LIÈGE université
GIGA

# Towards an accurate cancer diagnosis modelization: Comparison of Random Forest strategies

Ahmed DEBIT

11/30/2018

# Laboratory Context

- Diagnosis of Breast Cancer
- Breast Cancer treatment response
- Design of signatures

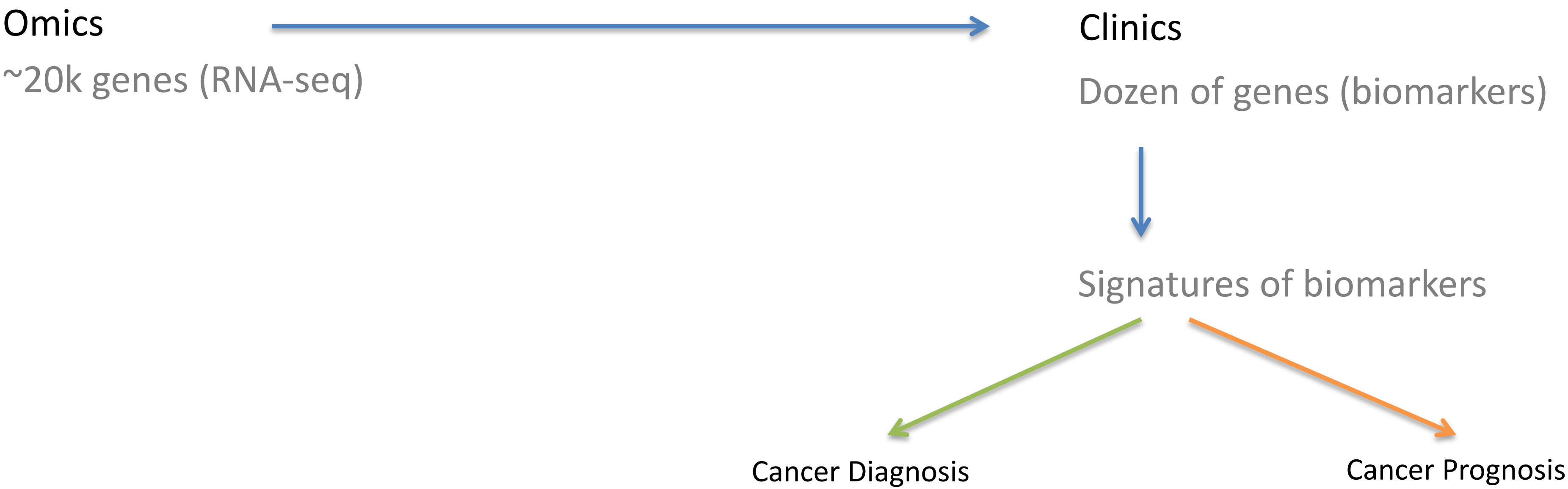
# From Omics to Clinics

Omics → Clinics

~20k genes (RNA-seq)

Dozen of genes (biomarkers)

# From Omics to Clinics



Omics

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Clinics

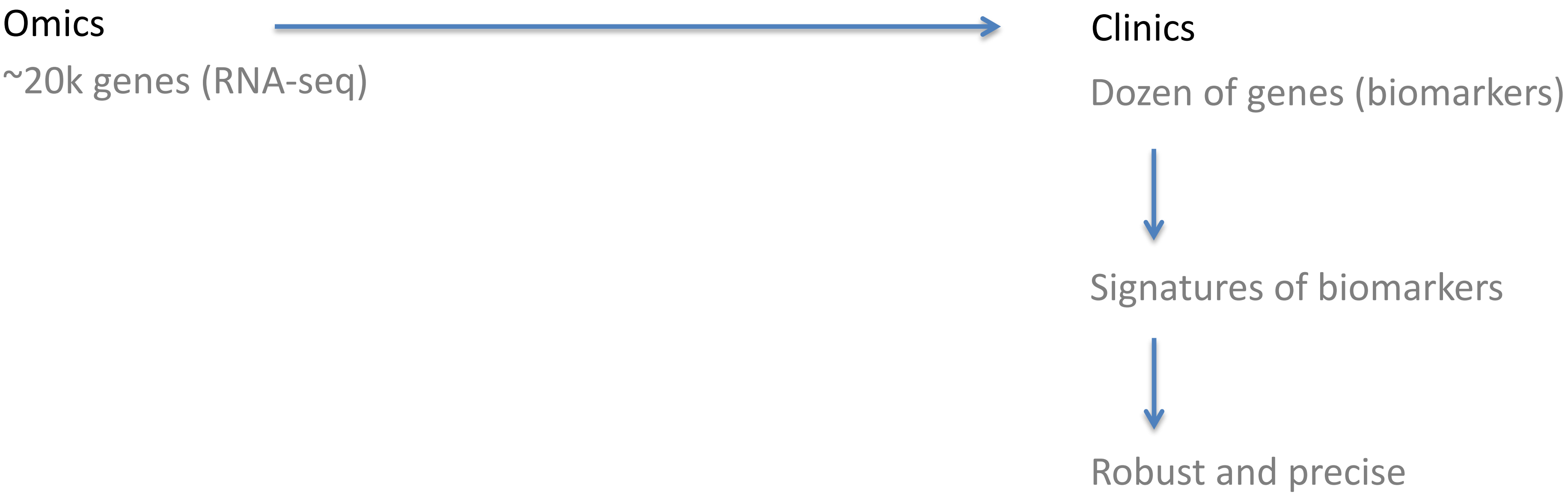
Dozen of genes (biomarkers)

Signatures of biomarkers

Cancer Diagnosis

Cancer Prognosis

# From Omics to Clinics



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Signatures of biomarkers

Robust and precise

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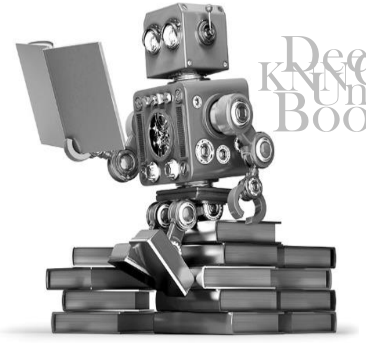

SVM

Deep Learning

KNN

Genetic Algorithm

Unsupervised Clustering

Boosting

Neural Networks

**Random Forest**

Signatures of biomarkers

Robust and precise
Models and signatures

# Random Forest

Omics

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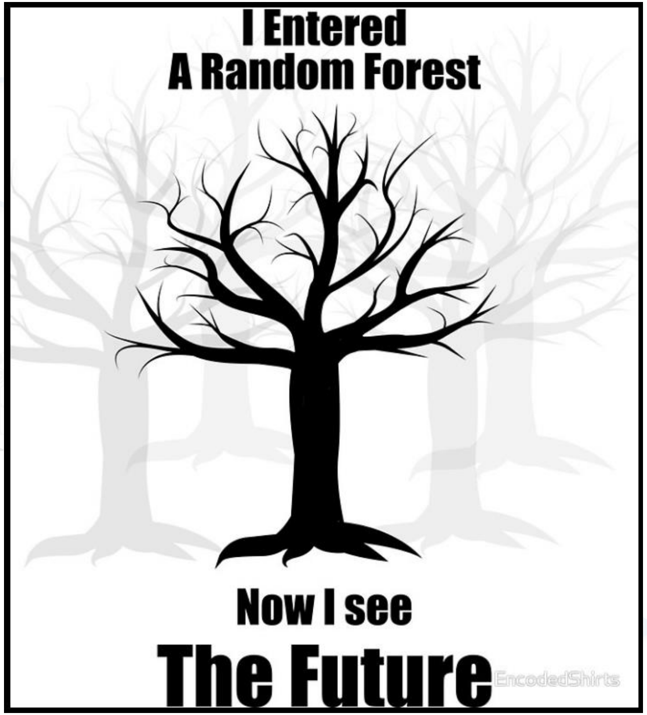

**Image source:** redbubble.com

Clinics

Dozen of genes (biomarkers)

Signatures of biomarkers

Robust and precise
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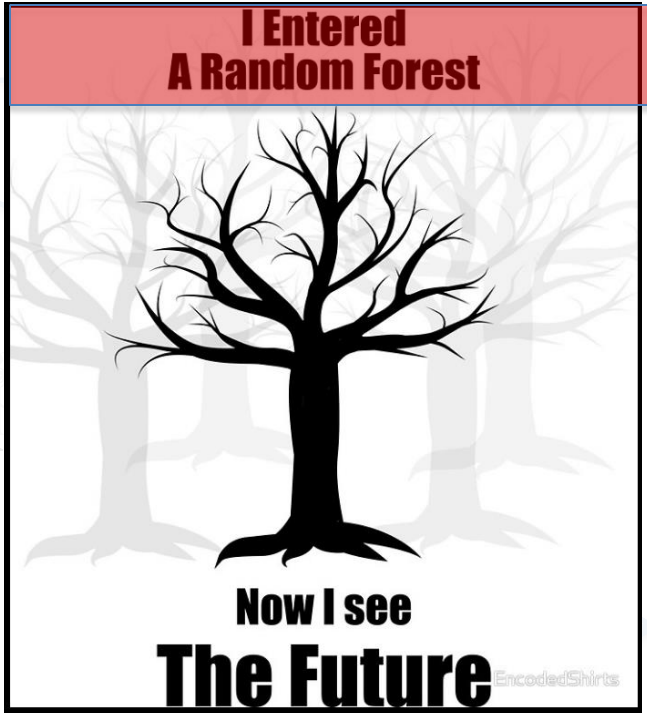

Training = modeling

**Image source:** redbubble.com

Clinics

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# Random Forest

Omics

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Training = modeling

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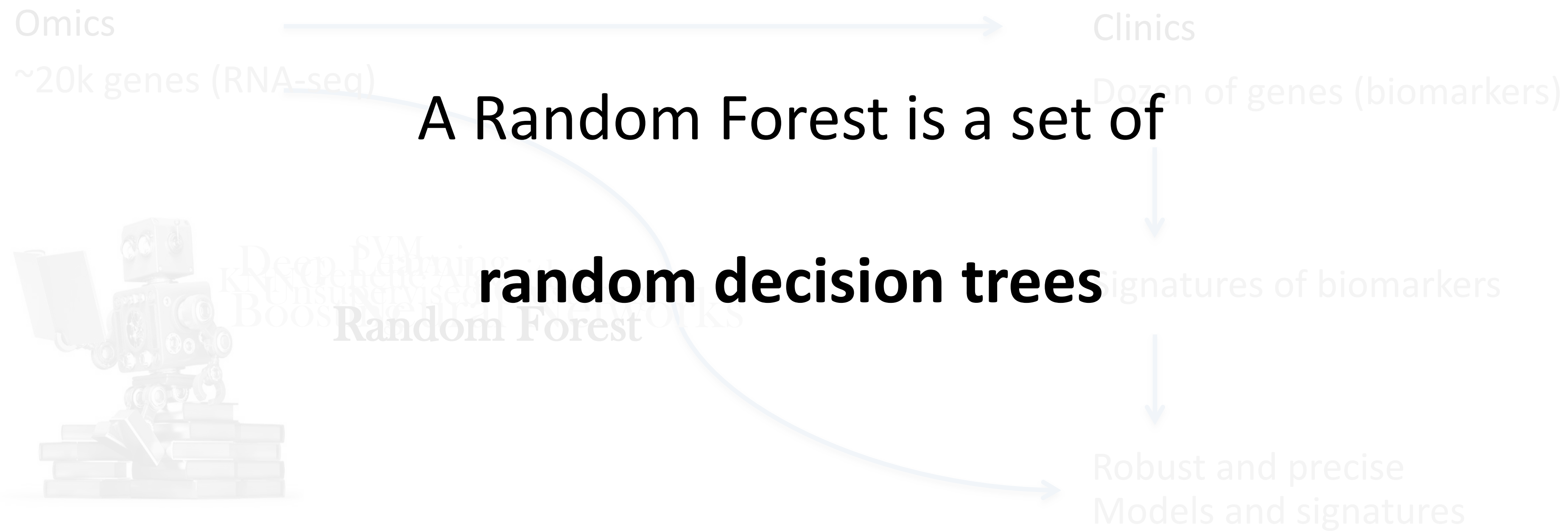
Robust and precise Models and signatures

Prediction

# Random Forest



A Random Forest is a set of

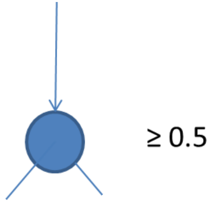
**random decision trees**

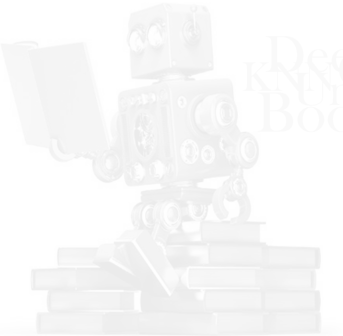
# A decision helps to stratify the data

Omics

~20k genes (RNA-seq)

es (biomarkers)





SVM
Deep Learning
KNN Genetic Algorithm
Unsupervised Cluste
Boosting Neural N
Random Fo

narkers

e
Models and signatures

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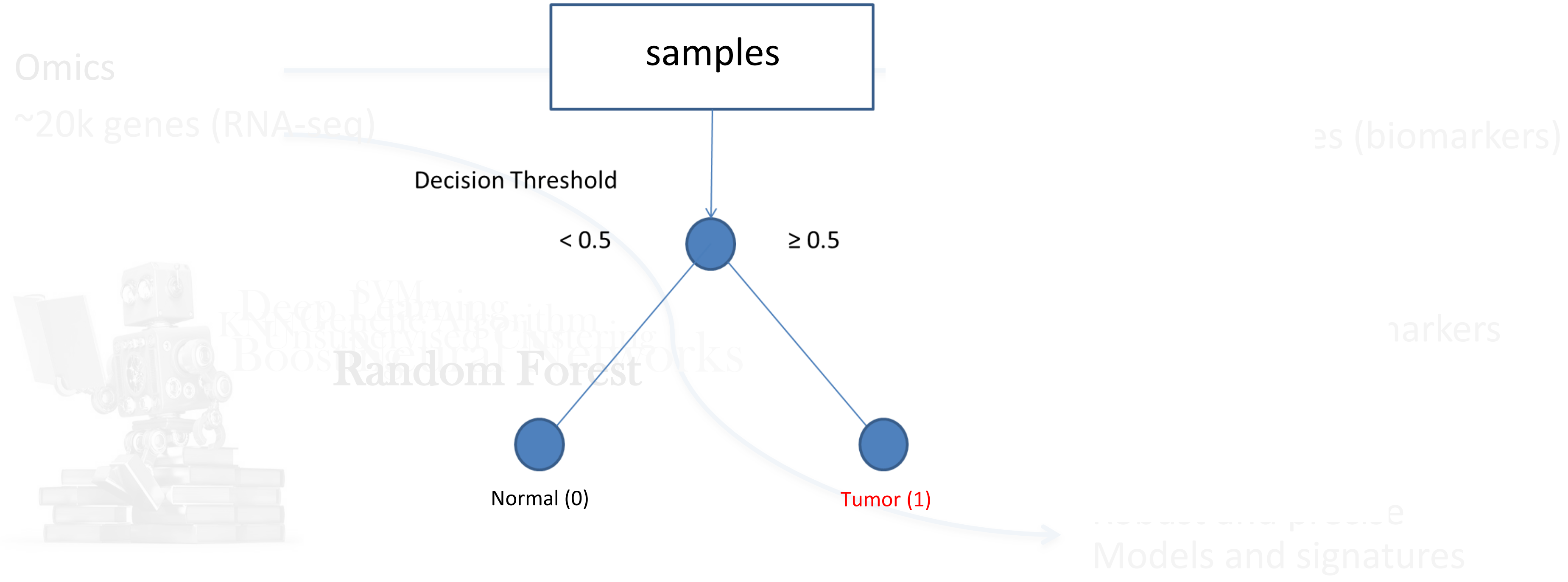


samples

Decision Threshold

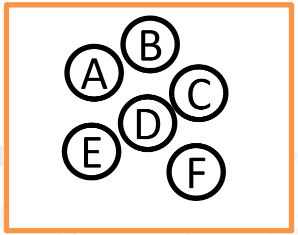
< 0.5

≥ 0.5

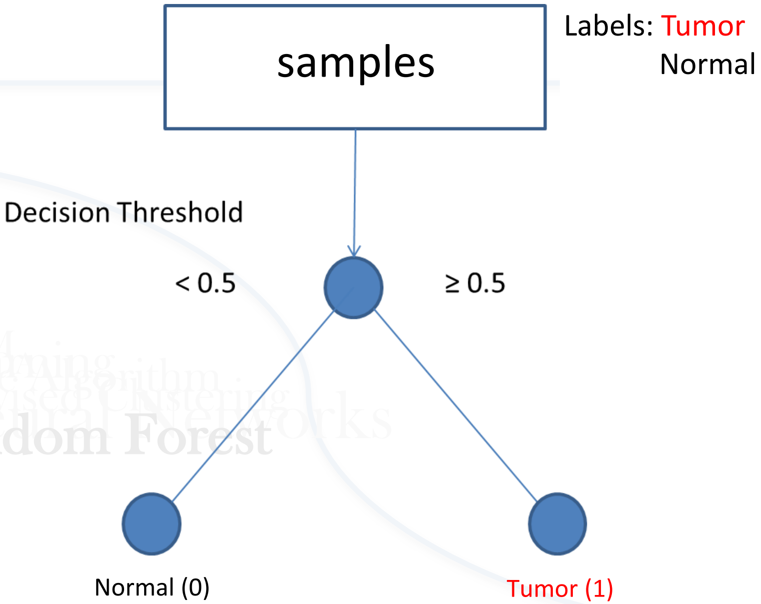
Normal (0)

Tumor (1)

# A decision helps to stratify the data



**Set of genes**



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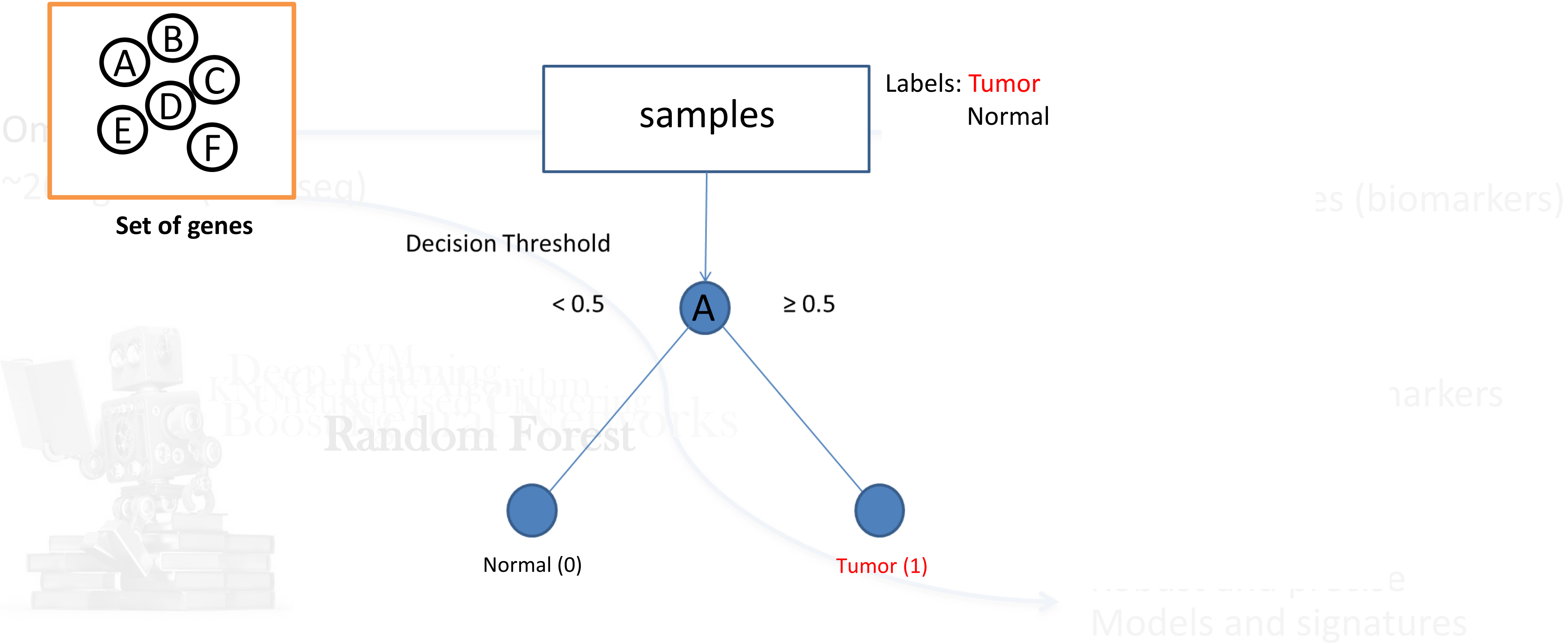

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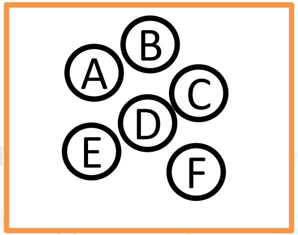

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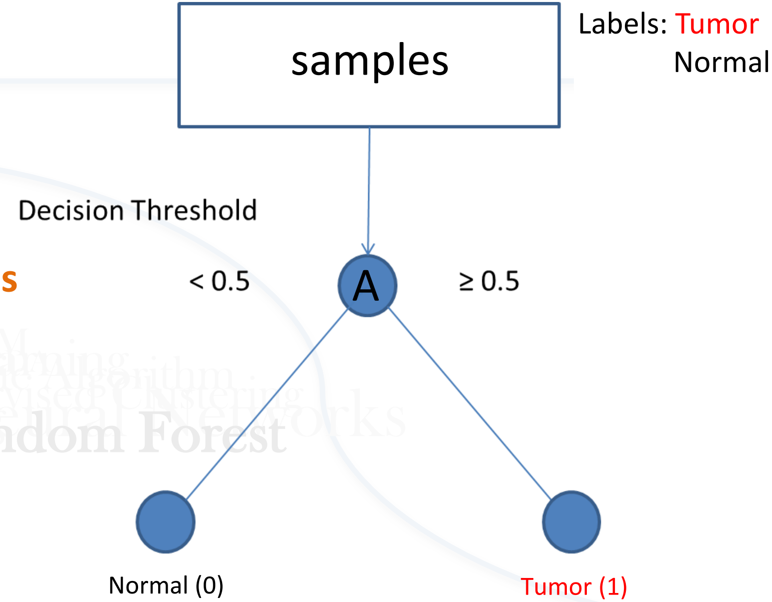
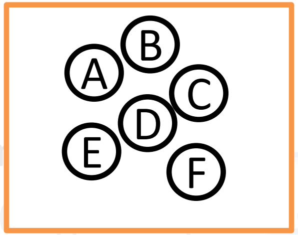


**Ability to discriminate groups of samples ➔ Importance**

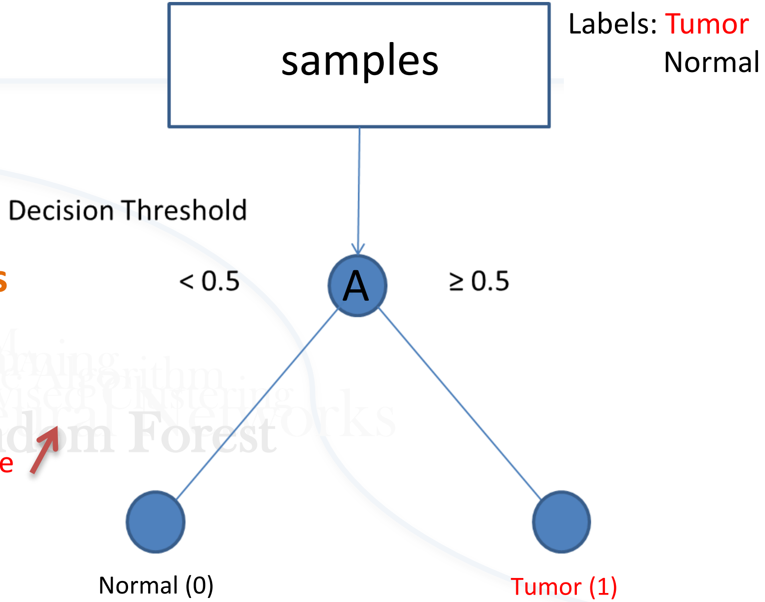
# A decision helps to stratify the data



**Set of genes**

**Ability to discriminate groups of samples ➔ Importance**

discriminative power ↗ ➔ importance ↗



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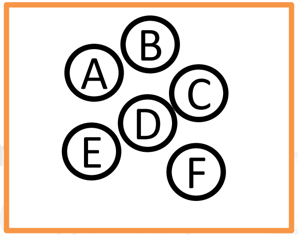
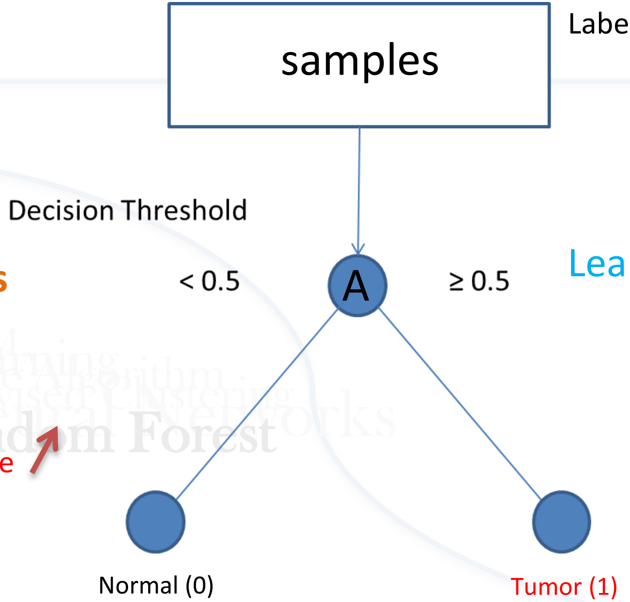


**Set of genes**



Labels: Tumor
Normal

Learning (training) process

Clinics

Dozen of genes (biomarkers)

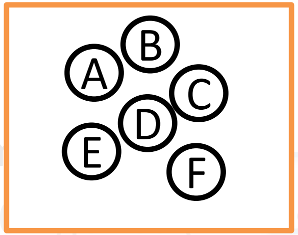
Signatures of biomarkers

Robust and precise
Models and signatures

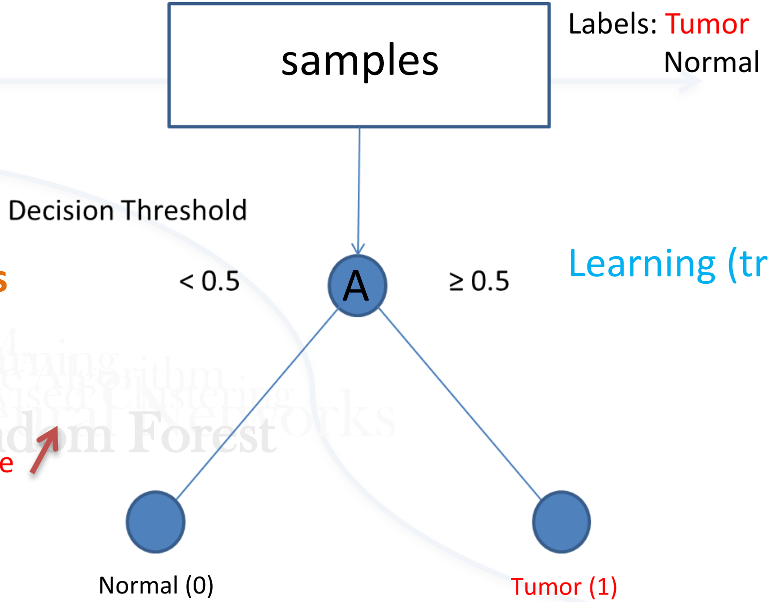
**Ability to discriminate groups of samples ➔ Importance**

discriminative power ↗ ➔ importance ↗

# A decision helps to stratify the data



Set of genes



Learning (training) process

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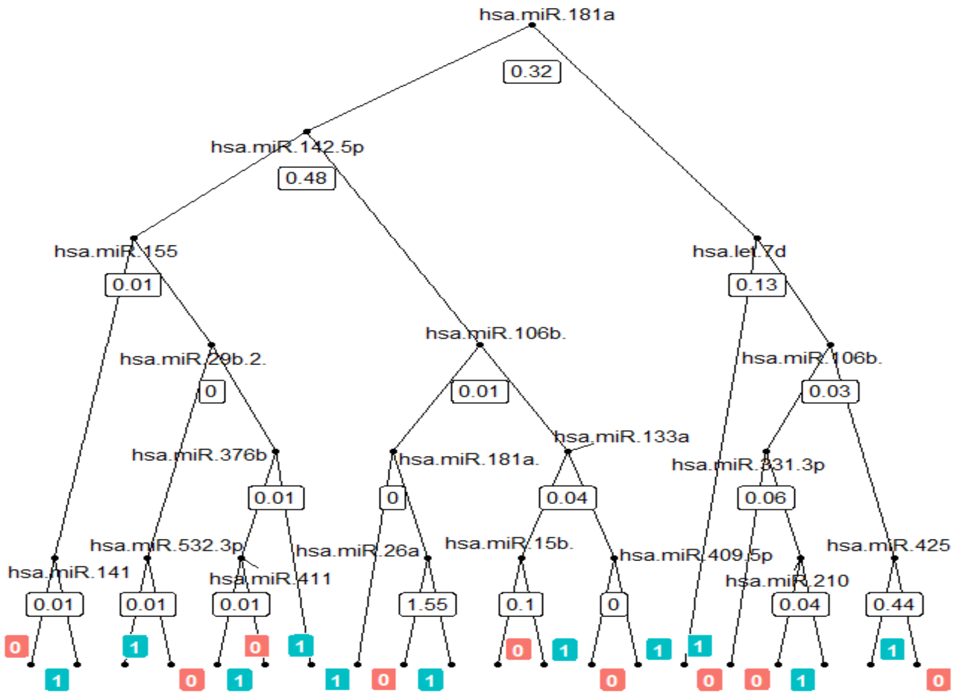
**Ability to discriminate groups of samples ➔ Importance**

discriminative power ↗ ➔ importance ↗

Random Forest

1 tree = Multiple decisions

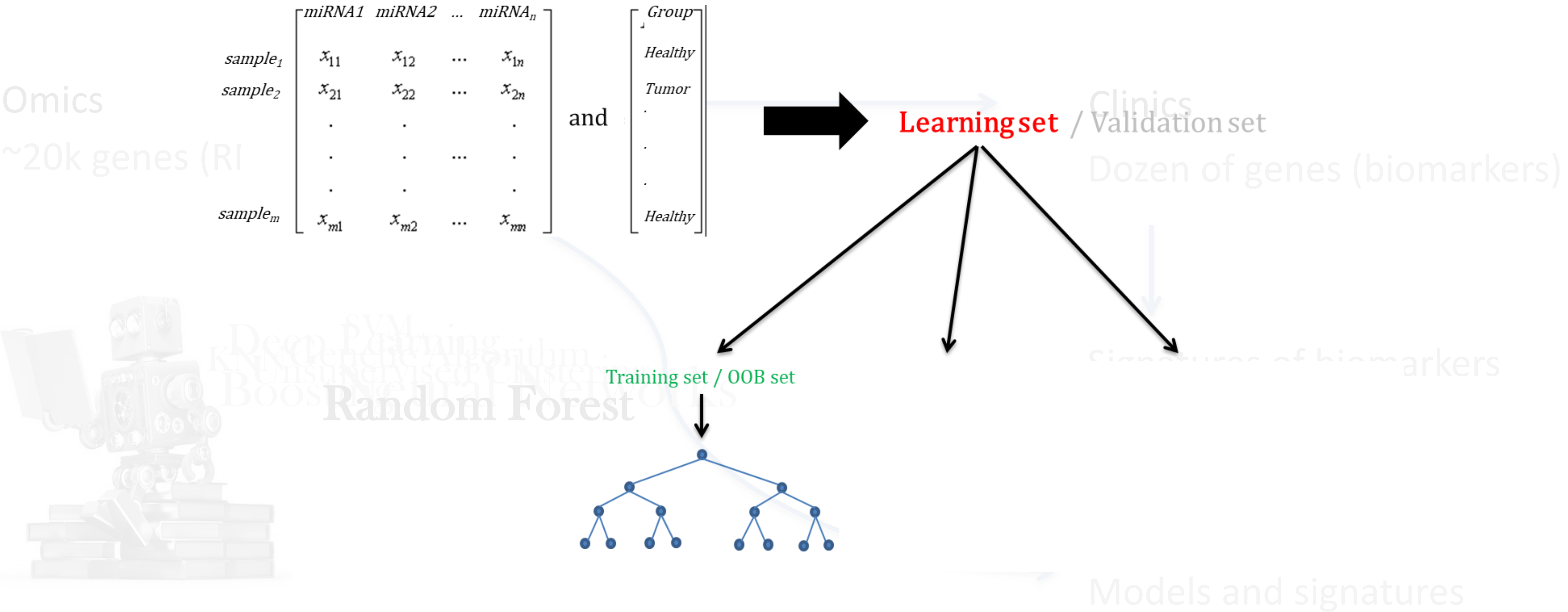
# Decision tree (real example)



Healthy: 0
Tumor: 1

1 tree = Multiple decisions

# Random Forest is a set of random trees

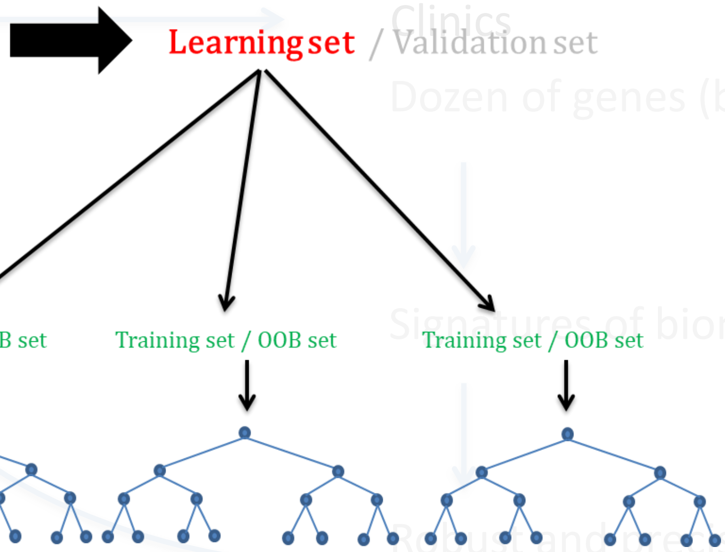


$$\begin{array}{c} \\ sample_1 \\ sample_2 \\ \\ \\ \\ sample_m \end{array} \begin{bmatrix} miRNA1 & miRNA2 & \dots & miRNA_n \\ x_{11} & x_{12} & \cdots & x_{1n} \\ x_{21} & x_{22} & \cdots & x_{2n} \\ . & . & & . \\ . & . & \cdots & . \\ . & . & & . \\ x_{m1} & x_{m2} & \cdots & x_{mn} \end{bmatrix} \text{ and } \begin{bmatrix} Group \\ Healthy \\ Tumor \\ . \\ . \\ . \\ Healthy \end{bmatrix}$$

1 Forest = Multiple trees

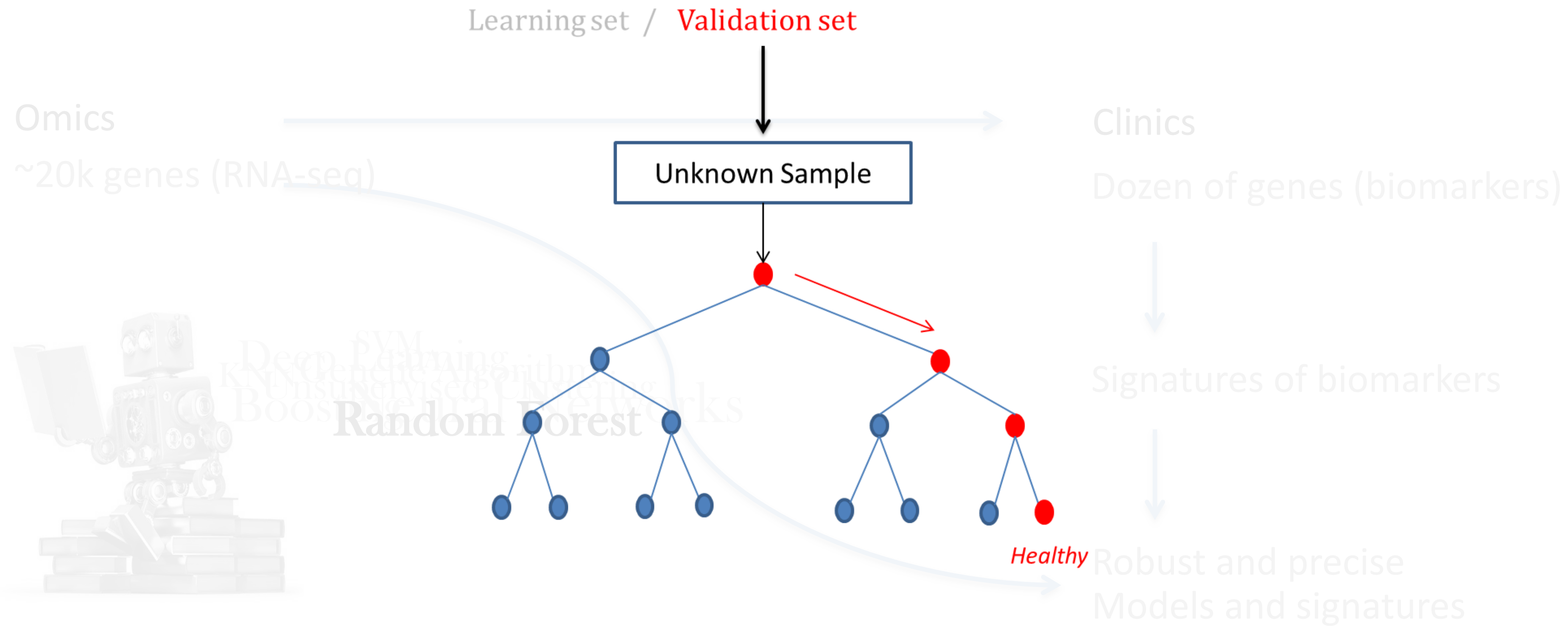
# Random Forest is a set of random trees

$$\begin{array}{c|cccc|} & miRNA1 & miRNA2 & \ldots & miRNA_n \\ sample_1 & x_{11} & x_{12} & \cdots & x_{1n} \\ sample_2 & x_{21} & x_{22} & \cdots & x_{2n} \\ & . & . & & . \\ & . & . & \cdots & . \\ & . & . & & . \\ sample_m & x_{m1} & x_{m2} & \cdots & x_{mn} \end{array} \quad \text{and} \quad \begin{bmatrix} Group \\ Healthy \\ Tumor \\ . \\ . \\ . \\ Healthy \end{bmatrix}$$



1 Forest = Multiple trees

# Prediction procedure



**One Tree prediction procedure**

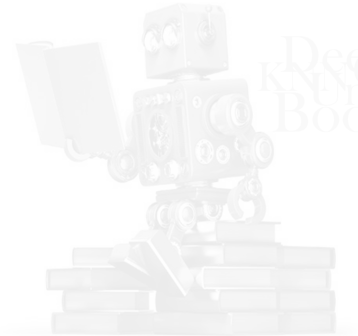
# Prediction procedure

Omics

~20k genes (RNA-seq)

Clinics

Dozen of genes (biomarkers)



SVM

Deep Learning

KNN

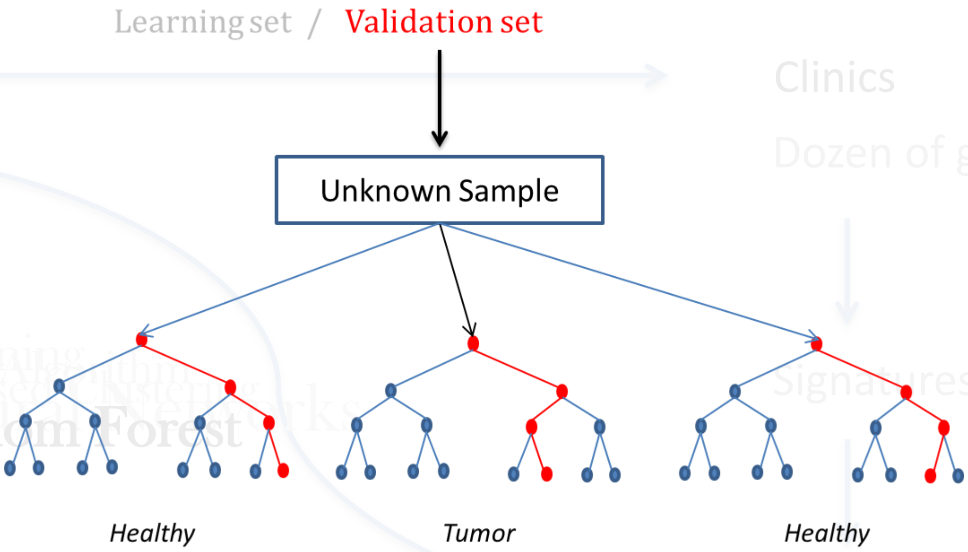
Genetic Algorithm

Unsupervised clustering

Boosting

Neural Networks

Random Forest



Signatures of biomarkers

Robust and precise
Models and signatures

**Multiple Trees prediction procedure**

# Prediction procedure

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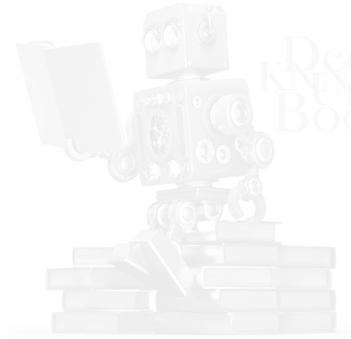

Deep Learning

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Genetic Algorithm

Unsupervised

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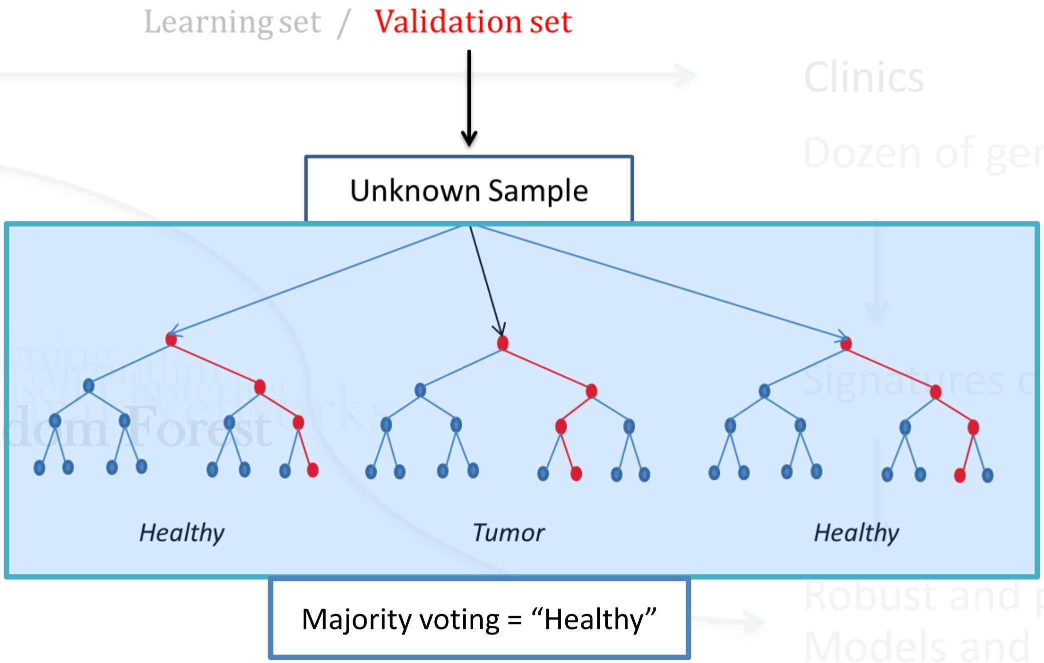
Random Forest



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**1 Forest = 1 Model**

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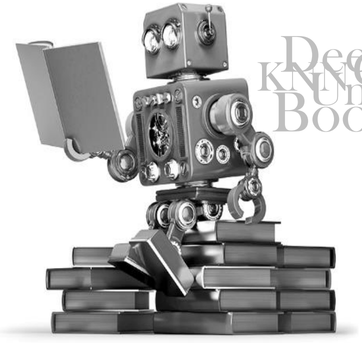

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Deep Learning
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Boosting Neural Networks

**Random Forest**

**R** implementation**s** of
Random Forest algorithm
proposed by *[Breiman et al. 2001]*

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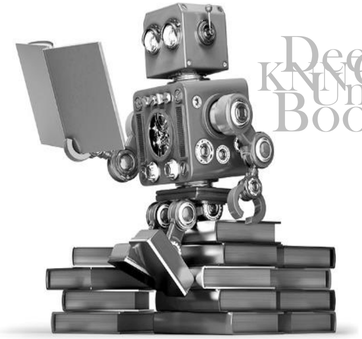
Models and signatures ???



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**R** implementation**s** of
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# Objectives

**Toward a robust RF method for the Biological question asked**

Which method is suitable for which dataset (platform/technology) ?

# Objectives

- Empirical comparison of random forest based methods
- Differences/Similarities of RF methods ➔ groups of methods
- Designing a high stability score to rank RF methods

**Toward a robust RF method for the Biological question asked**

Which method is suitable for which dataset (platform/technology) ?

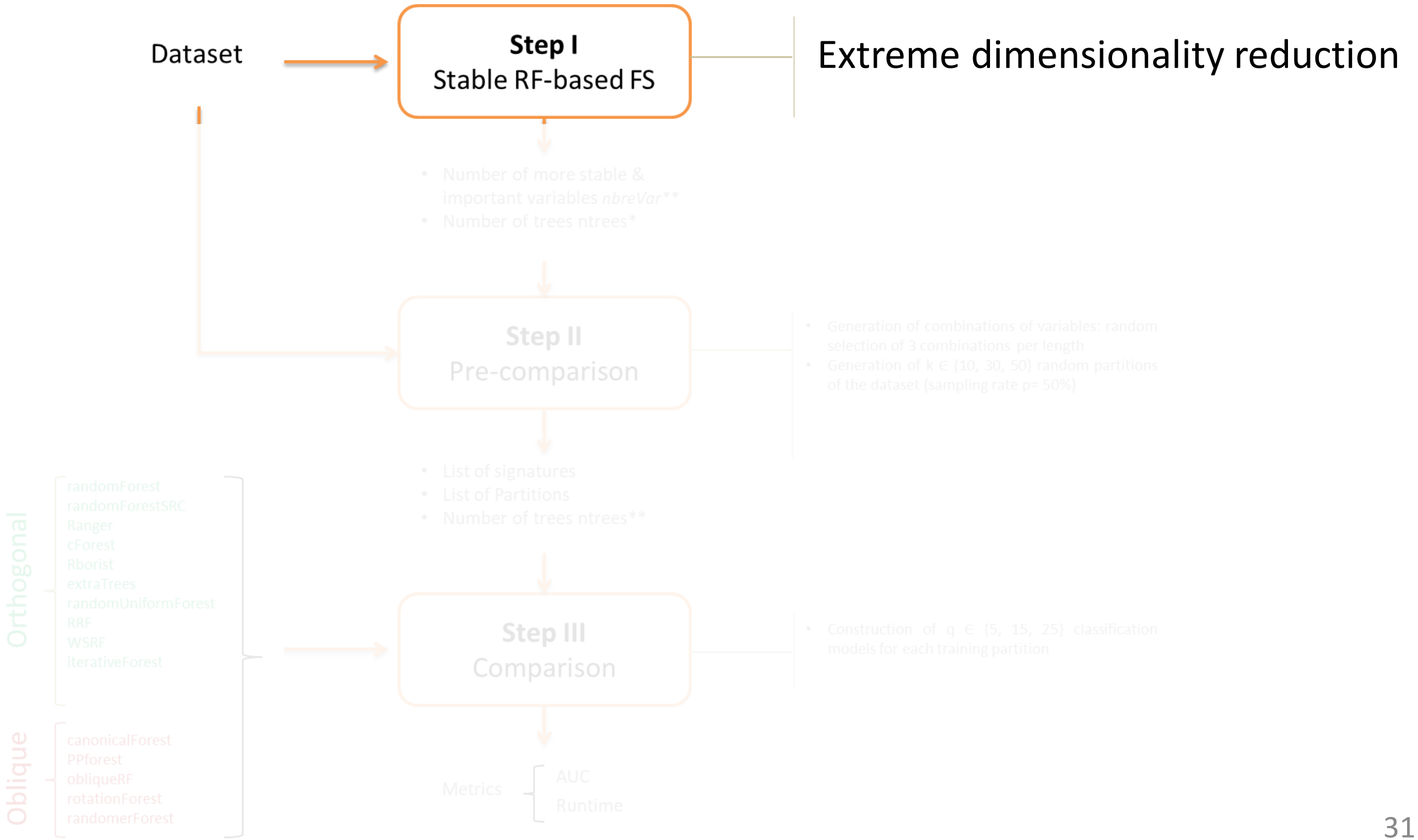
# Materials and Methods

- **Datasets (Perfectly balanced)**
  - TCGA-BRCA (RPKM): 182 samples x 9560 genes
  - TCGA-LUSC (RPKM): 96 samples x 9262 genes
  - TCGA-THCA (RPKM): 98 samples x 9353 genes

- **Main classification question**

The difference between paired **Tumor / Normal** samples will be used as a **strong classification** parameter, allowing for **strong** modeling only

# Overview of the method



Dataset

**Step I**
Stable RF-based FS

Extreme dimensionality reduction

- Number of more stable & important variables *nbreVar***
- Number of trees ntrees*

**Step II**
Pre-comparison

- Generation of combinations of variables: random selection of 3 combinations per length
- Generation of k ∈ {10, 30, 50} random partitions of the dataset (sampling rate p= 50%)

- List of signatures
- List of Partitions
- Number of trees ntrees**

Orthogonal

randomForest
randomForestSRC
Ranger
cForest
Rborist
extraTrees
randomUniformForest
RRF
WSRF
iterativeForest

Oblique

canonicalForest
PPforest
obliqueRF
rotationForest
randomerForest

**Step III**
Comparison

- Construction of q ∈ {5, 15, 25} classification models for each training partition

Metrics

AUC
Runtime

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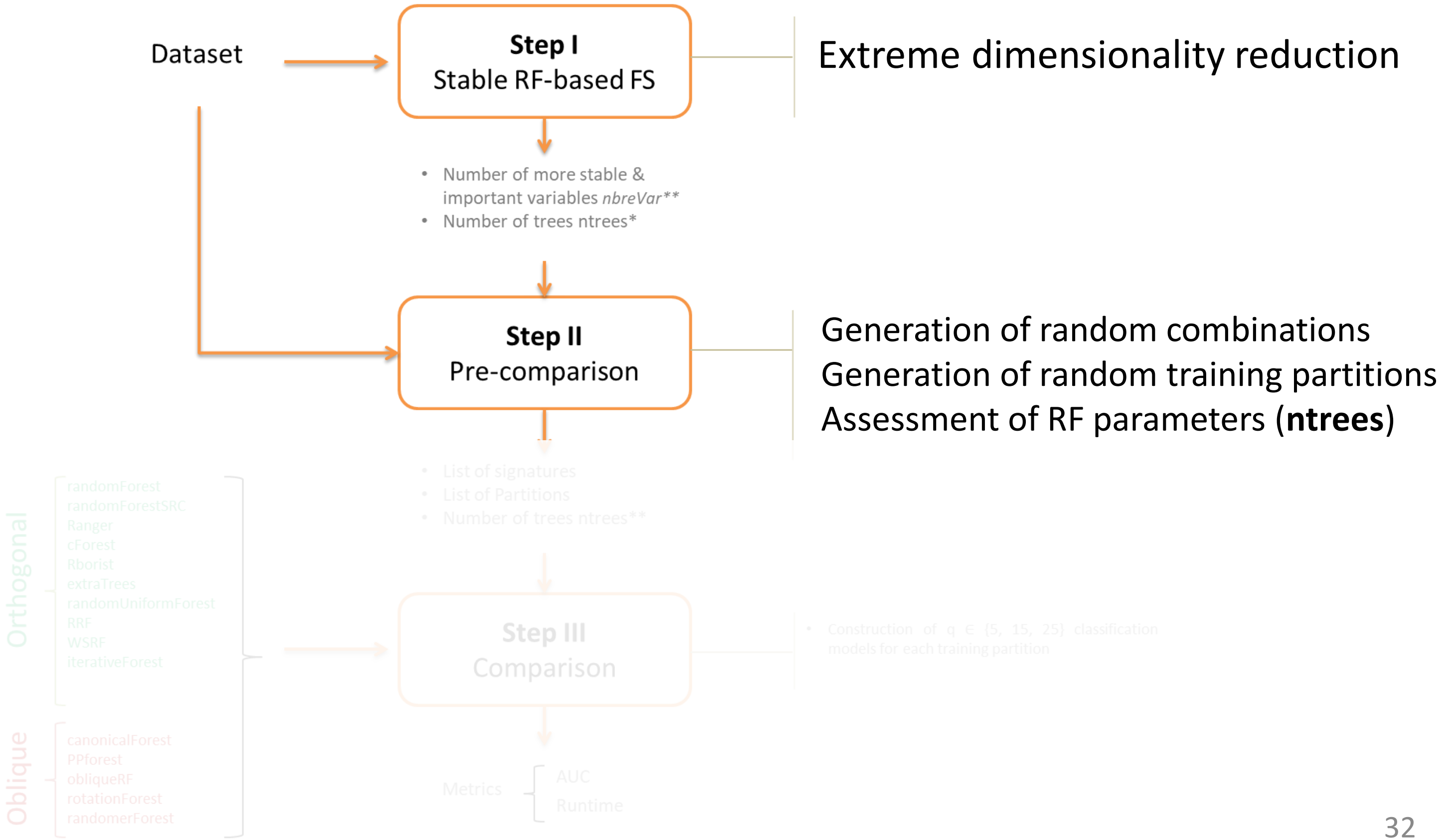

Dataset

**Step I**
Stable RF-based FS

- Number of more stable & important variables *nbreVar***
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Extreme dimensionality reduction

**Step II**
Pre-comparison

Generation of random combinations
Generation of random training partitions
Assessment of RF parameters (**ntrees**)

- List of signatures
- List of Partitions
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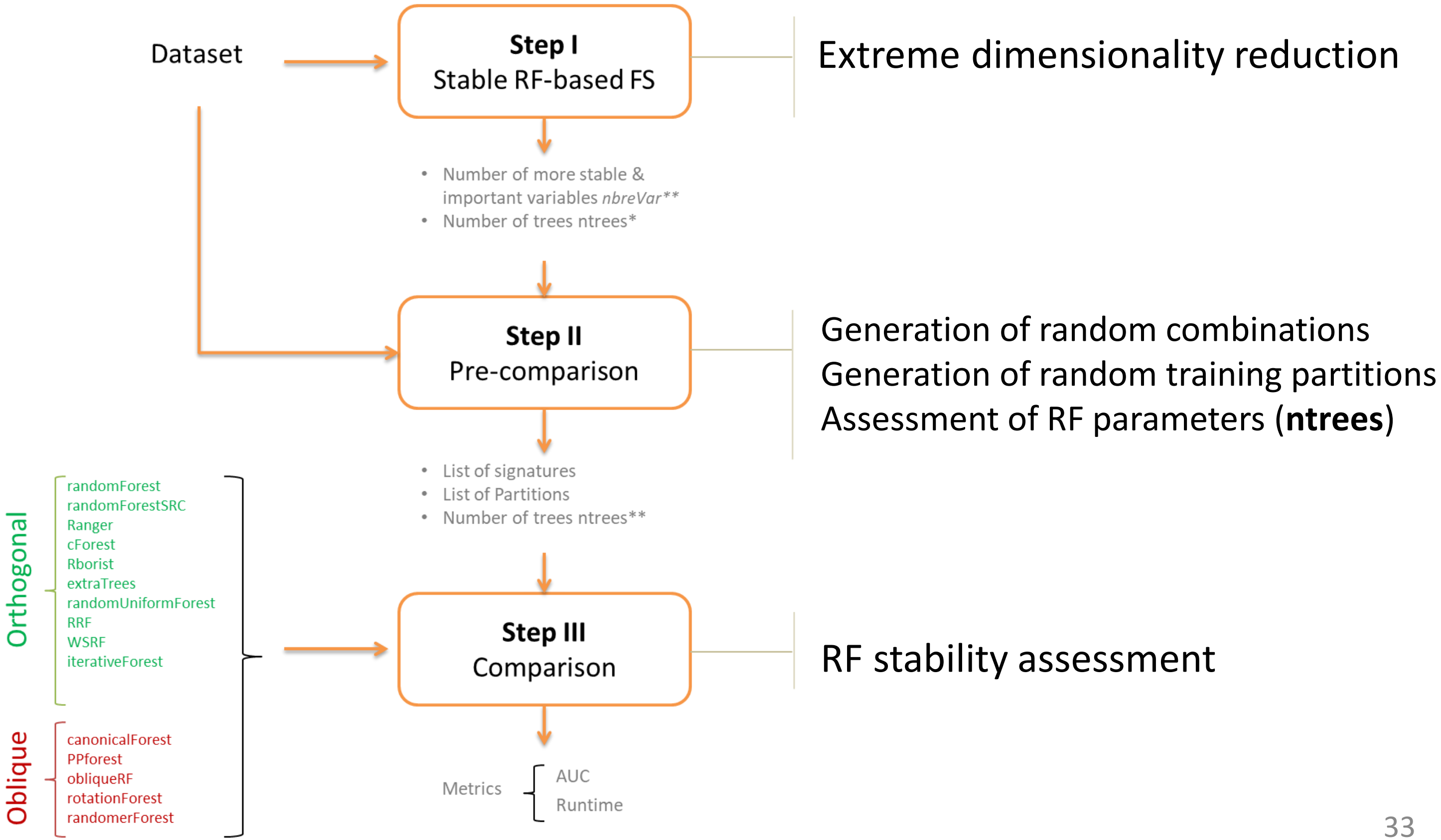

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randomerForest

**Step III**
Comparison

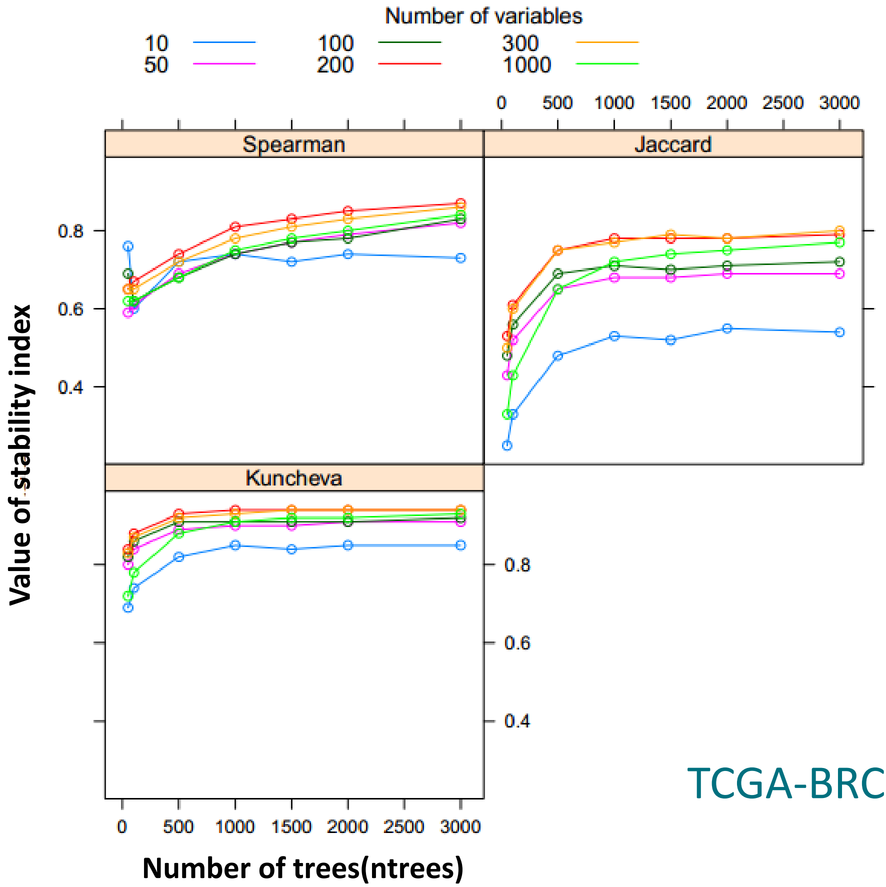
RF stability assessment

Metrics
AUC
Runtime

# Stable Feature Selection

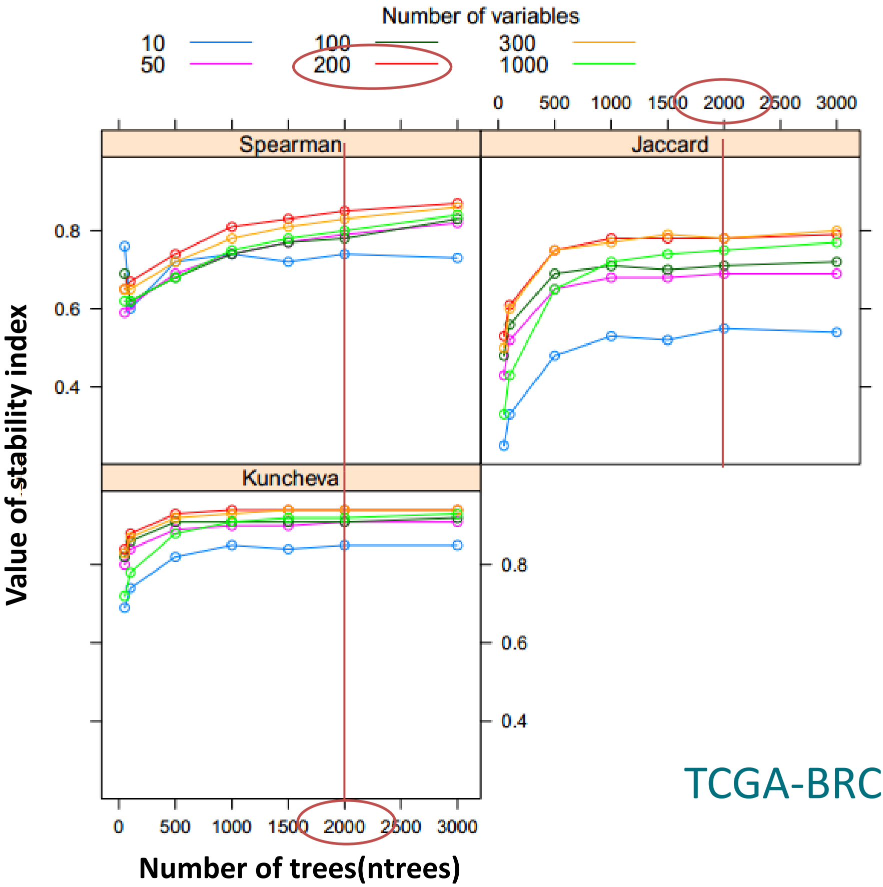
Extreme Dimensionality reduction

# First pass Feature Selection  results



TCGA-BRCA dataset

# First pass Feature Selection  results

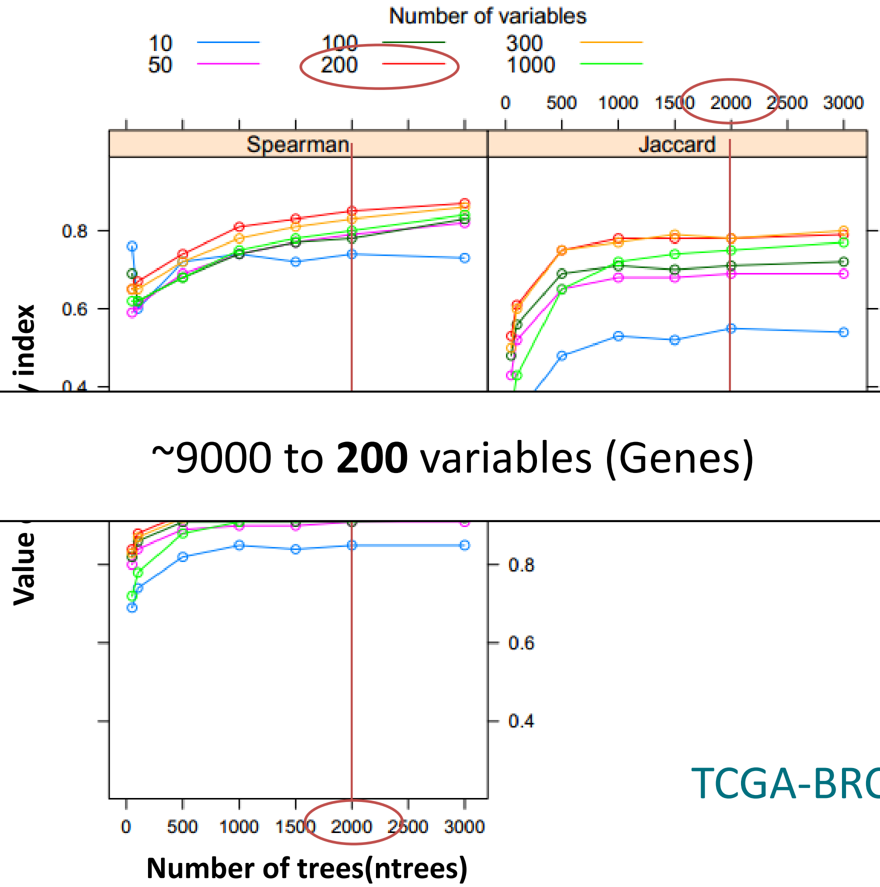


$ntrees^*$ = 2000

$nVar^*$ = 200

TCGA-BRCA dataset

# First pass Feature Selection  results



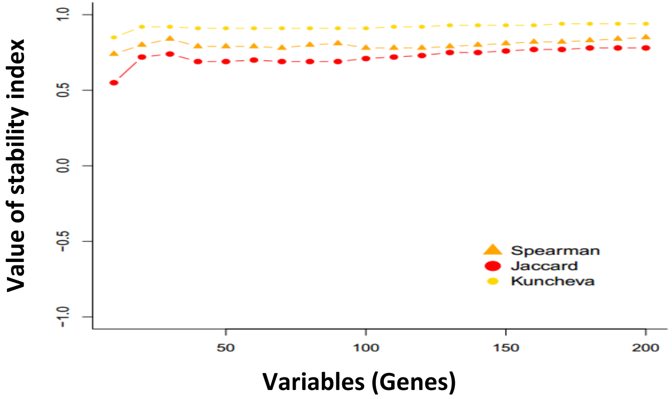
~9000 to **200** variables (Genes)

$ntrees^*$ = 2000

$nVar^*$ = 200

TCGA-BRCA dataset

# Second pass Feature Selection results



TCGA-BRCA dataset

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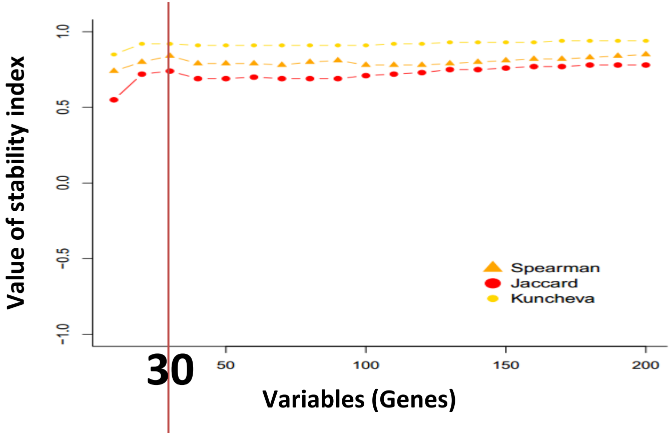
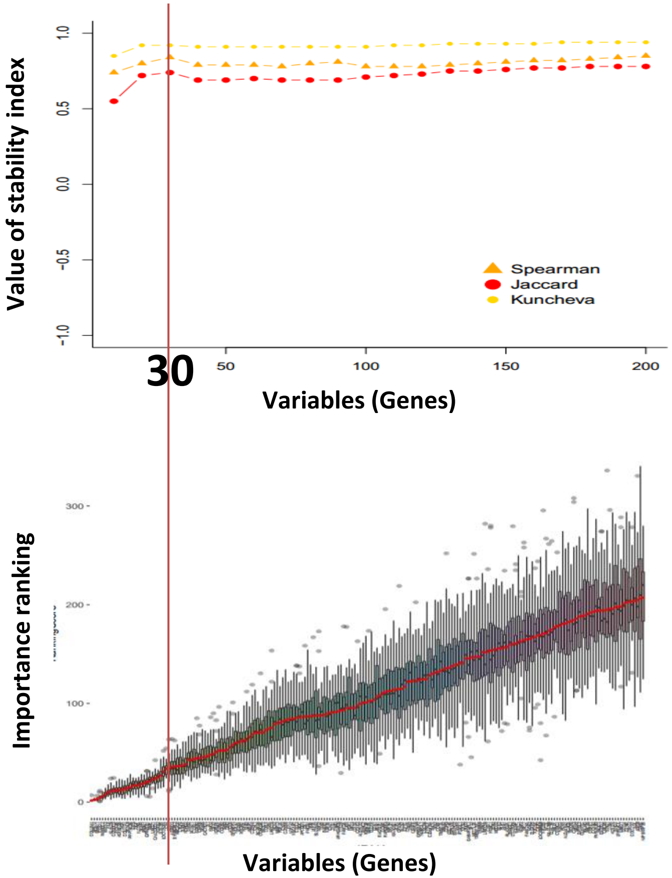


$$nVar^{**} = 30$$

TCGA-BRCA dataset

# Second pass Feature Selection results



$$nVar^{**} = 30$$

TCGA-BRCA dataset

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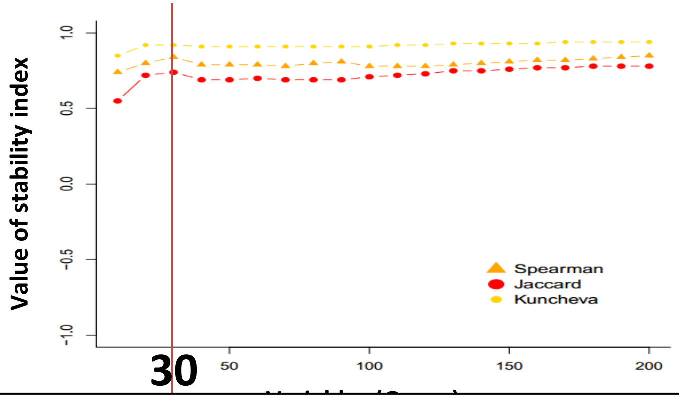
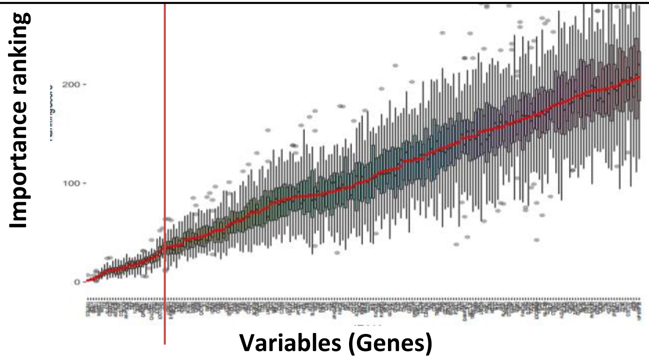


30

$$nVar^{**} = 30$$

~200 to **30** variables (Genes)



TCGA-BRCA dataset

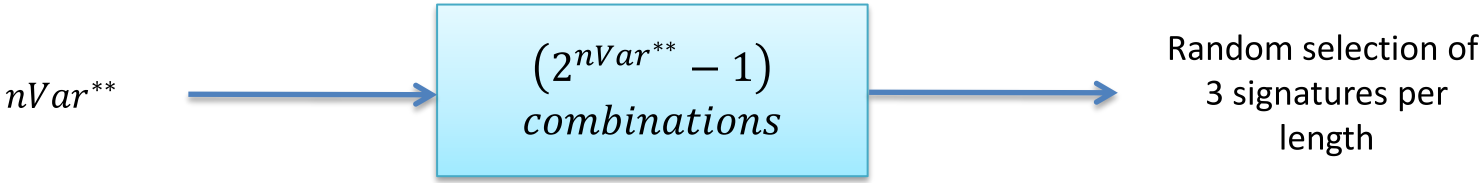
# Pre-Comparison

Assessment of RF parameters & Generation of random combinations

# Pre-comparison

## I- Generation of random combinations (Cancer signatures)

- Multiple predictive models using combinations of different lengths



$nVar^{**}$

$(2^{nVar^{**}} - 1)$ $combinations$

Random selection of 3 signatures per length

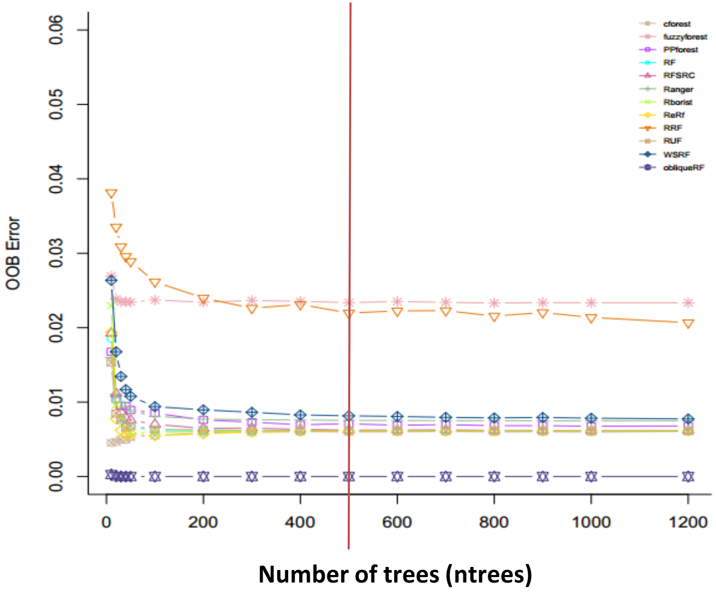
## II- Generation of random training partitions

- 50 random training partitions

training partition = a set of samples used to construct a model

# Pre-comparison

## III- Tuning the parameter $ntrees$ for each RF method



TCGA-BRCA dataset

# Pre-comparison

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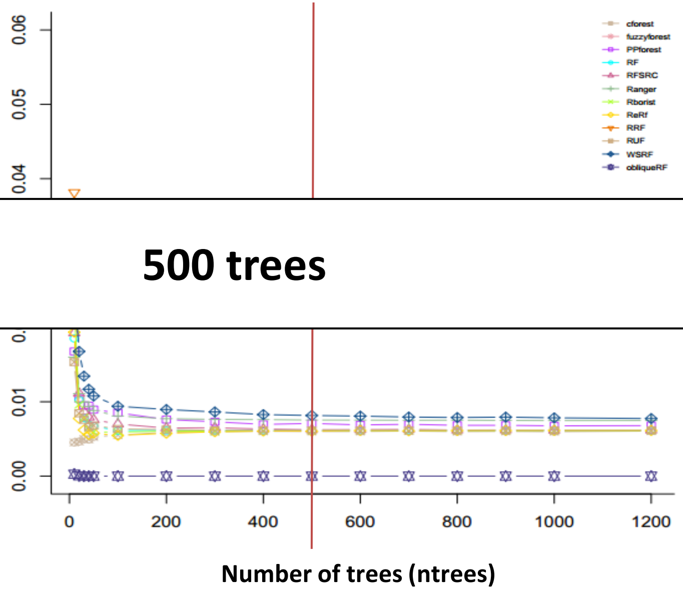


**500 trees**

TCGA-BRCA dataset

# Summary of step I + step II

| Dataset | $nVar$ | $nVar^{*}$ | $nVar^{**}$ | $ntrees^{*}$ | $ntrees^{**}$ | Nbre combinations |
|---|---|---|---|---|---|---|
| **TCGA-BRCA** | 9560 | 200 | 30 | 2000 | 500 | 78 |
| **TCGA-LUSC** | 9262 | 200 | 10 | 2000 | 500 | 21 |
| **TCGA-THCA** | 9353 | 200 | 40 | 2000 | 500 | 108 |

# Comparison

Random Forest stability assessment

# Random Forest Method Comparison

- Comparison of RF methods under perfect conditions
- Using **same** random training partitions
- Assessing the **same** signatures
- On computational cores of **same** characteristics

# Random Forest Method Comparison

- For each signature, we'll focus on:
    - **50 resampling** to build the Training and the Validation set.
    - **25 modeling and validations.**

- Analysis of:
    - **Coefficient of Variation of 1,250 models & AUCs**

**1,250 models & AUCs**

# Random Forest Method Comparison

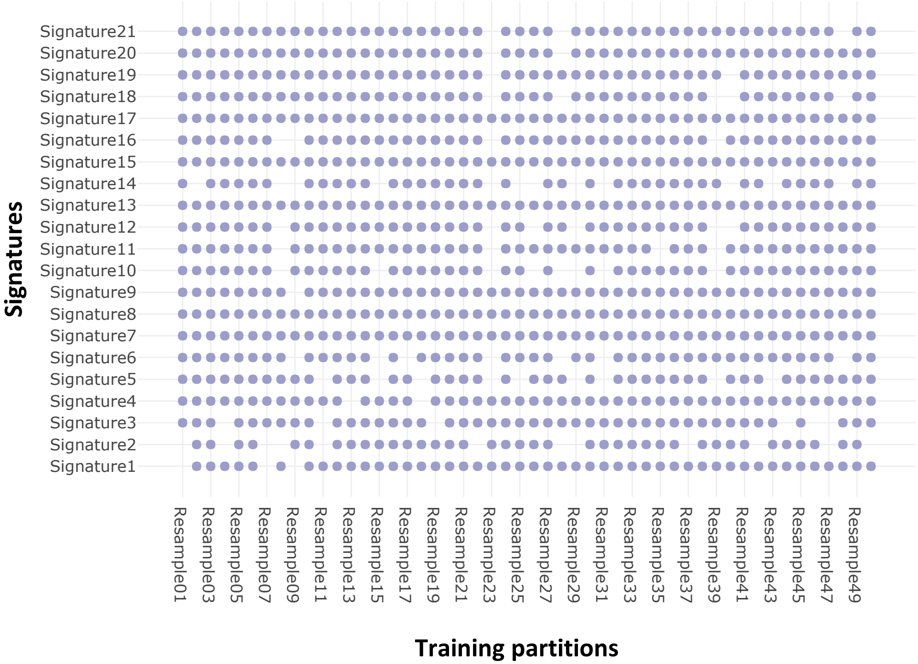
- For each signature, we'll focus on:
  - **50 resampling** to build the Training and the Validation set.
  - **25 modeling and validations.**

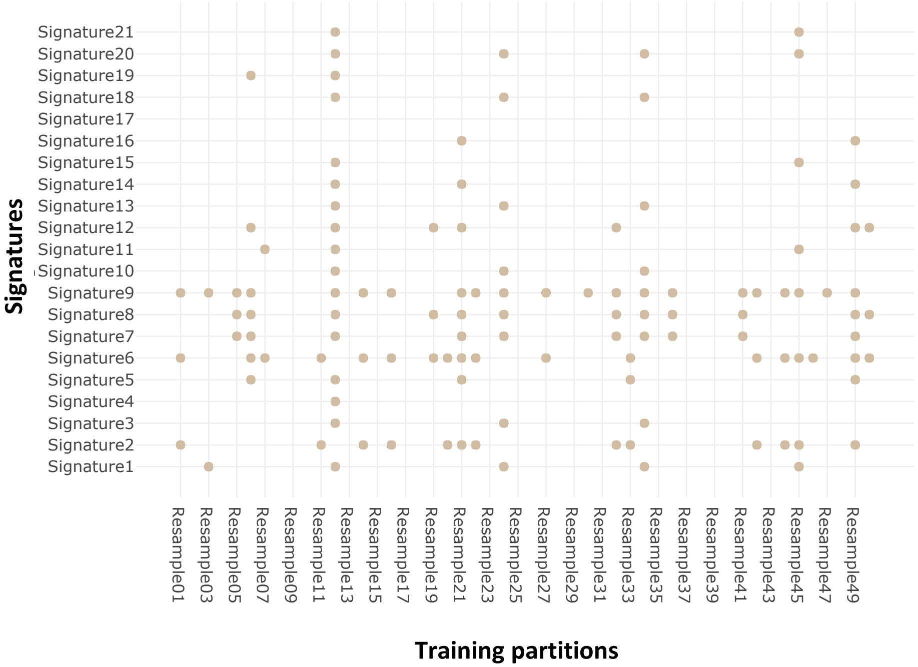
- Analysis of:
  - **Coefficient of Variation of 1,250 models & AUCs**

**1,250 models & AUCs**

**Clinics → Hyper Stability : CV == 0**

# Hyper Stability discriminates RF methods

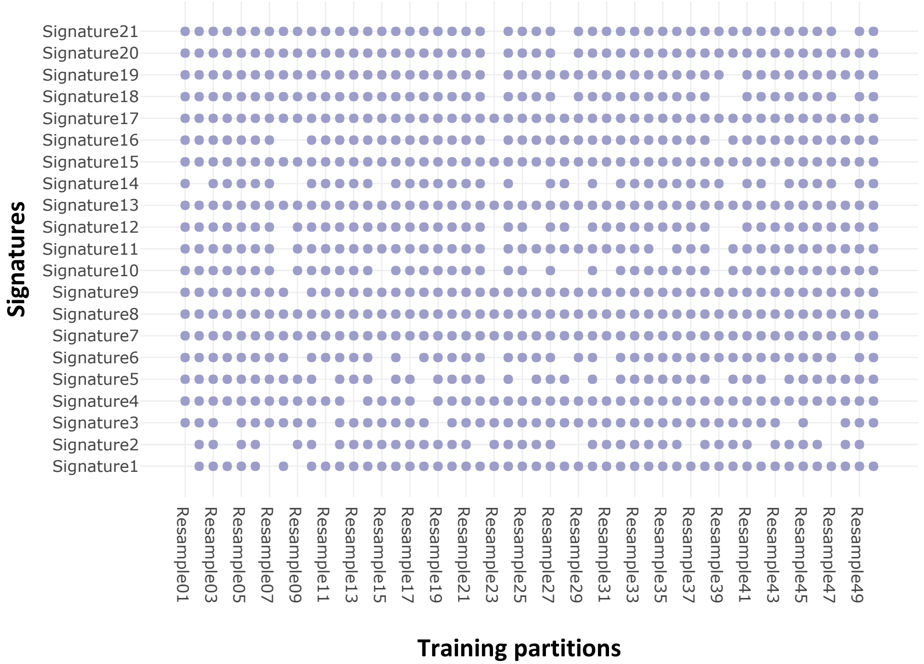




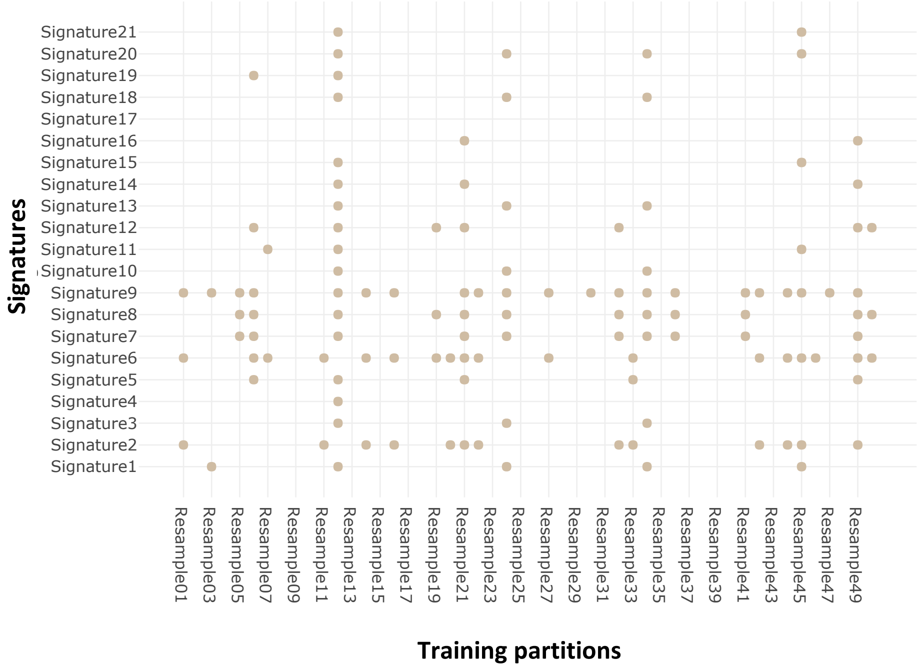
TCGA-LUSC dataset

# Hyper Stability discriminates RF methods

**Best Methods**

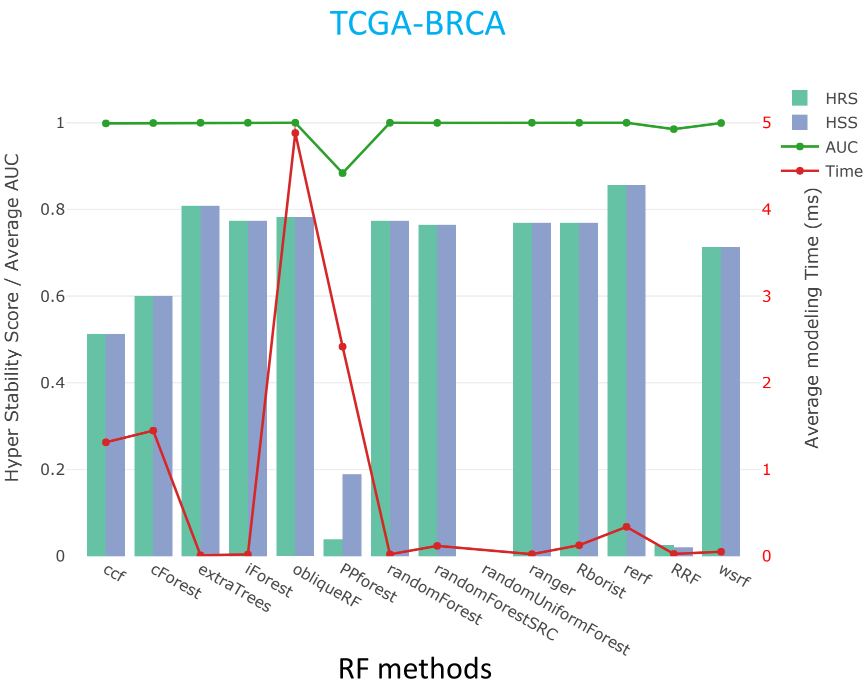


**Worst Methods**

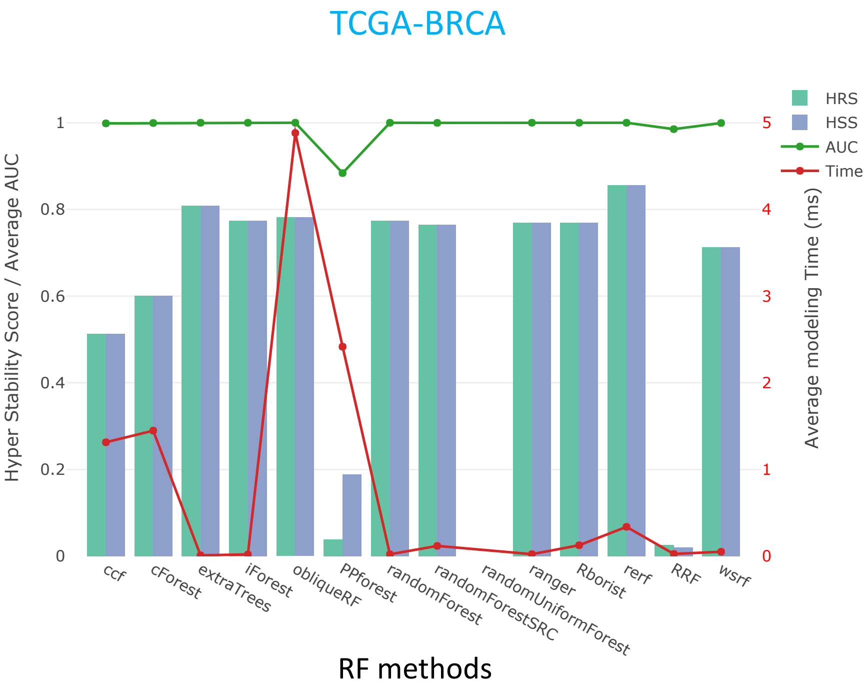


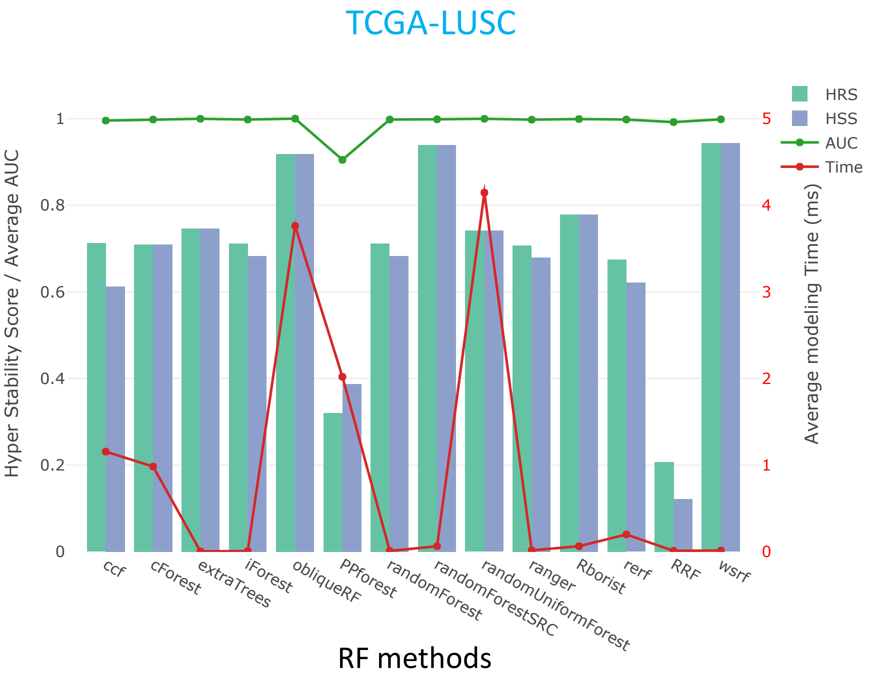
TCGA-LUSC dataset

# Hyper Stability Score helps finding the best method(s)



# Hyper Stability Score is dataset dependent





# Conclusions

- The AUC precision is dataset dependent
  - The Methods are dataset dependent.

- Trade-off:
  - AUC precision (hyper-stability)
  - Average AUC value
  - Modeling Time

Classification of classification methods

Towards robust signatures and predictions

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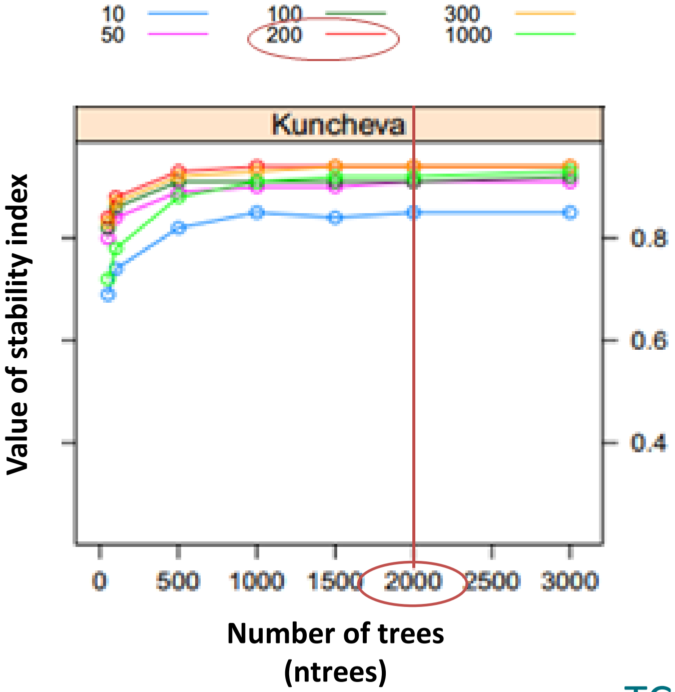
# First pass Feature Selection  results



$ntrees^*$ = 2000

$nVar^*$ = 200

TCGA-BRCA dataset