Overview

Useful For
Confirmation of diagnosis in patients suspected of having either Prader-Willi syndrome (PWS) or Angelman syndrome (AS) based on clinical assessment or previous laboratory analysis

Prenatal diagnosis in families at risk for PWS or AS

Genetics Test Information
Preferred first-tier test for diagnosis of Angelman (AS) and Prader-Willi syndrome (PWS). Multiplex ligation probe amplification (MLPA) is used to identify abnormal methylation of the PWS/AS region of chromosome 15.

Mayo Clinic Laboratories highly recommends that this test be ordered along with a routine chromosomal microarray analysis, CMACB / Chromosomal Microarray, Congenital, Blood, if the diagnosis of PWS or AS is not certain and chromosome analysis has not already been done.

Reflex Tests

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
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<tbody>
<tr>
<td>CULAF</td>
<td>Amniotic Fluid Culture/Genetic Test</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>MATCC</td>
<td>Maternal Cell Contamination, B</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

Testing Algorithm

For prenatal specimens only: If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture/genetic test will be added and charged separately. For any prenatal specimen that is received, maternal cell contamination studies will be added.

See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions.

Special Instructions
- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis
- Informed Consent for Genetic Testing (Spanish)

Method Name
Methylation-Sensitive Multiple Ligation-Dependent Probe Amplification (MLPA) (PCR is utilized pursuant to a license agreement with Roche Diagnostic Systems, Inc.)

NY State Available
Yes

Specimen
Specimen Type
Varies

Additional Testing Requirements
Mayo Clinic Laboratories highly recommends that this test be ordered along with a routine chromosomal microarray analysis, CMACB / Chromosomal Microarray, Congenital, Blood, if the diagnosis of PWS or AS is not certain and chromosome analysis has not already been done.

All prenatal specimens must be accompanied by a maternal blood specimen. Order MATCC / Maternal Cell Contamination, Molecular Analysis on the maternal specimen.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Prenatal specimens can be sent Monday through Thursday and must be received by 5 p.m. CST on Friday in order to be processed appropriately.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube:

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

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Prenatal Specimens

Due to the complexity of prenatal testing, consultation with the laboratory is required for all prenatal testing.

Specimen Type: Amniotic fluid

Container/Tube: Amniotic fluid container

Specimen Volume: 20 mL
Specimen Stability Information: Refrigerated (preferred)/Ambient

Acceptable:

Specimen Type: Confluent cultured cells

Container/Tube: T-25 flask

Specimen Volume: 2 flasks

Collection Instructions: Submit confluent cultured cells from another laboratory.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Forms

1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions

3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

Blood: 1 mL
Amniotic Fluid: 10 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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<th>Temperature</th>
<th>Time</th>
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Clinical and Interpretive

Clinical Information

Prader-Willi syndrome (PWS) is a congenital disorder characterized by a biphasic clinical course. Neonates with PWS are hypotonic, have a weak cry, and are poor feeders, but improve over time. In later infancy and childhood, individuals with PWS have global developmental delay, short stature, hypogonadism, small hands and feet, and marked hyperphagia leading to obesity. PWS is thought to be due to loss of function of paternally expressed genes, although specific genes have not yet been definitively implicated in the phenotype of PWS.

Etiology of Prader-Willi syndrome:
- Chromosome 15 deletion (15q11-13): approximately 70%-75%
- Maternal uniparental disomy (UPD): 20%-30%
- Imprinting defect: 1%-5%
- Chromosome rearrangement: rare

The phenotype caused by paternal deletions of 15q11-13 and by maternal UPD are generally identical with the exception of relative hypopigmentation being more common in patients with deletion PWS.

Angelman syndrome (AS) is a nonprogressive congenital disorder characterized by more significant developmental delay and mental retardation, ataxia, seizures, jerky arm movements, macrostomia, tongue thrusting, unprovoked laughter, brachycephaly, and virtual absence of speech. AS is due to loss of function of the maternally expressed gene \( UBE3A \).

**Etiology of Angelman syndrome:**

- Chromosome 15 deletion (15q11-13): approximately 70%-75%
- Paternal UPD: approximately 5%
- \( UBE3A \) mutation: approximately 10%
- Imprinting defect: 2%-5%
- Chromosome rearrangement: rare
- Unknown: approximately 10%

The phenotype of AS patients with maternal deletions is generally more severe than that associated with paternal UPD or imprinting defects, including a higher rate or severity of microcephaly, seizures, and motor difficulties. Patients with AS caused by paternal UPD or imprinting defects generally show better growth and higher developmental and language abilities.

Both chromosome 15 deletions and UPD most often occur as de novo events during conception and, thus, recurrence risk to siblings is very low. In rare cases, chromosome 15 deletions and UPD occur as a result of parental translocations or other rare cytogenetic rearrangements, and in these cases recurrence risks to siblings are increased.

The recurrence risk associated with imprinting defects is dependent on whether or not there is an identifiable mutation. \( UBE3A \) mutations can occur sporadically or be inherited in an autosomal dominant fashion. There is a 50% recurrence risk to siblings in cases of an inherited \( UBE3A \) mutation.

Due to the complex genetic etiology of PWS and AS and the corresponding variability in recurrence risks, careful cytogenetic and molecular testing and family assessment are necessary to provide accurate genetic counseling.

Initial studies to rule-out PWS or AS should include chromosomal microarray analysis to identify chromosome abnormalities that may have phenotypic overlap with PWS or AS, and methylation-sensitive multiple ligation-dependent probe amplification (MLPA) to identify deletions, duplications, and methylation defects. In cases where
methylhation-sensitive MLPA suggests either deletion or duplication, FISH can be used to confirm type I and type II deletions or characterize the disease mechanism, respectively. In cases where methylation-sensitive MLPA suggests abnormal methylation in the absence of a deletion or duplication, UPD studies can be used to characterize the disease mechanism.

Assessment of patients found to have a deletion in the PWS/AS critical region on routine cytogenetic analysis or chromosomal microarray can include confirmation of the deletion by FISH analysis and MLPA analysis to define parent of origin.

See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions for more information.

**Reference Values**
An interpretive report will be provided.

**Interpretation**
An interpretive report will be provided.

**Cautions**
In addition to disease-related probes, the multiple ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Methylation status cannot be assessed on chorionic villus specimens.

Rare cases of Prader-Willi syndrome or Angelman syndrome (AS) result from a subtle balanced translocation inherited from one of the parents. These may not be detected by this assay.

A negative molecular test result, especially in the case of a clinical suspicion of AS, does not rule out the diagnosis, because point mutations may not be detected by these methods.

**Clinical Reference**

Performance

Method Description
Methylation-sensitive multiple ligation-dependent probe amplification is utilized to test for the presence of large deletions, duplications and methylation defects in the Prader-Willi/Angelman syndrome critical region. (Unpublished Mayo method)

PDF Report
No

Day(s) and Time(s) Test Performed
Monday, Wednesday

Analytic Time
14 days

Maximum Laboratory Time
21 days

Specimen Retention Time
Whole Blood: 2 weeks (if available) Extracted DNA: 3 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
81331-SNRPN/UBE3A, (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis

Amniotic Fluid Culture/Genetic Test

88235-Tissue culture for amniotic fluid (if appropriate)

88240-Cryopreservation (if appropriate)

Maternal Cell Contamination, B
Test Definition: PWAS
Prader Willi/Angelman Mol Analysis

81265-Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing or maternal cell contamination of fetal cells (if appropriate)

LOINC® Information

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