Test Definition: HGEMS

HGEM, S

Overview

Useful For

Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC)

Evaluation of patients with abnormal newborn screens showing elevations of C4- acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies

Diagnosis of glutaric acidemia type 1

Aids in diagnosis of glutaric acidemia type 2

Genetics Test Information

Second-tier newborn screening for follow-up of C4 acylcarnitine and glutarylcarnitine (C5DC) elevations.

Differentiating diagnoses of short chain Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy.

Differentiating diagnoses of glutaric acidemia type I (GA-1) and glutaric acidemia type II (GA-2)

Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Serum Red

Necessary Information

Patient's age is required.

Specimen Required

Container/Tube: Red top

Submission Container/Tube: Plastic vial

Specimen Volume: 0.1 mL

Specimen Minimum Volume

0.02 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	90 days	
	Frozen	90 days	
	Ambient	4 days	

Clinical and Interpretive

Clinical Information

Acylcarnitine analysis is included in newborn screening blood testing and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxy glutaric acid (2OH-GA), 3-hydroxy glutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by LC-MS/MS allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers.

C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive; there is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements.

Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA.

Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1, also known as glutaric aciduria type 1, is caused by a deficiency of glutaryl-CoA dehydrogenase. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA-1 typically show elevations of glutaric acid and 3OH-GA, even in those considered to be "low excretors."

Glutaric acidemia (GA-2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA-2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood, and muscle weakness in childhood and adulthood. In addition to elevations in glutaric acid, individuals with GA-2 can also show increased EMA, MSA, and 2OH-GA.

The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

Reference Values

2-OH Glutaric acid < or =4.5 nmol/mL

3-OH Glutaric acid < or =0.7 nmol/mL

Glutaric acid < or =0.8 nmol/mL

Methylsuccinic acid < or =0.3 nmol/mL

Ethylmalonic acid < or =1.5 nmol/mL

Interpretation

Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl Co-A dehydrogenase (SCAD) deficiency.

Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy.

Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency.

Elevation of glutaric acid (GA) and 3-hydroxy glutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type 1 (GA-1).

Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia (GA-2).

Clinical Reference

1. Rinaldo P, Cowan TM, Matern D: Acylcarnitine profile analysis. 2008:10(2):151-156

2. Kolker S, Christensen E, Leonar JV, et al: Diagnosis and management of glutaric aciduria type I-revised recommendations. J Inherit Metab Dis 2011:34:677-694

3. Frerman FE, Goodman SI: Chapter 103: Defects of Electron Transfer Flavoprotein and Electron Transfer Flavoprotein-Ubiquinone Oxidoreductase: Glutaric Acidemia Type II. In Scriver's Online Metabolic and Molecular Bases of Inherited Disease. Edited by CR Scriver, AL Beaudet, D Valle, et al. Accessed 8/17/17. Available at www.ommbid.com

Performance

Method Description

An aqueous internal standard is added to the plasma specimen. The supernatant is evaporated under heated nitrogen and the residue is then reconstituted prior to injection onto a liquid chromatography-tandem mass spectrometry (LC-MS/MS). The MS/MS is operated in the multiple reaction monitoring (MRM) negative mode to follow the precursor to product species transitions. Separation of the structural isomers 2OH-GA and 3OH-GA as well as glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) is accomplished by the optimization of the LC separation. The ratios of the extracted peak areas of GA, EMA, and MSA to their respective internal standards as determined by LC-MS/MS are used to calculate the concentration of each analyte in the sample.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday, Wednesday; 8 a.m.

Analytic Time

2 days

Maximum Laboratory Time

10 days

Specimen Retention Time

2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

83918

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HGEMS	HGEM, S	92673-3

Result ID	Test Result Name	Result LOINC Value
36055	2-OH Glutaric acid	69845-6
36056	3-OH Glutaric acid	69851-4
36057	Glutaric acid	27301-1
36058	Methylsuccinic acid	69829-0
36059	Ethylmalonic acid	79476-8
36060	Interpretation (HGEMS)	59462-2
36061	Reviewed By	18771-6