MAYO CLINIC LABORATORIES

Test Definition: NEPHP

Comprehensive Nephrology Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of hereditary kidney disease

Establishing a diagnosis for a variety of hereditary kidney conditions including focal segmental glomerulosclerosis, nephritic/nephrotic syndrome, Alport syndrome, cystic kidney diseases (including polycystic kidney disease), nephronophthisis, tubulointerstitial disease, congenital anomalies of kidney and urinary tract, nephrocalcinosis, nephrolithiasis (kidney stones), renal electrolyte imbalances (including Bartter syndrome), C3 glomerulopathy, and complement-mediated thrombotic microangiopathy (also known as atypical hemolytic uremic syndrome)

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide, deletion-insertion, and copy number variants in 302 genes associated with hereditary kidney disease: *ABCC6, ACE, ACTN4, ADAMTS13, ADCY10, AGT, AGTR1, AGXT, AHI1, ALG1, ALG8, ALG9, ALMS1, ALPL, ANKS6, ANLN, ANOS1, APOA1, APOE, APOL1* [Chr22(GRCh37]:g.36661895-36661916 and g.36662023-36662062 only), *APRT, AP2S1, AQP2, ARHGAP24, ARHGDIA, ARL13B, ARL6, ATP6V0A4, ATP6V1B1, ATP7B, AVP, AVPR2, B9D1, B9D2, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BICC1, BSND, C2, C2CD3, C3, C5* [Chr9(GRCh37):g.123759950-123759973 only], *C8A, C8orf37, CA2, CACNA1D, CACNA1H, CASR, CC2D2A, CD151, CD2AP, CD46* (*MCP*), *CEP104, CEP120, CEP164, CEP290, CEP41, CEP83, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, CHD7, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CNNM2, COL4A1, COL4A3, COL4A4, COL4A5, COL4A6, COQ2, COQ6, COQ8B, CPLANE1, CRB2, CREBBP, CSPP1, CTNS, CUBN, CUL3, CYP11B1, CYP11B2, CYP24A1, CYP27B1, CYP2R1, DCDC2, DDX59, DGKE, DHCR7, DMP1, DNAJB11, DYNC2H1, DZIP1L, EGF, EMP2, ENPP1, EYA1, FAH, FAM20A, FAN1, FAT1, FGA, FGF20, FGF23, FGFR1, FGFR2, FN1, FOXI1, FOXP1, FRAS1, FREM1, FREM2, FXYD2, GALNT3, GANAB, GATA3, GLA, GLI3, GLIS2, GNA11, GPC3, GREB1L, GRHPR, GRIP1, GSN, HNF1B, HNF4A, HOGA1, HPRT1, HPSE2, HSD11B2, IFT122, IFT140, IFT172, IFT27, IFT43, IFT80, IFT81, INF2, INPP5E, INVS, IQCB1, ITGA3, ITGA8, ITGB4, JAG1, KANK2, KCNA1, KCNJ1, KCNJ10, KCNJ5, KIAA0556* (*KATNIP*), *KIAA0586, KIAA0753, KIF12, KIF14, KIF7, KL, KLHL3, LAMA5, LAMB2, LMNA, LMX1B, LRIG2, LRP2, LRP5, LYZ, LZTFL1, MAGED2, MAGI2, MAPKBP1, MEFV, MKKS, MKS1, MMACHC, MOCOS, MYH9, MYO1E, NEK1, NEK8, NLRP3, NOTCH2, NPHP1, NPHP3, NPHP4, NPHS1, NPHS2, NR3C2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, OCRL, OFD1, PAX2, PBX1, PCBD1, PDE6D, PDSS2, PHEX, PKD1, PKD2, PKHD1, PLCE1, PLCG2, PLG, PMM2, PODXL, PRKCSH, PRPS1, PTPRO, REN, ROBO2, RPGRIP1L, SALL1, SALL4, SARS2, SCARB2, SCLT1, SCNN1A, SCNN1B, SCNN1G, SDCCAG8, SEC61A1, SEC63, SGPL1, SIX1, SLC12A1, SLC12A3, SLC17A5, SLC22A12, SLC26A1, SLC2A2, SLC2A9, SLC34A1, SLC34A3, SLC3A1, SLC4A1, SLC4A4, ,SLC5A1, SLC5A2, SLC6A19, SLC7A7, SLC7A9, SLC9A3R1, SLIT2, SMARCAL1, TBC1D8B, TBX18, TCTN1, TCTN2, TCTN3, THBD, TMEM107, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, TRAF3IP1, TRIM32, TRPC6, TRPM6, TSC1, TSC2, TTC21B, TTC8, TTR, UMOD, VDR, VHL, VIPAS39, VPS33B, WDR19, WDR35, WDR72, WDR73, WNK1, WNK4, WNT4, WT1, XDH, XPNPEP3, ZMPSTE24, ZNF423.*
See Targeted Genes and Methodology Details for Comprehensive Nephrology Gene Panel and Method Description for additional details.
Identification of a pathogenic variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for a variety of hereditary kidney diseases.

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 Comprehensive Nephrology Gene Panel

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

NY State Available
Yes

Specimen

Specimen Type
Varies

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
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)

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
Monogenic kidney disease spans a clinical spectrum of conditions with etiologies that can include structural, metabolic, immune, or endocrine abnormalities. Many heritable kidney diseases exhibit overlapping or complex phenotypes leading to a broad clinical differential. This gene panel assesses over 300 genes associated with a diverse spectrum of monogenic kidney diseases spanning the structural, metabolic, immune, and endocrine phenotypes. Assessing genetic etiologies across this phenotypic spectrum may aid in differentiating the genetic etiology of complex or ambiguous clinical presentations.(1-6)

Renal phenotypes assessed on this panel include: focal segmental glomerulosclerosis, nephritic/nephrotic syndrome, Alport syndrome, cystic kidney diseases (including polycystic kidney disease), nephronophthisis, tubulointerstitial disease, congenital anomalies of kidney and urinary tract, nephrocalcinosis, nephrolithiasis (kidney stones), renal electrolyte imbalances (including Bartter syndrome), C3 glomerulopathy, and complement-mediated thrombotic microangiopathy (CM-TMA; also known as atypical hemolytic uremic syndrome [aHUS]).

Many hereditary kidney diseases exhibit autosomal dominant, autosomal recessive, and/or X-linked inheritance. However, some hereditary kidney diseases exhibit complex or multifactorial inheritance. These complex and environmental etiologies are not assessed on this gene panel.

Several risk alleles associated with increased susceptibility to kidney disease are also included on this panel to aid in risk assessment:
-*APOL1* Genotype: Two alleles, commonly called G1 and G2, have been associated with increased risk for development or progression of nondiabetic chronic kidney diseases.(7)
- *CFH*-H3 Risk Haplotype: The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated with an increased risk for development or progression of atypical hemolytic uremic syndrome..(8)
-*MCP*/*CD46* Risk Haplotype: The variants that comprise this risk haplotype are common in the general population, but in the context of additional pathogenic genetic and environmental factors, the presence of this risk haplotype is associated

with an increased risk for development or progression of atypical hemolytic uremic syndrome (8)
-Finally, two variants in *C5* (p.Arg885His and p.Arg885Cys) that are associated with poor response to eculizumab can be detected by this panel.(9)

Reference Values
An interpretive report will be provided.

Interpretation
All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) 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.

This gene panel does **not** include assessment or interpretation of the common *APOE* alleles e2, e3, or e4.

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 Comprehensive Nephrology 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.(10) 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. Lemaire M, Noone D, Lapeyraque AL, Licht C, Fremeaux-Bacchi V: Inherited kidney complement diseases. Clin J Am Soc Nephrol. 2021 Jun;16(6):942-956. doi:10.2215/CJN.11830720
2. Lanktree MB, Haghighi A, di Bari I, Song X, Pei Y: Insights into autosomal dominant polycystic kidney disease from genetic studies. Clin J Am Soc Nephrol. 2021 May 8;16(5):790-799. doi: 10.2215/CJN.02320220
3. Quinlan C, Rheault MN: Genetic basis of type IV collagen disorders of the kidney. Clin J Am Soc Nephrol. 2021 Jul;16(7) 1101-1109. doi: 10.2215/CJN.19171220
4. Downie ML, Lopez Garcia SC, Kleta R, Bockenhauer D: Inherited tubulopathies of the kidney: Insights from genetics. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):620-630. doi: 10.2215/CJN.14481119

5. Westland R, Renkema KY, Knoers NVAM: Clinical integration of genome diagnostics for congenital anomalies of the kidney and urinary tract. Clin J Am Soc Nephrol. 2020 Dec 31;16(1):128-137. doi: 10.2215/CJN.14661119
6. Li AS, Ingham JF, Lennon R: Genetic disorders of the glomerular filtration barrier. Clin J Am Soc Nephrol. 2020 Dec 7;15(12):1818-1828. doi: 10.2215/CJN.11440919
7. Parsa A, Kao WH, Xie D, et al: APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013 Dec 5;369(23):2183-2196. doi: 10.1056/NEJMoa1310345
8. Bernabeu-Herrero ME, Jimenez-Alcazar M, Anter J, et al. Complement factor H, FHR-3 and FHR-1 variants associate in an extended haplotype conferring increased risk of atypical hemolytic uremic syndrome. Mol Immunol. 2015 Oct;67(2 Pt B):276-286. doi: 10.1016/j.molimm.2015.06.021
9. Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med. 2014 Feb13;370(7):632-639. doi: 10.1056/NEJMoa1311084
10. 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) are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as 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 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 content, and repetitive sequences.(Unpublished Mayo method)

See Targeted Genes and Methodology Details for Comprehensive Nephrology Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.

Genes analyzed: *ABCC6, ACE, ACTN4, ADAMTS13, ADCY10, AGT, AGTR1, AGXT, AHI1, ALG1, ALG8, ALG9, ALMS1, ALPL, ANKS6, ANLN, ANOS1, APOA1, APOE, APOL1* [Chr22(GRCh37):g.36661895-36661916 and g.36662023-36662062 only]*, APRT, AP2S1, AQP2, ARHGAP24, ARHGDIA, ARL13B, ARL6, ATP6V0A4, ATP6V1B1, ATP7B, AVP, AVPR2, B9D1, B9D2, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BICC1, BSND, C2, C2CD3, C3, C5* [Chr9(GRCh37):g.123759950-123759973 only]*, C8A, C8orf37, CA2, CACNA1D, CACNA1H, CASR, CC2D2A, CD151, CD2AP, CD46 (MCP), CEP104, CEP120, CEP164, CEP290, CEP41, CEP83, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, CHD7, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CNNM2, COL4A1, COL4A3, COL4A4, COL4A5, COL4A6, COQ2, COQ6, COQ8B, CPLANE1, CRB2, CREBBP, CSPP1, CTNS, CUBN, CUL3, CYP11B1, CYP11B2, CYP24A1, CYP27B1, CYP2R1, DCDC2, DDX59, DGKE, DHCR7, DMP1, DNAJB11, DYNC2H1, DZIP1L, EGF, EMP2, ENPP1, EYA1, FAH, FAM20A, FAN1, FAT1, FGA,*

FGF20, FGF23, FGFR1, FGFR2, FN1, FOXI1, FOXP1, FRAS1, FREM1, FREM2, FXYD2, GALNT3, GANAB, GATA3, GLA, GLI3, GLIS2, GNA11, GPC3, GREB1L, GRHPR, GRIP1, GSN, HNF1B, HNF4A, HOGA1, HPRT1, HPSE2, HSD11B2, IFT122, IFT140, IFT172, IFT27, IFT43, IFT80, IFT81, INF2, INPP5E, INVS, IQCB1, ITGA3, ITGA8, ITGB4, JAG1, KANK2, KCNA1, KCNJ1, KCNJ10, KCNJ5, KIAA0556 (*KATNIP*), *KIAA0586, KIAA0753, KIF12, KIF14, KIF7, KL, KLHL3, LAMA5, LAMB2, LMNA, LMX1B, LRIG2, LRP2, LRP5, LYZ, LZTFL1, MAGED2, MAGI2, MAPKBP1, MEFV, MKKS, MKS1, MMACHC, MOCOS, MYH9, MYO1E, NEK1, NEK8, NLRP3, NOTCH2, NPHP1, NPHP3, NPHP4, NPHS1, NPHS2, NR3C2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, OCRL, OFD1, PAX2, PBX1, PCBD1, PDE6D, PDSS2, PHEX, PKD1, PKD2, PKHD1, PLCE1, PLCG2, PLG, PMM2, PODXL, PRKCSH, PRPS1, PTPRO, REN, ROBO2, RPGRIP1L, SALL1, SALL4, SARS2, SCARB2, SCLT1, SCNN1A, SCNN1B, SCNN1G, SDCCAG8, SEC61A1, SEC63, SGPL1, SIX1, SLC12A1, SLC12A3, SLC17A5, SLC22A12, SLC26A1, SLC2A2, SLC2A9, SLC34A1, SLC34A3, SLC3A1, SLC4A1, SLC4A4 ,SLC5A1, SLC5A2, SLC6A19, SLC7A7, SLC7A9, SLC9A3R1, SLIT2, SMARCAL1, TBC1D8B, TBX18, TCTN1, TCTN2, TCTN3, THBD, TMEM107, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, TRAF3IP1, TRIM32, TRPC6, TRPM6, TSC1, TSC2, TTC21B, TTC8, TTR, UMOD, VDR, VHL, VIPAS39, VPS33B, WDR19, WDR35, WDR72, WDR73, WNK1, WNK4, WNT4, WT1, XDH, XPNPEP3, ZMPSTE24, ZNF423*.

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
81401 x 2
81404 x 12

81405 x 8
81406 x 22
81407 x 13
81408 x 5
81479
81479 (if appropriate for government payers)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NEPHP	Comprehensive Nephrology Gene Panel	51966-0

Result ID	Test Result Name	Result LOINC® Value
618087	Test Description	62364-5
618088	Specimen	31208-2
618089	Source	31208-2
618090	Result Summary	50397-9
618091	Result	82939-0
618092	Interpretation	69047-9
618093	Additional Results	82939-0
618094	Resources	99622-3
618095	Additional Information	48767-8
618096	Method	85069-3
618097	Genes Analyzed	48018-6
618098	Disclaimer	62364-5
618099	Released By	18771-6