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Executive Summary

Pulmonary Fibrosis Foundation Position Statement on Genetic Testing

Introduction

Pulmonary fibrosis (PF) is a term used to describe a collection of disorders characterized by progressive scar accumulation within the lung. Common causes of PF include occupational, environmental and drug exposures and systemic autoimmune disease. Patients for whom no clear etiology can be identified are considered to have an idiopathic interstitial pneumonia, of which idiopathic pulmonary fibrosis (IPF) is the most common and deadly. It has become clear that heritable (genetic) factors play a major role in risk for IPF.

Genetic Basis of Pulmonary Fibrosis

Familial Pulmonary Fibrosis (FPF) – Pathogenic rare variants in more than 10 genes have been implicated in the development of FPF, including genes related to surfactant metabolism and telomere maintenance. Variants in surfactant-related genes SFTPA1, SFTPA2, SFTPC, ABCA3 and NKX2-1 have been found in 1-3% of FPF families. Variants in telomere-related genes (TERT, TERC, PARN, DKC1, NAF1, RTEL1, ZCCHC8, and TINF2) are found in a total of 20-30% of FPF cases and cause the telomeres to shorten. Pathogenic variants in the telomere-related genes may be associated with more rapid disease progression. Telomere length can be measured in blood cells and is a prognostic biomarker. In most FPF cases, mutations act in a “dominant” manner where carrying a single copy of a mutation is sufficient to confer FPF risk.

Sporadic IPF – In patients with IPF that does not appear to be familial, disease risk is known to be influenced by common genetic variants (single nucleotide polymorphisms, SNPs). These SNPs are generally found in at least 5- 10% of healthy individuals, but have higher frequency in IPF patients. The SNP most highly associated with IPF is found in the promoter for the gene encoding MUC5B. Individuals with one or two copies of the risk (T) SNP have 6-20 times greater risk for IPF than someone who does not have the risk SNP. At least 15 other IPF susceptibility SNPs have been identified, including near TOLLIP, DSP, TERT and AKAP13.

Clinical Scenarios Suggestive of a Genetic-mediated Pulmonary Fibrosis

FPF - A diagnosis of FPF should be suspected when a PF patient has at least one other closely related relative affected by pulmonary fibrosis. These patients should be considered for genetic counseling and testing.

Short telomere syndrome – Bone marrow disease, unexplained liver disease, and premature greying (onset in 20's or younger) in addition to pulmonary fibrosis are features of short telomere syndromes. Combinations of these processes within an individual or related family members should raise suspicion for underlying genetic variant in a telomere-related gene.

Syndromic- Classic features of Dyskeratosis Congenita, a prototypical short telomere syndrome, include a triad of dysplastic nails, lacy reticular pigmentation patterns on the upper chest/neck and oral leukoplakia. The combination of oculocutaneous albinism and pulmonary fibrosis, along with abnormal bleeding, should raise suspicion for Hermansky-Pudlak Syndrome (HPS). In contrast to FPF and short telomere syndromes, mutations in both copies of HPS genes are required for disease risk.

Genetic Testing Overview

Patients with possible or likely genetic forms of PF should be referred for genetic evaluation and counseling when possible. Such evaluation will help determine whether genetic testing is appropriate and help educate the patient about the risks and benefits of genetic testing. This can be done in their doctor's office, a PFF Care Center, a local medical genetics clinic, or through telehealth genetic services.

Genetic Testing Considerations- Genetic testing carries risks and benefits for not just the patient, but also their immediate and extended family members. For the patient, identifying a gene mutation may influence clinical management and confer prognostic information. Genetic counseling assists patients' understanding and helps them adapt to the medical, psychological and familial implications of genetic diseases. Genetic counseling should be performed prior genetic testing for FPF.

Gene mutation testing is traditionally performed using germline (or inherited) DNA extracted from a blood, saliva, cheek cells, or skin biopsy rather than somatic DNA from the lung. Germline testing assesses whether the DNA code in genes linked to FPF carries variation relative to the general population. DNA testing can take between 3-6 weeks to complete. Genetic testing results should be interpreted by specialists with expertise who can explain test results to patients and family members.

Potential Results of Genetic Tests - Up to 30% of cases of FPF will have a positive test for a causative mutation in a gene implicated in FPF. In this case, family members can undergo genetic testing to determine if they have the same mutation and are at increased risk for developing FPF. A positive result in another family member may prompt a recommendation for regular screening for signs of lung or extra-pulmonary disease associated with their genetic mutation. In some patients, genetic testing may identify a genetic mutation that has not been reported previously, and/or has unclear functional consequences. This finding is called a "Variant of uncertain significance" (VUS). A VUS may later be reclassified as either pathogenic (disease-causing) or benign based on emerging information such as telomere length testing or additional functional studies. A negative genetic test in an FPF patient may mean they either do not carry a disease causing variant, or they carry a mutation in a gene that has not been yet linked to FPF. A negative genetic test does not indicate other family members are not at risk for FPF. Additional genetic evaluation, primarily in a research setting, may be available to these patients at some centers.

Telomere length testing - Telomere length testing can be used alone or in combination with genetic testing when there is concern for a short telomere syndrome. Flow-cytometry-based telomere measurement (Flow-FISH)

is currently the only method of telomere length testing validated for clinical use. Telomere length does not perfectly discriminate between the presence and absence of a pathogenic telomere-related variant, but age-adjusted telomere length >50th percentile is less likely associated with a pathogenic variant.

Further study is needed to determine the role, if any, of telomere length testing in potential lung transplant recipients.

Cost - The cost of genetic testing varies significantly based on the nature of testing performed. Because the out-of-pocket cost may range from zero to several thousand dollars, proactively reviewing a specific lab's policies may have significant financial repercussions for the patient.

Genetic discrimination - The Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits health insurers and employers from discriminating on the basis of genetic information or family history. However, GINA does not extend these protections to life, long-term care or disability insurance. Therefore, it is prudent for asymptomatic individuals to obtain life and disability insurance before undergoing genetic testing.

Genetic Testing Recommendations

Key questions in considerations of genetic testing include whether the results of such testing would 1) influence disease management, 2) assist in risk stratification and/or 3) provide relevant information for the patient or patient's family. In general, the decision to perform genetic testing should be influenced by the likelihood of identifying a culprit mutation (pretest probability) in an individual.

Testing in FPF - Genetic testing should be discussed in patients with a high likelihood of FPF based on family history. It is important to remember that a wide range of ILD subtypes exist in families. A culprit variant will be identified in about 20-30% of patients with FPF. Telomere length testing can be employed as first line testing to screen for a likely telomere gene mutation, as in second line testing to assess potential pathogenicity of an identified variant after genetic testing and as an adjunct to genetic testing. Testing may be considered in families with young age of onset (<50 years) and/or pediatric cases of pulmonary fibrosis where surfactant-related genes or short telomere syndrome genes may be involved. If a culprit mutation is identified in an FPF patient, testing for their family's mutation can be offered to other family members.

Testing of asymptomatic individuals with a family history of FPF is generally not recommended if a pathogenic mutation is not known in their family. Testing is generally not recommended for children and minors younger than 18.

Syndromic ILD- Several specific features and syndromes warrant genetic testing regardless of family history. In patients with a personal or family history suggestive of short telomere syndrome, Dyskeratosis Congenita, or Hermansky-Pudlak Syndrome, genetic testing should be considered.

Genetic testing is generally not recommended for common genetic variants in sporadic or familial cases of IPF – Although numerous common polymorphisms are associated with increased susceptibility for IPF, these are found in 5-10% or more of the general population so are not useful as a screening or diagnostic tool.