Test Definition: PMSBB

Postmortem Screening, Bile and Blood Spot

Overview

Useful For

Postmortem evaluation of individuals at any age who died suddenly or unexpectedly; testing is particularly recommended under the following circumstances (risk factors):
-Family history of sudden infant death syndrome or other sudden unexpected deaths at any age
-Family history of Reye syndrome
-Maternal complications of pregnancy (acute fatty liver pregnancy, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count])
-Lethargy, vomiting, fasting in the 48 hours prior to death
-Allegation of child abuse (excluding obvious cases of trauma, physical harm)
Macroscopic findings at autopsy:
-Fatty infiltration of the liver
-Dilated or hypertrophic cardiomyopathy
-Autopsy evidence of infection that routinely **would not** represent a life-threatening event

Genetics Test Information

Acylcarnitine analysis in blood and bile specimens to evaluate cases of sudden or unexpected death. Confirmatory enzymatic and molecular studies of cultured fibroblasts may be recommended.

Testing Algorithm

For more information see Postmortem Screening Algorithm for Fatty Acid Oxidation Disorders and Organic Acidurias.

Special Instructions

- Request for Original Newborn Screening Card
- Postmortem Screening Algorithm for Fatty Acid Oxidation Disorders and Organic Acidurias

Highlights

Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual at any age.

Analysis facilitates the diagnosis of over 20 inborn errors of metabolism including fatty acid oxidation disorders and organic acidurias.

Abnormal results are not always sufficient to conclusively establish a diagnosis of a particular disease. When abnormal results are obtained, additional confirmatory testing is recommended.

Detailed reports for abnormal acylcarnitine profiles are provided that include an overview of the results and recommendations for follow-up.

Method Name

Flow Injection Analysis-Tandem Mass Spectrometry (FIA-MS/MS)

NY State Available

Yes

Specimen

Specimen Type
Whole blood

Necessary Information
Request the original newborn screening card from the state laboratory where the decedent was born. See Request for Original Newborn Screening Card. Provide patient name, date and time of birth and death, suspected cause of death, circumstances of death, relevant family history, and date and time of sample collection.

Biochemical Genetics Patient Information (T602) is recommended, but not required, to be filled out and sent with the specimen to aid in the interpretation of test results.

Specimen Required
Both bile and blood spots are required.

Supplies: Card-Postmortem Screening (Filter Paper) (T525)
Container/Tube:
Preferred: Card-Postmortem Screening Card (Filter Paper)
Acceptable: Whatman Protein Saver 903 paper or local newborn screening card
Specimen Volume: Properly completed screening card
Collection Instructions:
1. Collect blood in a heparin-containing tube and drop 25 mcL of blood onto the 2 circles labeled Blood.
2. Collect bile by direct puncture of the gallbladder and drop 25 mcL of bile onto the 2 circles labeled Bile.
3. Allow to dry at ambient temperature in a horizontal position for a minimum of 3 hours.
4. Fill out information on page 2 of collection card.
5. Do not expose specimen to heat or direct sunlight.
6. Do not stack wet specimens.
7. Keep specimen dry.

Forms
If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume
Bile spot: 1; Blood spot: 1

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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

Clinical & Interpretive

Clinical Information

Postmortem screening involves acylcarnitine analysis in blood and bile specimens to evaluate cases of sudden or unexpected death. Acylcarnitine analysis can diagnose disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs measured by this assay.(1) Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry. Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls.

In general, more than 20 inborn errors of metabolism can be identified using this method, including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections.

Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Urine organic acids can also be analyzed from urine spotted on filter paper. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age.

Disorders Detectable by Acylcarnitine Analysis*
Fatty Acid Oxidation Disorders:
-Short-chain acyl-CoA dehydrogenase deficiency
-Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
-Medium-chain acyl-CoA dehydrogenase deficiency
-Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and trifunctional protein deficiency
-Very long-chain acyl-CoA dehydrogenase deficiency
-Carnitine palmitoyl transferase type II deficiency
-Carnitine-acylcarnitine translocase deficiency
-Electron-Transferring Flavoproteins (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency; glutaric acidemia type II)

Organic Acid Disorders:
-Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I)
-Propionic acidemia
-Methylmalonic acidemia
-Isovaleric acidemia
-3-Hydroxy-3-methylglutaryl-CoA carboxylase deficiency
-3-Methylcrotonyl carboxylase deficiency
-Biotinidase deficiency
-Multiple carboxylase deficiency
-Isobutyryl-CoA dehydrogenase deficiency
-2-Methylbutyryl-CoA dehydrogenase deficiency
-Beta-ketothiolase deficiency
-Malonic aciduria
-Ethylmalonic encephalopathy
*Additional confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than one condition.

For more information see Postmortem Screening Algorithm for Fatty Acid Oxidation Disorders and Organic Acidurias.

Reference Values

Quantitative results are compared to a constantly updated range which corresponds to the 5 to 95 percentile interval of all postmortem cases analyzed in our laboratory.

Interpretation

Reports of abnormal acylcarnitine profiles will include an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) as indicated, name and phone number of contacts who may provide these studies, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Abnormal results are not always sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) or molecular genetic analyses are required using additional tissue such as skin fibroblasts from the deceased patient. If not available, molecular genetic analysis of a patient's parents may enable the confirmation of a diagnosis.

Cautions

Both blood and bile specimens must be collected to detect and independently confirm the largest possible number of disorders. However, if only one specimen type is available, testing is still beneficial.

In cases with a higher level of suspicion due to the recognition of 1 or more risk factors, collection of urine on filter paper and a skin biopsy is also recommended for further testing and enzymatic/molecular studies. Contact the Biochemical Genetic consultant or genetic counselor on call at 800-533-1710 to discuss high-risk cases.

In comparison to living individuals, profiles of postmortem blood specimens generally show a nonspecific increase of short chain species.

Patients with secondary carnitine deficiency may display uninformative acylcarnitine profiles in blood, but not in bile.

Several fatty acid oxidation disorders are not associated with abnormal acylcarnitine profiles (eg, carnitine palmitoyltransferase I [CPT I] deficiency, 3-hydroxy-3-methylglutaryl CoA synthase [HMG-CoA synthase] deficiency) and will not be detected.

Clinical Reference

1. Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S. ACMG Laboratory Quality Assurance Committee. Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(2):249-258
2. Rinaldo P, Matern D, Bennet BJ. Fatty acid oxidation disorders. Ann Rev Physiol. 2002;64:477-502
3. Rashed MS, Ozand PT, Bennett MJ, et al. Inborn errors of metabolism diagnosed in sudden death cases by acylcarnitine analysis of postmortem bile. Clin Chem. 1995;4(8 Pt 1):1109-1114
4. Pryce JW, Weber MA, Heales S, et al. Tandem mass spectrometry findings at autopsy for detection of metabolic disease in infant deaths: postmortem changes and confounding factors. J Clin Pathol. 2011;64(11):1005-1009. doi:10.1136/jclinpath-2011-200218
5. van Rijt WJ, Koolhaas GD, Bekhof J, et al. Inborn errors of metabolism that cause sudden infant death: A systematic review with implications for population neonatal screening programmes. Neonatology. 2016;109(4):297-302

Performance

Method Description

Blood and bile are collected on the same filter paper card; newborn screening filter paper cards are used. Blood drawn into heparin-containing tubes and bile collected by direct puncture of the gallbladder are spotted on a filter paper card. Two circles are labeled and used for blood, 2 circles are labeled and used for bile (each 25 mcL of volume). A 3/16" disk is punched out of the dried blood or 1/16" dried bile spot into an Eppendorf tube. The acylcarnitines are extracted by the addition of methanol and known concentrations of isotopically labeled acylcarnitines as internal standards. The extract is transferred to a Reacti-Vial, dried under a stream of nitrogen, and derivatized by the addition of *n*-butanol hydrochloric acid. The acylcarnitines are measured as their butyl esters by electrospray tandem mass spectrometry. The concentration of the analytes is established by computerized comparison of ion intensities of these analytes to that of the respective internal standards.(Chace DH, DiPerna JC, Mitchell BL, et al. Electrospray tandem mass spectrometry for analysis of acylcarnitines in dried postmortem blood specimens collected at autopsy from infants with unexplained cause of death. Clin Chem. 2001;47[7]:1166-1182; Miller MJ, Cusmano-Ozog K, Oglesbee D, Young S. ACMG Laboratory Quality Assurance Committee. Laboratory analysis of acylcarnitines, 2020 update: a technical standard of the American College of Medical Genetics and Genomics [ACMG]. Genet Med. 2021;23[2]:249-258)

PDF Report

No

Day(s) Performed

Wednesday

Report Available

7 to 16 days

Specimen Retention Time

Indefinitely

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

83789

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PMSBB	Postmortem Screening	In Process

Result ID	Test Result Name	Result LOINC® Value
22675	Specimen	31208-2
22676	Specimen ID	57723-9
22677	Source	31208-2
22678	Order Date	82785-7
22679	Reason For Referral	42349-1
22680	Method	85069-3
22684	Results	In Process
81931	Interpretation	59462-2
22681	Amendment	48767-8
22682	Reviewed By	18771-6
22683	Release Date	82772-5