Supervised ML Approaches for Predicting Survival Rate

Group 3
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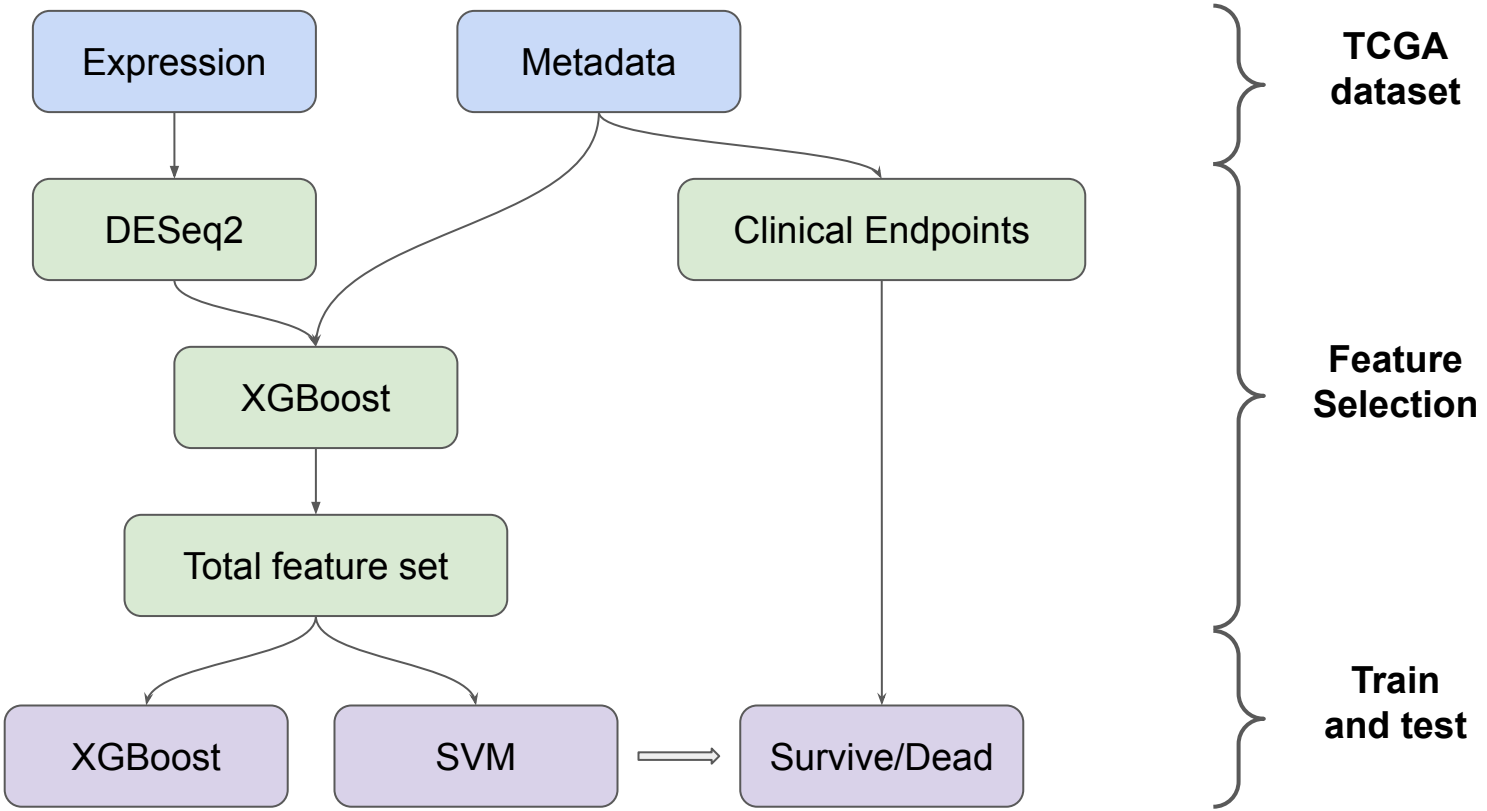
Background/Introduction

- **“How Long Have I Got?”**
- Most lung cancer patients worldwide [stage IV non small cell lung cancer (NSCLC)] have a poor survival: 25%–30% die <3 months.
- Of those surviving >3 months, 10%–15% (70,000–105,000 new patients worldwide per year) survive (very) long.
- **Goal:** develop and validate a survival prediction model in a cohort of different stages patients of lung cancer in TCGA.

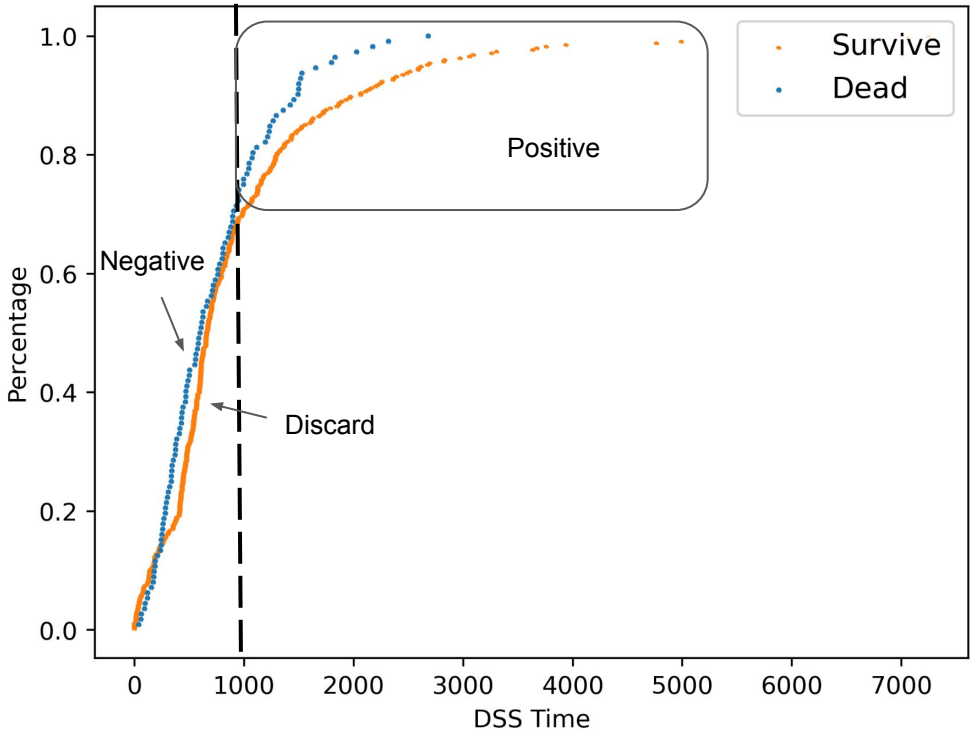
Guo et al.

Overview


Expression
Metadata
DESeq2
Clinical Endpoints
XGBoost
Total feature set
XGBoost
SVM
Survive/Dead
TCGA dataset
Feature Selection
Train and test

Clinical Endpoints

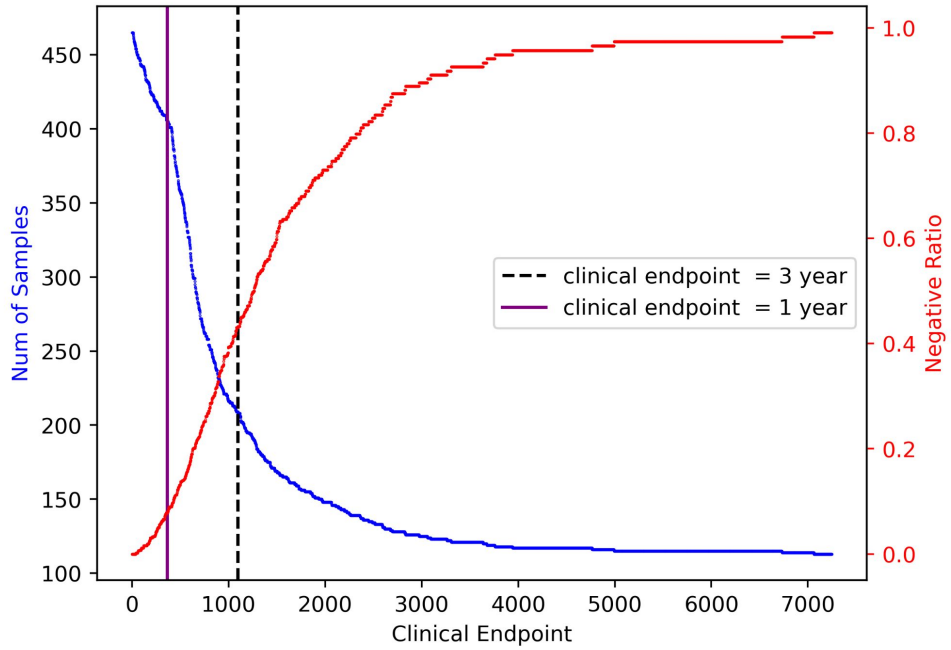
How to Define Negative/Positive Samples?



Clinical Endpoints

Trade-off between Sample Size and Sample Balance

Use two different clinical endpoints: 1 year and 3 year



Demographic Information

1 yr	N = 405	
Variable	**Living (N=373)**	**Deceased (N=32)**
Age (years)		
< 65(179)	163	16
≥65(226)	210	16
Sex		
Female (225)	210	15
Male(180)	163	17
Tumor stage		
Early(319)	293	26
Late(80)	74	6
Smoking status		
Smoker(256)	237	19
Non-smoker(149)	136	13

3 yr	N = 209	
Variable	**Living (N=119)**	**Deceased (N=90)**
Age (years)		
< 65(93)	49	44
≥65(116)	70	46
Sex		
Female(116)	66	50
Male(93)	53	40
Tumor stage		
Early(157)	99	58
Late(49)	18	31
Smoking status		
Smoker(134)	78	56
Non-smoker(75)	41	34

Data Preprocessing

Metadata

1. Age at diagnosis
2. Gender
3. Tumor stage:
   I, II as EARLY stage; III, IV as LATE stage
4. Smoking status:
   > 188 cigarettes/year as SMOKER
   ≤ 188 cigarettes/year as NON-SMOKER

Gene Expression

1. Remove all normal and recurrent samples
2. Log2 transformation

DESeq2 Result (Endpoint: 1 year)

- **DESeq2 pre-filtering**:
  Remove genes with less than 10 counts (remove 757 genes out of 19382 with nonzero total read count, 3.9%)
- **3,226** genes (15.7%) being significant with padj < 0.05

GENE	log2FoldChange	pvalue	padj
GPR77	-2.41267	8.29E-26	1.54E-21
MT1A	-3.5278	3.01E-16	2.80E-12
SCGB3A1	3.90002	1.11E-15	6.92E-12
AMDHD1	-2.60538	9.55E-15	4.45E-11
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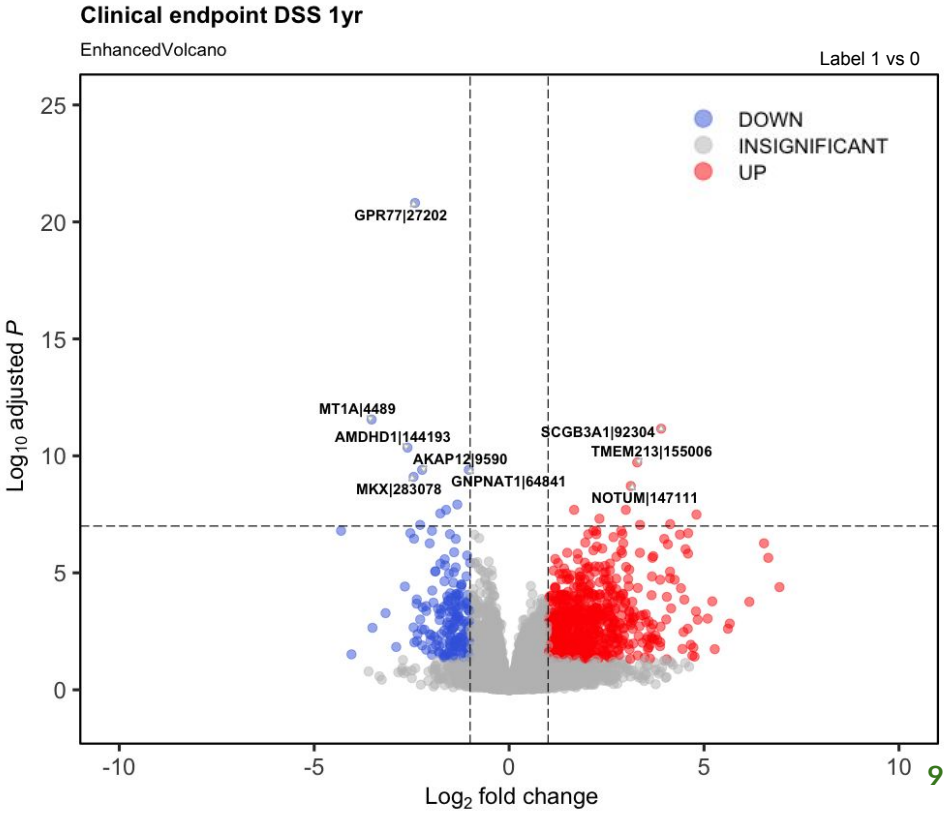

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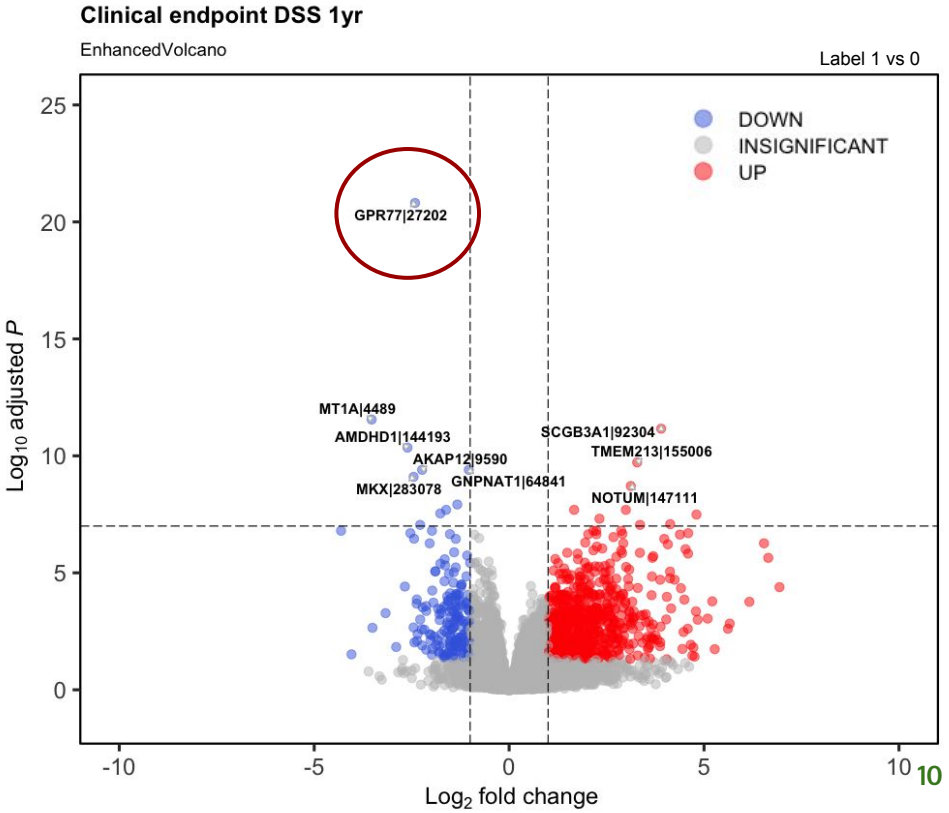
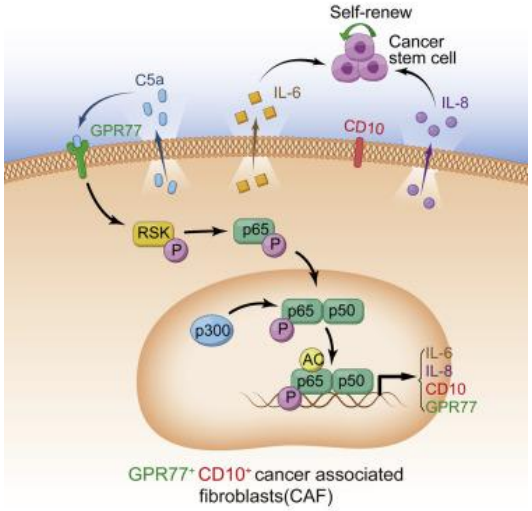
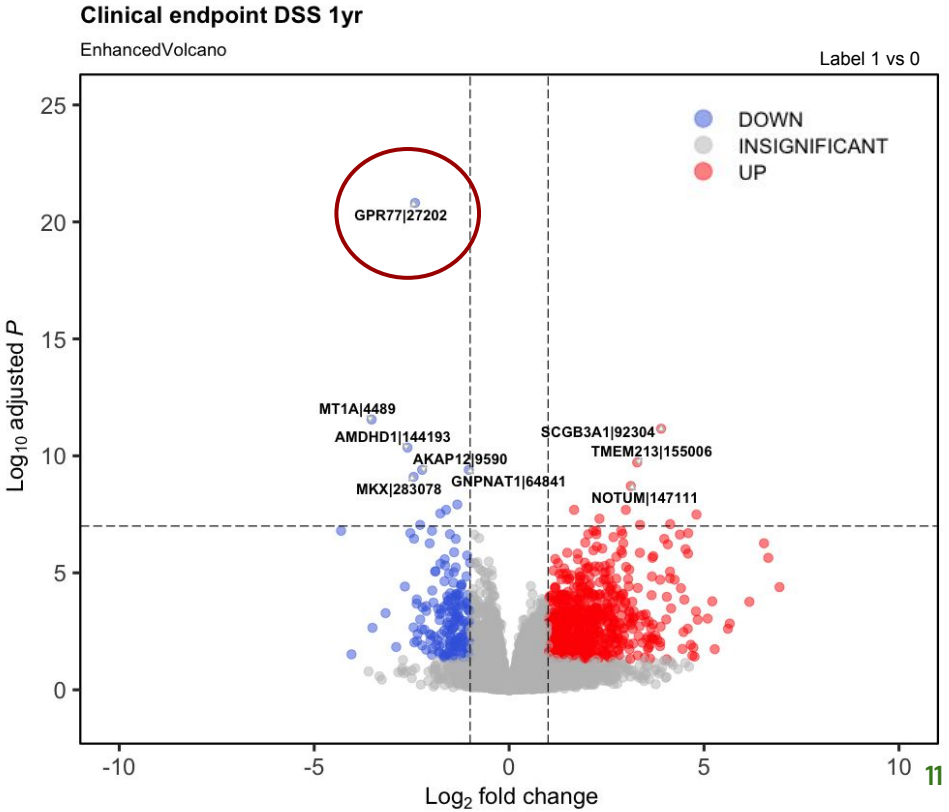


DESeq2 Result (Endpoint: 1 year)

- Role of GPR77 in lung cancer prognosis:
  GPR77+ carcinoma-associated fibroblasts (CAFs) sustain cancer stemness and promote tumor chemoresistance



Su et al., Cell (2018)



DESeq2 Result (Endpoint: 3 year)

- **DESeq2 pre-filtering**:
  Remove genes with less than 10 counts (remove 1126 genes out of 19163 with nonzero total read count, 5.9%)
- **1606** genes (7.8%) being significant with padj < 0.05

GENE	log2FoldChange	pvalue	padj
MAEL	3.81582	6.64E-17	1.20E-12
WIF1	3.07129	3.15E-15	2.84E-11
COL4A6	-2.22539	5.45E-15	3.28E-11
CIDEC	-3.94203	1.19E-14	5.36E-11
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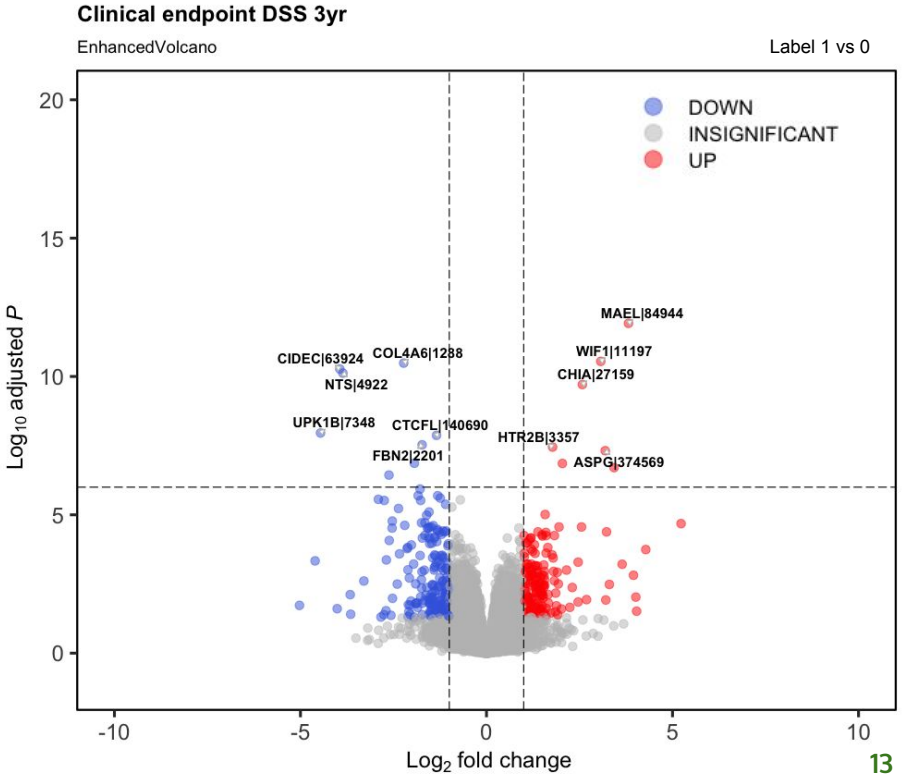

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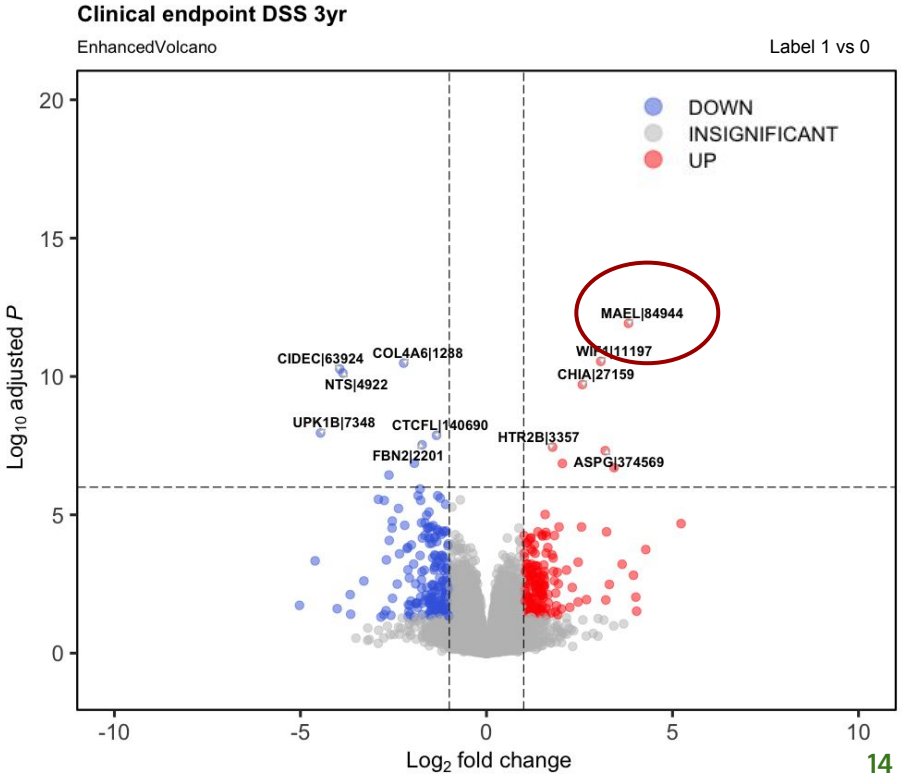
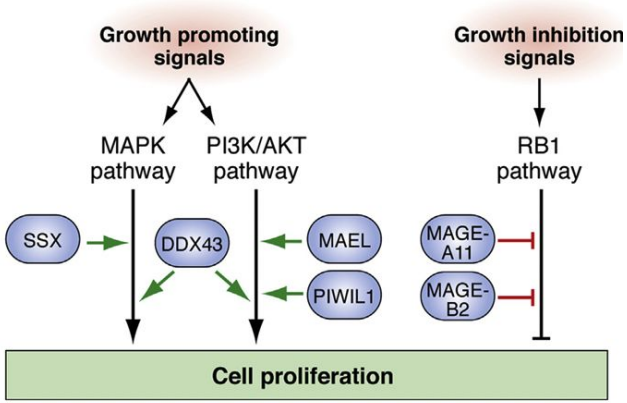


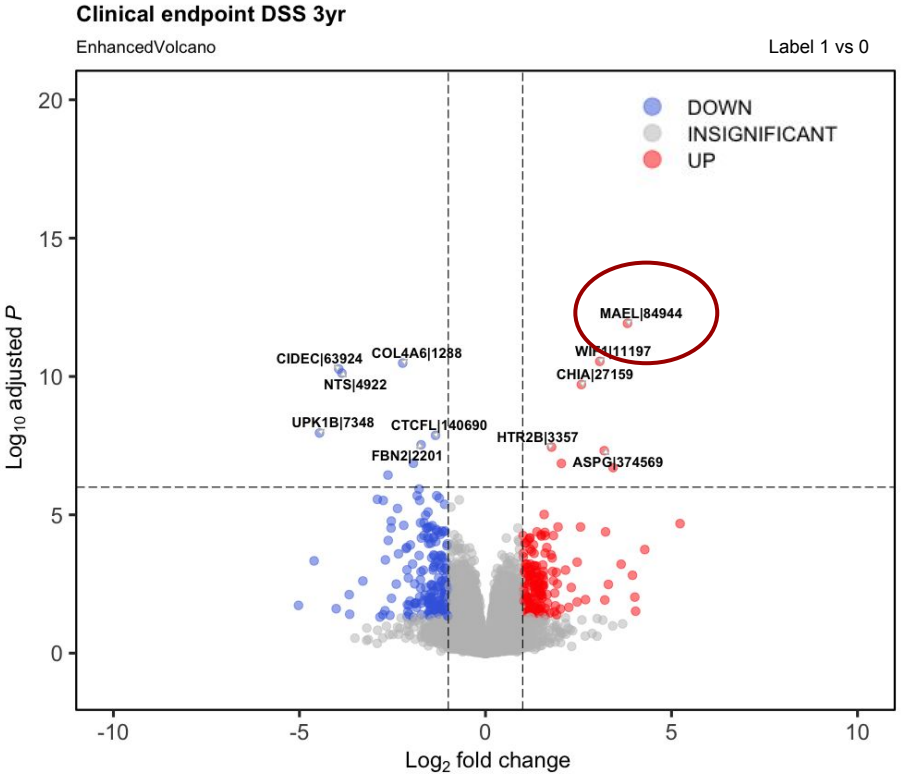
DESeq2 Result (Endpoint: 3 year)

- Roles of MAEL in lung cancer prognosis:

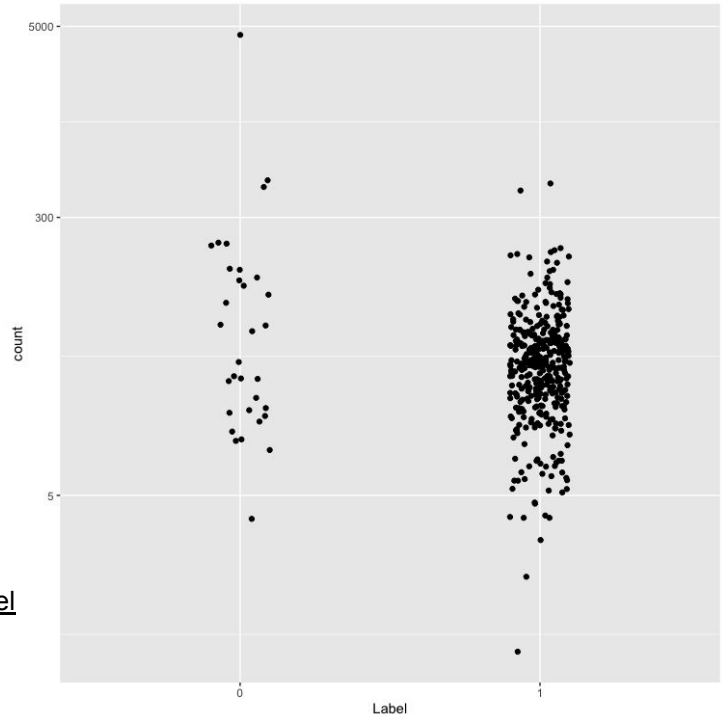
1. **Maelstrom (MAEL) is highly expressed in lung, liver, breast, bladder, and colorectal cancer**
2. **Correlated with epithelial-mesenchymal transition (EMT), tumor aggressiveness and poor prognosis outcome**



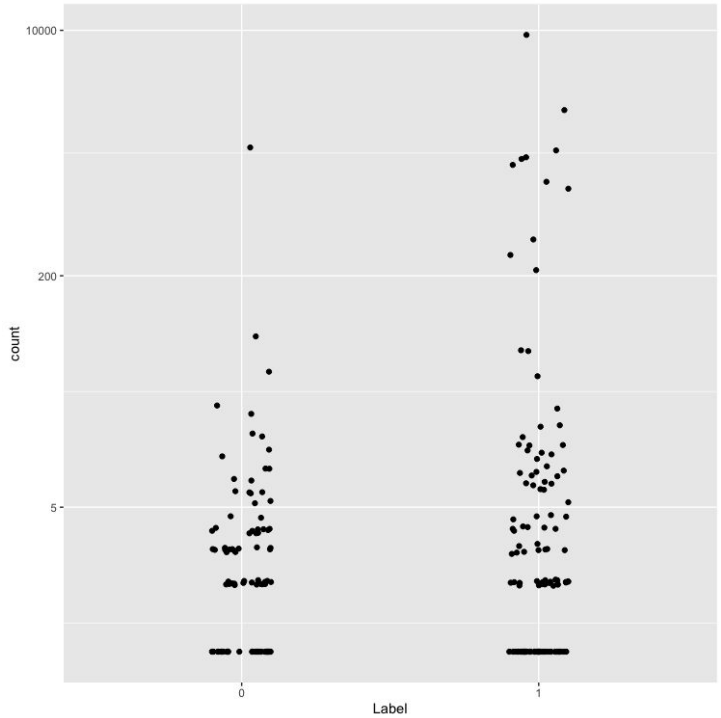
A.Van Tongelen et al. Cancer Letters (2017)



Read counts for the most significant genes



GPR77 (1 yr)



MAEL (3 yr)

Our classifier label
1 as living
0 as deceased

Feature Selection: XGBoost

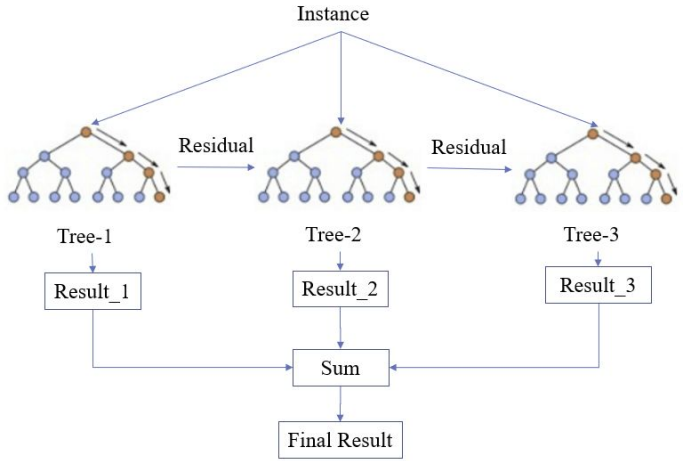
Selected Features for our models:

- Top 100 significant gene expression → DESeq2 Result
- Patient age → metadata dataset
- Tumor stage → metadata dataset
- Smoking status → metadata dataset
- Gender → metadata dataset
- Split our dataset into 80-20

Model: XGBoost

Combines weak predictive models (decision trees) to create a stronger predictive model

- Gradient boosting: each subsequent decision tree is trained to correct mistakes



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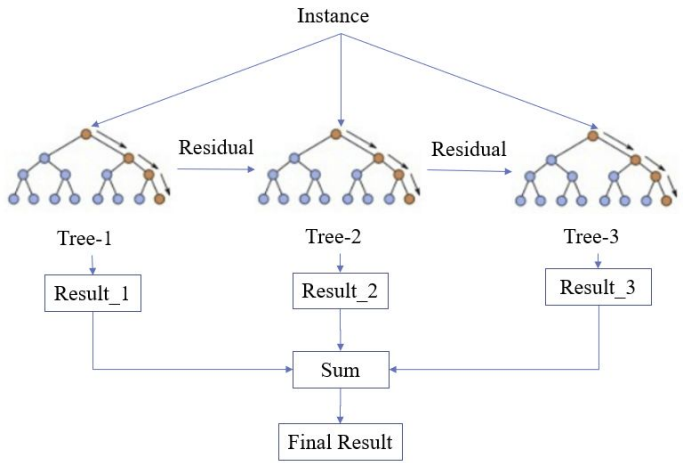
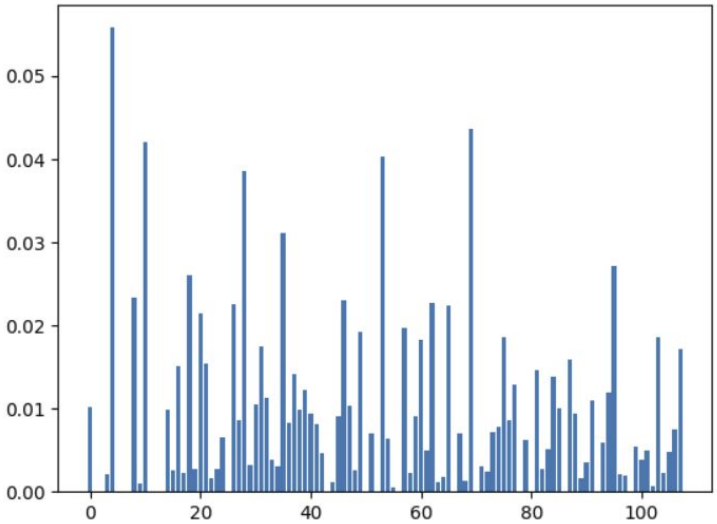


Parameters to vary:
- n_estimators
- max_depth
- learning_rate

Model: XGBoost

After training on the total feature set, XGBoost allows us to analyze the importance of the features using a significant threshold

- Features above the threshold were used for classification



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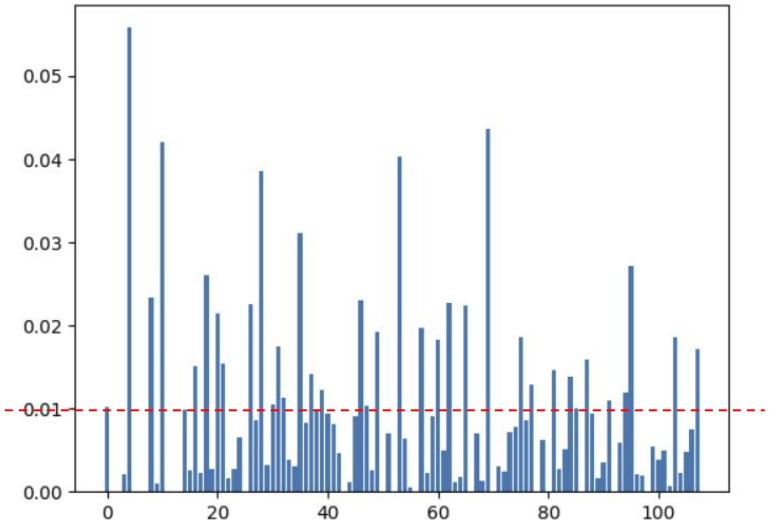

Iteration 1: threshold > 0.01

Model: XGBoost

After training on the total feature set, XGBoost allows us to analyze the importance of the features using a significant threshold

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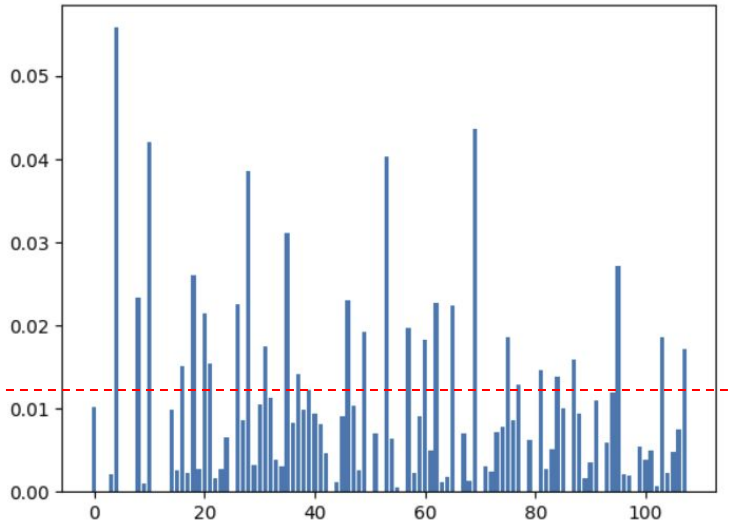

Iteration 2: threshold > 0.011

Model: XGBoost

After training on the total feature set, XGBoost allows us to analyze the importance of the features using a significant threshold

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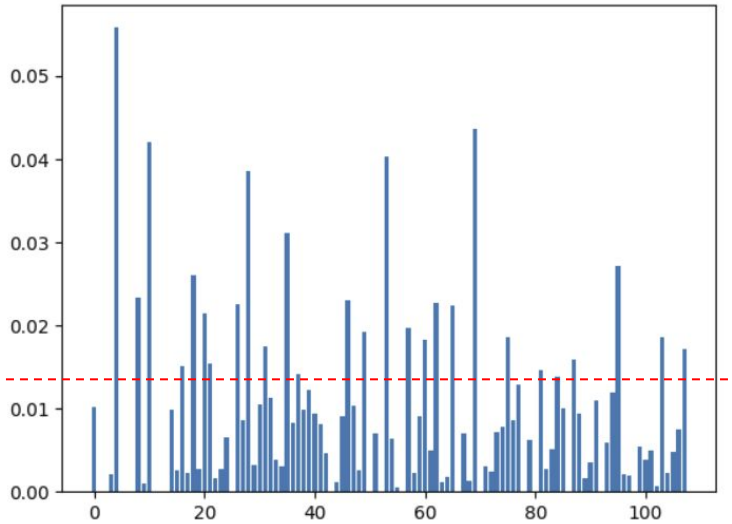

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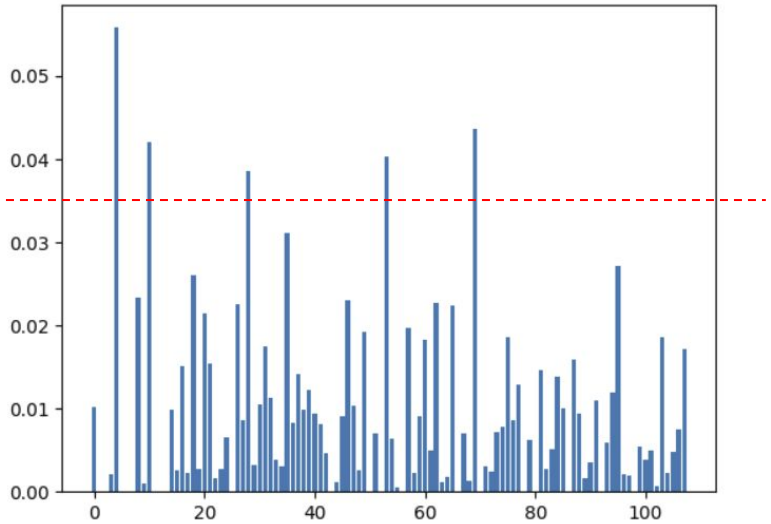
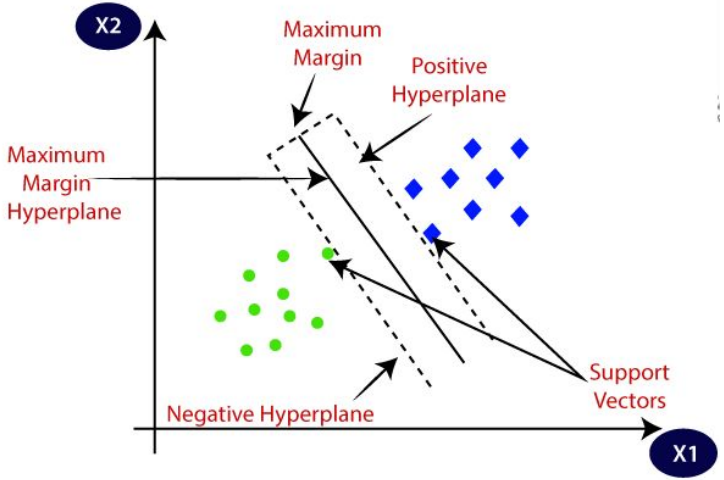


Model: SVM

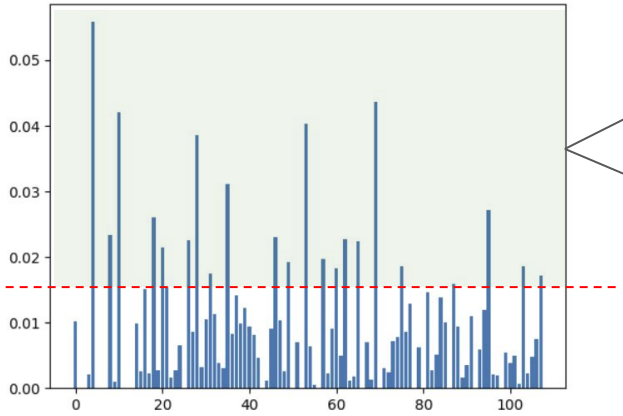
- Maps data to high-dimensional feature space to separate label data
- Looks to determine the optimal hyperplane that maximally separated the data points
  - Maximizing the margin
  - Maximizing the distance between the hyperplane and observations closest to the hyperplane
- Performed grid search varying the different parameter of SVM



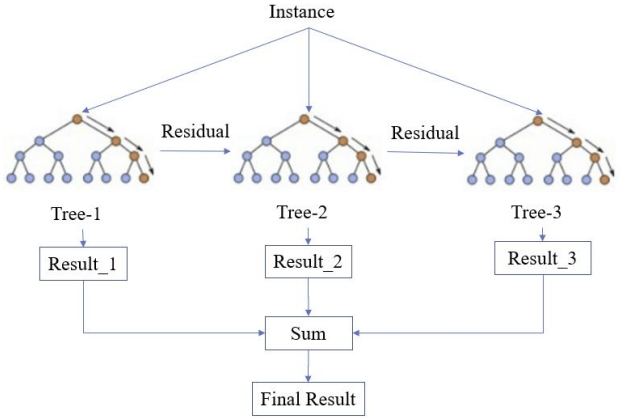
Parameters to Choose:
- Penalty
- kernel

Training/Testing

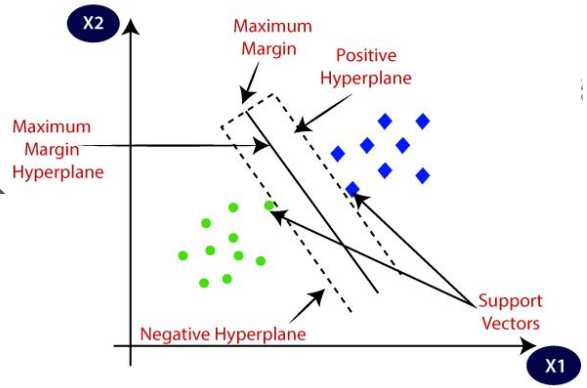
Feature Selection with XGBoost



XGBoost Classification



SVM Classification



Iterate over different significant thresholds + grid search over model parameters

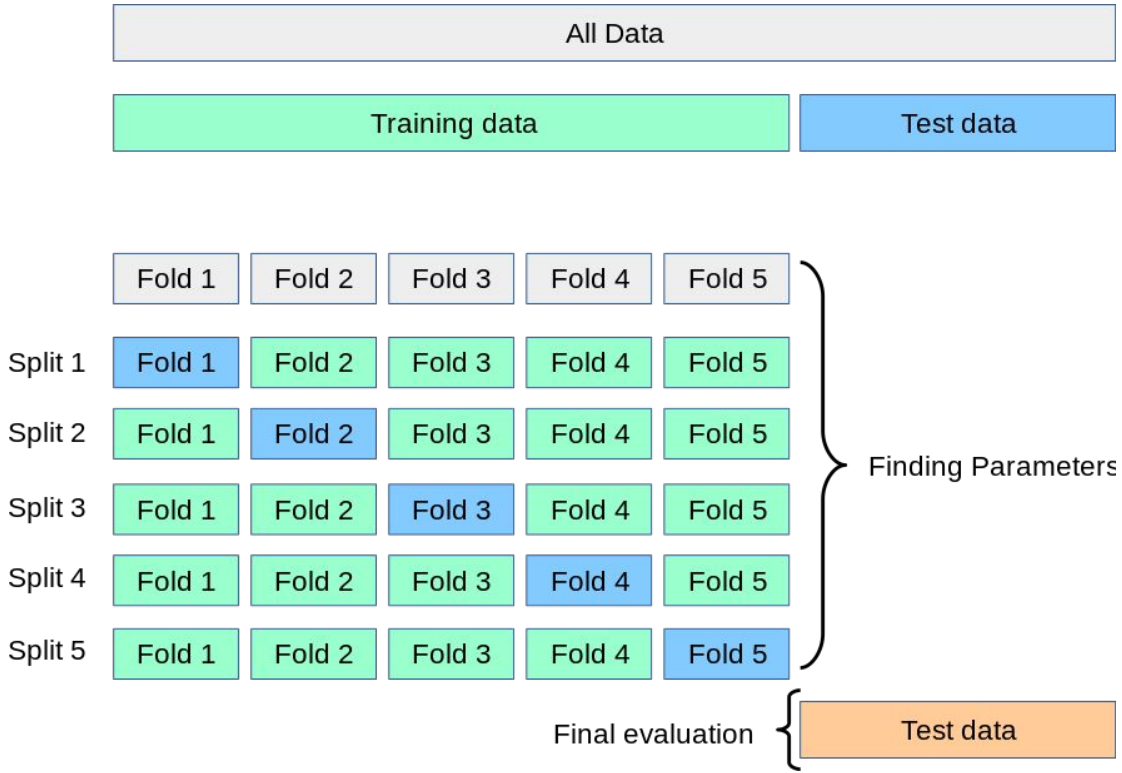
Training

Cross Validation

- 5 folds

Hyperparameter Tuning

- Grid search



Training

Cross Validation

- 5 folds

Hyperparameter Tuning

- Grid search

Parameters in XGBoost:
- N-estimators: 10, 50, 100
- Max_depth: 5, 10
- Learning_rate: 0.01, 0.1, 1, 10, 100

Parameters in SVM:
- C: 0.1, 0.5, 1, 2, 5, 10
- Kernel: Linear, RBF

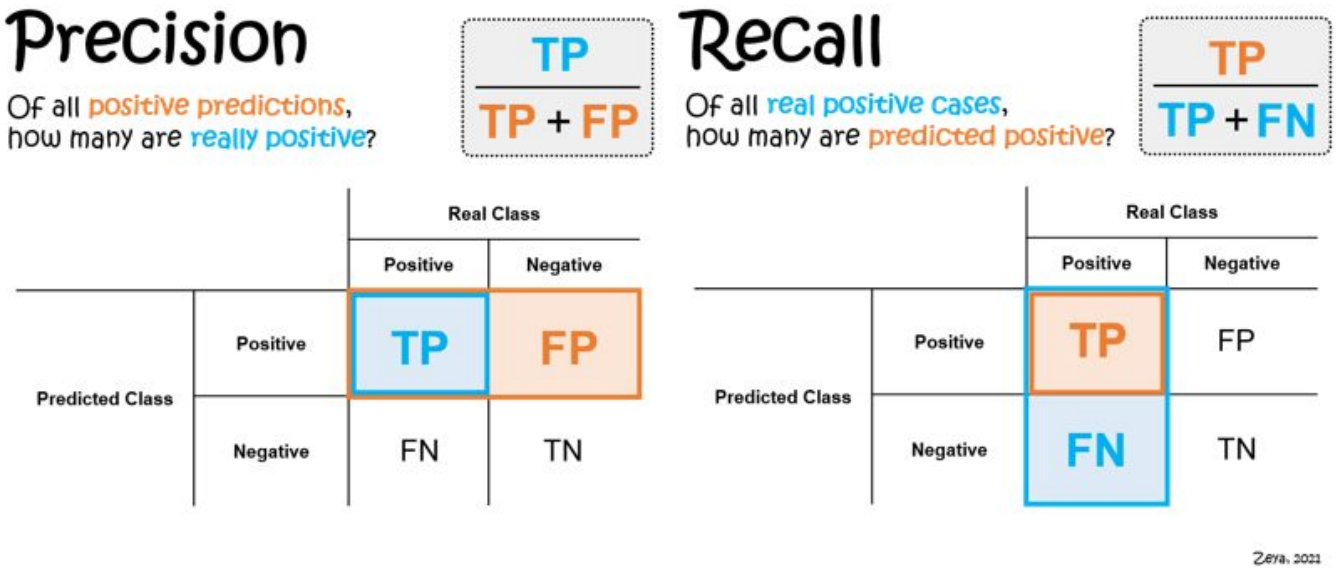
Evaluation

Accuracy:
0.85

Evaluation

Evaluation

- Accuracy
- F1-Score
  - **Imbalanced datasets**



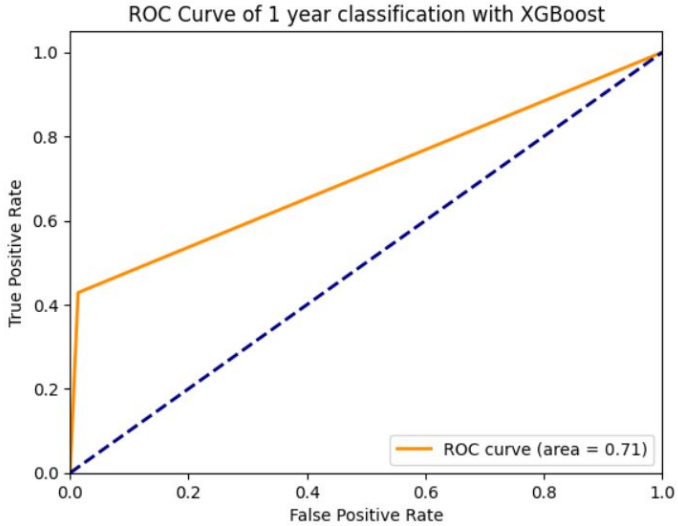
Evaluation

$$F1\ Score = 2 \times \frac{recall \times precision}{recall + precision}$$

RESULTS - 1 YEAR

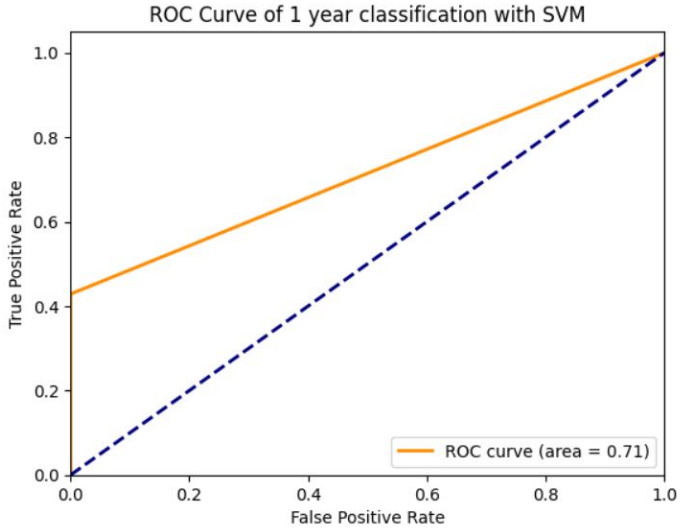
XGBoost

	Precision	Recall	F1
Alive	0.9481	0.9865	0.9669
Dead	0.7500	0.4286	0.5455
		Accuracy	0.9383



SVM

	Precision	Recall	F1
Alive	0.9487	1.0000	0.9737
Dead	1.0000	0.4286	0.6000
		Accuracy	0.9506



RESULTS - 1 YEAR

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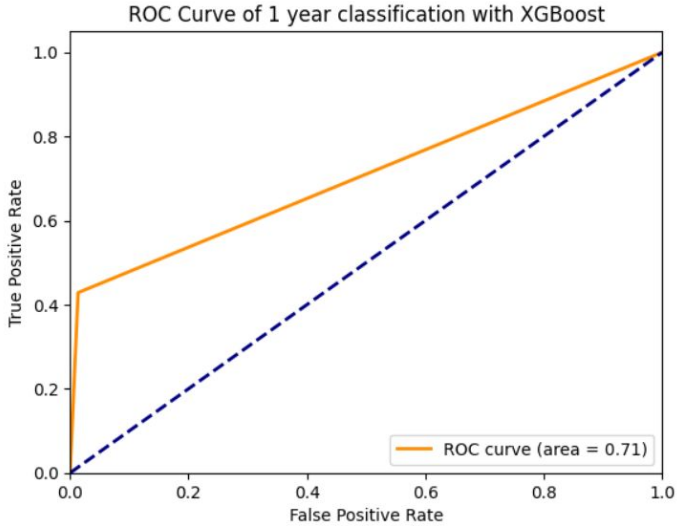

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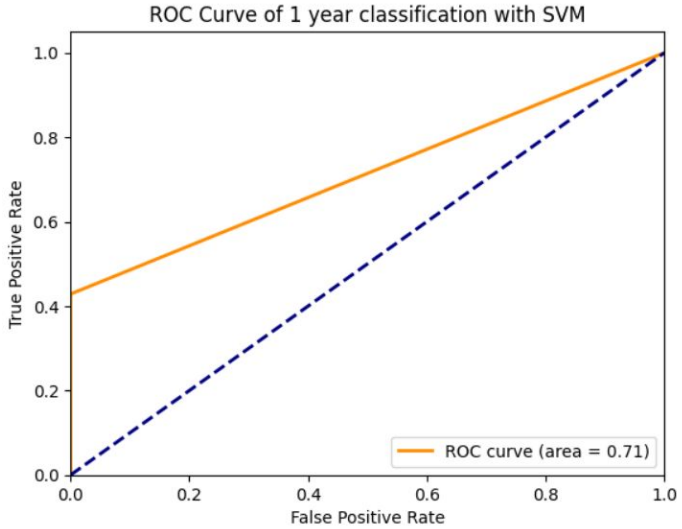

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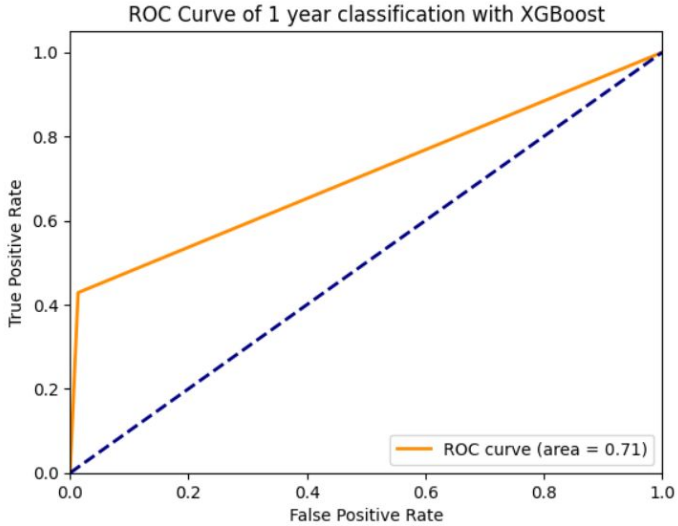
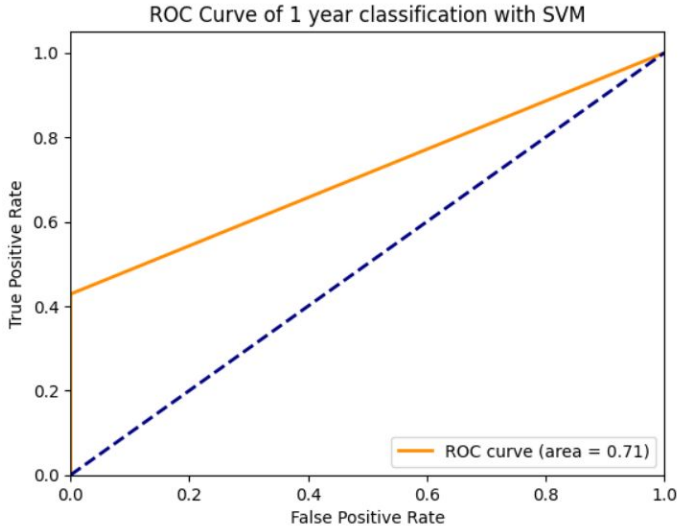


High accuracy expected, so we choose to focus on F1 score

SVM

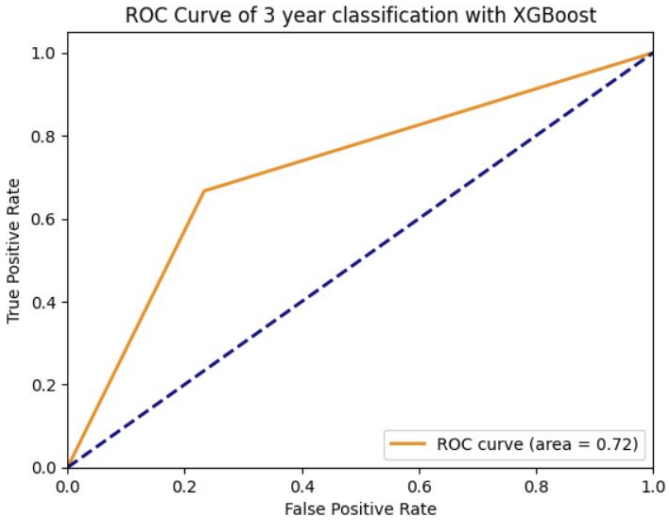
	Precision	Recall	F1
Alive	0.9487	1.0000	0.9737
Dead	1.0000	0.4286	0.6000
		Accuracy	0.9506



RESULTS - 3 YEAR

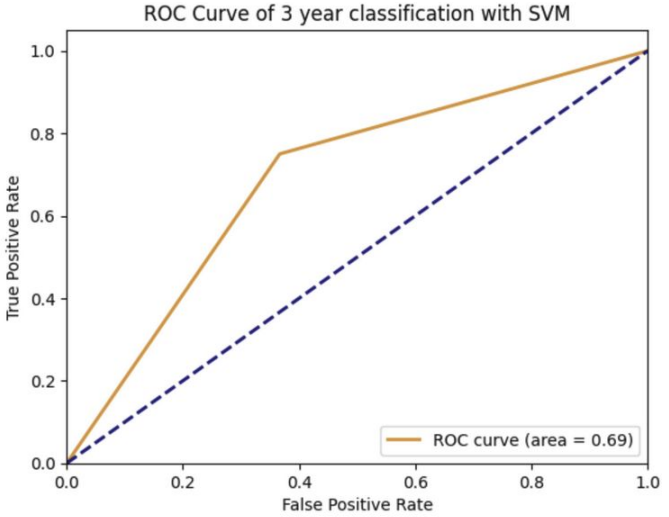
XGBoost

	Precision	Recall	F1
Alive	0.8148	0.7333	0.7719
Dead	0.4667	0.5833	0.5185
		Accuracy	0.6905



SVM

	Precision	Recall	F1
Alive	0.8696	0.6333	0.7308
Dead	0.4500	0.7500	0.5625
		Accuracy	0.6667



RESULTS - 3 YEAR

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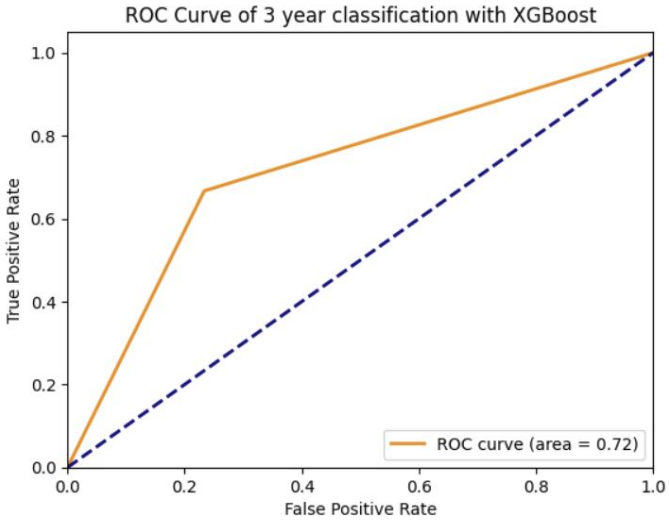

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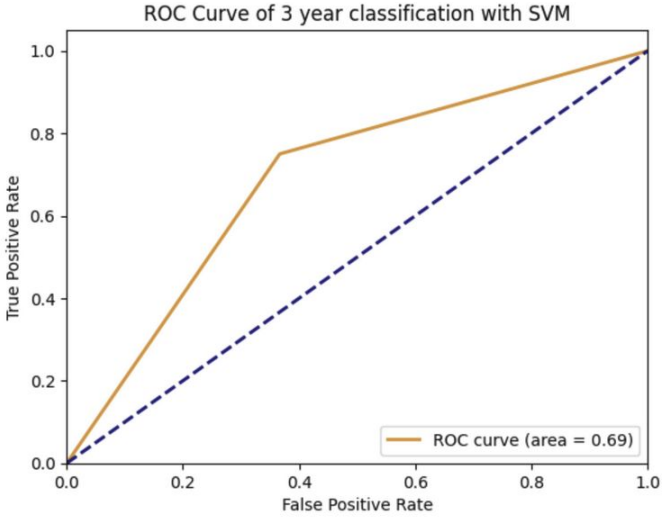
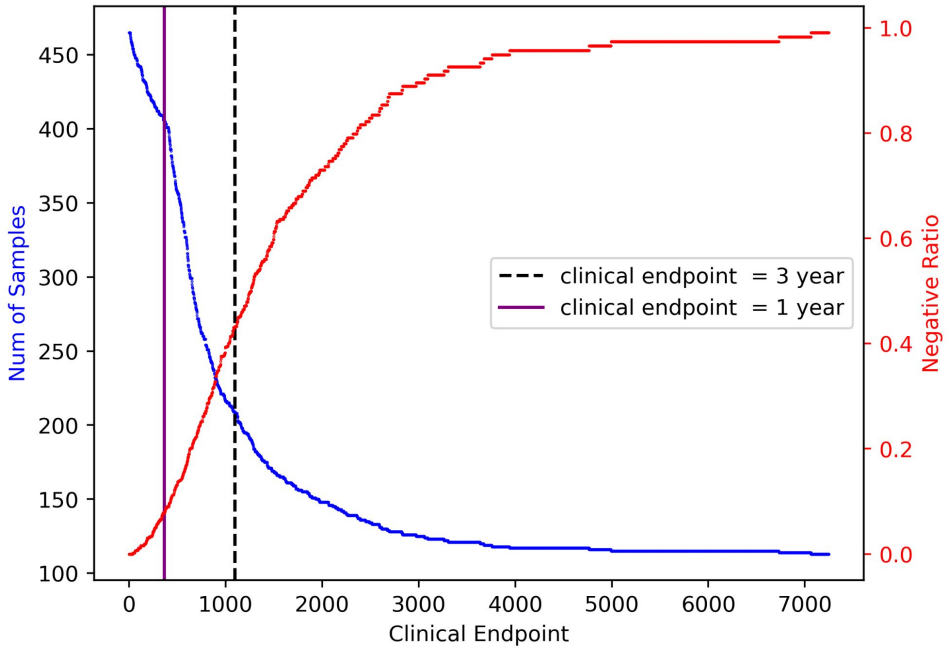


Discussion

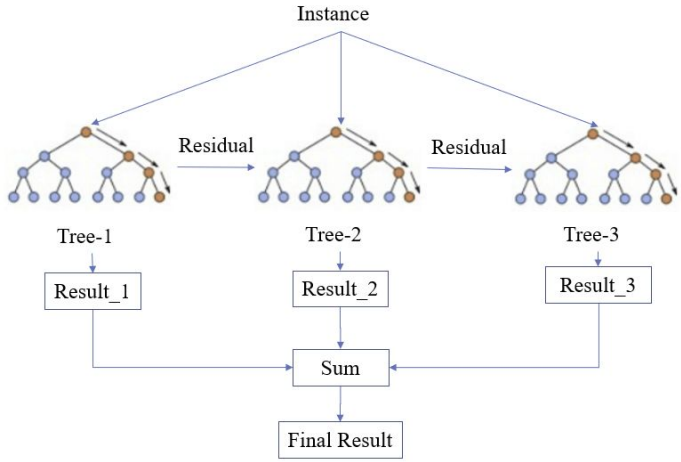
- Tradeoff between sample size and sample balance

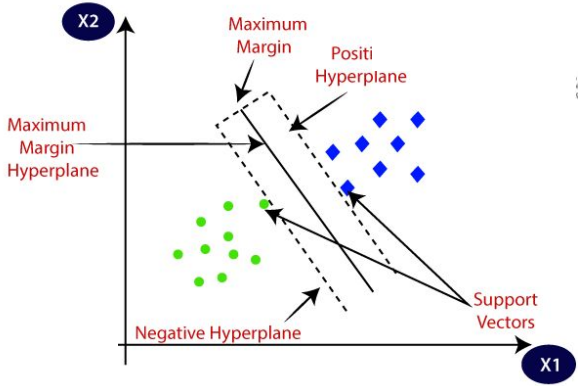


Discussion

- Trying different models
- Evaluation Metrics
  - Matthews Correlation Coefficient

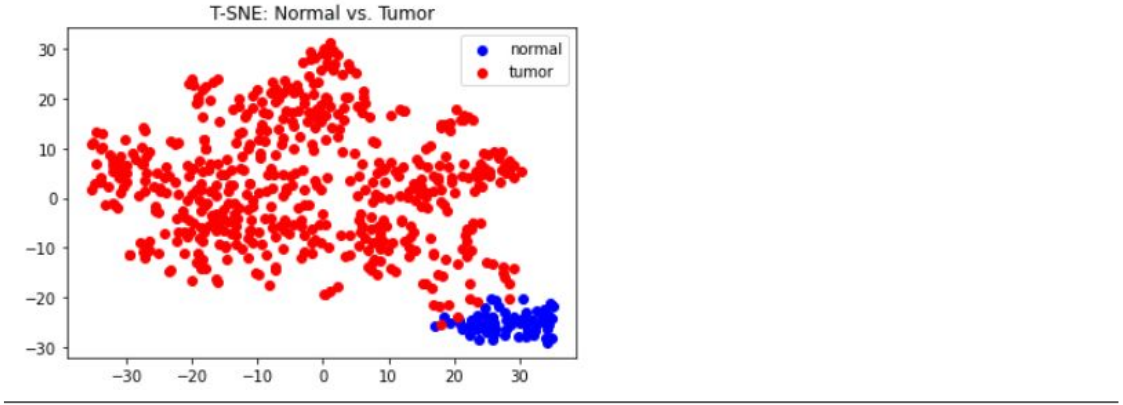
$$\mathrm{MCC} = \frac{\mathrm{TP} \times \mathrm{TN} - \mathrm{FP} \times \mathrm{FN}}{\sqrt{(\mathrm{TP}+\mathrm{FP})(\mathrm{TP}+\mathrm{FN})(\mathrm{TN}+\mathrm{FP})(\mathrm{TN}+\mathrm{FN})}}$$

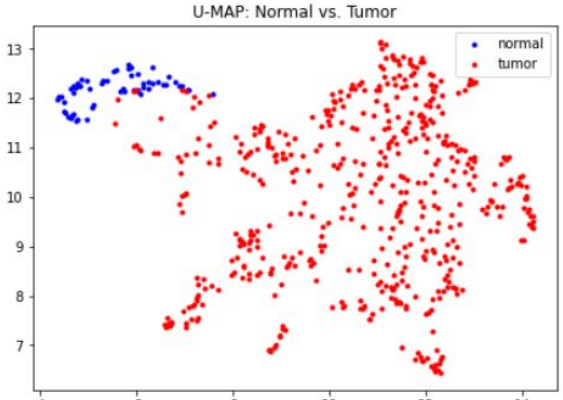




Discussion

- PCA, UMAP, t-SNE





Discussion

- Including mutation data
- Ran DESeq2 on training data vs. full

	patient_id	Hugo_Symbol	Entrez_Gene_Id	Center	NCBI_Build	Chromosome	Start_Position	End_Position	Strand	Variant_Classification
0	TCGA-05-4244	CPN1	0	.	GRCh37	10	101814119	101814119	+	Missense_Mutation
1	TCGA-05-4244	MKI67	0	.	GRCh37	10	129902901	129902901	+	Silent
2	TCGA-05-4244	NEBL	0	.	GRCh37	10	21104601	21104606	+	In_Frame_Del
3	TCGA-05-4244	RP11-445N18.7	0	.	GRCh37	10	45652518	45652518	+	RNA
4	TCGA-05-4244	ERCC6	0	.	GRCh37	10	50667200	50667200	+	Silent

THANK YOU!

- The coolest group, group 3