
Overview

Useful For

Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) using dried blood spot specimens

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

Aiding 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)

Special Instructions

- [Biochemical Genetics Patient Information](#)
- [Blood Spot Collection Card-Spanish Instructions](#)
- [Blood Spot Collection Card-Chinese Instructions](#)
- [Blood Spot Collection Instructions](#)

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Whole blood

Specimen Required

Supplies: Card-Blood Spot Collection (Filter Paper) (T493)

Container/Tube:

Preferred: Card-Blood Spot Collection (Filter Paper) from heel or finger stick

Acceptable: PerkinElmer (formerly Ahlstrom 226) filter paper, Munktell filter paper, Whatman Protein Saver 903 paper, available newborn screening card, blood collected in tubes containing heparin or EDTA and dried on filter paper

Specimen Volume: 2 Blood spots

Collection Instructions:

1. Do not use device or capillary tube containing ACD to collect specimen. Sodium heparin or EDTA are acceptable, but must be spotted on card the same day as collected.
2. Completely fill at least 2 circles on the filter paper card (approximately 100 microliters blood per circle).
3. Let blood dry on filter paper at room temperature in a horizontal position for 3 or more hours.
4. Do not stack wet specimens.
5. Do not expose specimen to heat or direct sunlight.
6. Keep specimen dry.

Additional Information:

1. For collection instructions, see [Blood Spot Collection Instructions](#) in Special Instructions.
2. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777) in Special Instructions.
3. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800) in Special Instructions.

Forms

1. [Biochemical Genetics Patient Information](#) (T602) in Special Instructions.
2. [If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request](#) (T798) with the

specimen.

Reject Due To

Blood spot: Shows serum rings Insufficient specimen Blood collected with ACD Nonapproved filter paper **Reject**

Specimen Minimum Volume

1 Blood spot

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Ambient (preferred)	123 days	FILTER PAPER
	Frozen	123 days	FILTER PAPER
	Refrigerated	123 days	FILTER PAPER

Clinical & Interpretive

Clinical Information

Acylcarnitine analysis is included in newborn screening blood tests 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-hydroxyglutaric acid (2OH-GA), 3-hydroxyglutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by liquid chromatography-tandem mass spectrometry 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.

Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type I (GA1) but is not differentiated from C10-OH acylcarnitine. GA1 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 GA1 typically show elevations of GA and 3OH-GA, even in those considered to be "low excretors."

Glutaric acidemia type II (GA2), 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. GA2 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 GA, individuals with GA2 can also show increased EMA, MSA, and 2OH-GA.

The American College of Medical Genetics and Genomics (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 =25 nmol/mL

3-OH Glutaric acid: < or =1.5 nmol/mL

Glutaric acid: < or =1.5 nmol/mL

Methylsuccinic acid: < or =0.45 nmol/mL

Ethylmalonic acid: < or =3.5 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-hydroxyglutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type I (GA1).

Elevation of GA, 2-hydroxyglutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia type II (GA2).

Cautions

No significant cautionary statements

Clinical Reference

1. Rinaldo P, Cowan TM, Matern D: Acylcarnitine profile analysis. *Genet Med.* 2008;10(2):151-156
2. Vockley J, Zschocke J, Knerr I, Vockley C, Michael Gibson KK: Branched chain organic acidurias. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. *The Online Metabolic and Molecular Bases of Inherited Disease*. McGraw-Hill; Accessed February 15, 2021. Available at <https://ommbid.mhmedical.com/content.aspx?bookid=2709§ionid=225085758>
3. Frerman FE, Goodman SI: Defects of electron transfer flavoprotein and electron transfer flavoprotein-ubiquinone oxidoreductase: Glutaric acidemia type II. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA. eds. *The Online Metabolic and Molecular Bases of Inherited Disease*. McGraw-Hill; Accessed February 15, 2021. Available at <https://ommbid.mhmedical.com/content.aspx?bookid=2709§ionid=225088261>
4. Larson A, Goodman S: Glutaric acidemia type 1. In: Adam MP, Ardinger HH, Pagon RA, et al. eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2019. Accessed April 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK546575/
5. Di Meo I, Lamperti C, Tiranti V: Ethylmalonic encephalopathy. In: Adam MP, Ardinger HH, Pagon RA, et al. eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2017. Accessed April 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK453432/
6. Wolfe L, Jethva R, Oglesbee D, et al: Short-chain acyl-CoA dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al. eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2011. Updated August 9, 2018. Accessed April 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK63582/

Performance**Method Description**

Internal standard is added to a dried blood spot. The extract is evaporated and reconstituted prior to injection onto a liquid chromatography-tandem mass spectrometry (LC-MS/MS) system. The ratios of the extracted peak areas of glutaric acid (GA), ethylmalonic acid (EMA), and methylsuccinic acid (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

Specimen Retention Time

2 years

Performing Laboratory Location

Rochester

Fees & Codes
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 US Food and Drug Administration.

CPT Code Information

83918

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
HGEM	HGEM, BS	92672-5

Result ID	Reporting Name	LOINC®
36048	2-OH Glutaric acid	75037-2
36049	3-OH Glutaric acid	82505-9
36050	Glutaric acid	82504-2
36051	Methylsuccinic acid	82503-4
36052	Ethylmalonic acid	82502-6
36053	Interpretation (HGEM)	59462-2
36054	Reviewed By	18771-6