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To

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Department of General Pediatrics
(General Pediatrics, Neurology, Metabolism, Gastroenterology, Nephrology)
Prof. Dr. med. G.F. Hoffmann
Chairman
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Metabolic Laboratory

Heidelberg, January 26th, 2018

ERNDIM QA Scheme for qualitative urinary organic acid analysis

Annual Report 2017

Participation

The geographical distribution of the active participants of the quality assurance scheme organized and distributed through the centre of Heidelberg in 2017 is shown in Table 1. Sheffield and Heidelberg participate in each other's scheme and the two centers work closely together under the auspices of the ERNDIM Scientific Advisory Committee.

Table 1: Geographical distribution of participants

Country	Number of laboratories		Country	Number of laboratories
Austria	3		Latvia	1
Belgium	1		Lithuania	1
Bulgaria	1		Luxembourg	1
Canada	9		New Zealand	1
China	2		Norway	1
Croatia	1		Philippines	1
Cyprus	1		Poland	2
Czech Republic	2		Serbia	1
Denmark	1		Slovakia	2
Estonia	2		Slovenia	1
France	5		Spain	2
Germany	17		Sweden	2
Greece	1		Switzerland	3
Hungary	1		The Netherlands	8
India	6		Ukraine	1
Italy	13		United Kingdom	1
Kingdom of Saudi Arabia	1		USA	14

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Samples and results

Three sets of three samples (total 9; sample numbers H241 - H249) were distributed to **111 laboratories**.

Table 2 shows the number of returned results for each circulation and the number of late returns.

Table 2: Receipt of results

Circulation	In time returns	Late returns	Total
1. circulation	105	1	106
2. circulation	108	1	109
3. circulation	106	3	109

Ninety-four percent of the participants returned results for all three circulations. One laboratory (1%) did not respond to any of the circulations (see also table 3)

Table 3: returned results

Circulations	Number of laboratories	%
3	104	94
2	6	5
1	0	0
0	1	1

Shipment of the samples

Date of sample dispatch: **06 April 2017**

The samples were sent out by the **Quality Control Center Switzerland (CSCQ)**.

As the years, before the samples for all three circulations were shipped together. This is only for organizational reasons, especially to keep the costs for participating in this scheme as low as possible.
Please remember, the idea of the scheme is to measure the samples evenly spread over the year and to report the results near to the closing date!

Table 4: Distribution of scores for individual samples (number of laboratories making returns)

		4	3	2	1	0
Sample H241	Normal pattern	101	5			
Sample H242	Tyrosinaemia type I	102	2		1	1
Sample H243	Normal pattern *)	100	6			
Sample H244	Normal pattern	101	8			
Sample H245	Isovaleric aciduria	109				
Sample H246	Phenylketonuria	108	1			
Sample H247	Methylmalonic aciduria	108	1			
Sample H248	Normal pattern	106	2	1		
Sample H249	3-methylcrotonyl-CoA carboxylase deficiency	105	2	2		

*) scores corrected

Scoring of results

In 2013 we changed the scoring system from the former scale (-2, -1, 0, +1, +2) to the four-point system (+1, +2, + 3, +4) which is used also in the DPT schemes. In this system a maximum of two points is given each for analytical results and interpretation, with the latter including suggestions for further testing/actions.

4 Correct/satisfactory
3 Helpful but incomplete
2 Unhelpful
1 Slightly misleading
0 Missleading

The total score achievable for a single circulation of three samples is twelve and thirty-six for the whole sample set of nine samples per year.

To obtain satisfactory performance a score of 22 or more should be achieved on three returns and 15 or more when two returns have been submitted.

Another criteria for satisfactory performance will be the absence of any “critical error” which is defined as an error resulting from seriously misleading analytical findings and /or interpretations with serious clinical consequences for the patient.

The final scoring and all proposed critical errors will need to be ratified by the Scientific Advisory Board (SAB).

Further information on the concept of ‘critical error’ can be found in the ERNDIM Newsletters 2015 at www.erndim.org.

Comments on performance

Sample H241:

Patient details: 15-year-old female, acute attacks of ataxia

Known diagnosis: Normal pattern

Analytical details: Nothing specifically

Overall Performance: Typical normal control sample with acceptable performance (94%)

Sample H242:

Patient details: 6-month-old boy presented with hepatosplenomegaly and active rickets, currently under medication

Known diagnosis: Tyrosinaemia type I

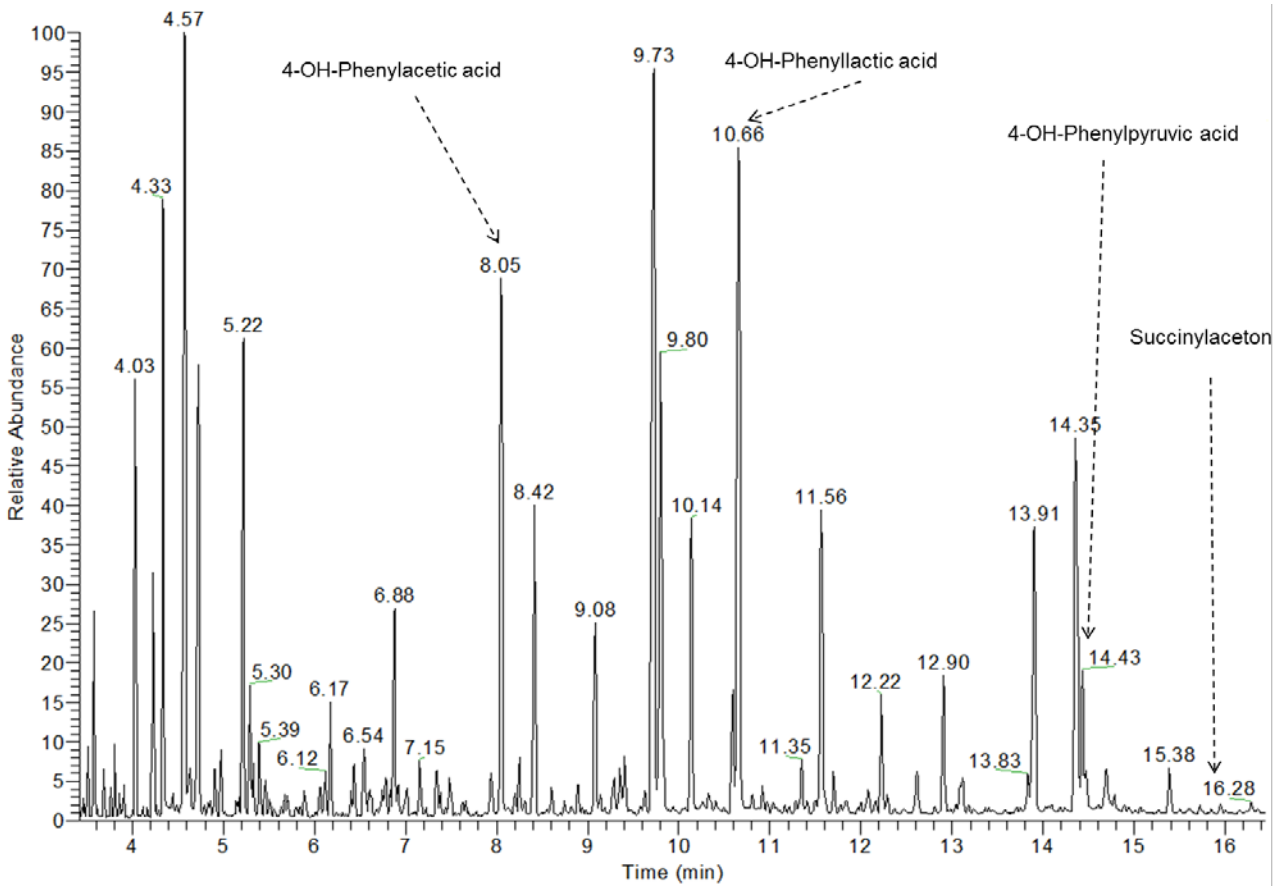
Analytical details: Elevated amount of 4-hydroxyphenylacetic acid, 4-hydroxyphenyllactic acid, 4-hydroxyphenylpyruvic acid.
Succinylacetone is detectable.

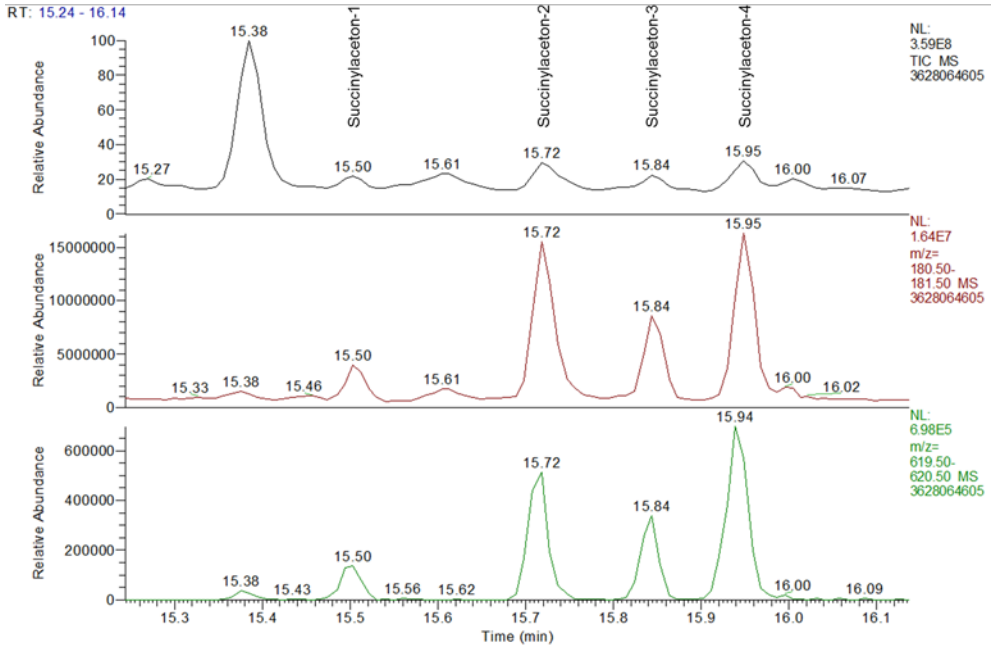
Analytical performance: Most of the labs identified the hydroxylated phenyl compounds (97%) whereas only 38% identified succinylacetone. The low performance for succinylacetone reflects the poor extraction efficiency of this metabolite.

Succinylacetone	mmol/mol creatinine
Heidelberg	8.0
Participants (N=6)	
Mean	2.5
Median	3.0
Min	0.8
Max	4.0

Diagnostic Performance:

Tyrosinaemia was diagnosed by 94% of the participants even though the majority of the labs could not detect succinylacetone.





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Sample H243:

Patient details:

3-year-old boy, hypotonic with seizures

Known diagnosis:

Normal pattern

Analytical details

Nothing specifically

Overall Performance: Quite normal profile with acceptable performance (94%)

Sample H244:

Patient details:

2-year old girl. Failure to thrive

Known diagnosis:

Normal pattern

Analytical details

Nothing specifically

Overall Performance: Rather normal sample. The performance of 92% results from overinterpretation of some analytical findings, mainly glycolic acid and oxalic acid, but also methylmalonic acid and ethylmalonic acid.

Sample H245:

Patient details:

5-year-old boy presented with vomiting and lethargy

Known diagnosis:

Isovaleric aciduria

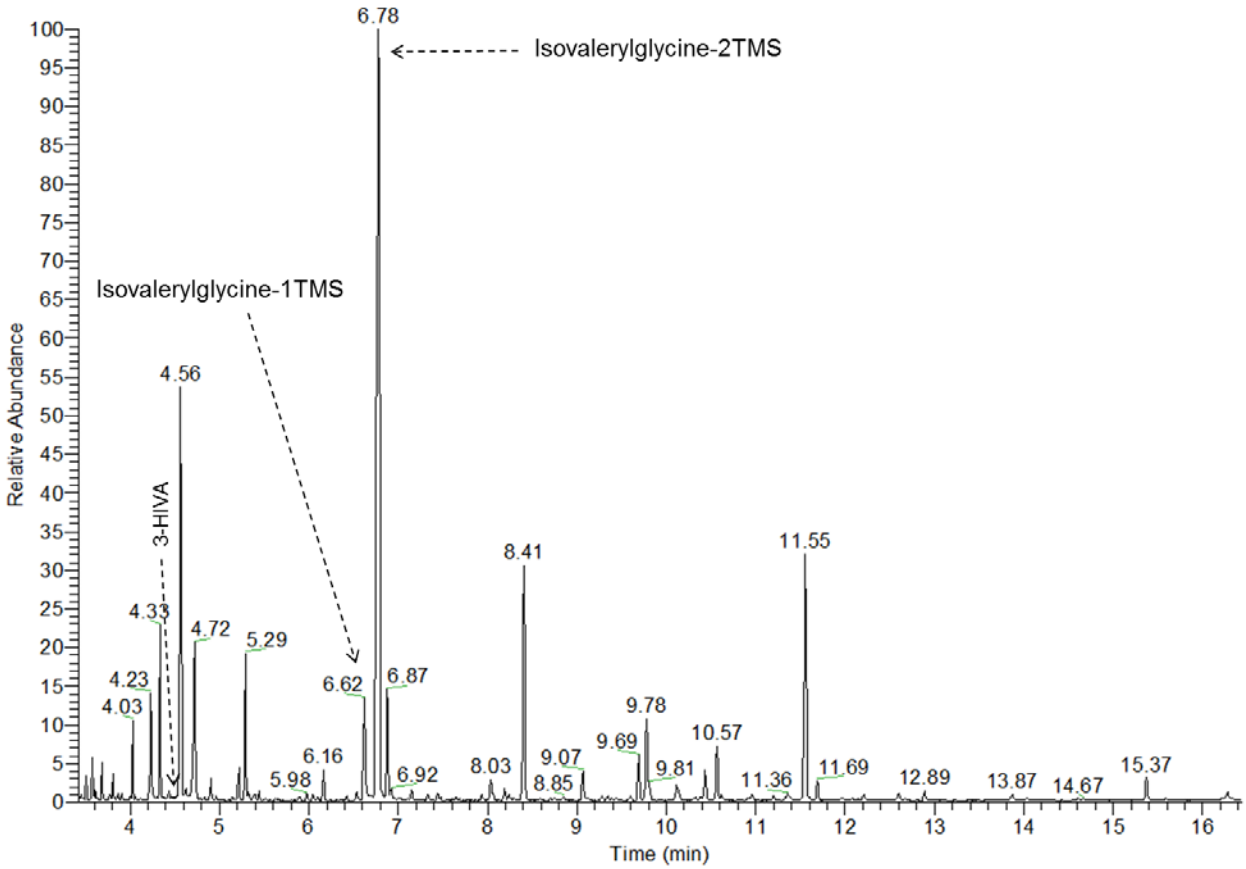
Analytical details:

Elevated amounts of isovalerylglycine

Overall Performance: 100%

The urine was collected from a treated patient in stable condition. Thus 3-hydroxyisovaleric acid was normal. Nevertheless all participants gave the correct diagnosis.

This appeared to be an easy sample for all labs.



Sample H246:

Patient details:

3-year-old boy with microcephaly and mental retardation

Known diagnosis:

Phenylketonuria

Analytical details:

Markedly elevated amounts of phenylacetic acid, mandelic acid, 2-hydroxyphenylacetic acid, phenyllactic acid, 4-hydroxyphenyllactic acid and phenylpyruvic acid.

Analytical performance:

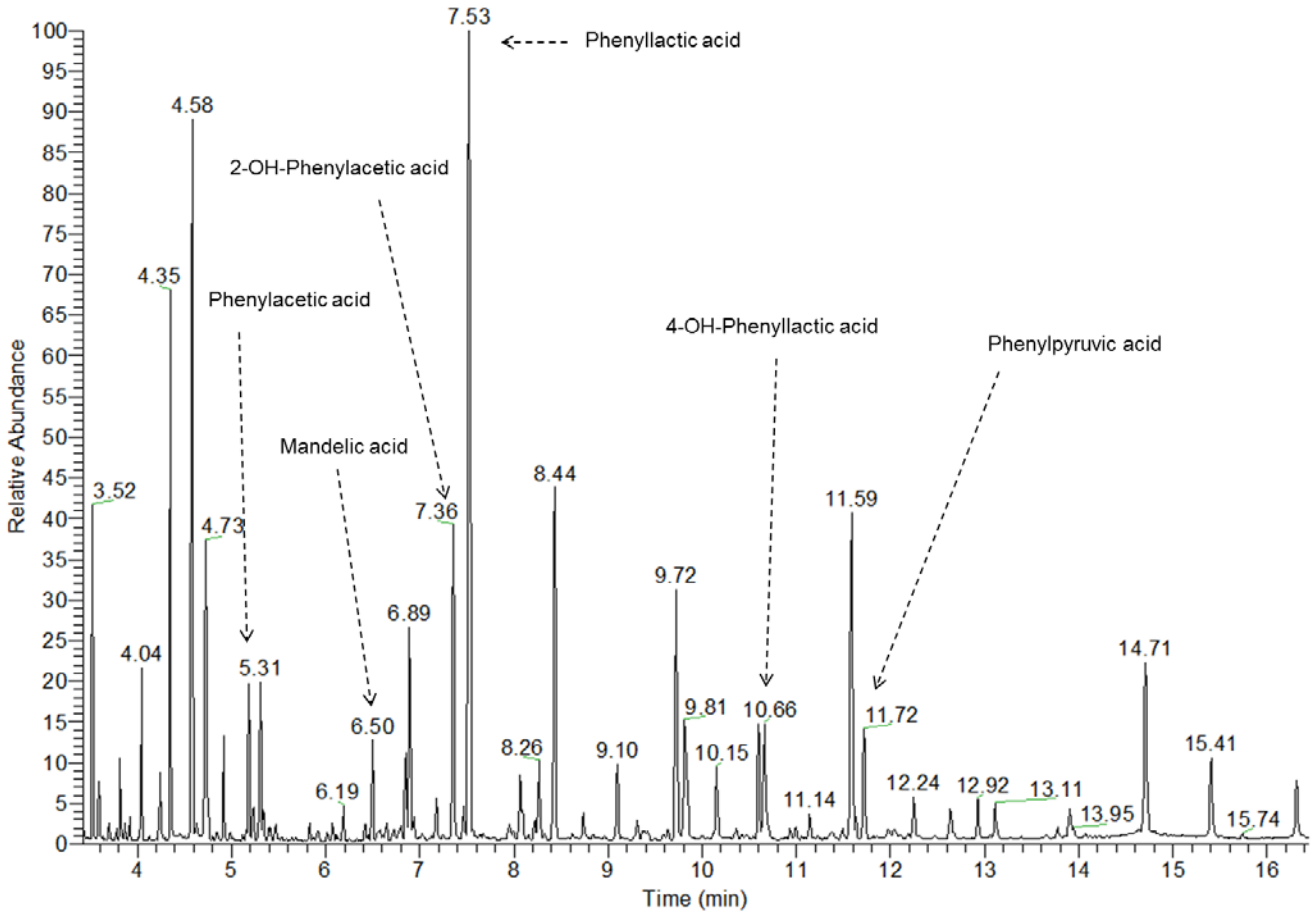
Phenyllactic acid was found by 96% followed by 2-hydroxyphenylacetic acid (81%) and phenylacetic acid (75%). Only 61% of the participants identified phenylpyruvic acid in this urine.

Further metabolites typically elevated in phenylketonuria were reported only by fifty percent of the labs (4-hydroxyphenyllactic acid: 57% and mandelic acid 51%).

Diagnostic Performance: Phenylketonuria was clearly diagnosed by nearly all participants.

One lab gave PKU as its second choice.

This was also a straightforward sample.



Sample 247:

Patient details:

12-month-old girl with developmental delay, seizures and metabolic acidosis

Known diagnosis:

Methylmalonic aciduria (Mut^0)

Analytical details:

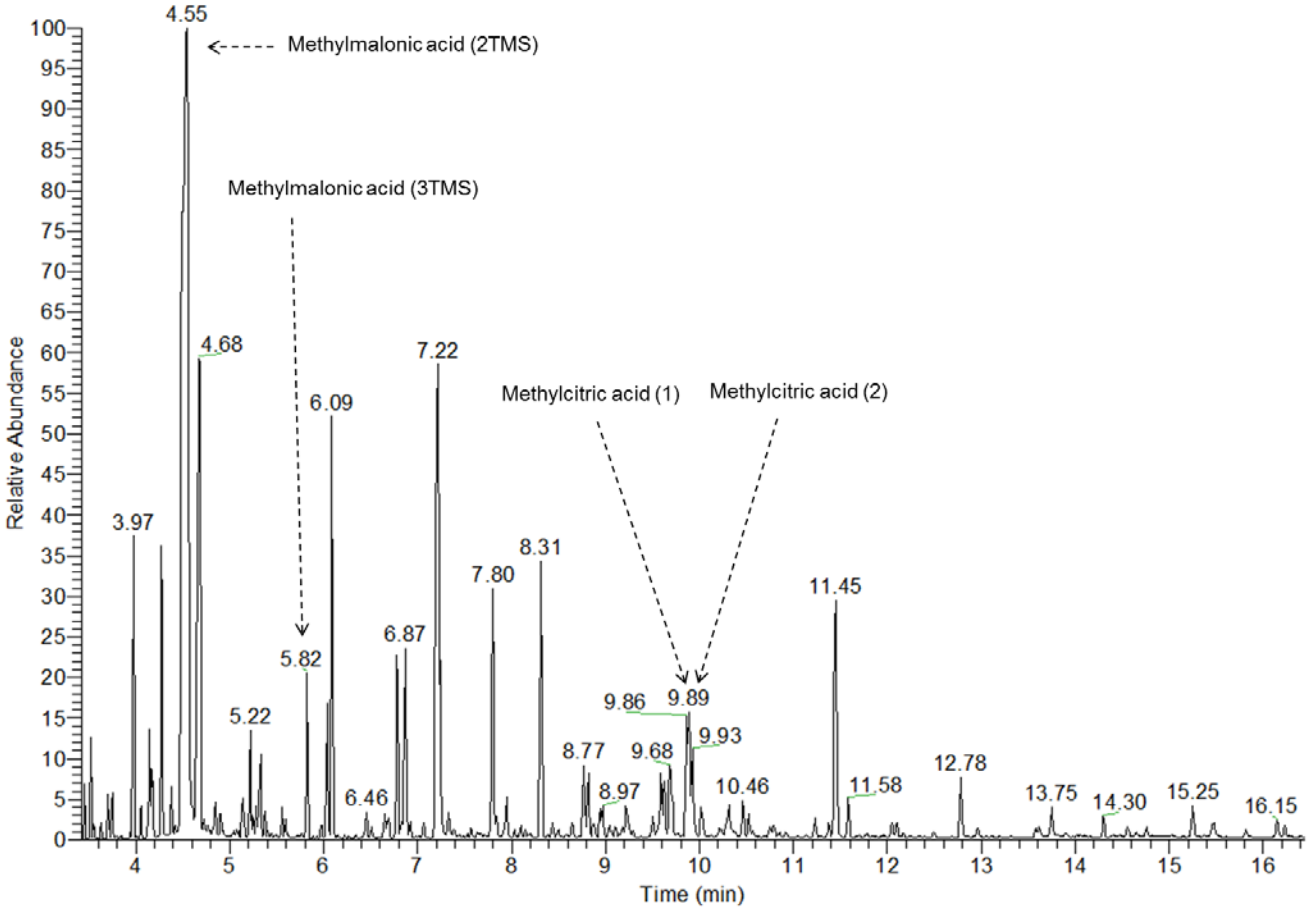
High excretion of methylmalonic acid and methylcitric acid consistent with Mut^0 variant.

The presence of drug metabolites (Levetiracetam) did not infer with the relevant metabolites.

Thus analytical performance was excellent.

Overall Performance: All participants identified the relevant metabolites (100%). The correct diagnosis was given by nearly all, only one lab suggested propionic aciduria in first place and methylmalonic aciduria as second.

As expected the Mut° subtyp of methylmalonic aciduria was not very challenging.



Sample 248:

Patient details:

7-year-old boy, developmental delay

Known diagnosis:

Normal pattern

Analytical details

Nothing specifically

Overall Performance: normal control sample with good performance (96%).

Sample 249:

Patient details:

10-year-old male with muscle weakness

Known diagnosis:

3-methylcrotonylglycinuria (3-methylcrotonyl-CoA carboxylase deficiency)

Analytical details:

Very high excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine.

Analytical Performance:

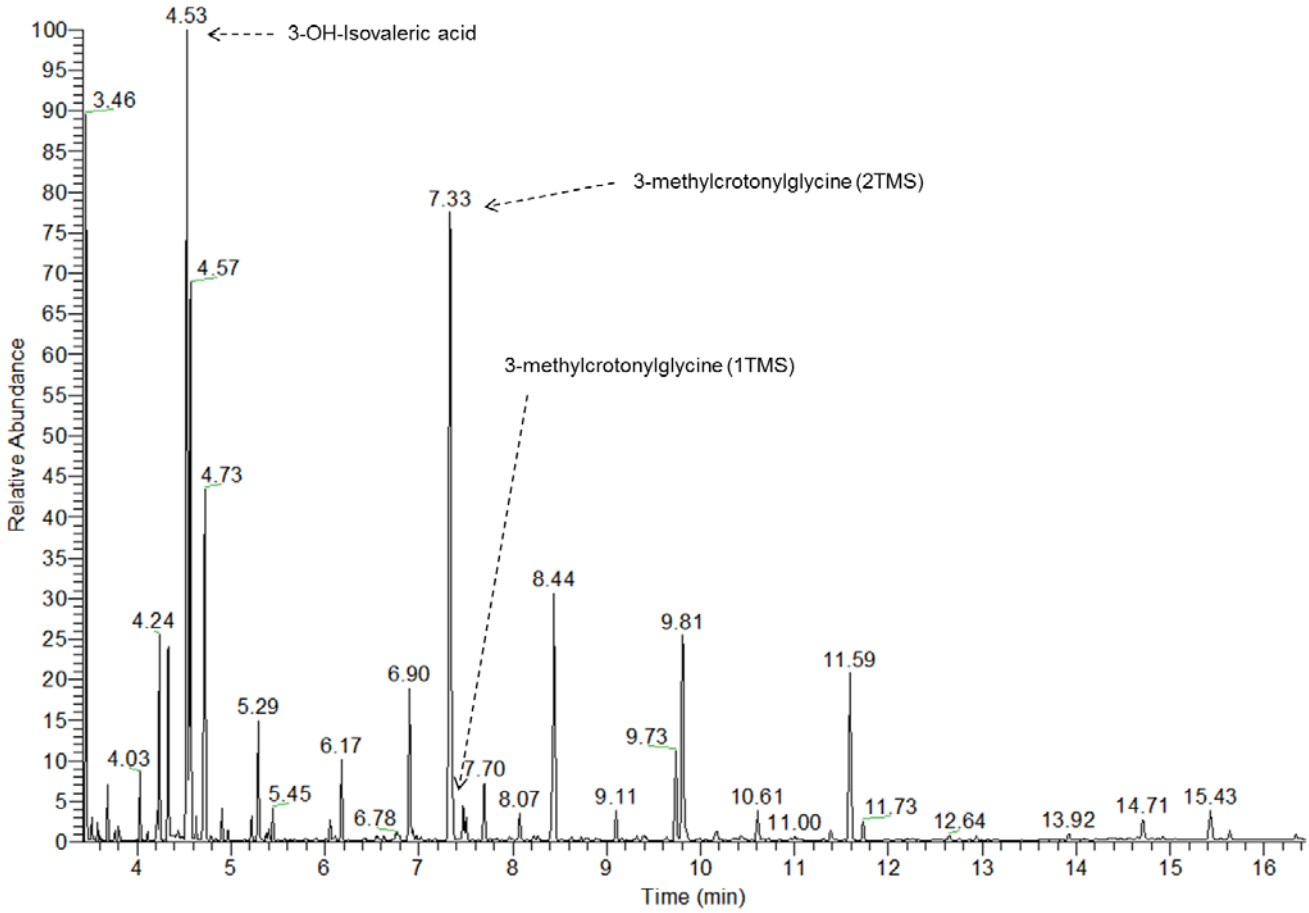
98% of the labs reported 3-hydroxyisovaleric acid and 3-methylcrotonylglycine.

Two labs did not identify 3-methylcrotonylglycine.

Diagnostic Performance:

95% of the participants correctly diagnosed 3-methylcrotonylglycinuria.

Four labs diagnosed a defect in biotin metabolism.



The participants´ cumulative scores are shown in table 5.
Cumulative scores are the scores for the whole year.

Table 5: Cumulative total scores 2013 - 2017
Number of all participants: all registered laboratories
Number of nonresponders: no results returned for any of the three circulations

	Percent of all participants				
Cumulative scores	**2017**	**2016**	**2015**	**2014**	**2013**
36	73	*Sample H235 not scored*	81	54	82
35	14		3	13	-
34	4		8	12	7
33	2		-	1	-
32	2	10	5	6	1
31	-	34	-	3	-
30	-	13	-	2	-
29	-	5	-	1	-
28	-	9	1	1	-
27	-	10	-	-	-
26	-	6	-	-	-
25	-	4	-	-	-
24	4	3	2	4	5
23	1	1	-	-	-
22	-	1	-	-	-
21	1	-	-	1	-
20	-	3	-	-	-
19	-	-	-	-	-
18	-	-	-	-	-
17	-	-	-	-	-
16	-	-	-	-	-
15	-	-	-	-	-
14	-	-	-	-	-
13	-	-	-	-	-
12	-	1	-	-	1
11	-	-	-	-	-
10	-	-	-	-	-
9	-	-	-	-	-
8	-	-	-	-	-
7	-	-	-	-	-
6	-	-	-	-	-
5	-	-	-	-	-
4	-	-	-	-	-
3	-	-	-	-	-
2	-	-	-	-	-
1	-	-	-	-	-
0	1	-	3	2	3
Number of all participants	111	105	103	101	94
Number of Nonresponders	1	1	4	2	3

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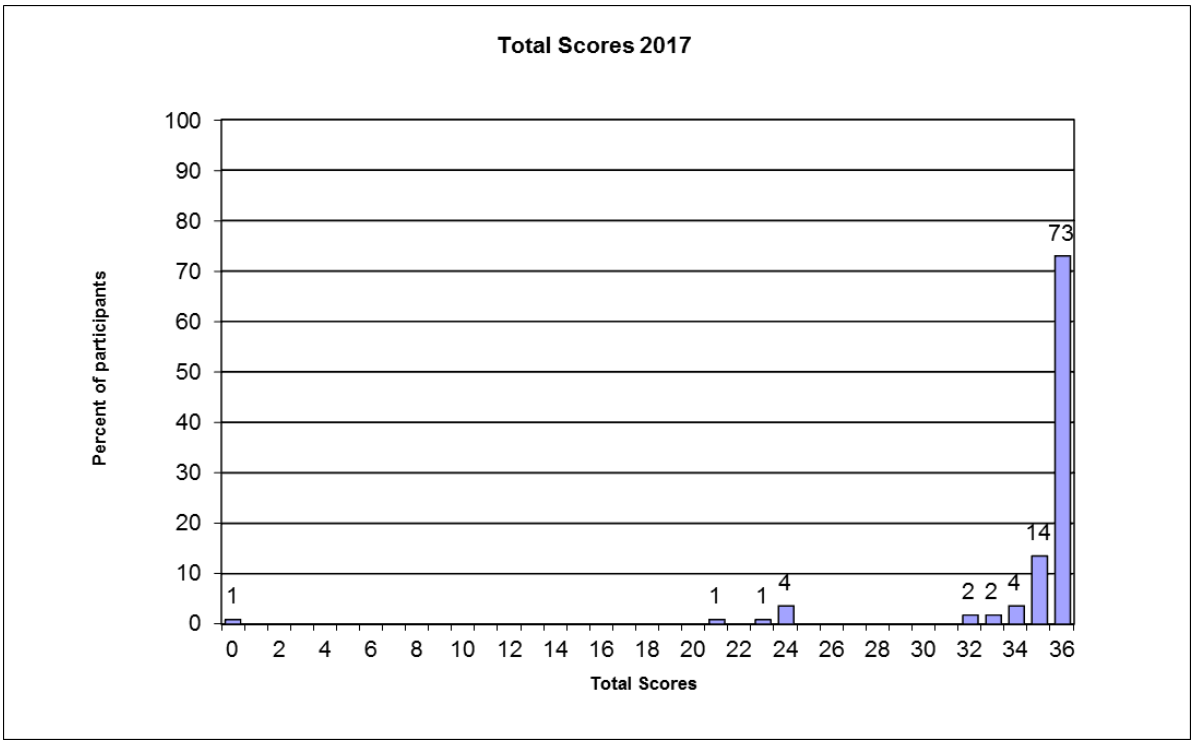
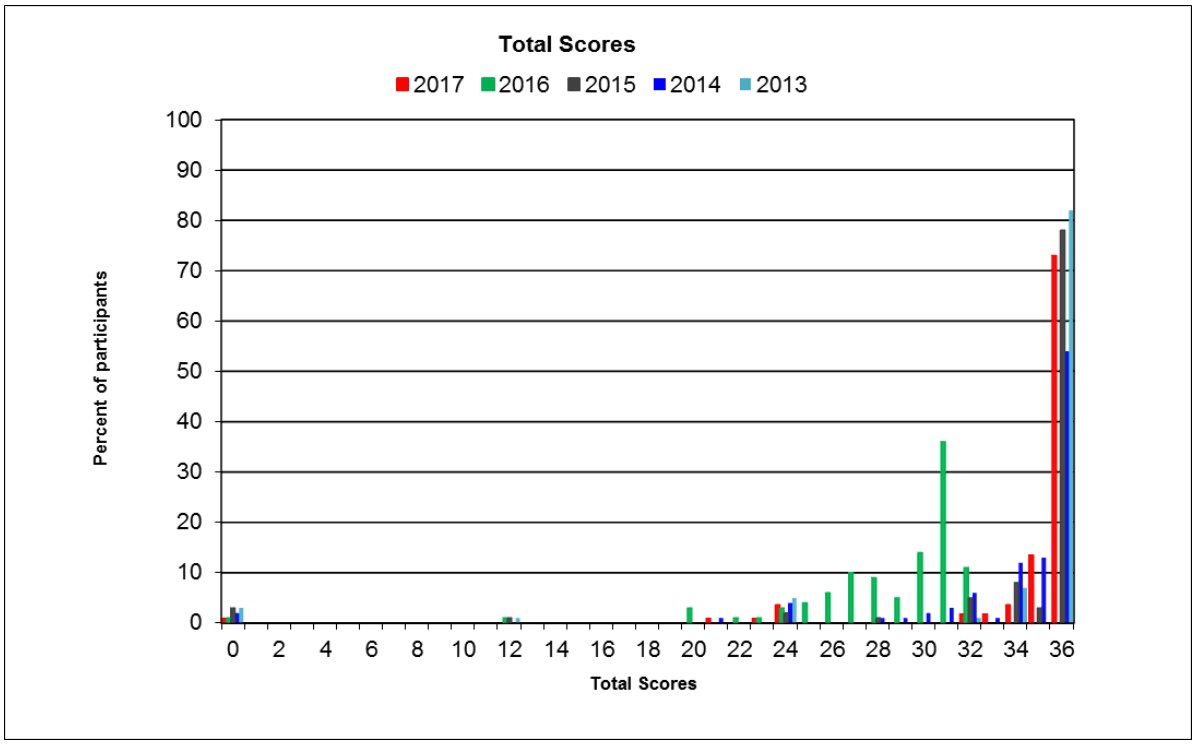
Cumulative scores 2017 (maximum achievable score: 36)





Your individual scores for Sample H241 – H249:

Sample H241:
Sample H242:
Sample H243:
Sample H244:
Sample H245:
Sample H246:
Sample H247:
Sample H248:
Sample H249:

Your total score 2017

Your total score for 2017 was:

Your number of returns in 2017 was:

General comments

We would just like to point out here that we are not able to accept returns sent in after the report for the corresponding circulation has been mailed because this would not be compatible with the overall intention of the scheme. We are conscious of the fact that posted results could get lost on a variety of ways. Therefore it would be a good advice to send in results by more than one route (e.g. FAX and email, regular mail and FAX or email).

Special thank for the laboratories that supported us last year with samples. This is critical for the success of the program and will keep the scheme interesting. Please **continue to support us with urine from patients. It is most appreciated. Please send us at least 300 ml urine of any interesting patients you may have. We will cover the costs.**

New in 2018:

1. Across the different Proficiency Testing Schemes, the score required for satisfactory performance was so far 60% of the total maximum score of a scheme year. Data published by Peters et al. in 2016 showed that proficiency in the Qualitative Organic Acids Scheme improved over the years (Peters V, Bonham JR, Hoffmann, GF, Scott C, Langhans CD; J Inherit Metab Dis 2016, 39, 683).

On this basis the Scientific Advisory Board (SAB) has decided in 2017 that the level required for satisfactory performance will be increased to **70% of the total maximum score** of a scheme year (**25 points on three returns, 17 points on two returns**).
This change was previously announced in the ERNDIM Newsletter 2017.

2. A further change concerns the **submission of results**. In 2017 a selected number of participants tested a website reporting system for the Qualitative Organic Acids Scheme which is already active in the DPT Schemes.
From 2018 on, reports of the samples will be submitted electronically on the website of the **Quality Control Center Switzerland CSCQ**. The website is accessible through https://cscq.hcuge.ch/cscq/ERNDIM/Initial/Initial.php.
For login the ERNDIM user name and the related password has to be used. More detailed information will be provided with the new sample sets.

The use of the website for reporting of the results is mandatory for all participants.

3. In 2018 a **third center for Qualitative Organic Acids** will start at the Biomedical Diagnostic Center (CDB) in Barcelona (Spain) with scheme advisor Dra. Judit García Villoria.

4.A new sample labelling system will be introduced. The serially numbered samples H250 to H258 will change to **QLOU-HD-2018A to QLOU-HD-2018I**

Yours sincerely,

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		Director
Laboratory of Metabolic Diseases	*Laboratory of Metabolic Diseases*	*Department of General Paediatrics*

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