antonios Papanicolau-Sengos, Kayla O'Donnell, Michael Newford, Mark R. Gilbert, Felix Sahm, Abigail K. Suwala, Andreas von Deimling, Yasin Mamatjan, Shirin Karimi, Farshad Nassiri, Gelareh Zadeh, Eytan Ruppin, Martha Quezado, and Kenneth Aldape

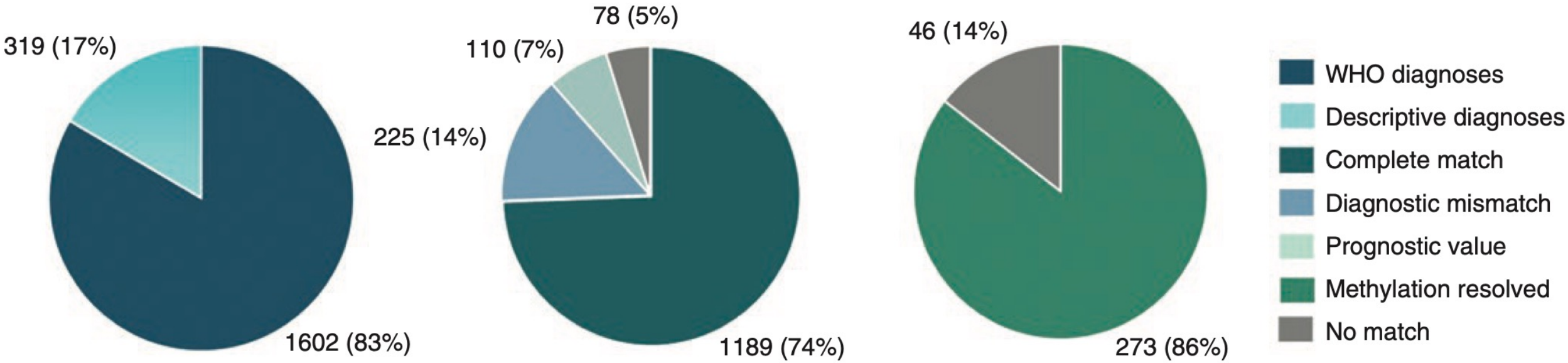
NYU prospective study to propose guidelines for use of DNA methylation in routine clinical practice

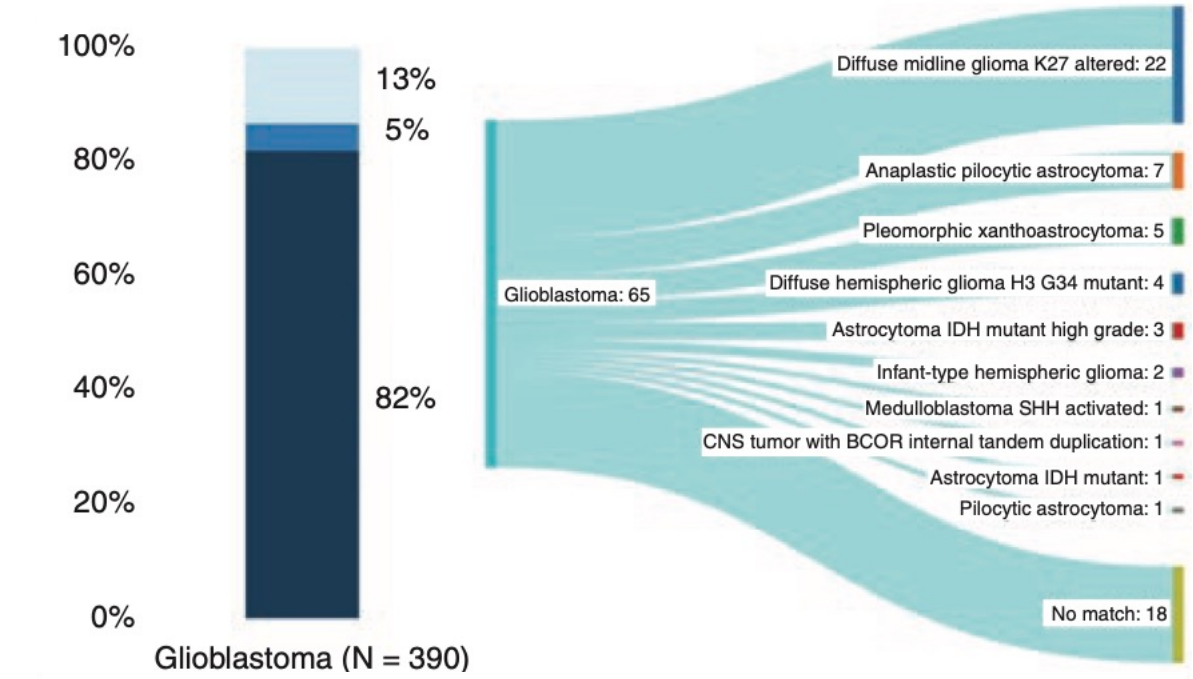
- Guidelines for the use of DNA methylation in clinical practice need to be developed
- We performed a prospective analysis of 1921 brain tumors diagnosed at NYU
- All tumors received the standard of care pathology diagnosis at the time of review and simultaneous whole genome DNA methylation profiling

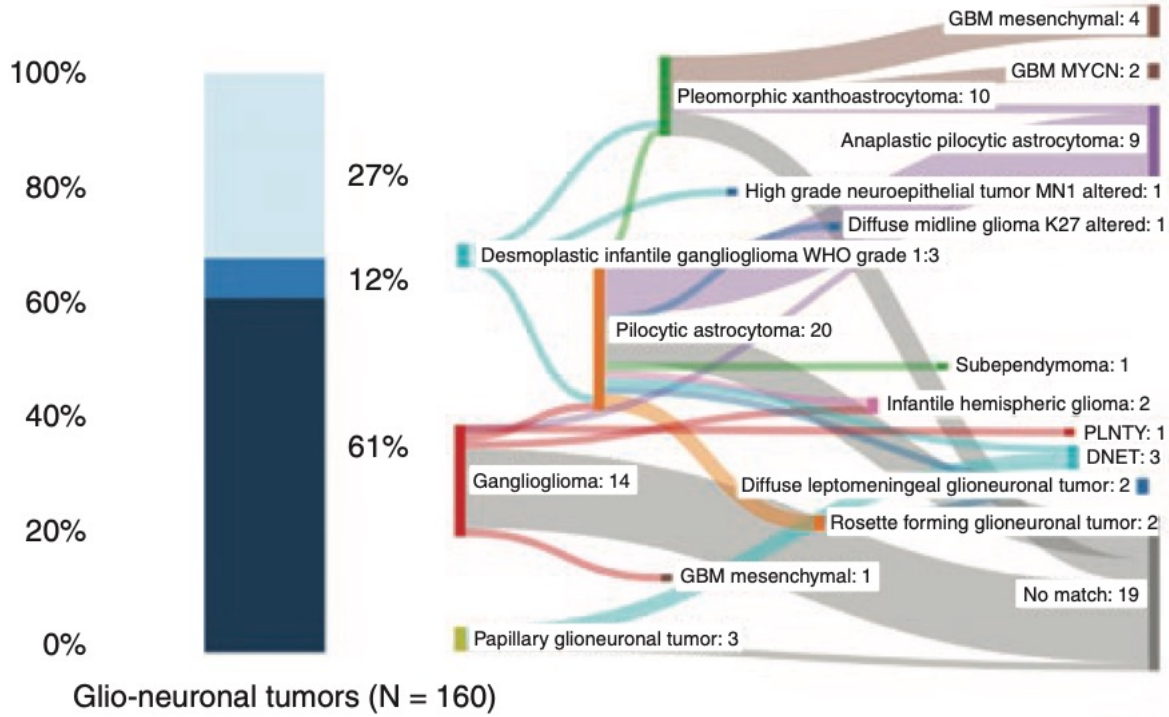
Table 1. Clinical Characteristics of the Cohort

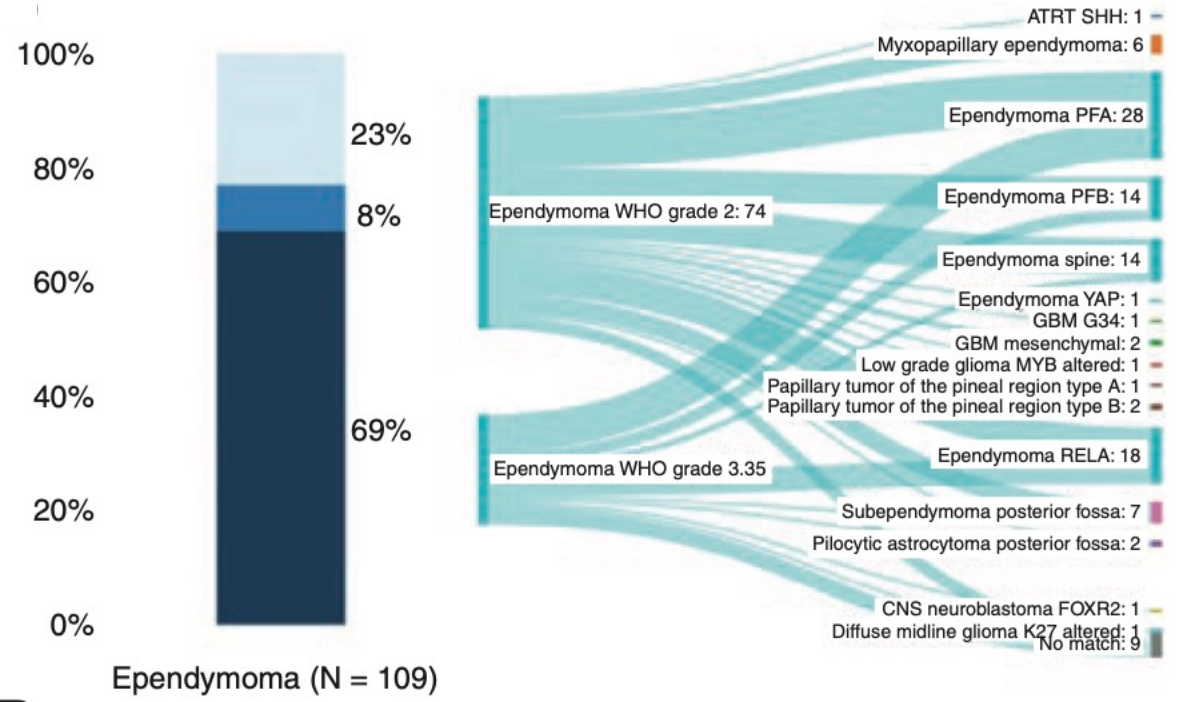
	N (%)
All tumors	1921
WHO recognized histologic diagnoses	67
Descriptive diagnoses	195
Methylation classes identified	88
Male	1006 (52%)
Female	915 (48%)
Adult	1303 (68%)
Pediatric	545 (28%)
Incomplete clinical data	73 (4%)

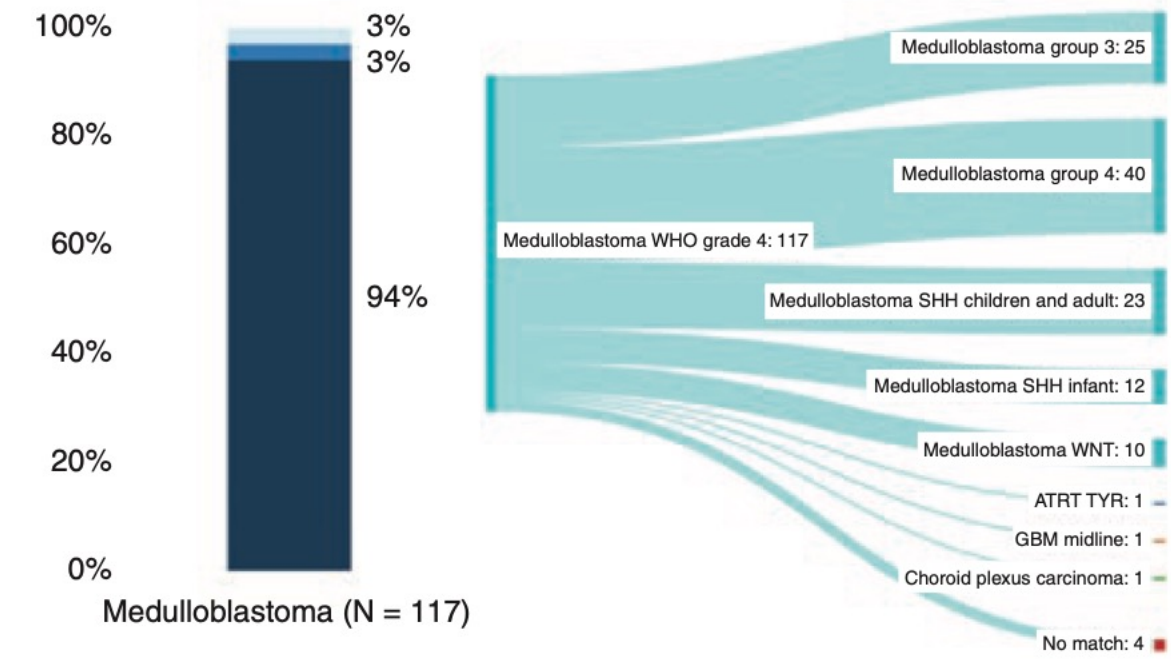
- Our cohort consisted of 1602 WHO recognized diagnoses and 319 descriptive diagnoses
- Of the 1602 WHO diagnoses, 225 (14%) of cases were a diagnostic mismatch with DNA methylation
- 110 cases received a diagnosis by DNA methylation that had prognostic significance
- 78 (5%) of cases did not match with any class by DNA methylation



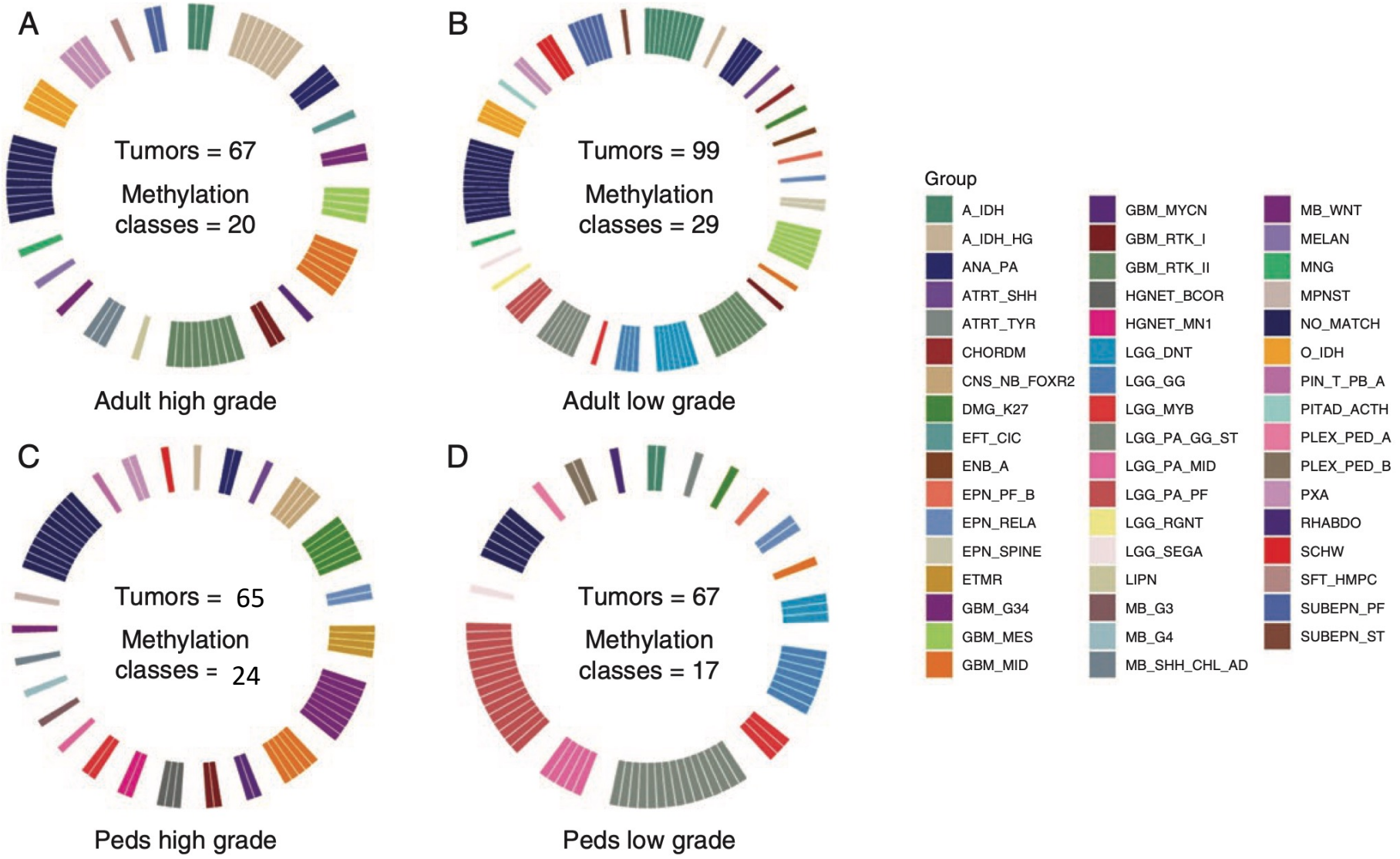

100%
80%
60%
40%
20%
0%
13%
5%
82%
Glioblastoma: 65
Diffuse midline glioma K27 altered: 22
Anaplastic pilocytic astrocytoma: 7
Pleomorphic xanthoastrocytoma: 5
Diffuse hemispheric glioma H3 G34 mutant: 4
Astrocytoma IDH mutant high grade: 3
Infant-type hemispheric glioma: 2
Medulloblastoma SHH activated: 1
CNS tumor with BCOR internal tandem duplication: 1
Astrocytoma IDH mutant: 1
Pilocytic astrocytoma: 1
No match: 18
Glioblastoma (N = 390)


100%
80%
60%
40%
20%
0%
27%
12%
61%
GBM mesenchymal: 4
GBM MYCN: 2
Pleomorphic xanthoastrocytoma: 10
Anaplastic pilocytic astrocytoma: 9
High grade neuroepithelial tumor MN1 altered: 1
Diffuse midline glioma K27 altered: 1
Desmoplastic infantile ganglioglioma WHO grade 1:3
Pilocytic astrocytoma: 20
Subependymoma: 1
Infantile hemispheric glioma: 2
PLNTY: 1
DNET: 3
Ganglioglioma: 14
Diffuse leptomeningeal glioneuronal tumor: 2
Rosette forming glioneuronal tumor: 2
GBM mesenchymal: 1
No match: 19
Papillary glioneuronal tumor: 3
Glio-neuronal tumors (N = 160)


100%
80%
60%
40%
20%
0%
23%
8%
69%
ATRT SHH: 1
Myxopapillary ependymoma: 6
Ependymoma PFA: 28
Ependymoma WHO grade 2: 74
Ependymoma PFB: 14
Ependymoma spine: 14
Ependymoma YAP: 1
GBM G34: 1
GBM mesenchymal: 2
Low grade glioma MYB altered: 1
Papillary tumor of the pineal region type A: 1
Papillary tumor of the pineal region type B: 2
Ependymoma WHO grade 3.35
Ependymoma RELA: 18
Subependymoma posterior fossa: 7
Pilocytic astrocytoma posterior fossa: 2
CNS neuroblastoma FOXR2: 1
Diffuse midline glioma K27 altered: 1
No match: 9
Ependymoma (N = 109)


100%
80%
60%
40%
20%
0%
3%
3%
94%
Medulloblastoma group 3: 25
Medulloblastoma group 4: 40
Medulloblastoma WHO grade 4: 117
Medulloblastoma SHH children and adult: 23
Medulloblastoma SHH infant: 12
Medulloblastoma WNT: 10
ATRT TYR: 1
GBM midline: 1
Choroid plexus carcinoma: 1
No match: 4
Medulloblastoma (N = 117)

DNA methylation accurately diagnosis 86% of tumors given descriptive diagnoses



Proposed criteria

Table 2. NYU Criteria for the Use of DNA Methylation in Clinical Practice

High Yield
• CNS tumors defined by DNA methylation signatures • All CNS tumors with descriptive diagnoses • Tumor entities with a high chance of diagnostic error in the absence of other molecular studies • Tumors with inconclusive or contradictory immunohistochemical or molecular results • Tumors where subclassification may affect clinical management or provides prognostic information
Intermediate yield
• Tumors in which DNA methylation could triage further molecular testing • Tumors with moderate chance of diagnostic error in the absence of other molecular studies • Tumors in which > 10 immunohistochemical stains and/or multiple molecular tests may be required for diagnosis (tissue preservation/cost efficiency)
Low yield
• Tumors with low chance of diagnostic error when using recommended techniques according to WHO required criteria) • Tumors in which other molecular tests have sufficiently established molecular drivers and tumor classification • No established prognostic value of molecular subclassification

WHO and DNA methylation

- DNA methylation defined entities
  - High grade astrocytoma with piloid features (HGAP)
  - Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
- Entities in which DNA methylation is included in diagnostic criteria

Diffuse Midline Glioma K27-altered

Essential:	
A diffuse glioma	
AND	
Loss of H3 p.K28me3 (K27me3) (immunohistochemistry)	
AND	
Midline location	
AND	
	Presence of an H3 p.K28M (K27M) or p.K28I (K27I) mutation (for H3 K27–mutant subtypes)
	OR
	Presence of a pathogenic mutation or amplification of *EGFR* (for the *EGFR*-mutant subtype)
	OR
	Overexpression of EZHIP (for the H3-wildtype with EZHIP overexpression subtype)
	OR
	Methylation profile of one of the subtypes of diffuse midline glioma
Desirable:	
Results from molecular analyses that enable discrimination of the H3.1 or H3.2 p.K28 (K27)-mutant subtype from the H3.3 p.K28 (K27)-mutant subtype	

Diagnostically challenging scenarios

- The tumor does not classify with any class (score of <0.3)
- The tumor classifies with a class that makes sense but with an indeterminant score (0.3-0.9)
- The tumor classifies with a class that doesn’t make sense with an indeterminant score (0.3-0.9)

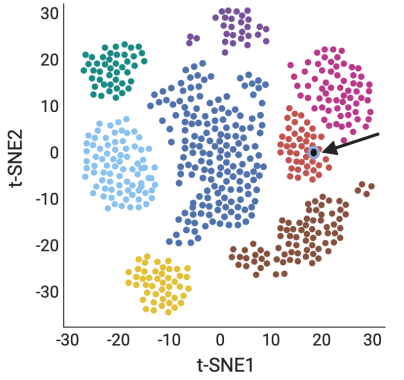
Reasons for poor classification

- Evaluating for lab error
- Reviewing H&E for tumor purity
  - DNA methylation is robust with a tumor content of 50% or higher
  - Infiltrating edge with normal can dilute the tumor content
  - Necrosis without inflammation doesn’t have a strong impact
- Additional molecular testing

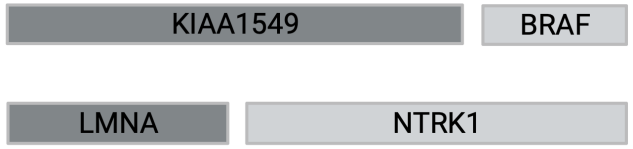
Diagnostic challenges

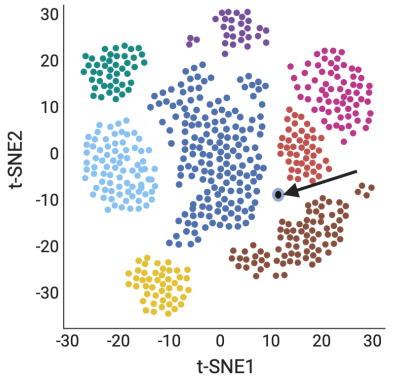
Brain tumor resection

Fusion analysis

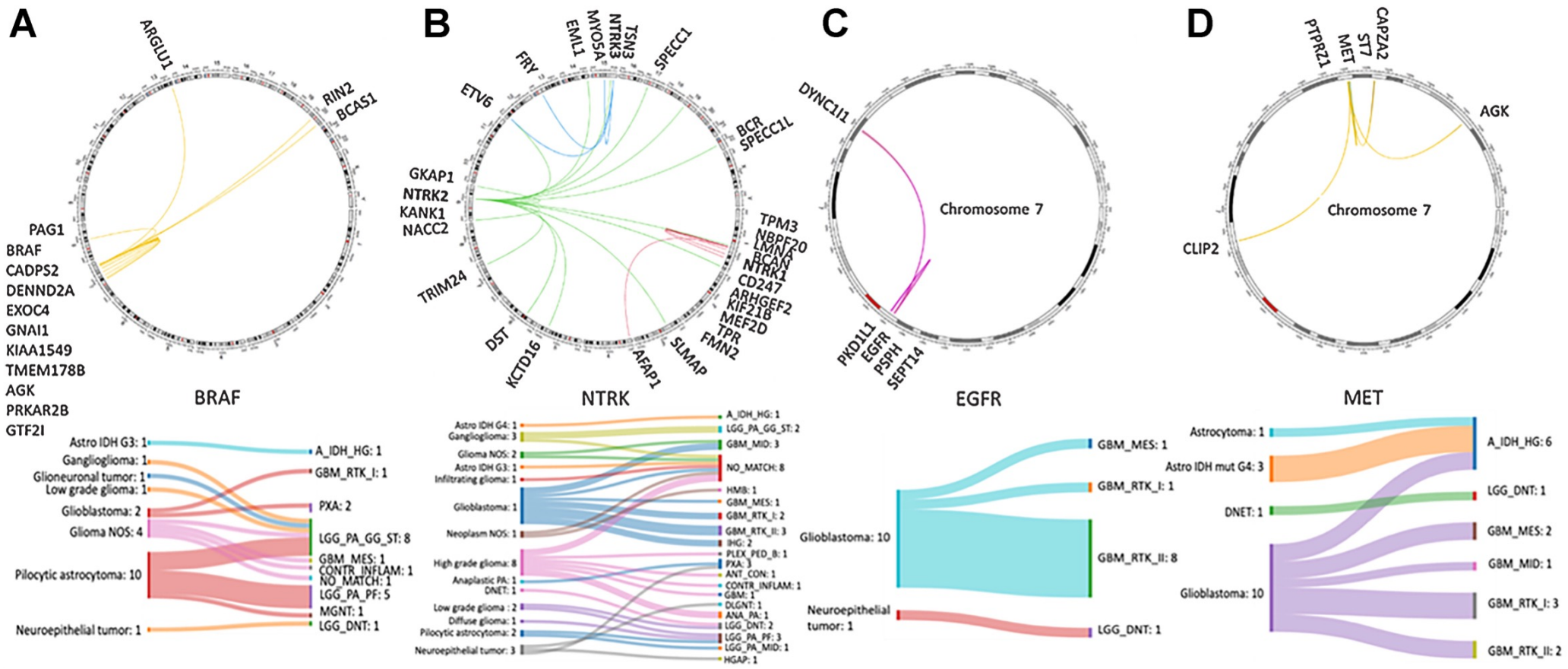


DNA methylation analysis





- Alterations for which the classifier was not trained can affect the classifier result
- We analyzed a cohort of 219 CNS tumors positive for fusion by RNA sequencing and with concurrent DNA methylation
- Tumors with disease defining gene fusions, for example BRAF-KIAA1549 in a pilocytic astrocytoma, were excluded from the cohort
- The cohort is comprised of cases from NYU, Cornell, MSKCC, and the NIH.
- RNA sequencing was performed using NYU FusionSEQer (NYU), Oncomine comprehensive V2 (Cornell), Illumina Truseq (NIH), and Archer FusionPlex (MSKCC)

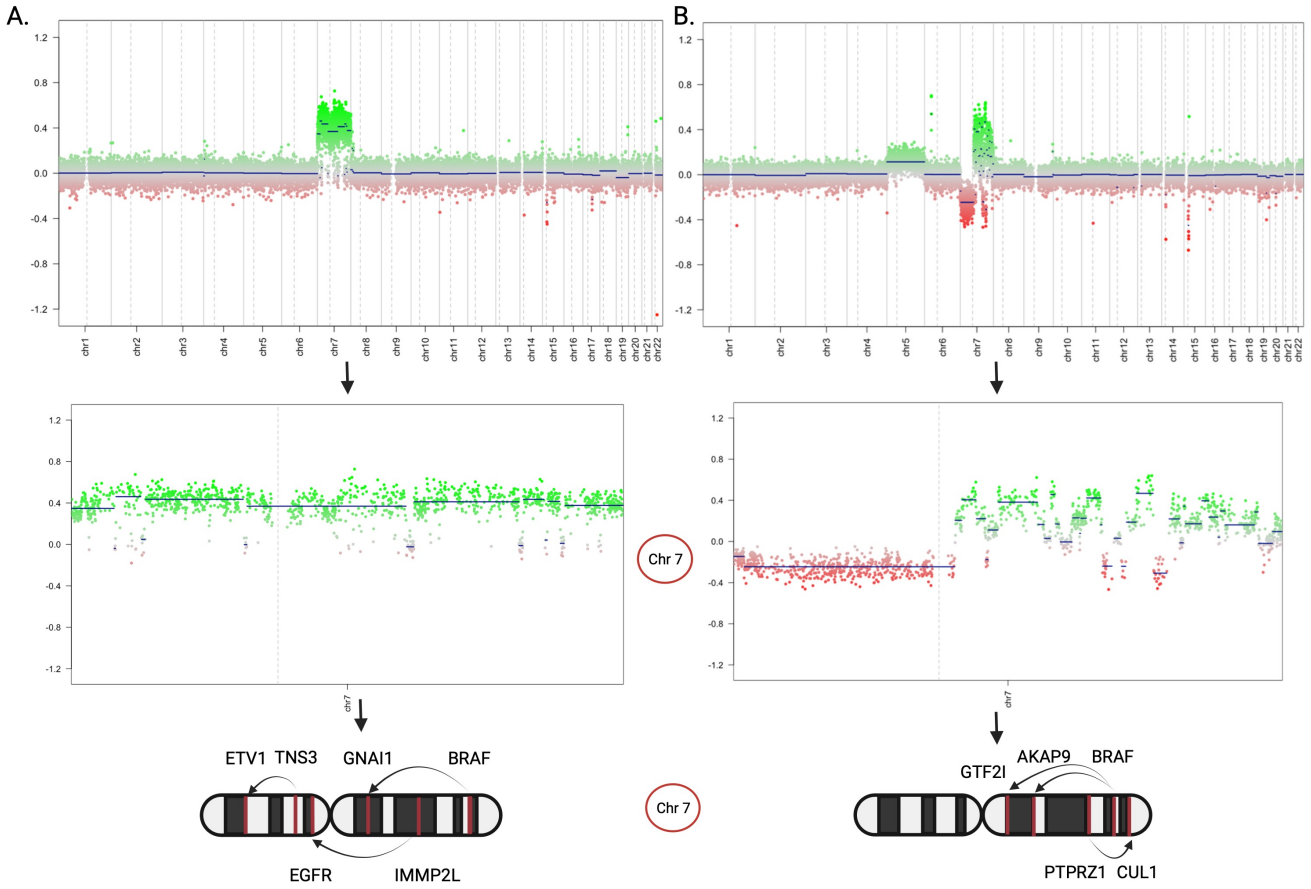


- NTRK fusions included many different partners and occurred across a wide variety of tumor types
- EGFR and MET fusions exclusively partnered with other genes on chromosome 7 and primarily occurred in glioblastomas
- BRAF fusions had a variety of different partners and occurred mainly in glioneuronal tumors and low grade gliomas

Fusions effect the classifier in two ways

- The diagnosis by histology and DNA methylation are concordant but below the calibrated score of 0.9
- The diagnosis is discordant between histology and DNA methylation

Tumors with multiple fusions

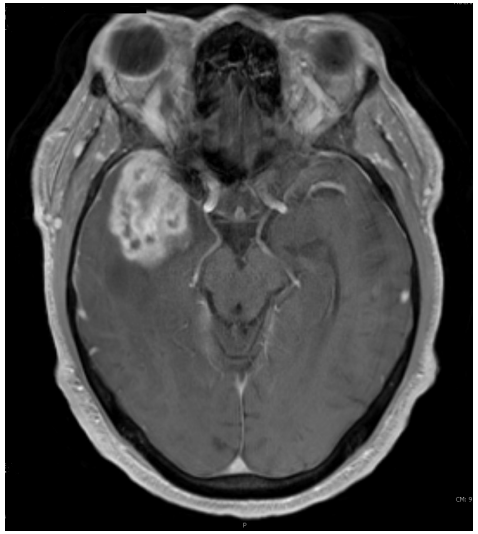


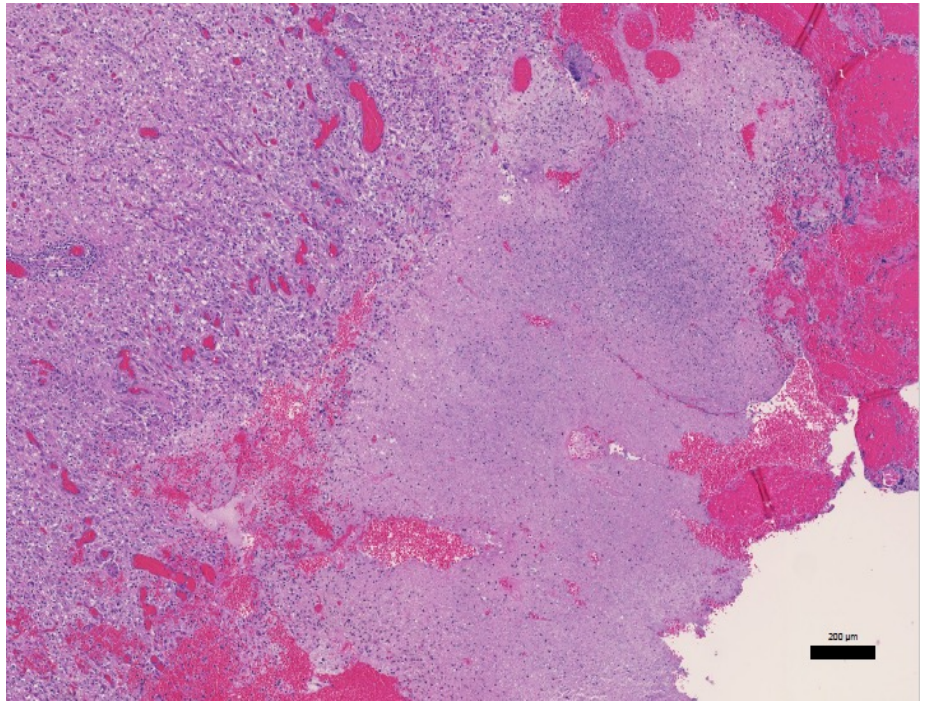
- We identified 6 tumors with multiple concurrent fusions
- Tumor on the left was diagnosed histologically as a low grade neuroepithelial tumor and classified poorly as a LGG_DNT with a score of 0.43
- Tumor on the right was diagnosed by histology and DNA methylation as a pilocytic astrocytoma with a calibrated score of 0.89
- Both tumors had 3 unique fusions involving 6 genes all on chromosome 7

Galbraith et al 2023 *Molecular cancer research*

Case 1

- 76 year old male with PMH of well-controlled HIV, prostate adenocarcinoma, and adrenal insufficiency
- Presented with 5 days of a right sided headache with accompanying right eye pain and tearing.
- Imaging showed an infiltrative, expansile, heterogeneously enhancing mass in the anterior temporal lobe. A subtotal surgical resection was performed





Diagnosis: Glioblastoma, CNS WHO grade 4

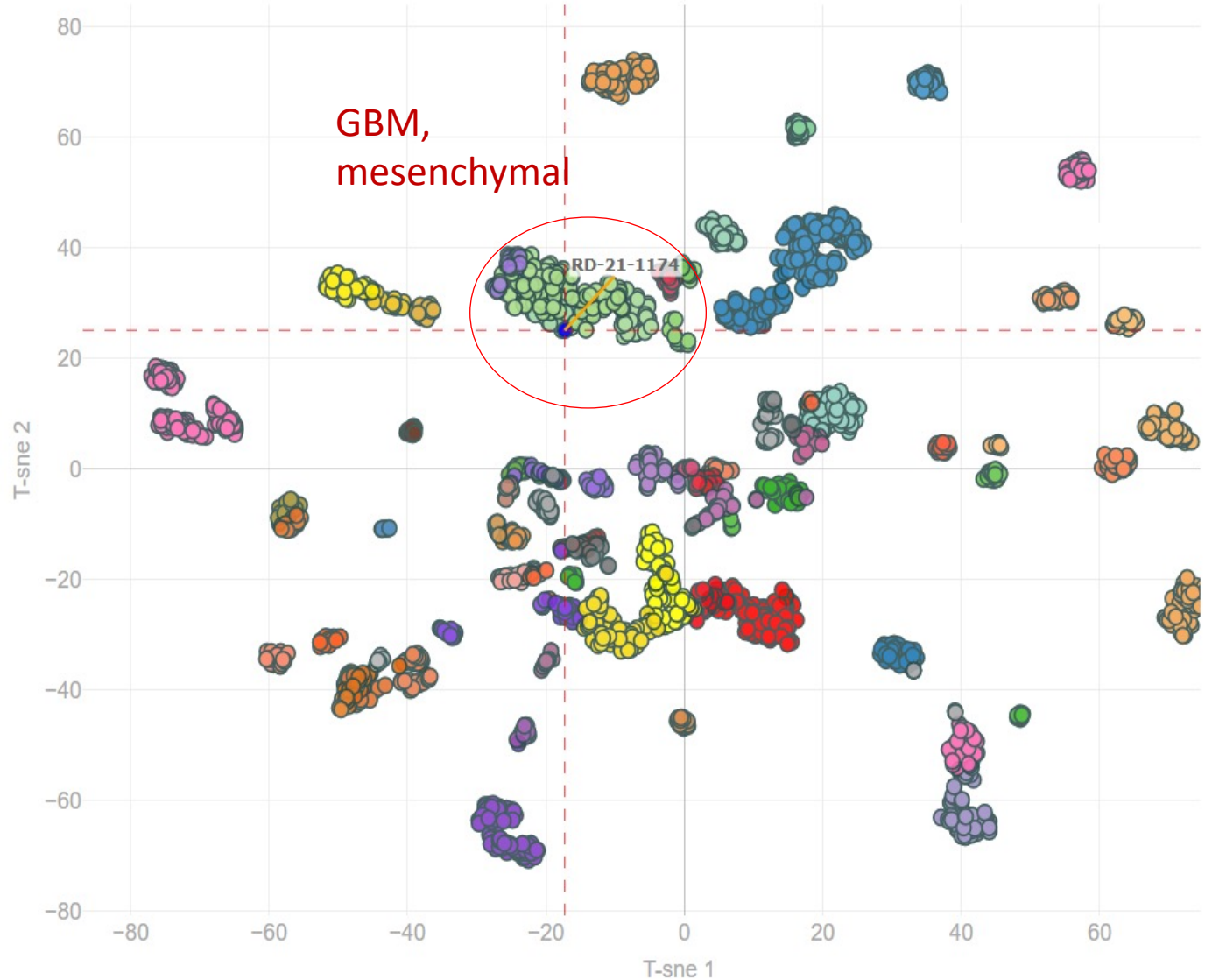
Class Score	Methylation Family	Interpretation
0.569	MTGF_GBM	Indeterminate
0.08	CONTR, REACT	
0.047	MTGF_PA	
0.041	CONTR, INFLAM	
0.026	LGG, SEGA	

Subgroup Score	Methylation Subgroup	Interpretation
0.555	GBM, MES	Positive
0.08	CONTR, REACT	
0.041	CONTR, INFLAM	
0.026	LGG, SEGA	
0.025	PXA	

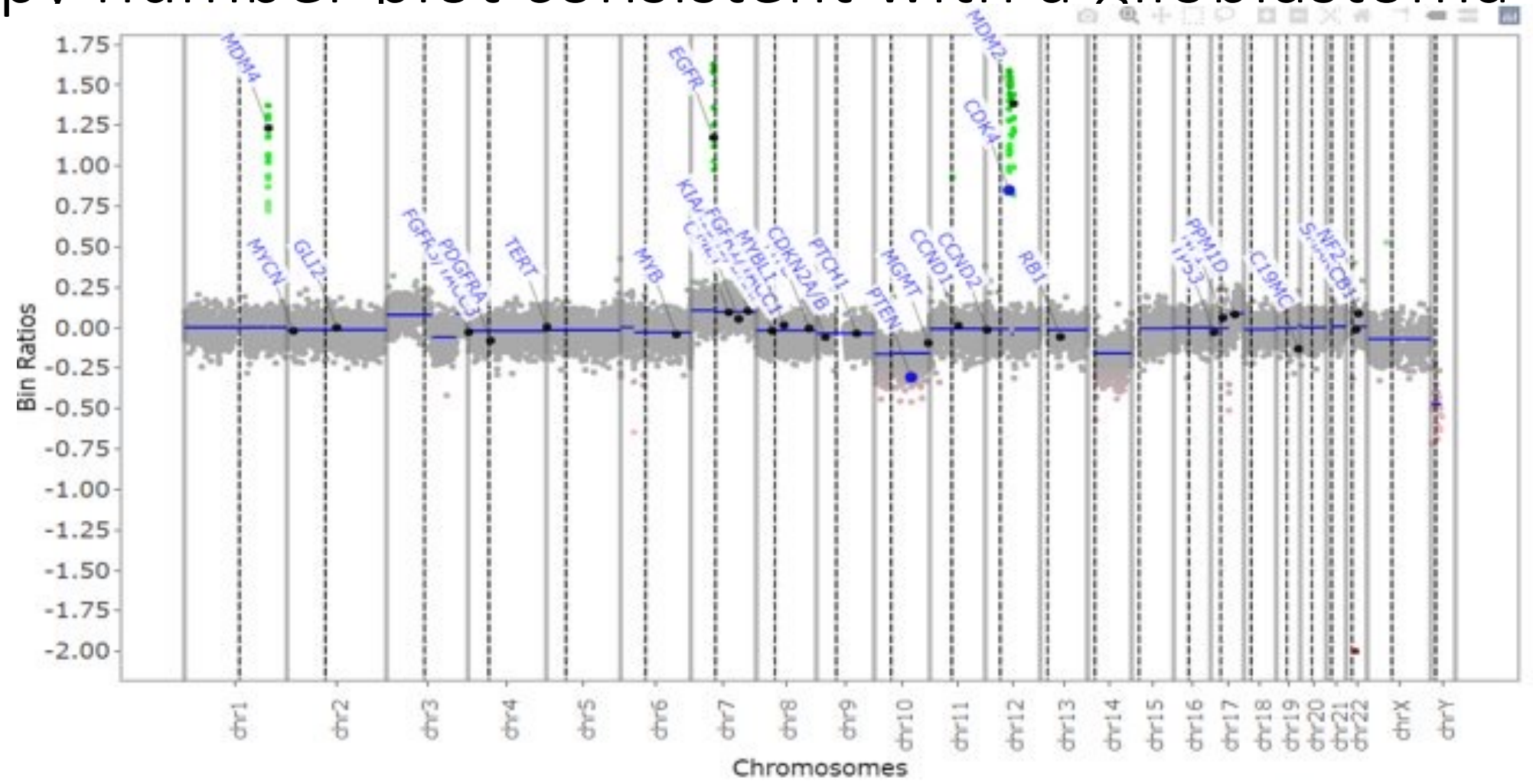
Interpretation Key

Positive indicates a positive match for methylation classifier (score >= 0.9) & Match to MC family member quality cases. (score >= 0.5)
Indeterminate indicates no determinate match (score < 0.9): possibly still relevant for low tumor content and low DNA. For subclass score, indeterminate value is <0.5 and >=0.1
Negative indicates no matching methylation class (score <0.3) and for classifier subclass score is <0.1

So what next…..


GBM,
mesenchymal
RD-21-1174
T-sne 2
T-sne 1
80
60
40
20
0
−20
−40
−60
−80
−80
−60
−40
−20
0
20
40
60

Copy number plot consistent with a glioblastoma

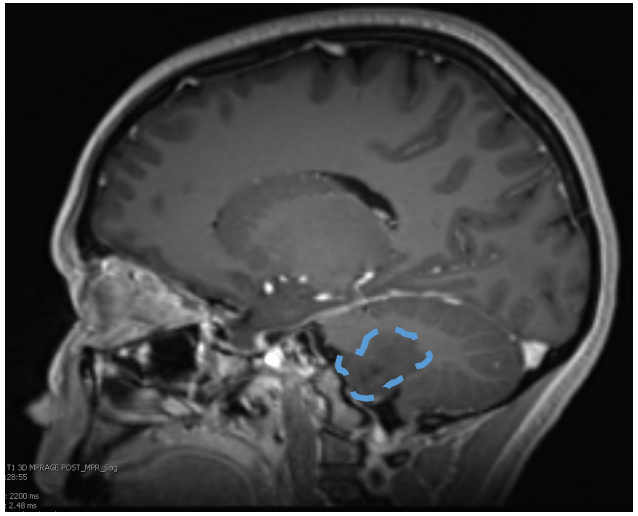


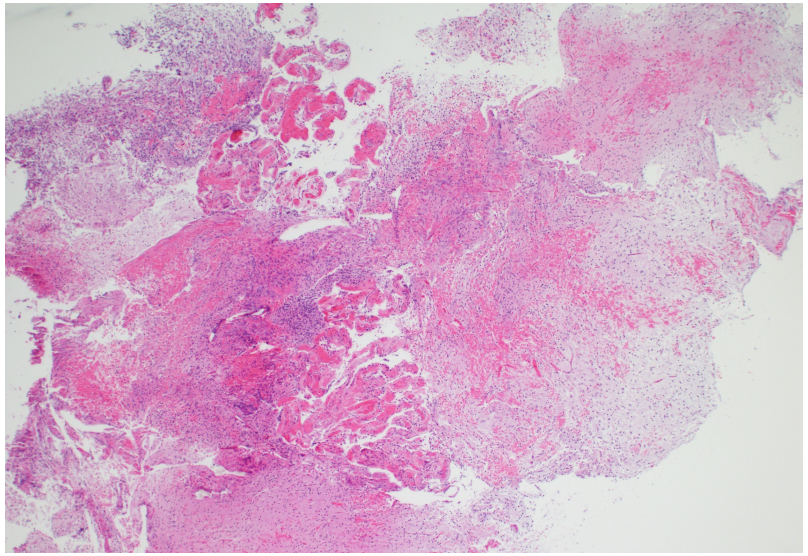
Classic histology: class match with a poor score

- Review the t-SNE: does it cluster with the expected class?
- Review the copy number plot: Are expected alterations present?
- Review the tumor cellularity of the slide for DNA methylation

Case 2

- 24 year old female with a syncopal episode directly after cutting her hand in the kitchen.
- Follow up at her primary care physician showed evidence of vertical nystagmus.
- An MRI scan demonstrated a tumor in the left cerebellum and cerebellopontine angle



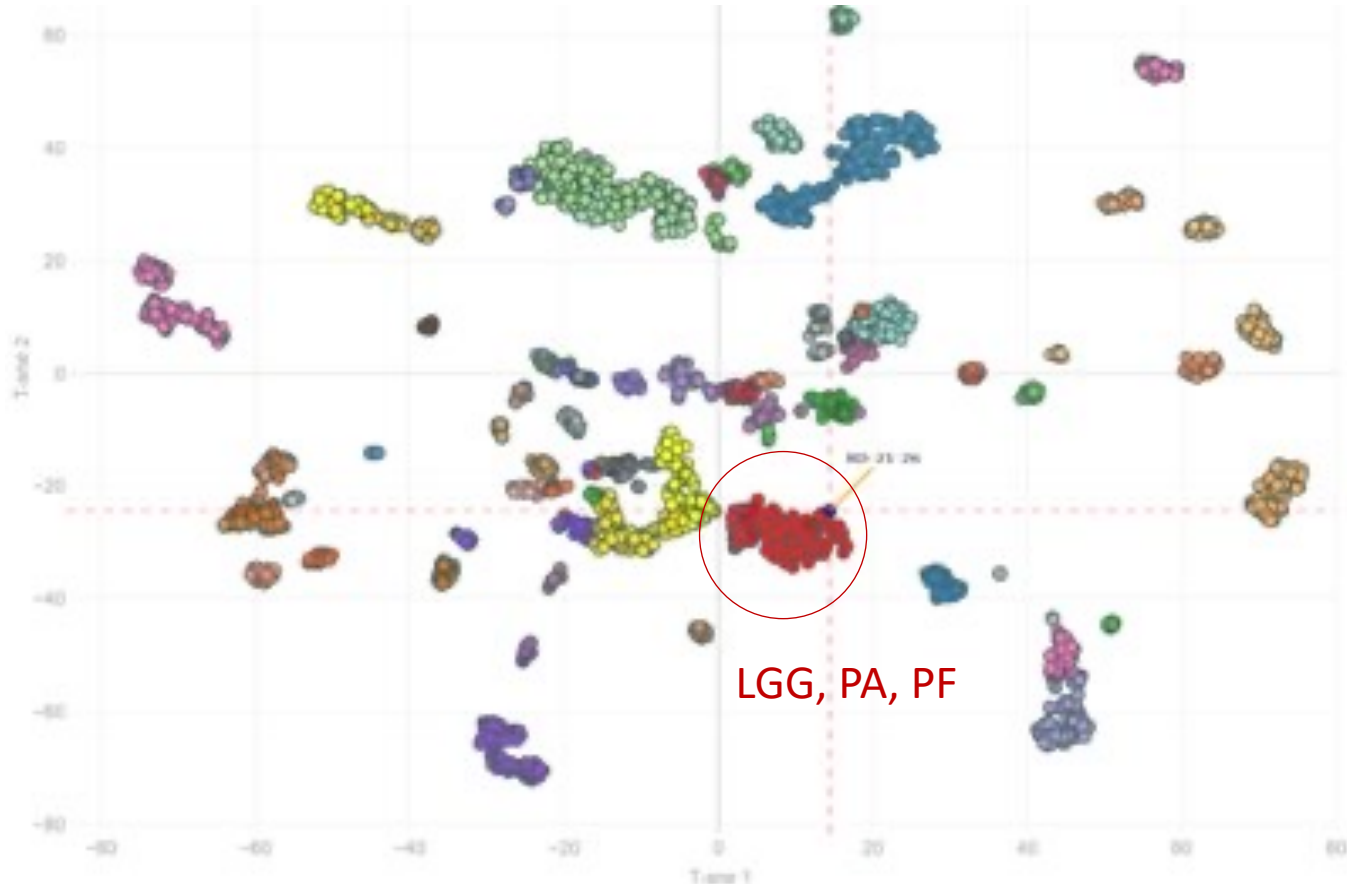


Diagnosis: Pediatric diffuse glioma, low grade

DNA methylation results

Class Score	Methylation Family	Interpretation
0.272	LGG, RGNT	Negative
0.16	MTGF_PA	
0.128	LGG, MYB	
0.042	MTGF_IDH_GLM	
0.04	LGG, DNT	

Subgroup Score	Methylation Subgroup	Interpretation
0.272	LGG, RGNT	Negative
0.154	LGG, PA PF	
0.128	LGG, MYB	
0.04	LGG, DNT	
0.04	ANA PA	


LGG, PA, PF

NYU Fusion SEQer

Class match with poor score: Rare driver

- Fusion can cause a low score match with an expected class
  - Low grade gliomas: NTRK fusions

Billing

- Current approaches include using a descriptive code or codes for MGMT or copy number analysis
- The process is underway to establish a specific CPT code dedicated to the DNA methylation classifier

Additional and future uses of DNA methylation

- Additional classifiers
  - Kidney
  - Sarcoma
  - Derm
  - Cancer of Unknown Primary
  - Lymphoma
- MGMT promoter methylation
- Copy number
- MLH1 promoter methylation

ARTICLE

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Sarcoma classification by DNA methylation profiling

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Thank you

Questions?

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