

Measurement of Uncertainty Qualitatively?



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SA for Sheffield Qualitative Urine
Organic Acid Scheme

What is ERNDIM -

- Formed in 1991 “*European Research Network* for evaluation and improvement of screening, diagnosis and treatment of **Inherited Disorders of Metabolism**”
- <http://www.erndim.org/home/about.asp>

The Schemes

Quantitative schemes

- Amino Acids
- Quantitative Organic Acids
- Urine Special Assays
- Urine Purines & Pyrimidines
- Special Assays in Serum
- Cystine in White Blood Cells
- Lysosomal Enzymes

Annual Report

- Accuracy
- Precision
- Recovery
- Linearity

..... measurement of uncertainty

Qualitative Schemes

- Proficiency schemes (*Sheffield, Basal, Prague, Lyon, Amsterdam*)
- Organic acids
- DBS acylcarnitines
- Congenital Disorders of Glycosylation
- Urine Mucopolysaccharides

Qualitatively urinary organic acid scheme

- **Nine heat treated urine samples per year from real patients with differing metabolic disorders**
- **Participants are asked to**
 - **Identify the major analytical findings**
 - **Indicate the most likely diagnosis**
 - **Suggest any further investigations needed to confirm or clarify the diagnosis**
 - **chromatograms**



ERNDIM Organic Acid QA
Response Form - Laboratory #

Sample 230

10 year old boy with myopathy
and developmental delay

Major analytical findings

The most likely diagnosis (one only)

Other possible diagnoses (if applicable)

Further investigations required to confirm/clarify the diagnosis

Additional comments (if required)



Major analytical findings

important increase of
ethylmalonic acid with presence
of methyl succinic acid

The most likely diagnosis (one only)

SCAD deficiency

This diagnosis is: Fairly certain

Tentative

Other possible diagnoses (if applicable)

Further investigations required to confirm/clarify the diagnosis

Additional comments (if required)

Sample 230 10 year old boy-myopathy and developmental delay

Major analytical findings

Significantly elevates ethylmalonic acid
Moderately elevated methylsuccinic acid.
(acylglycines ,lactic acid,2-hydroxyglutaric,adipic and Krebs metabolites are not elevated)
The presence of Paracetamol metabolites might obscure other findings

The most likely diagnosis (one only)

This diagnosis is: Tentative Ethylmalonic aciduria due to SCAD (short chain acyl CoA dehydrogenase) deficiency

Other possible diagnoses (if applicable)

ethylmalonic encephalopathy (EPEMA), mitochondrial respiratory chain defects, GAI (MADD)

Further investigations required to confirm/clarify the diagnosis

DBS acylcarnitine (attention to C4 butyrylcarnitine) and plasma carnitine (free/total)
ACAD5 sequencing (SCAD gene)-if normal or mild variant
Muscle biopsy+COX stain + cytochrome c oxidase activity
ETEI sequencing
Skin fibroblast fatty acid oxidation studies (not very specific)

Additional comments (if required)

Lactic acid and acyglycines are not elevated-suggesting a mild disorder
As the significance of SCADD is not entirely clear therefore other diagnostic approached could be pursued simultaneously.

Scoring

- **Scoring**

- **Satisfactory** 4
- **Helpful but incomplete** 3
- **Not helpful** 2
- **Slightly misleading** 1
- **Misleading** 0

- **Total annual achievable** 36

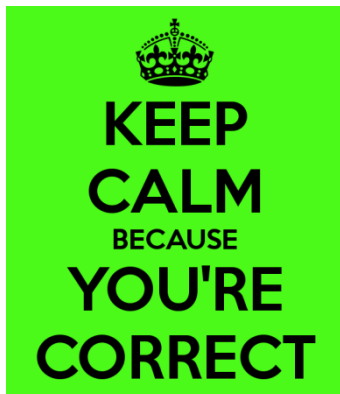
- Proficiency score
- satisfactory performance 22/36 or 15
- Critical error

Lab Number	No of returns in 2015	Total score 2015 out of 36 for 3 returns	Number of returns 2014	Total score 2014 out of 36 for 3 returns	Number of returns 2013	Total score 2013 out of 36 for 3 returns	Total score Over 3 years*.
82	3	34	3	33	3	36	103
83	2	20	3	15	3	34	69
84	3	36	3	36	3	36	108
85	1	10	3	24	3	32	66
86	3	26	-	-	-	-	-
87	2	20	-	-	-	-	-
88	3	36	3	24	-	-	-
89	3	36	-	-	-	-	-
90	3	32	3	36	3	36	104
91	3	28	3	38	3	30	96
92	3	31	3	29	3	31	91
93	2	22	-	-	-	-	-
94	3	32	3	34	3	36	102
95	3	36	3	34	-	-	-
96	3	29	3	32	3	32	93
97	3	35	3	36	2	20	91
98	2	22	-	-	-	-	-
99	3	36	3	36	-	-	-
100	3	30	3	32	-	-	-
101	3	28	3	36	-	-	-
102	3	24	-	-	-	-	-
103	2	24	-	-	-	-	-
104	3	36	-	-	-	-	-

Participant's 2016 =107

	2015	2014	2013	2012	2011	2010	2009
Argentina	3	3	2	2	2	2	2
Australia	6	6	6	6	6	6	6
Belgium	6	6	6	5	5	6	7
Brazil	2	2	2	2	2	-	1
Canada	1	1	1	1	1	1	1
Columbia	1	1	1	1	1	1	1
Chile	1	1	-	-	-	-	-
Czech Republic	-	-	-	-	1	-	-
Democratic Republic of China	1	1	1	1	2	2	1
Finland	2	2	2	1	1	1	1
France	15	15	15	15	15	13	13
Hong Kong	1	1	-	-	-	-	-
Germany†	1	1	1	1	1	1	1
Israel	3	3	3	3	3	4	3
Japan	2	2	1	1	1	1	1
Lebanon	1	1	1	1	1	1	1
Malaysia	3	3	3	3	3	4	3
New Zealand	1	1	1	1	1	1	1
People's Republic of China	9	9	9	8	10	7	7
Portugal	2	2	2	2	2	2	2
Republic of Korea	1	1	1	1	1	1	1
Republic of Ireland	1	1	1	1	1	1	1
Republic of Singapore	1	1	1	1	1	1	1
South Africa	2	2	2	2	2	2	1
Spain	6	6	6	6	6	6	6
Turkey	7	3	3	3	3	3	2
United Kingdom	18	18	18	18	18	19	20
USA	5	5	5	3	3	3	4
Uruguay	1	1	-	-	-	-	-
Venezuela	-	-	-	1	1	1	1
Vietnam	1	1	1	1	1	-	-
TOTAL	104	100	94	91	95	90	89

How well do we do?



Diagnosis	% Proficiency
MMA	95%
MCAD (non crisis)	86%
Ethylene glycol	95%
Fumerate hydratase deficiency	88%
SCAD	74%
PA	98%
MSUD	84%
Citrullinaemia	89%
3-methylglutaconic aciduria	87%
PKU	96%
MCC	95%
IVA	100%
LPI	79%
GA2	82%
Malonic acid	98%

Why IMD hard to get right?

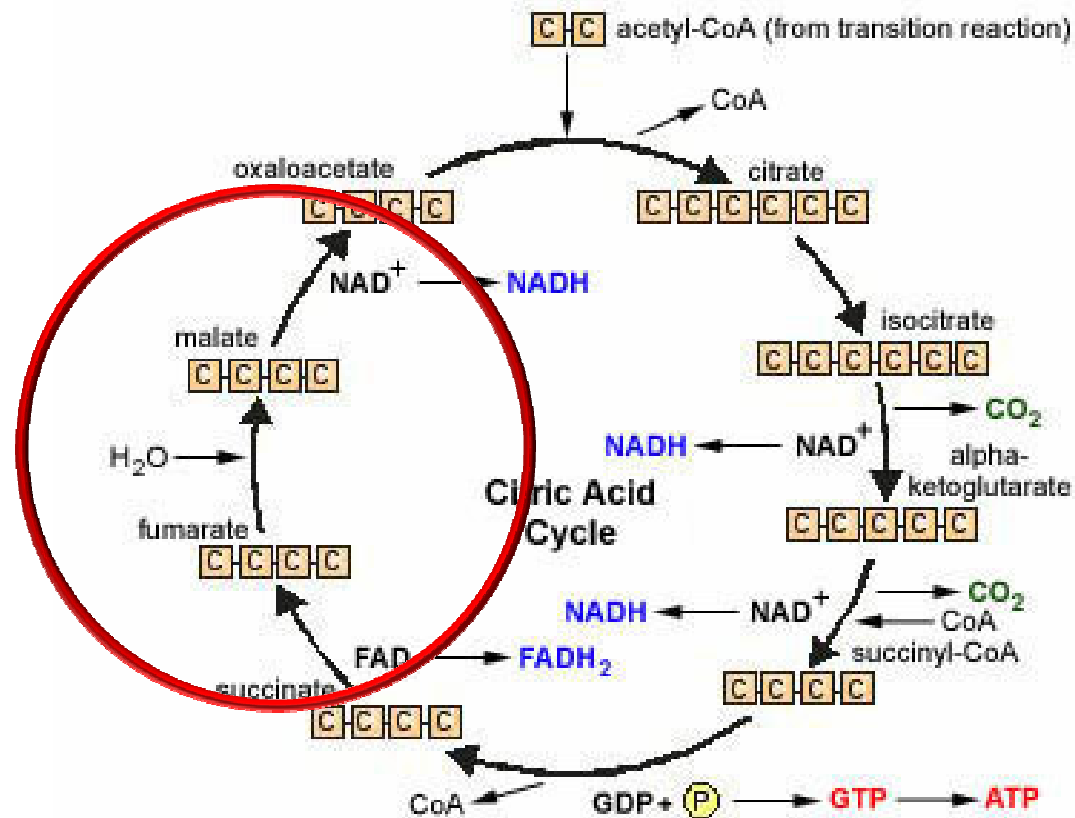
- **They are rare Zebras not horses....**



- **They are biochemically heterogeneous conditions**
- **They are clinically heterogeneous conditions**
- Small amounts of key compounds can be important
- The analyses are often qualitative rather than quantitative and the interpretation is therefore subjective
- Episodic excretion is common (e.g. intermittent MSUD)

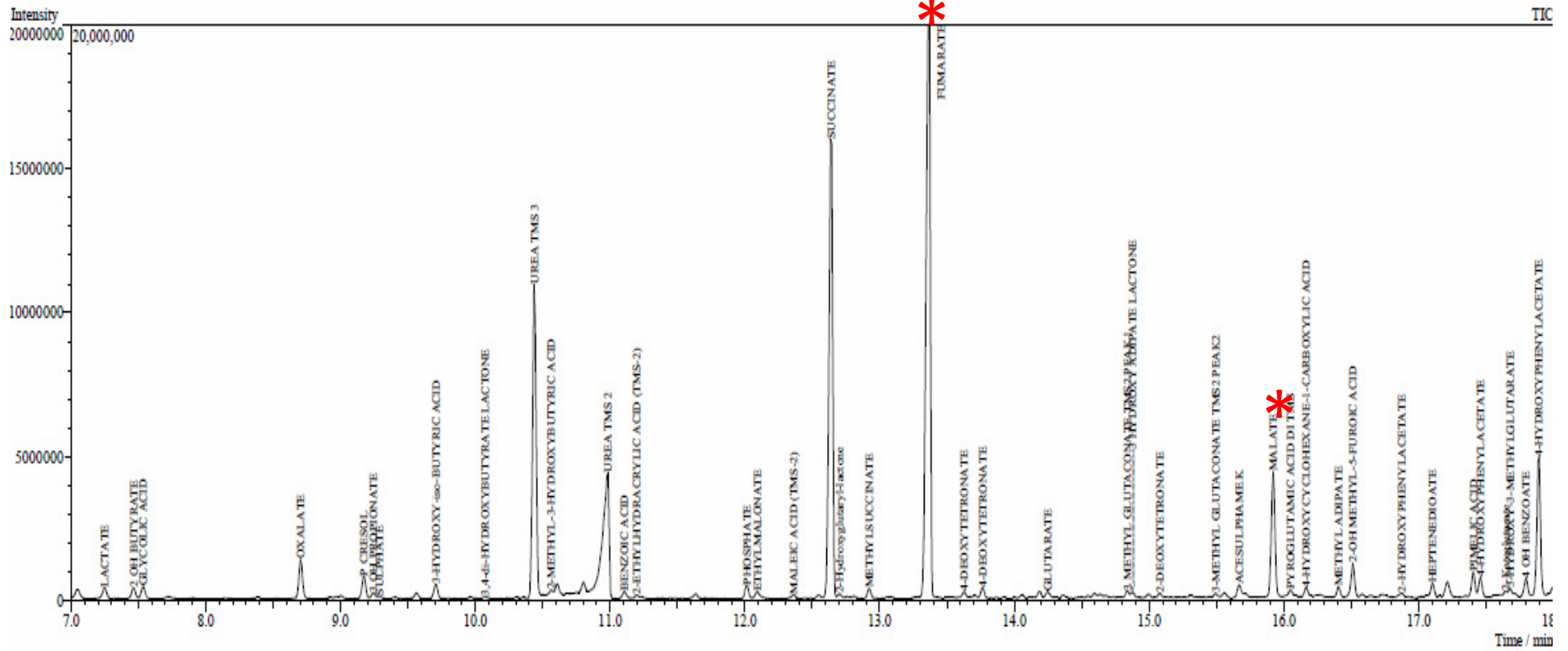
Fumarate Hydratase

88%



TCA cycle...

Fumarate Hydratase



Why IMD hard to get right?

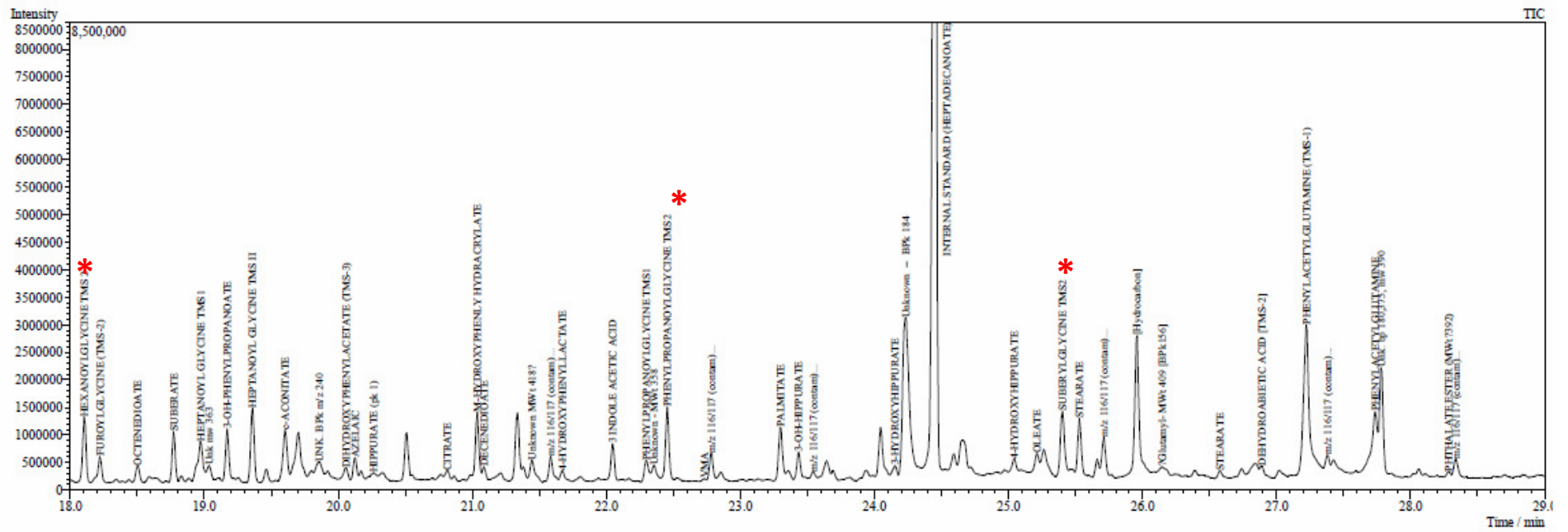
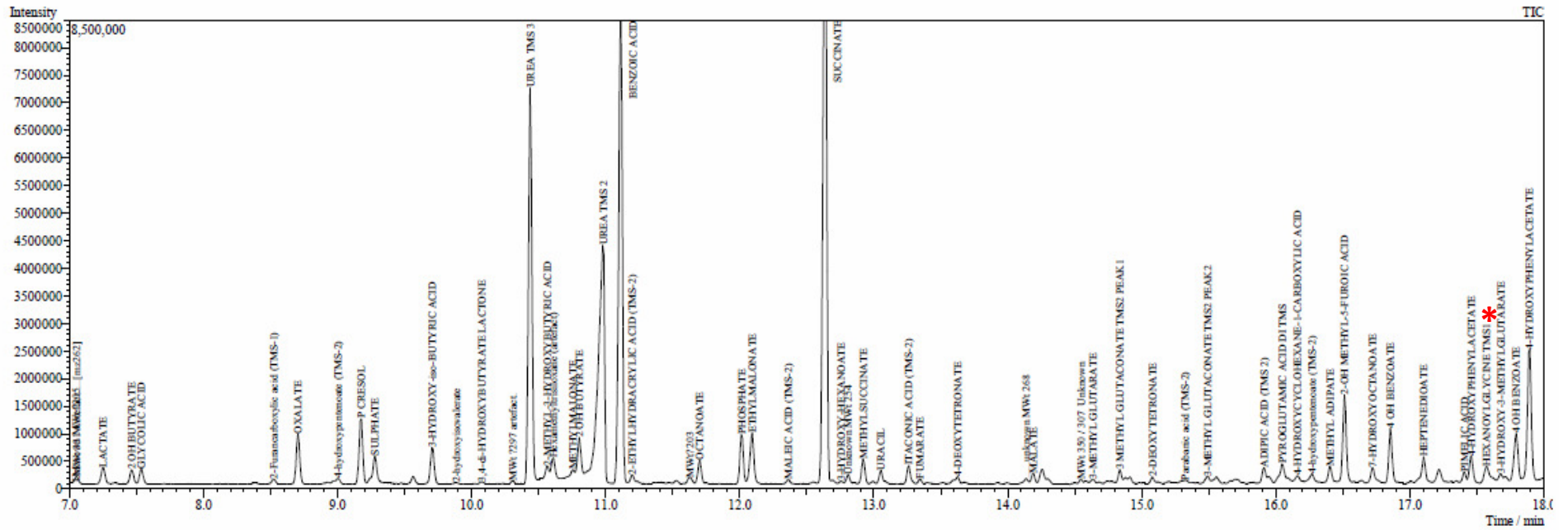
- They are rare Zebras not horses....



- They are biochemically heterogeneous conditions
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- Episodic excretion is common (e.g. intermittent MSUD)

MCAD none crisis sample

86%



How to do better and reduce uncertainty?

- Participation in EQA scheme's
- Training and accreditation
- Clinical details
- Repeat analysis
- Further analysis

Thank you for listening