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iPheGWAS in Action

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OUTLINE

- **iPheGWAS <- PheGWAS + Heuristic Method**
- **Application of iPheGWAS to Inspired Data**
- **Limitations**
- **Future Work**

COMPUTATIONAL APPROACHES DEVELOPED

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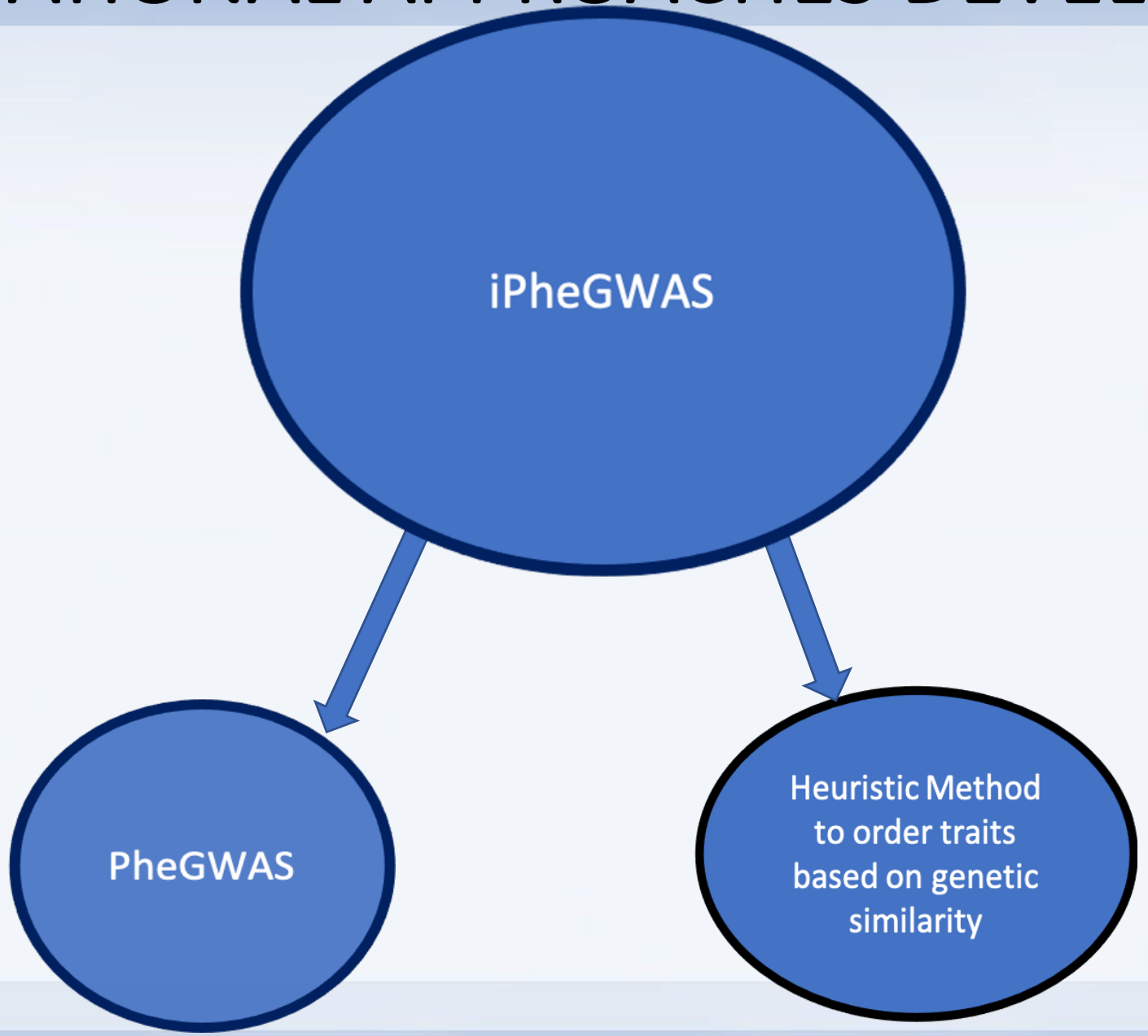

PheGWAS

- PheGWAS was developed with the broad aim of developing a visualization approach to explore ‘many variants-many phenotypes’ in one plot
- PheGWAS is capable of identifying independent signals
- Provides insights to
  - Pleiotropy
  - Local genetic correlation
- PheGWAS takes ~12 sec to complete(running in a 8 GB RAM machine).
  - Tested on 4 summary statistics files (HDL,LDL,TRIGS,TC from GLGC) having ~2.5 million SNPs

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Original Paper

Genetics and population analysis

PheGWAS: a new dimension to visualize GWAS across multiple phenotypes

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Abstract

Motivation: PheGWAS was developed to enhance exploration of phenome-wide pleiotropy at the genome-wide level through the efficient generation of a dynamic visualization combining Manhattan plots from GWAS with PheWAS to create a 3D ‘landscape’. Pleiotropy in sub-surface GWAS significance strata can be explored in a sectional view plotted within user defined levels. Further complexity reduction is achieved by confining to a single chromosomal section. Comprehensive genomic and phenomic coordinates can be displayed.
Results: PheGWAS is demonstrated using summary data from Global Lipids Genetics Consortium GWAS across

Heuristic Approach

- This heuristic approach provide insights about the pattern of genetic relationship among phenotypes

- We have shown that order of clustering of traits computed were consistent with the order produced by the genetic correlations calculated by the LDSC.

- Our method takes 1.5 minutes for computation as compared to 12 minutes in LDSC for ordering 14 traits based on their genetic similarity

iPheGWAS

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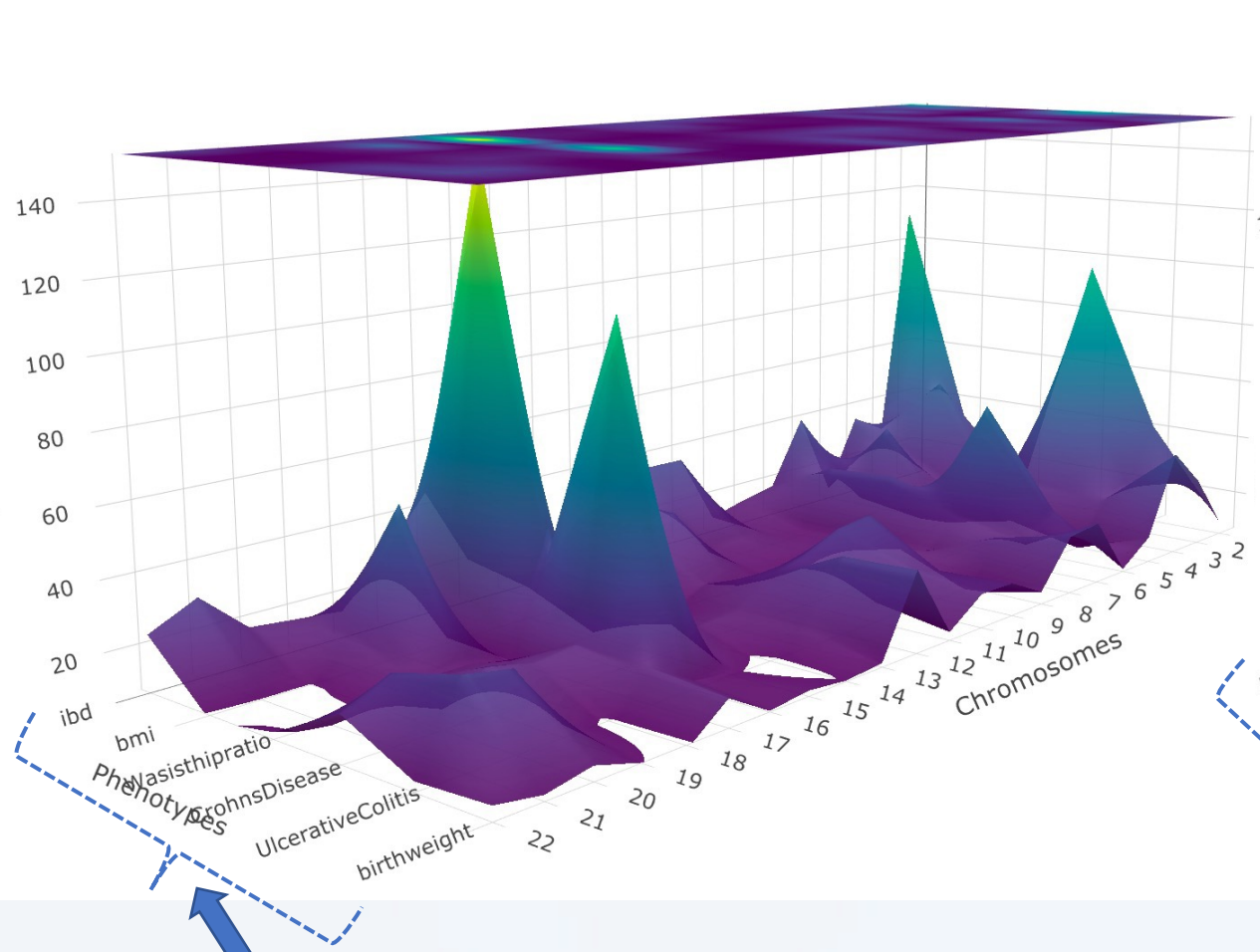
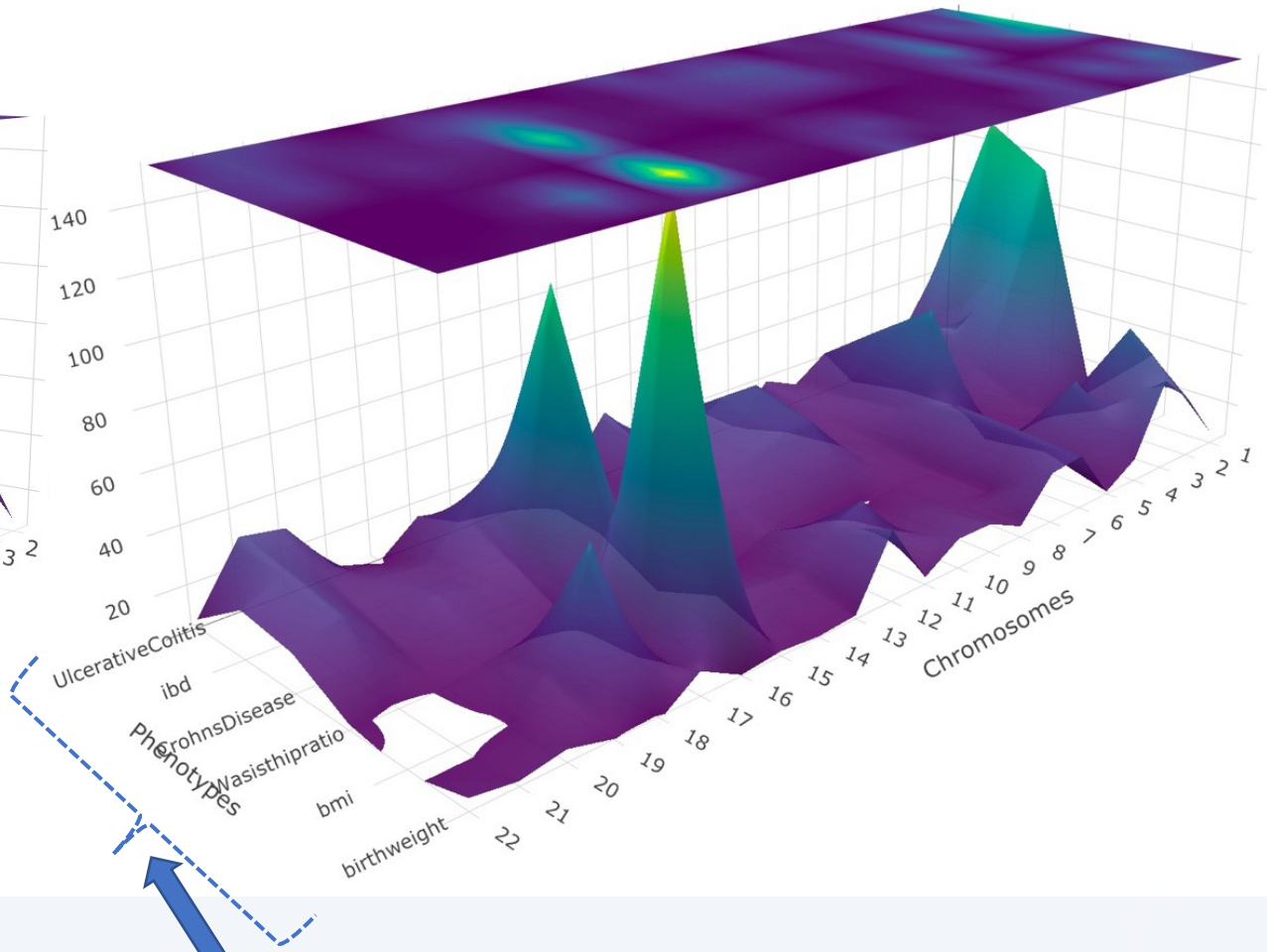


PheGWAS

The traits ordered in random order



iPheGWAS ← PheGWAS + Heuristic Method

The traits ordered by heuristic approach I developed

iPheGWAS retina traits in GoDARTS

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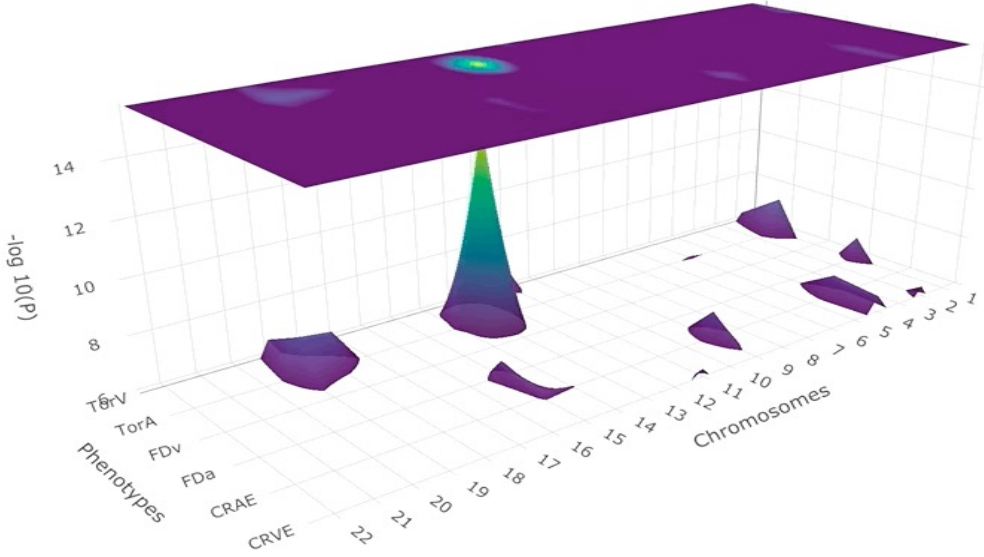
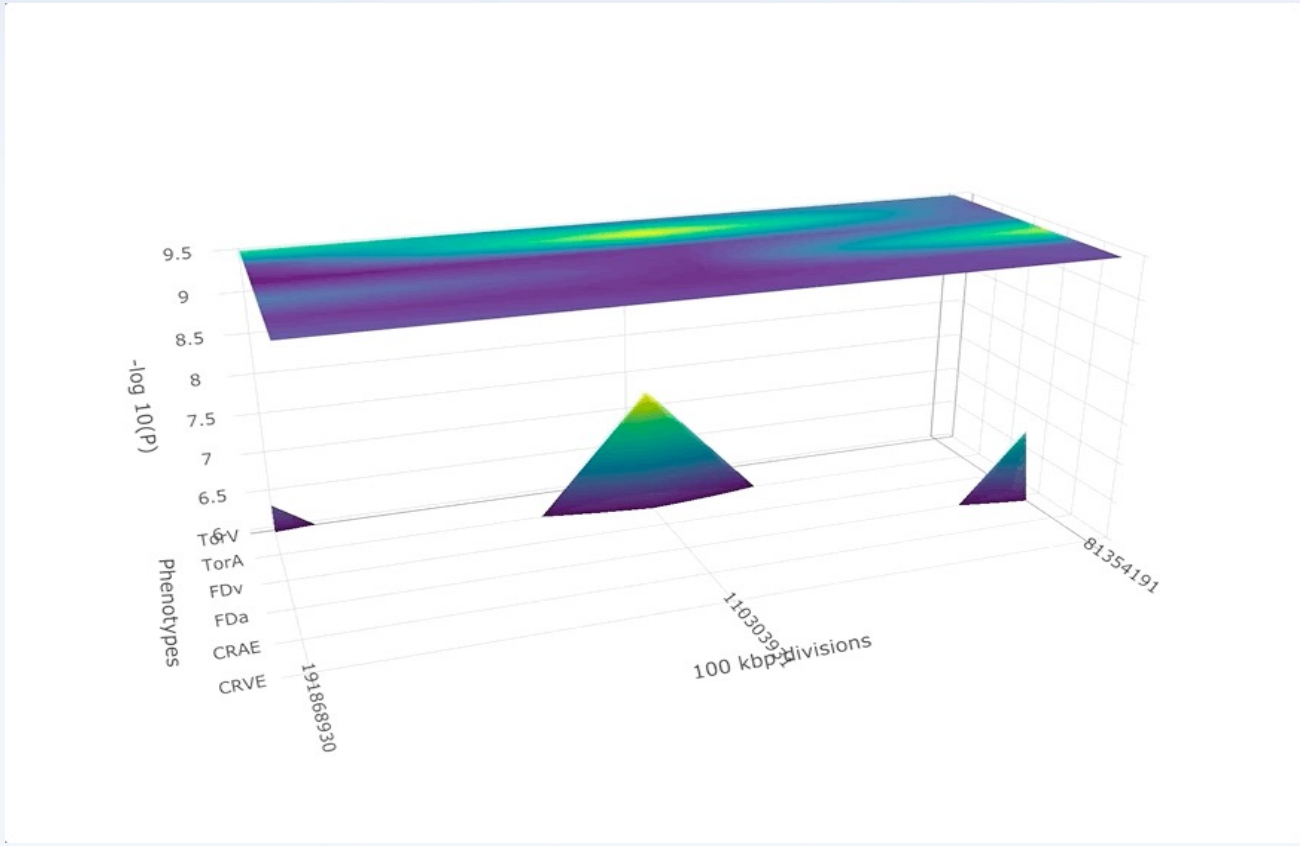
Genome View

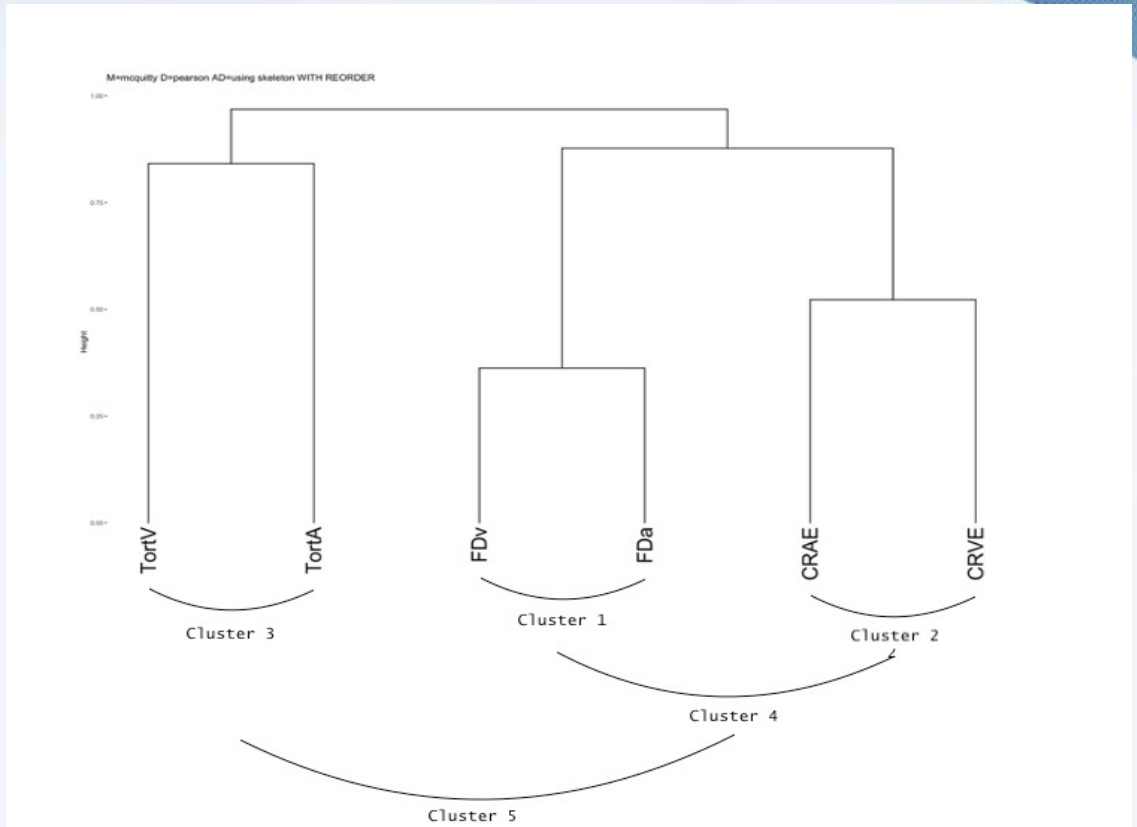


- Exploring all chromosomes suggest that there is no pleiotropic regions across the genome
- Seems reasonable that veins and artery measurements would cluster together in each of the measurement categories.
- Veluchamy et al .[] showed rs7991229 is associated with TortA which is in LD with rs9559797 that was found in chromosome 13 (r2 0.91). But this is not an independent confirmation.
- No other signals where identified in the literature

Chromosome 1 View



GoDARTS – Dendrograms



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Comparison of iPheGWAS of Clinical risk factors in GoDARTS & MDRF

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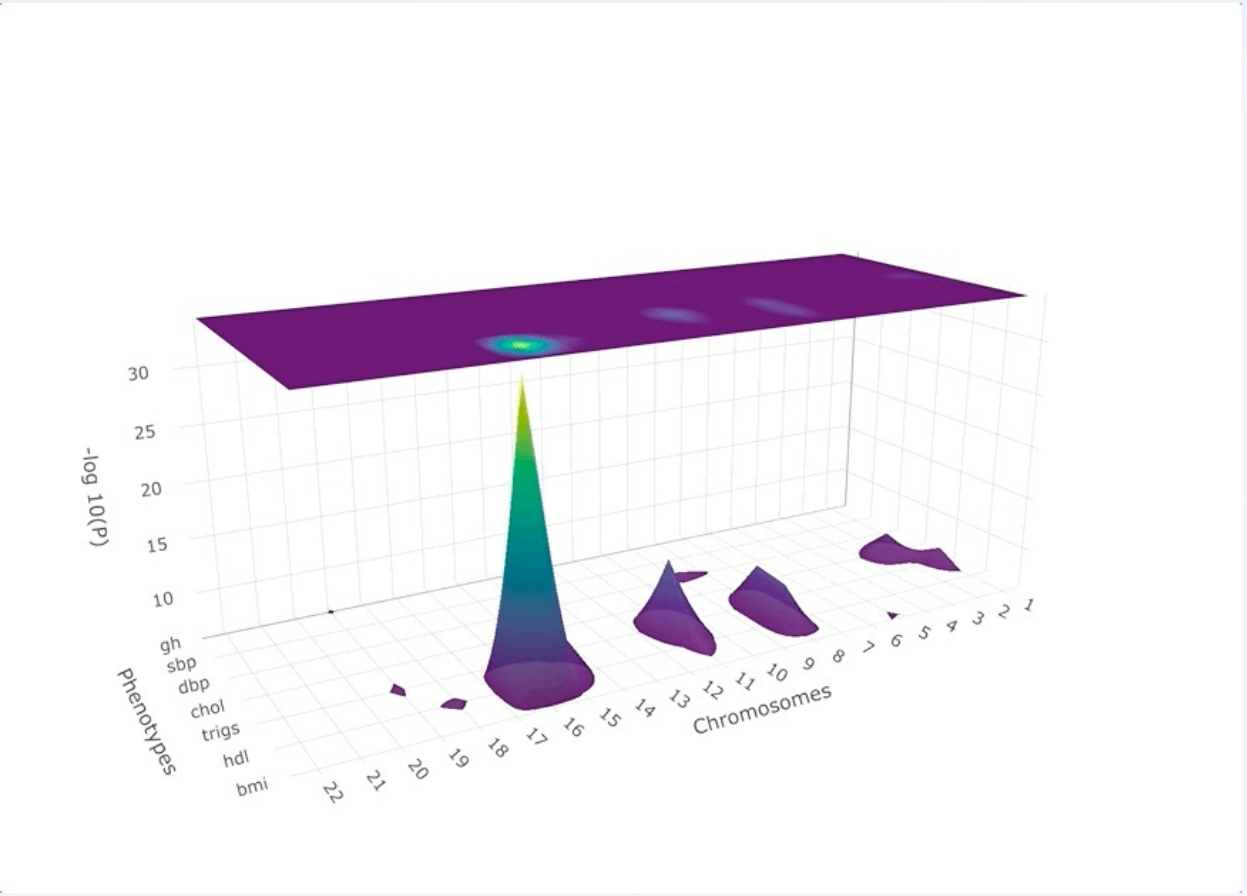
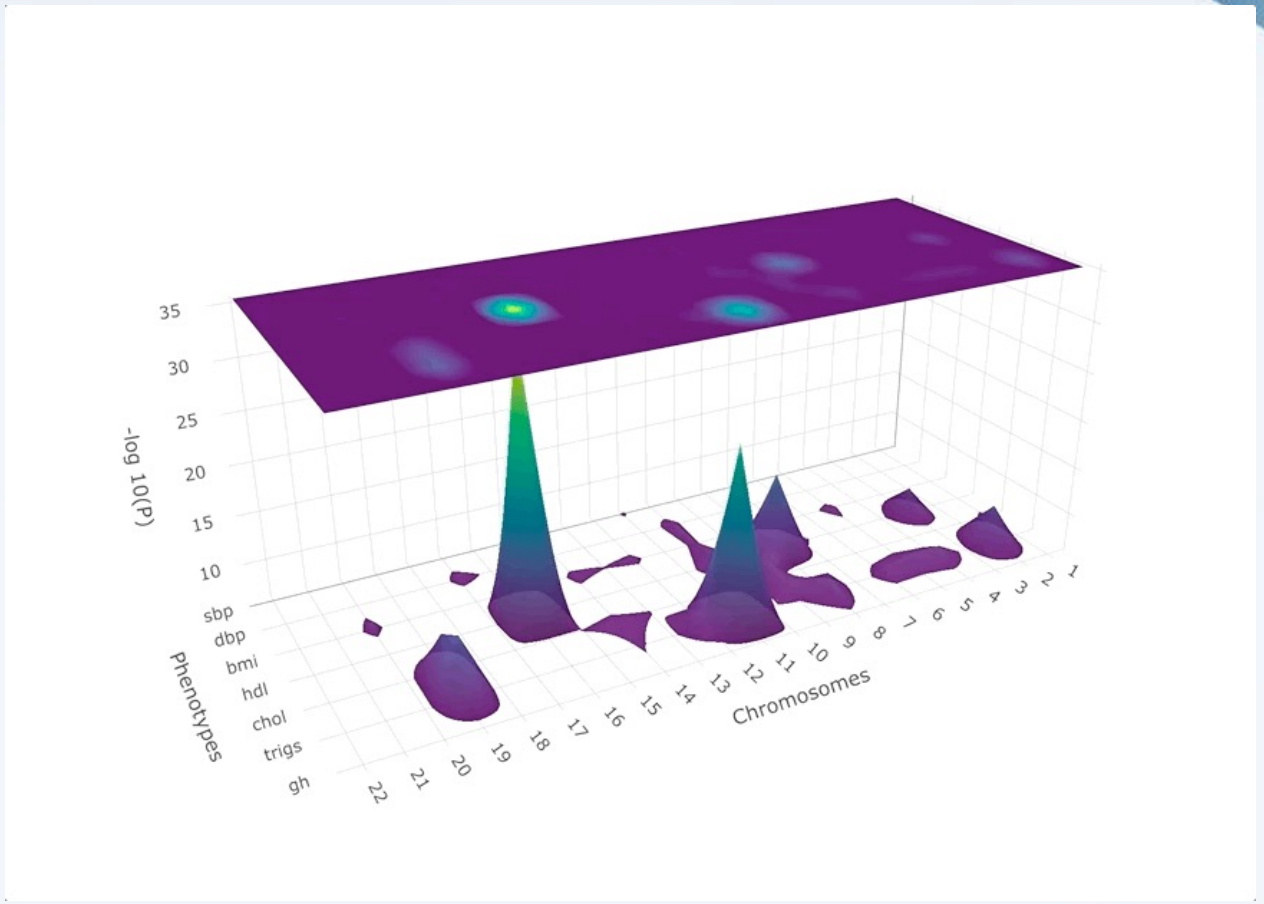
GoDARTS - Genome View



MDRF - Entire Genome View



Comparison of iPheGWAS of Clinical risk factors in GoDARTS & MDRF

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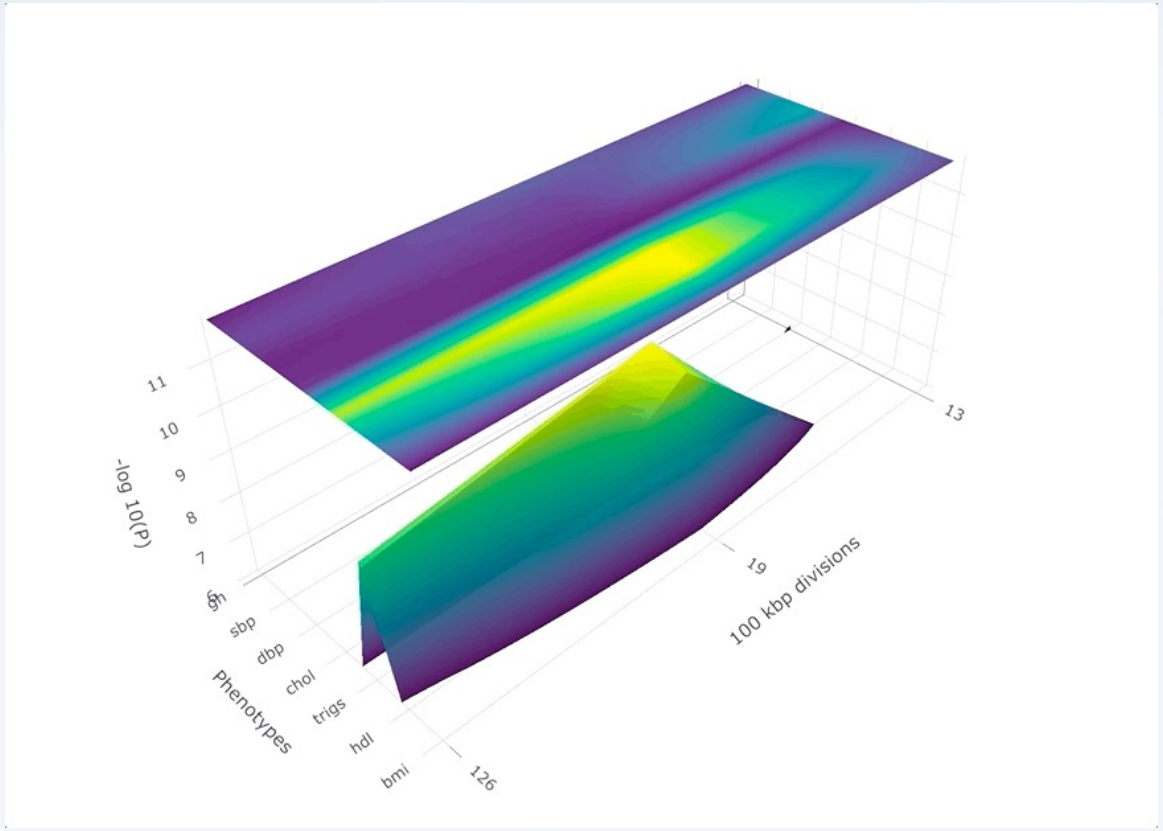
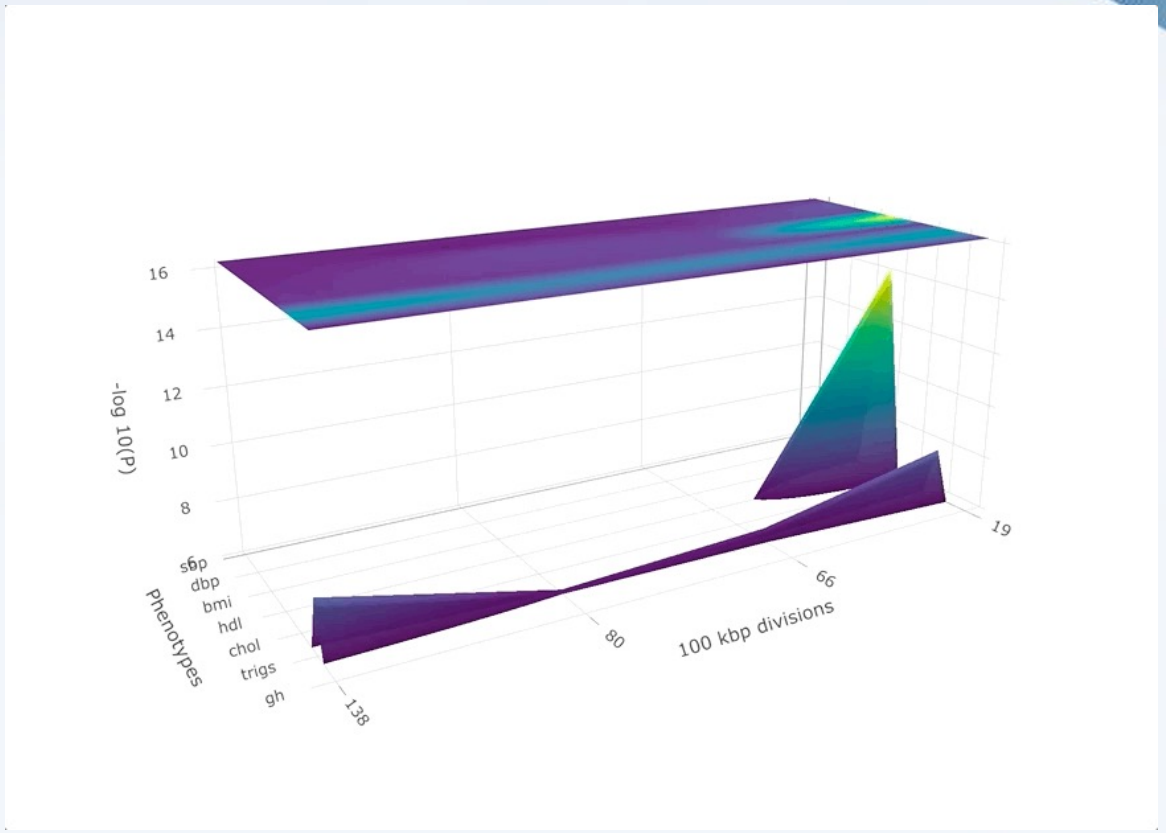
GoDARTS – Chromosome 8 View



MDRF – Chromosome 8 View



in chromosome 8, Position group 19, HDL and triglycerides shows pleiotropy in GoDARTS & MDRF

- From previous literatures rs3916027 and LPL gene in this region is associated with triglycerides*

* K. Musunuru et al., "Multi-ethnic analysis of lipid-associated loci: The NHLBI CARe project," PLoS One, vol. 7, no. 5, May 2012.

Comparison of iPheGWAS of Clinical risk factors in GoDARTS & MDRF

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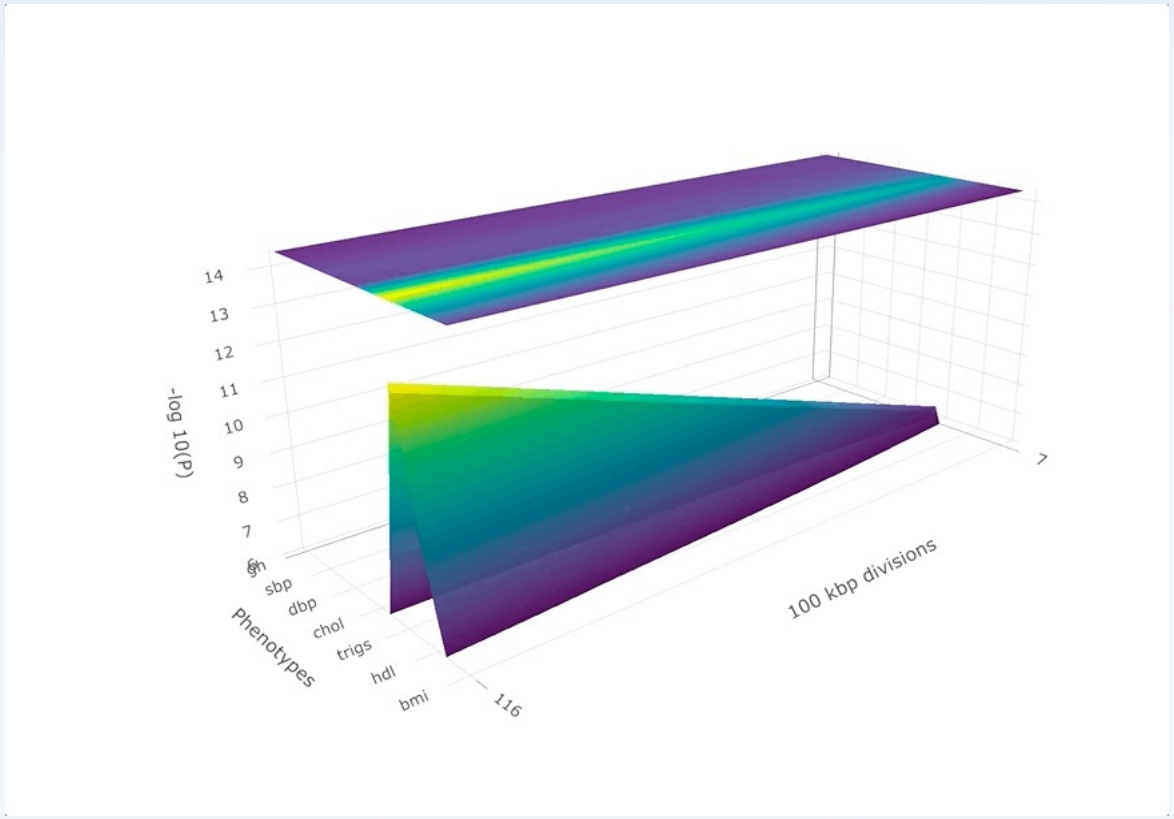
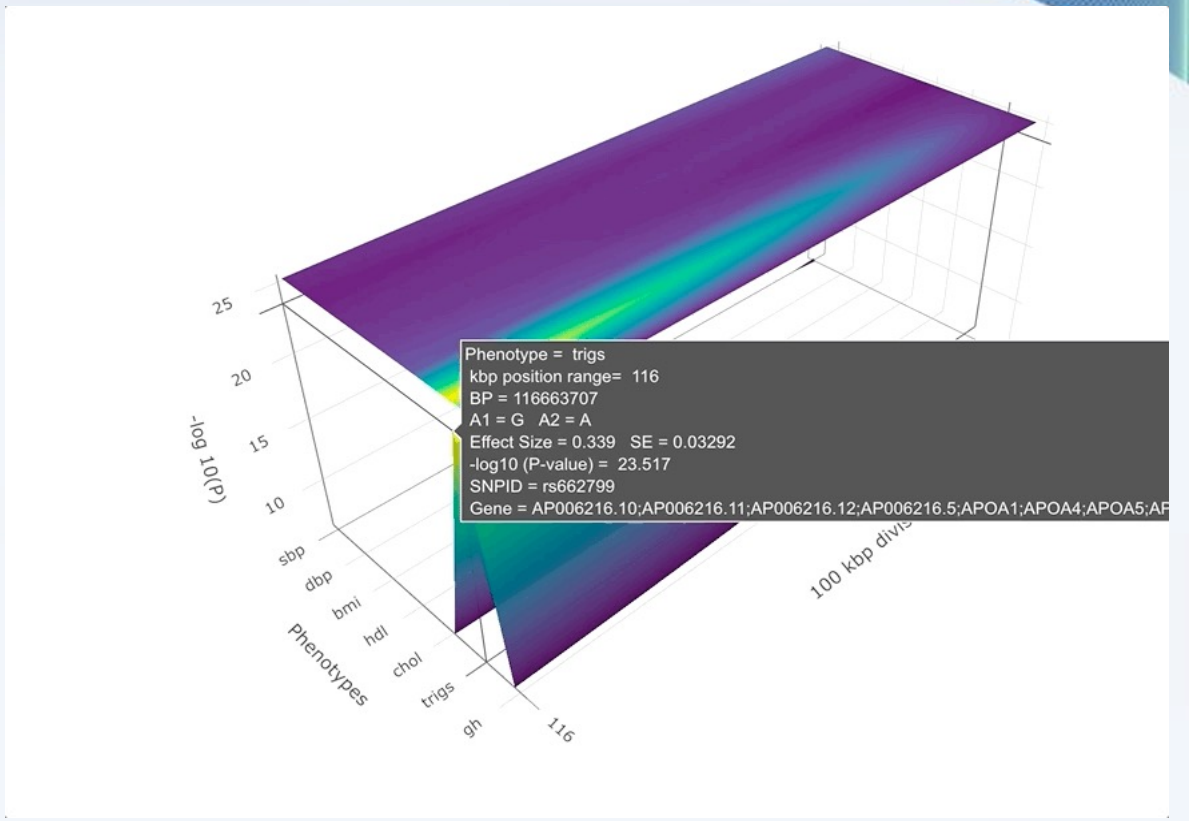
GoDARTS – Chromosome 11 View



MDRF – Chromosome 11 View



In chromosome 11, Position group 116 , HDL and triglycerides shows pleiotropy in GoDARTS. But for the same position group within the MDRF significance was only found with triglycerides.

- rs964184 and APOA5, APOC3, ZNF259 are associated with lipid traits [1]–[3].

[1] S. Kathiresan et al., “Common variants at 30 loci contribute to polygenic dyslipidemia,” Nat. Genet., vol. 41, no. 1, pp. 56–65, Jan. 2009.
[2] D. M. Waterworth et al., “Genetic variants influencing circulating lipid levels and risk ofcoronary artery disease,” Arterioscler. Thromb. Vasc. Biol., vol. 30, no. 11, pp. 2264–2276, Nov. 2010.
[3] C. T. Johansen et al., “Mutation skew in genes identified by genome-wide association study of hypertriglyceridemia,” Nat Genet, vol. 42, no. 8, pp. 684–687, 2010.

Comparison of dendrograms of Clinical risk factors in GoDARTS & MDRF

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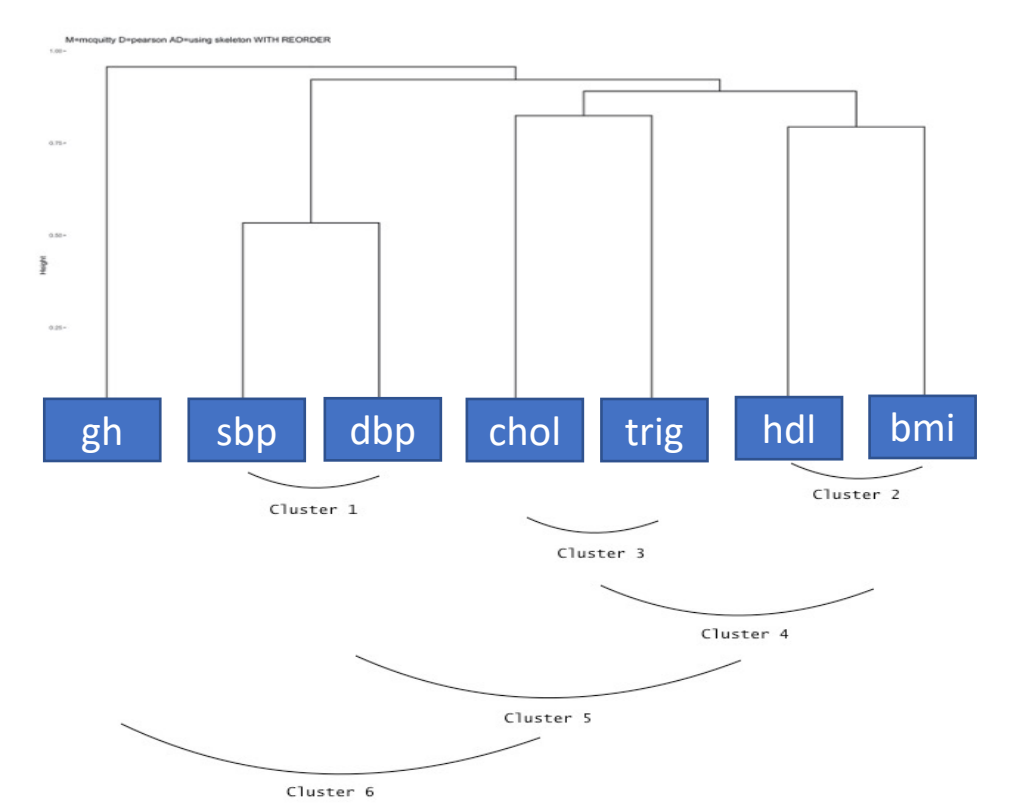
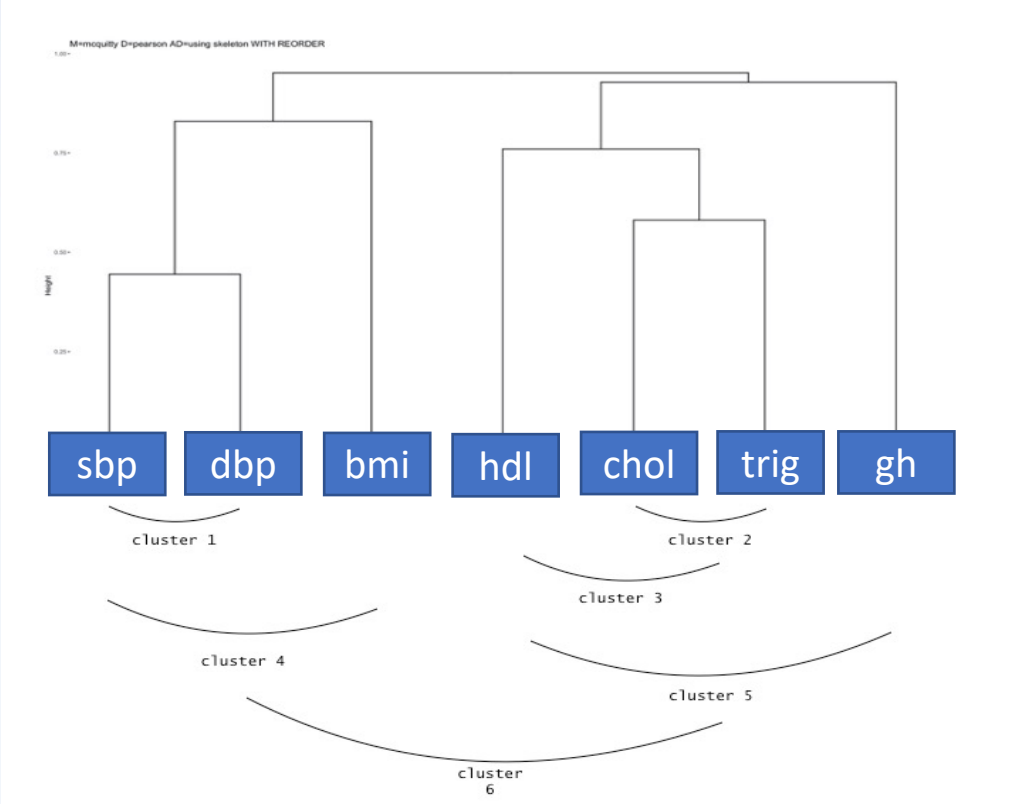
GoDARTS – Dendrograms



MDRF – Dendrograms



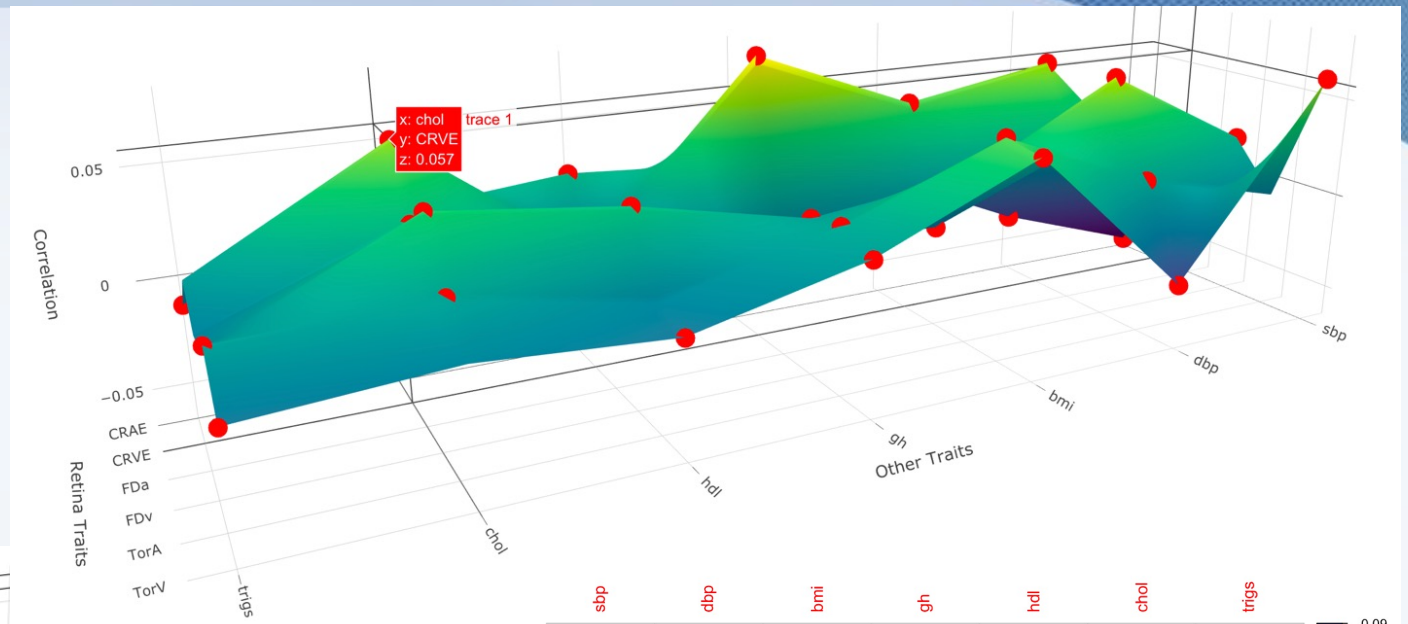
- These population differences that our tool is capable of capturing might be useful for biomedical researchers to open up avenues for further investigations.

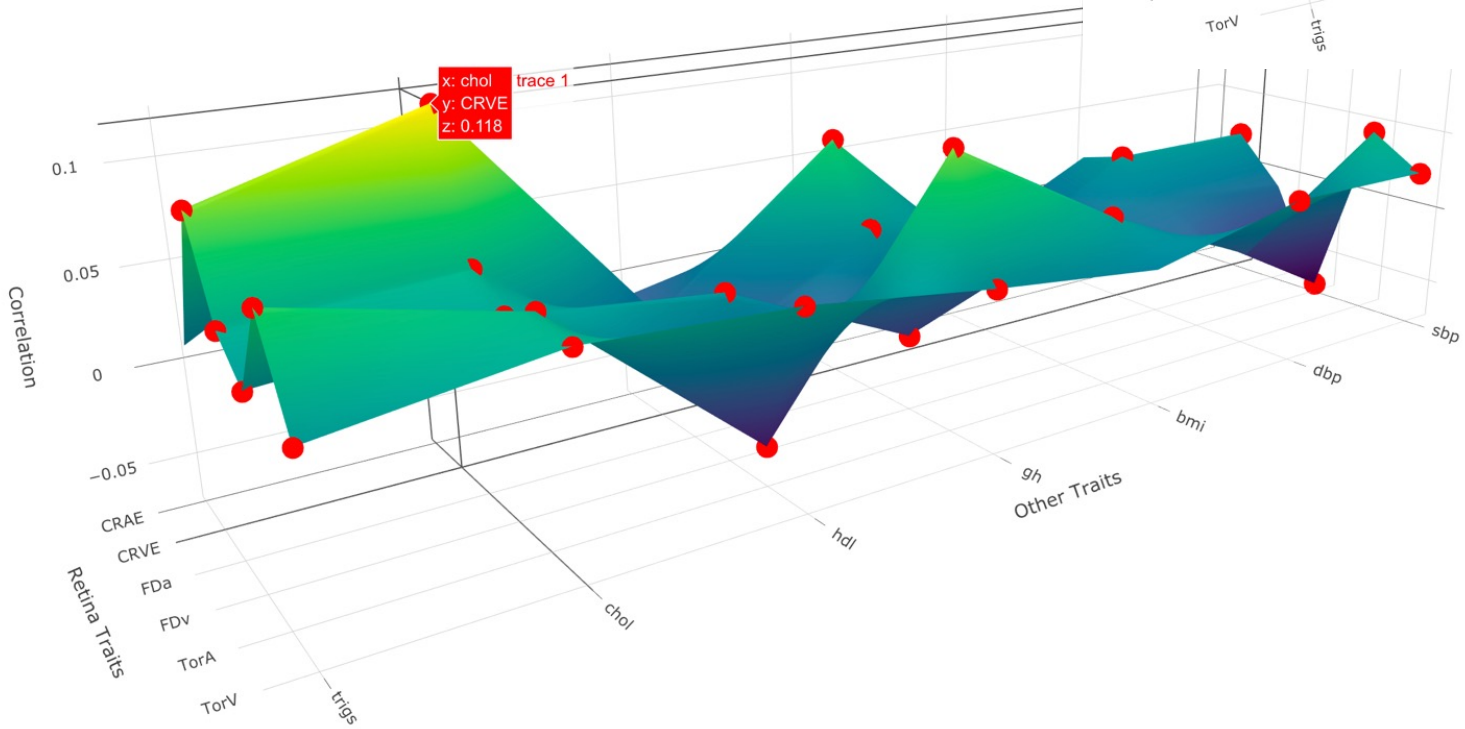
- Previous literature shows that genetic architecture of lipid traits differs by ethnicity and more ethnicity specific studies need to be conducted to clarify the underlying causes of such differences*

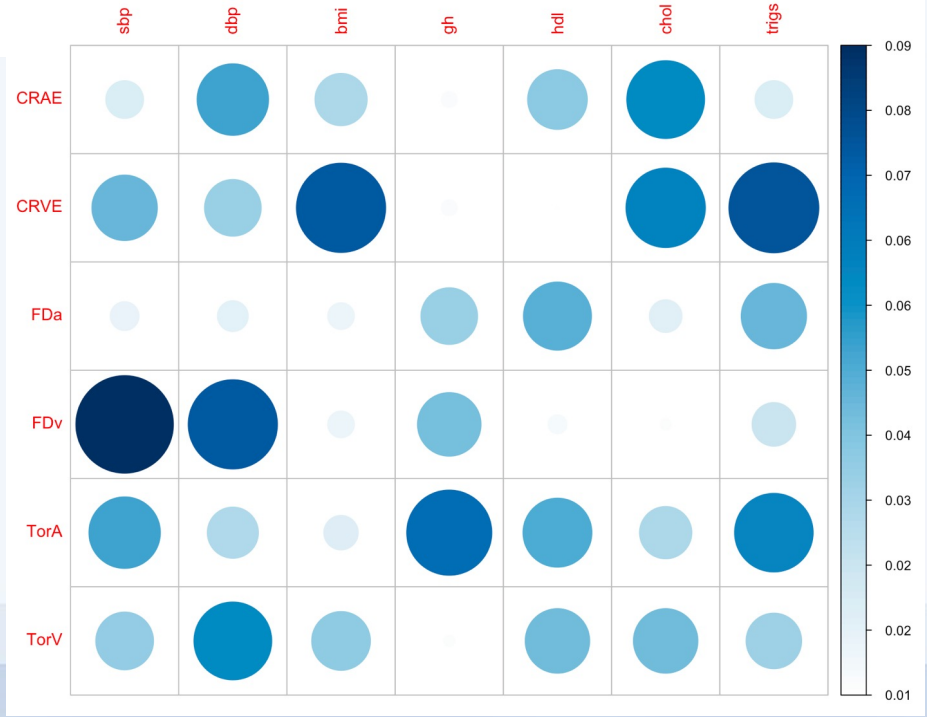
*J. G. Woo, J. A. Morrison, D. M. Stroop, L. A. Friedman, and L. J. Martin, "Genetic architecture of lipid traits changes over time and differs by race: Princeton Lipid Followup Study," J. Lipid Res., vol. 55, no. 7, pp. 1515–1524, 2014.

PhePheWAS of retina traits in GoDARTS and MDRF

Displays the phenome-phenome associations. This provides insights to explore the phenotypic relationship between multiple variables simultaneously.







LIMITATIONS

- iPheGWAS is considered to be an avenue for hypothesis generation, but for further assessments have to rely on other statistical softwares

- Our Heuristic method doesn’t show the sign of the genetic similarity. It only gives the strength of the association

- MDRF and GoDARTS (NHS data) are completely different health care systems and that can introduce some bias

FUTURE WORK

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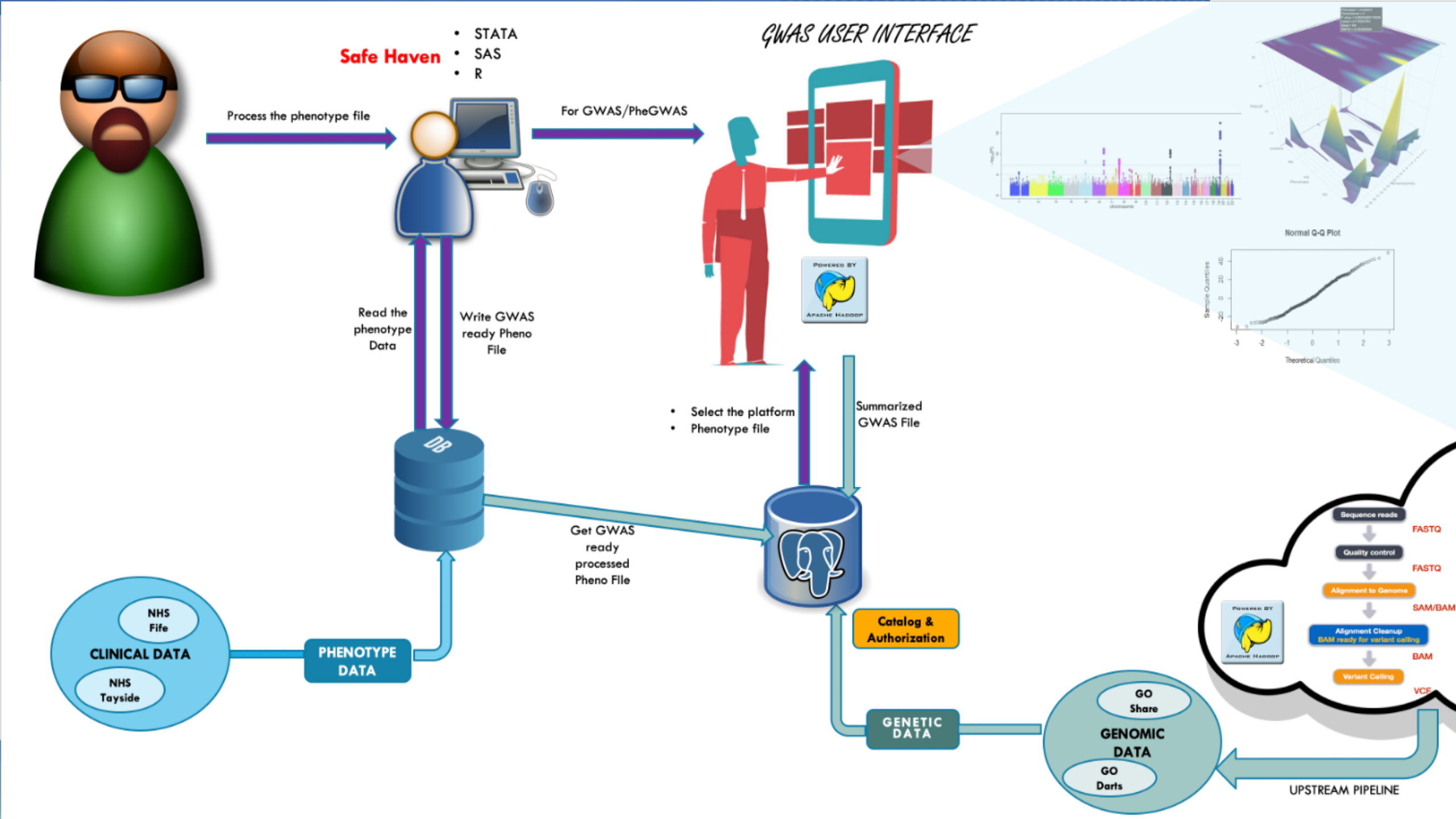
- Integrating other statistical softwares into iPheGWAS will take researchers towards “ONE-STOP-SHOP” concept
- Implementation of iPheGWAS along with other GWAS tools in HIC Hadoop-Spark cluster
- Applying PheGWAS on many traits (e.g. PheGWAS to prescription data in GoDARTS)
- It would be interesting to investigate more on the dendrogram difference in GoDARTS and MDRF populations.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Summarized GWAS File
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CLINICAL DATA
NHS Tayside
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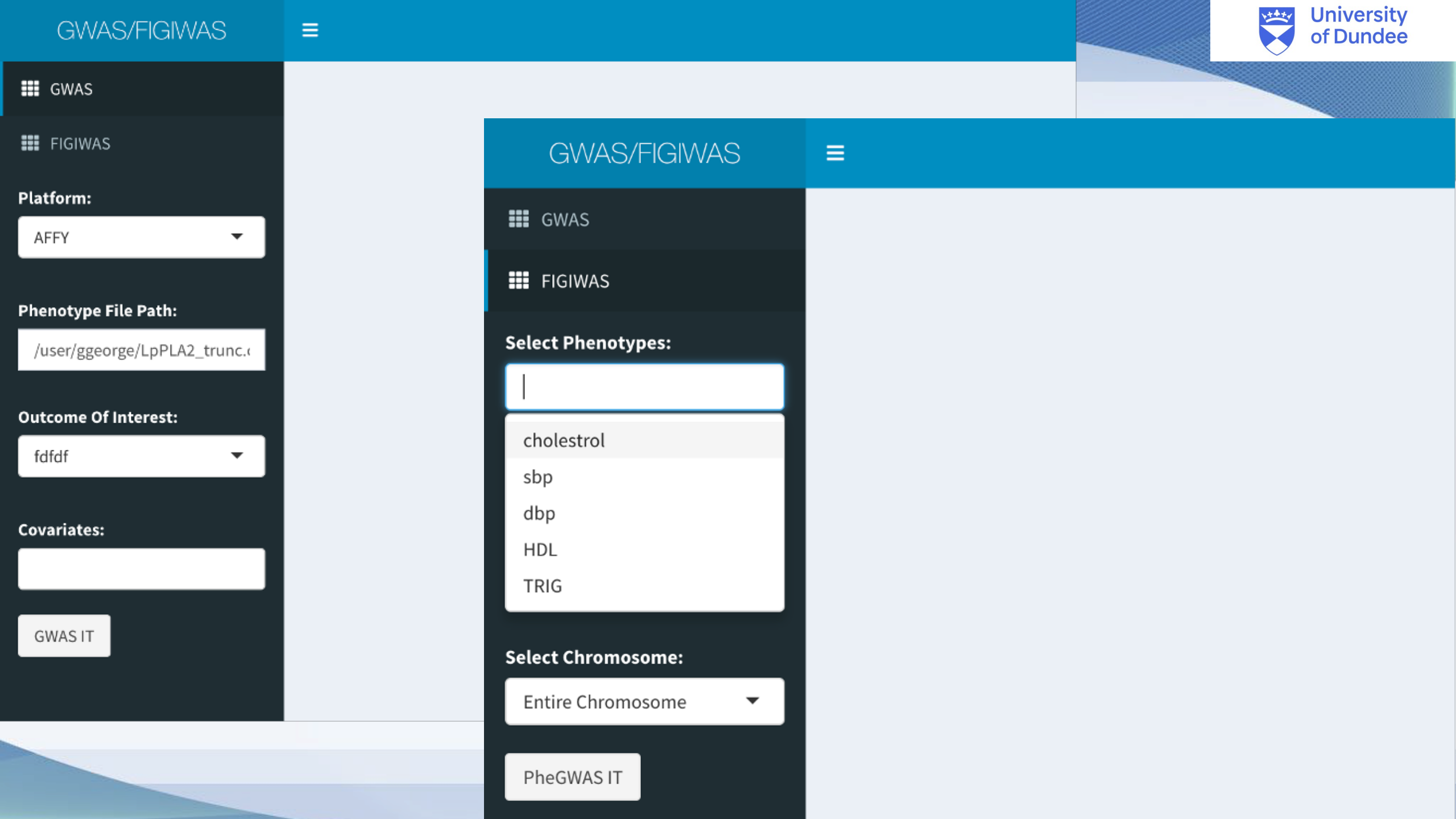
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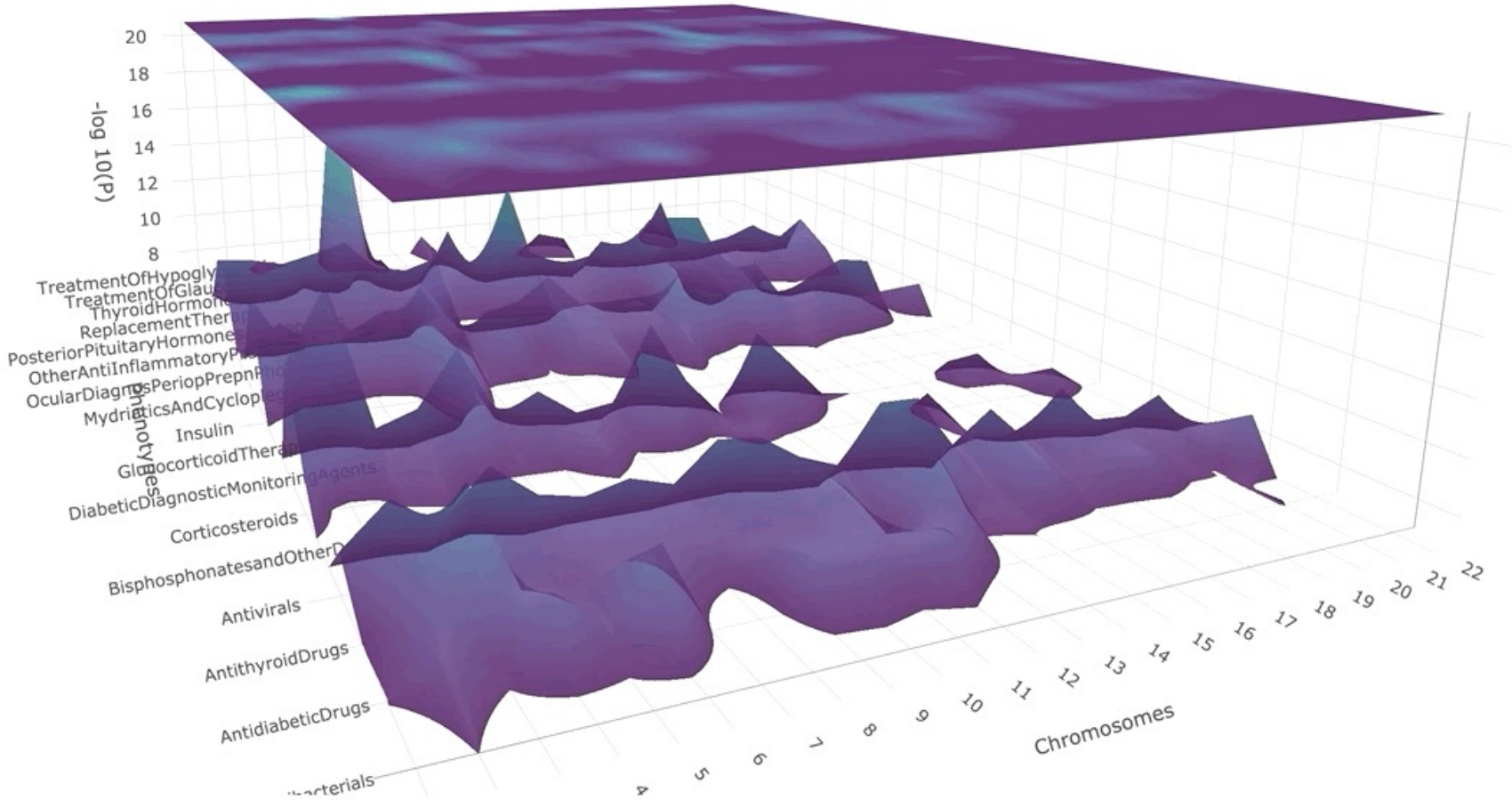
Prescription

- Cardiovascular system
- Endocrine system
- Eye



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