

Autosomal Dominant Severe Congenital Neutropenia and Cyclic Neutropenia via *ELANE* Gene Sequencing (Test #444)

Brief Description of Clinical Features: Severe Congenital Neutropenia (SCN; OMIM 202700) comprises a heterogeneous group of disorders of myelopoiesis with varying symptoms and patterns of inheritance. SCN is characterized by absolute neutrophil counts (ANC) consistently below 500/ μ l and severe systemic bacterial infections beginning in early infancy (see Boxer and Newburger *Pediatr Blood Cancer* 49:609-614, 2007). Patients typically have recurrent fevers and develop sinusitis, gingivitis and other soft tissue infections. SCN and cyclic neutropenia share the same symptoms, however with cyclic neutropenia ANCs rise and fall with a periodicity of ~ 21-days. A hallmark of SCN is bone marrow ‘maturation arrest’; neutrophils differentiate only to the promyelocyte/myelocyte stage (see Kostman *Acta Paediatr Scand* 64:362-368, 1975). About 95% of patients respond to treatment with recombinant granulocyte-colony stimulating factor (G-CSF) with an increase in ANC (Bellanne-Chantelot et al. *Blood* 103:4119-4125, 2004; Freedman et al. *Blood* 96:429-436, 2000), however treated patients are still at risk of sepsis (Donini et al. *Blood* 109:4716-4723, 2007). SCN is a premalignant condition; patients are at an elevated risk of developing myelodysplastic syndrome and acute myeloblastic leukemia (MDS/AML). The risk of developing a malignancy increases upon G-CSF treatment (Gilman et al. *Blood* 36:576-585, 1970; Freedman et al. *Blood* 96:429-436, 2000; Rosenberg et al. *Blood* 107:4628-4635, 2006). In contrast to patients with SCN, MDS/AML have not been diagnosed in patients with cyclic or idiopathic neutropenia.

Genetics: It is estimated that approximately 35%-63% of patients with neutropenia have heterozygous mutations in the *ELANE* gene (OMIM 130130) (Rosenberg et al. *Blood* 107:4628-4635, 2006; Bellanne-Chantelot et al. *Blood* 103:4119-4125, 2004). Causative mutations are primarily missense and nonsense mutations. *ELANE* encodes neutrophil elastase, a serine protease that cleaves cellular and extracellular proteins and is expressed exclusively in neutrophils and monocytes. Recent reports suggest that mutated elastase in the ER triggers the unfolded protein response in neutrophils causing apoptosis and neutropenia (see Ward and Dale *Curr Opin Hematol* 16:9-13, 2009). In comparison to other neutropenia-related genes, mutations in *ELANE* correlate with a more severe expression of the disease, particularly in cases of congenital neutropenia (Bellanne-Chantelot et al. *Blood* 103:4119-4125, 2004).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 5 exons of the *ELANE* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000019.9 mRNA: NM_001972.2 Protein: NP_001963.1 (CCDS 12045.1)

Indications for Test: Patients with recurring bacterial infections, a family history of SCN, or neutropenia unrelated to other syndromes (e.g. Chediak-Higashi Syndrome, Hermansky Pudlak Syndrome, or Griscelli Syndrome).

Sensitivity of Test: *ELANE* mutations are the most common cause of SCN and the only known cause of cyclic neutropenia.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of Requisition Form

Price: Sequencing of *ELANE* \$ 520

CPT Codes							
Test	83890 x1	83891 x1	83898 x5	83904 x5	83894 x1	83912 x1	Total
<i>ELANE</i>	\$30	\$40	\$130	\$200	\$30	\$90	\$520

Accreditation: CLIA ID #52D1027685 (expires 1/18/13) CAP #7185561, AU ID:1407125 (expires 12/20/12)

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