Genetic Testing: Diagnostic Evaluation of Interstitial Lung Disease

MEDICAL POLICY NUMBER: 178

Effective Date: 10/1/2023

Last Review Date: 7/2023

Next Annual Review: 7/2024

INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☒ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

The use of genomic sequencing classifiers for diagnostic evaluation of interstitial lung disease (e.g., Envisia® Genomic Classifier by Veracyte, Inc.) are considered **not medically necessary**.

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Interstitial Lung Disease (ISD)

Interstitial lung disease is characterized by a large group of disorders, which causes progressive scarring of lung tissue.[1] This scarring eventually affects the ability to breathe and get enough oxygen into the bloodstream. The primary signs and symptoms include shortness of breath at rest or aggravated by exertion and dry cough. Risk factors include age, exposure to environmental toxins, uncontrolled gastroesophageal reflux disease (GERD), smoking, radiation and chemotherapy. Some types of interstitial lung disease include:

- Interstitial pneumonia
- Idiopathic pulmonary fibrosis
- Nonspecific interstitial pneumonitis
- Hypersensitivity pneumonitis

According to the Mayo Clinic, identifying and determining the cause of interstitial lung disease is challenging.[1] The symptoms of ISD mimic a wide range of medical conditions, and these must be ruled out before making a definitive diagnosis. Treatments include medications, pulmonary rehabilitation, and oxygen therapy.

Envisia® Genomic Classifier

According to the manufacturer, the Envisia® Genomic Classifier is the first commercially available genomic test to improve the diagnosis of idiopathic pulmonary fibrosis (IPF).[2] The test is intended for patients undergoing evaluation for interstitial lung disease, including IPF. Envisia uses RNA whole-transcriptome sequencing and a machine learning algorithm to interrogate 190 genes in bronchial biopsy samples. This allows Envisia to identify the genomic pattern and differentiate IPF from other interstitial lung diseases without surgical lung biopsy.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of genomic classifiers for the diagnostic evaluation of interstitial lung disease. Below is a summary of the available evidence identified through May of 2022.

- In2023, Hayes conducted a genetic test evaluation report assessing the Envisia® Genomic Classifier (Veracyte®).[3] Hayes identified three studies evaluating Envisia. Only two of these studies addressed the analytic validity, one study evaluated the clinical validity, and no studies reported on the clinical utility of the test. Studies demonstrated the analytic and clinical validity of the Envisia genomic classifier; however, no studies were conducted to demonstrate changes in patient management or patient outcomes. The overall body of evidence was rated very low due to the limited number of studies and data to support the test. Hayes concluded with the following rating:

  > **D2 (insufficient evidence)**: for use of the Envisia Genomic Classifier that uses RNA sequencing to assess the genomic profile of transbronchial biopsy samples and uses machine learning to identify the genomic pattern for usual interstitial pneumonia in order to distinguish idiopathic pulmonary fibrosis from other interstitial lung diseases in combination with high-resolution computed tomography and clinical information during the diagnostic workup without the need for surgical lung biopsy.[3]

- In 2019, Raghu and colleagues published an industry-funded prospective validation study on the use of molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples.[4] Forty-nine patients undergoing evaluation for interstitial lung disease were included in the study. Samples were obtained from surgical or transbronchial biopsy or cryobiopsy

for pathology. Experienced pathologists completed the histopathological diagnoses, utilizing available high-resolution chest CT (HRCT). Transbronchial lung biopsy samples were collected for RNS sequence data. The primary endpoint of the study was to determine the validity of the classifier by comparing results to histopathology. The authors stated that in order to assess utility, the compared agreement and confidence level of diagnoses made by central multidisciplinary teams based on clinical information, radiology results, and either molecular classifier or histopathology results.

Envisia classifier identified usual interstitial pneumonia in transbronchial lung biopsy samples from 49 patients with 88% specificity (95% CI 70–98) and 70% sensitivity (47–87). Among 42 of these patients who had possible or inconsistent usual interstitial pneumonia on HRCT, the classifier showed 81% positive predictive value (95% CI 54–96) for underlying biopsy-proven usual interstitial pneumonia. In the clinical utility analysis, they found 86% agreement (95% CI 78–92) between clinical diagnoses using classifier results and those using histopathology data. Diagnostic confidence was non-significantly improved by the molecular classifier results compared with histopathology results in 18 with IPF diagnoses (p=0.0339) and in all 48 patients with non-diagnostic pathology or non-classifiable fibrosis histopathology (p=0·0412).

This study had a number of limitations, including small sample size, unrepresentative patient sample, and ineffective surrogate endpoint to determine clinical utility. Agreement and confidence in diagnosis with the addition of the Envisia classifier does not capture the effects of the classifier on patient-related objective outcomes such as treatment efficacy or quality of life. Therefore, this study shows the Envisia classifier has clinical validity, but does offer data to prove clinical utility. Envisia is not less invasive than standard of care, and therefore its diagnostic use should be superior to standard of care.

- In 2020, Kheir and colleagues published a retrospective study on the impact of using data from bronchoscopic cryobiopsies (BLC) and genomic classifiers on diagnostic impression and confidence of multidisciplinary discussions in the evaluation of interstitial lung disease (ILD).[5] Two multidisciplinary discussion (MDD) teams reviewed 24 patients with ILD without a definitive usual interstitial pneumonia (UIP) pattern. One team sequentially reviewed clinical-radiologic findings, BLC, and genomic classifiers, while the second team sequentially reviewed genomic classifiers before BLC. The first team had a significant increase (p=0.023) in diagnostic confidence in patients with probable UIP after reviewing genomic classifiers. The second team had a nonsignificant increase in diagnostic confidence (p=0.074) after adding BLC to genomic classifiers. The authors concluded that genomic classifiers increased diagnostic confidence when added to BLC for patients with a probable UIP pattern, and it may be appropriate to use genomic classifiers without BLC in some clinical settings. They also found that BLC had the greatest impact regarding specific diagnosis when the likelihood of UIP was considered low following clinical-radiographic review.

  This study had a number of limitations and a high risk of bias: BLC and genomic classifiers were not directly compared, therefore conclusions cannot be made on whether genomic classifiers are effective without reviewing BLC; small sample size; single institution patient sample; primary outcomes of confidence levels are not validated surrogate outcomes for objective, patient-centered outcomes. Further studies are needed with direct comparison of diagnoses with and without genomic classifiers to determine if the addition of classifiers changes treatment protocols and improves patient outcomes.

- In 2021, ECRI published a genetic test assessment of Envisia Genomic Classifier (Veracyte, Inc.) for Aiding Diagnosis of Idiopathic Pulmonary Fibrosis.[6] The review included 2 clinical validity studies reporting on 190 patients, both prospective cohort studies. They found that both studies suggested that Envisia may aid in idiopathic pulmonary fibrosis diagnosis, but the sample sizes were too small to be conclusive. Furthermore, they found not clinical utility studies on Envisia. They concluded that the evidence is unconclusive.

CLINICAL PRACTICE GUIDELINES

No evidence-based clinical practice guidelines were identified which address the use of genomic classifiers for the diagnostic evaluation of interstitial lung disease.

EVIDENCE SUMMARY

There is insufficient published evidence to support the medical necessity of genomic classifiers for the diagnostic evaluation of interstitial lung disease. Additional studies are required to demonstrate changes in patient management and patient outcomes due to the Envisia® genomic classifier. Additionally, no clinical practice guidelines recommend the use of genomic classifiers for evaluation of interstitial lung disease. Therefore, Envisia genomic classifier is considered not medically necessary for the diagnostic evaluation of interstitial lung disease.

BILLING GUIDELINES AND CODING

CODES*		
CPT	81479	Unlisted molecular pathology procedure
	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	

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for

Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Mayo Clinic. Interstitial Lung Disease. https://www.mayoclinic.org/diseases-conditions/interstitial-lung-disease/symptoms-causes/syc-20353108. Published 2023. Accessed 6/12/2023.
2. Veracyte. Envisia Genomic Classifier. https://www.veracyte.com/diagnostics/interstitial-lung-diseases. Published 2023. Accessed 6/12/2023.
3. Hayes. Molecular Test Evaluation: Envisia Genomic Classifier (Veracyte). https://evidence.hayesinc.com/report/gte.envisia4708. Published 2023. Accessed 6/13/2023.
4. Raghu G, Flaherty KR, Lederer DJ, et al. Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study. *Lancet Respir Med.* 2019;7(6):487-496.
5. Kheir F, Alkhatib A, Berry GJ, et al. Using Bronchoscopic Lung Cryobiopsy and a Genomic Classifier in the Multidisciplinary Diagnosis of Diffuse Interstitial Lung Diseases. *Chest.* 2020;158(5):2015-2025.
6. ECRI. Envisia Genomic Classifier (Veracyte, Inc.) for Aiding Diagnosis of Idiopathic Pulmonary Fibrosis. https://www.ecri.org/components/ECRIgene/Documents/EG0164.pdf. Published 2021. Accessed 6/12/2023.

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
10/2023	Changed denial type from “investigational” to “not medically necessary.”