Dyskeratosis Congenita and Telomere Disorders Panel

Genes Tested:

ACD	*CTC1*	*DKC1*	*NAF1*
NHP2	*NOP10*	*PARN*	*POT1*
RTEL1	*STN1*	*TERC*	*TERF2IP*
TERT	*TINF2*	*WRAP53*	

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.

Additional conditions associated with telomere dysfunction include pulmonary fibrosis, acute myelogenous leukemia, apparently acquired aplastic anemia, and cerebroretinal microangiopathy with calcifications and cysts.

Genetics:

Telomere disorders have been reported in association with autosomal dominant, autosomal recessive, and X-linked conditions. 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 some families with telomere disorders. Asymptomatic parents of affected children are at risk of carrying pathogenic variants.

Indications:

Dyskeratosis Congenita and Telomere Disorders 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 variant.

Gene Specific Sequencing:

- Confirmation of genetic diagnosis in a patient with DC and/or telomere disorders and in whom a specific genetic diagnosis is suspected.

Cincinnati Children's®
changing the outcome together

Laboratory of Genetics and Genomics
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www.cincinnatichildrens.org/genetics

Variant 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 variant(s) have been identified in the proband with DC and/or telomere disorders
- Prenatal diagnosis of an at-risk fetus, after confirmation of variant(s) in the parent(s) and by prior arrangement only.

Specimen:

At least 3 mLs whole blood in a lavender top (EDTA) tube or saliva in an Oragene saliva kit. Please call 513-636-4474 for a free saliva collection kit.

Note: For post-transplant patients, we accept pre-transplant samples or post-transplant skin fibroblasts ONLY (blood, saliva, and cytobrushes are not accepted). Culturing of skin fibroblasts is done at an additional charge.

Testing Methodology:

Dyskeratosis congenita and Telomere Disorders Panel: This test is performed by enrichment of the coding exons, flanking intronic and untranslated regions (5′ and 3′), as well as known pathogenic variants (HGMD 2018.4) in the promoter and deep intronic regions of the genes specified above using oligonucleotide probe hybridization followed by next-generation sequencing with >50X coverage at every target base. All pathogenic and likely pathogenic variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing. Regions with <50X will be filled in by Sanger sequencing. A detailed non-coding variant list is available upon request.

Gene Specific Sequencing: PCR-based sequencing of the entire coding region and intron/exon boundaries of the specified gene and selected known pathogenic variants in the promotor and deep intronic regions.

Variant Specific Analysis: Sanger sequencing following PCR amplification of the targeted variant(s) of the specified gene.

Test Sensitivity:

Clinical Sensitivity: Approximately 70% of individuals who meet clinical criteria for DC will have positive genetic testing.

Limitations: Variants in regulatory regions and non-reported variants in untranslated regions may not be detected by this test. Large deletions/ duplications, large insertions and other complex genetic events will not be identified using sequencing methodology.

Note: Single gene sequencing and targeted variant analysis is also available for all genes on the Dyskeratosis Congenita and Telomere Disorders Panel. Deletion/duplication is available for many of the genes on this panel. For further details, visit: www.cincinnatichildrens.org/deldup.

Turn-Around Time:

- Dyskeratosis congenita and Telomere Disorders NGS Panel: up to 6 weeks
- Single gene sequencing: up to 28 days

CPT Codes:

- **Dyskeratosis congenita and Telomere Disorders NGS Panel:** 81443
- **Single gene sequencing, targeted variant analysis, and deletion/duplication:** call for information.

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

Results:

Results will be reported to the referring physician or health care provider as specified on the requisition form.

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

References:

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Newton, C.A., K. Batra, et al. (2016). Telomere-Related Lung Fibrosis is Diagnostically Heterogeneous but Uniformly Progressive. Eur Resp J 48(6): 1710-20.

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Savage, S. A. (2018). Beginning at the ends: telomeres and human disease. F1000Res 1:7 pii. F1000 Faculty Rev-524.

Townsley, D. M., Dumitriu, B., & Young, N. S. (2014). Bone marrow failure and the telomeropathies. Blood, 124(18), 2775-2783.