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

Prenatal specimens only:

If an amniotic fluid specimen is received, an amniotic fluid culture will be performed at an additional charge.

If a chorionic villi, cultured chorionic villi, or cultured amniocyte specimen is 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.

For more information see Beckwith-Wiedemann and Russell-Silver Syndromes: Laboratory Approach to Diagnosis

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Beckwith-Wiedemann and Russell-Silver Syndromes: Laboratory Approach to Diagnosis

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.

Specimen Required

Submit only 1 of the following specimens:

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

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA) or yellow top (ACD)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information.
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 are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell

contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

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, 2 mL with skirted conical base
Acceptable: Matrix tube, 1 mL
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: Prenatal 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.

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

Specimen Minimum Volume

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.

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, a multisystem genetic disorder that causes intrauterine growth restriction (IUGR), skeletal anomalies, adrenal insufficiency, and congenital anomalies of the genitourinary tract in males. The CDKN1C variants associated with IMAGe syndrome tend to be missense variants occurring in the PCNA-binding domain, on the maternal copy 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.

Russell-Silver syndrome 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. Sporadic cases of RSS are typically caused by hypomethylation of IC1 (H19) or maternal uniparental disomy (UPD) of chromosome 7, and are rarely caused by 11p15.5 duplications or chromosome 7 duplications.

CDKN1C variants have also been identified as a rare 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;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;70(3):604-611
3. Shuman C, Kalish JM, Weksberg R. Beckwith-Wiedemann Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet], University of Washington, Seattle; 1993-2025. Updated September 21.2023. Accessed April 17, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1394/
4. Brioude F, Netchine I, Praz F, et al. Mutations of the Imprinted CDKN1C Gene as a Cause of the Overgrowth Beckwith-Wiedemann Syndrome: Clinical Spectrum and Functional Characterization. Hum Mutat. 2015;36(9):894-902. doi:10.1002/humu.22824
5. Binder G, Ziegler J, Schweizer R, et al. Novel mutation points to a hot spot in CDKN1C causing Silver-Russell syndrome. Clin Epigenetics. 2020;12(1):152. Published 2020 Oct 19. doi:10.1186/s13148-020-00945-y
6. Schrier Vergano SA, Deardorff MA. IMAGe Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews[Internet]. University of Washington, Seattle; 1993-2025. Updated August 5,2021. Accessed April 17, 2025. Available at: www.ncbi.nlm.nih.gov/books/NBK190103/

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: 28 days (if available); Extracted DNA: 3 months

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

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