Breakout Session 4: Track B

Optimizing Diagnostic and Prognostic Biomarkers of CASH using Machine Learning

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Optimizing Diagnostic and Prognostic Biomarkers of CASH using Machine Learning

Optimizing and Sharing Data for Machine Learning [ML] Analyses of Multiomic Biomarkers of Cavernous Angiomas with Symptomatic Hemorrhage [CASH]

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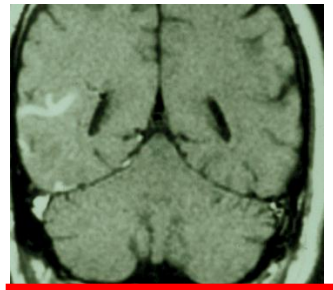
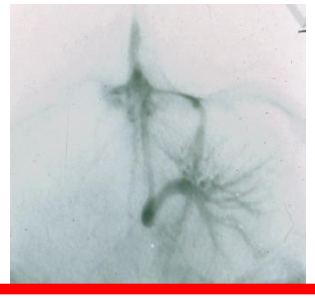
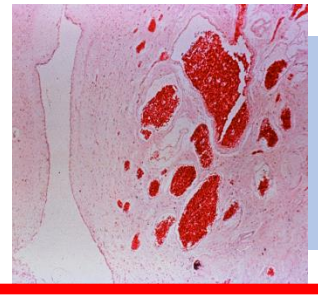
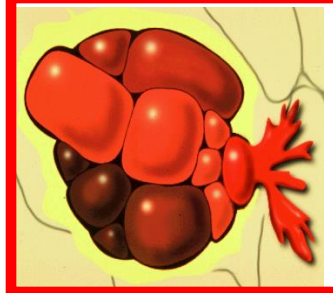
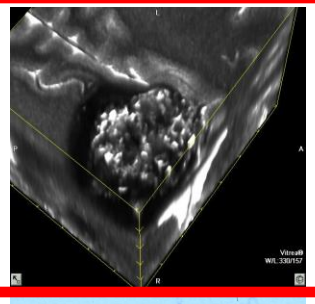
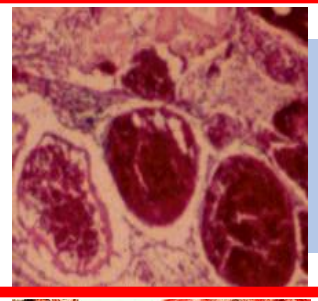
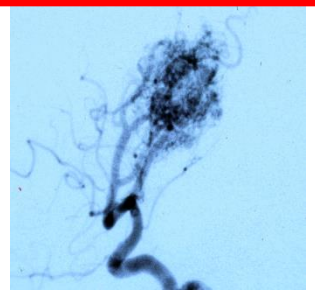
Cavernous Angiomas (CAs) are fairly common cerebrovascular anomalies

VENOUS ANGIOMA
Venous developmental anomaly
Regional venous dysmorphism

CAVERNOUS MALFORMATION
Hemorrhagic proliferative dysangiogenesis


ARTERIOVENOUS MALFORMATION
Arteriovenous shunting

Cerebral CAs behavior is unpredictable

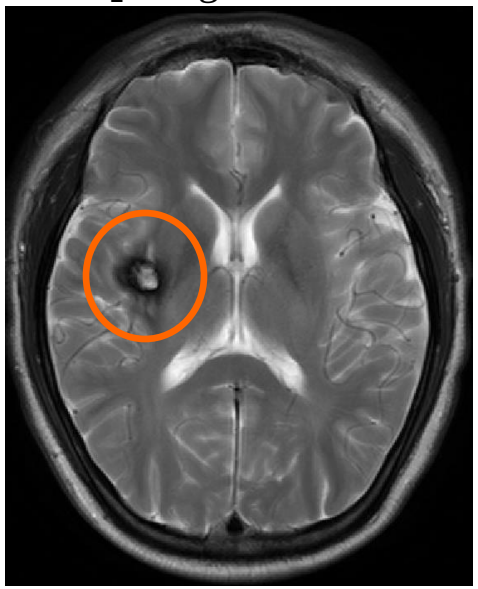
- CAs are abnormal clusters of enlarged capillary vessels embedded in normal brain or spinal cord tissue

- 2 forms : sporadic/solitary or familial/multifocal

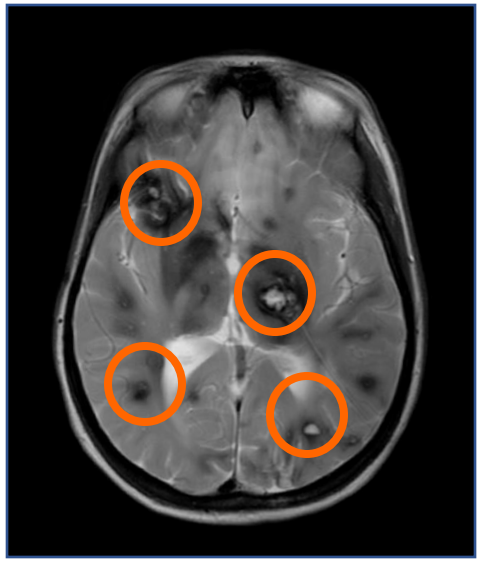
- CA without prior symptomatic hemorrhage (SH)
  - ➢ Low initial risk of SH (0.4 to 2.4% per year)

- CA with recent SH
  - ➢ High risk of rebleeding after initial SH (*Al-Shahi et al., 2012*)
    - 10-fold increase
    - 3.8 to 29.5% per year

T_2-weighted MRI

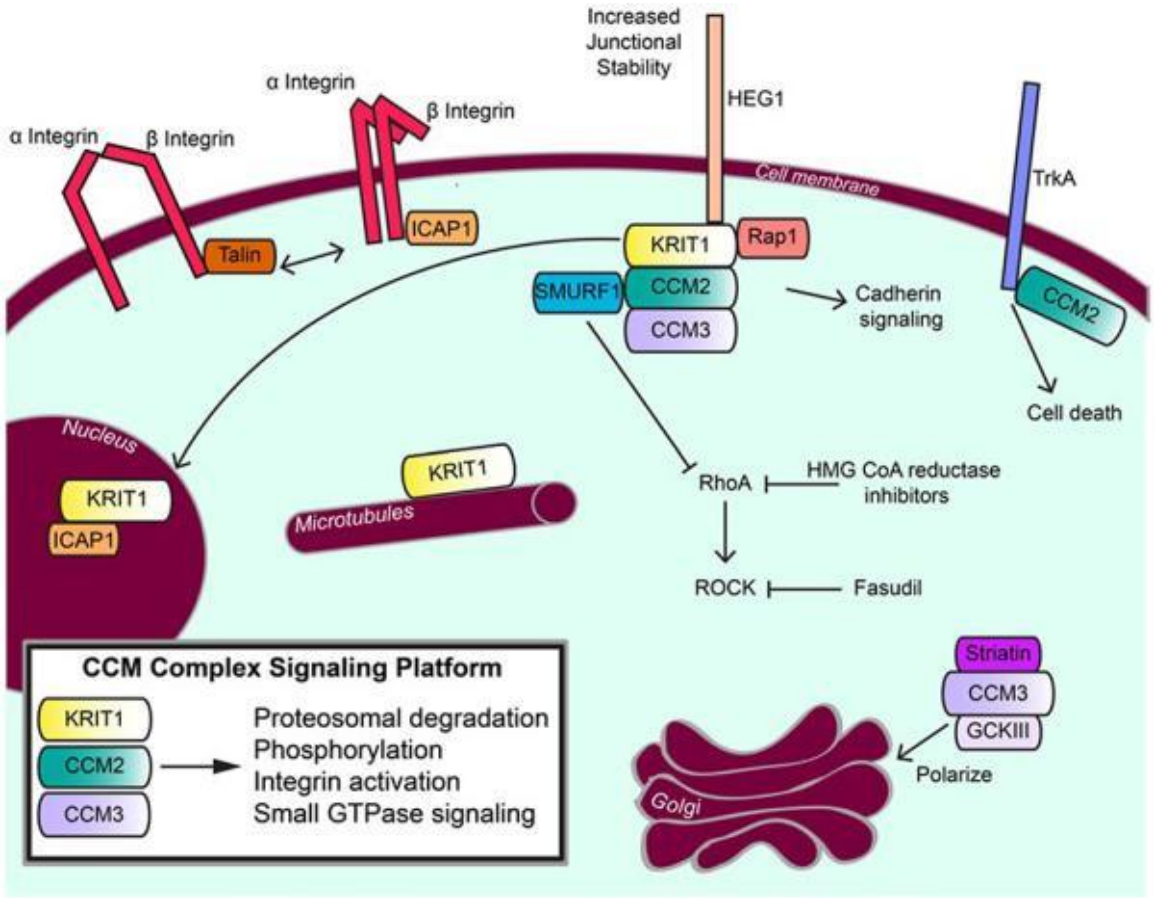


in sporadic patient



in familial patient

A complex interplay of angiogenesis and inflammatory processes



Fisher & Boggon, 2014

Double hit mutations on one of the CCM genes (stochastic and/or inherited)

↓

Signaling aberration

↓

Disruption of endothelial cell junctions

↓

Vascular hyper-permeability

↓

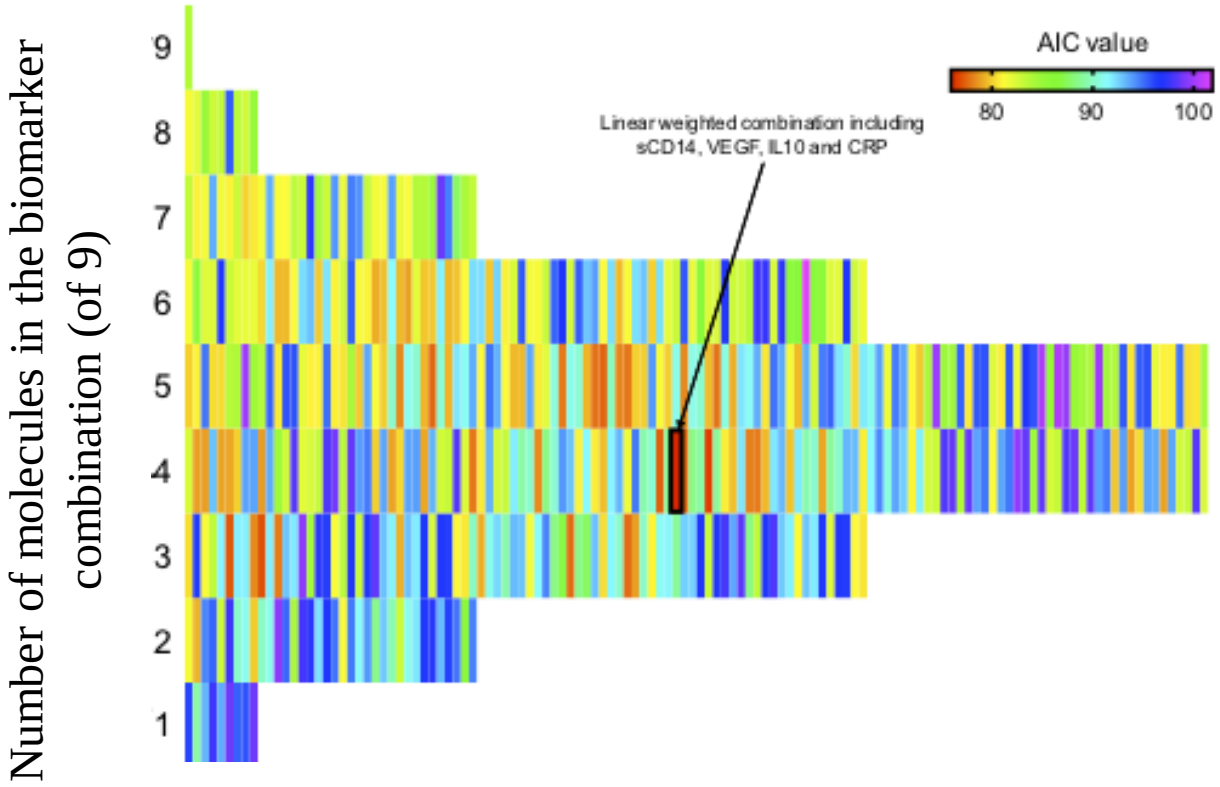
Hemorrhage and iron deposition

4 categories of biomarkers defined by the FDA-NIH Biomarker Working Group

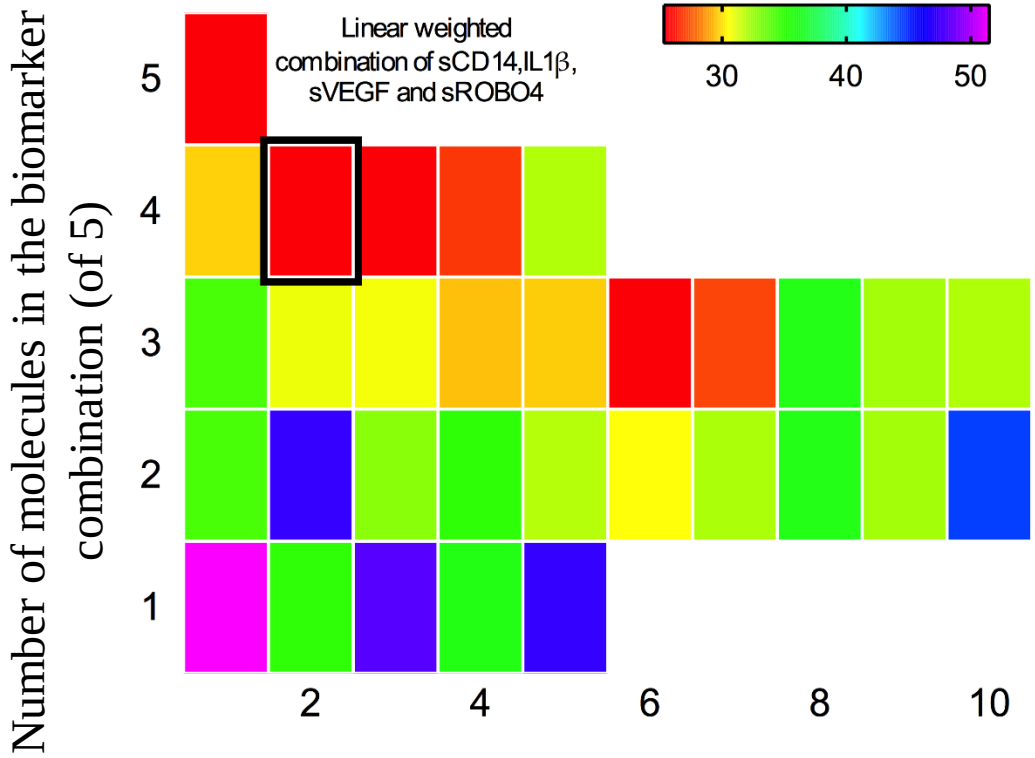
- A relevant biomarker may reflect chronic disease over the patient's lifetime, recent acute clinical activity or predict future events (Amur et al., 2015).

- 4 categories of biomarkers:
  - ✓ **Diagnostic** distinguish patients with a particular disease.
  - ✓ **Prognostic** provide information on the likely course of disease in an untreated individual.
  - ✓ **Predictive** provide a forecast of the potential responses (favorable or unfavorable) to one or more specific treatments.
  - ✓ **Response** are dynamic assessments of a biological response after a therapeutic intervention, include:
    - ➢ **Safety** indicating biological adverse effects in response to treatment.
    - ➢ **Pharmacodynamic** indicating the intended activity of the drug.
    - ➢ **Efficacy-response or surrogate endpoints** predicting a specific disease-related clinical outcome.

Plasma molecules effectively combine into a diagnostic and prognostic biomarker of hemorrhagic activity of CCM

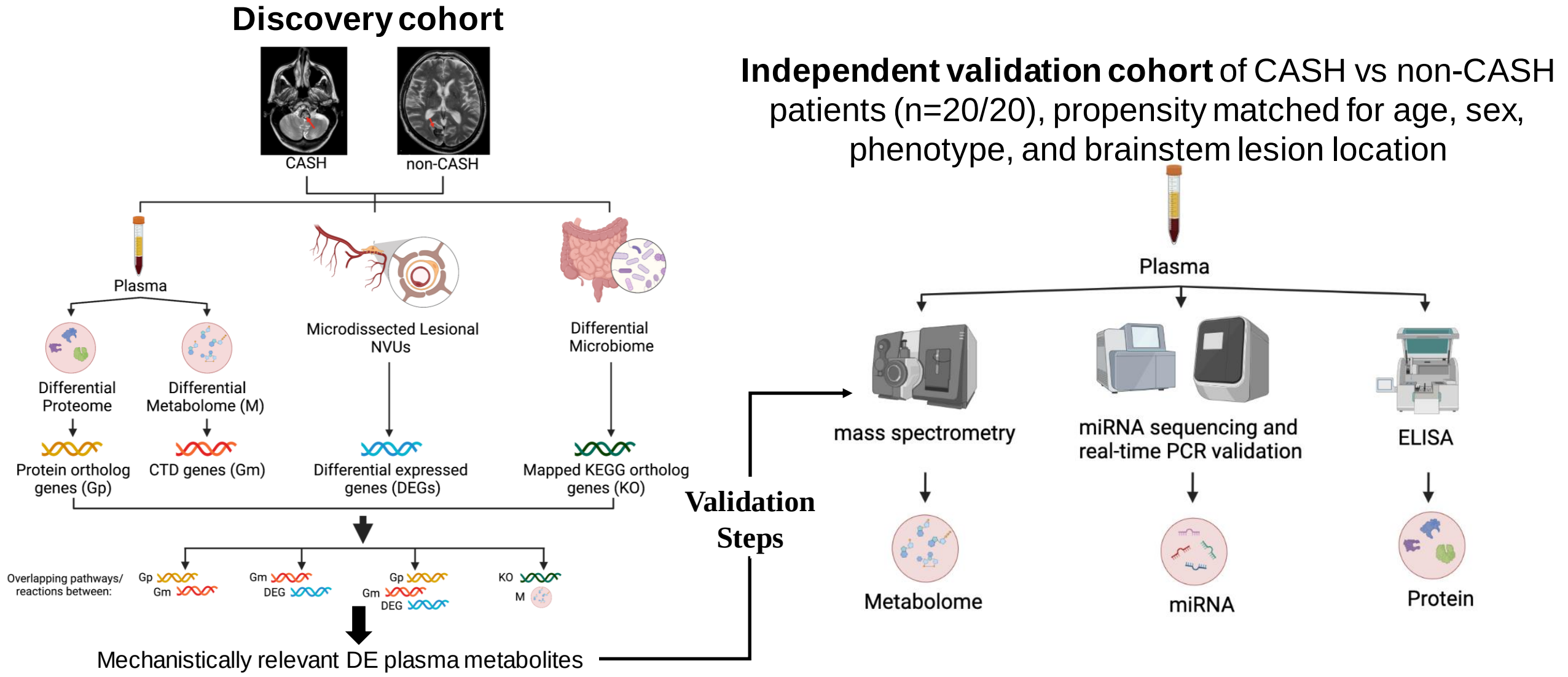


Lyne et al., 2019



Girard et al., 2018

Methodology to Identify Candidate Biomarkers

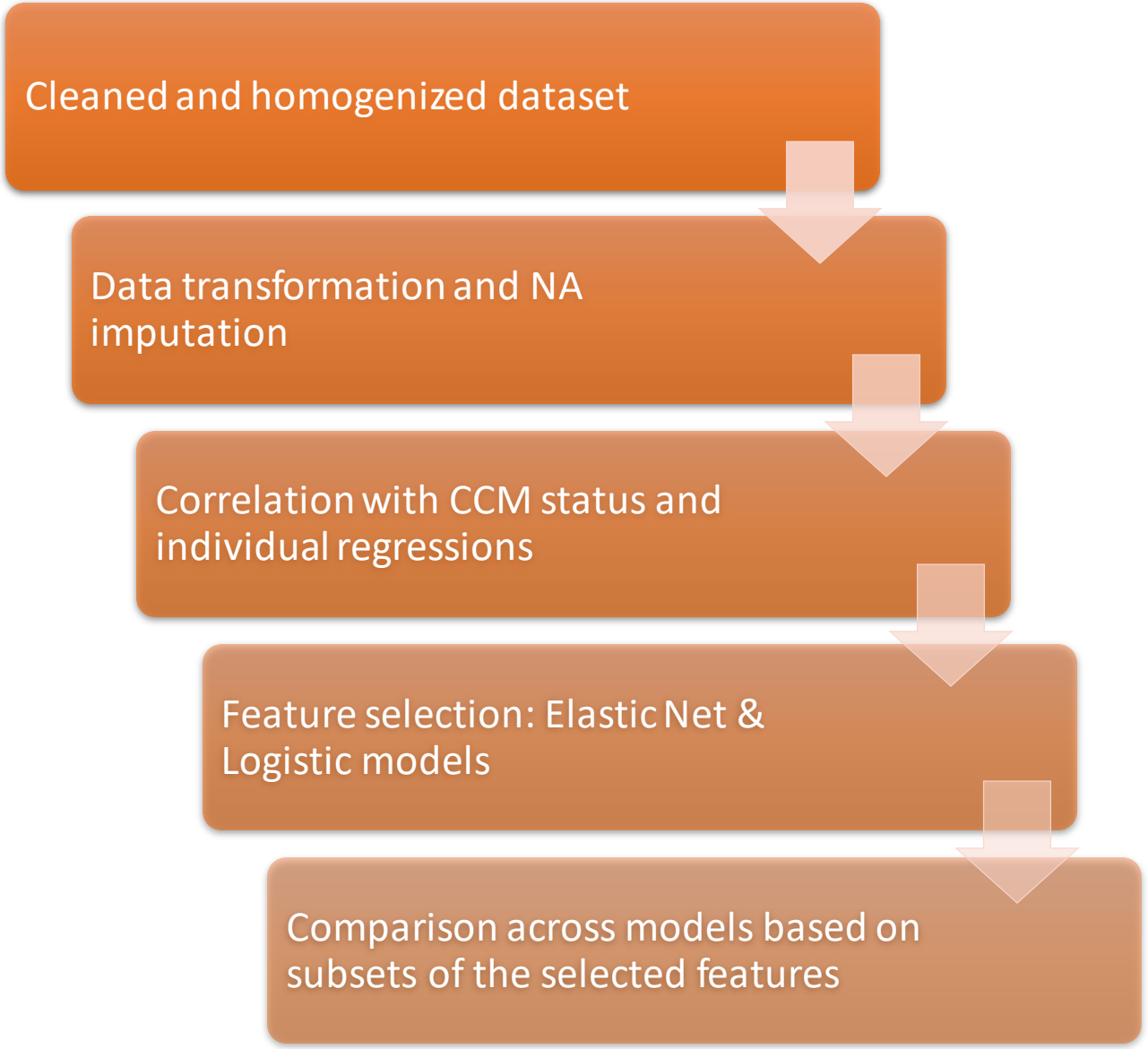


Srinath et al., 2023

Multi-Omic Datasets in Diagnostic and Prognostic Discovery Cohorts

	Assay	Diagnostic	Prognostic
Metabolites	LC-MS/MS	11	11
Proteins	ELISA	16	16
miRNA	ddPCR	5	-
Patients		**20/20**	**15/15**

Pilot cohorts: General Workflow



Pilot cohorts: General Workflow

Cleaned and homogenized dataset

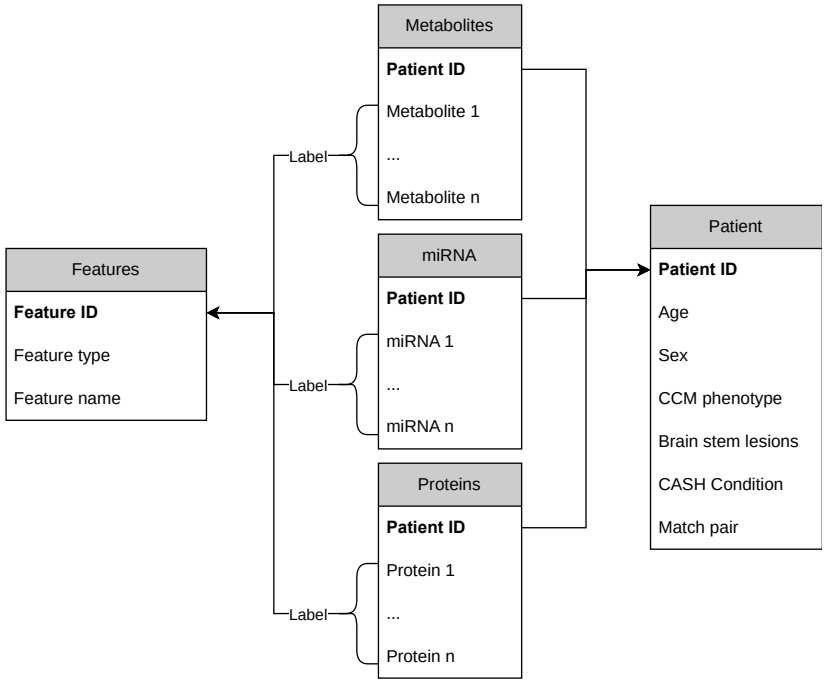
Data transformation and NA imputation

Correlation with CCM status and individual regressions

Feature selection: Elastic Net & Logistic models

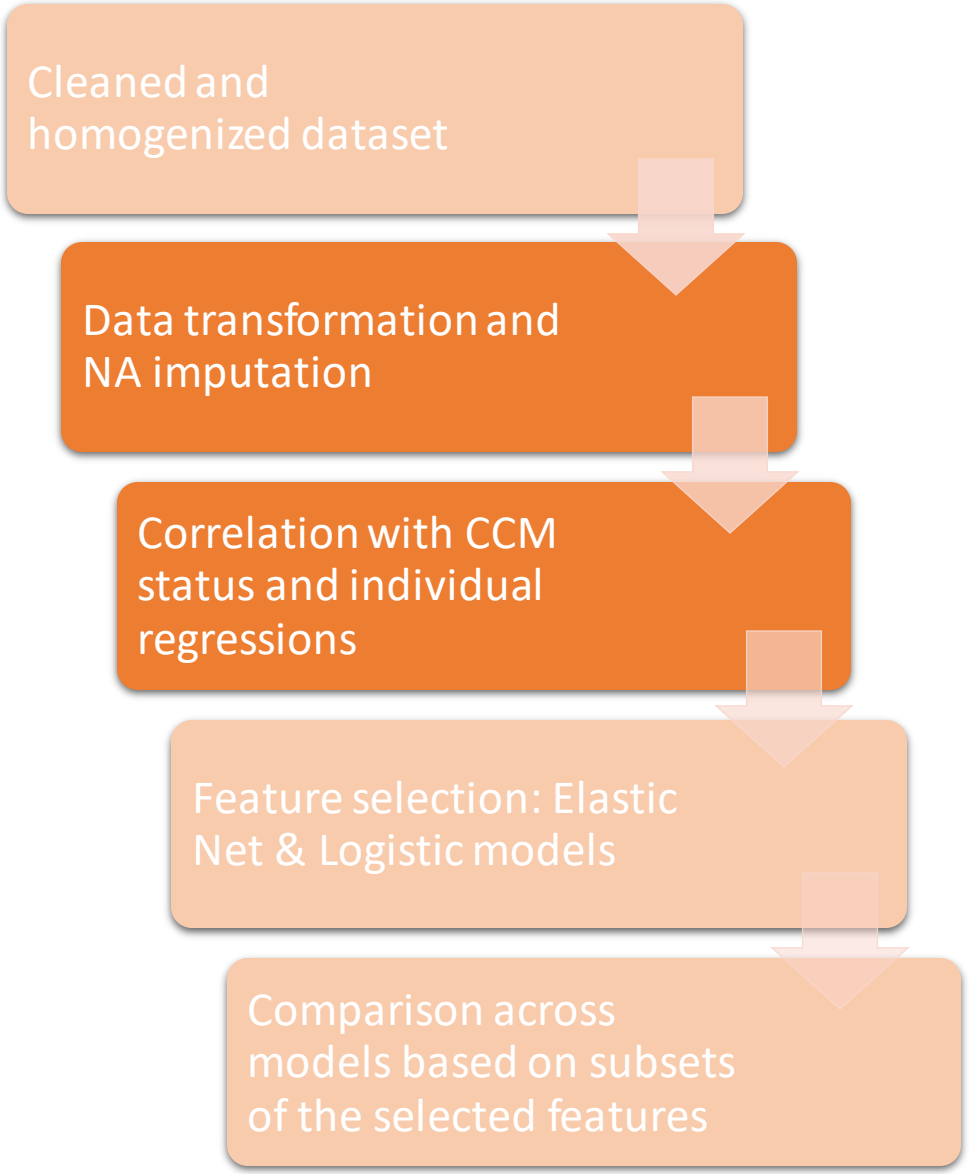
Comparison across models based on subsets of the selected features

Database structure



- Homogeneity across tables: Universal patient ID.
- Tidy format for data analysis and repository sharing.

Pilot cohorts: General Workflow



Data transformation

Test of normality (Shapiro-Wilk test)

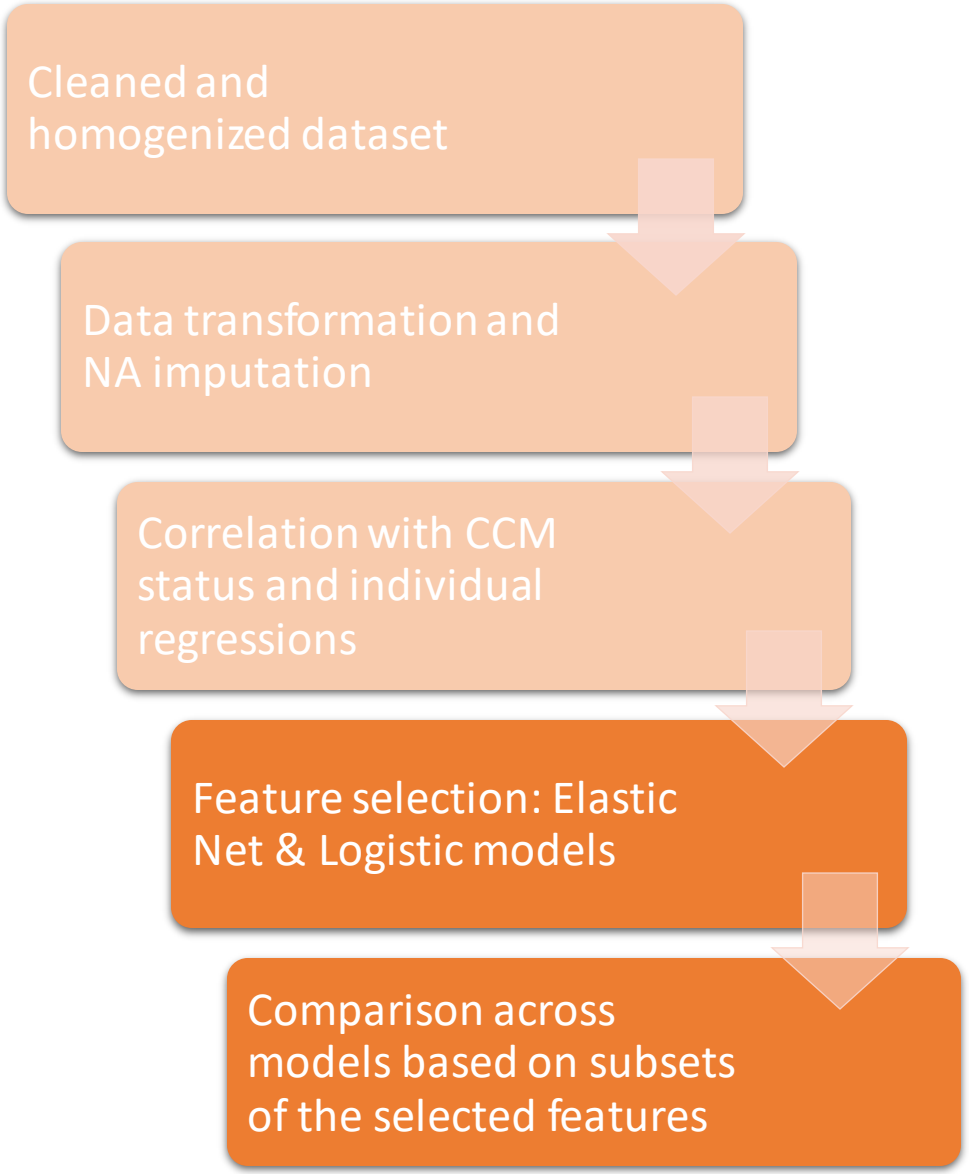
- Metabolites: linear
- Proteins: $\log_2$
- miRNA $\log_2$

NA imputation

- Model-based imputation method
- Hot-Deck initialized

Individual logistic regression

Pilot cohorts: General Workflow



Feature selection

- **Elastic Net** optimized for **accuracy** and **repeated k-fold** cross-validation.
- Logistic regression over the complete set and conditional logistic regression to evaluate the performance of propensity-match.

Reduced models

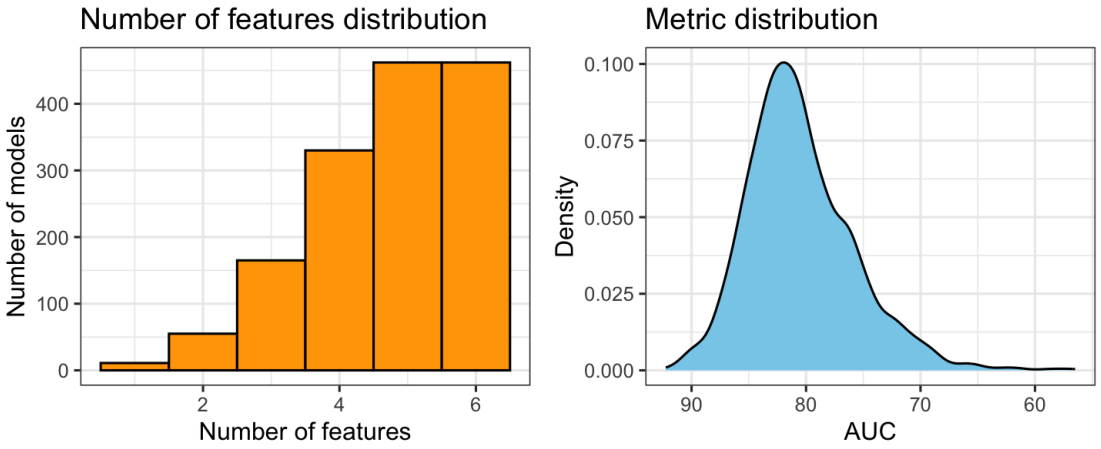
- Subset combinations of n elements, arranged by highest AUC.

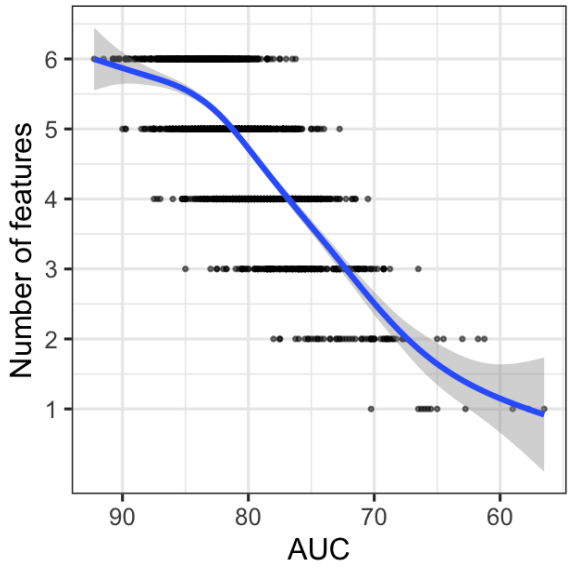
Best models criteria

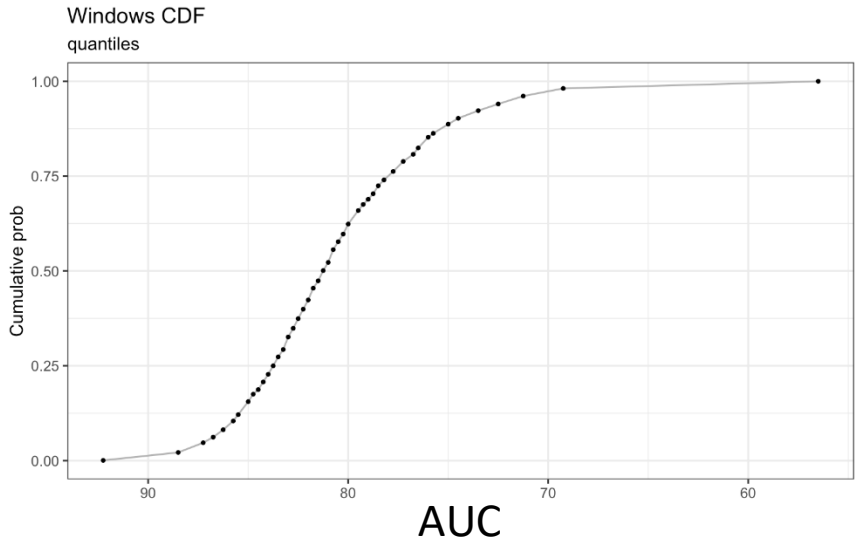
- Highest AUCs for a given number of features and lowest number of unique molecule types.

Subset models - AUC Comparison

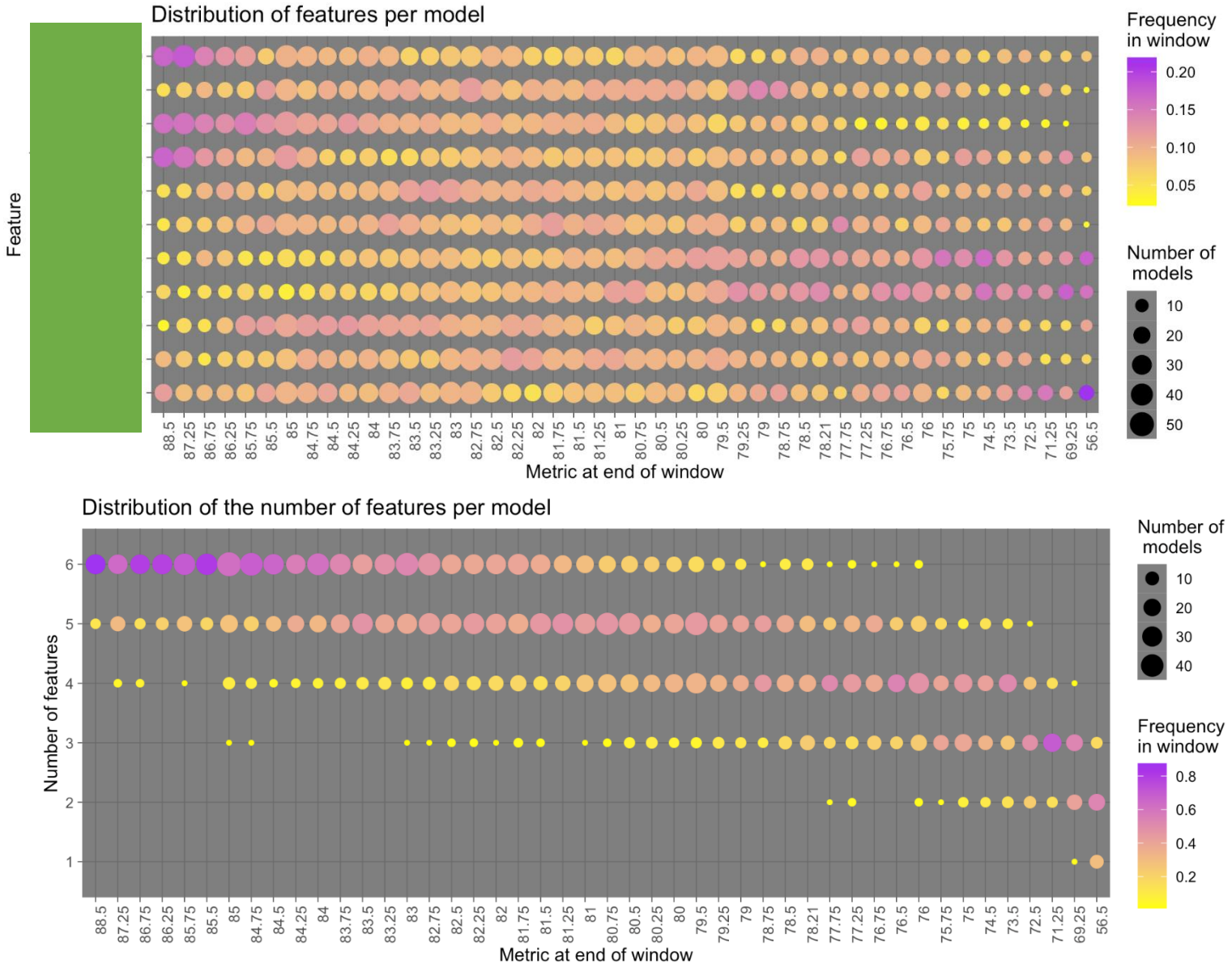
Total model considered: 9948 (Combinations from 1 to 6 elements max)







Subset models - AUC Comparison



Future work and Perspective

- Identification of the best diagnostic and prognostic models.
- Best models evaluation in testing cohorts: n > 260 patients.
- Model performance in relation of the known confounders of CCM clinical activity (e.g., CCM phenotype, lesion localization, gender and age).