Telomere Biology Disorders (TBDs), including Dyskeratosis Congenita (DC), are complex, genetic, multi-system disorders causing premature aging of cells and organs. The clinical symptoms of TBDs are varied and require multi-disciplinary diagnosis, monitoring and management.

Immunology

TBDs affect rapidly proliferating cells - therefore T & B lymphocytes are particularly vulnerable, leading to apoptosis (numerical deficit) or senescence (functional deficit)

Immune defects are common and usually subtle (especially adult onset) and may present as

1. CVID combined immunodeficiency or SCID- predominantly antibody deficiency
2. HPV (and maybe other virus susceptibility – mucosal intraepithelial neoplasia) may be severe especially in early childhood onset which can present as severe combined immune deficiency

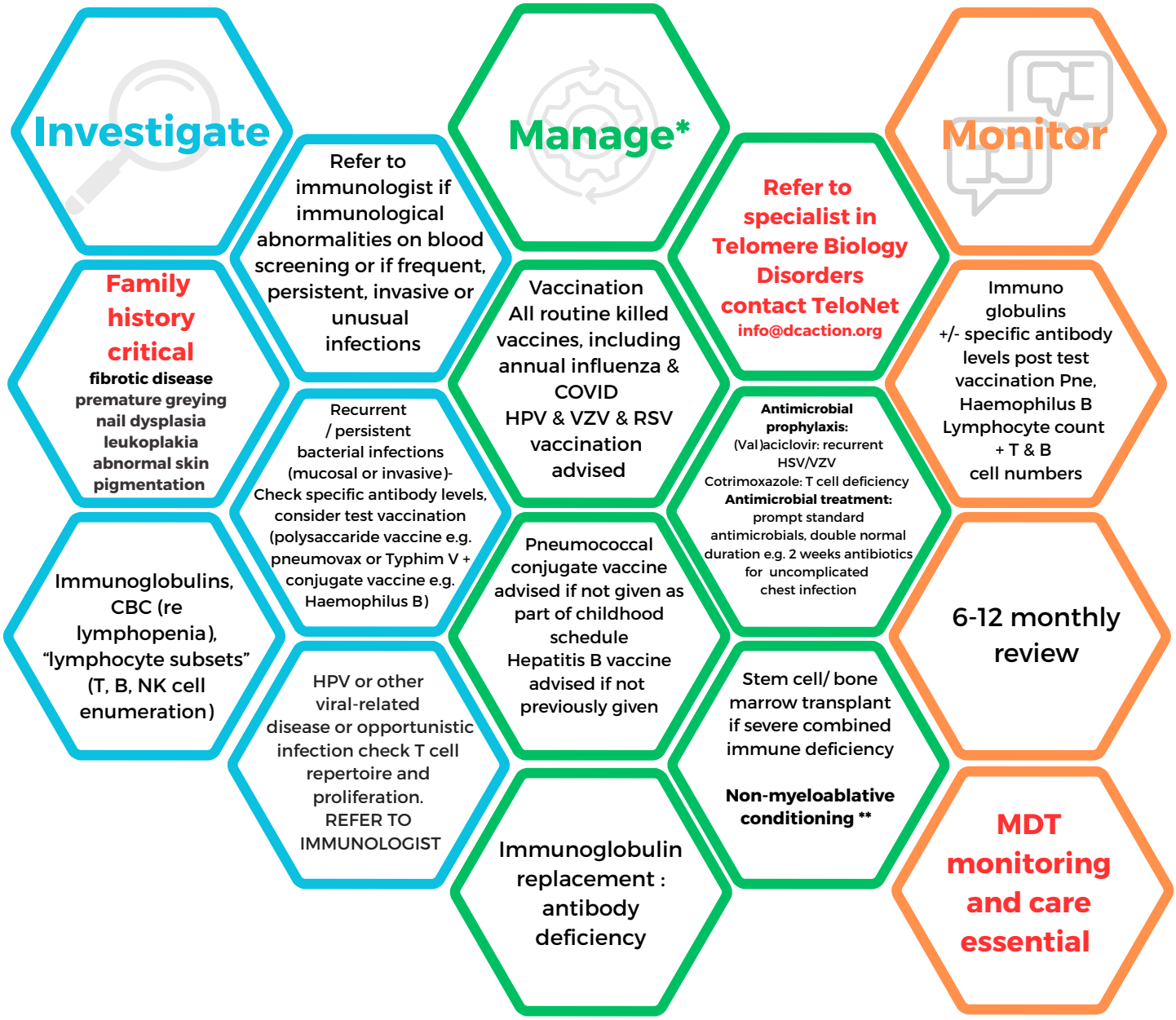
There is evidence that T cell immune deficiency rather than chromosome instability predisposes patients with short telomere syndromes to squamous cell cancers

Armanios M. The Role of Telomeres in Human Disease. Annu Rev Genomics Hum Genet. 2022 Aug 31;23:363-381. doi: 10.1146/annurev-genom-010422-091101.

Benjamin Rolles et al. Telomere biology disorders may manifest as common variable immunodeficiency (CVID), Clinical Immunology, Volume 257, 2023, 109837, SSN 1521-6616, doi.org/10.1016/j.clim.2023.109837

Schratz KE et al. T cell immune deficiency rather than chromosome instability predisposes patients with short telomere syndromes to squamous cancers. Cancer Cell. 2023 Apr 10;41(4):807-817.e6. doi: 10.1016/j.ccell.2023.03.005.

Tummala, H., Walne, A., & Dokal, I. (2022). The biology and management of dyskeratosis congenita and related disorders of telomeres. Expert Review of Hematology, 15(8), 685–696. doi.org/10.1080/17474086.2022.2108784



Savage SA, Niewisch MR. Dyskeratosis Congenita and Related Telomere Biology Disorders. 2009 Nov 12 [Updated 2023 Jan 19]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. https://www.ncbi.nlm.nih.gov/books/NBK22301/

*No specific treatments currently indicated but danazol/other attenuated androgen, metformin or other telomere-preserving treatments may be helpful

** Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines, Second Edition https://teamtelomere.org/telomere-biology-disorders-diagnosis-and-management-guidelines-downloads/

Telomere Biology Disorders (TBD) affect progenitor stem cell production and cell replication in multiple organ systems. Dyskeratosis Congenita (DC) is a severe TBD presenting in early childhood with a clinical triad of nail dysplasia, oral leukoplakia, and abnormal skin pigmentation associated with bone marrow failure. Mutations in ACD, TINF2, DKC1, DCLRE1B, NHP2, NOP10, NPM1, POT1, RPA1, PARN, RTEL1, TERT, TERC, MDM4, ZCCHC8, WRAP53, TYMS-ENOSFI, POLA1, POLA2 and RPA2 genes, all involved in telomere maintenance, have been identified in patients with a spectrum of clinical manifestations including immune deficiency, pulmonary fibrosis, emphysema, cryptogenic liver cirrhosis, lacrimal duct, oesophageal and urethral stenosis, avascular necrosis of hips and shoulders, periodontal disease, an increased predisposition to epithelial and haematologic malignancies plus dermatological features and premature greying of hair. Classical DC is characterised by very short telomeres but alterations in telomere maintenance genes produce variable phenotypes, differing in severity and age of onset.
NB:GE panel R15 PID lists some but not all known genes associated with Telomere Biology Disorders

References	
A report on the clinical incidence and severity of infections, as well as laboratory evidence of immunodeficiency in 83 patients with Telomere Biology Disorders. TERT and TERC were the most commonly mutated genes, others included DKC1, PARN, TINF2, CTC1, RTEL1, and NAF1. Of 49 patients with laboratory data available, the majority (65%) had depressed CD4 counts with 11 immunodeficient patients, 21 immune impaired patients, and 17 patients with normal counts.	Characterizing Immunodeficiency in Patients with Telomere Biology Disorders Nidhi Aggarwal, Xiaoyang Ma, Fernanda Gutierrez-Rodrigues, Ruba Shalhoub, Ivana Darden, Bhavisha A. Patel, Colin O. Wu, Neal S. Young, Emma M. Groarke Blood (2022) 140 (Supplement 1): 5826–5827. https://doi.org/10.1182/blood-2022-163264
A 39-marker panel of metal-labeled antibodies and mass cytometry (CyTOF) was used to assess the subsets of lymphocytes, monocytes, and dendritic cells (DC) in 20 patients and 10 healthy individuals. Results revealed a distinct immunophenotype in telomeropathies, comprising de□cient or skewed maturation of certain subsets, an aged phenotype of B and T cells, aberrant lymphocyte activation and very low levels of circulating MAIT cells, which might be indicators of ongoing in ammatory processes, tied with dysregulated cytokine levels. This immune perturbance may contribute to the clinical onset of telomeropathies and increase the risk of infections, cirrhosis, IPF and cancer development.	Immune Signature in Telomere-Biology Disorders Willian R. Gomes, MSc, Vinicius S. Carvalho, MsC, Edson Z. Martinez, PhD, Shan Hama, MSc ,Mohammad M. Karimi, PhD, Giorgio Napolitani, PhD, Ghulam Mufti, DM, FRCPath, Rodrigo T. Calado, MD PhD Blood 142 (2023) 4099–4100 https://doi.org/10.1182/blood-2023-187126
Transcriptional programs of T cells from telomerase mutation carriers, diverged from older adults with normal TL. Short telomere T cells upregulated DNA damage and intrinsic apoptosis pathways, while older adult T cells upregulated extrinsic apoptosis pathways and programmed cell death 1 (PD-1) expression. T cells from mice with short TL also showed an active DNA-damage response, in contrast with old WT mice, despite their shared propensity to apoptosis. Our data suggest there are TL-dependent and TL-independent mechanisms that differentially contribute to distinct molecular programs of T cell apoptosis with aging	Short telomere syndromes cause a primary T cell immunodeficiency Christa L. Wagner, Vidya Sagar Hanumanthu, C. Conover Talbot Jr., Roshini S. Abraham, David Hamm, Dustin L. Gable, Christopher G. Kanakry, Carolyn D. Applegate, Janet Siliciano, J. Brooks Jackson, Stephen Desiderio, Jonathan K. Alder, Leo Luznik, and Mary Armanios, J Clin Invest. 2018;128(12):5222-5234. https://doi.org/10.1172/JCI120216.
Gene mutations were identified by whole-exome and direct sequencing in two juvenile patients with DC. One had a DKC1 mutation and one a PARN mutation. Lymphocyte subset analysis showed B and NK cytopenia, an inverted CD4:CD8 ratio, and decreased naïve CD4 and CD8 cells. A significant increase in CD21 low B cells and skewed numbers of helper T cells (Th), regulatory T cells (Treg), follicular regulatory T cells (Tfr), and follicular helper T cells (Tfh) were also detected. Short telomere lengths, increased CD57 expression, and an expansion of CD8 effector memory T cells re-expressing CD45RA (TEMRA) were also found in both patients.	Zeng T, Lv G, Chen X, Yang L, Zhou L, Dou Y, Tang X, Yang J, An Y, Zhao X. CD8+ T-cell senescence and skewed lymphocyte subsets in young Dyskeratosis Congenita patients with PARN and DKC1 mutations. J Clin Lab Anal. 2020 Sep;34(9):e23375. doi: 10.1002/jcla.23375.
A review of the clinical records of 88 TBD patients (median age [range] = 35 [5-76]; 93% with a known germline mutation) followed at NHLBI since 2002. Significant infections were defined as opportunistic, recurrent (two or more severe infections in one year, three or more respiratory infections in one year, or the need for antibiotics for two months per year), or infections that required hospitalization. Longitudinal data of blood counts and T, B, and NK (TBNK) cell immunophenotyping were available for 88 and 55 patients, respectively. 32/88 (36%) had a clinically significant infection history: 8/32 (25%) opportunistic, 16/32 (50%) recurrent, and 21/32 (65%) requiring hospitalization. Of 88 patients, 41 were lymphopenic and only 3 were neutropenic. Of 55 patients with available data for TBNK subsets, 29 were immunodeficient. Twenty-three had decreased CD3 counts, including 22 patients with decreased CD4 count and 13 patients with decreased CD8 count. B lymphopenia was observed in 16 patients. Median age was similar between groups with normal and abnormal blood counts and TBNK subsets.	T Lymphopenia and Aged Immune System Characterize Immunodeficiency in Adult Patients with Telomere Biology Disorders Luiz Fernando Bazzo Catto MD, Nidhi Aggarwal BS , Ruba Shalhoub , Natthakan Thongon PhD , Tania Rene Machado RN, BSN , Ivana Darden RN , Jennifer Lotter PA-C , Bhavisha A. Patel MD 7 Geraldine Aubert PhD , Colin O. Wu PhD , Simona Colla PhD , Cynthia E. Dunbar MD, Fernanda Rodrigues PhD , Emma M. Groarke MD. Blood Volume 144, Supplement 1, 5 November 2024, Page 4094 https://doi.org/10.1182/blood-2024-207500
Immunodeficiency is prevalent in adults with telomere biology disorders (TBDs), characterized by T lymphopenia and associated with increased infection risk and lower survival rates. This study highlights the clinical and molecular features of immunodeficiency in a predominantly adult cohort of TBD patients. • 88 TBD patients studied, median age 37 years (range 6-76). • 90% of patients were over 18 years old; 45% had TERT mutations, 32% had TERC mutations. • 36% experienced significant infections, with 47% showing lymphopenia and 3% severe neutropenia. • Absolute lymphocyte counts (ALC) <0.96 and <1.1 x10^3/μL linked to increased infection risk and lower overall survival. • Decreased CD3+ T-cells, both CD4+ and CD8+, associated with BMF, increased infection risk, and reduced survival. • Low CD3+ and CD4+ associated with solid cancers. The study reveals a significant correlation between immunodeficiency and various clinical features, including infections and cancer predisposition.	Catto LFB, Aggarwal N, Shalhoub RN, Ma X, Darden I, Machado T, Zhang Y, Redekar N, Thongon N, Colla S, Aubert G, Dunbar CE, Wu CO, Young NS, Patel BA, Gutierrez-Rodrigues F, Groarke EM. Clinical and molecular features of immunodeficiency in patients with telomere biology disorders. Blood. 2025 Jun 25:blood.2024026735. doi: 10.1182/blood.2024026735.