TIPIT project

Prediction of the patient's outcome in Non-small cell lung cancer from baseline 18F-FDG PET scans

institut Curie

Inserm
La science pour la santé
From science to health

LITO

Outlines

1. Introduction

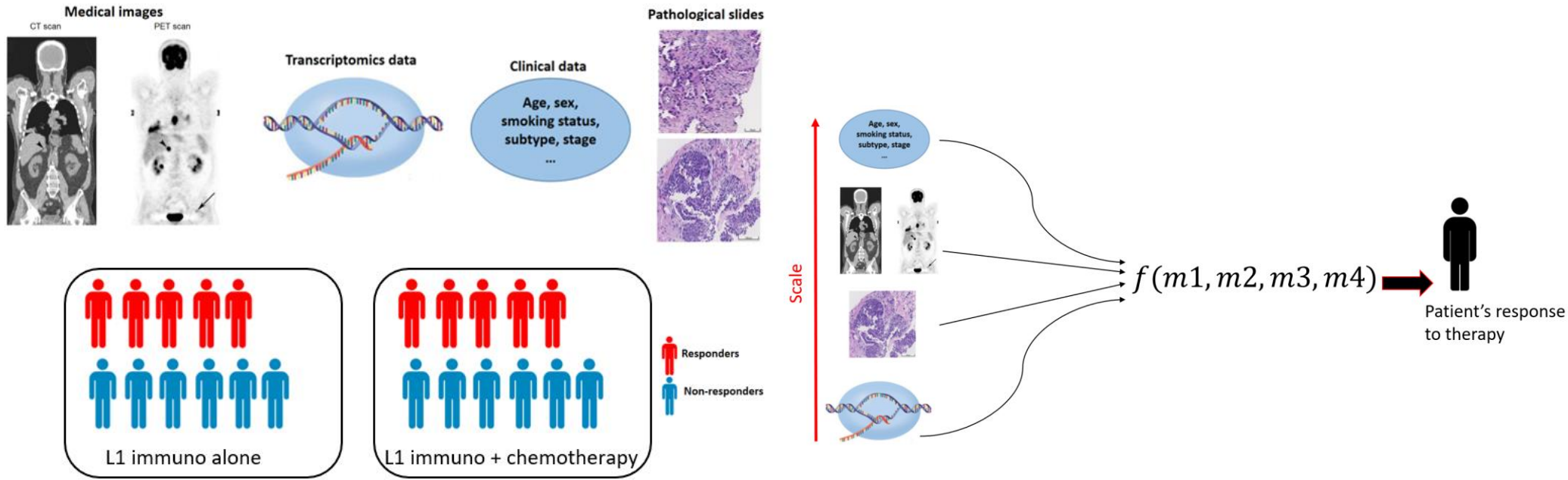
2. A basic example of multimodal Machine Learning with TCGA

3. Simple ML strategies for baseline PET predictions

4. An interpretation tool at the lesion level based on Shapley values

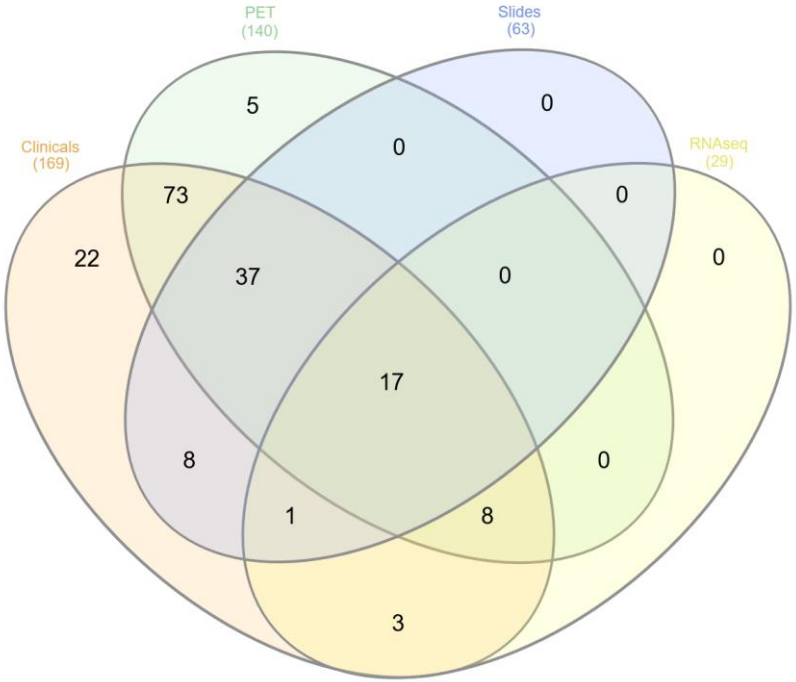
TIPIT project – multimodal predictions in NSCLC

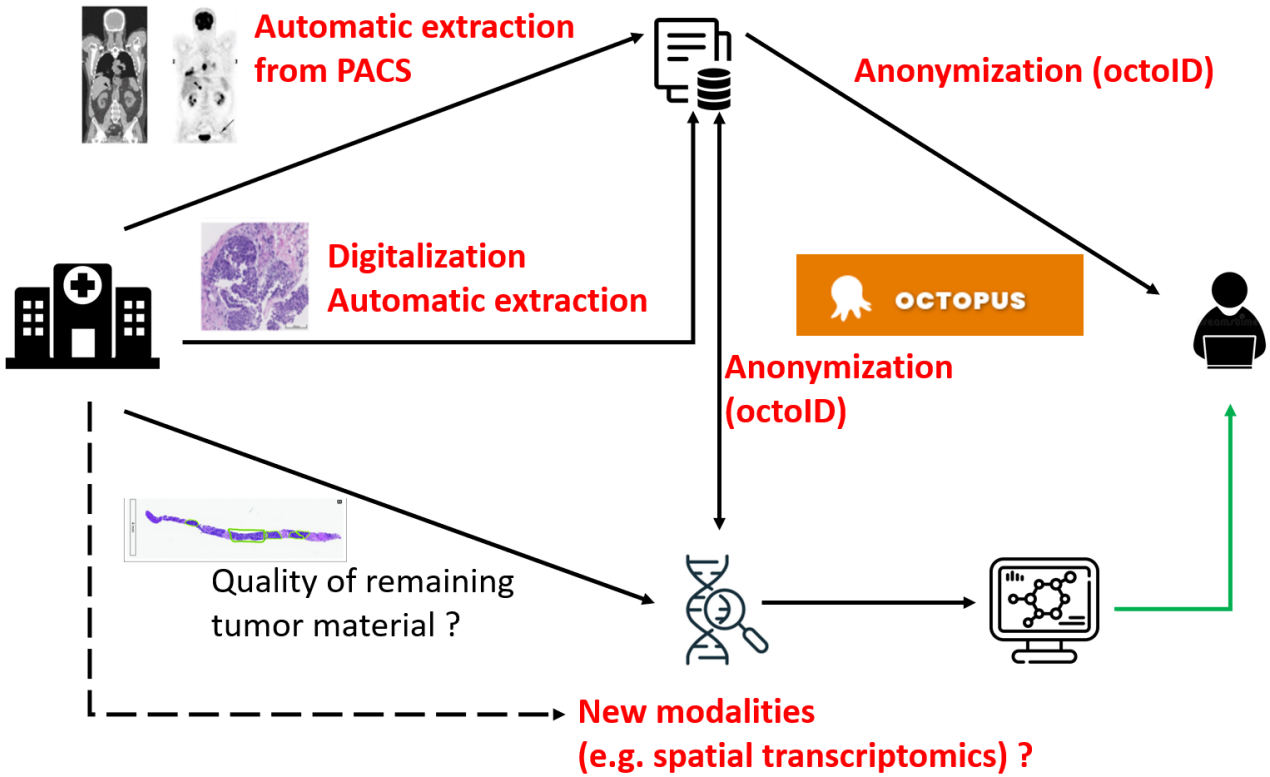
Can we use multimodal supervised Machine Learning to build new powerful and interpretable biomarkers for the response to immunotherapy for metastatic NSCLC patients ?



*Like many terms in Machine Learning "multimodality" is used for a lot of different things and by a lot of different people

The difficult challenge of building a multimodal cohort



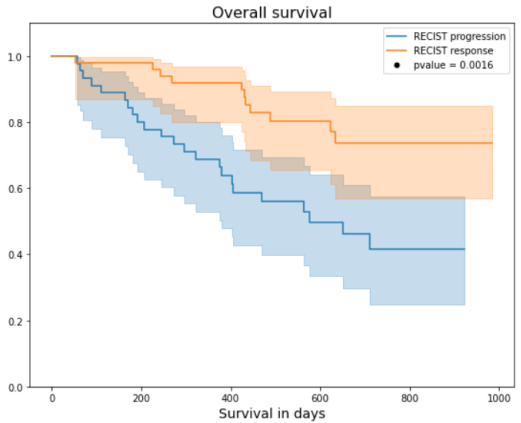


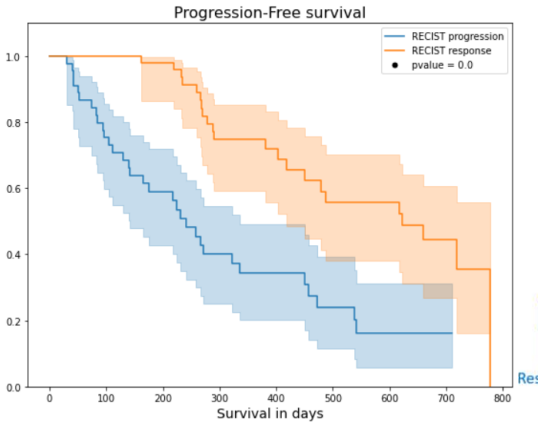
The extraction pipeline is composed of many steps and obstacles we do not have much impact on them

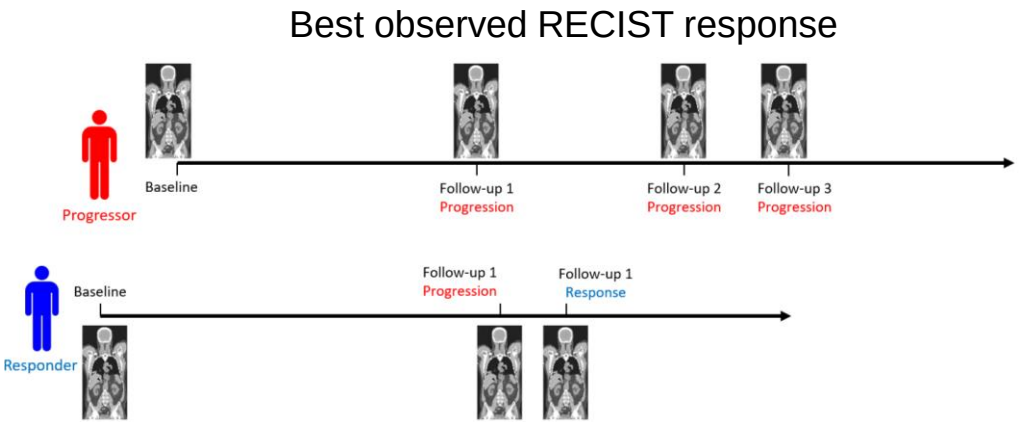
A more realistic use of Machine Learning in the TIPIT project

- With all the patients treated with immunotherapy, we cannot assess whether each patient benefitted from the treatment or not.

- We are more likely to build **prognostic biomarkers** (independent from the treatment) than **predictive biomarkers**







The predictiveness of our models should be assessed in further experiments (e.g clinical trials)

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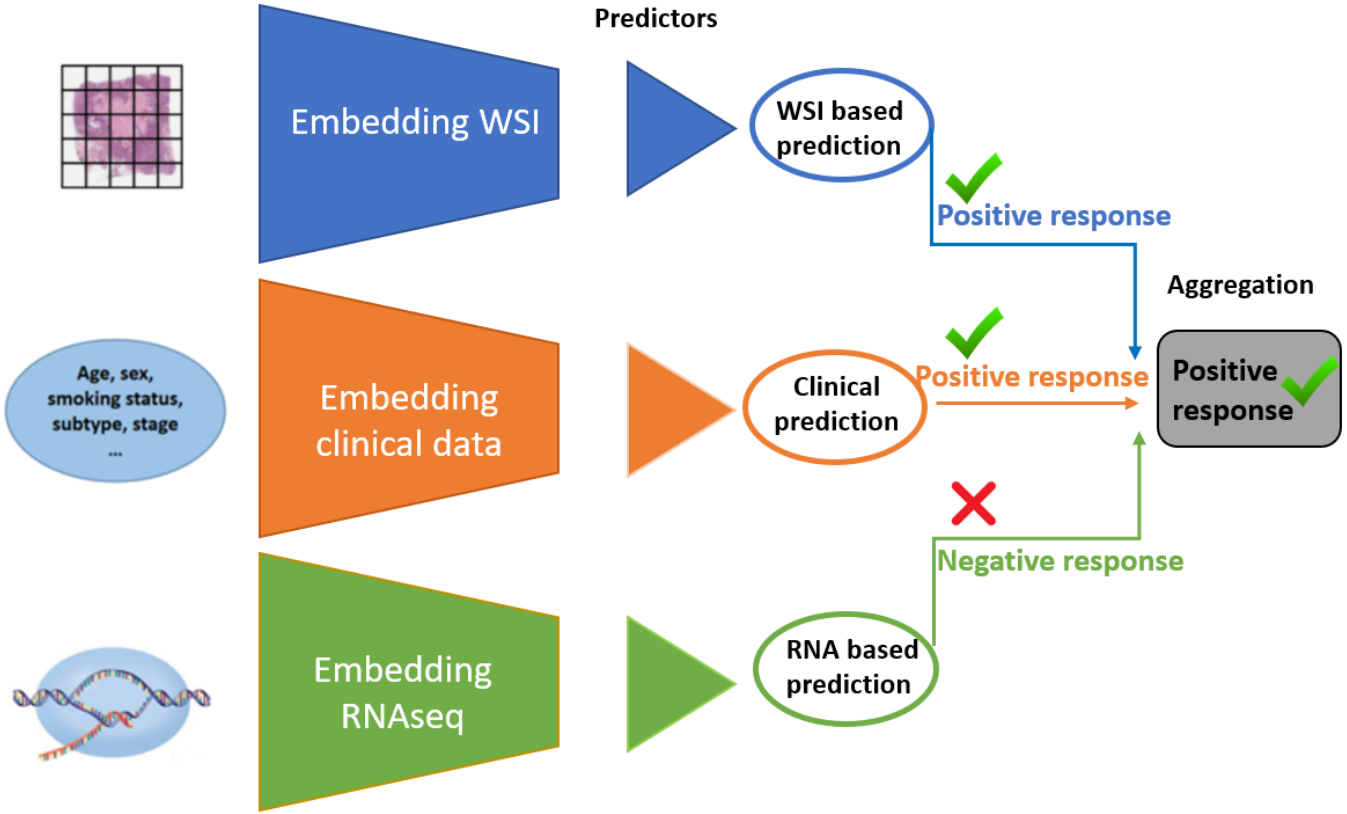
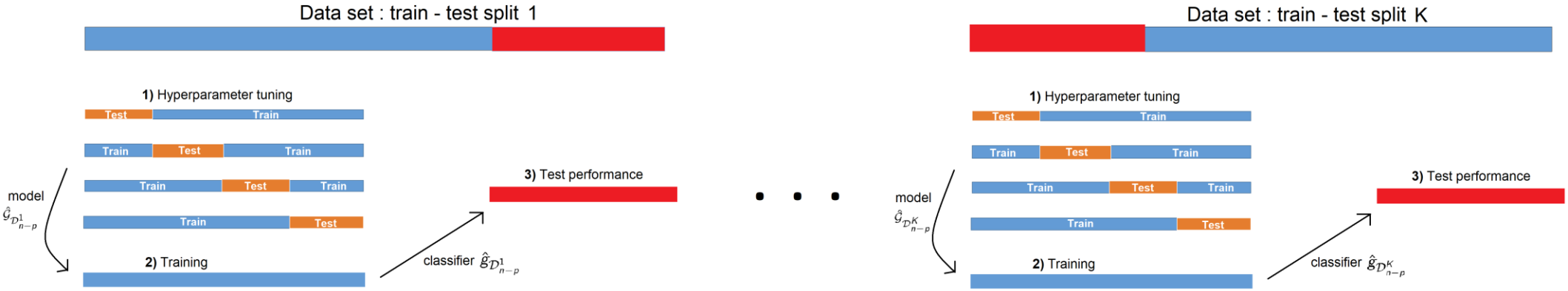
A late fusion scheme for TCGA adenocarcinoma patients

Can we predict the overall survival (OS) of **460 TCGA patients** from transcriptomic data, pathological slides (both extracted from solid biopsies) and clinical data ?



- Each modality is trained **independently** from the others
- Their predictions are **aggregated**

Combine hyperparameter tuning and cross-validation

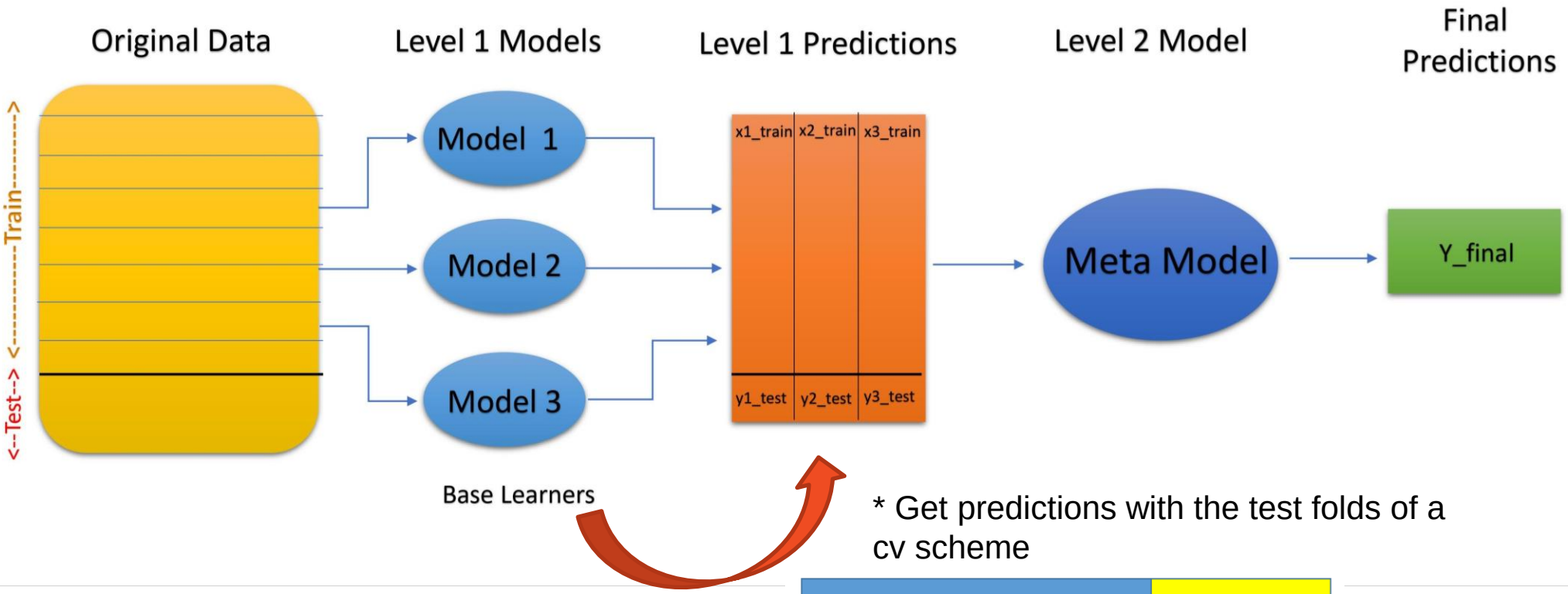


- The final result gives us and estimate of the performance we could get if we perform **hyperparameter tuning + training on the data set with the optimal hyperparameters** on the **full data set**

- It allows us to perform **stability analysis** (e.g feature selection)

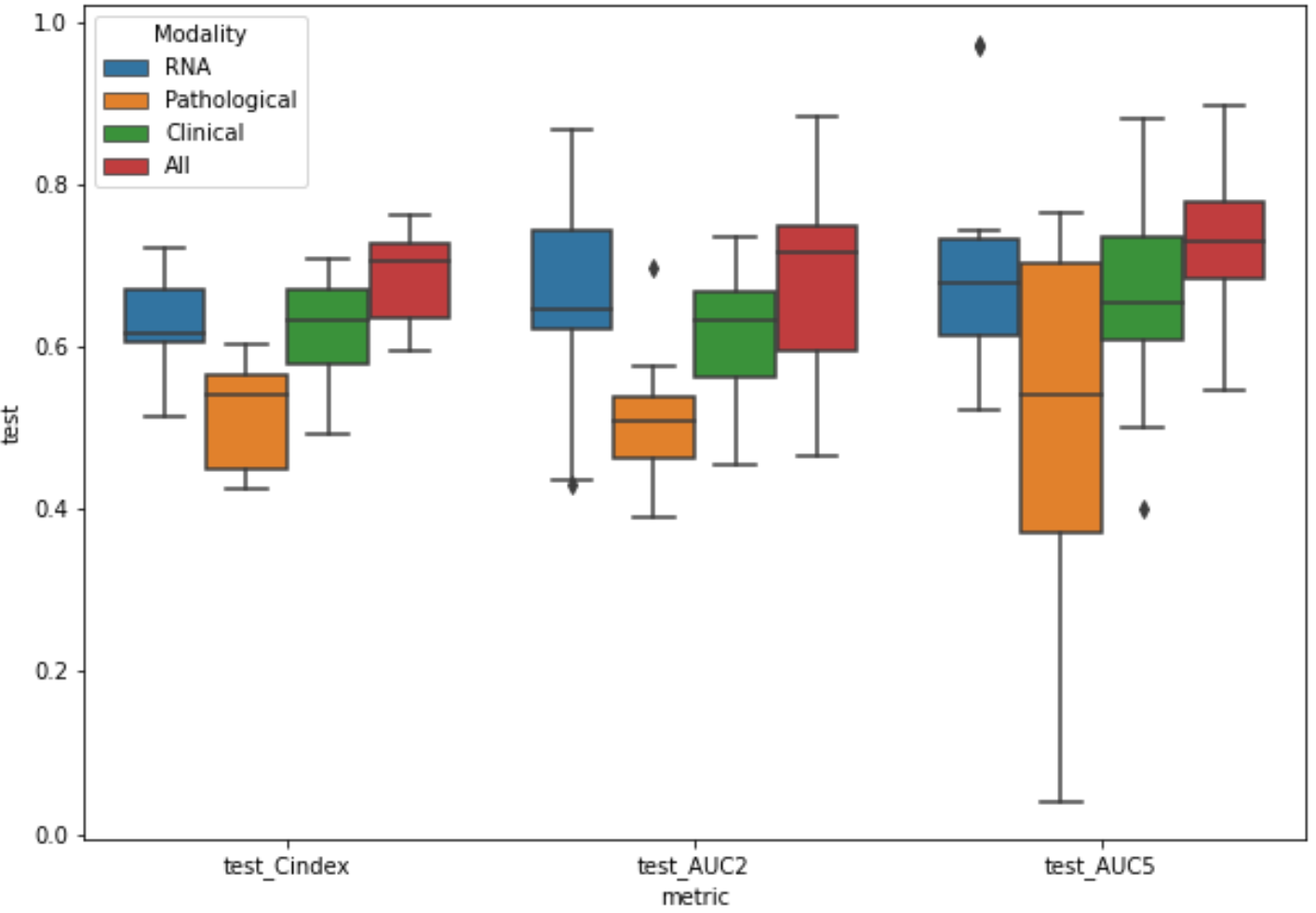
- We can apply more complex schemes than simple CV (e.g Monte-Carlo CV, repeated K-fold CV…)

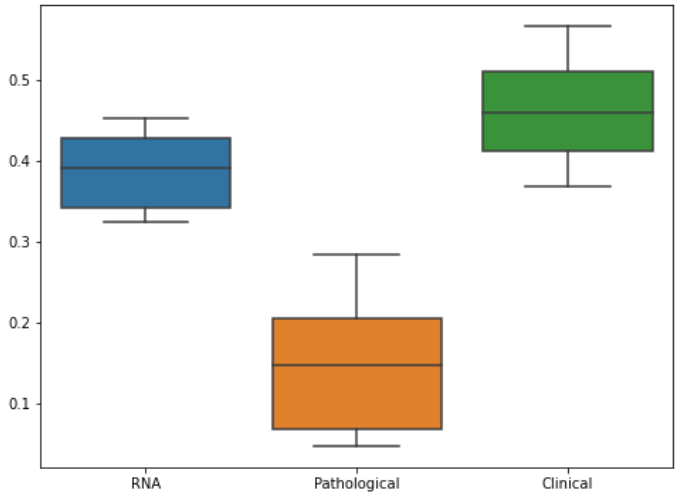
Stacking/Meta Learning for weighted aggregation



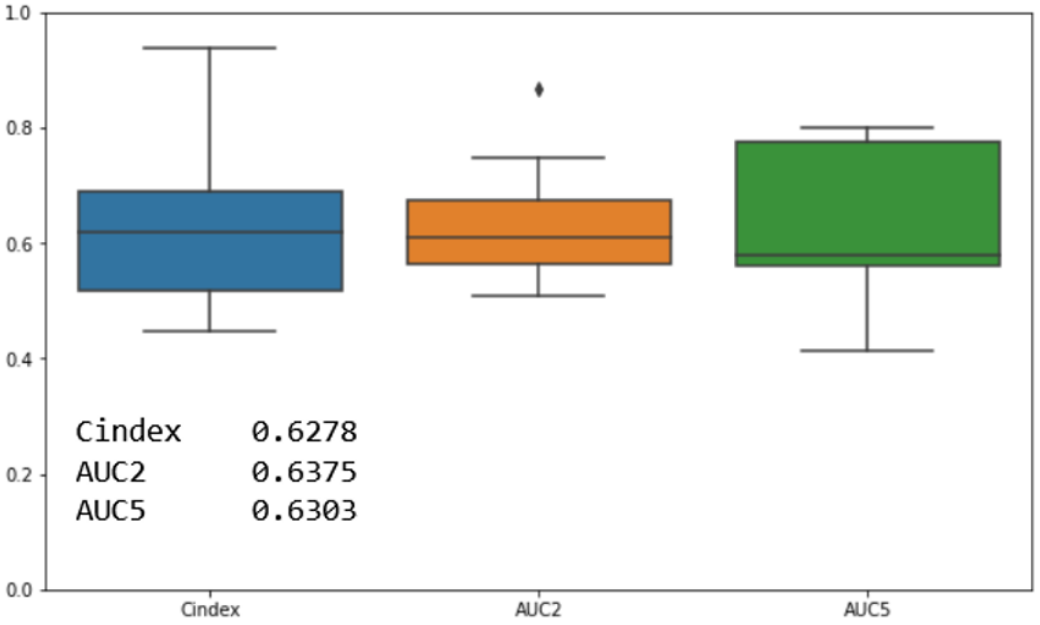
* Get predictions with the test folds of a cv scheme

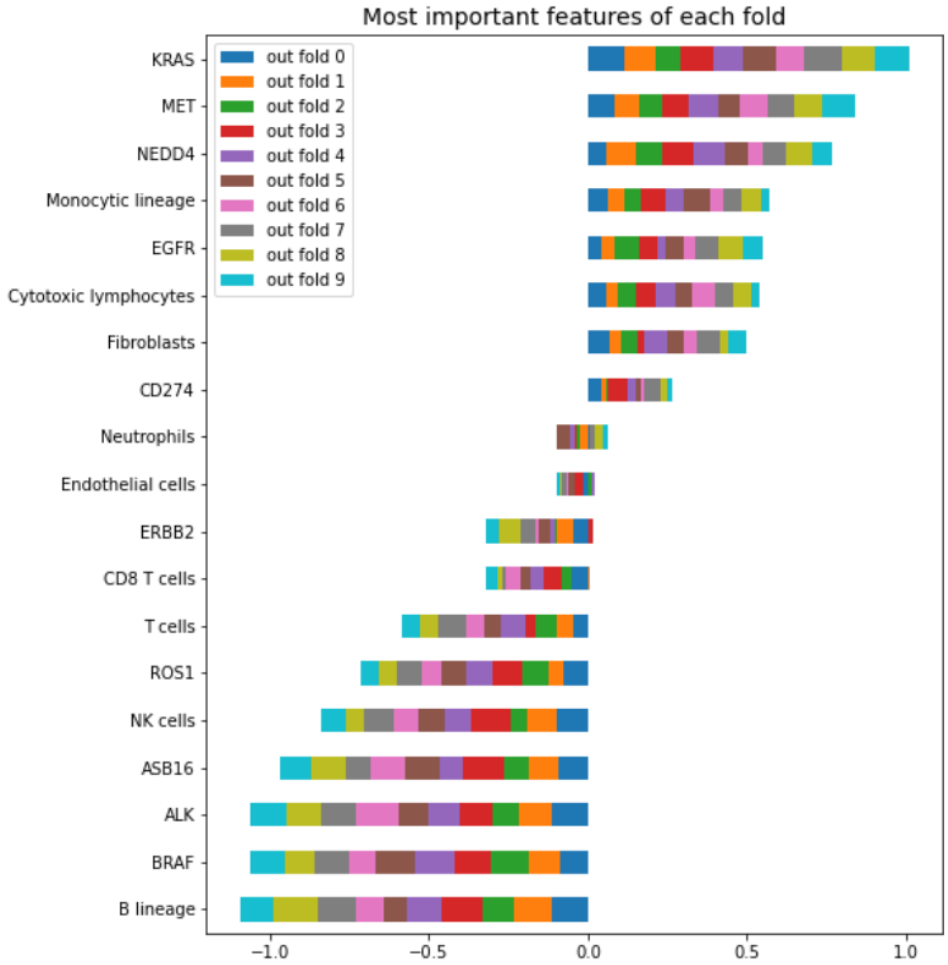
Results – Late fusion improves performances





Results – Interpretation of the transcriptomic model





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A brief overview of our images

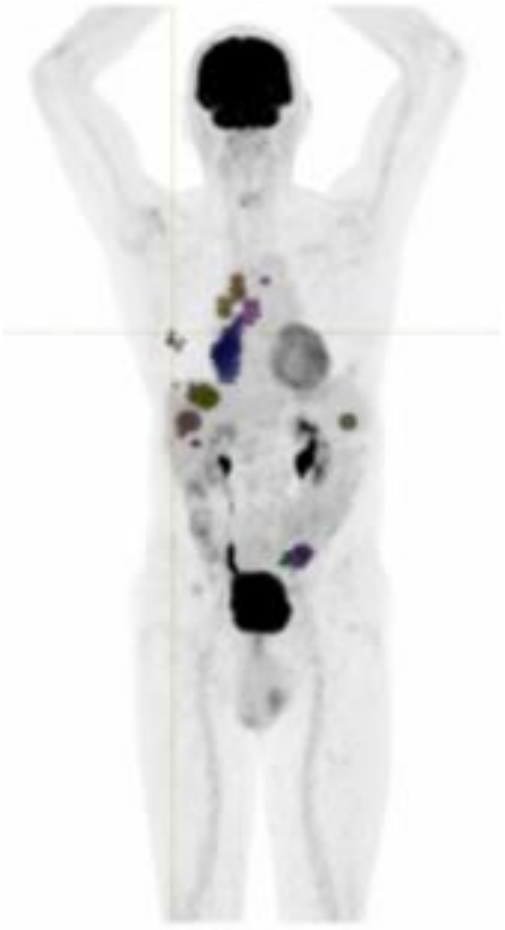
100 TIPIT patients with baseline PET

Manual segmentation and anatomical annotation by Marie

+

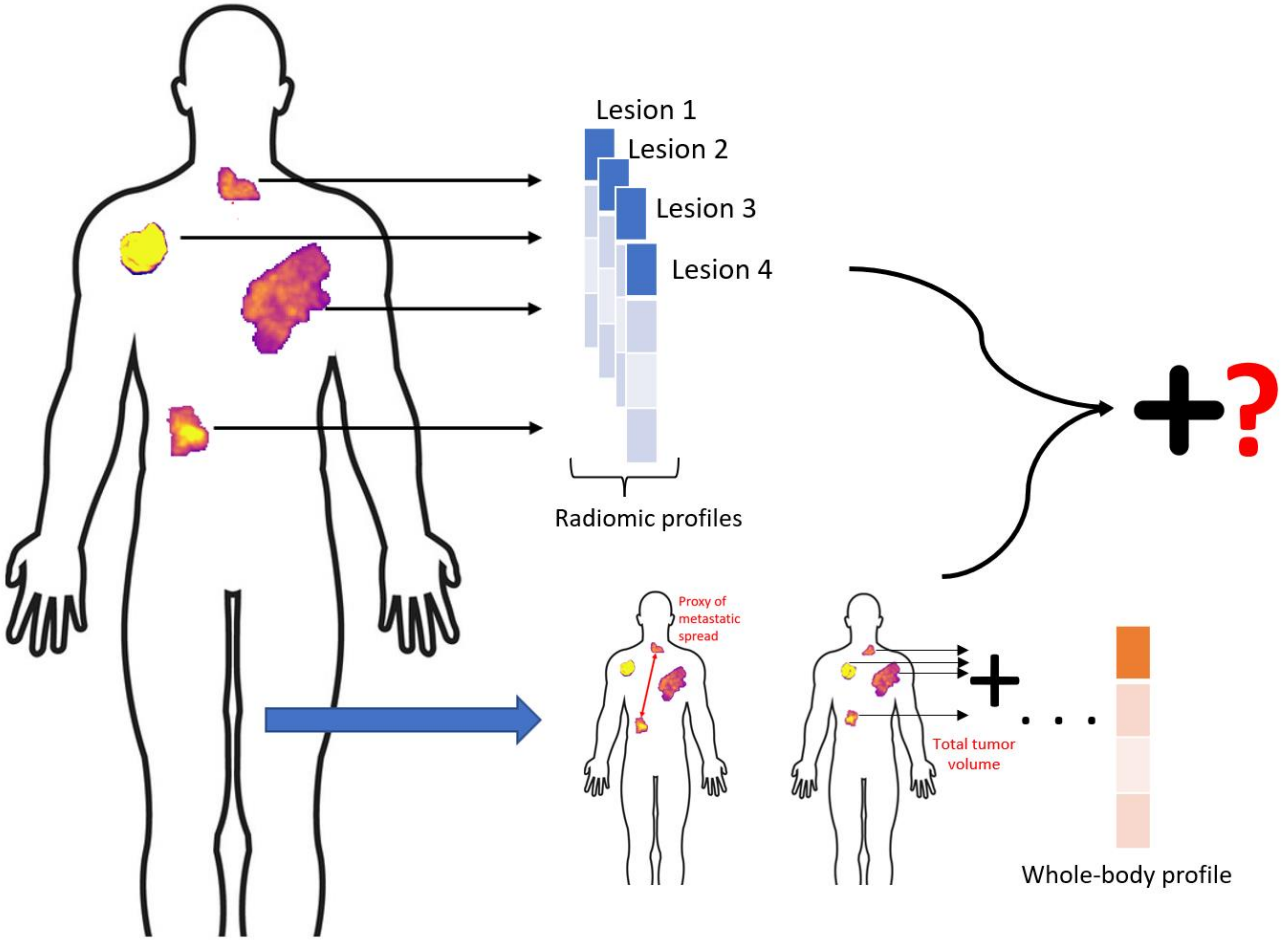
Manual corrections by Narinée and I

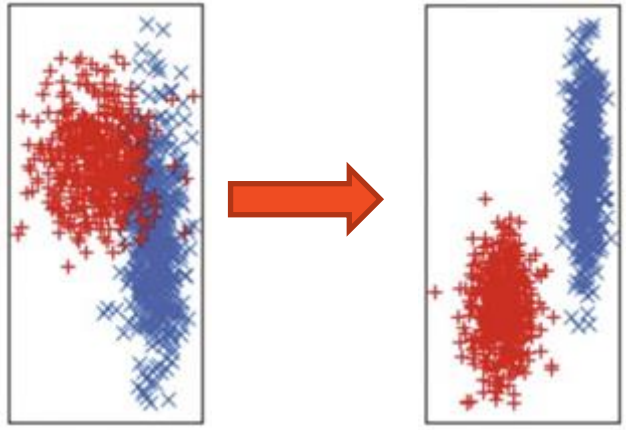
- Remove outlier voxels
- Add Necrosis
- Separate spatially disjoint areas
- Correct and harmonize annotations
- Redo some ROIs from scratch



* For all the lesions of all the patients we extracted radiomics features using a custom wrapper of Pyradiomics **(available on LITO GitHub)**

Leverage all the metastases of each patient





Improve sample representation by leveraging richer information

Different classes of hand-crafted aggregated features

Binary variables for the presence of metastases in different anatomical sites

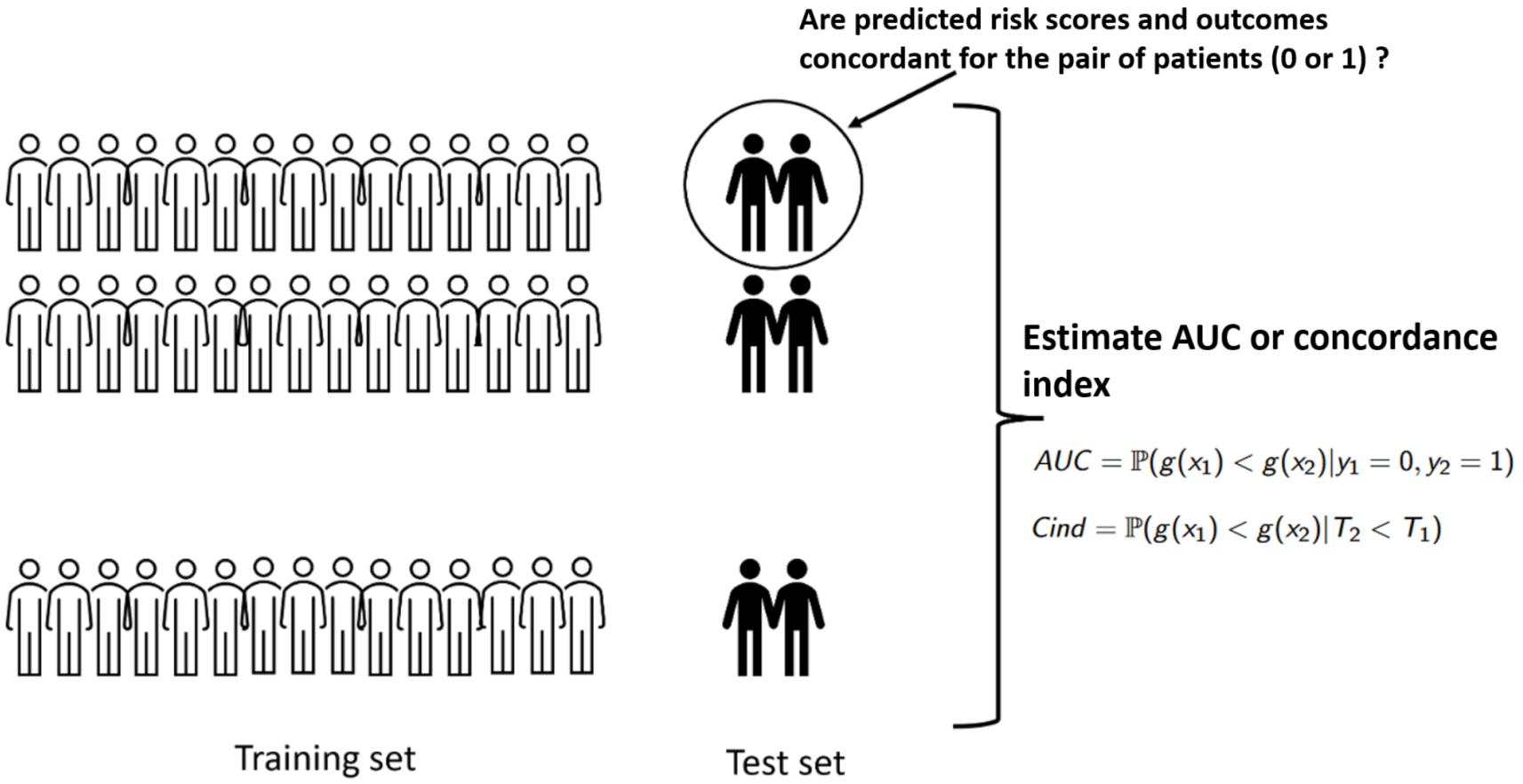
Base whole-body model (Total volume, Dmax, liver and spleen metabolism…)

Clinical variables (sex, age, BMI, Pack-year, PDL1, oncogene mutations, histology…)

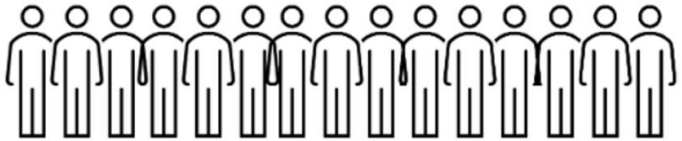
Volume and SUVmax aggregated at the TNM localizations level

Aggregation of radiomic features measured on each lesion (mean, max, std) – Multiple Instance Learning

LPOCV scheme to train an test with a maximum of patients



Late fusion strategy to keep things simple



Model 1

Model 2

Model 3

Model 4

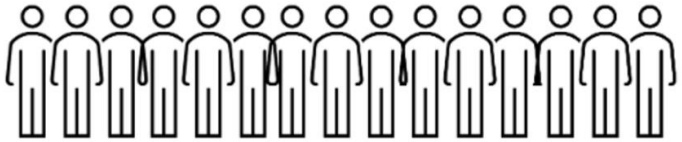
Model 5

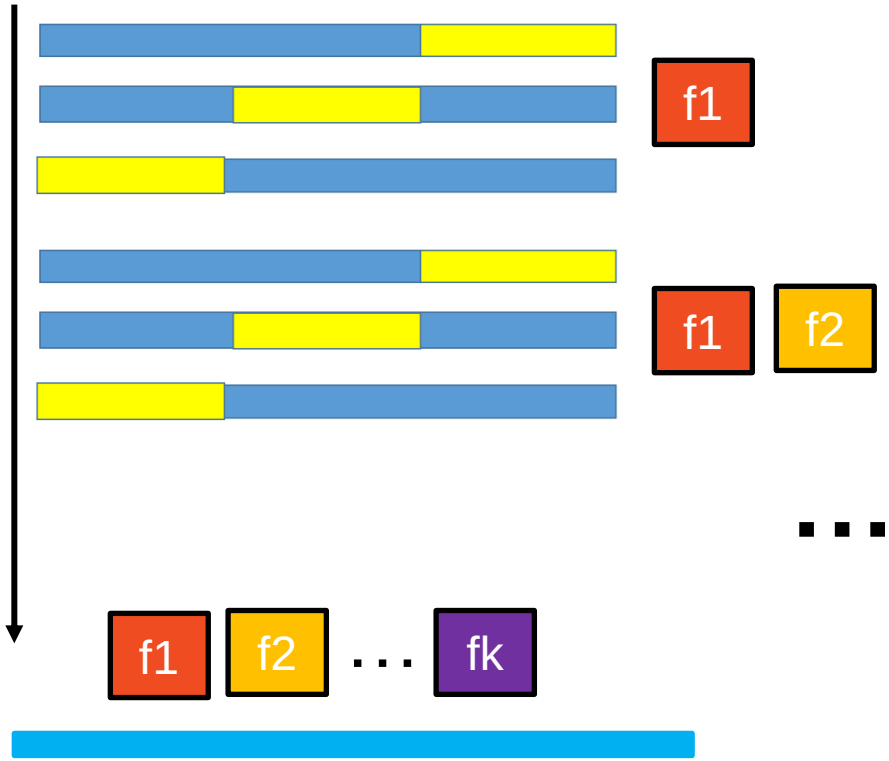
Cox's model + learn **mean** and **std** of the risk scores of each model

Sum the standardized risk scores of each model

* Weights can be learnt by measuring the performance of each model on the training set with a cv scheme

Recursive Feature Addition strategy to keep things simple





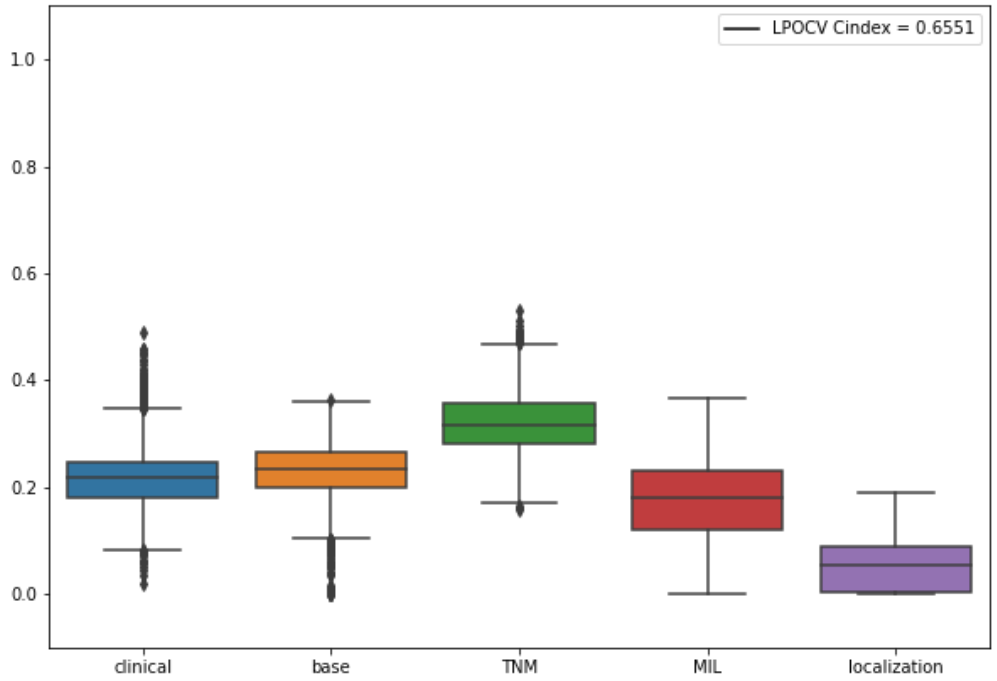
Select best feature with CV

Select best feature with CV if the gain in performance exceed a given threshold

Predict with the final model

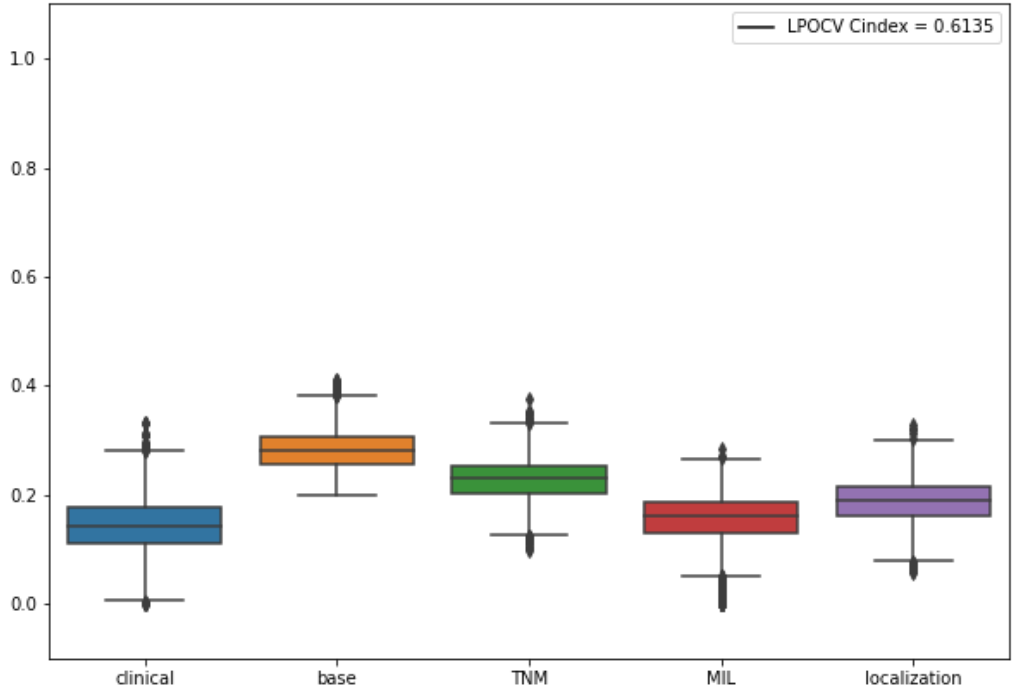
Train the final model on the full training set

Results - late fusion OS and PFS



Overall Survival

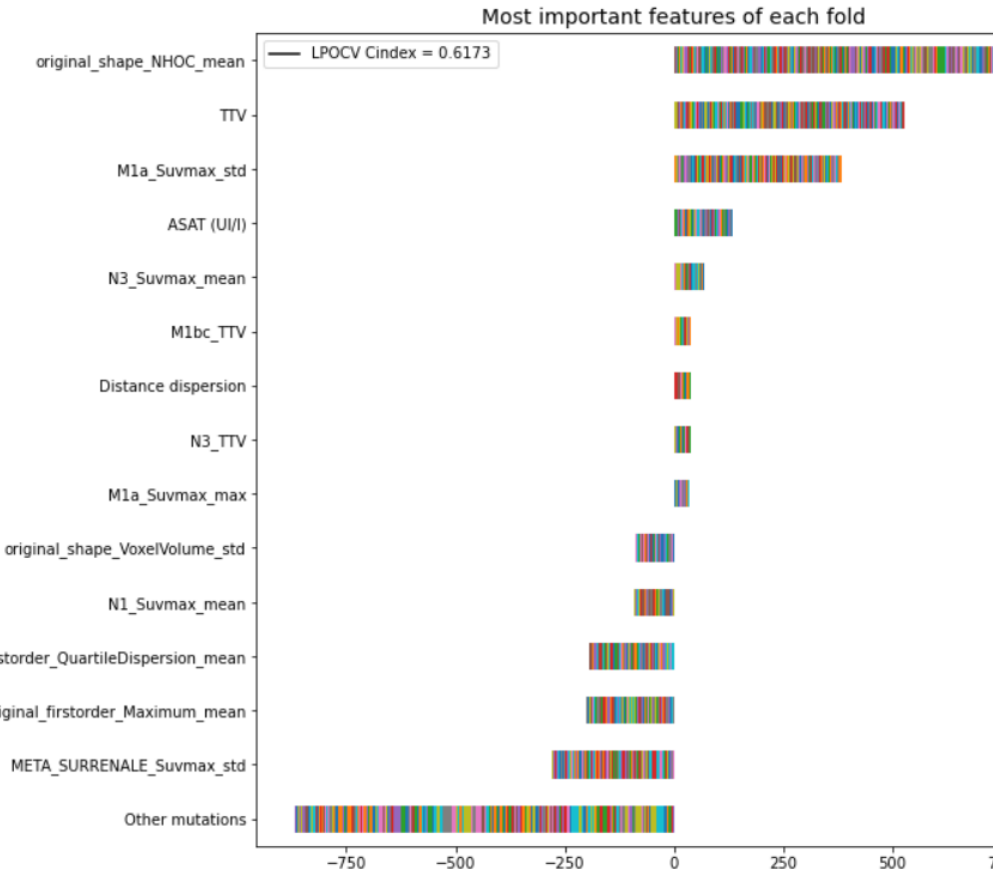
Without weights: 0.6703



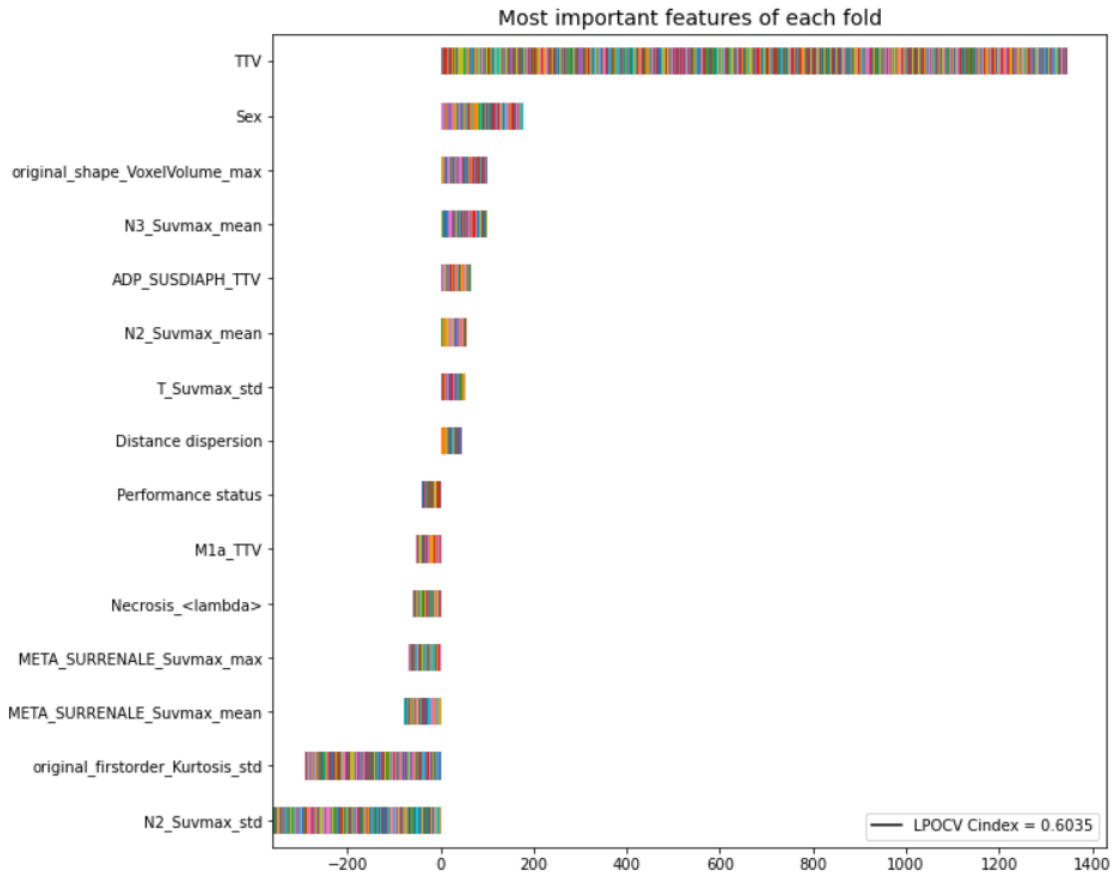
Progression-Free Survival

Without weights: 0.6346

Results – RFA OS and PFS

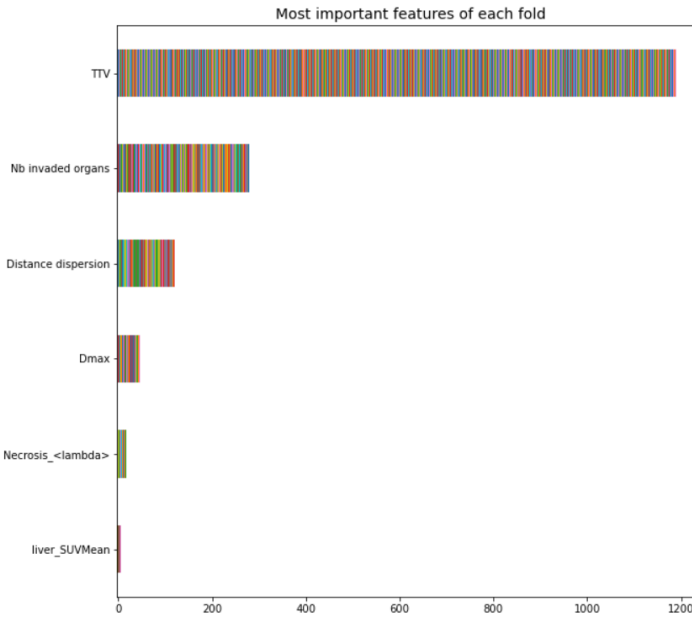


Overall Survival

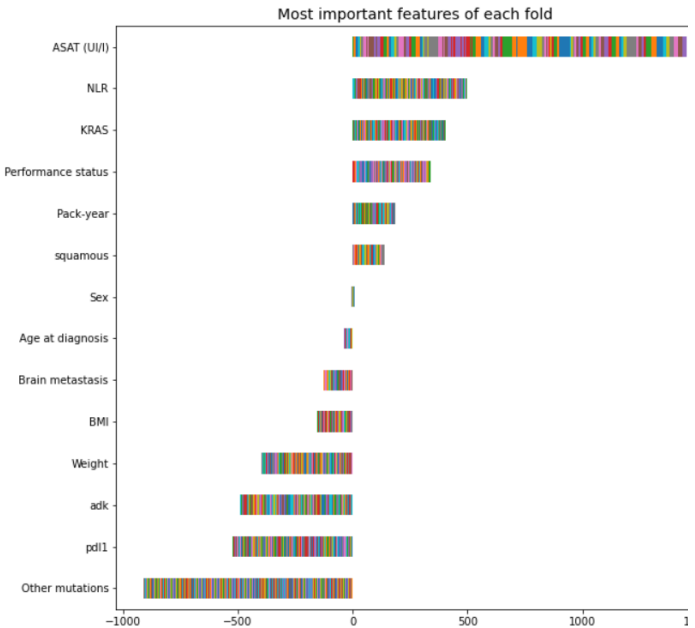


Progression-Free Survival

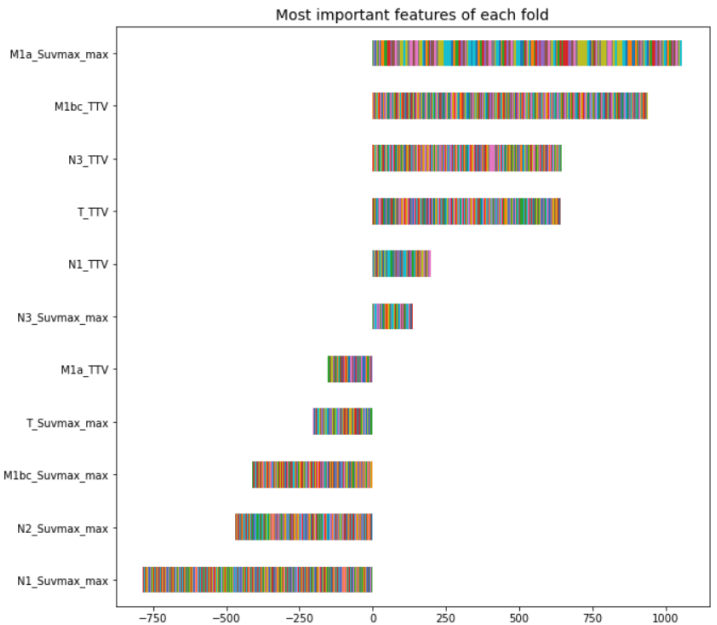
Results – feature importance late fusion OS



Base model



Clinical model



TNM model

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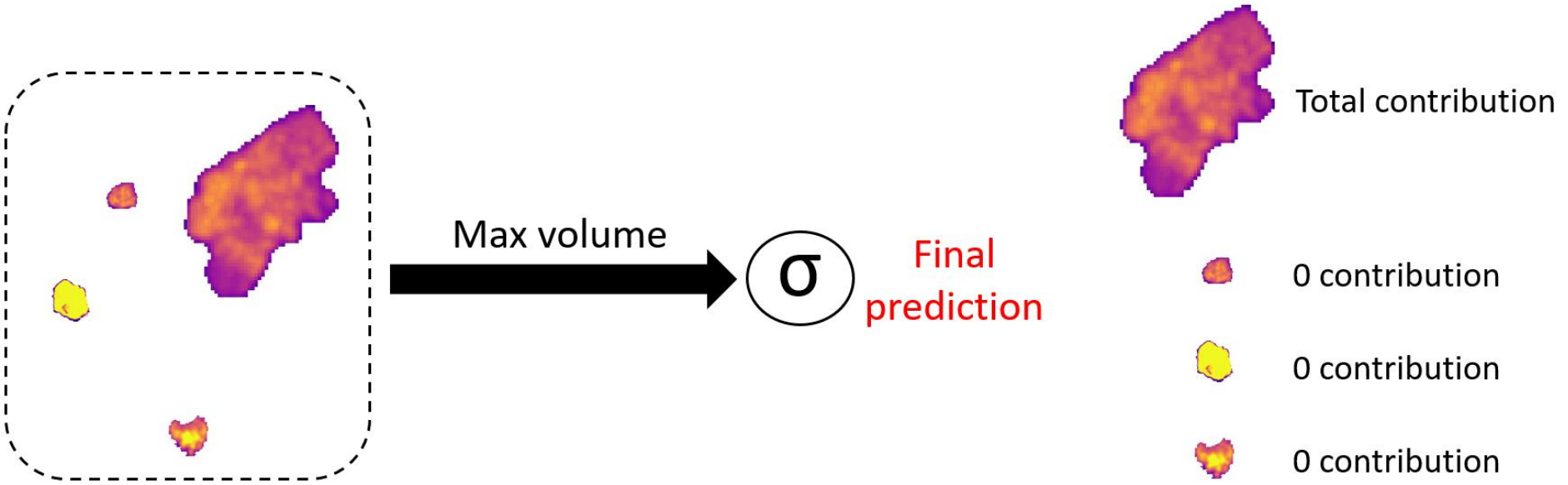
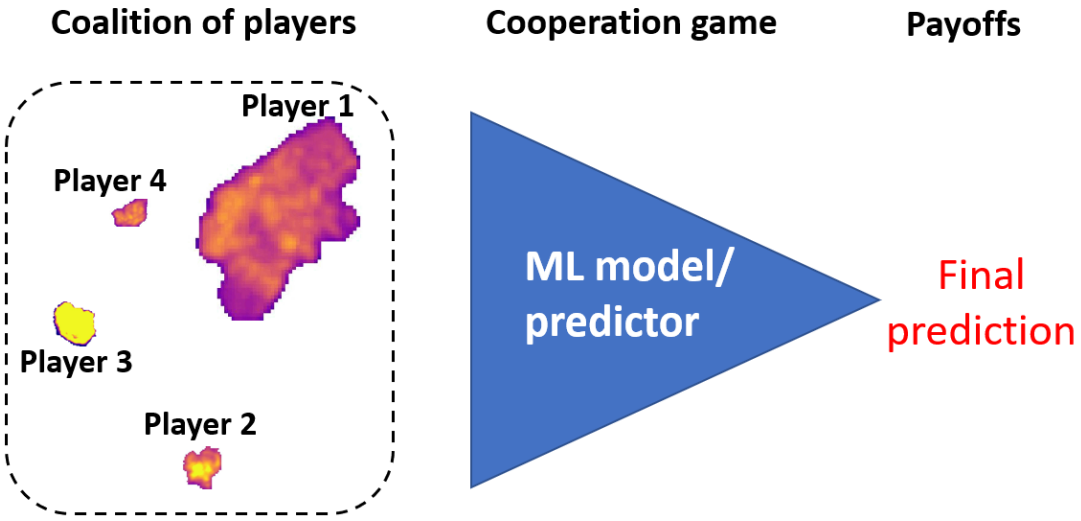
An interpretation tool at the lesion level

For a given aggregated model and for one patient, how to measure the impact of each of his lesions on the final prediction ?



How to generalize such and approach to any kind of aggregated predictive model ?

Shapley values to measure contributions



- All metastases (i.e players) cooperate to obtain the final prediction.
- We can borrow Shapley values from cooperative game theory for measuring the impact of each lesion to the final prediction.

$$\phi_i = \frac{1}{n} \sum_{S \subseteq N - \{i\}} \binom{n-1}{|S|}^{-1} \underbrace{(pred(S \cup \{i\}) - pred(S))}_{\text{marginal contribution of i}}$$

* It is the only payment rule satisfying Efficiency, Symmetry, Linearity and Null-player properties.

Independent contributions are not Shapley values !

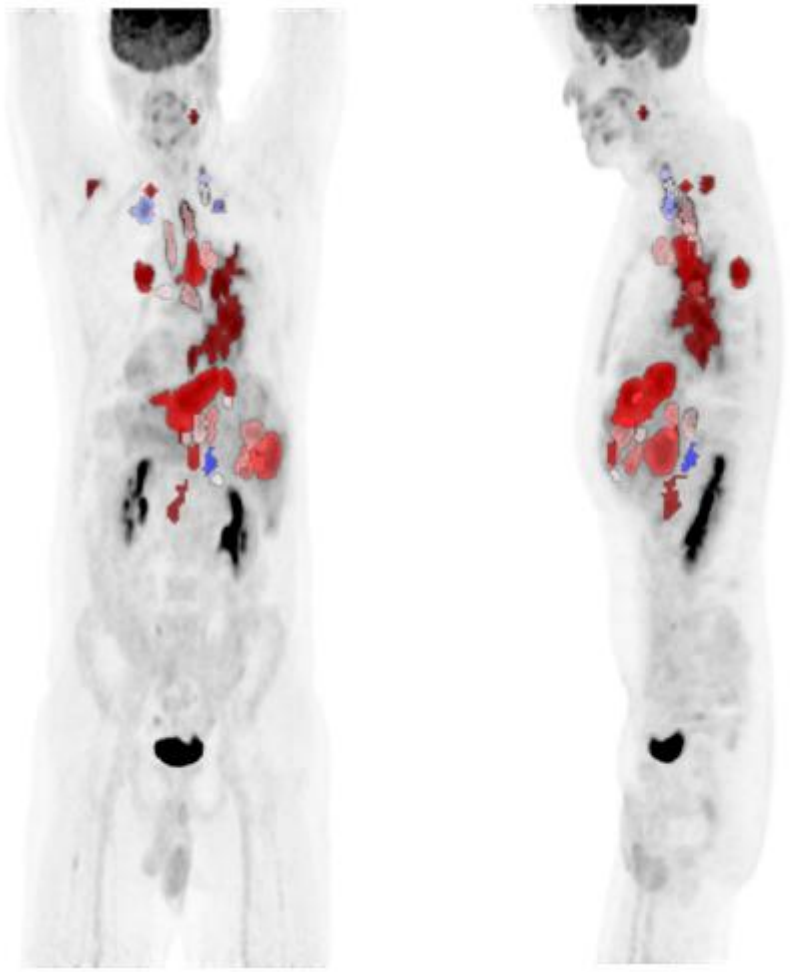
Let us consider a game g with two players x1, x2 such that the result obtained by each player separately is null and the result obtained from their cooperation is maximal:

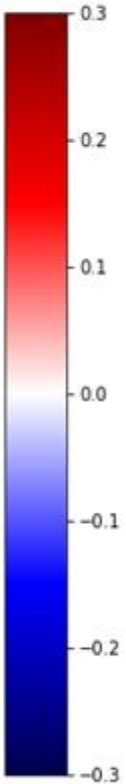
$$g(x_1) = g(x_2) = 0 \quad , \quad g(x_1, x_2) = 1 \quad , \quad g(\emptyset) = 0 \,(\text{no player involved})$$

$$\phi_1 = \frac{1}{2}(g(x_1) - g(\emptyset)) + \frac{1}{2}(g(x_1, x_2) - g(x_2)) = \frac{1}{2} \times 0 + \frac{1}{2} \times 1 = 0.5$$

$$\phi_2 = \ldots = 0.5$$

Application of Shapley values to OS late fusion model

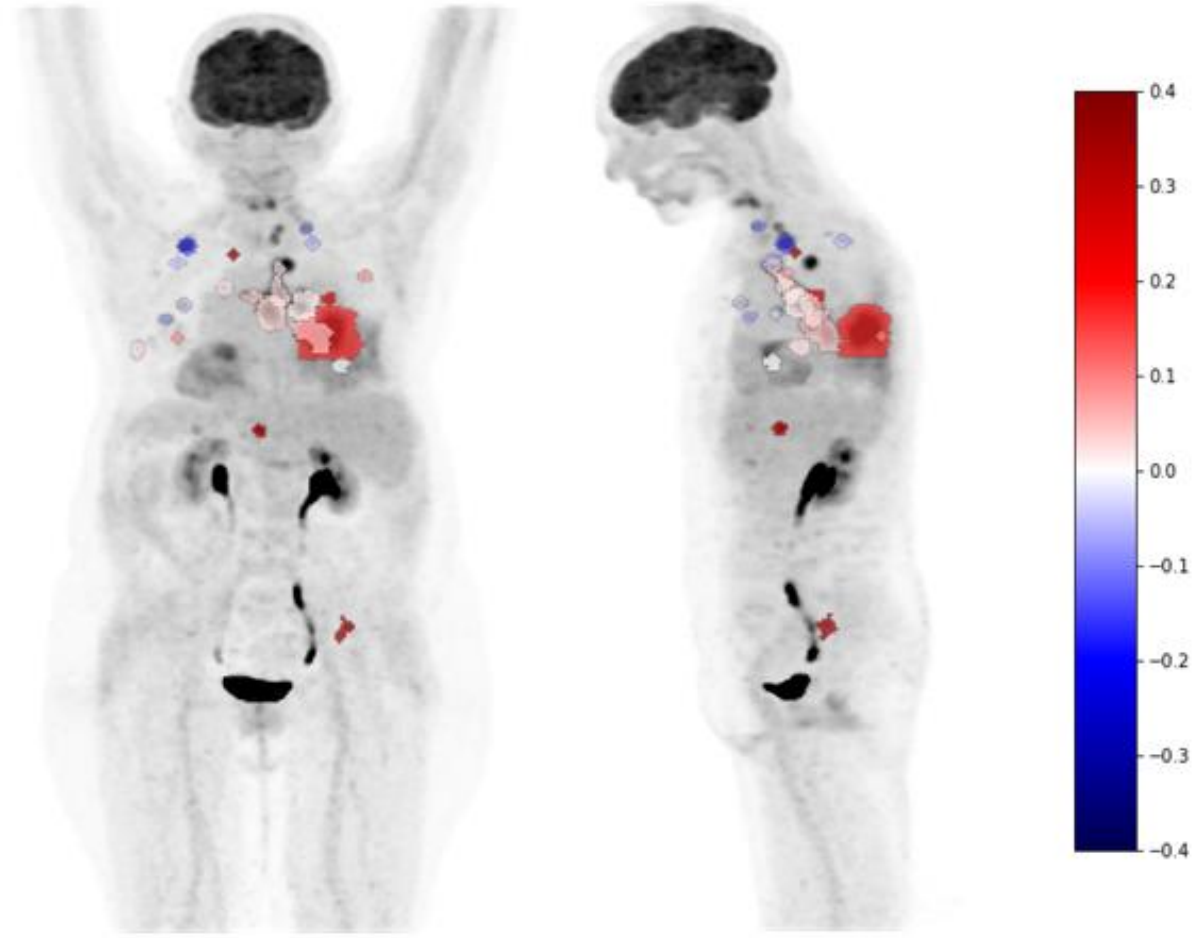




ADP_SOUSDIAPH_1	0.271069
ADP_CERV_HL_1	0.265905
META_OS	0.262040
PRIMITIF_PULM	0.257341
ADP_SOUSDIAPH_2	0.247039
ADP_SUSCLAV_CL	0.213111
META_FOIE_9	0.212359
META_PULM_CL	0.199501
META_FOIE_6	0.156821
ADP_MED_HL_2	0.132304
META_FOIE_8	0.109982
META_FOIE_10	0.079329
META_FOIE_4	0.067177
META_FOIE_5	0.055741
ADP_MED_HL_3	0.051112

Patient with highest predicted risk score

Application of Shapley values to OS late fusion model



META_OS	0.359036
META_PULM_CL_8	0.356151
ADP_SOUSDIAPH	0.290743
META_PULM_HL_1	0.244817
PRIMITIF_PULM	0.163355
META_PULM_CL_7	0.096740
META_PULM_HL_6	0.061479
ADP_MED_HL_4	0.037290
ADP_MED_CL	0.035760
ADP_MED_HL_2	0.029251
META_PULM_CL_1	0.022470
META_PULM_CL_5	0.018182
ADP_MED_HL_1	0.016128
ADP_MED_HL_3	0.001359
META_PULM_HL_5	-0.001487

Patient with high predicted risk score

Thank you for your attention !