



# European Respiratory Society statement on familial pulmonary fibrosis

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**Genetic predisposition to interstitial lung diseases (ILDs) is well known. The statement aims to assist health professionals with the care of monogenic pulmonary fibrosis and familial ILD patients and their relatives.** <https://bit.ly/3h9hvQ6>

**Cite this article as:** Borie R, Kannengiesser C, Antoniou K, *et al.* European Respiratory Society statement on familial pulmonary fibrosis. *Eur Respir J* 2023; 61: 2201383 [DOI: 10.1183/13993003.01383-2022].

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Received: 9 July 2022  
Accepted: 26 Oct 2022

## Abstract

Genetic predisposition to pulmonary fibrosis has been confirmed by the discovery of several gene mutations that cause pulmonary fibrosis. Although genetic sequencing of familial pulmonary fibrosis (FPF) cases is embedded in routine clinical practice in several countries, many centres have yet to incorporate genetic sequencing within interstitial lung disease (ILD) services and proper international consensus has not yet been established. An international and multidisciplinary expert Task Force (pulmonologists, geneticists, paediatrician, pathologist, genetic counsellor, patient representative and librarian) reviewed the literature between 1945 and 2022, and reached consensus for all of the following questions: 1) Which patients may benefit from genetic sequencing and clinical counselling? 2) What is known of the natural history of FPF? 3) Which genes are usually tested? 4) What is the evidence for telomere length measurement? 5) What is the role of common genetic variants (polymorphisms) in the diagnostic workup? 6) What are the optimal treatment options for FPF? 7) Which family members are eligible for genetic sequencing? 8) Which clinical screening and follow-up parameters may be considered in family members? Through a robust review of the literature, the Task Force offers a statement on genetic sequencing, clinical management and screening of patients with FPF and their relatives. This proposal may serve as a basis for a prospective evaluation and future international recommendations.

## Introduction

Genetic predisposition to pulmonary fibrosis is suggested by a 10-fold increase in disease prevalence in families of patients with a diagnosis of idiopathic pulmonary fibrosis (IPF) [1–3]. Initial studies of familial

clustering of interstitial lung disease (ILD) led to the discovery of mutations in genes implicated in telomere homeostasis (telomere-related genes (TRGs)) and surfactant homeostasis (surfactant-related genes (SRGs)) (table 1 and supplementary table S1) [3, 4]. These studies showed that the disease phenotype in families was not limited to IPF, but included a spectrum of potentially progressive pulmonary fibrosis, including non-specific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis and rheumatoid arthritis-associated ILD [5–10]. Furthermore, ILD morphological patterns are often indeterminate or contain overlapping features and do not necessarily fit within established diagnostic ILD categories [11]. On the other hand, the presence of mutations in TRGs or SRGs is associated with clinical characteristics, such as age, gender, pulmonary phenotype, extrapulmonary disease and survival. The presence of clear familial inheritance, associated with a single gene variant, such as TRGs or SRGs, segregating with the presence of ILD, strongly supports the conclusion that ILD in these cases is a monogenic (single gene) disorder.

Due to the wealth of scientific reports and the public's increased awareness of heritable diseases, genetic sequencing in patients with pulmonary fibrosis is finding a place in the clinical routine, with a potentially profound impact on patient care. However, the 2018 and 2022 international guidelines for IPF do not address this topic [12, 13]. French national practical guidelines for IPF in 2017 were the first to suggest genetic sequencing in patients with familial pulmonary fibrosis (FPF) [14]. In other countries, individual physicians and ILD clinics implement genetic sequencing in daily practice or offer genetic sequencing in a research setting [15]. The current lack of a consensus statement or recommendations has resulted in a multitude of opinions and approaches, without proper international consensus on genetic sequencing in FPF.

Numerous monogenic disorders can be associated with ILD. However, the present statement is limited to two groups of genes, TRGs and SRGs, as the most common cause of FPF. Patients with cystic lung disease, Hermansky–Pudlak syndrome, pulmonary alveolar proteinosis, lysinuric protein intolerance, lysosomal storage disorders, interferon-related gene mutations and pulmonary alveolar microlithiasis present with rare but specific syndromes and require dedicated separate statements (supplementary table S1).

The target audience for this statement includes adult and paediatric pulmonologists, genetic counsellors and clinical geneticists caring for patients with ILD. By reviewing the existing literature on genetic findings in ILD, we aim to outline the diagnostic, prognostic and therapeutic value of genetic sequencing, and provide a statement on the management of FPF.

## Methods

This Task Force is an international and multidisciplinary effort supported by the European Respiratory Society (ERS). Nine members are pulmonologists, two are geneticists, one paediatrician, one pathologist,

### BOX 1 Glossary of terms [1]

<b>Anticipation</b>	Apparent earlier age of onset and increased severity of a disease in successive generations.
<b>Complex disease</b>	A disorder in which the cause is considered to be a combination of genetic effects and environmental influences.
<b>Monogenic disorder</b>	Disorder caused by one or more mutations in a single gene, e.g. cystic fibrosis. Such disorders are also sometimes referred to as Mendelian diseases.
<b>Mutation</b>	A mutation is a change in the DNA sequence. Germline mutations (that occur in eggs and sperm) can be passed on to offspring, while somatic mutations (that occur in body cells) are not passed on.
<b>Penetrance</b>	The frequency (in percent) with which a dominant or homozygous recessive gene or gene combination manifests itself in the phenotype of the carriers.
<b>Pathogenicity (class)</b>	Each variant found through genetic sequencing is currently classified according to several criteria and reported as benign, likely benign, of unknown significance (“variant of unknown significance”), likely pathogenic or pathogenic.
<b>Phenocopy</b>	A phenotypic condition that resembles the trait expressed by a certain genotype, in the absence of carriage of the genotype.
<b>Polymorphism</b>	A chromosome or DNA variant that is observed in natural populations. A gene locus is defined as polymorphic if the minor allele has a frequency of 0.01 (1%) or more. The most common type of polymorphism involves variant at a single nucleotide (also called a single nucleotide polymorphism).
<b>Predisposition</b>	A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder. When such a variant (or mutation) is inherited, development of symptoms is more likely, but not certain.

TABLE 1 Telomere- and surfactant-related genes associated with interstitial lung disease (ILD)

Gene	Mode of inheritance	Age of presentation of pulmonary symptoms	Non-ILD pulmonary and extrapulmonary phenotype	Frequency	Most frequent radiological patterns	Implication for management/therapy for pulmonary disease <sup>#</sup>	References
<b>Telomere-related disease</b>							
<i>TERT</i>	AD <sup>n</sup>	>30 years in cases with ILD as single manifestation of short telomere syndrome	Mucocutaneous features: buccal leukoplakia, abnormal pigmentation, nail dystrophy, premature hair greying (canitia); aplastic anaemia, myelodysplastic syndrome, leukaemia; liver disease; osteoporosis	15–22%	UIP, NSIP, HP, PPFE or an indeterminate pattern	Antifibrotic drugs according to guidelines/market agreement. Lung transplantation may be considered with specific concern about haematological disease and cytomegalovirus infection.	[3, 8, 10, 58, 134–136]
<i>TERC</i>	AD <sup>n</sup>			2–5%			[3, 10, 21, 30, 88, 137, 138]
<i>RTEL1</i>	AD <sup>n</sup>			5–10%			[10, 58, 88, 139, 140]
<i>PARN</i>	AD <sup>n</sup>			1–5%			[141, 142]
<i>DKC1</i>	X			Rare			[143–145]
<i>TINF2</i>	AD			Rare			[146]
<i>NOP10</i>	AD			Ultra-rare			[147]
<i>NHP2</i>	AD			Ultra-rare			[148]
<i>ACD</i>	AD			Ultra-rare			[149]
<i>NAF1</i>	AD			Ultra-rare			[150]
<i>ZCCHC8</i>	AD			Ultra-rare			[151]
<i>RPA</i>	AD			Ultra-rare			[152]
<i>POT1</i>	AD			Ultra-rare			
<b>Surfactant-related disease</b>							
<i>SFTPA1</i>	AD	All ages, rare in children	Lung cancer	<5%	Unclassifiable pulmonary fibrosis: predominant diffuse ground-glass opacities, septal thickening and bilateral cysts of variable size, with a preferential distribution in the upper lobes and in subpleural areas	Optimal treatment in childhood ILD may differ from adult ILD. No cohort evaluation of drug effects in adults. Steroids? Hydroxychloroquine? Macrolides? Antifibrotic drugs? Lung transplantation may be considered.	[11, 58, 80]
<i>SFTPA2</i>	AD	All ages, rare in children	Lung cancer	<5%			[11, 79, 81]
<i>SFTPC</i>	AD	All ages, more frequent in children		<5%			[73, 153]
<i>NKX2.1</i>	AD	All ages, mainly in children	Lung–brain–thyroid syndrome: chorea and hypothyroidism	Rare			[76, 154]
<i>ABCA3</i>	AR	All ages, mainly in children		Rare			[59, 61, 74, 75]

AD: autosomal dominant; AR: autosomal recessive; X: X-linked; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonitis; HP: hypersensitivity pneumonitis; PPFE: pleuro-parenchymal fibroelastosis. <sup>#</sup>: see Narrative Question 6 for background information; <sup>n</sup>: AR in severe cases.

**TABLE 2** Narrative questions addressed by the Task Force

1	Which patients may benefit from genetic sequencing and clinical counselling?
2	What is known on the natural history of FPF (with or without evidence of genetic mutation)?
3	Which genes are usually tested?
4	What is the evidence for telomere length measurement?
5	What is the role of common genetic variants (polymorphisms) in the diagnostic workup?
6	What are the optimal treatment options for FPF?
7	Which family members are eligible for genetic sequencing?
8	Which clinical screening and follow-up parameters may be considered in family members?

FPF: familial pulmonary fibrosis.

one genetic counsellor, one patient representative and one librarian (Nienke van der Werf). The Chairs (R. Borie and C. van Moorsel) selected the other Task Force members based on their expertise in ILD and in genetics. Conflicts of interest of all Task Force members were declared and managed according to ERS policy (for full disclosure, see supplementary material). An early meeting of the Chairs took place in January 2020. At this meeting, suggestions were made on the creation of three working groups within the Task Force and the specific narrative (or non-PICO (Population, Intervention, Comparator, Outcomes) [16]) questions to be addressed within the groups (table 2). Subsequently, the literature search and review of the relevant studies between 1945 and 2020 was performed within the working groups using MEDLINE and Embase databases (supplementary figure). The search was restricted to articles available in English, reporting on human studies. A secondary search reviewed the reference lists of relevant articles. From 2020 onwards, Task Force members were asked to provide additional key literature they were aware of. At the second Task Force meeting (October 2020), the results of the individual reviews were presented and discussed by the whole Task Force. Based on these discussions, each group assembled the most important statements (“claims”) addressing a specific area, and the statements were evaluated by all Task Force members for correctness and importance. In the absence of evident consensus, two web-based surveys dedicated to specific questions were offered, including 1) definition of FPF and 2) screening of asymptomatic relatives. The definition with the majority of the votes was retained (supplementary tables S2 and S3). Although Task Force members had initially favoured the term “familial ILD”, as not all familial ILD is fibrotic at presentation, a subsequent vote revealed a preference for the term “familial pulmonary fibrosis (FPF)”, as the most commonly used in the literature, to avoid confusion.

Based on this selection, the first draft of the manuscript was written. This draft was discussed at the third and fourth Task Force meetings (January and May 2022); the main points of the statement were finalised together and studies published after the first Task Force meeting were included. The final document combines an evidence-based approach, relying on the reviewed publications, with the clinical expertise of the Task Force members and can be compared with the recent American Pulmonary Fibrosis Foundation Genetic Testing Work Group proposal [17].

## Results

### *Narrative Question 1: Which patients may benefit from genetic sequencing and clinical counselling?*

#### *Statement*

*In the following clinical contexts, the Task Force members usually offer genetic sequencing:*

- Any patient with fibrotic ILD and one or more first- or second-degree family members with fibrotic ILD
- Any patient with a relative carrying a pathogenic/likely pathogenic variant known to cause ILD
- Any patient with suspected short telomere syndrome (table 3) [18]
- Any patient with an idiopathic fibrosing ILD before the age of 50 years

**TABLE 3** Criteria used by Task Force members to suspect short telomere syndrome [18]

Pulmonary fibrosis and one or more of the following in the patients and/or family members:
• Pulmonary fibrosis
• Haematological abnormalities: macrocytosis, neutropenia, lymphopenia, thrombocytopenia, myelodysplasia, acute leukaemia and/or
• Hepatic abnormalities: cryptogenic elevated liver enzymes, portal hypertension, hepato-pulmonary syndrome, liver cirrhosis and/or
• Early hair greying (significant greying before age 30 years)
• Recognised telomere disease such as dyskeratosis congenita

### Summary of evidence

Although there is no consensus definition, in the research setting FPF has been usually defined as a case of fibrotic ILD with one or more relatives with a fibrotic form of ILD [19–22]. In this statement we define FPF as: *as any fibrotic ILD in at least two blood relative first- or second-degree family members*. The Task Force also considered the term “genetic pulmonary fibrosis” particularly for patients carrying a pathogenic variant known to cause ILD in the absence of any family relative with pulmonary fibrosis. Although the term holds promise for the future, it is currently not often used and not yet well defined. For now, the Task Force chose the term “FPF”, which has the advantage of helping pulmonologists recognise the phenotype and understand its impact on family members. We defined it to include sporadic cases of ILD with identified variants or suspicion of genetic variants. The presence of familial disease increases the likelihood of a progressive pulmonary fibrosis (occurring despite management appropriate for the individual entity). The impact on disease evolution of having relatives with non-fibrotic forms of ILD, such as sarcoidosis or non-fibrotic hypersensitivity pneumonitis, has not been studied, but observational case series of familial sarcoidosis and non-fibrotic hypersensitivity pneumonitis do not suggest a predilection towards progressive fibrotic ILD [23–25]. The Task Force members usually restrict genetic sequencing to fibrotic ILD.

Adults with FPF are essentially indistinguishable from sporadic patients in terms of clinical presentation, radiographic findings and histopathology [2, 26–28]. However, they are usually younger and disease evolves towards progressive fibrosing ILD with limited survival [2, 26–28]. A common genetic background in idiopathic and non-idiopathic ILD has been reported [5–7, 29]. Indeed all forms of fibrotic ILD in young adults, either idiopathic or non-idiopathic, are indicative of a possible TRG or SRG mutation [6, 8, 10, 11, 30].

In patients with TRG mutations and pulmonary fibrosis, anaemia is present in 17–27%, macrocytosis in 24–41% and thrombocytopenia in 8–54% [8, 10, 31]. *DKC1*, *TINF2* and *TERC* mutation carriers seem more prone to develop haematological involvement than *TERT*, *PARN* or *RTEL1* mutation carriers [10], but further studies are required to assess whether this could be related to an age difference between the cohorts. Established myelodysplasia and acute leukaemia are probably even more suggestive of TRG mutation carrier status in young patients, though rarer [8, 32, 33]. Indeed, in a patient with ILD, unexplained macrocytosis, thrombocytopenia, myelodysplasia and acute leukaemia are indicative signs of a possible TRG mutation (table 3).

The hepatic phenotype associated with TRG mutations is heterogeneous, ranging from asymptomatic increased liver enzymes reported in 5–27% to cryptogenic or secondary cirrhosis [8, 10, 34]. *GORGY et al.* [35] highlighted the high frequency of hepato-pulmonary syndrome associated with TRG mutations. Indeed the presence of cryptogenic elevated liver enzymes, hepato-pulmonary syndrome or cirrhosis (idiopathic or not) is indicative of a possible TRG mutation.

TRG mutations were initially reported in dyskeratosis congenita, a rare multisystemic disorder including a specific cutaneous triad (table 1) and often bone marrow failure. Most of the TRG carrier ILD patients do not present the cutaneous triad, but 15–40% of mutation carriers present early hair greying (before the age of 30 years) [8, 36]. Although there is no consensus definition of the age and percentage of early hair greying at which to consider TRG mutations, significant hair greying at the age of 30 years is indicative of a possible TRG mutation.

Short telomere syndrome may also include manifestations such as primary immunodeficiency, retinal or neurological disorders [37]. The need for genetic sequencing should be discussed in multidisciplinary team meetings for other rare manifestations suspected to be related to TRG mutation [18, 38]. Given the relatively young age at which most patients with TRG mutations are diagnosed with ILD (mean age 58 years), lung transplantation is often discussed and offered to these patients [8, 10, 30, 39, 40] as evidenced by the 11.8% and 24.2% reported prevalence of rare TRG variants in two cohorts of 262 and 149 IPF patients referred for lung transplantation (table 4) [41, 42]. More research is needed to determine whether all fibrotic ILD patients should undergo telomere length measurement and genetic sequencing before lung transplantation. FPF patients are potential candidates for lung transplantation, but may require a tailored immunosuppressive regimen in case of an underlying short telomere syndrome (see Narrative Question 6).

Informing patients on the impact of familial disease and genetic sequencing has become an important part of care in familial disease, and enables shared and informed decision making. The Task Force members usually offer genetic counselling prior to genetic sequencing. Genetic counselling is the process of helping

TABLE 4 Main results for the prevalence of telomere-related gene (TRG) variants in interstitial lung disease (ILD)

First author [ref.]	Year	Patients (n)	Phenotype of population included	Genes analysed	Technology	Main results
ARMANIOS [134]	2007	73	FPF	<i>TERT, TERC</i>	Direct sequencing	6 carriers (15%) of <i>TERT</i> or <i>TERC</i> mutation
TSAKIRI [135]	2007	90	FPF (n=46) and sporadic ILD (n=44)	<i>TERT, TERC</i>	Direct sequencing	7 <i>TERT</i> (7.7%) and 1 <i>TERC</i> (1.1%) mutations; 7 in FPF (15.2%) and 1 sporadic ILD (2.2%)
PARRY [33]	2011	10	FPF or familial bone marrow failure and pulmonary fibrosis	<i>TERT, TERC</i>	Direct sequencing	10 carriers of <i>TERT</i> (7) or <i>TERC</i> (3) mutation
COGAN [137]	2015	188	FPF	<i>RTEL1</i>	WES (n=25) and direct sequencing (n=163)	9 carriers (4.7%) of <i>RTEL1</i> mutation
KANNENGISSER [138] <sup>#</sup>	2015	35	FPF	<i>RTEL1</i>	WES	4 carriers of <i>RTEL1</i> mutation
STANLEY [155]	2015	292	COPD	<i>TERT, TERC</i>	WES	3 <i>TERT</i> mutation
STUART [88]	2015	99	FPF	<i>PARN, RTEL1</i>	WES	6 <i>PARN</i> (6%) and 5 <i>RTEL1</i> (5%) mutations
BORIE [8]	2016	237	153 FPF and 84 telomere syndrome	<i>TERT, TERC</i>	Direct sequencing	40 carriers (16.8%) of <i>TERT</i> or <i>TERC</i> mutation; young age, macrocytosis and low platelet count associated with presence of mutation; heterogeneous ILD patterns
NEWTON [10]	2016	115	ILD and carriers of a TRG mutation	<i>TERT, TERC, RTEL1, PARN</i>	Direct sequencing	Heterogeneous ILD, including secondary ILD, discordant diagnoses among families; patients with <i>TERC</i> younger (51 years) than patients with <i>PARN</i> mutation (64 years) and present more haematological diseases
JUGE [6]	2017	101	RA-ILD	<i>TERT, TERC, PARN, RTEL1, SFTPC</i>	WES	12 carriers (11.8%) of rare variants in <i>TERT, RTEL1, PARN</i> or <i>SFTPC</i>
PETROVSKI [42]	2017	262	Transplanted pulmonary fibrosis (81.3% IPF); sporadic (87%)	<i>TERT, RTEL1, PARN</i>	WES	31 rare variants of TRG (11.8%): <i>TERT</i> (5%) <i>RTEL1</i> (2.3%) and <i>PARN</i> (2.7%)
BORIE [30] <sup>#</sup>	2018	256	151 FPF or telomere syndrome and 101 RA-ILD without <i>TERT</i> and <i>TERC</i> mutations	<i>RTEL1</i>	WES	17 carriers of <i>RTEL1</i> mutation; heterogeneous ILD; less haematological disease compared to <i>TERT</i> or <i>TERC</i> mutation
DRESSEN [107]	2018	1739	3 IPF clinical trials and 2 ILD cohorts	<i>TERT, TERC, PARN, RTEL1</i>	WES	149 carriers (8.5%) of a rare variant of <i>TERT, PARN, TERC</i> or <i>RTEL1</i> ; earlier mean age of disease (65.1 versus 67.1 years) compared to non-carriers
POPESCU [37]	2018	42	Lung transplant IPF	TRG panel	Direct sequencing	4 pathogenic TRG mutations among 15 rare TRG variants: <i>TERT</i> (1), <i>RTEL1</i> (2) and <i>PARN</i> (1)
LEY [156]	2019	353	Hypersensitivity pneumonitis	<i>TERT, TERC, DKC1, PARN, TINF2</i>	Direct sequencing	33 carriers (9.3%) of a rare TRG variant; patients with a variant from 1 of 2 cohorts had more frequent family history of ILD TRG (31.2% versus 5.5%)
VAN BATENBURG [157]	2020	32	IPF with low lung biopsy telomere length	<i>TERT, RTEL1, TINF2, PARN, DKC1, TERC, NAF1</i>	WES	2 carriers (6%) of <i>RTEL1</i> mutation and 1 carrier (3%) of <i>PARN</i> mutation; lung biopsy telomere length in the range of lung biopsy telomere length of pulmonary fibrosis patients carrying a <i>TERT</i> mutation

Continued

TABLE 4 Continued

First author [ref.]	Year	Patients (n)	Phenotype of population included	Genes analysed	Technology	Main results
ALDER [41]	2021	431	IPF	<i>TERT</i> , <i>TERC</i> , <i>RTEL1</i> , <i>PARN</i> , <i>TINF2</i> , <i>NAF1</i> , <i>DKC1</i>	WGS	36/149 carriers of rare TRG variants in lung transplanted group (24.2%) versus 33/282 in non-transplanted group (11.7%); 20 pathogenic variants in lung transplanted group (13.4%) versus 11 in non-transplanted group (3.9%)
VAN DER VIS [93] <sup>¶</sup>	2021	99	FPF probands	<i>ACD</i> , <i>DKC1</i> , <i>PARN</i> , <i>RTEL1</i> , <i>TERC</i> , <i>TERT</i> , <i>TINF2</i> , <i>ZCCHC8</i>	WES	8 <i>RTEL1</i> (8%), 1 <i>TERC</i> (1%), 7 <i>TERT</i> (7%) and 2 <i>ZCCHC8</i> (2%)
VAN MOORSEL [58] <sup>¶</sup>	2021	221	FPF probands	TRG panel	WES	35.8% TRG mutation: 21.8% <i>TERT</i> , 2.7% <i>TERC</i> , 6.3% <i>RTEL1</i> , 3.2% <i>PARN</i> , 0.5% <i>TINF2</i> and 1.4% <i>ACD</i>
PLANAS-CEREZALES [158]	2021	20	Progressive fibrotic ILDs undergoing lung transplant	TRG panel	WES	55% TRG mutation: 25% <i>RTEL1</i> , 15% <i>TERT</i> , 10% <i>DKC1</i> and 5% <i>PARN</i>
MANALI [159]	2022	150	FPF, telomere syndrome and young age	TRG panel	Direct sequencing or WES	19 carriers of a pathogenic TRG variant (8 <i>TERT</i> , 5 <i>TERC</i> , 2 <i>RTEL1</i> , 2 <i>PARN</i> , 1 <i>NOP10</i> and 1 <i>NHP2</i> )

FPF: familial pulmonary fibrosis; RA-ILD: rheumatoid arthritis ILD; IPF: idiopathic pulmonary fibrosis; WES: whole-exome sequencing; WGS: whole-genome sequencing. #: patients from KANNENGIESSER *et al.* [138] are included in BORIE *et al.* [30]; ¶: part of patients from VAN DER VIS *et al.* [93] are included in VAN MOORSEL *et al.* [58].

people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. There is wide international variation in laws, health systems and cultures regarding genetic counselling [43]. In some countries trained counsellors are assigned to the task, while in other countries it is the task of the treating physician. Prior to this statement, the Task Force group performed a survey of patients, relatives and pulmonologists about experiences and needs on genetic sequencing in ILD to evaluate the current situation and identify future strategies. In the majority of cases, pulmonologists take care of patient's and relative's information on genetic sequencing and communication of the results. Patients, relatives and pulmonologists agreed on the need for more information and awareness [44].

### *Narrative Question 2: What is known on the natural history of FPF?*

#### *Statement*

*Familial or monogenic fibrotic ILD in adults is usually progressive and frequently associated with a poor prognosis, independently of disease entity.*

*In children, ILD is usually monogenic and disease course is dependent on the involved gene and mutations.*

#### *Summary of evidence*

The dominant phenotype in FPF is a chronic and progressive fibrotic ILD [2, 26–28, 45]. The clinical presentation of patients carrying causal mutations for adult and paediatric ILD is similar to sporadic ILD, with dyspnoea, cough, inspiratory crackles and, in a minority, clubbing.

Lung function decline in FPF has been compared with sporadic IPF, although the inevitably small numbers of FPF patients in each study make estimates imprecise. In a study of 46 FPF patients, 54.3% with definite usual interstitial pneumonia (UIP), 21.8% with possible UIP and 23.9% inconsistent with UIP, different rates of forced vital capacity (FVC) and diffusing lung capacity of the lung for carbon monoxide ( $D_{LCO}$ ) decline were seen depending on the different high-resolution computed tomography (HRCT) patterns [26]. One study suggested a trend towards a more rapid rate of FVC decline (9.9% per year) in 21 familial IPF index cases compared to 4.9% per year in 54 patients with sporadic IPF, although this difference did not reach statistical significance ( $p=0.12$ ) [28]. In 115 ILD patients carrying a TRG mutation, of whom 46% had IPF, a 300 mL decline per year in FVC was seen regardless of the gene involved and of the ILD entity [10].

Survival of FPF has been investigated in several studies, with close similarities between adult fibrotic FPF, regardless of the underlying entity, and sporadic IPF [46]. Overall survival was low in familial and gene-specific cohorts, although different methodologies were used, thereby hampering direct comparisons. Median survival from diagnosis in FPF is 2.4–7.3 years [9, 26, 27, 45].

A recent study including 1262 ILD patients found a significantly worse survival in familial IPF and non-IPF FPF compared with their sporadic counterparts (hazard ratio for death or transplant 1.8 for IPF patients (95% CI 1.37–2.37;  $p<0.001$ ) and 2.08 (95% CI 1.46–2.96;  $p<0.001$ ) for non-IPF patients), while no difference between non-IPF FPF and sporadic IPF was found [46]. Several other retrospective cohorts have not identified a difference between sporadic ILD and FPF [4, 27, 45].

A similarly low survival was reported in gene-specific ILD cohorts, including a median transplant-free survival of 2.9–4.2 years after diagnosis in patients with a TRG mutation [8, 10, 30, 36].

There are only a few studies comparing survival between different clinical entities of familial patients. NEWTON *et al.* [10] showed that within the group with telomere-related disease, the median survival of patients with a diagnosis of IPF (2.8 years) did not differ from that seen in the non-IPF patient group (3.1 years). Although these findings suggest that in FPF, survival is independent of the ILD entity, more confirmatory data are needed.

For ILD in childhood there are several older small case series on basket cohorts with pulmonary fibrosis [47–50]. 10–30% of the childhood ILDs have some evidence of fibrosis [51]. Cohorts of potentially fibrotic and molecularly defined ILDs range from stable to progressive fatal disease [52–56] in early and late adulthood [57, 58]. For *ABCA3*, a strong genotype–phenotype correlation exists [59, 60]. Biallelic null mutations lead to early death in infancy, whereas residual function mutations lead to chronic ILD, with a broad clinical spectrum including presentation in late adulthood [59–62].



### Narrative Question 3: Which genes are usually tested?

#### Statement

Telomere- and surfactant-related genes are usually analysed.

Targeted genetic sequencing of other genes can be discussed on a case-by-case basis, depending on the phenotype, and are beyond the scope of this paper.

#### Summary of evidence

Causative mutations in FPF include mutations in TRGs and SRGs (table 1).

#### Telomere-related genes

Telomeres are non-coding DNA sequences (TTAGGG) located at the end of chromosomes. They play a role in chromosome integrity maintenance. Telomeres shorten with each cell division, ultimately leading to cell senescence. Telomere shortening is associated with ageing. To counteract telomere shortening, the enzymatic ribonucleoprotein telomerase complex adds telomeric repeats. The telomerase complex refers to the group of proteins and RNA that catalyses the addition of nucleotide repeats to chromosome ends. There are numerous components to the telomere complex, including telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC), essential for normal telomere function and integrity. TRG mutations are often associated with shorter telomeres [63]. TRG mutations that cause short telomere syndromes have been associated with numerous disease manifestations, including progressive fibrotic ILD [63].

*TERT* and *TERC* mutations were the first TRGs identified in FPF [64]. Numerous studies of FPF cases and their kindred have identified mutations in various TRGs, and more than 12 TRGs are currently associated with FPF (table 1) [65]. Indeed, the presence of personal or familial extrapulmonary signs of short telomere syndrome has been shown to correlate with the rate of TRG mutations in sporadic or familial ILD (table 4).

A typical UIP pattern on chest CT was initially reported in up to 74% of ILD cases with TRG mutations, but was subsequently found in only 46–55% of cases [8, 10, 31]. Unusual features found in 13–20% of cases included upper-lung predominance of fibrosis, peribronchovascular predominance or a pleuro-parenchymal fibroelastosis (PPFE) pattern [8, 10, 31, 66]. Overall, 14–40% of cases show a combined pulmonary fibrosis and emphysema (CPFE) pattern [67]. The CT scan and histological patterns may vary and overlap, even within the same family, between UIP, NSIP, hypersensitivity pneumonitis, PPFE and unclassifiable fibrosis. Indeed all forms of fibrotic ILD can be associated with a TRG mutation [6, 8, 10, 30].

The extrapulmonary phenotype associated with TRG mutations is heterogeneous (table 3).

#### Surfactant-related genes

Surfactant is synthesised and secreted by type II alveolar epithelial cells. Surfactant is composed of 90% lipids and 10% proteins [68]. Surfactant-associated protein (SP)-A and SP-D are important for lung defence, while the hydrophobic proteins SP-B and SP-C are important for surfactant function. The corresponding genes are *SFTPA*, *SFTPB*, *SFTPC* and *SFTPD* [68]. Lamellar bodies contain SP-B and SP-C and the surfactant lipids. The latter are transported into the lamellar bodies by the ATP binding cassette family A, member 3 (*ABCA3*) transporter encoded by *ABCA3* [69]. Thyroid transcription factor 1 (TTF1), encoded by *NKX2.1*, is a transcription factor expressed in the lung, thyroid and central nervous system which regulates surfactant protein and *ABCA3* gene transcription [70, 71].

Homozygous or compound heterozygous *SFTPB* mutations have been identified as the cause of neonatal respiratory distress syndrome, but have not been identified in adult ILD [68]. *SFTPD* mutations have not been associated with lung disease.

Both paediatric and adult ILD have been linked to *SFTPC* mutations, but their frequency is usually <5% in FPF (table 5) [3, 58, 72, 73]. Transmission is autosomal dominant. *De novo* mutations are frequent and may explain as many as 50% of cases [56]. Although homozygous and compound heterozygous *ABCA3* mutations are usually associated with respiratory failure in the newborn [59], several adult ILD patient carriers of homozygous/compound heterozygous *ABCA3* mutations have been reported [61, 62, 74, 75].

Heterozygous *NKX2.1* mutations are classically associated with the triad of lung disease (neonatal respiratory distress syndrome, recurrent bronchitis or pneumonia and ILD), hypothyroidism and neurological anomalies (hypotonia, delayed development and chorea) [76, 77]. These mutations may be

TABLE 5 Main results for the prevalence of surfactant-related gene (SRG) variants in interstitial lung disease (ILD)

First author [ref.]	Year	Patients (n)	Phenotype of population included	Genes or SNP analysed	Technology	Major results
LAWSON [160]	2004	135	Adult sporadic ILD: 89 UIP and 46 NSIP	<i>SFTPC</i>	Direct sequencing	10 carriers of variants; only one pathogenic variant (0.7%)
CAMERON [130]	2005	116	chILD	<i>SFTPC</i> , I73T	Direct sequencing	7 <i>SFTPC</i> (6.1%) mutation
BULLARD [161]	2007	325	chILD	<i>SFTPC</i>	Direct sequencing	55 <i>SFTPC</i> (16.9%) mutation
GUILLOT [162]	2009	121	ILD	<i>SFTPC</i>	Direct sequencing	10 patients with I73T and 8 patients with other <i>SFTPC</i> mutations
WANG [79]	2009	59	FPF without <i>TERT</i> and <i>TERC</i> mutation	<i>SFTPA2</i>	Direct sequencing	2 probands; <i>SFTPA2</i> mutations associated with ILD and cancer
VAN MOORSEL [4]	2010	22	FPF	<i>SFTPC</i>	Direct sequencing	5 carriers of <i>SFTPC</i> mutation
TURCU [163]	2013	427	chILD	<i>SFTPC</i> , <i>ABCA3</i> , <i>SFTPB</i>	Direct sequencing	25 carriers (5.8%) of <i>SFTPB</i> , <i>SFTPC</i> or <i>ABCA3</i> mutation (0–10 years)
FLAMEIN [69]	2012	47	chILD	<i>ABCA3</i>	Direct sequencing	2 homozygous, 5 compound heterozygous and 3 heterozygous patients; 5 died shortly after birth and 5 developed chronic ILD
WAMBACH [59]	2014	632	chILD without <i>SFTPC</i> and <i>SFTPB</i> mutation	<i>ABCA3</i>	Direct sequencing	185 homozygous or compound heterozygous (29.2%); patients with null/null mutations died within the first months of life, those with non-null had variable presentation and outcome
KRÖNER [56]	2015	595	chILD	<i>SFTPC</i>	Direct sequencing	17 patients, follow-up median (range) age 3 (0.3–19) years; 1 patient healthy, 6 sick-better, 7 sick-same, 3 sick-worse
VAN MOORSEL [81]	2015	157	39 FPF and 118 idiopathic ILD	<i>SFTPA2</i>	Direct sequencing	3 probands from FPF (7.7%), 1 from sporadic (0.8%); mutations associated with ILD and lung cancer
KRÖNER [60]	2016	242	chILD	<i>ABCA3</i>	Direct sequencing	40 homozygous or compound heterozygous (16.5%); patients with null/null mutations died within the first months of life, those with non-null had variable presentation and outcome
NATHAN [80]	2016	12	FPF	<i>SFTPA1</i> , <i>SFTPA2</i>	Direct sequencing	1 family with ILD and cancer with <i>SFTPA1</i> mutation
LEGENDRE [11]	2020	14	FPF carriers of <i>SFTPA1</i> or <i>SFTPA2</i> mutation	<i>SFTPA1</i> , <i>SFTPA2</i>	Direct sequencing	28 patients (median (range) age 45 (0.56–65) years) with heterogeneous ILD and lung cancer
VAN MOORSEL [58] <sup>#</sup>	2021	221	FPF probands	SRG panel	WES	7.9% SRG mutation: 3.6% <i>SFTPC</i> , 2.3% <i>SFTPA2</i> , 1.4% <i>ABCA3</i> and 0.5% <i>HPS1</i> mutation

UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; FPF: familial pulmonary fibrosis; chILD: childhood ILD. #: patients from VAN MOORSEL *et al.* 2010 [4] and 2015 [81] are included in VAN MOORSEL *et al.* 2021 [58].

associated with ILD without hypothyroidism or neurological anomalies in up to a third of cases, including adult cases in which the most common HRCT pattern is atypical for UIP [76].

Biallelic *ABCA3* mutations and heterozygous *NKX2.1*, *SFTPA1*, *SFTPA2* and *SFTPC* mutations in adults may share similar clinical and radiological presentation. The most frequent radiological pattern is often described as unclassifiable pulmonary fibrosis and characterised by predominant diffuse ground-glass opacities and lung fibrosis [11, 58]. Septal thickening and bilateral cysts of variable size, with a preferential distribution in the upper lobes and in subpleural areas, may be observed [11, 58]. Differentiating emphysema from cysts is sometimes difficult [78]. Histologically, the most frequently related pattern in adults is UIP, but a mixed feature of NSIP, organising pneumonia, alveolar proteinosis or desquamative interstitial pneumonia has also been reported. Moderate inflammation and centrilobular fibrosis can be observed [4]. In younger patients, histology may show areas of NSIP, alveolar proteinosis or desquamative interstitial pneumonia alone or in combination in the same specimen [56, 60].

Heterozygous *SFTPA1* and *SFTPA2* germline mutations are unique in that these mutations are associated with a high prevalence of lung cancer, although the mechanisms are poorly understood [11, 58, 79–81]. Three cases of lung cancer associated with ILD in patients with *NKX2.1* mutation have been reported [82]. However, data are lacking to offer SRG sequencing for a sporadic patient with ILD and lung cancer. SRGs are usually tested in patients with PPF, or with idiopathic fibrotic ILD before the age of 50 years, as discussed in Narrative Question 1.

#### Methodological considerations

Genetic sequencing of the PPF gene panel (TRGs and SRGs) searching for new and previously described ultra-rare variants in coding regions may be performed by different techniques: whole-exome sequencing (WES), whole-genome sequencing (WGS) or next-generation sequencing panel, each with their advantages and limits: cost, availability and coverage. The complete panel may be targeted at once and determination of pathogenicity should follow international standards [83]. By WES or WGS, not only TRG and SRG, but also variants present in other syndromes (supplementary table S1) that may manifest as ILD can be determined in one analysis. However, availability of techniques, national health or insurance policies and the generation of many unresolvable variants of unknown significance may require more targeted approaches. In childhood ILD, SRG mutations are the most frequently found; in adults, pathogenic TRG variants are more common than SRGs. Table 1 and published mutation spectra show genes with the highest yields in PPF [41, 58].

#### Narrative Question 4: What is the evidence for telomere length measurement?

##### Statement

*Telomere length sometimes provides additional information to genetic sequencing and is sometimes performed when available in suspected telomere-related disease.*

##### Summary of evidence

##### Telomere length measurement

Telomere length is measured in peripheral blood, and may be expressed as an absolute number (kb) or as a relative length compared to a control population and corrected for age. The latter is preferred, as stated in the following paragraph.

Several methods for telomere length measurement exist (supplementary material and table 6). Quantitative PCR and Flow-FISH are currently the two more widely available techniques, with Flow-FISH reported as the more reproducible. Although shorter telomeres are a logical consequence of TRG pathogenic variants, only a few studies have explored the direct correlation between telomere length and TRG variants, with conflicting results. Because telomere length decreases with age in the healthy population, telomere length should always be age-adjusted [84]. Younger patients with short telomere syndromes usually present more severe phenotypes such as dyskeratosis congenita with associated very short age-adjusted telomere length (less than the 1st percentile) [85]. However, adult patients with a TRG mutation with only liver or lung disease do not necessarily present markedly short telomere length [85]. ILD patients carrying a pathogenic TRG variant display on average telomeres shorter than age-matched controls, most often lower than the 25th percentile [86]. However 15% of *TERT* mutation carriers presented normal telomere length in one cohort [36]. In another cohort, almost all ILD patients, older than 60 years, with *TERT*, *TERC* or *RTEL1* mutations, had a telomere length less than the 1st percentile, with 50% having a telomere length greater than the 10th percentile [86].

TABLE 6 Comparison of main telomere length measurement methods

Method	Principle	Pros	Cons	Main references
Quantitative PCR	Estimation of the telomere signal (T) compared to a reference signal (S)	Easy and relatively fast; cheap; from DNA; low amount of DNA; possible automation; validated for clinical use	High intra- and inter-centre variability (>10%); duplicate or triplicate needed	[164, 165]
Telomere fragment analysis by Southern blot	Measuring telomere length with a TTAGGG-labelled probe	Reproducible; applicable to several tissues	High amount of DNA (2 µg); time consuming; radioactive probe; difficult to detect very short telomeres	[166]
STELA (single telomere length analysis)	Specific PCR after primer ligation; detection by Southern blot	Very low amount of DNA; accurate	High expertise; radioactive probe; not validated for clinical use	[166, 167]
Flow-FISH (fluorescence <i>in situ</i> hybridisation)	Combining FISH and flow cytometry	Accurate; large number of samples at once; high reproducibility; validated for clinical use	Requires living cells (blood); requires expertise; time consuming; relatively expensive	[88, 168]

Short telomere length in peripheral blood mononuclear cells is usually linked to pathogenic TRG variants [87, 88]. However, telomere length within normal values is frequently observed in families with pulmonary fibrosis and telomere length yields insufficient information to exclude the presence of a short telomere syndrome or the risk of pulmonary disease, especially in subjects aged >60 years [10, 85, 86, 89–91]. Of note, some TRG variants may not affect telomere length but rather telomere function, with similar clinical consequences [92]. Telomere length measurement might be used to screen for TRG mutations. In FPF patients without an identified mutation, a short telomere length may identify patients with a mutation in an unknown TRG or a phenocopy, where patients inherited very short telomeres from their parents [93].

Shorter telomere length is associated with a poor outcome in IPF and other fibrotic ILDs [7, 34, 94]. Shorter telomere length may also influence the prognosis after lung transplantation [95, 96].

In summary, telomere length can be determined when available, but normal or unavailable telomere length does not usually discourage genetic sequencing.

#### **Narrative Question 5: What is the role of common genetic variants (polymorphisms) in the diagnostic workup?**

##### **Statement**

*Pending new studies, the majority of Task Force members do not include the common genetic variants associated with IPF or FPF in the genetic diagnostic workup.*

##### **Summary of evidence**

Common genetic variants (also known as polymorphisms) are present in any region of the genome and have an allele frequency >1%. Some of these common variants are robustly associated with specific diseases, although their functional consequence is not always known.

Multiple common polymorphisms predisposing to fibrotic ILD have been identified, although their effect size is usually low [97]. The rs35705950 *MUC5B* promoter gene polymorphism has been the most extensively studied. Mucin 5B is a protein constituent of respiratory mucus. The minor allele of the promoter variant rs35705950 (11-1241221-G-T (GRCh37)) is found in approximately 10% of European populations, which is equivalent to approximately 20% of carriers (heterozygotes) of the minor allele and 1% homozygotes for the minor allele. This minor allele variant is significantly more frequent in European people with sporadic IPF and FPF (34–38%) [22, 98]. The presence of the *MUC5B* promoter polymorphism is also associated with other fibrotic ILDs, including rheumatoid arthritis-associated ILD [5], sporadic fibrotic hypersensitivity pneumonitis [7], asbestosis [29] and progressive fibrotic interstitial lung abnormalities [99], but not with systemic sclerosis-associated ILD, pulmonary sarcoidosis or autoimmune myositis-associated ILD [100–102].

The rs35705950 T-allele is associated with increased *MUC5B* expression in terminal bronchioles [103, 104] and one study suggested this association was seen in UIP/IPF but not NSIP [101]. Of note, in IPF patients, carriers of the *MUC5B* promoter variant may be associated with better survival and slower progression [105–108].

The *MUC5B* promoter variant is not specifically associated with the occurrence of familial or early-onset lung fibrosis. However, some groups suggest screening for the *MUC5B* promoter variant in FPF when variants classically associated with FPF as a monogenic disease (telomerase/surfactant-related) are not found [3].

In the context of screening relatives of IPF patients, the presence of the *MUC5B* promoter polymorphism along with interstitial abnormalities could be predictive of subsequent fibrosis and progression [9, 109, 110]. However, given the high prevalence of the *MUC5B* rs35705950 minor allele and its associated low penetrance, genotyping of the variant is currently not part of the FPF gene investigations. Further research is needed to evaluate whether this promoter polymorphism plays a role in variable expressivity in FPF with monogenic disease.

*MUC5B* genotyping is useful to stratify patients such as those with interstitial lung abnormalities or rheumatoid arthritis at risk of developing lung fibrosis and is sometimes used in the clinical routine.

#### **Narrative Question 6: What are the optimal treatment options for FPF?**

##### **Statement**

*For patients with IPF or progressive pulmonary fibrosis (despite standard management), including those with FPF or a known monogenic disease, the Task Force agrees with current international guidelines [13] recommending antifibrotic drugs.*

*Treatment of childhood ILD is essentially based on expert opinion. Childhood ILD should be included in therapeutic trials when available.*

*Task Force members would consider lung transplantation in patients with monogenic disease or FPF, when appropriate. In case of short telomere syndrome, the post-transplant immunosuppressive regimen should be carefully monitored and adjusted when indicated.*

##### **Summary of evidence**

###### **Drug treatment in adults**

Clinical trials testing antifibrotic treatment in IPF and progressive pulmonary fibrosis included patients independently of familial or genetic associations. Antifibrotic treatment has been approved for progressive pulmonary fibrosis, and retrospective analysis of patients with a TRG variant treated with antifibrotics showed a reduction in FVC decline after treatment initiation and a safety profile comparable to previous IPF trial observations [111]. *Post hoc* analysis of trial data suggested that pirfenidone treatment was beneficial regardless of telomere length [107].

In contrast to these encouraging findings for antifibrotics are the negative findings for treatment with immunosuppressive drugs in pulmonary patients with short telomeres or carrying a TRG mutation. In a *post hoc* analysis of IPF trial data, the adverse outcomes (death, lung transplantation or FVC decline) associated with immunosuppressive treatment were observed preferentially in patients with leukocyte telomere length less than the 10th percentile [112]. Moreover, in a retrospective study of patients with fibrotic hypersensitivity pneumonitis, patients with telomere length in the lowest quartile did not benefit from treatment with mycophenolate mofetil, in contrast to patients with longer telomere length [113]. For adult patients with SRG mutations, no specific drug trials have been performed.

In this small number of studies, patients carrying a TRG mutation or with short telomere length seem to have a different disease evolution and to respond differently to immunosuppressive treatment. However, it is unknown if FPF patients with specific inflammatory features may benefit from immunosuppressive treatment, and a direct comparison between immunosuppressive and antifibrotic treatment is currently lacking.

###### **Drug treatment in children**

In children, only empirical data from case reports or small series have been published on treatment of clinically evident ILD. Results of a phase 2 randomised controlled trial of hydroxychloroquine in childhood ILD showed no difference between placebo and hydroxychloroquine groups in response to treatment, assessed as oxygenation or other end-points including health-related quality of life and pulmonary function [114]. A trial of nintedanib in fibrosing childhood ILD assessed safety and pharmacokinetics [115]. At least one study is currently dedicated to treatment with danazol in patients aged >15 years with pulmonary fibrosis associated with TRG mutation, with results expected in 2023 (ClinicalTrials.gov: NCT03710356). Currently available data do not justify the prescription of danazol

outside of clinical trials. Inclusion of children with ILD in clinical trials should be encouraged and all adult trials should have a Paediatric Investigational Plan.

Patients with SRG mutations are usually referred to reference centres and discussed in specialised multidisciplinary meetings. Based on the randomised trial of hydroxychloroquine [114], the Task Force members undertake a careful case-by-case assessment of ongoing prescriptions. In children, and as suggested by European and American statements, treatment of ILD caused by SRG mutations may include immunosuppression (prednisolone pulse or continuous therapy, steroid-sparing drugs) on a purely empirical basis, as there are no randomised trials in SRG on steroids yet, or macrolide usage for extended periods [38, 116, 117].

### Lung transplant

In advanced disease, evidence shows that patients with monogenic pulmonary fibrosis may benefit from lung transplantation, when appropriate. The 5-year survival after lung transplantation in infants with SRG mutations was 55% [118], and a recent study suggests similar survival rates in younger and older children [119]. In adults, lung transplantation outcomes in patients with FPF were comparable to sporadic ILD patients [120]. Because lung cancer development has been documented in up to 37% of *SFTPA1/SFTPA2* mutation carriers [58], Task Force members would consider early referral and bilateral transplantation.

Several studies have shown that transplantation in pulmonary fibrosis patients with TRG mutations has similar outcomes as in patients without such mutations [39, 41, 96, 121, 122]. Thrombocytopenia with the need for platelet transfusion is frequent, and myelodysplastic syndrome and/or bone marrow failure are reported in some patients [37, 96, 121–123]. A recent retrospective study did not report higher risk of haematological complications in *TERT*, *RTEL1* or *PARN* rare variant carriers [96], but confirmatory observations are needed. Standard regimens of immunosuppressive post-transplant treatment can be poorly tolerated and increase the risk of developing haematological complications or renal disease [121–123]. Adjustment of the immunosuppressive regimen has therefore been suggested, with avoidance of cytotoxic drugs such as azathioprine [37, 39]. In summary, FPF patients are considered by Task Force members as potential candidates for lung transplantation, but may require a tailored immunosuppressive regimen in case of an underlying short telomere syndrome [37, 39].

### *Narrative Question 7: Which family members are eligible for genetic sequencing?*

#### *Statement*

*For families with proven monogenic disease, the Task Force supports offering genetic sequencing according to national directives or legislation.*

#### *Summary of evidence*

In genetic disease, family members are at significantly increased risk of developing the disease. Inheritance in FPF is most commonly dominant, which results in a 50% chance of inheriting the deleterious allele in first-degree family members (parents, sibs and children). Genetic sequencing in asymptomatic family members can be performed in case of proven monogenic disease (identification of a (likely) pathogenic mutation in an affected relative) which may be followed by cascade genetic sequencing in subsequent first-degree relatives. However, local health and insurance policies may determine possibilities for genetic sequencing of asymptomatic relatives. Furthermore, because results of genetic sequencing have a psychological, social and financial impact it is advised that asymptomatic relatives are not tested before they can make their own informed decision, usually >18 years of age [124]. Due to high penetrance, the predictive power for disease development of genetic sequencing of SRG is relatively high [58]. TRG mutations transmitting more often in an autosomal dominant manner are associated to incomplete penetrance and variable expressivity. Other more unusual features are present in TRG families: the inheritance of the shortened telomeres leads to anticipation and sometimes to the occurrence of pulmonary phenocopies. While the presence of a mutation associates with a high risk for disease, the absence of the mutation in TRG families does not exclude increased risk for disease due to other inherited telomere abnormalities [93]. Further research on the predictive power of genetic sequencing in families with pathogenic TRG mutations is needed.

### *Narrative Question 8: Which clinical screening and follow-up parameters may be considered in family members?*

#### *Statement*

*The majority of Task Force members offer to all asymptomatic first-degree relatives of patients with FPF a periodic clinical evaluation for (early) ILD identification. Frequency is unknown at present.*

*In their clinical practice, the majority of Task Force members advise all first-degree relatives of patients with FPF to have a chest CT scan and lung function tests at least when experiencing persistent respiratory symptoms, such as dyspnoea or cough.*

*The majority of Task Force members include a complete blood count and hepatic enzyme evaluation in first-degree relatives of patients with short telomere syndrome.*

*All known risk factors of pulmonary fibrosis such as smoking or other inhalational exposures should be avoided in first-degree relatives of patients with FPF.*

#### Summary of evidence

The disease course can be subdivided into a clinical (symptomatic) and a pre-clinical (asymptomatic) phase. Considering that at diagnosis many adult patients have irreversibly lost up to 50% of diffusion capacity, early detection of ILD is warranted. Comparison of age at onset of symptoms with age at diagnosis shows that there is a diagnostic 1–3 years delay in FPF [27, 28, 72]. Furthermore, screening may detect disease before the onset of symptoms. In one study, in familial patients, the age at diagnosis after screening was 58.5 years, whereas the age of patients diagnosed after onset of symptoms was 61.4 years [72].

Screening for pre-clinical disease is offered to first-degree relatives in several countries in a clinical or research setting. There are no guidelines, standardisation or, even less, evidence-based practice regarding which tests to include in the screening, age at which it should start and its frequency. The risk of disease correlates with age and the specific gene. The most common inheritance pattern is autosomal dominant with high penetrance, causing risk of disease of up to 50% in first-degree relatives.

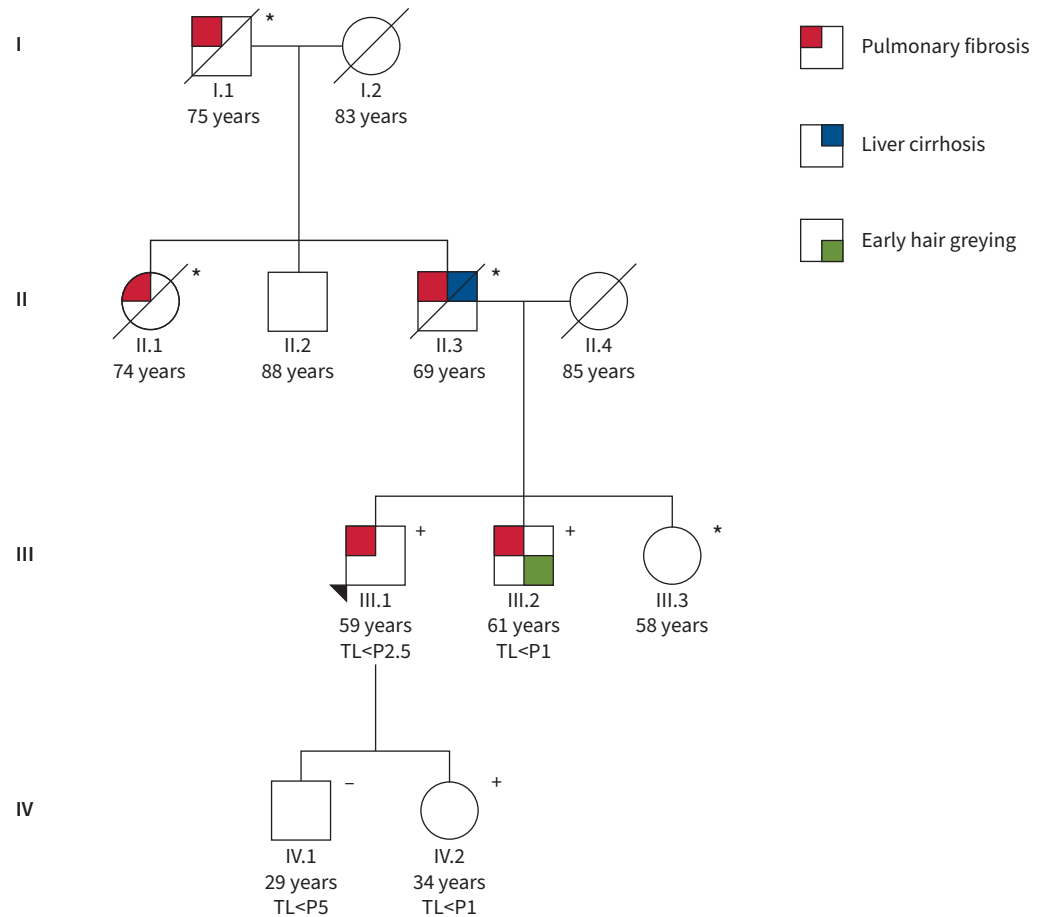
The median age at diagnosis of 91 adult patients carrying SRG mutations was 45 years (range 18–72 years) [58]. Among SRG carriers, the median age in *SFTPC* mutation carriers was significantly lower than that of *SFTPA1/SFTPA2* mutation carriers (37 versus 48 years) [58]. Only one paediatric patient with an *SFTPA* mutation has been reported versus 51 adult cases, which indicates that the risk for disease in *SFTPA1/SFTPA2* is commonly restricted to adults. In contrast, *SFTPC*- and *ABCA3*-related disease may present at all ages [58].

In TRG mutation carriers, the median age at diagnosis of ILD is 62 years (range 35–79 years) [58]. Within TRG mutation carriers, patients carrying a *TERC* mutation were diagnosed at a significantly earlier age than those with a *PARN* mutation in one cohort (51±11 versus 64±8 years) [10]. While the sex ratio for surfactant-related disease is 50/50 for all ages [58], male predominance has been reported for telomere-related disease. In a study of 134 subjects with heterozygous *TERT* mutations, pulmonary fibrosis was identified in 38% of men and 14% of women aged <60 years, and in 60% of men and 50% of women aged ≥60 years [31]. However, multiple studies of relatives of patients with FPF show that only age, and not sex, associates with HRCT abnormalities at screening [21, 110, 125, 126].

The phenomenon of anticipation in families with TRG mutations further complicates matters. Patients with TRG mutations transmit their short telomeres independently of transmission of the mutation and telomeres shorten at a younger age in subsequent generations [34, 127]. This inheritance explains the phenomenon of genetic anticipation, which is defined as an earlier and more severe disease with each generation (figure 1) [34, 93, 127, 128]. Age at diagnosis was highly correlated among affected family members of the same generation [2, 26] and decreased over generations by a mean of 6–18 years in FPF [10, 26, 28]. In patients <30 years of age, pulmonary fibrosis as the single manifestation of short telomere syndrome is uncommon. While risk of disease development increases with age and is dependent on the gene or type of mutation and genetic anticipation, there is insufficient evidence for gene- or age-specific screening advice. Several SRGs cause pulmonary disease in childhood, whereas pulmonary disease as the only manifestation of telomere-related disease in childhood has not been reported.

Little is known on the pathogenesis of pre-clinical disease, defined as the period between the initiation of pathogenic processes and the onset of disease symptoms. In FPF, relatives are at increased risk for disease. Several lines of evidence suggest that additional genetic factors such as *MUC5B* risk allele carriage and environmental exposures, including a strong effect of cigarette smoking, play a role in the development of pulmonary fibrosis [2, 21, 110].

Previous studies using HRCT as a screening tool are surprisingly congruent on the prevalence of interstitial changes on HRCT in asymptomatic at-risk relatives of familial patients. These studies included relatives aged >18, 40–65 [21], >40 [110, 126], >48 [129] or within 10 years of the age at diagnosis of the



**FIGURE 1** Representative pedigree of a family with a telomere-related gene mutation associated with pulmonary fibrosis, liver cirrhosis and hair greying, of autosomal transmission with genetic anticipation and telomere shortening. The proband is indicated by an arrowhead. Relatives IV.1 and IV.2 underwent pre-symptomatic screening. Age is indicated. +: carrier of the mutation; -: non-carrier of the mutation; \*: unknown genetic status. TL: telomere length; P: percentile.

youngest family member and reported a prevalence of 14–25% interstitial changes on HRCT at first screening visit [21, 110, 125, 126, 129],

Risk factors for interstitial HRCT abnormalities in asymptomatic relatives include older age, shorter peripheral telomere length, alveolar epithelial cell telomere length, and elevated plasma concentration of SP-D and matrix metalloproteinase-7 [2, 21, 110, 126].

The rate of progression of interstitial HRCT abnormalities towards clinical disease in FPF has been understudied. One study described changes in radiological abnormalities in 129 self-reported unaffected first-degree relatives of patients with FPF without extensive interstitial lung abnormalities at first visit, of whom 25 (19.4%) developed extensive HRCT abnormalities or clinical ILD 5 years after enrolment [126]. Of note, 63.3% of patients with limited interstitial lung abnormalities at enrolment experienced progression compared to only 6.1% of patients with normal HRCT at baseline [126].

Although sparsely evaluated in relatives at risk, preliminary studies suggest that changes visible on HRCT may coincide with a reduction in lung function. Asymptomatic screened relatives with HRCT findings consistent with early ILD had a mean  $D_{LCO}$  of 97% predicted, which was significantly lower than the mean  $D_{LCO}$  of 105% predicted in the relatives with a normal HRCT scan [125]. Similarly, SALISBURY *et al.* [126] found that at-risk relatives with interstitial lung abnormalities had a  $D_{LCO}$  of 89% versus 93% predicted in relatives without interstitial lung abnormalities. In asymptomatic relatives of patients with



familial or sporadic ILD, those with interstitial abnormalities had a significantly lower  $D_{LCO}$  of 73% predicted compared to a  $D_{LCO}$  of 87% predicted in those without interstitial abnormalities [129]. FVC is usually in the normal value in relatives with asymptomatic interstitial abnormalities [21]. Lung function within the normal range therefore does not exclude pre-clinical disease; however, lung function should be part of the initial evaluation and follow-up. Lung function measurement is a relatively non-invasive procedure and annual repetition may detect significant reductions or subnormal values suggesting the presence of ILD.

In families with a TRG mutation, asymptomatic carriers of the mutation were shown to exhibit ILD changes on HRCT and slightly reduced  $D_{LCO}$  when compared with age-matched non-carriers. In the age-matched asymptomatic subjects from families with pulmonary fibrosis, *TERT* mutation carriers had a significantly decreased  $D_{LCO}$  of 77% versus 88% predicted in non-carriers [36]. Additionally, differences in short telomere syndrome-associated abnormalities, such as lower red blood cell and platelet counts, and higher mean corpuscular volume and mean corpuscular haemoglobin concentration, more frequent earlier hair greying and shorter telomere length, were present in asymptomatic *TERT* mutation carriers [36].

Disease penetrance in SRG mutation carriers is high and documented asymptomatic mutation carriers are rare [58]. Screening of such relatives revealed subclinical disease with below normal lung function or the presence of ILD changes on HRCT in adults [62, 130–132]. Little is known on asymptomatic paediatric carriers. However, some children with surfactant-related disease manifesting in the neonatal period recover with disappearance of disease symptoms [56, 133]. Their long-term prognosis is not yet known.

**TABLE 7** Markers for the identification of pre-clinical disease in asymptomatic relatives at risk

Pulmonary disease marker	Findings in screening asymptomatic relatives	Remarks from Task Force
<b>Physical examination, symptoms</b>		
Dyspnoea/MRC-5	May be present; not predictive for pre-clinical pulmonary fibrosis	
Frequent cough	May be present; not predictive for pre-clinical pulmonary fibrosis	
Clubbing	May be present	
Inspiratory crackles	May be present	
<b>Pulmonary function</b>		<b>Can be performed in subjects from age 6 years onward</b>
FVC	Below normal values rare	
$D_{LCO}$	Below normal values may be present; lower in subjects with ILD changes than without ILD changes on HRCT	
TLC	Below normal values rare; lower in subjects with ILD changes than without ILD changes on HRCT	
<b>Radiology HRCT</b>	14–25% have ILD changes on HRCT or a diagnosis of ILD on first screening visit	One-third of <i>SFTPA1/SFTPA2</i> mutation carriers may develop lung cancer
<b>Genetic sequencing</b>	Disease-causing variants in TRGs and SRGs	In families with a (likely) pathogenic SRG mutation: family members without the mutation are not at increased risk for FPF; in families with a (likely) pathogenic TRG mutation: family members without the mutation may have inherited short telomeres and may be at risk of development of STS
<b>Extrapulmonary signs and symptoms of STS</b>		<b>In all families with unknown cause or TRG mutation</b>
Haematological markers	Mean corpuscular volume above normal; red blood cells or platelets below normal	Abnormalities in one or several haematological cell lines are a sign of marrow dysfunction in asymptomatic carriers of TRG mutations
Liver enzymes	Elevated liver enzymes	Abnormalities in liver enzymes are a sign of hepatic disease in asymptomatic carriers of TRG mutations
Hair greying	Before 30 years of age	No consensual definition
Telomere length	<10th percentile	Low values for age associate with marrow dysfunction in asymptomatic carriers of TRG mutations

MRC: Medical Research Council; FVC: forced vital capacity;  $D_{LCO}$ : diffusing lung capacity of the lung for carbon monoxide; TLC: total lung capacity; HRCT: high-resolution computed tomography; STS: short telomere syndrome; ILD: interstitial lung disease; TRG: telomere-related gene; SRG: surfactant-related gene; FPF: familial pulmonary fibrosis.

Results from studies screening relatives at risk for pre-clinical ILD are summarised in table 7. Screening markers include HRCT, lung function in the case of a family with unknown genetic cause of disease, and haematological and hepatic evaluation for relatives of a patient with a TRG mutation.

Possibilities for screening are country specific. Relatives at risk include all first-degree family members of patients with monogenic or familial ILD as defined earlier. The appropriate age at which to start screening is unknown, and may depend on the gene involved and the age at disease onset in family members, although this requires further study [2, 10, 26, 128].

However, in families with age at onset of pulmonary fibrosis >60 years, without a disease-causing mutation and without evidence for disease anticipation, Task Force members usually offer screening to all first-degree relatives of FPF patients, with chest HRCT scan at a minimum, starting from the age of 50 years, or earlier if experiencing persisting respiratory symptoms or if auscultation abnormalities are identified [129].

In children, medical history details usually include neonatal respiratory adaptation (which respiratory support necessary, how long), prolonged pulmonary infections (>2 weeks), tachypnoea/dyspnoea between respiratory tract infections, any chronic respiratory disease up to the present, clubbing and changes in pulmonary function. Overall, interstitial changes on HRCT may suggest pre-clinical disease, but HRCT is not usually repeated on a yearly basis. Abnormal haematological values and extrapulmonary symptoms may inform on the development of short telomere syndrome.

In siblings of affected children, Task Force members usually offer a regular complete assessment. However, the optimal age for carrying out the examinations and the frequency of monitoring will have to be specified in the future.

### Conclusions

This statement aims to assist health professionals, FPF patients and their family members with the care of monogenic pulmonary fibrosis and FPF. While the available data and facilities are currently limited, we hope this statement will help in the implementation of genetic sequencing in daily practice worldwide, although we highlight the importance of performing genetic sequencing in highly specialised centres where all competences are available. In addition, this statement summarises the most relevant information regarding SRG/TRG genetics in ILD and advocates for future clinical trials in order to increase the evidence base for robust international guidelines.

This document was endorsed by the ERS Executive Committee on 29 November 2022.

Conflict of interest: R. Borie reports grants from Boehringer Ingelheim, consulting fees from Sanofi, lecture honoraria from Boehringer Ingelheim, Roche and Sanofi, and travel support from Boehringer Ingelheim, outside the submitted work. K. Antoniou reports consulting fees from Boehringer Ingelheim, Roche and GlaxoSmithKline, lecture honoraria from Boehringer Ingelheim, Roche, Chiesi, Menarini, GlaxoSmithKline and AstraZeneca, outside the submitted work. F. Bonella reports lecture honoraria from Boehringer Ingelheim, Fujirebio, Galapagos NV and Roche, travel support from Boehringer Ingelheim and Roche, participation on advisory boards with Boehringer Ingelheim, BMS, Fujirebio, Galapagos NV, GlaxoSmithKline, Roche and Takeda, outside the submitted work. B. Crestani reports grants from BMS, Boehringer Ingelheim and Roche, consulting fees from Apellis, lecture honoraria from Boehringer Ingelheim, BMS, Roche, Sanofi, Novartis, AstraZeneca and Chiesi, and is in receipt of equipment from Translate Bio, outside the submitted work. A. Froidure reports grants and consulting fees from Boehringer Ingelheim, lecture honoraria from Boehringer Ingelheim and GlaxoSmithKline, and travel support from Sanofi, outside the submitted work. L. Galvin reports travel support from the European Lung Foundation, European Respiratory Society and European Pulmonary Fibrosis Federation, leadership roles with the European Pulmonary Fibrosis Federation, Irish Lung Fibrosis Association, European Lung Foundation and European Reference Network On Rare Respiratory Diseases, outside the submitted work. M. Griesse reports grants and travel support from Boehringer Ingelheim, outside the submitted work. M. Molina-Molina reports grants from Roche and Boehringer Ingelheim, consulting fees from Esteve-Teijin, Ferrer, Roche and Boehringer Ingelheim, and lecture honoraria from Chiesi, Roche and Boehringer Ingelheim, outside the submitted work. V. Poletti reports lecture honoraria from AMBU, Boehringer Ingelheim, ERBE and Roche, outside the submitted work. E. Renzoni reports grants from Boehringer Ingelheim, and lecture honoraria from Boehringer Ingelheim, Roche and Novartis, outside the submitted work. C.H.M. van Moorsel reports grants from the European Respiratory Society supporting the present manuscript, grants and lecture honoraria from Boehringer Ingelheim, and a leadership role as co-chair of the European Respiratory Society Task Force for genetics in pulmonary fibrosis, outside the submitted work. All other authors have nothing to disclose.

Support statement: This work was supported by the European Respiratory Society. Funding information for this article has been deposited with the Crossref Funder Registry.

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