Disorder:
Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome caused by defects in the telomere maintenance pathway. The prevalence of DC is estimated to be 1 in 1,000,000. Patients with DC have varied clinical presentations, which may include the classic diagnostic triad of dysplastic nails, lacy reticular pigmentation of the chest and neck, and oral leukoplakia. Patients with DC are predisposed to bone marrow failure, acute myelogenous leukemia, myelodysplastic syndrome, solid tumors, and pulmonary fibrosis. Bone marrow failure is the primary cause of early mortality. There is significant variation in clinical manifestation between affected individuals, even between those in the same family. A broad phenotypic spectrum exists in individuals with telomere maintenance defects, ranging from the severe, Hoyeraal Hreidarsson and Revesz syndromes to idiopathic aplastic anemia and pulmonary fibrosis. Nearly all individuals with DC have abnormally short telomeres compared to healthy age-matched controls.

Genetics:
Dyskeratosis congenita is a genetically heterogeneous disorder. To date, mutations in eight genes have been identified in patients with DC: DKC1, NHP2, NOP10, RTEL1, TERC, TERT, TINF2, and WRAP53. The inheritance of DC can be X-linked recessive (DKC1), autosomal dominant (RTEL1, TERC, TERT, TINF2), or autosomal recessive (NHP2, NOP10, RTEL1, TERT, WRAP53). There is a high frequency of sporadic cases of DC, due to the incidence of de novo mutations in the X-linked and dominant genes. Genetic anticipation has been reported in families with mutations in the autosomal dominant genes. Thus, some asymptomatic parents of individuals with mutations in TERC, TERT, and TINF2 may also carry a familial mutation.

Indications:
Dyskeratosis Congenita Panel by NGS
Confirmation of diagnosis in a patient with the following symptoms:
- Two or more features of the common clinical triad: dysplastic nails, lacy reticular pigmentation of the chest and neck, oral leukoplakia
- Four or more features of Hoyeraal Hreidarsson syndrome (growth retardation, developmental delay, microcephaly, bone-marrow failure, immunodeficiency, and cerebellar hypoplasia)
- One feature of the classic triad plus bone-marrow failure, plus two or more of the following: epiphora, developmental delay, pulmonary disease, blepharitis, abnormal eyelashes, premature graying, alopecia, periodontal disease, taurodontism, short stature, microcephaly, hypogonadism, esophageal stenosis, urethral stenosis, liver disease, leukemia, osteoporosis, avascular necrosis of the hips or shoulders
- Two or more features of DC associated with telomeres shorter than the 1st centile
- Aplastic anemia, myelodysplastic syndrome or pulmonary fibrosis associated with a telomerase mutation.

Gene Specific Sequencing:
- Confirmation of genetic diagnosis in a patient with DC and in whom a specific genetic diagnosis is suspected.

Mutation Specific Analysis:
- Presymptomatic testing of at-risk siblings and/or parents for medical management and prior to bone marrow donation.
• Carrier identification in individuals in whom specific mutation(s) have been identified in the proband with DC
• Prenatal diagnosis of an at-risk fetus, after confirmation of biallelic mutations in the parents (by prior arrangement only).

**Specimen:**
At least 5 mLs whole blood in a lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection.

**Testing Methodology:**

**Dyskeratosis congenita Panel by NGS:** This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5' and 3') of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with >20 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown significance, as determined bioinformatically, are confirmed by Sanger sequencing.

**Gene Specific Sequencing/ Mutation Specific Analysis:** Sanger sequencing following PCR amplification of the specified coding and exon/intron boundaries of the specified gene.

**Test Sensitivity:**

**Clinical Sensitivity:** Approximately 50% of patients with classic dyskeratosis congenita (individuals with the triad of nail dystrophy, skin pigmentation, and oral leukoplakia) have an identifiable mutation in one of the seven genes currently known to be associated with DC. Up to 10% of individuals with idiopathic pulmonary fibrosis, acute myelogenous leukemia, or apparently acquired aplastic anemia have mutations in *TERC* or *TERT.*

**Analytical Sensitivity:** The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. The majority of mutations responsible for DC are point mutations or small deletions that can be detected by sequencing. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events have been reported in *DKC1* and *TERC* and will not be identified using this test methodology. Somatic mutations are likely to be detected when they are present in >20% of cells analyzed.

**Note:** Targeted deletion and duplication analysis of every gene on this panel is clinically available at an additional charge.

**Turn-Around Time:**
• Dyskeratosis congenita NGS Panel: 42 days
• Single gene sequencing: up to 42 days

**Cost:**
Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

**CPT Codes:**
• Dyskeratosis congenita NGS Panel: 81479x8
• Mutation specific analysis: 81403
• Deletion/duplication analysis of single gene: 81479
• Deletion and duplication analysis of entire panel: 81479x8

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

**Shipping Instructions:**
Please enclose test requisition with sample. **All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

**Ship to:**
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474
Results:
Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for the clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

References:


