**Telomere Biology Disorders (TBD), including Dyskeratosis Congenita (DC)** are complex 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.

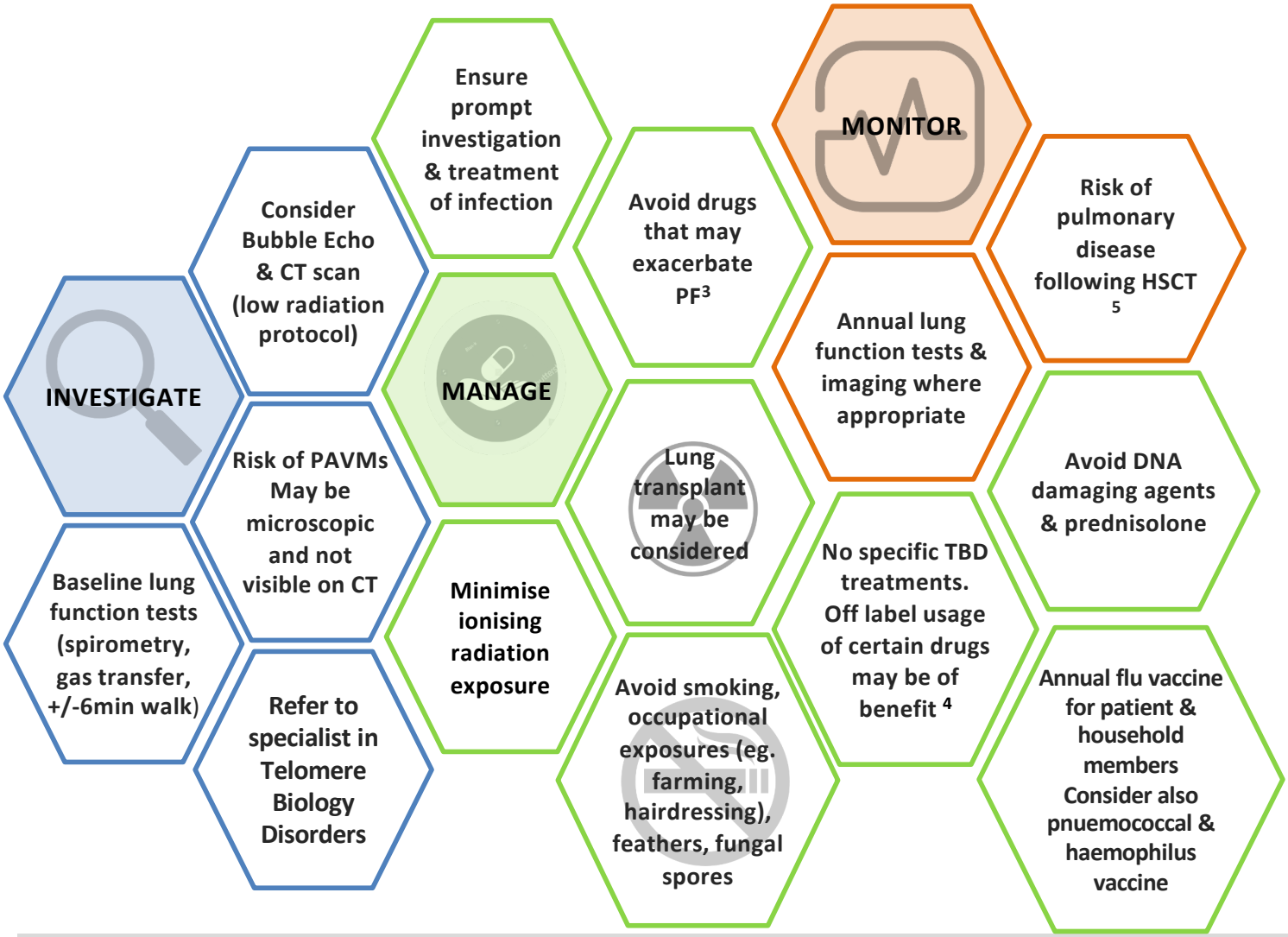
## Respiratory

Pulmonary disease including interstitial lung disease (ILD) idiopathic pulmonary fibrosis (IPF), familial pulmonary fibrosis (FPF), organising pneumonia, restrictive, arteriovenous fistulus /malformations, hepatopulmonary syndrome. [1,2]

**DC Variants:** Respiratory symptoms may occur in absence of other DC features, especially in older adults. If PF main/only presenting feature (esp. familial) check for other DC features (skin, nail, oral and blood anomalies). Respiratory symptoms typically occur later than bone marrow failure in children diagnosed with DC, but not always.

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/

*Differential diagnosis: infection, including opportunistic infection (pneumocystis, bacterial, viral or fungal pneumonia, especially if immunosuppressed or post transplantation)*




[1] Newton CA, Molyneaux PL and Oldham JM (2018) Clinical Genetics in Interstitial Lung Disease. Front. Med. 5:116

[2] Kropski *et al (2017)* Genetic Evaluation and Testing of Patients and Families with IPF. Am J Respir Crit Care Med:195:11, pp 1423–1428

[3] Including methotrexate, long term nitrofurantoin, bleomycin, busulphan, amiodarone and as per www.pneumotox.org

[4] Limited evidence - danazol, metformin, sirolimus, PARP inhibitors (RTEL1 only)

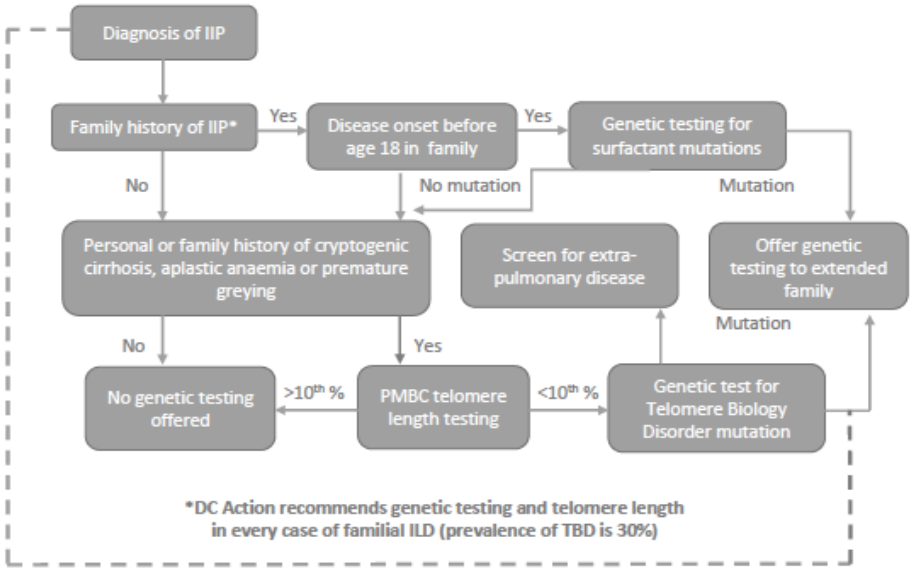
[5] Giri N, Ravichandran S, Wang Y, et al. Prognostic significance of pulmonary function tests in dyskeratosis congenita, a telomere biology disorder. ERJ Open Res 2019; 5: 00209- 2019 [https://doi.org/10.1183/23120541.00209-2019].

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

ADVOCACY EDUCATION SUPPORT

Please contact us. We welcome your feedback

**Idiopathic Interstitial Pneumonia (IIP) / Interstitial Lung Disease (ILD) Differential Diagnosis considerations**:
Chronic Hypersensitivity Pneumonitis (CHP) is associated with short telomeres. Mutations in the promotor region of mucin gene MUC5B and Single Nucleotide Polymorphisms (SNPs) in or near TOLLIP (TOLL-Interacting Protein) influence IPF susceptibility, mortality and treatment outcomes. [1]
The most common telomere biology gene related mutation associated ILD is idiopathic pulmonary fibrosis (IPF) or Familial Pulmonary Fibrosis (FPF). Up to 1/3rd of adult FPF and 1:10 sporadic IPF cases have shortened telomeres or carry a telomere maintenance gene mutation. Regardless of ILD phenotype, individuals with short telomeres and/or known telomere-related gene mutations have more rapid disease progression and shorter lung transplant–free survival.
Telomere Biology Disorders (TBD) due to mutations in in TERT, TERC, RTEL1, PARN, NAF1, TINF2 or DKC1 are associated with ILD and some with Rheumatoid Arthritis associated ILD. [1,2,3,4,5,6,7,8]




Adapted from: Kropski JA *et al*. Genetic Evaluation and Testing of Patients and Families with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2017:195, 11, p1423

**Management recommendations**
Consider antifibrotic agents for those with an IPF phenotype and early referral to a transplant centre. Patients with ILD being considered for transplant should be screened for short telomeres and telomere gene mutations if there is a significant family history of pulmonary fibrosis or evidence of extrapulmonary organ dysfunction associated with a short telomere syndrome. Post-transplant management of recipients with telomere-related mutations should include careful adjustment of immunosuppression regimens on the basis of bone marrow reserve. Pulmonary fibrosis may develop following HSCT [8].

**Pulmonary Arteriovenous Malformations (PAVMs)**
Vascular complications such as bleeding due to gastrointestinal telangiectatic anomalies, pulmonary arteriovenous malformations, hepatopulmonary syndrome, and retinal vessel abnormalities are being reported in patients with telomere biology disorders more frequently than previously described. A multi-institutional retrospective review of medical records evaluated patients diagnosed with both DC / TBD and PAVMs. This case series establishes PAVMs as a clinically important pulmonary phenotype in DC / TBD and one that may occur in the absence of overt hepatopulmonary syndrome, in the absence of symptoms, and in patients of any age, genotype or phenotype. [9,10,11]

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3. Wolters PJ *et al*. Time for a change: is idiopathic pulmonary fibrosis idiopathic and only fibrotic? Lancet Respir Med. 2018 February ; 6(2): 154–160.
4. Parry EM *et al*. Syndrome complex of bone marrow failure and pulmonary fibrosis predicts germline defects in telomerase. Blood 2011; 117:5607–11
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7. Courtright AM and El-Chemaly S. Telomeres in Interstitial Lung Disease: The Short and the Long of It. Ann ATS 2019, Vol 16:2
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