THE OHIO STATE UNIVERSITY

Providing molecular insight for resource-strained patients with machine learning-based workflows

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Division of Neuropathology

Distribution of Pathology Expertise Globally

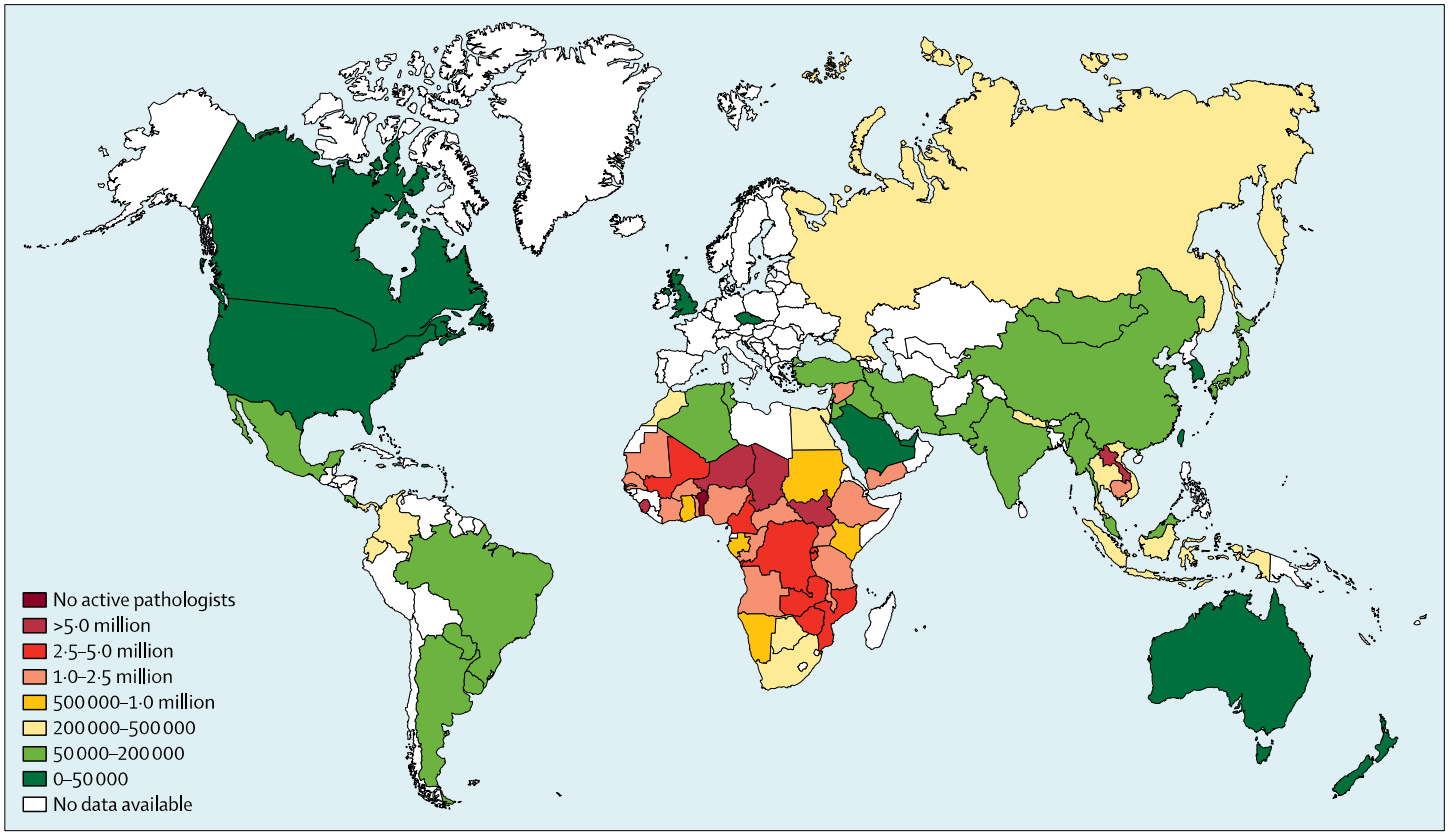

Figure 3: **Global workforce capacity in pathology and laboratory medicine (PALM)**
Data derived from previous studies[66–70] and the survey data shown in the appendix.

Wilson, et al., The Lancet 2018, vol 391, pg 1927

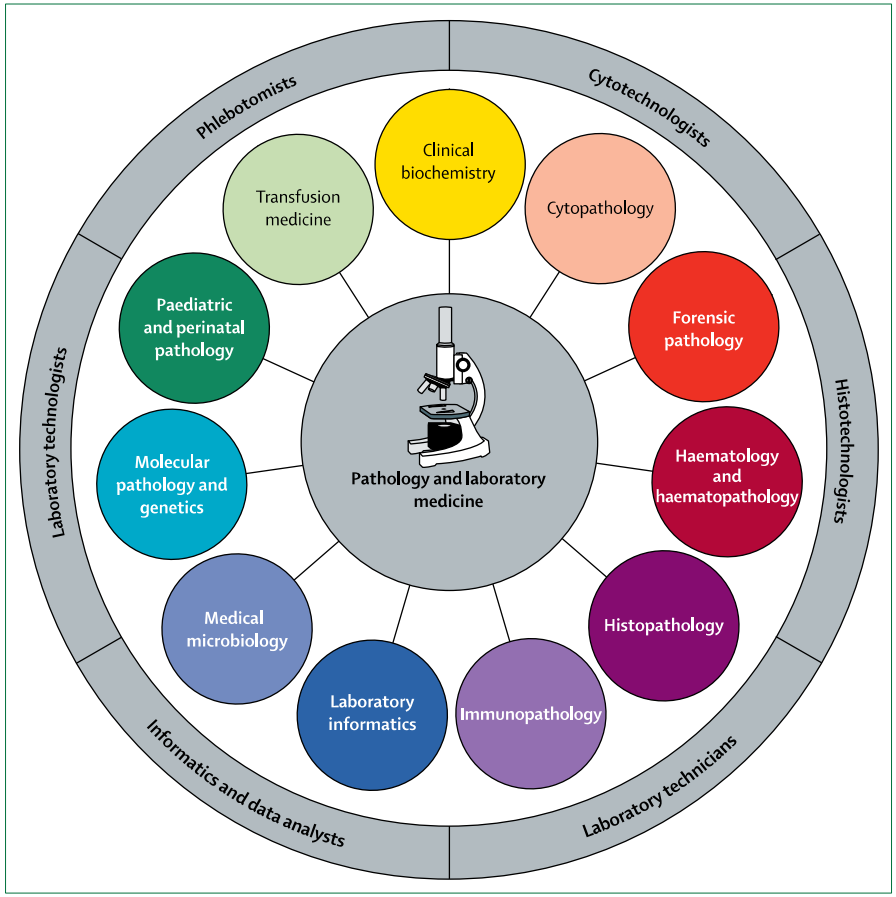

Figure 2: **The organisation and integrated structure of pathology and laboratory medicine (PALM)**
PALM is a highly complex and integrated set of medical and technical subdisciplines that must function as a coordinated team to provide the scope of services needed for contemporary health care.

Modern Pathology Workflows Require Integrated Expertise and Infrastructure

Infrastructure Problems include

- Lack of training.
- Lack of equipment.
- Lack of clear S.O.P. for workflows, Quality Control, Quality Assurance.

Wilson, et al., The Lancet 2018, vol 391, pg 1927

Pathology Infrastructure is Challenged

Grossing Station

Ohio State University

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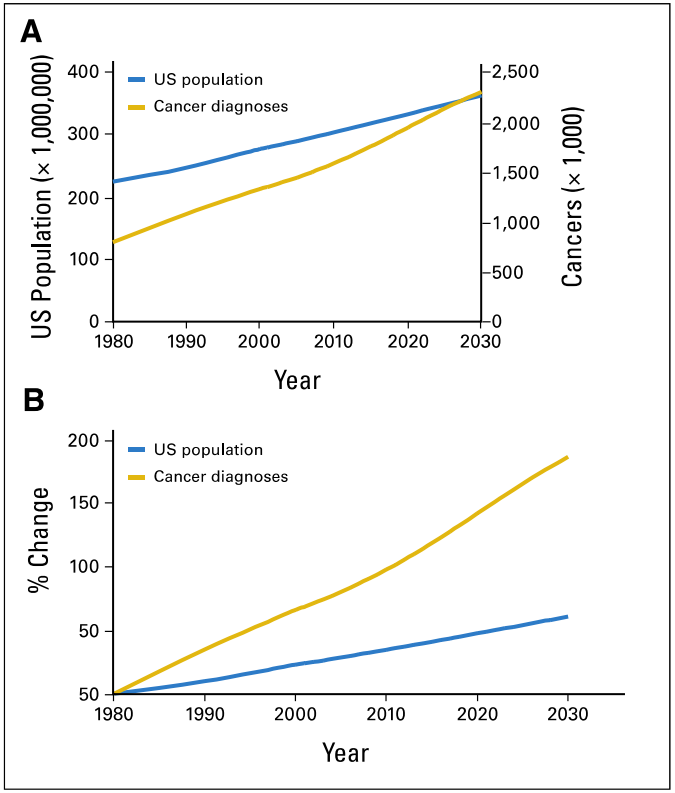
Developed country, by World Bank Criteria



Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol. 2009 Jun 10;27(17):2758-65. doi: 10.1200/JCO.2008.20.8983. Epub 2009 Apr 29. PMID: 19403886.

FIGURE 10.4

Number of new cancer cases in 2018 vs. 2040: impact of demographic projections by 2040

American Cancer Society, https://canceratlas.cancer.org/wp-content/uploads/2019/09/CA3_TheBurdenofCancer.pdf

Emerging Trend in Brain Cancer Diagnostics

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
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Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
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Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

2016 WHO Classification of CNS Tumors represented the first instance in solid tumors where molecular characterization was necessary for diagnosis

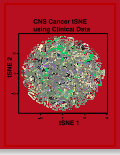
- ***Many molecular assays are not well reimbursed.***

The 2021 WHO Classification of CNS Tumors will expand this molecular classification, and will include entities such as Anaplastic Astrocytoma with Piloid Features which are only delineated through methylation.

- ***No reimbursement model has been generated yet.***

<u>The development of these diagnostic insights has been advanced rapidly without much thought as to how this can be deployed nationally and internationally.</u>

How can we meet this challenge?



Machine Learning can help

- Improve workflows.
- Fill a gap in human resources by applying clinical diagnostic aids.
- Help make informed decisions about when to perform non-reimbursable tests.

Challenges to ML/AI implementation in Brain Cancer Diagnostics

- Primary Brain Cancers are Rare
- Worldwide, primary malignant brain cancer incidence is ***3.7 per 100,000 males and 2.6 per 100,000 females*** (Bondy et al., 2008).
- The current practice is to obtain high resolution data and integrate tissue architecture with molecular features to generate an integrated diagnosis.
  - Problem of low number of subjects with multiple features to model.
  - Not all testing is appropriate for each tumor entity, making many GB datasets fraught with missing data values.
  - Current repositories, such as TCGA and CGGA, may show H&E stained sections of flash frozen tissue, which do not recapitulate actual morphology seen in routine practice. ***Features learned from these data are not generalizable to current workflows.***

How do we solve this problem?

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Thought Experiment:

Simulation of the WHO diagnostic grading scheme.

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Methodology

A **meta-analysis** of the scientific literature pertaining to the classification of gliomas was performed. We focused on common entities. We then constructed a database model using public domain data from the scientific literature to compose a model patient database.

We call this a simulated brain cancer population.

We tabulated several features in 4 general types of data

[1] "Age"
[2] "ATRX.loss"
[3] "BRAF.V600E.mutation"
[4] "calcifications"
[5] "chicken.wire"
[6] "columns.cords"
[7] "desmoplasia"
[8] "displastic.neurons"
[9] "EGFR.amplification"
[10] "Endothelial.Proliferation"
[11] "eosinophil.granular.bodies"
[12] "FISH_codeletion_1p19q"
[13] "Gender"
[14] "GFAP"
[15] "high.celullarity"
[16] "idh1.2.mutation"
[17] "idh1.R132H"
[18] "infiltrative.diffusse"
[19] "ki67"
[20] "LOH_codeletion_1p19q"
[21] "low.cellularity"
[22] "medium.celullarity"
[23] "MGMT"
[24] "microcystic"
[25] "multilayered.rosettes"
[26] "my_diagnosis"
[27] "myxoid.areas"
[28] "Necrosis"
[29] "nodular"
[30] "p53"
[31] "perivascular.lymphocytes"
[32] "perivascular.pseudorosettes"
[33] "pseudopapillar.papillary"
[34] "rosental.fibers"
[35] "site"
[36] "Solid.discohesive"
[37] "solid.with.infiltration"
[38] "storiform"

Methodology

We generated samples of data using either normal distributions of means (eg., mean age, ki67, etc.)

The patients in this database are “modeled patients”, ie, a theoretical population model based on public domain data which was extracted from our meta-analysis.

We then pooled these data into one large database containing 102359 modelled patients.

NOTE, WE ARE NOT INCLUDING IN THIS MODEL INCIDENCE NOR PREVALENCE.

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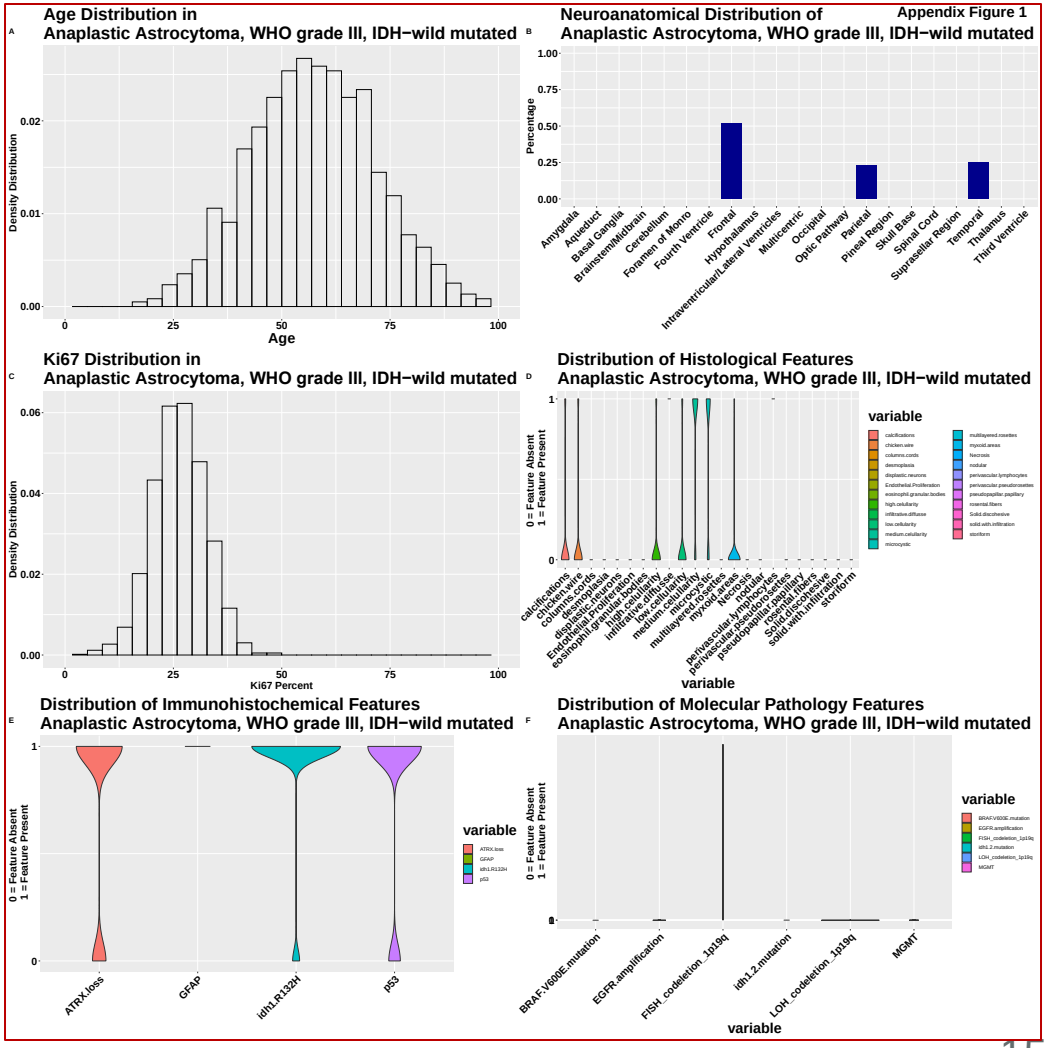
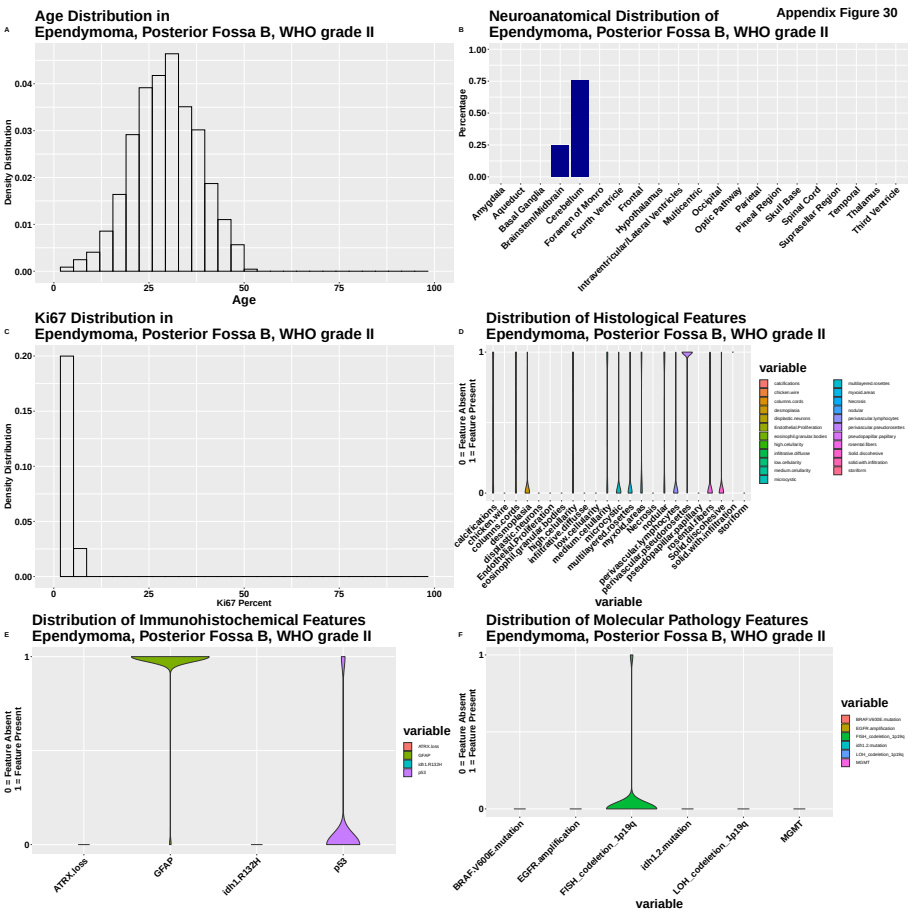
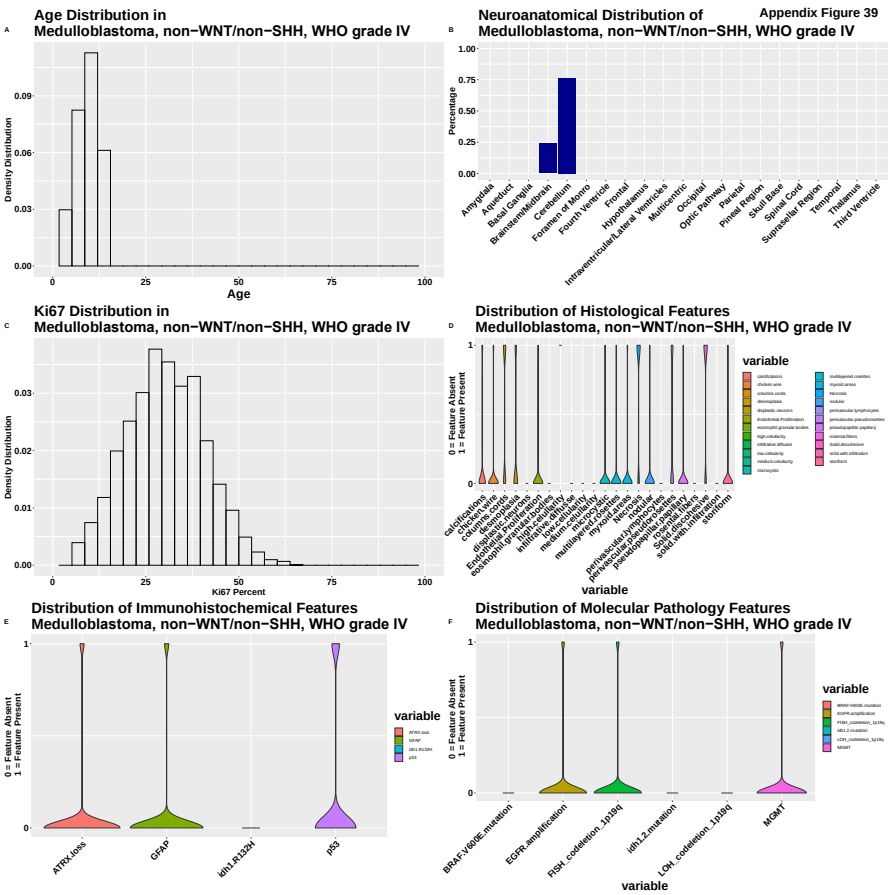
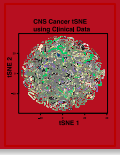


Example of Two Different Posterior Fossa Tumor Types



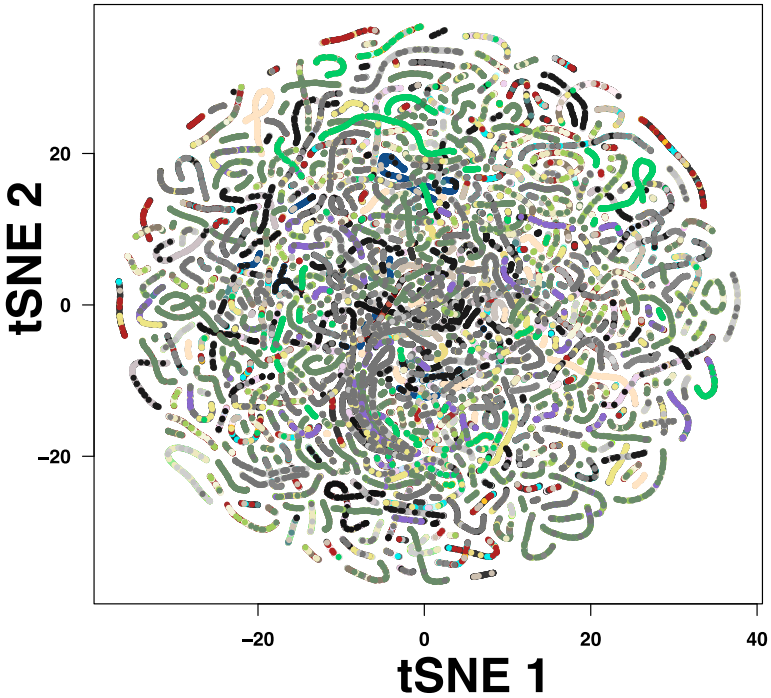


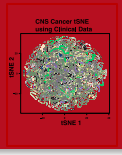


WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

CNS Cancer tSNE using Clinical Data





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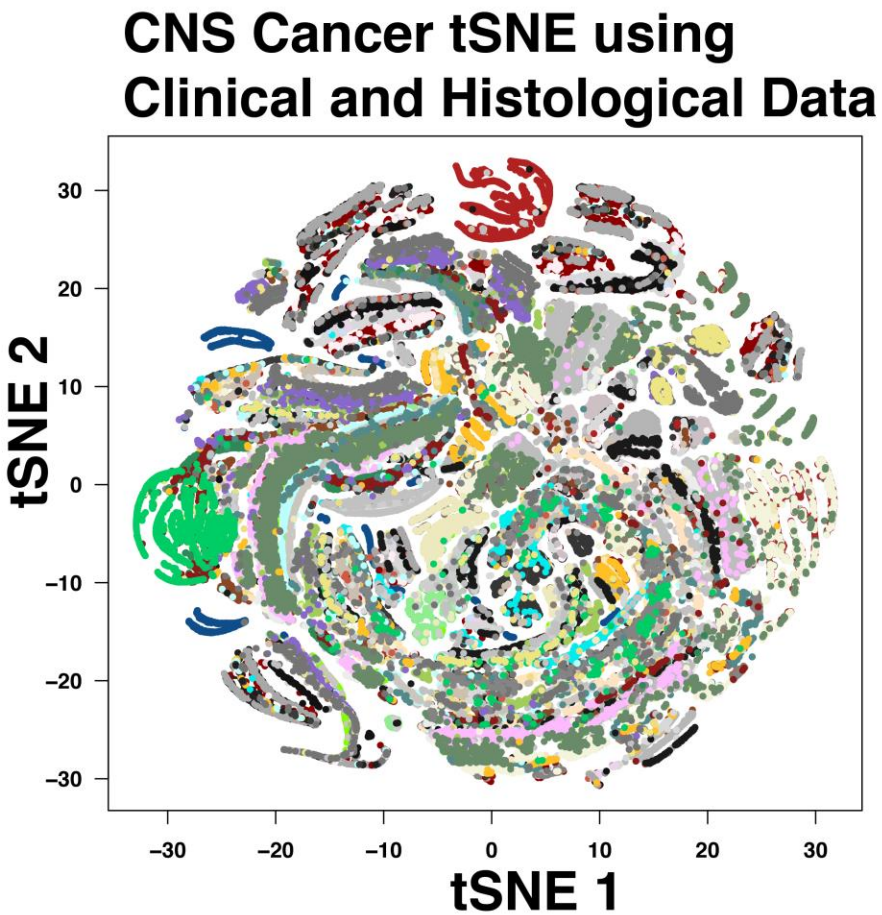
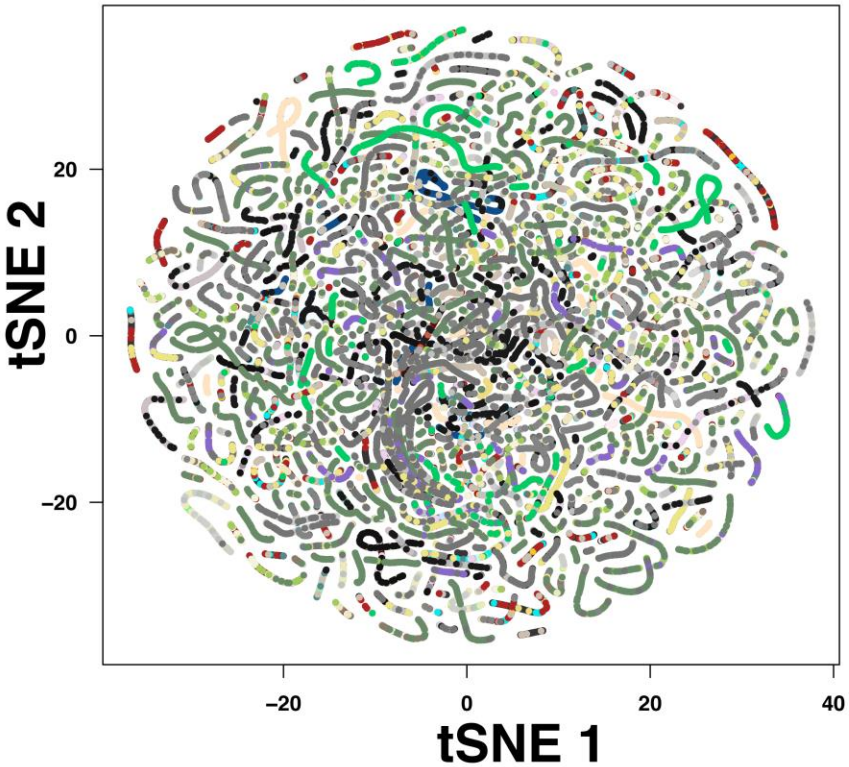
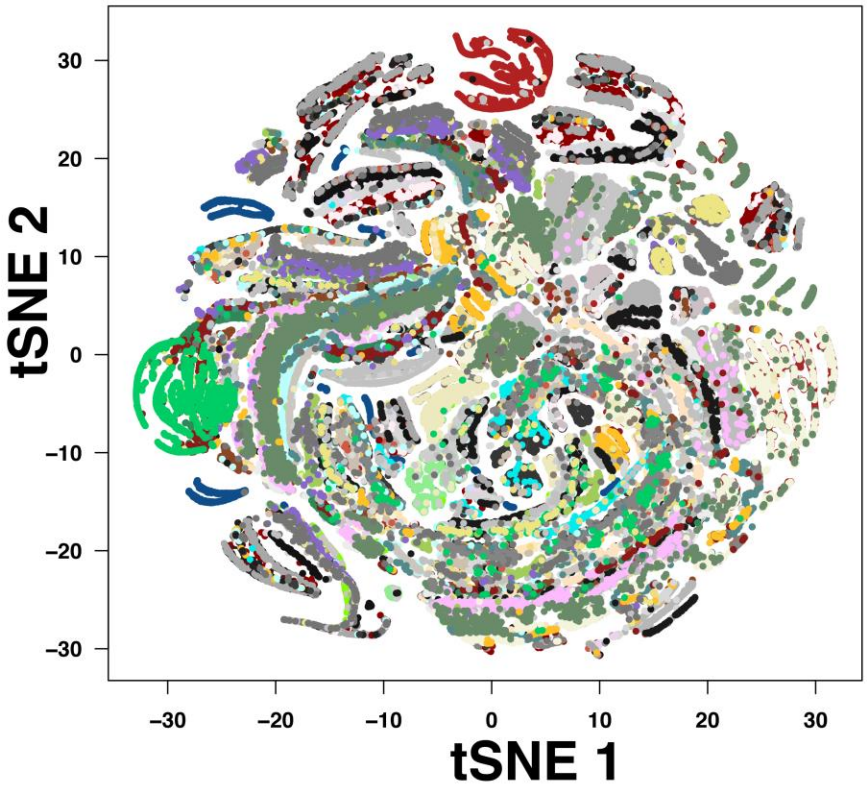


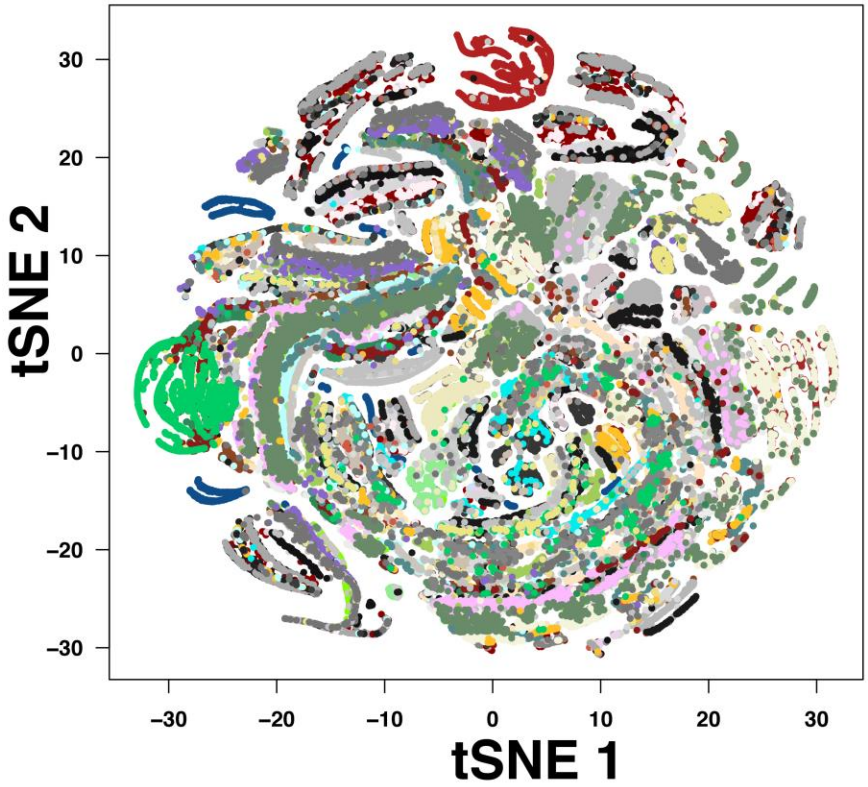
CNS Cancer tSNE using Clinical Data



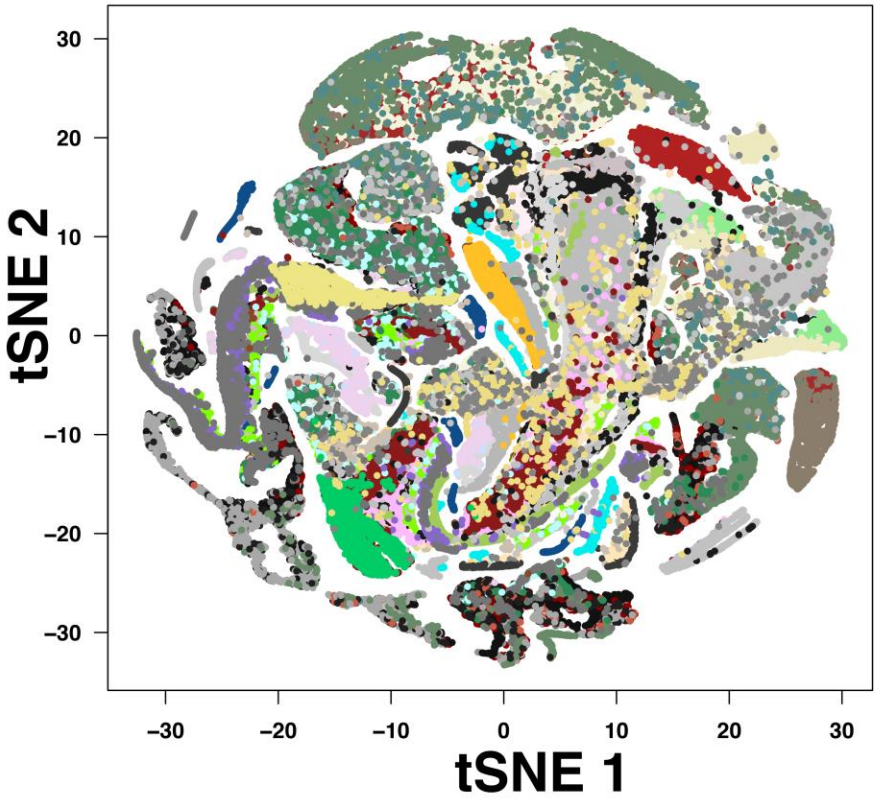
CNS Cancer tSNE using Clinical and Histological Data



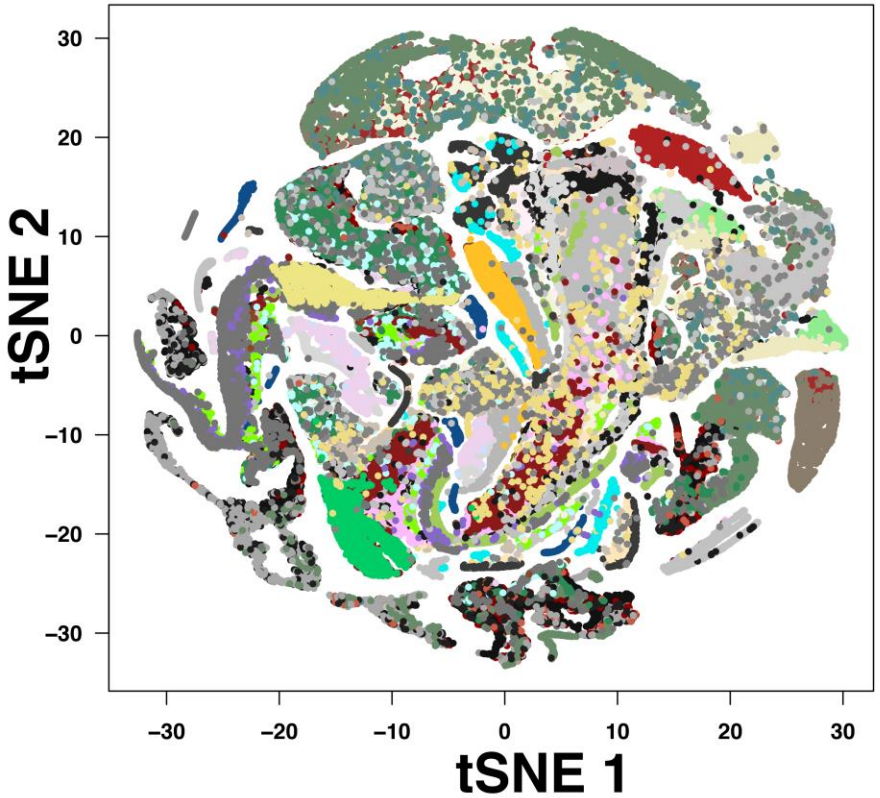
CNS Cancer tSNE using Clinical and Histological Data



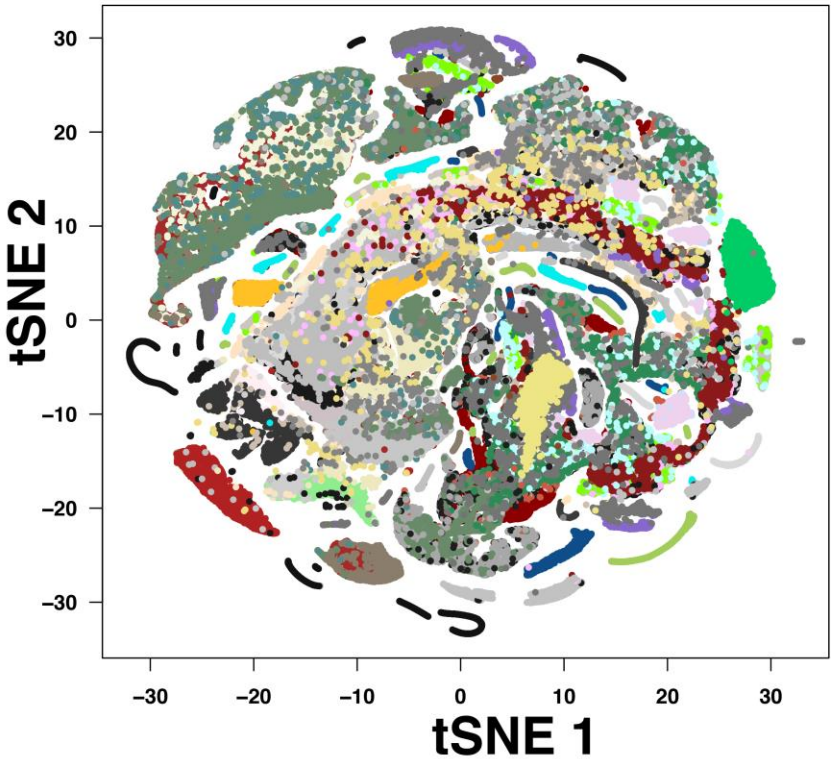
CNS Cancer tSNE using Clinical, Histological, and Immunohistochemical Data



CNS Cancer tSNE using Clinical, Histological, and Immunohistochemical Data



CNS Cancer tSNE using Clinical, Histological, Immunohistochemical, and Molecular Data



Conclusions:

-Visual inspection of the tSNE shows very little gain in clustering after the immunohistochemistry.

-What additional things can we learn from this simulated population model?

Information Theory: a mathematical representation of the conditions and *parameters* affecting the *transmission* and *processing of information*.

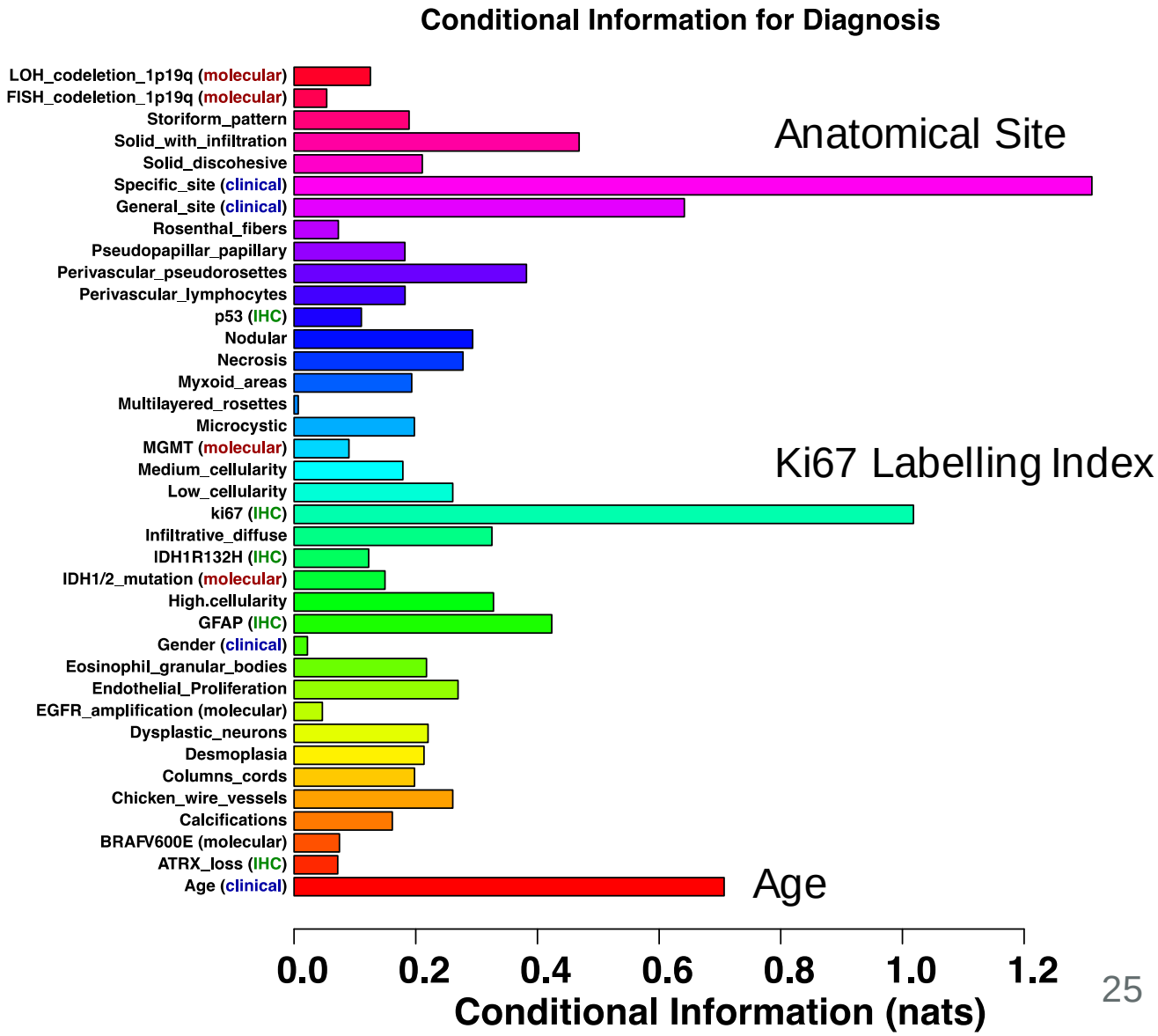
- Routinely used in engineering and computer science, and is the basis for many ML/AI algorithms.
- Has been used in basic neuroscience research to interrogate circuits in networks.
- Our implementation is based on transmitting data to the pathologist for diagnosis.

What Data Points Provide the most information in our brain cancer population simulation?

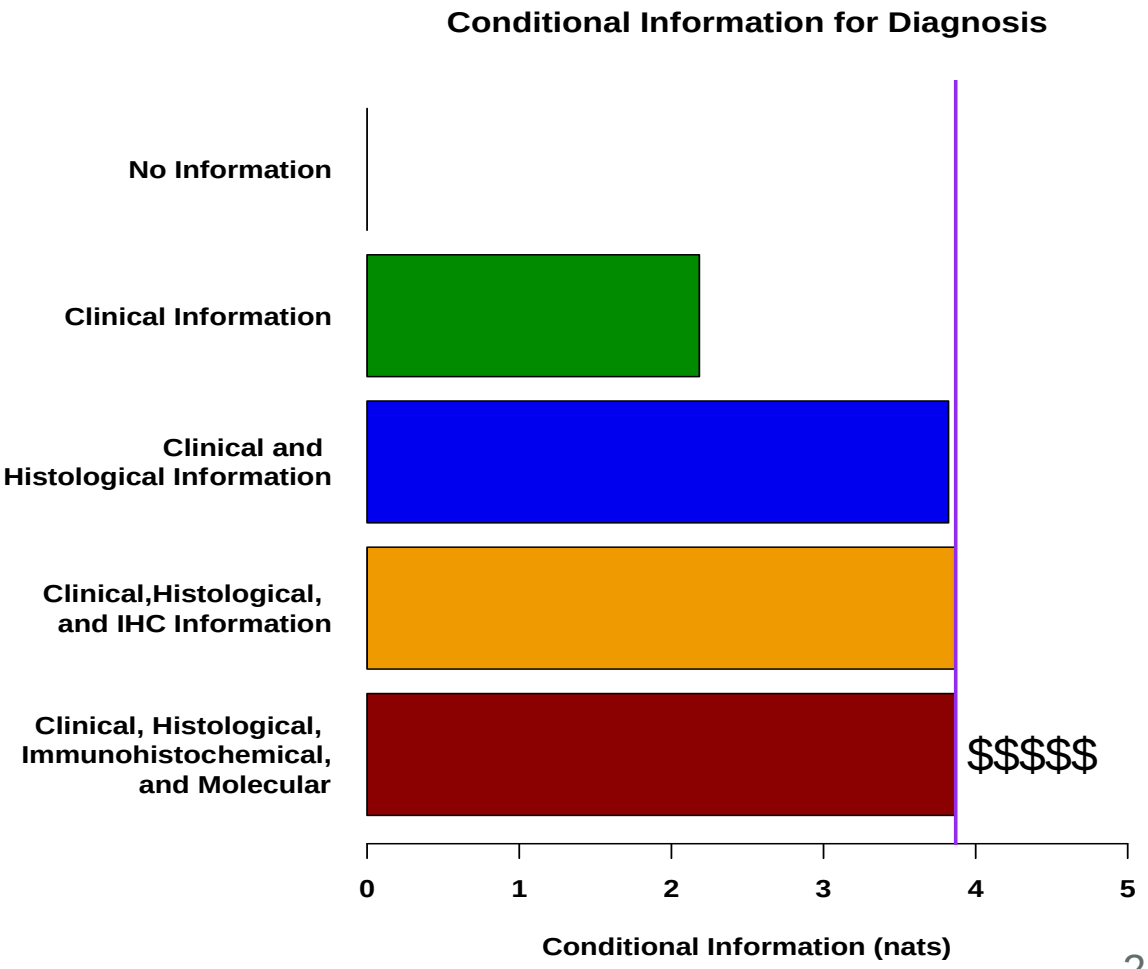
Experiment: Calculate the mutual information of each feature in the brain cancer simulation to identify its information gain.

Not all features induce the same amount of information gain.

Many ML/AI algorithms would probably highly weigh Site, Age, and Ki67 labelling.



Pooling Information Shows that Clinical and Histological Features Provide Nearly all Information



Practical Challenge: The molecular tests offer significant prognostic information and treatment plan information.

- *Different tumor classes share molecular features and prognostication varies as a function of tumor class*

Most information gain exists in non-molecular features.

Our approach: Generate focused ML/AI workflows to solve *SPECIFIC PROBLEMS*.

Diffusely infiltrating gliomas (Grade II/III)

Commonly present primary brain tumors in young adults

Astrocytoma and oligodendroglioma have distinct clinical courses

- Survival (astro = ~ 7 yrs mos, oligo = ~ 14 yrs mos)
- Responsiveness to chemotherapeutics

Diffusely infiltrating gliomas (Grade II/III)

2016 WHO classification

- Oligodendroglioma diagnosis requires molecular IDH 1or 2 mutation and chromosome 1p/19q codeletion
- Since 2016, there has been an expansion of 1p19q codeletion testing which has changed the sensitivity and specificity of 1p19q codeletion test

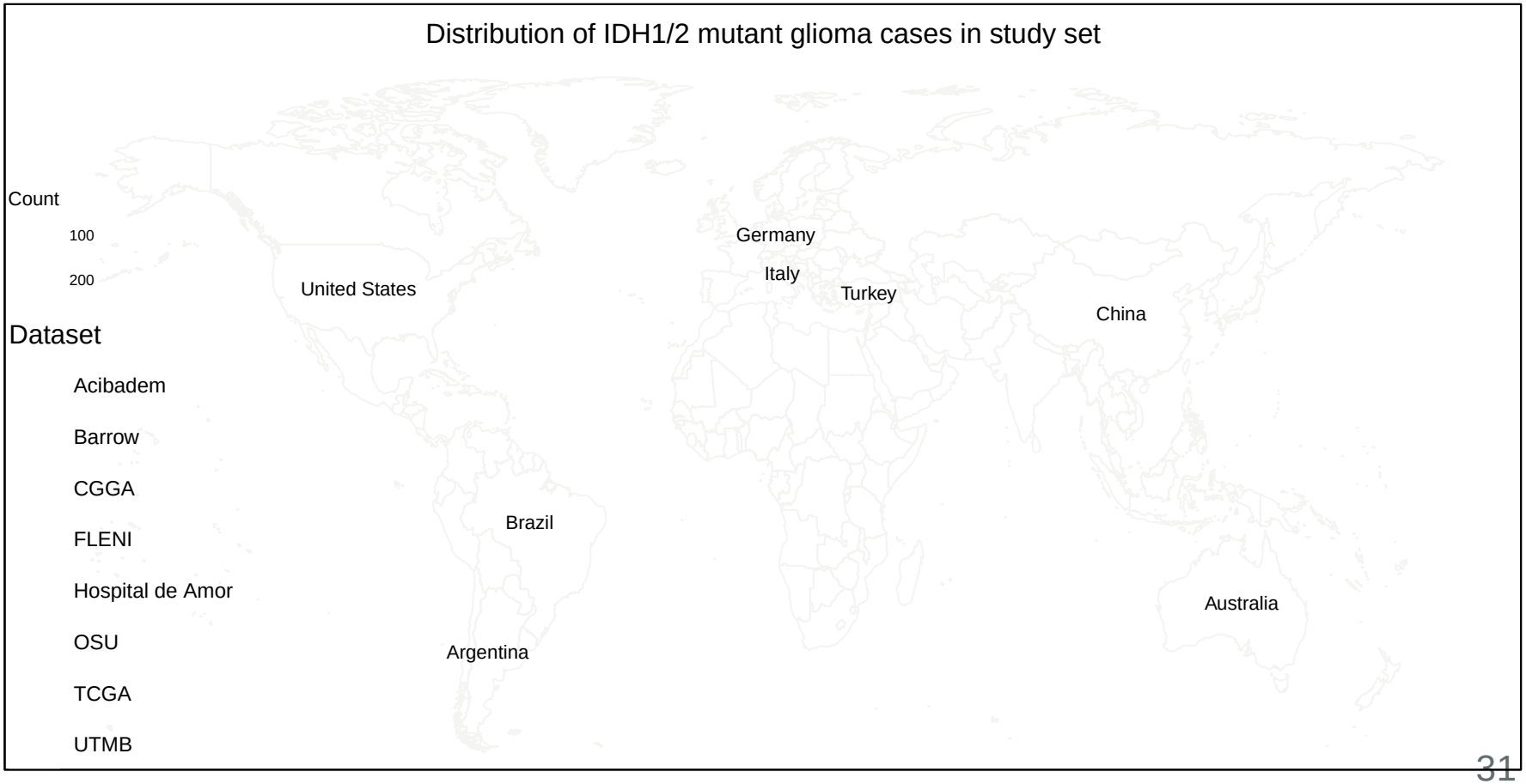
Most common methods for 1p19q codeletion

- FISH (fully reimbursable in the US and deployed in most countries, **5% false positives**, has a *very high negative predictive value*)
- LOH (considered by some as Gold standard, not reimbursable in the US)
- NGS (only reimbursable if it is an FDA approved test)

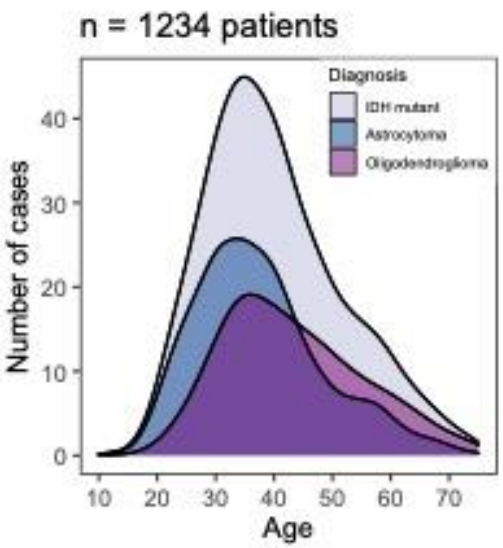
When should we order a non-reimbursable test, when the 1p19q codeletion is positive by FISH?

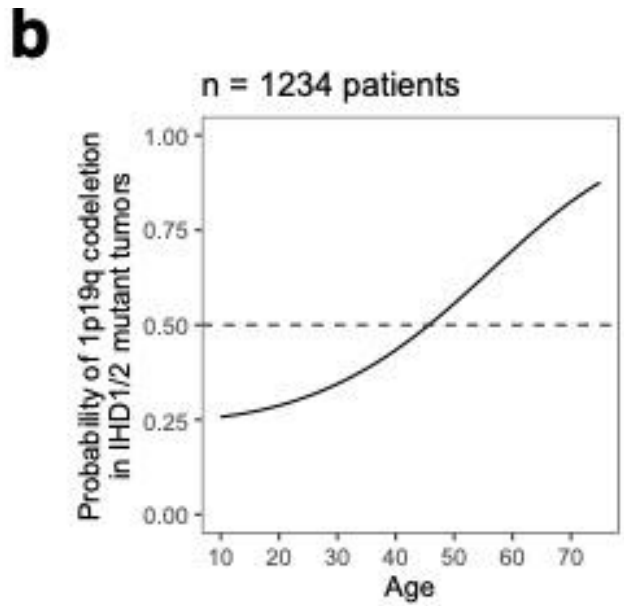
Collected Data from Diffuse Gliomas Throughout the World

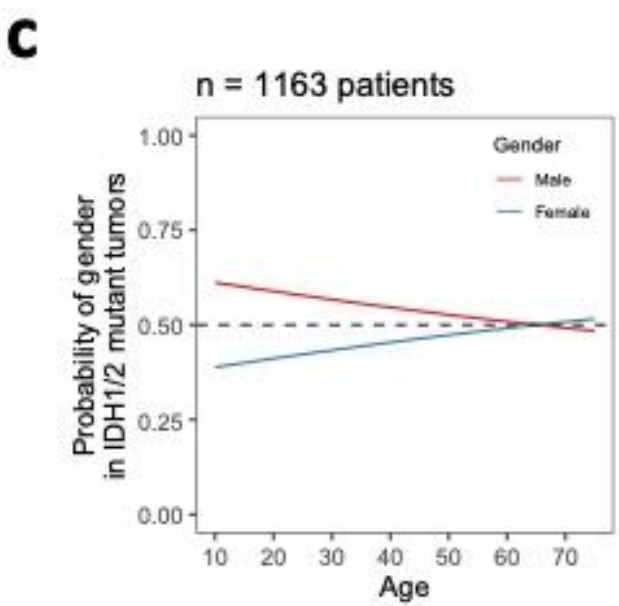
d



Large, global dataset is only ~1200 cases







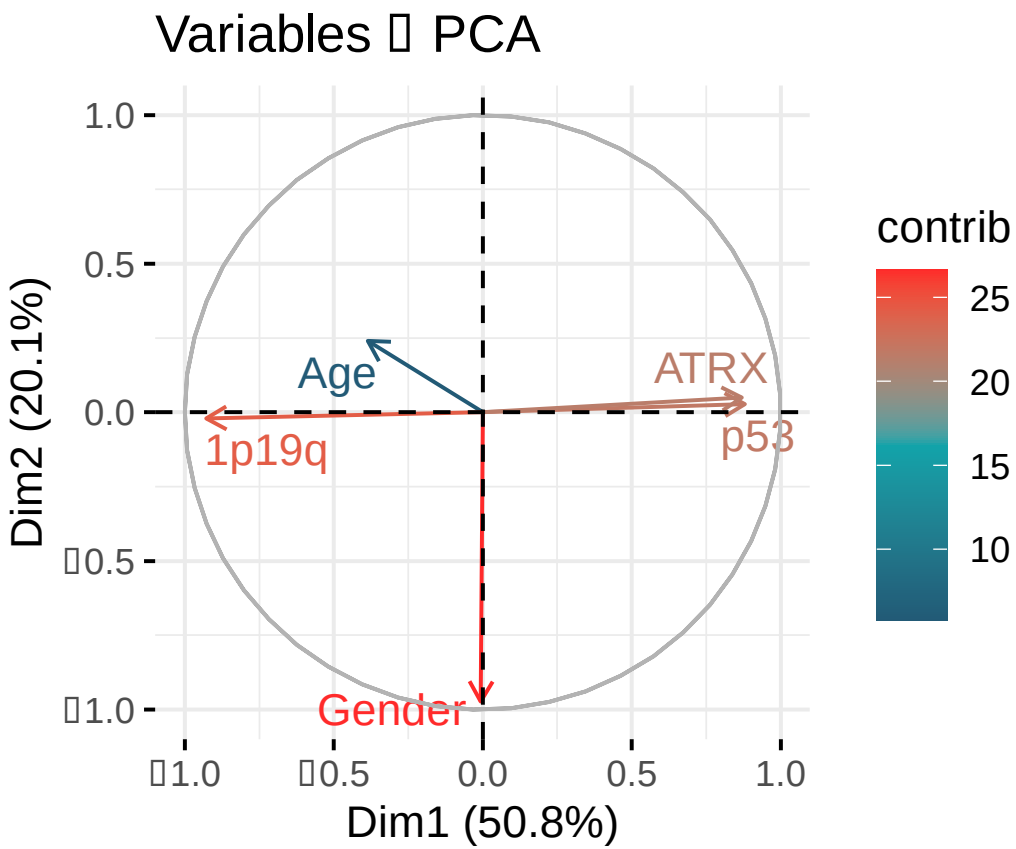
Probability of Oligo. INCREASES with age but fewer cases exist in older patients

From These Patients we obtained the following features in a structured data table:

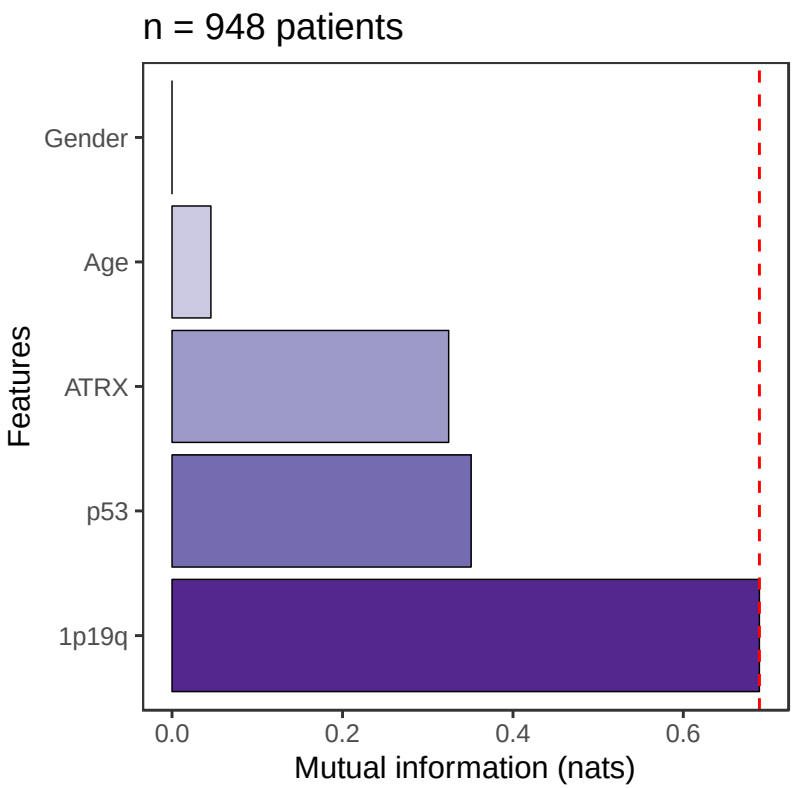
- Age
- Gender
- ATRX status (+/-)
- P53 (+/-)
- **1p19q codeletion status**

We generated dummy variables, and performed a principal component analysis.

Principal Component Analysis of Diffuse Glioma Dataset



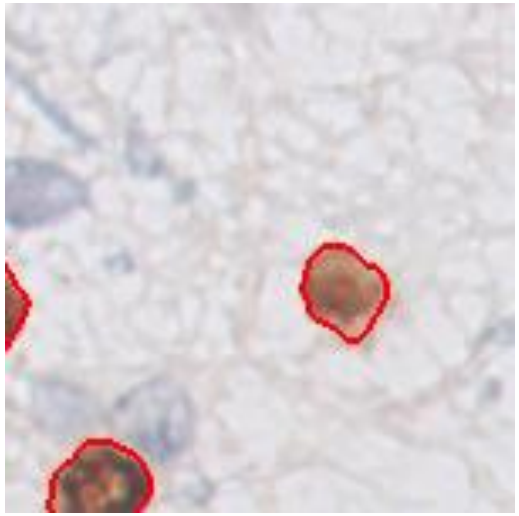
Information Gain on Diagnosis



Can we generate an imaging workflow to distinguish astrocytoma from oligodendroglioma?

Ground truth

GIMP + R



Comparison of segmentation methods

- Regions of interest from gliomas immunostained with OLIG2 WSI (40x resolution)

- 10 images (512 x 512 pixel)

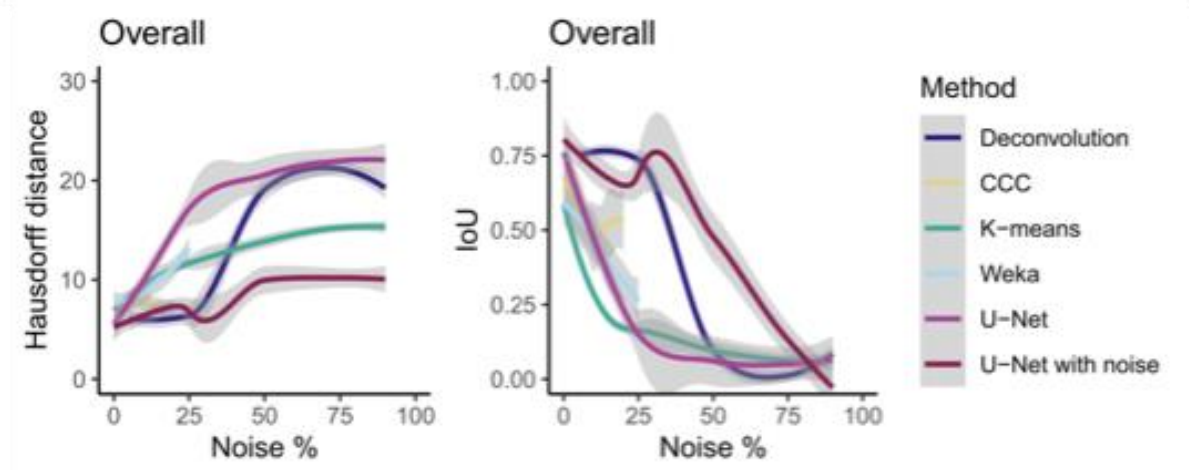
Approaches:

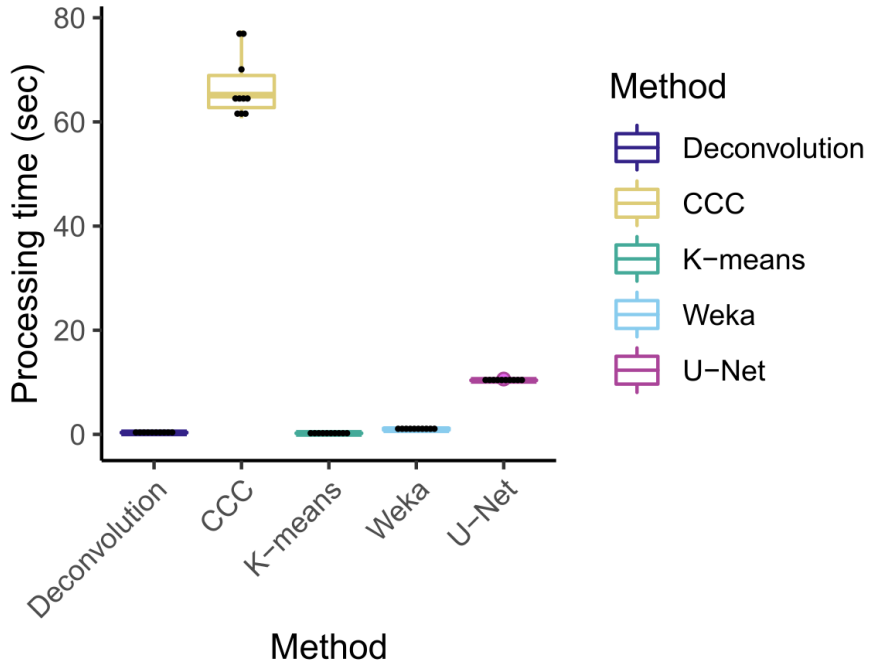
Unsupervised:

• **Deconvolution with otsu**	**RStudio**
• **CCC (Cut-Cluster-Classify)**	**Spyder (Python)**
• **K-means clustering**	**Rstudio**

Supervised:

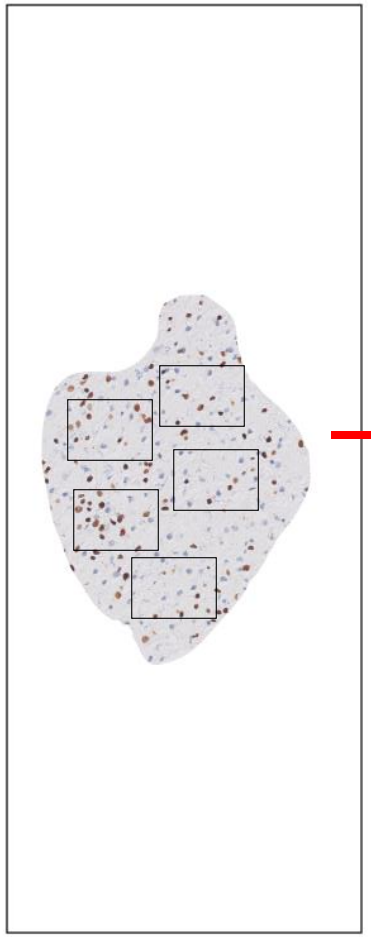
• **Weka Segmentation**	**Fiji (Java based)**
• **U-Net**	**Spyder (Python)**

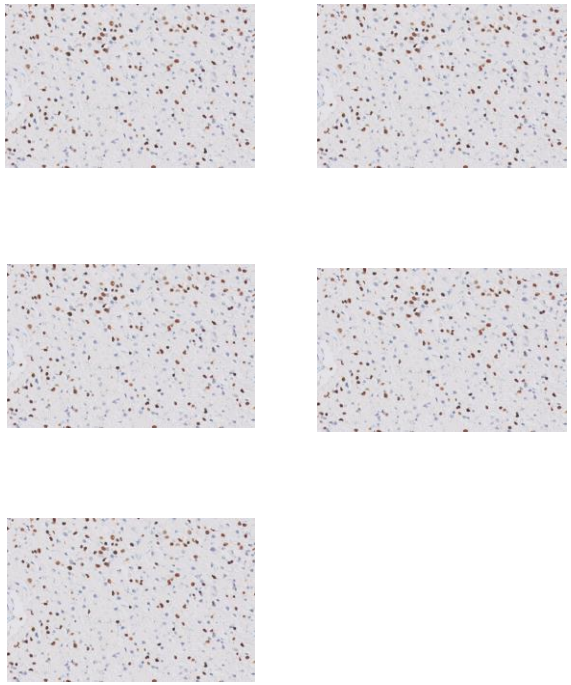

Overall
Hausdorff distance
30
20
10
0
0
25
50
75
100
Noise %
Overall
IoU
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
Noise %
Method
Deconvolution
CCC
K−means
Weka
U−Net
U−Net with noise


Processing time (sec)
80
60
40
20
0
Deconvolution
CCC
K−means
Weka
U−Net
Method
Method
Deconvolution
CCC
K−means
Weka
U−Net

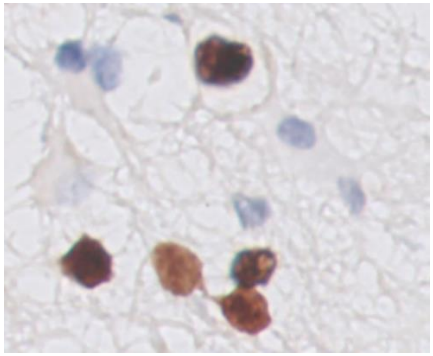
91 cases

695 tiles





271524 objects

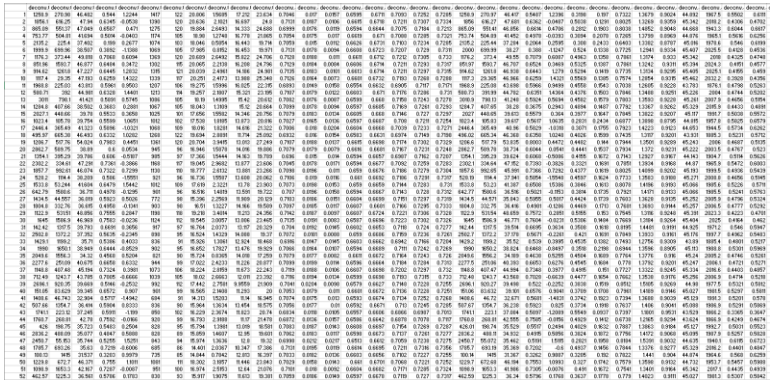


39

PCA for dimensionality reduction

```
Importance of components:
                          PC1    PC2    PC3     PC4     PC5     PC6     PC7     PC8
Standard deviation     8.6925 7.7644 5.0261 3.46008 2.82380 2.1695 1.93138 1.76884
Proportion of Variance 0.3547 0.2830 0.1186 0.05621 0.03744 0.0221 0.01751 0.01469
Cumulative Proportion  0.3547 0.6378 0.7564 0.81258 0.85002 0.8721 0.88963 0.90431
```

213 features



8 features

Capturing 90% of data variance

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
1	1258.94	270.979	46.4819	0.544	1.22444	1417	122	20.8062	1.56845	17.2123
2	1856.06	616.247	47.9403	0.63451	-0.05385	1390	120	20.6361	2.10213	16.6967
3	865.089	551.369	47.0491	0.65867	0.471	1275	120	19.8836	2.64934	14.3326
4	753.769	504.812	41.6937	0.50145	-0.0403	1174	105	18.9799	1.2748	16.778
5	2135.22	225.4	37.4018	0.19896	0.26768	1074	103	18.0463	0.58545	16.4425
6	1999.94	699.96	38.5071	0.38916	-1.13882	1069	105	17.9848	0.81518	16.4533
7	1176.3	373.443	49.8181	0.70676	0.60938	1369	120	20.6893	2.6492	15.8217
8	851.959	1593.71	46.8765	0.64839	0.34723	1302	115	20.0653	2.21376	16.2077
9	914.62	1261.77	47.2273	0.64452	1.28323	1315	121	20.0386	2.49614	14.1859
10	1117.37	29.3503	47.1931	0.62591	1.43223	1339	117	20.2509	2.41727	13.9877
11	1968.8	225.027	43.8132	0.59612	0.95034	1207	106	19.2752	1.59956	16.0251
12	580.706	392.004	44.9809	0.63283	1.44012	1213	114	19.2574	2.18075	15.3206
13	3010.97	798.099	41.4206	0.58914	0.57451	1086	105	18.1902	1.49954	15.4201
14	1284.76	407.658	38.5022	0.36829	0.28809	1067	105	18.0431	1.31089	15.1202
15	2027.07	448.663	39.7802	0.5533	0.36585	1025	101	17.6563	1.55821	14.3457
16	1023.38	105.784	39.7544	0.55985	1.06512	1012	102	17.5385	1.81851	13.8729
17	2446.37	365.488	41.3235	0.5896	-1.03207	1068	109	18.0158	1.82809	14.6158

Density (d10, d20, d40, d60)

For every object
- d10
- d20
- d40
- d60

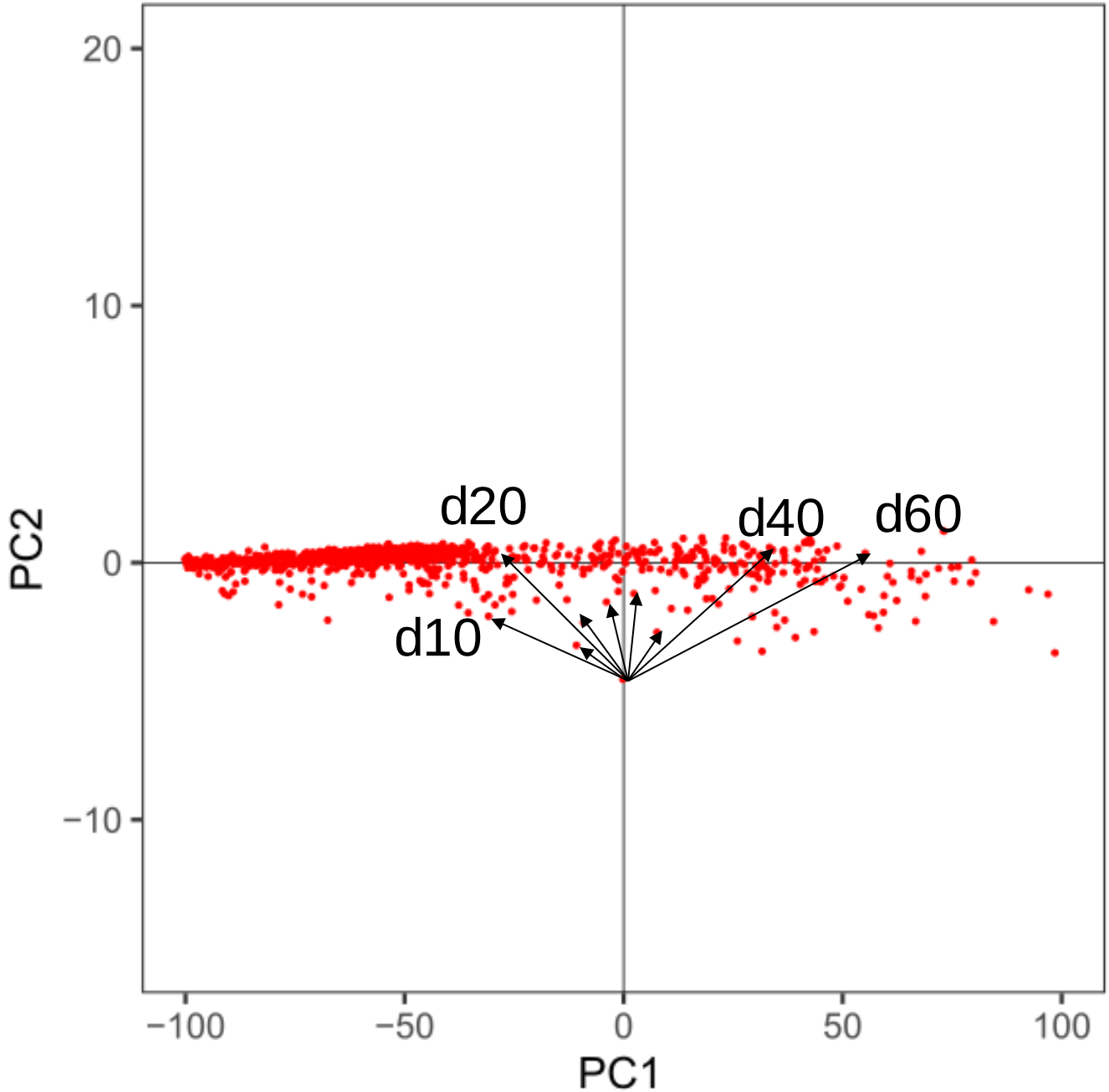
Central tendency measurements
- Mean
- Median
- sd

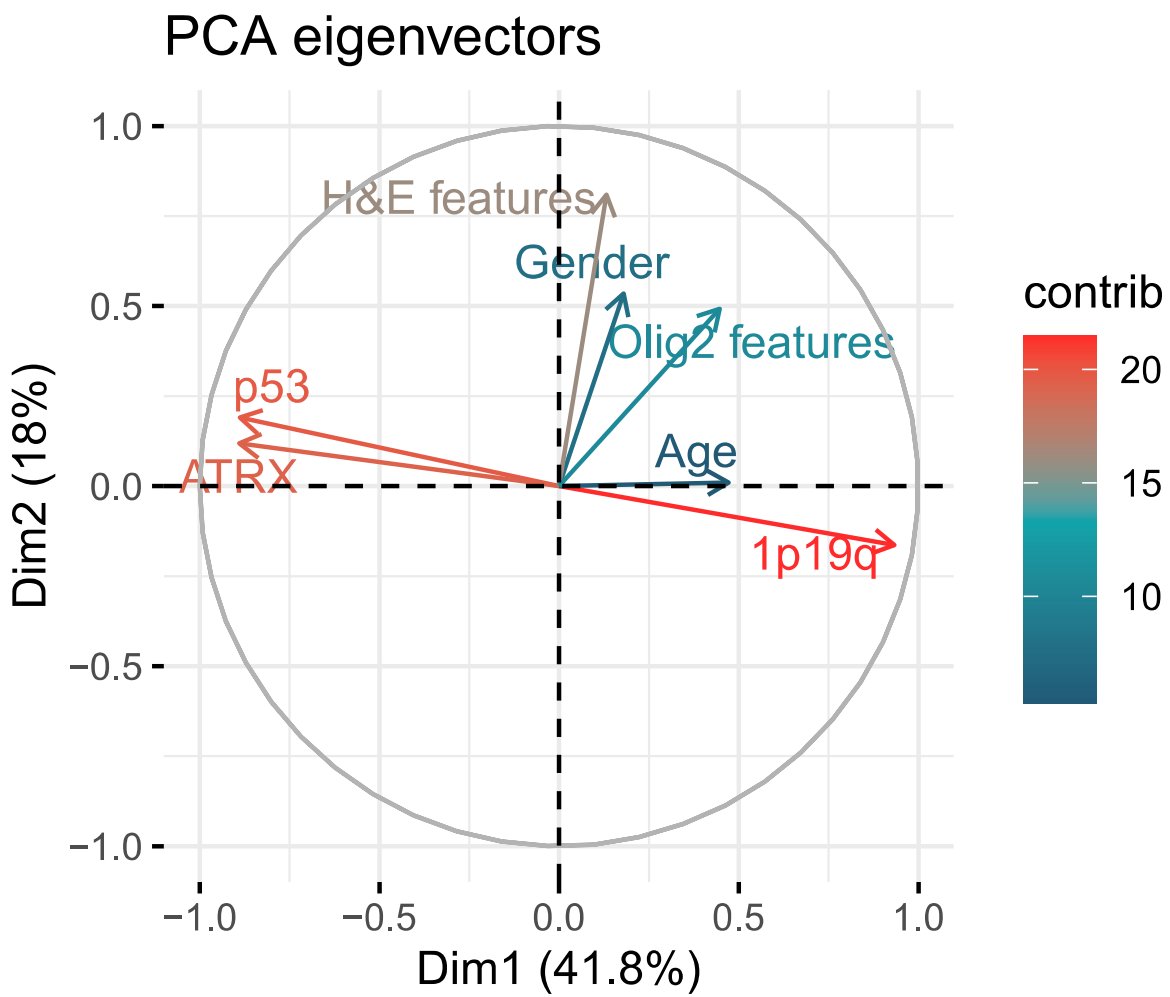
We took advantage that Oligodendroglioma is more morphologically monomorphic than Astrocytoma.

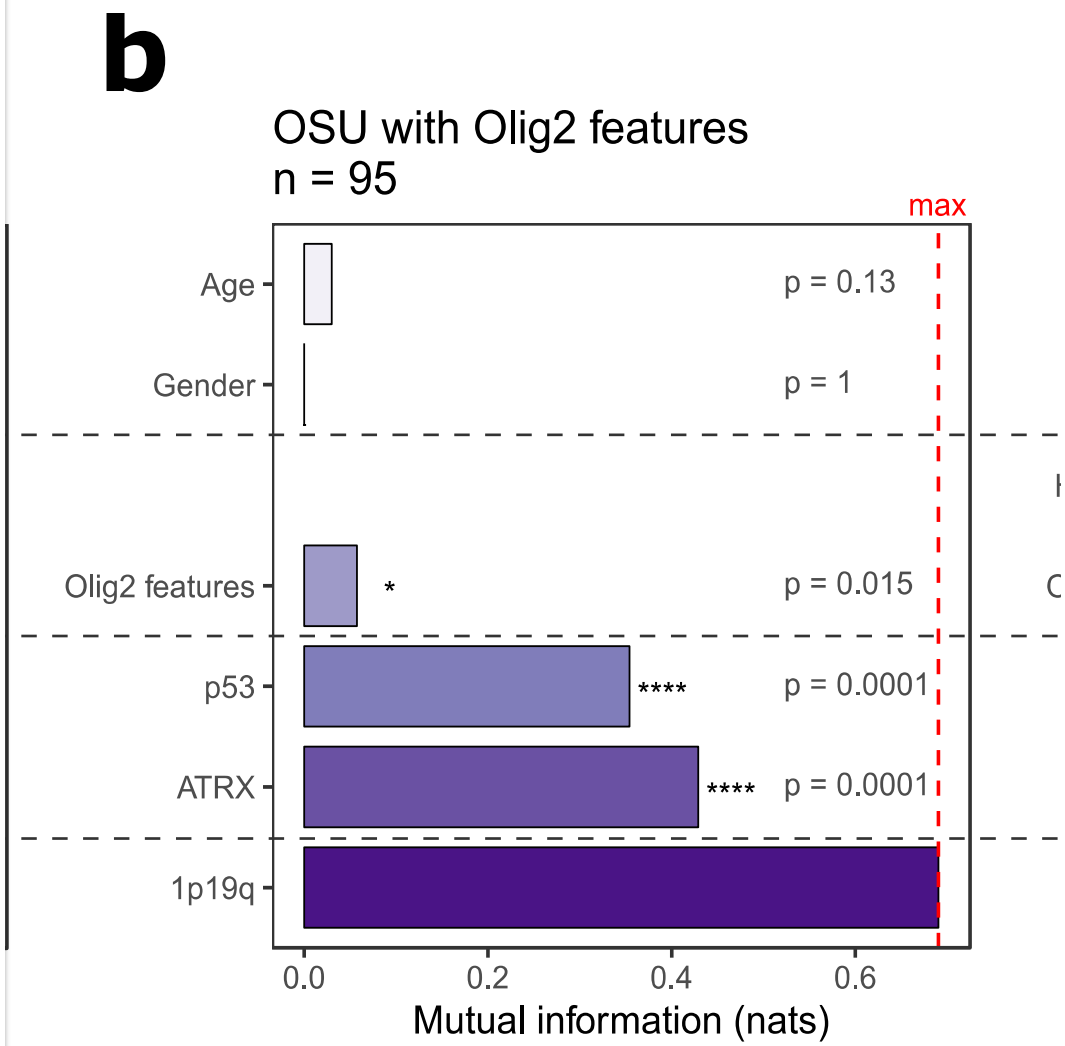
And used density in high dimensionality space as a measure of this morphological variation in the specimen.

WE ARE NOT REFERRING TO CELLULAR DENSITY SUCH AS CELLS/VOLUME

41


20
10
0
−10
PC2
−100
−50
0
50
100
PC1
d20
d40
d60
d10


PCA eigenvectors
H&E features
Gender
Olig2 features
p53
ATRX
Age
1p19q
1.0
0.5
0.0
−0.5
−1.0
Dim2 (18%)
−1.0
−0.5
0.0
0.5
1.0
Dim1 (41.8%)
contrib
20
15
10

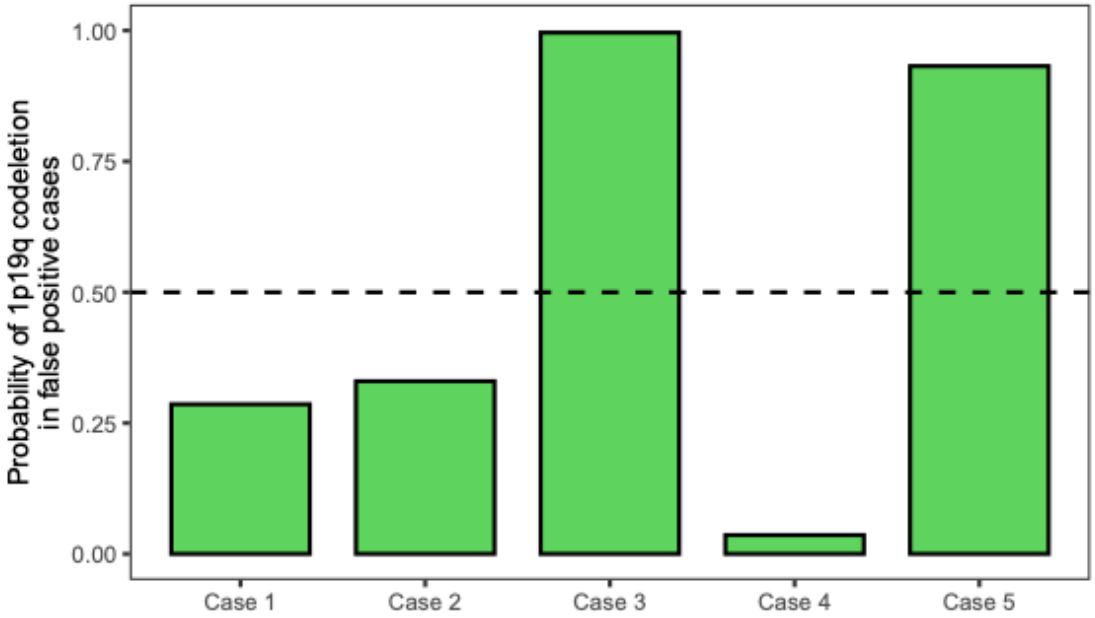

b
OSU with Olig2 features
n = 95
max
Age
Gender
Olig2 features
p53
ATRX
1p19q
p = 0.13
p = 1
p = 0.015
p = 0.0001
p = 0.0001
*
****
****
0.0
0.2
0.4
0.6
Mutual information (nats)

Concluding Remarks and Proposed Clinical Guidelines

Generate a random forest classification model.

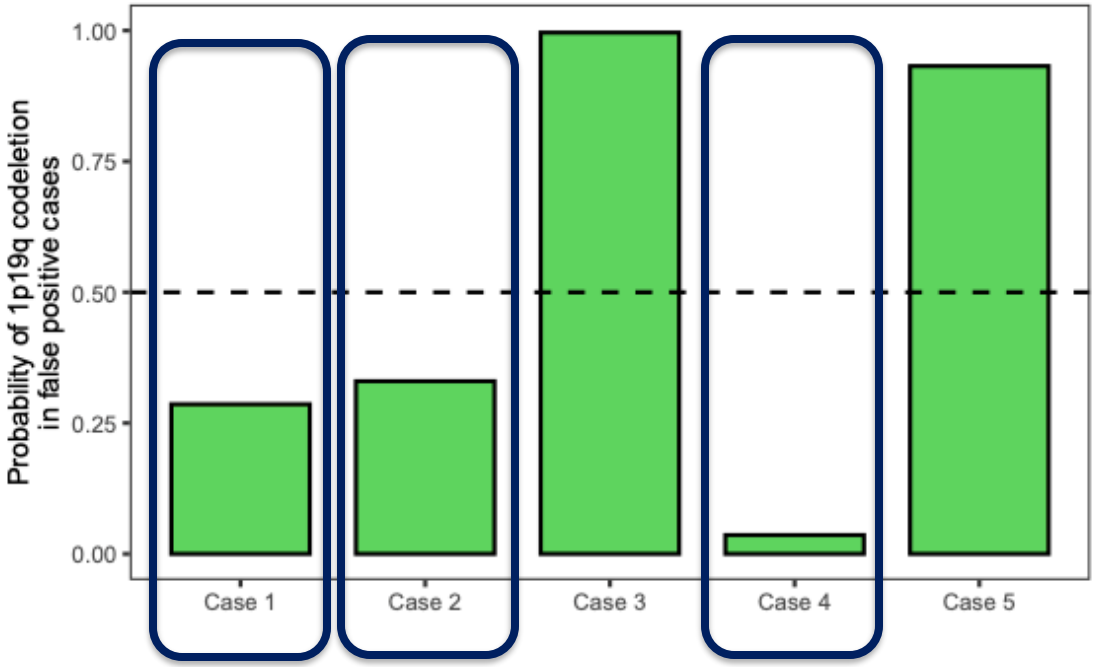
- **Diagnosis is a function of ATRX, P53, Age probability, and OLIG2 features**

Random Forest Votes



	LGG	LGG	LGG	LGG	LGG (ctrl)
Age	55	39	40	35	37
p53	+	+	-	+	-
ATRX	+	-	-	+	-
1p19q codel	+ FISH	+ FISH	+ FISH	+ FISH	+ FISH

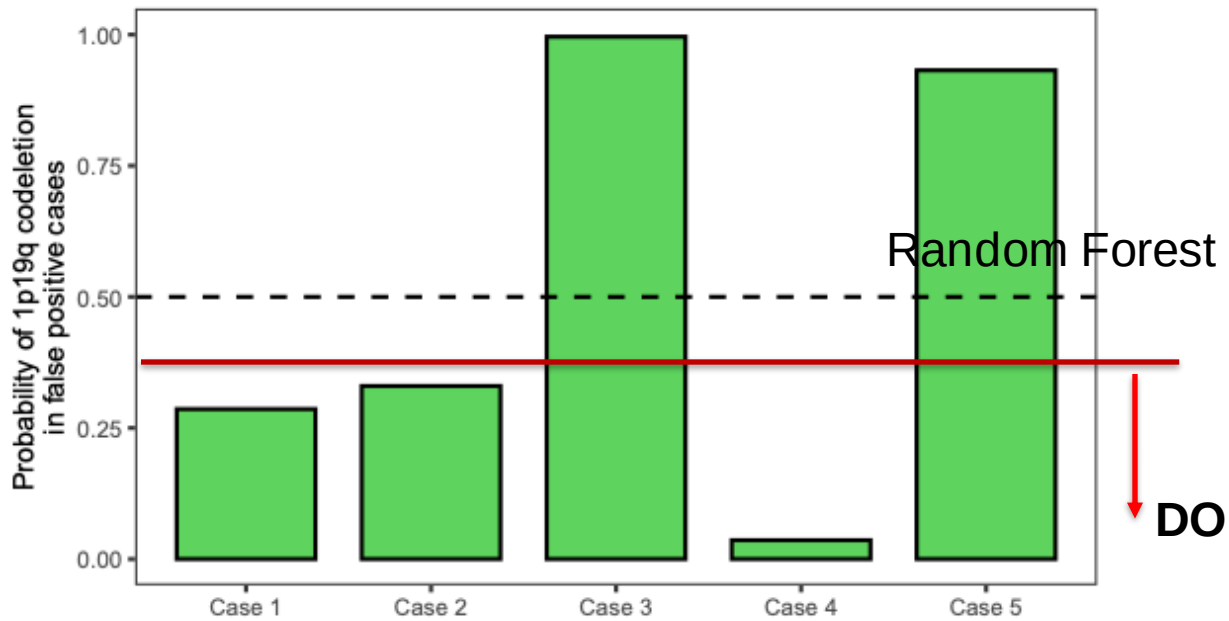
Random Forest Votes



	Case 1	Case 2	Case 3	Case 4	Case 5
	LGG	LGG	LGG	LGG	LGG (ctrl)
Age	55	39	40	35	37
p53	+	+	-	+	-
ATRX	+	-	-	+	-
1p19q codel	+ FISH	+ FISH	+ FISH	+ FISH	+ FISH

False Positive FISH
Negative LOH

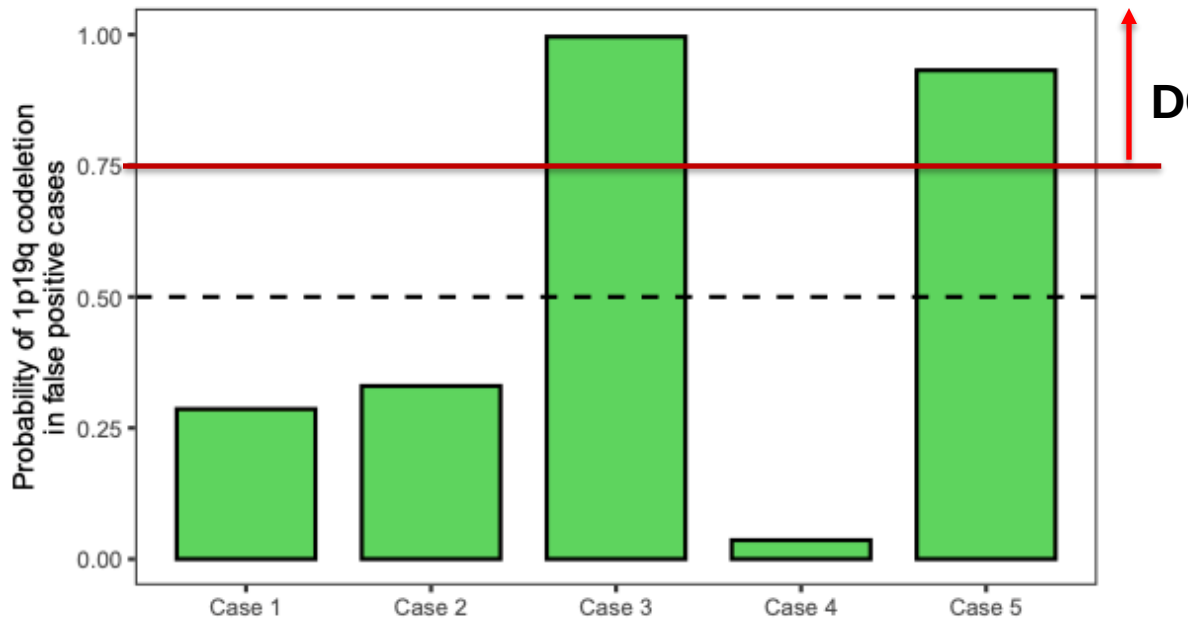
Guideline Recommendations



DO NOT ORDER 1P19Q FISH

	LGG	LGG	LGG	LGG	LGG (ctrl)
Age	55	39	40	35	37
p53	+	+	-	+	-
ATRX	+	-	-	+	-
1p19q codel	+ FISH	+ FISH	+ FISH	+ FISH	+ FISH

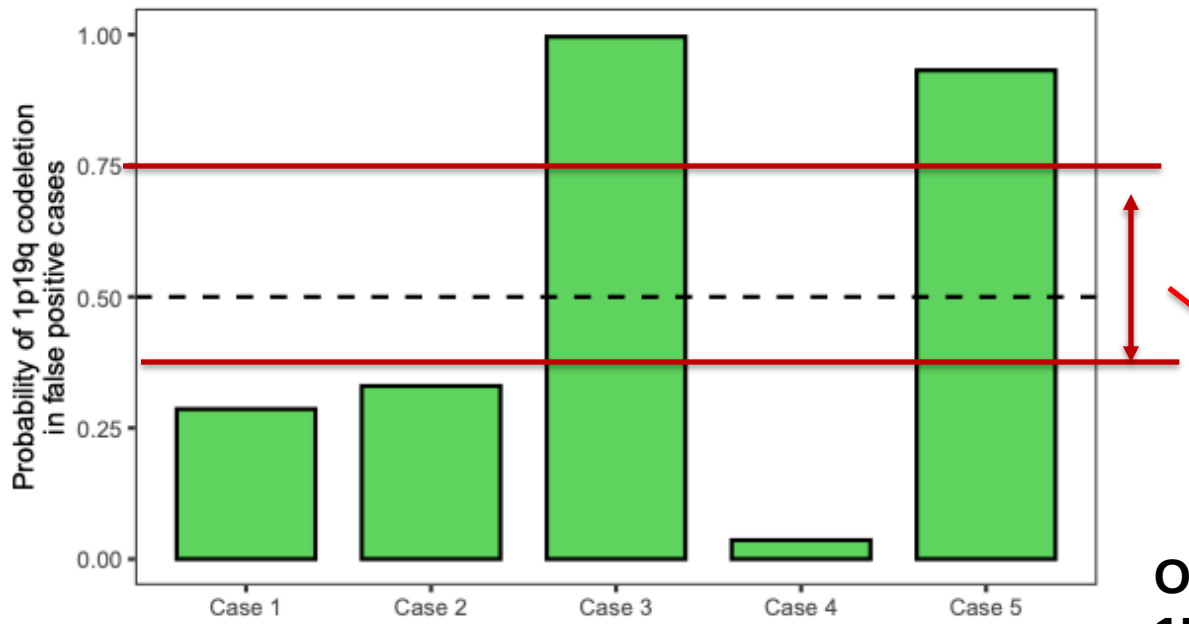
Guideline Recommendations



DO NOT ORDER 1P19Q LOH

	LGG	LGG	LGG	LGG	LGG (ctrl)
Age	55	39	40	35	37
p53	+	+	-	+	-
ATRX	+	-	-	+	-
1p19q codel	+ FISH	+ FISH	+ FISH	+ FISH	+ FISH

Guideline Recommendations



	LGG	LGG	LGG	LGG	LGG (ctrl)
Age	55	39	40	35	37
p53	+	+	-	+	-
ATRX	+	-	-	+	-
1p19q codel	+ FISH	+ FISH	+ FISH	+ FISH	+ FISH

ORDER 1P19Q LOH WHEN 1P19Q FISH IS POSITIVE

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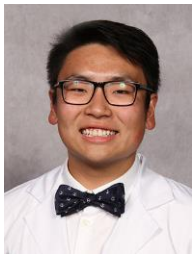

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