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MAYO CLINIC LABORATORIES

# Test Definition: RBART

Bartter Syndrome Gene Panel, Varies

## Overview

### Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of Bartter syndrome

Establishing a diagnosis of Bartter syndrome

### 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

This test utilizes next-generation sequencing to detect single nucleotide, deletion-insertion, and copy number variants in 6 genes associated with Bartter syndrome: *BSND, CLCNKA, CLCNKB, KCNJ1, MAGED2*, and *SLC12A1*. See Targeted Genes and Methodology Details for Bartter Syndrome Gene Panel in Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for Bartter syndrome.

### Testing Algorithm

**Prenatal specimens:**

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. If viable cells are not obtained, the client will be notified.

**Cord blood**:

For cord blood specimens that have an accompanying maternal blood specimen, maternal cell contamination studies will be performed at an additional charge.

### Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Hereditary Renal Genetic Testing Patient Information
- Targeted Genes and Methodology Details for Bartter Syndrome Gene Panel

### Method Name

Sequence Capture and Amplicon-Based Next-Generation Sequencing (NGS)

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Ordering Guidance

The genes associated with Gitelman syndrome (*SLC12A3*) and autosomal dominant familial hypocalciuric hypercalcemia (*FHH*, *CASR*) are not included on this panel. If testing for these disorders and Bartter syndrome on a single panel is desired, order RSCGP / Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel, Varies. It is inappropriate to order both this test and RSCGP on the same patient because the genes on this panel are included on the RSCGP panel.

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.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information, see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies. To modify this panel via CGPH, use the Hereditary Renal Conditions disease state for step 1 on the Custom Gene Ordering Tool.

### Specimen Required

**Patient Preparation** 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.

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood
**Container/Tube:**

**Preferred:** 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 or tissue
**Container/Tube**: T-25 flask
**Specimen Volume**: 2 Flasks
**Collection Instructions**: Submit confluent cultured fibroblast cells from a skin or tissue 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 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, 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**: Confluent cultured amniocytes
This does not include cultured chorionic villi.
**Container/Tube**: T-25 flask
**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.

**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 is 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. Hereditary Renal Genetic Testing Patient Information (T918)
3. If not ordering electronically, complete, print, and send a Renal Diagnostics Test Request (T830) 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

Bartter syndrome (BS) is a rare, hereditary tubulopathy of highly variable severity that can cause renal salt-wasting in infants and young children due to impaired sodium/chloride reabsorption in the thick ascending limb of the nephron.(1)

Characteristic clinical features are hypokalemic, hypochloremic metabolic alkalosis and normal blood pressure despite hyperreninemia and hyperaldosteronism.(1) Children with BS have hypercalciuria and normal serum magnesium levels and may present with symptoms in early childhood or before birth. These symptoms distinguish BS from a more common and milder renal salt-wasting disorder called Gitelman syndrome, which features hypocalciuria and low serum magnesium levels and typically presents after 6 years. Autosomal dominant hypocalcemia may resemble Bartter syndrome in patients with a markedly activating gain-of-function variant but is distinguishable from BS by mode of inheritance and the presence of hypocalcemia and hypomagnesemia.

Age of onset and disease severity is highly variable in Bartter syndrome. The most severe form, antenatal Bartter syndrome (also known as hyperprostaglandin E syndrome or neonatal Bartter syndrome), typically results in polyhydramnios, leading to premature birth. Infants often demonstrate failure to thrive and have significant polyuria

resulting in risk for life-threatening salt and water loss.

There are four subtypes of Bartter syndrome that typically present antenatally. BS type 1, caused by biallelic alterations in *SLC12A1*, may also feature fever, vomiting, and nephrocalcinosis in infancy. BS type 2, caused by biallelic variants in *KCNJ1*, causes symptoms like BS type 1, but patients may demonstrate transient hyperkalemia and acidosis. BS type 4a, caused by biallelic alterations in *BSND*, and BS type 4b, caused by alterations in *CLCNKA* and *CLCNKB*, may be accompanied by sensorineural deafness in addition to renal salt-wasting and related symptoms. Type 4b is also inherited in an autosomal recessive (or biallelic) pattern or can result from digenic inheritance.

Classic Bartter syndrome, also known as type 3, is the second major form of BS and is caused by alterations in *CLCNKB*. All BS type 3 patients have marked hypochloremia. Age of onset varies in BS type 3 and may correlate with genotype, with individuals with truncating variants presenting earlier in life. Individuals with BS type 3 may present antenatally with polyhydramnios, during infancy with failure to thrive and lethargy, or in adolescence or adulthood with symptoms of chronic hypokalemia, such as constipation, muscle cramps, salt-craving, nocturia, and vomiting. Nephrocalcinosis is uncommon in BS type 3, and patients are usually normocalciuric but may still have severe electrolyte imbalances.

A third from of BS called transient neonatal Bartter syndrome (BS type 5), is associated with severe polyhydramnios and extreme salt wasting at birth that spontaneously resolves in the first few months of life in surviving patients. BS type 5 is caused by variants in *MAGED2* inherited in an X-linked recessive pattern.

Although there is some phenotypic overlap between Bartter syndrome, Gitelman syndrome, and autosomal dominant hypocalcemia, they have different genetic causes.

This panel does not include the genes associated with Gitelman syndrome (*SLC12A3*) or autosomal dominant hypocalcemia (*CASR*). If simultaneous genetic testing for Bartter syndrome, Gitelman syndrome and/or autosomal dominant hypocalcemic hypercalciuria is desired, order RSCGP / Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel, Varies.

## Reference Values

An interpretive report will be provided.

## Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

## Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the

Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic mutations and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.
If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukocyte reduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(2) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools are interpreted with caution and professional clinical judgement.

Rarely, incidental findings or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

### Clinical Reference

1. Fulchiero R, Seo-Mayer P. Bartter Syndrome and Gitelman Syndrome. Pediatr Clin North Am. 2019;66(1):121-134
2. 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

## Performance

### Method Description

Capture-based and amplicon-based next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See the Targeted Genes and Methodology Details for Bartter Syndrome Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *BSND, CLCNKA, CLCNKB, KCNJ1, MAGED2*, and *SLC12A1*

### PDF Report

No

### Day(s) Performed
Varies

### Report Available
21 to 35 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
81404
81406
81407
81479
81479 (if appropriate for government payers)

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| RBART | Bartter Syndrome Gene Panel | 51966-0 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 618101 | Test Description | 62364-5 |
| 618102 | Specimen | 31208-2 |
| 618103 | Source | 31208-2 |
| 618104 | Result Summary | 50397-9 |
| 618105 | Result | 82939-0 |
| 618106 | Interpretation | 69047-9 |

| | | |
|---|---|---|
| 618107 | Additional Results | 82939-0 |
| 618108 | Resources | 99622-3 |
| 618109 | Additional Information | 48767-8 |
| 618110 | Method | 85069-3 |
| 618111 | Genes Analyzed | 48018-6 |
| 618112 | Disclaimer | 62364-5 |
| 618113 | Released By | 18771-6 |