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Overview of ‘Critical Errors’ in the evaluation of interpretive schemes

On behalf of ERNDIM Scientific Advisory Board
George Ruijter
Madrid 9-10-2025

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Critical error briefly

- A critical error is an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management

- A confirmed critical error will lead automatically to the classification ‘failure to achieve satisfactory performance’

- Since 2014

EuroGentest

HARMONIZING GENETIC TESTING ACROSS EUROPE

CE is applied in Qualitative & hybrid ERNDIM schemes

Qualitative Schemes
Diagnostic Proficiency Testing [5 centres]
Organic acids [3 centres]
Acylcarnitines in DBS [3 centres]
Mucopolysaccharides
Congenital Disorders of Glycosylation
Amino Acids Interpretation

Scoring by Scientific Advisor (incl Critical error)

Hybrid Schemes
Cystine in White Blood Cells
Lysosomal Enzymes in Fibroblasts
Neurotransmitters in CSF
Pterins in urine

Data evaluation by statistical analysis
+
Scoring by Scientific Advisor (incl CE)

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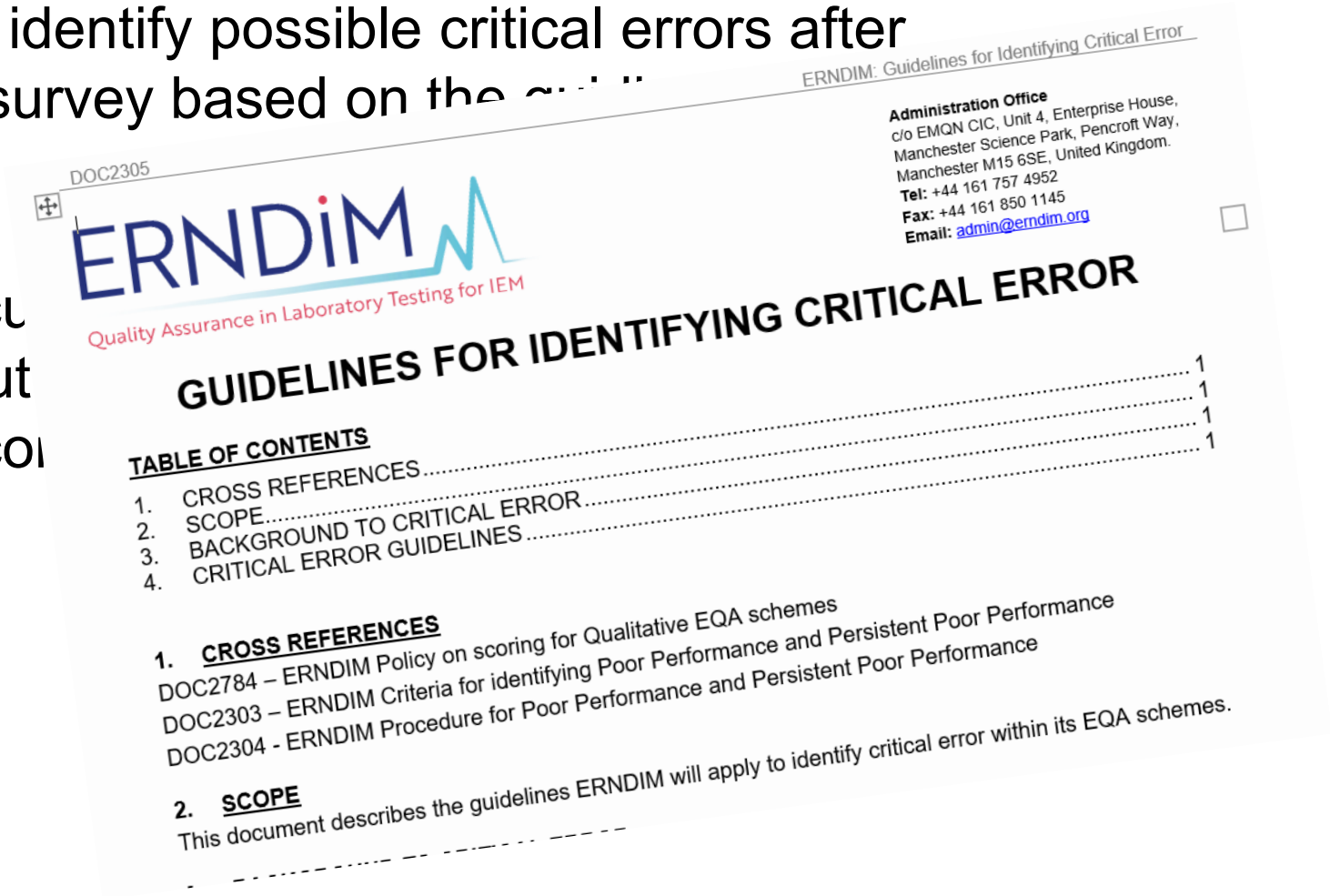
Guiding principles to identify critical error

- If clinical harm is to be expected as a result of wrong conclusions
- Failure to perform a relevant test (DPT only)
- Failure to identify a relevant metabolite(s)
- Failure to establish a diagnosis when proficiency is high (e.g. >95%)
- Lack of useful recommendations when a diagnosis is missed

- Samples with no IEM known generally can NOT result in critical error

Procedure to establish critical error

- Scientific Advisors identify possible critical errors after completion of the survey based on the g... principles
- Proposals are discu... Board during its Aut... discussion either co...



DOC2305

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ERNDIM: Guidelines for Identifying Critical Error

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GUIDELINES FOR IDENTIFYING CRITICAL ERROR

TABLE OF CONTENTS

1. CROSS REFERENCES

DOC2784 – ERNDIM Policy on scoring for Qualitative EQA schemes
DOC2303 – ERNDIM Criteria for identifying Poor Performance and Persistent Poor Performance
DOC2304 - ERNDIM Procedure for Poor Performance and Persistent Poor Performance

2. SCOPE

This document describes the guidelines ERNDIM will apply to identify critical error within its EQA schemes.

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UMPS 2024-B
MPS VII

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Sample ID:	UMPS-NL-2024--B
Clinical features: **Scoring criteria:**	Male, 16 years old GAG abnormal (1p), DS/CS (1p), different combinations including VII (2p)
Analytical findings:	Analytical Performance (AP): 79.5 % Diagnostic Performance (DP): 42.6 % Total Performance (TP): 61.0 %
Correct Diagnosis:	MPS-VII
Acceptable recommendations:	None
% of participants with correct diagnosis:	MPS-VII (33/88, 37.5%), normal profile/no diagnosis (n=15) A number of labs (n=7) missed points in the diagnostic follow-up of the results. MPS-VII was not mentioned in the differential diagnosis. …22.4%) and was educational in 2018. …considered eligible for CE. …ional labs with satisfactory performance …minimum, 70% of 20p).

Low proficiency
CE: sample not eligible

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QLOU-Heidelberg 2024-D Alkaptonuria

Sample ID:	D (Alkaptonuria)
Clinical features:	Man aged 45 years with severe back pain.
Analytical findings:	Homogentisic acid elevated → 2 pts (720 mmol/mol CTN)
Correct Diagnosis:	Alkaptonuria → 2 pts
Acceptable recommendations:	genetics, enzyme activity
% of participants with correct diagnosis:	70/74 (95%)

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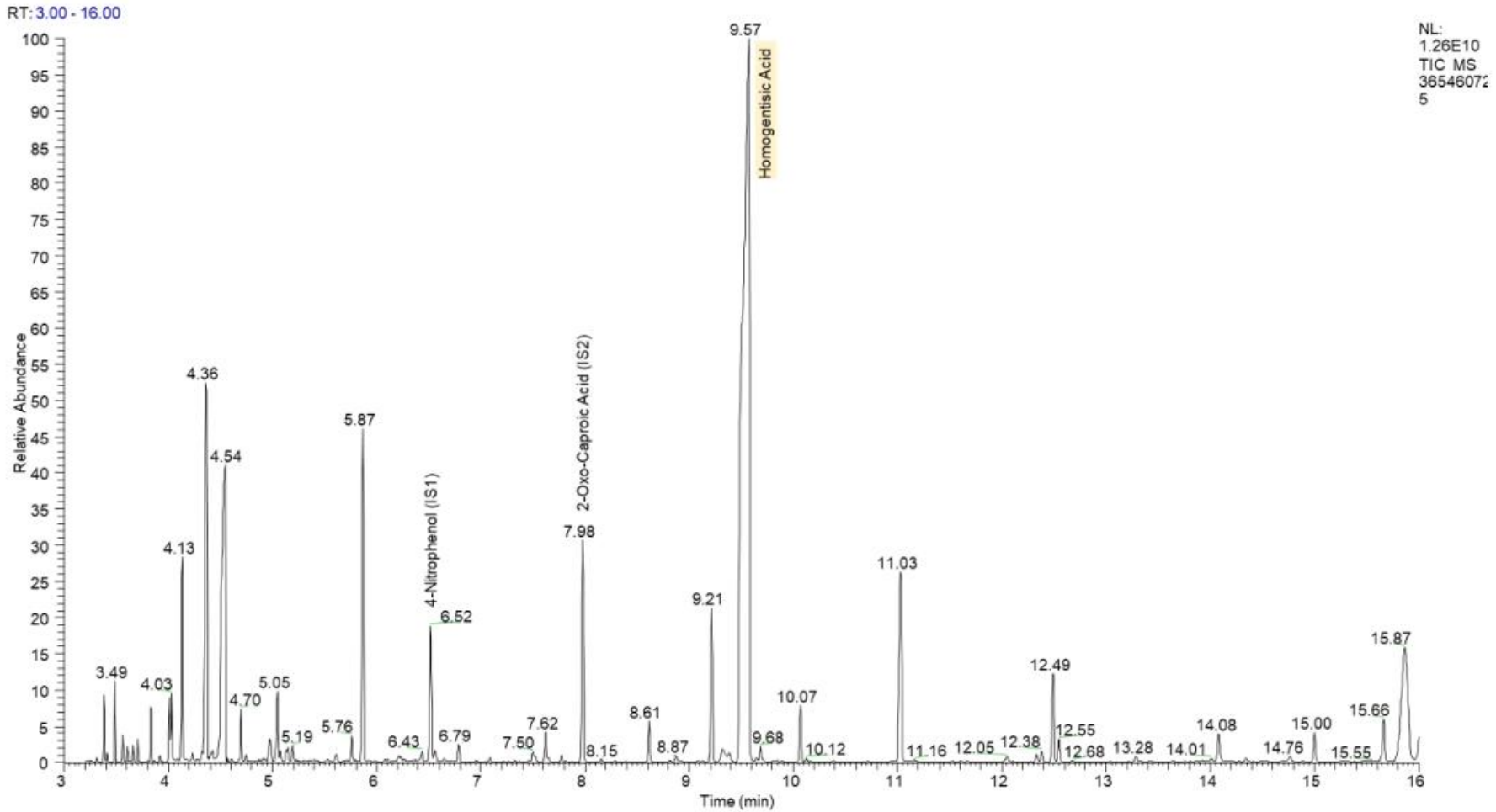
QLOU-Heidelberg 2024-D Alkaptonuria



Example chromatogram for sample D highlighting the key metabolite, homogentisic acid.

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QLOU-Heidelberg 2024-D
Alkaptonuria

Lab ID (do not use ERN code)	**CE agreed?**	**Diagnosis given**	**Alternate diagnoses suggested**	**Recommendations**	**Notes on analytical findings** (SAs review)
Lab 38	**Yes**	Malonic aciduria	-	Genetics for “the particular muration”	malonic, malic, citric, 4OH-phenyllactic: GE lactic, succinic, methyl-malonic, homovanillic: E
Lab 48	**Yes**	no abnormalities	-	no further investigation is required	glycolic acid: E
Lab 50	**Yes**	dietary behaviour, paracetamol	mild hyperoxaluria 1	Anamnesis of medication, dietary habits and history of urolithiasis.	glycolic, 3OH-propionic, 5-oxoproline: E
Lab 76	**Yes**	Malonic acidemia		ACs in blood, genetics	malonic acid: E

Clear abnormalities
Treatable disorder
CE: incorrect diagnosis & lack of useful recommendations
n=4

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QLOU-Barcelona 2024-F
GA I

Sample ID:	QLOU-EB-2024-F
Clinical features:	Patient diagnosed at 15 months of age with movement disorders and psychomotor retardation. Currently he is under treatment and presents with a tetraparesia.
Analytical findings:	Detection of glutarate and 3-hydroxyglutarate
Correct Diagnosis:	Glutaric aciduria type I, low excretor
Acceptable recommendations:	Amino acids, Acylcarnitines, molecular analysis
% of participants with correct diagnosis:	96% (68/71)

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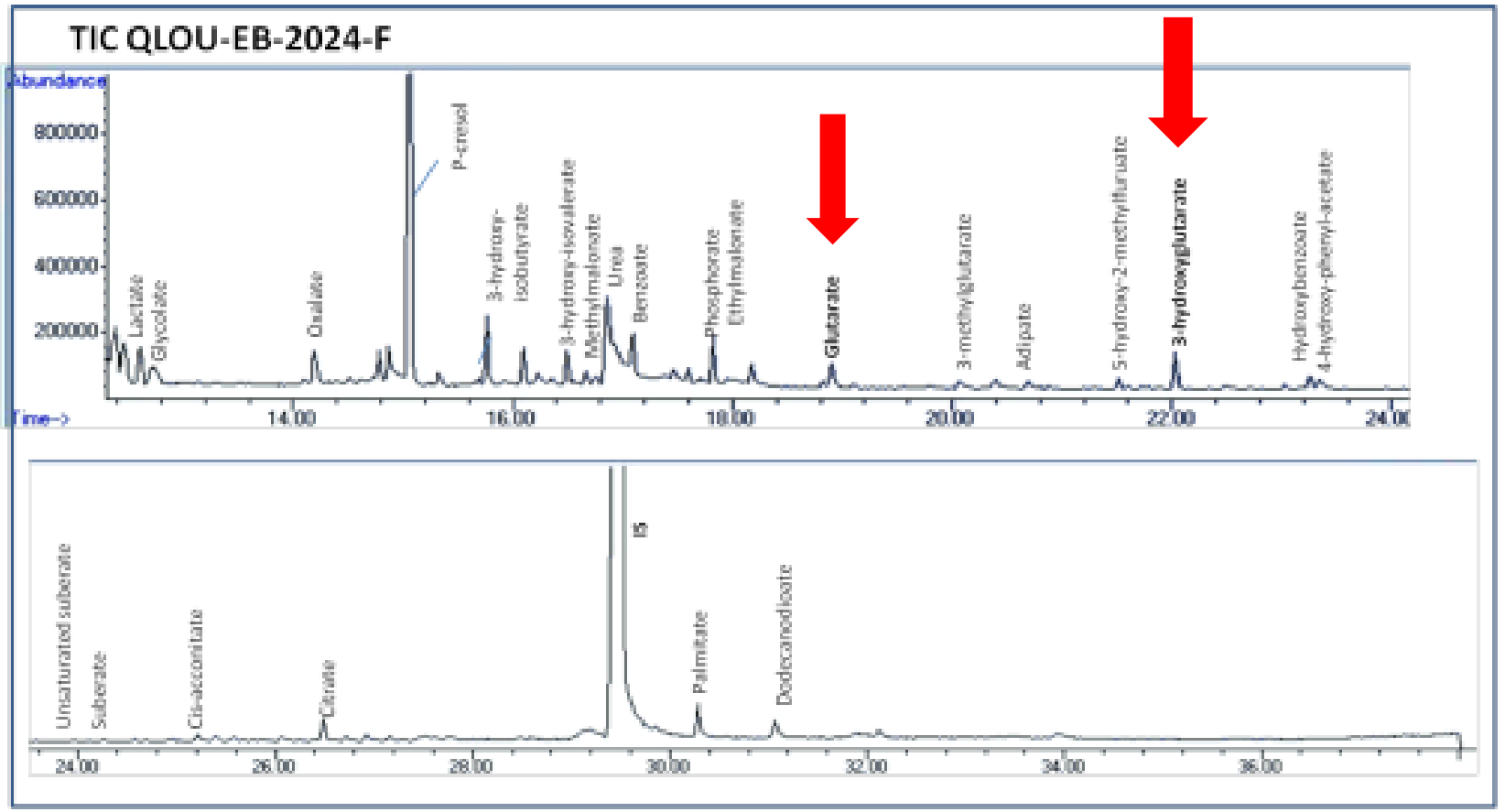
QLOU-Barcelona 2024-F
GA I



TIC QLOU-EB-2024-F

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QLOU-Barcelona 2024-F
GA I

Lab ID (do not use ERN code)	**CE agreed?**	**Diagnosis given**	**Alternate diagnoses suggested**	**Recommendations**	**Notes on analytical findings** (SAs review)
Lab 1	**Yes**	D-2-hydroyglutaric aciduria	L-2-hydroyglutaric aciduria	Acylcarnitines and NGS	*Increase of glutarate and D-2-OHglutarate*
Lab 2	**Yes**	Lipoic acid deficiency	None	Genetics related lipoic acid disorders	*Increase of 2-Ohbutyric acid, 3-OH-glutaric acid, 2 ketoglutaric acid*
Lab 3	**Yes**	3-methylglutaconic aciduria	None	Molecualr testinf for 3MGA	Icrease of 3-methylglutaconic acid, 3-methylglutaric acid and 3-Ohisovaleric acid

Clear abnormalities
Treatable disorder
CE: incorrect diagnosis & lack of useful recommendations
n=3

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DPT-CZ 2024-B
α-mannosidosis

Sample ID:	Sample B
Clinical features:	This girl was referred at the age of 1 year for facial dysmorphia.
Analytical findings:	oligosaccharides profile characteristic for alpha-mannosidosis
Correct Diagnosis:	alpha-mannosidosis
Acceptable recommendations:	enzyme activity, mutation analysis
% of participants with correct diagnosis:	75 (12/16)

NB. Multiple α-mannosidosis circulated in DPT-CZ (2020-C, 2021-A, 2022-D)

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DPT-CZ 2024-B
α-mannosidosis

Lab ID (do not use ERN code)	**CE agreed?**	**Diagnosis given**	**Alternate diagnoses suggested**	**Recommendations**	**Notes on analytical findings** (SAs review)
Lab 1	**Yes**	No metabolic disorder.	Other genetic disorders with facial dysmorphia.	WES (or WGS) in order to determine the diagnosis.	Normal profile of both glycosaminoglycans and oligosaccharides.
Lab 2	**Yes**	The patient does not suffer from a disease that can be diagnosed by the performed analyses. There is unremarkable excretion of oligosaccharides and electrophoresis of GAG **(analyses performed by our cluster laboratory),** which together with the normal quantitative GAG exclude several oligosaccharidoses and mucopolysaccharidoses.			
Lab 3	**Yes**	Disorder of pyrimidine degradation	Other disorders/syndromes causing dysmorphism	When available pyrimidines should be analysed in urine. Nowadays panel WES of pyrimidine	Normal profile of oligosaccharides Elevated beta-alanine
Lab 4					not

Treatable disorder
Despite relatively low proficiency
CE: incorrect diagnosis & lack of useful recommendations
n=3

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DPT-F 2024-D
Adenylosuccinate lyase def

Sample ID: D	
Clinical features:	Boy, 5 years. He presents severe psychomotor retardation with stereotypies since 10 months old. His brother also presents the same clinical picture.
Analytical findings:	S-Ado : median = 95 mmol/mol creat SAICAr : median = 73 mmol/mol creat
Correct Diagnosis:	Adenylosuccinate lyase deficiency
Acceptable recommendations:	Confirm diagnosis by *ADSL* genetic analysis Perform purines & pyrimidines if not done
% of participants with correct diagnosis:	75 (16/20) 4 / 20 : cystathioninuria; 2 of them recommended to perform purines & pyrimidines analysis

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DPT-F 2024-D
Adenylosuccinate lyase def

Lab ID (do not use ERN code)	**CE Agreed?**	**Diagnosis given**	**Alternate diagnoses suggested**	**Recommendations**	**Notes on analytical findings** (SAs review)
Lab 1	**No**	Cystathionuria	-	Plasma AA, acylcarnitines, *CTH* gene	
Lab 2	**No**	Cystathionuria	Remethylation defect	Plasma AA, total homocystein, **Bratton-Marshall test**	
Lab 3	**No**	Cystathionuria	-	Plasma AA, total homocystein, **purines & pyrimidines**, *CTH* gene	
Lab 4	**No**	Cystathionuria	-	No clinical significance	

NOT a treatable disorder
Relatively low proficiency
Sample not eligible for Critical Error

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ACDB-Heidelberg 2024-D
HMG-CoA lyase deficiency

Sample ID:	**D (HMG CLD)**
Clinical features:	Boy of eight years who presented first 3 years ago with hepatomegaly and seizures.
Analytical findings:	C5OH (/C4DC) elevated → 1pt C6DC (/me-glut) elevated → 1pt
Correct Diagnosis:	HMG CLD as principal diag. → 2pts HMG CLD as alt. diag. → 1 pt (+1 for useful recommendations)
Acceptable recommendations:	UOA, suitable genetics panel
% of participants with correct diagnosis: (41 submissions)	90% (37/41) 82.9% analytical prof. 90.2% interpretation prof.

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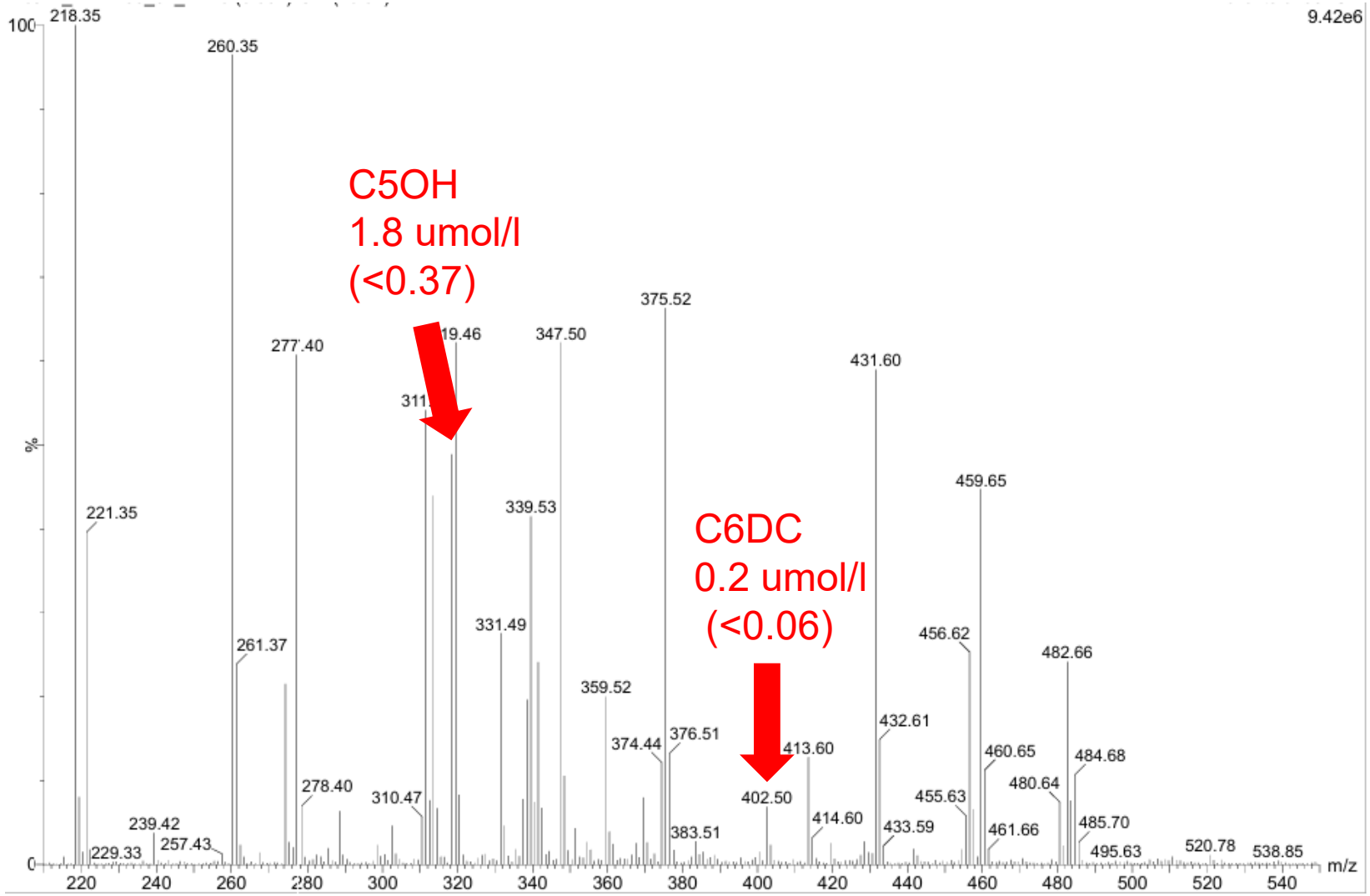
ACDB-Heidelberg 2024-D
HMG-CoA lyase deficiency



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ACDB-Heidelberg 2024-D
HMG-CoA lyase deficiency

Lab ID (do not use ERN code)	**CE agreed?**	**Diagnosis given**	**Alternate diagnoses suggested**	**Recommendations**	**Notes on analytical findings** (SAs review)
Lab 9	No	MMA or MGA, type I	-	**UOA profile**	**C5OH**/C4DC: E (1 pt)
Lab 14	No	B12 metabolism disorder	B12 deficiency, MMA	**UOA** and AA profiles, B12 measurement	**C5OH**/C4DC: GE (1 pt)
Lab 42	**Yes**	IVA	-	-	C0 & C3 normal, "C5 OH 3OH ISOVALERYL": E (1 pt)
Lab 43	No	MADD	-	**UOA**, plasma OA, genetics	**C6DC**: E (1 pt) C16OH, C16:1OH, C18OH: E

Treatable disorder

CE: incorrect diagnosis & lack of useful recommendations

n=1

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ACDB-London 2024-D
VLCAD deficiency

Sample ID:	ACDB-UL-2024-D
Clinical features:	Sibling with metabolic disorder. On treatment.
Analytical findings:	37/44 identified increased C14:1 and/or increases in appropriate ratios 4/44 abnormalities associated with CPT2 deficiency 3/44 normal profile
Correct Diagnosis:	VLCADD (subtle abnormalities)
Acceptable recommendations:	Genetic analysis of *ACADVL* gene Enzyme analysis (VLCAD specifically or FAOD flux studies) Plasma acylcarnitines Urine organic acids
% of participants with correct diagnosis:	86% (38/44) Others suggested CPT2 but gave appropriate follow-up tests to identify VLCADD including plasma acylcarnitines

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Lab ID (do not use ERN code)	**CE agreed?**	**Diagnosis given**	**Alternate diagnoses suggested**	**Recommendations**	**Notes on analytical findings** (SAs review)
Lab 3	**No** (0 score agreed)	Normal	None	None	N/A

Treatable disorder
Acylcarnitine abnormalities subtle
Sample not eligible for Critical Error

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Conclusions

1) In short: A critical error is an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management

2) Critical errors are must be ratified by the Scientific Advisory Board

3) Absence of critical error is required to achieve satisfactory performance in a scheme

4) Critical errors are applied on the basis of guidelines

Questions & suggestions: Scientific Advisors