Molecular Testing for Interstitial Lung Disease

Effective: February 1, 2024

Next Review: November 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Interstitial lung diseases (ILDs) can cause irreversible and progressive damage to lung tissue. Distinguishing between ILDs can be challenging, and diagnostic testing for these disorders includes histopathology and radiology testing. Gene expression testing has been proposed as a method for identifying patients with idiopathic pulmonary fibrosis, one of the most common ILDs.

MEDICAL POLICY CRITERIA

Gene expression testing for the diagnosis of interstitial lung diseases is considered **investigational**, including but not limited to the use of the Envisia® Genomic Classifier for idiopathic pulmonary fibrosis.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Genetic Testing for Alpha-1 Antitrypsin Deficiency, Genetic Testing, Policy No. 61
2. Molecular Testing in the Management of Pulmonary Nodules, Laboratory, Policy No. 73

BACKGROUND

INTERSTITIAL LUNG DISEASE AND IDIOPATHIC PULMONARY FIBROSIS

Interstitial lung disease (ILD), also known as diffuse parenchymal lung disease, describes a group of disorders that are characterized by damage to the tissues that support the alveoli of the lungs, called the pulmonary interstitium. These diseases generally cause lung damage through inflammation and fibrosis of the interstitial tissue, which is irreversible and may get worse over time. They can affect children as well as adults.

A number of genetic and environmental factors can contribute to the development of ILD, including smoking, lung infections, certain medications, radiation therapy, and exposure to hazardous materials such as asbestos.[1] Individuals with certain autoimmune disorders, including rheumatoid arthritis, are also at increased risk of developing ILD. The diagnostic work-up of ILD may include chest x-rays, computed tomography (CT) scans, pulmonary function tests, bronchoscopy, and lung biopsy.[1]

ILDs may classified by their clinical presentation and by their cause. Examples of ILDs include eosinophilic pulmonary diseases, pulmonary Langerhans cell histiocytosis (granulocytosis), lymphangioleiomyomatosis, pulmonary alveolar proteinosis, and sarcoidosis.[2] However, in many cases there is no cause identified, and these are known as idiopathic interstitial pneumonias (IIPs). The American Thoracic Society has classified IIPs into the following groups:[3]

- Major idiopathic interstitial pneumonias
    - Idiopathic pulmonary fibrosis
    - Idiopathic nonspecific interstitial pneumonia
    - Respiratory bronchiolitis–interstitial lung disease
    - Desquamative interstitial pneumonia
    - Cryptogenic organizing pneumonia
    - Acute interstitial pneumonia
- Rare idiopathic interstitial pneumonias
    - Idiopathic lymphoid interstitial pneumonia
    - Idiopathic pleuroparenchymal fibroelastosis
- Unclassifiable idiopathic interstitial pneumonias

Idiopathic pulmonary fibrosis (IPF) a form of chronic, progressive, fibrosing interstitial pneumonia, and the diagnosis of IPF is made when other causes of ILD have been excluded.[3] Histologically, IPF is generally characterized by a pattern known as usual interstitial pneumonia (UIP), which may be identified in biopsy specimens or using high-resolution computed tomography (HRCT).[4]

The risk of developing IPF increases with age. The primary symptoms are nonproductive cough and shortness of breath, particularly with exertion. IPF is a progressive disease, and although the clinical course is variable, prior to the availability of antifibrotic medications, the

median survival for IPF patients was three to five years following diagnosis.[5] The use of antifibrotic medications is associated with slower progression.[6]

GENE EXPRESSION PROFILING FOR DIAGNOSIS OF IPF

Gene expression profiling is used to measure the expression of specific genes in a tissue, and this type of testing has been proposed as a method for evaluating ILD.

The Envisia® Genomic Classifier (Veracyte) uses a machine-learning algorithm to evaluate gene expression profiles from transbronchial lung biopsy samples.[7] The test is designed to identify UIP, which is the hallmark characteristic of IPF.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on three main principles: (1) analytic validity, which refers to the technical accuracy of the test; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility, which refers to how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on clinical validity and utility, particularly evidence from well-designed studies related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention; and
- Improve health outcomes as a result of those decisions

While a number of studies have evaluated associations between gene expression patterns and interstitial lung disease, only the Envisia® Genomic Classifier (Veracyte) is commercially available and marketed for this purpose. No randomized controlled trials (RCTs) of the Genomic Classifier have been published, and the evidence for this test is limited to nonrandomized studies.

Clinical Validity

The development of the Envisia® Genomic Classifier was published by Pankratz (2017).[8] Exome-enriched RNA sequencing was performed on transbronchial biopsy (TBB) specimens from 113 individuals with suspected ILD, with up to five specimens per individual. Of these, 25 individuals were excluded for nondiagnostic pathology or unclassifiable fibrosis (n=18), histopathology requiring unblinded review for diagnosis (n=6), or lung cancer (n=1). Four additional participants were excluded for unusable RNA sequencing data. Pathologic diagnoses were categorized as either UIP or non-UIP, and this information was used to generate an algorithm for classification with machine learning, using data from 54 patients (training group). The highest-performing algorithm was tested on an additional test group, with a similar distribution of UIP/non-UIP pathologies to the training group. Only patients that had sufficient samples for pooling were included in the performance analysis, which further reduced the training group to 38/53 (72%) and the test group to 27/31 (87%), with the additional exclusion of an addition test participant for unusable sequencing data. The classifier algorithm had a sensitivity of 59% (95% confidence interval [CI] 33% to 82%) and a specificity

of 100% (95% CI 66% to 100%) for UIP pathology in the remaining 26 participants in the test group (17 with UIP and nine with non-UIP pathology).

Results from a company-sponsored validation study called the Bronchial Sample Collection for a Novel Genomic Test (BRAVE) study were published by Raghu (2019).[9] The study included 237 patients undergoing evaluation for interstitial lung disease at multiple centers in the U.S. and Europe. Histopathologic diagnoses were made based on surgical or TBB specimens and, when available, high-resolution chest CT (HRCT). RNA sequencing for the genomic classifier test was performed on pooled patient samples composed of three to five TBB samples per patient. Diagnosis and RNA sequencing data from 90 of the patients was used to train the machine-learning algorithm to discriminate between UIP and non-UIP, and then the classifier was tested on TBB samples from 49 patients. In this test group, the classifier identified UIP with 88% specificity (95% CI 70% to 98%) and 70% sensitivity (95% CI 47% to 87%). A subgroup analysis of the BRAVE study patients that had HRCT performed was published by Richeldi (2021), which reported that the HRCT identified UIP in 18 of 53 patients with UIP histopathology, while genomic classifier test identified an additional 24.[10]

A systematic review by Kheir (2022) included the three studies above and an additional study that measured diagnostic confidence related to the use of the test.[11] In the meta-analysis, the pooled sensitivity of the test was 68% (95% CI 55% to 73%) and the specificity was 92% (95% CI 81% to 95%) for UIP pattern. However, the authors noted the moderate to very-low quality of the available evidence for measures of test characteristics, agreement, and confidence.

Chaudhary (2023) published a retrospective study of 192 patients who previously received diagnostic bronchoscopy along with genomic classifier UIP testing to investigate whether a positive genomic classifier UIP diagnosis is associated with a progressive IPF phenotype.[12] 104 patients had a positive genomic UIP classification, and 88 had a negative classification. In multivariable analysis, positive genomic UIP classification was associated with reduced progression-free survival (hazard ratio 1.58, 95% CI 0.86 to 2.92; p=0.14), but this did not reach statistical significance.

A retrospective study by Abdalla (2023) evaluated the concordance between transbronchial lung cryobiopsy and the Envisia Genomic Classifier at diagnosing interstitial lung disease.[13] Among 49 patients, imaging demonstrated a probable (n=14) or indeterminate (n=7) UIP pattern in 43% and an alternative pattern in 57% (n=28). Envisia Genomic Classifier results were positive for UIP in 37% (n=18) and negative in 63% (n=31). The concordance between the Envisia Genomic Classifier and transbronchial lung cryobiopsy was 76% (37 of 49) with discordant results seen in 24% (12 of 49) of patients.

Clinical Utility

While some studies have evaluated the impact of genomic classifier testing on diagnostic confidence[14] and decision making[15], no studies have been published that evaluate the impact of gene expression testing for ILDs on patient health outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN THORACIC SOCIETY, EUROPEAN RESPIRATORY SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND LATIN AMERICAN THORACIC SOCIETY

The American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society (2022) published guidelines on the diagnosis of IPF which did not include any recommendations related to gene expression testing.[16]

SUMMARY

There is not enough research to show that gene expression testing for the diagnosis of interstitial pulmonary fibrosis or other interstitial lung diseases (ILDs) can improve health outcomes for patients with these disorders. In addition, clinical guidelines do not recommend this type of testing. Therefore, this testing is considered investigational.

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CODES

Codes	Number	Description
CPT	81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP])
HCPCS	None	

Date of Origin: *December 2018*