Connecting metabolic biomarkers with biological pathways and clinical data to enable omics data interpretation

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Twitter: @SMaLLCaT4Sci and @BiGCaT_UM
Blog: http://smallcats4science.blogspot.nl
ORCID: 0000-0001-8449-1318

2019-10-04 DiseaseMaps2019, Sevilla

Maastricht University

Slides on:

10.6084/m9.figshare.9937922

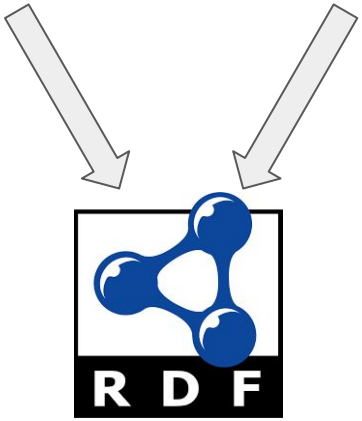
No problem taking pictures ;)

Metabolic Biomarkers
Biological Pathways
Clinical Data
Omics data Interpretation

Metabolic Biomarkers + Biological Pathways + Clinical Data → Omics data Interpretation

http://iembase.org/

www.wikipathways.org



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Pathways for the People

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Clin. Genetics Department

RDF

Cytoscape

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Genes + Proteins + Metabolites → Phenotype

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Gene, protein and metabolite logo's from: https://www.x-omics.nl/

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Biological Pathways

WIKIPATHWAYS
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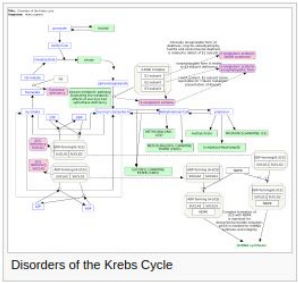
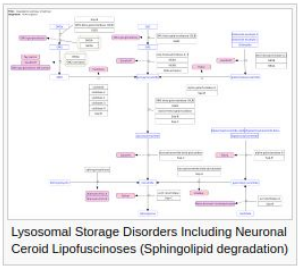
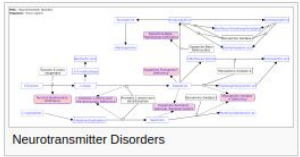
Ongoing effort since 2016 to digitise all PWs from:

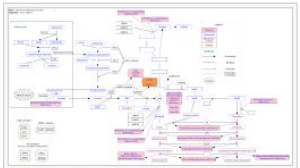
- Pathway:WP4236 - Chapter 20 "Disorders of the Krebs Cycle"
- Pathway:WP4153 - Chapter 25 "Lysosomal Storage Disorders Including Neuronal Ceroid Lipofuscinoses (Sphingolipid degradation)"
- Pathway:WP4220 - Chapter 31 "Neurotransmitter Disorders"
- Pathway:WP4224 - Chapter 41 "Purine Disorders"
- Pathway:WP4225 - Chapter 41 "Pyrimidine Disorders"


Disorders of the Krebs Cycle


Lysosomal Storage Disorders Including Neuronal Ceroid Lipofuscinoses (Sphingolipid degradation)


Neurotransmitter Disorders

Purine Disorders


Pyrimidine Disorders

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With help from various students and related projects/courses:
(and colleagues I kept bothering)

Biological Pathways

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With help from various students and related projects/courses: (and colleagues I kept bothering)

2017:
Create pathways, digitise Biomarker info as RDF

[DKE] Richard Delava ; Roel Hacking ; Herman Ritter
[FPN] Anne Friesacher ; Lisa Held
[LAW] Mzolisi Mtshaulana

(2018-current):
Create pathways, OMICS data analysis (mutations and functional prediction tools, transcriptomics, GO-analysis)

[BSc] Jesse Vercoulen
[MSc] Youssef Walid; Mick Eikelhof ; Irene Hemel

2019:
Create pathways, digitise Kinetic + Drug data as RDF

Evi Schoenmaker ; Lobke Meels ; Inge Budé ; Britt Pieters ; Eline Sanders

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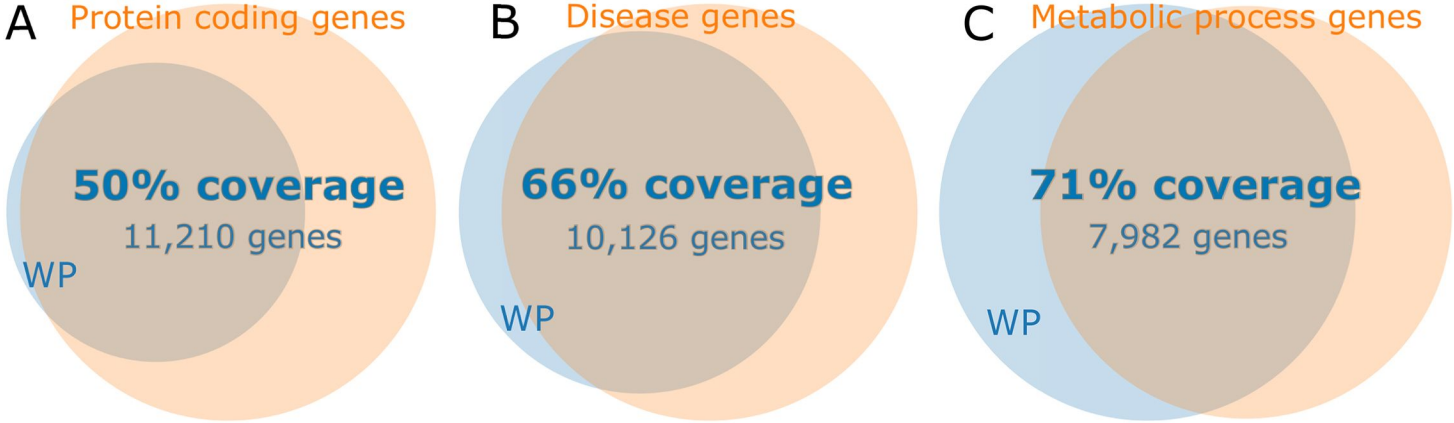

DOI: https://doi.org/10.1093/nar/gkx1064

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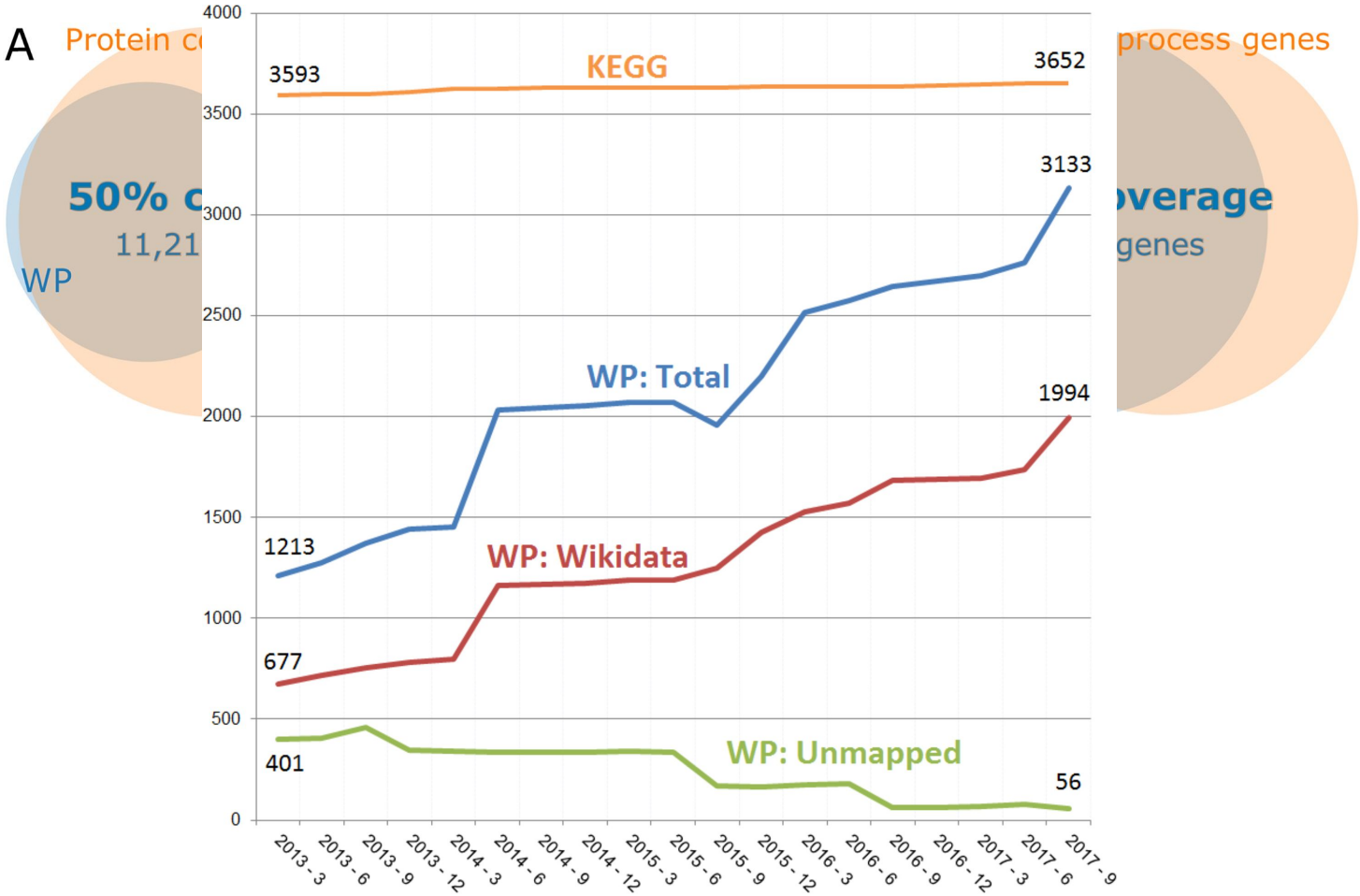

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Biological Pathways

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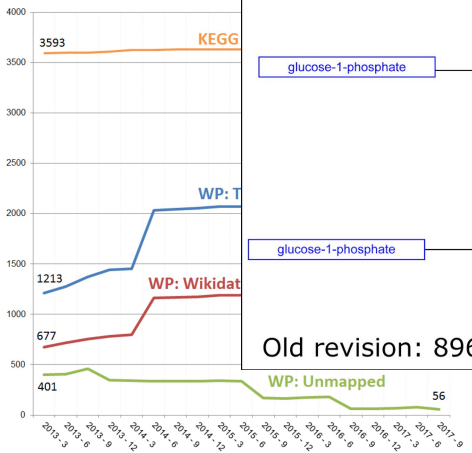
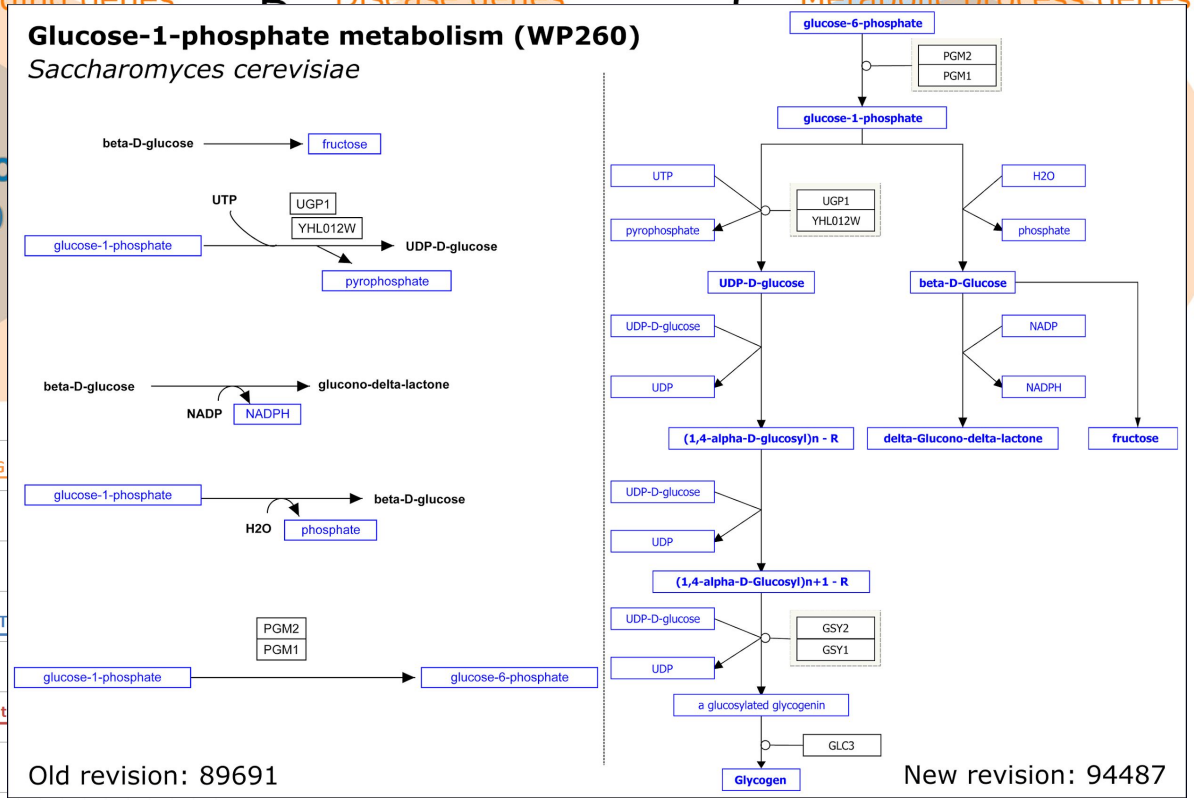
A Protein coding genes B Disease genes C Metabolic process genes

50% co
11,210
WP





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Genes + Proteins + Metabolites → Phenotype

RDF

Cytoscape

Gene, protein and metabolite logo's from: https://www.x-omics.nl/

Metabolic Biomarkers + Biological Pathways

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www.wikipathways.org

R D F

Bsc. thesis Biomedical Sciences
Josien Landman

Research Question:

Can we use biological pathway information to check if biomarkers are linked to diseases?

Workflow

RDF with disease-biomarker associations

Biological pathway information from WikiPathways

Conversion of disease associations from GPML-RDF to WP-RDF

SPARQL queries with Blazegraph

RDF with disease-biomarker associations

Input

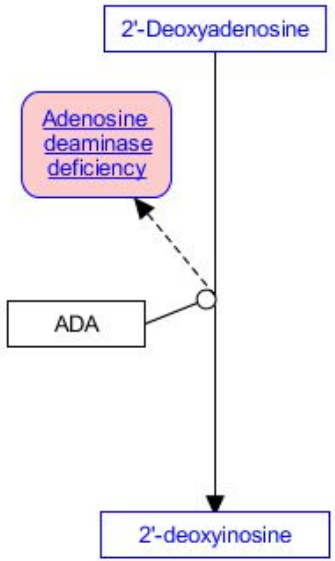
- "Physician's Guide to the Diagnosis, Treatment and Follow-Up of Inherited Metabolic Disorders"
  - ch 1. Disorders of Phenylalanine and Tetrahydrobiopterin (BH4) Metabolism
  - ch 11. Vitamin B6-Dependent and Responsive Disorders
  - ch 20. Disorders of the Krebs Cycle
  - ch 31. Neurotransmitter Disorders
  - ch 41. Purine and Pyrimidine Disorders

Output

- RDF file with 50 diseases and 58 unique biomarkers
- 103 biomarker-disease associations

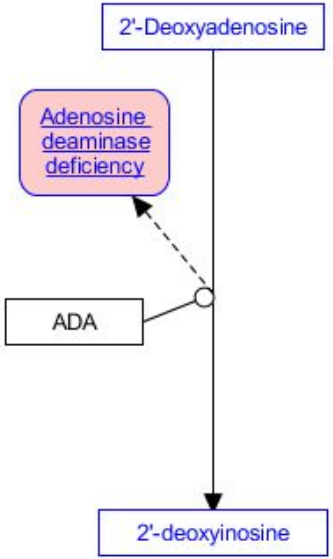
Blau, N., Duran, M., Gibson, K.M., Dionisi-Vici, C.; ISBN 978-3-642-40337-8, 2014

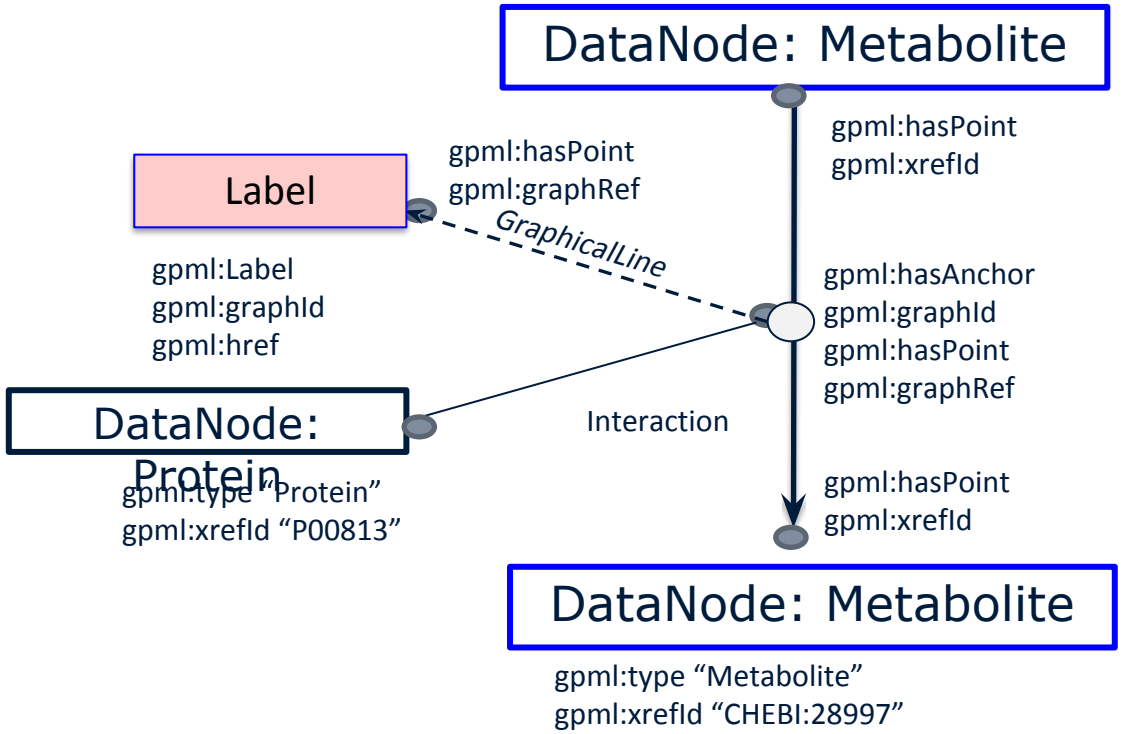
Adding disease associations from GPML-RDF to WP-RDF



Example disease interaction: www.wikipathways.org/instance/WP4224

Adding disease associations from GPML-RDF to WP-RDF





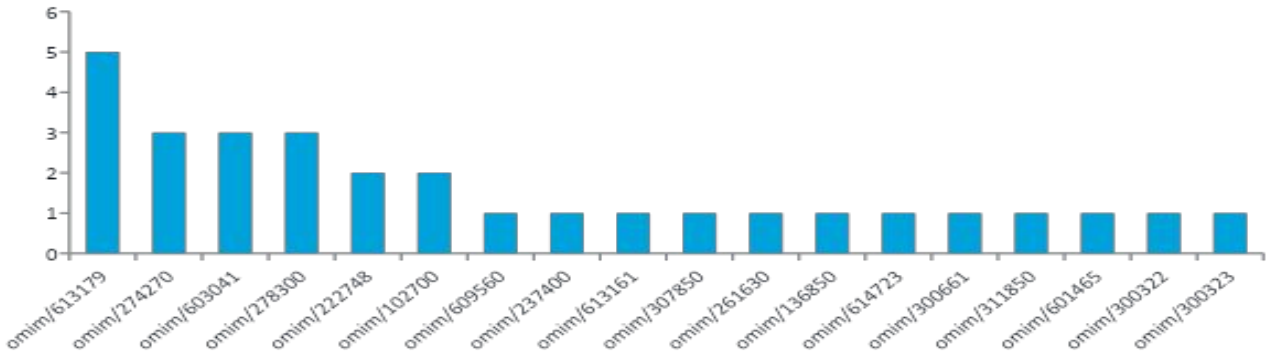
Example disease interaction: www.wikipathways.org/instance/WP4224

Co-occurence of disease and biomarker in the same biological pathway:

34 of the 50 diseases present* in WikiPathways connected to a biomarker

Disease is associated with an interaction that directly involves the biomarker:

18 of the 50 diseases present* in WikiPathways directly connected



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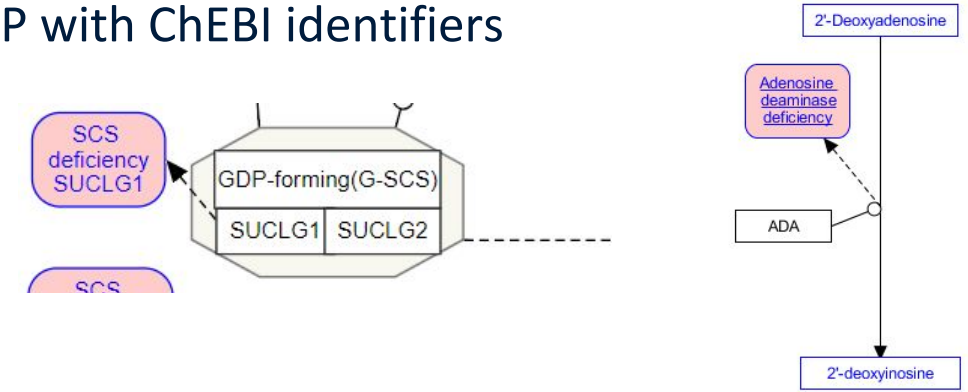
* Biomarker disease links were investigated for 5 different chapters

Challenges

- RDF with biomarker-disease associations annotated with Wikidata identifiers (biomarkers), metabolites in WP with ChEBI identifiers
- Not all diseases in pathways are connected to the interaction in similar manner



- Biomarkers present in pathway but not all biomarkers are directly linked to diseases

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RDF

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Gene, protein and metabolite logo's from: https://www.x-omics.nl/

Biological Pathways + Clinical Data

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Cytoscape

MSc. thesis Biomedical Sciences
Irene Hemel

Research Title:

Automated visualization of biomarkers for pyrimidine and urea cycle disorders in pathways

Differential diagnosis Urea and Pyrimidine Disorders

- Challenging
- Urea cycle disorders → accumulation carbamoyl phosphate → enters *de novo* synthesis of pyrimidines → altered pyrimidine metabolite concentrations [1,2]

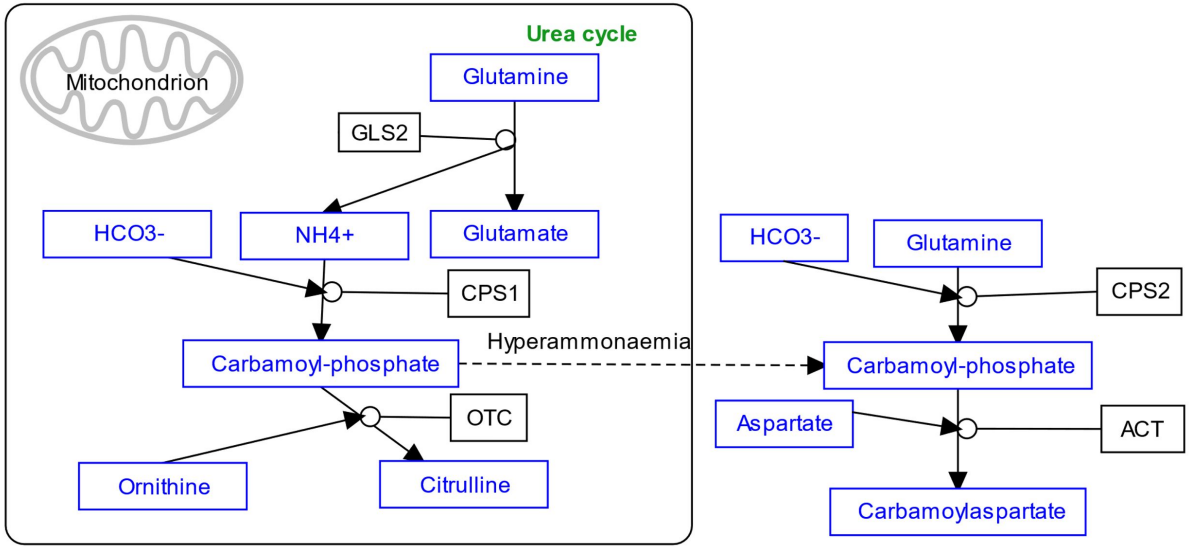
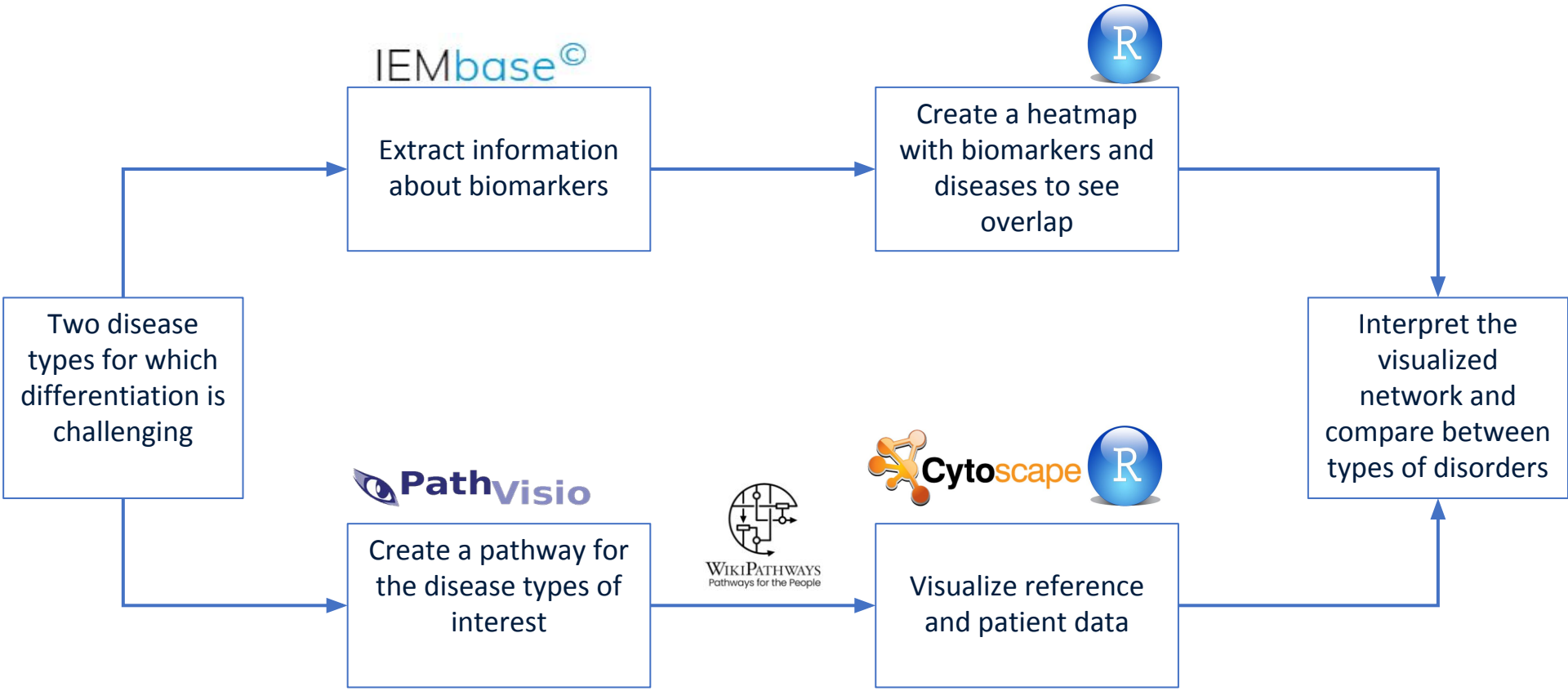


Image adapted from WP4225_104804

1 Leonard JV, Morris AA. (2002) Seminars in neonatology;
2 Burrage LC, et al. (2019) Genetics in medicine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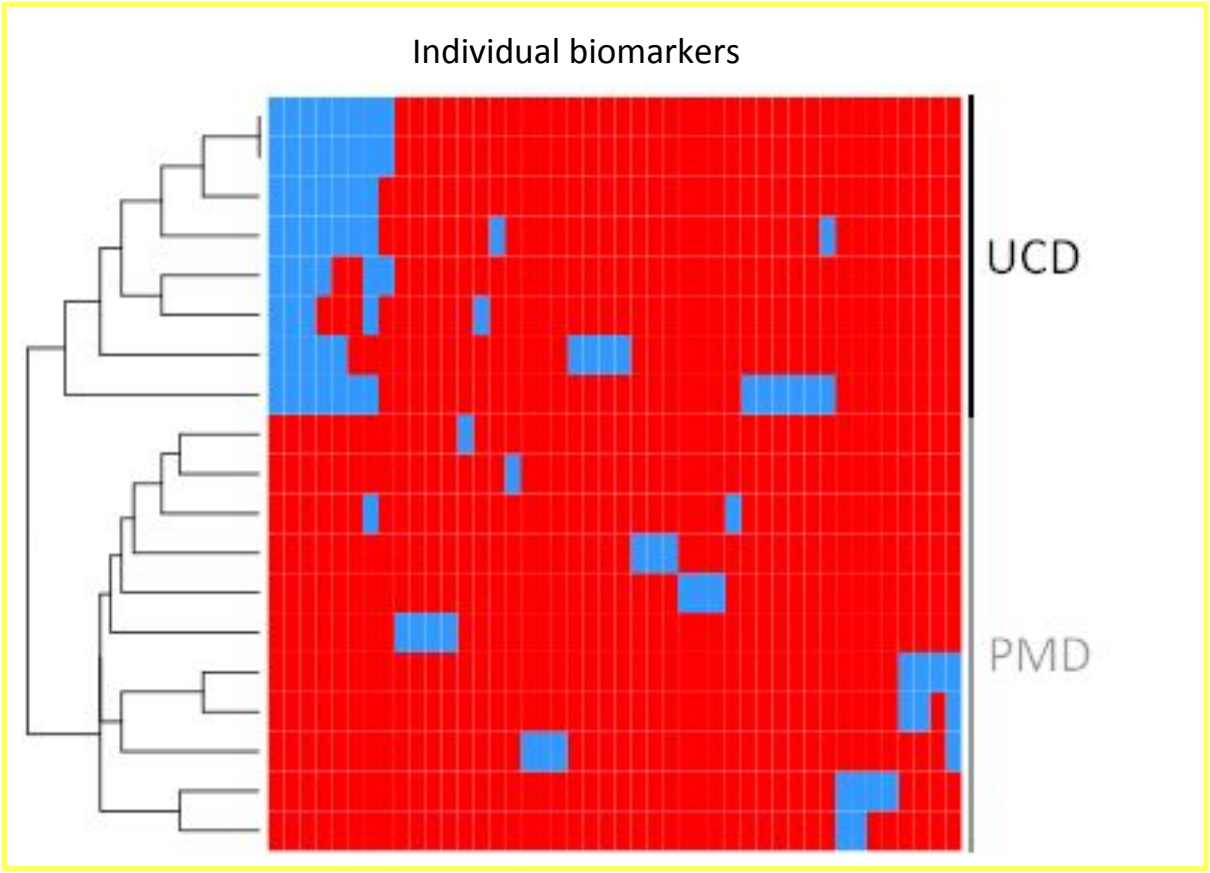
Extract information about biomarkers
R
Create a heatmap with biomarkers and diseases to see overlap
Two disease types for which differentiation is challenging
Interpret the visualized network and compare between types of disorders
PathVisio
Create a pathway for the disease types of interest
WikiPathways
Pathways for the People
Cytoscape
R
Visualize reference and patient data

Heatmap

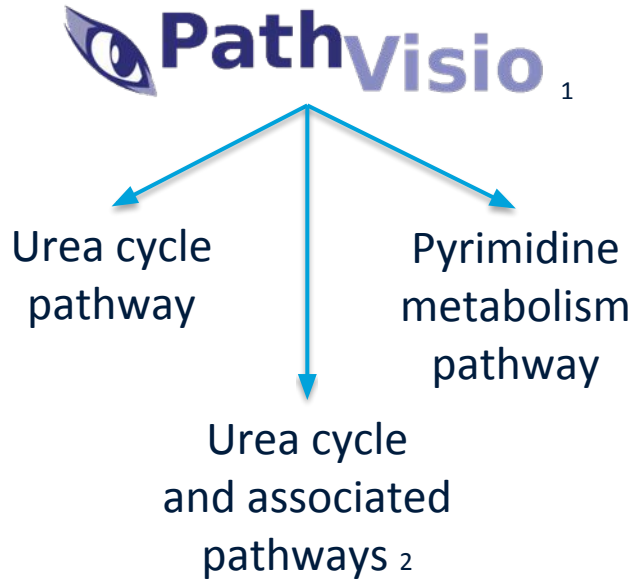
- Disease types form individual clusters

- Based on theoretical biomarkers differentiation seems possible
  - Not in practice



Every column represent an individual metabolite. Blue: Metabolite is biomarker for disease. Red: metabolite is NOT a biomarker for disease

Original Pathways



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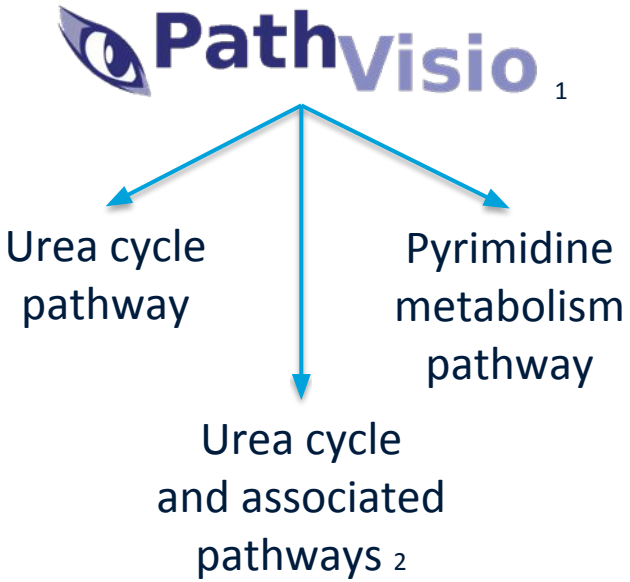
1 Kutmon M, et al. (2015) Plos computational biology
2 Blau N, et al. (2014) Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases, Ch 4
3 UniProt Consortium (2019) Nucleic Acids Research
4 Morgat A, et al. (2017) Nucleic Acids Research
5 Hastings J, et al. (2016) Nucleic Acids Research
6 OMIM (2019-04-12) https://omim.org/

Original Pathways



Proteins → Uniprot IDs [3]

Interactions → Rhea IDs [4]

Metabolites → ChEBI [5]

Diseases → OMIM [6]

1 Kutmon M, et al. (2015) Plos computational biology
2 Blau N, et al. (2014) Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases, Ch 4
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6 OMIM (2019-04-12) https://omim.org/

Comparing Biomarkers to Original Pathways

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Biomarker information [1]

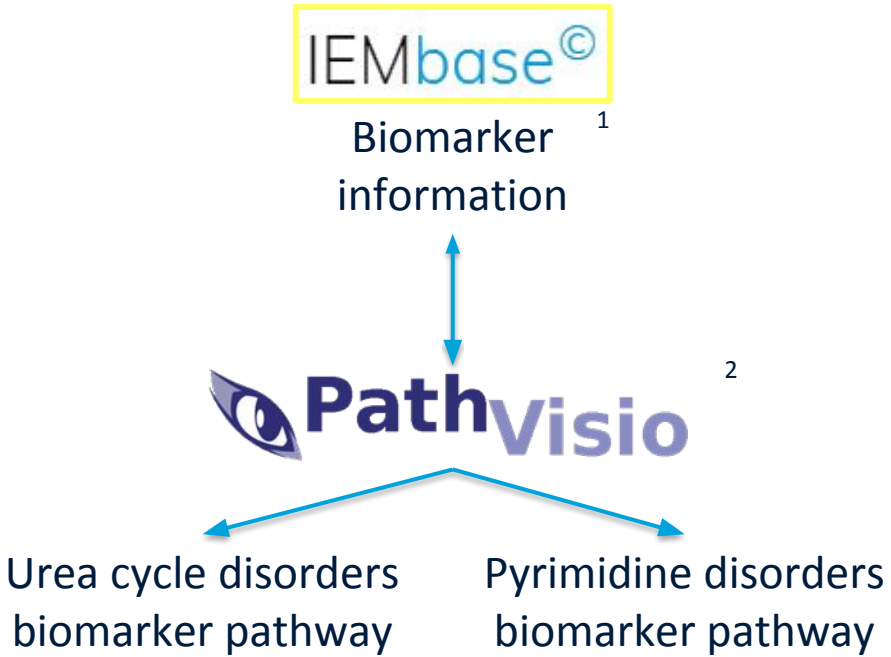
[2]

Challenges:

Not all biomarkers present in PWs

1 Lee JJY, et al. (2018) Genetics in medicine; last accessed: 2019-04-16
2 Kutmon M, et al. (2015) Plos computational biology

Comparing Biomarkers to Original Pathways



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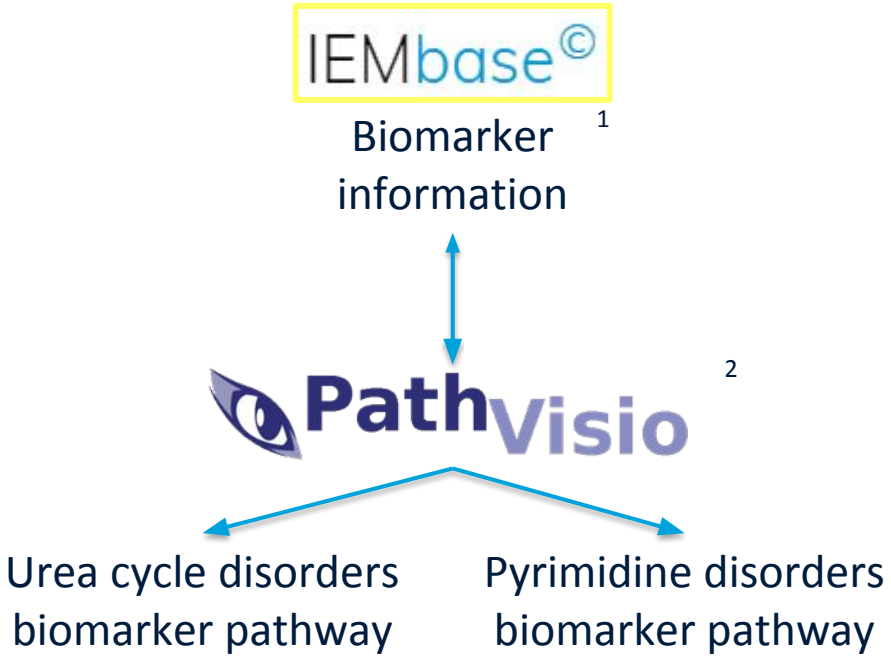
Comparing Biomarkers to Original Pathways



Challenges:

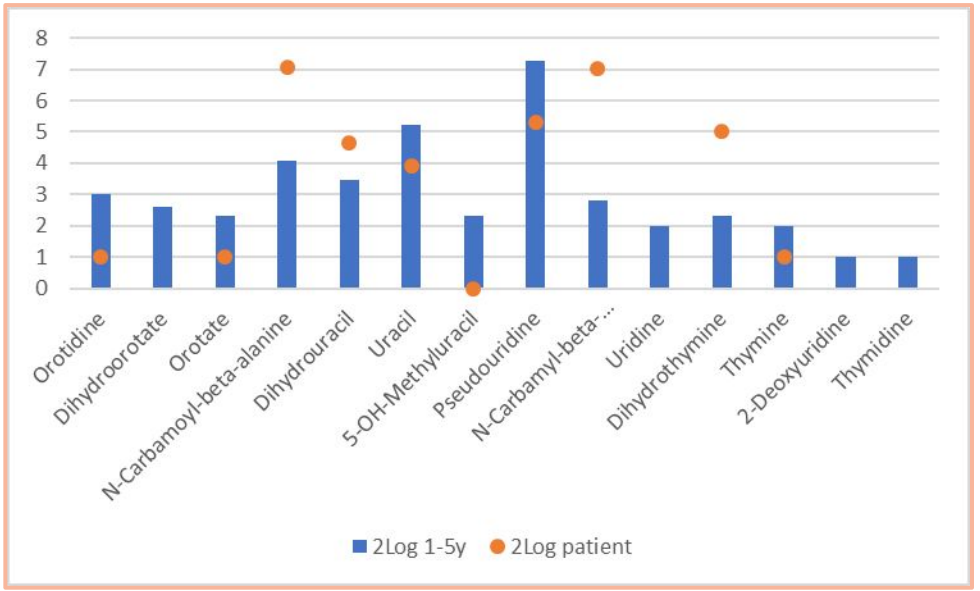
Mapping from HMDB to ChEBI (and vice versa)

Mapping charged and zwitterions metabolites to biomarkers

1 Lee JJY, et al. (2018) Genetics in medicine; last accessed: 2019-04-16
2 Kutmon M, et al. (2015) Plos computational biology

Possible visualization of Clinical data

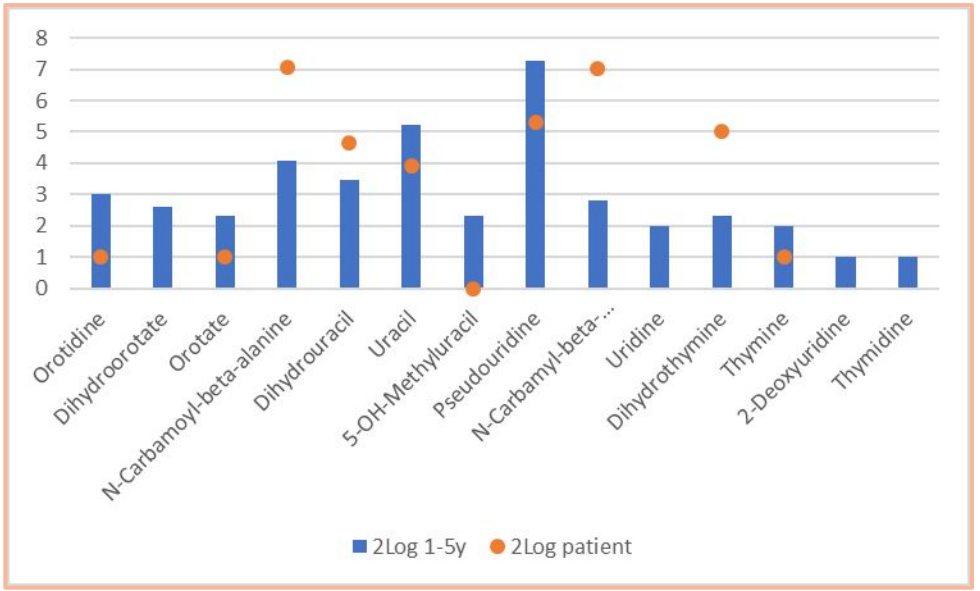
- Log transformed reference and patient data
- 4 metabolites with increased concentration



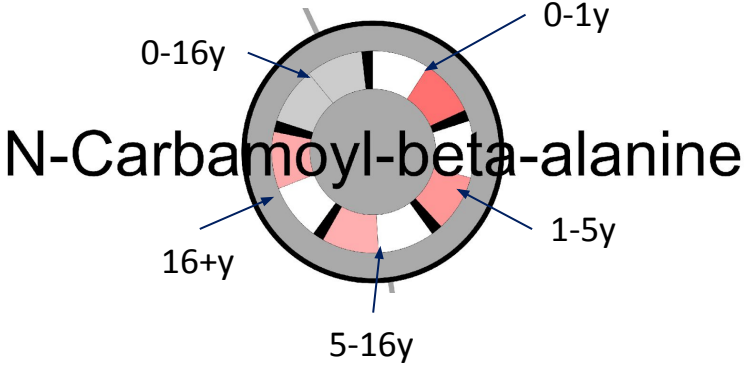
Possible visualization of Clinical data

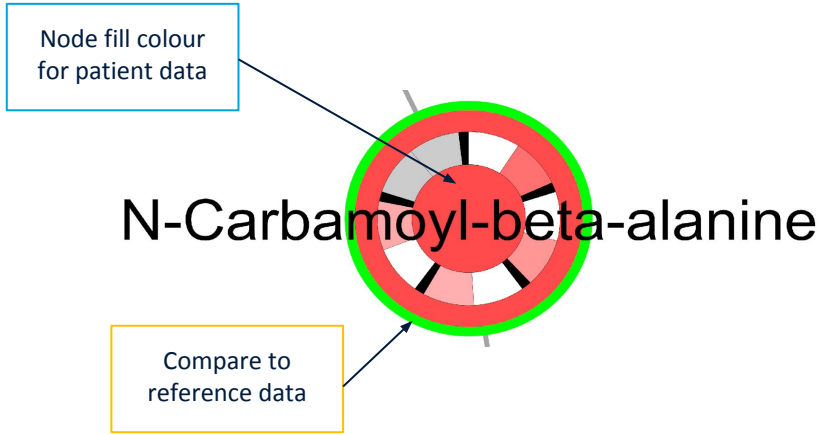
- Log transformed reference and patient data
- 4 metabolites with increased concentration

- But….
  - How are these metabolites connected?
  - Which protein(s) is/are involved?



Visualize reference data



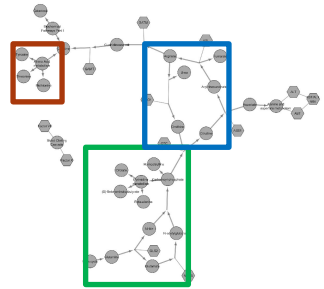


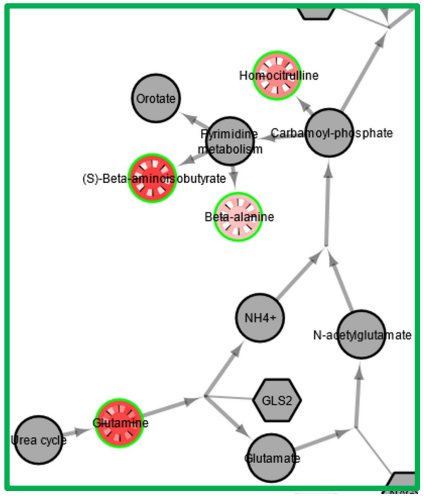
Example Result:

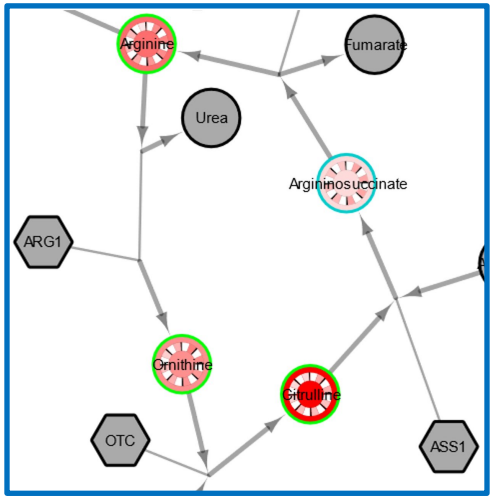
Patient with Citrullinemia type I

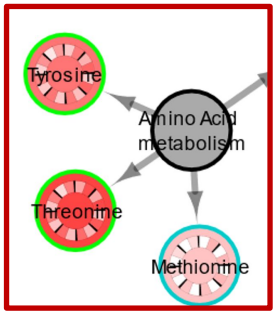
9 altered Urea cycle metabolites

- 2 metabolites part of Pyrimidine breakdown metabolism
- Citrulline more than 4 times the reference value









Results overview:

- Separation between patients (or groups of patients) was possible with network approach.
- Potentially affected proteins are directly visualised with metabolic data.
- Proteins can be traced back to original disorder.

Challenges

- Problems with identifier mapping
- Parts of the workflow not automated

- Differentiation seems possible with network analysis
- Not for all patients both metabolites panel measured
- Lack of large sample size
- Lack of diseases analysed

Metabolic Biomarkers + Biological Pathways + Clinical Data → Omics data Interpretation

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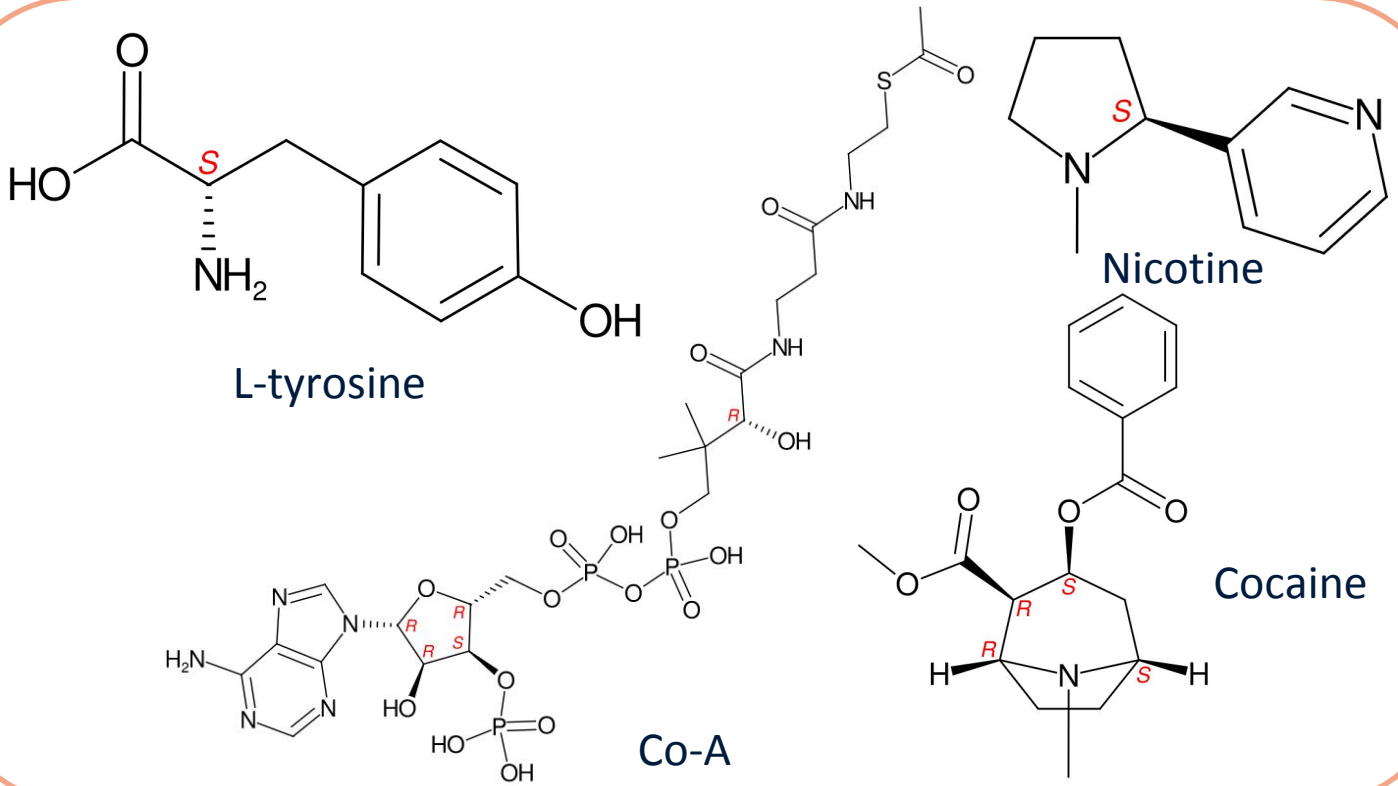
Cytoscape

Genes + Proteins + Metabolites → Phenotype

Gene, protein and metabolite logo's from: https://www.x-omics.nl/

Linking metabolomics data to pathways…



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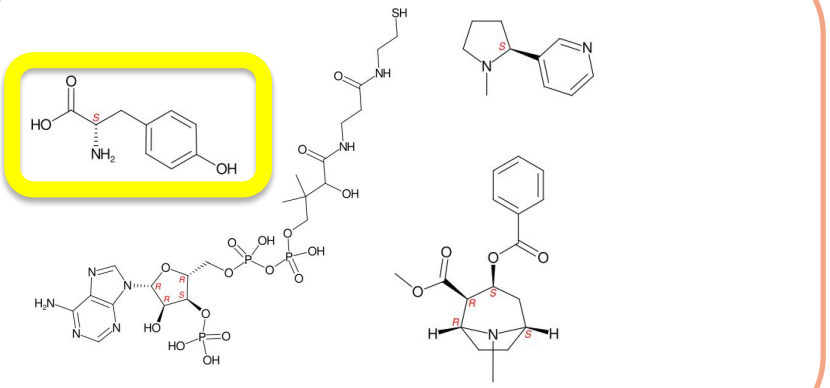
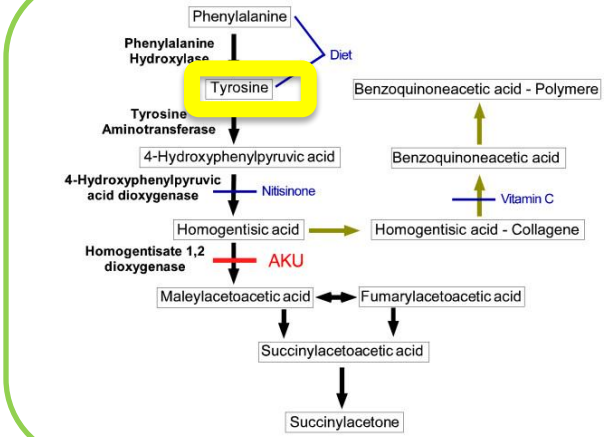
Structures obtained from Wikidata [2019-06-16] with CDK depict: https://github.com/cdk/depict
Willighagen *et al*. (2017) DOI: 10.1186/s13321-017-0220-4

Linking metabolomics data to pathways…





[1]

Sparseness of Data

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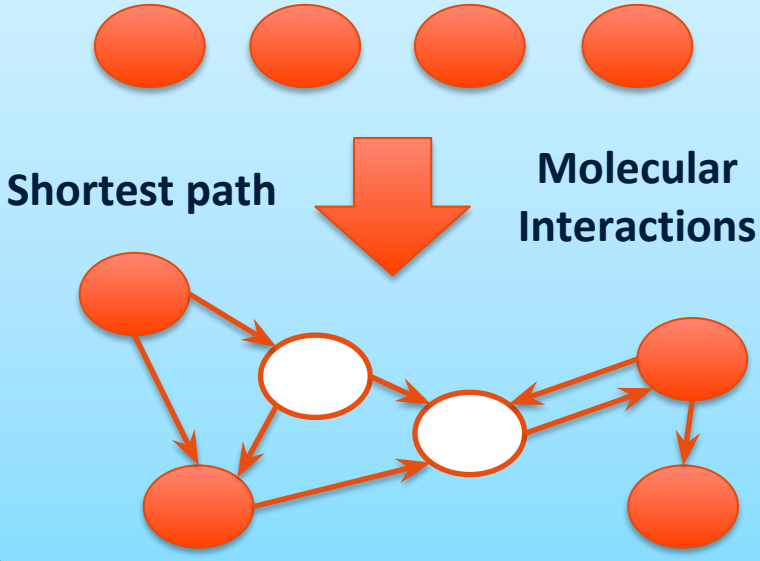
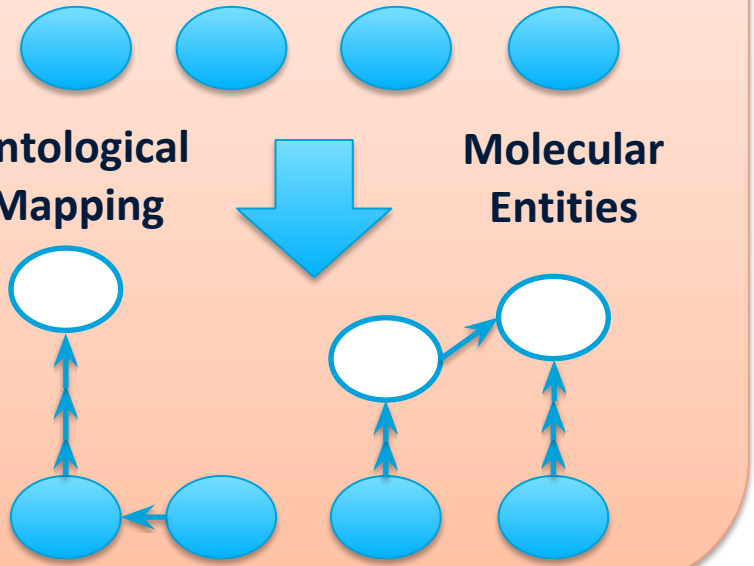
[1] Lindner, et al. BMC ophthalmology (2014)

Two approaches:

Network approach [1]



Ontological approach [2]



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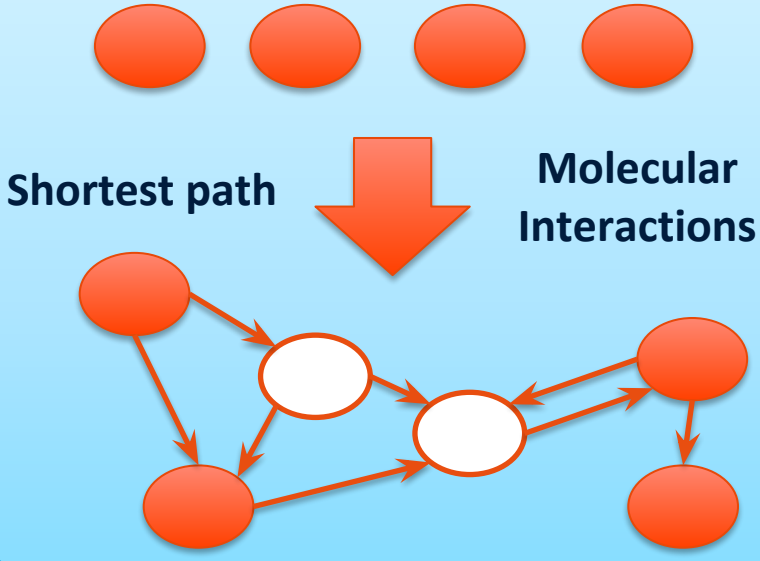
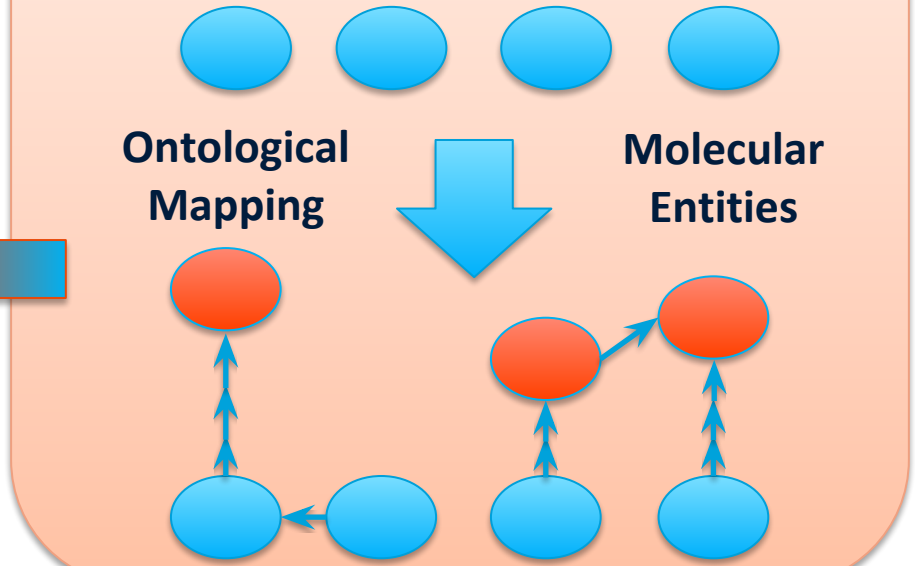
[1] DOI: 10.6084/m9.figshare.5234851.v1
[2] DOI: 10.6084/m9.figshare.6368921.v1

Two approaches:

Network approach [1]



Ontological approach [2]



Maastricht University

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Chris Evelo
All colleagues of BioInformatics who helped with this project

Jörgen Bierau
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Irene Hemel & Josien Landman
All other students involved!

Team of Nenad Blau
All authors of disease pathways

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3 PostDocs + 1 PhD

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