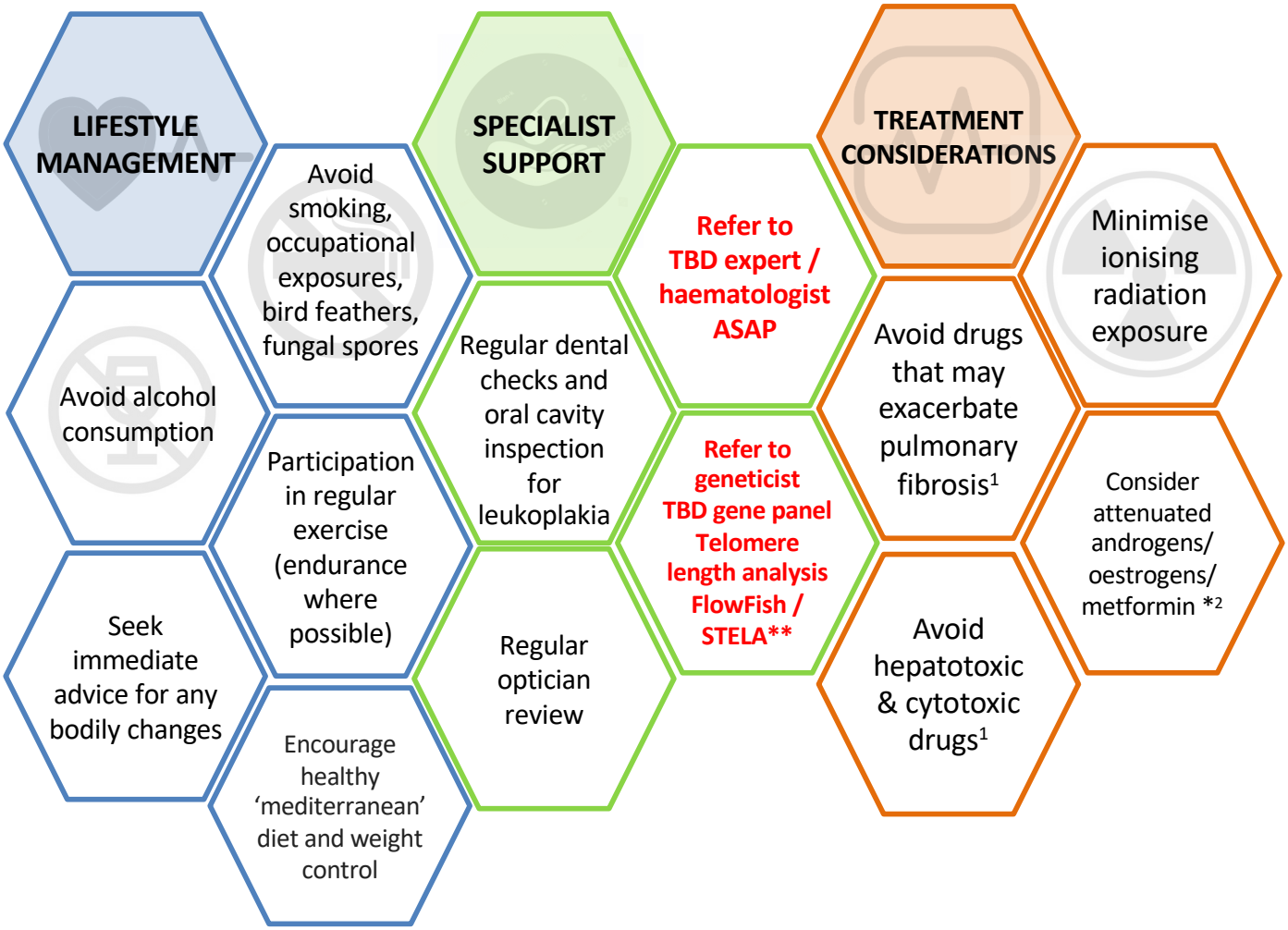
Telomere Biology Disorders (TBDs), including Dyskeratosis congenita (DC) are complex multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied.

Late onset/Adult population

Manifestations include bone marrow failure, 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 hematologic malignancies plus premature greying of hair. Extra consideration may also need to be given to those at risk of metabolic disorders and (pre)diabetes.

The presentation of TBDs in the adult population may differ from that in the child population.

Team Telomere Telomere Biology Disorders: Diagnosis and Management Guidelines 2022
https://teamtelomere.org/telomere-biology-disorders-diagnosis-and-management-guidelines-downloads/



Specialist involvement will vary between patients, however recommended minimum annual surveillance and intervention would include the following:

- Complete blood count
- Liver function assessment inc. bloods and fibro/fat scan
- Respiratory spirometry and gas transfer
- Dental and optician review
- Annual flu vaccine for patient and household members.

1 Including methotrexate, long term nitrofurantoin, bleomycin, busulphan, amiodarone and as per www.pneumotox.org
*Androgens/danazol are assumed acceptable as perceived benefit probably outweighs risk to liver.

2 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.

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

This information is based on reports from the medical literature. Please speak to your doctor if you have concerns about your condition

ADVOCACY EDUCATION SUPPORT

We value your feedback. Please contact us.

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, CTC1, DKC1, DCLRE1B, NHP2, NOP10, NPM1, POT1, RPA1, STN1, TCAB1, PARN, RTEL1, TERT, TERC, MDM4 and ZCCHC8, 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 anemia. 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.