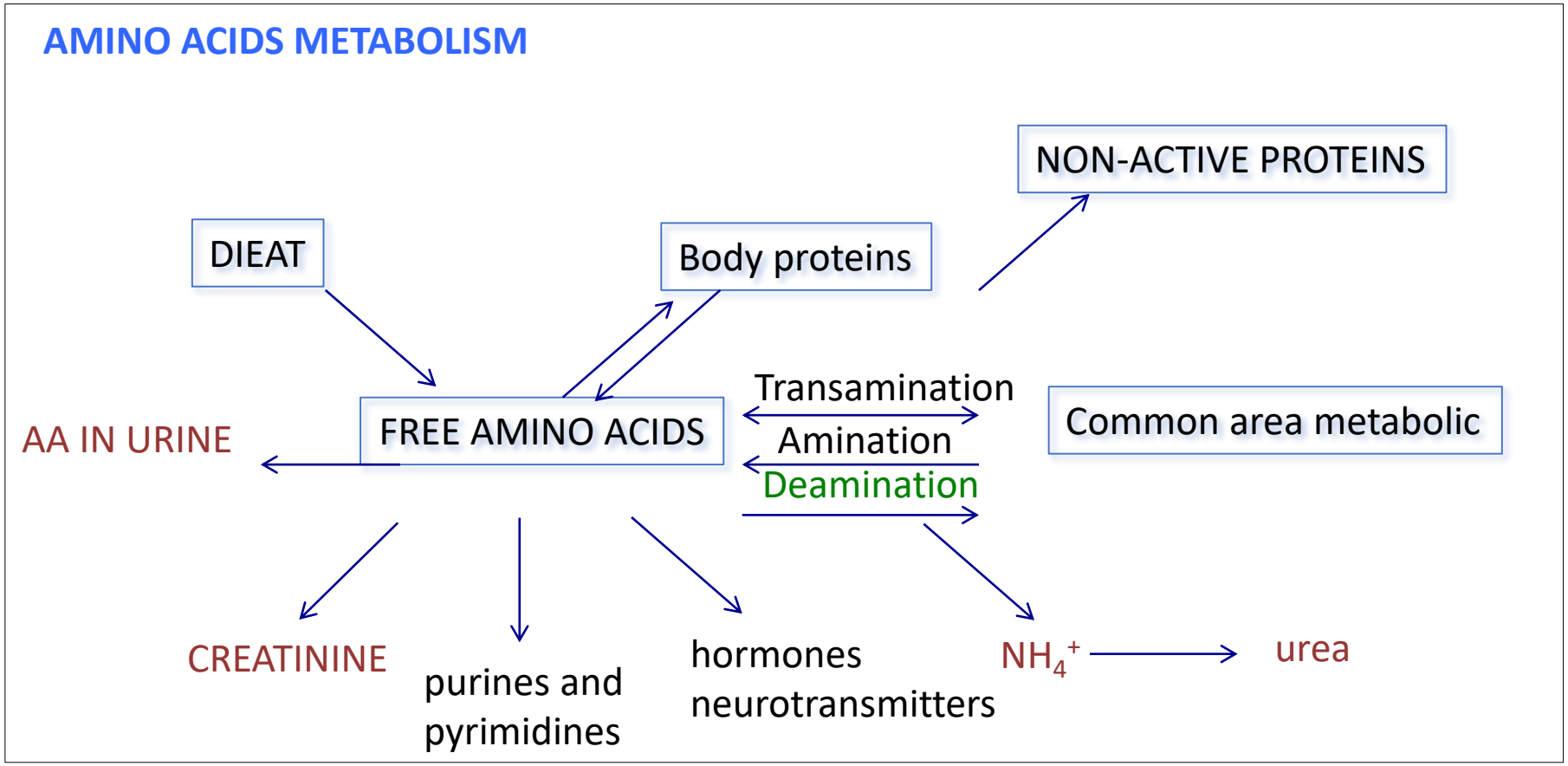
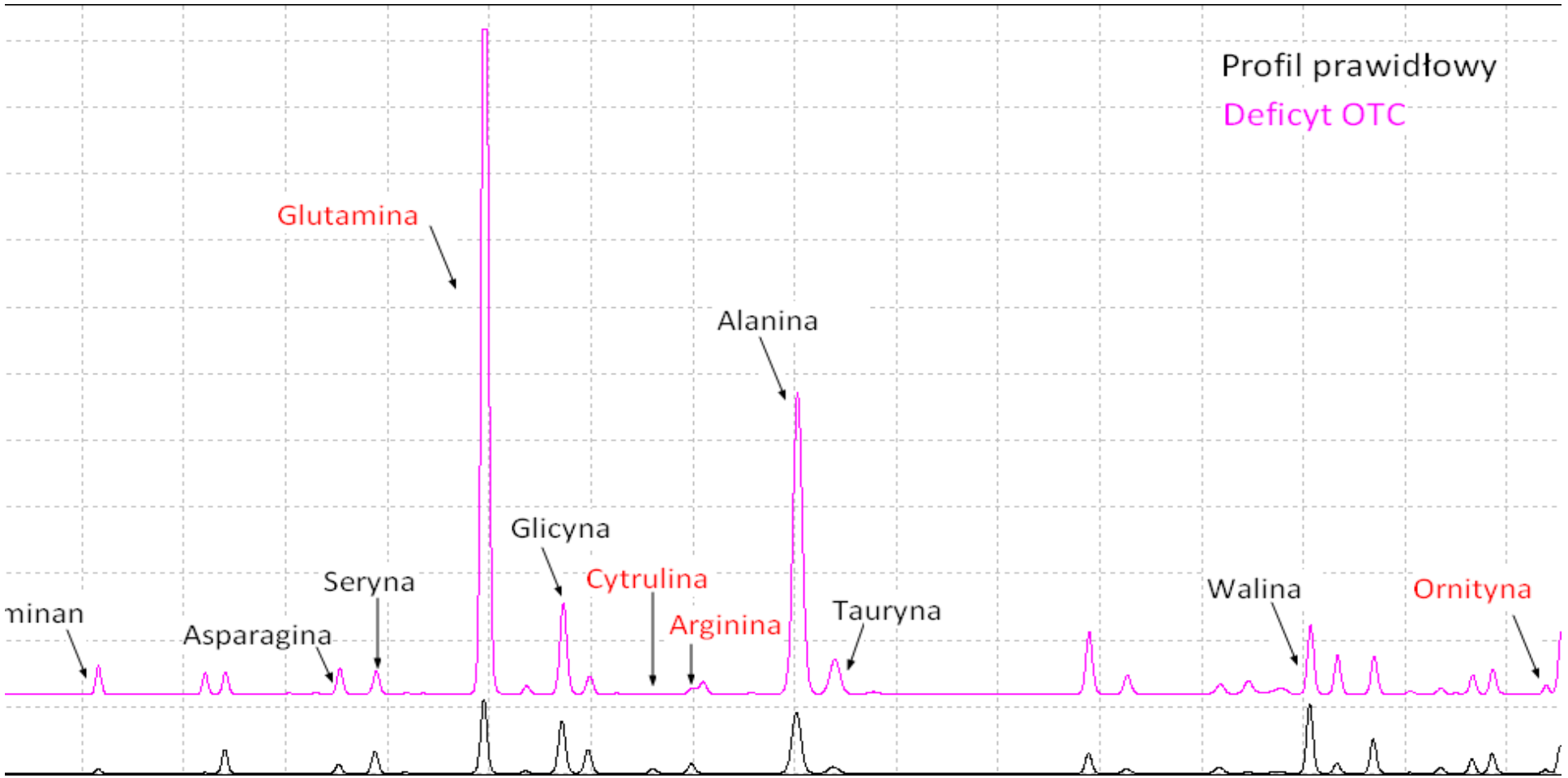
Diagnosis of Inborn errors of metabolism – follow-up

Katarzyna Kuśmierska

During the growth phase, the balance between amino acids and proteins is shifted in favor of proteins, which means that protein synthesis processes prevail over protein breakdown.

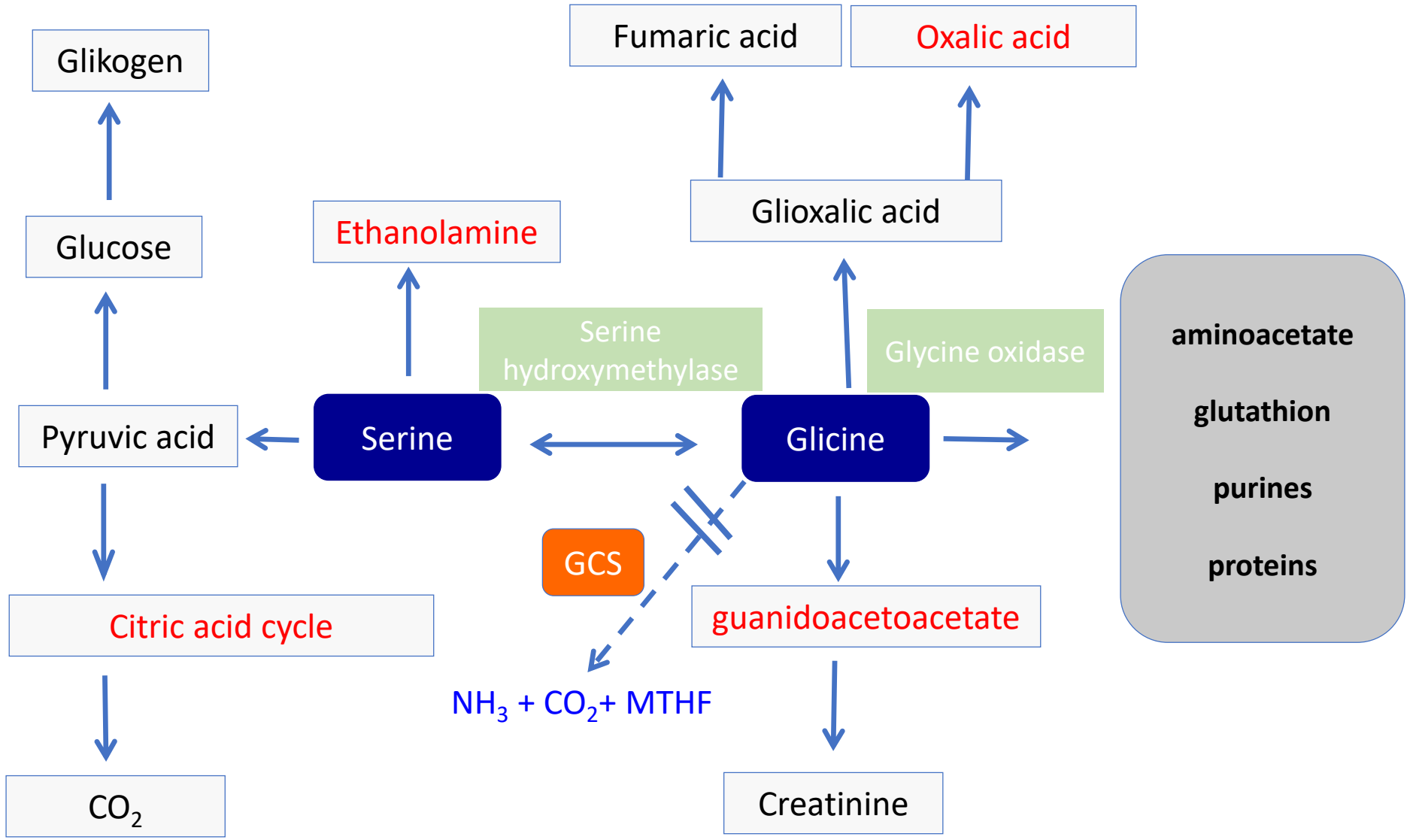



Profil prawidłowy
Deficyt OTC
Glutamina
Alanina
Glicyna
Seryna
Cytrulina
Arginina
Tauryna
Walina
Ornityna
Asparagina
minan

Def. OTC

Amino acids	Pacjent 1	Pacjent 2	Ref. range
Serine	88	107	68 -160
Homocysteine	5,0	15	3,3 – 8,3
Glutamine	412	740	396 – 740
Glicine	166	296	123 – 319
Threonine	67	33	102 - 190
Citruline	15	7,7	16 – 46
Arginine	48	40	46 – 128
Alanine	137	294	182 – 552
Taurine	22	17	6 – 126
Tyrosine	37	28	35 – 84
Valine	124	103	144 – 269
Methionine	18	16	12 – 32
Isoleucine	17	29	34 – 84
Ornitine	17	30	27 – 98
Leucine	75	55	78 – 160
Proline	72	115	88 - 290

Glicine and folic acids metabolism



Patient with non-ketotic hyperglicinemia

Aminokwasy	*Patient* plasma	Patient CSF	Ref. Range plasma	Ref. Range CSF
Serine	123	53	68 -160	21 - 63
Homocysteine	5,0	ND	3,3 – 8,3	ND
Glutamine	467	592	396 – 740	352 - 680
Glicine	456	112	123 – 319	3 - 9
Threonine	112	41	102 - 190	14 - 45
Citruline	15	2	16 – 46	1 - 6
Arginine	49	23	46 – 128	13 – 25,5
Alanine	237	42	182 – 552	13 – 48
Taurine	29	6	6 – 126	4 - 14
Tyrosine	43	11	35 – 84	8 - 14
Valine	187	19,1	144 – 269	9 - 19
Methionine	23	4,1	12 – 32	1 – 5
Isoleucine	45	3,5	34 – 84	2,5 – 6,5
Ornitine	78	3	27 – 98	2,4 - 9
Leucine	98	12	78 – 160	6,5 - 16
Proline	134	0,3	88 - 290	<0,5

Amino acids metabolism disorders

Amino acids	Patient (Citrulinemia)	Patient (Tyrosinemia)	Ref. range
Serine	79	111	90 -221
Homocysteine	3,8	5,4	3,3 – 8,3
Glutamine	382	490	178 – 740
Glicine	86	225	100 – 324
Threonine	109	109	76 - 192
Citruline	**150**	20	6 – 50
Arginine	30	55	18 – 125
Alanine	182	178	144 – 418
Taurine	40	57	18 - 162
Tyrosine	45	**501**	32 - 98
Valine	84	155	79 – 273
Methionine	18	25	9 – 51
Isoleucine	32	39	28 – 92
Ornitine	26	20	9 - 123
Leucine	66	90	53 – 164
Proline	93	94	53 - 254

Amino acids metabolism disorderskwasów

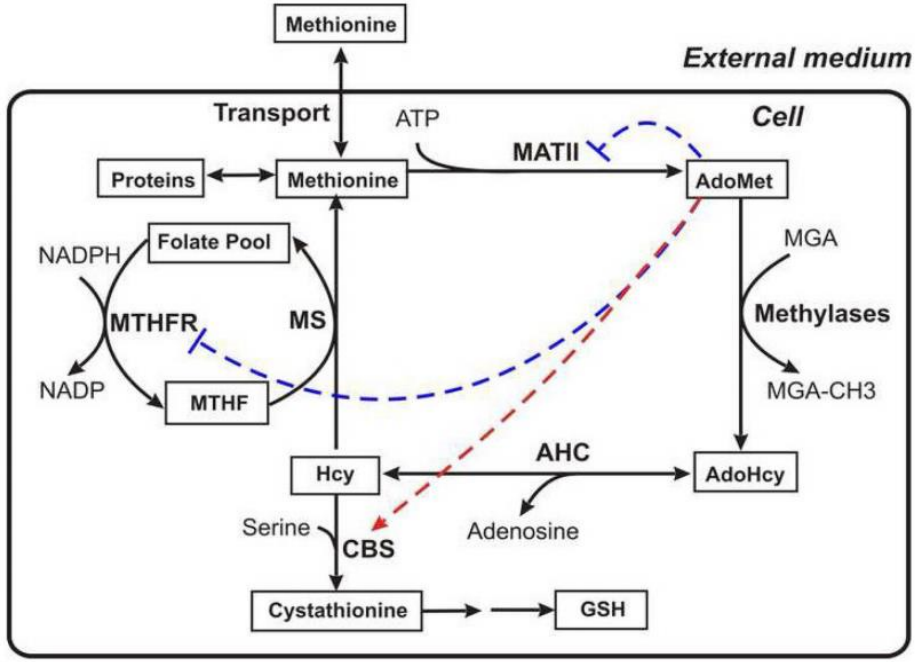
Amino acids	Patient (MMA)	Patient (PA)	Ref. range
Serine	137	148	90 -221
Homocysteine	4,4	7	3,3 – 8,3
Glutamine	301	379	178 – 740
Glicine	314	709	100 – 324
Threonine	363	97	76 - 192
Citruline	14,1	24	6 – 50
Arginine	45	45	18 – 125
Alanine	515	430	144 – 418
Taurine	50	52	18 - 162
Tyrosine	25	59	32 - 98
Valine	105	91	79 – 273
Methionine	22	22	9 – 51
Isoleucine	52	25	28 – 92
Ornitine	14	44	9 - 123
Leucine	74	53	53 – 164
Proline	141	120	53 - 254

„1-carbon metabolism”

- shows that the most important processes occurring in the cell are based on the transfer of a single carbon atom from one molecule to another.
- a molecule consisting of one carbon atom and three hydrogen atoms, which is the main element of the process, is responsible for such transport

metylation – methyl group *(–CH3)*

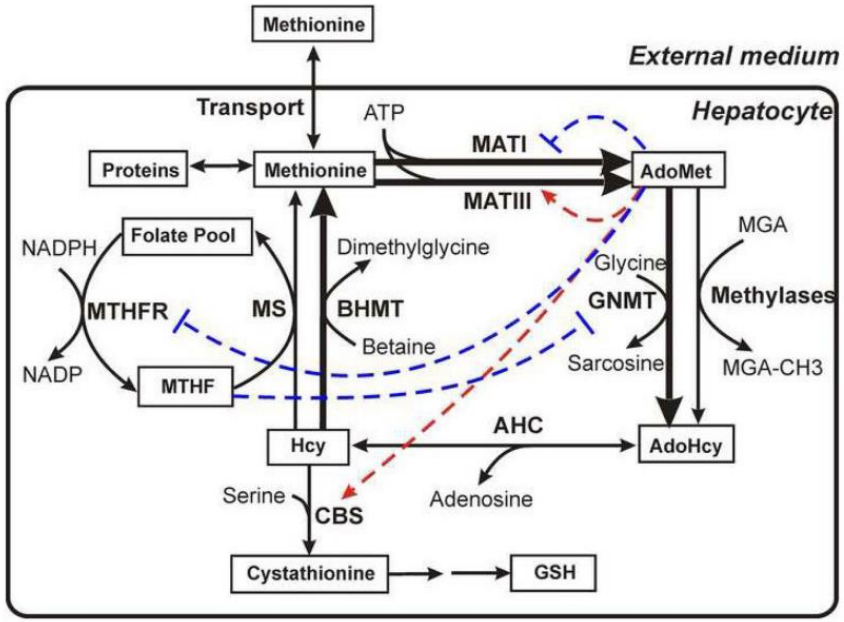
The basic amino acids involved in the transport of methyl groups are **sulfur amino acids**.



SAM:
- activates CBS
- inhibits MAT II
- inhibits MTHFR

SAM:
- activates CBS
- activates MAT III
- inhibits MAT I
- inhibits MTHFR

MTHF:
- inhibits GNMT



Sulfur amino acids

- Methionine, Homocysteine, Cystathionine, Cysteine, Taurine, Sulfocysteine

- Disorders of sulfur amino acid metabolism include enzyme deficiency :

- on the **transsulfuration** pathway, which involves the conversion of sulfur from methionine through homocysteine and cysteine into sulfate

- in the homocysteine to methionine **remethylation** pathway.

- in the **transmethylation** and synthesis pathway of SAM and SAH..

Methionine and cistine

The metabolism of methionine and cysteine in body tissues determines the concentration of several metabolites with different biological activities

SAA	MAT I/III (1)	MAT I/III (2)	Ref. range
Methionine	632	212	16 – 29
Sarcosine	2,06	0,96	0,91 – 2,24
SAM	0,08	0,102	0,048 – 0,072
SAH	0,021	0,014	0,01 – 0,021
Hcy	23,9	9,7	6,9 – 13,0
Cystathionine	0,258	0,206	0,09 – 0,29
Cysteine	199	195	204 – 292
Glutathion	6,64	4,43	3,9 – 8,9
Hypotaurine	0,32	0,46	0,49 – 1,12
sulphites	0,029	0,091	0,14 – 0,62
Thiosulphate	0,029	0,016	0,43 – 2,93
Dimethylglycine	12,4	5,14	2,5 – 4,7
Betaine	405	89,4	26,5 – 50,2
Choline	11,7	13,4	5,5 – 9,5

Zaburzenia metabolizmu aminokwasów siarkowych

Amino acids	Patient1 (Homocystynuria)	Patient2 (Homocystynuria)	Ref. V.
Serine	137	72	90 -221
Homocysteine	738	208	3,3 – 8,3
Glutamine	641	515	178 – 740
Glicine	502	260	100 – 324
Threonine	249	139	76 - 192
Citruline	31	33	6 – 50
Arginine	121	61	18 – 125
Alanine	376	353	144 – 418
Taurine	165	37	18 - 162
Tyrosine	59	49	32 - 98
Valine	142	165	79 – 273
Methionine	196	185	9 – 51
Isoleucine	64	34	28 – 92
Ornitine	55	41	9 - 123
Leucine	95	81	53 – 164
Prolina	101	179	53 - 254

Organic acids profile in urine

- Organic acids are intermediates and end products in metabolic processes.

- Organic acid analysis in urine useful for:

- detection of malfunctions in the metabolism of:

a/ amino acids

b/ lipids

c/ carbohydrates

d/ purines/pyrimidines

e/ neurotransmitters

- Follow-up and therapy monitoring

Urinary organic acid profile also includes **exogenic substances from:**

- Food components: caffeine, sweetener
- Drug metabolites: valproate, ethosuximid, aspirin
- Skin care products: glycerol
- Bacterial metabolism products: succinate, uracil, 2-OH-glutarate
- Artefacts from sample preparation: e.g. waste products of
- pentafluorobenzylhydroxylamine

- Interpretation of Organic Acid Profiles
- Search for
  - characteristic pattern of abnormalities
  - diagnostic key metabolites
- Limitations
  - Overlap of diagnostic metabolites with other compounds
    - Severe metabolic decompensation
    - Ketosis
  - Only slight elevations of diagnostic metabolites
    - e.g. defects in cobalamine metabolism

Interpretation of Organic Acid Profails

- Exact clinical description is helpful and important

► Direct search for specific metabolites (e.g. hexanoylglycine)

► Organic acid pattern could be normal if urine is not taken during acute crisis

► Abnormal pattern could result from diseases other than IEM (e.g. neuroblastoma)

- Information about medication

► Possible overlap of endogenous metabolites and drug metabolites

► “Some Phenomenon”: 4-hydroxybutyric acid:

- Information about special diet

✓MCT feeding: could result in an organic acid pattern similar to ß-oxidation defects (odd-numbered dicarboxylic acids like sebacic acid, 5-hydroxyhexanoic acid, 7-hydroxyoctanoic acid)

Interpretation - Pitfalls

Glutaric aciduria type 1 :

- 3-hydroxyglutaric acid is difficult to separate from 2- hydroxyglutaric acid
- Only small amounts of glutaric acid in “low excretors”

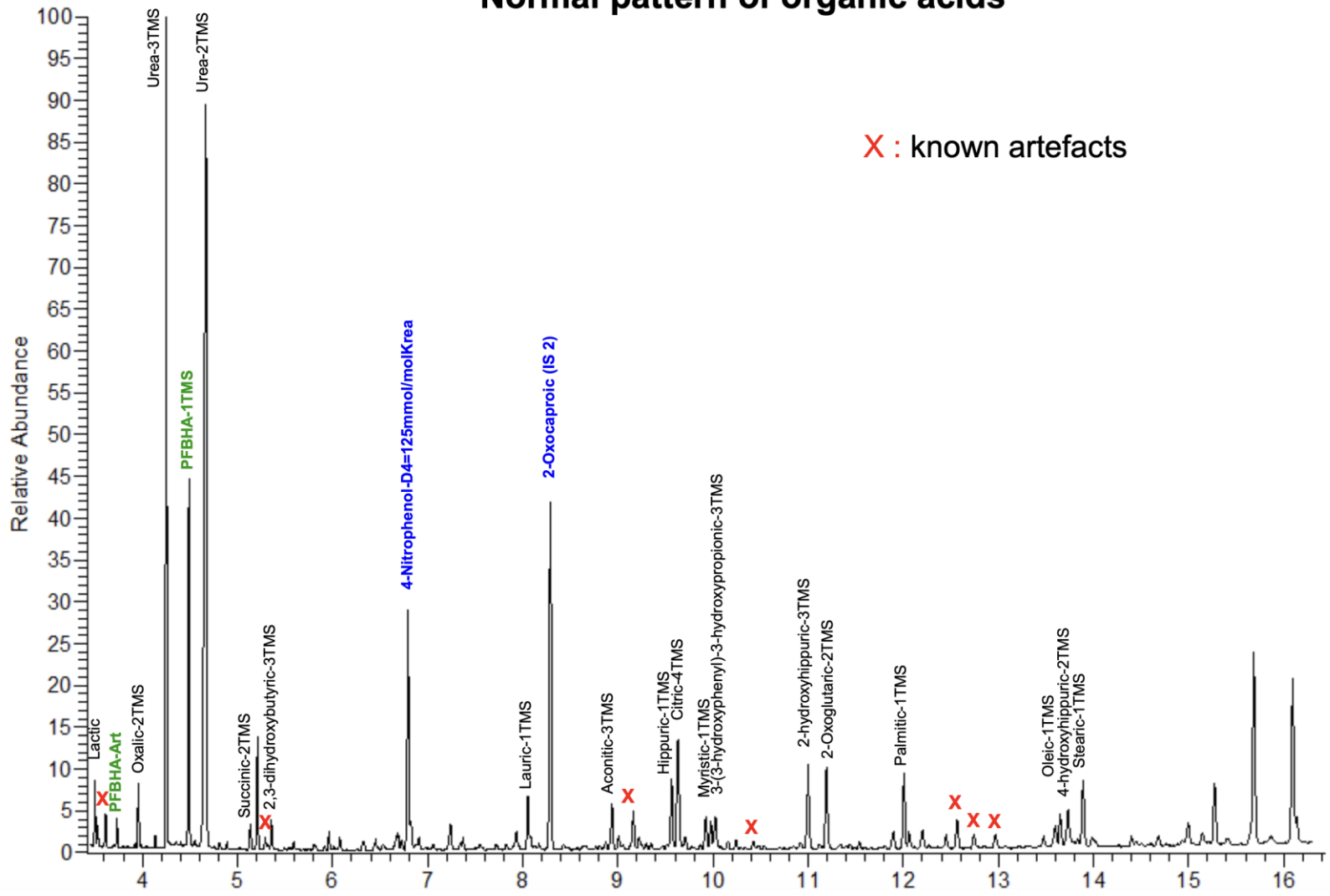
Tyrosinemia type 1:

- Increased phenolic acids also seen in severe liver disease (but no succinylacetone!)
- N-acetyltyrosine is contained in i.v. amino acids
- Succinylacetone is only present in small amounts in urine

SSADH deficiency :

- 4-hydroxybutyric acid could be masked by a huge urea peak

Normal pattern of organic acids



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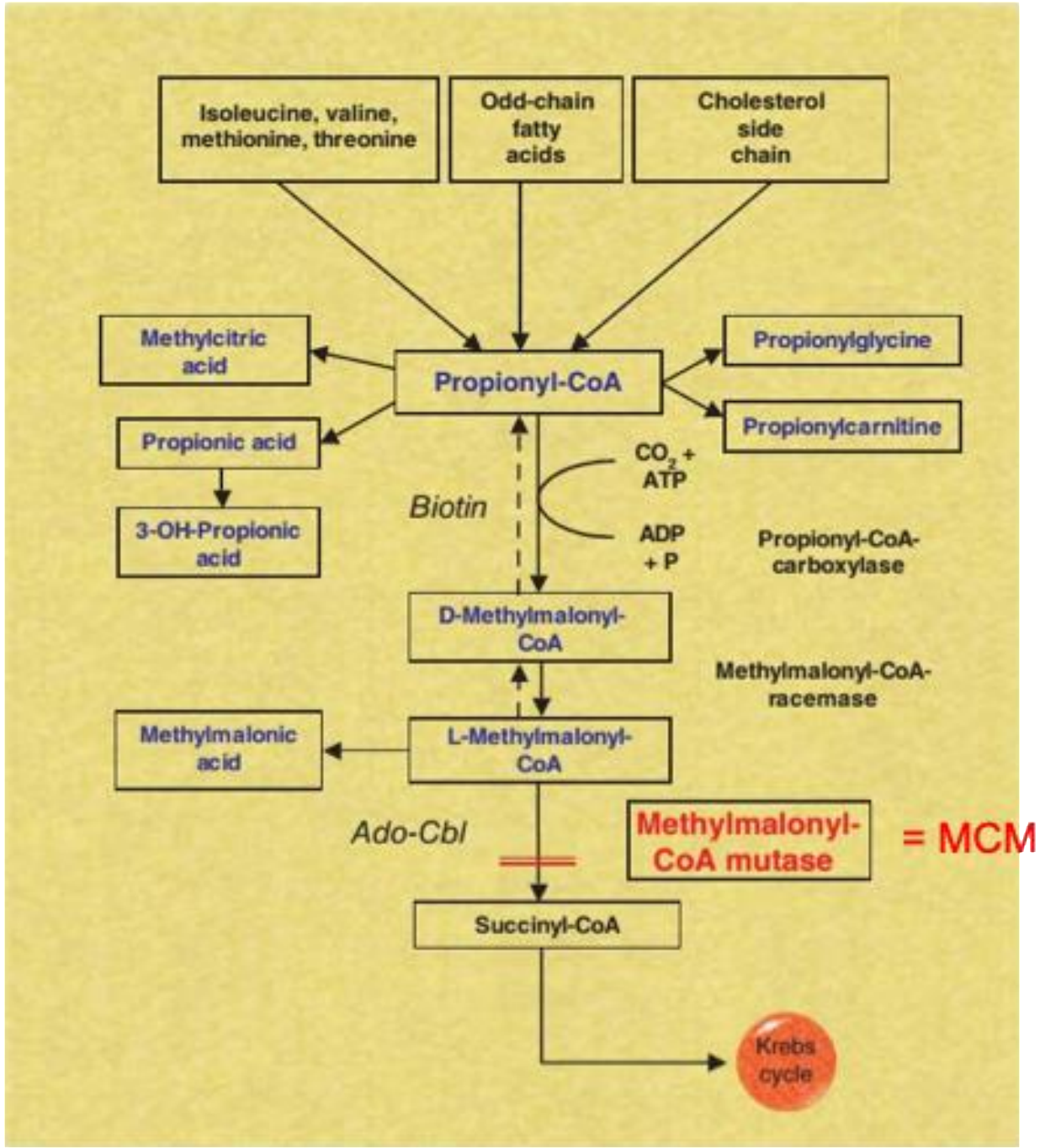
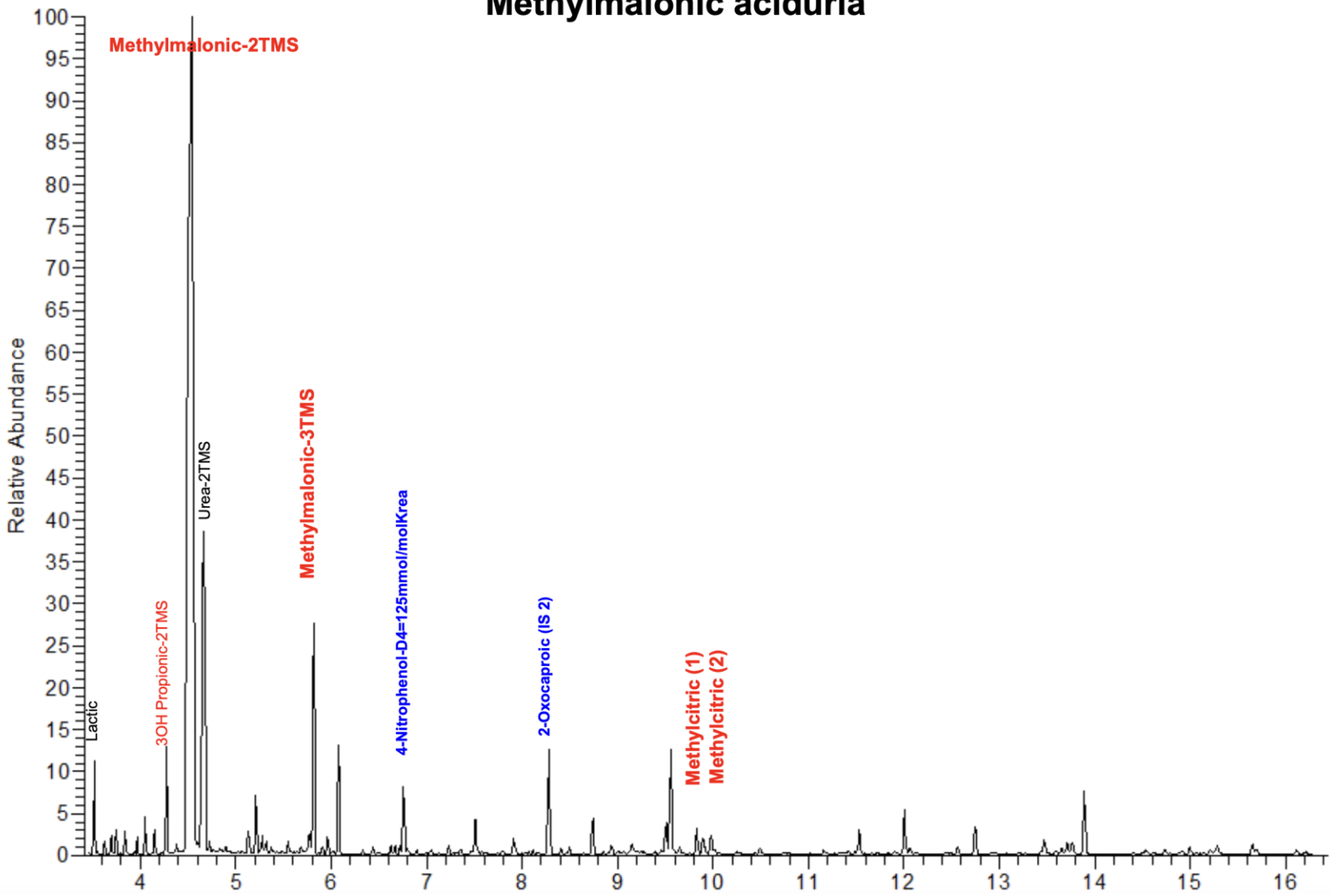


Hoffmann GF, Burlina A, Barshop BA; Organic acidurias In: Pediatric Endocrinology and Inborn Errors of Metabolism, Sarafoglou K (ed), sec ed. 2017, McGraw-Hill

Methylmalonic aciduria



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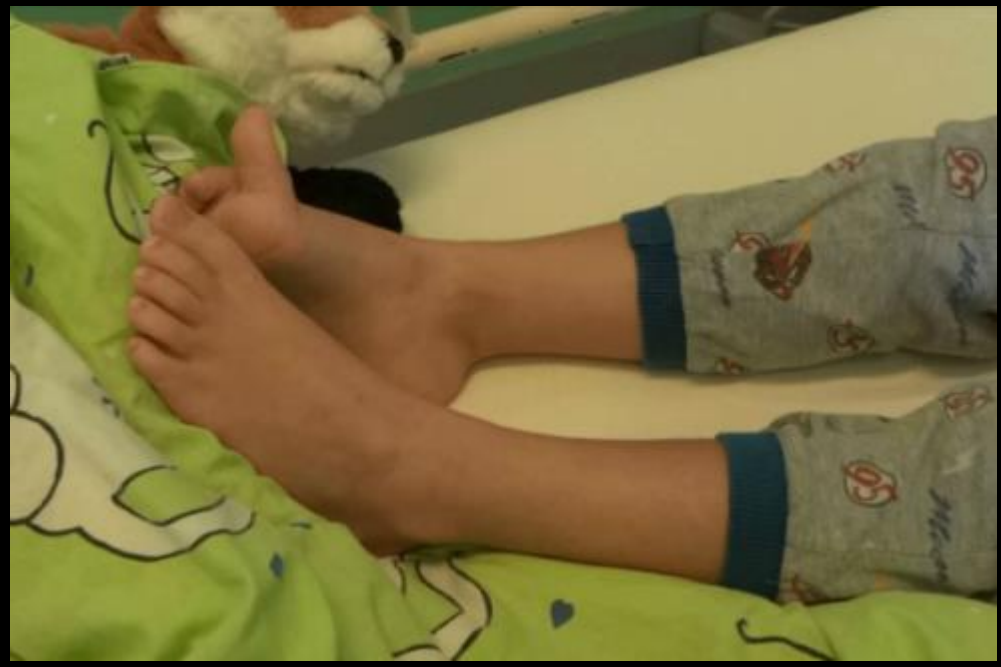
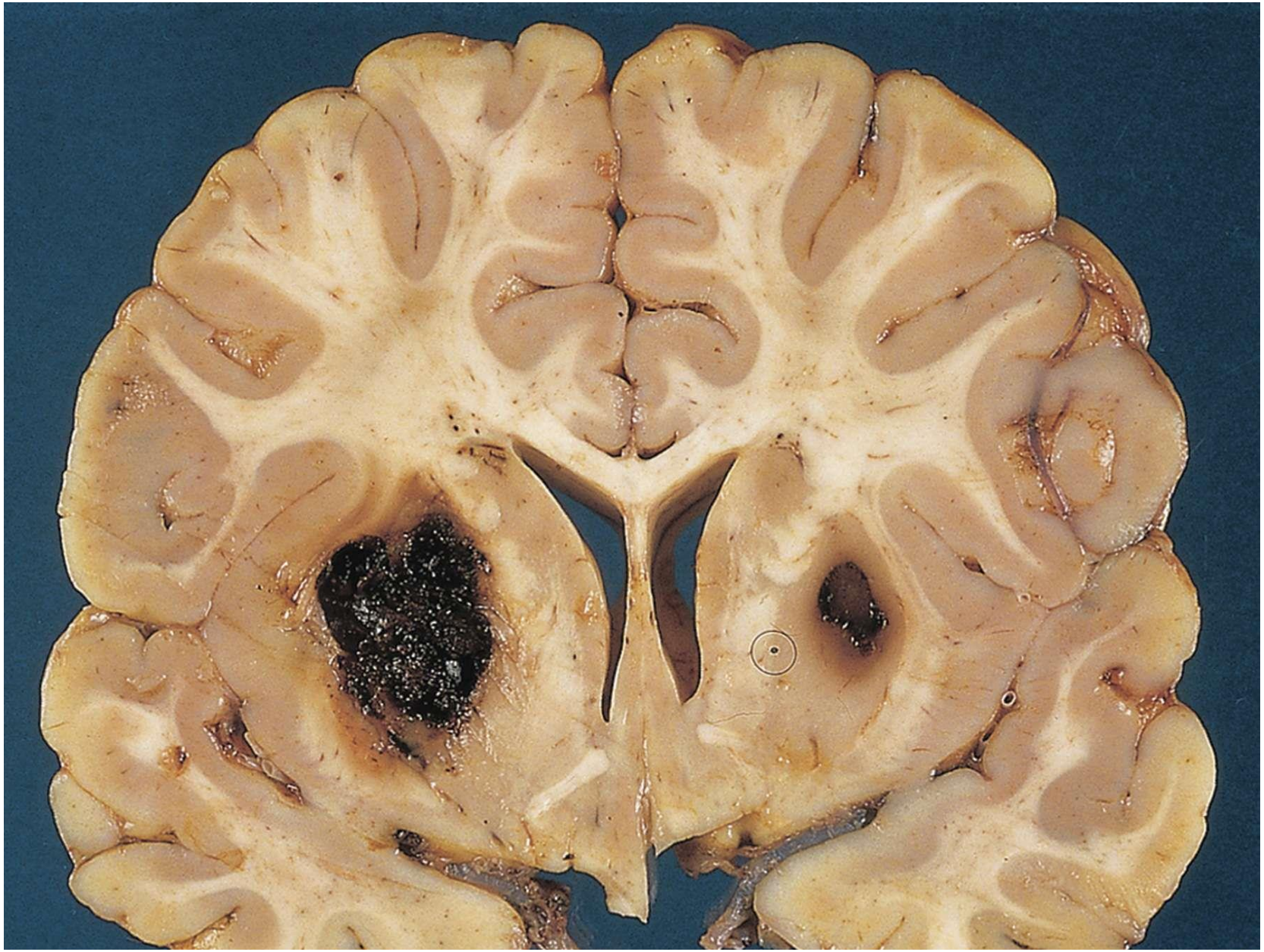
METHYLMALONIC ACIDURIA

metylomalonyl-CoA MUTASE DEFICIENCY

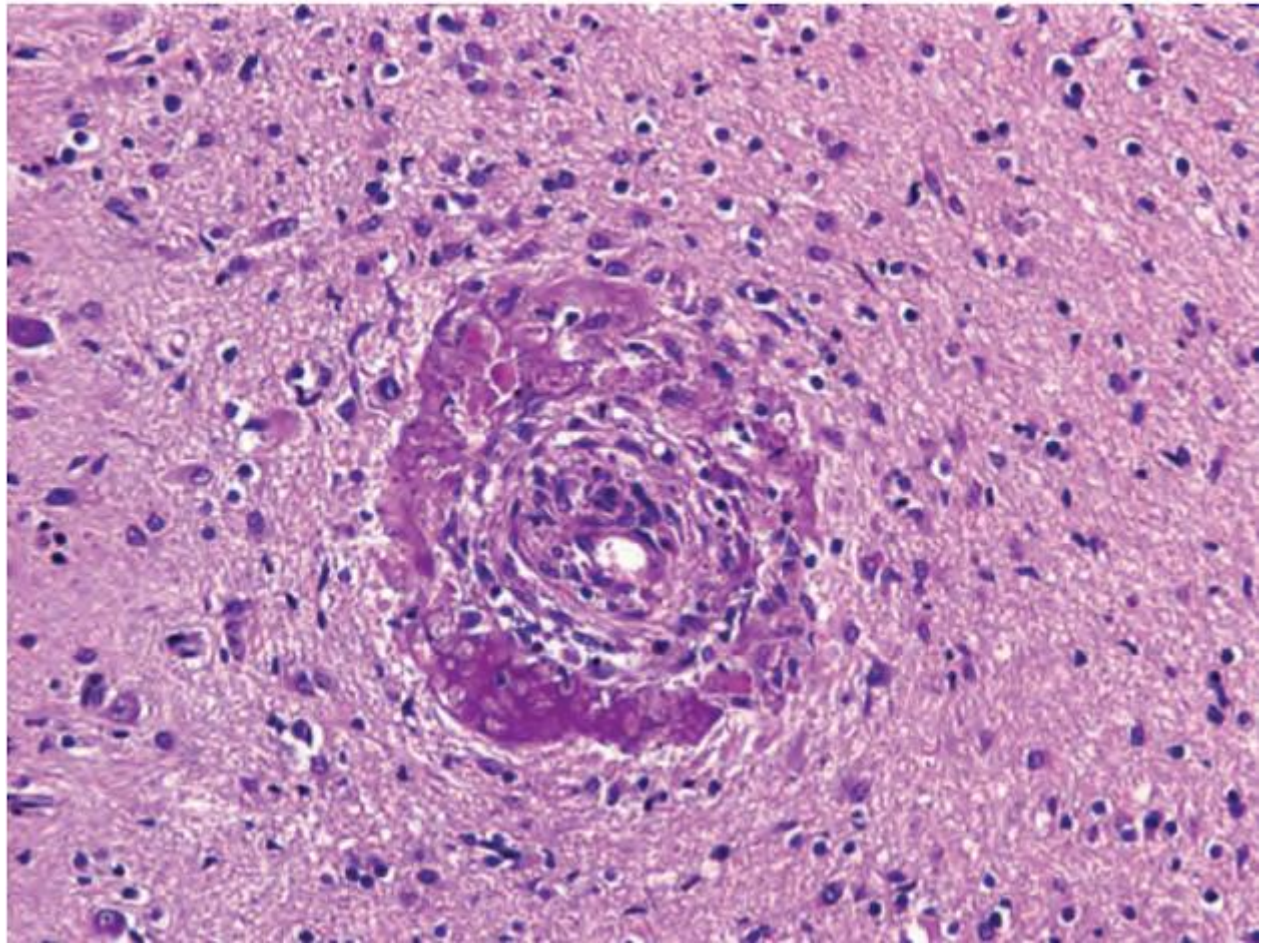


INTOXICATION SYNDROME
METABOLIC DECOMPENSATION
(METABOLIC RIFICATION)



MMA – BILATERAL BLEEDING SHEL?

Greenfield's Neuropathology 2008

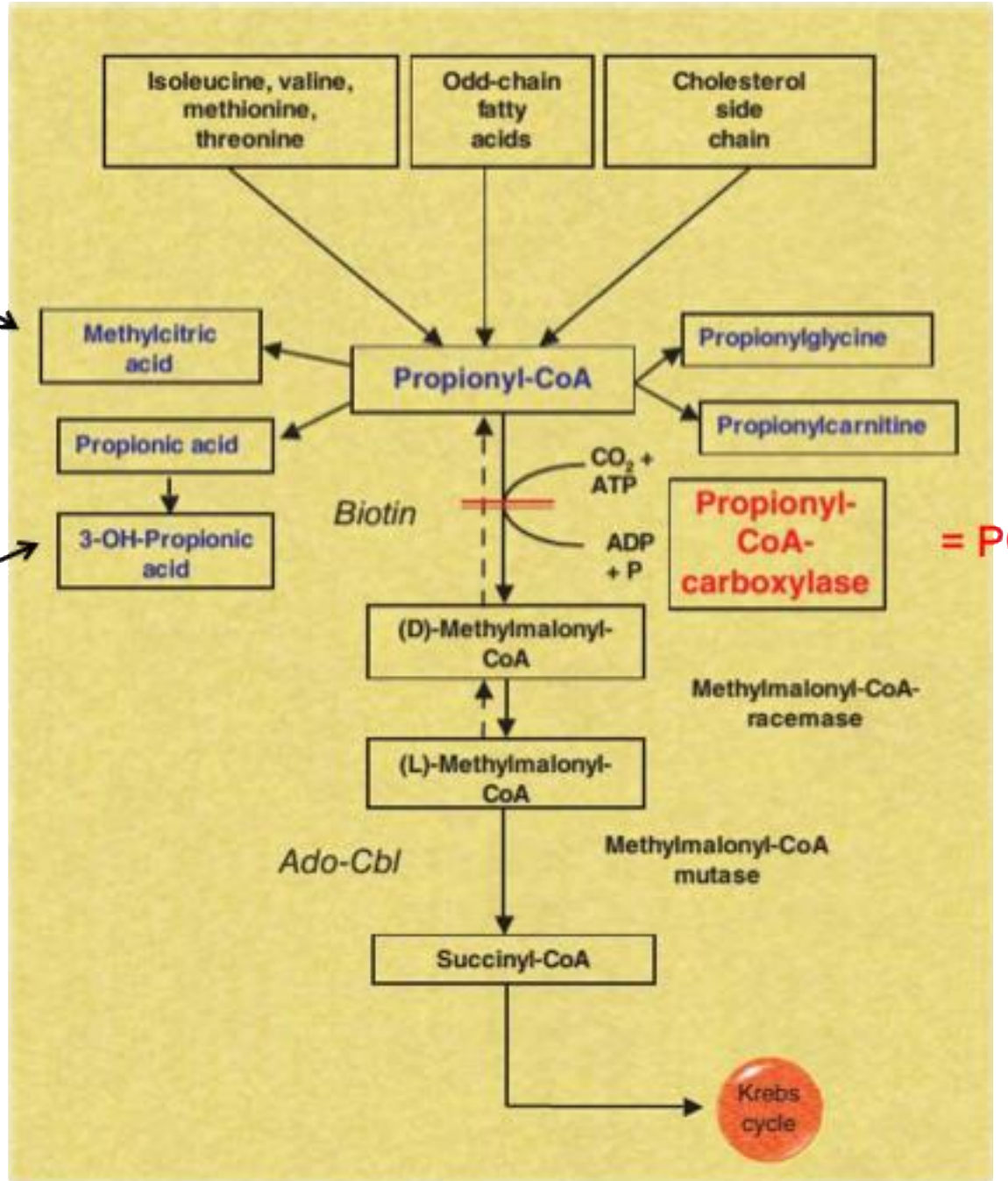


METYLMALONIC ACIDURIA- ANGIOPATHY WITH ENDOTHELIAL PROLIFERATION, INCREASED ENDOTHELIAL PERMEABILITY

Developmental Neuropathology red. Adle-Biassette H, et al

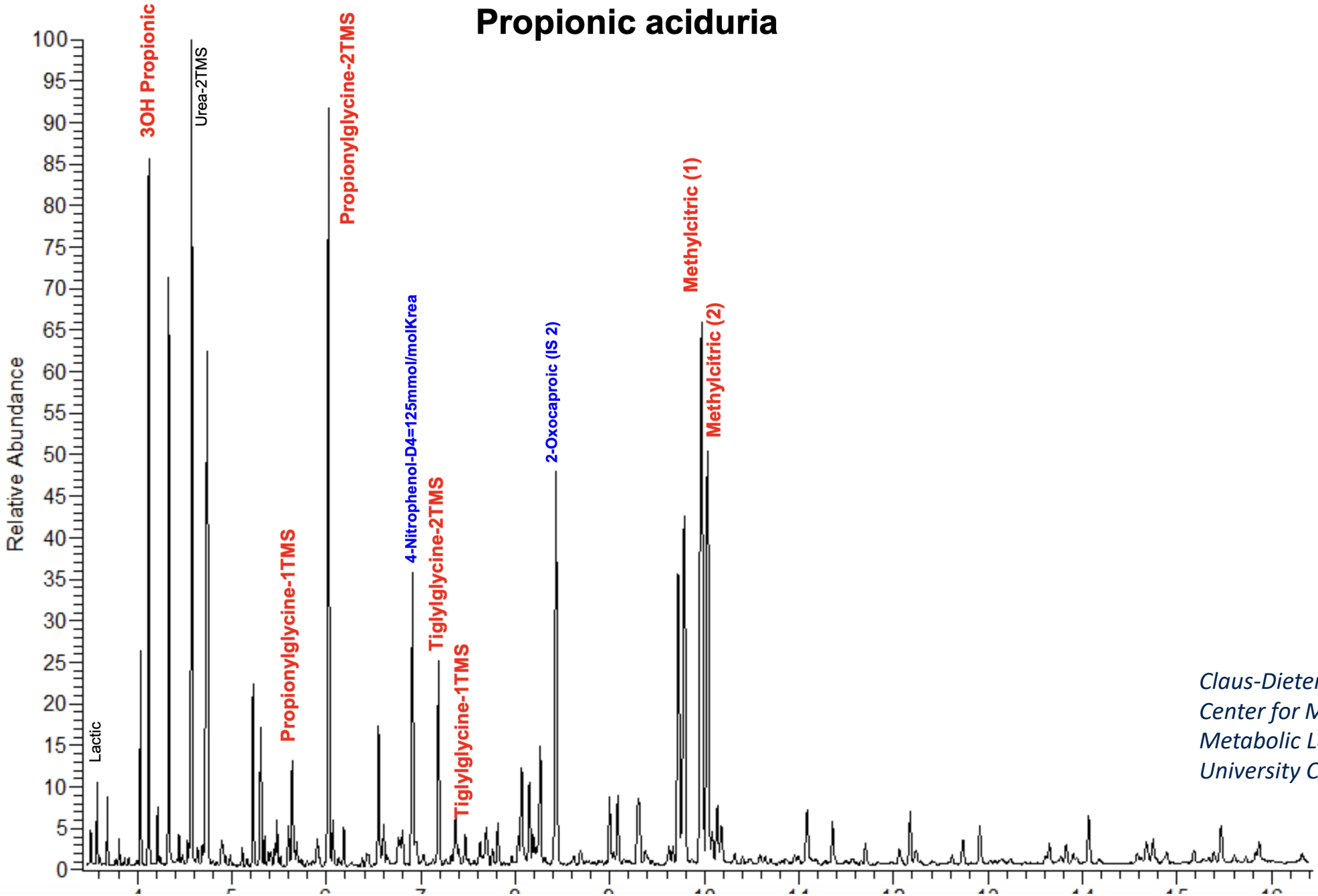
Condensation product of oxaloacetate with propionyl-Co A

β- or ω-oxidation of propionyl-Co A



Hoffmann GF, Burlina A, Barshop BA; Organic acidurias In: Pediatric Endocrinology and Inborn Errors of Metabolism, Sarafoglou K (ed), sec ed. 2017, McGraw-Hill

Propionic aciduria



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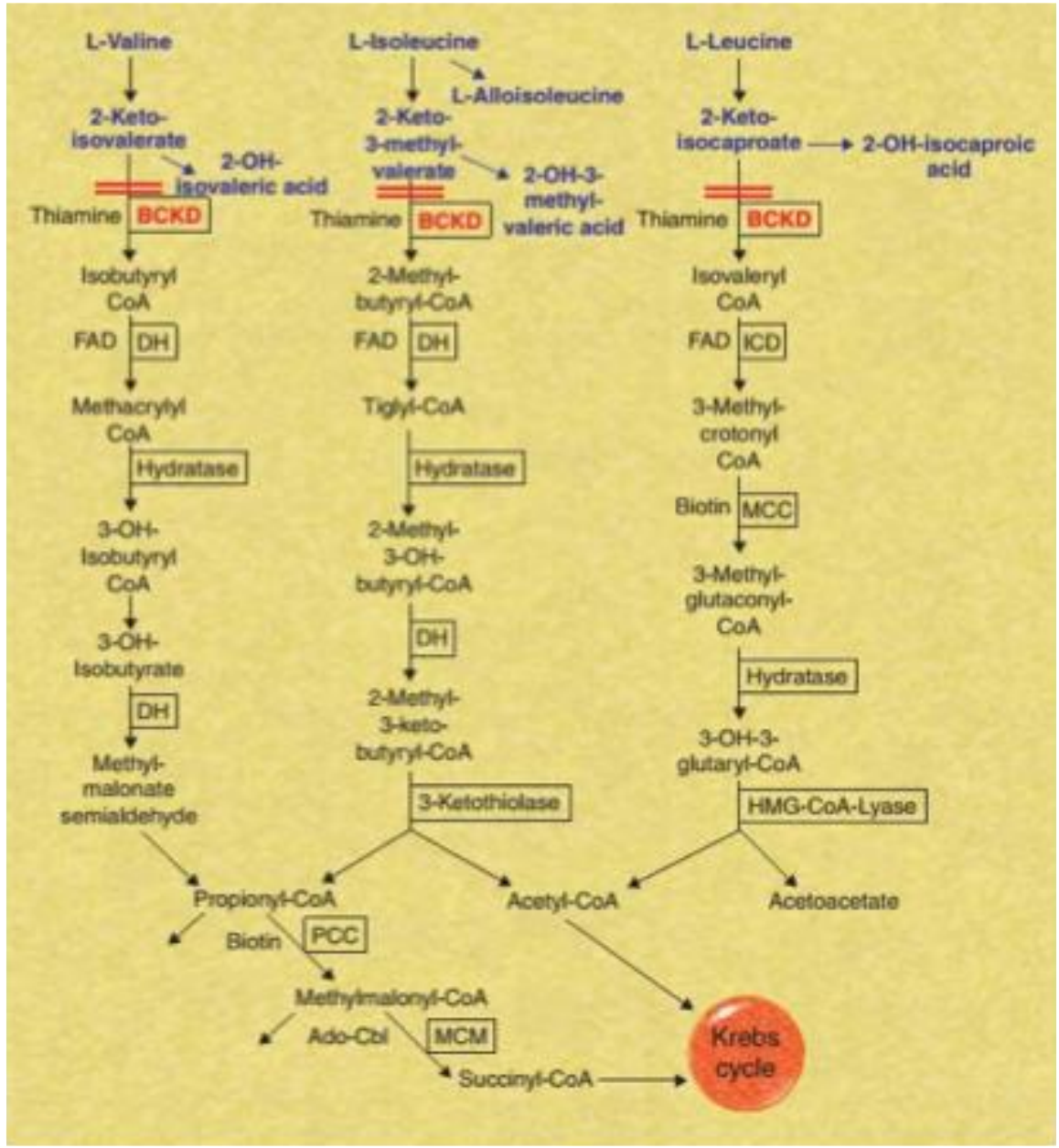
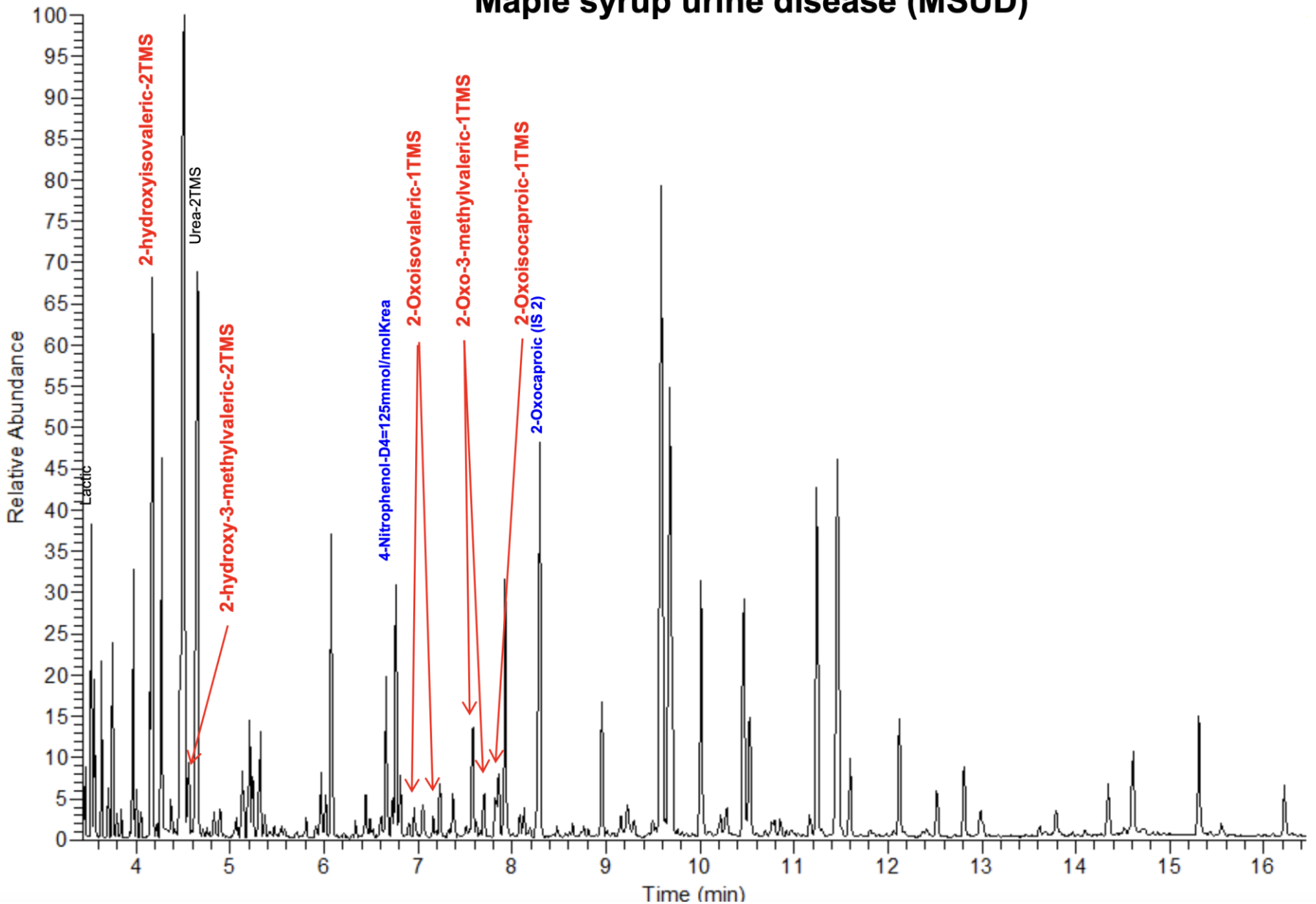


Hoffmann GF, Burlina A, Barshop BA; Organic acidurias In: Pediatric Endocrinology and Inborn Errors of Metabolism, Sarafoglou K (ed), sec ed. 2017, McGraw-Hill

Maple syrup urine disease (MSUD)



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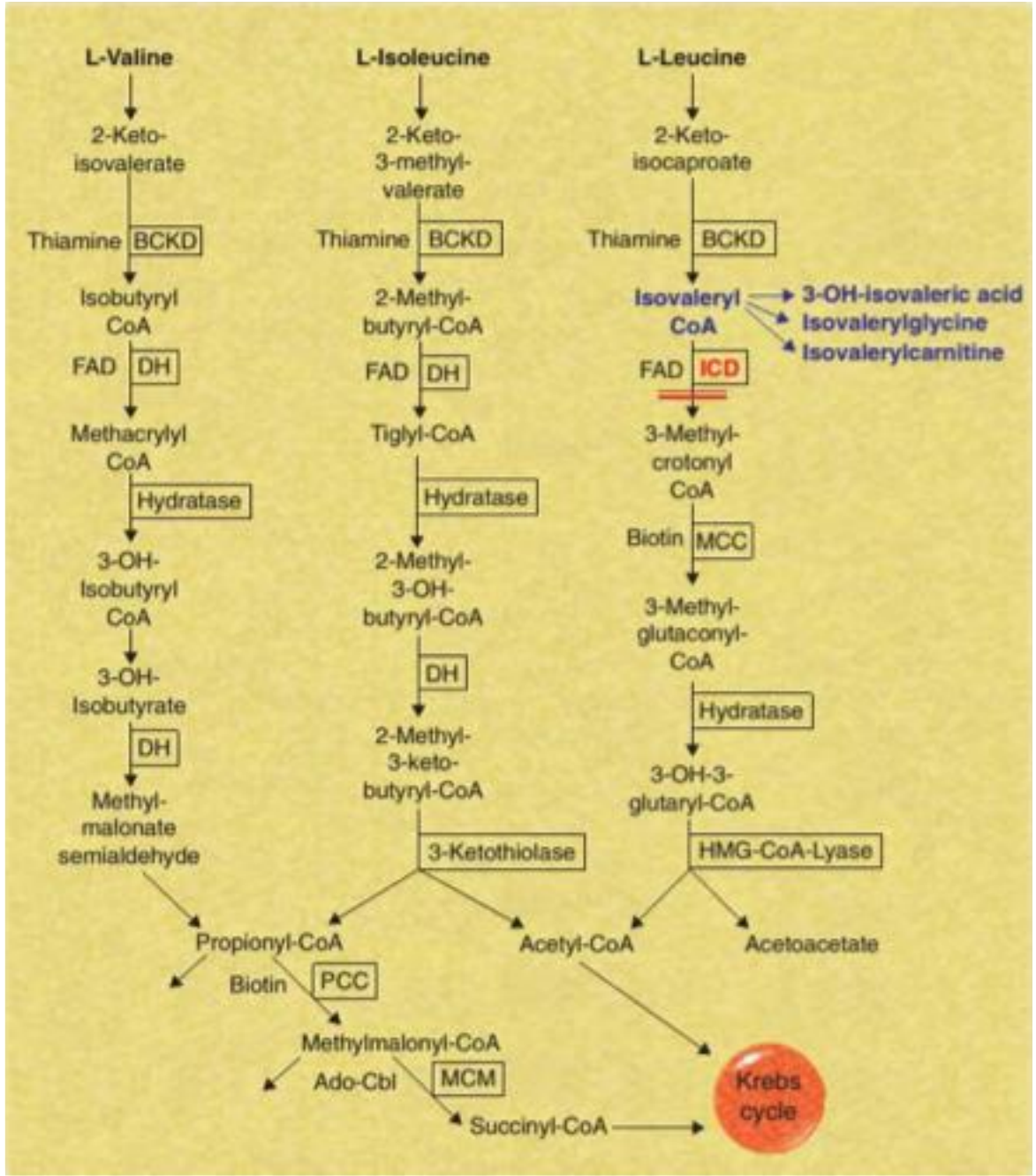

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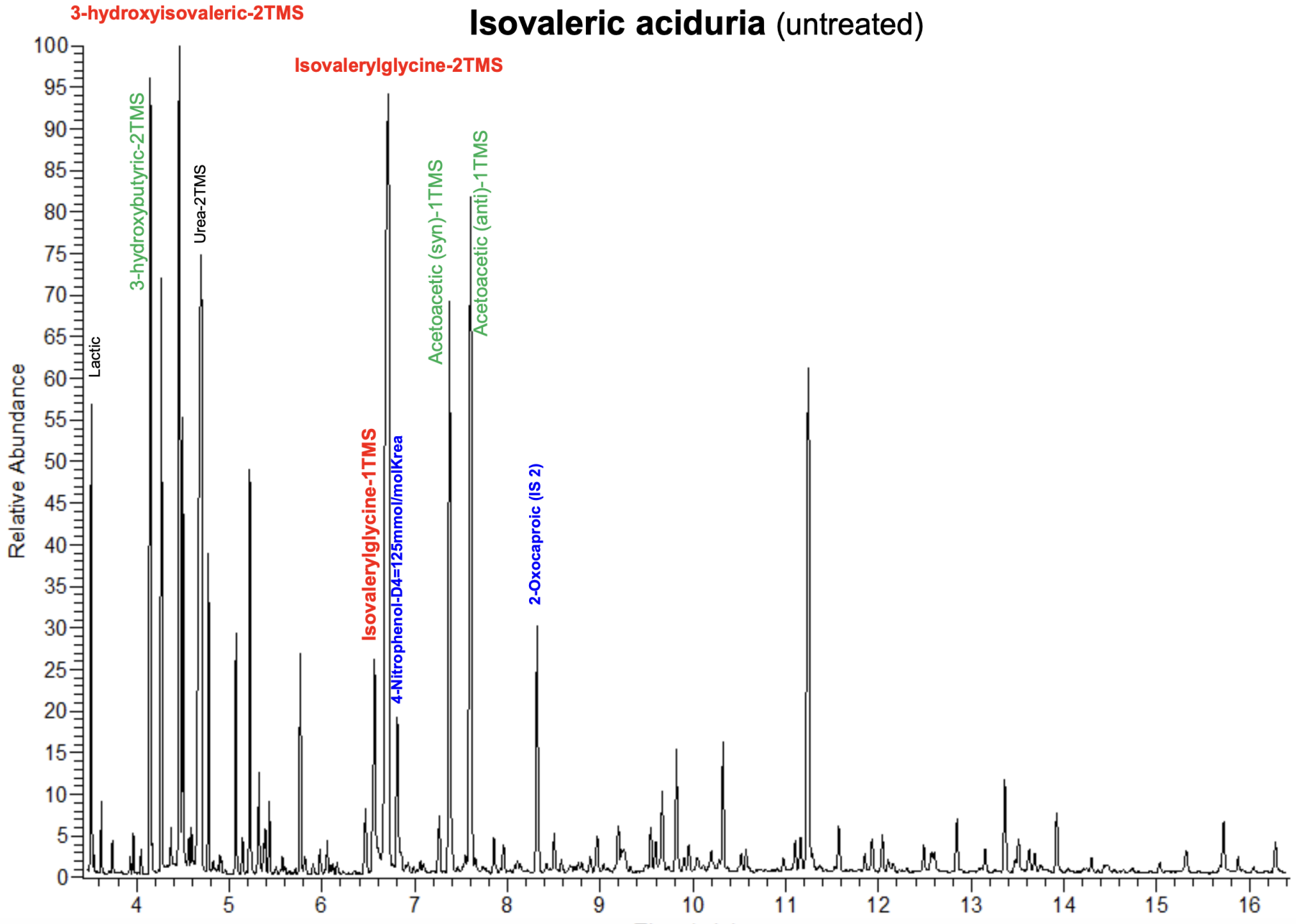

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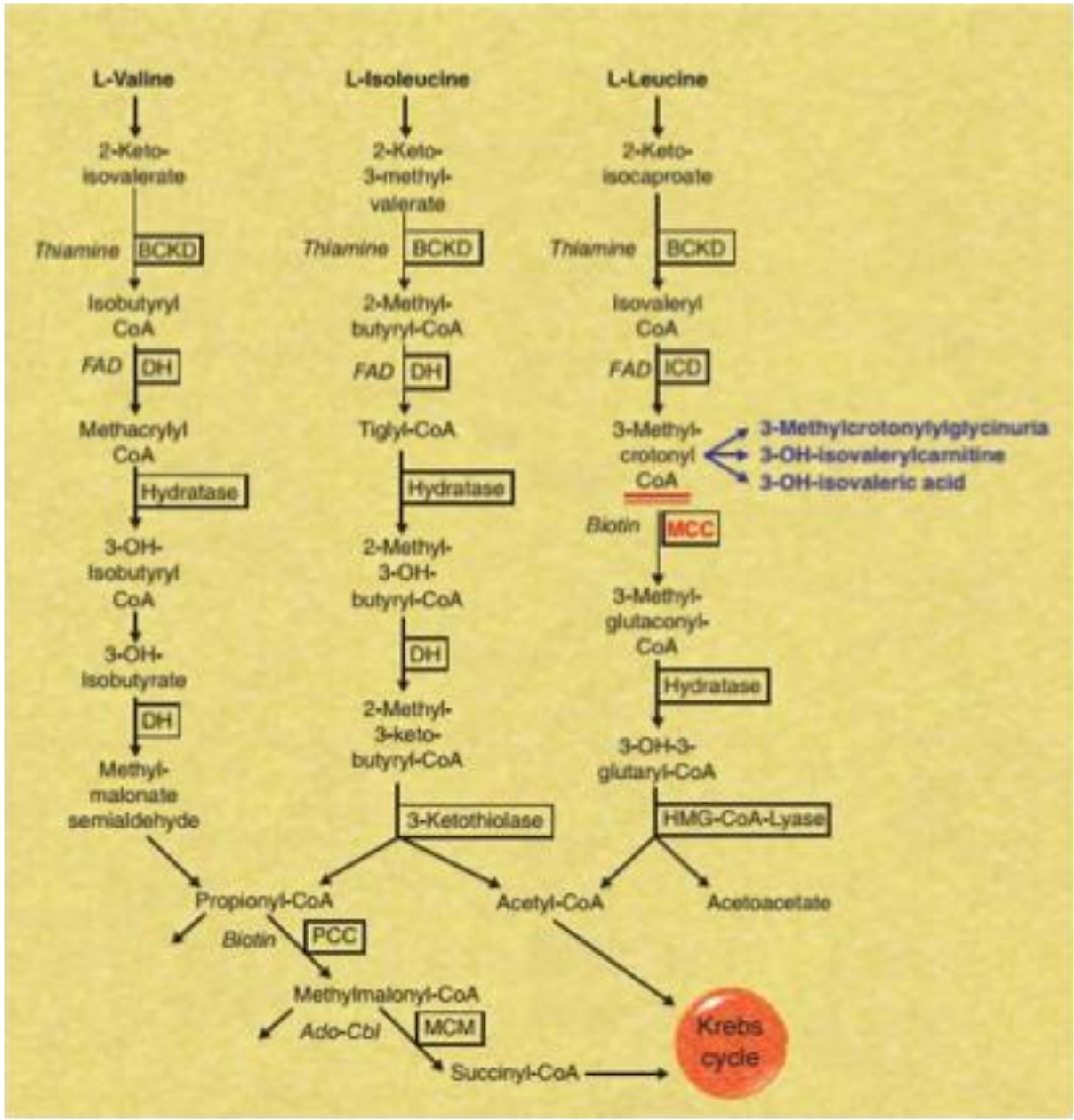
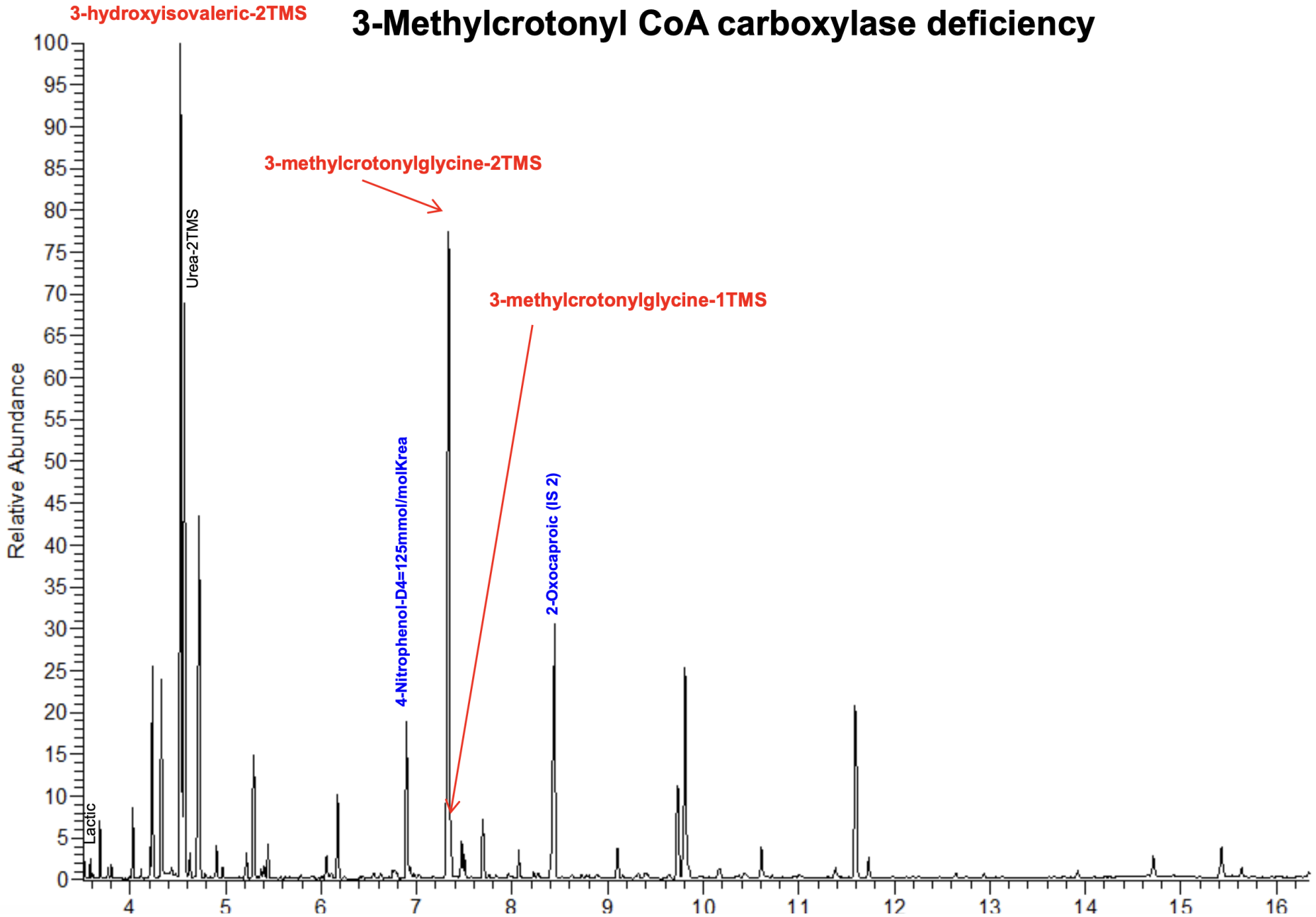


Hoffmann GF, Burlina A, Barshop BA; Organic acidurias In: Pediatric Endocrinology and Inborn Errors of Metabolism, Sarafoglou K (ed), sec ed. 2017, McGraw-Hill

3-Methylcrotonyl CoA carboxylase deficiency



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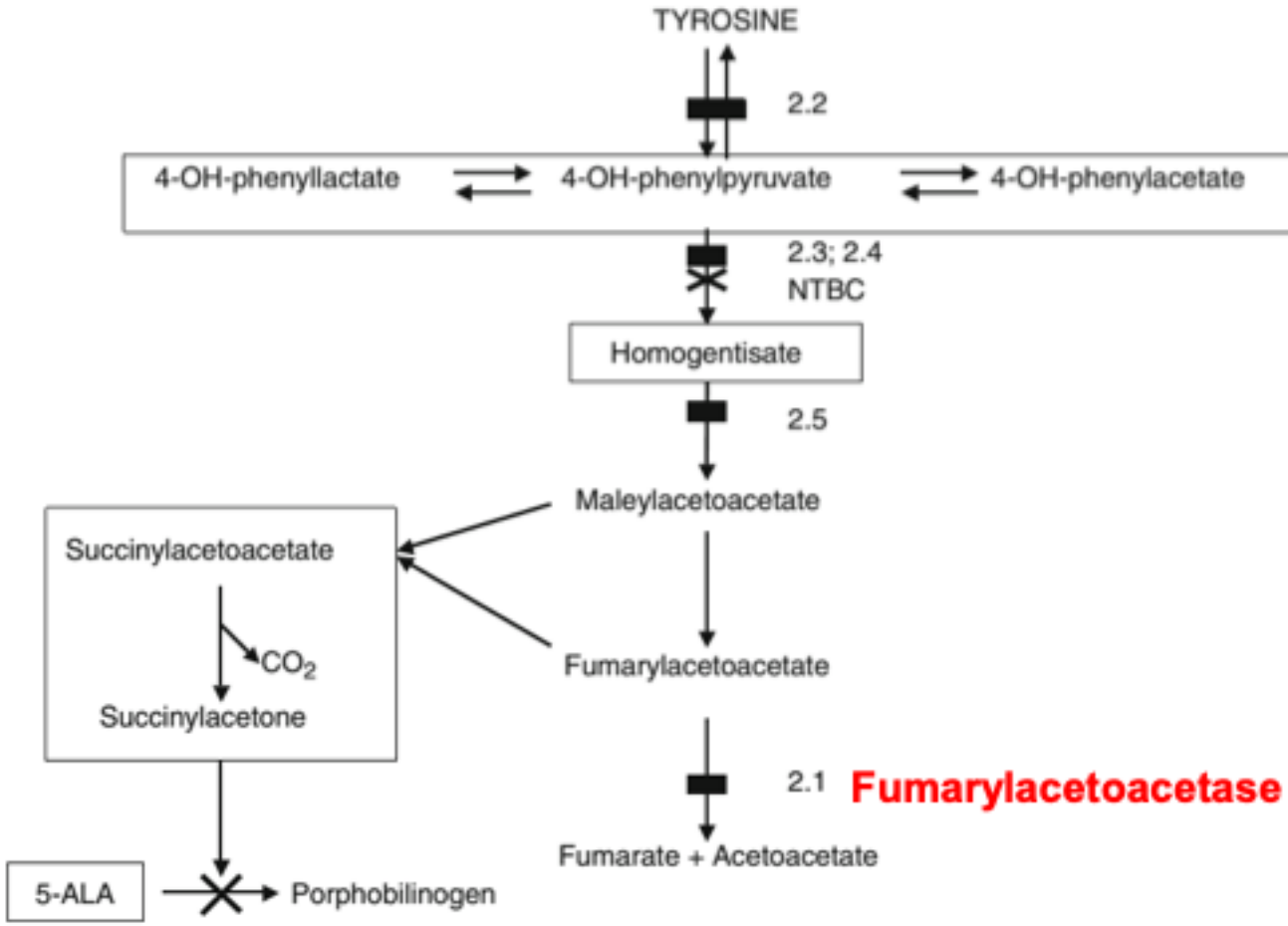
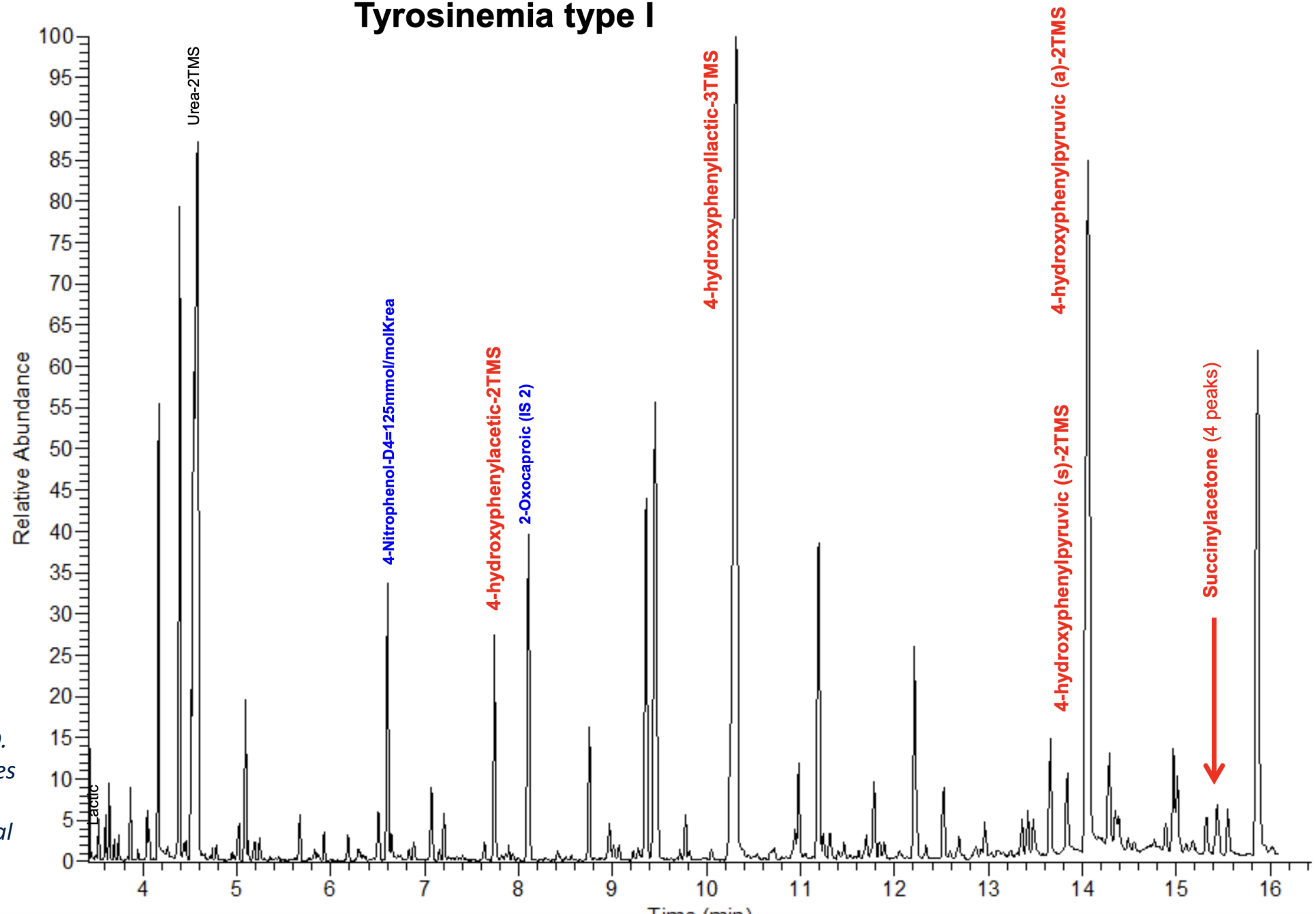


Holme E, Mitchell GA
In: Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases, Blau N et al (eds), 2014, Springer Heidelberg

Tyrosinemia type I



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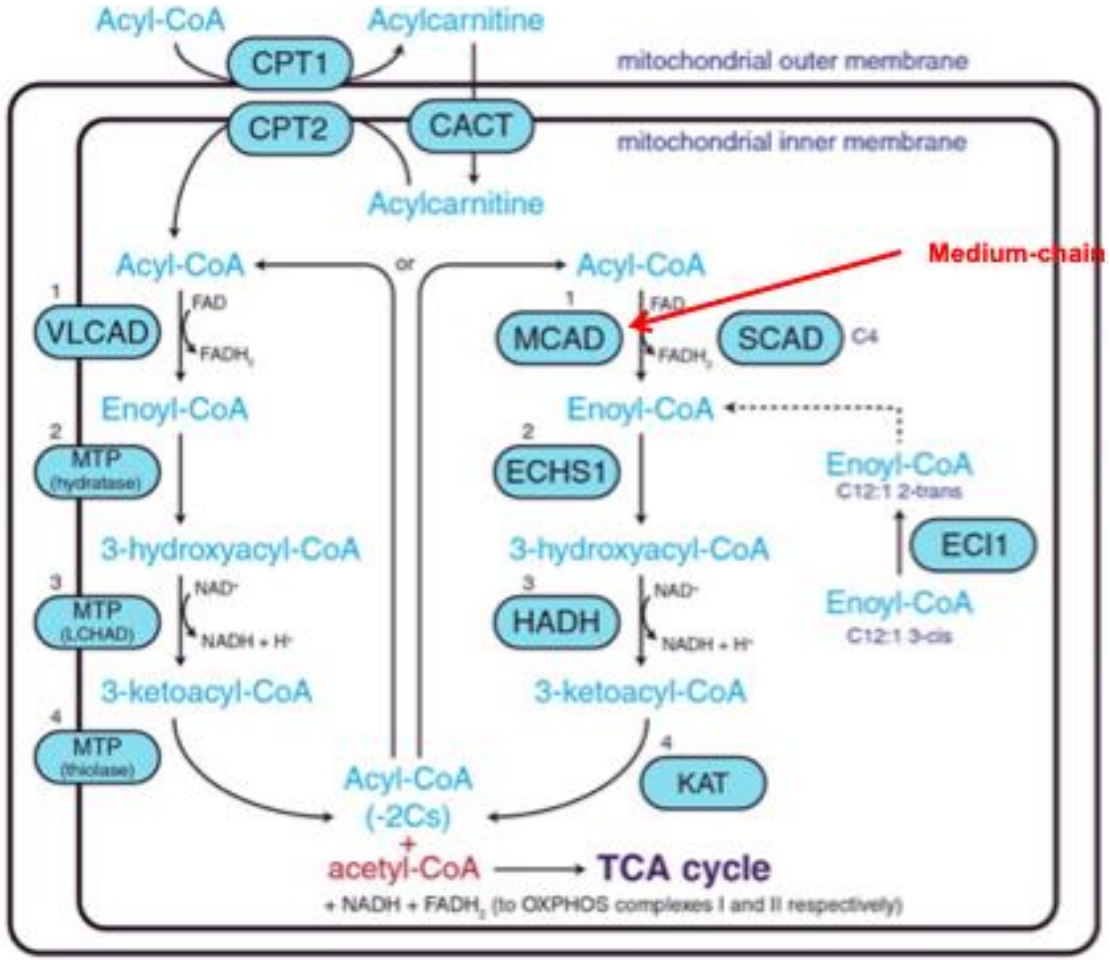
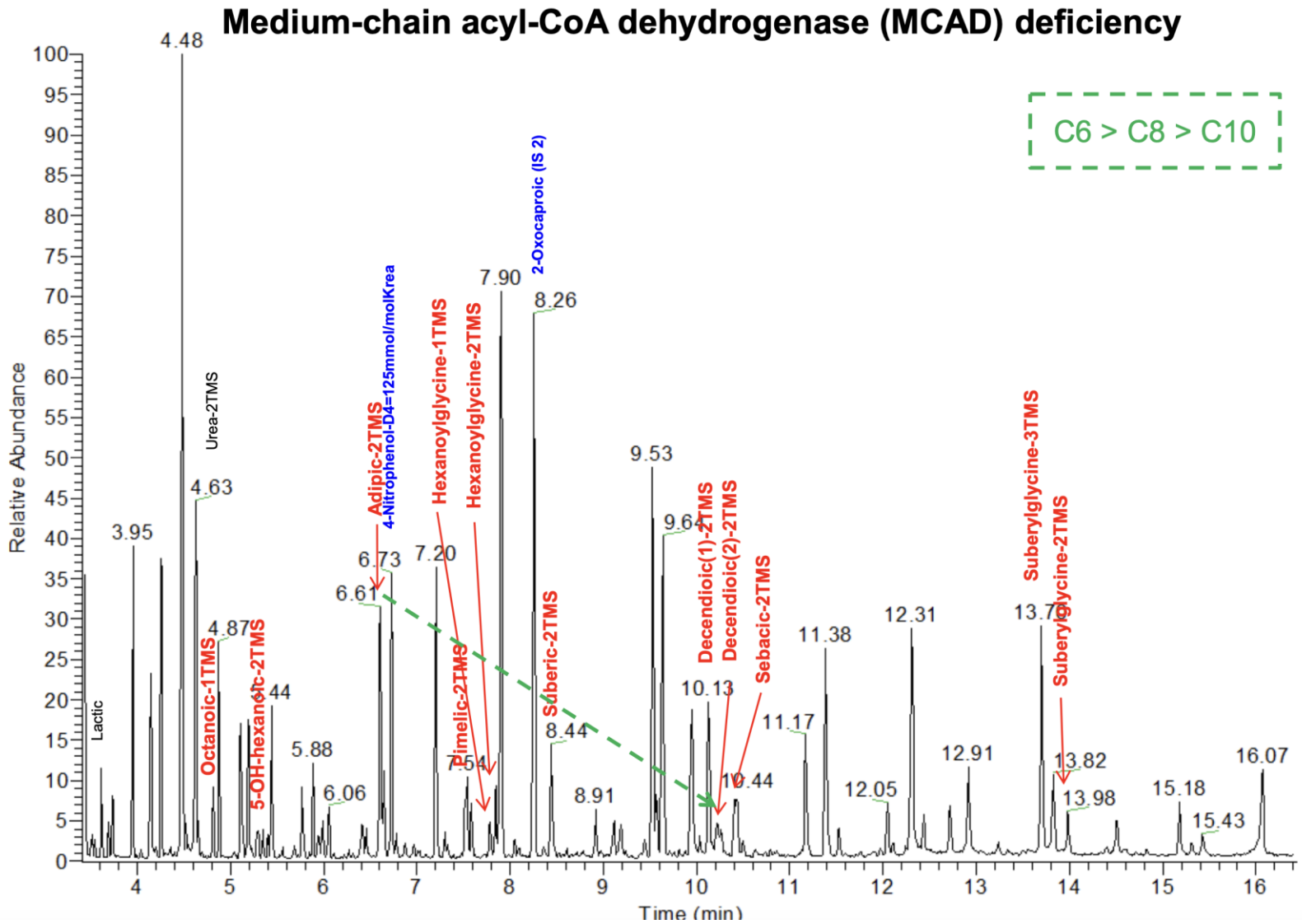
beta-Oxidation Defects



Medium-chain dicarboxylic acids
C6, C8, C10

Hexanoylglycine
Suberylglycine

Nsiah-Sefaa A, McKenzie M
Bioscience Reports 2016, 36



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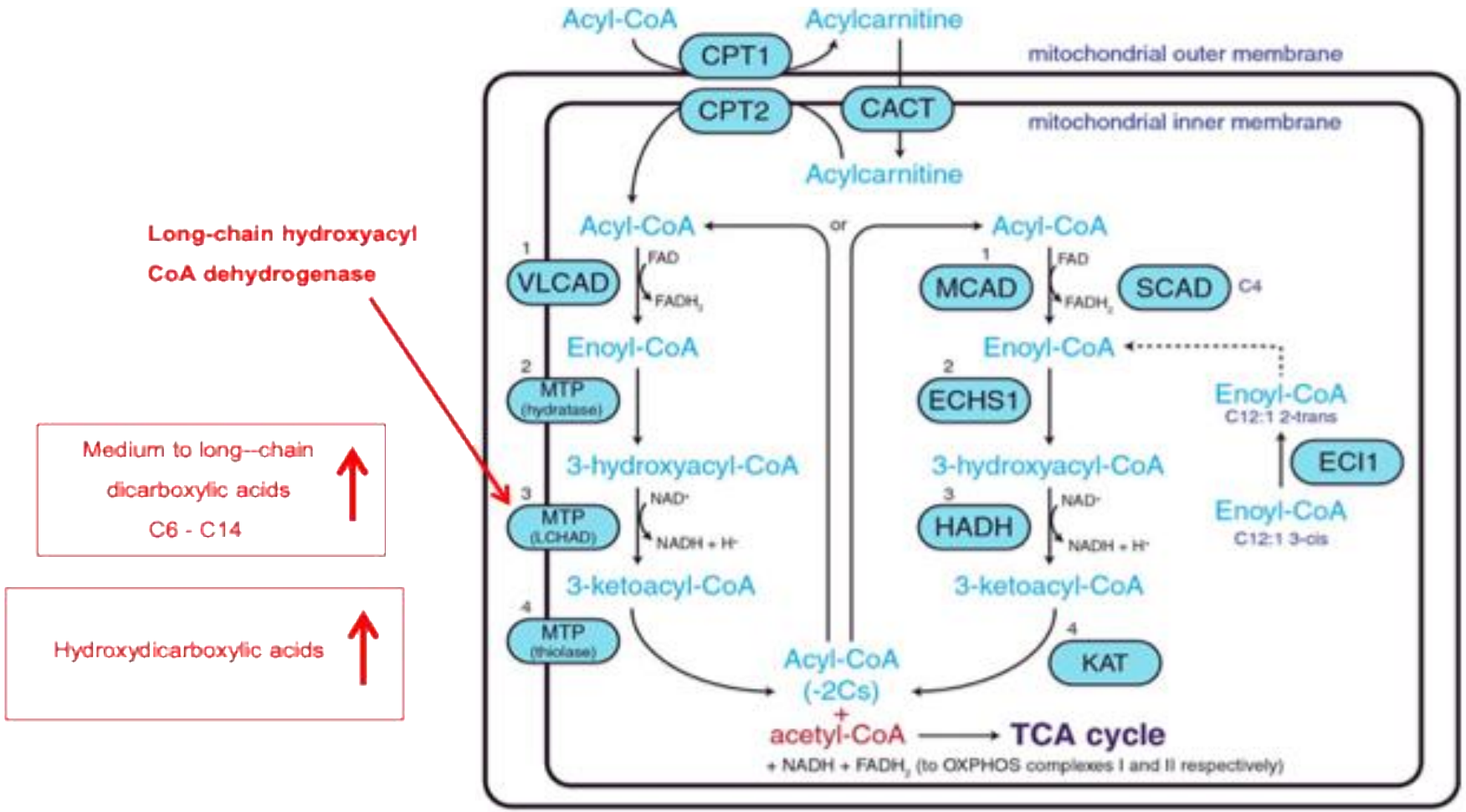
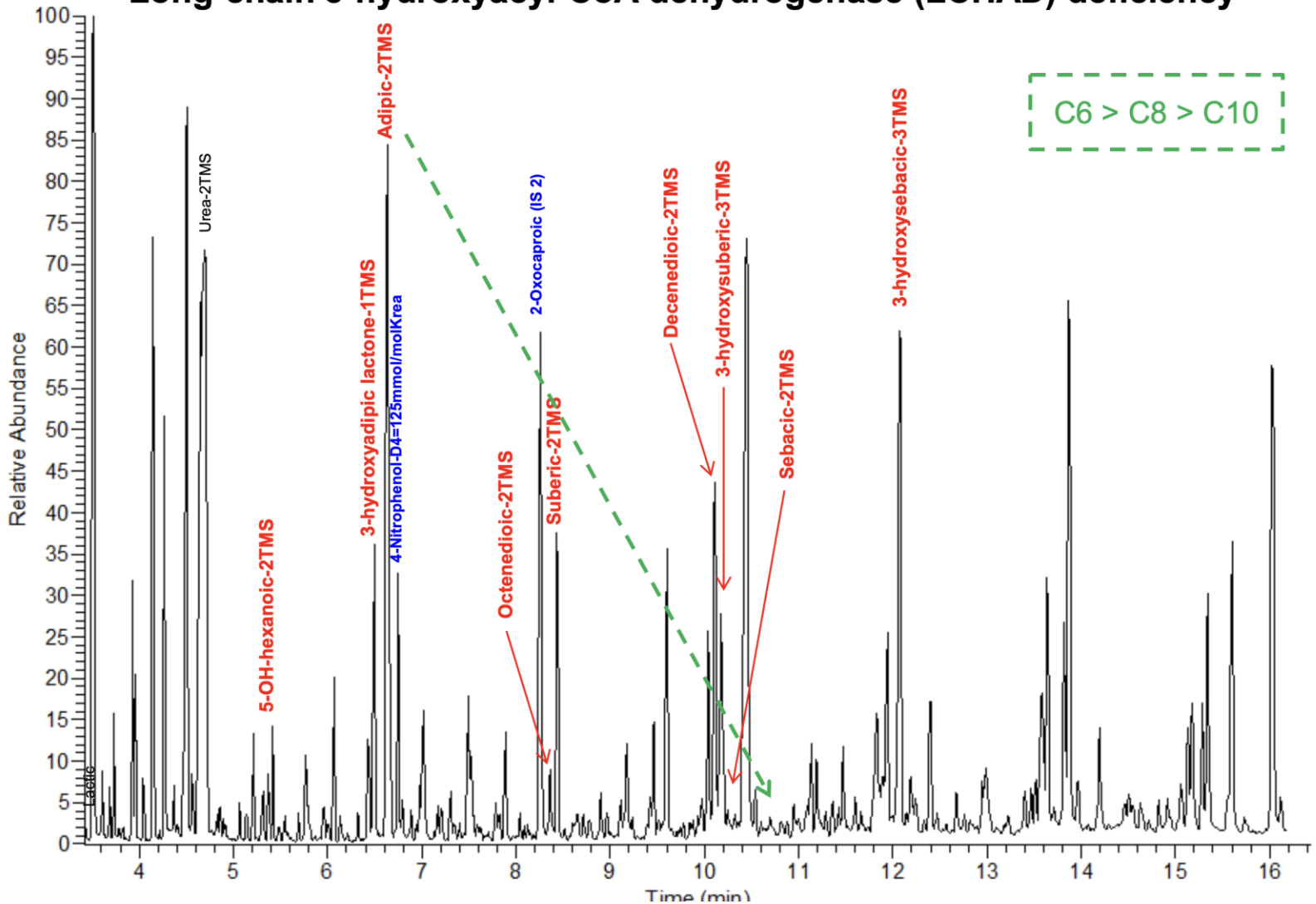
beta-Oxidation Defects



Nsiah-Sefaa A, McKenzie M
Bioscience Reports 2016, 36

Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency



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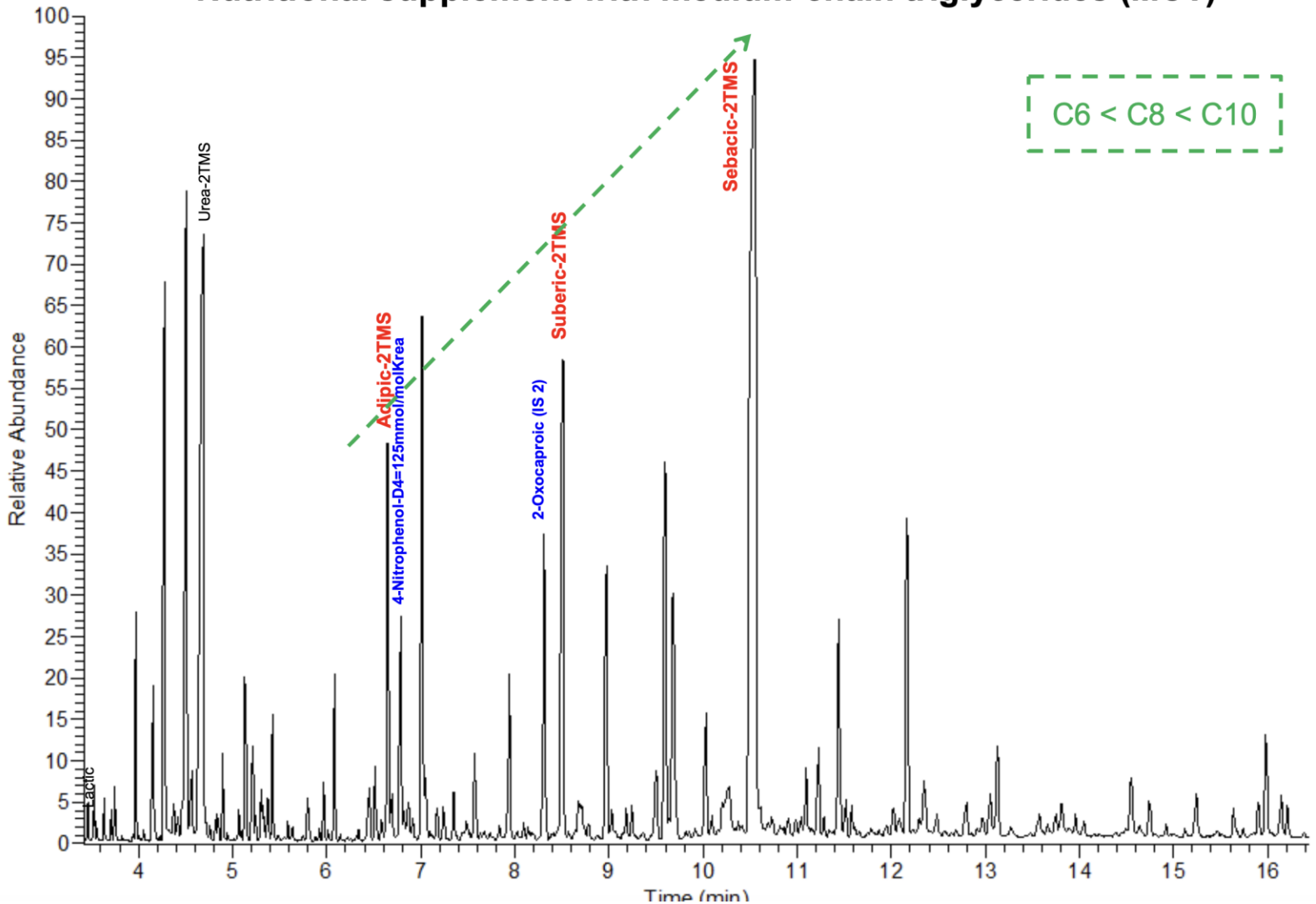
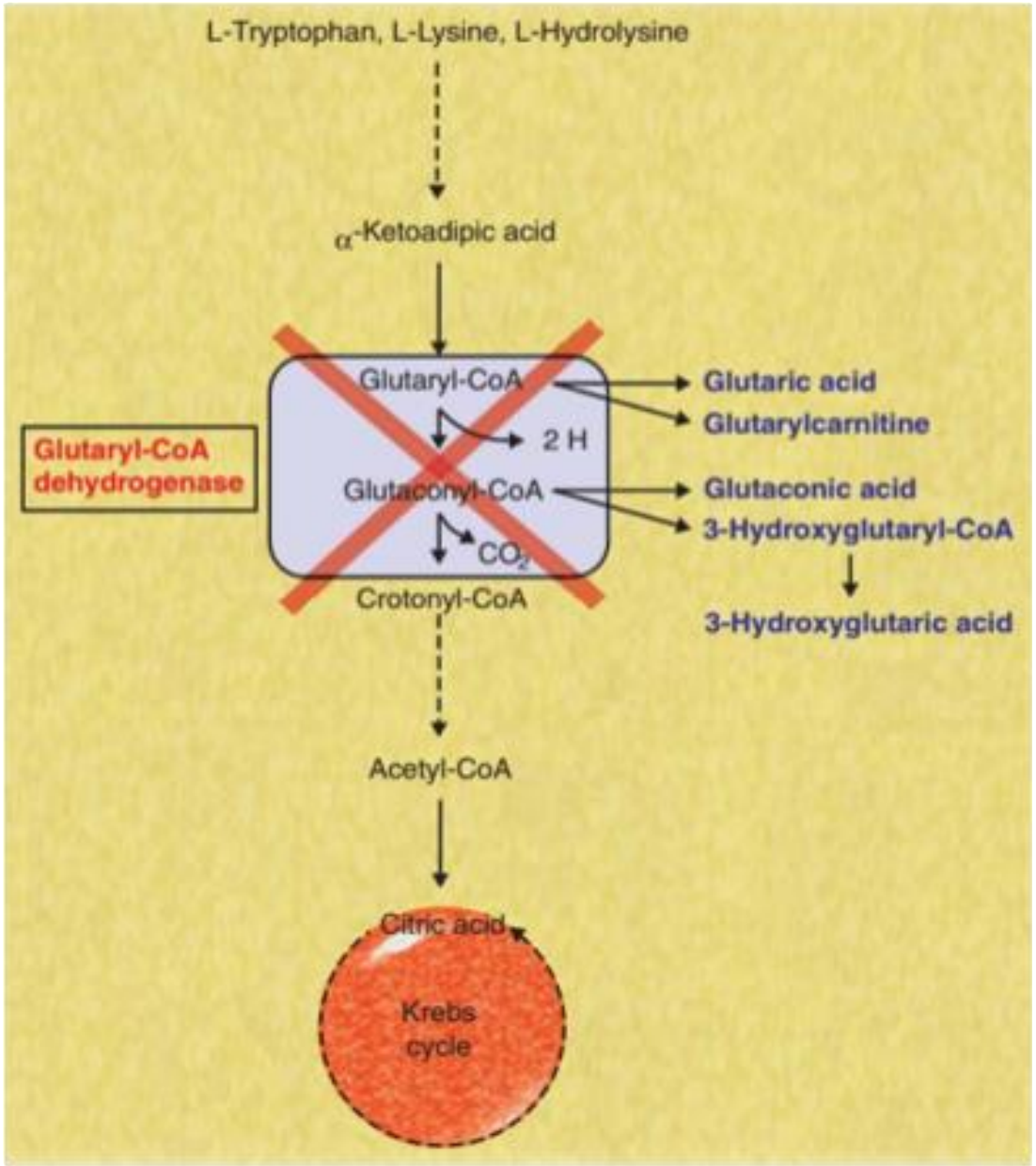
Nutritional supplement with medium-chain triglycerides (MCT)





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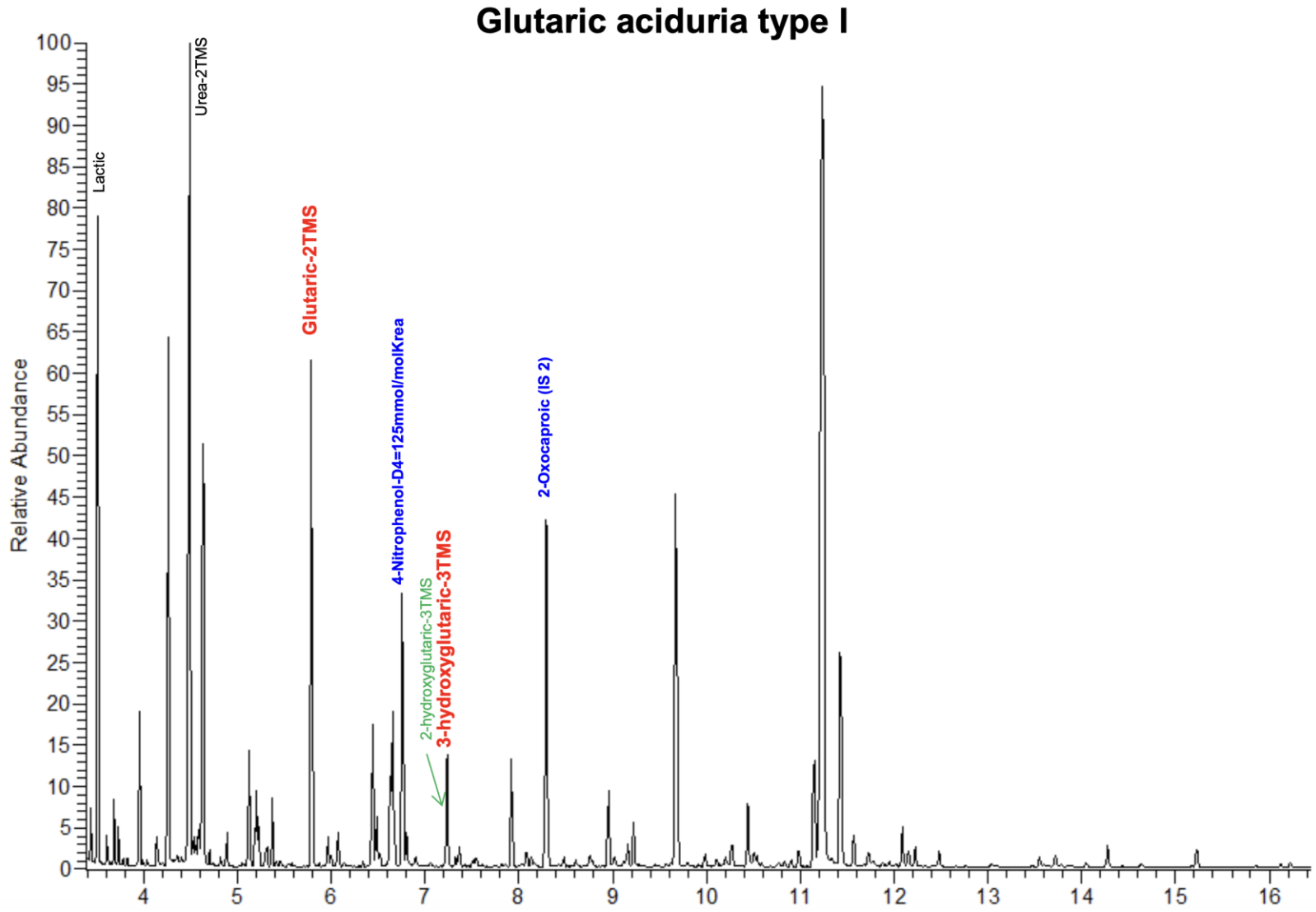

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MISDIAGNOSES

- familial bigocephalus

  cerebral palsy – extrapyramidal syndrome

  encephalitis

  post-inflammatory Parkinsonism

  post-vaccination encephalopathy
- Reye's syndrome

  sudden infant death syndrome

  abused child syndrome!!!!

  Confirmation of the initial diagnosis **GC-MS; TANDEM**

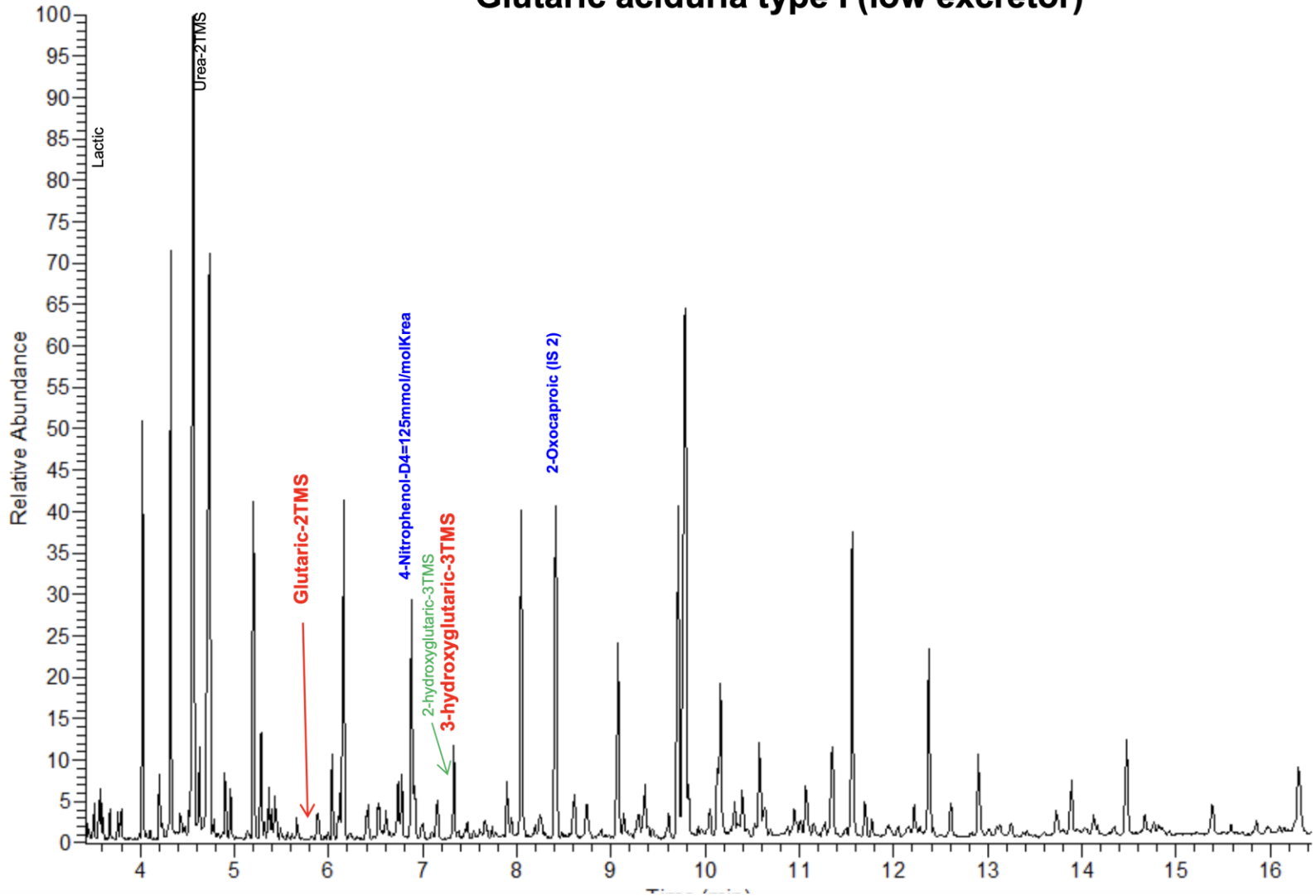
PATIENT MW

FETAL-PERINATAL PERIOD -
fetal history**– 1x** infection in the mother in the second trimester**,**
LOW BLOOD PRESSURE **WITH episode of dizziness and disturbances of consciousness;**

PSN w 39 hbd, oceniona w 1’ na 7p., w 5’8p, z m.c. 3000g, dł. 57cm, o.gł. 33 cm,
hyperbilirubinemia in the neonatal period
HEAD CIRCUMFERENCE AT THE AGE OF 3 YEARS OLD **75 C**

GLOBAL HYPOTONIA
RM BRAIN
TREATMENT

Glutaric aciduria type I (low excretor)



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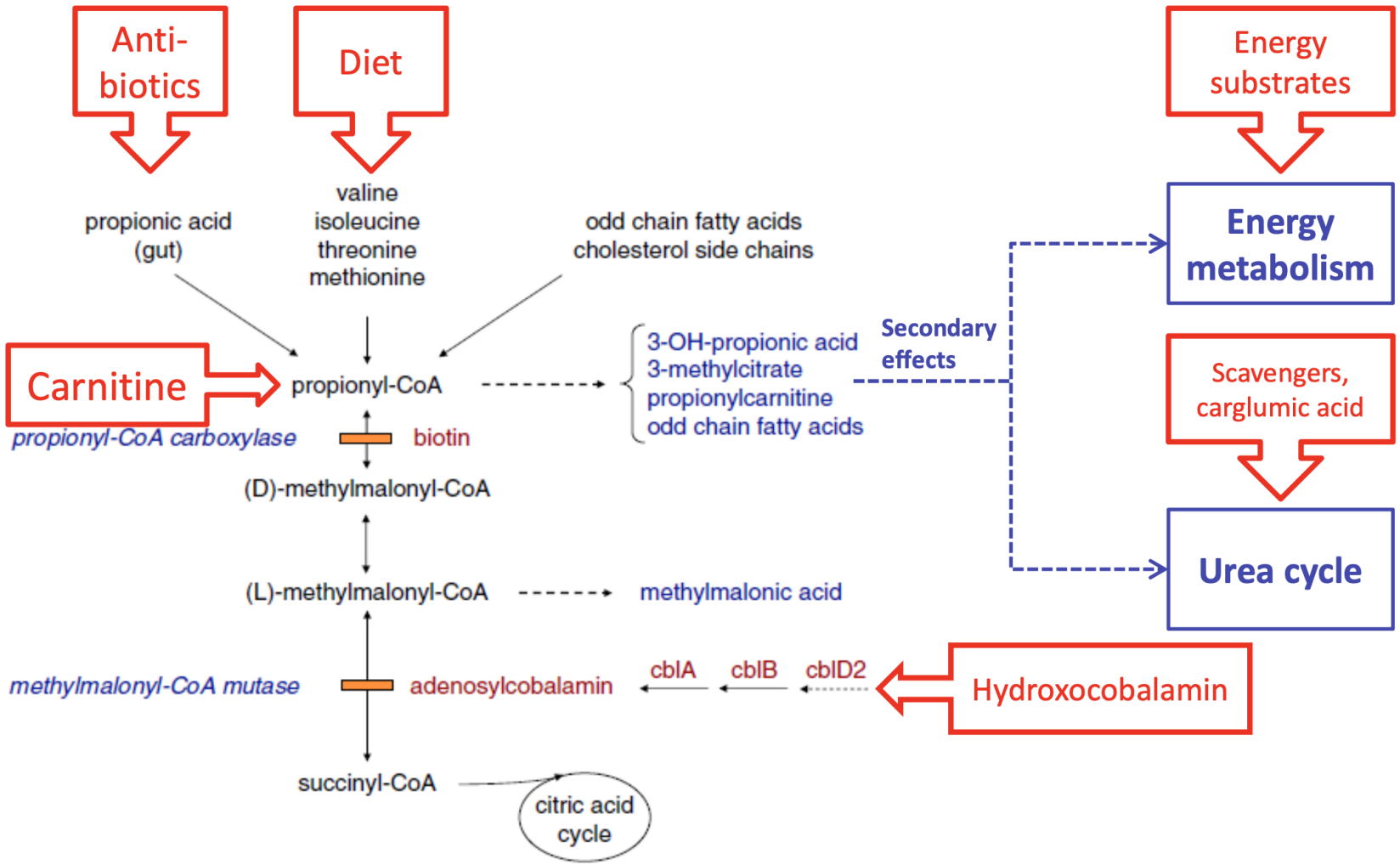
Therapeutic options

Maintenance treatment	Disease
Diet	MMA (Cbl-nonresponsive), PA, IVA (?), GA-I
Carnitine	MMA, PA, IVA, GA-I
Glycine	IVA (?)
Cofactor	MMA (Cbl-responsive), L2-OH-GA (Riboflavin)
Oral antibiotics	PA, MMA

Emergency treatment	Disease
Intermittent reduction/ stop of protein intake	All
Carbohydrates PO / glucose IV (+ insulin)	All
Cofactor	MMA (Cbl-responsive), L2-OH-GA (Riboflavin)
Sodium benzoate, carglumic acid	PA, MMA (Cbl-nonresponsive), (IVA)
Extracorporeal detoxification	PA, MMA (Cbl-nonresponsive)

General strategy

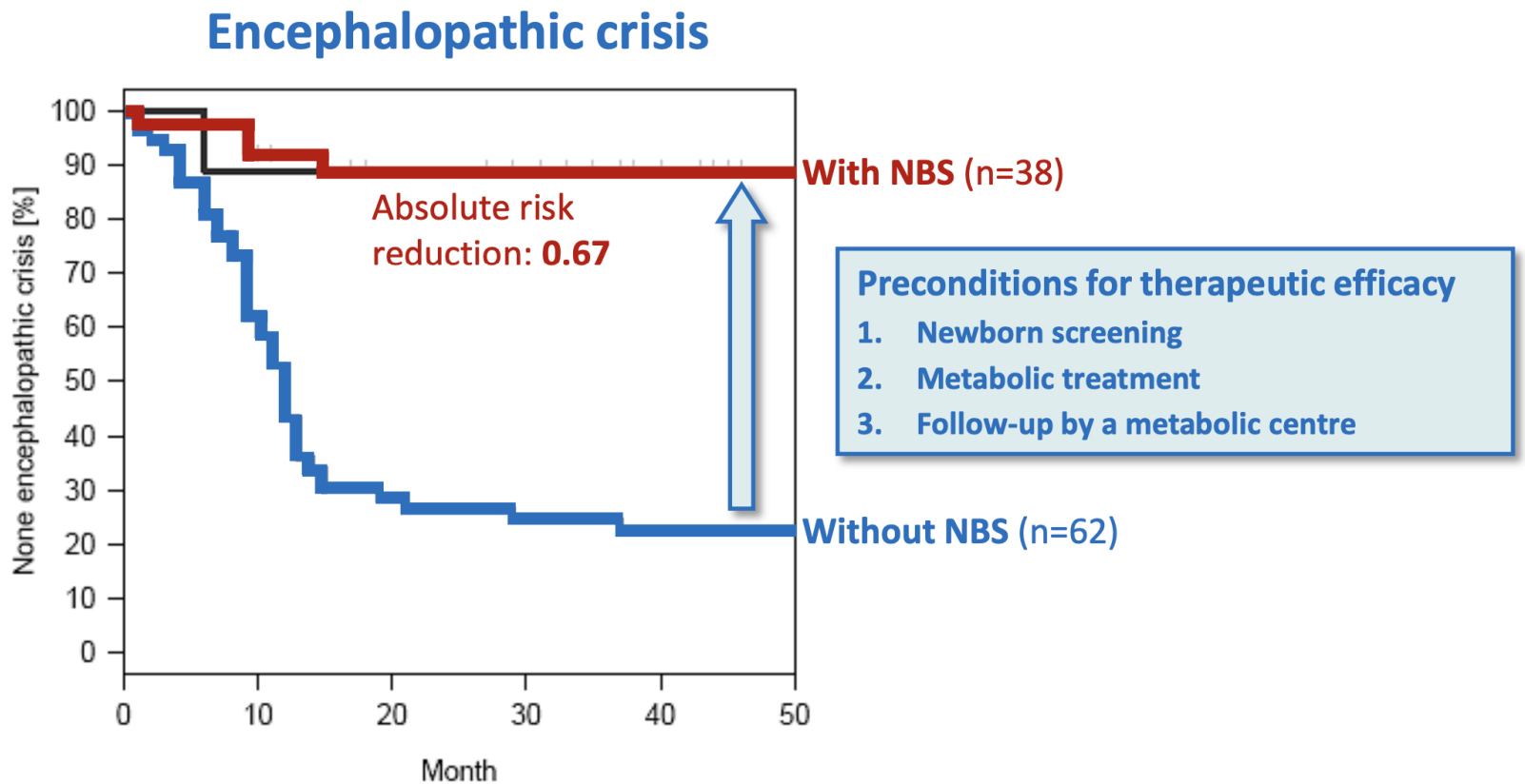
Reduced production and forced removal of toxic metabolites



Baumgartner et al. Orphanet J Rare Dis 2014

Can we prevent neurological manifestations?

Example: Glutaric aciduria type I



Kölker et al. Pediatr Res; 62: 357-363 (2007)
Heringer et al. Ann Neurol; 68: 743-752 (2010)

Conclusion

- Long-term disease course of classic OADs is incompletely understood.
- Multiple organ manifestations in adolescents and adults (who have remained ”metabolically stable“ for years).

- Complex pathomechanism (toxic metabolites): energy impairment, activation of ROS, autophagy and inflammation, and long-term epigenetic modification of gene expression.
- Conventional metabolic therapy: often insufficient to prevent long-term organ damage.