MAYO CLINIC LABORATORIES

Test Definition: RSCGP

Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of a hereditary form of nephrocalcinosis, nephrolithiasis, or renal electrolyte imbalance

Establishing a diagnosis for a variety of hereditary conditions associated with renal salt wasting or abnormal salt retention; impaired acid-base, water, and calcium homeostasis; or kidney crystallization

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide, deletion-insertion, and copy number variants in 72 genes associated with nephrocalcinosis, nephrolithiasis, and renal electrolyte imbalance: *ABCC6, ADCY10, AGXT, ALPL, AP2S1, APRT, AQP2, ATP6V0A4, ATP6V1B1, ATP7B, AVP, AVPR2, BSND, CA2, CASR, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CNNM2, CUL3, CYP11B1, CYP11B2, CYP24A1, CYP27B1, CYP2R1, DMP1, EGF, ENPP1, FAM20A, FGF23, FOXI1, FXYD2, GALNT3, GATA3, GNA11, GRHPR, HNF4A, HOGA1, HPRT1, KCNJ1, KCNJ5, KL, KLHL3, MAGED2, MOCOS, NR3C2, OCRL, PHEX, PRPS1, SCNN1A, SCNN1B, SCNN1G, SLC12A1, SLC12A3, SLC22A12, SLC26A1, SLC2A9, SLC3A1, SLC34A1, SLC34A3, SLC4A1, SLC4A4, SLC7A9, SLC9A3R1, TRPM6, UMOD, VDR, WNK1, WNK4,* and *XDH*. See Targeted Genes and Methodology Details for Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for hereditary forms of nephrocalcinosis, nephrolithiasis, and renal electrolyte imbalance.

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 Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

A next-generation sequencing (NGS) panel of the 6 genes associated with Bartter syndrome, a rare renal salt-wasting disorder, is available. See RBART / Bartter Syndrome Gene Panel, Varies. It is inappropriate to order both RBART and this test on the same patient because the genes on the RBART panel are included on this panel.

Testing for *CASR* is available individually. See CASRG / CASR Full Gene Sequencing with Deletion/Duplication, Varies.

With a few exceptions, this panel is focused on conditions where the primary phenotype is impaired osmoregulation that may result in secondary extrarenal symptoms. If interested in testing for syndromic disorders that are associated with kidney disease but feature broader clinical phenotypes and multisystem involvement, see NEPHP / Comprehensive Nephrology Gene Panel, Varies.

Targeted testing for familial variants (also called site-specific or known mutations/variants 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.

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. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
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 specimen in original tube. **Do not aliquot.**
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:
-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 1 of the following forms with the specimen:
-Renal Diagnostics Test Request (T830)

-Biochemical Genetics Test Request (T798)

Specimen Minimum Volume
1 mL

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
Dehydration, certain medications, diet, and digestive disorders are common factors that can increase the risk for electrolyte imbalances or the development of kidney stones. However, renal tubular loss of electrolytes or protein, or the development of kidney calculi can also signal underlying metabolic, endocrine, or renal tubular dysfunction that is genetic in origin, especially when symptoms present in utero, infancy, or adolescence.

When the presence or severity of electrolyte imbalance or kidney stones observed in a patient cannot be explained by acquired causes or there are multiple cases clustered within a family, genetic testing for the inherited causes of kidney or extrarenal impairment of osmoregulation may be considered. This gene panel assesses 72 genes associated with heritable causes of electrolyte imbalance and kidney stones. A thorough clinical and laboratory evaluation prior to genetic testing is often essential for correct genetic diagnosis. While many symptoms associated with kidney stone formation and/or electrolyte imbalance may overlap, most disorders are identifiable by distinct clinical features and a biochemical "signature" established by plasma electrolyte profiles, blood volume status, urine biochemistries, and kidney stone analysis.

Genes on this panel are associated with disorders of:
1) Renal salt wasting (Gitelman and Bartter syndromes, pseudohypoaldosteronism type 1, congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency, and glucocorticoid remediable aldosteronism)
2) Salt retention (pseudohypoaldosteronism type 2, Liddle syndrome, familial hyperaldosteronism types 1 and 3)
3) Acid-base homeostasis (proximal or distal renal tubular acidosis)
4) Water handling (nephrogenic diabetes insipidus, neurohypophyseal diabetes insipidus, and nephrogenic syndrome of inappropriate antidiuresis)
5) Calcium homeostasis (familial hypocalciuric hypercalcemia, autosomal dominant hypocalcemia), parathyroid function, and vitamin D metabolism
6) Kidney crystallization inhibitors, such as magnesium, uromodulin, and pyrophosphate
7) Kidney crystallization promoters such as oxalate (calcium oxalate nephrolithiasis), phosphate (hypophosphatasia, Dent disease, familial tumoral calcinosis), urate (Lesch-Nyhan syndrome, xanthinuria), cystine (cystinuria), and 2,8-dihydroxyadenine (adenine phosphoribosyltransferase deficiency)

This panel also includes genes associated with 3 syndromic disorders for which kidney stones or involvement have been reported: Wilson disease (low-molecular weight proteinuria, microscopic hematuria, and Fanconi syndrome that can result in kidney failure); amelogenesis imperfecta, type IG ("enamel-renal syndrome"; nephrocalcinosis); and Fanconi renotubular syndrome 4, with maturity-onset diabetes of the young (MODY; nephrocalcinosis).

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants 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

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 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.

Deletion/Duplication Analysis:
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 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. Refer to the Targeted Genes and Methodology Details for Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel for the most up to date list of genes included in this test. 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 blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories at 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers 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.(1) 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. 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. Singh P, Harris PC, Sas DJ, Lieske JC: The genetics of kidney stone disease and nephrocalcinosis. Nat Rev Nephrol. 2022 Apr;18(4):224-240

Performance

Method Description

Capture-based and amplicon-based next-generation sequencing (NGS) 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-insertion (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-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.(Unpublished Mayo method)

See Targeted Genes and Methodology Details for Nephrocalcinosis, Nephrolithiasis, and Renal Electrolyte Imbalance Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.

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

Genes analyzed: *ABCC6, ADCY10, AGXT, ALPL, AP2S1, APRT, AQP2, ATP6V0A4, ATP6V1B1, ATP7B, AVP, AVPR2, BSND, CA2, CASR, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CNNM2, CUL3, CYP11B1, CYP11B2, CYP24A1, CYP27B1, CYP2R1, DMP1, EGF, ENPP1, FAM20A, FGF23, FOXI1, FXYD2, GALNT3, GATA3, GNA11, GRHPR, HNF4A, HOGA1, HPRT1, KCNJ1, KCNJ5, KL, KLHL3, MAGED2, MOCOS, NR3C2, OCRL, PHEX, PRPS1, SCNN1A, SCNN1B, SCNN1G, SLC12A1, SLC12A3, SLC22A12, SLC26A1, SLC2A9, SLC3A1, SLC34A1, SLC34A3, SLC4A1, SLC4A4, SLC7A9, SLC9A3R1, TRPM6, UMOD, VDR, WNK1, WNK4*, *XDH*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (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 x 4
81405 x 2
81406 x 8
81407 x 2
81479
81479 (if appropriate for government payers)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
RSCGP	Renal Stone/Electrolyte Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
618129	Test Description	62364-5
618130	Specimen	31208-2
618131	Source	31208-2
618132	Result Summary	50397-9
618133	Result	82939-0
618134	Interpretation	69047-9
618135	Additional Results	82939-0
618136	Resources	99622-3
618137	Additional Information	48767-8
618138	Method	85069-3

618139	Genes Analyzed	48018-6
618140	Disclaimer	62364-5
618141	Released By	18771-6