ELANE (ELA2) Gene Analysis in Severe Congenital Neutropenia or Cyclic Neutropenia

**Disorder also known as:** SCN1, congenital autosomal dominant or sporadic neutropenia, infantile genetic agranulocytosis, Kostmann disease (historically); cyclic hematopoiesis

**Clinical Features:**
Severe congenital neutropenia (SCN) and cyclic neutropenia (CN) are severe disorders of neutrophil production that cause lifelong problems with recurrent infections. Congenital neutropenia is characterized by very low non-oscillating neutrophil counts with normal hemoglobin and platelet levels. Typical infections include omphalitis, pneumonia, sinusitis and gingivitis. The bone marrow shows a selective defect in neutrophil formation with promyelocytic maturation arrest. While all types of severe congenital neutropenia sometimes are called Kostmann disease, the extended family studied by Kostmann had a recessive disorder now known to be caused by mutations in HAX1, not ELANE.

Cyclic neutropenia often, but not always, follows a 3-week cycle of neutropenia, fever and mouth ulcers. Diagnosis is usually made in infancy and infections may lessen in severity with age.

**Genetics:**
Autosomal dominant, with pathogenic variants that usually occur de novo in SCN and may be inherited in CN.

**Test Methods:**
Analysis is performed by bi-directional sequencing of the coding regions and splice sites of exons 1-5 of the ELANE gene. Pathogenic variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test Sensitivity:**
In various studies, 35-88% of patients with SCN$^{1,2}$ and 44-100% of patients with CN$^{1,2,3}$ have had ELANE variants. The sequence analysis performed by GeneDx is expected to detect at least 98% of ELANE variants associated with these dominant disorders.

**Variant spectrum:**
Both disorders are associated with the production of stable neutrophil elastase proteins of near-normal sequence resulting from missense variants, small deletions, use of alternate
splice sites, and distal truncations. Promoter variants resulting in excess normal protein production have been postulated.

References: