Artificial intelligence in medicine from genomic to personalize medicine

Maurizio Polano
IRCCS CRO AVIANO

WORKSHOP GARR 2020
NET MAKERS
Consortium GARR

Experimental and Clinical Pharmacology Division

- Develop precision medicine approach base on genomic and molecular profile of the tumour.
- Develop clinical trials (phase 1-phase 2)
- Develop nano drugs and therapies using CART cells.
- **Develop computational approach on big data for personalised medicine**

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Inferno - Canto ventesimo

Da Wikipedia, l'enciclopedia libera.

Il **canto ventesimo** dell'*Inferno* di Dante Alighieri si svolge nella quarta bolgia dell'ottavo cerchio, ove sono puniti gli indovini e i maghi; siamo all'alba del 9 aprile 1300 (Sabato Santo), o secondo altri commentatori del 26 marzo 1300.

Dante, dopo una descrizione generale, indica tra i peccatori, attraverso le parole di Virgilio, cinque indovini antichi (quattro dei quali mitologici) e tre moderni. Durante la presentazione dell'indovina Manto c'è una lunga digressione sulle origini di Mantova.

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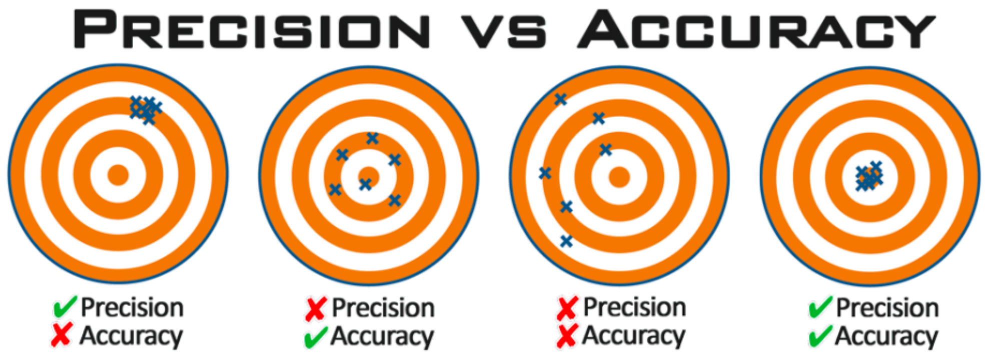
Personalized medicine vs Precision Medicine

- Personalised medicine is an emerging practice of medicine that uses an individual’s genetic profile to guide decision made in regard to the prevention , diagnosis and treatment of disease.

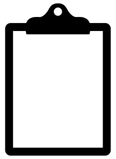
- Precision medicine are term more appropriate for the description of the approach the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors

- **Pharmacogenomics** is the study of how genes affect a person’s response to particular drugs.

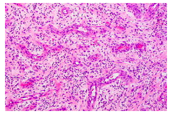


DATA
Make knowledge from comics

Health records

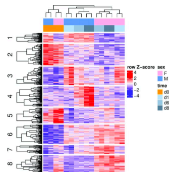


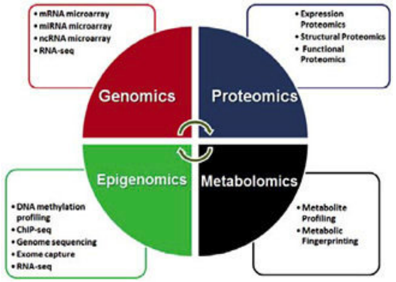
Pathology Images



Drugs

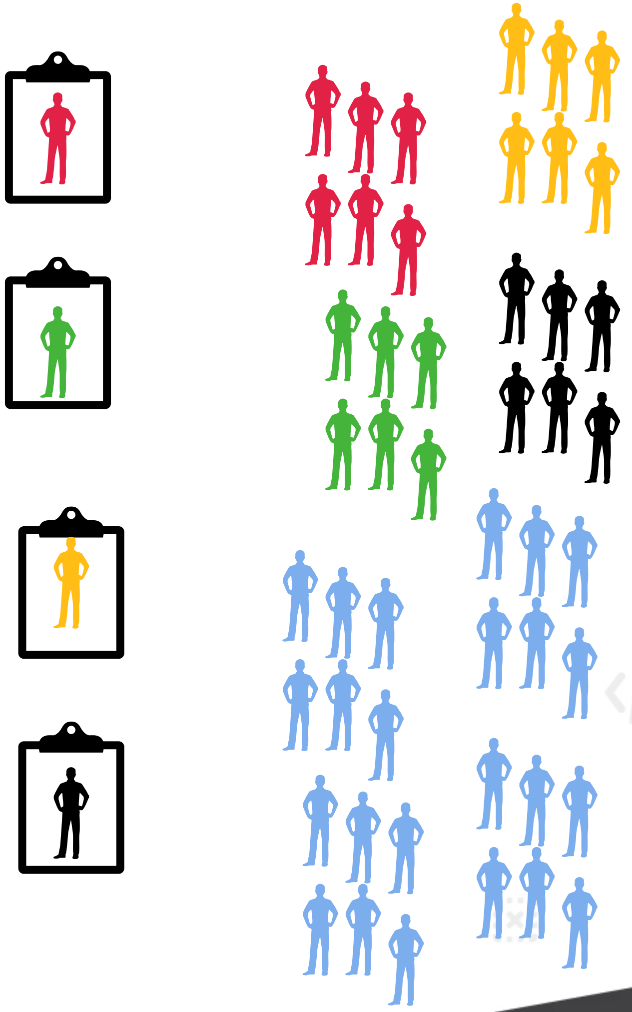
Genomic Data



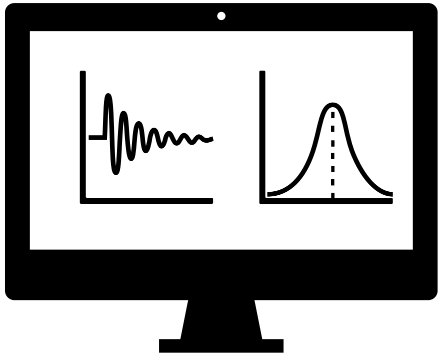


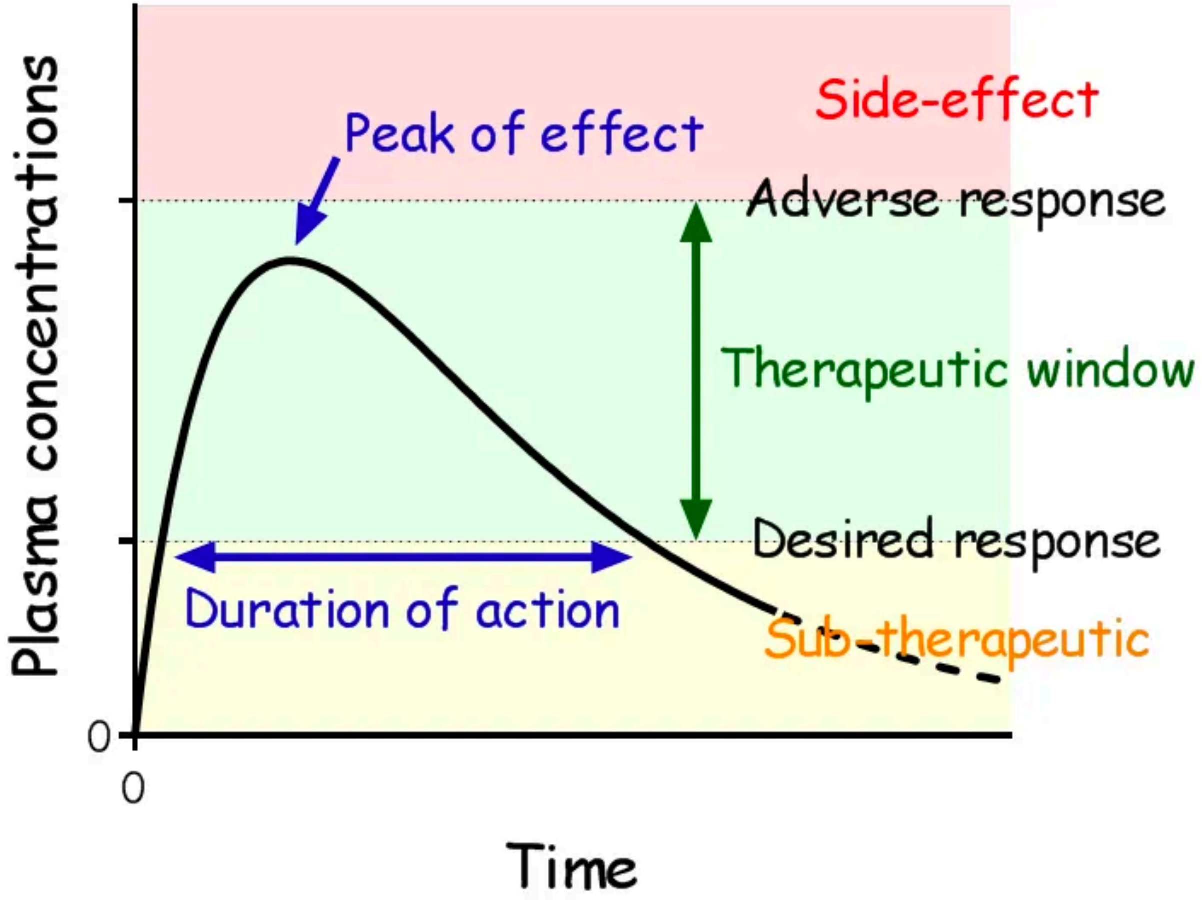
KNOWLEDGE
Predict clinical phenotype

ACTION
Select optimal therapy



Therapeutic Window and Therapeutic Index





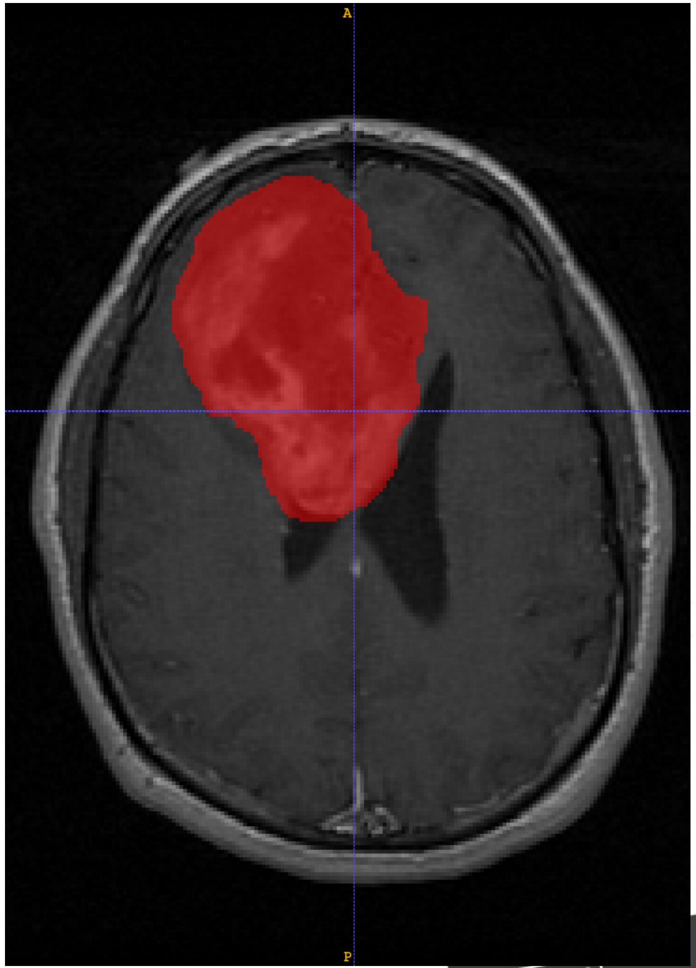
GLIOBLASTOMA

Glioblastoma (GBM) is a devastating disease for both patients and caregivers.

It is the most aggressive primary brain tumour – a tumour that originates in the brain – and despite available therapies, prognosis is extremely poor.

The majority of patients do not survive for more than two years following diagnosis, and the median survival is generally less than a year.[1]

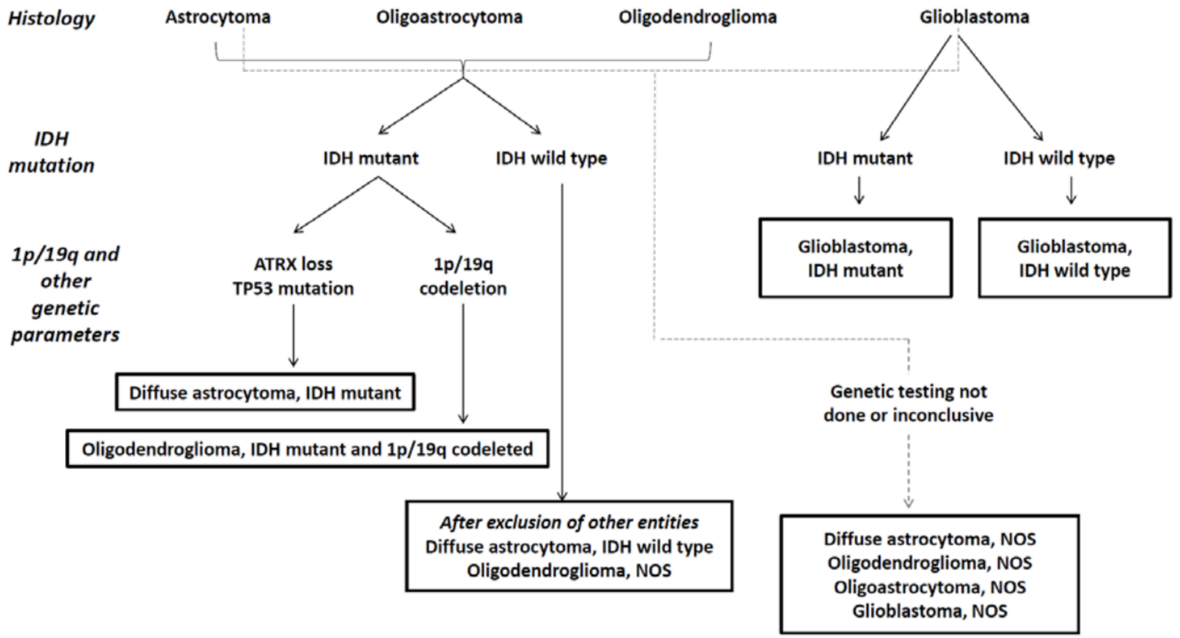
The average 5-year survival rate is less than 3%



Pre-operative T1 Neuronavigator image

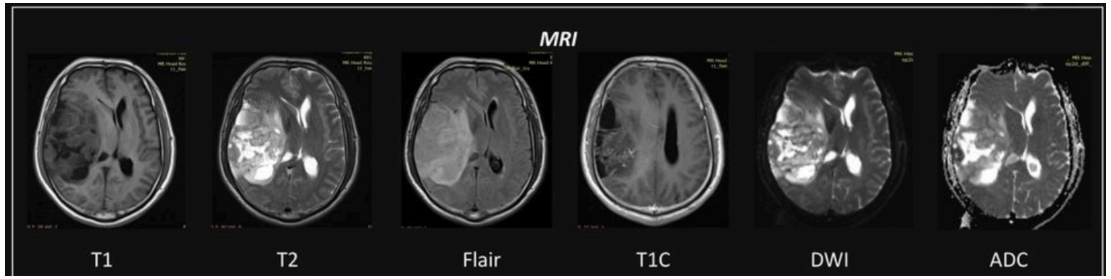
GLIOBLASTOMA

Standard treatment based on surgery, radiotherapy with concomitant temozolomide followed by 6 or more cycles of adjuvant temozolomide: medial overall survival (OS) is 14.6 months, progression free survival (PFS) 6.9 months (Stupp et al 2005)

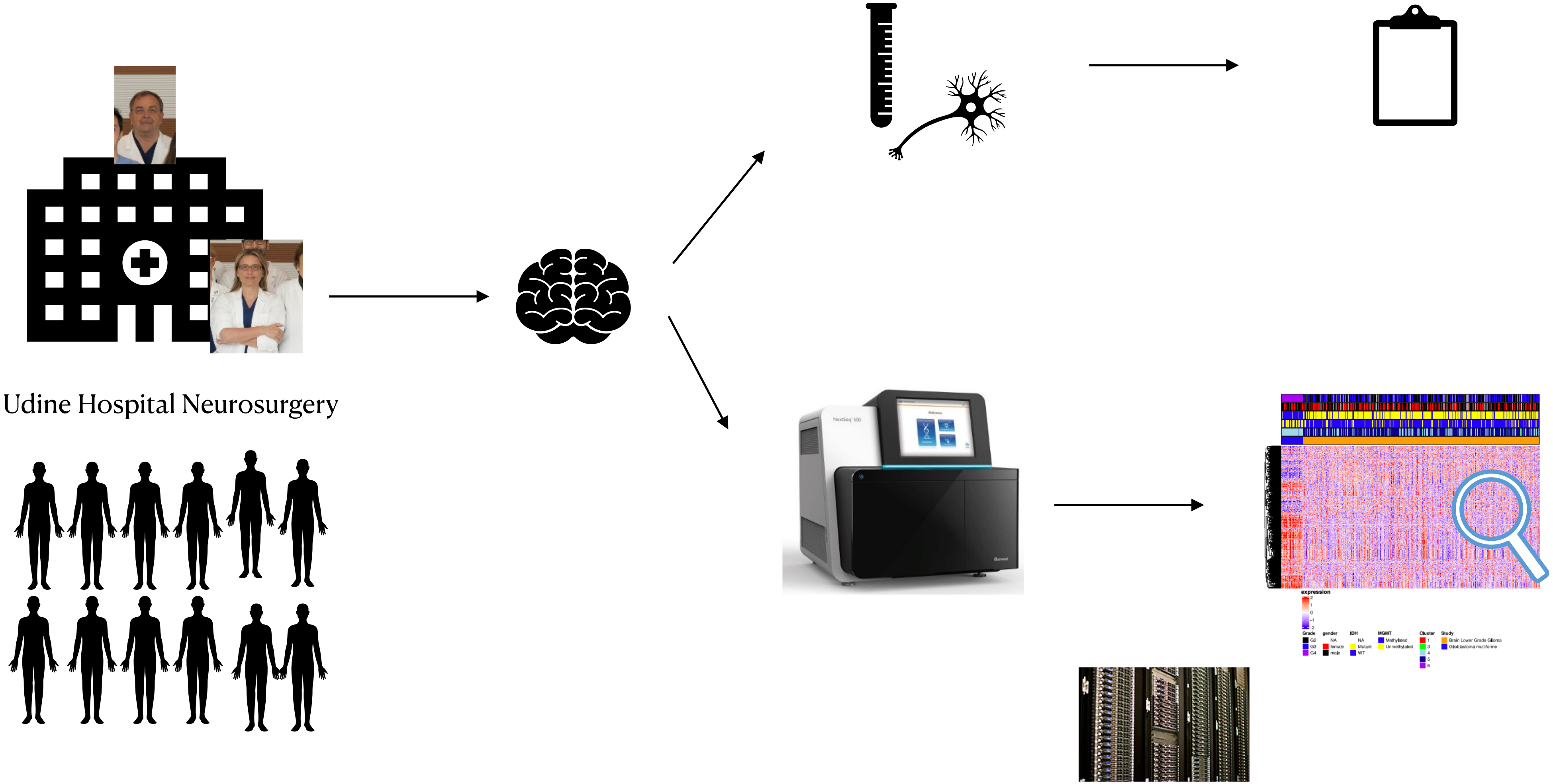


Parametri molecolari prognostici e predittivi.

	Prognostico	Predittivo
Metilazione *MGMT*	X	X*
Co-delezione 1p/19q	X	X
Mutazione *IDH1/IDH2*	X	



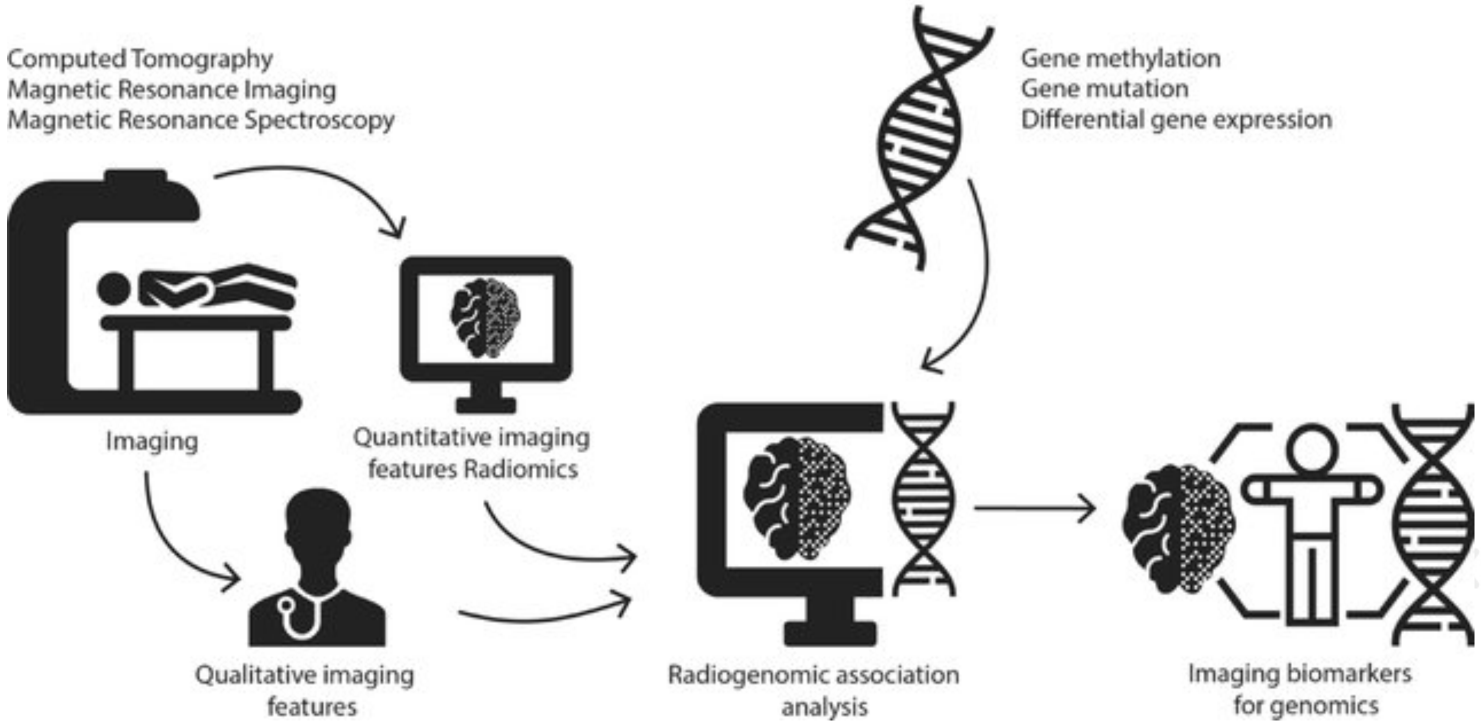
GLIOBLASTOMA



RADIOGENOMICS

Radiogenomics *is a relatively recently coined term to denote the relationship between the imaging features of a particular disease and various genetic or molecular features. The former is referred to as an imaging phenotype, whereas the later as genomic phenotype.*

Radiogenomics, therefore, provides a tool for clinicians to correlate imaging traits to molecular markers of diseases processes (such as cancer) in an effort to guide tailored therapy



Machine learning and glioma imaging biomarkers

Table 1
Recent studies applying machine learning to the development of neuro-oncology monitoring biomarkers.

Author(s)	Prediction	Dataset	Method	Results
Cha *et al.*, 2014[40]	True progression	35 CBV & ADC	Retrospective Multivariate logistic regression, longitudinal subtraction of ADC & CBV histograms	Mode of rCBV AUC: 0.877
Park *et al.*, 2015[44]	Early true progression	162 (training = 108 & testing = 54) DWI, DSC, DCE	Retrospective Volume-weighted, MP clustering	Sensitivity: 87% Specificity: 87.1% AUC: 0.96
Yun *et al.*, 2015[42]	True progression	33 DCE	Prospective Multivariate logistic regression, K_{trans}, v_e, v_p	K_{trans} Accuracy: 76% Sensitivity: 59% Specificity: 94%
Artzi *et al.*, 2016[49]	Pseudoprogression	20 longitudinal patients DCE & MRS (training = 25/44 DCE & MRS studies; testing = 19/44 studies)	Prospective Voxel-wise SVM with K_{trans}, v_e, K_{ep}, v_p	Sensitivity: 98% Specificity: 97%
Tiwari *et al.*, 2016[47]	Radiation necrosis	58 (training = 43 & testing = 15) MRI	Retrospective 119 features, mRmR feature selection, SVM. Sequence independent	AUC: 0.79 AUC (primary): 0.77 AUC (metastatic): 0.72
Qian *et al.*, 2016[36]	True progression	35 longitudinal DTI	Retrospective Spatiotemporal dictionary learning & SVM classification	Accuracy: 86.7% AUC: 0.92
Ion-Margineanu *et al.*, 2016[50]	True progression	29 T1, T1 C, DKI, DSC	Prospective Compared 7 classifiers over various global and local features	T1 C Max BAR (balanced accuracy rate) value: 0.96 for AdaBoost
Yoon *et al.*, 2017[45]	True progression	75 MRI, DWI, DSC, DCE	Retrospective, unsupervised MP clustering of ADC, rCBV, IAUC	Sensitivity: 96.4% Specificity: 81.8% AUC: 0.95
Booth *et al.*, 2017[12]	True progression	50 feature estimation. 24 (training = 17 & testing = 7) T2	Prospective testing set. SVM using Minkowski functionals	Accuracy: 88% AUC: 0.9
Kebir *et al.*, 2017[30]	True progression	14 18F-FET-PET	Retrospective, unsupervised Consensus clustering, 19 conventional and textural features	Sensitivity: 90% Specificity: 75% NPV: 75%
Nam *et al.*, 2017[43]	True progression	37 DCE	Retrospective Multivariate logistic regression using pharmacokinetic parameters	K_{ep} Accuracy: 70.3% AUC: 0.75 Sensitivity: 71.4% Specificity: 90%
Jang *et al.*, 2018[31]	Pseudoprogression	78 (training = 59 & testing = 19) T1 C MRI, Age, Gender, MGMT status, IDH mutation, radiotherapy dose & fractions, follow up interval	Retrospective 9 T1 C axial slices centred on lesion, CNN	AUC: 0.83 AUPRC: 0.87 F1 score: 0.74
Ismail *et al.*, 2018[37]	True progression	105 (training = 59 & testing = 46) MRI	Retrospective SVM using global & local features of lesion & peritumour habitat	Accuracy: 90.2% Sensitivity: 100% Specificity: 94.7%
Kim *et al.*, 2018[38]	Early true progression	95 (training = 61 & testing = 34) T1 C, FLAIR, DWI, DSC	Retrospective Generalised linear model, LASSO feature selection on multiparametric first- & second-order statistics	AUC: 0.85 Sensitivity: 71.4% Specificity: 90%

^{18}F-FET-PET, [^{18}F]-fluoroethyl-L-tyrosine positron emission tomography; NPV, negative predictive value; T1 C, post contrast T1-weighted; MGMT, O^6-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; CNN, convolutional neural network; AUC, area under the receiver operator characteristic curve; AUPRC, area under the precision-recall curve; DCE, dynamic contrast-enhanced imaging; MRS, ^{1}H-magnetic resonance spectroscopy; SVM, support vector machine; mRmR, minimum redundancy and maximum relevance; CBV, cerebral blood volume (rCBV, relative CBV); ADC, apparent diffusion coefficient; IAUC, initial area under the curve; MP, multiparametric; DWI, diffusion-weighted imaging; DSC, dynamic susceptibility weighted; LASSO, least absolute shrinkage and selection operator; DTI, diffusor tensor imaging; DKI, diffusor kurtosis imaging.

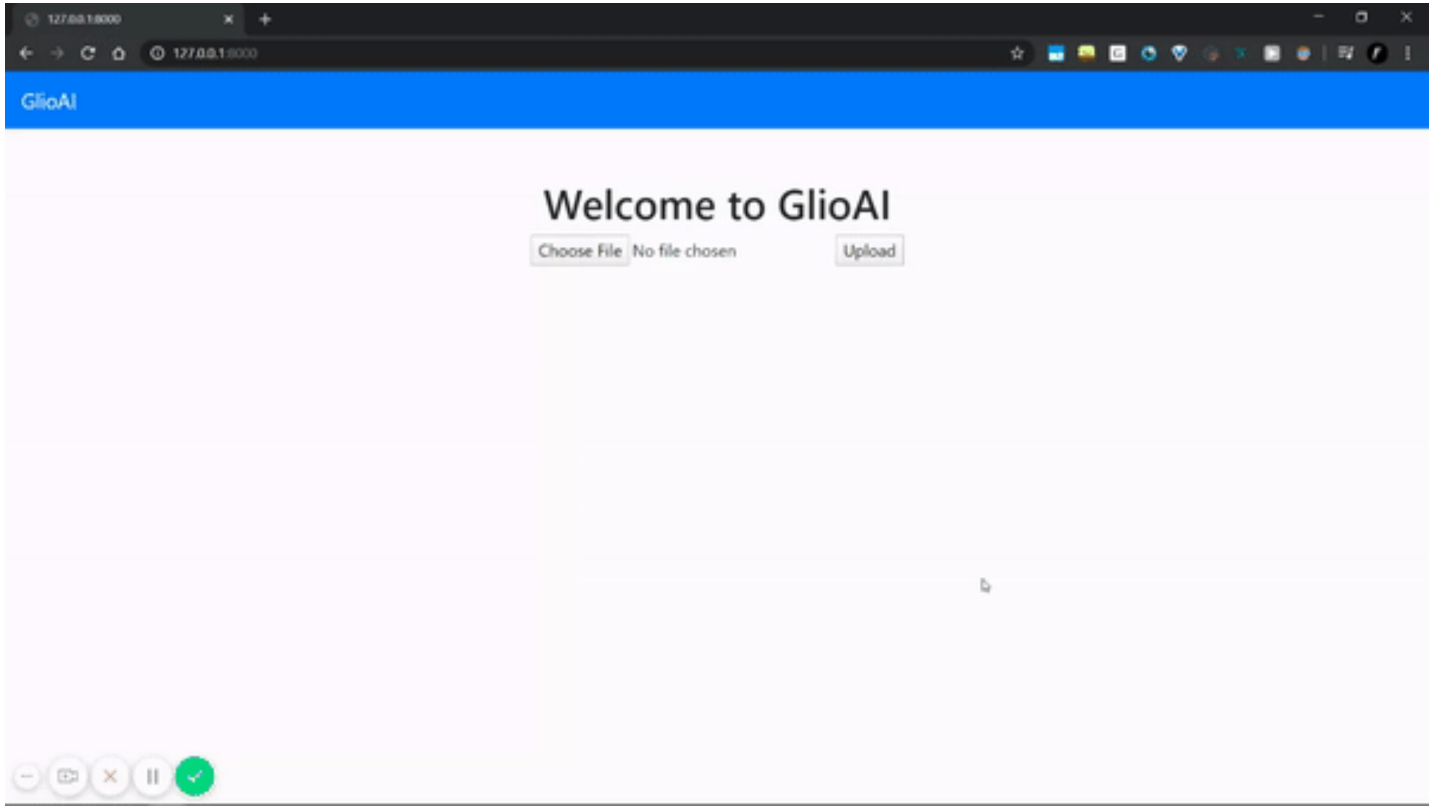
T.C. Booth et al. / Clinical Radiology 75 (2020) 20e32

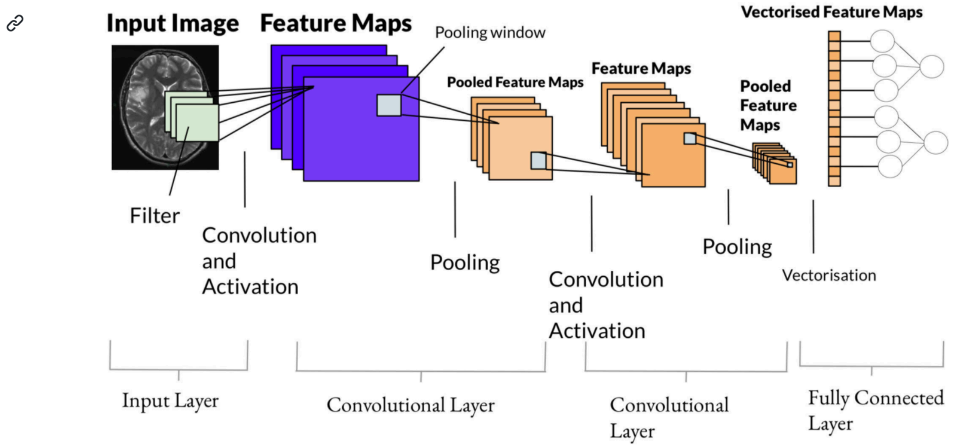
Table 2
Recent studies applying machine learning to the development of neuro-oncology prognostic biomarkers.

Author(s)	Dataset	Method	Results
Choi *et al.*, 2015[60]	61 preoperative DCE	Retrospective Multivariate Cox regression using MRI, pharmacokinetic, & clinical parameters	C-index: 0.82
Kickingereder *et al.*, 2016[61]	119 (training = 79 & testing = 40) T1, T1 C, FLAIR, DWI, DSC	Retrospective Supervised principal component analysis with Cox regression analysis	C-index: 0.70
Chang *et al.*, 2016[62]	126 (training = 84 & testing = 42) patients T1, T2, FLAIR, T1 C, DWI	Retrospective Random forest on radiomic features (including Laws, Haralick)	Accuracy: 76%
Liu *et al.*, 2016[63]	147 rs-fMRI and DTI	Retrospective SVM using clinical features & network features of structural & functional network	Accuracy: 75%
Nie *et al.*, 2016[64]	69 T1 C, rs-fMRI, DTI	Prospective SVM using supervised CNN-derived features	Accuracy: 89.9% Sensitivity: 96.9% Specificity: 83.8% PPR: 84.9% NPR: 93.9%
Macyszyn *et al.*, 2016[51]	134 (training = 105 & testing = 29) T1, T1 C, T2, FLAIR, DTI, DSC	Prospective SVM for OS <6 months & SVM for OS <18 months	Accuracy (<6 months): 82.76% Accuracy (<18 months): 83.33% Accuracy (combined): 79%
Zhou *et al.*, 2017[65]	32 TCGA T1 C, FLAIR, T2 & 22 T1 C, FLAIR, T2	Retrospective Group difference features to quantify habitat variation Supervised forward feature ranking with SVM	Accuracy: 87.5%, 86.4%
Dehkordi *et al.*, 2017[66]	33 pre-treatment DCE	Retrospective Adaptive neural network with fuzzy inference system using K_{trans}, K_{ep} and v_e	Accuracy: 84.8%
Lao *et al.*, 2017[67]	112 (training = 75 & testing = 37) pre-treatment T1, T1 C, T2, FLAIR	Retrospective Multivariate Cox regression analysis using radiomic features as well as "deep features" from pre-trained CNN	C-index: 0.71
Liu *et al.*, 2017[68]	133 T1 C	Retrospective Recursive feature selection with SVM	Accuracy: 78.2% AUC: 0.81 Sensitivity: 79.1% Specificity: 77.3%
Li *et al.*, 2017[69]	92 (training = 60, testing = 32) T1, T1 C, T2, FLAIR. TCGA data used.	Retrospective Random forest for segmentation into 5 classes Multivariate LASSO-Cox regression model	C-index: 0.71
Chato & Latifi, 2017[52]	163 T1, T1 C, T2, FLAIR. Short-, mid-, long-term survivors	Retrospective SVM, KNN, linear discriminant, tree, ensemble & logistic regression applied to volumetric, statistical & intensity texture, histograms & deep features	Accuracy: 91% Linear discriminant using deep features
Ingrisch *et al.*, 2017[70]	66 T1 C	Retrospective Random survival forests using 208 global & local features from segmented tumour	C-index: 0.67
Li *et al.*, 2017[71]	92 (training = 60 & testing = 32) T1, T1 C, T2, FLAIR. TCGA data used.	Retrospective LASSO Cox regression to define radiomics signature	C-index: 0.71
Bharath *et al.*, 2017[72]	63 TCGA preoperative: T1 C, FLAIR	Retrospective LASSO Cox regression using age, KPS, DDIT3 & 11 principal component shape coefficients	C-index: 0.86
Shboul *et al.*, 2017[73]	163 T1, T1 C, T2, FLAIR	Retrospective Recursive feature selection & random forest regression	Accuracy: 63%
Peeken *et al.*, 2018[74]	189 T1, T1 C, T2, FLAIR & clinical data.	Retrospective Multivariate Cox regression using VASARI features and clinical data	C-index: 0.69
Kickingereder *et al.*, 2018[75]	181 (training = 120 & testing = 61) pretreatment MRI	Retrospective Penalised Cox model for radiomic signature construction	C-index: 0.77
Chaddad *et al.*, 2018[76]	40 (training = 20 & testing = 20) preoperative MRI, T1 & FLAIR.	Retrospective Random forest on multi-scale texture features	AUC: 74.4%
Bae *et al.*, 2018[77]	217 (training = 163 & testing = 54) pre-operative MRI, T1 C, T2, FLAIR, DWI	Retrospective Variable hunting algorithm for selection & random forest classifier	iAUC: 0.65

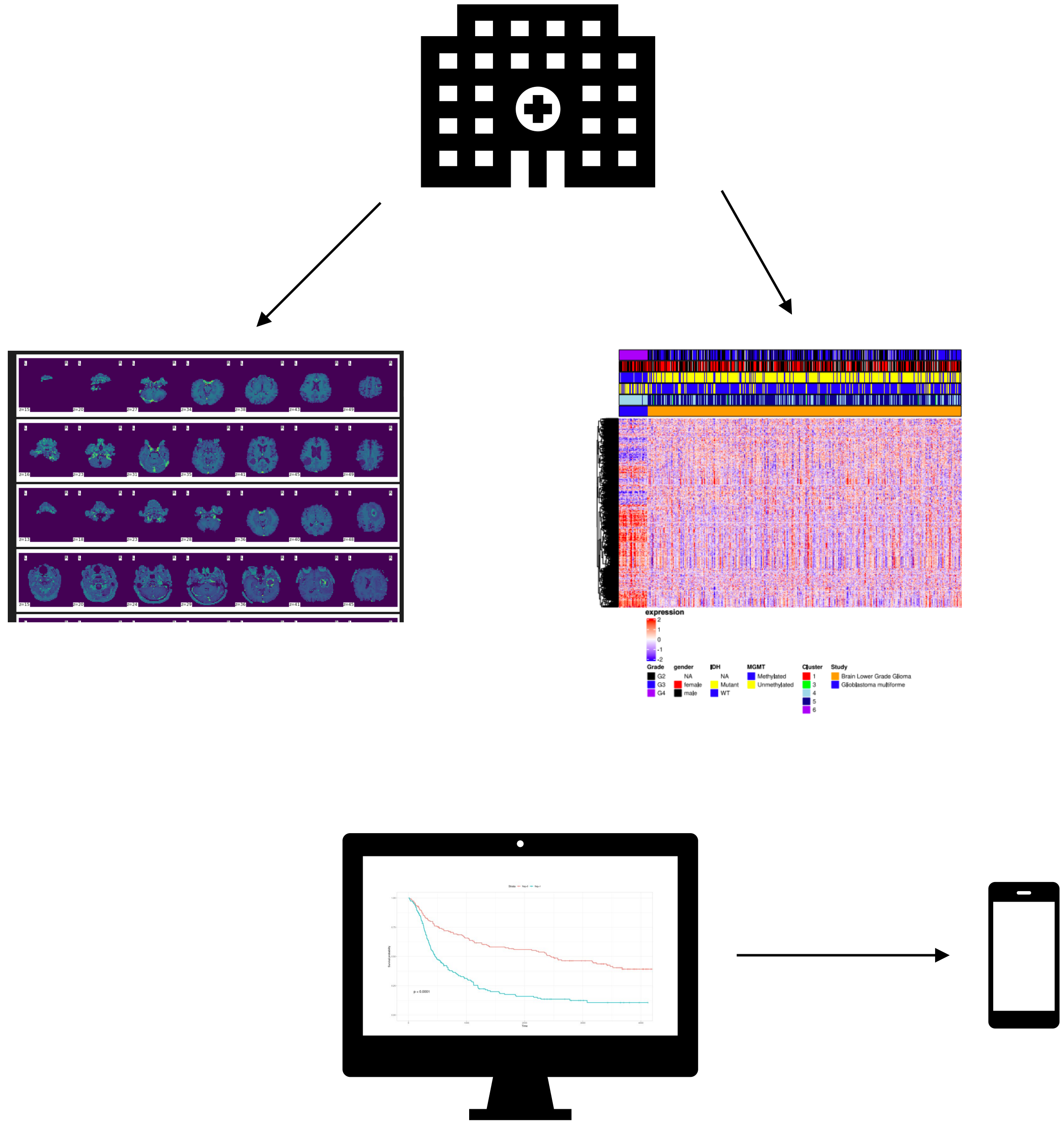
TCGA, The Cancer Genome Atlas; T1 C, post contrast T1-weighted; SVM, support vector machine; DCE, dynamic contrast-enhanced imaging; CNN, convolutional neural network; KNN, k-nearest neighbours/rs-fMRI, resting state functional MRI; KPS, Karnofsky performance status; DDIT3, DNA damage inducible transcript 3; DTI, diffusor tensor imaging; DSC, dynamic susceptibility weighted; OS, overall survival.

GlioAI: Automatic Brain Tumor Detection System





GLIOBLASTOMA



Machine learning on glioblastoma

S.O.C. GESTIONE DELLE TECNOLOGIE CLINICHE

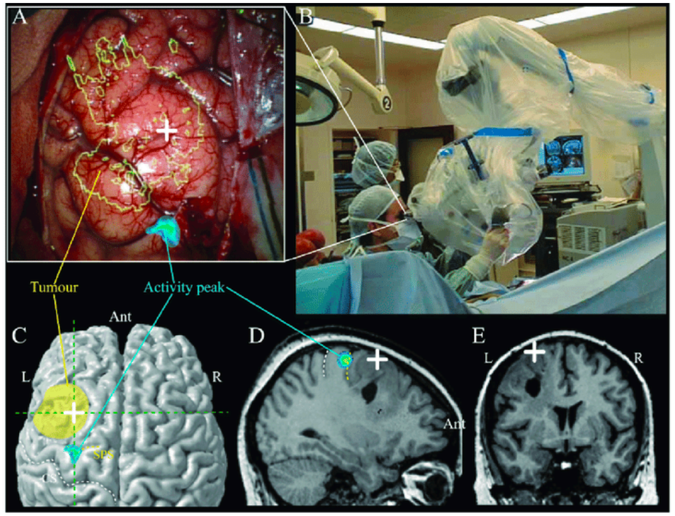
Head: Ricci Roberto

Consortium GARR

Nvidia Tesla V100 **GPUs**.

Machine learning on glioblastoma

Pre-Operative MRI for Neuronavigation



RADIOMICS

Docs » Welcome to pyradiomics documentation!

Edit on GitHub

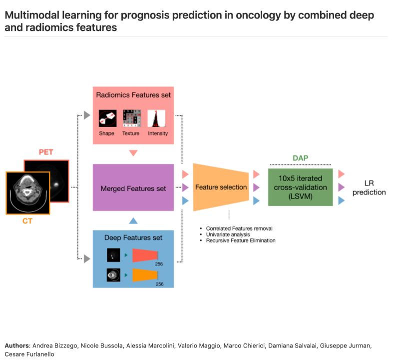
Welcome to pyradiomics documentation!

This is an open-source python package for the extraction of Radiomics features from medical imaging. With this package we aim to establish a reference standard for Radiomic Analysis, and provide a tested and maintained open-source platform for easy and reproducible Radiomic Feature extraction. By doing so, we hope to increase awareness of radiomic capabilities and expand the community. The platform supports both the feature extraction in 2D and 3D and can be used to calculate single values per feature for a region of interest ("segment-based") or to generate feature maps ("voxel-based").

DEEP LEARNING

Deep learning is a subset of machine learning consisting of computational units of multiple layers resembling the multilayered human cognition system.

Several studies using deep learning to predict glioma grading, glioma genetic mutation or survival.



Emanuele Fabbiani
Università di Pavia

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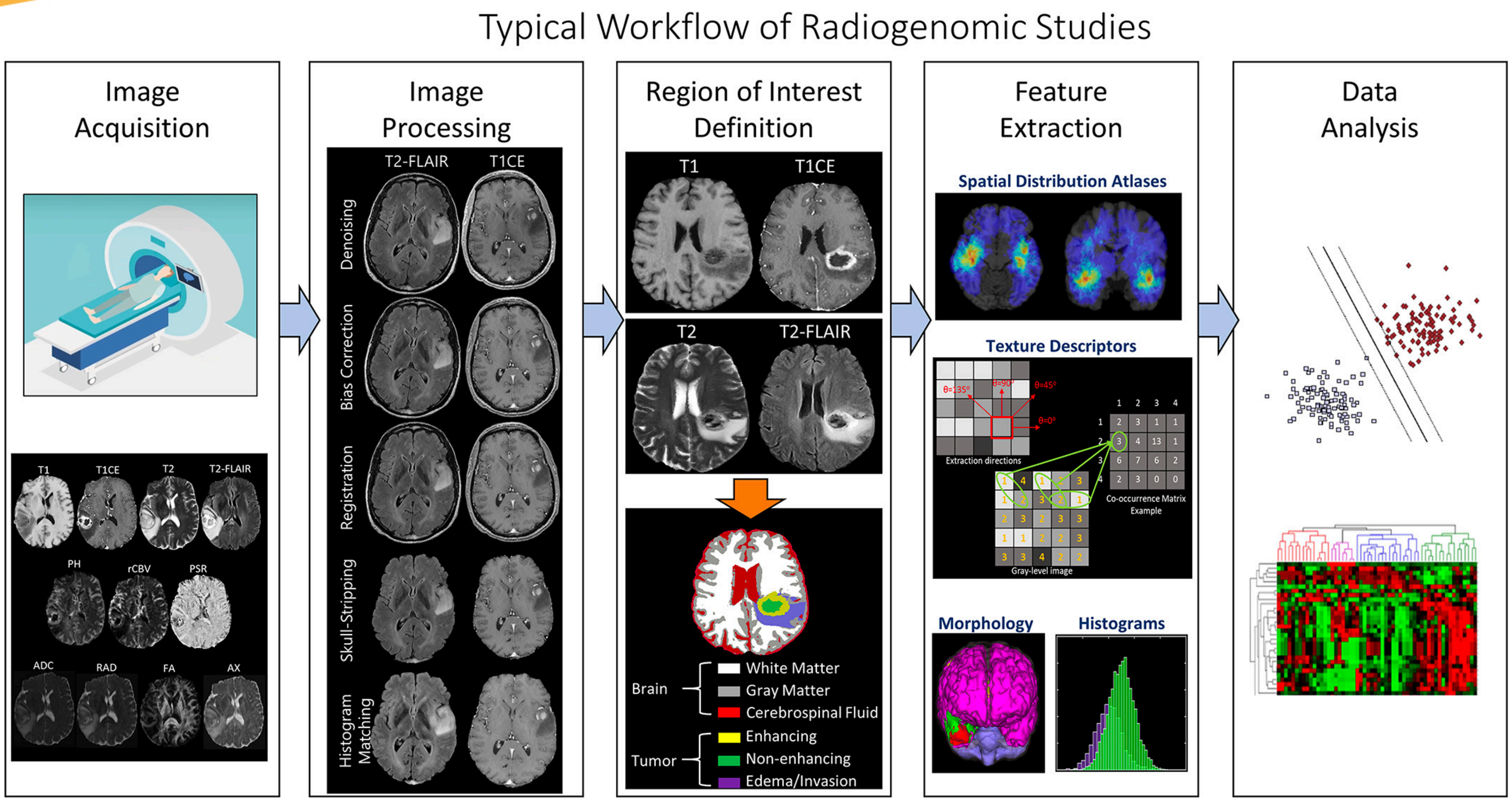
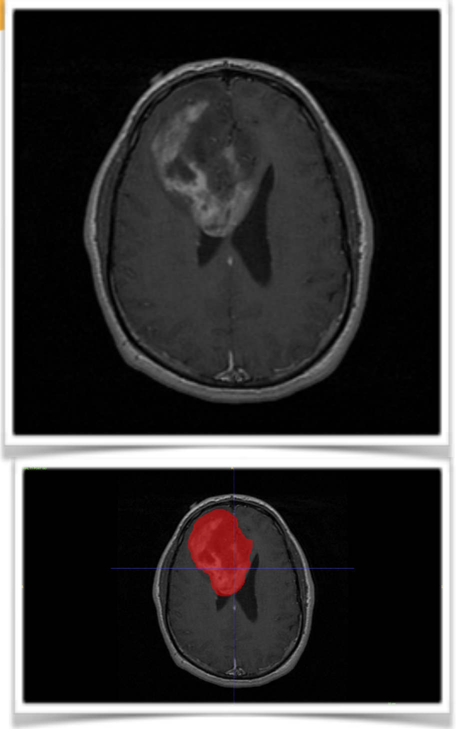
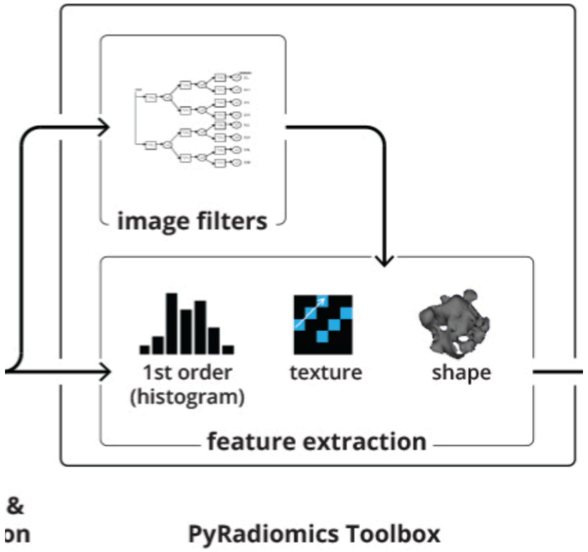
Machine learning on glioblastoma

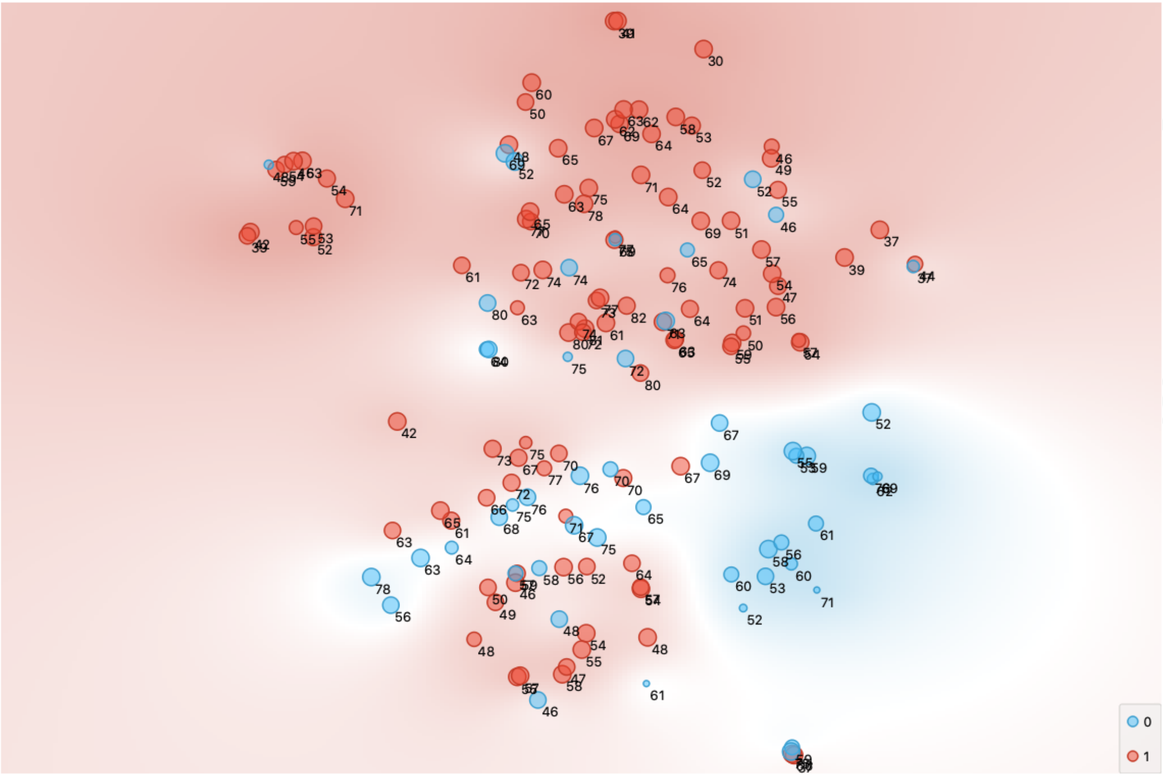


Machine learning on glioblastoma





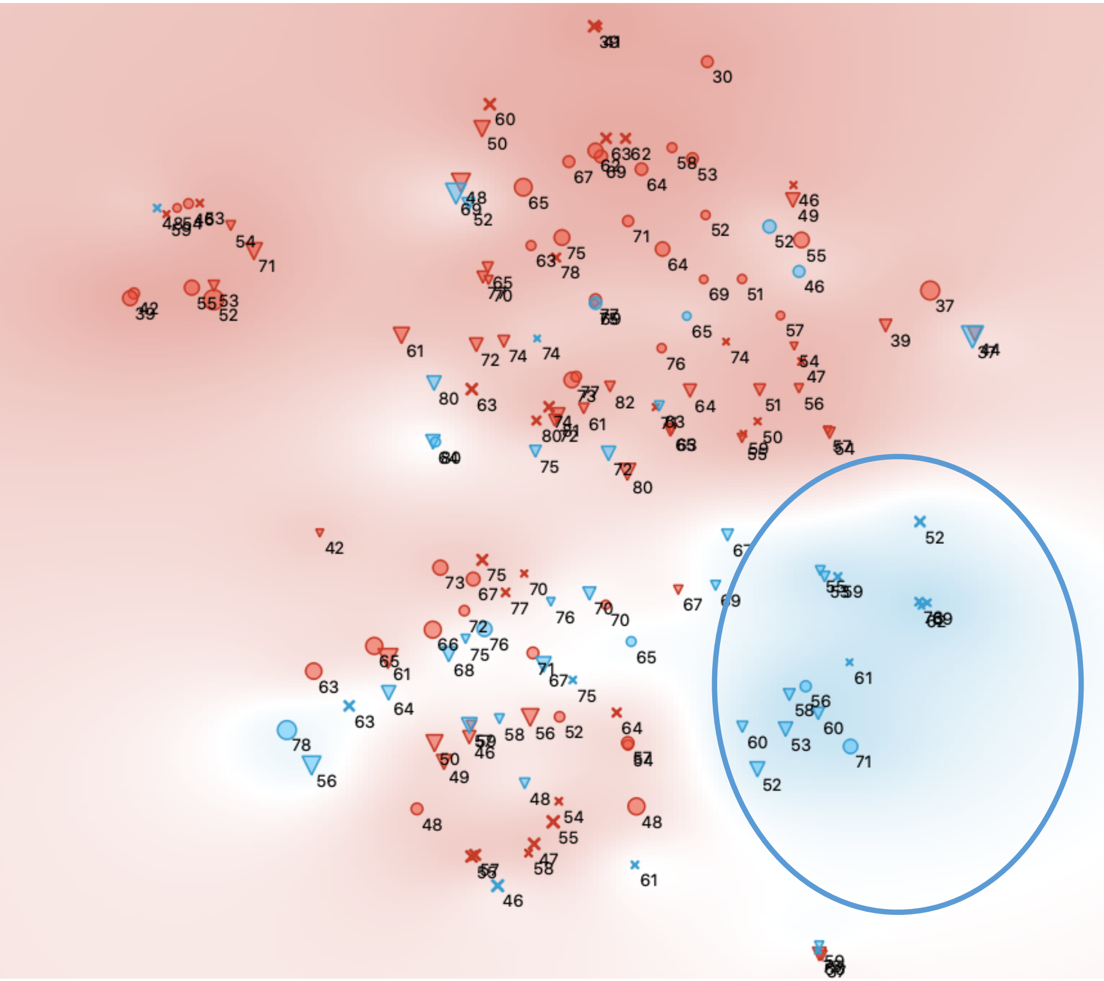
PyRadiomics Toolbox



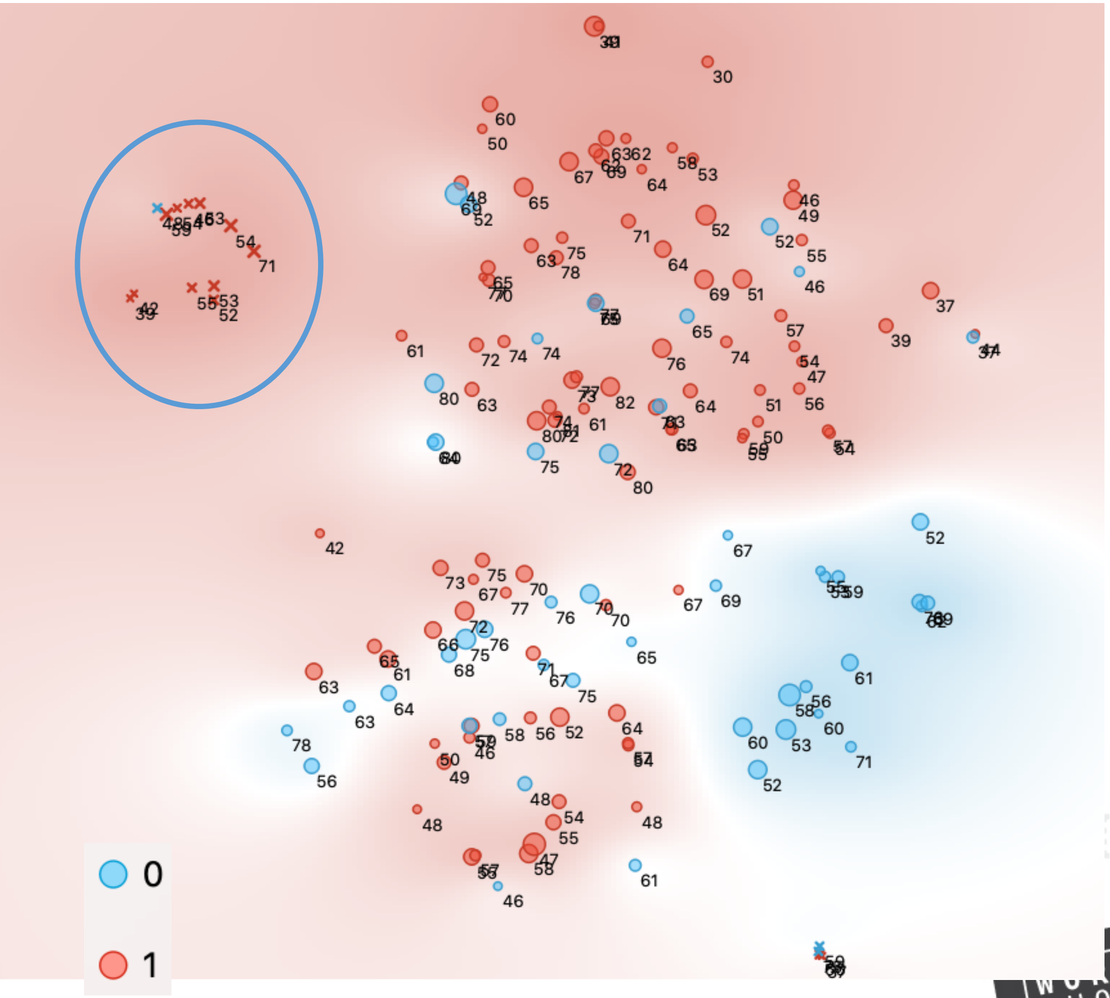
pfs_6mesi_binary	type: Count	Philips	Siemens	Total
	0	24.0	27.0	**51.0**
	1	50.0	57.0	**107.0**
	Total	**74.0**	**84.0**	**158.0**

pfs_6mesi_binary		sex: Aggregate	0	1	Total
	0	**Mean**	89.559	89.059	**89.392**
		Median	92.5	95.0	**95.0**
	1	**Mean**	96.958	97.222	**97.047**
		Median	100.0	100.0	**100.0**
	Total	**Mean**	**94.562**	**94.604**	**94.576**
		Median	**98.0**	**98.0**	**98.0**

Machine learning on glioblastoma

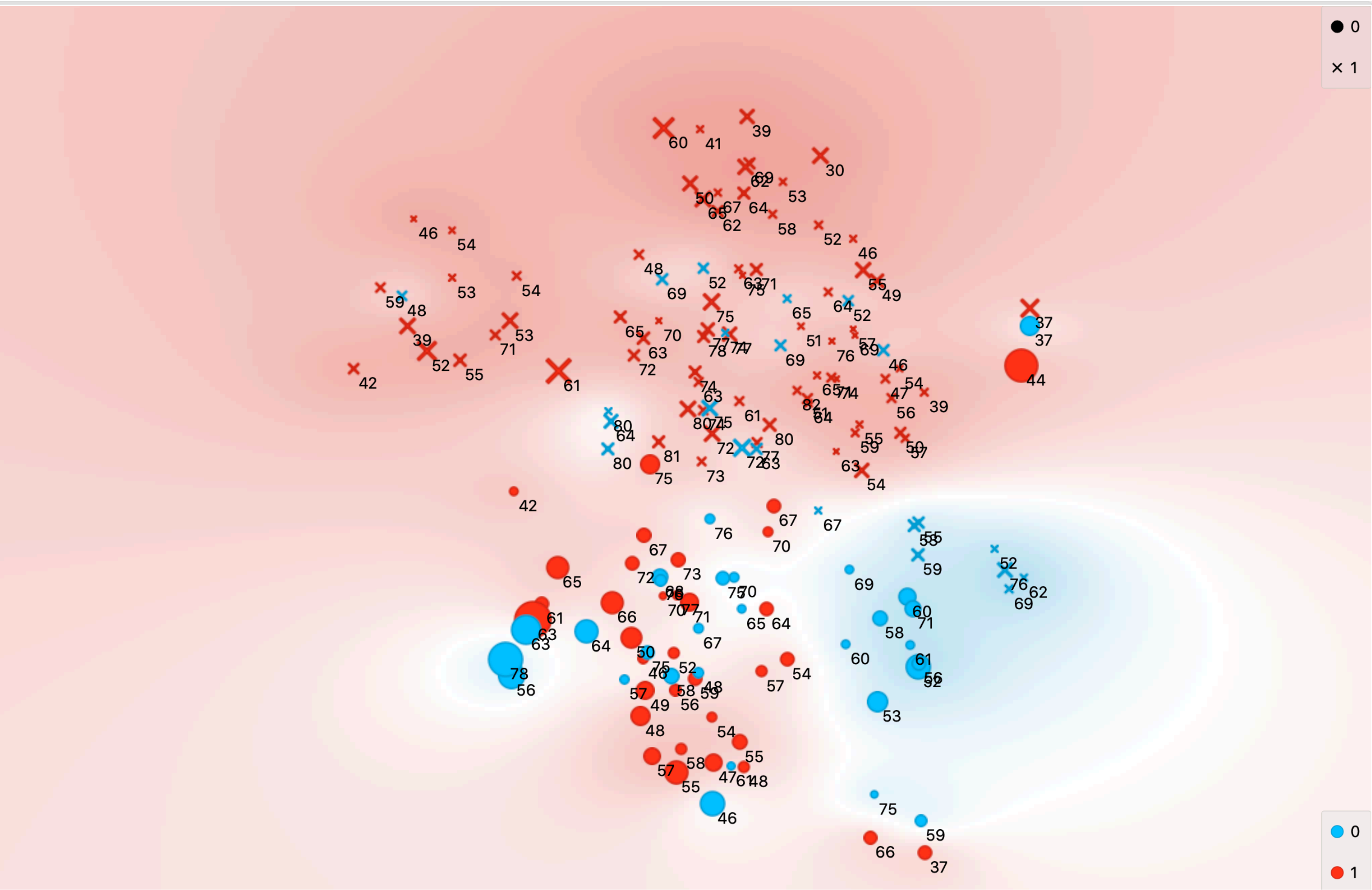


Volume T2 pre



IDH mutation an survival

Machine learning on glioblastoma



Mgmt

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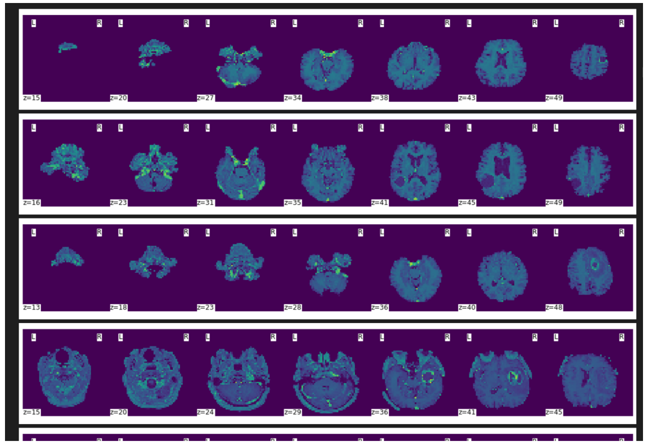
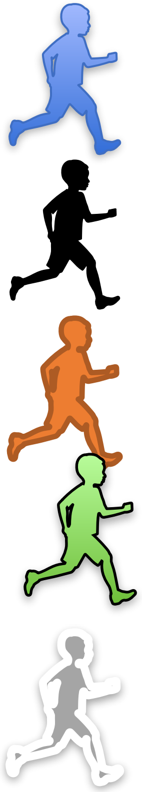
Machine learning on glioblastoma



185 patients anonymous

Preprocessing

Kubernetes



PyTorch
Computer application

PyTorch

PyTorch is an open source machine learning library based on the Torch library, used for applications such as computer vision and natural language processing, primarily developed by Facebook's AI Research lab. It is free and open-source software released under the Modified BSD license. Wikipedia

License: BSD

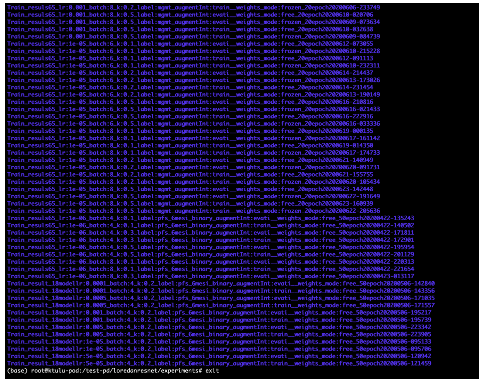
Developer(s): Facebook's AI Research lab (FAIR)

Original author(s): Adam Paszke; Sam Gross; Soumith Chintala; Gregory Chanan

Stable release: 1.6.0 / 28 July 2020; 2 months ago

Initial release: September 2016; 4 years ago

Written in: Python, C++, CUDA



Machine learning on glioblastoma

Kubernets

Resnet-18

Resnet-34

Resnet-50

Resnet-30

Resnet-105

PyTorch

Computer application

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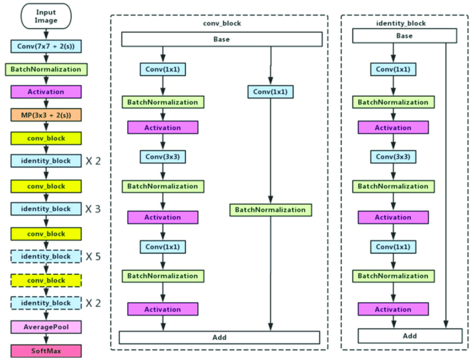
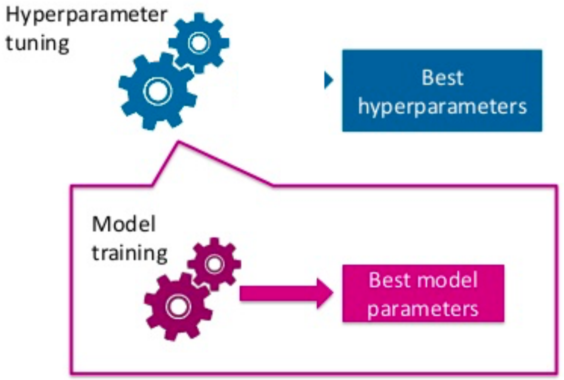
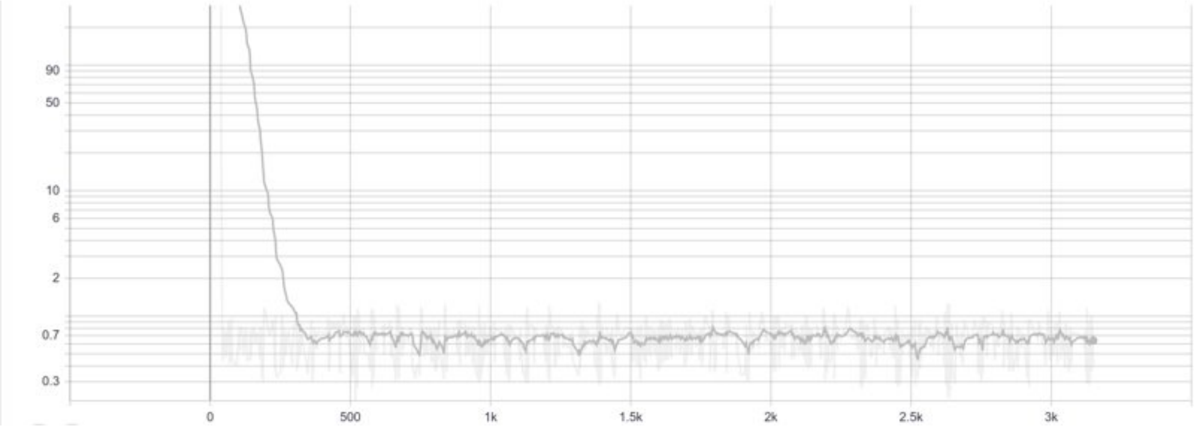


Hyperparameter tuning vs. model training

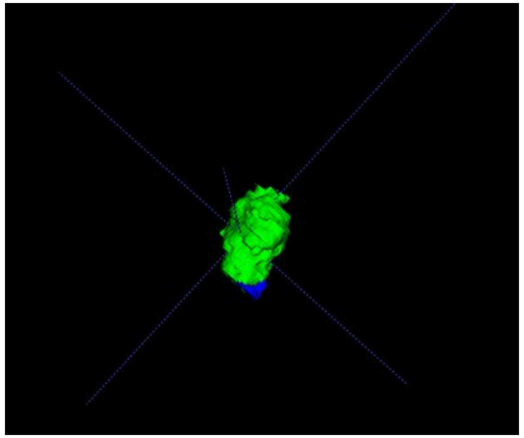


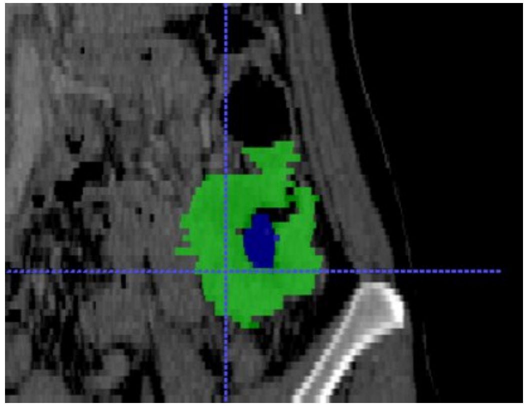
Parameters: 17861314
Total Parameters : 5102134

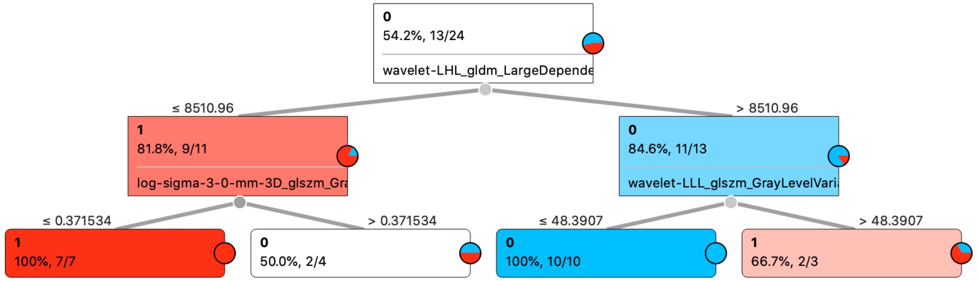
Resnet 18: Transfer learning using Medical Net 50 epoch



OTHER EXPERIENCE: COLON CANCER







Cancer Management and Research

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ORIGINAL RESEARCH

A radiomics-based formula for the preoperative prediction of postoperative pancreatic fistula in patients with pancreaticoduodenectomy

This article was published in the following Dove Press journal:
Cancer Management and Research

Wenyu Zhang[1,2]
Wei Cai[1,2]

Objective: The objective of the study was to develop and validate a radiomics-based formula for the preoperative prediction of postoperative pancreatic fistula (POPF) in patients undergoing

Table 3 Rad-score calculation formula

Rad-score= –6.34907–0.002009672*log-sigma-1–0-mm-3D_firstorder_Kurtosis
+0.0002217893*log-sigma-3–0-mm-3D_firstorder_Maximum
+0.08755741*log-sigma-4–0-mm-3D_firstorder_Skewness
–4.839234*HHH_gldm_SmallDependenceLowGrayLevelEmphasis
+3.12135*LHL_glcm_Imc2
+1.333126*LHL_glrlm_RunEntropy
–9.788694*LHL_glszm_SmallAreaLowGrayLevelEmphasis
+7.885982*LHH_glcm_Imc2
–3.23331*HHL_gldm_SmallDependenceLowGrayLevelEmphasis
–0.01287862*HLH_firstorder_Kurtosis
–0.2409615*HLH_glszm_ZoneEntropy

Notes: L and H indicate a low-pass (ie, scaling) and a high-pass (ie, wavelet) function, respectively. The decompositions are constructed in this manner, applying their respective ordering of low- or high-pass filtering in x, y and z-direction. For example, LHH is then interpreted as the high-pass sub band, resulting from directional filtering of X with a low-pass filter along x-direction, a high-pass filter along y-direction and a high-pass filter along z-direction.
Abbreviation: Rad-score, radiomics score.

FUTURE


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Thanks all for the Attention