USEFUL FOR

- Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of congenital neutropenia, cyclic neutropenia, or other primary immunodeficiency presenting with significant neutropenia
- Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved
- Identifying variants within genes known to be associated with primary immunodeficiencies characterized by significant neutropenia allowing for predictive testing of at-risk family members

GENETICS TEST INFORMATION

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for the genes listed on the panel.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for all genes on this panel. See KVAR1 / Known Variant Analysis-1 Variant; KVAR2 / Known Variant Analysis-2 Variants; or KVAR3 / Known Variant Analysis-3+ Variants. Contact Mayo Medical Laboratories to confirm the appropriate test code for targeted testing if testing for a gene not included on this panel, or if testing for more than 5 variants is needed.

CLINICAL INFORMATION

Severe congenital neutropenia is characterized by severe and recurrent bacterial infections, such as otitis media, bronchitis, pneumonia, osteomyelitis, and cellulitis, typically with the absence of pus at the infected site. Susceptibility to fungal infections may also be observed. Neutropenia may be an isolated finding or may be part of a syndrome. This panel includes genes associated with neutropenia as a major presenting feature; other panels may be more appropriate when neutropenia is identified but not as the main finding.

REFERENCE VALUES

An interpretive report will be provided.

ANALYTIC TIME

6 weeks
Pathogenic variants in **ELANE**, which encodes neutrophil elastase, can result in severe congenital neutropenia type 1 (SCN1) or cyclic neutropenia. SCN1 often presents immediately with omphalitis, while diarrhea, pneumonia, and deep abscesses affecting the liver, lungs, or subcutaneous tissues are noted within the first year. Patients are at risk for development of myelodysplastic syndrome or acute myelogenous leukemia, presumably due to acquired mutations in **CSF3R** (which may also be identified in the presence of congenital neutropenia due to variants in genes other than **ELANE**, see below). Biallelic mutations in **CSF3R** have also been recently reported to be associated with severe congenital neutropenia. Cyclic neutropenia typically presents in the first year of life with 3-week-long oscillations in cell counts along with intervals of fever, oral ulcerations, and ulcers; between intervals, patients are generally healthy. Unlike SCN1, cyclic neutropenia is not associated with risk of malignancy. Both SCN1 and cyclic neutropenia are inherited in an autosomal dominant pattern from an affected parent, although de novo mutations have been identified. Studies have demonstrated pathogenic variants in **ELANE** in nearly 100% of cases with well-documented classical cyclic neutropenia, while in some cases with atypical presentations (ie, oscillations that are not 3 weeks) a variant in **ELANE** is not identified. **ELANE** variants are identified in 38% to 80% of cases of congenital neutropenia, depending on the criteria used to identify patients. Although there is some overlap, generally, variants at the active site of neutrophil elastase result in cyclic neutropenia, while variants that prevent normal folding or packaging of the enzyme cause congenital neutropenia.

In addition to variants in **ELANE**, severe congenital neutropenia—where the predominant finding is neutropenia—can be inherited as a result of pathogenic variants in other genes. Dominant variants in **GFI1** (encoding growth factor independent 1) result in severe congenital neutropenia type 2 (SCN2). Pathogenic variants in **G6PC3** (encoding glucose-6-phosphate 3), which are inherited in an autosomal recessive manner, can result in a phenotypic spectrum from isolated nonsyndromic severe congenital neutropenia to classic G6PC3 deficiency (severe neutropenia along with cardiovascular and urogenital abnormalities) to severe G6PC3 deficiency (also known as Dursun syndrome, which includes features of classic G6PC3 deficiency along with severe lymphopenia, primary pulmonary hypertension, thymic hypoplasia, among other features). Kostmann disease or severe congenital neutropenia type 3 (SCN3) is due to recessive inheritance of pathogenic variants in **HAX1** (which encodes HCLS1-associated protein X-1) and may result in seizures and developmental delay in addition to neutropenia. Along with neutropenia, variants in **VPS45** inherited in an autosomal recessive manner (also known as severe congenital neutropenia type 5 [SNC5]) are associated with neutrophil dysfunction, bone marrow fibrosis, and nephromegaly due to renal extramedullary hematopoiesis. While loss-of-function variants in **WAS** (which is located on the X chromosome, cause Wiskott-Aldrich syndrome [characterized by thrombocytopenia, eczema, and recurrent infections]), gain-of-function variants affecting the autoinhibitory structure of the protein, have been associated with congenital neutropenia, along with variable lymphopenia, decreased lymphocyte proliferation, and impaired phagocyte activity. Pathogenic variants in **WIPF1** can present with similar findings to Wiskott-Aldrich syndrome.

Severe neutropenia may also be present as part of a multisystem disorder. Barth syndrome, due to pathogenic variants in **TAZ**, which is located on the X-chromosome, is characterized by neutropenia, cardio- and skeletal myopathy, growth delay, and distinctive facial features. Biallelic variants in **C16orf57** manifest as poikiloderma with neutropenia; the neutropenia may be cyclical. In Cohen syndrome, an autosomal recessive disorder due to variants in **COH1** (also known as **VPS13B**), neutropenia is accompanied by hypotonia, developmental delays, microcephaly, failure to thrive in infancy, truncal obesity in adolescent years, ophthalmologic findings, joint hypermobility, a cheerful disposition, and characteristic facial features. Glycogen storage disease type 1 (GSD1), caused by biallelic pathogenic variants in either **G6PC3** or **SLC37A4**, when untreated can result in chronic neutropenia and impaired neutrophil and monocyte function, as well as the characteristic findings that include accumulation of glycogen and fat in the liver and kidneys. Pathogenic variants in **LAMTOR2/MAKPPIP** have been shown to result in neutropenia, decreased cytotoxic activity of CD8+ T-cells, short stature, and hypopigmented skin. Persistent or intermittent neutropenia is often a presenting feature of Shwachman-Diamond syndrome (SDS), which is also characterized by exocrine pancreatic dysfunction (with malabsorption, malnutrition, and growth failure), bone abnormalities, and hematologic abnormalities (single- or multilineage cytopenias along with predisposition to myelodysplastic syndrome and acute myelogenous leukemia). SDS is an autosomal recessive disorder due to pathogenic variants in **SDS**. Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome is characterized by neutropenia in addition to hypogammaglobulinemia, and susceptibility to human papillomavirus. It is due to autosomal dominant pathogenic variants in **CXCR4**. Although most forms of Hermansky-Pudlak syndrome do not include significant neutropenia, type 2 caused by variants in **AP3B1** can be associated with persistent neutropenia and increased infections in addition to the typical findings of tyrosinase-positive oculocutaneous albinism, platelet storage pool deficiency, pulmonary fibrosis, and granulomatous colitis. Few patients with **RAC2** pathogenic variants have been identified, but neutrophil dysfunction appears to be a feature, though CD11b expression and specific granule release appear to be preserved. Both individuals with dominant and individuals with recessive inheritance have been identified, with and without additional associated phenotypic findings.

GATA-binding protein (GATA2) deficiency demonstrates a wide spectrum of clinical presentations, including neutropenia. Most variants appear to arise de novo (spontaneously) and are then transmitted in an autosomal dominant manner. If the clinical phenotype strongly suggests GATA2 deficiency, this gene is available as a stand-alone test (see test code GATA2). This panel does not evaluate for somatic (acquired) ASXL1 mutations associated with GATA2 deficiency.