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

General Practice considerations: TBDs in children

Alterations in telomere associated genes result in short telomeres and impaired cell replication and together with environmental factors, have been shown to affect telomere maintenance leading to chromosome instability and premature cell death. Dyskeratosis congenita (DC) and Høyeraal-Hreidarsson (HH) syndrome present with the most severe multi-organ clinical manifestations but alterations in an array telomere maintenance genes can show variable penetrance and phenotype with disease onset possible in childhood or later life.

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. Available from: https://www.ncbi.nlm.nih.gov/books/NBK22301/

Specialist involvement will vary between patients, however recommended minimum annual surveillance should include

- Complete blood count
- Liver function assessment inc. bloods and fibro/fat scan
- Respiratory spirometry and gas transfer
- Dental (six monthly) + ENT / oral review
- Optician
- Nutritional status review

*Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines 2022
https://teamtelomere.org/telomere-biology-disorders-diagnosis-and-management-guidelines-downloads/
Chapter 25 Routine Healthcare for Children with Telomere Biology Disorders

** Single Telomere Length Analysis https://www.telonostix.com/

Charity No. 1167150 | www.dcaction.org | info@dcaction.org

Telomere Biology Disorders (TBDs) are genetic disorders that affect progenitor stem cell production and cell replication in multiple organ systems. Dyskeratosis congenita (DC) is a severe TBD that commonly presents in early childhood with a clinical triad of nail dysplasia, oral leukoplakia and abnormal skin pigmentation associated with bone marrow failure but mutations in an array of telomere maintenance genes can produce variable phenotypes differing in severity, in childhood or later into adulthood. Mutations in ACD, TINF2, DKC1, DCLRE1B, NHP2, NOP10, NPM1, POT1, RPA1, PARN, RTEL1, TERT, TERC, MDM4, ZCCHC8, WRAP53 and TYMS-ENOSFI, all involved in telomere biology, have been identified in patients with a spectrum of clinical manifestations including bone marrow failure, pulmonary fibrosis; emphysema; cryptogenic liver cirrhosis; lacrimal duct, oesophageal, and urethral stenosis; avascular necrosis of hips and shoulders; periodontal disease; and an increased predisposition to epithelial and hematologic malignancies and premature graying of hair. The symptoms of TBD can appear at any age and adult-onset bone marrow failure can be difficult to distinguish from idiopathic aplastic anaemia. The effects of Telomere Biology Disease can be variable in severity and clinical prognosis is difficult to predict. As multi-system complications can emerge at any time during a patient's life, lifelong follow-up and monitoring is required. The heterogenous course of possible clinical development make recommendations for frequency of monitoring difficult but blood tests, bone marrow examinations, pulmonary function tests etc. on an annual basis are advisable. **Liaison with a specialist centre providing multi-disciplinary monitoring, treatment and care is vital.**

Savage SA. Dyskeratosis congenita and telomere biology disorders. Hematology Am Soc Hematol Educ Program. 2022 Dec 9;2022(1):637-648. doi: 10.1182/hematology.2022000394.

Medical Management of Bone Marrow Failure

Significant peripheral cytopenia should be managed with supportive therapy ie: blood and platelet transfusions. Anabolic steroids or androgens may be used to treat bone marrow failure and preserve telomere length. NB: No androgen or steroid therapy is licensed for treatment of Telomere Biology Disorders. Prescriptions are likely to be personalised by a specialist haematologist or a specialist in TBDs.

Townsley DM et al. Danazol Treatment for Telomere Diseases. N Engl J Med. 2016 May 19;374(20):1922-31. doi:10.1056/NEJMoa1515319.
Team telomere Telomere Biology Disorders: Diagnosis and Management Guidelines Chapter 10 Medical Management of Bone Marrow Failure in Telomere Biology Disorders. https://teamtelomere.org/wp-content/uploads/2022/04/Chapter-10_-Medical-Management-of-Bone-Marrow-Failure-in-Telomere-Biology-Disorders.pdf

Stem Cell Transplantation and conditioning regimens

At the present time, allogeneic hematopoietic stem cell transplantation (HSCT) is the only option for progressive marrow failure, myelodysplastic syndrome, or leukaemia related to dyskeratosis congenita and telomere biology disorders. Underlying chromosomal instability and sensitivity to chemotherapy and radiation preclude traditional conditioning regimens. Non-myeloablative conditioning regimens designed for TBD patients are recommended prior to HSCT.

Dietz AC et al. Disease-specific hematopoietic cell transplantation: nonmyeloablative conditioning regimen for dyskeratosis congenita. Bone Marrow Transplant. 2011 Jan;46(1):98-104. doi: 10.1038/bmt.2010.65.
Nelson AS et al. A Reduced-Intensity Conditioning Regimen for Patients with Dyskeratosis Congenita Undergoing Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2016 May;22(5):884-8. doi: 10.1016/j.bbmt.2016.01.026.
Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines 2022. Chapter 13 Hematopoietic Stem Cell Transplantation. https://teamtelomere.org/wp-content/uploads/2022/04/Chapter-13_-Hematopoietic-Stem-Cell-Transplantation.pdf

Pulmonary Fibrosis and Liver Cirrhosis

Pulmonary fibrosis and liver cirrhosis can be primary manifestations of Telomere Biology Disease. Consider an inherited telomeropathy in early onset cirrhosis or lung fibrosis.

Kapuria D. et al. The Spectrum of Hepatic Involvement in Patients With Telomere Disease. Hepatology. 2019 Jun;69(6):2579-2585. doi: 10.1002/hep.30578.
Alder JK, Armanios M. Telomere-mediated lung disease. Physiol Rev. 2022 Oct 1;102(4):1703-1720. doi: 10.1152/physrev.00046.2021.
Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines 2022. Chapter 14 Pulmonary Fibrosis. https://teamtelomere.org/wp-content/uploads/2022/04/Chapter-14_-Pulmonary-Fibrosis.pdf
Chapter 18 Hepatic Complications https://teamtelomere.org/wp-content/uploads/2022/04/Chapter-18_-Hepatic-Complications.pdf

Dental and Oral Manifestations

A diagnosis of DC or other inherited Telomere Biology Disorder should be considered in young persons with oral leukoplakia. There is
evidence that there is an increased risk of oral cancers in Telomere Biology Disorders. Periodontal hygiene critical in HSCT.

Atkinson JC. et al. Oral and dental phenotype of dyskeratosis congenita. Oral Dis. 2008 Jul;14(5):419-27. doi: 10.1111/j.1601-0825.2007.01394.x.
Fatehi et al. Squamous cell carcinoma of the tongue in a patient with Dyskeratosis congenita: a rare entity. Br. J. of Oral and Maxillofacial Surgery: 57(2019) 79-81.
Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines 2022. Chapter 8 Dental and Oral Complications. https://teamtelomere.org/wp-content/uploads/2022/04/Chapter-8_-Dental-and-Oral-Complications.pdf

Cancer Risk

There is evidence of increased risk of cancers in Dyskeratosis congenita (DC) /Telomere Biology Disorders, especially head and neck and epithelial cell cancers.

Alter et al. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. Haematologica 2018 Volume 103(1):30-39.
Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines 2022. Chapter 9 Solid Tumors. https://teamtelomere.org/wp-content/uploads/2022/04/Chapter-9_-Solid-Tumors.pdf
Tummala H, Walne A, Dokal I. The biology and management of dyskeratosis congenita and related disorders of telomeres. Expert Rev Hematol. 2022 Aug;15(8):685-696. doi: 10.1080/17474086.2022.2108784.