Local Coverage Determination (LCD): MolDX: Envisia, Veracyte, Idiopathic Pulmonary Fibrosis Diagnostic Test (L37887)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
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LCD Information

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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim lacking the necessary documentation to process the claim.

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Ch. 16, §50.5 Jurisdiction of Laboratory Claims, §60.12 Independent Laboratory Specimen Drawing, §60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes".

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a laboratory test which will assist physicians caring for patients who have developed pulmonary (lung) scarring.

This policy provides limited coverage for the Envisia Genomic Classifier (Veracyte, Inc., South San Francisco, CA), 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.

Summary of Evidence

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[1]. 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[2]. The incidence of IPF is estimated to be between 8-17 per 100,000 person-years in the general population[3], and mean survival after diagnosis is 2 to 5 years[2]. 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[4].

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[5]. 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[6, 7]. 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[8]. 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[9]. 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[10].

Diagnosis of IPF by HRCT alone is challenging. As shown in Table 1, 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)[11]. 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[12]. 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[2]. 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[13].

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[14]. 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 IPF15. These findings highlight the need for more sensitive and specific diagnostic techniques to identify IPF.

Table 1. High Resolution Computed Tomography Criteria for UIP Pattern (Raghu AJRCCM 2011)

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP (see third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (see third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

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[2]. 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[16]. 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%[17]. 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[18]. 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%[19]. 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[2].

Professional Society Clinical Practice Guidelines

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[2]. 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[23]. 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.

This contractor consulted several ILD specialists in the development of this policy including clinicians from:

- Mayo Clinic
- Columbia University
- USC Medical Center

Test Description and Intended Use

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.

Analytical Validation

The Envisia classifier was developed to identify UIP without the need for surgical lung biopsy by assessing gene expression profiles from lung tissue collected from non-surgical TBBs. The classifier was validated utilizing patient samples obtained from the BRAVE trial (BRonchial sAmple collection for a noVel gEnomic test; BRAVE). The BRAVE trial includes 26 study sites in U.S. and Europe and is an IRB-approved study prospectively enrolling patients with suspected ILD undergoing a planned lung biopsy procedure that consent to the collection of an additional five TBBs for classifier development and validation. Final pathologic diagnoses used as the reference standard were made by expert lung pathologists in each of the three study arms from surgical lung biopsy (BRAVE-1), transbronchial biopsy

(BRAVE-2), or cryobiopsy (BRAVE-3) against which the classifier performance is compared to calculate test performance of sensitivity and specificity.

Clinical Validation

The first clinical validation of the genomic classifier by Pankratz et al included 140 enrolled patients. After predefined exclusion criteria, 84 eligible patients provided 283 TBB samples paired with same-patient final reference pathology diagnoses. Machine learning was used to train an algorithm with high specificity using TBB samples from 53 patients, and performance was evaluated on an independent test set of 31 patients. The TBB classifier distinguished UIP from non-UIP conditions with an area under the curve of 0.86, specificity of 86% [CI:71%-95%] and sensitivity of 63% [CI: 51%-74%]. Importantly, this study explored the feasibility of a single molecular test result per subject by combining multiple TBBs from upper and lower lobes. Performance improved to an AUC of 0.92 when a minimum of three and up to five TBB samples per subject are combined at the RNA level for testing[20].

A second clinical validation by Choi et al., utilized 3-5 pooled TBB samples from 139 patients enrolled in the BRAVE study. Samples from 90 patients were utilized for classifier training, and the final Envisia classifier was validated on an independent, blinded test set of 49 patients. In the independent test set final pathology diagnoses were assigned by expert ILD pathologists using samples from surgical lung biopsy (53%, BRAVE-1), TBB (4%, BRAVE-2) and cryobiopsy (43%, BRAVE-3). The Envisia classifier predicted histopathologic UIP from TBB samples with a high specificity (88%; CI: 70%-98%) and modest sensitivity (70%; CI:47%-87%), surpassing the ability of both local and expert central HRCT evaluation to predict histopathologic UIP suggesting this classifier has utility in clinical practice to guide patient management in lieu of surgical lung biopsy[21].

Clinical Utility

Investigators have sought to assess the utility of the Envisia classifier in making a categorical IPF vs non-IPF clinical diagnosis. In a randomized, blinded analysis of 98 prospectively enrolled patients from the BRAVE trial two independent, 3-member, central multidisciplinary teams (CMDTs) made up of expert ILD clinicians received clinical information, centrally reviewed HRCT, and either centrally reviewed histopathology or the Envisia classifier result for each patient case. Cases were randomly assigned between CMDTs and each subject is therefore reviewed twice, once each by the two CMDTs using histopathology or Envisia classifier results. The primary objective was to compare the intra-patient agreement for clinical diagnoses. Interim results for approximately half of cases (n=56) showed a 92% categorical agreement in IPF vs Non-IPF diagnosis. These findings suggest that the Envisia classifier is capable of informing a clinical diagnosis without the need for surgical lung biopsy or expert pathology[22].

Criteria for Coverage

The Envisia classifier is reasonable and necessary when all of the following conditions are met:

- That are 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) showing one of the following:
    - A “Probable UIP” pattern (See comment below) as defined by the 2018 Fleischner Society White paper (https://www.ncbi.nlm.nih.gov/pubmed/29154106), or
    - An "Indeterminate for UIP” pattern as defined by the 2018 Fleischner Society White paper (https://www.ncbi.nlm.nih.gov/pubmed/29154106)

- 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

Situations in which Envisia should not be used:

1. "Typical UIP" pattern on HRCT as defined by the 2018 Fleischner Society White paper (https://www.ncbi.nlm.nih.gov/pubmed/29154106)
2. "CT features most consistent with non-IPF diagnosis" on HRCT as defined by the 2018 Fleischner Society White paper (https://www.ncbi.nlm.nih.gov/pubmed/29154106).
3. 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%.

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality: Moderate
Strength: Limited
Weight: Limited

The clinical utility of the Envisia genomic classifier to aid in the diagnosis of patients with an ILD of unknown cause and suspected of IPF, as defined in the intended use above, is quite promising. This contractor believes that forthcoming clinical studies in these patients will demonstrate improved patient clinical outcomes. Continued coverage for Envisia testing is dependent on annual review by this contractor of such data and publications.

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service.

Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type.Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

N/A

Group 1 Codes:

CODE	DESCRIPTION
81479	UNLISTED MOLECULAR PATHOLOGY PROCEDURE

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

ICD-10 CODE	DESCRIPTION
D86.0	Sarcoidosis of lung
J60	Coalworker's pneumoconiosis
J67.0	Farmer's lung
J67.1	Bagassosis
J67.2	Bird fancier's lung
J67.3	Suberosis
J67.4	Maltworker's lung
J67.5	Mushroom-worker's lung
J67.6	Maple-bark-stripper's lung

ICD-10 CODE	DESCRIPTION
J67.7	Air conditioner and humidifier lung
J67.8	Hypersensitivity pneumonitis due to other organic dusts
J67.9	Hypersensitivity pneumonitis due to unspecified organic dust
J84.09	Other alveolar and parieto-alveolar conditions
J84.10	Pulmonary fibrosis, unspecified
J84.111	Idiopathic interstitial pneumonia, not otherwise specified
J84.112	Idiopathic pulmonary fibrosis
J84.113	Idiopathic non-specific interstitial pneumonitis
J84.114	Acute interstitial pneumonitis
J84.115	Respiratory bronchiolitis interstitial lung disease
J84.116	Cryptogenic organizing pneumonia
J84.117	Desquamative interstitial pneumonia
J84.2	Lymphoid interstitial pneumonia
J84.89	Other specified interstitial pulmonary diseases
J84.9	Interstitial pulmonary disease, unspecified

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

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Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A56375 - Response to Comments: MolDX: Envisia, Veracyte, Idiopathic Pulmonary Fibrosis Diagnostic Test
LCD(s)
DL37887 - MolDX: Envisia, Veracyte, Idiopathic Pulmonary Fibrosis Diagnostic Test

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