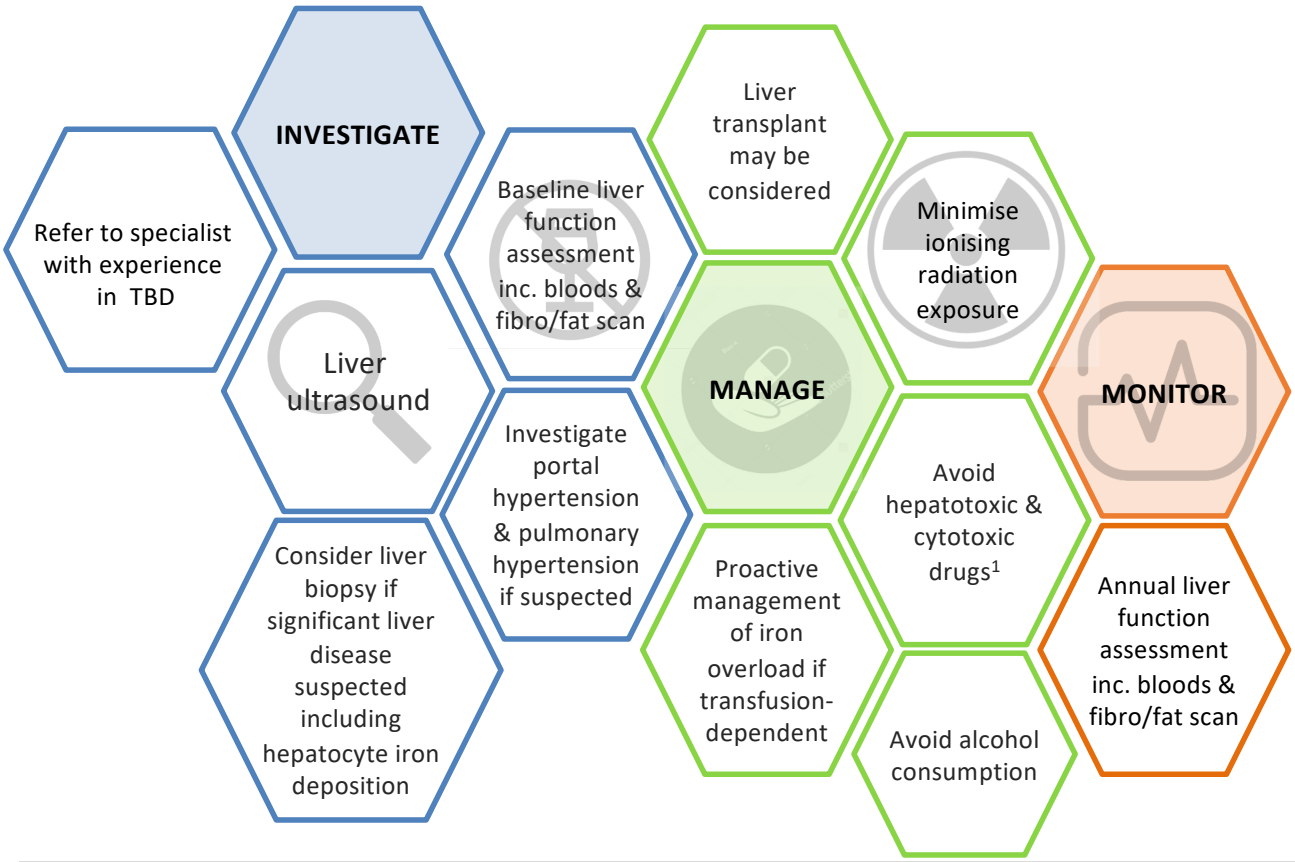
Telomere Biology Disorders (TBD), including Dyskeratosis congenita are complex, genetic multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied. A person diagnosed with a TBD may not experience all of the symptoms listed below.

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[1] and post transplant complications including Graft Versus Host Disease (GVHD)[2].

TBD Variants: Liver disease may occur in absence of other classical DC features, especially in older adults[1]. 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).



Refs. Calado *et al*, 2009 PLoS ONE 4(11): e7926. doi:10.1371/journal.pone.0007926. Carulli and Anzivino. World J Gastroenterol. 2014 May 28; 20(20): 6287–6292. Donati and Valenti, Int. J. Mol. Sci. 2016, 17, 383; doi:10.3390/ijms17030383

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

[2]associated with veno-occlusive disease and rapidly progressive cirrhosis. Risk may be reduced by non/minimally myeloablative regimens.

This information is based on reports from the medical literature. Please see your doctor if you have concerns about TBD.

Please contact us. We welcome your feedback.

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.
Glousker G *et al.* Unraveling the pathogenesis of Høyeraal–Hreidarsson syndrome, a complex telomere biology disorder British Journal of Haematology, 2015,170,457 - 471.

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

Early onset cirrhosis / fibrosis
Evidence from two studies show that mutations in TERC or TERT genes are associated with cirrhosis.

Calado RT *et al.*	Hepatology 2011;53:1600 - 1607	10/134 patients = 7.5%
Hartmann D *et al.*	Hepatology 2011;53:1608 - 1617	16/521 patients = 3.1%
Donati B and Valenti L.	Telomeres NAFLD and Chronic Liver Disease. Review Int. J. Mol. Sci. 2016, 17, 383.	

Telomere-mediated disease may be manifest in adults as isolated or syndromic clustering of idiopathic pulmonary fibrosis (IPF), liver cirrhosis, and bone marrow failure.
Armanios M. Annu Rev Genomics Hum Genet. 2009; 10: 45

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.
Gorgy A *et al.* Chest 2015; 148(4): 1019 - 1026.

See also:
A Spectrum of Severe Familial Liver Disorders Associate with Telomerase Mutations. Calado RT *et al.* (2009) PLoS ONE 4(11): e7926. doi:10.1371/journal.pone.0007926

A longitudinal study of patients with telomere disease, with a median follow-up of 2.4 years, concluded that the liver is involved in patients with telomere disease at much higher rates than previously appreciated, and these patients also have significant morbidity and mortality.
Kapuria D *et al.* The Spectrum of Hepatic Involvement in Patients With Telomere Disease. Hepatology 2019;69:2579-2585.

Eighty six blood samples from subjects with end-stage liver disease, randomly selected from a tissue repository, were tested for the presence of telomere complex variants in the following genes: TERT, TERC, RTEL1, DKC, NOP10, NHP2, TINF2, and WRAP53. Twenty per cent had likely deleterious variants. The presence of any telomerase variant was associated with an increased number of readmissions within 1 year after transplantation demonstrated by an incident rate ratio (IRR) of 3.15 (95% CI, 1.22 to 8.57). Among patients who underwent liver transplantation, the presence of any exonic missense variant was associated with a longer postoperative length of stay with an IRR of 2.16 (95% CI, 1.31 to 3.68).
Chiu V *et al*. Telomerase Variants in Patients with Cirrhosis Awaiting Liver Transplantation. Hepatology 2019;69:2652-2663.

In a study of 12/27 patients with telomere diseases, treated with 800mg daily danazol and analysed by intention to treat, 11 had reduced telomere attrition. Of 6 patients with cirrhosis at baseline, 3 showed improvements, while one deteriorated, probably due to continued alchohol abuse.
Townsley DM *et al.* N Engl J Med 2016; 374: 1922 - 31. doi: 10.1056/NEJMoa1515319.

Mutations in DKC1, TERC, TERT, CTC1, NHP2, NAF1, NOP10, WRAP53, TINF2, RTEL1, PARN, ACD, STN1 and ZCCHC8 have so far been identified in patients with a spectrum of clinical manifestations.
Niewisch MR & Savage SA. (2019) An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. Expert Review of Hematology, 12:12, 1037-1052, DOI: 10.1080/17474086.2019.1662720
Savage SA. Dyskeratosis congenita 2009 (updated 2019 Nov 21) in Adam MP, Ardinger HH, Pagon RA *et al.,* Eds. Gene Reviews® [internet] Seattle (WA): University of Washington Seattle; 1993-1019.
Bookshelf URL https://ncbi-nlm.nih.gov/books/