

## Methylmalonic Aciduria Gene Panel, Varies

**Test ID:** MMAGP

**Explanation:** On the effective date, the test algorithm will be updated to include a reflex test when necessary. Additionally, the Genetics Information, Ordering Guidance and Specimen Required sections will be updated as indicated below.

### Current Genetics Information

- This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 25 genes associated with methylmalonic aciduria: *ABCD4*, *ACSF3*, *ALDH6A1*, *AMN*, *CD320*, *CUBN*, *CBLIF*, *HCFC1*, *LMBRD1*, *MCEE*, *MMAA*, *MMAB*, *MMACHC*, *MMADHC*, *MTHFR*, *MTR*, *MTRR*, *MMUT*, *PRDX1*, *SUCLA2*, *SUCLG1*, *TCN1*, *TCN2*, *THAP11*, *ZNF143*. For additional details see Method Description or [Targeted Genes and Methodology Details for Methylmalonic Aciduria Gene Panel](#).
- Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for methylmalonic aciduria.

### New Genetics Information

- This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 25 genes associated with methylmalonic aciduria: *ABCD4*, *ACSF3*, *ALDH6A1*, *AMN*, *CD320*, *CUBN*, *CBLIF*, *HCFC1*, *LMBRD1*, *MCEE*, *MMAA*, *MMAB*, *MMACHC*, *MMADHC*, *MTHFR*, *MTR*, *MTRR*, *MMUT*, *PRDX1*, *SUCLA2*, *SUCLG1*, *TCN1*, *TCN2*, *THAP11*, *ZNF143*. For additional details see Method Description or [Targeted Genes and Methodology Details for Methylmalonic Aciduria Gene Panel](#).
- Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for methylmalonic aciduria.
- This test is not recommended for detection of the benign *MTHFR* variants c.665C>T (p.C677T, p.Ala222Val) and c.1286A>C (A1298C, p.Glu429Ala) due to limited clinical utility (3-6).

### Current Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

### New Algorithm

#### Prenatal specimens only:

- If an amniotic fluid specimen or cultured amniocytes are received, an amniotic fluid culture will be performed at an additional charge.
- If a chorionic villi specimen or cultured chorionic villi are received, a fibroblast culture will be performed at an additional charge.
- For any prenatal specimen that is received, maternal cell contamination testing will be performed at an additional charge.

#### Skin biopsy or cultured fibroblast specimens:

For skin biopsy or cultured fibroblast specimens, a fibroblast culture will be performed at an additional charge.

Current Reflex Tests			
Test ID	Reportable Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

New Reflex Tests			
Test ID	Reportable Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No

Current Ordering Guidance
<ul style="list-style-type: none"> <li>The recommended first-tier tests to screen for methylmalonic aciduria include plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Random, Urine), and homocysteine (HCYSP / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum).</li> <li>Customization of this panel and single gene analysis for any gene present on this panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.</li> <li>Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.</li> </ul>

New Ordering Guidance
<ul style="list-style-type: none"> <li>The recommended first-tier tests to screen for methylmalonic aciduria include plasma acylcarnitine profile (ACRN / Acylcarnitines, Quantitative, Plasma), quantitative plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma), urine organic acids (OAU / Organic Acids Screen, Random, Urine), and homocysteine (HCYSP / Homocysteine, Total, Plasma or HCYSS / Homocysteine, Total, Serum).</li> <li>Customization of this panel and single gene analysis for any gene present on this panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies. To modify this panel via CGPH, please use the Inborn Errors of Metabolism disease state for step 1 on the <a href="#">custom gene ordering tool</a>.</li> <li>Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.</li> </ul>

Current Specimen Required
<p><b>Patient Preparation:</b> A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.</p> <p><b>Submit only 1 of the following specimens:</b></p> <p><b>Specimen Type:</b> Whole blood  <b>Container/Tube:</b> Lavender top (EDTA) or yellow top (ACD)  <b>Specimen Volume:</b> 3 mL  <b>Collection Instructions:</b>  1. Invert several times to mix blood.  2. Send whole blood specimen in original tube. <b>Do not aliquot.</b>  <b>Specimen Stability Information:</b> Ambient (preferred) 4 days/Refrigerated 14 days</p>

New Specimen Required
<p><b>Patient Preparation:</b> A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.</p> <p><b>Submit only 1 of the following specimens:</b></p> <p><b>Specimen Type:</b> Whole blood  <b>Container/Tube:</b>  <b>Preferred:</b> Lavender top (EDTA) or yellow top (ACD)  <b>Acceptable:</b> Green top (Sodium heparin)  <b>Specimen Volume:</b> 3 mL  <b>Collection Instructions:</b>  1. Invert several times to mix blood.  2. Send whole blood specimen in original tube. <b>Do not aliquot.</b>  <b>Specimen Stability Information:</b> Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days  <b>Additional Information:</b></p>

**Specimen Type: Skin biopsy**

**Supplies:** Fibroblast Biopsy Transport Media (T115)

**Container/Tube:** Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

**Specimen Volume:** 4-mm punch

**Specimen Stability Information:** Refrigerated (preferred)/Ambient

**Additional Information:** A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Type: Cultured fibroblast**

**Container/Tube:** T-25 flask

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will **not** be accepted.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated (<24 hours)

**Additional Information:** A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

**Specimen Type: Blood spot**

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

**Container/Tube:**

**Preferred:** Collection card (Whatman Protein Saver 903 Paper)

**Acceptable:** PerkinElmer 226 (formerly Ahlstrom 226) filter paper or blood spot collection card

**Specimen Volume:** 5 Blood spots

**Collection Instructions:**

1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see [How to Collect Dried Blood Spot Samples](#).

2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.

3. Do not expose specimen to heat or direct sunlight.

4. Do not stack wet specimens.

5. Keep specimen dry.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Additional Information:**

1. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.

2. For collection instructions, see [Blood Spot Collection Instructions](#)

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.

2. To ensure minimum volume and concentration of DNA is met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

**Specimen Type: Cord blood**

**Container/Tube:**

**Preferred:** Lavender top (EDTA) or yellow top (ACD)

**Acceptable:** Green top (Sodium heparin)

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.

2. Send cord blood specimen in original tube. **Do not aliquot.**

**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days

**Additional Information:**

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.

2. To ensure minimum volume and concentration of DNA is met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

3. While a properly collected cord blood sample may not be at risk for maternal cell contamination, unanticipated complications may occur during collection. Therefore, maternal cell contamination studies are recommended to ensure the test results reflect that of the patient tested and are available at an additional charge. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**Specimen Type: Saliva**

**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

**Supplies:** Saliva Swab Collection Kit (T786)

**Specimen Volume:** 2 Swabs

**Collection Instructions:** Collect and send specimen per kit instructions.

**Specimen Stability Information:** Ambient (preferred) 30 days/Refrigerated 30 days

**Additional information:** Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

**Specimen Type: Blood spot**

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

**Container/Tube:**

**Preferred:** Collection card (Whatman Protein Saver 903 Paper)

**Acceptable:** PerkinElmer 226 filter paper or blood spot collection card

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

**Specimen Type: Saliva**

**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

**Supplies:** Saliva Swab Collection Kit (T786)

**Specimen Volume:** 1 Swab

**Collection Instructions:** Collect and send specimen per kit instructions.

**Specimen Stability Information:** Ambient 30 days

**Additional Information:** Due to lower concentration of DNA yielded from saliva, it is possible that additional specimen may be required to complete testing.

**Specimen Volume:** 2 to 5 Blood spots

**Collection Instructions:**

1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see [How to Collect a Dried Blood Spot Sample](#).

2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.

3. Do not expose specimen to heat or direct sunlight.

4. Do not stack wet specimens.

5. Keep specimen dry

**Send:** Ambient (preferred)/Refrigerated

**Additional Information:**

1. Blood spot specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from blood spots, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

2. Due to lower concentration of DNA yielded from blood spot, it is possible that additional specimen may be required to complete testing.

3. For collection instructions, see [Blood Spot Collection Instructions](#)

4. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777)

5. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800)

**Specimen Type: Cultured fibroblasts**

**Source:** Skin

**Container/Tube:** T-25 flask

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured fibroblast cells from a skin biopsy. Cultured cells from a prenatal specimen will not be accepted.

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and/or extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.

2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

**Specimen Type: Skin biopsy**

**Supplies:** Fibroblast Biopsy Transport Media (T115)

**Container/Tube:** Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

**Specimen Volume:** 4-mm punch

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and/or extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

**Specimen Type: Extracted DNA**

**Container/Tube:**

**Preferred:** Screw Cap Micro Tube, 2mL with skirted conical base

**Acceptable:** Matrix tube, 1mL

**Collection Instructions:**

1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred) 1 year/Ambient/Refrigerated

**Additional Information:** DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

**PRENATAL SPECIMENS**

**Due to its complexity, consultation with the laboratory is required** for all prenatal testing; call 800-533-1710 to speak to a genetic counselor.

**Specimen Type: Amniotic fluid**

**Container/Tube:** Amniotic fluid container

**Specimen Volume:** 20 mL

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:** Specimen will only be tested after culture.

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid. An additional 2 to 3 weeks are required to culture amniotic fluid before genetic testing can occur.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**Specimen Type: Confluent cultured amniocytes**

This does not include cultured chorionic villi.

**Container/Tube:** T-25 flask

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured cells from another laboratory

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**Specimen Type:** Chorionic villi

**Container/Tube:** 15-mL tube containing 15 mL of transport media

**Specimen Volume:** 20 mg

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:** Specimen will only be tested after culture.

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**Specimen Type:** Cultured chorionic villi

**Container/Tube:** T-25 flasks

**Specimen Volume:** 2 full flasks

**Collection Instructions:** Submit confluent cultured cells from another laboratory

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

## Questions

Contact Michelle Rath, Laboratory Resource Coordinator at 800-533-1710.