Metabolomic Differences Between Black and White Men with Metastatic Prostate Cancer

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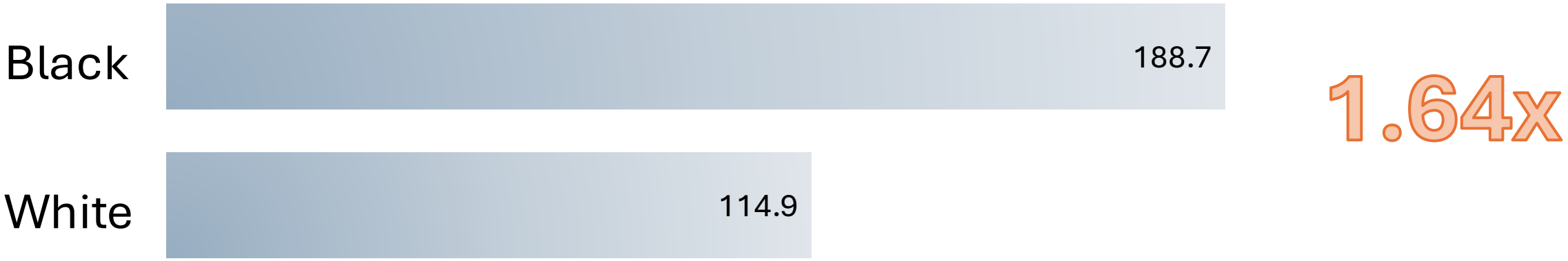
“Prostate cancer has the **largest** racial disparities of any cancer in the United States.” [1]

Incidence Rate

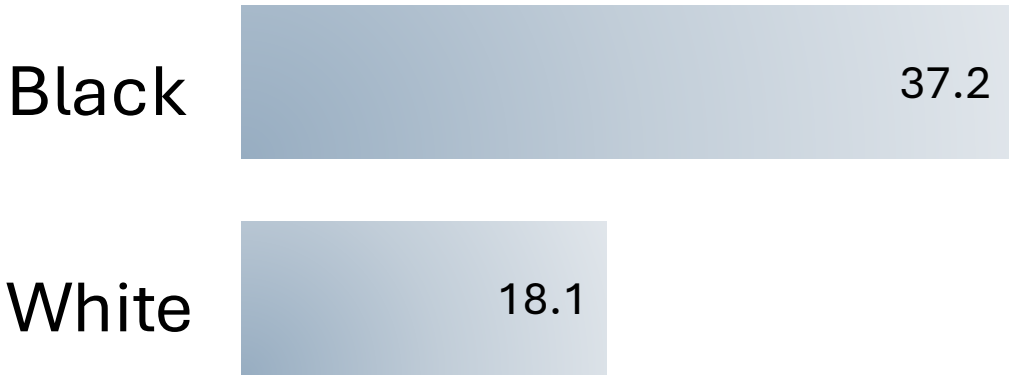
Per 100,000 persons (2017–2021, Age-Adjusted)



National Cancer Institute (https://seer.cancer.gov/statfacts/html/prost.html)

Death Rate

Per 100,000 persons (2017–2021, Age-Adjusted)



2.06x

National Cancer Institute (https://seer.cancer.gov/statfacts/html/prost.html)

Previous Evidence

- Among Black men
  - Upregulated lipid metabolism in prostatectomy specimens [2]
  - Acyl carnitines and sphingolipid enrichment in prostatic fluid [3]
- Few studies used blood samples
  - White-dominant populations [4-7] || prostate cancer vs. prostate cancer-free [8]
  - None on Black–White differences

Aim

Introduce a pilot study that bridges the gap

Research Question

What is the difference in blood-based metabolomic profiles between Black and White men with metastatic hormone-sensitive prostate cancer (mHSPC) in the United States?

PICO

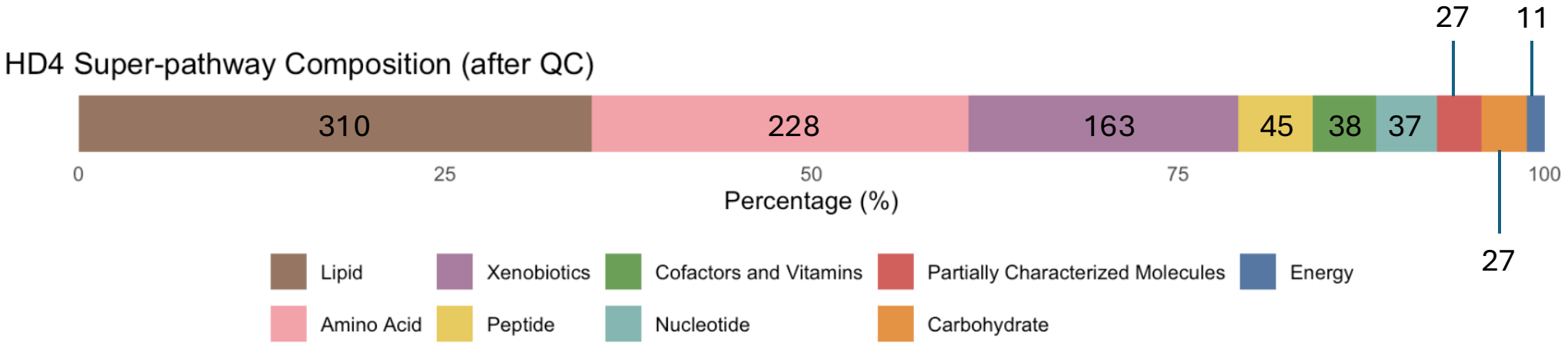
- P: 34 men (17 Black, 17 White) with mHSPC enrolled from the International Registry for Men with Advanced Prostate Cancer
- I: Black Race
- C: White Race
- O: Metabolomic profile from blood plasma

“Table 1”

	Overall (n = 34)	Black (n = 17)	White (n = 17)
Age at Enrollment (n, %)			
50 – 59 years	8 (23.4)	5 (29.4)	3 (17.6)
60 – 69 years	16 (47.1)	7 (41.2)	9 (52.9)
70 – 79 years	10 (29.4)	5 (29.4)	5 (29.4)
Body Mass Index (n, %)			
< 25 kg/m^2	9 (26.5)	4 (23.5)	5 (29.4)
25 - < 30 kg/m^2	11 (32.4)	4 (23.5)	7 (41.2)
$\geq$ 30 kg/m^2	12 (35.2)	7 (41.2)	5 (29.4)
Not Available	2 (5.8)	2 (11.8)	0

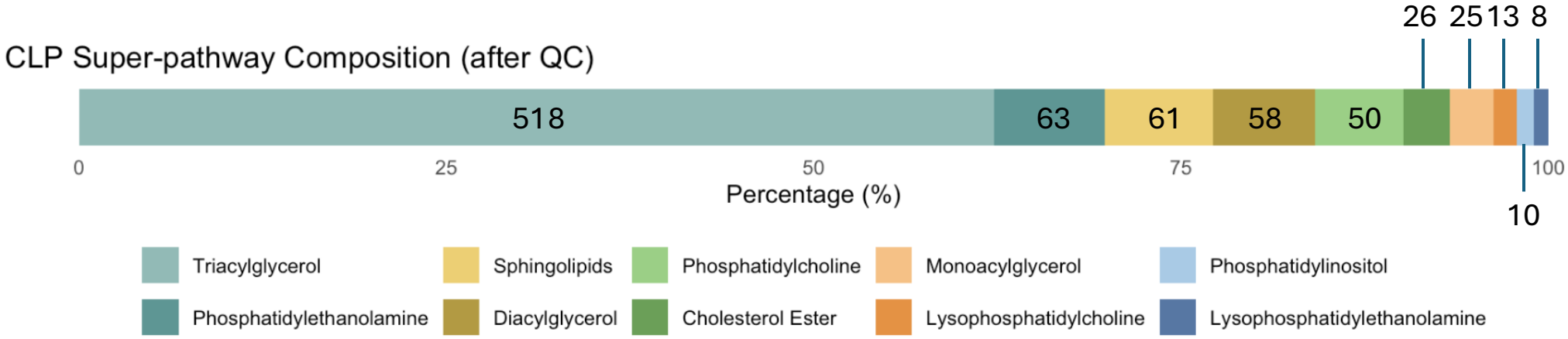
Two Panels (Part I)

1. Global Discovery Panel (HD4)
- Quantified various classes of metabolites
- Total after quality control: 886 metabolites



Two Panels (Part 2)

2. Complex Lipidomics Panel (CLP)
   - Quantified lipids only
   - Total after quality control: 832 lipids



Statistical Analyses

- Welch’s t-test
- Principal Component Analysis (PCA)
- Partial Least Square-Discriminant Analysis (PLS-DA)
- Random Forest

All analyses were performed in Jupyter Notebook with an R kernel (version 4.3.1); Some visualizations were enhanced using Photoshop.

Motivation

Look for metabolites consistently found across all analyses

Welch’s T-Test

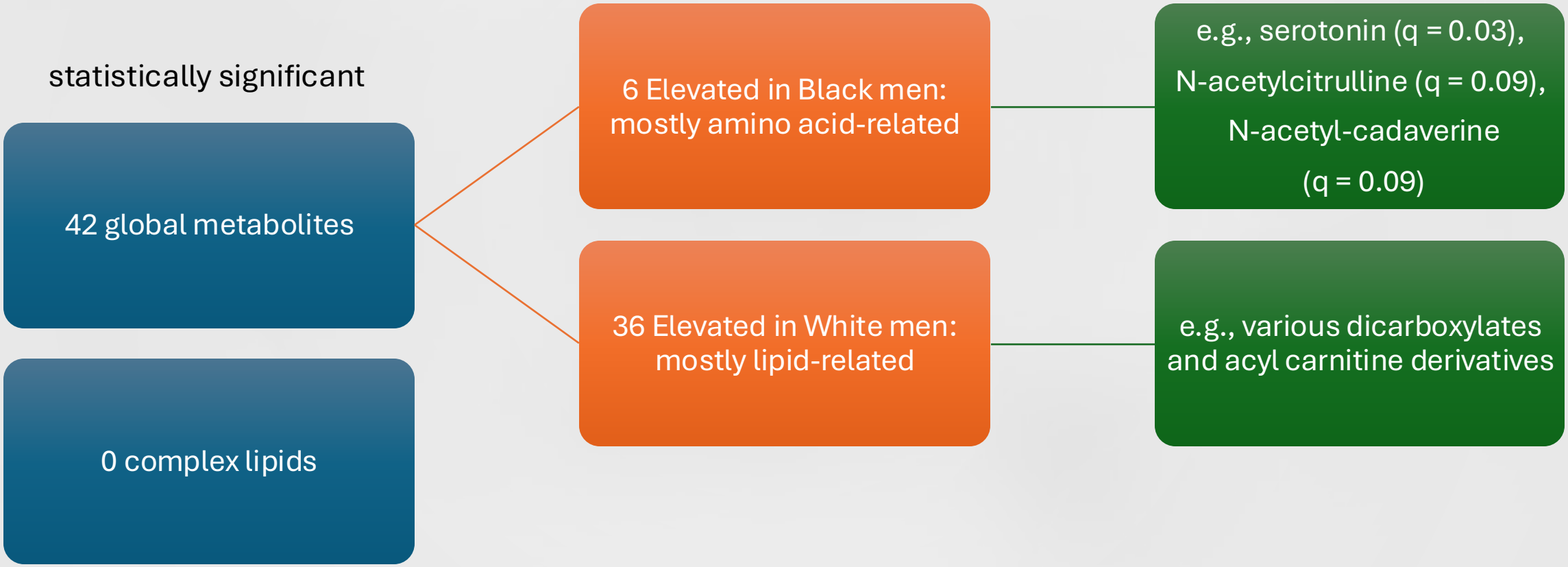
Motivation

- Compare mean metabolite concentrations (Black vs White)

Multiple hypothesis testing

- Performing ~1,700 t-tests can inflate false positive (Type I error)
- Used false discovery rate adjusted q-values
- Statistical significance: $q < 0.1$

T-Test Results



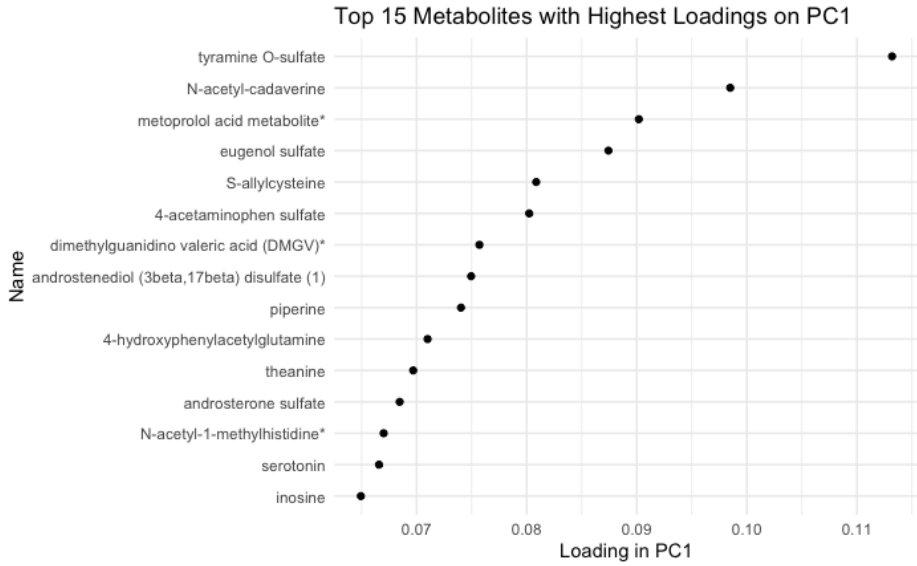
PCA

- Motivation
  - reduce high-dimensional metabolite data into a few principal components (PC) to capture the major patterns of variation

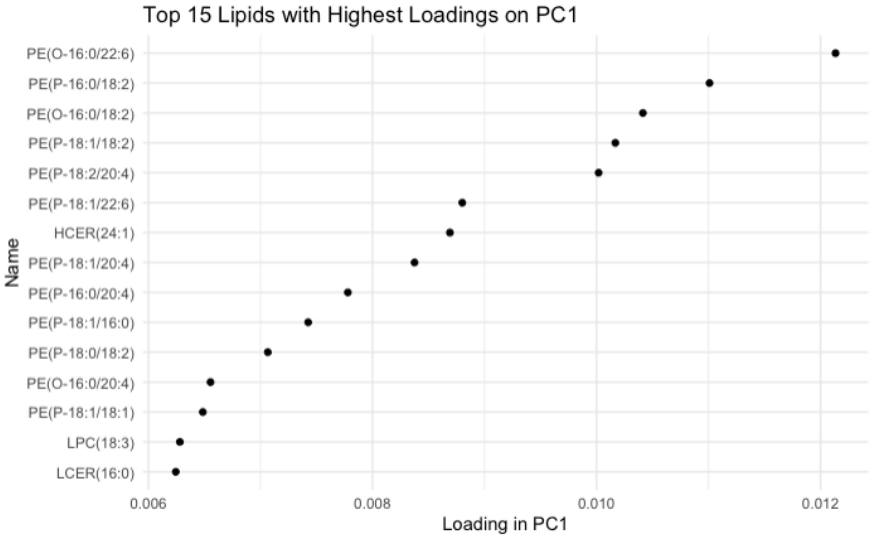
Top 15 Compounds with Highest Loading

- Loading: weight of a metabolite's contribution to PC1
- HD4: Serotonin and N-acetyl-cadaverine from t-test again
- CLP: Phosphatidylethanolamine (PE)

HD4



CLP



PLS-DA

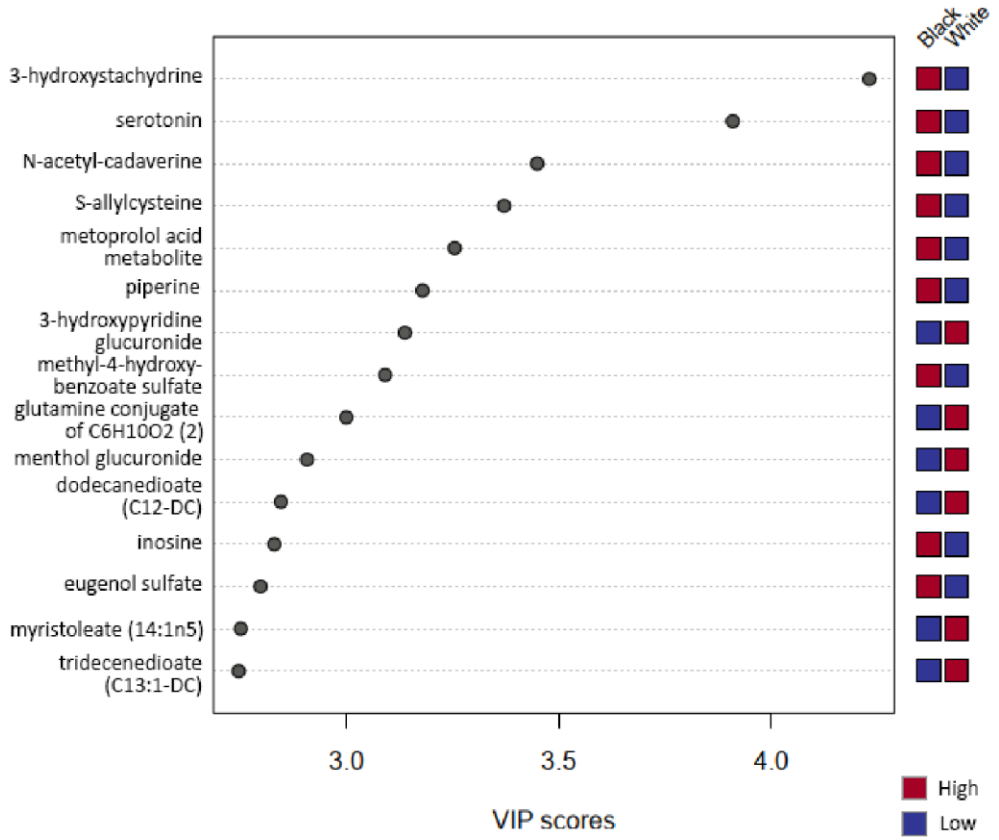
- Motivation
  - a supervised dimensionality reduction method
  - maximizes the separation between Black and White individuals

VIP Scores

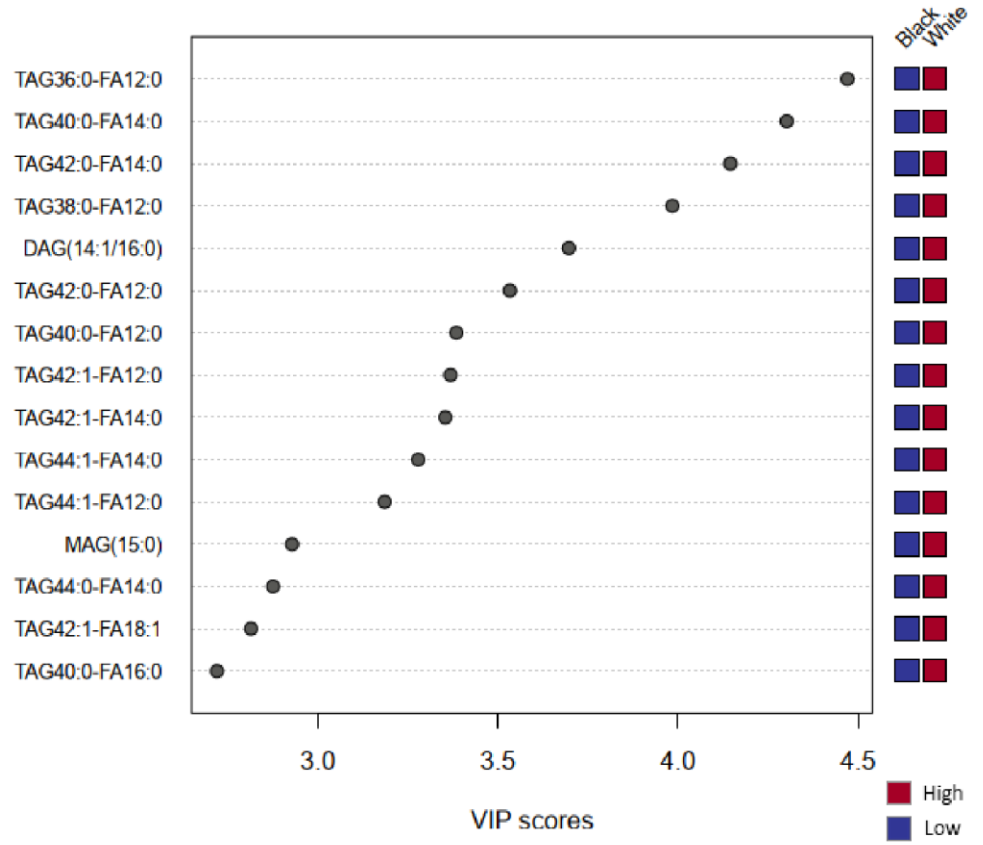
- Variable Importance in Projection
- Quantifies a metabolite’s importance in the model’s ability to distinguish between groups

- HD4: Serotonin and N-acetyl-cadaverine again! 3-hydroxystachydrine highest
- CLP: Triacylglycerol (TAG) class

a HD4

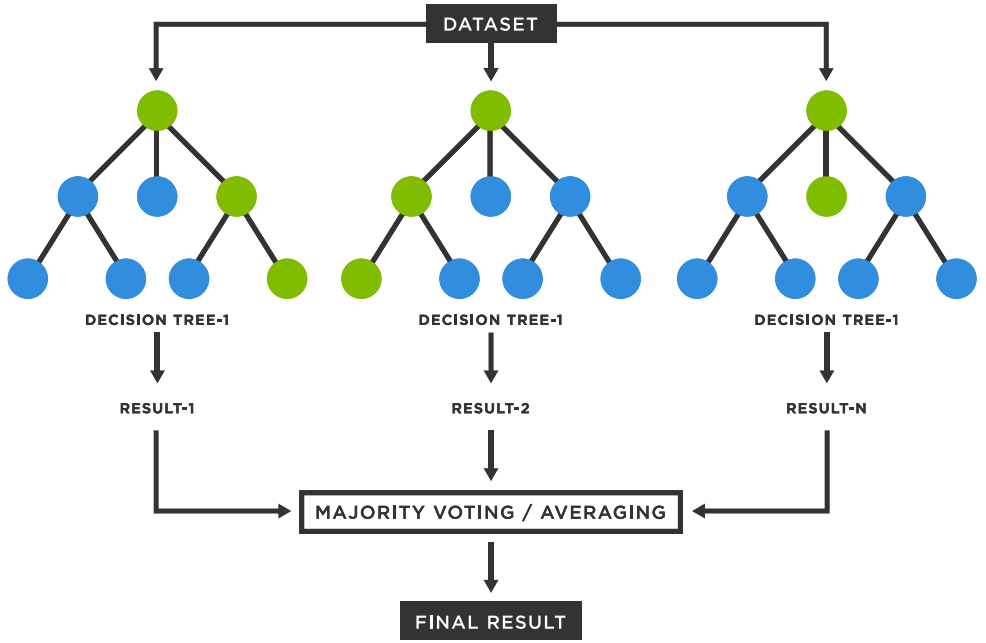


b CLP



Random Forest (RF)

- Motivation
  - a machine learning classifier

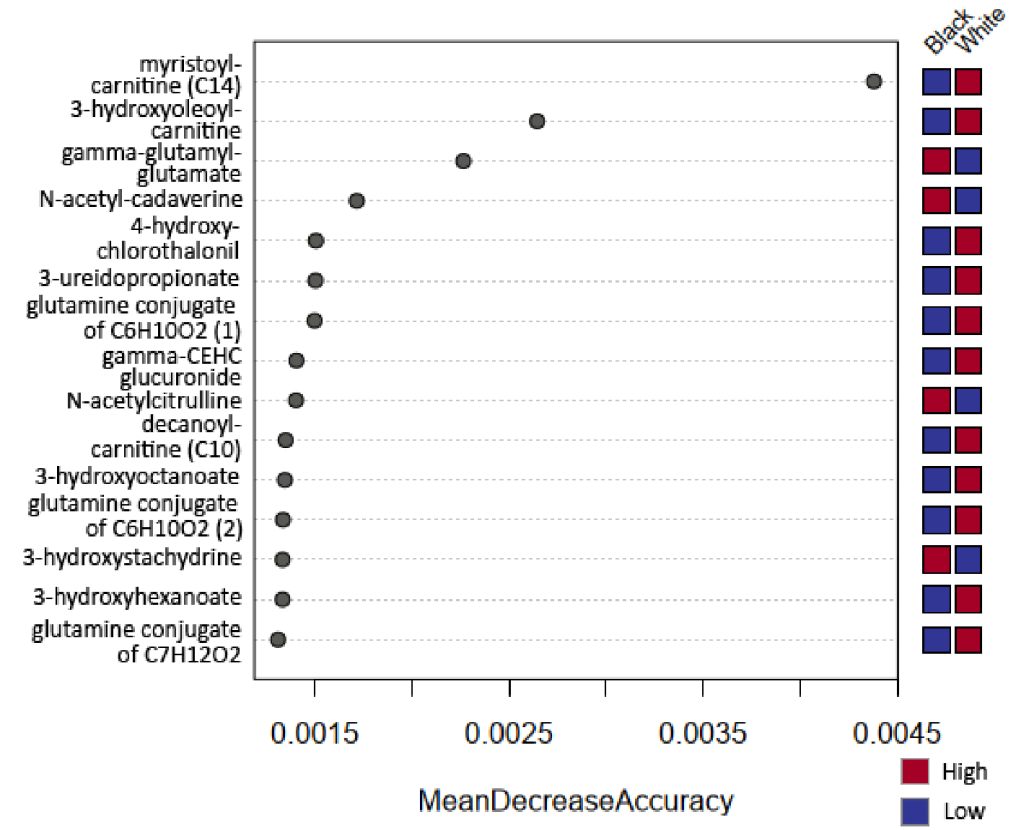


MDA Scores

- Mean Decrease Accuracy
- Measures how much the model's accuracy drops when we permute the values of that metabolite across all samples

- HD4
  - N-acetyl-cadaverine (from t-test and PLS-DA) and N-acetylcitrulline (from t-test) again
  - 3-hydroxystachydrine (from PLS-DA) again
  - Acyl carnitine derivatives and glutamine derivatives were also found
- CLP
  - TAG again

a



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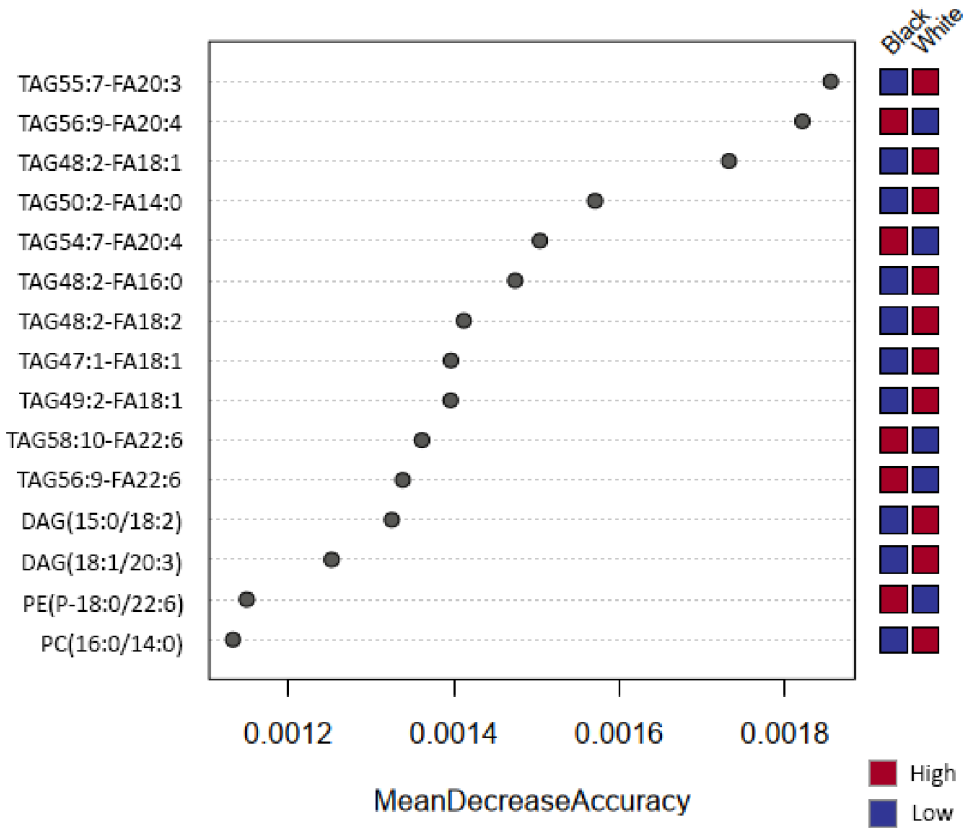

Conclusion

- HD4: Serotonin, N-acetylcitrulline, and N-acetyl-cadaverine were consistently found across multiple analyses
- CLP: TAGs were found across multiple analyses
- Ontological perspectives
  - Serotonin: synapse
  - N-acetylcitrulline: arginine synthesis
  - N-acetyl-cadaverine: brain GABA (inhibitory neurotransmitter) synthesis
  - TAGs: related to PE conversion (cell membrane)

Limitations

- Limited statistical power
  - Small sample size (n = 50)

Thank you all!

- Especially
  - Professor Rebecca Graff at UCSF
  - Professor John Witte at Stanford
  - And also my Chinese “family” :3

References

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