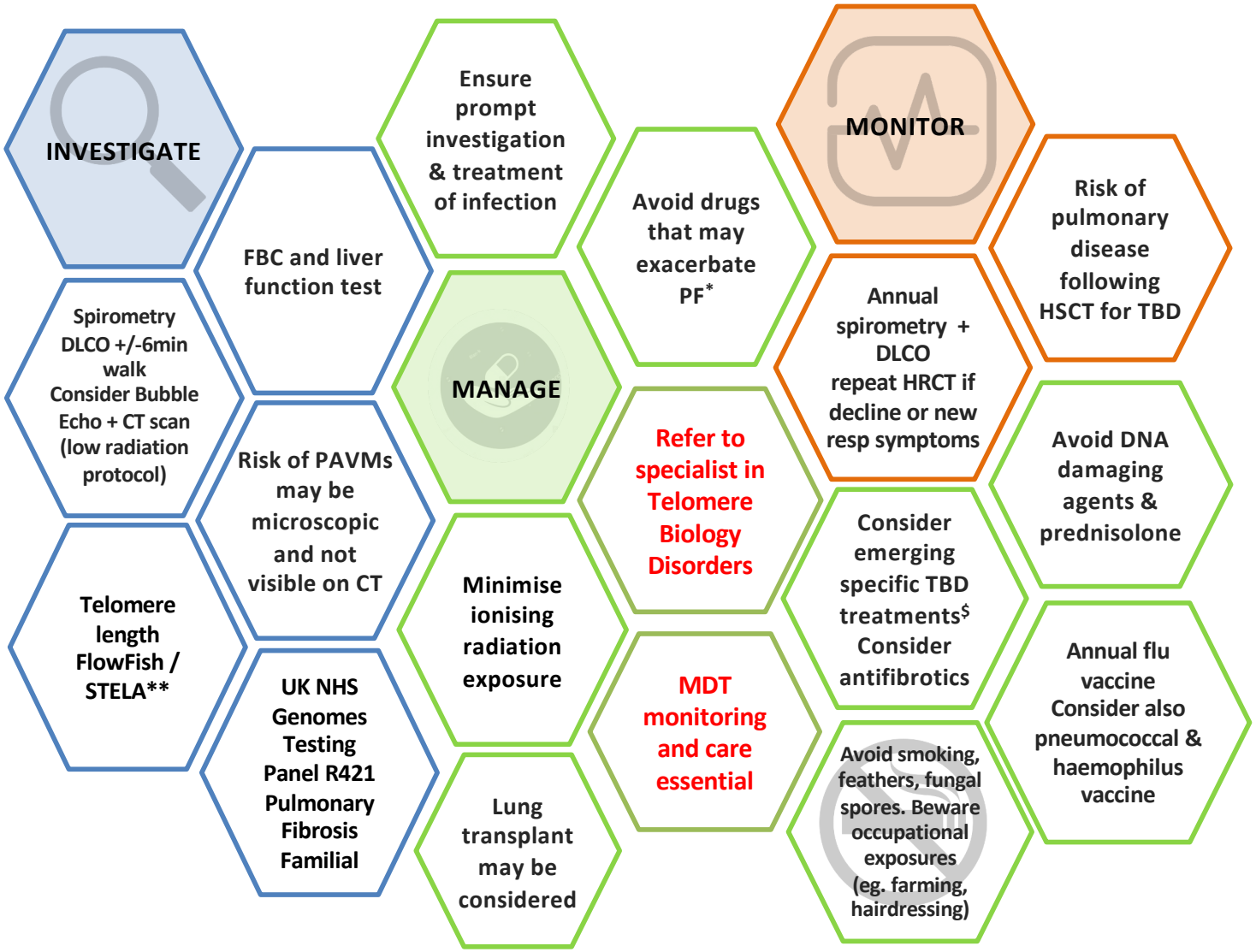
Telomere Biology Disorders (TBD) including Dyskeratosis Congenita (DC) are complex multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied but can include IPF, bone marrow failure, liver fibrosis and a pre-dispostion to cancer.

Respiratory

Pulmonary disease including interstitial lung disease (ILD) idiopathic pulmonary fibrosis (IPF), familial pulmonary fibrosis (FPF), organising pneumonia, restrictive, arteriovenous fistulas /malformations. The mean age of ILD diagnosis in patients with a TBD mutation is approximately 58 years. Respiratory symptoms may occur in absence of other TBD features, especially in older adults but check for idiopathic liver disease – steatohepatitis / portal hypertension / cirrhosis, hepatopulmonary syndrome, cytopenia, macrocytosis, oral leukoplakia, stenosis, all features of TBDs. Respiratory symptoms typically occur later than bone marrow failure in children, but not always. PF can occur post HSCT.

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/



* Including methotrexate, long term nitrofurantoin, bleomycin, busulphan, amiodarone and as per www.pneumotox.com/drug/index/

$ Limited evidence - danazol, metformin, sirolimus, PARP inhibitors (RTEL1 only)

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

Stanel SC, Callum J, Rivera-Ortega P. Present and future perspectives in early diagnosis and monitoring for progressive fibrosing interstitial lung diseases. Front Med (Lausanne). 2023 Feb 15;10:1114722. doi: 10.3389/fmed.2023.1114722.

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

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

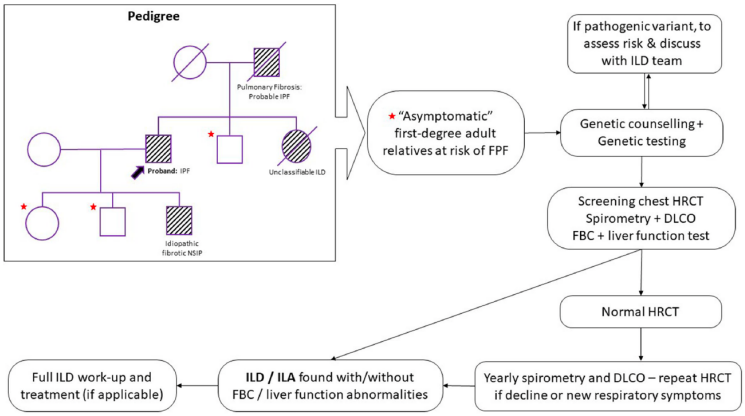
ADVOCACY EDUCATION SUPPORT

Please contact us. We welcome your feedback

ILD and Telomere Biology Disorders (TBD)

Differential diagnosis considerations: Chronic Hypersensitivity Pneumonitis (CHP) – also associated with short telomeres. Mutations in the promotor region of mucin gene MUC5B and SNPs in or near TOLLIP (toll-interacting protein) influence IPF susceptibility, mortality and treatment outcomes. The most common telomere-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 mutations have more rapid disease progression and shorter lung transplant–free survival. Telomere Biology Disorders (TBD) due to mutations in TERT, TERC, PARN, RTEL1, NAF1, DKC1, NHP2, TINF2, NOP10, NHP2, ACD, RPA1, POT1, ZCCHC8 are associated with ILD and some with Rheumatoid Arthritis associated ILD. Also consider CTC1, DCLRE1B, NPM1, STN1, TCAB1, MDM4 and WRAP53. [1,2,3,4]

Diagnostic recommendations



UK NHS National Genomic Test Directory – Testing Criteria for Rare and Inherited Disease, version 5.1, May 2023
R421 Pulmonary Fibrosis Familial testing criteria: ILD and ONE of the following:
1. ILD, no identifiable cause or association, and age < 50 years.
2. Family history of ILD regardless of identifiable cause or association.
3. For suspected telomerase complex mutations, testing to be considered in the absence of 1. and 2. above if one or more of the following are present in addition to ILD: • Unexplained hematological abnormalities including macrocytosis, anemia, thrombocytopenia, leukopenia and/or lymphopenia; premature greying, • Or unexplained liver function abnormalities. • Consideration of lung transplantation.

From Stanel SC, Callum J, Rivera-Ortega P. Present and future perspectives in early diagnosis and monitoring for progressive fibrosing interstitial lung diseases. Front Med (Lausanne). 2023 Feb 15;10:1114722. doi: 10.3389/fmed.2023.1114722.

Assess telomere length (FlowFish **/ STELA***). Genetic testing for inherited mutations if the peripheral blood leukocyte telomere length falls below the 10th percentile recommended. Cascade testing of pathogenic or likely pathogenic variants in at-risk family members. ***Whole blood or DNA to TeloNostiX Cardiff https://www.telonostix.com/**

Management recommendations

Initiation of antifibrotic agents for those with an IPF phenotype and early referral to a transplant centre. MDT monitoring and care essential. Screen patients with ILD for short telomeres and telomere gene mutations if 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. People with DC/TBD are at increased risk for progressive bone marrow failure, myelodysplastic syndrome or acute myelogenous leukaemia and solid tumours (usually squamous cell carcinoma of the head/neck or anogenital cancer). MDT monitoring and care is essential. Pulmonary fibrosis may develop following HSCT.[3,5]

Pulmonary Arteriovenous Malformations (PAVMs)

Vascular complications such as bleeding due to gastrointestinal telangiectatic anomalies, PAVMs, hepatopulmonary syndrome and retinal vessel abnormalities are reported in patients with Telomere Biology Disorders (TBD). A multi-institutional retrospective review of medical records evaluated patients diagnosed with both Dyskeratosis congenita (DC) / TBD and PAVMs and established PAVMs as a clinically important pulmonary phenotype that may occur in the absence of overt hepato-pulmonary syndrome or in the absence of symptoms in patients of any age, genotype or phenotype. [3,6,7,8]

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