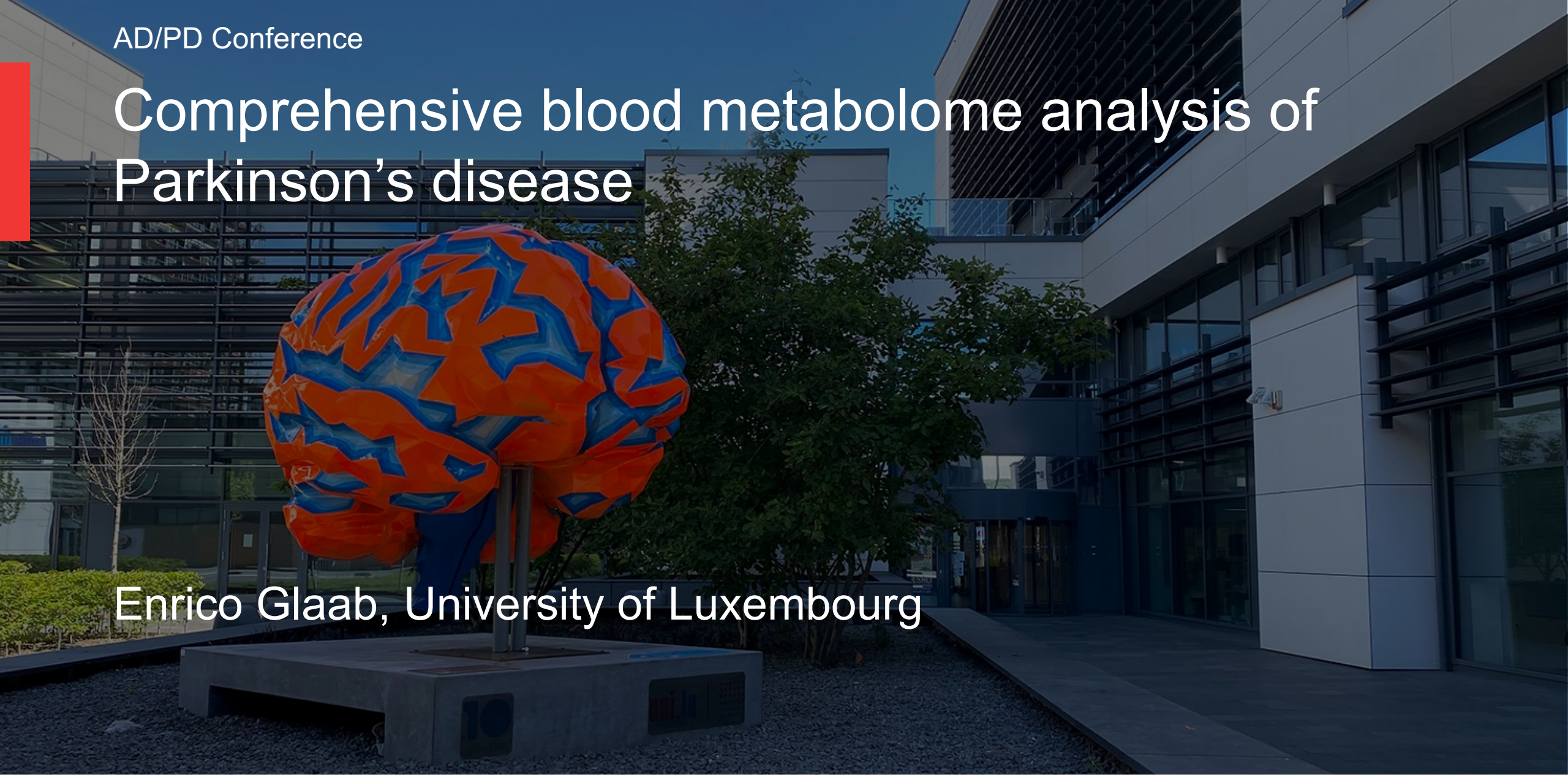
AD/PD Conference

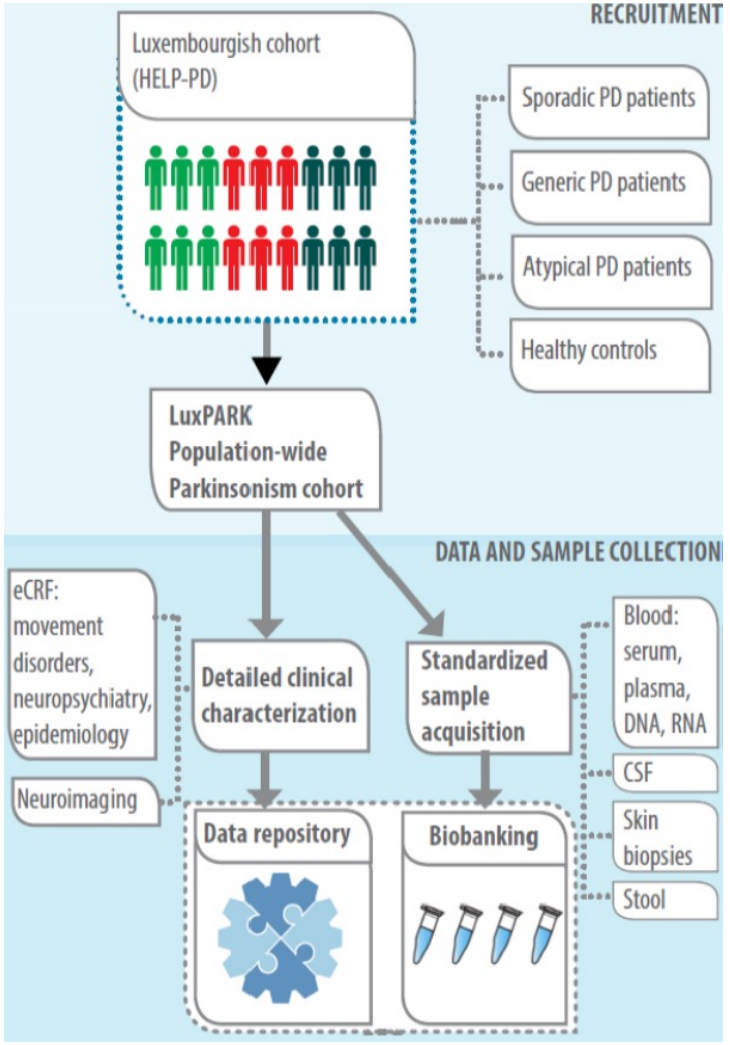
Comprehensive blood metabolome analysis of Parkinson’s disease



Enrico Glaab, University of Luxembourg

The Luxembourg Parkinson Study (LuxPARK)

- a nationwide, monocentric, observational, longitudinal study; coordinator: Prof. Rejko Krüger
- covers ~800 patients with typical or atypical parkinsonism and ~800 controls
- Patients: annual follow-up, controls: after 4 years
- **Clinical data**: Motor symptoms (MDS-UPDRS), Non-motor symptoms (Cognition, Sleep, Quality of Life, Environment, among others)
- **Biosampling**: Blood, DNA, RNA, Urine, Saliva, Nasal Washes, Stool, CSF, Skin & Colon biopsies



LuxPARK Metabolomics Study - Overview

Goals: - Characterize blood metabolomics changes in PD vs. controls & PD sub-groups

- Interpret cellular pathway/network alterations & build prediction models for clinical outcomes

Data: LC-MS metabolomics (Metabolon) for 1500 blood plasma samples, covering 1409 metabolites

Baseline analysis
(1300 samples)

- PD (593, including 56 *de novo* PD) and Controls (592)
- PD with dementia (46)
- Atypical forms of parkinsonism (PSP: 46, MSA-P: 12, CBS: 11)

Longitudinal analysis
(200 samples)

- Annual follow-up visits 1 & 2 for 100 PD patients in the baseline analysis
- Balanced sexes (50/50)

Differential statistical analysis

Goal: Identify PD-associated metabolite changes, independent from medication, age and sex effects

Method:

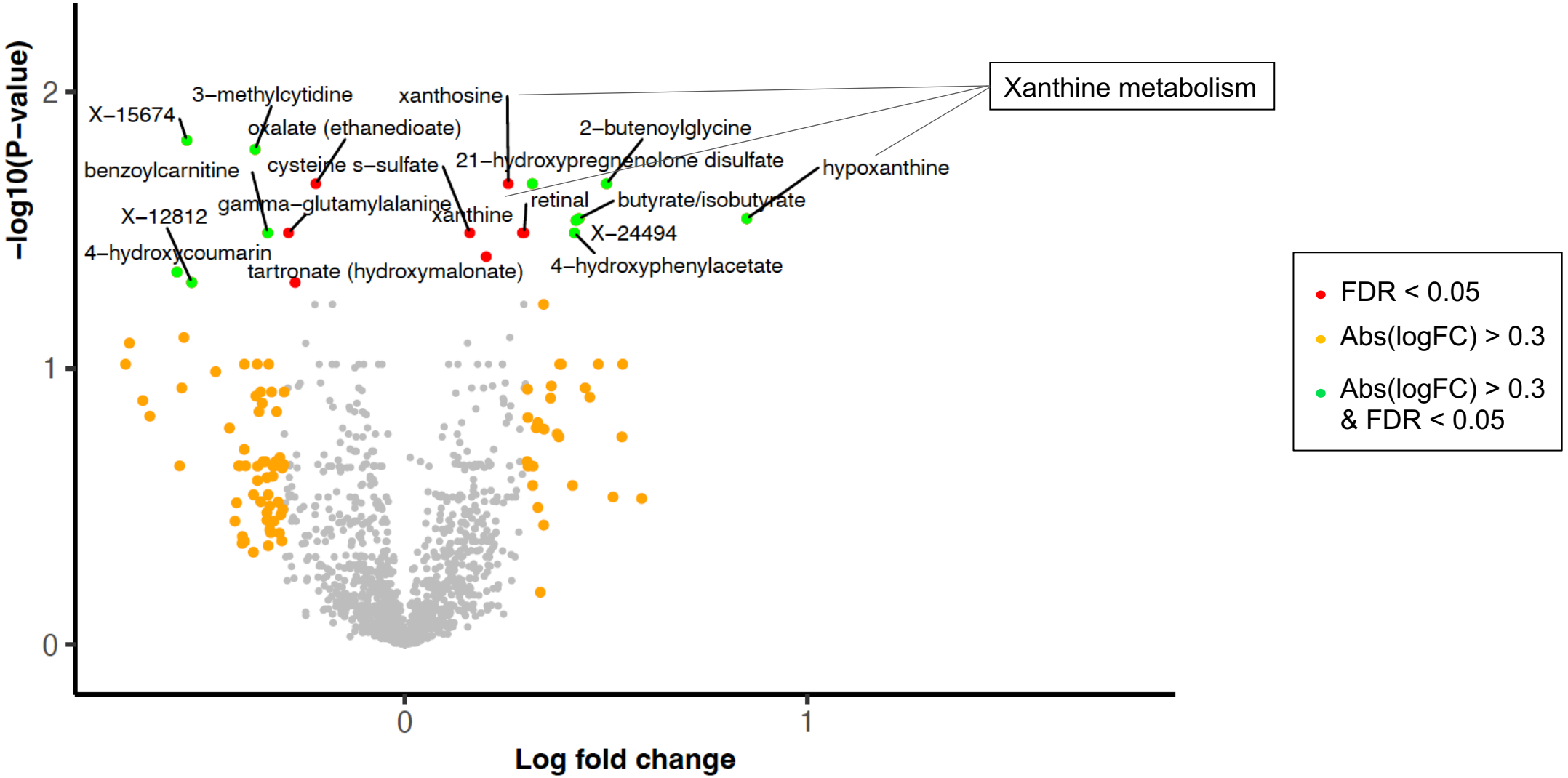
- Differential abundance analysis: PD vs. Controls

  Statistical test: empirical Bayes moderated t-statistic

- Confounder adjustment: age, sex, treatment effects (L-Dopa treatment captured using 3-O-Methyldopa metabolite) + compare with *de novo* PD vs. controls results

- Check for other confounders: Principal variance component analysis (PCVA) does not suggest the presence of additional confounders with major effects in our clinical data

De novo PD vs. control - Volcano plot

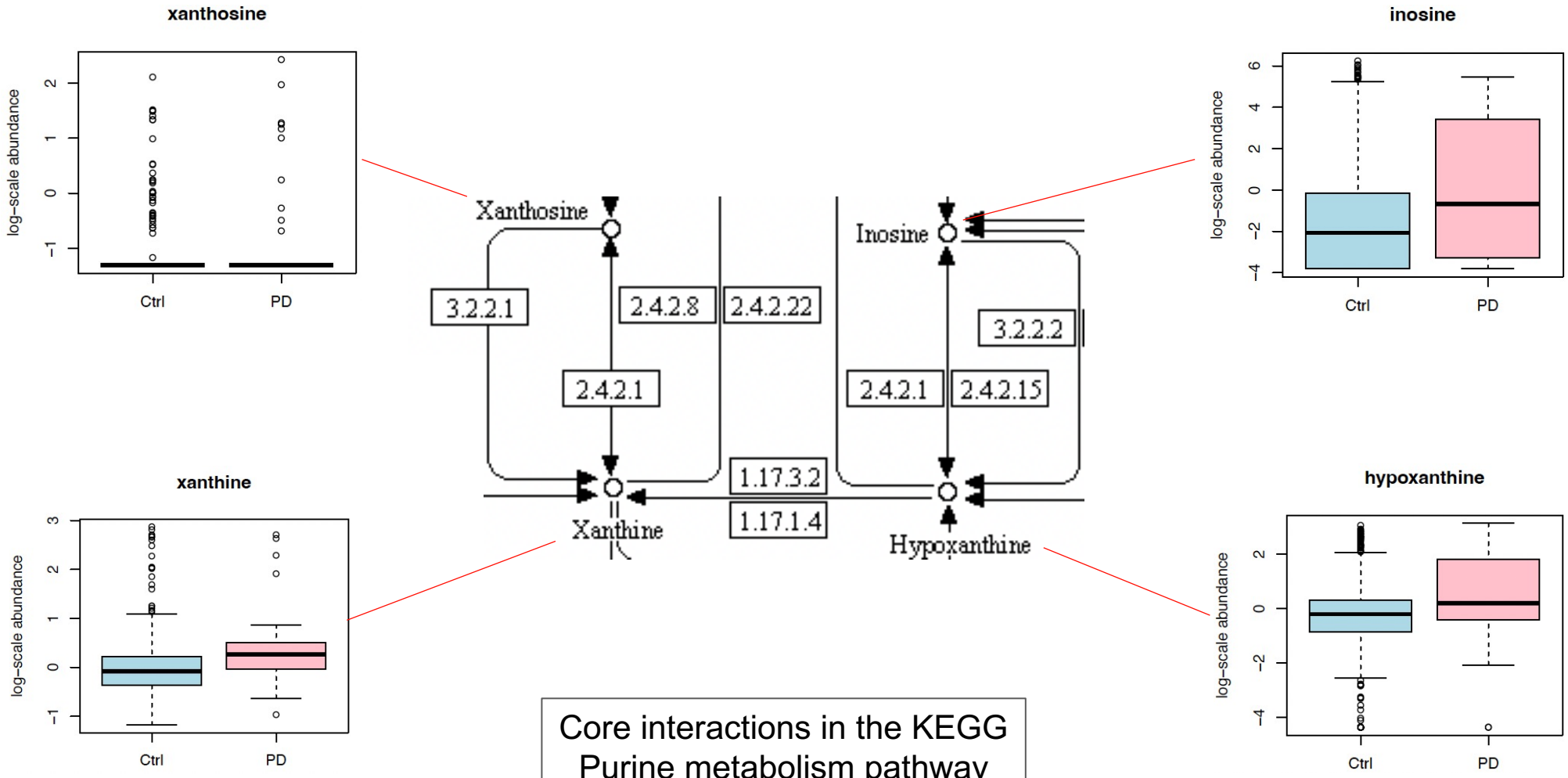


Shared significant metabolites – *de novo* PD & all PD analysis

	***De novo* PD vs. Control**			**All PD vs. Control (adjusted)**		
Metabolite	**logFC**	**P-Value**	**adj. P-Value**	**logFC**	**P-Value**	**adj. P-Value**
inosine	1.79	4.44E-06	3.19E-03	0.63	3.57E-03	3.71E-02
hypoxanthine	0.85	2.00E-04	2.87E-02	0.45	2.26E-04	5.92E-03
gamma-glutamylalanine	-0.29	0.000323	0.032301	-0.13	4.71E-03	4.44E-02
benzoylcarnitine	-0.34	3.64E-04	3.23E-02	-0.25	9.15E-06	7.76E-04
retinal	0.30	3.73E-04	3.23E-02	0.13	3.30E-03	3.48E-02
4-hydroxycoumarin	-0.57	5.92E-04	4.48E-02	-0.30	1.10E-03	1.62E-02
tartronate (hydroxymalonate)	-0.27	7.12E-04	4.89E-02	-0.18	3.45E-04	7.65E-03
X-12812	-0.53	7.14E-04	4.89E-02	-0.28	1.28E-03	1.80E-02

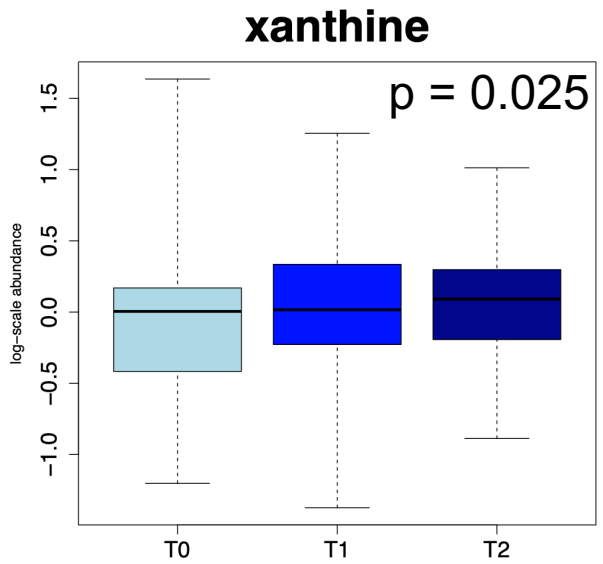
Blue = xanthine metabolites

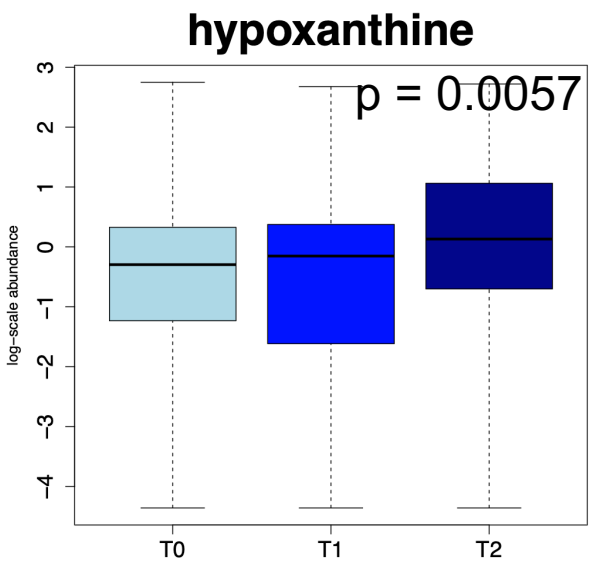
Xanthine/purine metabolism in *de novo* PD vs. controls

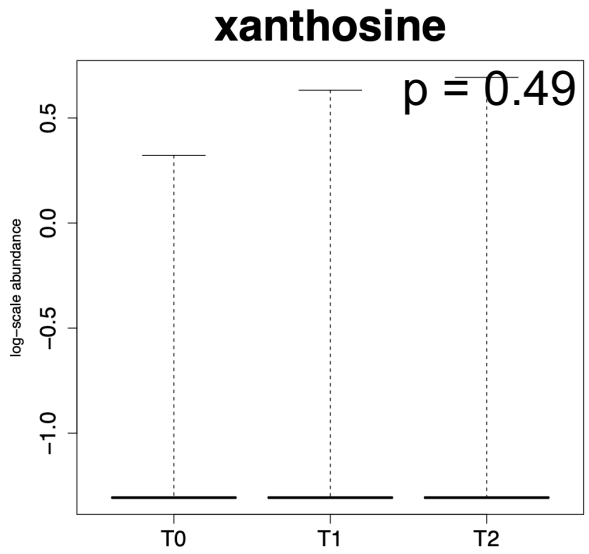


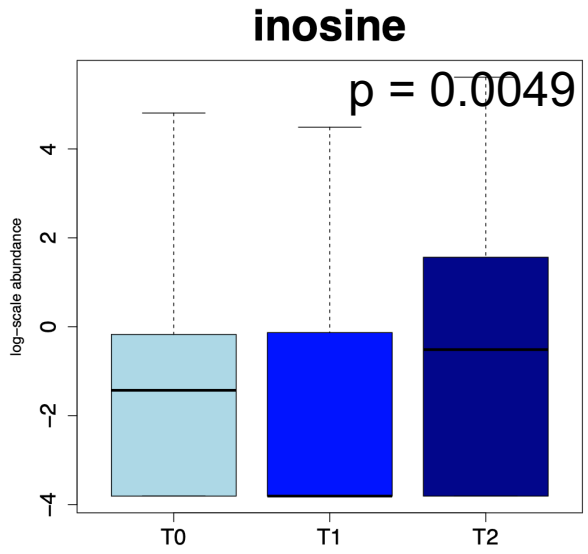
Core interactions in the KEGG Purine metabolism pathway

Metabolite changes over time in PD – Xanthine metabolism





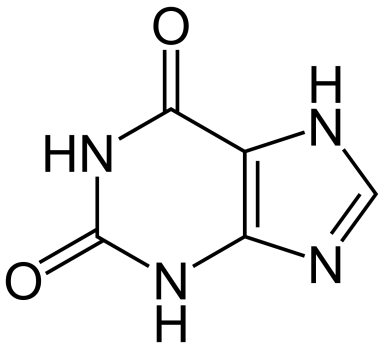




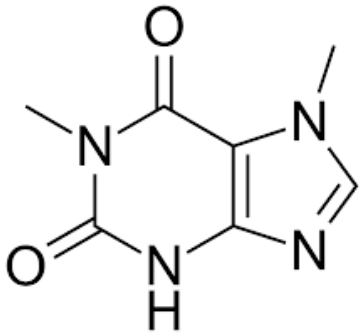
Significant increase over time in 3 out of 4 xanthines (Spearman correlation test)

Prior links between xanthines and PD

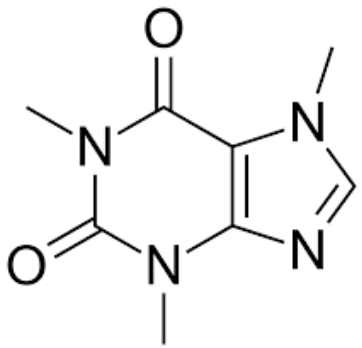
- **Drug candidates**: Xanthine derivatives show benefits in PD patients and mouse models (Xu et al., 2010)
- **Scaffold for drugs**: Xanthine is a sub-structure of various drugs, including Istradefylline (an A2A receptor antagonist)
- **Mechanisms**: - **A2A Receptor Antagonism**: enhances dopaminergic signaling
  - **MAO-B Inhibition**: reduces dopamine breakdown



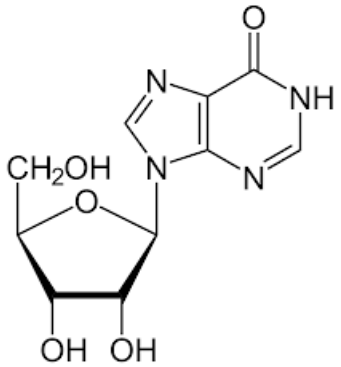
xanthine



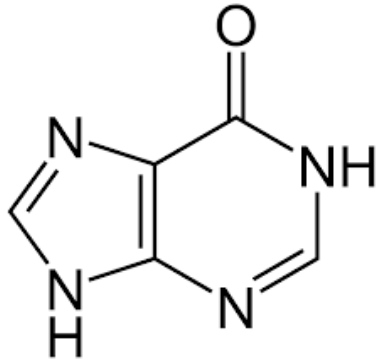
paraxanthine



caffeine

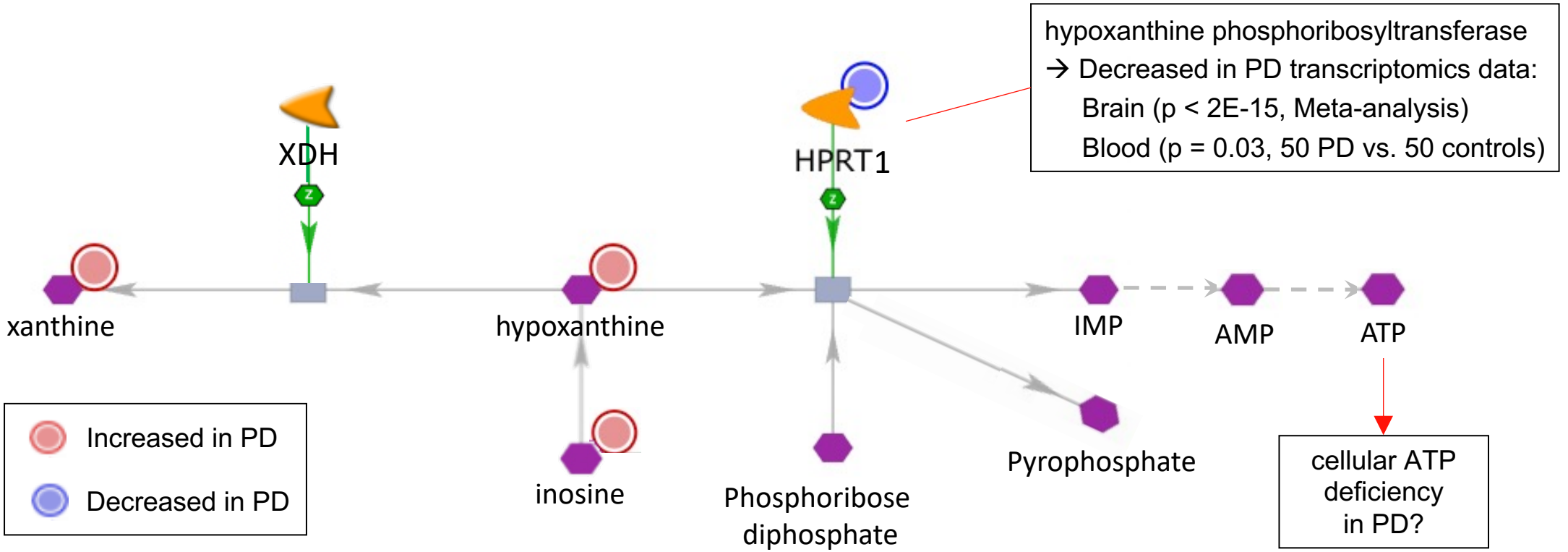


inosine



hypoxanthine

Joint metabolomics & transcriptomics network analysis



Machine learning: *de novo* PD vs. control classification

Metabolite	Linear AUC (Train)	Linear AUC (Test)	Radial AUC (Train)	Radial AUC (Test)	Avg. AUC
Xanthine	0.68	0.71	0.63	0.72	0.68
2-ketocaprylate	0.58	0.74	0.54	0.78	0.66
Glutarylcarnitine (C5-DC)	0.64	0.68	0.62	0.66	0.65
4-hydroxyphenylpyruvate	0.57	0.68	0.61	0.66	0.63
N-palmitoyl-sphingadienine (d18:2/16:0)	0.57	0.58	0.70	0.65	0.63
3-hydroxyoleoylcarnitine	0.57	0.62	0.64	0.68	0.62
3-hydroxybutyroylglycine	0.61	0.62	0.66	0.60	0.62
Cortisol	0.53	0.70	0.56	0.69	0.62
Hypotaurine	0.60	0.66	0.59	0.63	0.62
Palmitoleoylcarnitine (C16:1)	0.59	0.65	0.57	0.66	0.62

Ranking of the top 10 known metabolite features for supervised sample classification of *de novo* PD vs. control samples, by the sum-of-ranks of the Area Under the ROC Curve (AUC) for linear and radial Support Vector Machine (SVM) classifiers.

Summary

- **Metabolite-level analysis**

  → statistically significant alterations in *de novo* PD vs. controls,
  particularly in xanthines (e.g., inosine, hypoxanthine, xanthine, xanthosine)

- **Pathway- & network-level analysis**

  → coordinated PD-associated changes in purine / xanthine metabolism

  → integrated analysis with transcriptomics data suggests *HPRT1* as a key regulator

- **Machine learning analysis**

  → Discriminate *de novo* PD vs. control with avg. AUCs up to 68%,
  xanthine is top-ranked predictor

Acknowledgments

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- Biomedical Data Science Group
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References

1. E. Gómez de Lope, … , R. Krüger, E. Glaab, Comprehensive blood metabolomics profiling of Parkinson's disease reveals coordinated alterations in xanthine metabolism, npj Parkinson's Disease (2024), 10, 68
2. M. Soudy, S. Le Bars, E. Glaab, Sex-Dependent Molecular Landscape of Alzheimer's Disease Revealed by Large-Scale Single-Cell Transcriptomics, Alzheimer's & Dementia (2025), 21, 2
3. M. Ali, P. Garcia, L.P. Lunkes, A. Sciortino, M. Thomas, T. Heurtaux, K. Grzyb, R. Halder, A. Skupin, L. Buée, D. Blum, M. Buttini, E. Glaab, Temporal Transcriptomic Changes in the THY-Tau22 Mouse Model of Tauopathy Display Cell Type- and Sex-Specific Differences, Acta Neuropathologica Communications (2025), 13, 9
4. M. Ali, P. Garcia, L.P. Lunkes, A. Sciortino, M. Thomas, T. Heurtaux, K. Grzyb, R. Halder, D. Coowar, A. Skupin, L. Buée, D. Blum, M. Buttini, E. Glaab, Single cell transcriptome analysis of the THY-Tau22 mouse model of Alzheimer's disease reveals sex-dependent dysregulations, Cell Death Discovery (2024), 10, 119
5. R.T.J. Loo, L. Pavelka, G. Mangone, F. Khoury, M. Vidailhet, J.-C. Corvol, R. Krüger, E. Glaab, Interpretable Machine Learning for Cross-Cohort Prediction of Motor Fluctuations in Parkinsons Disease, Movement Disorders (2025), in press (doi:10.1002/mds.30223)
6. A. Rauschenberger, Z. Landoulsi, M. A. van de Wiel, E. Glaab. Penalized regression with multiple sources of prior effects, Bioinformatics (2022), 39(12), doi: 10.1007/s12035-022-02985-2.
7. M. Ali, O. Uriarte Huarte, T. Heurtaux, P. Garcia, B. Pardo Rodriguez, K. Grzyb, R. Halder, A. Skupin, M. Buttini, E. Glaab. Single-Cell Transcriptional Profiling and Gene Regulatory Network Modeling in Tg2576 Mice Reveal Gender-Dependent Molecular Features Preceding Alzheimer-Like Pathologies, Mol Neurobiol (2022), doi:10.1007/s12035-022-02985-2.
8. A. Rauschenberger, E. Glaab. Predicting Dichotomised Outcomes from High-Dimensional Data in Biomedicine, Journal of Applied Statistics, (2023), doi: 10.1080/02664763.2023.2233057.
9. L. C. Tranchevent, R. Halder, E. Glaab. Systems level analysis of sex-dependent gene expression changes in Parkinson's disease, NPJ Parkinson's Disease, (2022), 9, 8.
10. A. Rauschenberger, E. Glaab, Predicting correlated outcomes from molecular data, Bioinformatics (2021), 37(21), 3889–3895
11. R. Diaz-Uriarte, E. Gómez de Lope, R. Giugno, H. Fröhlich, P. V. Nazarov, I. A. Nepomuceno-Chamorro, A. Rauschenberger, E. Glaab, Ten Quick Tips for Biomarker Discovery and Validation Analyses Using Machine Learning, PLoS Computational Biology (2022), doi:10.1371/journal.pcbi.1010357
12. E. Glaab, J.P. Trezzi, A. Greuel, C. Jäger, Z. Hodak, A. Drzezga, L. Timmermann, M. Tittgemeyer, N. J. Diederich, C. Eggers, Integrative analysis of blood metabolomics and PET brain neuroimaging data for Parkinson's disease, Neurobiology of Disease (2019), Vol. 124, No. 1, pp. 555
13. S. Köglsberger, M. L. Cordero-Maldonado, P. Antony, J. I. Forster, P. Garcia, M. Buttini, A. Crawford, E. Glaab, Gender-specific expression of ubiquitin-specific peptidase 9 modulates tau expression and phosphorylation: possible implications for tauopathies, Molecular Neurobiology (2017), 54(10), pp. 7979
14. N. Vlassis, E. Glaab, GenePEN: analysis of network activity alterations in complex diseases via the pairwise elastic net, Statistical Applications in Genetics and Molecular Biology (2015), 14(2), 221
15. E. Glaab, Using prior knowledge from cellular pathways and molecular networks for diagnostic specimen classification, Briefings in Bioinformatics (2015), 17(3), pp. 440
16. E. Glaab, R. Schneider, Comparative pathway and network analysis of brain transcriptome changes during adult aging and in Parkinson's disease, Neurobiology of Disease (2015), 74, 1-13
17. E. Glaab, R. Schneider, RepExplore: Addressing technical replicate variance in proteomics and metabolomics data analysis, Bioinformatics (2015), 31(13), pp. 2235
18. E. Glaab, A. Baudot, N. Krasnogor, A. Valencia. Extending pathways and processes using molecular interaction networks to analyse cancer genome data, BMC Bioinformatics, 11(1):597, 2010
19. E. Glaab, A. Baudot, N. Krasnogor, R. Schneider, A. Valencia. EnrichNet: network-based gene set enrichment analysis, Bioinformatics, 28(18):i451-i457, 2012
20. E. Glaab, A. Rauschenberger, R. Banzi, C. Gerardi, P. Garcia, J. Demotes-Mainard, and the PERMIT Group, Biomarker discovery studies for patient stratification using machine learning analysis of omics data: a scoping review, BMC Open (2021), 11, e053674
21. D. M. Hendrickx, P. Garcia, A. Ashrafi, A. Sciortino, K. J. Schmit, H. Kollmus, N. Nicot, T. Kaoma, L. Vallar, M. Buttini, E. Glaab, A new synuclein-transgenic mouse model for early Parkinson's reveals molecular features of preclinical disease, Molecular Neurobiology (2020), 58, 576-602
22. C. Brzenczek, Q. Klopfenstein, T. Hähnel, S. Sapienza, J. Klucken, H. Fröhlich, E. Glaab, Integrating digital gait sensor data with metabolomics and clinical data to predict clinically relevant outcomes in Parkinsons disease, npj Digital Medicine (2024), 7, 235
23. S. Le Bars, E. Glaab, Single-Cell Cortical Transcriptomics Reveals Common and Distinct Changes in Cell-Cell Communication in Alzheimer's and Parkinson's Disease, Molecular Neurobiology (2024), 10.1007/s12035-024-04419-7