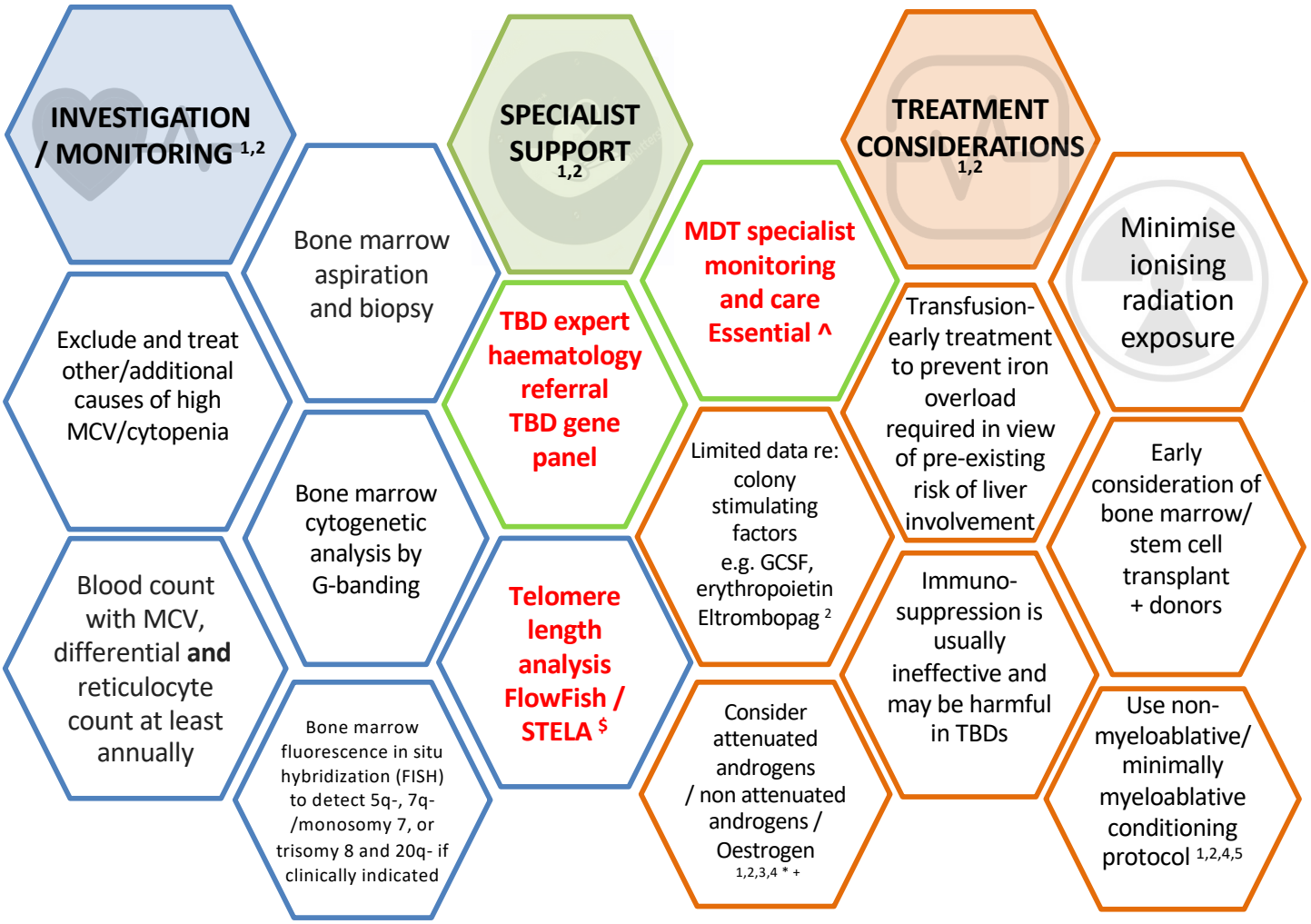
Telomere Biology Disorders (TBD), including Dyskeratosis Congenita (DC) are complex, genetic, multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied and require multi-disciplinary diagnosis and management.

HAEMATOLOGY MANIFESTATIONS

Childhood or adult-onset bone marrow hypoplasia or bone marrow failure resulting in cytopaenias, raised MCV, raised HbF, Myelodysplasia, CML, Low urate.

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/



^ Recommended minimum annual MDT surveillance and intervention to include:

- Liver function assessment inc. bloods and fibro/fat scan
- Respiratory spirometry and gas transfer
- Dental and optician review

[1] 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.

[2] **Team Telomere** Telomere Biology Disorders Diagnosis and Management Guidelines Second Edition 2022. https://teamtelomere.org/telomere-biology-disorders-diagnosis-and-management-guidelines-downloads/

[3] Townsley DM *et al* N Engl J Med 2016;374:1922-31. DOI: 10.1056/NEJMoa1515319

[4] Islam A, Rafiq S, Kirwan M, Walne A, Cavenagh J, Vulliamy T, Dokal I. Haematological recovery in dyskeratosis congenita patients treated with danazol. Br J Haematol. 2013 Sep;162(6):854-6. doi: 10.1111/bjh.12432..

[4] Dietz AC *et al.* Bone Marrow Transplantation (2011) 46, 98–104.doi: 10.1038/bmt.2010.65

[5] Nelson AS *et al.* Biol Blood Marrow Transplant. 2016 May 22(5): 884-888.doi: 10.1016/j.bbmt.2016.01.026

* Non-attenuated androgens / oxymetholone. Low dose danazol (200mg daily). Oestrogens in females not deleterious and may be beneficial

+ There are no currently licensed treatments for TBDs

$ Single Telomere Length Analysis https://www.telonostix.com/ TeloNostiX Ltd. Central Biotechnology Services, Henry Wellcome Building, Heath Park, Cardiff, CF14 4XN, UK.

This information is based on the medical literature. Speak to your doctor if you have concerns about TBD

ADVOCACY **EDUCATION** **SUPPORT**

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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 but mutations in ACD, TINF2, CTC1, DKC1, DCLRE1B, NHP2, NOP10, NPM1, POT1, RPA1, STN1, TCAB1, PARN, RTEL1, TERT, TERC, MDM4, ZCCHC8 WRAP53 genes, all involved in telomere biology, have been identified in patients with a spectrum of clinical manifestations. These include 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. Classical DC is characterized by extremely short telomeres but different gene mutations in an array of telomere maintenance genes can produce variable phenotypes, differing in severity, in childhood or later into adulthood. The symptoms of TBD can appear at any age and adult-onset bone marrow failure can be difficult to distinguish from idiopathic aplastic anaemia. [1,2,3,4]

For a suggested diagnostic algorithm for germline telomere diseases see: Townsley DM *et al*. Bone marrow failure and the telomeropathies. *Blood*. 2014;124(18):2775–2783. doi:10.1182/blood-2014-05-526285

Medical Management of Bone Marrow Failure

Significant peripheral cytopenia should be managed with supportive therapy (blood and platelet transfusions). Khincha *et al* describe the use of the anabolic steroid oxymetholone to treat bone marrow failure.[5] Also Danazol was found to be effective in preserving and elongating telomeres in association with a haematological response in patients with telomere diseases.[6,7] A personal observation by Prof Inderjeet Dokal suggests patients with TBDs can respond to a dose as low as 0.25 mg oxymetholone/kg per day which can be increased, if necessary, to 2-5 mg/kg per day.[1,2] However a 2018 retrospective observational study found that telomere length for age shortened over time in patients with Dyskeratosis Congenita, irrespective of treatment with androgens and recommend that prospective long-term research is needed. [8] NB: No androgen therapy is licensed for treatment of TBD.

Stem Cell Transplantation and conditioning regimens

At the present time, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for progressive marrow failure, myelodysplastic syndrome, or leukaemia related to DC and TBDs. Underlying chromosomal instability and sensitivity to chemotherapy and radiation preclude traditional conditioning regimens. Reduced intensity conditioning regimens are recommended. [1,2,9,10]

1. 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.
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6. Townsley DM *et al*. Danazol Treatment for Telomere Diseases. N Engl J Med. 2016 May 19;374(20):1922-31. doi:10.1056/NEJMoa1515319.
7. Islam A, Rafiq S, Kirwan M, Walne A, Cavenagh J, Vulliamy T, Dokal I. Haematological recovery in dyskeratosis congenita patients treated with danazol. Br J Haematol. 2013 Sep;162(6):854-6. doi: 10.1111/bjh.12432.
8. Khincha PP *et al*. Similar telomere attrition rates in androgen-treated and untreated patients with dyskeratosis congenita. Blood Adv. 2018 Jun 12;2(11):1243-1249. doi: 10.1182/bloodadvances.2018016964.
9. 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.
10. Nelson AS, Marsh RA, Myers KC, Davies SM, Jodele S, O'Brien TA, Mehta PA. 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.