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REVIEW

Genetic Testing in Interstitial Lung Disease: Potential Benefits and Unintended Risks

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Abstract

Purpose of Review This review aims to summarize the recent evidence supporting the role of genetic testing across the spectrum of interstitial lung diseases and identifying barriers and unintended risks of genetic testing.

Recent Findings There is increasing interest among patients and their relatives in pursuing testing and no significant negative psychological impact of testing has been identified. Specific group of individuals who would most benefit from genetic testing (younger age at diagnosis, familial pulmonary fibrosis, features of short telomere syndrome, Hermansky-Pudlak syndrome, and relatives of individuals with known pathogenic genetic variants) and those who would likely not benefit from testing have been recently addressed. Gene sequencing can be used to identify known pathogenic variants in the surfactant-related genes and telomere-related genes. Peripheral blood leukocyte telomere length measurement may be of prognostic value and evidence for using this to guide clinical decision-making is evolving. Practical aspects like cost and availability of genetic testing are major barriers to genetic testing in the USA.

Summary Though genetic testing is not currently a part of routine clinical practice, there is a role for testing in specific situations. Future research should focus on how the results of genetic testing can guide clinical decision-making in pulmonary fibrosis.

Keywords Genetic testing · Familial pulmonary fibrosis · Familial interstitial pneumonia · Short telomere syndrome · Surfactant-related genes · Telomere-related genes · Telomere length

Introduction

Interstitial lung disease (ILD) is a broad category of diffuse parenchymal lung diseases which are often chronic and characterized by progressive fibrosis of the lungs.

Idiopathic pulmonary fibrosis (IPF) is one of the most progressive ILDs. Recent studies have identified several genetic variants that increase the susceptibility to develop IPF [1–5]. Some of these variants have also been noted in association with ILDs other than IPF such as rheumatoid arthritis-related ILD (RA-ILD) [6], fibrotic hypersensitivity pneumonitis (FHP) [7], and unclassifiable fibrotic ILDs as well as interstitial lung abnormalities (ILAs) [8, 9].

Pulmonologists often encounter patients who are interested in whether their ILD has a genetic basis and whether their children are at risk for developing the disease. Family members of individuals diagnosed with ILD may want to know their risk for the development of ILD and ways to modify this risk. In current clinical practice, testing for genetic variants is not routine since there are no well-established guidelines on when to test and how to use the test results for the management of ILD.

A study by Grant-Orser et al. showed that 67% of patients and first-degree relatives of individuals with ILD who were interviewed had an interest in testing for genes associated with ILD [10]. With growing interest in genetic testing, it is imperative for both patients and providers to understand the potential benefits and risks with genetic testing.

This review describes the current landscape of the genetics of pulmonary fibrosis, factors to consider when pursuing genetic testing in patients and relatives with ILD, and potential benefits and unintended risks with genetic testing.

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Familial Pulmonary Fibrosis

When two or more first or second-degree relatives are diagnosed with pulmonary fibrosis, it is referred to as familial interstitial pneumonia (FIP) or familial pulmonary fibrosis (FPF). Up to 20% of patients with a diagnosis of IPF have a family history of ILD. The presence of a family history of ILD has been shown to be a strong risk factor for developing IPF [11] and is associated with worse outcomes [12].

Families of Individuals with Pulmonary Fibrosis: What We Know

It has been noted that there is a clustering of ILD diagnosis in families which led to further work on identifying the genetic variants that are associated with increased risk for developing ILD. In studies looking at individuals who have a family history of ILD, a known pathogenic gene variant associated with increased risk of ILD is only identified in up to 20–30% of the time [13]. There are both common and rare genetic variants that have been associated with increased risk of developing ILD. These common and rare variants and their pattern of inheritance are discussed below (Table 1).

McGroder et al. looked at asymptomatic relatives of individuals with both sporadic and familial forms of ILD and found that first-degree relatives of both sporadic and familial forms of fibrotic ILD have increased prevalence of ILAs as well as early ILDs. In their study, there was a higher prevalence of ILAs when there was a family history of ILD (19% prevalence of ILAs in those with family history vs 8% in sporadic ILD). This study also included asymptomatic relatives of individuals with non-IPF forms of fibrotic ILDs (fibrotic hypersensitivity pneumonitis, connective tissue disease-related ILD (CTD-ILD), and unclassifiable fibrotic ILD) [14].

Hunninghake et al. also studied asymptomatic first-degree relatives of those with pulmonary fibrosis and found 31% of their cohort had undiagnosed ILA and 19% had ILD. However, in this study, there was no difference in the prevalence of ILAs or ILD between sporadic and familial forms in multivariable analysis [15].

It is important to note that among individuals diagnosed with ILD, those who have a familial history of ILD are typically younger than those without a family history of ILD [12, 16]. It is also reported that those with a family history have an earlier age at death than those without familial forms of ILD [12, 16]. However, the presence of a common variant known as MUC5b promoter polymorphism (MUC5B rs35705950) is paradoxically noted to be associated with increased survival from diagnosis of ILD compared to those without this variant, and the reason for this is unclear [17].

The phenomenon of anticipation, when the symptoms of a specific genetic condition appear at earlier ages in successive generations, has been noted in the presence of mutations involving telomere-related genes.

ILAs and Associated Risks

Interstitial lung abnormalities are incidentally detected findings in non-dependent areas in high-resolution computed tomography (HRCT) affecting more than 5% of any lung zone when there is no previously diagnosed ILD. Radiographically, ILAs can be ground glass opacities, reticulations, traction bronchiectasis or bronchiolectasis, honeycombing, architectural distortion, and non-emphysematous cysts. Between 20 and 73% of these ILAs progress to ILD [18, 19]. The presence of ILAs is associated with increased all-cause mortality [18, 20, 21]. ILAs and ILDs share common genetic SNP associations in genome-wide association studies (GWAS) [22]. ILAs are also associated with decreased leukocyte telomere length in multiple cohorts [23].

With an increasing number of chest CT scans performed for lung cancer screening and cardiac screening and with increasing awareness of ILAs and their implications, clinicians are also identifying more individuals with ILAs. Currently, when an ILA is identified, it is difficult to ascertain whether the individual will progress to ILD. Genetic testing may be a way to risk-stratify these individuals.

Types of Genetic Variants

Genetic variants have been implicated in both sporadic and familial forms of pulmonary fibrosis. Both common and rare genetic variants have been described in association with familial pulmonary fibrosis.

A common variant is one that is present at a higher frequency in the general population. A single nucleotide substitution of one base for another that occurs with a minor allele frequency of more than 1% of the general population is known as a single nucleotide polymorphism (SNP). Common variants typically have a low effect size.

Genome-wide association studies have uncovered several common genetic variants that are associated with IPF. These studies establish association that may influence disease but do not confer causality. Since common variants are, by definition, common and are not thought to be entirely causal for the development of disease, there is currently low utility in offering testing for these variants outside of research studies.

Rare variants are those that are typically present with a minor allele frequency of $<0.1\%$ in the population. However, these rare variants are often associated with high effect size. Rare variants are found clustered among families with disease.

Table 1 Glossary of terminology

Terminology	Explanation
Allele	There are typically one or more versions of a DNA sequence in a particular location on the genome, these versions are called alleles. A person inherits one allele from each parent. If the person is homozygous for that allele, then both the inherited versions are the same for that location on the genome
Allele frequency	Proportion of chromosomes or genes in a population having the specific allele
Anticipation	Phenomenon of anticipation is when the symptoms of a specific genetic condition appear at earlier ages in successive generations
Complex disease in genetics	When multiple factors, both genetic and non-genetic factors (such as environmental exposures) play a role in developing disease
Dominant	When the presence of a single copy of the allele is required to express the trait, that trait is referred to as a dominant trait
Epigenetics	It is the study of changes in the expression of the DNA that do not involve alterations in the sequence of the nucleotides. Chemical modifications such as DNA methylation and histone acetylation are epigenetic changes. Epigenetic changes can be due to environmental stresses and medications and can also be passed on during cell division
Exome	Portion of the genome containing the sequences of DNA, which is transcribed and present in mRNA, typically involves the coding regions but may also include non-coding regions of the genome. The exome only constitutes 1–2% of the genome. The rest of the genome consists of introns
Genomic variation	The differences in DNA sequence in individuals or populations. Some genomic variations can cause disease, and some do not
Kindred	A group of individuals who are genetically related
Mendelian inheritance	When the inheritance pattern can be explained by the Mendelian model like Autosomal or X linked and dominant or recessive, it is referred to as Mendelian inheritance
Penetrance	The likelihood of developing the disease, when there is a particular pathogenic variant associated with the disease, is present in an individual
Single nucleotide polymorphism	When 2 or more variant forms of a DNA sequence can occur in a population. A type of polymorphism is SNP or single nucleotide polymorphism. This refers to variation in a single nucleotide base at a certain location on the genome, and when this variation is present in typically more than 1% of the population
Variant	When there is a change in the DNA sequence, it is referred to as a genetic variant **Pathogenic variant**: disease-causing variant is called the pathogenic variant. This is usually confirmed by very strong evidence in studies **Likely pathogenic variant**: variant with strong but no definitive evidence of pathogenicity **Variant of uncertain significance (VUS):** when there is contradicting evidence for disease pathogenicity or when criteria for other classifications is not met **Likely benign variant:** when the variant has some evidence but not conclusive that it is not causing disease **Benign variant:** when there is strong evidence that a particular variant is established to be present in a healthy population and not associated with disease

Common Variants

In 2011, Seibold et al. reported the association of a SNP in the promoter region of the MUC5B gene with IPF [4]. Minor allele rs35705950 in the MUC5B gene has a higher allele frequency in those with IPF compared to the general population and confers a significantly higher risk of developing IPF. This MUC5B promoter SNP has been associated with other non IPF-ILDs including rheumatoid arthritis-associated ILD (RA-ILD) and fibrotic hypersensitivity pneumonitis (FHP). However, this MUC5B promoter polymorphism appears to be specific to the risk of the usual interstitial pneumonia (UIP) pattern [6].

Another notable common variant that has been reported in association with FPF is in the rs5743890 polymorphism in the TOLLIP gene (Toll interacting protein). The presence of this SNP may be associated with varying responses to therapy with N-acetyl cysteine and is being further studied [24].

Rare Variants

In the context of genetic testing for ILD, it is more useful to test for rare variants. Rare variants typically cause monogenic diseases. Rare variants that are well established in ILDs belong to two groups—surfactant-related genes (SRG) and telomere-related genes (TRG). Mutations identified in these two groups of genes and their inheritance pattern are shown in Table 2. Up to 35% of patients with FPF have a mutation in the telomere-related genes and 1–2% of patients with FPF have a mutation in surfactant-related genes [25].

Table 2 Rare genetic variants associated with risk of ILD and their Mendelian inheritance patterns. (Adapted and reproduced with permission of the ERS 2023: European Respiratory Journal 61 (3) 2,201,383; https://doi.org/10.1183/13993003.01383-2022 Published 16 March 2023)

Genes	Telomere (TRG) vs surfactant (SRG) related genes	Inheritance pattern
TERT	TRG	AD
TERC	TRG	AD
RTEL1	TRG	AD
PARN	TRG	AD
SFTPA1	SRG	AD
SFTPA2	SRG	AD
SFTPC	SRG	AD
ABCA3	SRG	AR
DKC	TRG	X linked

Role of Telomeres and Telomere Length in ILD

Telomeres are present at the ends of chromosomes and are composed of nucleotide repeats and specific proteins. They prevent the fusion of chromosomes and maintain the genomic integrity. Telomerase is the enzyme complex that generates and maintains telomeres. It has 2 essential components—telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC), which are RNA templates. Telomerase is expressed mainly in embryonic and adult stem cells. Exceptions are lymphocytes and select epithelial and testicular cells which also express telomerase. Over time, somatic tissue telomeres shorten, eventually triggering cell senescence and apoptosis [26].

The average length of telomeres in human leukocytes is based on the presence of variants in the telomere maintenance genes and the inherited telomere length [25]. Telomere length decreases with cell replication, and telomere length is shorter with aging. When a group of telomeres reaches a critical threshold (which could be around 100 base pairs), the cell may be triggered to go into apoptosis or cell cycle arrest due to a DNA damage response signal [25]. Cells with high turnover like skin and bone marrow are frequently affected in children with short telomere defects. In adults, liver and lungs which have slower tissue turnover are implicated in disease. Lung disease is the predominant manifestation of short telomere syndromes in adults, whereas bone marrow failure is most common in children.

Telomeres are considered to be short when age-adjusted telomere length is less than the 10th percentile in peripheral blood leukocytes. Telomere length is typically reported in a nomogram so that it is adjusted for age and comparable to distribution based on age across the population.

Short telomeres have been identified in up to 35–40% of the patients with familial pulmonary fibrosis and 25% of sporadic pulmonary fibrosis [27]. Telomere shortening maybe innate from mutations or acquired. Whether this shortening is from increased proliferation of immune cells is not completely clear [28]. Individuals with the shortest telomeres in the population have an increased risk for pulmonary fibrosis whether the shortening is from telomere-related gene mutations or not.

Table 3 Clinical features of short telomere syndrome that can be noted in individuals presenting with ILD or in their family history. (Adapted and reproduced with permission of the ERS 2023: European Respiratory Journal 61 (3) 2,201,383; https://doi.org/10.1183/13993003.01383-2022 Published 16 March 2023)

Clinical features
History of pulmonary fibrosis
Premature graying of hair
Cryptogenic cirrhosis
Bone marrow failure (aplastic anemia, myelodysplasia, leukemia)
Anemia, macrocytosis, thrombocytopenia, leukopenia
Nail dystrophy

It is thought that telomere shortening leading to alveolar stem cell senescence is dependent on both the genetic factors affecting telomere length as well as "second hits" like cigarette smoking, radiation, and other forms of lung injury acquired over time with aging. Of note, short telomeres are known to predispose individuals to both pulmonary fibrosis and emphysema.

Shorter telomere length predicts worse survival in patients with IPF [29] and across other ILDs [30, 31]. Extrapulmonary clinical manifestations of short telomere syndrome include premature graying of hair (in the second and third decade of life), cryptogenic cirrhosis, aplastic anemia and bone marrow failure, myelodysplasia or leukemia, and nail dystrophy (Table 3). Two or more of these features in an individual or family are suggestive of short telomere syndrome. Extrapulmonary manifestations of short telomeres in a patient with IPF are associated with decreased survival [32].

The presence of pathogenic variants in the telomere-related genes may not always correlate with telomere shortening. Also, when short telomeres are noted, the presence of identified mutations in the telomere-related genes is not always seen [25, 33, 34]. However, it is unusual to see mutations in telomere-related genes when age-adjusted leukocyte telomere length is greater than the 50th percentile [34]. Telomere length measurement should be considered when short telomere syndrome is suspected. However, when there is high suspicion for TRG mutations, further testing for gene variants may need to be pursued even if age-adjusted telomere length is not decreased.

Potential Benefits of Genetic Testing in ILD

Benefits of genetic testing may be classified as risk modification, life planning, monitoring for pulmonary and extrapulmonary disease, prognostication, and therapeutic management of the lung disease.

Risk Modification

Individuals who are at risk for developing ILD based on the result of genetic testing and those at high risk of disease progression can be counseled regarding risk mitigation.

Smoking has been well established to be a risk factor for the development of IPF and RA-ILD [35]. Smoking increases the risk of development and progression in ILAs [36] and ILD [37]. History of maternal smoking is also found to be an independent risk factor for the development of IPF [38].

Other modifiable risk factors for the development of ILD are exposure to inhalational organic and inorganic dusts (e.g., mold, avian antigens) that can lead to hypersensitivity pneumonitis in predisposed individuals [39, 40]. Air pollution with particulate matter less than 2.5 μm (PM2.5) in diameter has been shown to increase the risk for more severe fibrotic ILD, progression of ILD, and increased mortality [41]. Exposure to particulate dusts known to cause pneumoconiosis (asbestos, coal mining, silica dust, fiberglass dust, etc.) is also a known risk factor for fibrotic ILD.

Risk modification in these individuals would involve smoking cessation, change in occupation for those working in industries with particulates, and mitigating strategies for decreasing air pollution or moving to areas with less air pollution from PM2.5.

Decreasing the risk of lung injury from pulmonary infections should also be considered. Pulmonary fibrosis after severe illness from COVID-19 has been shown to be associated with decreased leukocyte telomere length. In this study, it was shown that with every 10% decrease in age-adjusted telomere length, there were 1.35 times increased odds of developing a fibrotic pattern on HRCT [42]. MUC5B promoter minor allele has also been shown to increase the risk of development of acute respiratory distress syndrome (ARDS). Hence, vaccination against pneumococcal strains, influenza, and COVID-19 would be considered prudent in those at risk for pulmonary fibrosis. Family members and patients who seek genetic testing do report change in health behaviors based on genetic testing in one study [10].

Life Planning

It is important to make the patient and family members aware that there are laws in the USA (Genetic Information Non-discrimination Act 2008) that prohibit discrimination in obtaining health insurance coverage for pre-existing conditions which include genetic mutations in the individual and family medical history. Individuals at risk who do not have health insurance may choose to obtain health insurance. Employment decisions to hire or fire employees based on genetic information are also prohibited. However, these laws do not apply to coverage for life insurance, long-term care insurance, or disability insurance in the USA. Hence, when an individual is considering testing, they should routinely be counseled on these factors. Individuals may choose to obtain appropriate life or disability insurance coverage prior to undergoing genetic testing.

Another important aspect of genetic testing is in young individuals who are making decisions regarding family planning. Couples planning a pregnancy may decide to undergo genetic testing if there are multiple family members with ILD or if they are at risk for conditions like the Hermansky-Pudlak syndrome (HPS) or Dyskeratosis congenita (DKC) or have a family history of surfactant protein mutations.

Monitoring of Pulmonary Disease

In individuals who are identified to have short telomeres, as well as those with variants in telomere-related genes, there is decreased transplant-free survival.

Early antifibrotic use at the time of ILD diagnosis may be considered in these individuals to slow down the rate of decline in lung function. Both nintedanib and pirfenidone are found to be safe and effective for those with familial pulmonary fibrosis and specifically those with mutations in TRG [43, 44]. However, there is no evidence currently to consider antifibrotic use in individuals without ILD and in those with ILAs, unless there is progressive fibrosis [45, 46]. If ILAs are recognized in asymptomatic relatives of individuals with ILD, close monitoring of pulmonary function tests and HRCT for the progression of the disease should be considered. However, there are no clear guidelines currently on how often pulmonary function tests and HRCT should be performed in those with ILAs.

It is important to discuss with asymptomatic relatives at risk and make them aware of symptoms and signs of pulmonary disease to monitor (dyspnea, persistent cough, decreased exercise capacity, frequent respiratory exacerbations, chest tightness, clubbing, bibasilar inspiratory crackles on lung exam, oxygen desaturation). They should be advised to obtain chest HRCT when they do develop symptoms. These pulmonary symptoms are not specific to ILD and may initially be attributed to other respiratory diseases, and hence, they should be encouraged to seek medical care in a center with expertise in ILD.

Early referral to a center capable of performing lung transplants should also be considered in those at high risk for progression (especially those with short telomeres, mutations in TRG and SRG, and those with HPS). Telomere length is found to be an independent predictor in the outcome of IPF and non IPF-ILDs, including interstitial pneumonia with autoimmune features (IPAF) and unclassifiable ILD, with shorter telomeres increasing the risk of worse outcomes [47]. There is evidence of decreased

survival and increased chronic lung allograft dysfunction in those undergoing lung transplant in individuals with short telomeres [48, 49]. Some lung transplant centers routinely check leukocyte telomere length to modify the immunosuppressive regimen post-transplant. However, measuring telomere length in individuals undergoing lung transplant evaluation is not routine practice [50]. Irrespective of telomere length, there appears to be improved survival and quality of life with lung transplant in those with pulmonary fibrosis [51].

Individuals who are found to have mutations in SFTPA1 and SFTPA2 are at increased risk for developing lung cancer in addition to pulmonary fibrosis. Hence, screening for lung cancer should be considered in these individuals.

Monitoring for Extrapulmonary Disease

When short telomeres or known pathogenic variants in TRG are identified, monitoring for extrapulmonary manifestations of short telomere syndrome should be considered. This would include checking liver function tests and complete blood count to screen for abnormalities in the liver and bone marrow, respectively. Primary cause of mortality in adults with short telomere syndrome is pulmonary fibrosis, and the next cause of mortality is disorders of bone marrow including aplastic anemia, myelodysplasia, and leukemia.

Prognostication

As mentioned above, individuals with short telomeres and those with mutations in TRG are at increased risk of ILD at younger age, increased rates of disease progression, and decreased transplant-free survival. Genetic testing will help identify those at increased risk for worse outcomes. Though MUC5B promoter polymorphism with a minor allele has been associated with an increased risk of developing IPF and RA-ILD, individuals with this SNP have been shown to have longer survival from the time of diagnosis compared to those without this polymorphism, conferring a better prognosis.

Decisions Affecting the Management of Lung Disease

Some of the benefits of genetic testing regarding ILD management have been discussed above (risk modification, lung cancer screening, early antifibrotic use, and early referral to a lung transplant center). Other potential benefits of genetic testing in management decisions are discussed in this section.

Newton et al. showed that there was an increased risk of ILD progression and a higher risk of death and lung transplantation in patients with IPF who had short leukocyte telomeres [52].

Immunosuppressive therapy has been widely used to manage non IPF-ILDs including chronic hypersensitivity pneumonitis (CHP). This raises the concern that immunosuppressive therapy used for the management of CHP may also affect outcomes based on leukocyte telomere length. In a study by Adegunsoye et al. looking at the interaction between immunosuppressive therapy with mycophenolate mofetil (MMF) and telomere length in 189 patients with CHP, they found that survival was in fact better with MMF in those with telomere lengths in the second to fourth quartiles. Those with the lowest quartile telomere length did not have improved survival with MMF. This interaction must be evaluated further in future studies; however, it is reassuring that the use of immunosuppressive therapy in a non-IPF diagnosis in those without short telomeres does not seem to portend harm.

Oldham et al. found a significant interaction between the TT genotype in TOLLIP SNP where N-acetyl cysteine (NAC) therapy in IPF was associated with a reduced risk of the composite endpoint of death, transplantation, and hospitalization, whereas the CC genotype was associated with a trend toward harm [24]. Results from an ongoing randomized clinical trial evaluating the benefit of NAC in individuals with IPF with TT genotype are awaited [53].

With certain rare variants described next, the radiologic manifestations are not always consistent with UIP. In individuals with SFTPC and ABCA3 mutations, HRCT features reported are the presence of cysts especially in upper lobes, in addition to ground glass opacities, septal thickening, and reticulations. The HRCT pattern for adults with SFTPA1, SFTPA2, and NKX2-1 mutations is not typically UIP, and increased ground glass opacities and septal thickening have been described [1, 3, 54–57].

The presence of cysts would render the HRCT pattern as inconsistent with UIP according to the 2018 ATS guidelines [58]. A surgical lung biopsy may be avoided in these individuals when it is known that they have a rare variant that would lead to atypical presentations for ILD. In children with surfactant protein mutations, the use of hydroxychloroquine and corticosteroids has been described; however, this is not studied in adults [59].

Unintended Risks and Barriers to Genetic Testing

Although the discussion so far has focused on the potential benefits of genetic testing in ILD, there are downsides and risks involved with such testing.

Practical Aspects and Cost

Genetic counseling can help explain the risks and benefits, weigh the options, and understand the implications of genetic testing to an individual's health, psychological well-being, and implications to other family members. Hence, it is advisable to undergo genetic counseling before pursuing testing. Certified genetic counselors are not easily accessible which can be a barrier to pursuing testing and understanding the full implications of genetic testing.

The other practical aspect to consider is the cost of testing. Health insurance typically does not cover the cost of genetic testing for ILD, and hence, out of pocket costs may be a significant barrier for some individuals who are interested in testing. Costs are also variable and may reach a few thousand dollars based on the laboratory and the panel of genes tested.

Lack of Established Guidelines

Until recently, there were no well-established guidelines currently that provided recommendations on when and which genetic tests to pursue. In 2022, the European Respiratory Society published a statement on familial pulmonary fibrosis which aims to address these issues [60]. In North America, there was a document by a working group involved in the Pulmonary Fibrosis Foundation that provided some perspectives by researchers and clinicians on the role of genetic testing in pulmonary fibrosis [61]. Hopefully, these documents will provide a common framework for pulmonologists and patients to identify situations where genetic testing would be beneficial.

Uncertainty of Effect

Penetrance measures the proportion of individuals in a population who carry the specific gene and express the related trait (Table 1). Many of the rare variants described in this discussion (TERT, TERC, RTEL1, PARN, SFTPA1, SFTPA2, SFTPC) are inherited in an autosomal dominant manner. Rare variants in SRG typically have a high penetrance. However, the variants in TRG typically have incomplete penetrance. As discussed above, though the presence of a mutation is associated with a high risk for disease, the absence of the mutation in TRG does not exclude an increased risk for disease. Hence, when pathogenic variants are not found on genetic testing, this does not exclude familial forms of pulmonary fibrosis.

Gene expression is affected by epigenetic modifications and genetic testing to identify rare disease-causing variants does not account for epigenetic factors in risk of developing disease.

Though ILAs have been associated with similar genetic risks as ILD and associated with increased risk of all-cause mortality, the proportion of ILAs that progress is variable in studies. When an ILA is identified on HRCT, there is no consensus on whether there is a risk of progression to ILD in a particular individual [8, 19, 21–23]. In up to 50% of individuals, these ILAs may resolve or improve. Since these individuals must be monitored with serial lung function testing and HRCTs, this results in unnecessary anxiety, cost, and radiation exposure.

Anxiety Regarding Testing

It may be useful to ascertain the intent in pursuing genetic testing in patients and families who seek testing. Finding out their genetic predisposition for the disease may give some individuals peace of mind in answering the question, "Why did I get this disease?" and maybe a motivation for pursuing testing. When a patient with ILD has been identified to have disease-causing variant, this may provoke anxiety in related family members regarding their risk of developing disease. It is reassuring that Carmichael et al. found that there was no decisional regret in 90% of the relatives of individuals with pulmonary fibrosis who were screened for pulmonary fibrosis [62].

Results from a gene sequencing panel may reveal variants of uncertain significance or VUS (Table 1). Only a quarter of the genes involved in familial pulmonary fibrosis are currently known. Since only a small fraction of genetic variants have been identified to be associated with increased risk of developing ILD, when no known genetic variants are identified, this does not rule out the absence of a genetic risk to develop ILD.

Several direct-to-consumer DNA testing kits (e.g., 23andMe) are now available to detect variants in cystic fibrosis and alpha1 antitrypsin deficiency. It is likely that these kits may include tests for the risk of pulmonary fibrosis in the future, and providers should be prepared to counsel patients regarding these situations.

Lack of Actionable Mutations

Unlike therapies that are available for other pulmonary disorders with a genetic basis like cystic fibrosis, there are no approved therapies that would significantly alter the course of disease in ILD. Antifibrotics have shown to slow the rate of lung function decline in familial pulmonary fibrosis. However, antifibrotics would likely be offered to individuals with progressive pulmonary fibrosis, and genetic testing may not add to the management of progressive disease. In individuals at risk for ILD, modifiable risk factors (smoking cessation, avoidance of particulate dusts, antigen avoidance) should be recommended in any case, and hence, genetic testing would not change these recommendations.

The Role of Race and Ethnicity

Prevalence of these genetic variants is best studied in the non-Hispanic White population. The prevalence and implications of these common and rare variants in non-white populations are not as extensively studied. For example, the MUC5B promoter minor allele was rare in the Chinese population [63], it was associated with IPF in the Mexican population but not in the Korean population [64, 65]. South Asian Indians have similar prevalence and risk as that of the Caucasian white population [66]. Pathogenic variants in SRG have been well characterized in the Dutch cohort. The prevalence of these rare variants and clinical manifestations with mutations related to SRG or TRG in non-White populations is not clear. Hence, further studies are required to explore these variants in non-White populations.

Situations Where It May Be Beneficial to Test

There is some consensus that diagnosis of ILD in individuals with the following characteristics may warrant discussion regarding genetic testing [13, 60, 61]. In these individuals, potential benefits of testing may outweigh the risks of testing.

- Young age at ILD diagnosis (age less than 50)
- Syndromic features (Hermansky-Pudlak syndrome, Dyskeratosis congenita)
- Presence of extrapulmonary manifestations of short telomere syndrome
- Pathogenic variants identified in family members

It is currently a matter of debate whether all individuals with a diagnosis of ILD and who have a family history of ILD (those with familial pulmonary fibrosis) should be offered genetic testing. In these situations, it could be offered on a case-by-case basis. Providers and patients may choose not to pursue testing if it will not affect clinical decision-making regarding further management of their ILD.

Situations Where Testing Is Unlikely to Be Beneficial

There is also some agreement that genetic testing is unlikely to be of significant benefit in sporadic forms of ILD when there are none of the features above (younger age, syndromic features, short telomere features) [13, 60, 61].

Which Genetic Test to Do?

Methods of Testing

The choices to consider when pursuing testing are (a) whether to look for known pathogenic variants in genes (gene sequencing) or (b) measure leukocyte telomere length testing or (c) perform both. Whole genome sequencing (WGS) or whole exome sequencing (WES) can be used to identify specific variants associated with ILD, though the latter is more accessible and more affordable. Clinical practice varies across institutions and is based on availability, familiarity with the test, and cost. Those with suspected risk for variants in SRG should undergo gene sequencing.

Peripheral blood leukocyte telomere length is the most typically measured and used as a surrogate for germline telomere length if individuals do not have hematologic diseases. Flow FlSH or flow fluorescence in-site hybridization technique is standardized and reproducible but less commonly available. Telomere length is reported in a nomogram so that it is adjusted for age and comparable to distribution based on age across the population. Other techniques used for telomere length measurement are quantitative PCR (qPCR), next-generation sequencing, and southern blotting. Most widely available test uses the qPCR technique but is less reproducible than the flow FISH technique. Various research studies use different techniques to measure leukocyte telomere length, and hence, there is a lack of consistency in reporting. This may affect reproducibility across studies and hence external validity and reliability [23, 25, 32, 47, 52, 67–71].

If peripheral blood leukocyte telomere length testing identifies short telomeres ($< 10^{th}$ percentile), this may be followed by testing for variants in TRG. This is especially important in those who have a personal or family history of features of short telomere syndrome or features of DKC.

If the individual is young(age < 50) or if there is a family history of ILD in childhood, checking for variants in SRG may be considered. Adults with pathogenic variants in SRG (ABCA3, SFTPA1/A2, SFTPC, and NKX2) have been described to have a spectrum of radiographic and histologic features, often categorized as unclassifiable pattern.

If there are features of bleeding diathesis from platelet dysfunction, neutropenia, and oculocutaneous albinism in addition to ILD in a younger patient, testing for the Hermansky-Pudlak syndrome should be considered [61, 72, 73].

Tests for common variants like MUC5B promoter SNP are less likely to be of benefit. Based on the results of the ongoing PRECISIONS-IPF study, there may be utility in testing for the TOLLIP rs3750920 TT genotype in the future [53].

Conclusions

Scientific knowledge of genetic factors affecting susceptibility for pulmonary fibrosis, risk of disease progression, response to therapy, and survival is constantly evolving. Genetic variants have been identified in both sporadic and familial pulmonary fibrosis. Some of these variants associated with disease have similar effect across the spectrum of various interstitial lung diseases and not just IPF. Recently identified genetic variants have improved our understanding of pulmonary fibrosis, provided potential targets for therapy that are being investigated, but also raise several questions on their current clinical utility.

Though there are several benefits in pursuing genetic testing in a specific subgroup of individuals and families with ILD, this should be done after extensive counseling regarding the health, financial, and psychological implications to the individual and their family members.

There is an increasing need for guidelines that integrate the role of genetic testing to clinical practice. The scientific community across North America and Europe has made recent efforts to address this issue [60, 61].

Compliance with Ethical Standards

Conflicts of Interest Dr. Krishna reports receiving institutional funds for serving as Site Principal Investigator for multisite clinical trials with United Therapeutics and from Biobridge Therapeutics, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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