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

Pulmonary disease including interstitial lung disease (ILD) idiopathic pulmonary fibrosis (IPF), familial pulmonary fibrosis (FPF), organising pneumonia, restrictive, arteriovenous fistulus /malformations. The mean age of ILD diagnosis in patients with a TBD mutation is 58 years. Respiratory symptoms may occur in the 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/

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.

Niewisch MR, Beier F, Savage SA. Clinical manifestations of telomere biology disorders in adults. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):563-572. doi: 10.1182/hematology.2023000490.

Investigate

- Spirometry
  DLCO
  +/-6min walk
  Consider Bubble Echo
  + CT scan (low radiation protocol)
- Risk of Pulmonary Arteriovenous Malformations
  May be microscopic and invisible on CT
- Telomere length
  FlowFish / STELA**
- FBC and Liver Function Test
- Ensure prompt investigation & treatment of infection
- **Family History Critical**
  Genomes England Pulmonary Fibrosis Familial panel R421

Manage

- Minimise ionising radiation exposure
- **Refer to specialist in Telomere Biology Disorders contact TeloNet**
  info@dcaction.org
- Avoid DNA damaging agents & prednisolone
- + Fibrotic hypersensitivity pneumonitis and unclassifiable ILD patients who have age-adjusted leukocyte telomere length <10th percentile may experience reduced survival when exposed to immunosuppression, similar to IPF patients

Monitor

- Annual spirometry + DLCO
  Repeat HRCT if decline or new respiratory symptoms
- **MDT monitoring and care essential**
- Risk of pulmonary disease following HSCT for Telomere Biology Disorders

- Consider emerging specific TBD treatments$
  Consider antifibrotics
- Consider lung transplant
- Annual flu & Covid vaccine
  Consider also pneumococcal & haemophilus vaccine
- Avoid smoking, feathers, fungal spores
  Beware occupational exposures

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

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

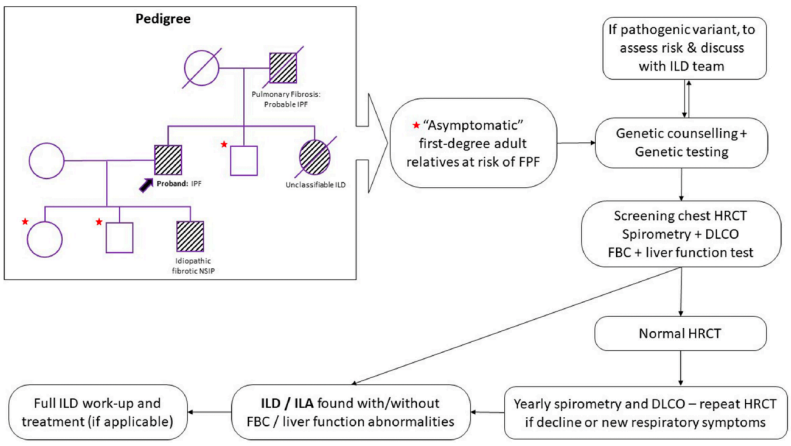
** Single Telomere Length Analysis https://www.telonostix.com/

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

+Zhang D, et al. Telomere length and immunosuppression in non-idiopathic pulmonary fibrosis interstitial lung disease. Eur Respir J. 2023 Nov 29;62(5):2300441. doi: 10.1183/13993003.00441-2023

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, MDM4 and WRAP53. 1,2,3,4,5

Diagnostic recommendations 2



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.

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: MDT monitoring and care essential.
Initiation of antifibrotic agents for those with an IPF phenotype and early referral to a transplant centre. Screen patients with ILD being considered for transplant 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). Monitor for liver disease. Baird et al describe a patient with Short Telomere Syndrome presenting with pulmonary fibrosis, liver cirrhosis and hepatopulmonary syndrome.5 MDT monitoring and care is essential. Pulmonary fibrosis may develop following HSCT. 3,6

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. 3,6,7,8,9,10

1. Papiris SA, Kannengiesser C, Borie R, Kolilekas L, Kallieri M, Apollonatou V, Ba I, Nathan N, Bush A, Griese M, Dieude P, Crestani B, Manali ED. Genetics in Idiopathic Pulmonary Fibrosis: A Clinical Perspective. Diagnostics (Basel). 2022 Nov 23;12(12):2928. doi: 10.3390/diagnostics12122928. PMID: 36552935; PMCID: PMC9777433.
2. 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.
3. Team Telomere Diagnosis and Management Guidelines 2022 https://teamtelomere.org/telomere-biology-disorders-diagnosis-and-management-guidelines-downloads/
4. Juge et al. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J 2017; 49:
5. Borie R, Kannengiesser C, Antoniou K, Bonella F, Crestani B, Fabre A, Froidure A, Galvin L, Griese M, Grutters JC, Molina-Molina M, Poletti V, Prasse A, Renzoni E, van der Smagt J, van Moorsel CHM. European Respiratory Society statement on familial pulmonary fibrosis. Eur Respir J. 2023 Mar 16;61(3):2201383. doi: 10.1183/13993003.01383-2022.
6. Baird A. et al. Short Telomere Syndrome presenting with pulmonary fibrosis, liver cirrhosis and hepatopulmonary syndrome: a case report BMC Pulmonary Medicine (2023) 23:114 https://doi.org/10.1186/s12890-023-02378-8
7. Swaminathan AC et al. Lung Transplant Outcomes in Patients With Pulmonary Fibrosis With Telomere-Related Gene Variants. Chest. 2019 Sep;156(3):477-485. doi: 10.1016/j.chest.2019.03.030.
8. Higgs C et al. Clinical Care Consortium for Telomere-associated Ailments (CCCTAA). Understanding the evolving phenotype of vascular complications in telomere biology disorders. Angiogenesis. 2019 Feb;22(1):95-102. doi: 10.1007/s10456-018-9640-7.
9. Khincha PP et al. Pulmonary arteriovenous malformations: an uncharacterised phenotype of dyskeratosis congenita and related telomere biology disorders. Eur Respir J. 2017 Jan 25;49(1):1601640. doi: 10.1183/13993003.01640-2016.
10. Fernandez L et al. Dyskeratosis Congenita Presenting with Pulmonary Arteriovenous Malformation (PAVMs): A Case Report. American Journal of Respiratory and Critical Care Medicine 2017;195:A6 https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts A6083