**Medical Coverage Policy |** Envisia for Idiopathic Pulmonary Fibrosis

**EFFECTIVE DATE:** 01|01|2021
**POLICY LAST UPDATED:** 03|01|2023

## OVERVIEW

The Envisia genomic classifier is a multianalyte assay with algorithm analyses that analyzes gene expression of 190 genes to deliver a categorical UIP or Non-UIP result. The Envisia classifier is intended for patients with interstitial lung disease (ILD) suspected of idiopathic pulmonary fibrosis (IPF) and who do not have a definitive usual interstitial pneumonia (UIP) pattern by high resolution computed tomography (HRCT) or other known cause The Envisia genomic classifier is intended to provide a categorical UIP or Non-UIP result that along with clinical and radiographic information may guide treatment without the need for surgical lung biopsy reducing patient risk.

The following test is addressed in this policy:

- Envisia Genomic Classifier (Veracyte)

## MEDICAL CRITERIA

**Medicare Advantage Plans**

The Envisia Genomic Classifier may be considered medically necessary when all of the following criteria are met:

- The patient is healthy enough to undergo a bronchoscopy with transbronchial biopsies, and
- High-resolution CT scan of the chest (defined by high kernel ~1mm axial reconstructions, including both inspiratory and expiratory imaging) shows one of the following:
  - A "Probable UIP" pattern (See definition below) or
  - An "Indeterminate for UIP" pattern (See definition below)
- Exclusion of autoimmune disease by clinical evaluation and serologic testing, including, when indicated, an evaluation by a rheumatologist
- Absence of a definitive occupational, environmental, medication-related, or other cause of the patient's lung disease

*Definitions of High-Resolution Computed Tomography Scanning Patterns*

*Usual Interstitial Pneumonia (UIP)*

- *Subpleural and basal predominant; distribution is often heterogeneous (occasionally diffuse, may be asymmetrical)*
- *Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis*

*Probable UIP*

- *Subpleural and basal predominant; distribution is often heterogeneous (occasionally diffuse, may be asymmetrical)*
- *Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*
- *May have mild ground-glass opacities (GGO)*

*Indeterminate for UIP*

- *Subpleural and basal predominant*
- *Subtle reticulation; may have mild GGO or distortion ("early UIP pattern")*
- *CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate for UIP")*

**Commercial Products**

Not applicable

## PRIOR AUTHORIZATION

**Medicare Advantage Plans**

Prior authorization is required for the following test:

- Envisia Genomic Classifier

**Commercial Products**

Not applicable

**Note**: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

## POLICY STATEMENT

**Medicare Advantage Plans**

The Envisia Genomic Classifier may be considered medically necessary when the medical criteria above are met.

**Commercial Products**

The Envisia Genomic Classifier is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory and not medically necessary/not covered benefits/coverage.

## BACKGROUND

Envisia Genomic Classifier (Veracyte, Inc., South San Francisco, CA), is a tissue based multi-analyte assay with algorithm analysis test (hereafter called Envisia) for interstitial lung disease (ILD) patients who are suspected of idiopathic pulmonary fibrosis (IPF) and who do not have a definitive usual interstitial pneumonia (UIP) pattern by high resolution computed tomography (HRCT) or other known cause of ILD. IPF suspicion increases significantly in patients greater than 60 years of age when HRCT is not definitive, and comorbidities in this population make clinicians reluctant to perform surgical lung biopsy to obtain a diagnosis due to significant procedure morbidity and mortality. Envisia testing is performed on less-invasive bronchoscopy transbronchial biopsy samples and is intended to provide a categorical UIP or Non-UIP result that along with clinical and radiographic information may guide treatment without the need or risk of surgical lung biopsy.

Interstitial lung disease (ILD) is a heterogenous group of lung disorders, for which an accurate diagnosis is critical to determining appropriate intervention for a given patient. Idiopathic Pulmonary Fibrosis (IPF) is one the most common interstitial lung diseases and frequently implicated when there is no other known cause of ILD, and often necessitates surgical lung biopsy to obtain a diagnosis. The natural history of IPF is described as progressive decline in pulmonary function until eventual death from respiratory failure or complicating comorbidity. Patients with IPF under age 50 are rare, with disease typically presenting in the

sixth and seventh decades of life and incidence increasing with older age. The incidence of IPF is estimated to be between 8-17 per 100,000 person-years in the general population, and mean survival after diagnosis is 2 to 5 years. A study evaluating Medicare claims data from 2000 to 2011 found that the incidence of IPF in the Medicare population is significantly higher, 93.7 per 100,000 person years, than observed in the general population.

Historically, lung transplantation has been the only proven treatment for IPF, but its use has been limited due to supply of donor organs and poor survival for IPF patients relative to other candidates. Recent clinical trials evaluating the efficacy of anti-fibrotic therapy in patients diagnosed with IPF have demonstrated a 50% reduction in the proportion of patients that have absolute pulmonary function decline of 10% or greater, an increase in the rate of patients with no pulmonary function decline, and improved progression free survival. These findings suggest an improvement in patient outcomes when IPF is accurately diagnosed and treated.

The pattern of usual interstitial pneumonia (UIP) is the hallmark of an IPF diagnosis. The development of evidence based diagnostic criteria for IPF in 2011 by an international consortium of pulmonary societies including the American Thoracic Society (ATS) requires exclusion of known causes of ILD, a definitive UIP pattern by HRCT, or specific combinations of UIP by HRCT and surgical pathology. Despite efforts to standardize these criteria, interobserver agreement of categorical UIP diagnosis by HRCT following the ATS guideline is moderate (52%) among expert thoracic radiologists. And recent studies suggest that a minority (13%) of patients being evaluated for IPF obtain a definitive UIP diagnosis by HRCT, necessitating surgical biopsy as the next diagnostic step.

Diagnosis of IPF by HRCT alone is challenging. A diagnosis of UIP by HRCT requires the coexistence of multiple radiographic features of a UIP pattern and absence of features inconsistent with UIP. Those features consistent with IPF may also be found in patients with other common ILDs of known cause such as chronic hypersensitivity pneumonitis (HP). Although guidelines place significant importance upon a thorough clinical history to identify ILDs of known cause, up to 30% of patients with HP are ultimately diagnosed without identifying a known cause, further complicating clinician's ability to distinguish these diseases. Additional non-surgical biopsy approaches to diagnosing ILDs of known cause that may be utilized include bronchoalveolar lavage (BAL) for the identification of lymphocytosis which may suggest occult hypersensitivity pneumonitis, and transbronchial lung biopsy (TBB) which is useful in diagnosing granulomatous disorders such as sarcoidosis. While highly specific for these indications and significantly less risk than a surgical biopsy, pathologic review of BAL and TBB specimens have not shown to be sensitive for detecting a UIP pattern.

A patient survey led by the Pulmonary Fibrosis Foundation suggests that at least half of patients with IPF are misdiagnosed at least once, and for up to 4 in 10 patients it takes a year to reach a final diagnosis. These data suggest that many patients with IPF are being missed by HRCT and non-surgical biopsy alone.
Missing an IPF diagnosis can prove fatal. The PANTHER trial challenged the paradigm of treating patients that may have IPF with steroid and immunosuppressive combination therapy that is the standard of care for many ILDs of known cause. The trial demonstrated that the use of prednisone, azathioprine and N-acetylcysteine (NAC) combination therapy compared to placebo had an increased rate of death (8 to 1, $p=0.01$) and hospitalization (3.2 to 1, $p<0.001$) in patients with diagnosed IPF. These findings highlight the need for more sensitive and specific diagnostic techniques to identify IPF.

When a definitive UIP pattern cannot be established by HRCT, ATS guidelines recommend physicians consider surgical lung biopsy as the next step and require the multidisciplinary integration of clinical, radiographic and pathologic features against a series of formal diagnostic criteria to make a diagnosis of IPF. While this leaves only a minority of scenarios where clinicians are unable to categorically assign a diagnosis, clinicians are increasingly reluctant to perform surgical lung biopsy in patients with unclassifiable ILD due to significant safety concerns. Among five clinical trials conducted since the year 2000 utilizing predominantly video-assisted thoracoscopy for surgical biopsy for the diagnosis of IPF, common complications include prolonged airway leaks (6-12%), pneumothorax, hemothorax, pleural effusion, and a 30-day mortality rate of 3-4%. Procedure risks are increased in patients with high oxygen requirements, pulmonary hypertension,

rapid disease progression, severely reduced forced vital lung capacity, multiple coexisting conditions, or frailty. ATS guidelines recommend clinicians consider the unique clinical situation of each individual patient as to whether the risks of surgical lung biopsy outweigh the benefits of establishing a diagnosis of IPF.

Over the past decade transbronchial cryobiopsy has been investigated by major lung disease centers as an alternative to surgical lung biopsy. Cryobiopsy provides a larger biopsy specimen than TBB, which is generally associated with a greater diagnostic yield. Cryoprobes work by applying cooling agents under high pressure causing pulmonary tissue to adhere to the cold probe tip and the tissue is then extracted. A recent meta-analysis of diagnostic yield using cryobiopsy in the diagnosis of ILD showed a mean yield of 73% with significant heterogeneity across 27 independent studies where diagnostic yield ranged from 40% to 95%. Complication rates of cryobiopsy are not insignificant and most commonly include pneumothorax and significant bleeding. The pooled incidence of pneumothorax was 9.4%, significant bleeding was 14.2%, and 30-day mortality 0.3%. The authors conclude that cryobiopsy when compared to TBB increases diagnostic yield, however there is a significant concomitant increase in the risks of pneumothorax (from 0.7-2% to 9.4%) and significant bleeding (from 1-4% to 14.2%). The authors recommend patients be carefully selected and cryobiopsy be performed at centers with considerable experience.

Significant investigation into genetic factors of familial IPF have shown strong associations with specific gene variants. Familial forms of IPF affecting two or more members of the same family contribute to only 5% of all IPF cases and therefore hereditary genetic testing is not currently recommended. 2011 ATS guidelines called for greater research into gene expression and the genomic factors contributing to IPF for earlier diagnosis and treatment.

The development of diagnostic criteria for IPF in 2011 by an international consortium of guidelines including the American Thoracic Society requires exclusion of known causes of ILD, a definitive UIP pattern by HRCT, or specific combinations of UIP by HRCT and histopathology obtained through surgical lung biopsy. ATS guidelines recommend physicians consider surgical lung biopsy as the next step in obtaining a diagnosis when patients do not meet all criteria to establish a UIP diagnosis by HRCT. Further, ATS guidelines recommend clinicians consider the unique clinical situation of each individual patient as to whether the risks of surgical lung biopsy outweigh the benefits of establishing a secure diagnosis of IPF.

In 2018 the Fleischner Society published a white paper on the diagnostic criteria for IPF with an emphasis on radiographic features of UIP in diagnosing IPF. The Fleischner Society recommendations and diagnostic criteria are largely consistent with the 2011 American Thoracic Society recommendations in establishing categorical determinations of the presence of UIP by HRCT and surgical pathology to distinguish IPF from other ILDs of known cause with an emphasis on multi-disciplinary assessment of clinical, radiographic and pathological factors. The statement authors suggest that molecular diagnosis with machine learning, with reference to Envisia, will play an increasing role in the diagnosis of IPF when considered along with clinical and imaging features.

Findings suggest that the Envisia classifier is capable of informing a clinical diagnosis without the need for surgical lung biopsy or expert pathology.

Situations in which Envisia should not be used:

- Typical UIP pattern on HRCT (See definitions in Medical Criteria section).
- "CT features most consistent with non-IPF diagnosis" on HRCT (See definitions in Medical Criteria section).
- When a positive Envisia result is considered unlikely to lead to a confident diagnosis of IPF (>90% confidence).

Comment regarding Probable UIP pattern on HRCT
• A "Probable UIP" pattern in an adult >70 years of age with extensive reticulation (>1/3 of the lung fields) is unlikely to benefit from ENVISIA since the likelihood of a histological pattern of UIP is already >90%.

• A "Probable UIP" pattern in a man >50yo or a woman >60 years of age with moderate-to-severe traction bronchiectasis is unlikely to benefit from ENVISIA since the likelihood of a histological pattern of UIP is already >90%.

## CODING

The following CPT code is covered for Medicare Advantage Plans when medical criteria above are met and is not medically necessary for Commercial Products:

This code can be used for Envisia Genomic Classifier:

**81554** Pulmonary isease (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])

## RELATED POLICIES

Genetic Testing Services

## PUBLISHED

Provider Update, May 2023
Provider Update, January 2021

## REFERENCES


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