Chapter 14

Pulmonary Fibrosis

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Introduction

Pulmonary fibrosis is one of the most serious and life-threatening complications of the telomere biology disorders (TBDs). Pulmonary fibrosis represents a heterogeneous group of conditions termed the fibrotic Interstitial Lung Diseases (ILDs), which are characterized by the deposition of collagen and extracellular matrix in the space between alveolar epithelial cells and capillary endothelial cells.

Pulmonary fibrosis can manifest across the age spectrum in patients with TBDs. Pulmonary fibrosis in young patients with dyskeratosis congenita (DC) has been

described after hematopoietic cell transplantation (HCT) for bone marrow failure. Pulmonary fibrosis in this setting may be accelerated by exposure to conditioning regimens for hematopoietic cell transplantation [1, 2]. In patients who have received a HCT, respiratory symptoms develop early in life (median 14 years), with survival to early adulthood [3]. Pulmonary fibrosis may also occur in patients with DC later in life, in the absence of HCT, and may also be found concurrently with cytopenias [4, 5]. For this group of DC/TBD patients, respiratory symptoms develop later (median 37 years), and median survival is longer. Finally, pulmonary fibrosis may be the dominant, and only, clinical manifestation of telomere-mediated disease [6-9]. Patients presenting in this manner are typically older and do not have the mucocutaneous findings or severe bone marrow failure associated with DC, although they may have a family or personal history of less severe DC-associated phenotypes. The most common diagnosis for this last group of patients is Idiopathic Pulmonary Fibrosis (IPF), which is typically diagnosed after the fifth decade of life [10]. Regardless of when the pulmonary fibrosis starts, it is usually relentlessly progressive and leads to respiratory failure. Considering that the prevalence of IPF associated with TBDs is estimated to be greater than the prevalence of classic DC, IPF is recognized as one of the most common TBD presentations [11].

Clinical Presentation

Patients typically present with respiratory complaints including exertional dyspnea (shortness of breath) and chronic cough. They may have inspiratory rales and digital clubbing on physical exam. The disease is associated with a restrictive pattern on

pulmonary function testing and decreased diffusion capacity for carbon monoxide (DL_{CO}). Screening chest X-rays may appear normal during the early stages of disease, which is why high-resolution computed tomography (HRCT) imaging of the chest is the gold-standard diagnostic study. HRCT often demonstrates diffuse interstitial markings (reticulations), architectural distortion of the airways (traction bronchiectasis), and loss of normal lung parenchyma in scarred tissue (cysts, honeycombing).

The pattern of lung involvement is often complex in patients with DC and pulmonary fibrosis. Lung histopathology generally features a mixture of cellular inflammatory infiltrates and interstitial fibrosis that does not typically mirror the findings in older adults. Assessing these patients may be particularly difficult not only because the clinical findings and histopathology are non-specific, but because of the range of possible differential diagnoses, including lung involvement of graft versus host disease after HCT, opportunistic infection, and drug-induced lung injury.

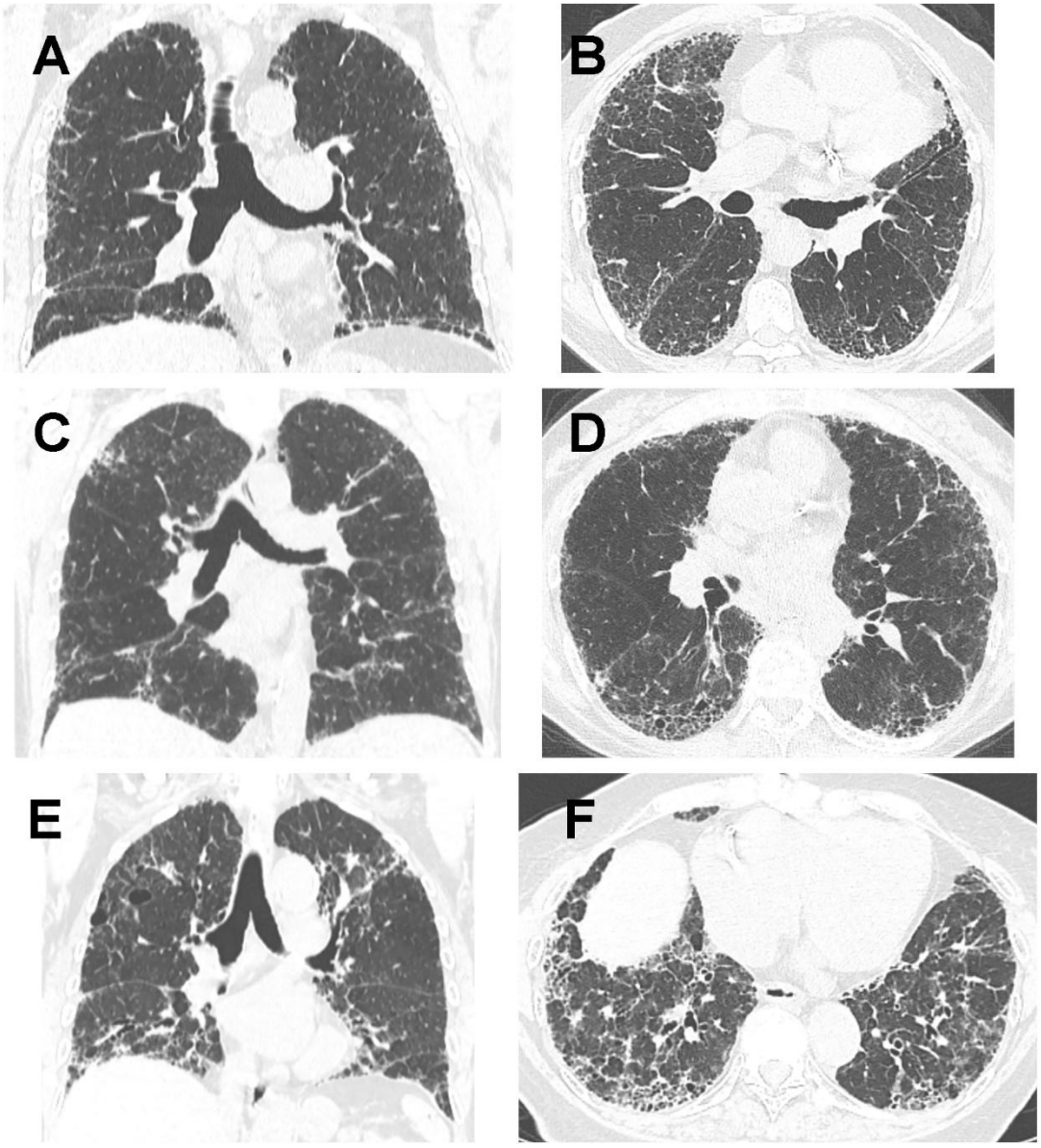

Figure. Representative high-resolution computed tomography (HRCT) chest images from adult pulmonary fibrosis patients with rare, deleterious variants in telomere related genes. A 78 year old man heterozygous for *TERT* p.Cys76Stop (**A**, **B**), a 55 year old man heterozygous for *PARN* c.1222+1G>T (**C**, **D**), and an 81 year old female heterozygous for *RTEL1* p.Ile110frameshift (**E**, **F**). Coronal images at the level of the carina are shown in **A**, **C**, and **E**. Axial images are shown in **B**, **D.** and **F**.

Guidelines for providing an accurate ILD diagnosis in adults have evolved over the last decade [12-14]. As with any chronic lung disease, a thorough medical history is

necessary to determine if there are underlying environmental insults or comorbidities that may be contributing to the lung disease. In certain clinical contexts, when there is no clear cause of the pulmonary fibrosis, a diagnosis of IPF is considered. This diagnosis requires a definite or probable radiographic pattern of usual interstitial pneumonitis (UIP) on HRCT. In cases in which the radiographic pattern is indeterminate or not consistent with UIP, evaluation of lung tissue is often needed to make a definitive diagnosis. However, the risks and benefits of a surgical lung biopsy should be carefully weighed, as surgical biopsy has been associated with increased mortality in patients with TBDs [15], and no significant difference in survival has been found in patients with different fibrotic ILD diagnoses [10]. Thus, clinical work-up, including the least invasive procedures, and multidisciplinary discussion are recommended.

Telomere-Related Genetic Variants Associated With Pulmonary Fibrosis

Rare, damaging, protein-coding variants in several telomere-related genes linked to DC are enriched in patients with fibrotic ILDs (see also Chapter 4, The Genetics of Dyskeratosis Congenita and Telomere Biology Disorders and Chapter 5, Genetic Counseling for Families). In older adults, they are found most (~25%) in patients with a family history of pulmonary fibrosis (FPF) and less commonly (~5%) in those with sporadic IPF [16]. Pathogenic variants in the telomerase genes (*TERT, TERC*) are most commonly represented [6, 7, 17], followed by variants in *PARN* and *RTEL1* [18-22]. Fewer FPF kindreds and cases have been described with pathogenic variants in *NAF1* [23], *DKC1* [24, 25], *NHP2* [26], *TINF2* [27-29], *NOP10* [30, 31] and *ZCCHC8* [32].

Individuals with deleterious variants in telomere biology genes have evidence of short telomeres (see also Chapter 3, Diagnosing TBDs). The manifestations of TBDs follow the general trend that affected pediatric patients have mean lymphocyte telomere lengths far below the 1st percentile for their age, those presenting in early adulthood have telomere lengths <1st percentile, and patients >50 years of age have more modest telomere shortening, i.e., <10th percentile for their age [33]. When evaluating for short telomeres in individuals with rare variants in telomere-related genes, a cutoff of mean lymphocyte telomere length <1st percentile by flow-FISH (see Chapter 3, Diagnosing TBDs) is usually employed to implicate a diagnosis of DC [34]. The appropriate cutoff for adults is less well established.

Fibrotic ILD Associated With Short Telomeres and Telomere Biology Gene Pathogenic Variants

Heterozygous rare, deleterious, genetic variants in telomere biology genes have been linked with different clinical ILD diagnoses that can lead to progressive forms of pulmonary fibrosis [10]. For adults, a clinical diagnosis of IPF is typically the most common, accounting for about 50% of cases [10]. Unclassifiable ILD, chronic hypersensitivity pneumonitis (CHP), connective tissue disease-associated ILD (CTD-ILD) pleuroparenchymal fibroelastosis, and other idiopathic interstitial pneumonias make up the other half of cases [10, 35]. Extra-pulmonary manifestations, including macrocytosis, thrombocytopenia, liver disease, and cutaneous abnormalities, may be prevalent in carriers of rare genetic variants [8, 17].

Age at the time of pulmonary fibrosis diagnosis correlates with gene mutation and degree of telomere shortening. DC/TBD patients with *DKC1, NHP2*, or *TINF2* mutations have a younger age of ILD onset than those with *TERT* or *TERC* mutations [15]. For adult-onset pulmonary fibrosis, patients with *TERC* mutations are diagnosed with a fibrotic ILD at an earlier age (mean 51 years), than those with *TERT* (58 years), *RTEL1* (60 years), or *PARN* (65 years) mutations [10].

Fibrotic ILD Associated With Short Telomeres, With No Identifiable Telomere Biology Gene Pathogenic Variant(s)

The telomere length cutoff considered to be “short” is not well established for adults with pulmonary fibrosis. Age-adjusted peripheral blood leukocyte telomere length <10th percentile is frequently seen in patients with FPF and sporadic IPF without identifiable telomere-related mutations [36, 37]. There are now at least 12 independent IPF cohorts across the globe that demonstrate evidence of telomere shortening of this degree [17, 19, 37-43]. The percentage of patients with various non-IPF fibrotic ILDs, such as CHP [44], unclassifiable ILD [45], rheumatoid arthritis-associated ILD [46], and other CTD-ILDs [47], with age-adjusted telomere length <10th percentile is higher than would be predicted, but to a lesser degree than what is observed for IPF. Mendelian randomization studies suggest that telomere length, identified from a polygenic risk score, is causally related to the development of IPF, but not COPD, in the UK Biobank [48]. Thus, short telomeres are a common finding in, and are likely causally related, to a wide array of fibrotic ILDs.

The explanation for short telomeres in patients with no identifiable rare genetic mutation in a telomere biology gene is unclear. Combinatorial effects from common genetic variants associated with short telomeres may explain some proportion of patients [49, 50]. Environmental factors, such as cigarette smoking, may contribute [51]. Additionally, epigenetic inheritance of short telomeres may contribute to this heritability gap. Family members of telomere biology gene variant carriers with pulmonary fibrosis, who did not inherit the mutation themselves, may harbor short telomeres [52].

There is an inverse association between telomere length and lung transplant-free survival for patients with IPF [19, 38-40, 42], CHP [53], and interstitial fibrosis with autoimmune features (IPAF) [46], independent of patient age, sex, ethnicity, and baseline Forced Vital Capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}). Similarly, the rate of FVC decline is faster for IPF, CTD-ILD, and IPAF patients with leukocyte telomere length <10^{th} percentile versus those with ≥10^{th} percentile [46]. Thus, telomere length is a biomarker that can inform clinically relevant outcomes for adults with a variety of fibrotic ILDs.

Medical Treatment

Immunosuppression poses increased risk of adverse outcomes in patients with IPF, particularly in those with short telomeres [15, 43]. Similarly, in patients with CHP, immunosuppression shows no efficacy in those with the shortest telomere lengths [54]. As such, patients with pulmonary fibrosis and short telomeres should be treated with

immunosuppressive therapies only when benefits outweigh risks, such as after lung transplantation, and should be carefully monitored for infectious complications.

One phase 1-2 clinical trial showed that danazol, a synthetic sex hormone with androgenic properties, was associated with telomere elongation and hematologic response in some patients with TBDs and pancytopenia [55]. The effect of danazol in slowing pulmonary fibrosis is currently unknown but is undergoing study in ongoing clinical trials.

Clinical trials that have led to FDA approval of pirfenidone [56] and nintedanib [57] as antifibrotic therapies for IPF have not enrolled or stratified patients by telomere length. These studies have included large numbers of patients and have shown that the rate of FVC decline was significantly lower among patients who received an antifibrotic than among those who received placebo. Meta-analysis of ~13,000 patients with IPF across 26 studies have shown improved survival and fewer acute exacerbations in those patients taking these antifibrotics [58]. Lower risk of all-cause mortality and hospitalization of patients with IPF taking antifibrotics as compared to patients with no treatment have also been seen by analyzing large US insurance databases [59]. Recently, nintedanib was also FDA approved for progressive fibrosing ILD, based on a double-blind, placebo-controlled, phase 3, international clinical trial [60].

Only a handful of studies have evaluated treatment of TBD-mediated pulmonary fibrosis with antifibrotic medications. Post-hoc analysis of two phase 3 clinical trials indicates a reduced rate of FVC decline in IPF patients with short telomeres randomized to

treatment with pirfenidone as compared to placebo [19]. Safety and efficacy of the antifibrotics for IPF patients who carry a telomere biology gene pathogenic variant have been reported [61].

Thus, it is our recommendation that TBD patients with IPF or progressive pulmonary fibrosis should be started on an antifibrotic medication. Those with interstitial lung abnormalities (ILA) in a non-fibrotic or a non-UIP pattern should be followed with serial pulmonary function tests annually or more frequently depending on symptom progression. Repeat HRCT scans can be performed if there are progressive symptoms or pulmonary function test (PFT) decline to determine if there is progressive pulmonary fibrosis.

Screening for Pulmonary Fibrosis

There are few studies assessing the utility of screening protocols for pulmonary fibrosis in DC/TBD. Some providers feel that chest imaging poses too high a risk from medical radiation for children relative to its potential benefit. Pulmonary function testing affords no exposure to radiation, and thus, is safer means of determining functional limitations. Given the risk of pulmonary complications after HCT, all patients should have careful assessment of lung function prior to HCT. Additionally, current consensus guidelines suggest lung function tests every 3 months for 2 years following HCT [62]. For individuals with persistently diminished lung function, further work-up with imaging and bronchoscopy should be considered.

Asymptomatic carriers of telomere biology gene pathogenic variants have a very high prevalence of pulmonary fibrosis, which increases with age. ILAs, which are subtle and often incidentally found, are thought to represent early ILD in high-risk individuals [63]. In one study, fifty percent of at-risk family members with rare *TERT* variants were found to have ILA and a DL_{CO} less than 80% predicted [64]. Similarly, adults with just a family history of fibrotic lung disease are at higher risk for pulmonary fibrosis. The estimated prevalence of early or subclinical manifestations of pulmonary fibrosis in relatives of individuals with familial pulmonary fibrosis ranges from 15-22% [65, 66]. Development of ILA in family members of patients affected with sporadic IPF or pulmonary fibrosis due to other etiologies is dependent on the presence of environmental risk factors (such as cigarette smoking) and common genetic variants, including the *MUC5B* promoter risk allele (rs35705950) [67].

Given that the FDA approved therapies for fibrotic ILD are not curative and do not reverse fibrosis, their utility in slowing down the rate of progression is best if implemented early in the course of disease. Thus, for family members at high risk of disease (such as mutation carriers or those with a strong family history of disease), we recommend a screening HRCT scan of the chest, spirometry, and plethysmography 10-15 years before the earliest manifestation of ILD in the family. The age at which to start screening should consider effects of genetic anticipation related to accelerated telomere shortening.

In symptomatic individuals with a family history of pulmonary fibrosis and/or evidence of a personal or family history of a TBD (such as early graying of hair before 30 years of

age, idiopathic liver disease, cytopenia, macrocytosis), we recommend telomere length testing as part of the workup [68]. We recommend genetic testing for inherited mutations if the peripheral blood leukocyte telomere length falls below the 10th percentile, with cascade testing of pathogenic or likely pathogenic variants in at-risk family members. Individuals with a family history of pulmonary fibrosis without evidence of a TBD may wish to undergo genetic testing, but the likelihood of discovering pathogenic or likely pathogenic variants is typically low, especially if there are few affected individuals in the kindred. Currently, we do not recommend telomere length testing in individuals with sporadic pulmonary fibrosis without a personal or family history suggestive of a TBD.

Exposures to Avoid

The development of pulmonary fibrosis is associated with various environmental, occupational, and iatrogenic exposures. Vigilance is needed to avoid these insults, especially for those that have a genetically inherited susceptibility to ILD. The following list, although not comprehensive, includes:

- **Smoking.** Cigarette smoking is known to accelerate the onset of lung disease and is associated with various ILDs [69]. Smoking of cigarettes, cigars, pipes, e-cigarettes, vaping, hookahs, and recreational drugs all lead to lung injury and increased risk of ILD. Smoking should be strongly discouraged, and multi-disciplinary effort should be made to support patients in avoiding both

primary and secondary sources of smoke. Referral to support groups, counseling, and medication aides should be considered in high-risk populations.

- **Cytotoxic medications and radiation.** Ionizing radiation should be minimized and procedures for aggressive lung shielding should be implemented [70]. Cytotoxic medications used as conditioning agents prior to HCT should be avoided whenever possible [1, 2]. Preparative agents with the smallest potential for pulmonary toxicity should be considered.
- **Medications.** Several medications are strongly associated with pulmonary toxicity [71], such as amiodarone [72] and nitrofurantoin [73]. A growing number of checkpoint inhibitors are associated with increased incidence of ILD. Some anti-depressants are associated with increased risk of ILD in older adults [74]. These medications should be avoided when possible.
- **Surgical risk.** Exacerbations of lung disease in adults with ILD have been well-documented following both pulmonary and non-pulmonary surgeries. The risk should be weighed in planning elective procedures because these complications can be fatal. Pirfenidone has been shown to be safe and promising for reducing the risk of acute exacerbations of IPF in patients undergoing lung cancer surgery [75] but has not been studied in patients with TBD. When feasible, elective surgery is preferably pursued using regional anesthesia to avoid aspiration or high partial pressure oxygen, which can cause alveolar epithelial injury.

- **Occupational and environmental risk factors.** Occupations and exposures that have been associated with an increased risk of ILA progression in individuals at risk for familial ILD include aluminum smelting as well as lead, bird, and mold exposure [76]. Exposure to a number of organic antigens (most commonly bird feathers, fungal, and bacterial antigens) can result in chronic hypersensitivity pneumonitis (CHP), which can mimic IPF and other fibrosing ILDs. Changing occupations is not feasible for many individuals. In these cases, implementing respiratory protection plans that include wearing a particulate-filtering respiratory may reduce hazards associated with these exposures.
- **Respiratory illness.** Infections suspected or confirmed to be caused by bacterial pathogens should be promptly and appropriately treated with antibiotics. Immunizations to respiratory tract pathogens should be offered.

Lung Transplantation

Lung transplantation is the only known modality that cures fibrotic ILD. Please refer to Chapter 15, Lung Transplantation for more details.

Conclusion

Pulmonary fibrosis is one of the most common and life-threatening complications of the TBDs. Treatment with antifibrotic agents offers promise for patients with IPF or progressive pulmonary fibrosis in slowing the rate of respiratory decline, but current medications do not halt or reverse the disease. Additional studies are needed to

specifically study the effects of antifibrotic medications in patients with TBDs. Thus, screening for pulmonary fibrosis in high-risk individuals, avoidance of environmental contributors to fibrosis, and consideration of early implementation of antifibrotic treatment should be cornerstones of clinical management.

References

1. de la Fuente J, and Dokal I. Dyskeratosis congenita: advances in the understanding of the telomerase defect and the role of stem cell transplantation. *Pediatric transplantation.* 2007;11(6):584-94.
2. Dietz AC, Orchard PJ, Baker KS, Giller RH, Savage SA, Alter BP, et al. Disease-specific hematopoietic cell transplantation: nonmyeloablative conditioning regimen for dyskeratosis congenita. *Bone Marrow Transplant.* 2011;46(1):98-104.
3. Giri N, Lee R, Faro A, Huddleston CB, White FV, Alter BP, et al. Lung transplantation for pulmonary fibrosis in dyskeratosis congenita: Case Report and systematic literature review. *BMC Blood Disord.* 2011;11:3.
4. Parry EM, Alder JK, Qi X, Chen JJ, and Armanios M. Syndrome complex of bone marrow failure and pulmonary fibrosis predicts germline defects in telomerase. *Blood.* 2011;117(21):5607-11.
5. Gansner JM, Rosas IO, and Ebert BL. Pulmonary fibrosis, bone marrow failure, and telomerase mutation. *N Engl J Med.* 2012;366(16):1551-3.
6. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med.* 2007;356(13):1317-26.
7. Tsakiri KD, Cronkhite JT, Kuan PJ, Xing C, Raghu G, Weissler JC, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proc Natl Acad Sci U S A.* 2007;104(18):7552-7.
8. Diaz de Leon A, Cronkhite JT, Katzenstein AL, Godwin JD, Raghu G, Glazer CS, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. *PLoS ONE.* 2010;5(5):e10680.

9. Giri N, Ravichandran S, Wang Y, Gadalla SM, Alter BP, Fontana J, et al. Prognostic significance of pulmonary function tests in dyskeratosis congenita, a telomere biology disorder. *ERJ Open Res.* 2019;5(4).

10. Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J.* 2016;48(6):1710-20.

11. Armanios M. Telomerase and idiopathic pulmonary fibrosis. *Mutation research.* 2012;730(1-2):52-8.

12. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med.* 2013;188(6):733-48.

13. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2018;198(5):e44-e68.

14. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2020;202(3):e36-e69.

15. Wang P, and Xu Z. Pulmonary fibrosis in dyskeratosis congenita: a case report with a PRISMA-compliant systematic review. *BMC Pulm Med.* 2021;21(1):279.

16. Borie R, Le Guen P, Ghanem M, Taille C, Dupin C, Dieude P, et al. The genetics of interstitial lung diseases. *European respiratory review : an official journal of the European Respiratory Society.* 2019;28(153).

17. Borie R, Tabeze L, Thabut G, Nunes H, Cottin V, Marchand-Adam S, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. *Eur Respir J.* 2016;48(6):1721-31.

18. Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, et al. An Exome Sequencing Study to Assess the Role of Rare Genetic Variation in Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2017;196(1):82-93.

19. Dressen A, Abbas AR, Cabanski C, Reeder J, Ramalingam TR, Neighbors M, et al. Analysis of protein-altering variants in telomerase genes and their association with MUC5B common variant status in patients with idiopathic pulmonary fibrosis: a candidate gene sequencing study. *The lancet Respiratory medicine.* 2018;6(8):603-4.

20. Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. *Nat Genet.* 2015;47(5):512-7.

21. Cogan JD, Kropski JA, Zhao M, Mitchell DB, Rives L, Markin C, et al. Rare Variants in RTEL1 are Associated with Familial Interstitial Pneumonia. *Am J Respir Crit Care Med.* 2015;191(6):646-55.

22. Kannengiesser C, Borie R, Menard C, Reocreux M, Nitschke P, Gazal S, et al. Heterozygous RTEL1 mutations are associated with familial pulmonary fibrosis. *Eur Respir J.* 2015;46(2):474-85.

23. Stanley SE, Gable DL, Wagner CL, Carlile TM, Hanumanthu VS, Podlevsky JD, et al. Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema. *Sci Transl Med.* 2016;8(351):351ra107.

24. Kropski JA, Mitchell DB, Markin C, Polosukhin VV, Choi L, Johnson JE, et al. A novel dyskerin (DKC1) mutation is associated with familial interstitial pneumonia. *Chest.* 2014;146(1):e1-7.

25. Hisata S, Sakaguchi H, Kanegane H, Hidaka T, Ichinose M, Kojima S, et al. A Novel Missense Mutation of DKC1 In Dyskeratosis Congenita With Pulmonary Fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2013;30(3):221-5.

26. Benyelles M, O'Donohue MF, Kermasson L, Lainey E, Borie R, Lagresle-Peyrou C, et al. NHP2 deficiency impairs rRNA biogenesis and causes pulmonary fibrosis and Hoyeraal-Hreidarsson syndrome. *Hum Mol Genet.* 2020;29(6):907-22.

27. Alder JK, Stanley SE, Wagner CL, Hamilton M, Hanumanthu VS, and Armanios M. Exome sequencing identifies mutant TINF2 in a family with pulmonary fibrosis. *Chest.* 2015;147(5):1361-8.

28. Fukuhara A, Tanino Y, Ishii T, Inokoshi Y, Saito K, Fukuhara N, et al. Pulmonary fibrosis in dyskeratosis congenita with TINF2 gene mutation. *Eur Respir J.* 2013;42(6):1757-9.

29. Hoffman TW, van der Vis JJ, van Oosterhout MF, van Es HW, van Kessel DA, Grutters JC, et al. TINF2 Gene Mutation in a Patient with Pulmonary Fibrosis. *Case Rep Pulmonol.* 2016;2016:1310862.

30. Kannengiesser C, Manali ED, Revy P, Callebaut I, Ba I, Borgel A, et al. First heterozygous NOP10 mutation in familial pulmonary fibrosis. *Eur Respir J.* 2020;55(6).

31. Walne AJ, Vulliamy T, Marrone A, Beswick R, Kirwan M, Masunari Y, et al. Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. *Hum Mol Genet.* 2007.

32. Gable DL, Gaysinskaya V, Atik CC, Talbot CC, Jr., Kang B, Stanley SE, et al. ZCCHC8, the nuclear exosome targeting component, is mutated in familial

pulmonary fibrosis and is required for telomerase RNA maturation. *Genes Dev.* 2019;33(19-20):1381-96.

33. Armanios M, and Blackburn EH. The telomere syndromes. *Nat Rev Genet.* 2012;13(10):693-704.

34. Savage SA, Niewisch MR. Dyskeratosis Congenita and Related Telomere Biology Disorders. 2009 Nov 12 [updated 2022 Mar 31]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Mirzaa GM, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

35. Newton CA, Batra K, Torrealba J, Meyer K, Raghu G, and Garcia CK. Pleuroparenchymal fibroelastosis associated with telomerase reverse transcriptase mutations. *Eur Respir J.* 2017;49(5).

36. Cronkhite JT, Xing C, Raghu G, Chin KM, Torres F, Rosenblatt RL, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2008;178(7):729-37.

37. Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. *Proc Natl Acad Sci U S A.* 2008;105(35):13051-6.

38. Planas-Cerezales L, Arias-Salgado EG, Buendia-Roldan I, Montes-Worboys A, Lopez CE, Vicens-Zygmunt V, et al. Predictive factors and prognostic effect of telomere shortening in pulmonary fibrosis. *Respirology.* 2019;24(2):146-53.

39. Snetselaar R, van Batenburg AA, van Oosterhout MFM, Kazemier KM, Roothaan SM, Peeters T, et al. Short telomere length in IPF lung associates with fibrotic lesions and predicts survival. *PLoS One.* 2017;12(12):e0189467.

40. Dai J, Cai H, Li H, Zhuang Y, Min H, Wen Y, et al. Association between telomere length and survival in patients with idiopathic pulmonary fibrosis. *Respirology.* 2015;20(6):947-52.

41. Popescu I, Mannem H, Winters SA, Hoji A, Silveira F, McNally E, et al. Impaired Cytomegalovirus Immunity in Idiopathic Pulmonary Fibrosis Lung Transplant Recipients with Short Telomeres. *Am J Respir Crit Care Med.* 2019;199(3):362-76.

42. Stuart BD, Lee JS, Kozlitina J, Noth I, Devine MS, Glazer CS, et al. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. *The lancet Respiratory medicine.* 2014;2(7):557-65.

43. Newton CA, Zhang D, Oldham JM, Kozlitina J, Ma SF, Martinez FJ, et al. Telomere Length and Use of Immunosuppressive Medications in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2019;200(3):336-47.

44. Ley B, Torgerson DG, Oldham JM, Adegunsoye A, Liu S, Li J, et al. Rare Protein-Altering Telomere-related Gene Variants in Patients with Chronic Hypersensitivity Pneumonitis. *Am J Respir Crit Care Med.* 2019;200(9):1154-63.

45. Ley B, Liu S, Elicker BM, Henry TS, Vittinghoff E, Golden JA, et al. Telomere length in patients with unclassifiable interstitial lung disease: a cohort study. *Eur Respir J.* 2020;56(2).

46. Newton CA, Oldham JM, Ley B, Anand V, Adegunsoye A, Liu G, et al. Telomere length and genetic variant associations with interstitial lung disease progression and survival. *Eur Respir J.* 2019;53(4).

47. Snetselaar R, van Moorsel CH, Kazemier KM, van der Vis JJ, Zanen P, van Oosterhout MF, et al. Telomere length in interstitial lung diseases. *Chest.* 2015;148(4):1011-8.

48. Duckworth A, Gibbons MA, Allen RJ, Almond H, Beaumont RN, Wood AR, et al. Evidence that Telomere Length is Causal for Idiopathic Pulmonary Fibrosis but not Chronic Obstructive Pulmonary Disease: A Mendelian Randomisation Study *medRxiv.* 2020.

49. Li C, Stoma S, Lotta LA, Warner S, Albrecht E, Allione A, et al. Genome-wide Association Analysis in Humans Links Nucleotide Metabolism to Leukocyte Telomere Length. *Am J Hum Genet.* 2020;106(3):389-404.

50. Codd V, Wang Q, Allara E, Musicha C, Kaptoge S, Stoma S, et al. Polygenic basis and biomedical consequences of telomere length variation. *Nat Genet.* 2021;53(10):1425-33.

51. Astuti Y, Wardhana A, Watkins J, Wulaningsih W, and Network PR. Cigarette smoking and telomere length: A systematic review of 84 studies and meta-analysis. *Environ Res.* 2017;158:480-9.

52. Xing C, and Garcia CK. Epigenetic inheritance of telomere length obscures identification of causative PARN locus. *J Med Genet.* 2016;53(5):356-8.

53. Ley B, Newton CA, Arnould I, Elicker BM, Henry TS, Vittinghoff E, et al. The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study. *The lancet Respiratory medicine.* 2017;5(8):639-47.

54. Adegunsoye A, Morisset J, Newton CA, Oldham JM, Vittinghoff E, Linderholm AL, et al. Leukocyte telomere length and mycophenolate therapy in chronic hypersensitivity pneumonitis. *Eur Respir J.* 2021;57(3).

55. Townsley DM, Dumitriu B, Liu D, Biancotto A, Weinstein B, Chen C, et al. Danazol Treatment for Telomere Diseases. *N Engl J Med.* 2016;374(20):1922-31.

56. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370(22):2083-92.

57. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370(22):2071-82.

58. Petnak T, Lertjitbanjong P, Thongprayoon C, and Moua T. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. *Chest.* 2021;160(5):1751-63.

59. Dempsey TM, Sangaralingham LR, Yao X, Sanghavi D, Shah ND, and Limper AH. Clinical Effectiveness of Antifibrotic Medications for Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2019;200(2):168-74.

60. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med.* 2019;381(18):1718-27.

61. Justet A, Klay D, Porcher R, Cottin V, Ahmad K, Molina Molina M, et al. Safety and efficacy of pirfenidone and nintedanib in patients with Idiopathic Pulmonary Fibrosis and carrying a telomere related gene mutation. *Eur Respir J.* 2020.

62. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401 e1.

63. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *The lancet Respiratory medicine.* 2020;8(7):726-37.

64. Diaz de Leon A, Cronkhite JT, Yilmaz C, Brewington C, Wang R, Xing C, et al. Subclinical lung disease, macrocytosis, and premature graying in kindreds with telomerase (TERT) mutations. *Chest.* 2011;140(3):753-63.

65. Rosas IO, Ren P, Avila NA, Chow CK, Franks TJ, Travis WD, et al. Early interstitial lung disease in familial pulmonary fibrosis. *Am J Respir Crit Care Med.* 2007;176(7):698-705.

66. Kropski JA, Pritchett JM, Zoz DF, Crossno PF, Markin C, Garnett ET, et al. Extensive phenotyping of individuals at risk for familial interstitial pneumonia reveals clues to the pathogenesis of interstitial lung disease. *Am J Respir Crit Care Med.* 2015;191(4):417-26.

67. Hunninghake GM, Quesada-Arias LD, Carmichael NE, Martinez Manzano JM, Poli De Frias S, Baumgartner MA, et al. Interstitial Lung Disease in Relatives of

Patients with Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2020;201(10):1240-8.

68. Kropski JA, Young LR, Cogan JD, Mitchell DB, Lancaster LH, Worrell JA, et al. Genetic Evaluation and Testing of Patients and Families with Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2017;195(11):1423-8.

69. Dawod YT, Cook NE, Graham WB, Madhani-Lovely F, and Thao C. Smoking-associated interstitial lung disease: update and review. *Expert Rev Respir Med.* 2020;14(8):825-34.

70. Stanley SE, Rao AD, Gable DL, McGrath-Morrow S, and Armanios M. Radiation Sensitivity and Radiation Necrosis in the Short Telomere Syndromes. *Int J Radiat Oncol Biol Phys.* 2015;93(5):1115-7.

71. Camus P. Drug history and remote exposure to drugs. A cause of lung disease? *Eur Respir J.* 2000;16(3):381-4.

72. Hamilton D, Sr., Nandkeolyar S, Lan H, Desai P, Evans J, Hauschild C, et al. Amiodarone: A Comprehensive Guide for Clinicians. *Am J Cardiovasc Drugs.* 2020;20(6):549-58.

73. Mir E, Malik JA, Lone SA, Mohi-Ud-Din R, and Khalil M. Spontaneous resolution of nitrofurantoin-induced chronic pulmonary toxicity presenting with respiratory failure. *Adv Respir Med.* 2017;85(6):333-8.

74. Hubbard R, Venn A, and Britton J. Exposure to antidepressants and the risk of cryptogenic fibrosing alveolitis: a case-control study. *Eur Respir J.* 2000;16(3):409-13.

75. Iwata T, Yoshino I, Yoshida S, Ikeda N, Tsuboi M, Asato Y, et al. A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: West Japan Oncology Group 6711 L (PEOPLE Study). *Respir Res.* 2016;17(1):90.

76. Salisbury ML, Hewlett JC, Ding G, Markin CR, Douglas K, Mason W, et al. Development and Progression of Radiologic Abnormalities in Individuals at Risk for Familial Interstitial Lung Disease. *Am J Respir Crit Care Med.* 2020;201(10):1230-9.