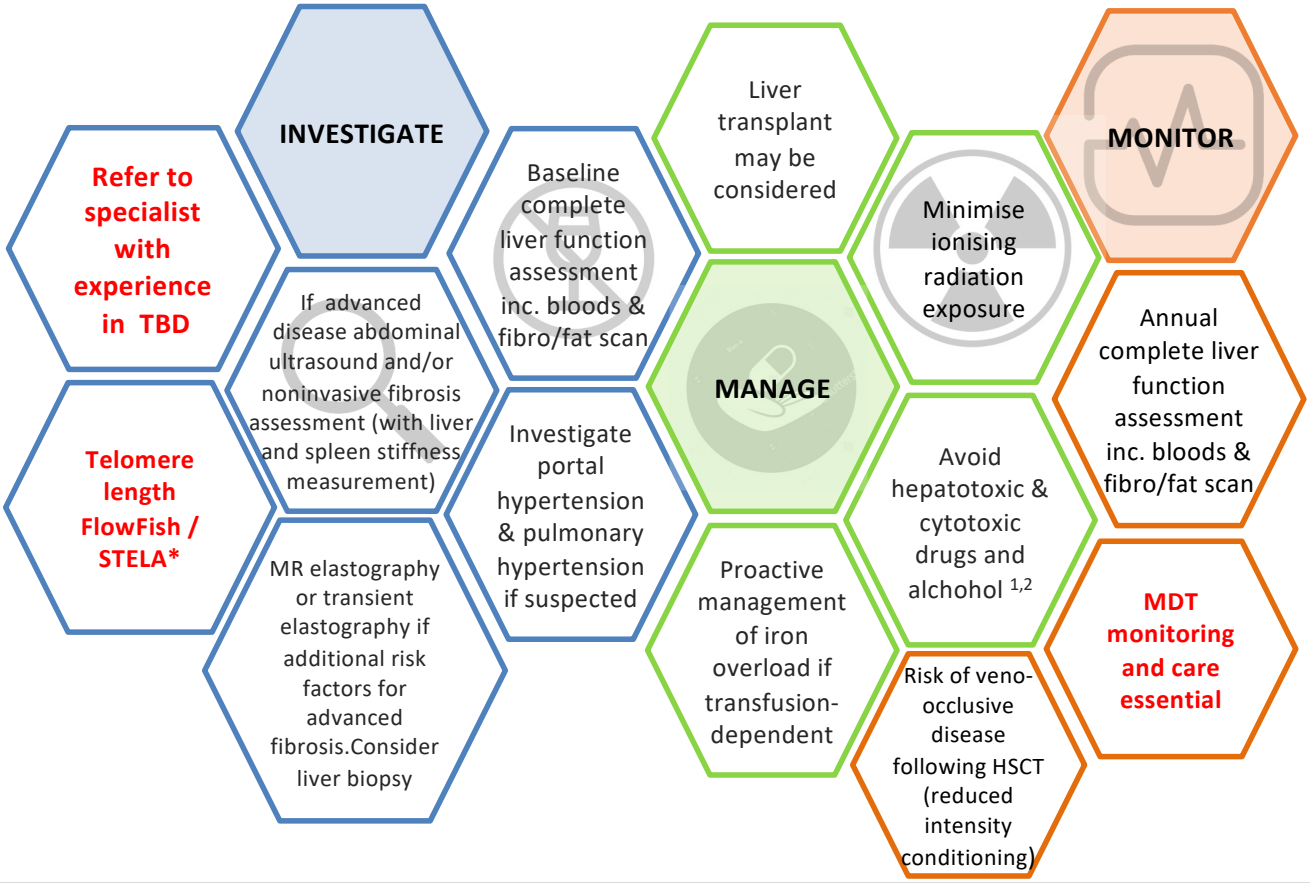
Telomere Biology Disorders (TBD), including Dyskeratosis Congenita (DC) are complex, genetic multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied. A person diagnosed with a TBD may not experience all of the symptoms listed below.

Hepatology

Liver disease, non-cirrhotic portal hypertension, hepatopulmonary syndrome, hepatocellular cancer, chronic liver disease and fulminant liver failure may be a feature of TBD. Liver involvement may also manifest as portal hypertension (causing splenomegaly, oesophageal varices etc.) or hepatopulmonary syndrome (manifest as exertional dyspnoea). Adverse environmental factors contribute to an increased risk of liver disease, including alcohol consumption, hepatotoxic drugs and post transplant complications including Graft Versus Host Disease **TBD Variants:** Liver disease may occur in absence of other classical DC features, especially in older adults. Liver disease symptoms typically occur later than bone marrow failure in children diagnosed with a TBD, but not always.
Differential diagnosis: Features of primary liver involvement may be mistaken for complications of bone marrow failure (e.g. thrombocytopenia) or pulmonary inflammation/fibrosis (e.g. hepatopulmonary syndrome).

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/



[1]Androgens/danazol for treatment of cytopaenias are assumed acceptable as perceived benefit probably outweighs risk. See Townsley DM *et al.* N Engl J Med 2016;374:1922-31. DOI: 10.1056/NEJMoa1515319

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

* 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 TBD.

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In the severe Telomere Biology Disorders (TBD) Høyeraal-Hreidarsson (HH) Syndrome and Dyskeratosis Congenita (DC) presenting in childhood with short telomeres, liver fibrosis unrelated to alcohol or a viral cause is a clinical feature and may be associated with portal hypertension even in the absence of cirrhosis[1]. Mutations in TERT, TERC, PARN, RTEL1, NAF1, DKC1, NHP2, TINF2, NOP10, NHP2, ACD, RPA1, POT1, ZCCHC8 CTC1, DCLRE1B, NPM1, STN1, TCAB1, MDM4 and WRAP53, all involved in telomere maintenance have so far been identified with a spectrum of clinical manifestations. [2,3]

Shortened telomere lengths are common in liver disease but it is important to consider inherited TBD in:

Early onset cirrhosis / fibrosis

Mutations in the TERT and TERC genes have been observed at a higher prevalence in patients with liver disease compared with the general population; however, there is evidence that other TBDs mutations are associated with cirrhosis.[4,5]
A cohort of 134 patients with cirrhosis of common aetiology and 528 healthy subjects were screened for variation in the TERT and TERC genes by direct sequencing and 528 healthy subjects were screened for variation in the TERT and TERC genes by direct sequencing; an additional 1,472 controls were examined for the most common genetic variation observed in patients. Nine of the 134 patients with cirrhosis (7%) carried a missense variant in TERT, resulting in a cumulative carrier frequency significantly higher than in controls (P = 0.0009). The allele frequency for the most common missense TERT variant was significantly higher in patients with cirrhosis (2.6%) than in 2,000 controls (0.7%; P = 0.0011). One additional patient carried a TERC mutation.[6]

In another study, the telomerase RNA component (TERC) and the telomerase reverse transcriptase (TERT) were sequenced in 521 patients with cirrhosis induced by chronic liver disease and 600 non-cirrhotic controls. An increased incidence of telomerase mutations was detected in cirrhosis patients (allele frequency 0.017) compared to non-cirrhotic controls (0.003, P value 0.0007; relative risk [RR] 1.859; 95% confidence interval [CI] 1.552-2.227). [7]

In a cohort of nine patients with TBD (5TERC 4TERT) first diagnosed in adulthood, patients showed normal to slightly elevated liver function test parameters. Hepatic ultrasound revealed inhomogeneous parenchyma in seven (77.7%) and increased liver echogenicity in four patients (44.4%). Median liver stiffness was 10.7 kilopascal (kPa) (interquartile range 8.4, 15.7 kPa). Using 7.1 kPa as cut-off, 88.8% of patients were classified as moderate fibrosis to cirrhosis. Subclinical chronic liver involvement is frequent in patients with adult-onset TBD. [8]

Nodular Regenerative Hyperplasia

A study of 42 cases of short telomere syndrome identified the hepatopulmonary syndrome in 9 cases (21%). Age at presentation was significantly younger than those initially presenting with pulmonary fibrosis and emphysema (median, 25 years vs 55 years; P .001). Nodular regenerative hyperplasia, in the absence of cirrhosis, was the most common feature. Dyspnoea and portal hypertension were progressive, and the median time to death or liver transplantation was 6 years.[9]

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