MAYO CLINIC LABORATORIES

Test Definition: TELDP

Telomere Biology Disorders Gene Panel, Varies

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of a telomere biology disorder

Establishing a diagnosis of a telomere biology disorder, allowing for appropriate management and surveillance for disease features based on the gene and/or variant involved

Identifying disease-causing variants within genes known to be associated with increased risk for telomere defects, allowing for predictive testing of at-risk family members

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 18 genes associated with telomere biology disorders: *ACD, CTC1, DKC1, LIG4, NAF1, NHP2, NOP10, PARN, POT1, RPA1, RTEL1, STN1, TERC, TERT, TINF2, USB1, WRAP53,* and *ZCCHC8*. See Targeted Genes and Methodology Details for Telomere Biology Disorders Gene Panel and Method Description for additional details.

This test may aid in the diagnosis of a telomere biology disorder. This test is not intended or validated for detection of somatic variants and cannot distinguish between germline variants associated with telomere biology disorders versus somatic (oncogenic, nongermline) variants, which may be associated with hematologic neoplasms. Therefore, this test does not provide diagnostic, prognostic, or therapeutic information for somatic variants. Variants detected by this test are interpreted as germline unless otherwise noted in the interpretation. If a patient has active hematological malignancy, skin biopsy is recommended (instead of whole blood) for detection of germline variants.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for telomere biology disorders.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture 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
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Telomere Biology Disorders Gene Panel
- Congenital Neutropenia, Bone Marrow Failure, Telomere Defects, and Pulmonary Fibrosis (IPF) Patient Information

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

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
Upon request and after initial testing is complete, WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies may be added to this test. To obtain more information about this option or add WESPR testing, call 800-533-1710.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about testing option, call 800-533-1710.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Specimen Required
Patient Preparation: 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.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated

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.

Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing, Chorionic Villi/Products of Conception/Tissue. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. **Cultured cells from a prenatal specimen will not be accepted**.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing, Chorionic Villi/Products of Conception/Tissue. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521)
3. Congenital Neutropenia, Bone Marrow Failure, Telomere Defects, and Pulmonary Fibrosis (IPF) Patient Information

Specimen Minimum Volume

Whole blood: 1 mL; Skin biopsy or cultured fibroblasts: See Specimen Required

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Telomeres are highly specialized structures composed of TTAGGG nucleotide repeats and proteins that protect chromosome ends. Under normal circumstances, telomeres shorten with every cycle of DNA replication. Telomerase is an enzyme complex that can extend the length of the telomere, thus helping to slow the shortening process. Telomerase is most active in highly proliferative tissues, such as lymphocytes, skin, intestine, and bone marrow.

Telomere biology disorders (TBD) include a complex group of syndromes characterized by abnormally short telomeres. Telomere length analysis in leukocyte subsets is usually performed by flow fluorescent in situ hybridization. The severity

of TBD syndromes is variable, and they may present in children or adults. Symptoms of TBD include bone marrow failure, pulmonary fibrosis, liver disease, gastrointestinal disease, and mucocutaneous abnormalities. The prevalence of cancer in the short telomere syndromes is increased. These cancers are mainly hematological malignancies, such as myelodysplastic syndrome and acute myelogenous leukemia, although some solid tumor prevalence is also increased (eg, oral squamous cell carcinoma). Recognition and diagnosis of underlying TBD is important, as it can help guide treatment decisions.

Dyskeratosis congenita (DC) was the first TBD to be described. The subsets of DC include classic DC, Hoyeraal Hreidarsson syndrome (HHS), Revesz syndrome, DC-like conditions, Coats plus syndrome, and isolated subtypes.

Patients with the classic forms of DC are usually diagnosed in childhood with a triad of mucocutaneous features, including dysplastic nails, anomalies of skin pigmentation, and oral leukoplakia. Other features may include bone marrow failure, gastrointestinal disease, liver disease, pulmonary fibrosis, a predisposition to certain cancers, and other medical problems. Alternatively, some patients may have one of the 3 classic features of classic DC along with a hypocellular bone marrow. These patients all have very short telomeres (<1% percentile of age) in leukocytes.

Patients with HHS have the features of classic DC but additionally have cerebellar hypoplasia, neurological conditions, and severe immunodeficiency. They can also have low T-cell numbers with severe B and natural killer (NK) cell lymphopenia (T+/-B- NK-) reminiscent of severe combined immunodeficiency.

In Revesz syndrome, patients have bilateral exudative retinopathy along with other features of DC. Coats plus syndrome is also characterized by bilateral exudative retinopathy in addition to gastrointestinal problems and other symptoms.

When a TBD manifests in adulthood, the presentation can be variable according to the severity of the telomere length defect relative to age. A broad umbrella of clinical features could include bone marrow failure, pulmonary fibrosis, liver disease not otherwise classified, myelodysplastic syndrome, acute myeloid leukemia, or early onset of malignancies within the DC grouping.

A classification of DC-like may be applied for patients who do not meet the diagnostic criteria of DC but have several features reminiscent of the disease. This could include presence of bone marrow failure, developmental delay, familial history of pulmonary fibrosis, and no other clear diagnosis.

The TBD can be inherited in a variety of patterns, including X-linked recessive, autosomal dominant, and autosomal recessive. Approximately 60% to 80% of patients with TBD have variants in the genes evaluated by this panel. In autosomal dominant DC, phenotypes may present at a younger age and more severely in successive generations (genetic anticipation). The genetic anticipation is mediated by the shortened telomeres that are inherited together with the disease-causing variant.

It is increasingly recognized that TBD also include syndromes characterized by abnormally long telomeres. Telomere length is controlled, and like short telomeres, long telomeres also have consequences, mainly increased risk of cancers. The genetic basis of these short and long telomere syndromes may be linked to different disease-causing variants in the same genes. Loss-of-function variants in *TERT* lead to short telomere syndromes as described earlier, whereas gain-of-function variants lead to increased telomere length and autosomal dominant familial melanoma. Similarly, disease-causing variants in *ACD* and *TINF2* have been described to cause both long and short telomers. Long telomeres caused by these variants lead to increased cancer risk (familial melanoma and thyroid cancer).

Reference Values

An interpretive report will be provided

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders,

Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For the most up to date list of genes included in this test and detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukoreduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants**:**
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(1) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424
2. Podlevsky JD, Bley CJ, Omana RV, Qi X, Chen JJL. The telomerase database. Nucleic Acids Res. 2008;36(Database issue):D339-343. doi:10.1093/nar/gkm700
3. Armanios M. The role of telomeres in human disease. Annu Rev Genomics Hum Genet. 2022 Aug;23:363-381. doi:10.1146/annurev-genom-010422-091101

4. Bluteau O, Sebert M, Leblanc T, et al: A landscape of germ line mutations in a cohort of inherited bone marrow failure patients. Blood. 2018 Feb 15;131(7):717-732. doi: 10.1182/blood-2017-09-806489
5. Lai TP, Wright WE, Shay JW: Comparison of telomere length measurement methods. Philos Trans R Soc Lond B Biol Sci. 2018 Mar 5;373(1741):20160451. doi: 10.1098/rstb.2016.0451
6. Niewisch MR, Savage SA: An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. Expert Rev Hematol. 2019;12(12):1037-1052. doi:10.1080/17474086.2019.1662720
7. Grill S, Nandakumar J. Molecular mechanisms of telomere biology disorders. J Biol Chem. 2021;296:100064. doi:10.1074/jbc.REV120.014017

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions/insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See Targeted Genes and Methodology Details for Telomere Biology Disorders Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ACD, CTC1, DKC1, LIG4, NAF1, NHP2, NOP10, PARN, POT1, RPA1, RTEL1, STN1, TERC, TERT, TINF2, USB1, WRAP53, ZCCHC8*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts, skin biopsy: 1 month

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

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

CPT Code Information

81443

88233- Tissue culture, skin, solid tissue biopsy (if appropriate)

88240- Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
TELDP	Telomere Disorders Gene Panel	35463-9

Result ID	Test Result Name	Result LOINC® Value
619887	Test Description	62364-5
619888	Specimen	31208-2
619889	Source	31208-2
619890	Result Summary	50397-9
619891	Result	82939-0
619892	Interpretation	69047-9
619893	Additional Results	82939-0
619894	Resources	99622-3
619895	Additional Information	48767-8
619896	Method	85069-3
619897	Genes Analyzed	82939-0
619898	Disclaimer	62364-5
619899	Released By	18771-6