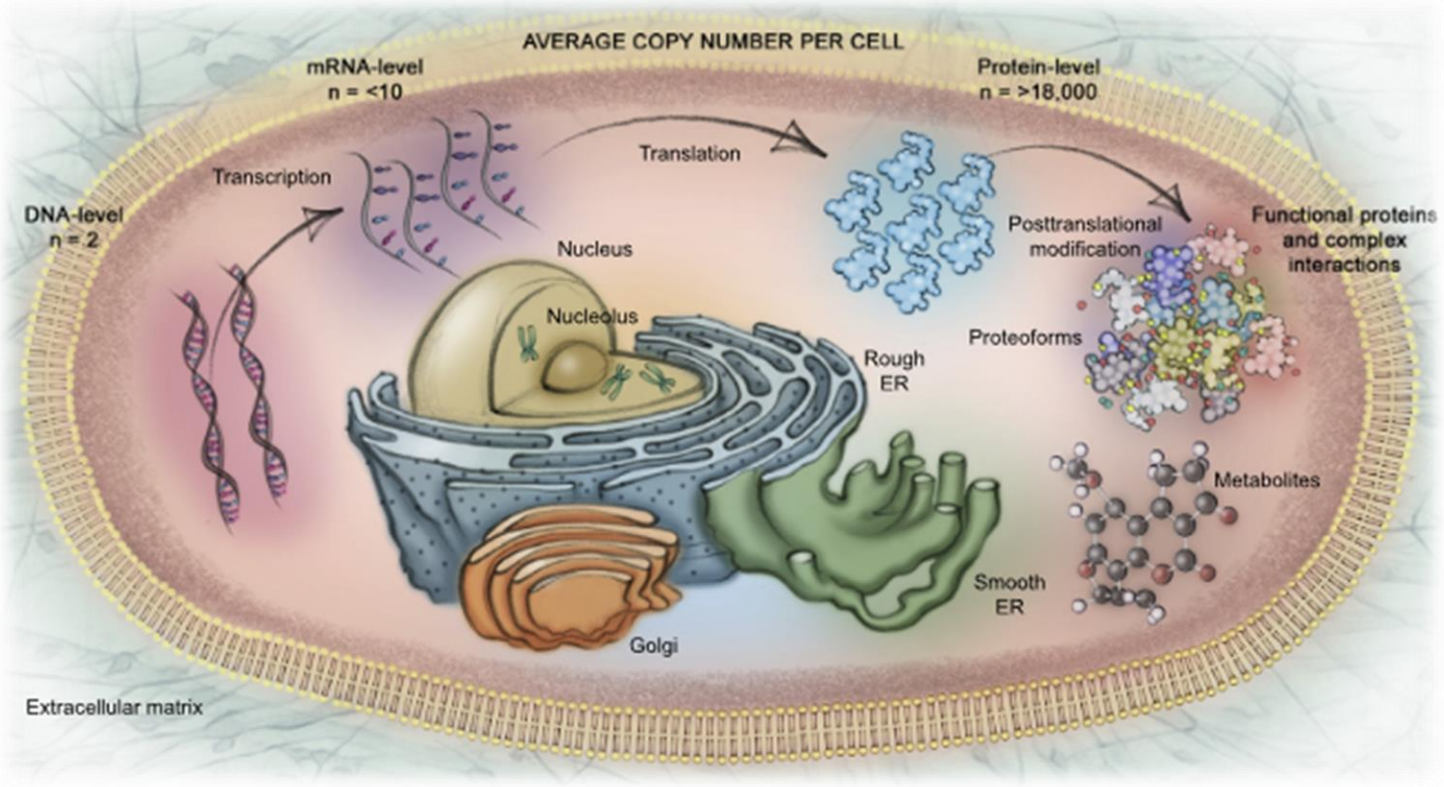
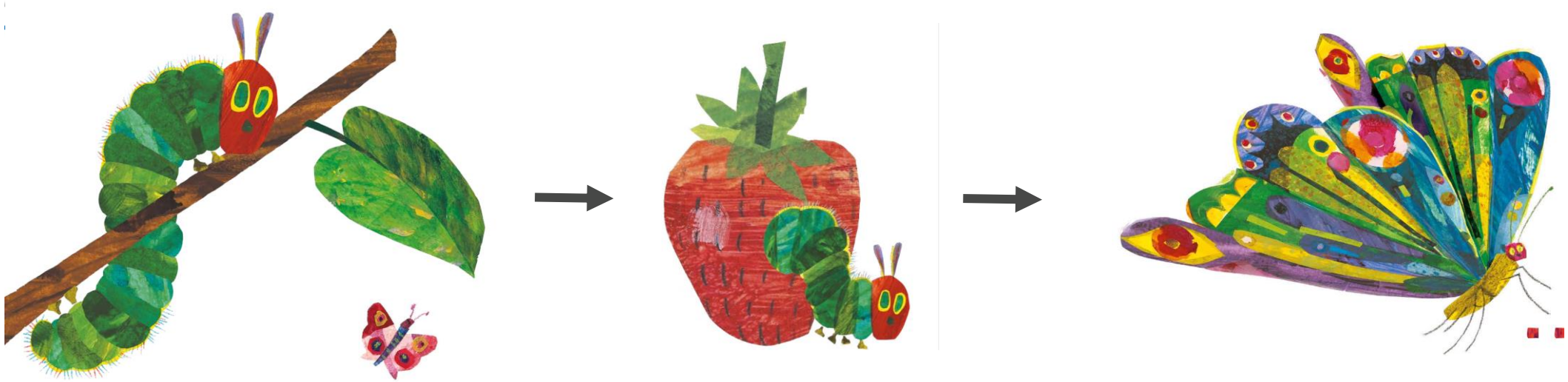
Proteomics for Precision Healthcare: Illuminating Cardiovascular Disease

Why do proteomics?

- A human being consists of about 100 Billion (10^{14}) cells
- Each cell contains a nucleus and other organelles (mitochondria, ER, …)
- Each cell has the complete set of genetic information but different proteins



Caterpillar and Butterfly – same gene, but another phenotype

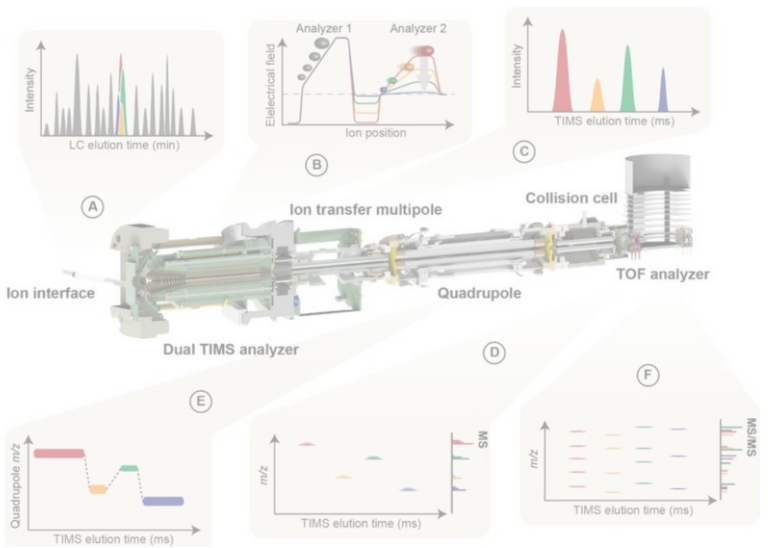


- Proteins are the functional actuators → direct measurement = best measurement
- Function of proteins (phenotype) are modulated from transcription to post-translational levels
- Specific proteoform can carry a particular biological function

Adapted from: The very hungry caterpillar (Eric Carle)

Long-term missions of our department

Constant technological developments

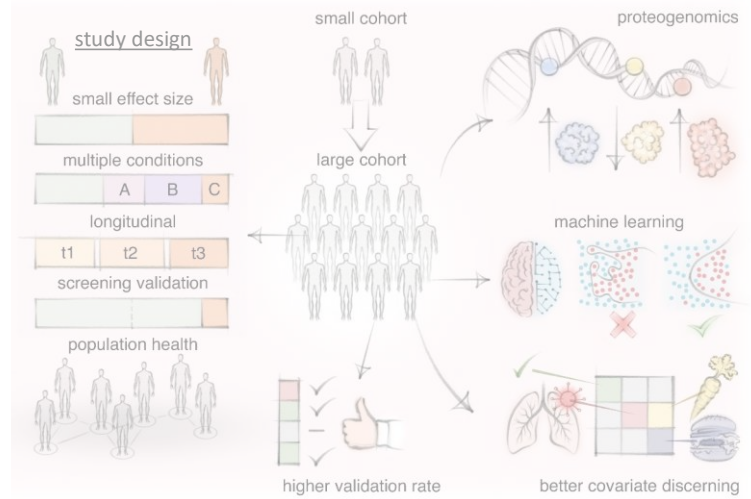


Open source MS software

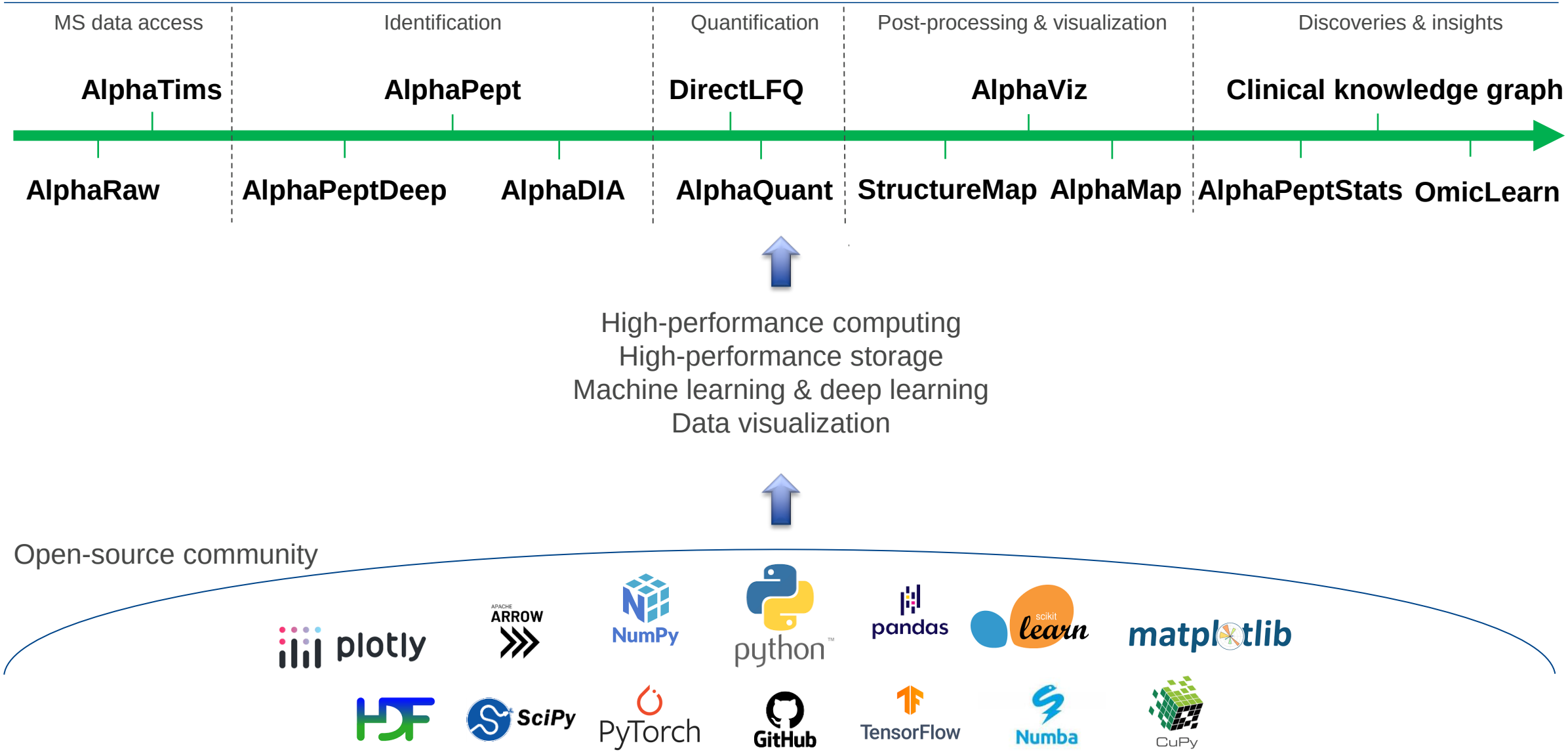
The alpha universe

Mann Labs

High biological and clinical relevance



Overview of AlphaX packages



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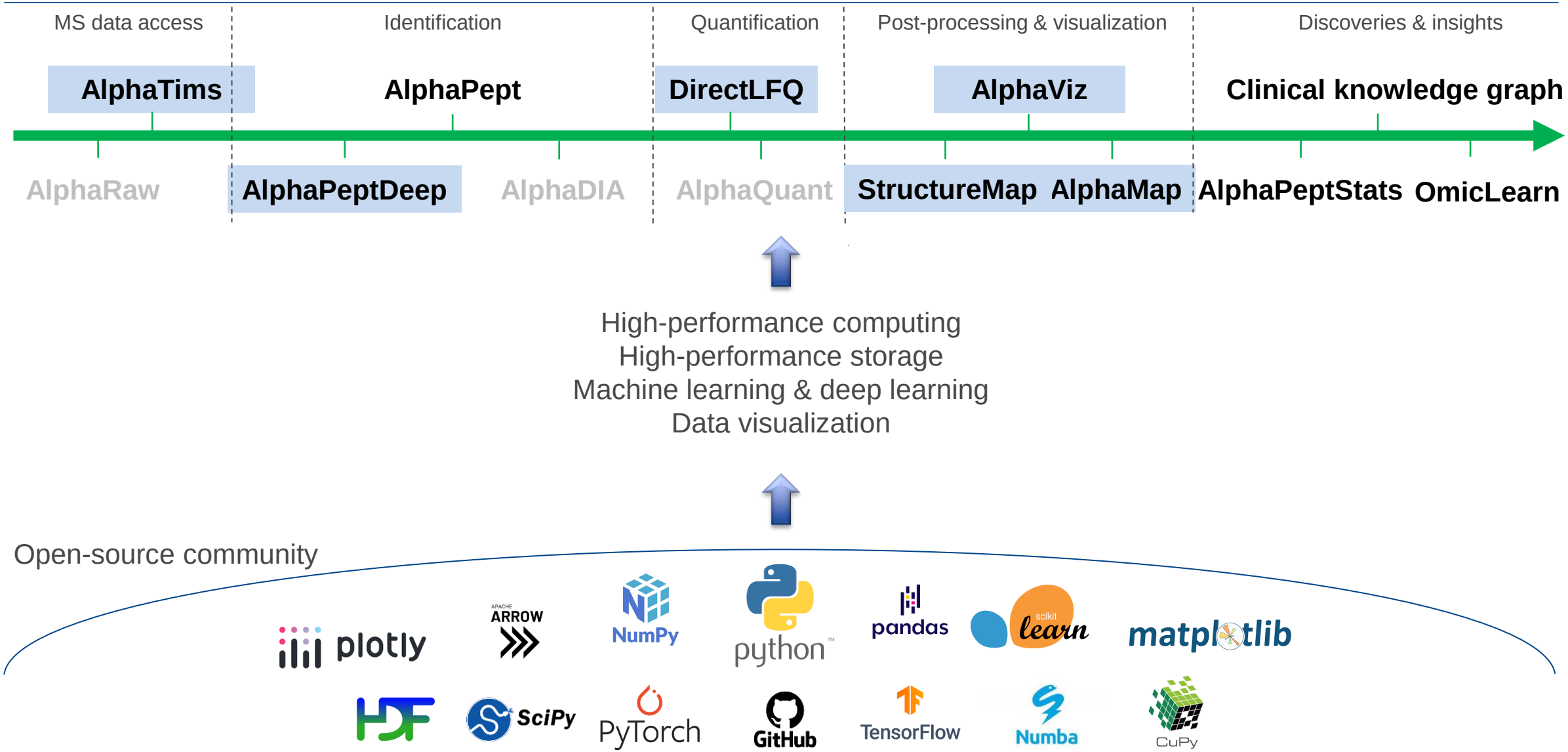
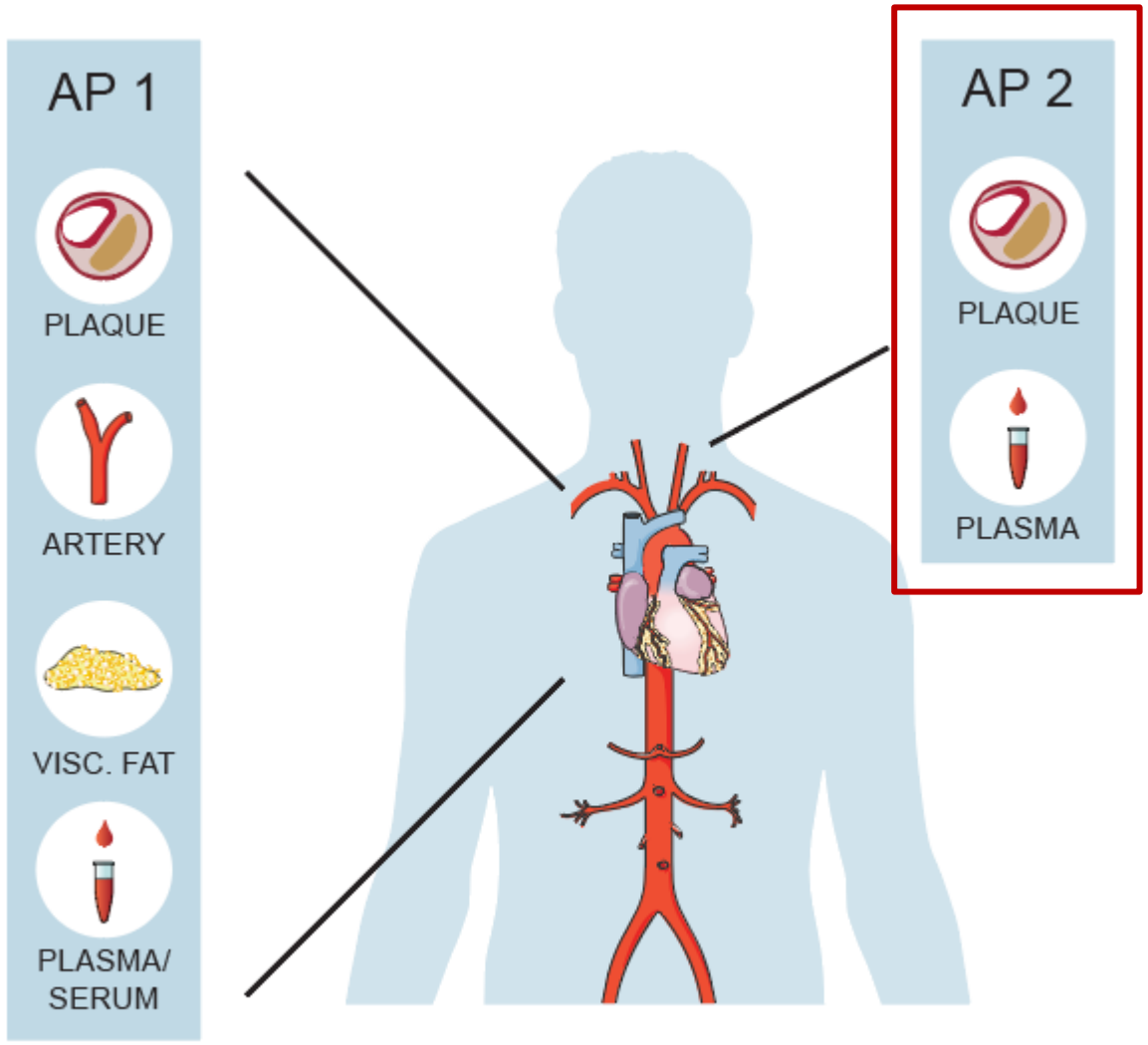


DigiMed – P4 medicine for Coronary Heart Disease



DigiMed Bayern

AP 1: ***P4 medicine for coronary heart disease (CHD)***

AP 2: ***P4 medicine for carotid stenosis and stroke***

Deutsches Herzzentrum München
des Freistaates Bayern
Klinik an der Technischen Universität München

Klinikum rechts der Isar
Technische Universität München

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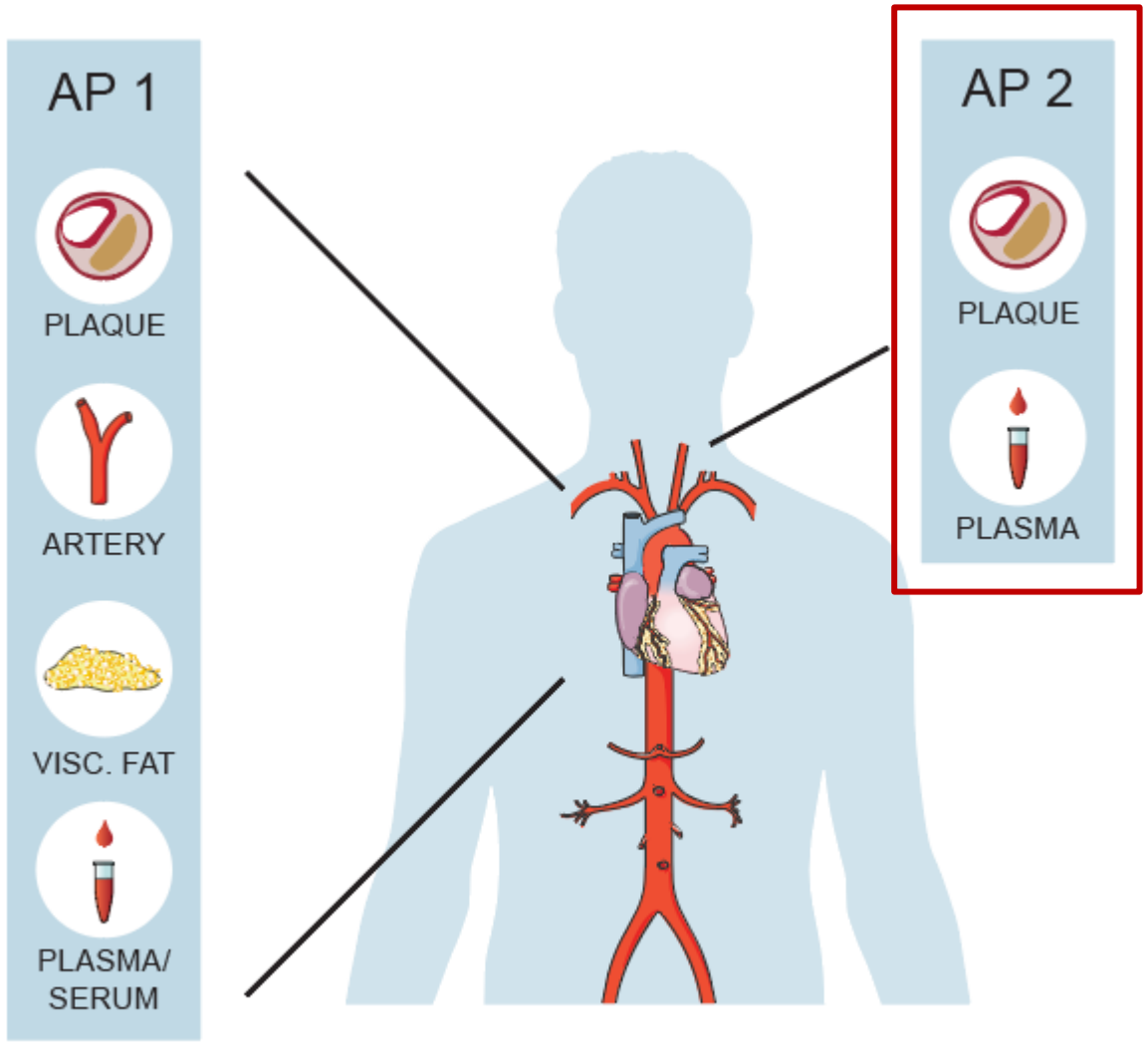
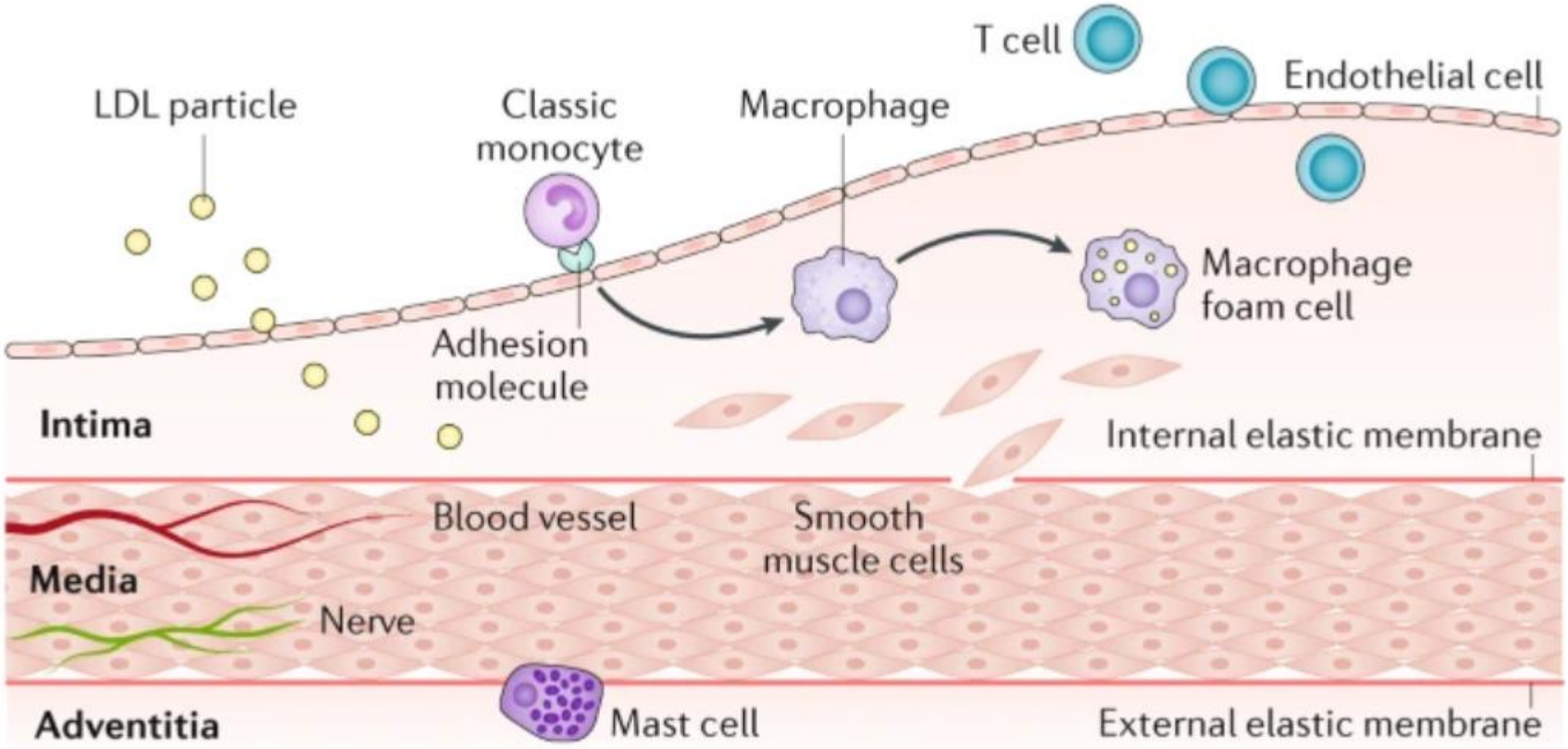


DigiMed Bayern

AP 2: ***P4 medicine for carotid stenosis and stroke***

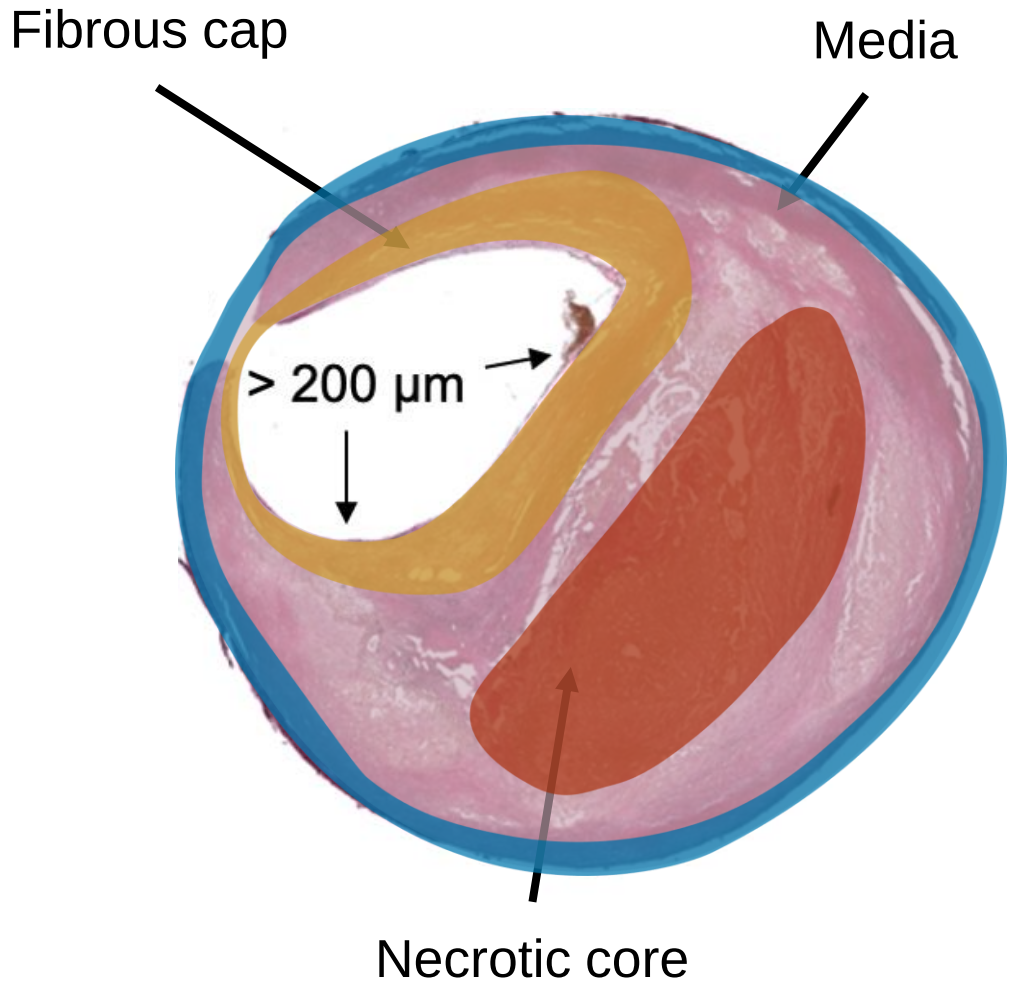
→ How plaque subregions contribute to plaque stability risks?

Pathogenesis of atherosclerotic plaques



The three histomorphologically distinct subregions inside carotid artery plaques

- **Media**
  - Outer layer, surrounds the intima
  - VSMCs, organised ECM proteins
- **Necrotic core**
  - Largest component of the plaque, forms in the intima
  - Necrotic cells, cell debris, inflammatory cells, foam cells and lipids
  - Extensive intra-plaque hemorrhage
- **Fibrous cap**
  - Protective barrier around the arterial lumen
  - ECM proteins, activated VSMCs, macrophages, lymphocytes



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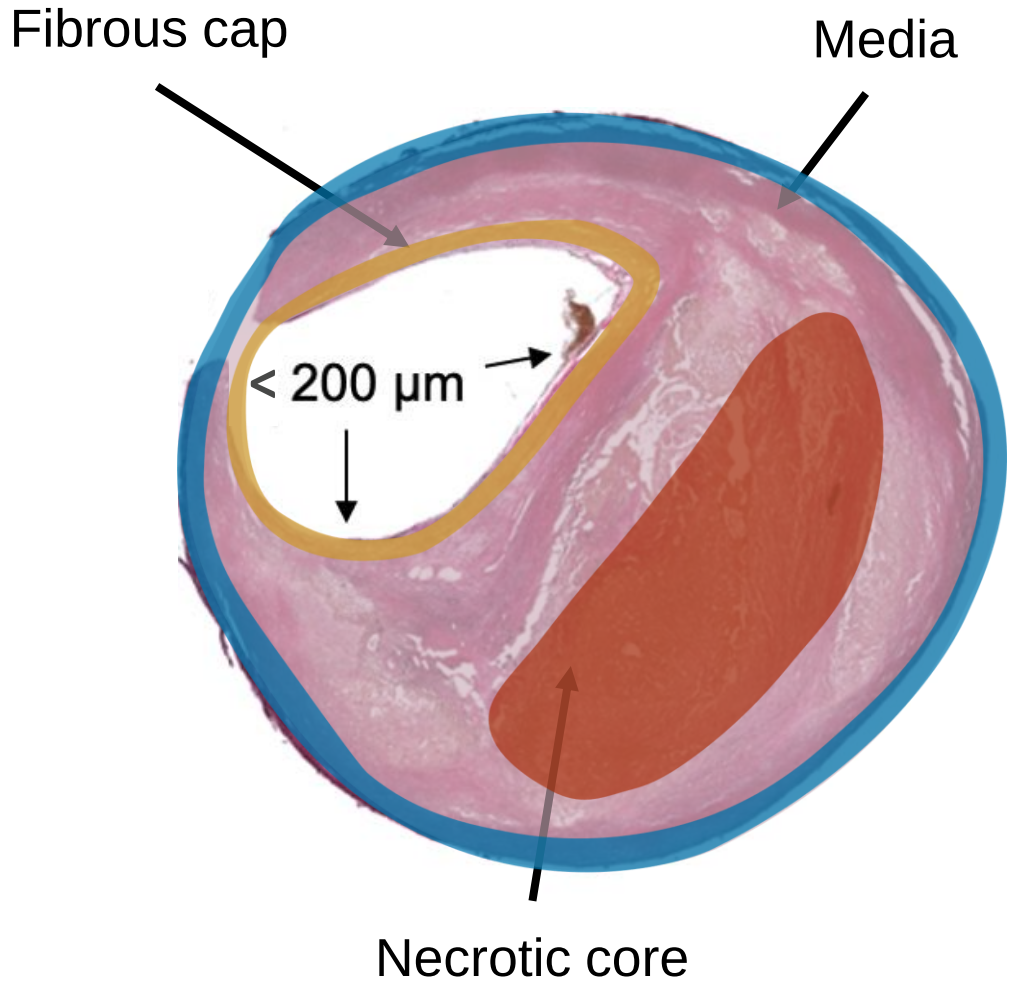
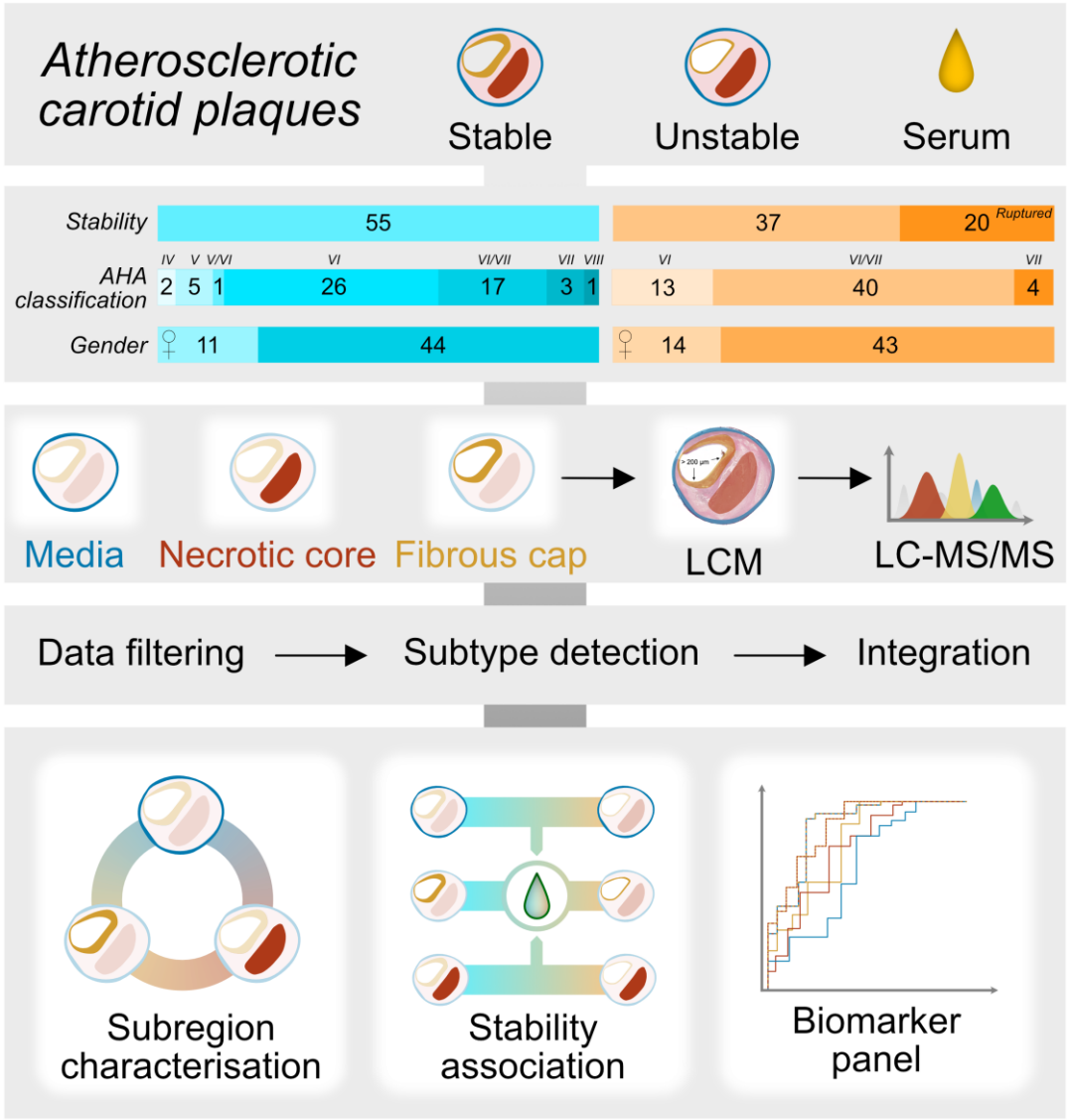


→ ***How do the subregions differentially associated with the stability status of carotid plaques?***

Study overview



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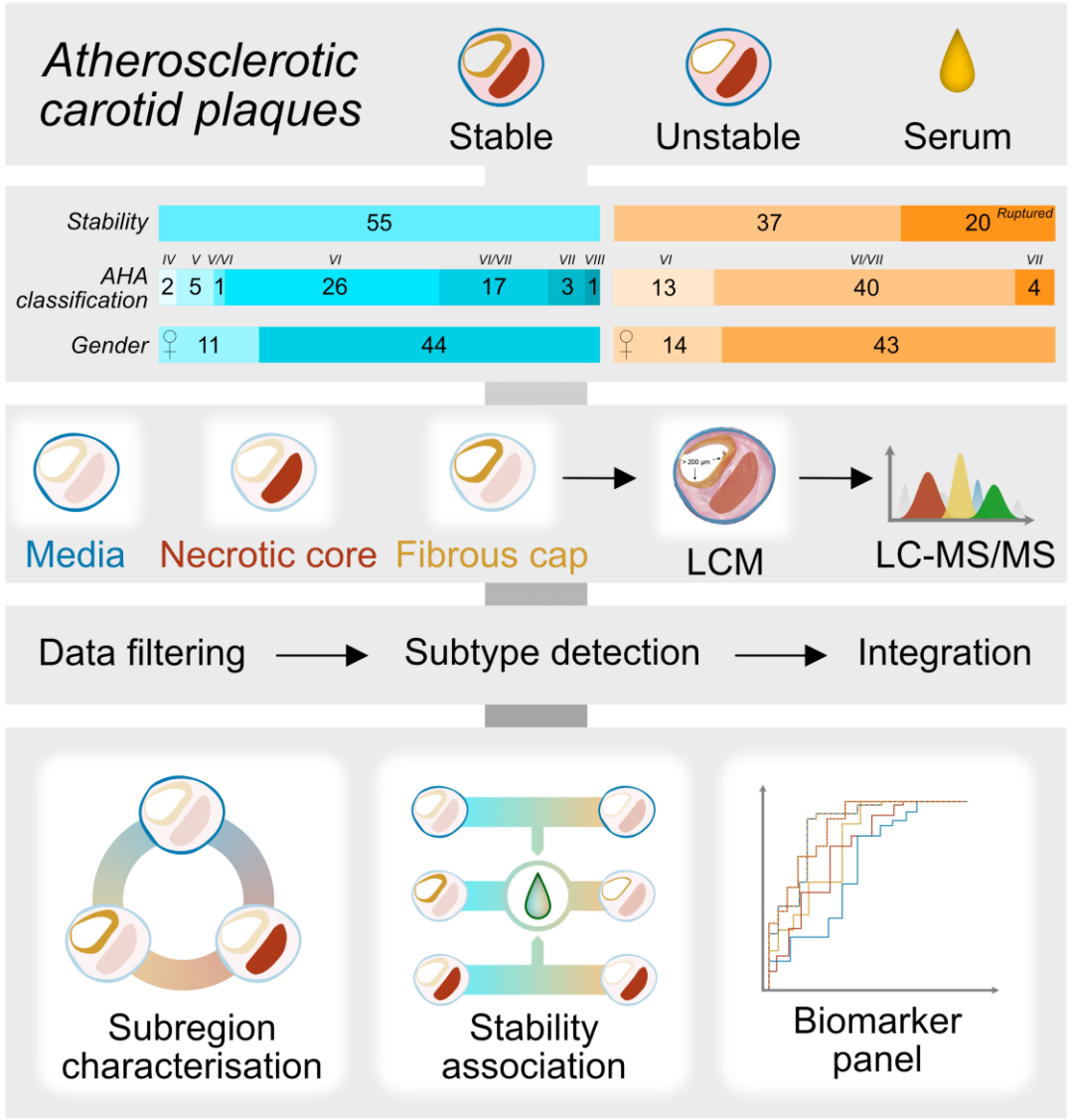

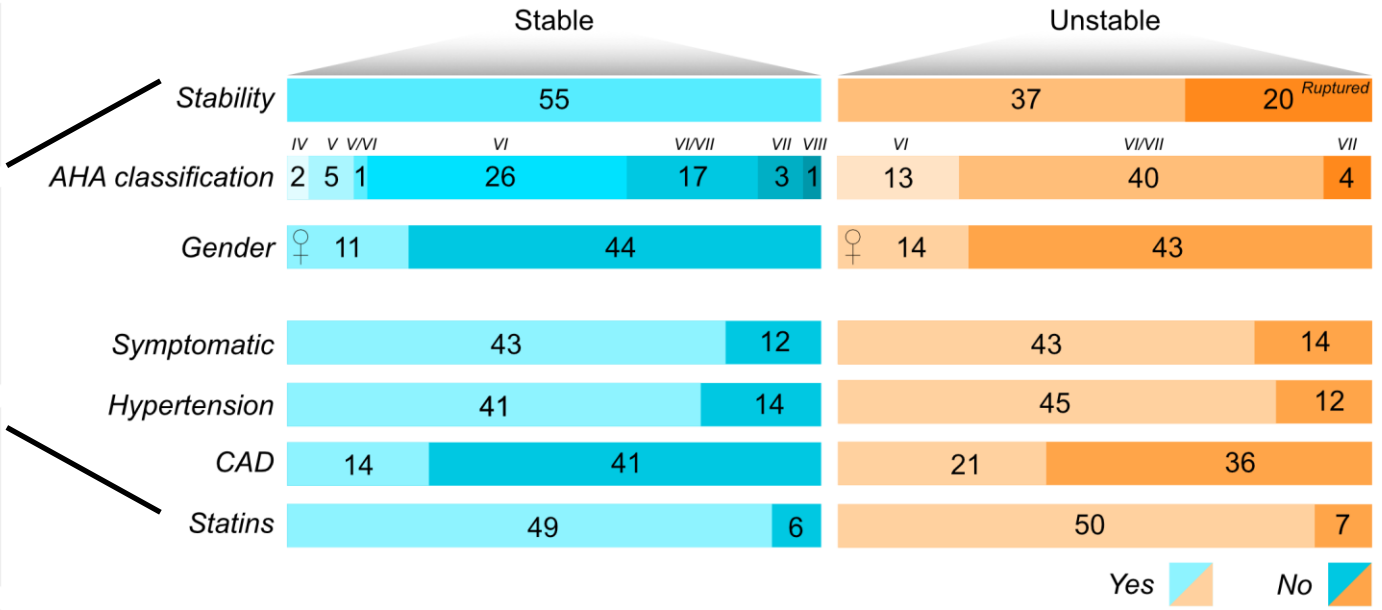

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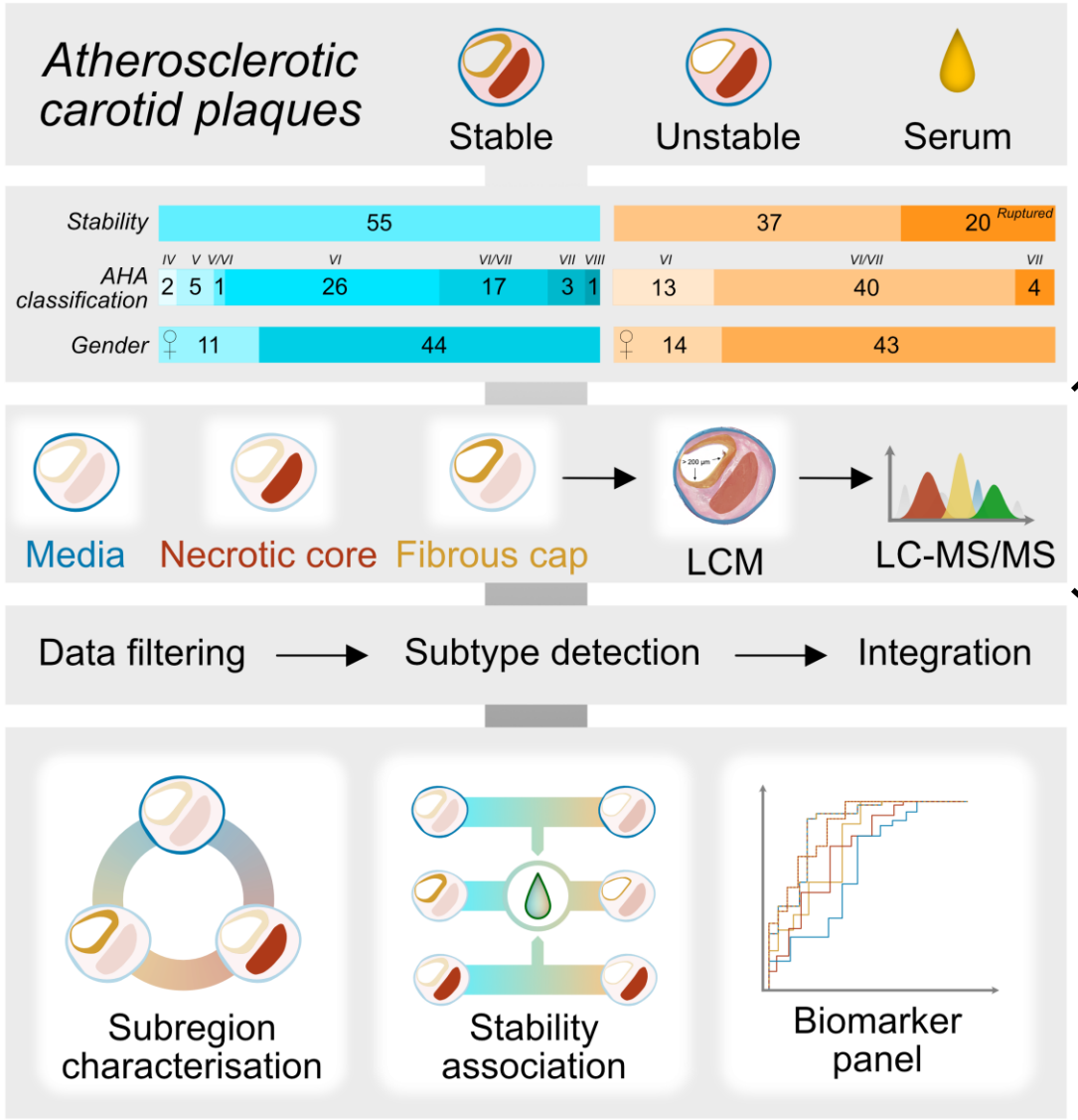
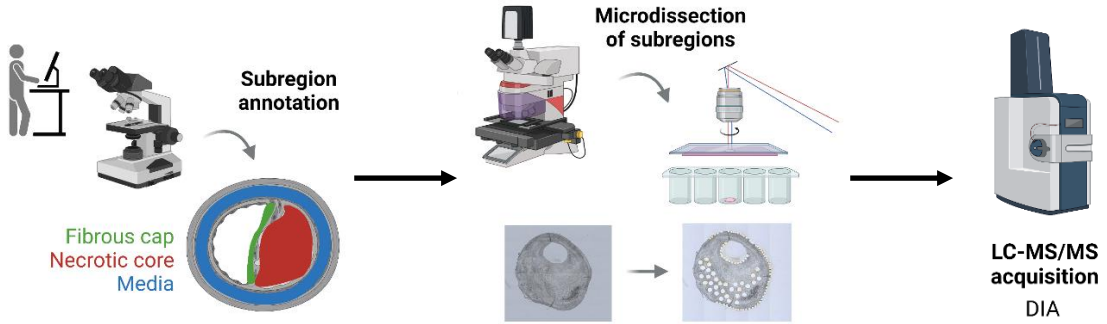
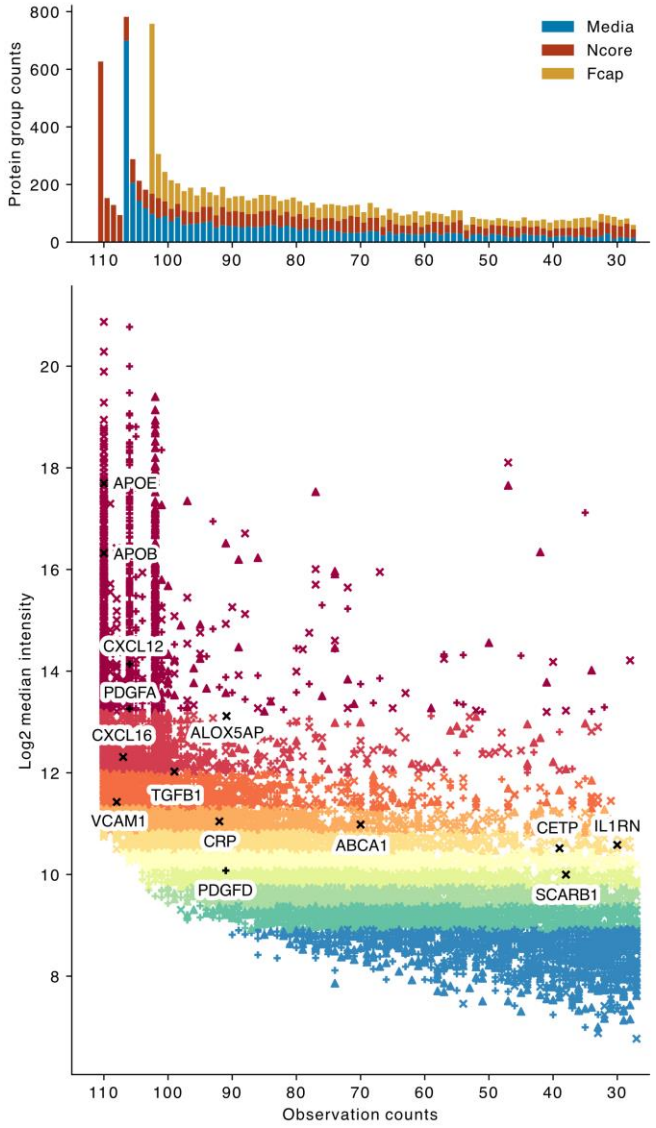


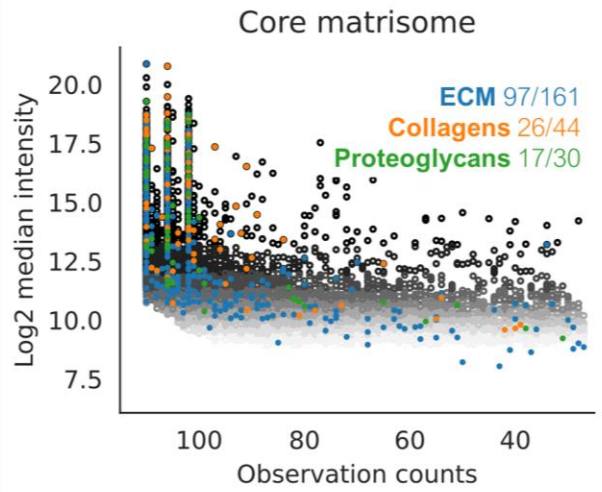
Key concepts:

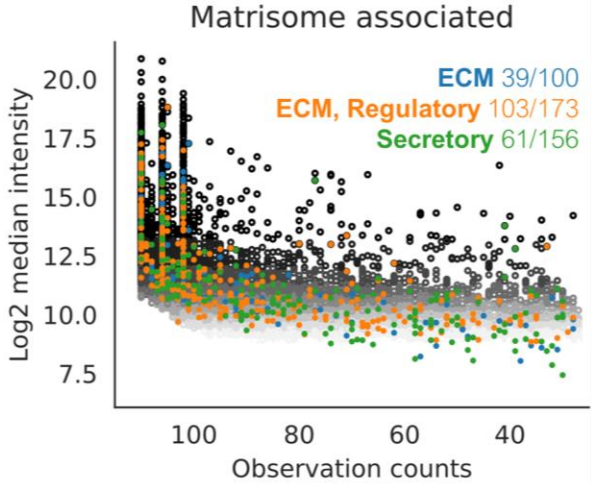
Proteomics characterization → Carotid plaque → Histological subregion → Plaque stability

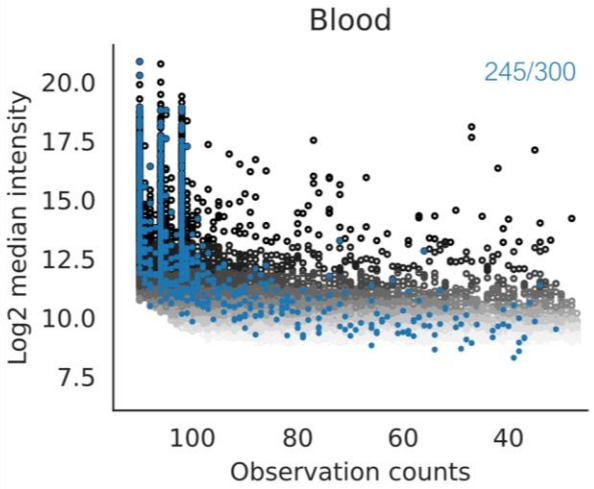


Proteomics reliably quantifies ECM and other atherosclerosis related proteins

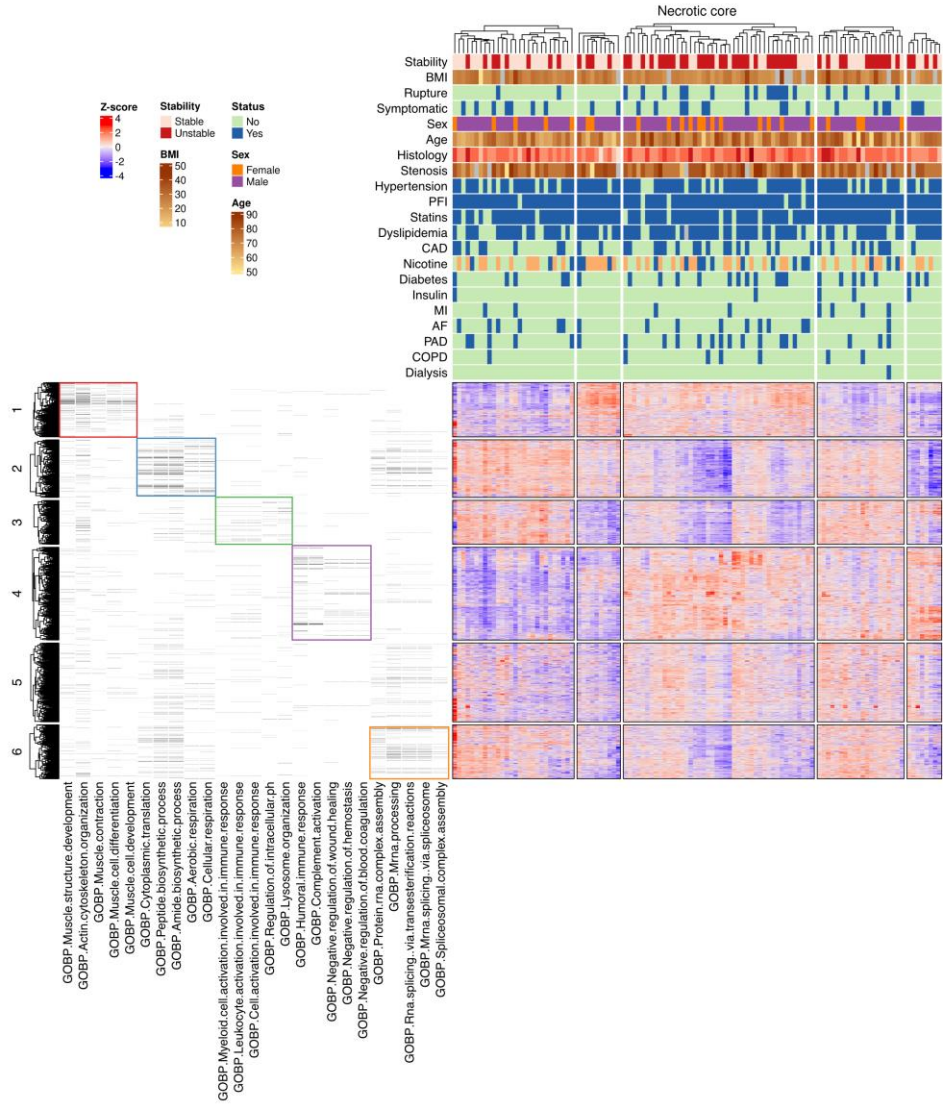








Proteomics identifies patient and protein subtypes



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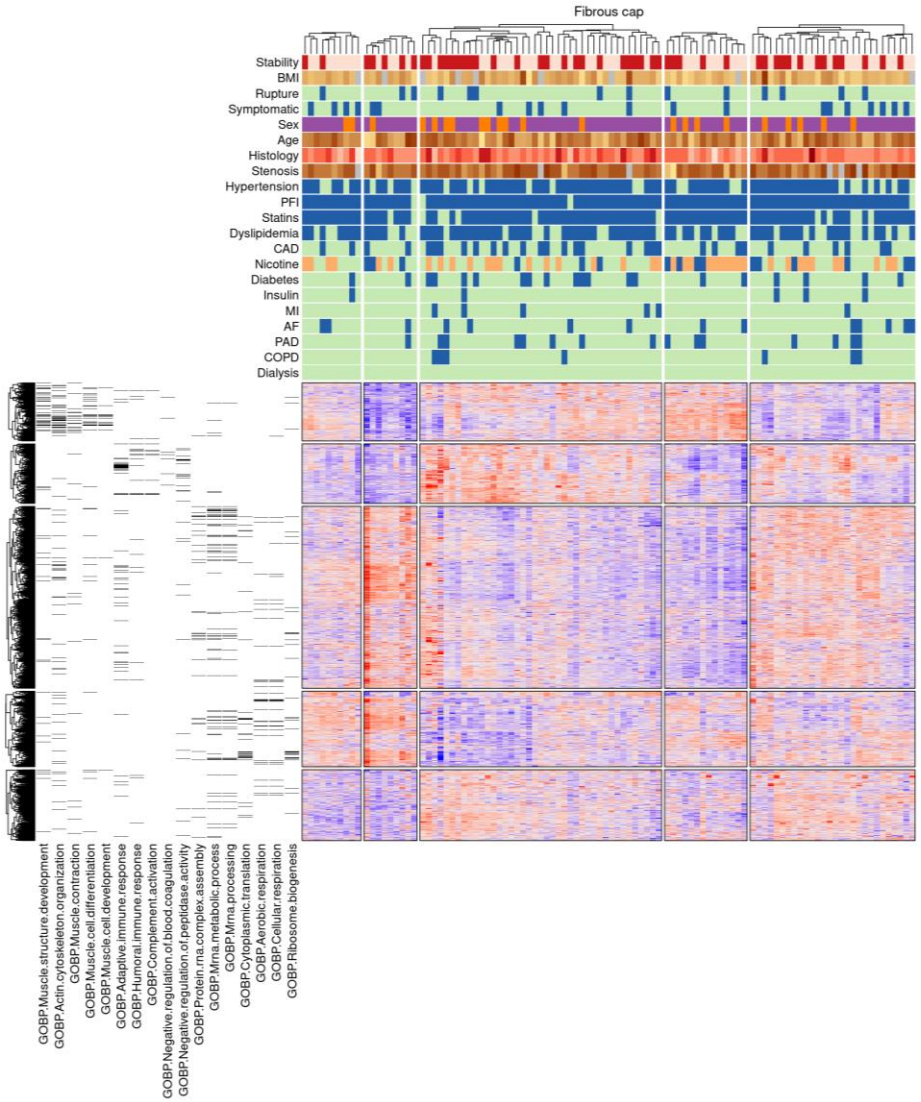
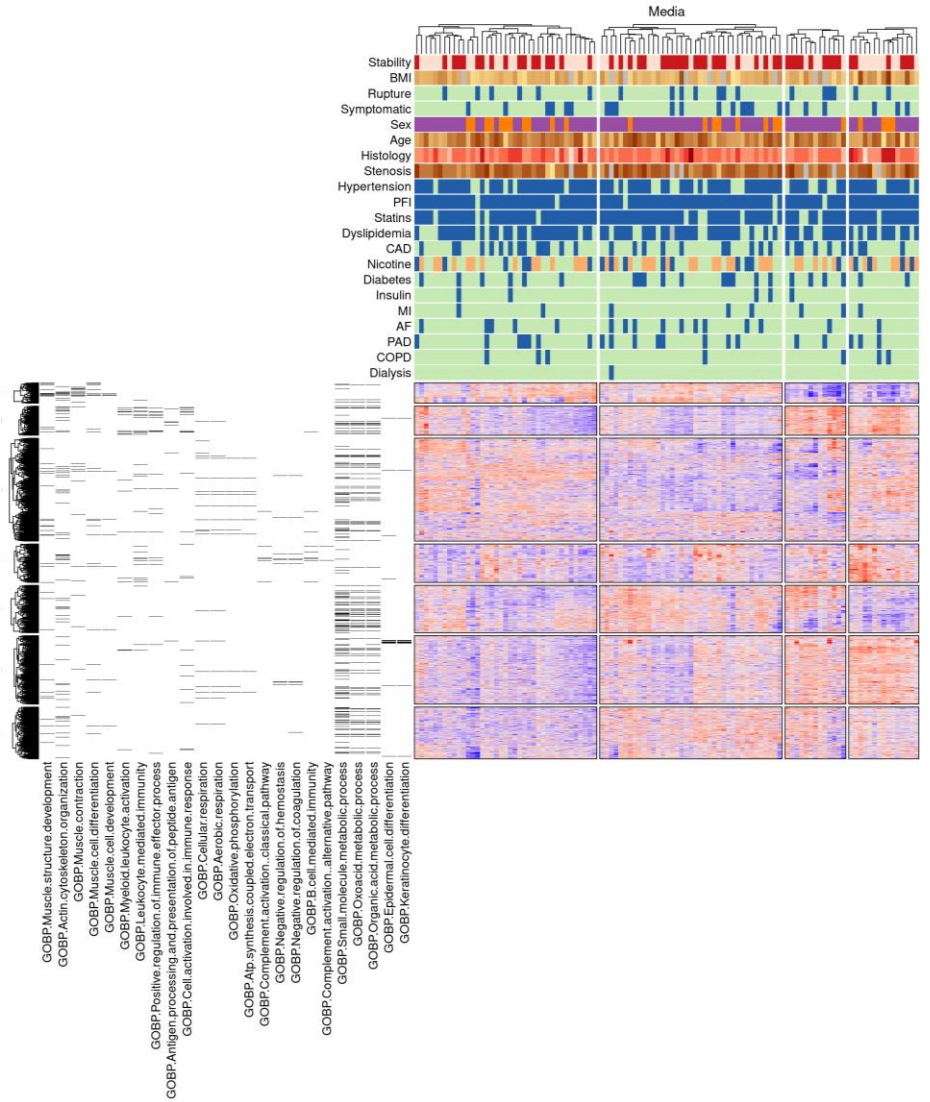
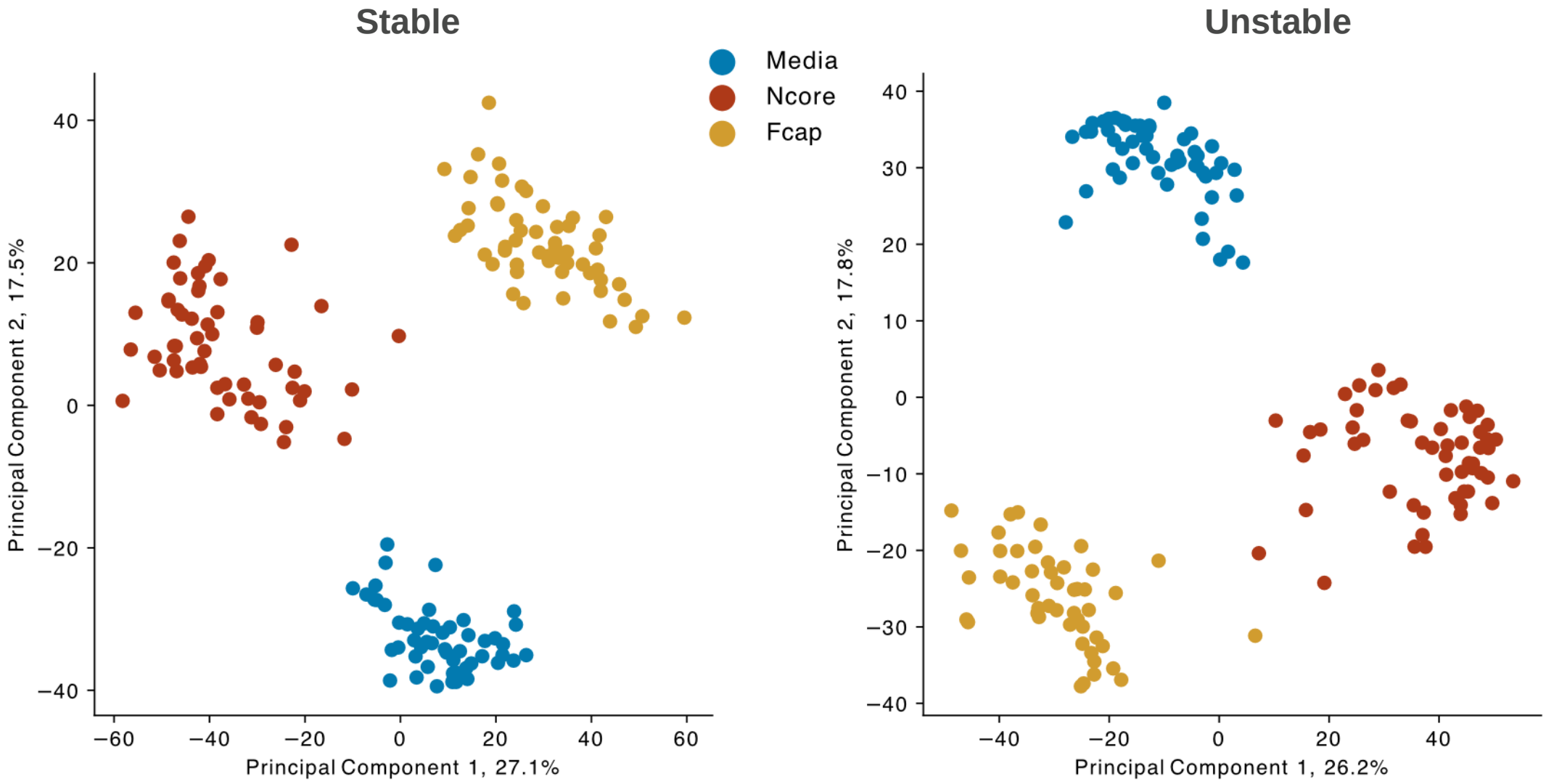




How do the plaque subregions differ in proteomics?



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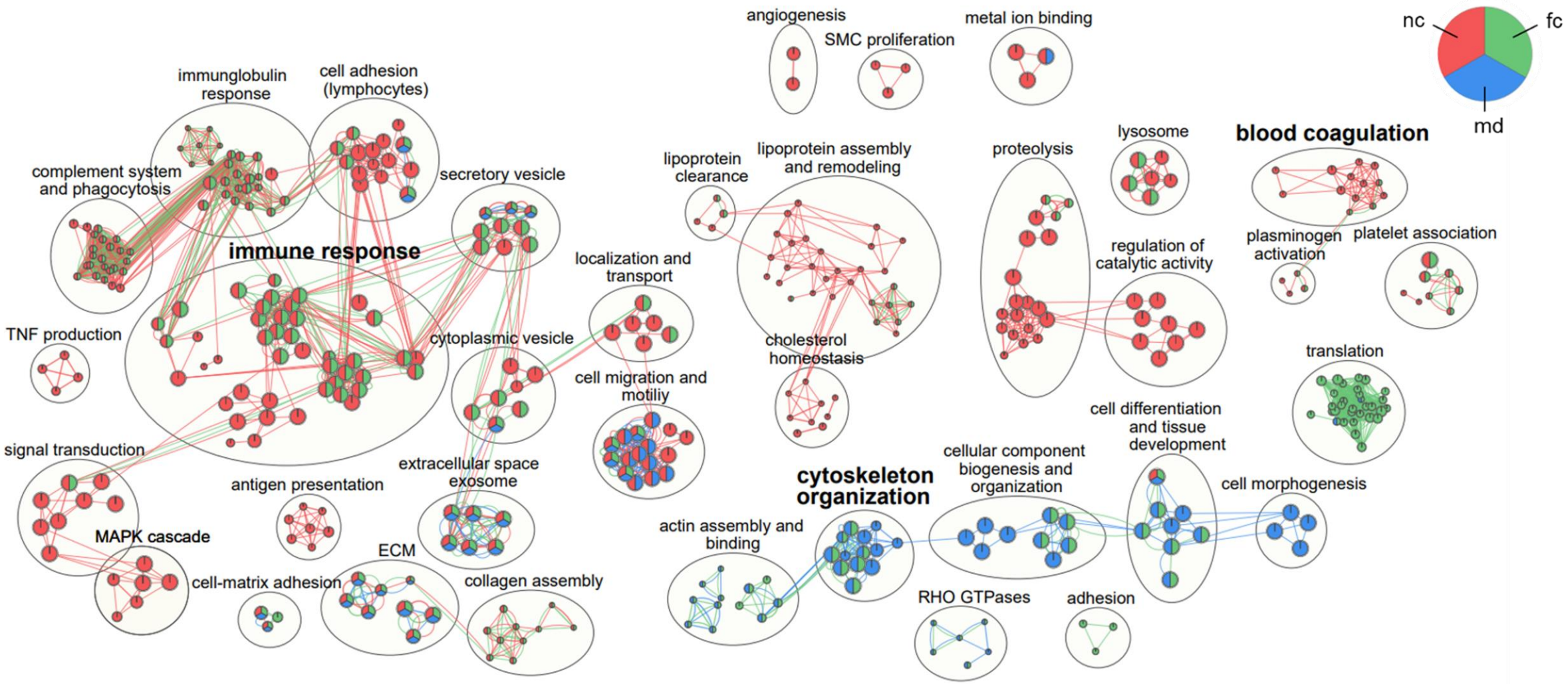
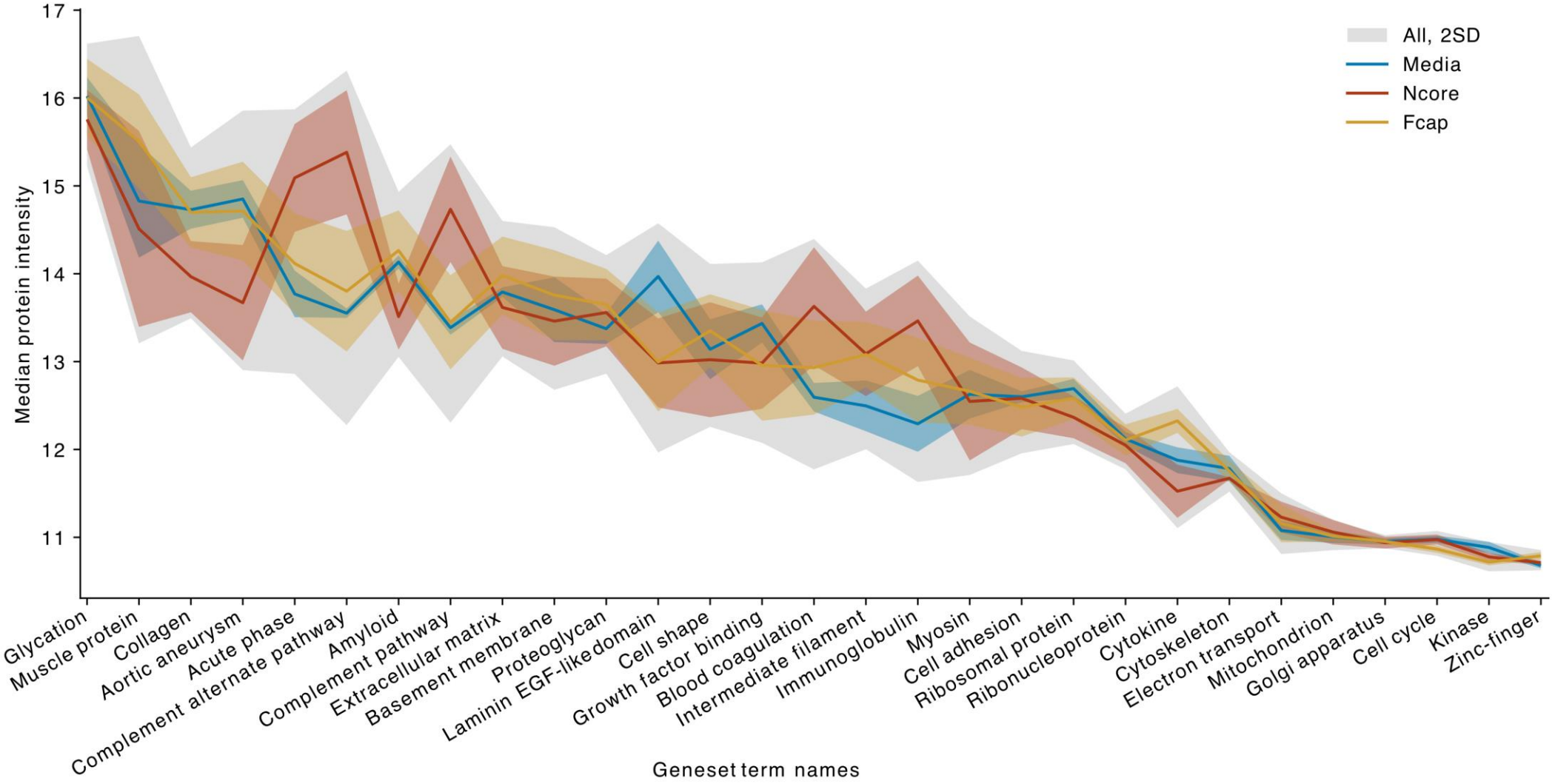
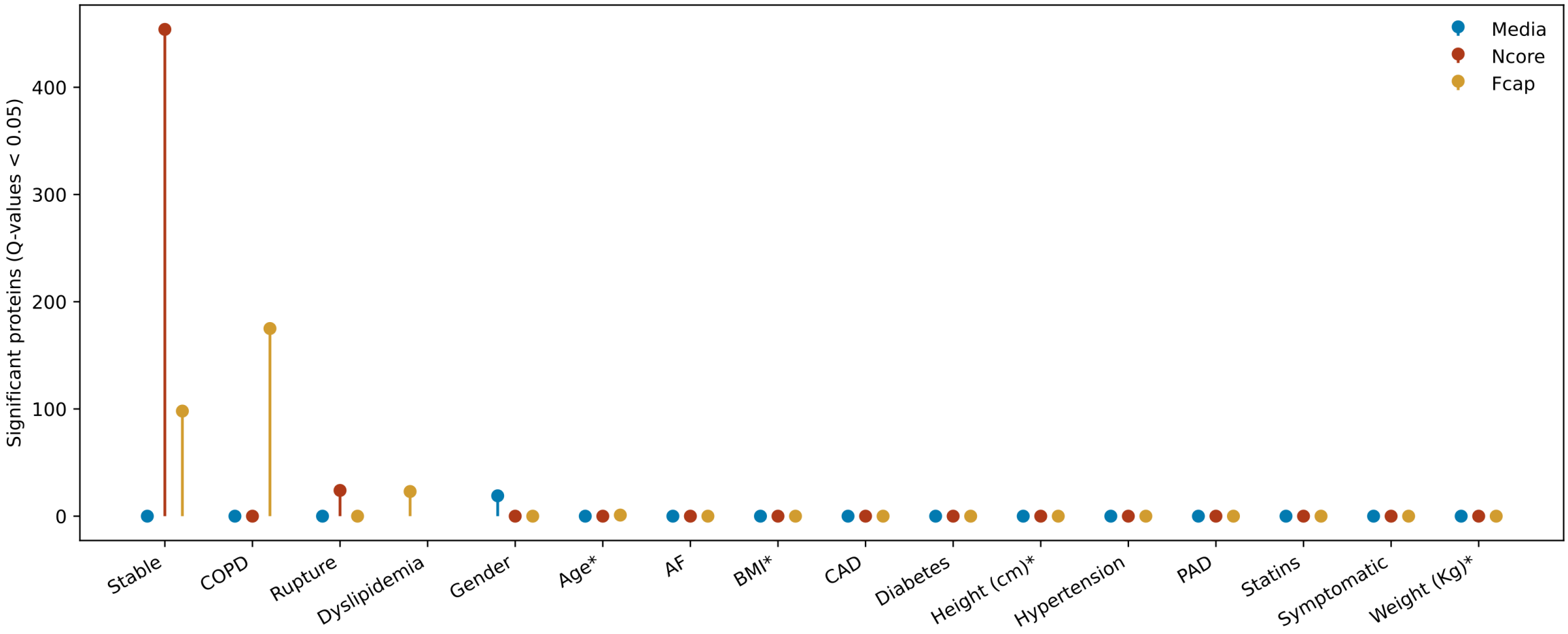


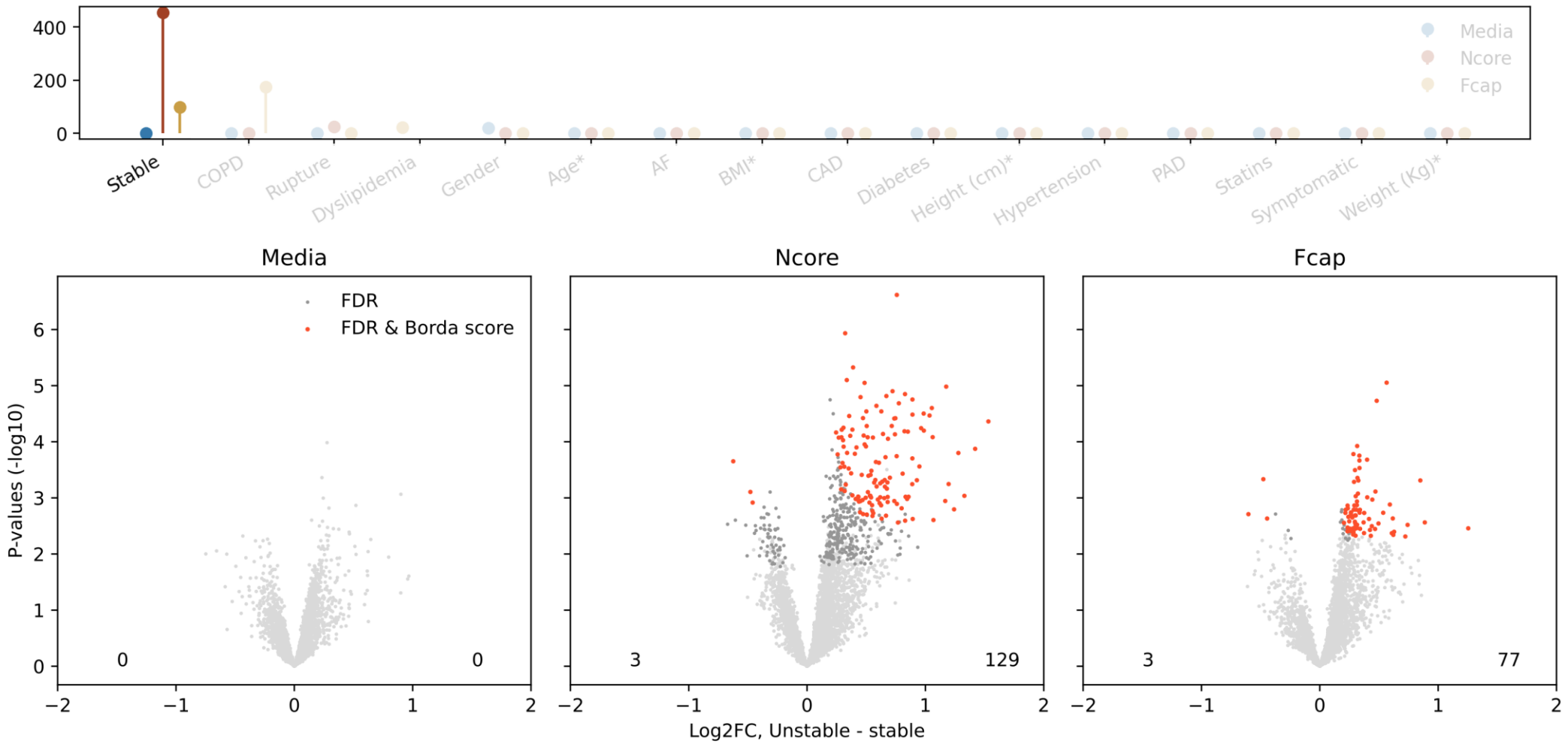
ECM proteins vary the most between the subregions



How are the plaque region proteomes associated with clinical covariates?



Media is unchanged with plaque stability status



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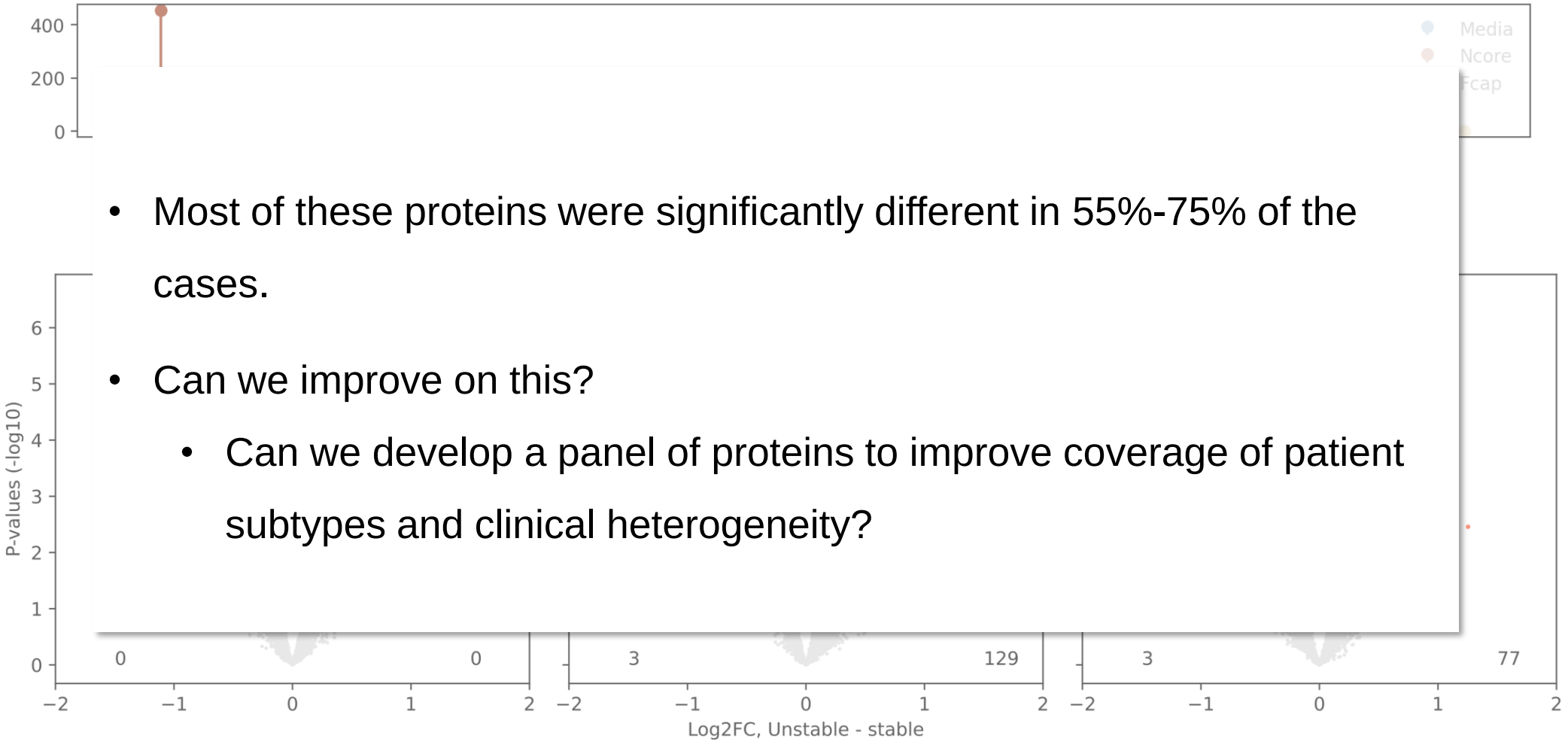

- Most of these proteins were significantly different in 55%-75% of the cases.
- Can we improve on this?
  - Can we develop a panel of proteins to improve coverage of patient subtypes and clinical heterogeneity?

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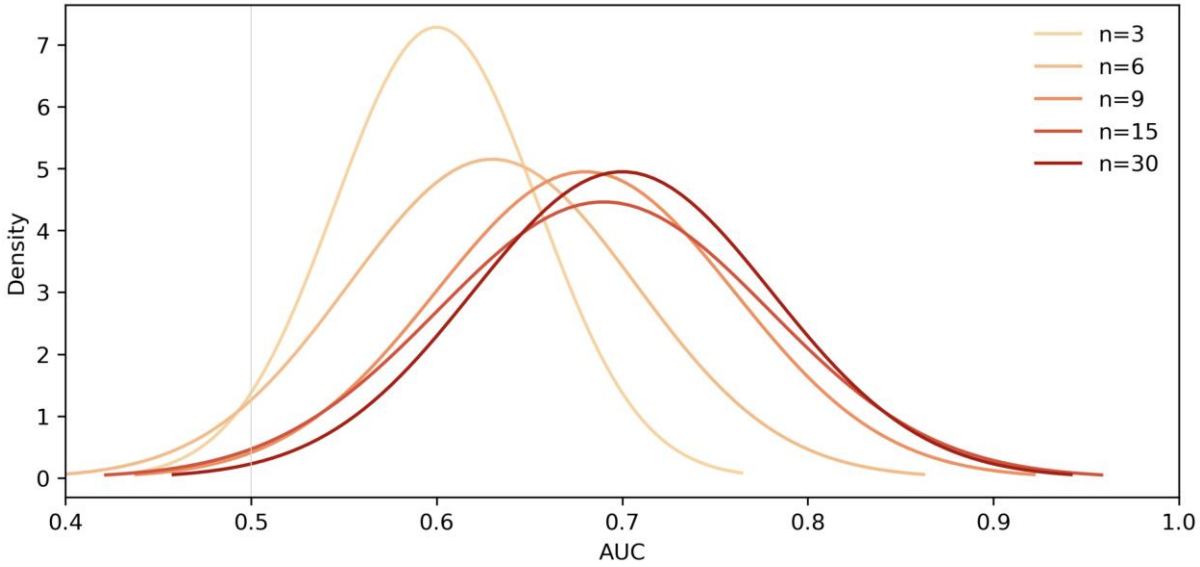

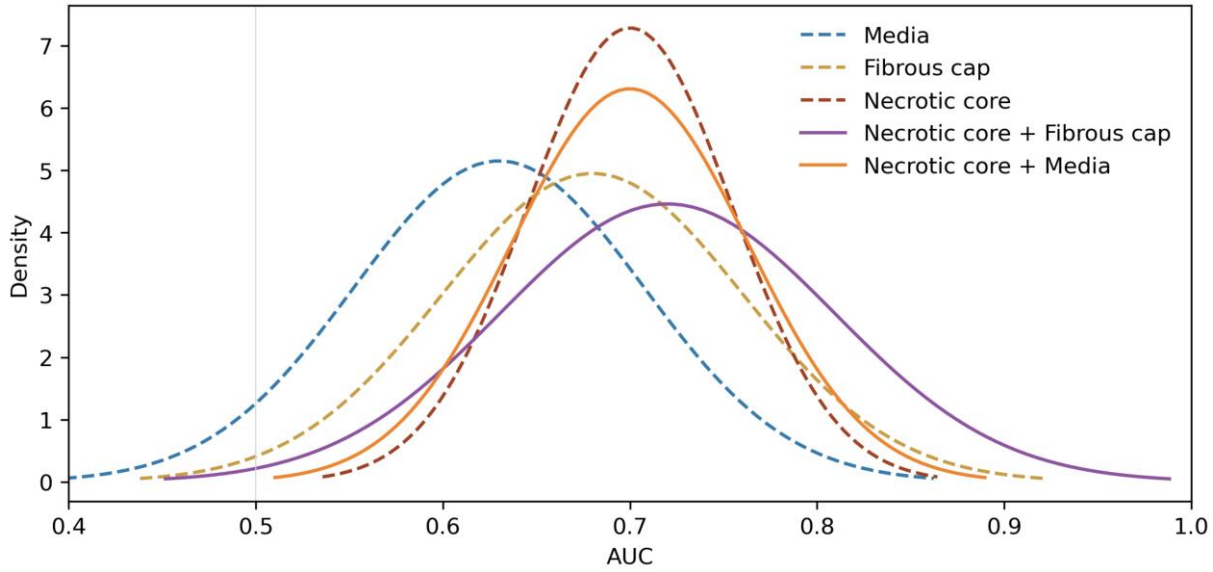

→ A panel of 9 proteins can reliably detect stability status across different patient subtypes

→ Protein panel made from necrotic core and fibrous cap provides highest classification accuracy

Summary

- Histological subregions greatly differ in ECM-related proteins
- Subcluster analysis reveals that MS-based proteomics drives patient subclustering
- MS-based proteomics identifies proteins significantly associated with plaque stability status that could act as biomarkers and therapeutic target proteins
- Protein panels can confidently detect stability status, and a protein panel assembled from multiple subregions outperforms single subregion panels

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