Overview

Useful For
Evaluation of patients with an abnormal newborn screen showing elevations of glutaryl carnitine (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 glutaryl carnitine (C5DC) elevations.

Differentiating diagnoses of short chain acyl-CoA 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
Plasma

Necessary Information
Patient's age is required.

Specimen Required

Collection Container/Tube:

Preferred: Green top (sodium heparin)

Acceptable: Lavender top (EDTA) plasma

Submission Container/Tube: Plastic vial

Specimen Volume: 0.1 mL

Forms
If not ordering electronically, complete, print, and send an Inborn Errors of Metabolism Test Request (T798) with the specimen.
**Test Definition: HGEMP**

**HGEM, P**

**Specimen Minimum Volume**
0.02 mL

**Reject Due To**

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<tr>
<td>Gross icterus</td>
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**Specimen Stability Information**

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**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 glutaryl carnitine/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.

Glutaryl carnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase and 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).

**Cautions**

No significant cautionary statements

**Clinical Reference**


**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), ethylmalonic acid (EMA), and methylsuccinic acid (MSA) 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**

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