Untargeted Metabolomic Profiling in Inborn Errors of Metabolism

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Disclosure

A fixed portion of my salary is paid by Baylor Genetics Laboratories but compensation is not tied to laboratory revenue

Outline

- Common practice and limitations of current routine testing for IEMs
- Global Metabolomic Assisted Pathway Screen (Global MAPS®) - Methods
- Validation for common IEMs
- Confirmation of DNA variant pathogenecity
- Discovery of Novel Biomarkers

CURRENT RECOMMENDATIONS FOR INTELLECTUAL DISABILITY EVALUATION

AAN Recommendations for Intellectual Disability (2011)

- Screening for inborn errors of metabolism (IEMs) in children with GDD/ID has a **yield of between 0.2% and 4.6%**, depending on the presence of clinical indicators and the range of testing performed (Class III).
- Testing for congenital disorders of glycosylation has a yield of up to 1.4%, and testing for creatine disorders has a yield of up to 2.8% (Class III).

1st Tier: Non-Targeted screening to identify 54 (60%) treatable IEMs

Blood:

- ammonia, lactate
- plasma amino acids
- total homocysteine
- acylcarnitine profile
- copper, ceruloplasmin

Urine:

- organic acids
- purines & pyrimidines
- creatine metabolites
- oligosaccharides
- glycosaminoglycans

2nd Tier: Targeted testing to identify 35 (40%) treatable IEMs requiring 'specific testing'

- **according to patient's symptomatology patient (Table 4) & clinician's expertise**
- **utilization of textbooks & digital resources** (WebApp: *www.treatable-ID.org*)
- **consider the following biochemical / molecular analyses:**
  - whole blood manganese
  - plasma cholestanol
  - plasma 7-dehydroxy-cholesterol:cholesterol ratio
  - plasma pipecolic acid & urine AASA
  - plasma very long chain fatty acids
  - plasma vitamin B12 & folate
  - serum & CSF lactate:pyruvate ratio
  - enzyme activities (leucocytes): arylsulphatase A, biotinidase, glucocerebrosidase, fatty aldehyde dehydrogenase
  - urine deoxypyridonoline
  - CSF amino acids
  - CSF neurotransmitters
  - CSF: plasma glucose ratio
  - CoQ measurement fibcroblasts
  - molecular: *CA5A, NPC1, NPC2, SC4MOL, SLC18A2, SLC19A3, SLC30A10, SLC52A2, SLC52A3, PDHA1, DLAT, PDHX, SPR, TH*

van Karnebeek CDM et al., Mol Genet & Metab 111:428-38, 2014

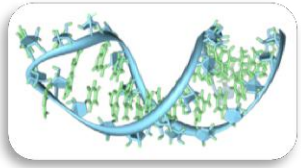
Current Challenges

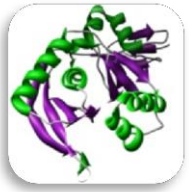
- For undifferentiated phenotypes, such as intellectual disability, seizures, recurrent vomiting, failure to thrive etc. many different tests are needed
- Various fluid types (blood, urine, cerebrospinal fluid) may be needed for diagnosis
- Cost for multiple tests may be prohibitive and many are rare, so no good way to tier testing

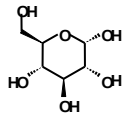
Methods/Tests

- HPLC – amino acids
- GC/MS – organic acids
- MS/MS
  - Acylcarnitines
  - Newborn screening
  - Individual specialized tests
    - Purines & Pyrimidines
    - Creatine & guanidinoacetate
    - Pyridoxine responsive seizure panels
    - Bile acids
    - CSF Neurotransmitters
    - Etc!

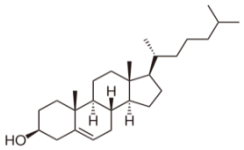
Rationale for Metabolomic Approach



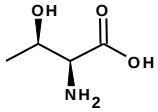




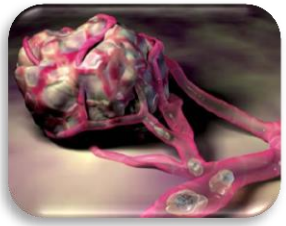
glucose



cholesterol



threonine



DNA

RNA

Proteins

Biochemicals

Mechanistic Insight into Phenotype

Biochemistry Advantages

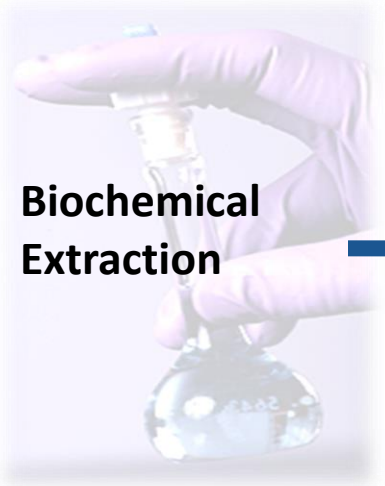
- Any sample type
- Condensed & information rich
- Actionable
- Bridge between genome & phenotype

METHODS

Metabolon, a global leader in metabolomics

Pioneering the emerging field of global biochemical pathway analysis for biomarker discovery and the development of innovative diagnostic tests

- Founded in 2000
- Over 150 employees worldwide with expertise in biochemistry, mass spectrometry and software development
- 54,000 sq. ft. facility in Research Triangle Park, NC and Sacramento
- CLIA-certified lab onsite



Biochemical Extraction

UHPLC-MS/MS (+ESI) Early/Polar

UHPLC-MS/MS (+ESI) Late/Lipid

UHPLC-MS/MS (-ESI)

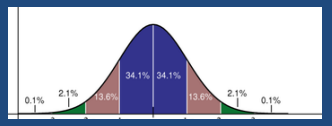
UHPLC (HILIC)-MS/MS

Library Search
RT, Mass, MS/MS

Data Reduction

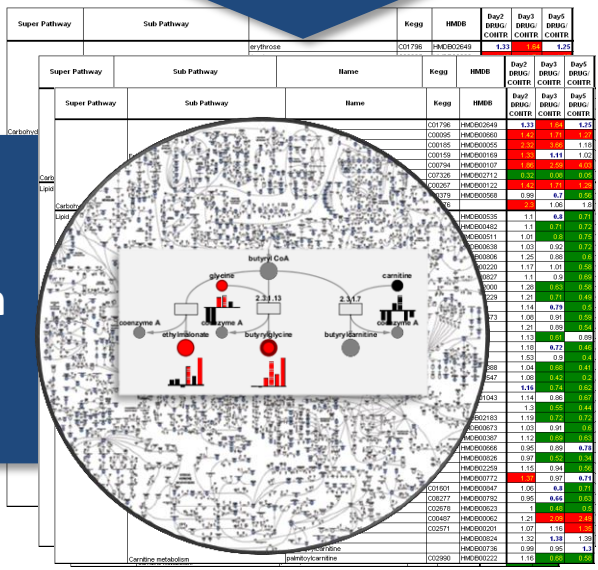
Compound ID

QA/QC



Statistical Analysis

Pathway Visualization: Metabolync™ plugin to Cytoscape developed to overlay analyte findings onto metabolic pathways



Interpretation

Biomarkers
Mechanistic Understanding
Drug MoA
Cellular Characteristics

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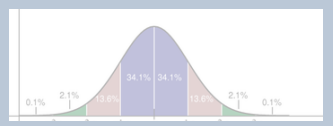
Enrich 50-1500 Da small molecule analytes



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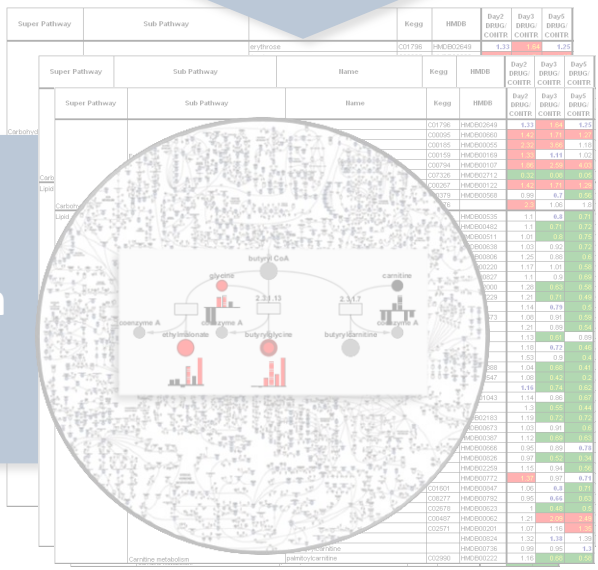

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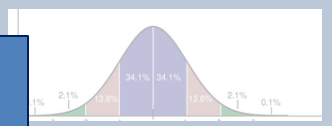
QA/QC

- Q exactive MS/MS - Orbitrap based MS/MS (Thermo)
- Accurate to 1 ppm vs 100 ppm for quadrupole analyzers
- Cost ~2X quadrupole



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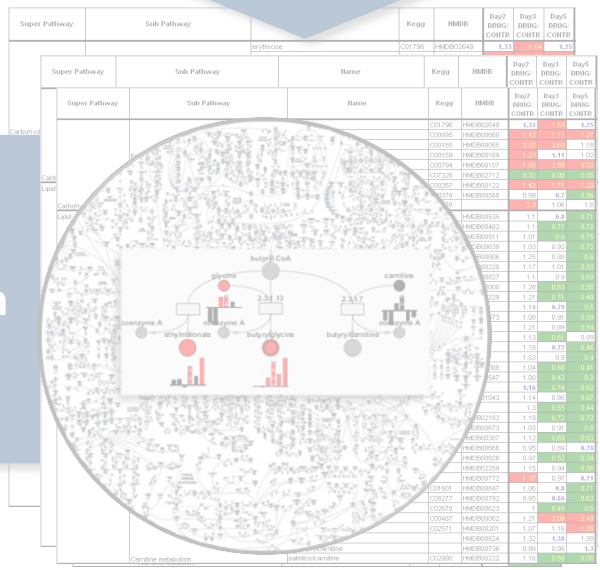

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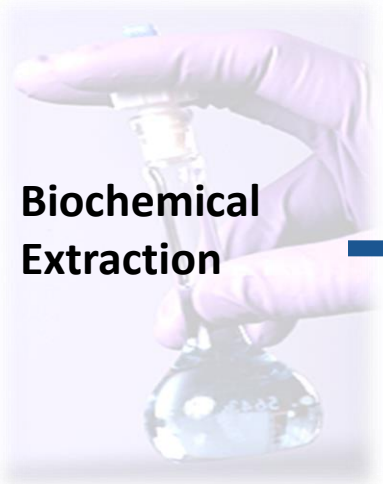

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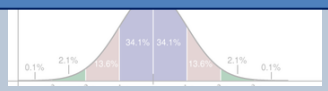
•Library of ~2500 human metabolites



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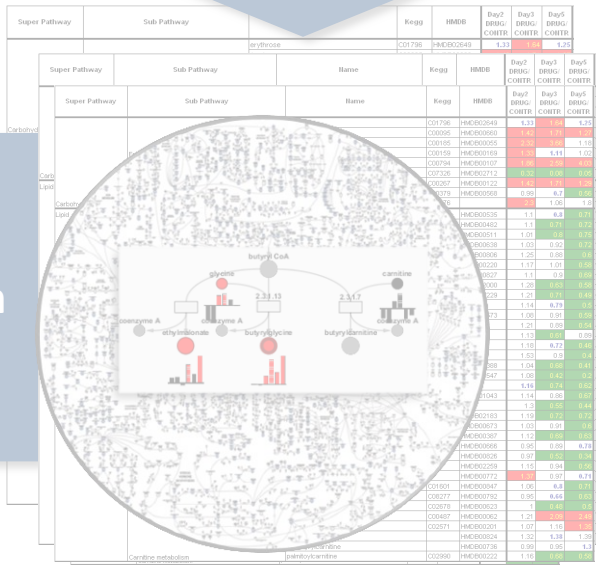

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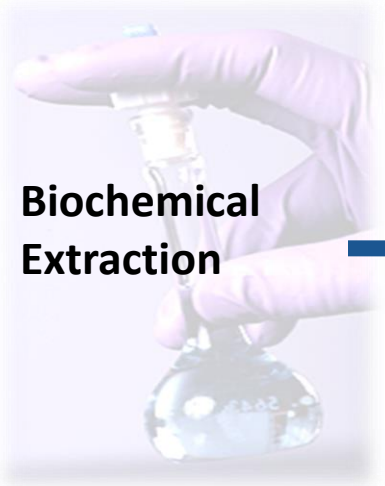

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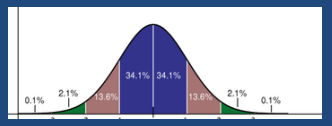

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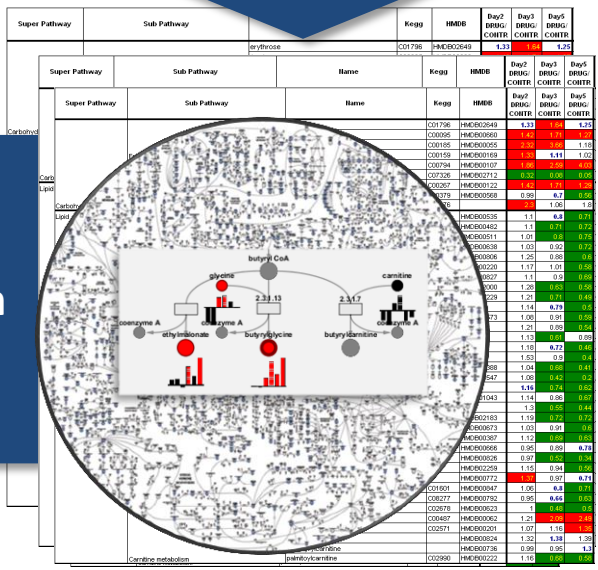

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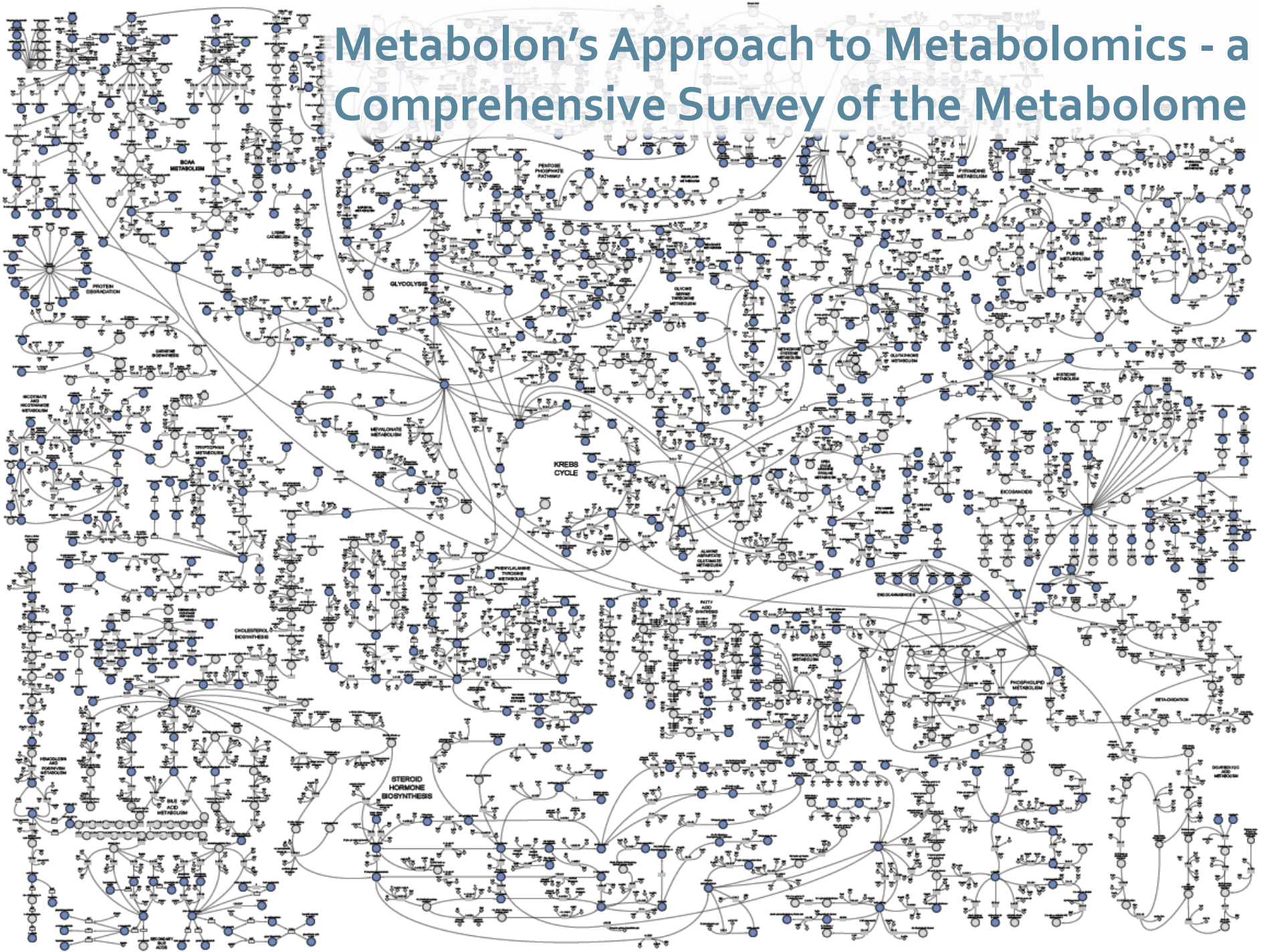
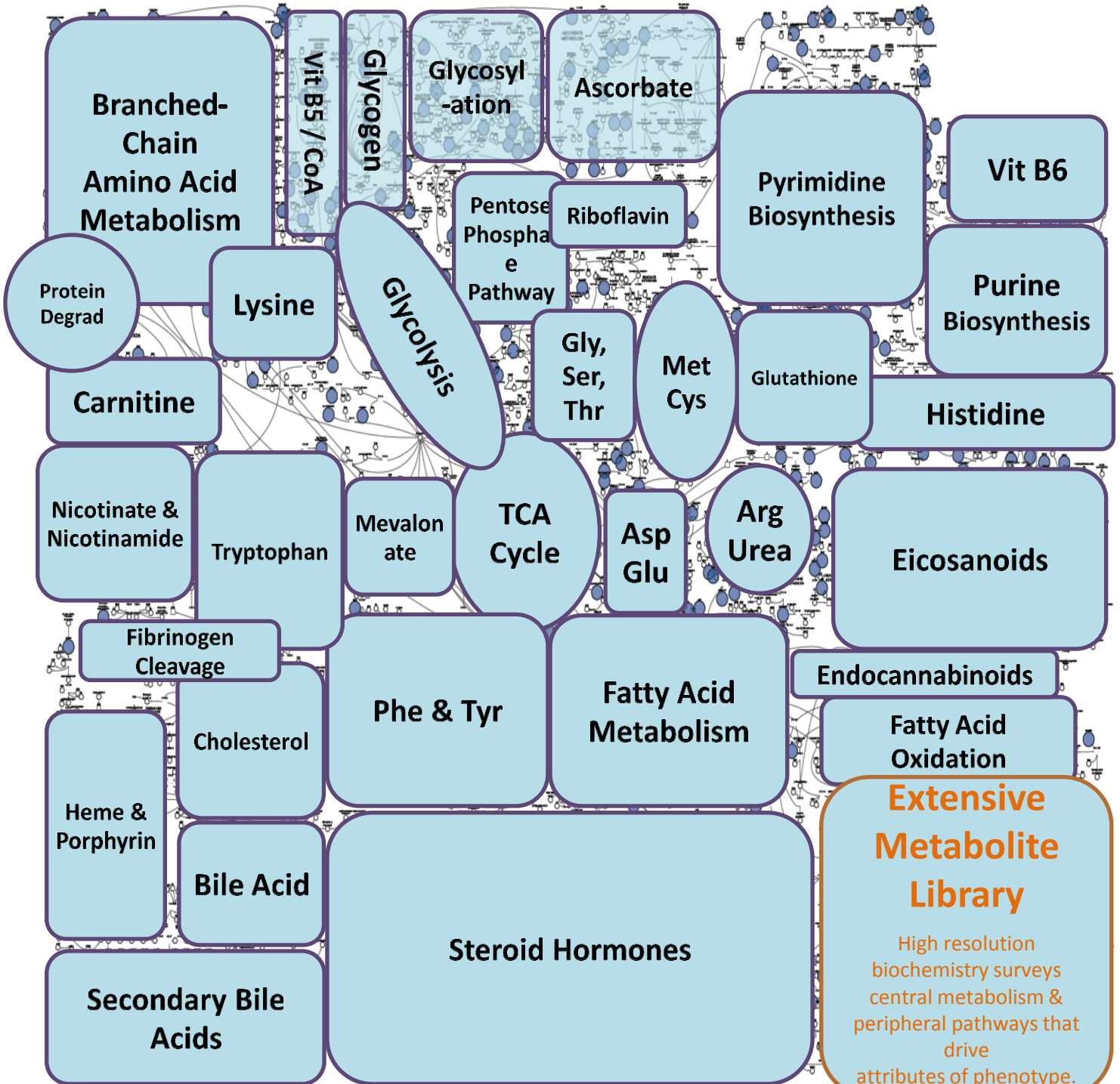
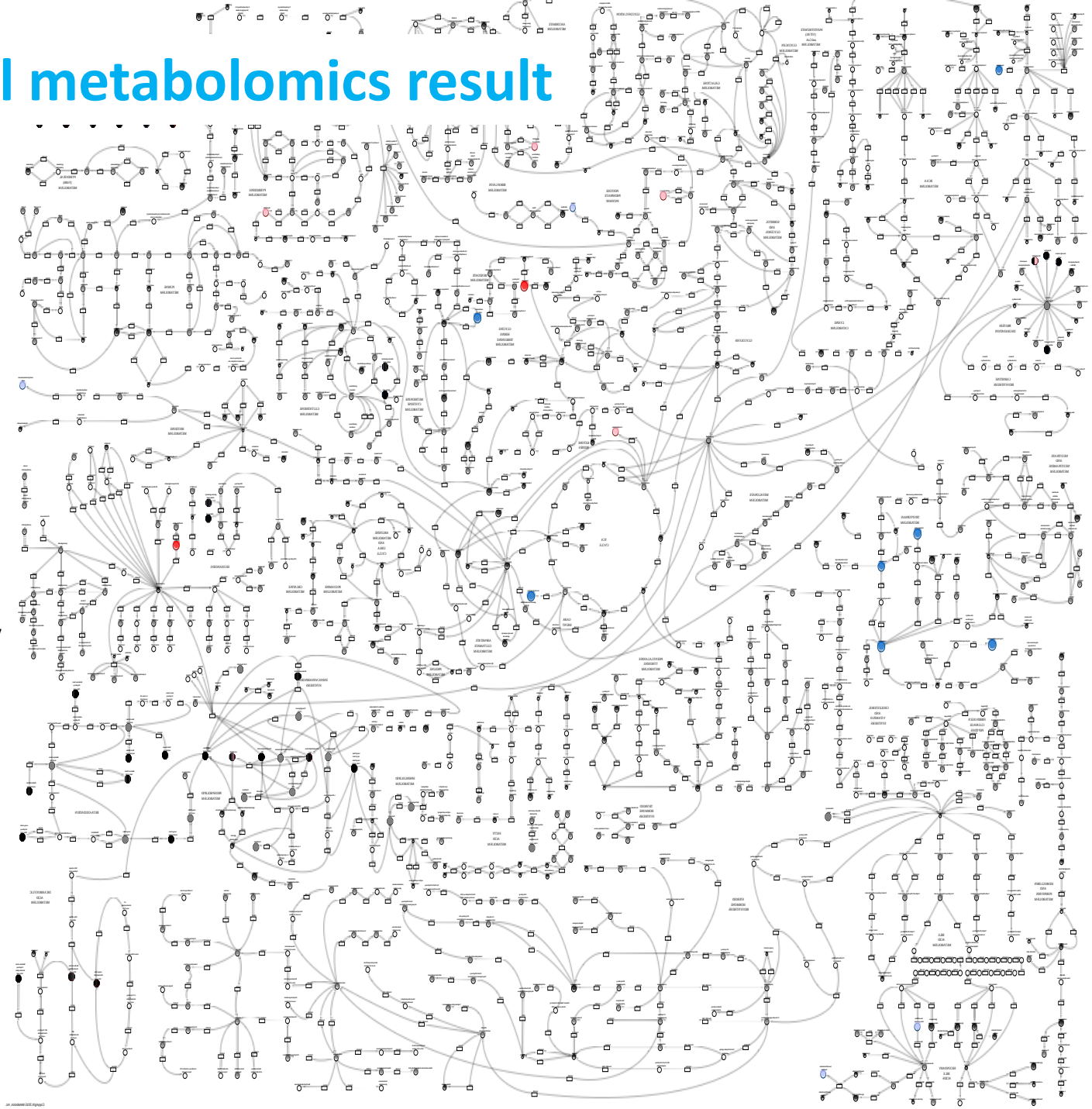
Metabolon's Approach to Metabolomics - a Comprehensive Survey of the Metabolome




Branched-Chain Amino Acid Metabolism
Vit B5 / CoA
Glycogen
Glycosyl-ation
Ascorbate
Pyrimidine Biosynthesis
Vit B6
Pentose Phospha e Pathway
Riboflavin
Protein Degrad
Lysine
Glycolysis
Purine Biosynthesis
Gly, Ser, Thr
Met Cys
Glutathione
Carnitine
Histidine
Nicotinate & Nicotinamide
Tryptophan
Mevalon ate
TCA Cycle
Asp Glu
Arg Urea
Eicosanoids
Fibrinogen Cleavage
Endocannabinoids
Cholesterol
Phe & Tyr
Fatty Acid Metabolism
Fatty Acid Oxidation
Heme & Porphyrin
Bile Acid
Steroid Hormones
Secondary Bile Acids
Extensive Metabolite Library
High resolution biochemistry surveys central metabolism & peripheral pathways that drive attributes of phenotype.

Normal metabolomics result



- High
- Low
- -1.5 - +1.5
- Molecule in library but not detected
- Molecule not in library

Circle size relative to Z-score

Global MAPS

Global Metabolomic Assisted Pathway Screen

- Metabolic pathway screen for perturbations in levels of analytes and relative abundance
  - Screens for >2500 small molecules (50-1500 Da)
  - Z-scores provided (not absolute values)
- Small molecule metabolomic analysis
  - Plasma
    - ~750-900 analyte identifications per plasma sample
  - CSF
    - ~300 analyte identifications per CSF sample
  - Urine
    - ~1200 analyte identifications per urine sample

Limitations of test

1. Inappropriate for identification of
    - Analytes >1500 Da or <50 Da
        - Proteins/large peptides
        - Complex oligosaccharides
        - Large lipids
        - Elements (K, Na, etc.)
2. Analytes requiring special extraction/chromatographic separation
        - Homocysteine (requires reductant treatment)
3. Screening tool to identify metabolic perturbations
4. Values are not quantitative
5. Not for acute assessments

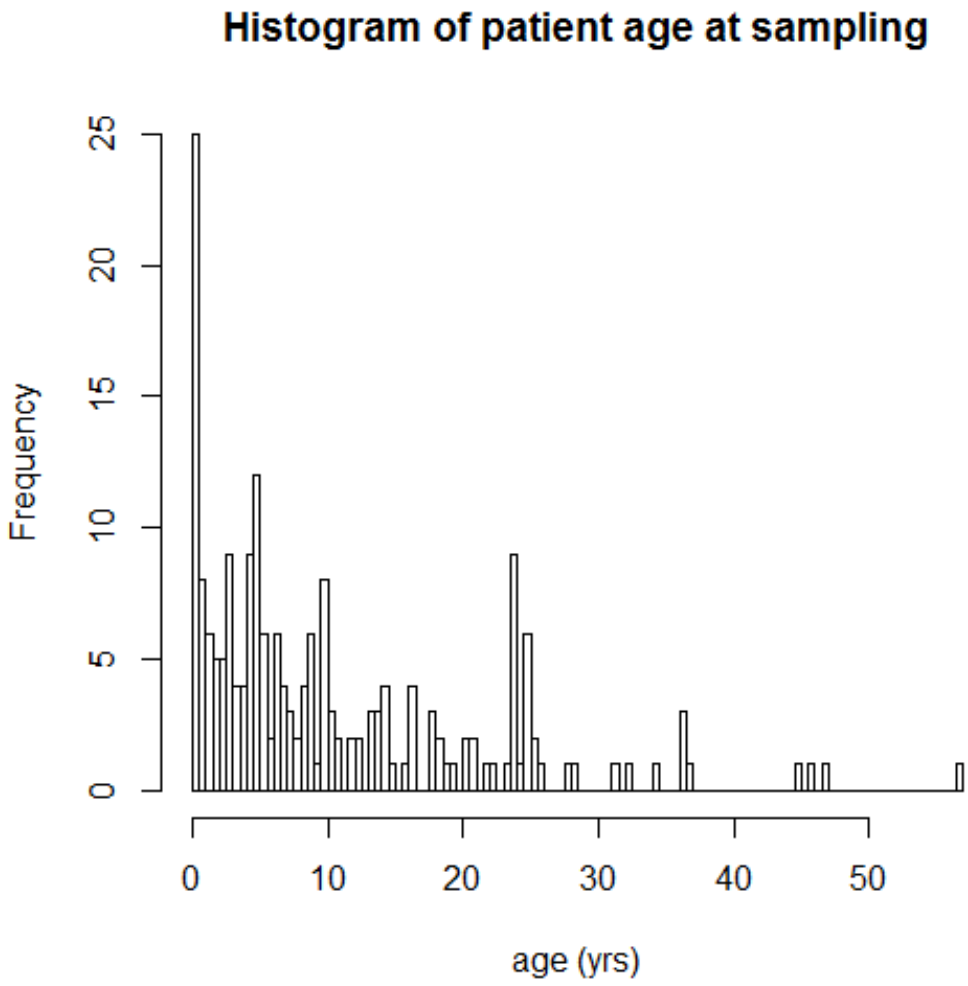
If you are interested in a specific compound we can provide information on detection rates, accuracy, and analyte stability.

Sample collection/validation

- Retrospectively collected from stored lab samples
  - Na-Heparin treated plasma, stored -20 C for up to 3 months
  - 83% from Texas Children's Hospital
- "Normal Controls"
  - Patient that came to our lab for testing but for whom no abnormal analytes were detected
  - Roughly age and sex matched to known patient samples

Overview of Plasma Samples

- **200 total**
  - 128 from patients with diagnosis of IEM
  - 72 “Normal Controls”
- **27 different IEMs**
- **Majority of patients on treatment**



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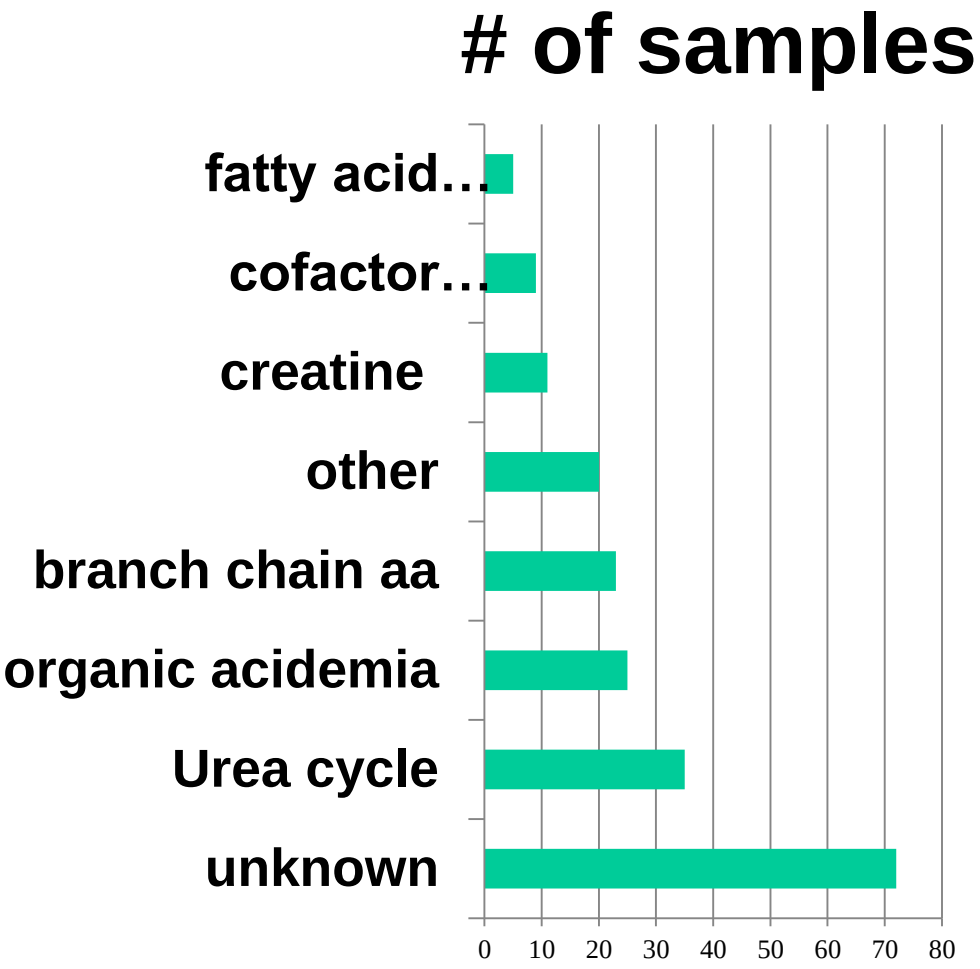
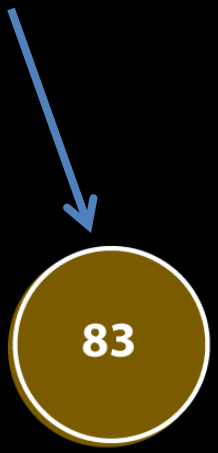
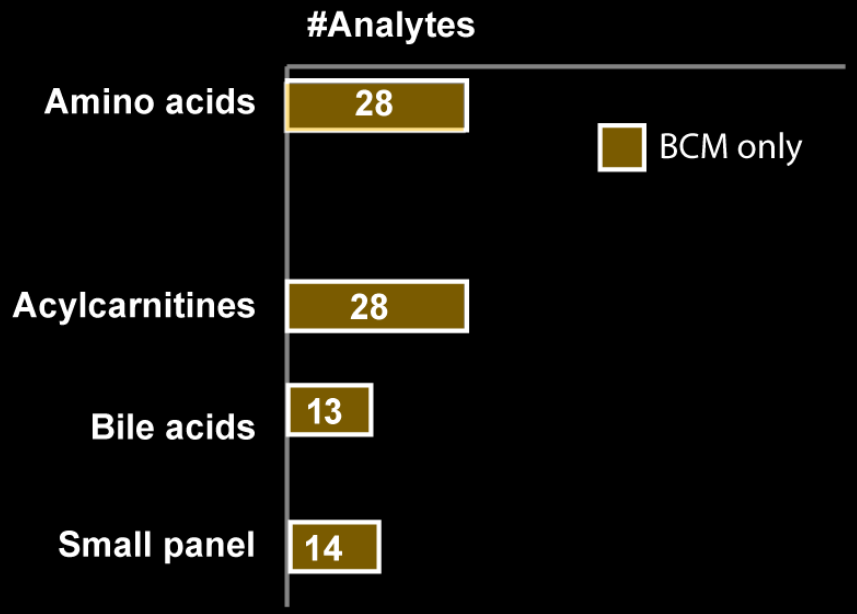


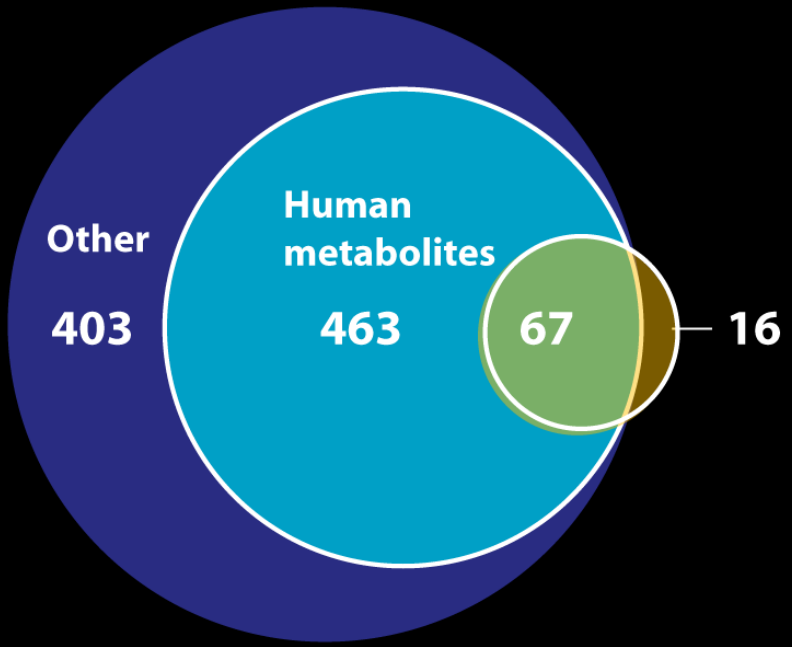
Current analyte detections possible in our lab

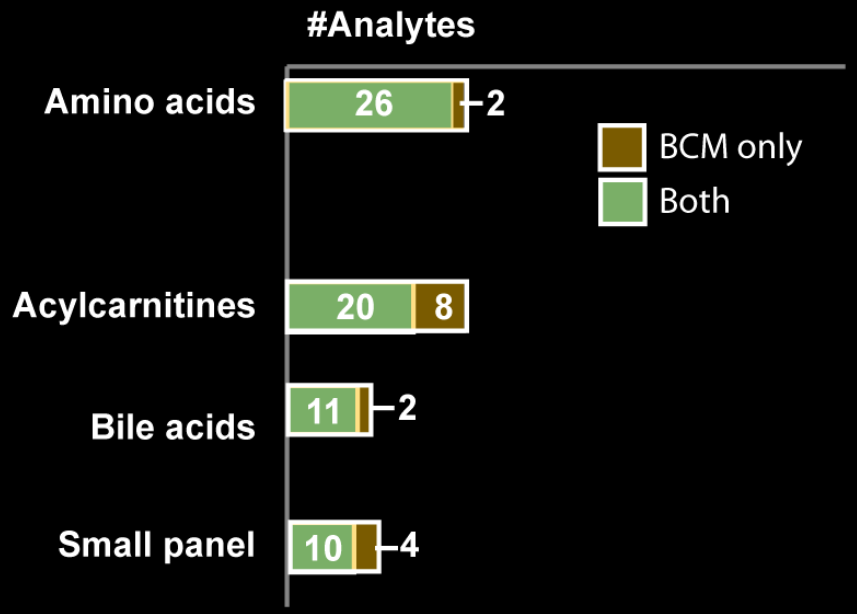
All biochem lab plasma tests





Average metabolomic detection in plasma





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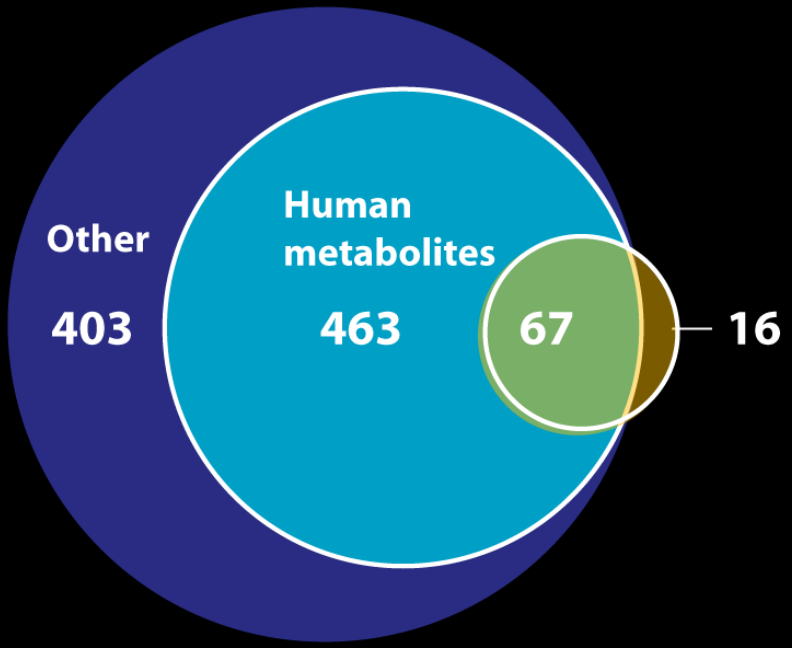
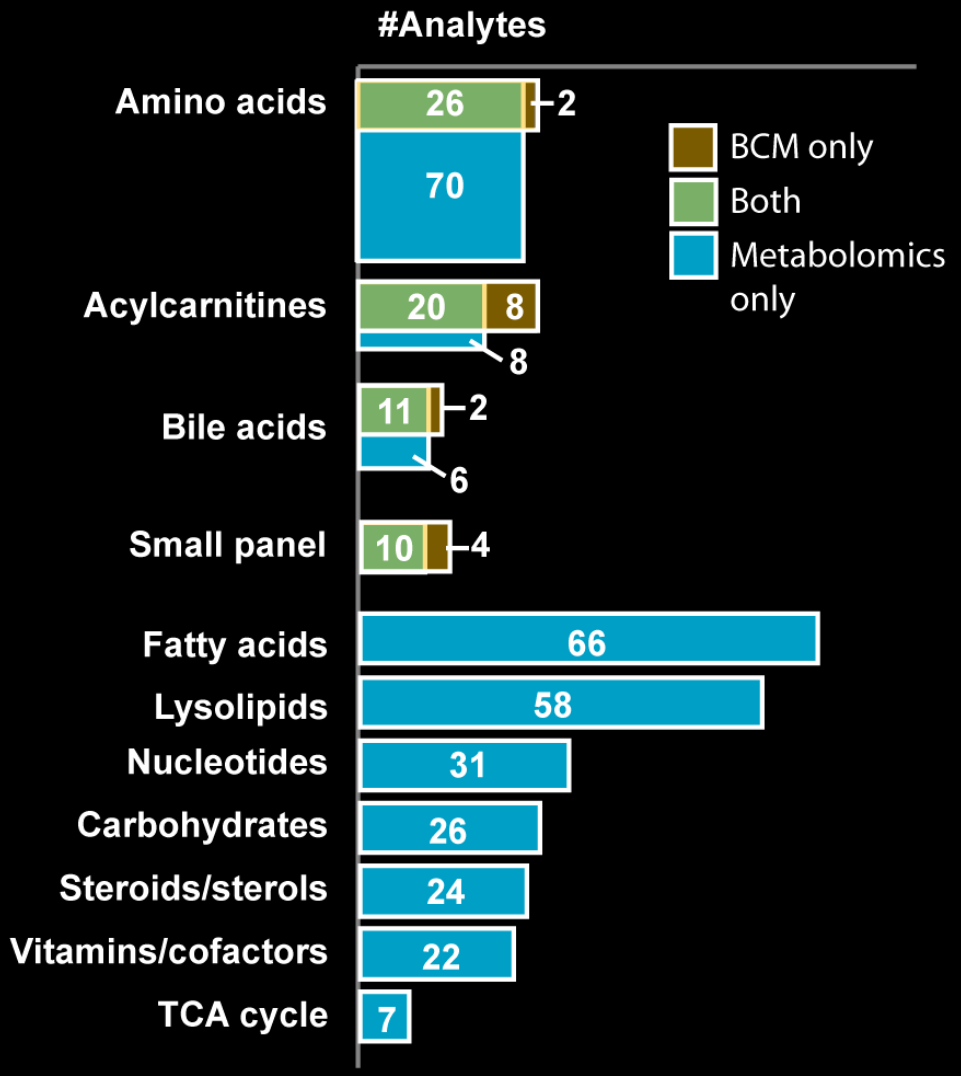
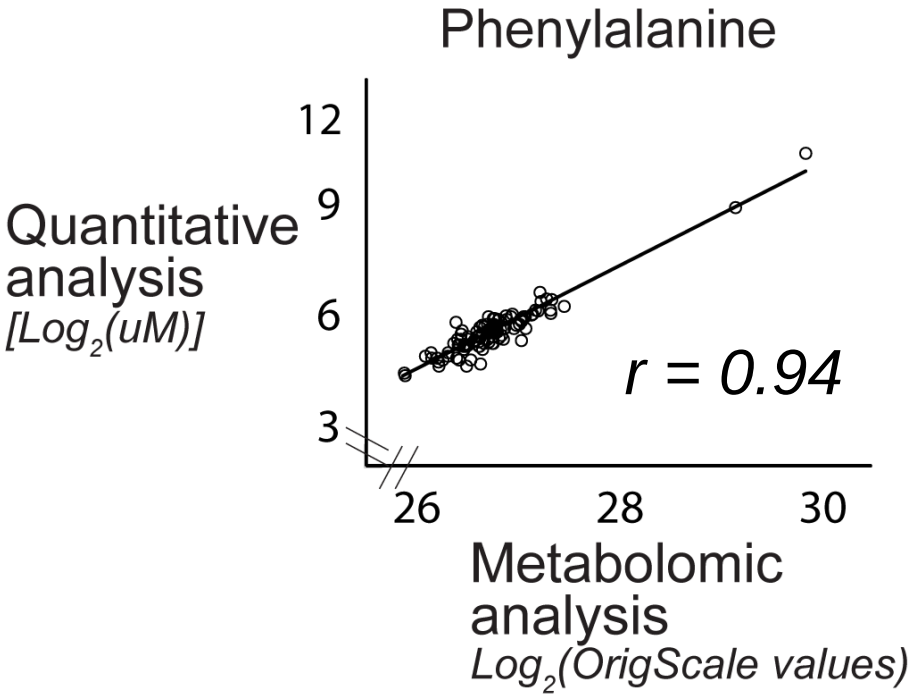


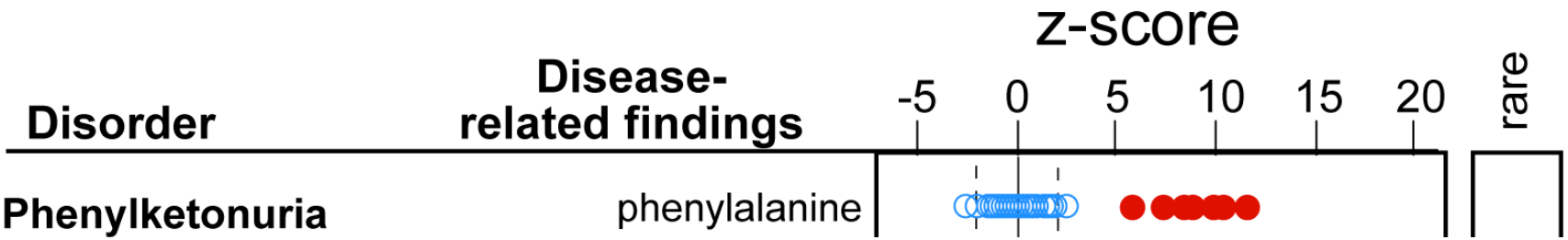


Clinical validation experiments

- Intra-assay precision
  - median=10.47% (IQR= 5.55-22.04%)
- Linear detection
  - 34 acylcarnitines and amino acids
  - median r=0.9, IQR r= 0.84-0.95
- Stability
  - Plasma separation time course studies- 30 mins to >1 day



Expected IEM-related analyte elevations were detected



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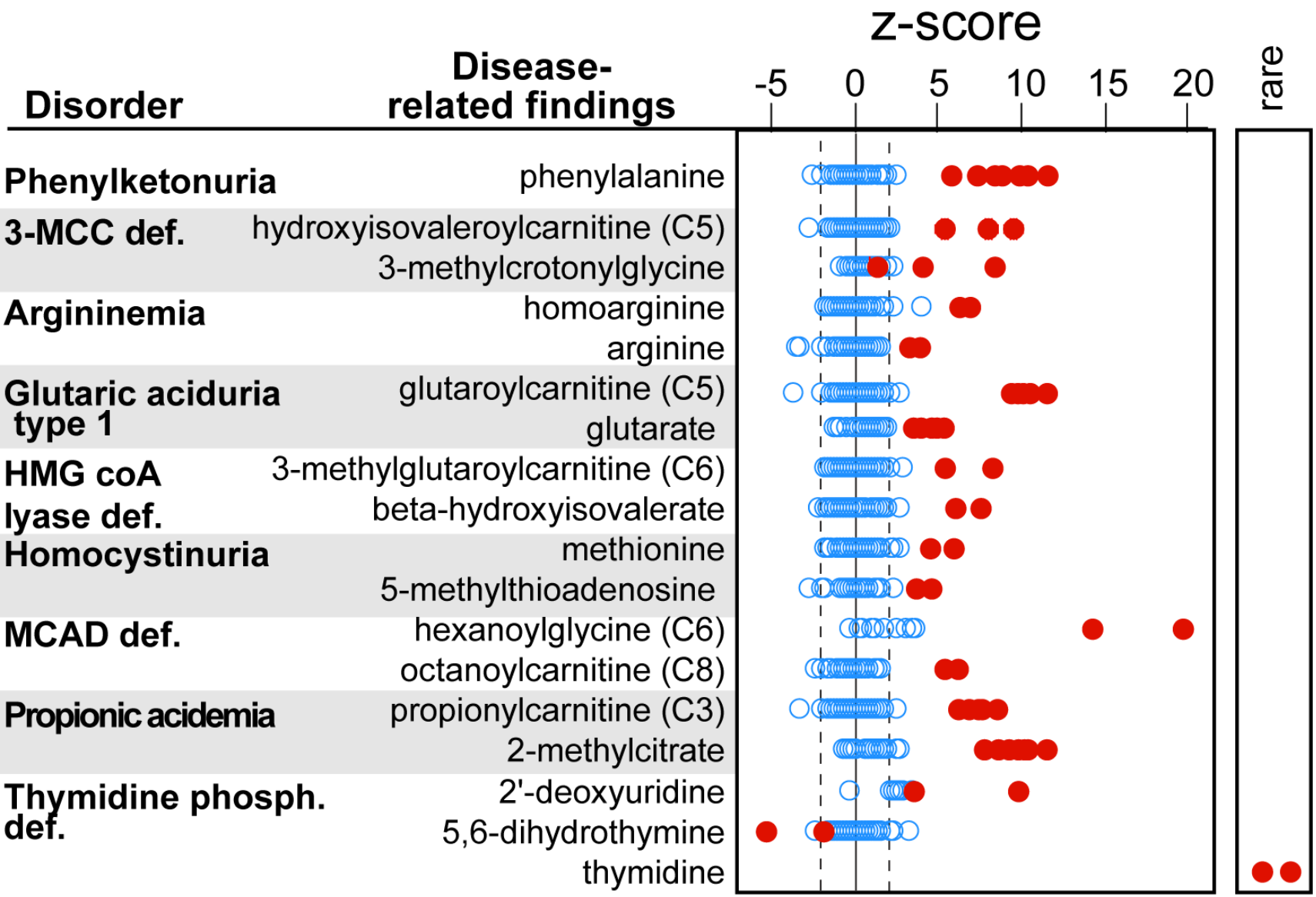
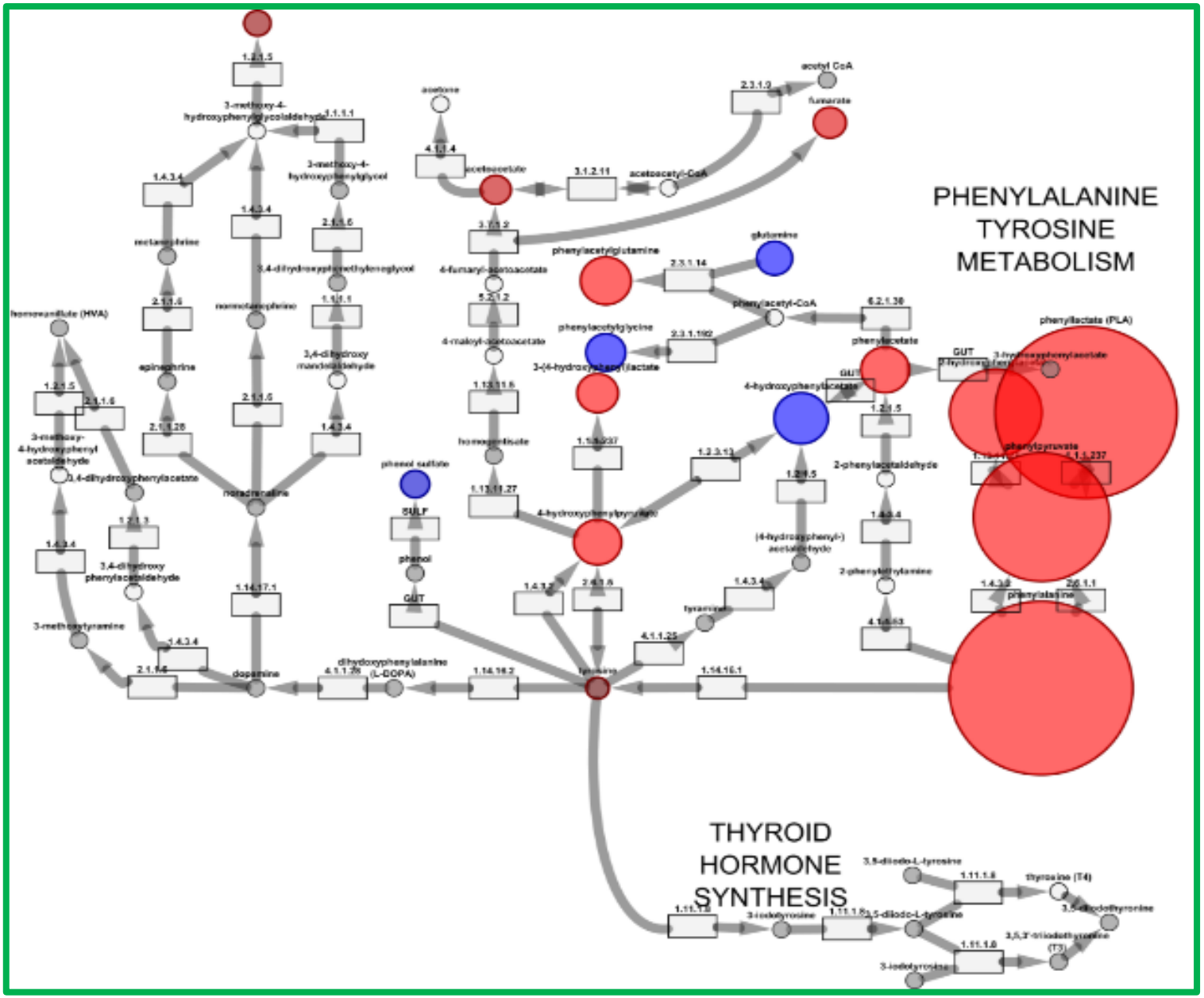
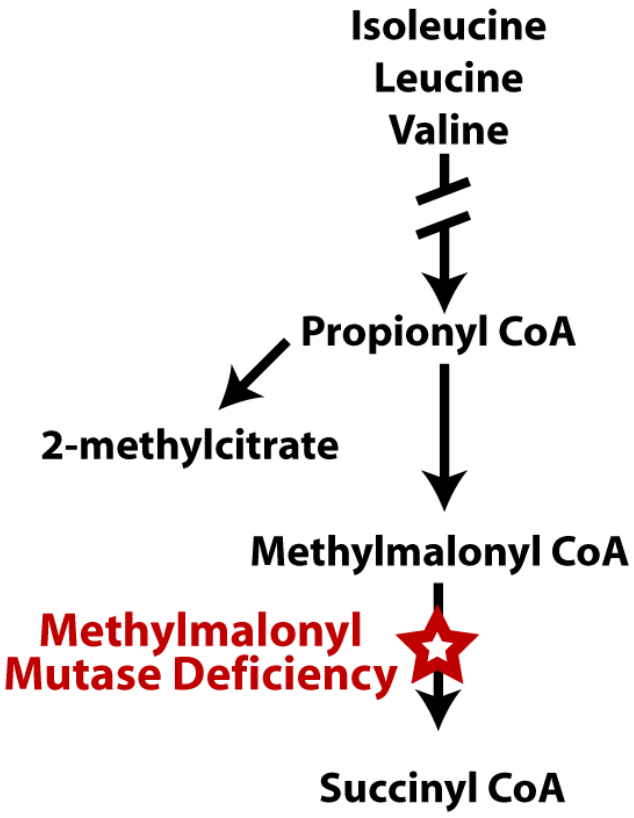
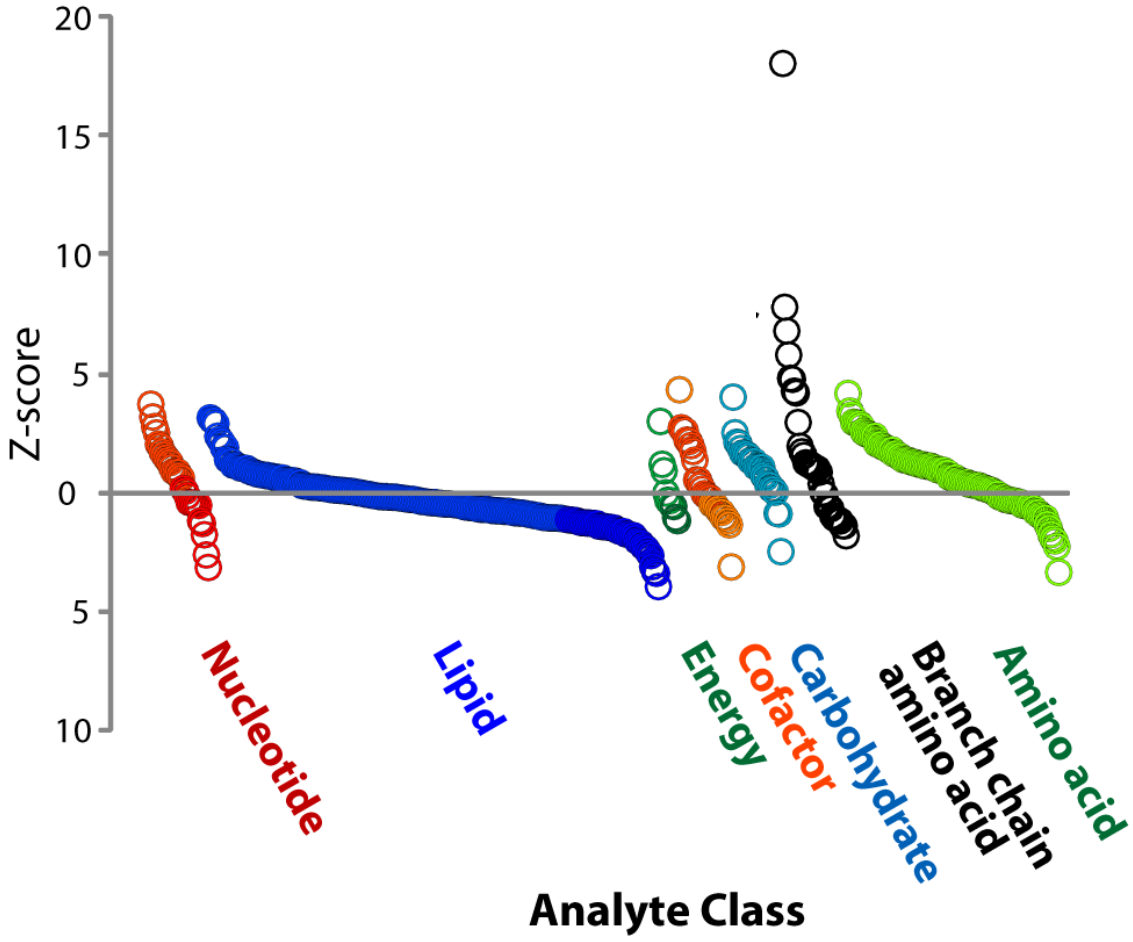


PKU

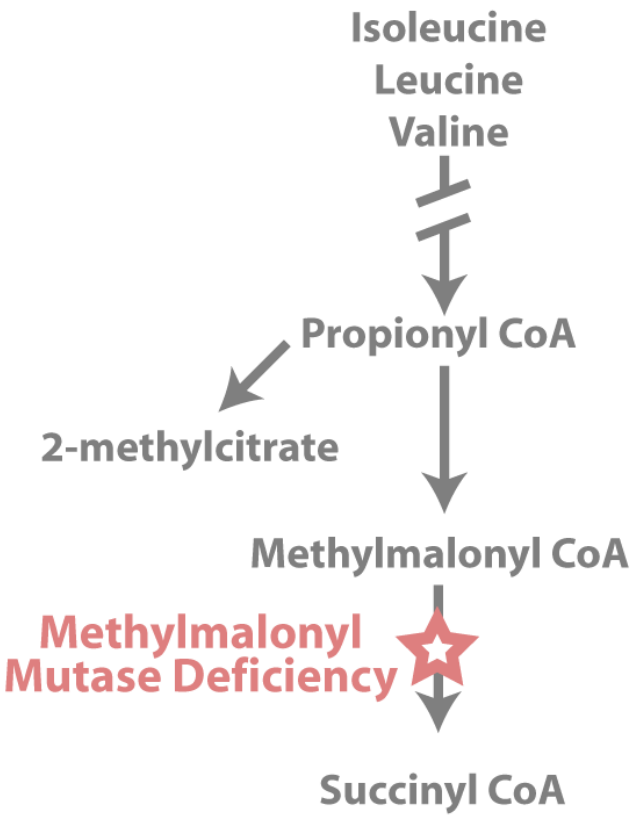

PHENYLALANINE
TYROSINE
METABOLISM
THYROID
HORMONE
SYNTHESIS
acetone
acetoacetate
acetoacetyl-CoA
acetyl CoA
fumarate
glutamine
phenylacetylglutamine
phenylacetyl-CoA
phenylacetylglycine
3-(4-hydroxyphenyl)lactate
4-hydroxyphenylacetate
phenyllactate (PLA)
phenylacetate
phenylpyruvate
2-phenylacetaldehyde
2-phenylethylamine
phenylalanine
4-hydroxyphenylpyruvate
(4-hydroxyphenyl-)
acetaldehyde
tyrosine
tyramine
dihydroxyphenylalanine
(L-DOPA)
dopamine
3-methoxytyramine
noradrenaline
adrenaline
normetanephrine
metanephrine
3-methoxy-4-
hydroxyphenylglycol
3-methoxy-4-
hydroxyphenylglycolaldehyde
3,4-dihydroxyphenylglycol
3,4-dihydroxy
mandelaldehyde
3,4-dihydroxyphenylacetate
3,4-dihydroxy
phenylacetaldehyde
3-methoxy-
4-hydroxyphenyl
acetaldehyde
homovanillate (HVA)
phenol sulfate
SULF
phenol
GUT
3,5-diiodo-L-tyrosine
3-iodotyrosine
thyroxine (T4)
3,5,3'-triiodothyronine
(T3)
3-iodotyronine

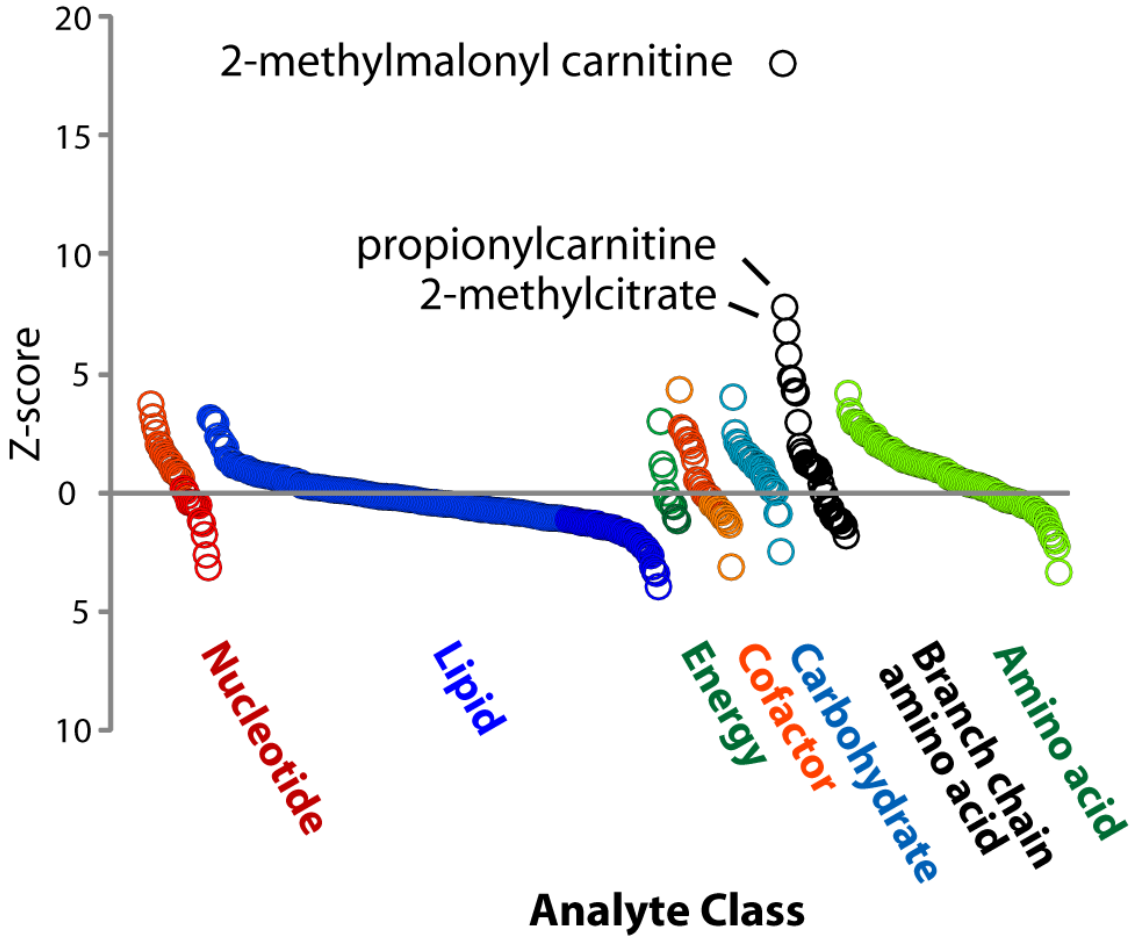
Methylmalonic acidemia

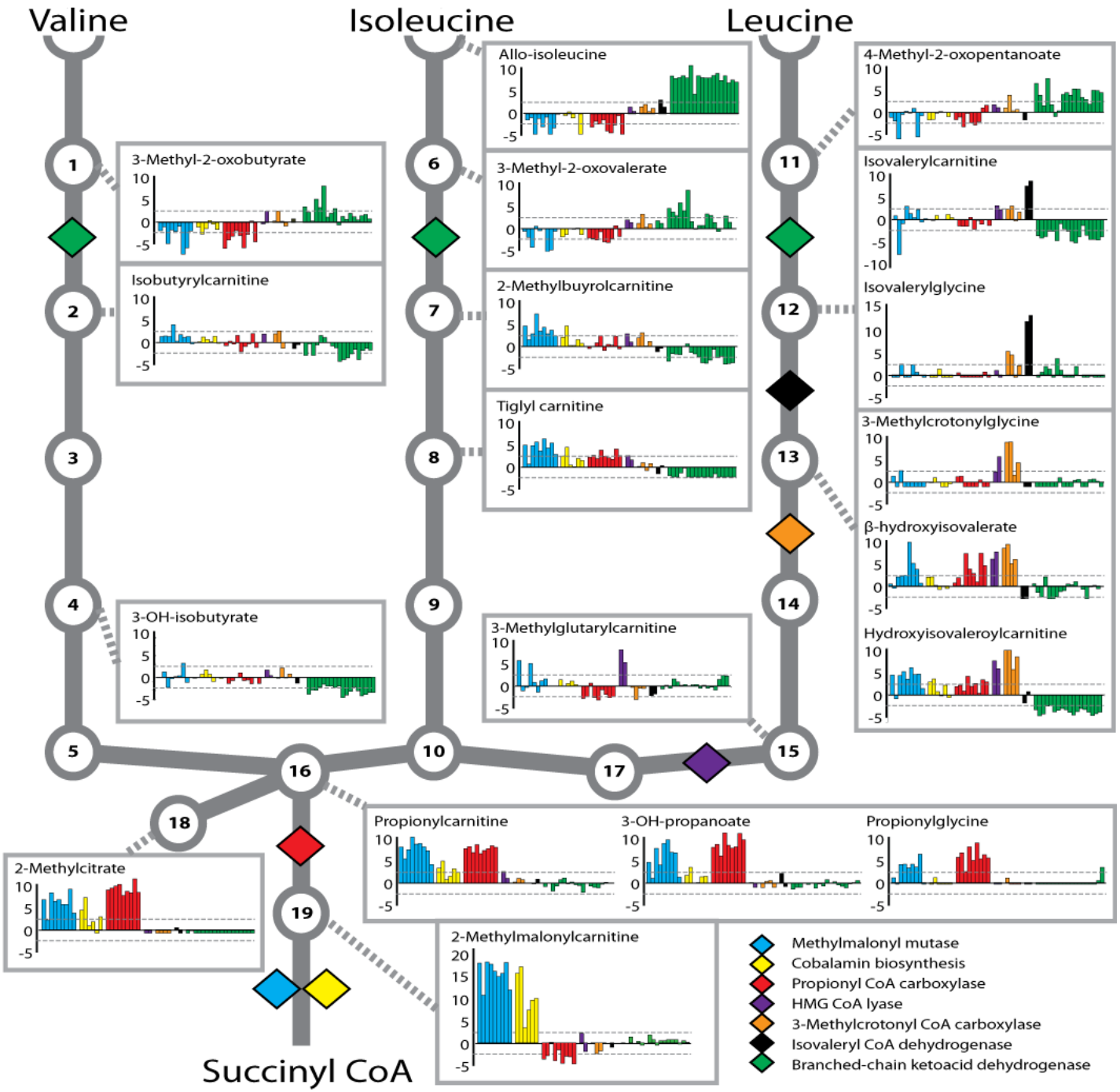




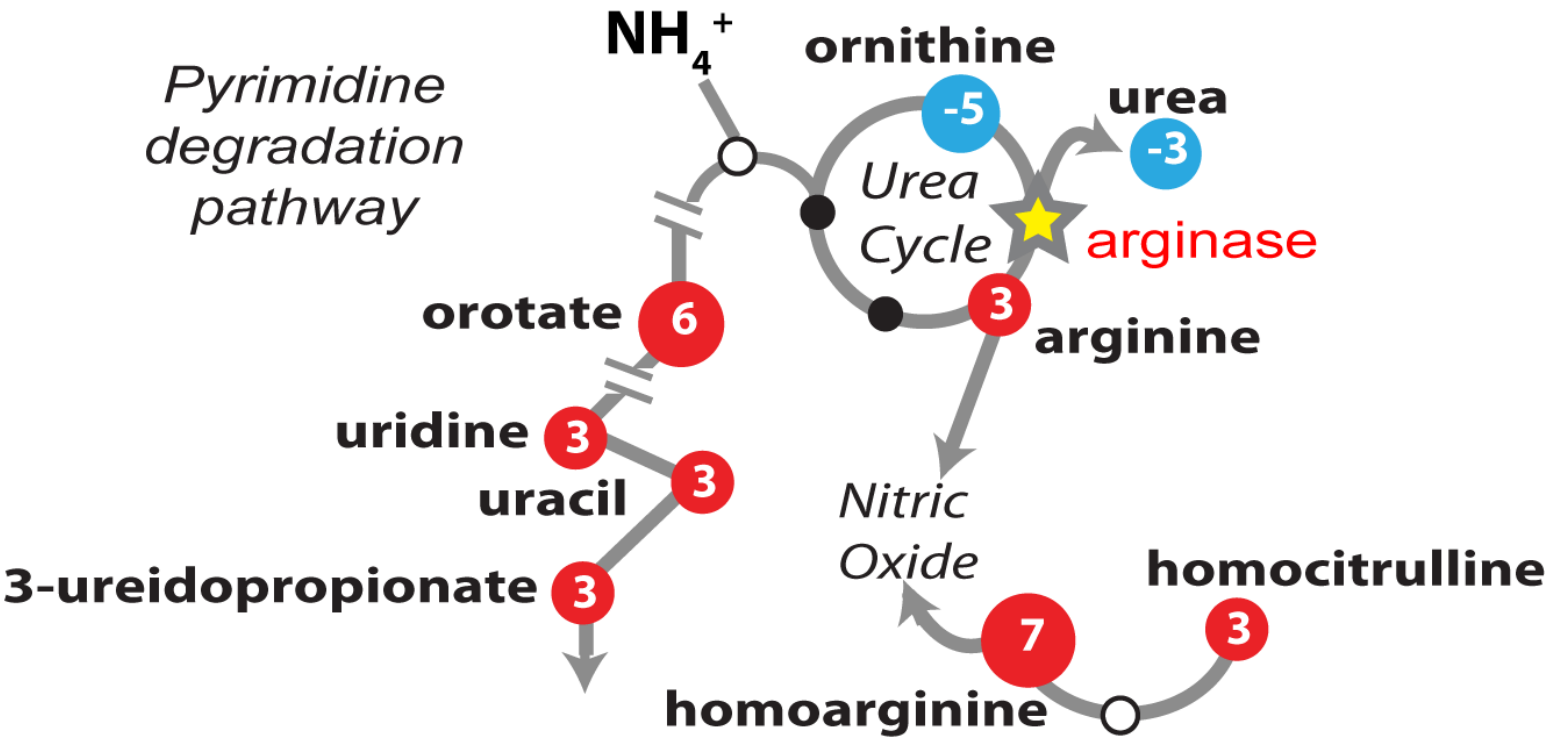
Methylmalonic acidemia






Valine
Isoleucine
Leucine
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
3-Methyl-2-oxobutyrate
Isobutyrylcarnitine
3-OH-isobutyrate
Allo-isoleucine
3-Methyl-2-oxovalerate
2-Methylbuyrolcarnitine
Tiglyl carnitine
3-Methylglutarylcarnitine
4-Methyl-2-oxopentanoate
Isovalerylcarnitine
Isovalerylglycine
3-Methylcrotonylglycine
β-hydroxyisovalerate
Hydroxyisovaleroylcarnitine
2-Methylcitrate
Propionylcarnitine
3-OH-propanoate
Propionylglycine
2-Methylmalonylcarnitine
Succinyl CoA
Methylmalonyl mutase
Cobalamin biosynthesis
Propionyl CoA carboxylase
HMG CoA lyase
3-Methylcrotonyl CoA carboxylase
Isovaleryl CoA dehydrogenase
Branched-chain ketoacid dehydrogenase

Metabolomic Results: *Argininemia*



Plasma metabolomic analysis successfully screened for 20 different IEMs

- **Urea cycle disorders**
  - Arginase def
  - Argininosuccinate lyase def
  - Citrullinemia
  - Ornithine transcarbamylase def
- **Amino acid disorders**
  - Homocystinuria (CBS)
  - Maple syrup urine disease
  - Phenylketonuria
- **Fatty acid oxidation disorders**
  - MCAD
  - VLCAD
- **Organic acidemias**
  - 3-methylcrotonyl-CoA carboxylase def
  - Cobalamin disorders
  - Glutaric acidemia type I
  - HMG-CoA lyase def
  - Isovaleric acidemia
  - Methymalonic acidemia
  - Propionic acidemia
- **Other**
  - Guanidinoacetate methyltransferase def
  - Holocarboxylase synthetase def
  - Thymidine phosphorylase def
  - TMLHE def

J Inherit Metab Dis (2015) 38:1029–1039
DOI 10.1007/s10545-015-9843-7

ORIGINAL ARTICLE

Untargeted metabolomic analysis for the clinical screening of inborn errors of metabolism

Marcus J. Miller[1] · Adam D. Kennedy[2] · Andrea D. Eckhart[2] · Lindsay C. Burrage[1] · Jacob E. Wulff[2] · Luke A.D. Miller[2] · Michael V. Milburn[2] · John A. Ryals[2] · Arthur L. Beaudet[1] · Qin Sun[1] · V. Reid Sutton[1] · Sarah H. Elsea[1]

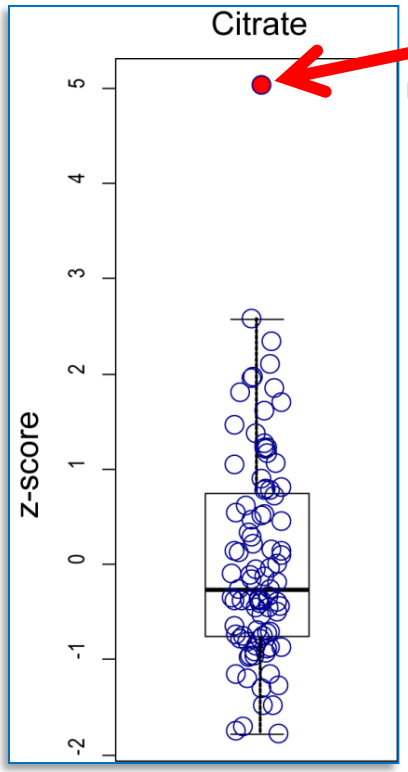
Neurologic phenotypes

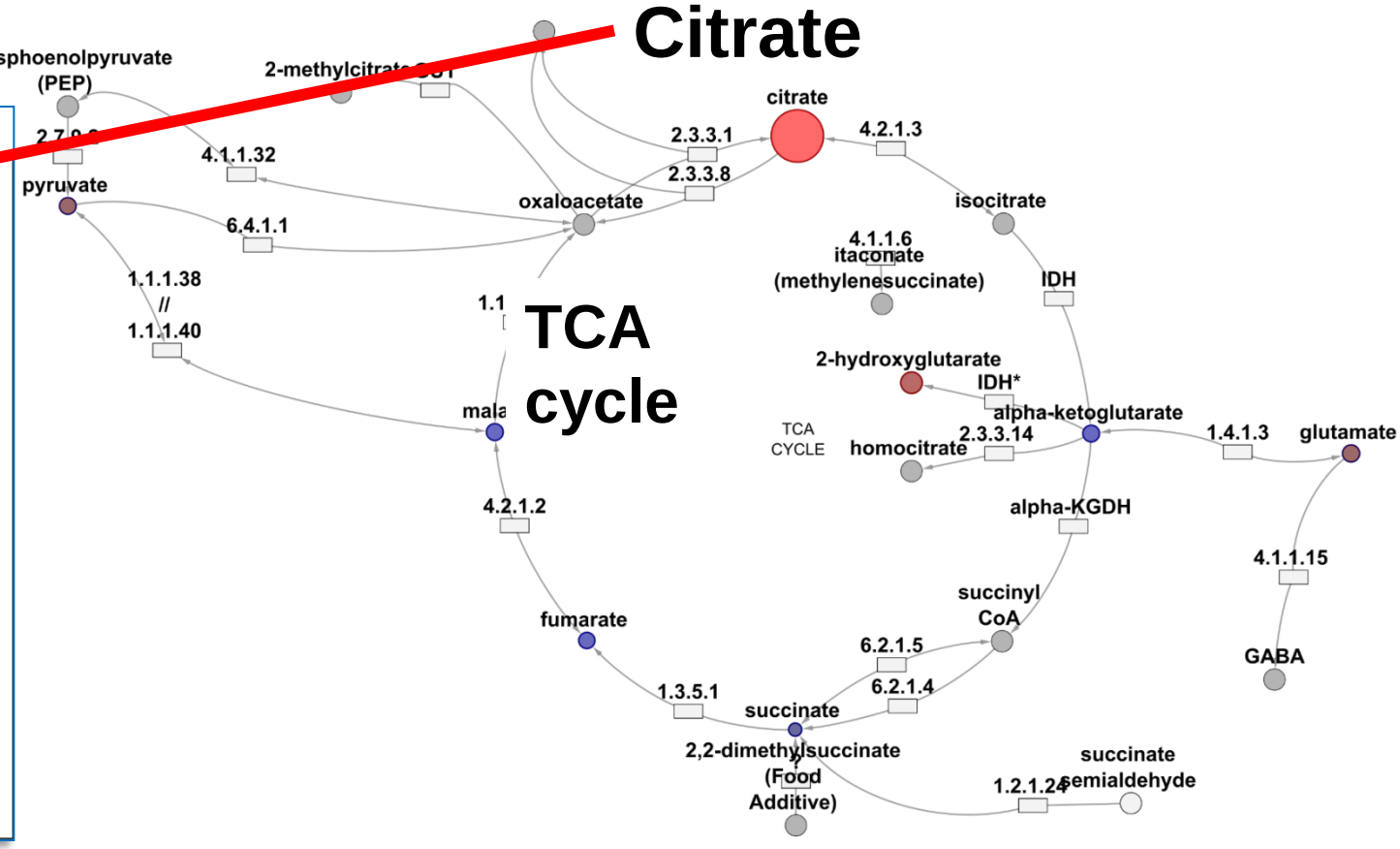
FUNCTIONAL VALIDATION OF DNA VARIANTS OF UNCERTAIN SIGNIFICANCE

Case 1 – Citrate Transporter Deficiency

EXOME Findings

- *trans mutations in SLC13A5*
  - c.997C>T (p.R333X) and c.680C>T (p.T227M)
- Disorder: AR citrate transporter def.

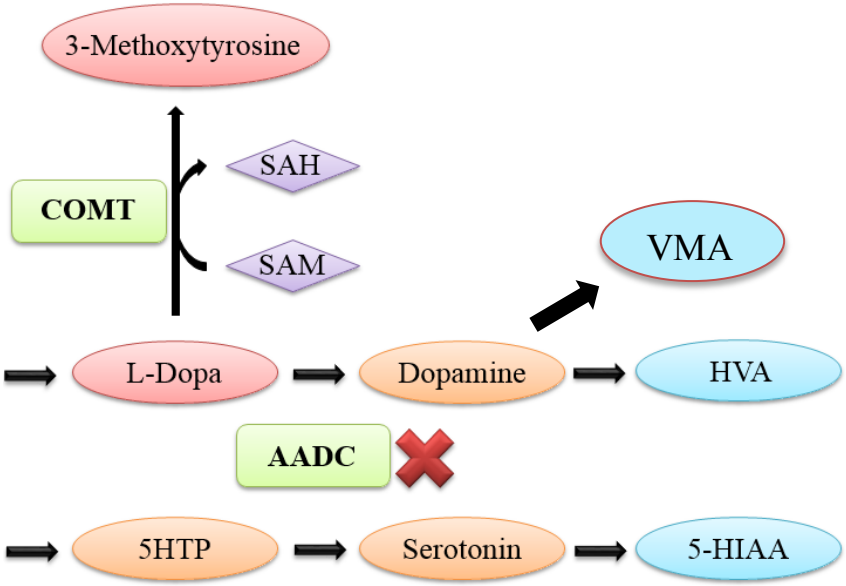


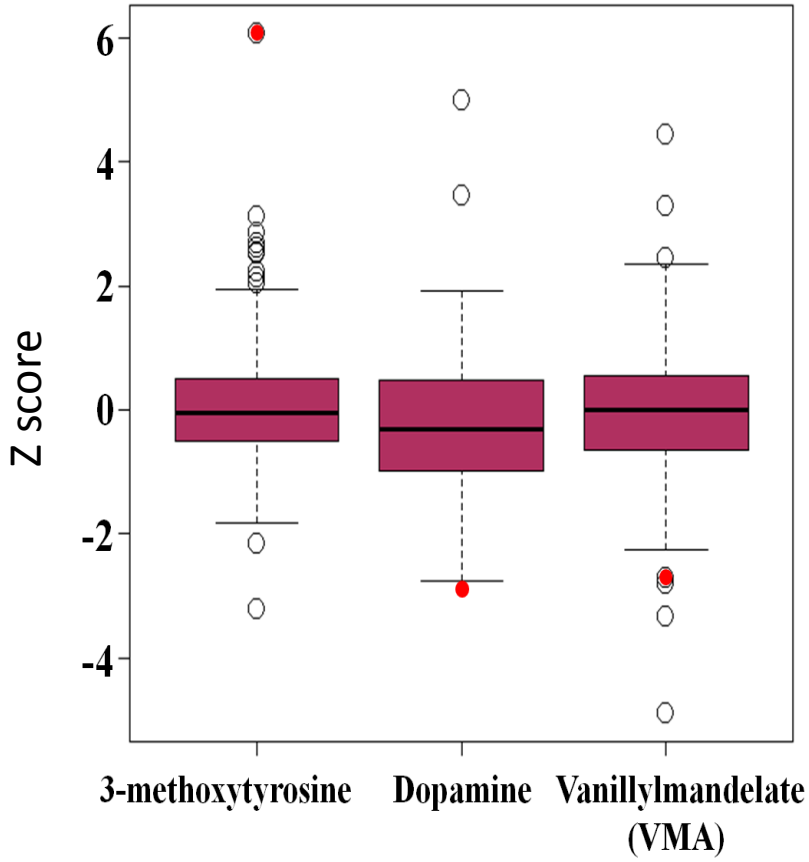


Case 2 - Aromatic Amino Acid Decarboxylase Deficiency

- 4 year old infant with developmental delay and hypotonia; initial presentation 11 months
- Tests performed previously– VLCFA, LSD panel, urine MPS, CMA,PAA, UOA, ACP, NH3, lactate, CK, CSF glucose/protein, muscle biopsy, ETC analysis, mitochondrial genome/depletion, MRI brain
- WES – 2 VUS (trans), c.286G>A (p.G96R) and c.260C>T (p.P87L) in the *DDC* gene

Case 2 - Pathway and Results

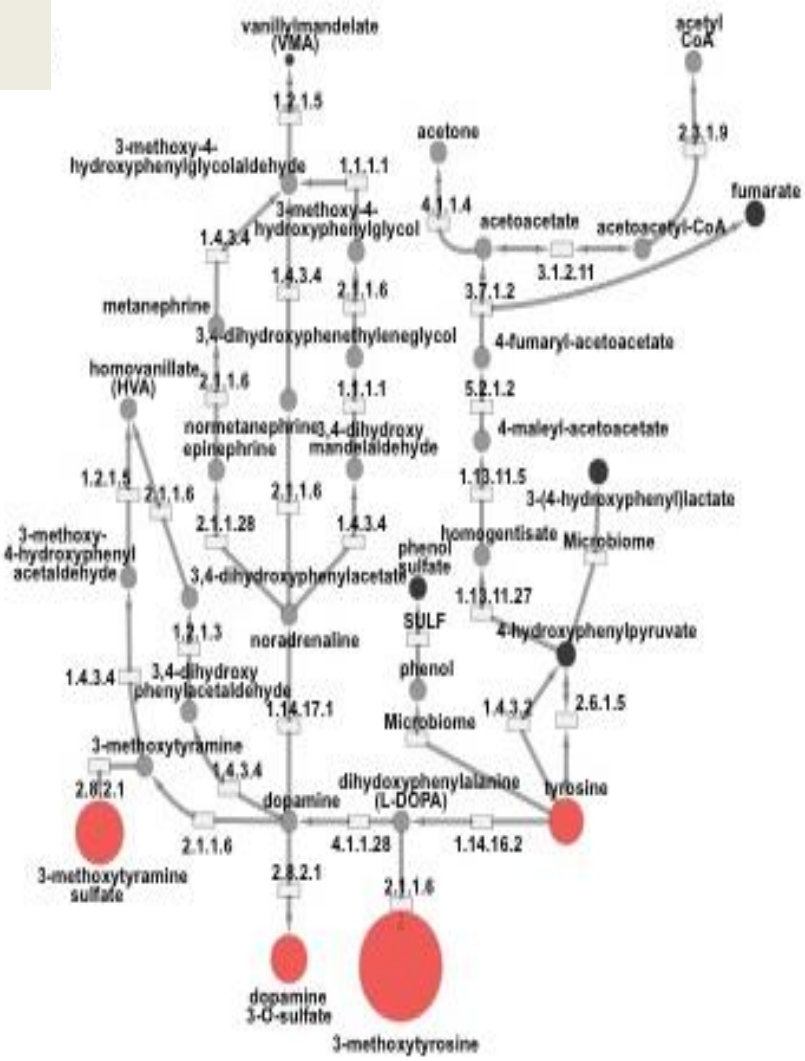


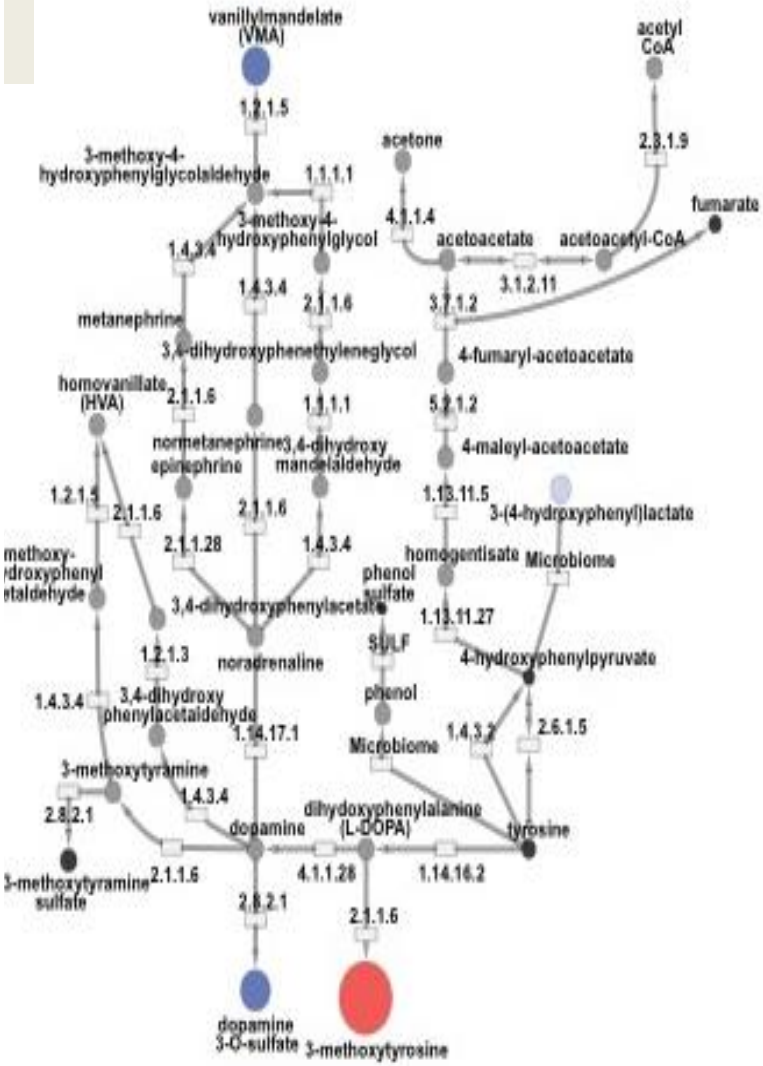


Patient is shown in red

Dopa-containing medications

Aromatic amino acid decarboxylase deficiency





High

Low

-1.5 - +1.5

Molecule in library but not detected

Molecule not in library

Circle size relat
Z-score

Case 3

- 19 month old male
  - Global developmental delay
  - Hypotonia
  - Abnormal movements
  - Abnormal MRI (delayed myelination)
  - Oculomotor apraxia
  - Facial hemangioma
  - Constipation
- Prior normal workup
  - Microarray
  - Metabolic workup
    - Plasma amino acids
    - Lactate
    - Ammonia
    - Urine organic acids
    - CSF amino acids
    - CSF neurotransmitter profile

Whole exome sequencing and metabolomics ordered

Case 3 WES Results

- Single heterozygous pathogenic variant
  - *UROC1*, novel c.1448_1449delCT (p.S483fs)
    - Urocanase deficiency [MIM #276880]
- Two heterozygous VUS
  - *ABAT,* novel: c.454C>T (p.P152S) and c.1393G>C (p.G465R)
    - GABA transaminase deficiency [MIM #613163]

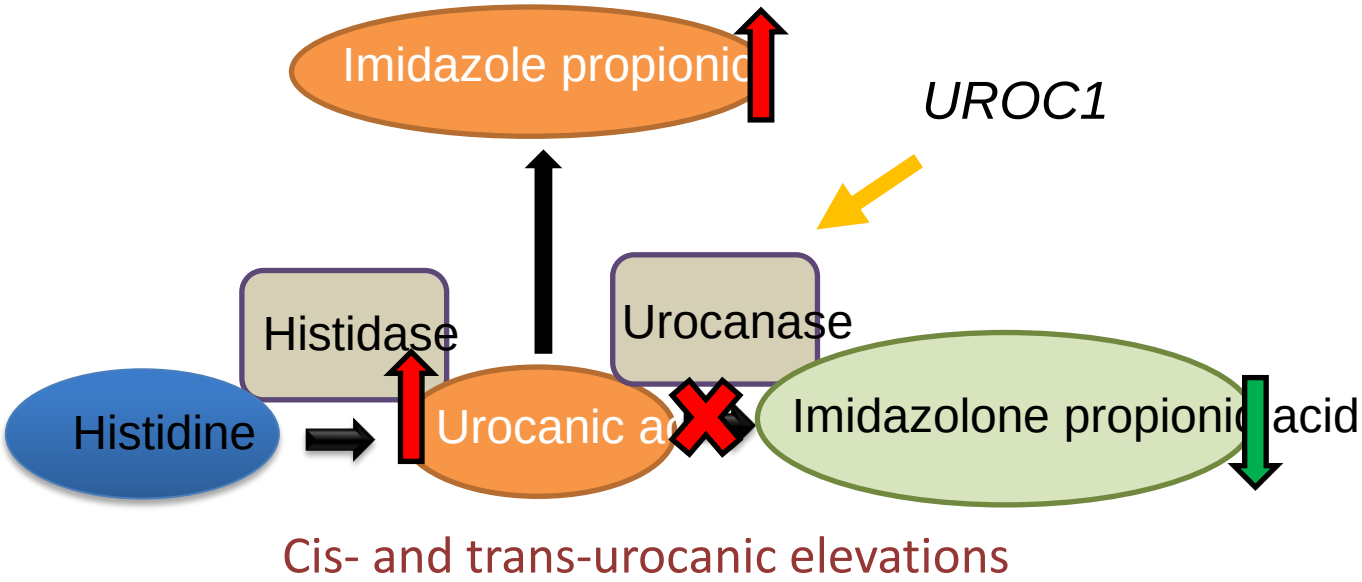
Single heterozygous VUS

- ***ACAD9***, ACAD9 deficiency
- ***ATM***, Ataxia-telangiectasia
- ***UPB1***, Beta-ureidopropionase deficiency
- ***DARS*****,** Hypomyelination with brainstem and spinal cord involvement and leg spasticity
- ***CSPP1***, Joubert syndrome 21
- ***HERC2***, Mental retardation, autosomal recessive 38
- ***TH*****,** Segawa syndrome, recessive
- ***SPG11***, Spastic paraplegia 11, autosomal recessive
- ***AP4B1***, Spastic paraplegia 47, autosomal recessive

Case 3 WES Results

- Single heterozygous pathogenic variant
  – ***UROC1***, novel c.1448_1449delCT (p.S483fs)
    - Confirmed by Sanger sequencing: Coverage = 100%
      - »Father heterozygous
      - »Mother negative
    - Urocanase deficiency [MIM #276880]
- Two heterozygous VUS
  – *ABAT,* novel: c.454C>T (p.P152S) and c.1393G>C (p.G465R)
    - GABA transaminase deficiency [MIM #613163]

Case 3 - Metabolomic Results



No significant alterations of molecules in histidine pathway.

Second pathogenic variant likely not present.

Diagnosis likely not urocanase deficiency.

Case 3 WES Results

- Single heterozygous pathogenic variant
  - ***UROC1***, novel c.1448_1449delCT (p.S483fs)
    - Confirmed by Sanger sequencing: Coverage = 100%
      - »Father heterozygous
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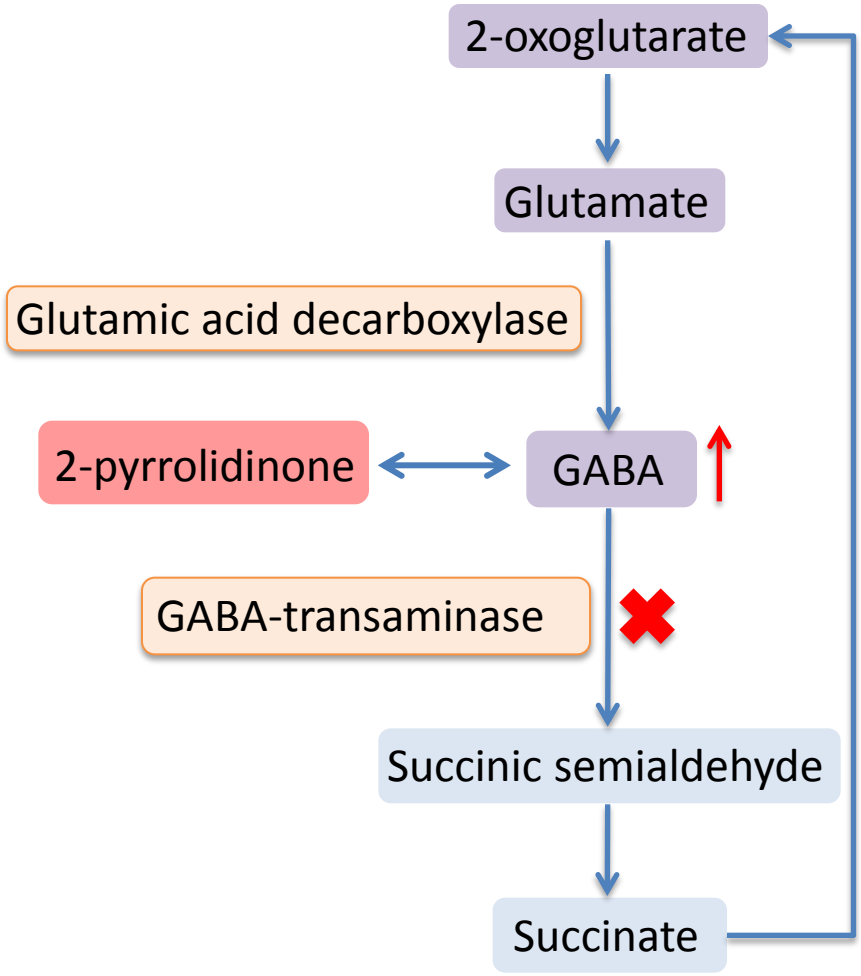
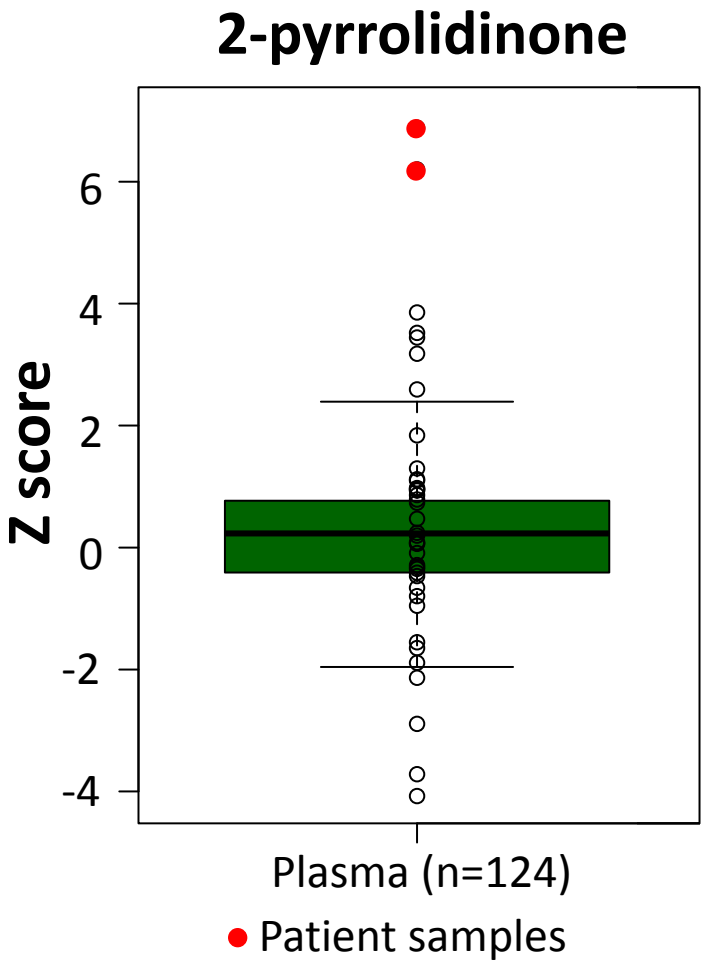
    - Urocanase deficiency [MIM #276880]
- Two heterozygous VUS
  - *ABAT,* novel: c.454C>T (p.P152S) and c.1393G>C (p.G465R)
    - c.454C>T (p.P152S), novel, inherited from mother
    - c.1393G>C (p.G465R), novel, inherited from father
    - Both variants predicted to be deleterious using sift and polyphen
    - GABA transaminase deficiency [MIM:#613163]

GABA transaminase (ABAT) deficiency (*Plasma!*)



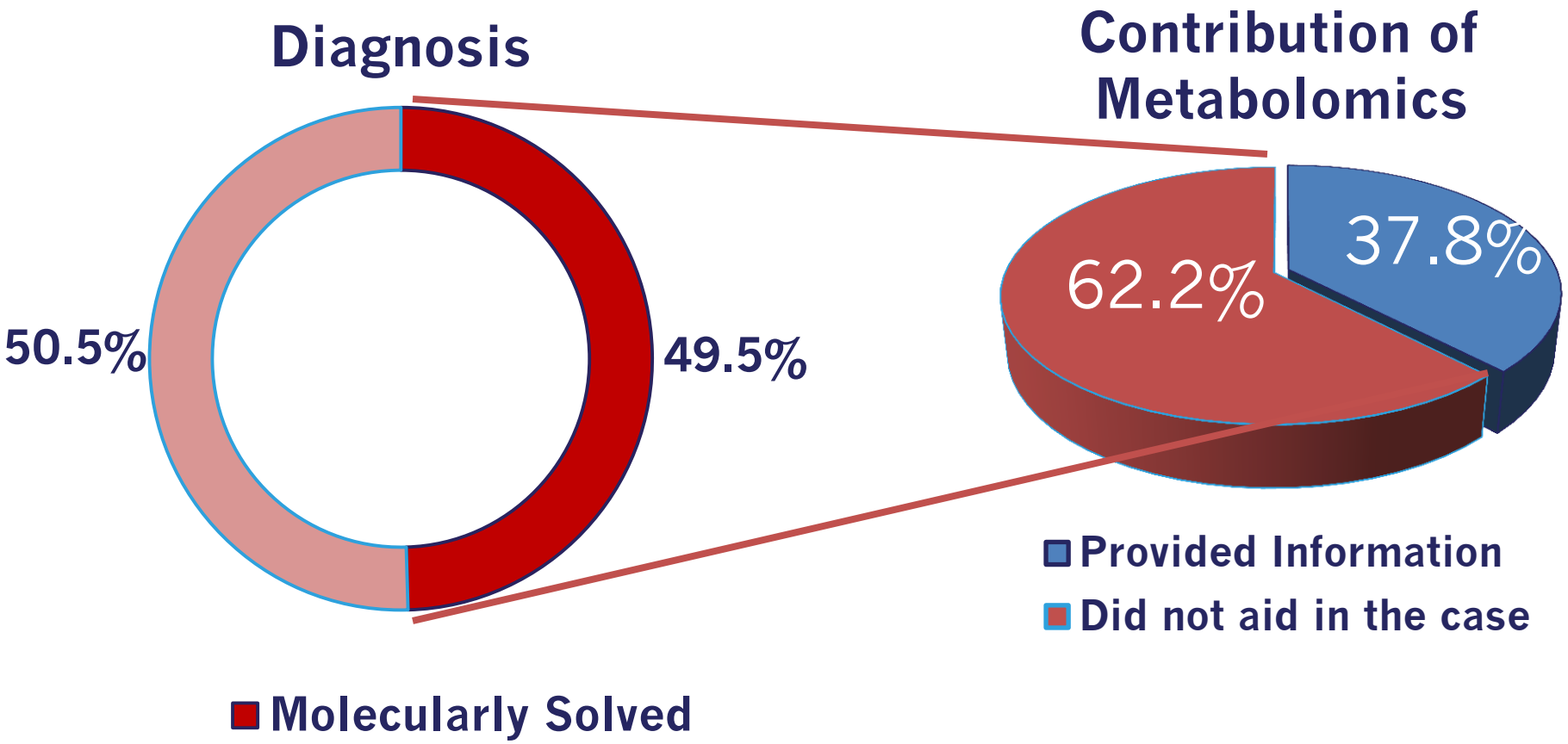


2-pyrrolidinone - a new biomarker for ABAT deficiency

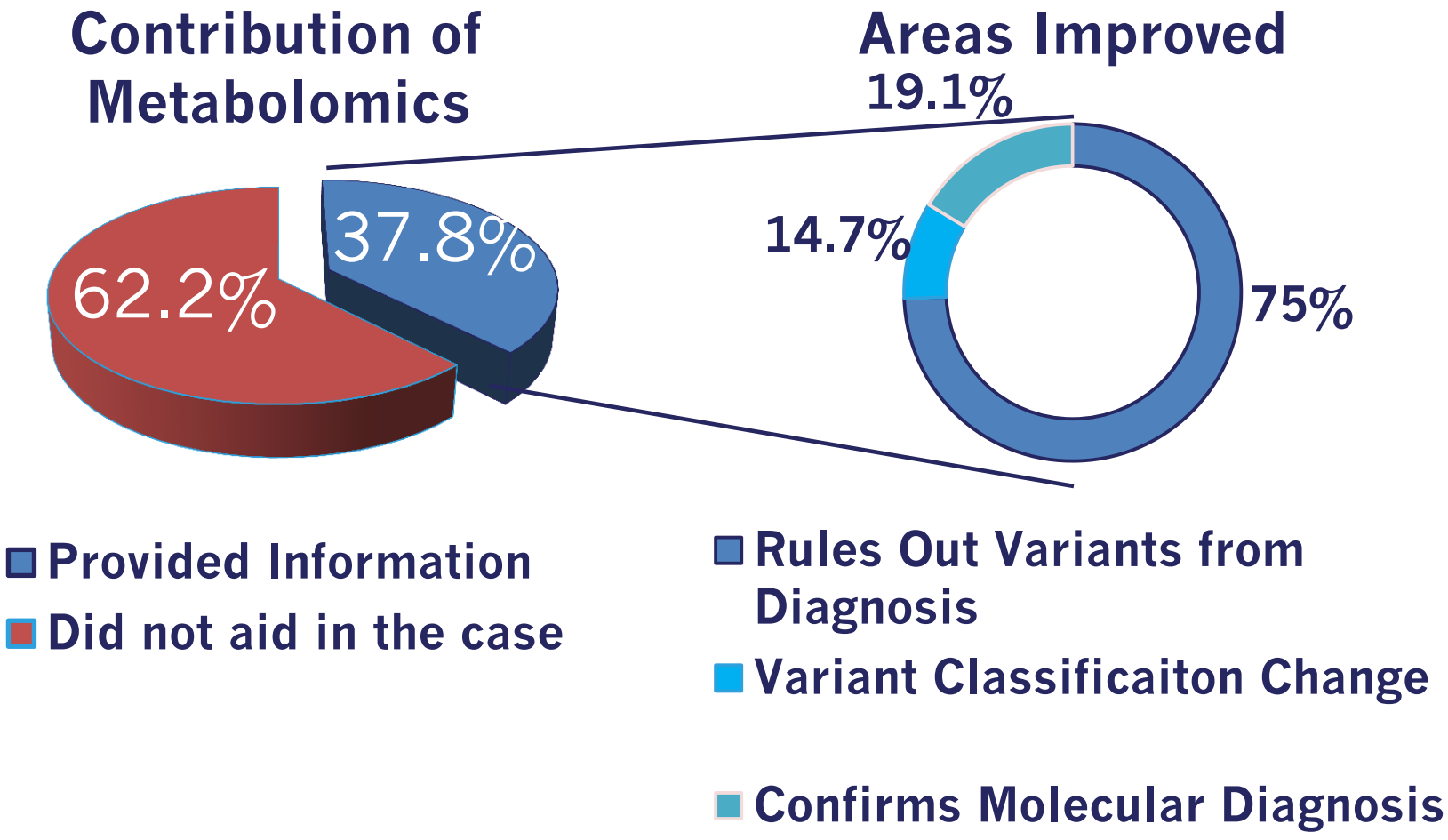
Exome + Metabolomics

- 180 Cases with both clinical exome and clinical metabolomic testing
- Assessed diagnostic rate of platforms
- Assessed when metabolomics contributed to variant re-classification [Alaimo, ASHG 2017]

Contribution of Metabolomics to Genomics

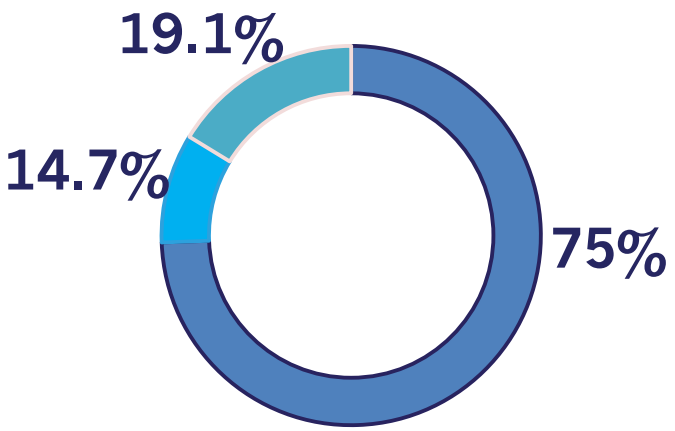


Contribution of Metabolomics to Genomics



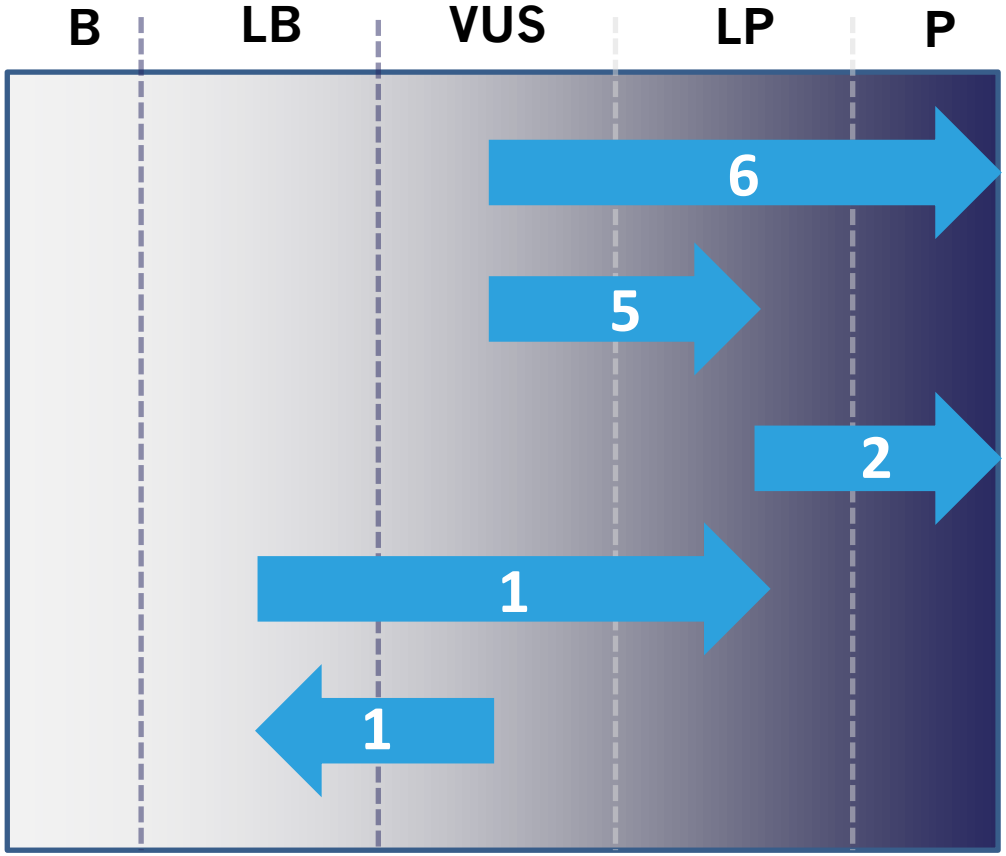
Contribution of Metabolomics to Variant Interpretation

Areas Improved



- Rules Out Variant from Diagnosis
- Variant Classification Change
- Confirms Molecular Diagnosis

Variant Classification Changes



B = benign
LB = likely benign
VUS = variant of uncertain significance
LP = likely pathogenic
P = pathogenic

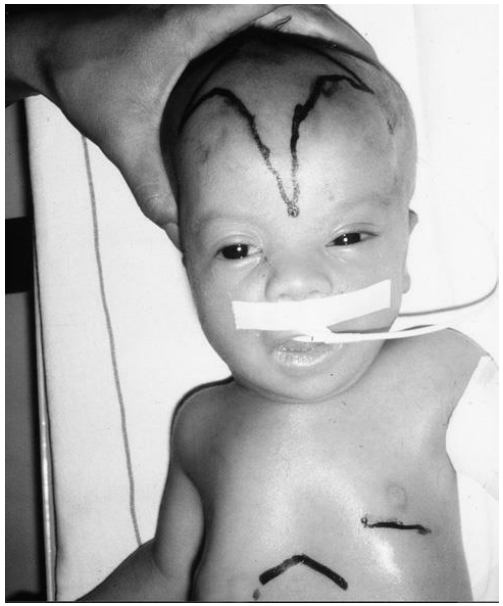
Peroxisomal Biogenesis disorders (PBD)

FURTHER VALIDATION AND NEW DISCOVERIES

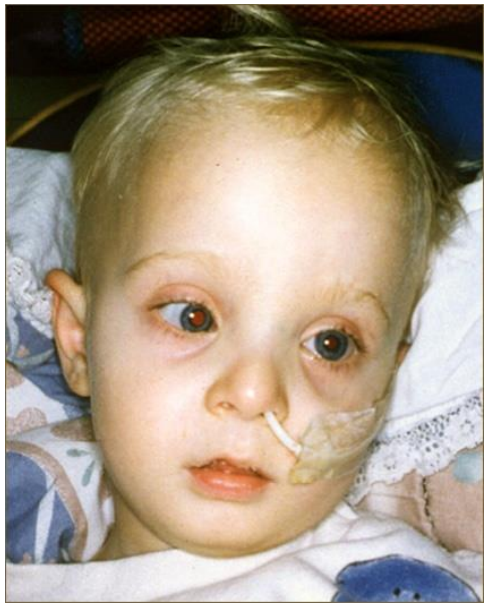
PBD are a clinical spectrum of disease

Disease Phenotype

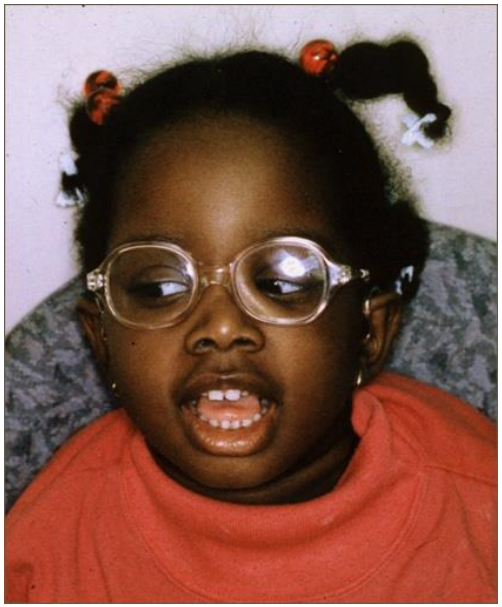
Classic Zellweger



Neonatal Adrenoleukodystrophy



Infantile Refsum



Disease Severity

Biochemical Phenotype

↑ ↑ VLCFA's
Absent or deficient peroxisomes

↑ or normal VLCFA's
Reduced # peroxisomes

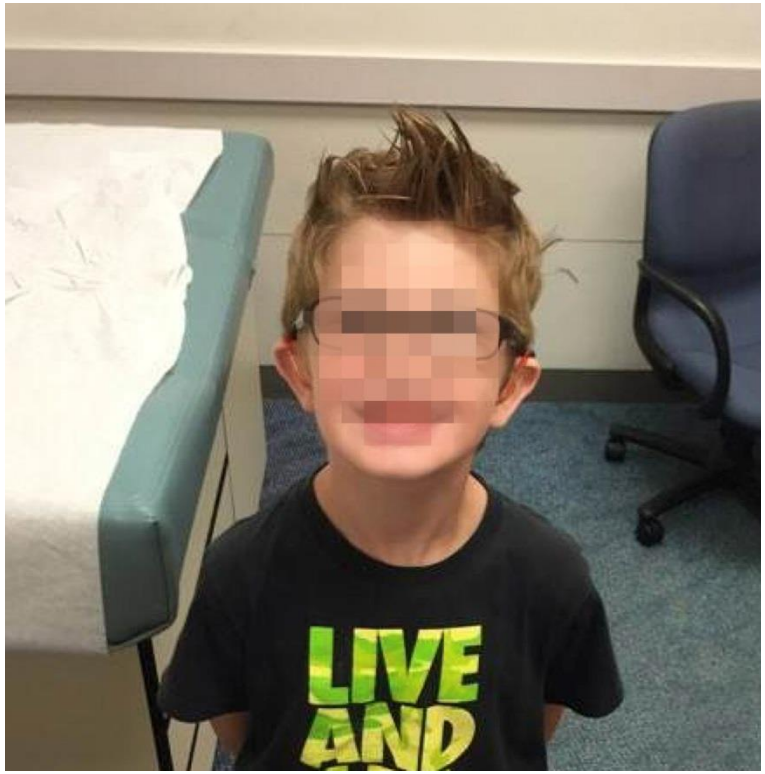
PEX alleles

Severe hypomorphic or null

Mild hypomorphic

Pictures from Inborn Metabolic Diseases 4th edition and SIMD NAMA

Mild PBD

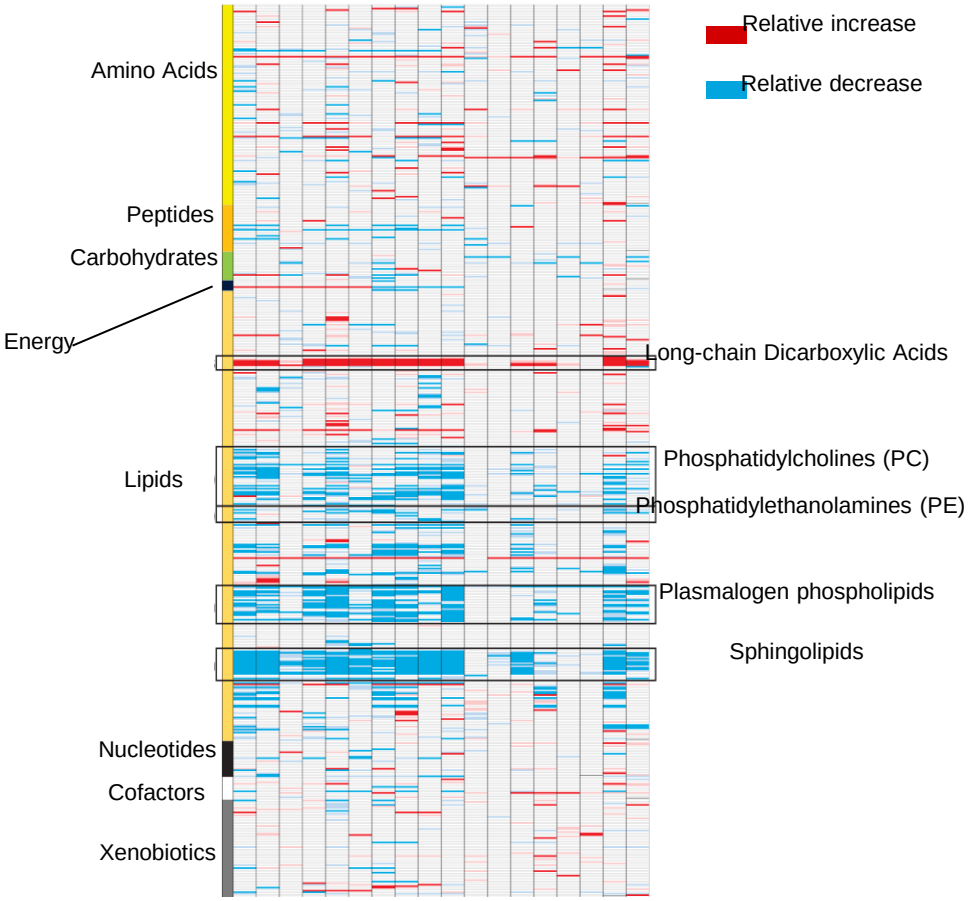


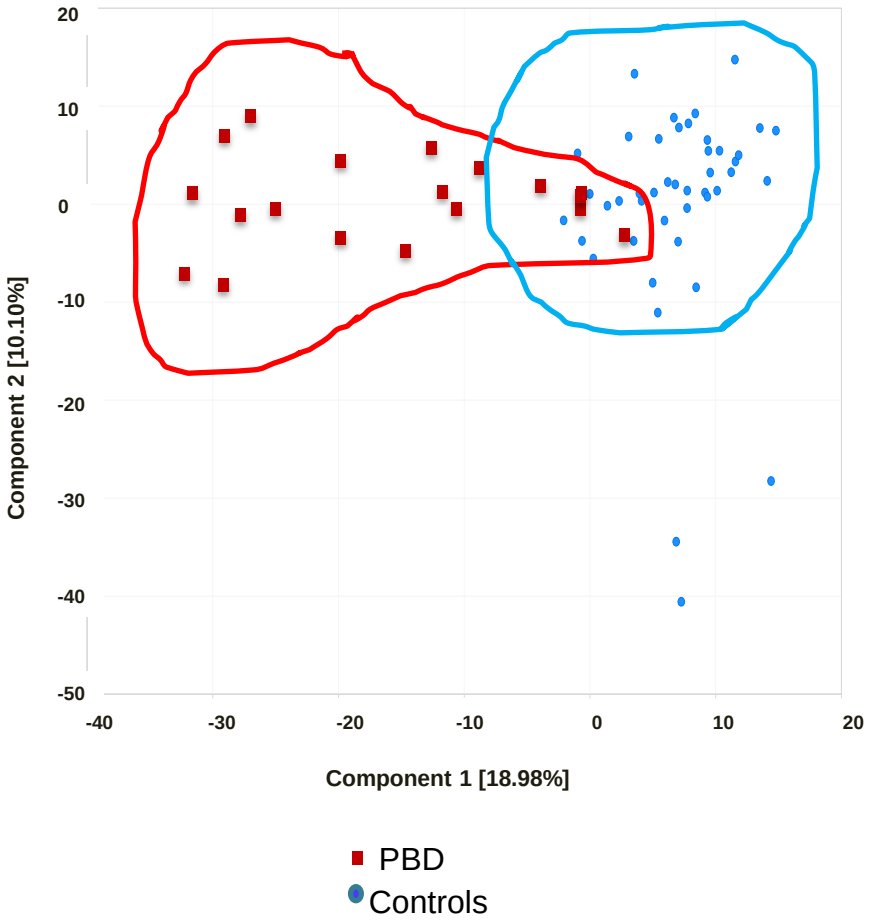
- 7 year old
- Phenotype mimicking Usher syndrome with hearing loss and pigmentary retinopathy, normal cognition, diagnosed by research sequencing study for Usher
- *PEX1* G843D homozygote

Zellweger-spectrum disorders

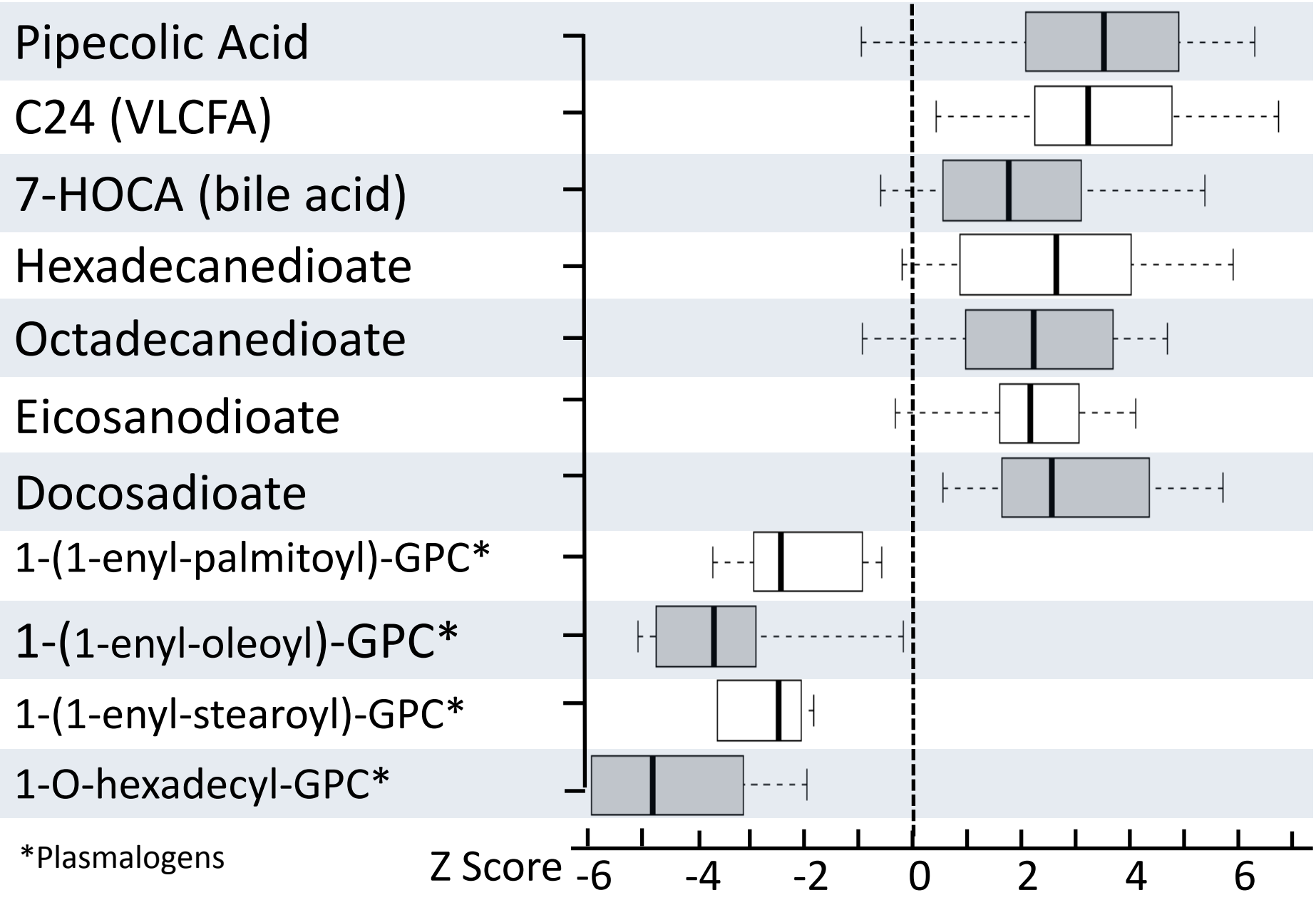
Metabolomics

~650 named molecules identified in each plasma sample, N=19



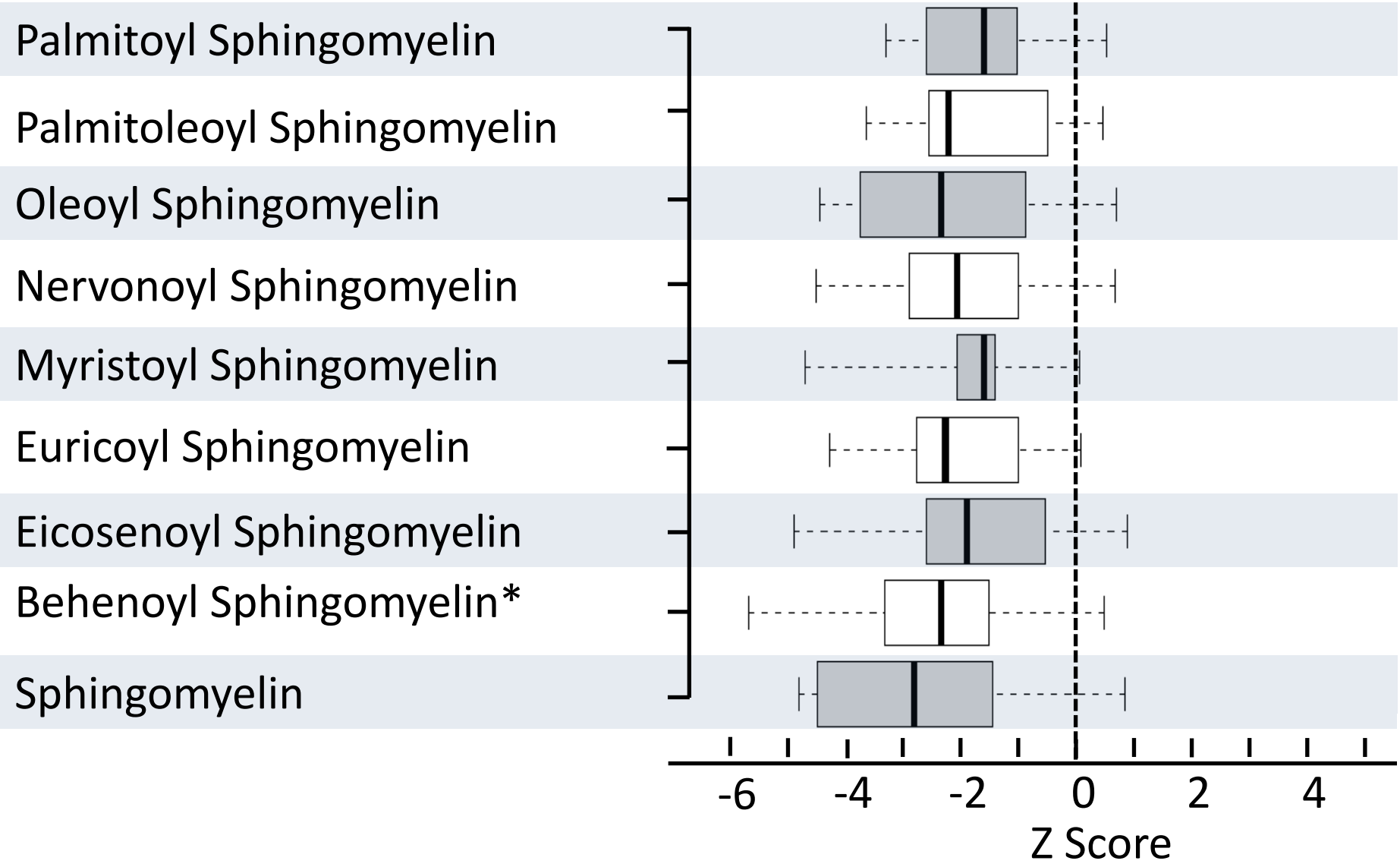


Results: Untargeted metabolomic analysis



*Plasmalogens

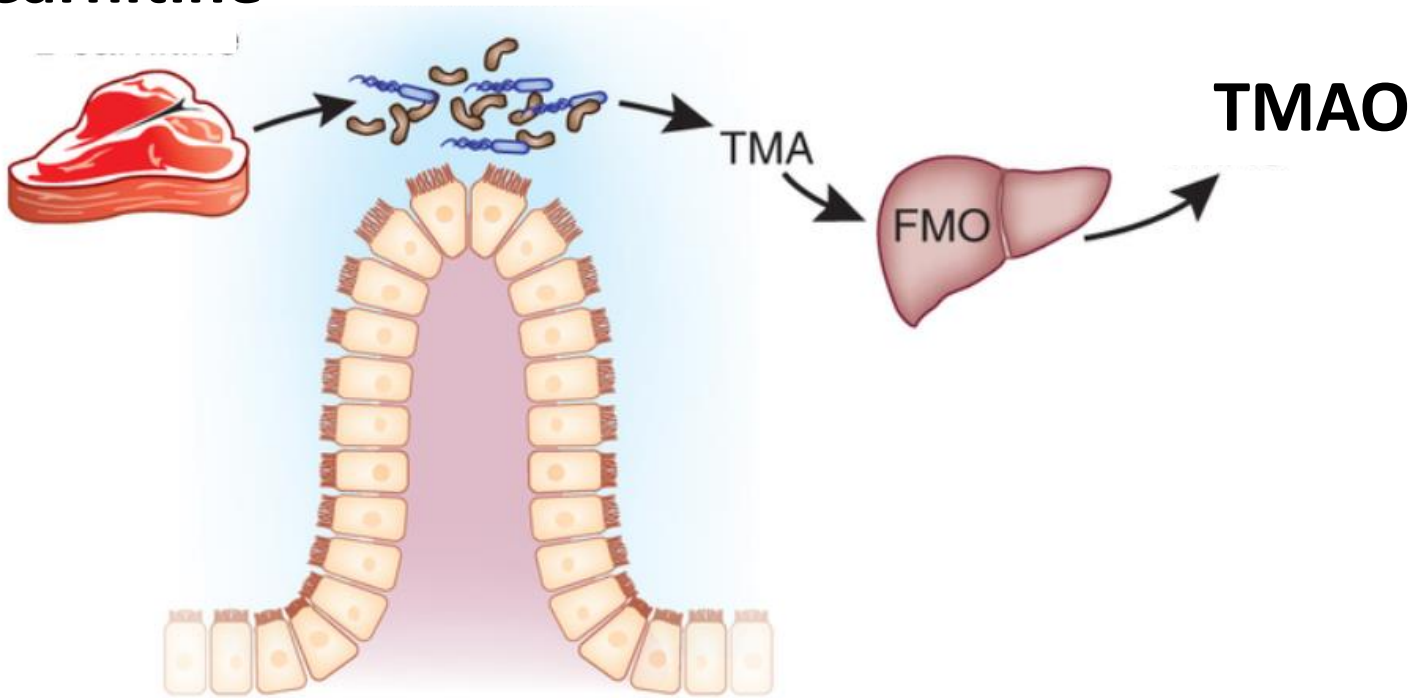
Results: Sphingomyelins as new biomarkers for PBD-ZSD



NEW DISCOVERIES!

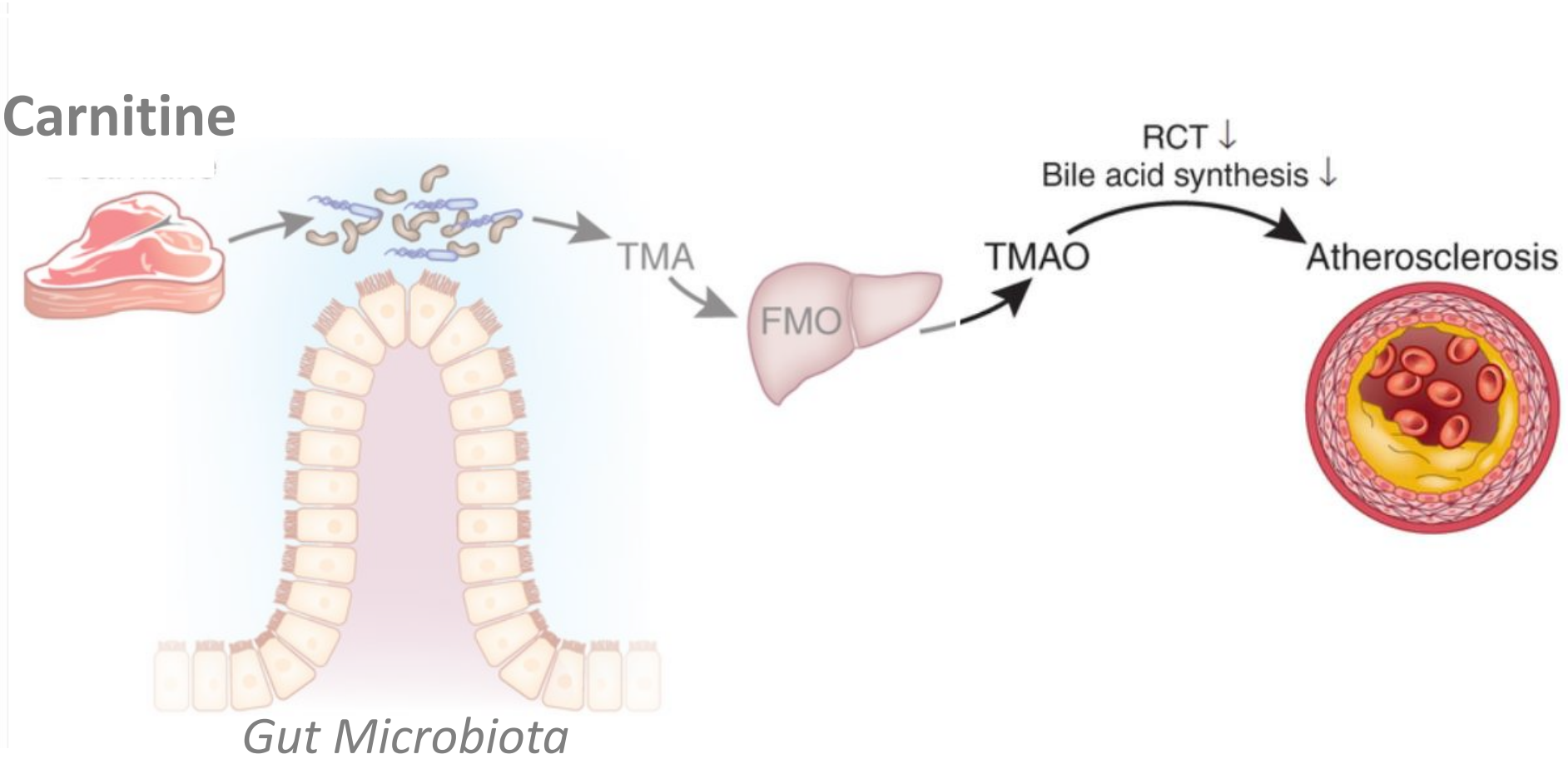
Oral Carnitine is converted to Trimethylamine N-oxide (TMAO)

Carnitine



Backhed F., Nature Medicine (2013) PMID: 23652100

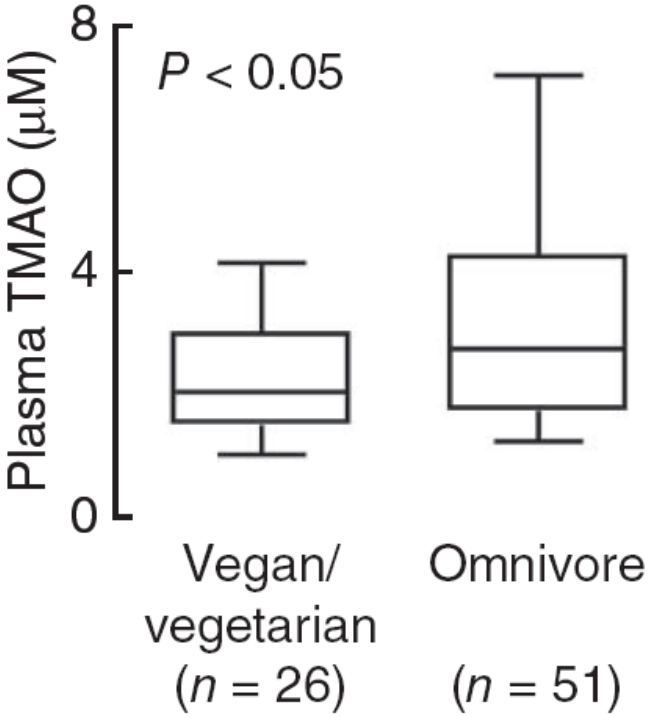
Oral Carnitine is converted to Trimethylamine N-oxide (TMAO)



Koeth R.A., et al., Nature Medicine (2013) PMID:23563705

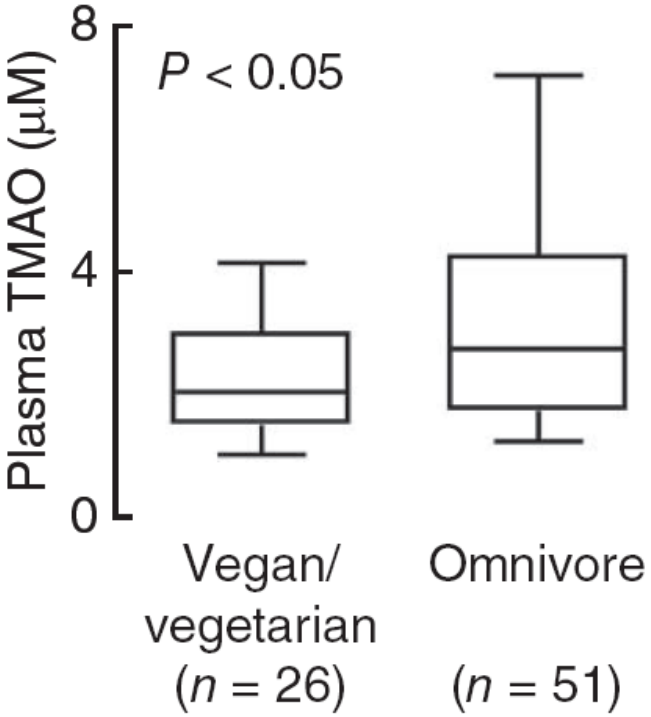
Backhed F., Nature Medicine (2013) PMID: 23652100

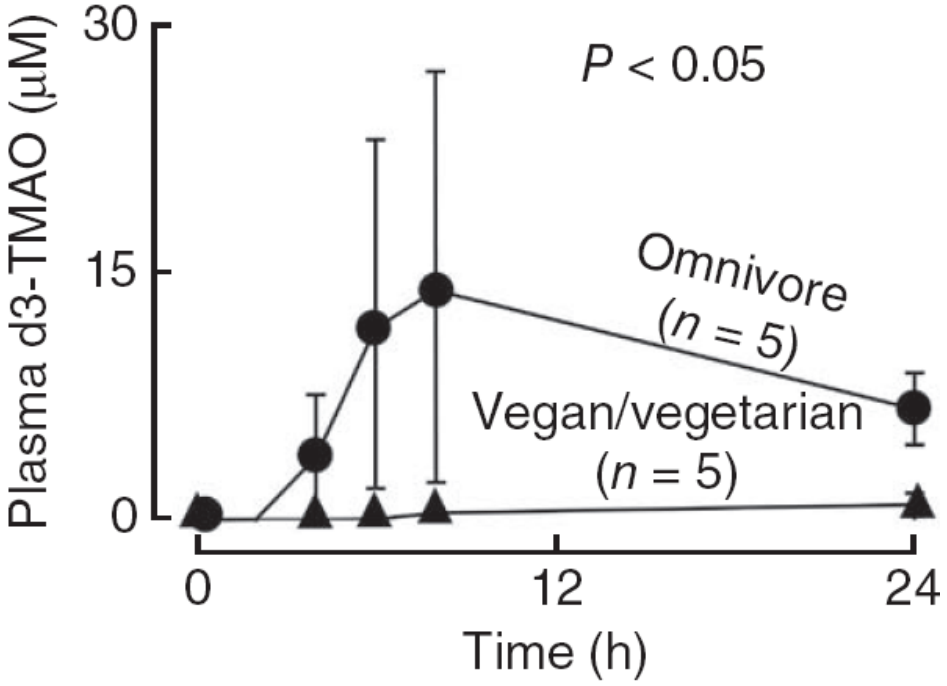
Diet & baseline production of TMAO



Koeth R.A., et al., Nature Medicine (2013) PMID: 23563705

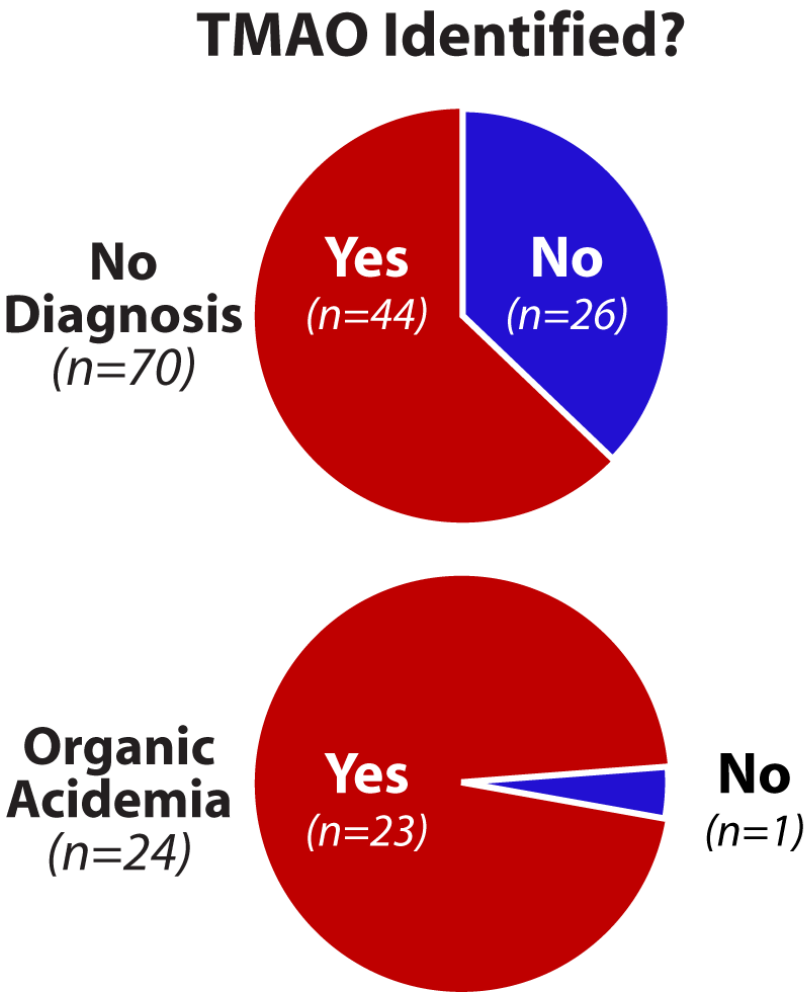
Dietary influence of carnitine-challenge on TMAO production



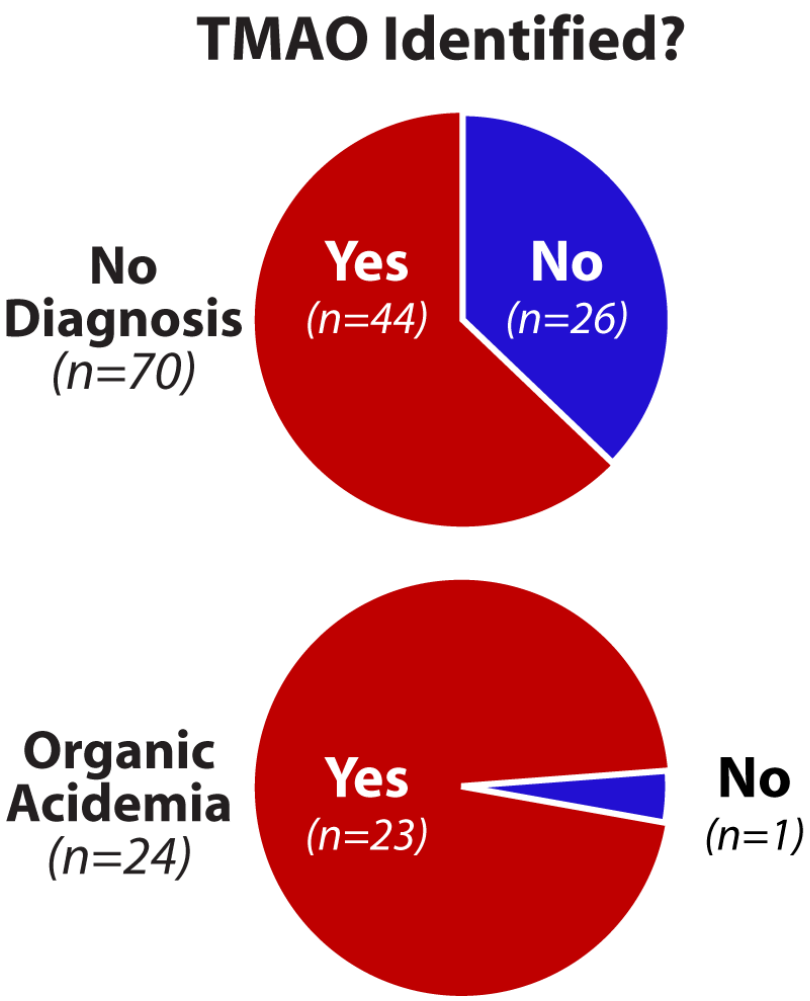


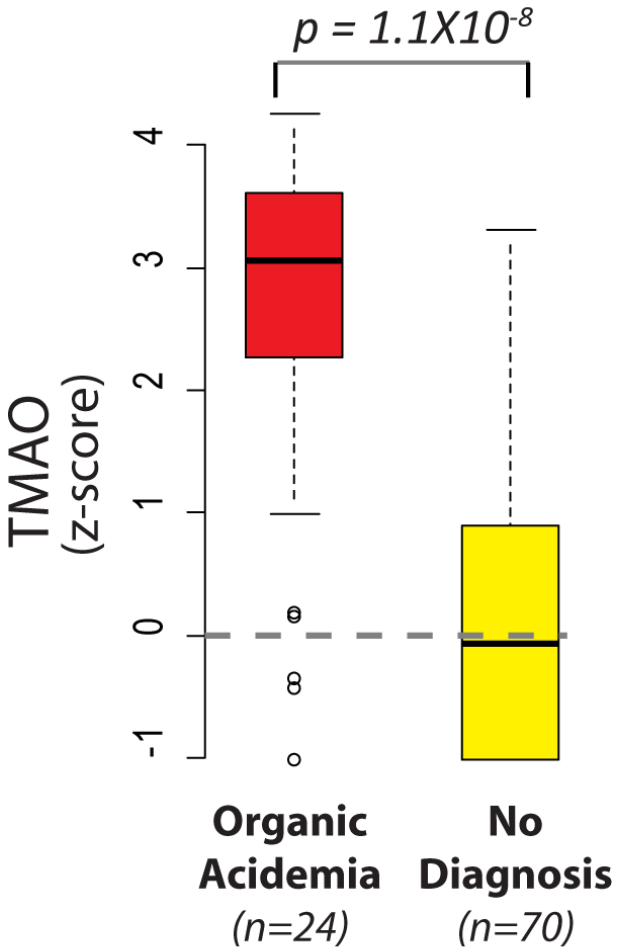
Koeth R.A., et al., Nature Medicine (2013) PMID: 23563705

Plasma TMAO elevations in Global MAPS validation cohort



Plasma TMAO elevations in Global MAPS validation cohort





Meat restriction and oral carnitine supplementation

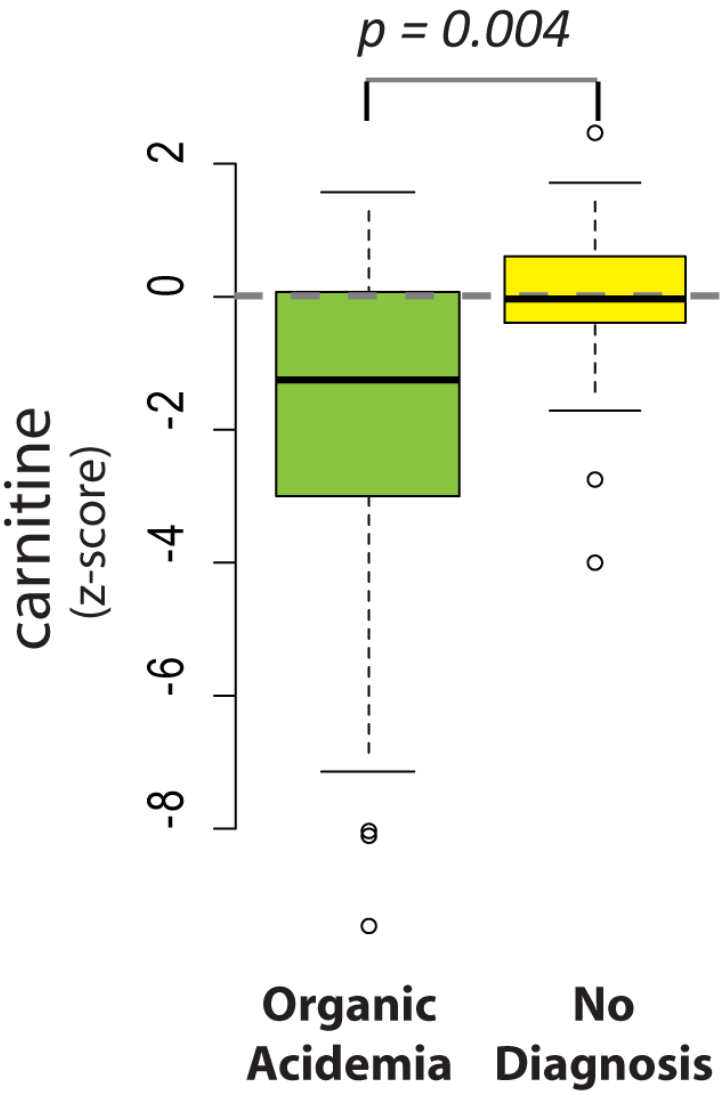
- Clinical notes on 19 of 24 patients
- All on Chronic PO carnitine (range 17-145 mg/kg/day)
- *All highly discouraged from consuming meat*

Meat restriction and oral carnitine supplementation

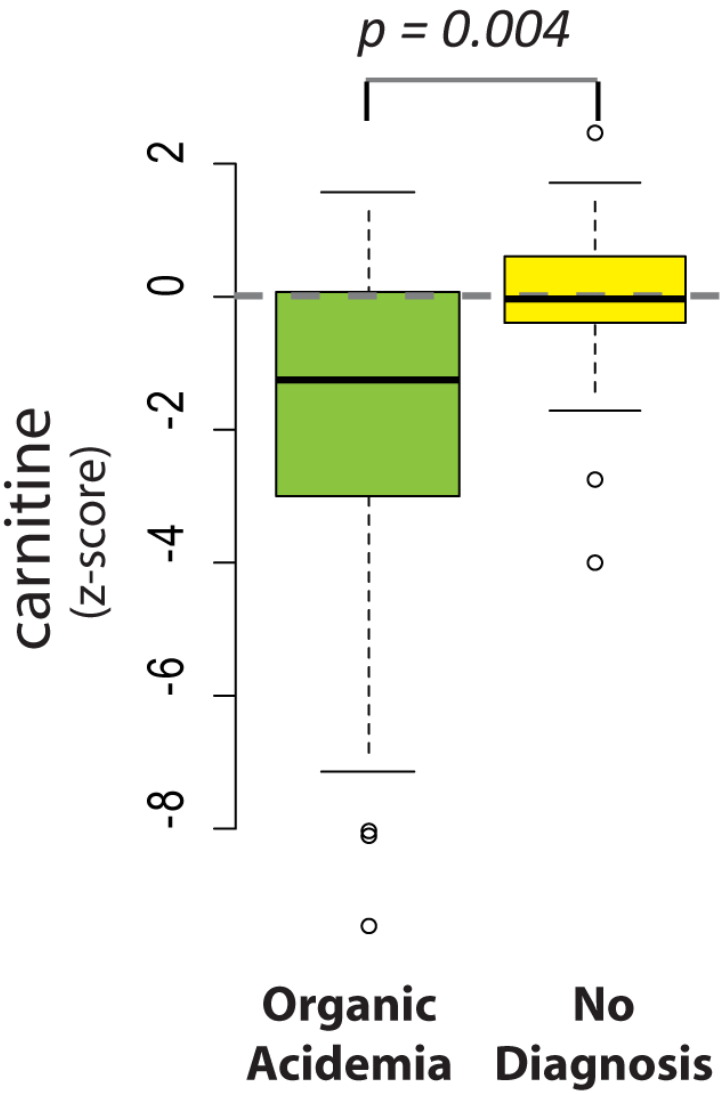
- Clinical notes on 19 of 24 patients
- All on Chronic PO carnitine (range 17-145 mg/kg/day)
- *All highly discouraged from consuming meat*

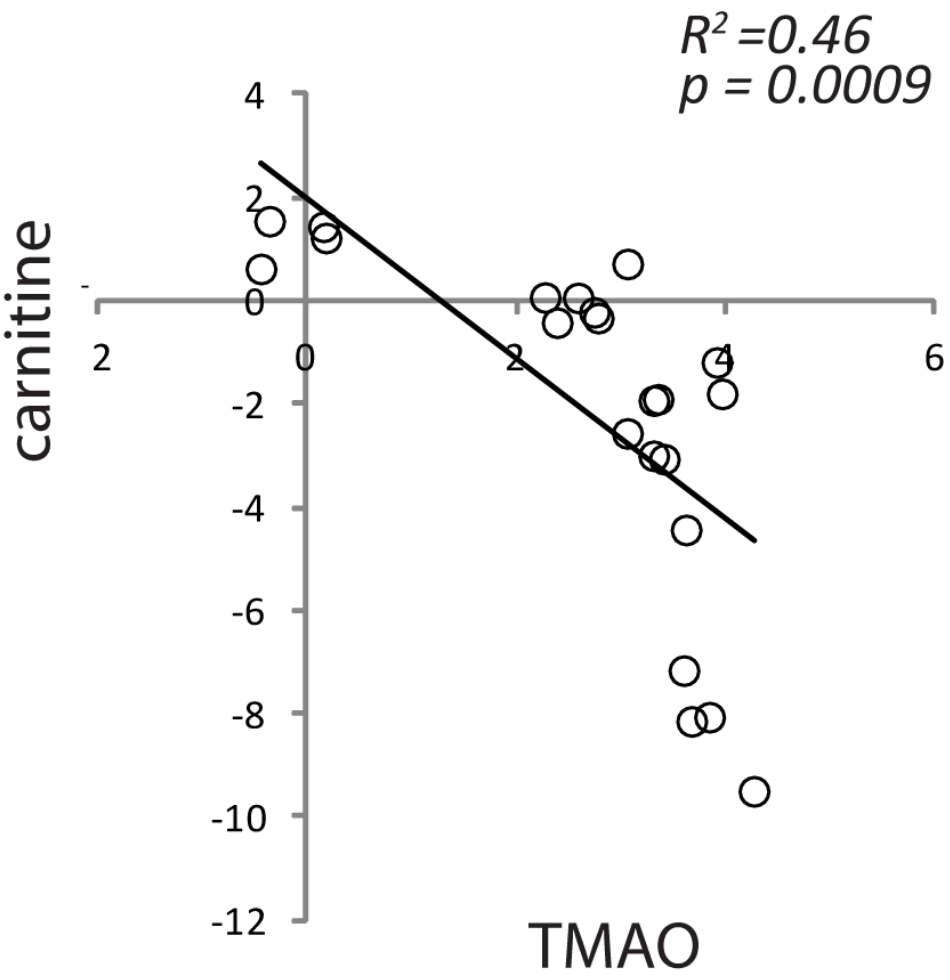
Disorder	3-methylhistidine *(average z-score)*	p value
organic acidemia	-0.70	5.02E-04
urea cycle	-0.73	1.82E-05
pku	-0.57	7.96E-03
no diagnosis	0.00	NA

Plasma Carnitine
is decreased in patients with organic acidemias



Plasma Carnitine is decreased in patients with organic acidemias





TEST REPORTING

Reporting Format

- Analysis of data
- Interpretation provided by laboratory director
- Tables of analytes with Z-score >+2 or <-2
  - Human metabolites
  - Drugs
  - Xenobiotics
  - Dietary
- Analytes categorized by pathway

Global MAPS℠

Global Metabolomic Assisted Pathway Screen℠

635422-1441968

INTERPRETATION:

We understand this is a 3 year old male with developmental delay, ocular motor apraxia, and seizures. Molecular testing revealed a de novo 12q11.2 duplication (361 Kb). This region contains 8 genes: RNASE7, RNASE8, SOLO, SNF219, HNRNPC, RPGRIP1, SUPT16H, and CHD8. His family history includes two brothers, ages 14 months and 5 years old, who are also affected. The 14 month old has a similar clinical presentation, while the 5 year old suffered from delayed speech development which has since resolved. In addition, his 56 year old maternal grandmother has a history of Crohn's disease and Type 2 diabetes. Analysis of plasma amino acids, urine organic acids, plasma acylcarnitines, and plasma creatine/guandinoacetate were negative. Plasma was submitted for analysis of perturbations in metabolic pathways that may be relevant to these clinical symptoms and molecular findings.

All significant analytes are listed in Tables 1-4. N6-succinyladenosine is significantly elevated. Accumulation of this compound is associated with adenylosuccinase deficiency (OMIM 103050), a disorder of de novo purine synthesis. Suggest urine purine analysis for confirmation of this finding. Needs clinical correlation.

Results are dependent upon sample quality, diet, medications, and other physiological conditions. Use of special diets or supplements may mask metabolic abnormalities. Clinical indications, medications, and diet are required for proper interpretation. An expanded report is available upon request.

RESULTS:

1. Significantly altered analytes (z-score >2 or <-2) possibly related to the patient's phenotype

Analyte	z-score '	Superpathway	Subpathway	HMDB ID ^
N6-succinyladenosine	**7.3**	Nucleotide	Purine Metabolism, Adenine containing	HMDB00912
2-palmitoyl-GPE* (16:0)*	**3.1**	Lipid	Lysolipid	
phenylacetylglycine	**2.4**	Amino Acid	Phenylalanine and Tyrosine Metabolism	HMDB00821
1-dihomo-linolenoyl-GPE (20:3n3 or 6)*	**2.4**	Lipid	Lysolipid	
orotate	**2.3**	Nucleotide	Pyrimidine Metabolism, Orotate containing	HMDB00226
dimethylglycine	**2.3**	Amino Acid	Glycine, Serine and Threonine Metabolism	HMDB00092
isovalerylglycine	**2.0**	Amino Acid	Leucine, Isoleucine and Valine Metabolism	HMDB00678
tyrosine	**2.0**	Amino Acid	Phenylalanine and Tyrosine Metabolism	HMDB00158
butyrylcarnitine (C4)	**-2.2**	Lipid	Fatty Acid Metabolism (also BCAA Metabolism)	HMDB02013
3-methoxytyrosine	**-4.0**	Amino Acid	Phenylalanine and Tyrosine Metabolism	HMDB01434

Summary Global MAPS

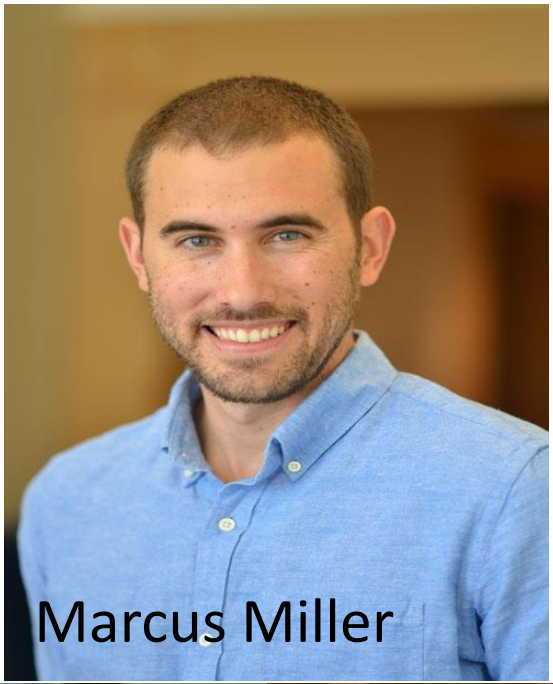
- Identifies all common IEMs studied to date screened on PAA/UOA/ACP
- Screening tool for undifferentiated phenotypes
  - Developmental Delay/Intellectual disability/Hypotonia
  - Seizures (non-specific)
- Does not replace PAA, UOA, etc. for diagnostic testing or management nor can it detect large molecules (MPS, CDG)
- Validate DNA results and can identify IEMs for which no biochemical testing available (Citrate transporter deficiency)
- Potential to diagnose neurotransmitter disorders on a plasma specimen (AADC & GABA transaminase)
- Discovery of Novel Biomarkers for IEMs (PBDs)
- Understand effects of therapies in IEMs

BAYLOR GENETICS

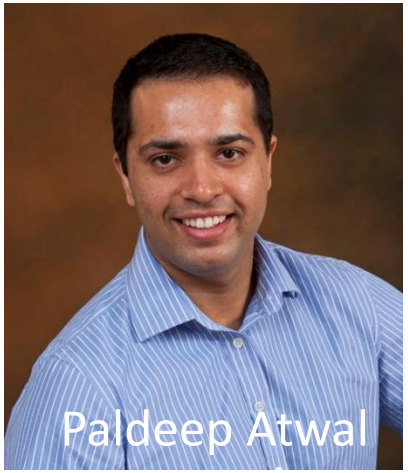

Michael Wangler

Baylor College of Medicine
GIVING LIFE TO POSSIBLE


Sarah Elsea


Marcus Miller


Taraka Donti


Paldeep Atwal


Qin Sun


Adam Kennedy


Leroy Hubert

METABOLON


Lisa Emrick


Bret Bostwick

What does Global MAPS test for?

- Disorders of amino acid metabolism: plasma amino acids $220
- Organic acidemias: urine organic acids and acylglycines $500
- Purine disorders: urine purine panel $260
- Pyrimidine disorders: (urine pyrimidine panel $280
- Neurotransmitter disorders: plasma thymidine; urine pyrimidines; plasma/urine creatine & guanidinoacetate; **csf**: succinyladenosine, 5HIAA, HVA, 3OMD, lactate, & glucose $1330 (exclusive of LP costs)
- Cholesterol Metabolism & PBDs $850
- Creatine disorders: plasma/ urine creatine and guanidinoacetate $280
- Bile acid disorders: plasma/urine bile acids $917
- Urea cycle disorders: plasma amino acids & urine orotic acid $300
- Fatty acid oxidation disorders: acylcarnitine profile, acylglycines, & urine organic acids $770
- Certain mitochondrial disorders:
  - MNGIE: plasma thymidine $200

Total cost: > $5000!