Clin. Lab. 2024;70:XXX-XXX

ORIGINAL ARTICLE

Result of a Pilot External Quality Assessment Scheme for Clinical Diagnosis of Inherited Metabolic Disorders in China

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SUMMARY

Background: **We aimed to evaluate the diagnostic capabilities of Chinese laboratories for inherited metabolic disorders (IMDs) using gas chromatography-mass spectrometry (GC-MS) on urine samples. Meanwhile, based on the result of the pilot external quality assessment (EQA) scheme, we hope to establish a standardized and reliable procedure for future EQA practice.**

Methods: **We recruited laboratories that participated in the EQA of quantitative analysis of urinary organic acids with GC-MS before joining the surveys. In each survey, a set of five real urine samples was distributed to each participant. The participants should analyze the sample by GC-MS and report the "analytical result", "the most likely diagnosis", and "recommendation for further tests" to the NCCL before the deadline.**

Results: **A total of 21 laboratories participated in the scheme. The pass rates were 94.4% in 2020 and 89.5% in 2021. For all eight IMDs tested, the analytical proficiency rates ranged from 84.7% - 100%, and the interpretational performance rate ranged from 88.2% - 97.0%. The performance on hyperphenylalaninemia (HPA), 3-methylcrotonyl-CoA carboxylase deficiency (MCCD), and ethylmalonic encephalopathy (EE) samples were not satisfactory.**

Conclusions: **In general, the participants of this pilot EQA scheme are equipped with the basic capability for qualitative organic acid analysis and interpretation of the results. Limited by the small size of laboratories and samples involved, this activity could not fully reflect the state of clinical practice of Chinese laboratories. NCCL will improve the EQA scheme and implement more EQA activities in the future.**

(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2023.230909)

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Manuscript accepted October 12, 2023

Supplementary Data

Table S1. Basic information and clinical features of quality control samples.

Batch number	Patient information (age, gender and specific clinical features)	Inherited metabolic disorder	Abnormal organic acid for diagnosis	Recommended further diagnostic strategies
202011	A 2-year-old boy with hypoevolutism, twitching, hypomyotonia, metabolic acidosis and craniocerebral injury	Methylmalonic acidemia (MMA)	Methylmalonic acid, Methylcitric acid, 3-hydroxy-propionic acid	Amino acids and acylcarnitine profile in blood or plasma; Measurement of homocysteine levels in blood or urine; Evaluatioin of responsiveness for parenteral vitamin B12; Genetic testing for deficiencies of MMUT (OMIM #251000), MMAA (OMIM #251100), MMAB (OMIM #251110) and truncating mutations towards the N-terminal in the MMADHC gene (OMIM #277410)
202012	A 10-year-old boy with seizures, abnormal muscle tone, microcephaly, intellectual-motor backwardness, poor limb coordination, yellowing hair and malnutrition.	Hyperphenylalaninemia (HPA)	Phenylacetic acid, Phenyllactic acid, Phenylpyruvic acid	Blood phenylalanine level testing; Urinary pteridine analysis; Measurement of dihydropteridine reductase (DHPR) activity in blood; Genetic testing for phenylalanine hydroxylase (*PAH*); Evaluation of responsiveness for tetrahydrobiopterin
202013	A 14-month-old girl with intellectual motor regression after six months of birth, cerebral basal ganglia damage, increase in head circum ference, feeding intolerance, malnutrition, hypomyotonia, hypoevolutism and retardation of bone age	Glutaric acidemia type I (GA I)	Glutaric acid, 3-hydroxyglutaric acid	Amino acids and acylcarnitine profile in blood; Medical imaging tests, such as Magnetic Resonance Imaging (MRI) or CT scans; Enzyme analysis for glutaryl-CoA dehydrogenase (GCDH); Genetic testing for *GCDH* gene
202014	A 3-year-and-3-months-old girl with vomitting, diarrhea, hypoevolutism, dyskinesia, skin lesions, partial seizure and myocardiopathy	3-methylcrotonyl-CoA carboxylase deficiency (MCCD)	3-hydroxy-isovaleric acid, 3-Methylcro-tonylglycine	Amino acids and acylcarnitine profile in blood; Enzyme analysis for biotinidase; Genetic testing for methylcrotonyl-CoA carboxylase subunit 1 (*MCCC1*) and methylcrotonyl-CoA carboxylase subunit 2 (*MCCC2)* genes
202015	A 7-year-old boy with anorexia, drowsiness and hypoevolutism	Negative control	NA	Amino acids and acylcarnitine profile in blood; Further differential diagnosis in conjunction with clinical consultation
202111	An 18-month-old boy with vomitting, drowsiness, and metabolic acidosis after infection	Isovaleric acidemia (IVA)	Isovalerylglycine, 3-hydroxy-isovaleric acid	Amino acids and acylcarnitine profile in blood; Medical imaging test (brain MRI); Enzyme analysis of Isovaleric acid-CoA dehydrogenase (IVD) activity; Genetic testing for *IVD* gene
202112	A 6-year-old girl with ataxia after infection	Negative control	NA	Amino acids and acylcarnitine profile in blood; Further differential diagnosis in conjunction with clinical consultation
202113	A 4-year-and-1-month-old girl with hypoevolutism, epilepsy and dystonia	Succinic semialdehyde dehydrogenase deficiency (SSADHD)	4-hydroxy-butyric acid	Amino acids and acylcarnitine profile in blood; Medical imaging test (brain MRI); Enzyme analysis for Succinic semialdehyde dehydrogenase (SSADH) activity; Genetic testing for *ALDH5A1* (aldhehyde dehydrogenase 5a1) gene
202114	A 22-month-old boy with hypoevolutism, convulsion and cardiomyopathy with liver damage	Propionic acidemia (PA)	3-hydroxy-propionic acid, Methylcitric acid	Amino acids and acylcarnitine profile in blood; Electrocardiogram (ECG); Medical imaging test (brain CT and MRI); Genetic testing for propionyl-CoA carboxylase subunit alpha (*PCCA*) and propionyl-CoA carboxylase subunit beta (*PCCB*) genes
202115	A 5-month-and-10-day-old boy with hydrocephalus, epilepsy, intelligence and motor delayed and hypomyotonia	Ethylmalonic encephalopathy (EE)	Ethylmalonic acid	Amino acids and acylcarnitine profile in blood; Medical imaging test (brain CT and MRI); Genetic testing for ETHE1 persulfide dioxygenase (*ETHE1*) gene

Table S2. Score Scheme.

Grade	Analytical findings	The most likely diagnosis	Recommendation for further test	Requirements
Excellent	4’	11 - 12’	4’	Consistent with reference results, with the accurate diagnosis and/or follow-up protocols
Good	3’	8 - 10’	3’	Similar to reference results, with the acceptable diagnosis and/or follow-up
Neutral	2’	5 - 7’	2’	Partially similar to the reference result, with no help to diagnosis and/or follow-up, but no harm
Poor	1’	1 - 4’	1’	Different from reference results, result in wrong diagnosis and/or follow-up
Very poor	0’	0’	0’	Different from reference results, result in serious diagnostic errors and/or inappropriate follow-up

Table S3. The schedule of the pilot EQA scheme.

Survey	Sample number	Sample testing date	Results submitted deadline	Quality assessment grades posted date
First	202011, 202012, 202013, 202014, 202015	2020/11/5	2020/11/20	2020/11/30
Second	202111, 202112, 202113, 202114, 202115	2021/11/22	2021/11/30	2022/1/20

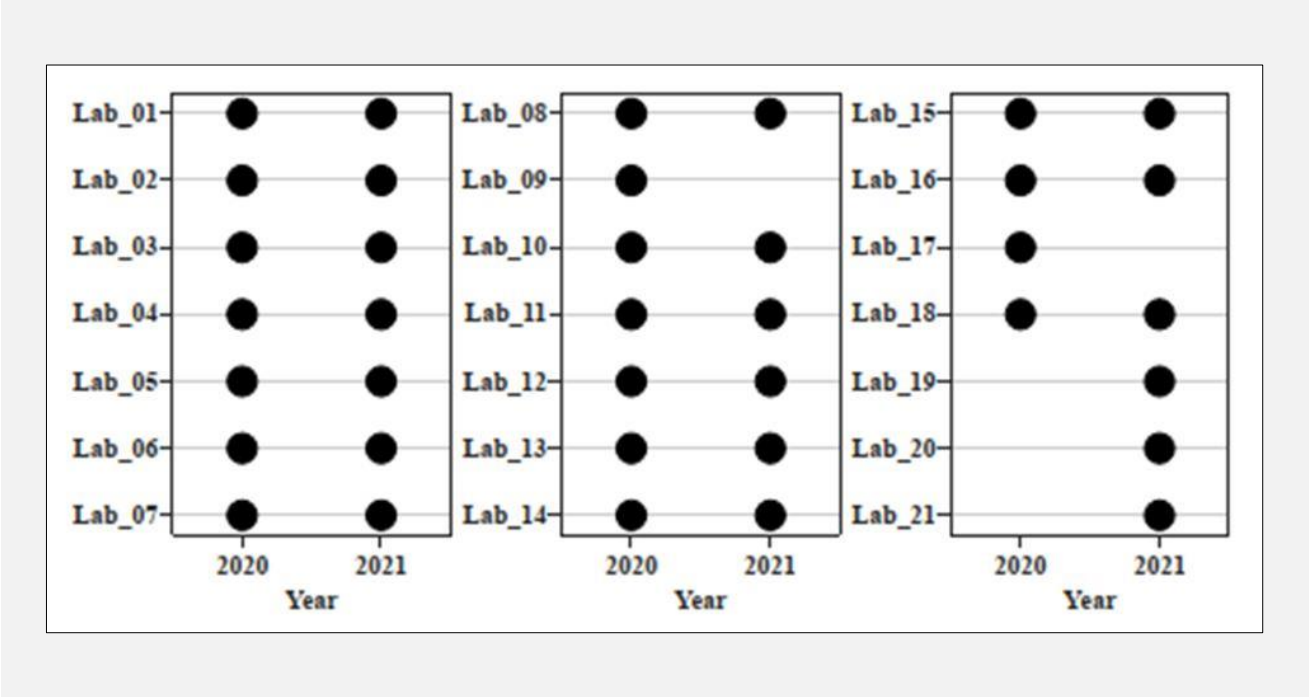

Figure 1. Laboratory attendance chart of the surveys in 2020 and 2021.

A total of 21 laboratories enrolled for this pilot EQA scheme, 16 participated in both surveys, 2 participated in 2020 only, and 3 participated in 2021 only.

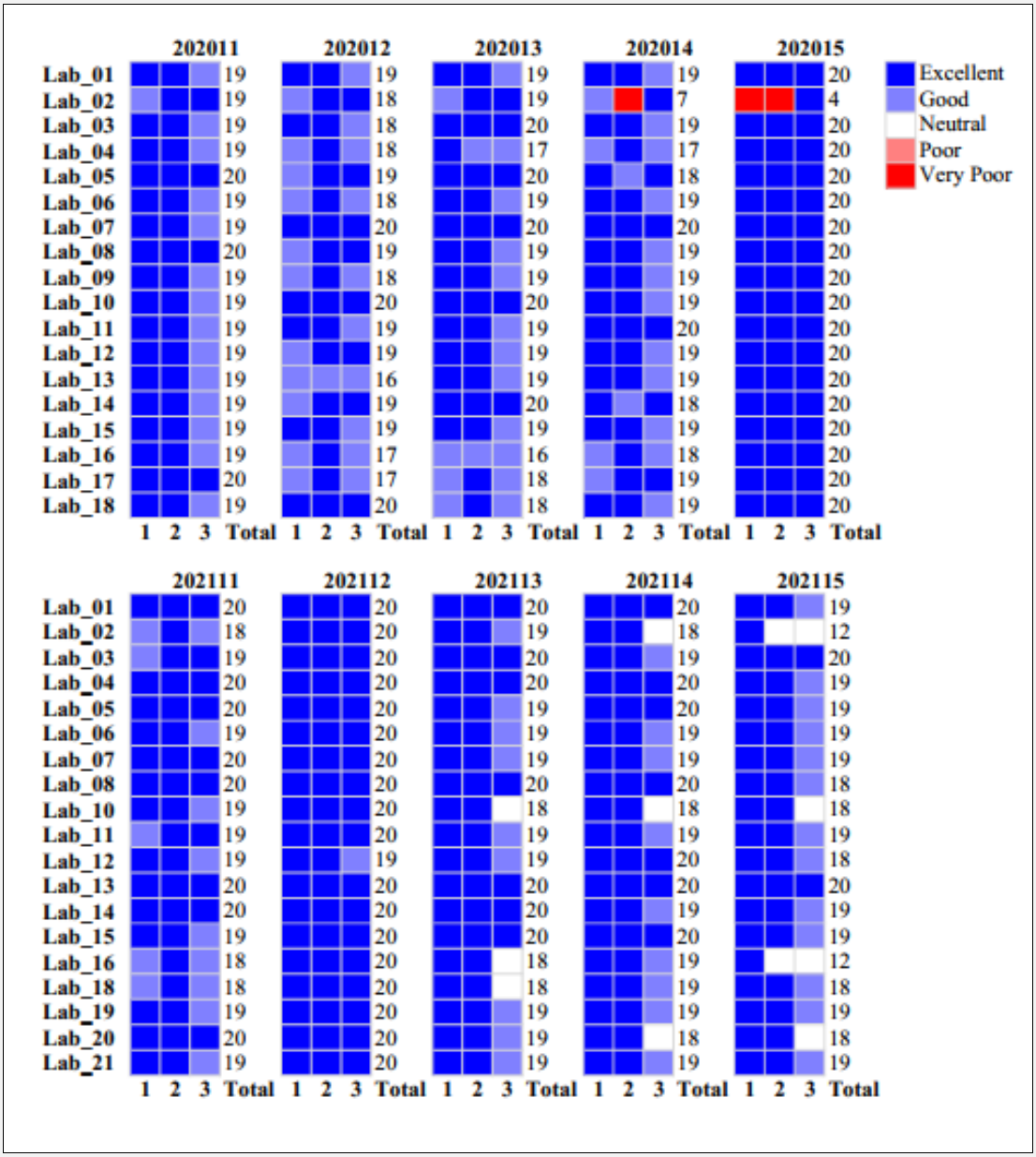

Figure 2. Grade of each participant in the pilot EQA scheme.

Individual grade for each aspect and the total score of each sample achieved by each laboratory. In each batch, five samples were tested. The numbers represent the aspect of the assessment: 1, "analytical result", 2, “the most likely diagnosis”, 3, "recommendation for further tests". Total refers to the final score the participant received for the sample is particularly significant in this scheme. The detailed scoring scheme is shown in Supplemental Table 2.