CHEST

# The Role of Genetic Testing in Pulmonary Fibrosis

## A Perspective From the Pulmonary Fibrosis Foundation Genetic Testing Work Group

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Patients with familial pulmonary fibrosis represent a subset of patients with pulmonary fibrosis in whom inherited gene variation predisposes them to disease development. In the appropriate setting, genetic testing allows for personalized assessment of disease, recognition of clinically relevant extrapulmonary manifestations, and assessing susceptibility in unaffected relatives. However currently, the use of genetic testing is inconsistent, partly because of the lack of guidance regarding high-yield scenarios in which the results of genetic testing can inform clinical decision-making. To address this, the Pulmonary Fibrosis Foundation commissioned a genetic testing work group comprising pulmonologists, geneticists, and genetic counselors from the United States to provide guidance on genetic testing in patients with pulmonary fibrosis. This *CHEST* special feature presents a concise review of these proceedings and reviews pulmonary fibrosis susceptibility, clinically available genetic testing methods, and clinical scenarios in which genetic testing should be considered. CHEST 2022; 162(2):394-405

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Pulmonary fibrosis encompasses a group of more than 100 diffuse lung disorders that result in parenchymal scarring, cause substantial morbidity and mortality, and can cluster in families. Familial pulmonary fibrosis (FPF) is a diagnostic modifier

**ABBREVIATIONS:** DC = dyskeratosis congenita; flow-FISH = flow cytometry with fluorescent in situ hybridization; FPF = familial pulmonary fibrosis; HPS = Hermansky-Pudlak syndrome; SNP = single nucleotide polymorphism; TL = telomere length; VUS = variant of uncertain significance

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conveyed to families with two or more members with pulmonary fibrosis within three degrees of relationship.[1] Currently, it is estimated that 20% of patients with pulmonary fibrosis fulfill the FPF designation and may experience worse survival.[2-4] Genetic studies have identified numerous rare genetic variants in multiple genes that cause disease manifestations. In aggregate, results from these studies suggest that genetic determinants underlying FPF may inform clinical decision-making for individual patients and their relatives.

Despite the growing appreciation of the role of inherited genetic variants in disease development, indications for genetic testing in clinical practice are not well described, and such testing is used inconsistently when high-yield indications are present. To address these uncertainties and inconsistencies, the Pulmonary Fibrosis Foundation commissioned the Genetic Testing Work Group comprising US-based pulmonologists, geneticists, and genetic counselors who participate in the care of patients with pulmonary fibrosis to provide guidance on genetic testing in these patients. The goals of the Genetic Testing Work Group guidelines were (1) to summarize genetic variation in FPF, (2) to describe clinically available genetic testing methods, (3) to review indications for genetic testing, and (4) to discuss special considerations for genetic testing. Two documents were produced as part of this work group, one for care providers and one for patients.[5,6] This *CHEST* special feature details the findings and recommendations of the care provider document produced by the Pulmonary Fibrosis Foundation Genetics Testing Work Group.

## Genetic Underpinnings of FPF

Within FPF, associated variants can be categorized as common or rare based on their allele frequency within the population. Common variants, otherwise known as single nucleotide polymorphisms (SNPs), occur in approximately every 1,000 nucleotides in the human genome and have a frequency of 1% or higher in a population.[7] Disease-associated SNPs also can be found in healthy individuals, generally reside at specific loci within noncoding regions, and may influence gene expression.[8] For example, the rs35705950 SNP in the promoter region of the *MUC5B* gene is associated strongly with idiopathic pulmonary fibrosis risk.[9] Although common variants influence risk of disease development, they usually are insufficient to cause disease in isolation. In contrast, rare variants are found infrequently in the general population at less than 1%. Instead, their frequency is enriched in patients and families with pulmonary fibrosis, with penetrance that increases with age. The rare variants tend to cosegregate with disease in families across multiple generations and affect distant relatives who may have had no knowledge of each other. In addition, rare variants generally occur at variable loci within coding regions of disease-associated genes, resulting in impaired gene products, and alone can cause disease.[10] Therefore, clinical genetic testing in FPF kindred focuses primarily on identifying rare heritable variants.

### *FPF*

Collectively, prior studies indicate that only 20% to 30% of kindred with FPF harbor an identifiable causative genetic variant.[11] The reason for the relatively low positivity rate may be the result of multiple factors, including yet to be identified genetic variants that contribute to disease risk, additive effects of lower effect-size variants, or the effect of genetic plus certain environmental exposures. Multiple disease-associated genes and multiple variants within those genes have been identified to date, so no one gene or variant causes pulmonary fibrosis in all patients or families. In addition, individuals within families may manifest variable forms of pulmonary fibrosis, suggesting that additional genetic or environmental factors may influence phenotype.[12] To date, rare variants in two biologic pathways contribute to the known genetic heritability of FPF: surfactant metabolism and telomere maintenance, with the latter being significantly more common.

### *Rare Surfactant Gene Variants*

Surfactant is a mixture of lipid and proteins produced by type II alveolar epithelial cells that reduces alveolar surface tension and modulates the innate immune response.[13] Rare pathogenic variants in surfactant-related genes cause improper protein trafficking, leading to endoplasmic reticulum stress, defects in autophagy, and type II alveolar cell toxicity.[14-16] To date, six surfactant-related genes have been implicated in FPF. Heterozygous variants in surfactant protein C *(SFTPC)* have been reported in patients ranging from neonates to elderly adults with variable pulmonary fibrosis phenotypes.[17,18] Surfactant protein A *(SFTPA1, SFTPA2)* variants have been associated with concomitant familial pulmonary fibrosis and lung adenocarcinoma in a small number of families.[19,20] Rare

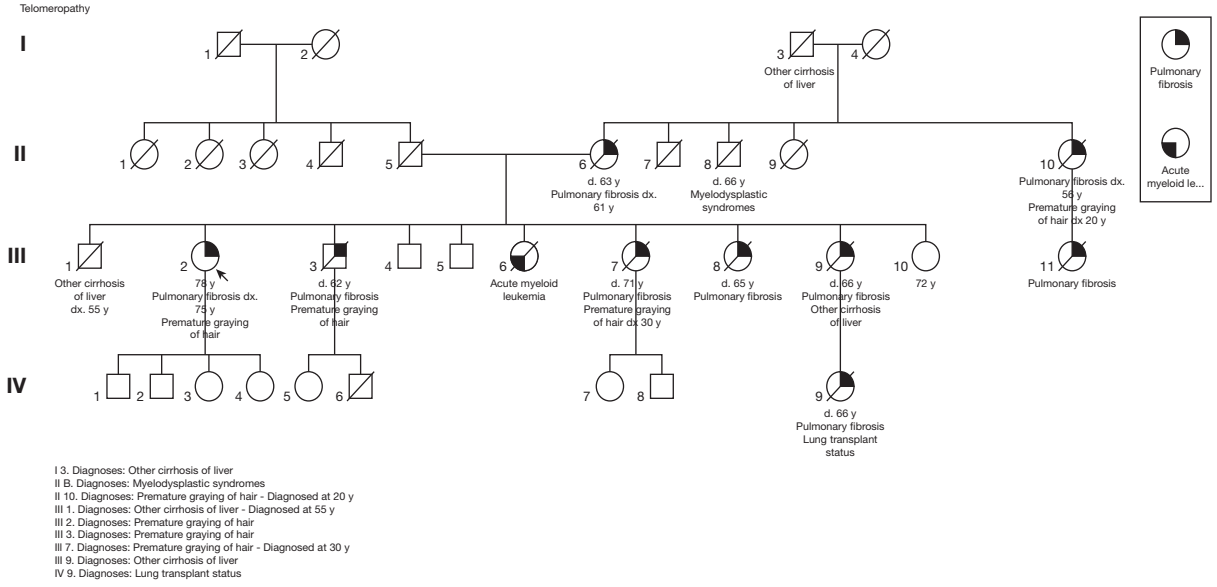
variants in surfactant protein B (*SFTPB*) and ATP-binding cassette-type 3 (*ABCA3*) are associated more commonly with neonatal respiratory distress syndrome and pediatric-onset interstitial lung disease.[21-24] In the case of *ABCA3*, a genotype-phenotype correlation exists whereby homozygous loss-of-function variants are associated with respiratory failure at birth, whereas compound heterozygous variants result in variable presentation often with less severe disease.[25,26] Monoallelic *ABCA3* variants have been reported in FPF, but a causal role has not been established clearly.[21,27] Variants in the transcription factor *NKX2-1* also have been reported in FPF.[28]

Collectively, surfactant gene rare variants are estimated to occur in 1% to 3% of kindred with FPF,[29] of whom the affected relatives often demonstrate disease across the age spectrum ranging from the neonatal period through late adulthood. Apart from brain and thyroid disease in patients with *NKX2-1* mutations, rare variants in surfactant genes are not associated with extrapulmonary manifestations.

### Rare Telomere Gene Variants

Telomeres are specialized structures comprising six nucleotide repeat sequences (TTAGGG) located at the ends of chromosomes that serve as a buffer to prevent DNA loss during cell division. Telomere structure is maintained and protected by specialized proteins; dysfunction of these proteins leads to abnormal telomere shortening. To date, pathogenic variants in a number of telomere genes have been implicated in the development of adult-onset FPF. These genes are responsible for maintaining telomere length (*TERT* and *TERC*),[30,31] formation of the telomerase complex (*PARN*, *DKC1*, *NAF1*, *ZCCHC8*, and *NOP10*),[32-36] unwinding telomere structure during DNA replication (*RTEL1*),[32,37,38] and maintaining integrity of the telomere end (*TINF2*).[39] Of note, heterozygous mutations in *NOP10* have been reported in only one family to date.[35,36] Pathogenic variants generally are inherited through an autosomal dominant pattern with variable penetrance,[12,30,31,40,41] except for *DKC1*, which causes X-linked inheritance.[42] A single report of biallelic (ie, recessive) *PARN* rare variants has been published.[43]

Pathogenic variants in telomere genes as well as short TL are associated with a variety of clinical manifestations including pulmonary fibrosis, pulmonary emphysema, liver dysfunction, bone marrow dysfunction, and premature graying of hair (Fig 1).[44,45] Patients with




Legend: ○ = Females; □ = Males; ⊘ = Deceased; ◧ = Pulmonary fibrosis; ◪ = Acute myeloid leukemia; Arrow points to the Proband or index case; Roman Numerals represent the generations from oldest to youngest; Individuals are identified by Roman numeral generation and number in order (e.g., III.7)

Figure 1 – *Example of a pedigree demonstrating features of short telomere syndrome across multiple generations. Arrow points to the proband or index patient. Roman numerals represent the generations from oldest to youngest. Individuals are identified by Roman numeral generation and number in order (eg, III.7).*

**TABLE 1** ] Clinical Features Within Patients or Families That Suggest a Possible Genetically Driven Process Stratified by Gene Pathways

| Clinical Feature | Telomere Pathway | Surfactant Pathway | Hermansky-Pudlak Syndrome |
|---|---|---|---|
| Pulmonary fibrosis < 50 y of age | Yes | Yes | Yes |
| 2+ Members with pulmonary Fibrosis within family (proband plus ≥ 1 relative(s)) | Yes | Yes | Yes |
| Bone marrow abnormalities: acute myeloid leukemia, aplastic anemia, myelodysplastic syndrome, macrocytosis, chronic anemia | Yes | No | No |
| Bone marrow abnormalities: atypical cells (eg, macrophages), bleeding diathesis resulting from platelet dysfunction, neutropenia | No | No | Yes |
| Integumentary features: premature greying (teens or 20s), alopecia, dysplastic nails, oral leukoplakia, reticular skin pigmentation on chest or neck | Yes | No | No |
| Integumentary features: oculocutaneous albinism, iris transillumination | No | No | Yes |
| Liver disease or cirrhosis | Yes | No | No |
| Head or neck malignancy (< 50 y of age) | Yes | No | No |
| Bone disorders: premature osteoporosis, avascular necrosis of hips or shoulders | Yes | No | No |
| Pediatric-onset ILD with or without brain or thyroid disorders | No | Yes | No |
| Pulmonary fibrosis with lung adenocarcinoma | No | Yes | No |

telomere gene variants may manifest a wide variety of pulmonary fibrosis subtypes and are at risk of rapid progression and poor survival.[12,46] Pathogenic variants in telomere genes are found in 20% to 30% of unselected familial pulmonary fibrosis kindreds and up to 80% in selected cohorts with strong clinical histories that include bone marrow failure in first-degree relatives.[47,48] *TERT* is by far the most commonly affected gene in FPF and is found in approximately 10% to 20% of kindreds, followed by *RTEL1*, *PARN*, and *TERC* at 2% to 5%.[12,30-32,40,41]

### *TL in FPF*

Leukocyte telomere length (TL) is a surrogate marker for telomere-mediated lung disease risk. Short age-adjusted TL is common in individuals with pathogenic variants in telomere genes; however, the magnitude of telomere shortening is variable among the telomere genes and depends on the age at diagnosis, with shorter TL being associated with more severe disease.[32,47] Telomere shortening can occur in the absence of an identifiable rare telomere-related variant[40,49] and may be associated with bone marrow failure even in the absence of a family history. As such, TL alone does not discriminate perfectly between the presence or absence of a rare telomere gene variant, especially in patients older than 40 years. However, age-adjusted TL at or longer than the 50th percentile by clinically validated flow cytometry with fluorescent in situ hybridization (flow-FISH) may have a negative predictive value.[47]

## Pedigree Construction

Family history ascertainment is a critical step in identifying potential kindred with FPF and may influence disease outcomes[50]; therefore, a detailed family history should be obtained for all patients with pulmonary fibrosis. The family pedigree should include medical history from relatives within at least three generations, with particular focus on phenotypes associated with known genetic pathways (Table 1). Patients with pulmonary fibrosis with a family history of disease or relevant extrapulmonary manifestation should be suspected of having FPF, and genetic testing should be considered strongly, given the high yield.[48]

## Clinical Genetic Testing Methods

For patients with FPF, two clinically available genetic testing options offer different, yet complementary, information: (1) gene sequencing and (2) TL measurement.

### *Gene Sequencing*

Gene sequencing includes the detailed assessment of genomic DNA code extracted from cells within blood, saliva, buccal swabs, or skin biopsies. Multiple gene sequencing technologies are available to

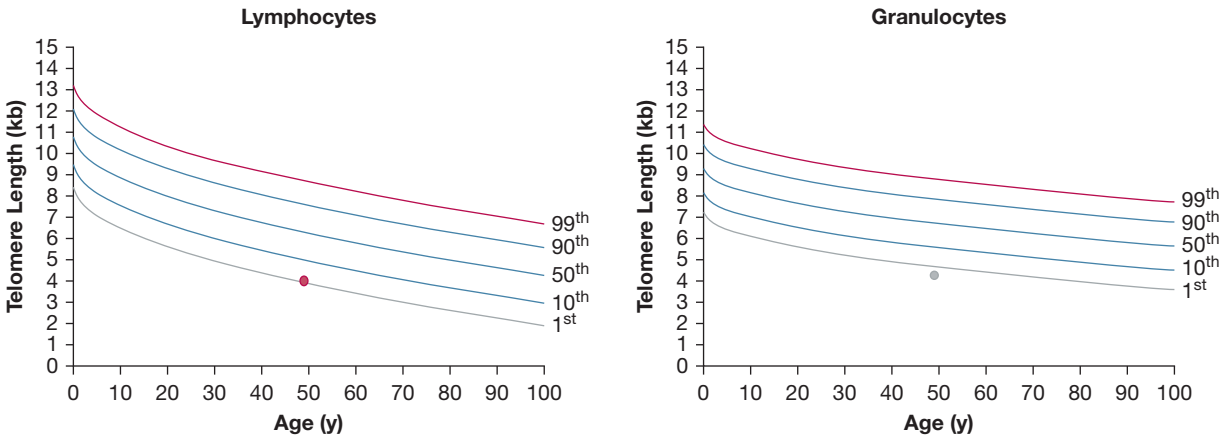



Figure 2 – *A, B, Graphs showing examples of clinical reports of telomere length in lymphocytes (A) and granulocytes (B) for a patient with familial pulmonary fibrosis. The points on the telograms represent the telomere length values relative to the expected age-adjusted distribution. Telomere length was measured by flow cytometry and fluorescent in situ hybridization.*

clinicians, including whole genome, whole exome, and gene panel testing. Although whole genome and exome sequencing assess the entire genome or exome of the patient, gene panel testing sequences only the subset of genes that have been implicated previously in FPF, and therefore is preferred both for cost and expedience. Gene sequencing results can be complex and should be interpreted by clinicians with genetic expertise who can explain the meaning of test results to patients and their family members.

Genetic variants identified through gene sequencing are reported according to standards outlined by the American College of Medical Genetics, which include pathogenic, likely pathogenic, uncertain significance, likely benign, and benign descriptions.[51,52] These designations are derived by assimilating known information about the specific variant in question, including the functional consequence, variant prevalence within the population, previous associations, or cosegregation with disease.[53] Within this context, positive results are found in up to 30% of patients with FPF, indicating that the patient harbors a pathogenic or likely pathogenic variant in a gene that was implicated previously in FPF. In contrast, negative results are the more common finding in unselected patients, indicating that the patient does not have a causative genetic variant in the genes tested, but still may harbor a causative variant that is yet to be identified. Rarely, negative results may be the result of technological limitations such as variants located deep within introns. In many patients with FPF, gene sequencing identifies a variant of uncertain significance (VUS) that either has not been reported previously, but is linked to pulmonary fibrosis, or has insufficient data to determine if the variant is pathogenic or benign. Private or unreported rare missense variants present a unique challenge. As such, variants are reported as VUSs because functional studies to ascertain pathogenicity better may not be available. However, a VUS later may be reclassified as either pathogenic or benign based on emerging information from additional clinical genetic databases and functional studies. Among individuals with variants in telomere maintenance genes, TL testing may help to determine the significance of a VUS.

### *TL Measurement*

Clinical TL measurement is performed using peripheral blood leukocytes or DNA extracted from these cells. Multiple methods quantify leukocyte TL, such as flow-FISH, terminal restriction fragment length, quantitative polymerase chain reaction, and estimations from whole genome sequencing, each of which has limitations. Among these, flow-FISH has high interlaboratory reproducibility. Several clinical indications exist for TL

**TABLE 2** ] Clinical Scenarios in Which Clinicians May Consider Genetic Testing and the Potential Yield for Identifying a Variant

| Clinical Scenario | Consider Testing and Potential Yield for Variant |
|---|---|
| Patient with pulmonary fibrosis with family history of pulmonary fibrosis | Yes, high yield |
| Patient with pulmonary fibrosis (sporadic or familial) with personal or family history of telomeropathy manifestations | Yes, high yield |
| Syndromic presentations (short telomere syndrome, Hermansky-Pudlak syndrome) | Yes, high yield |
| Targeted testing in unaffected family members (> 18 y of age) of proband with known pathogenic variant in disease-causing gene | Yes, high yield |
| Young age at PF onset (< 50 y) | Yes, low yield |
| Personal or family history of coexistent pulmonary fibrosis with lung adenocarcinoma | Consider, low yield |
| Sporadic pulmonary fibrosis with no suggestive extrapulmonary manifestations | Not currently recommended |
| Unaffected relative if proband has not undergone genetic testing, or recent comprehensive testing showed negative results for disease-causing variant | Not currently recommended |
| Common variants in sporadic pulmonary fibrosis (eg, *MUC5B*) | Not currently recommended |
| Evaluation before lung transplantation | Not currently recommended |

testing, and flow-FISH is considered the gold standard for diagnosis of telomere-related disease in children and young adults.[47] Given that telomeres normally shorten with age, the measured absolute TL is compared with that of a reference population to calculate age-adjusted values. Clinical reporting of TL provides both the absolute length in kilobases and age-adjusted percentiles, which often are represented graphically on telograms (Fig 2).

## Considerations for Genetic Testing in FPF

Genetic testing is considered for patients with FPF when the results (1) would influence patient-specific disease management, (2) would inform individual risk stratification, (3) would provide context for extrapulmonary disease manifestations, (4) would provide relevant information for the patient or their relatives, or a combination thereof. Scenarios in which genetic testing should be considered and their likelihood of a genetic diagnosis are outlined below and summarized in Table 2.

### *Patients With FPF*

Panel-based gene sequencing should be considered for all patients with a diagnosis of and with a family history of pulmonary fibrosis because identification of a rare genetic variant within risk genes offers actionable information for individual patients and their relatives. For example, pathogenic variants in the telomere genes *TERT*, *TERC*, *PARN*, and *RTEL1* convey high risk for rapid progression and poor survival, regardless of the specific pulmonary fibrosis diagnosis.[12] In such cases, clinicians may consider deferring invasive surgical lung biopsy because histopathologic analysis may be less prognostically informative, and instead may opt for frequent monitoring, early initiation of appropriate therapies, and referral to lung transplant centers.[12] Further, patients who harbor rare pathogenic variants may be at risk for nonpulmonary fibrosis manifestations that warrant surveillance, such as lung cancer in those with *SFTPA1/2* variants and liver disease and bone marrow dysfunction in those with telomere-related variants.

For patients with FPF, TL testing alone is an imprecise screening tool for the presence of a telomere-related gene variant because the length varies among telomere genes.[32,54] However, broadly speaking, age-adjusted TL of more than the 50th percentile is less likely to coexist with a pathogenic telomere gene variant, whereas TL of less than the first percentile increases the likelihood of a telomere gene variant; therefore, sequencing could focus on telomere genes. Isolated TL testing can aid in the evaluation of patients with a personal or family history of multisystem manifestations suggestive of a short telomere syndrome: coexistent pulmonary fibrosis, liver disease, bone marrow failure, myelodysplastic syndrome or acute myeloid leukemia, premature hair graying, or a combination thereof. In this scenario, a short telomere syndrome is considered unlikely when age-adjusted TL is more than the 50th percentile, but is more likely when TL is less than the first percentile even when no mutation is identified.

When performed in conjunction with gene sequencing, TL testing may offer additional insight into the potential

pathogenicity of an identified telomere-related variant. In this setting, short age-adjusted TL may argue for pathogenicity depending on the variant and clinical history, whereas longer TL is less helpful in this regard. Available data suggest that a TL threshold-based approach is age dependent and cannot predict mutation pathogenicity accurately alone in all patients, but requires additional clinical data, including family history, for adequate interpretation.[47]

### Family Member Testing

The presence of a disease-causing variant in an affected family member offers potential actionable information for their relatives. In such cases, genetic counseling with targeted gene sequencing for the specific variant should be offered to other interested relatives to aid in susceptibility risk stratification. Those relatives who also harbor the variant should be considered at higher risk for disease development; however, disease penetrance and severity are highly variable, and currently no known interventions exist that prevent disease onset. In general, the risk of inheriting an identified variant and of disease developing is gene dependent and may range from 0% to 50%, depending on how the gene is inherited (autosomal dominant, autosomal recessive, or X-linked recessive). Autosomal dominant inheritance is the most common scenario in FPF, resulting in a 50% chance that the parents, children, and siblings of individuals with positive test results will inherit the same mutation. Because pulmonary fibrosis usually manifests in middle to late adulthood, asymptomatic individuals may not suspect that they carry a disease-causing variant until they undergo genetic testing. Genetic anticipation can be observed in kindreds harboring rare telomere gene variants resulting from progressive shortening of TL across generations. This can result in earlier age of pulmonary fibrosis onset and higher risk of bone marrow failure developing as the initial manifestation in subsequent generations.[12,48,55,56]

### Syndromic Presentations

Genetic testing should be considered in patients (with sporadic or familial disease) when personal or family history is suspicious for defined genetic syndromes such as short telomere syndromes, including dyskeratosis congenita, Hermansky-Pudlak syndrome, or young age at disease onset (adults younger than 50 years or pediatric patients). Dyskeratosis congenita (DC) is the first historically recognized short telomere syndrome that classically manifests dysplastic nails, lacy reticular skin pigmentation on the upper chest or neck, and oral leukoplakia. Most patients with DC experience bone marrow failure, which is the leading cause of death. Pulmonary fibrosis may manifest in late adolescence or early adulthood, often after bone marrow transplantation. To date, rare variants in at least 11 genes have been implicated in DC (*ACD*, *CTC1*, *DKC1*, *NHP2*, *NOP10*, *PARN*, *RTEL1*, *TERC*, *TERT*, *TINF2*, and *WRAP53*) and are transmitted through various modes of inheritance (X-linked, autosomal recessive, and autosomal dominant).[57,58] Heterozygous variants in *TERT*, *TERC*, *RTEL1*, and *PARN* are associated with disease, but biallelic variants rarely cause more severe forms of DC (eg, Hoyeraal-Hreidarsson and Revesz syndromes) or adult-onset FPF.[43] Patients with suspected DC should undergo TL testing with or without gene sequencing, because all patients with DC have short age-adjusted TL, but only 70% harbor a currently identifiable pathogenic variant in previously identified telomere genes.[59] This classic form of DC comprises only less than 10% of all short telomere syndrome manifestations, with the most common form being FPF.[47]

Hermansky-Pudlak syndrome (HPS) is characterized by oculocutaneous albinism and bleeding diathesis, and some patients with HPS also exhibit pulmonary fibrosis, granulomatous colitis, or immunodeficiency. If pulmonary fibrosis is present, it often manifests in the third decade of life. At least 10 genes (*AP3B1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, and less commonly, *AP3D1*, *BLOC1S3*, *BLOC1S6*, and *DTNBP1*) have been implicated in HPS and are inherited in an autosomal recessive manner.[60] The *HPS1*, *HPS4*, and *AP3B1* genes seem to be associated most strongly with pulmonary fibrosis, with many specific variants being more prevalent in certain populations (eg, those of Puerto Rican or Ashkenazi Jewish ancestry). In patients with clinical history or features suggestive of HPS, platelet electron microscopy and gene sequencing should be considered.[60]

Several surfactant metabolism genes also have been observed in patients with a pulmonary alveolar proteinosis phenotype in the neonatal period; variants in genes encoding for the GM-CSF receptor *CSF2RA*, *CSF2RB, MARS*, *SLC7A7* and *GATA2* also have been implicated in patients with pulmonary alveolar

proteinosis.[61–64] Variants in *COPA*, *TMEM173*, and *FOXF1* have been associated with syndromic presentations that may include interstitial lung disease.[65–67] The complete spectrum of disease associated with these genes has not yet been defined, but currently, it is not clear that adult presentations of isolated pulmonary fibrosis are seen in patients with these mutations.

## Scenarios When Genetic Testing Generally Is Not Indicated

Although genetic testing may provide high-yield results in the appropriate clinical setting, widespread genetic testing is not yet justified for all patients with pulmonary fibrosis because the relevance of such results remains unclear in many settings. Genetic testing generally is not recommended for the following indications.

### *Sporadic Pulmonary Fibrosis*

Genetic sequencing generally is not recommended for patients with sporadic pulmonary fibrosis unless they or their family members display features suggestive of a genetic syndrome. Although presence of the *MUC5B* promoter polymorphism greatly increases the risk of sporadic idiopathic pulmonary fibrosis, an estimated 20% of people of European ancestry carry this polymorphism,[9,68,69] and it is found at substantially lower frequencies in non-European populations,[70] limiting its usefulness as a screening tool. This is true of other common SNPs identified to date. Additionally, although several common SNPs have been linked to differential survival and treatment response in patients with idiopathic pulmonary fibrosis and other forms of pulmonary fibrosis, the role of these in clinical decision-making has yet to be defined.

The role of TL testing is understood incompletely and remains an active area of research. Short age-adjusted TL has been shown in retrospective studies to offer prognostic information across a variety of pulmonary fibrosis subtypes.[71–74] In addition, idiopathic patients with pulmonary fibrosis with short TL experience higher mortality and hospitalization rates when exposed to immunosuppressant medications.[75] Patients with the very short TL, even in sporadic PF, may have increased risk for myelosuppression after lung transplantation, and some TL patterns by flow-FISH also are associated with the development of myelodysplastic syndrome and acute myeloid leukemia.[49,56] Additional studies are needed to determine if and how TL measurement should be integrated into clinical practice.

Prior small case series and retrospective studies have identified unique management challenges after transplantation encountered in patients with pathogenic variants in telomere genes or short age-adjusted TL.[76–82] In some cases, short TL in idiopathic patients with pulmonary fibrosis has been associated with infectious complications occurring after transplantation and are indicative of an underlying immunodeficiency that may be unmasked by immunosuppressive medications.[78,83] Given the limited data currently available, genetic testing (gene sequencing or TL testing) is not recommended to inform lung transplant candidacy for patients with sporadic pulmonary fibrosis. However, future studies are needed to determine how and if this information can improve patient care after transplantation.

### *Unaffected Relatives*

Genetic testing is not currently recommended for unaffected relatives if the affected proband either has not undergone genetic testing or has shown negative results for genetic sequencing. In the genetics professions, it is considered best practice to initiate genetic testing in the individual most likely to be informative, ideally a family member with a diagnosis of the disease of interest.[84,85] Because current testing identifies a genetic cause in only 20% to 30% of probands, cascade testing of relatives is expected to have clinical usefulness only in these families. Without knowing the genetic cause in a family, negative results or VUS findings in an unaffected relative are considered indeterminate results with significant limitations for interpretation of risk. In these patients, ancillary testing such as TL may be warranted, educating the unaffected relatives that they may be at higher risk for development of disease given their family history, and we recommend age-appropriate medical screening examinations and avoidance of known risk factors and fibrogenic exposures. Of note, Carmichael et al[86] found that unaffected first-degree relatives undergoing clinical and genetic screening for FPF felt little regret over their decision to be tested or negative feelings on learning of a genetic risk factor.

## Genetic Testing Considerations

### *Genetic Counseling*

Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease and should be offered to all individuals before undergoing genetic testing.[87] Genetic counselors are health-care professionals with specialized training in

both medical genetics and psychosocial counseling. In addition to helping patients understand the risks and benefits of genetic testing, genetic counselors can help clinicians to identify the appropriate testing method, can help to facilitate testing, and can assist in the interpretation of the results. Therefore, we advocate for the inclusion of genetic counselors in the care pathway for all patients considering genetic testing.

### *Cost*

The cost of genetic testing varies significantly based on the number of genes tested, the technology used, and the specific laboratory selected. The out-of-pocket cost to the patient will depend on the list price for the test, insurance coverage, and whether preauthorization is required. Several laboratories offer to perform a benefit analysis before proceeding with testing and will contact the patient if the cost will be more than a specified amount. Because the out-of-pocket cost may range from zero to several thousand dollars, proactively reviewing the laboratory's policies may have significant financial repercussions for the patient.

### *Genetic Discrimination*

Patients often inquire if positive genetic test results could impact their ability to obtain health insurance. Although each state may have their own laws, the Genetic Information Nondiscrimination Act of 2008 is a federal law that prohibits health insurers from discriminating based on genetic information, including family history, and prohibits employers from using genetic information in employment decisions. However, the Genetic Information Nondiscrimination Act does not extend these protections to companies with fewer than 15 employees to life, long-term care, or disability insurance. The Genetic Information Nondiscrimination Act excludes military members in Tricare or the Veterans Affairs system, federal employees, and Indian Health Service because these entities already have their own protections in place. Therefore, it is prudent for asymptomatic individuals to obtain life and disability insurance before undergoing genetic testing. For this reason, it is not recommended that minors undergo genetic testing until they can understand the implications of genetic testing and provide informed consent.

## Alternatives to Genetic Testing

Although genetic testing should be offered in the appropriate clinical setting, some patients may decline to undergo testing after being counseled on the risks and benefits of testing. Because of the paucity of immediate clinical usefulness, low yield on mutation identification rate, possible high out-of-pocket costs, and hesitation from unaffected family members, genetic testing ultimately is up to the patient. In these situations, clinicians should continue standard management practices that include regular monitoring and institution of appropriate therapies. In addition, clinicians also should consider that the patient may have an unidentified genetic determinant of disease and remain diligent regarding possible extrapulmonary manifestations and risk for rapid pulmonary fibrosis progression.

Participation in DNA banking programs allows patients to preserve DNA samples until a later time when more is known about pulmonary fibrosis and its genetic underpinnings. Several commercial laboratories offer reasonable prices to store DNA for a patient or family members. This approach can allow for more informed genetic counseling even after a patient is no longer available. Alternatively, patients may elect to participate in research activities in which DNA banking is part of the research protocol.

## Conclusions

Significant advances have been made in identifying heritable genetic variants that underpin FPF. Genetic testing provides an opportunity to identify variants within patients and their relatives that serves as a powerful adjunct to inform clinical decision-making. The bench-to-bedside concept is in place; however, integrating the system into clinical practice remains challenging. Identifying patients with the highest yield for a genetic cause historically has been entrusted to specialist centers or genetics professionals who may not be familiar with the diagnosis and its complexity. This article attempts to provide the basic tools for the nongenetic pulmonary specialists to recognize, evaluate, and determine genetic testing candidacy for patients with FPF. However, as the field evolves, incorporating genetics into the multidisciplinary discussion may provide additional insights into patient- and family-specific clinical decision-making.[88,89] Although this statement was organized by a US-based panel, we acknowledge that health-care delivery can differ widely in other countries. As such, a European-based task force is developing a statement on the impact of genetics in pulmonary fibrosis.[90] It is our hope that these statements become a starting point for integrating genetic medicine in the care of patients with pulmonary fibrosis.

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