Test Definition: SCCNP

Severe Congenital and Cyclic Neutropenia
Gene Panel, Varies

Overview

Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of severe congenital neutropenia and/or cyclic neutropenia

Establishing a diagnosis of an inherited congenital neutropenia and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 30 genes associated with severe congenital neutropenia and cyclic neutropenia: *AK2, AP3B1, AP3D1, CD40LG, CEBPE, CLPB, CSF3R, CXCR2, CXCR4, DNAJC21, EFL1, ELANE, G6PC3, GATA2, GFI1, GINS1, HAX1, JAGN1, LYST, RAC2, SBDS, SLC37A4, SMARCD2, SRP54, TAZ(TAFAZZIN), USB1, VPS13B, VPS45, WAS,* and *WIPF1*. See Targeted Genes and Methodology Details for Severe Congenital and Cyclic Neutropenia Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for severe congenital neutropenia and cyclic neutropenia.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Severe Congenital and Cyclic Neutropenia Gene Panel
- Congenital Neutropenia, Bone Marrow Failure, Telomere Defects, and Pulmonary Fibrosis (IPF) Patient Information

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type
Varies

Ordering Guidance
Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about testing option, call 800-533-1710.

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.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
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) 4 days/Refrigerated

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: Refrigerated (preferred)/Ambient
Additional Information: 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.

Specimen Type: Cultured fibroblasts
Container/Tube: T-25 flask

Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: 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.

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. Congenital Neutropenia, Bone Marrow Failure, Telomere Defects, and Pulmonary Fibrosis (IPF) Patient Information

Specimen Minimum Volume

Blood: 1 mL; Skin biopsy or cultured fibroblasts: 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

Inherited congenital neutropenia refers to a subset of primary immunodeficiencies impacting neutrophil maturation and function. The severity of the clinical manifestations in these disorders typically reflects the degree of neutropenia. Most cases of neutropenia are due to acquired (non-genetic) causes. Severe congenital neutropenia (SCN) is characterized by chronically low neutrophil count and recurrent, often life-threatening infections beginning in the first few months of life. Some individuals with SCN may also have an increased risk for myelodysplastic syndrome or acute myelogenous leukemia.(1-3) Cyclic neutropenia (CN) is characterized by periods of severe neutropenia and infections that last 3 to 5 days and recur at regular intervals.(1-5) Individuals with SCN or CN may also exhibit recurrent fevers, sinusitis, gingivitis, cellulitis, oral ulcers, colonic ulcers, and other manifestations of chronic infections.(1-5) Bone marrow biopsy on affected individuals may show arrest in myelopoiesis at the promyelocyte/myelocyte stage.(1-3)

The prevalence of inherited severe congenital neutropenia and cyclic neutropenia is estimated to range from 1:500,000 to 1:100,000 live births.(1-5) The genetic etiology of inherited congenital neutropenia is most commonly due to disease-causing variants in genes that play a role in neutrophil differentiation.(1) Inheritance can be autosomal recessive, autosomal dominant, or X-linked.

The most common causes of isolated congenital neutropenia are disease-causing variants in the *ELANE* and *HAX1* genes, which encode neutrophil elastase and HCLS1(hematopoietic cell-specific Lyn substrate)-associated protein X-1, respectively. Autosomal dominant *ELANE*-related neutropenia is the most common cause of congenital neutropenia in children and may present with oral/colonic ulcers, recurrent upper and lower respiratory infections, and various infections of the soft tissue.(2,4,6) In addition, most cases of cyclic neutropenia are due to disease-causing variants in *ELANE*. Autosomal recessive Kostmann disease, caused by variants in the *HAX1* gene, is the second most common cause of congenital neutropenia in children and presents similarly to *ELANE*-related neutropenia.(2,4,6) X-linked *WAS*-related disorders lead to a spectrum of congenital neutropenia phenotypes including Wiskott-Aldrich syndrome and X-linked congenital neutropenia.(5,6) Isolated severe congenital neutropenia may more rarely be due to disease-causing variants in several additional genes including *CSF3R*, *CXCR2*, *GFI1* and *WIPF1*.(1,6)

Severe neutropenia may also be present as part of a multisystem disorder.(1) This panel assesses for many conditions in which neutropenia is seen in conjunction with extra-hematologic features, including but not limited to:
-Shwachman-Diamond syndrome, an autosomal dominant condition due to disease-causing variants in the *SBDS* gene, is also characterized by exocrine pancreatic dysfunction, bone abnormalities, and hematologic abnormalities.
-*GATA2*-deficieny (monocytopenia and mycobacterial infection [MonoMAC] syndrome), an autosomal dominant condition due to disease-causing variants in the *GATA2* gene, demonstrates a wide spectrum of clinical presentations ranging from mild chronic neutropenia with monocytopenia to Emberger syndrome and predisposition to acute myeloid malignancy.
-Barth syndrome, an X-linked condition due to disease-causing variants in the *TAZ* gene, is also characterized cardiomyopathy, skeletal myopathy, growth delay, and distinctive facial features.
-Cohen syndrome, an autosomal recessive condition due to disease-causing variants in the *VSP13B* gene, is also characterized by hypotonia, developmental delays, microcephaly, failure to thrive in infancy, truncal obesity, ophthalmologic findings, joint hypermobility, a cheerful disposition, and characteristic facial features.
-WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome, an autosomal dominant condition caused by variants in the *CXCR4* gene, is also characterized by hypogammaglobulinemia and susceptibility to human papillomavirus.

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) 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.

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 Severe Congenital and Cyclic Neutropenia 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 non-leukoreduced 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 health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

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.(7) 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 judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K: Severe congenital neutropenias. Nat Rev Dis Primers. 2017 Jun 8;3:17032. doi:10.1038/nrdp.2017.32
2. Fadeel B, Garwicz D, Carlsson G, Sandstedt B, Nordenskjold M: Kostmann disease and other forms of severe congenital neutropenia. Acta Paediatr. 2021 Nov;110(11):2912-2920. doi:10.1111/apa.16005
3. Tayal A, Meena JP, Kaur R, et al: A novel homozygous HAX1 mutation in a child With cyclic neutropenia: A case report and review. J Pediatr Hematol Oncol. 2022 Mar 1;44(2):e420-e423. doi:10.1097/MPH.0000000000002110
4. Dale DC, Makaryan V: ELANE-related neutropenia. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2002. Updated August 23, 2018. Accessed January 19, 2023. Available at www.ncbi.nlm.nih.gov/books/NBK1533/
5. Chandra S, Bronicki L, Nagaraj CB, et al: WAS-related disorders. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2004. Updated September 22, 2016. Accessed January 19, 2023. Available at https://www.ncbi.nlm.nih.gov/books/NBK1178/
6. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct:42(7):1473-1507. doi: 10.1007/s10875-022-01289-3
7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: 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

Next-generation sequencing (NGS) and/or Sanger sequencing are 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), and 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. See Targeted Genes and Methodology Details for Severe Congenital and Cyclic Neutropenia 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: *AK2, AP3B1, AP3D1, CD40LG, CEBPE, CLPB, CSF3R, CXCR2, CXCR4, DNAJC21, EFL1, ELANE, G6PC3, GATA2, GFI1, GINS1, HAX1, JAGN1, LYST, RAC2, SBDS, SLC37A4, SMARCD2, SRP54, TAZ(TAFAZZIN), USB1, VPS13B, VPS45, WAS,* and *WIPF1*

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; Cultured fibroblasts, skin biopsy: 1 month

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

81443
88233- Tissue culture, skin, solid tissue biopsy (if appropriate)
88240- Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
SCCNP	Congenital Neutropenia GenePanel	In Process

Result ID	Test Result Name	Result LOINC® Value
619873	Test Description	62364-5
619874	Specimen	31208-2
619875	Source	31208-2
619876	Result Summary	50397-9
619877	Result	82939-0
619878	Interpretation	69047-9
619879	Additional Results	82939-0
619880	Resources	99622-3
619881	Additional Information	48767-8
619882	Method	85069-3
619883	Genes Analyzed	82939-0
619884	Disclaimer	62364-5
619885	Released By	18771-6