MAYO CLINIC LABORATORIES

Test Definition: CDKZ

CDKN1C Gene, Full Gene Analysis, Varies

Overview

Useful For

Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome following a normal result on methylation analysis

Confirming a clinical diagnosis of IMAGe (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies) syndrome

Confirming a clinical diagnosis of Russell-Silver syndrome following a normal result on methylation analysis and uniparental disomy (UPD) 7 studies

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

Genetics Test Information

Testing includes full gene sequencing of the *CDKN1C* gene

Testing Algorithm

For prenatal specimens only:

-If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture will be added at an additional charge.
-If chorionic villus specimen (nonconfluent cultured cells) is received, fibroblast culture will be added at an additional charge.

For any prenatal specimen that is received, maternal cell contamination testing will be performed at an additional charge.

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.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing

- Informed Consent for Genetic Testing (Spanish)

Method Name
Polymerase Chain Reaction (PCR) followed by DNA Sequencing

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
This test is for CDKN1C gene sequencing. For a full evaluation of a possible diagnosis of Beckwith-Wiedemann Syndrome, the recommended first-tier test is BWRS / Beckwith-Wiedemann Syndrome/Russell-Silver Syndrome, Molecular Analysis, Varies.

Additional Testing Requirements
All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen as **this must be a different order number than the prenatal specimen**.

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

Specimen Required
Patient Preparation: 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.

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 whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Cultured fibroblasts

Container/Tube: T-75 or T-25 flask
Specimen Volume: 1 Full T-75 flask or 2 full T-25 flasks
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: 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. Tubes can be supplied upon request (Eagle's minimum essential medium 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.

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: Refrigerated (preferred)/Ambient
Additional information:
1. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid. An additional 2 to 3 weeks is required to culture amniotic fluid before genetic testing can occur.
2. **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: Refrigerated
Additional information:
1. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 2 to 3 weeks is required to culture chorionic villi before genetic testing can occur.
2. **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 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

Additional Information: All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521)

Specimen Minimum Volume

Blood: 1 mL; Other specimen types: See Specimen Required

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

The *CDKN1C* gene is an imprinted gene that has been associated with Beckwith-Wiedemann syndrome (BWS), IMAGe (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies) syndrome, and Russell-Silver syndrome (RSS). Imprinting describes a difference in gene expression based on parent of origin. The majority of autosomal genes exhibit biallelic (maternal and paternal) expression, whereas imprinted genes are normally expressed from only one parent. *CDKN1C* is typically expressed on the maternally inherited allele.

Beckwith-Wiedemann Syndrome:
Beckwith-Wiedemann syndrome is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%.

Most cases of BWS are caused by hypomethylation of *LIT1*, paternal uniparental disomy of chromosome 11, or hypermethylation of *H19*. Approximately 5% to 10% of sporadic BWS cases and approximately 40% of BWS cases with a positive family history are caused by *CDKN1C* variants. The appropriate first-tier test in the evaluation of a possible diagnosis of BWS is BWRS / Beckwith-Wiedemann Syndrome/Russell-Silver Syndrome, Molecular Analysis, Varies. This test may be considered when the results of BWS methylation analysis are negative, and there is still a strong clinical suspicion of BWS.

IMAGe Syndrome:

Variants in the *CDKN1C* gene have also been associated with IMAGe syndrome. The *CDKN1C* variants associated with IMAGe syndrome tend to be missense variants occurring in the PCNA-binding domain of the gene. Not every individual with a clinical diagnosis of IMAGe syndrome will have an identifiable *CDKN1C* variant.

Russell-Silver Syndrome:
Russell-Silver syndrome is a rare genetic condition with an incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth delay with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include cafe au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia.

RSS is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes: hypomethylation of *IC1* (*H19*), maternal uniparental disomy (UPD) of chromosome 7, 11p15.5 duplications (rare), and chromosome 7 duplications (rare).

CDKN1C variants have recently been identified as a cause of RSS in some families. This test may be considered when results of RSS methylation analysis and UPD 7 studies are negative and there is still a strong clinical suspicion of RSS

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of Beckwith-Wiedemann syndrome, IMAGe (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita and genital anomalies) syndrome, or Russell-Silver syndrome caused by *CDKN1C* may have a variant that is not identified by this method (eg, large genomic deletions, promoter variants). The absence of a variant, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of Beckwith-Wiedemann syndrome, IMAGe syndrome, or Russell-Silver syndrome. For carrier testing, it is important to first document the presence of a *CDKN1C* gene variant in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.
Rare variants (ie, 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 the interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424
2. DeBaun MR, Niemitz EL, McNeil DE, Brandenburg SA, Lee MP, Feinberg AP: Epigenetic alterations of H19 and LIT1

distinguish patients with Beckwith-Wiedemann syndrome with cancer and birth defects. Am J Hum Genet. 2002 Mar;70(3):604-611
3. Choufani S, Shuman C, Weksberg R: Beckwith-Wiedemann syndrome. Am J Med Genet. 2010 Aug;154C(3):343-354
4. Romanelli V, Belinchon A, Benito-Sanz S, et al: CDKN1C (p57[Kip2]) analysis in Beckwith-Wiedemann syndrome (BWS) patients: Genotype-phenotype correlations, novel mutations, and polymorphisms. Am J Med Genet A. 2010 Jun;152A:1390-1397. doi: 10.1002/ajmg.a.33453
5. Lam WWK, Hatada I, Ohishi S, et al: Analysis of germline CDKNIC (p57[Kip2]) mutations in familial and sporadic Beckwith-Wiedemann syndrome (BWS) provides a novel genotype-phenotype correlation. J Med Genet. 1999 Jul;36(7):518-523
6. Arboleda VA, Lee H, Parnaik R, et al: Mutations in the PCNA-binding domain of CDKN1C cause IMAGe syndrome. Nat Genet. 2012 May;44(7):788-792

Performance

Method Description
Bidirectional sequence analysis is performed to test for the presence of a variant in all coding regions and intron/exon boundaries of the *CDKN1C* gene (excluding c.481-c.595).(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Varies

Report Available
14 to 20 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts, skin biopsy, amniotic fluid, cultured amniocytes, chorionic villi, cultured chorionic villi: 1 month

Performing Laboratory Location
Rochester

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

81479
88233-Tissue culture, skin or solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)
88235-Amniotic fluid culture (if appropriate)
81265-Maternal cell contamination (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CDKZ	CDKN1C Gene, Full Gene Analysis	94193-0

Result ID	Test Result Name	Result LOINC® Value
53880	Result Summary	50397-9
53881	Result	82939-0
53882	Interpretation	69047-9
53883	Additional Information	48767-8
53884	Specimen	31208-2
53886	Released By	18771-6
53885	Source	31208-2