MAYO CLINIC LABORATORIES

# Test Definition: RFSGS

Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome Gene Panel, Varies

## Overview

### Useful For

Providing a genetic evaluation for patients with a personal or family history of steroid resistant nephrotic syndrome (SRNS)

Establishing a diagnosis of hereditary SRNS

Guiding treatment decisions in individuals with nephrotic syndrome

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide, deletion-insertion, and copy number variants in 56 genes associated with focal segmental glomerulosclerosis and nephrotic syndrome: *ACTN4, ALG1, ANLN, APOL1* [Chr22(GRCh37):g.36661895-36661916 and g.36662023-36662062 only], *ARHGAP24, ARHGDIA, CD2AP, CLCN5, COL4A3, COL4A4, COL4A5, COQ2, COQ6, COQ8B, CRB2, CUBN, DGKE, EMP2, FAN1, FAT1, FN1, INF2, ITGA3, ITGB4, KANK2, LAMA5, LAMB2, LMX1B, MAGI2, MYH9, MYO1E, NPHS1, NPHS2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, OCRL, PAX2, PDSS2, PLCE1, PLCG2, PMM2, PODXL, PTPRO, SCARB2, SGPL1, SMARCAL1, TBC1D8B, TRPC6, TTC21B, WDR73, WT1, ZMPSTE24*. See Targeted Genes and Methodology Details for Focal Segmental Glomerulosclerosis and Nephrotic 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 focal segmental glomerulosclerosis or nephrotic syndrome.

### 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 Focal Segmental Glomerulosclerosis and Nephrotic Syndrome Gene Panel

### Method Name

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

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

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## Ordering Guidance

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.

## Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

## Specimen Required

**Specimen Type:** Whole blood
**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 blood 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 a Renal Diagnostics Test Request (T830) with the specimen.

## 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

Nephrotic syndrome (NS) is a kidney disorder characterized by proteinuria, hypoalbuminemia, and edema. Many conditions can cause NS, including diseases that only affect the kidney and other more systemic disorders such as diabetes or lupus. Focal segmental glomerulosclerosis (FSGS), a histologic finding characterized by sclerosis involving part of the kidney glomeruli, is commonly found in patients with NS.(1)

Approximately 85% of nephrotic syndrome is steroid sensitive, while the remaining 15% is steroid resistant (SRNS). SRNS may be genetic or nongenetic. Nongenetic causes of NS/FSGS may be due to a circulating factor causing generalized injury to podocytes, structural renal abnormalities, viral or drug-induced causes, or other stress on the kidney such as obesity, congenital heart disease, malignancy, or hypertension.(2)

Genetic SRNS may result from disease-causing variants in genes encoding renal-specific proteins (renal-limited) or syndromic conditions with extrarenal features.(2) Autosomal recessive forms of nonsyndromic SRNS typically present in childhood and are caused by disease-causing variants in nephrin (*NPHS1*), podocin (*NPHS2*), *CD2AP*, *PLCE1*, *MYO1E*, and multiple other genes. Autosomal dominant SRNS is typically adult onset and may be caused by disease-causing variants in *TRPC6*, *ACTN4*, *INF2*, and other genes. Variants in type IV collagen genes, known to cause Alport syndrome, may also be identified in patients with familial or sporadic SNRS and present later in adolescence or adulthood.

In syndromic forms of SRNS, extrarenal manifestations may be prominent and diagnostic, but in some cases, extrarenal features may be subtle or develop later in the disease course, such as in Denys-Drash syndrome (DDS) and Frasier syndrome caused by disease-causing variants in *WT1*.

Other genes included on this panel cover a broad spectrum of conditions that may display proteinuria, NS, or FSGS, either as an isolated feature or as part of a more systemic presentation, including genes associated with congenital disorders of glycosylation, Alport syndrome, coenzyme Q10 deficiency, and others.

This test also includes assessment of the G1 and G2 alleles of the *APOL1* gene. The G1 and G2 alleles have been associated with increased risk for development or progression of nondiabetic chronic kidney diseases, including nonsyndromic SRNS.(3)

Despite some clinical and histologic overlap among the various categories of NS, management and prognosis may differ based on the underlying etiology. In particular, steroid sensitive NS may respond to treatment with corticosteroids, while SRNS, including those due to genetic causes, typically does not.(2) Therefore, identification of a genetic form of SRNS may impact evaluation for extra-renal manifestations, treatment decisions including transplantation, and genetic counselling.(4)

## Reference Values

An interpretive report will be provided.

## Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) 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.

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.

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 Focal Segmental Glomerulosclerosis and Nephrotic Syndrome 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 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.(5) 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. Chen YM, Liapis H: Focal segmental glomerulosclerosis: molecular genetics and targeted therapies. BMC Nephrol. 2015 Jul 9;16:101
2. De Vriese AS, Sethi S, Nath KA, et al: Differentiating primary, genetic, and secondary FSGS in adults: A clinicopathologic approach. J Am Soc Nephrol. 2018 Mar;29(3):759-774
3. Parsa A, Kao WH, Xie D, et al: APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013;369(23):2183-2196. doi: 10.1056/NEJMoa13103454
4. Rood IM, Deegens JKJ, Wetzels JFM: Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. Nephrol Dial Transplant. 2012 Mar;27(3):882-890
5. 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

## 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-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 Targeted Genes and Methodology Details for Focal Segmental Glomerulosclerosis and Nephrotic Syndrome Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions.(Unpublished Mayo method)

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

Genes analyzed: *ACTN4, ALG1, ANLN, APOL1* [Chr22(GRCh37):g.36661895-36661916 and g.36662023-36662062 only]*, ARHGAP24, ARHGDIA, CD2AP, CLCN5, COL4A3, COL4A4, COL4A5, COQ2, COQ6, COQ8B, CRB2, CUBN, DGKE, EMP2, FAN1, FAT1, FN1, INF2, ITGA3, ITGB4, KANK2, LAMA5, LAMB2, LMX1B, MAGI2, MYH9, MYO1E, NPHS1, NPHS2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, OCRL, PAX2, PDSS2, PLCE1, PLCG2, PMM2, PODXL, PTPRO, SCARB2, SGPL1, SMARCAL1, TBC1D8B, TRPC6, TTC21B, WDR73, WT1, ZMPSTE24*.

### 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
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

81408 x 2
81405 x 2
81406 x 4
81407 x 4
81479
81479 (if appropriate for government payers)

## LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| RFSGS | FSGS/Nephrotic Syndrome Gene Panel | 51966-0 |

| Result ID | Test Result Name | Result LOINC® Value |
|---|---|---|
| 618115 | Test Description | 62364-5 |
| 618116 | Specimen | 31208-2 |
| 618117 | Source | 31208-2 |
| 618118 | Result Summary | 50397-9 |
| 618119 | Result | 82939-0 |
| 618120 | Interpretation | 69047-9 |
| 618121 | Additional Results | 82939-0 |
| 618122 | Resources | 99622-3 |
| 618123 | Additional Information | 48767-8 |
| 618124 | Method | 85069-3 |
| 618125 | Genes Analyzed | 48018-6 |
| 618126 | Disclaimer | 62364-5 |
| 618127 | Released By | 18771-6 |