Anthem FINAL DRAFT – LOGO TO BE INSERTED UPON FINAL PRODUCTION DATE

Medical Policy

Subject:	Gene Expression Profiling for Idiopathic Pulmonary Fibrosis		
Document#:	GENE.00057	**Publish Date:**	07/07/2021
Status:	New	**Last Review Date:**	05/13/2021

Description/Scope

This document addresses the use of gene expression profiling to assist in the diagnosis or management of idiopathic pulmonary fibrosis.

Note: Please see the following related document for additional information:

- **TRANS.00009 Lung and Lobar Transplantation**

Position Statement

Investigational and Not Medically Necessary:

The use of gene expression profiling to assist in the diagnosis or management of idiopathic pulmonary fibrosis is considered investigational and not medically necessary in all situations.

Rationale

Interstitial lung disease is a broad and diverse group of parenchymal lung disorders that can be characterized by alveolar inflammation, fibrosis, and scarring. The scarring (also referred to as pulmonary fibrosis) and inflammation can make it difficult for the lungs to adequately oxygenate the blood. There are more than 150 recognized interstitial lung diseases. Various causes include genetics, medication, certain medical conditions, and environmental exposures. When the cause of scarring is unknown, this is referred to as idiopathic pulmonary fibrosis.

Healthy Blue Medical Policy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Individuals with idiopathic pulmonary fibrosis (IPF) commonly present with a condition called usual interstitial pneumonia (UIP). Diagnosis is usually made by lung biopsy or high-resolution computed tomography (HRCT). Alternating areas of fibrosis and normal lung can produce a honeycomb appearance. This heterogeneous distribution of disease may produce false-negative biopsies. It is often difficult to obtain sufficient tissue with transbronchial techniques and open surgical biopsy may then be needed. Although there is no cure for IPF, early diagnosis may provide benefit because antifibrotic medications are showing promise in slowing disease progression.

With the difficulty in diagnosis of IPF, a laboratory test using a minimally invasive transbronchial biopsy (TBB) has been proposed to assist in diagnosis. The method was developed using machine learning and whole-transcriptome next-generation ribonucleic acid (RNA) sequencing of 190 genes. Machine learning employs automated improvement of an algorithm through iterative analysis of data. To apply this to the diagnosis of IPF, genetic information from biopsy samples has been sequentially analyzed to detect a molecular signature for UIP. It is proposed that a genetic basis for diagnosis could overcome problems related with false negative pathology readings.

A 2017 industry-sponsored study by Pankratz and colleagues reported on the accuracy of a molecular classifier (genomic algorithm) that could detect a gene expression signature of UIP from TBB. The authors extracted RNA from 496 TBB samples of 113 subjects with suspected IPF. Biopsies were independently read by 2 pathologists. A third independent evaluation was obtained if there was disagreement between the first 2 diagnoses. Usable, high-quality sample data was found for 84 participants (60 from surgical lung biopsy, 17 from cryobiopsy, and 7 from TBB). Participants were randomly assigned to a derivation group (called the training set in the article, 53 subjects with 170 biopsy samples) or a validation group (called the test set in the article, 31 subjects with 113 biopsy samples). UIP was diagnosed by biopsy specimens in 33 of 53 subjects (62%) and 19 of 31 (61%) in the validation set. In the derivation set of 53 participants, receiver operator characteristic (ROC) area under the curve (AUC) was 0.85 when biopsy samples were scored separately. Sensitivity was 65% and specificity was 92%. For the validation set of 31 participants, the classifier showed an ROC-AUC of 0.86, with sensitivity of 63% and specificity of 86%. When the biopsy samples were pooled, the sensitivity was 93% and sensitivity was 74% in derivation subjects with sensitivity of 59% and specificity of 100% in the validation subjects. This study has several limitations. The population was small and focused on subjects suspected of having IPF. Low numbers of individuals with other fibrotic condition limits the ability to determine this test's ability to discriminate between different types of fibrotic lung disease.

Healthy Blue Medical Policy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

A 2019 industry-sponsored prospective study by Raghu and colleagues reports the clinical validity and utility of molecular diagnosis of UIP. Using the participant population from the 2017 Pankratz study, clinical validity of the classifier was assessed in 49 participants by comparison with diagnostic pathology. Clinical utility was assessed by comparing the agreement and level of diagnosis made by multidisciplinary teams using clinical information, radiology results, and either molecular classifier or pathology results. The classification showed sensitivity of 70% and specificity of 88%. Negative predictive value (NPV) was 77% and positive predictive value (PPV) was 84%. After excluding the participants with definite or probable UIP by local and central radiology (n=42), sensitivity was 76%, specificity was 88%, NPV was 85%, and PPV was 81%. There were 46 participants in this cohort who had HRCT scans available for review. Expert review of the scans identified 40 participants classified as possible UIP or diagnosis inconsistent with UIP. Clinical utility analysis showed an overall 86% agreement between molecular classifier results and histopathology diagnosis. This study only included participants who underwent lung biopsy to ascertain histopathological diagnosis. Accuracy in participants who have not had surgical lung biopsy is unknown. Since the cohort in this study came from the 2017 Pankratz population, the Rahgu study shares the same limitations as that study. The study was not designed or powered to determine agreement between biopsy types. For individuals with HRCT findings consistent with pattern other than UIP, the clinical relevance of a positive molecular classifier is unclear. Larger prospective trials with more diverse populations will be needed to evaluate the clinical utility of molecular classifier testing. Future studies addressing time to diagnosis, time to treatment, number of procedures, and progression and outcomes are necessary to address improved net health outcomes.

Another study looked at a new cohort of participants to validate the genomic classifier. Richeldi and colleagues (2020) reported on 96 participants with diagnostic pathology as a validation cohort. For the molecular testing, total RNA was extracted from three to five TBB specimens from each participant. In addition to TBB, 64% of participants had surgical lung biopsy and 35% had cryobiopsy to obtain a final histopathologic diagnosis. Based on histopathology, overall prevalence of UIP was 60.4%. In the validation cohort, sensitivity was 60.3% with specificity of 92.1%. PPV was 92.1% and NPV was 60.3%. There were 85 local HRCT scans available for review. Among the 53 cases of histopathologically identified UIP, 18 were identified as definite or probable by local computed tomography scans. Sensitivity for HRCT was 34% and specificity was 96.9%. When the molecular classifier results were used in combination with radiology, there were 24 additional participants with biopsy-proven UIP. The sensitivity for combined use of HRCT and the molecular classifier was 79.2% and specificity was 90.6%. NPV for HRCT was 47% and 72.5% with the

Healthy Blue Medical Policy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

addition of the molecular classifier. PPV was above 90% when molecular classifier results are used in combination to HRCT. While these results suggest the addition of molecular classifier to recognize a pattern of UIP, caution should be used when applying to all populations. Like the Raghu study, accuracy of the genomic classifier is unknown in those individuals with interstitial lung disease with a non-diagnostic pathological lung biopsy. It's also important to note that a finding of UIP is not synonymous with IPF. It can be present in other types of interstitial lung diseases as well.

In 2018 the American Thoracic Society published their Clinical Practice Guideline for diagnosis of idiopathic pulmonary fibrosis (Raghu, 2018). For individuals with newly detected interstitial lung disease of unknown cause with clinical suspicion of idiopathic pulmonary fibrosis and HRCT pattern of probable usual interstitial pneumonia, they suggest surgical lung biopsy. There were no recommendations made for or against TBB.

Larger prospective trials with more diverse populations will be needed to evaluate the clinical utility of molecular classifier testing. Future studies assessing time to diagnosis, time to treatment, number of procedures, and progression and outcomes are necessary to address improved net health outcomes through use of this testing.

Background/Overview

Idiopathic pulmonary fibrosis is a chronic disease which affects the tissue surrounding the alveoli in the lungs. Idiopathic pulmonary fibrosis is among the most common and most lethal of the group of interstitial lung diseases with an estimated prevalence of 14-60 cases per 100,000 persons per year. The lung tissue becomes thick and stiff and over time this can cause scarring in the lungs and difficulty breathing.

Definitions

Idiopathic pulmonary fibrosis: A disease with progressive lung scarring that occurs without an obvious cause.

Interstitial lung disease: a group of lung diseases characterized by varying patterns of inflammation and fibrosis.

Healthy Blue Medical Policy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Usual interstitial pneumonia: The hallmark of idiopathic pulmonary fibrosis identified by radiology or histopathology. Can appear on imaging as loss of lung volume and honeycombing.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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])** **Envisia® Genomic Classifier, Veracyte, Inc**

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. **Choi Y, Lu J, Hu Z, et al. Analytical performance of Envisia: a genomic classifier for usual interstitial pneumonia. BMC Pulm Med. 2017; 17(1):141.**
2. **Pankratz DG, Choi Y, Imtiaz U, et al. Usual interstitial pneumonia can be detected in transbronchial biopsies using machine learning. Ann Am Thorac Soc. 2017; 14(11):1646-1654.**

Healthy Blue Medical Policy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

3. **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.**
4. **Richeldi L, Scholand MB, Lynch DA, et al. Utility of a molecular classifier as a complement to HRCT to identify usual interstitial pneumonia. Am J Respir Crit Care Med. 2021; 203(2):211-220.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018; 198(5):e44-e68.**

Websites for Additional Information

1. **National Institutes of Health. National Heart. Lung, and Blood Institute. Idiopathic pulmonary fibrosis. Available at: https://www.nhlbi.nih.gov/health-topics/idiopathic-pulmonary-fibrosis. Accessed on February 17, 2021.**
2. **National Institutes of Health. National Heart, Lung, and Blood Institute. Interstitial lung diseases. Available at: https://www.nhlbi.nih.gov/health-topics/interstitial-lung-diseases. Accessed on February 17, 2021.**

Index

Document History

Status	Date	Action
New	05/13/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

Healthy Blue Medical Policy

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.