

General information (relevant for all patients):

R version 4.1.0 (2021-05-18); Platform: x86\_64-pc-linux-gnu (64-bit) ; cytoscapeVersion: "3.8.2"  
[1] "These biomarkers do not have an identifier mapping: cyshcys"  
[1] "These biomarkers are not annotated with a ChEBI ID: 2,8-dihydroxyadenine"  
[1] "These biomarkers (ChEBI IDs) are not in a pathway: 35621, 17755, 70744, 43433, 89698, 27596, 50599, 86498, 17261, 49015, 61511"

Patient A

[1] "Selected Patient ID is: A , age is between: 1 to 5 years old"  
[1] "There are 16 biomarkers relevant for patient A , the ChEBI-IDs are ch:17821 ch:17568 ch:16964 ch:17553 ch:18095 ch:18237 ch:17748 ch:7274 ch:17191 ch:15603 ch:17295 ch:57966 ch:57743 ch:17755 ch:15428 ch:15727"  
[1] "These biomarkers (as ChEBI IDs) are not in any pathway: 17755"

Relevant pathway models

pathway	pathwayTitle	CHEBIs in PWs	included CHEBIs
1 WP4584	Biomarkers for pyrimidine metabolism disorders	5	16964 17568 17748 17821 57966
2 WP4225	Pyrimidine metabolism and related diseases	5	17568 17748 17821 57743 57966
3 WP3925	Amino acid metabolism	5	15428 15603 17191 17295 18095
4 WP4022	Pyrimidine metabolism	3	17568 17748 17821
5 WP4595	Urea cycle and associated pathways	2	17568 57743

Data visualized on first three pathways (manual selection based on covering most biomarkers for this patient). One biomarker is not visualized now:

Dutch.name	Database.name	ID	log.Change
carnosine	Carnosine	CHEBI:15727	-0.26

Figure 1\_A: **left** five biomarkers [thymidine 6.78, uracil 3.71, 5-OH-methyluracil 3.67, thymidine 1.0, beta-alanine 0.26] visualized in WP4584 (yFiles hierarchical layout); **right top** one biomarker [citrulline] visualized in WP4225 (same layout); **right bottom** color scale for log2(change)-value

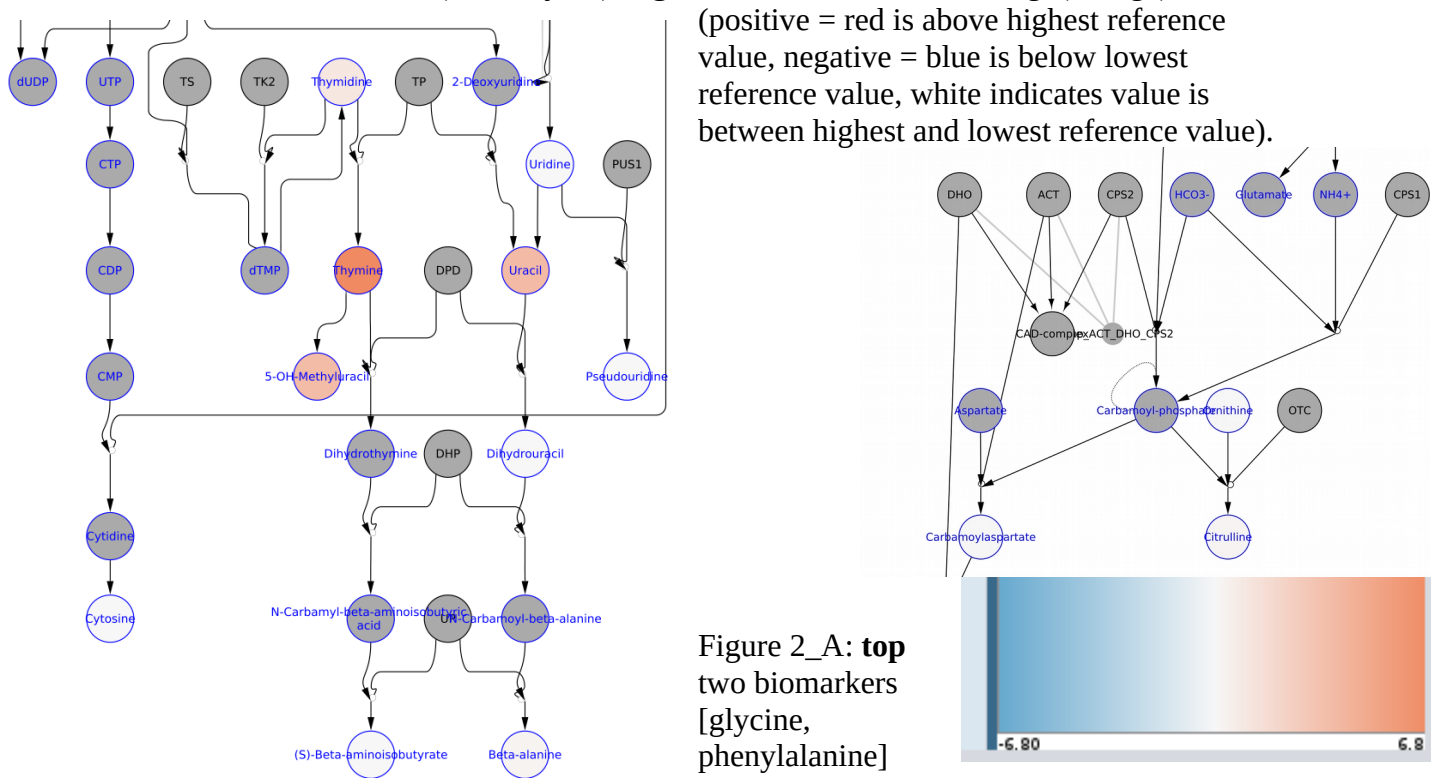
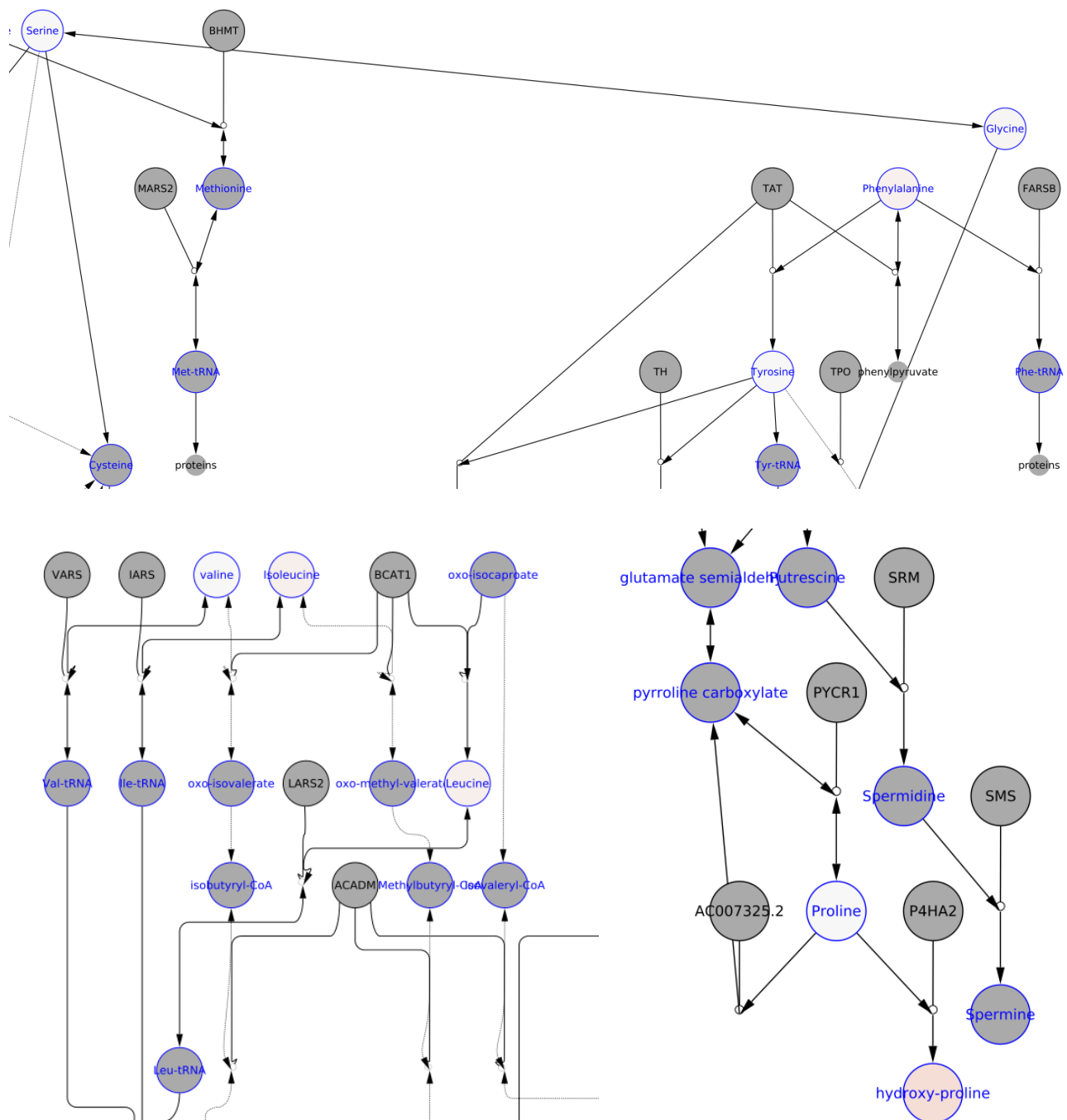


Figure 2\_A: **top** two biomarkers [glycine, phenylalanine] visualized in WP3925 (yFiles hierarchical layout); **bottom left** two biomarker [isoleucine, leucine] visualized in WP3925 (same layout); **bottom right** one biomarker [hydroxy-proline] visualized in WP3925 (same layout), mapped HMDB to ChEBI for WP3925. \*Same scale as previous Figure.



### Results interpretation 1: DPD

### Results interpretation 2:

Dihydropyrimidine dehydrogenase deficiency based on increased uracil, thymine and 5-OH-Me-Uracil.

A secondary increase as suggested by the figure is logical as thymine is a degradation product of thymidine. Relevant downstream markers in blue: dihydrouracil, beta-aminoisobutyrate, beta-alanine and carnosine.

Carbamoyl-Aspartate is a pyrimidine de novo biosynthesis biomarker. Feedback inhibition?

Cytosine perhaps same if de novo synthesis is the preferred source of CTP biosynthesis.

I cannot place the role of the altered amino acids in DPD deficiency.

Patient D

[1] "Selected Patient ID is: D , age is between: 0 to 1 years old"

A tibble: 16 x 4Rowwise:

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbl>
citrulline	Citrulline	CHEBI:57743	10.28
orootzuur	Orotate	CHEBI:30839	4.36
piperideine-6-carbonzuur	Piperideine carboxylic acid	CHEBI:49015	2.00
formimino-L-glutaminezuur	Formiminoglutamic acid	CHEBI:7274	1.79
asparagine	Asparagine	CHEBI:17196	1.67
arginine	Arginine	CHEBI:32682	1.22
fenylalanine	Phenylalanine	CHEBI:17295	0.95
histidine	Histidine	CHEBI:15971	0.94
alanine	Alanine	CHEBI:16977	0.74
serine	Serine	CHEBI:17115	0.66

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbl>
dihydro-uracil	Dihydrouracil	CHEBI:15901	0.51
threonine	Threonine	CHEBI:16857	0.48
pipecolinezuur	Pipecolic acid	CHEBI:30913	0.42
tyrosine	Tyrosine	CHEBI:17895	0.32
uracil	Uracil	CHEBI:17568	0.04
lysine	Lysine	CHEBI:18019	-0.84

[1] "There are 16 biomarkers relevant for patient D , the ChEBI-IDs are ch:30839 ch:15901 ch:17568 ch:17196 ch:17115 ch:16857 ch:57743 ch:16977 ch:7274 ch:30913 ch:17895 ch:17295 ch:15971 ch:18019 ch:32682 ch:49015"

[1] "These biomarkers (as ChEBI IDs) are not in a pathway: 49015"

pathway<chr>	pathwayTitle<chr>	CHEBIsInPWs<chr>	includedCHEBIs<chr>
1 WP3925	Amino acid metabolism	7	15971 16857 16977 17115 17196 17295 17895
2 WP4595	Urea cycle and associated pathways	5	16977 17568 30839 32682 57743
3 WP4225	Pyrimidine metabolism and related diseases	4	15901 17568 30839 57743
4 WP661	Glucose homeostasis	4	15971 17295 17895 18019
5 WP4583	Biomarkers for urea cycle disorders	4	16857 17895 32682 57743

Figure 1\_D: **left** four biomarkers [serine 0.66, threonine 0.48, tyrosine 0.32, phenylalanine 0.95] visualized in WP3925 (yFiles organic layout); **right** three biomarker [asparagine 1.67, histidine 0.94, alanine 0.74] visualized in WP3925 (same layout), mapped HMDB to ChEBI for WP3925.

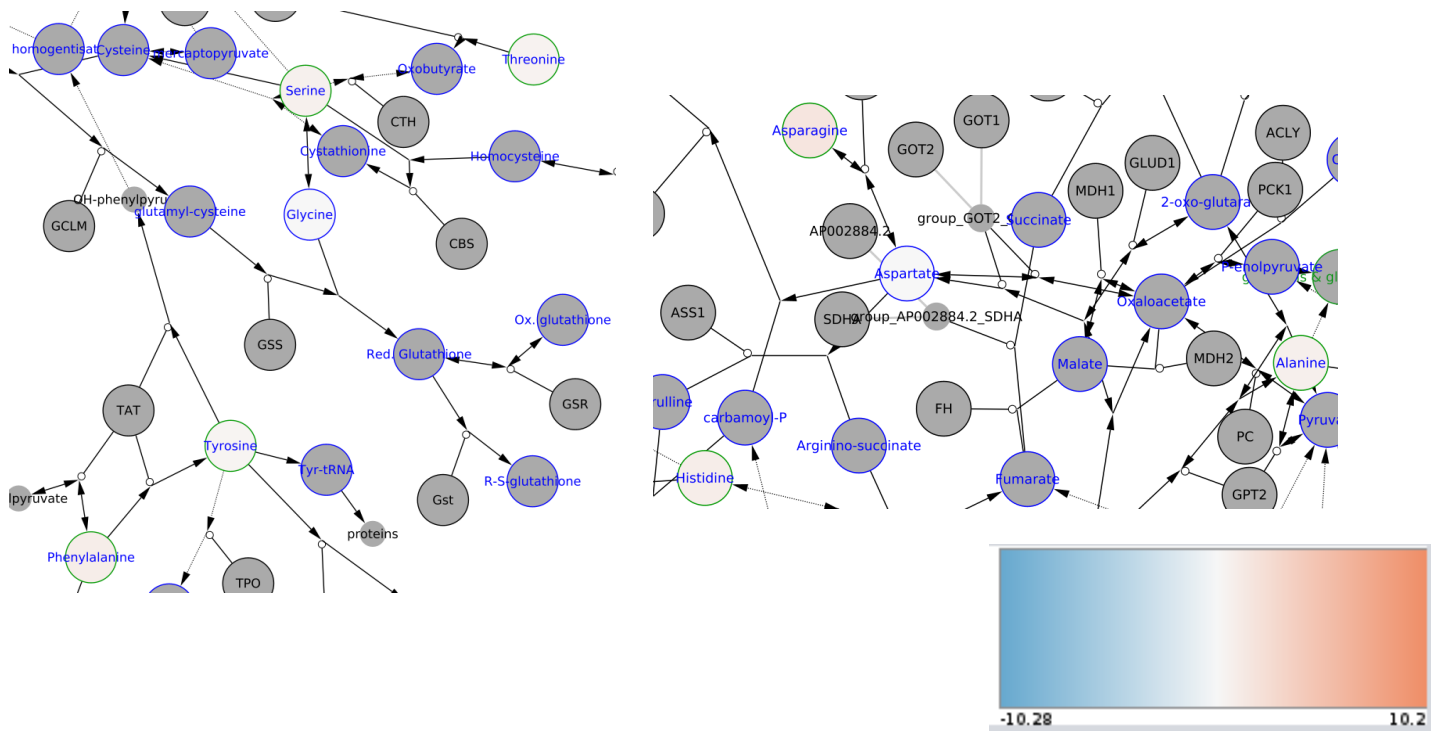
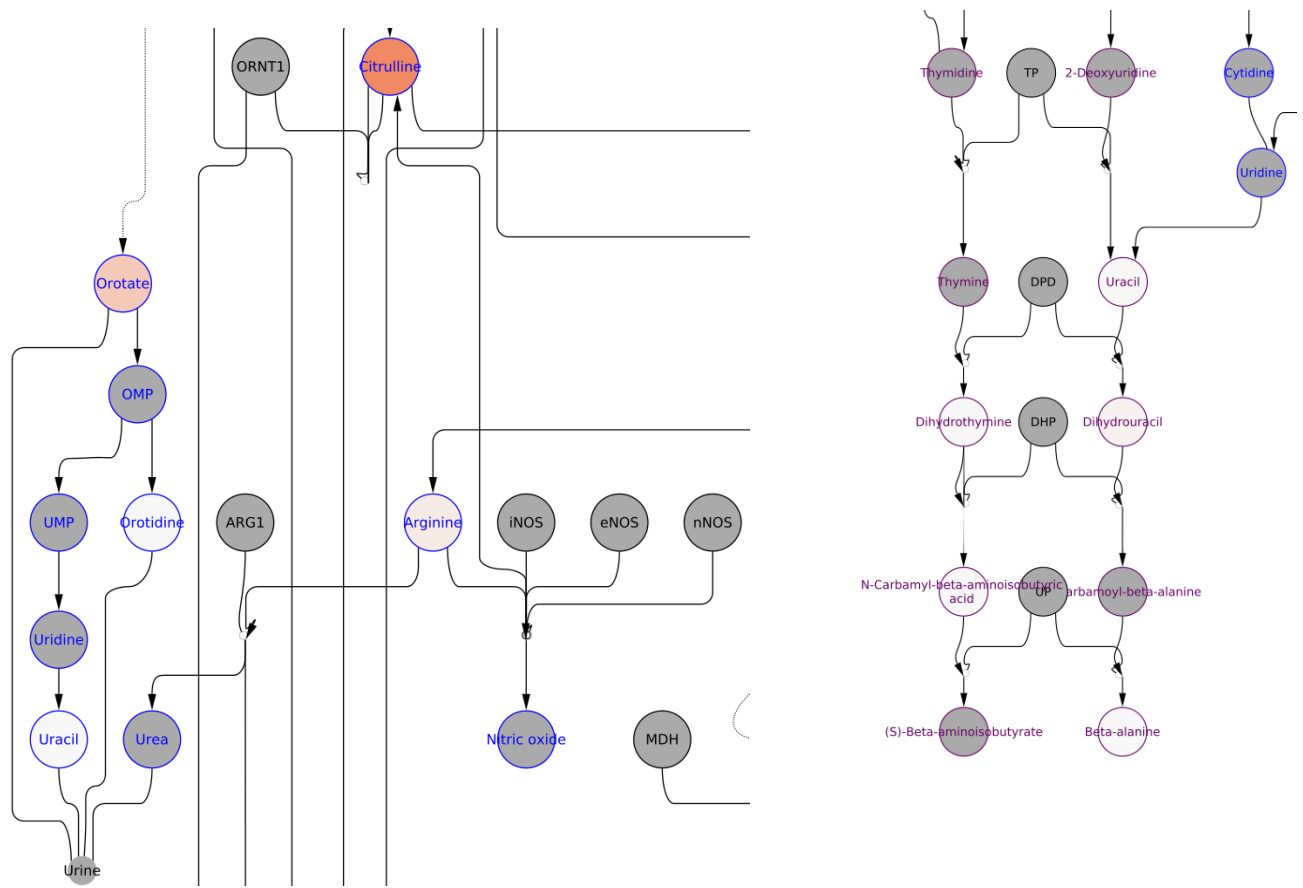


Figure 2\_D: **left** four biomarkers [citrulline 10.28, orotate 4.36, arginine 1.22, uracil 0.04] visualized in WP4595 (yFiles hierarchical layout); **right** two biomarker [uracil 0.04, dihydrouracil 0.51] visualized in WP3925 (same layout). \*Same scale as previous Figure.



**Results interpretation 1:**  
ASS (Citrullinemia Type I)

**Results interpretation 2:**  
Citrullinaemia with hyperammonaemia, based on high citrulline and orotate.

Patient E

[1] "Selected Patient ID is: E , age is between: 5 to 16 years old"

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbi>
thymine	Thymine	CHEBI:17821	3.12
uracil	Uracil	CHEBI:17568	3.02
hydroxyproline	Hydroxyproline	CHEBI:18095	2.58
glutaminezuur	Glutamic acid	CHEBI:18237	2.13
alfa-aminoboterzuur	AABA	CHEBI:35621	1.77
hydroxylysine	Hydroxylysine	CHEBI:86498	0.42
glycine	Glycine	CHEBI:15428	0.41
leucine	Leucine	CHEBI:15603	-0.38
ethanolamine	Monoethanolamine	CHEBI:16000	-0.47
valine	Valine	CHEBI:16414	-1.00

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbi>
serine	Serine	CHEBI:17115	-2.17
glutamine	Glutamine	CHEBI:58359	-4.64

[1] "There are 12 biomarkers relevant for patient E , the ChEBI-IDs are ch:17568 ch:17821 ch:18095 ch:17115 ch:58359 ch:15428 ch:18237 ch:35621 ch:16414 ch:16000 ch:15603 ch:86498"

[1] "These biomarkers (as ChEBI IDs) are not in a pathway: 35621, 86498"

pathway<chr>	pathwayTitle<chr>	CHEBIsInPWs<int>	includedCHEBIs<chr>
1 WP3925	Amino acid metabolism	5	15428 15603 16414 17115 18095
2 WP4225	Pyrimidine metabolism and related diseases	3	17568 17821 58359
3 WP3940	One-carbon metabolism and related pathways	3	15428 16000 17115
4 WP2525	Trans-sulfuration and one-carbon metabolism	2	15428 17115
5 WP4022	Pyrimidine metabolism	2	17568 17821

This biomarker will not be visualized:

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbi>
glutaminezuur	Glutamic acid	CHEBI:18237	2.13

Figure 1\_E: **left** two biomarkers [serine -2.17, glycine 0.41] visualized in WP3925 (yFiles hierarchical layout); **right top** two biomarker [valine -1, leucine -0.38] visualized in WP3925 (same layout); **right bottom** one biomarker [hydroxyproline 2.58] visualized in WP3925 (same layout), mapped HMDB to ChEBI for WP3925.

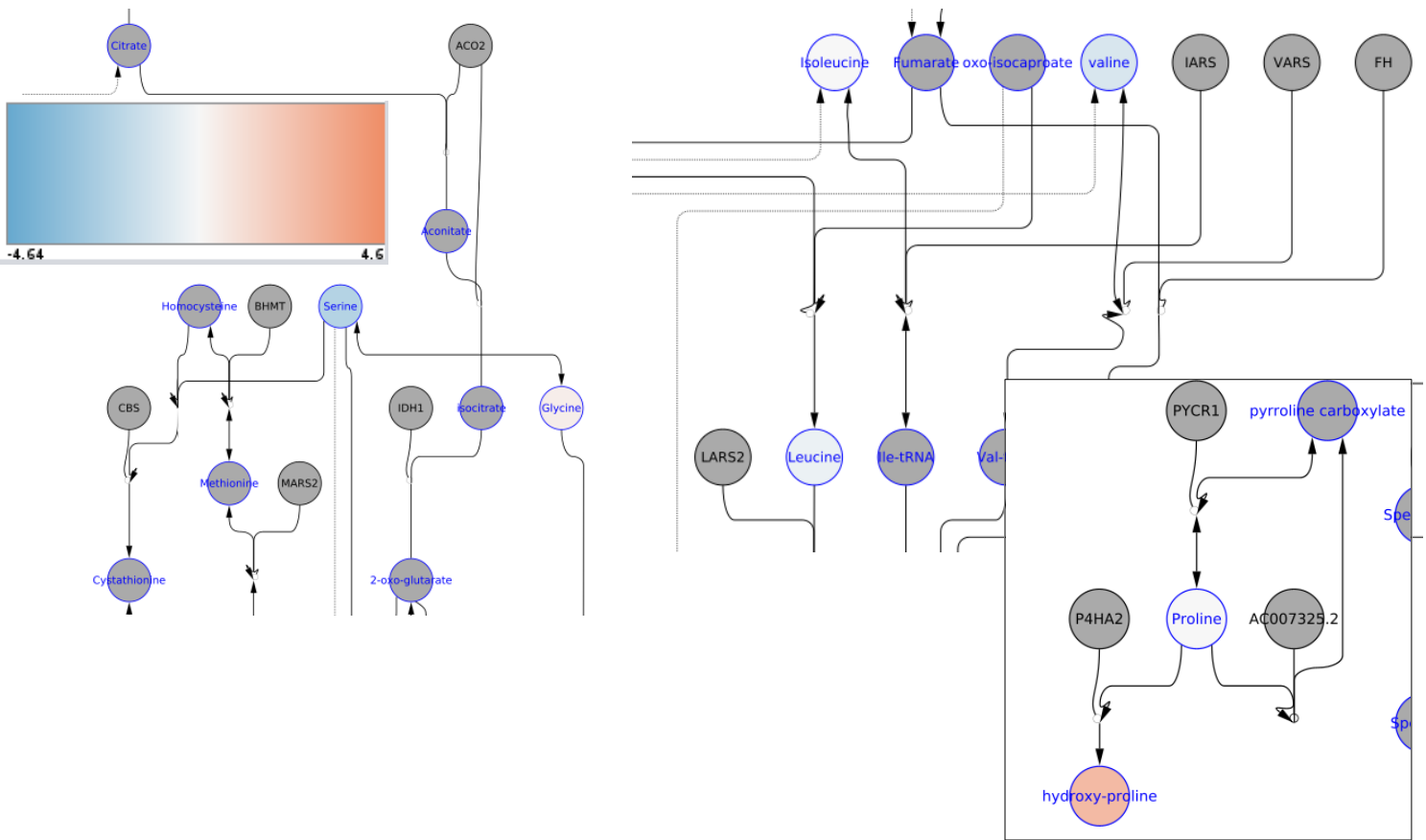
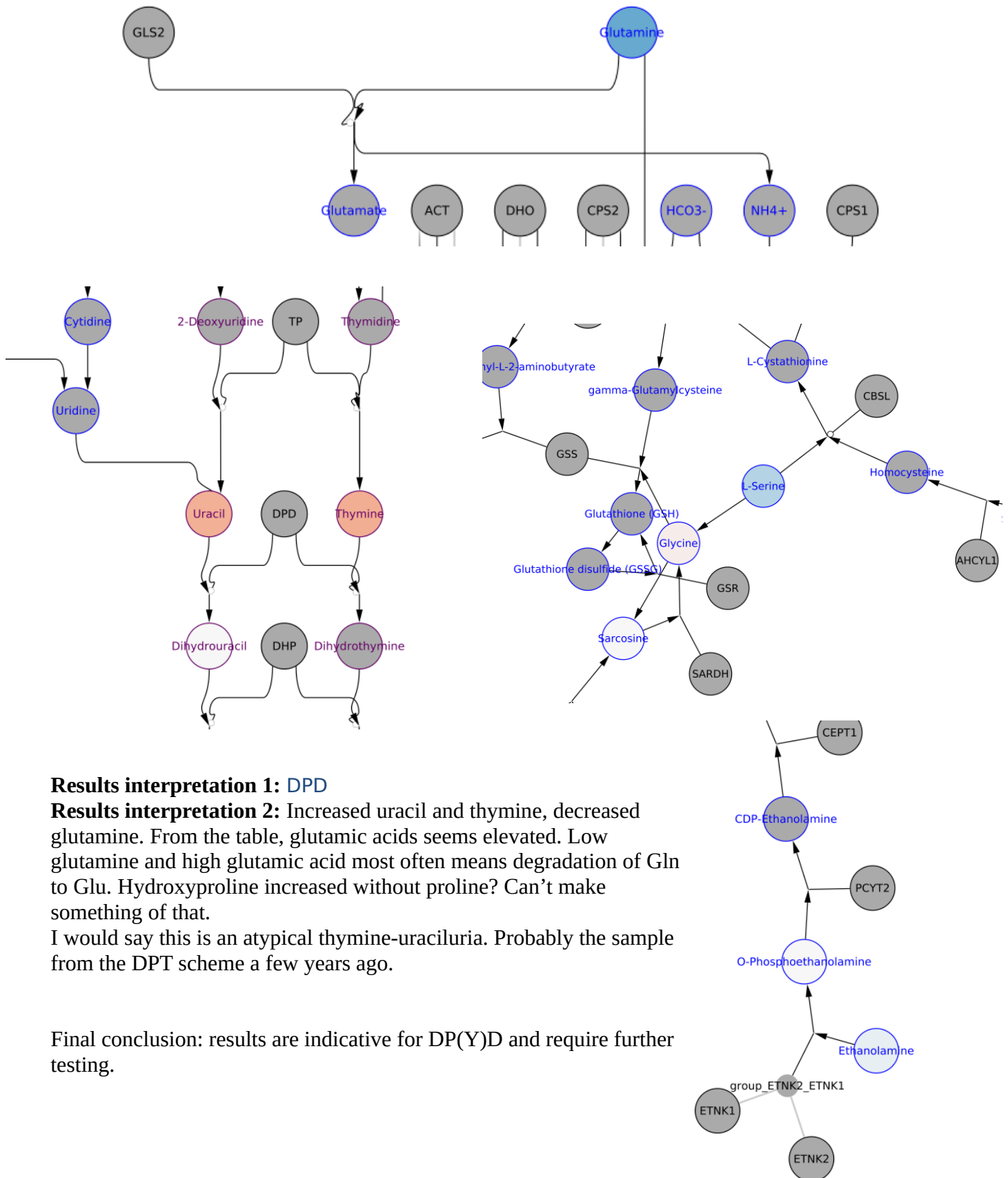


Figure 2\_E: **top** one biomarker [glutamine -4.64] visualized in WP4225 (yFiles hierarchical layout); **middle left** two biomarkers [uracil 3.02, thymine 3.12] visualized in WP4225 (same layout); **middle right** two biomarker [L-serine -2.17, Glycine 0.41] visualized in WP3940 (yFiles organic layout); **bottom right** one biomarker [ethanolamine -0.47] visualized in WP3940 (yFiles organic layout), mapped KEGG Compound to ChEBI for WP3940. \*Same scale as previous Figure.



### Results interpretation 1: DPD

**Results interpretation 2:** Increased uracil and thymine, decreased glutamine. From the table, glutamic acids seems elevated. Low glutamine and high glutamic acid most often means degradation of Gln to Glu. Hydroxyproline increased without proline? Can't make something of that.

I would say this is an atypical thymine-uraciluria. Probably the sample from the DPT scheme a few years ago.

Final conclusion: results are indicative for DP(Y)D and require further testing.

Patient F

[1] "Selected Patient ID is: F , age is between: 16+ years old"

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbl>
argininobarnsteenzuur	Argininosuccinate	CHEBI:57472	11.15
arginine	Arginine	CHEBI:32682	6.00
fosfoethanolamine	Phosphoethanolamine	CHEBI:17553	5.32
hydroxylysine	Hydroxylysine	CHEBI:86498	2.12
carnosine	Carnosine	CHEBI:15727	1.35
ethanolamine	Monoethanolamine	CHEBI:16000	1.28
3-methyl-histidine	3-Methyl-histidine	CHEBI:27596	1.27
sarcosine	Sarcosine	CHEBI:15611	1.00
citrulline	Citrulline	CHEBI:57743	1.00
homocarnosine	Homocarnosine	CHEBI:85981	1.00

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbl>
homocitrulline	Homocitrulline	CHEBI:58148	0.74
uracil	Uracil	CHEBI:17568	0.15

[1] "There are 12 biomarkers relevant for patient F , the ChEBI-IDs are ch:17568 ch:17553 ch:15611 ch:57743 ch:58148 ch:16000 ch:57472 ch:27596 ch:86498 ch:32682 ch:15727 ch:85981"

pathway<chr>	pathwayTitle<chr>	CHEBIsInPWs<int>	includedCHEBIs<chr>
1 WP4595	Urea cycle and associated pathways	4	17568 32682 57472 57743
2 WP4583	Biomarkers for urea cycle disorders	4	32682 57472 57743 58148
3 WP4571	Urea cycle and related diseases	3	32682 57472 57743
4 WP3940	One-carbon metabolism and related pathways	3	15611 16000 17553
5 WP2533	Glycerophospholipid biosynthetic pathway	2	16000 17553

[1] "These biomarkers (as ChEBI IDs) are not in a pathway: 27596, 86498"  
These biomarkers will not be visualized:

Dutch.name<chr>	Database.name<chr>	ID<chr>	log.Change<dbl>
carnosine	Carnosine	CHEBI:15727	1.35
homocarnosine	Homocarnosine	CHEBI:85981	1.00

Figure 1\_F: four biomarkers [argininosuccinate 11.15, arginine 6.0, citrulline 1, uracil 0.15] visualized in WP4595 (WikiPathways-As-Network layout).

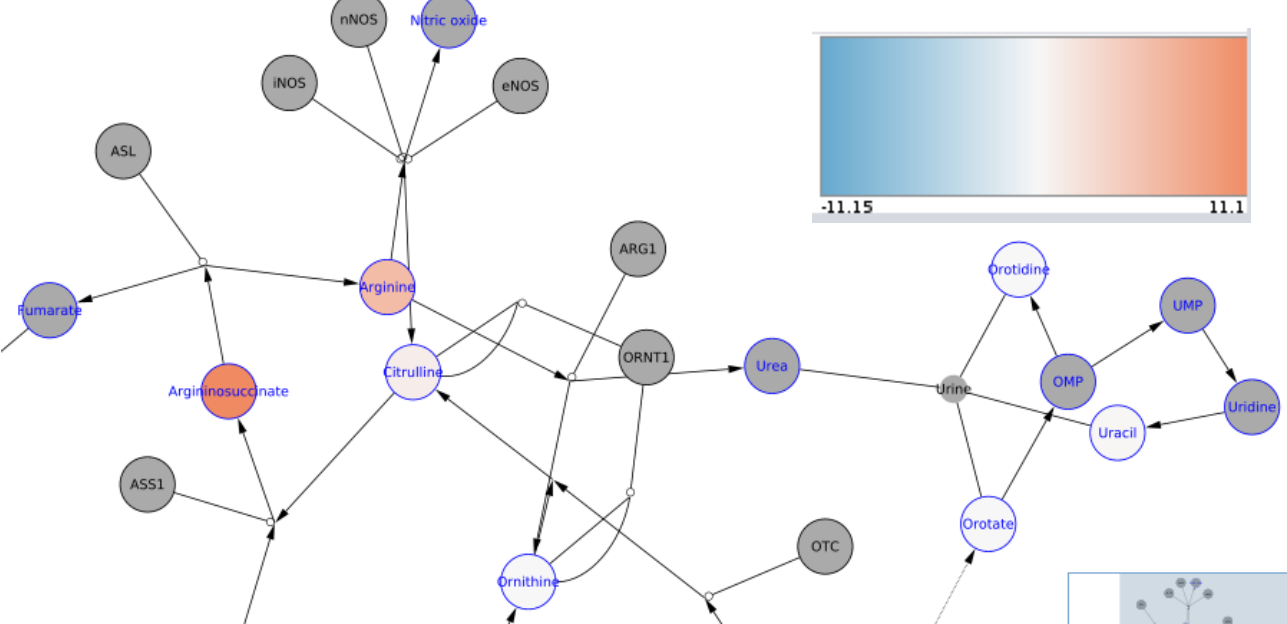


Figure 2\_F: **top** four biomarker [argininosuccinate 11.15, arginine 6.0, citrulline 1, homocitrulline 0.74] visualized in WP4583 (WikiPathways-As-Network layout); bottom three biomarker

[ethanolamine 5.32, O-phosphoethanolamine 1.28, sarcosine 1.0] visualized in WP3940 (same layout); mapped KEGG to ChEBI for WP3940. \*Same scale as previous Figure.

**Results interpretation 1:**  
ASL

**Results interpretation 2:**

Argininosuccinate lyase deficiency based on increased argininosuccinate. Patient is supplemented with arginine. No hyperammonaemia.

