**Overview**

**Useful For**
Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of telomeropathies
Establishing a diagnosis of a telomeropathy, in some cases, allowing for appropriate management and surveillance for disease features
Identifying pathogenic variants within genes known to be associated with increased risk for telomere defects 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.

**Testing Algorithm**
For skin biopsy or cultured fibroblast specimens, fibroblast culture and cryopreservation testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

**Special Instructions**
- Informed Consent for Genetic Testing
- Primary Immunodeficiencies Patient Information

**Highlights**
This test uses next-generation sequencing to test for variants in the *CTC1, DKC1, NHP2, NOP10, RTEL1, TERC, TERT, TINF2, US81 (C16ORF57), and WRAP53 (TCAB1)* genes.
Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

**Reflex Tests**

<table>
<thead>
<tr>
<th>Test Id</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
</tr>
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<tbody>
<tr>
<td>FIBR</td>
<td>Fibroblast Culture</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CRYOB</td>
<td>Cryopreserve for Biochem Studies</td>
<td>No</td>
<td>No</td>
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</table>

**Method Name**
Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

**NY State Available**
Yes
Test Definition: TELGP
Telomere Defects Gene Panel

Specimen Type
Varies

Ordering Guidance
This test is not for measuring telomere length. This test is a second-tier genetic test for hereditary telomere defects. Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Necessary Information
1. Primary Immunodeficiencies Patient Information (T791) is strongly recommended, but not required, to be filled out and sent with the specimen. This information aids in providing a more thorough interpretation of test results. Ordering providers are strongly encouraged to complete the form and send it with the specimen.
2. Include physician name and phone number with specimen.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:
Preferred:
Specimen Type: Whole blood
Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Specimen Type: Blood spot
Supplies: Card-Blood Spot Collection Filter Paper (T493)
Collection Instructions:
1. An alternative blood collection option for a patient <1 year of age is finger stick.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Specimen Type: Peripheral blood mononuclear cells (PBMCs)
Collection Instructions: Send as a suspension in freezing medium or cell pellet frozen on dry ice.
Specimen Stability Information: Frozen
Specimen Type: Cultured fibroblasts
Collection Instructions: T-75 or T-25 flask
Specimen Stability Information: 1 Full T-75 or 2 full T-25 flasks
Test Definition: TELGP
Telomere Defects Gene Panel

Additional Information: Indicate the tests to be performed on the fibroblast culture cells. A separate culture charge will be assessed under FIBR / Fibroblast Culture. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours
Specimen Type: Skin biopsy
Supplies: Fibroblast Biopsy Transport Media (T115)
Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin. Tubes of culture media can be supplied upon request (Eagle’s minimum essential medium with 1% penicillin and streptomycin [T115]).
Specimen Volume: 4-mm punch
Additional Information: A separate culture charge will be assessed under FIBR / Fibroblast Culture. An additional 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Stability Information: Refrigerated (preferred)/Ambient
Specimen Type: DNA
Container/Tube: 2 mL screw top tube
Specimen Volume: 100 mcL (microliters)
Collection Instructions:
1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms
1. New York Clients-Informed consent is required. Please document on the request form or electronic order that a copy is on file. An Informed Consent for Genetic Testing (T576) is available in Special Instructions.
2. Primary Immunodeficiencies Patient Information (T791) is required. See Special Instructions.

Reject Due To

Specimen Minimum Volume
Whole blood: 1 mL

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
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<tbody>
<tr>
<td>Varies</td>
<td>Varies (preferred)</td>
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Clinical & Interpretive

Clinical Information

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<tr>
<th>Gene (alias)</th>
<th>Protein</th>
<th>OMIM</th>
<th>Incidence</th>
<th>Inheritance</th>
<th>Phenotype disorder</th>
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<tbody>
<tr>
<td>CTC1</td>
<td>CST complex subunit CTC1</td>
<td>613129</td>
<td>Approximately 1-3% of DC</td>
<td>AR</td>
<td>Cereboretinal microangiopath</td>
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<td>Gene</td>
<td>Description</td>
<td>Reference SNV</td>
<td>Frequency in DC</td>
<td>Genotype</td>
<td>Disorder</td>
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<td>---------------</td>
<td>-----------------</td>
<td>----------</td>
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<tr>
<td>DKC1</td>
<td>H/ACA ribonucleoprotein in complex subunit 4 isoform 1</td>
<td>300126</td>
<td>Approximately 17-36% of DC</td>
<td>XL</td>
<td>Dyskeratosis congenita</td>
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<td>NHP2</td>
<td>H/ACA ribonucleoprotein in complex subunit 2 isoform a</td>
<td>606470</td>
<td>&lt;1% of DC</td>
<td>AR</td>
<td>Dyskeratosis congenita</td>
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<tr>
<td>NOP10</td>
<td>H/ACA ribonucleoprotein in complex subunit 3</td>
<td>606471</td>
<td>&lt;1% of DC</td>
<td>AR</td>
<td>Dyskeratosis congenita</td>
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<tr>
<td>RTEL1</td>
<td>Regulator of telomere elongation helicase 1 isoform 2</td>
<td>608833</td>
<td>Rare</td>
<td>AR, AD</td>
<td>Dyskeratosis congenita, pulmonary fibrosis and/or bone marrow failure,</td>
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<tr>
<td>TERC</td>
<td>Telomerase RNA component</td>
<td>602322</td>
<td>Approximately 6-10% of DC</td>
<td>AD</td>
<td>Dyskeratosis congenita, aplastic anemia, susceptibility to idiopathic pulmonary fibrosis</td>
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<td>TERT</td>
<td>Telomerase reverse transcriptase isoform 1</td>
<td>187270</td>
<td>Approximately 1-7% of DC</td>
<td>AR, AD</td>
<td>Dyskeratosis congenita, acute myeloid leukemia, cutaneous malignant melanoma, pulmonary fibrosis and/or bone marrow failure, telomere-related</td>
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<tr>
<td>TINF2</td>
<td>TERF1-interacti</td>
<td>604319</td>
<td>Approximately 1</td>
<td>AD</td>
<td>Dyskeratosis congenita</td>
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</table>
Reference Values
An interpretive report will be provided.

Interpretation
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. Information about these variants and common polymorphisms are available upon request.

The telomerase database is a useful tool for variant review and classification of telomere disorders that may be used in some cases.

Cautions
Clinical Correlations:
Some individuals who have involvement of one or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of disease. Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene variant in an affected family member.

Short telomeres may be present in leukocytes or buccal cells with a variety of malignancies. Short telomeres have also been reported in nonmalignant disorders such as metabolic conditions, cardiovascular disease, diabetes, and in smokers. At least half of patients with a BMFS or DC phenotype do not have a detectable variant in the 10 genes tested in the panel and, therefore, there may be additional genes that need to be discovered. Most cases of telomere disorders appear to occur sporadically with no prior family history, and this could be related to incomplete penetrance, variable expressivity, or de novo variants. It is important to correlate the genetic testing data with clinical phenotype and other relevant testing, including assessment of telomere length.
Test Definition: TELGP
Telomere Defects Gene Panel

Technical Limitations:
Next-generation sequencing may not detect all types of genetic variants. Additionally, rare alterations (ie, polymorphisms) may be present that could lead to false-negative or false-positive results. The variant detection software has lower detection efficiency for insertion/deletion variants as compared to single nucleotide variants. Therefore, small deletions and insertions greater than 8 nucleotides in length may not be detected by this test. Copy number variations (CNV) are not currently reported for any of the genes on this panel. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. In some cases, DNA variants of undetermined significance may be identified. If a diagnosis of one of the syndromes on this panel is still suspected, consider a Laboratory Director or genetic counselor consultation. A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants-Policy:
At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a healthcare provider, or team of healthcare providers, with expertise in genetics and primary immunodeficiencies, is recommended for interpretation of this result.

A list of benign and likely benign variants detected for this patient is available from the lab upon request.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient’s results.

Clinical Reference
1. Podlevsky JD: The Telomere Database. NAR 2008;36:D339-D343

Performance

Method Description
Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is
prepared for NGS using a custom Agilent Sure Select Target Enrichment System. Data is analyzed with a bioinformatics software pipeline. Supplemental Sanger sequencing may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. (Unpublished Mayo method)

Genes analyzed: CTC1, DKC1, NHP2, NOP10, RTEL1, TERC, TERT, TINF2, USB1 (C16ORF57), WRAP53 (TCAB1)

PDF Report
No

Specimen Retention Time
Extracted DNA: 2 months

Performing Laboratory Location
Rochester

Fees & Codes

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81479

LOINC® Information

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<th>Test ID</th>
<th>Test Order Name</th>
<th>Order LOINC Value</th>
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<td>Telomere Defects Gene Panel</td>
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<td>BA3919</td>
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