



Integrating the Envisia Genomic Classifier to Improve ILD Diagnostic and Prognostic Confidence

Moderator and Panelists



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Key Learning Objectives

- Discuss the importance of an accurate ILD diagnosis
- Review updated clinical guideline recommendations for the diagnosis of IPF/PPF
- Discuss how the Envisia Genomic Classifier can be integrated into the clinical work up for ILD

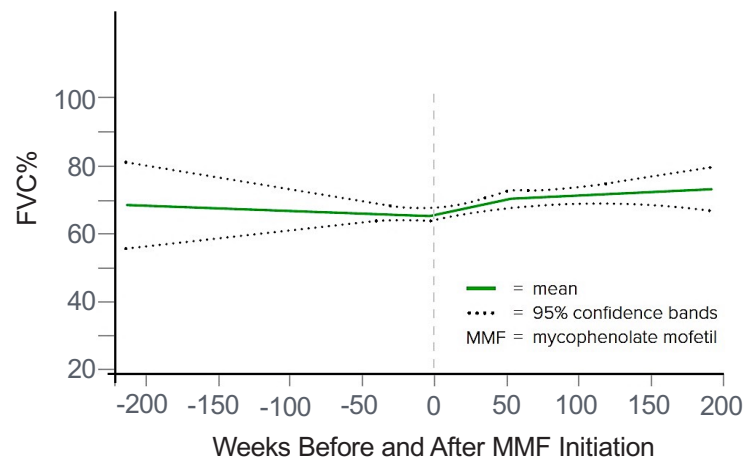


2022 ATS | ERS | JRS | ALAT Clinical Practice Guideline Updates

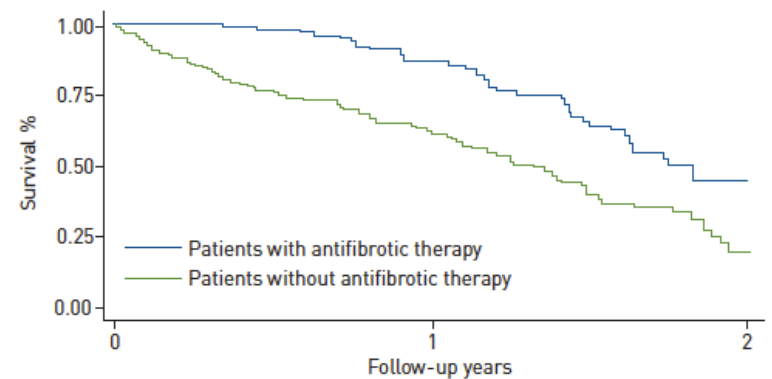
Mary Beth Scholand, MD

Accurate ILD Diagnosis is Important to Inform Initial Treatment

Immunosuppression may stabilize lung function in appropriately selected ILD patients¹⁻³ but is harmful for IPF patients⁴



Antifibrotics may slow disease progression in IPF⁵⁻⁸



| | | | |
|---------------------------|-----|-----|----|
| Patients at Risk n | | | |
| With Antifibrotic Therapy | 281 | 129 | 57 |
| No Antifibrotic Therapy | 252 | 139 | 93 |

1. Morisset et al. *Chest* 2017.

2. Fischer et al. *J Rheumatol* 2013.

3. Tashkin et al. *N Engl J Med* 2006.

4. The Idiopathic Pulmonary Fibrosis Clinical Research Network. *N Engl J Med* 2012.

5. Richeldi L, et al. *NEJM* 2014;370:2071-2082.

6. King TE Jr et al. *N Engl J Med* 2014;370:2083-2092.

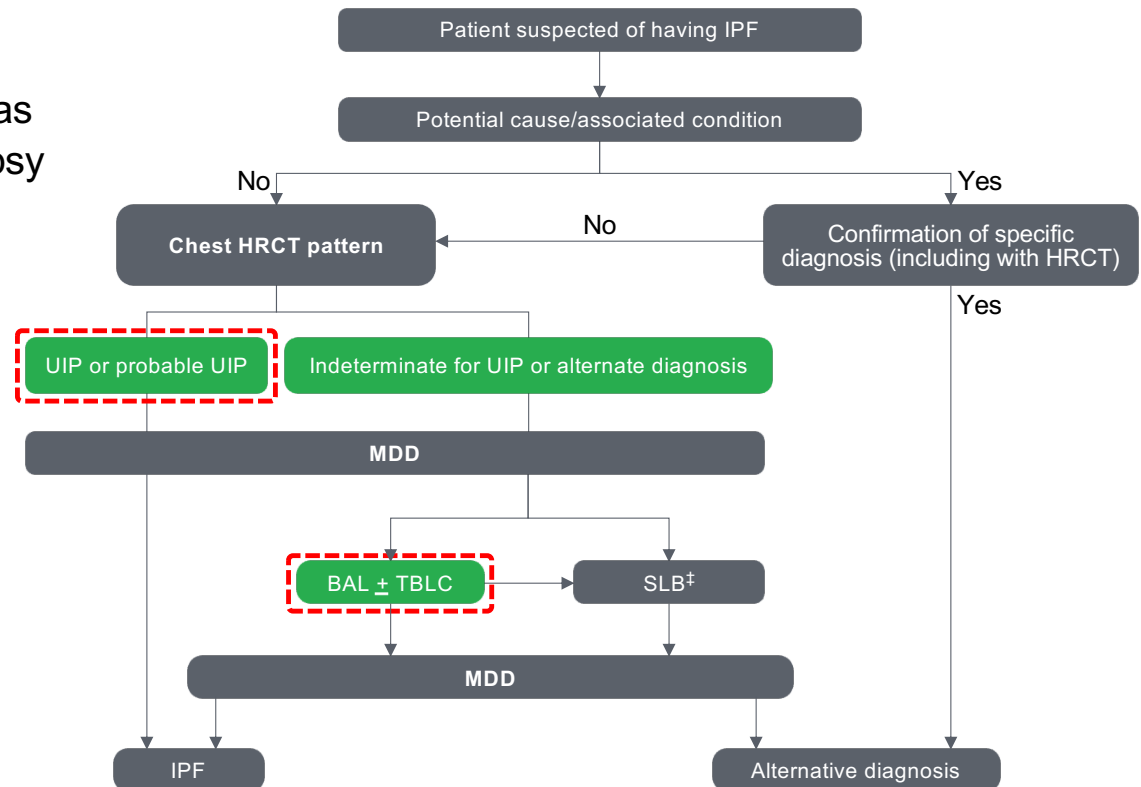
7. Canestaro et al. *CHEST* 2015;11.013.

8. Behr et al. *Eur Respir J* 2020; 56: 1902279.

2022 Updated Diagnostic Algorithm for IPF Diagnosis

Key Changes:

- Probable UIP by HRCT can be diagnosed as IPF after MDD discussion without lung biopsy confirmation in appropriate clinical setting (e.g. 60yr old male, smoker)
 - BAL may be appropriate in some patients with a probable UIP and may be performed before MDD
- Transbronchial lung cryobiopsy may be preferred over SLB in centers with appropriate expertise with or without BAL



Definition of Progressive Pulmonary Fibrosis (PPF) Per the Newly Released ATS Guidelines

Definition

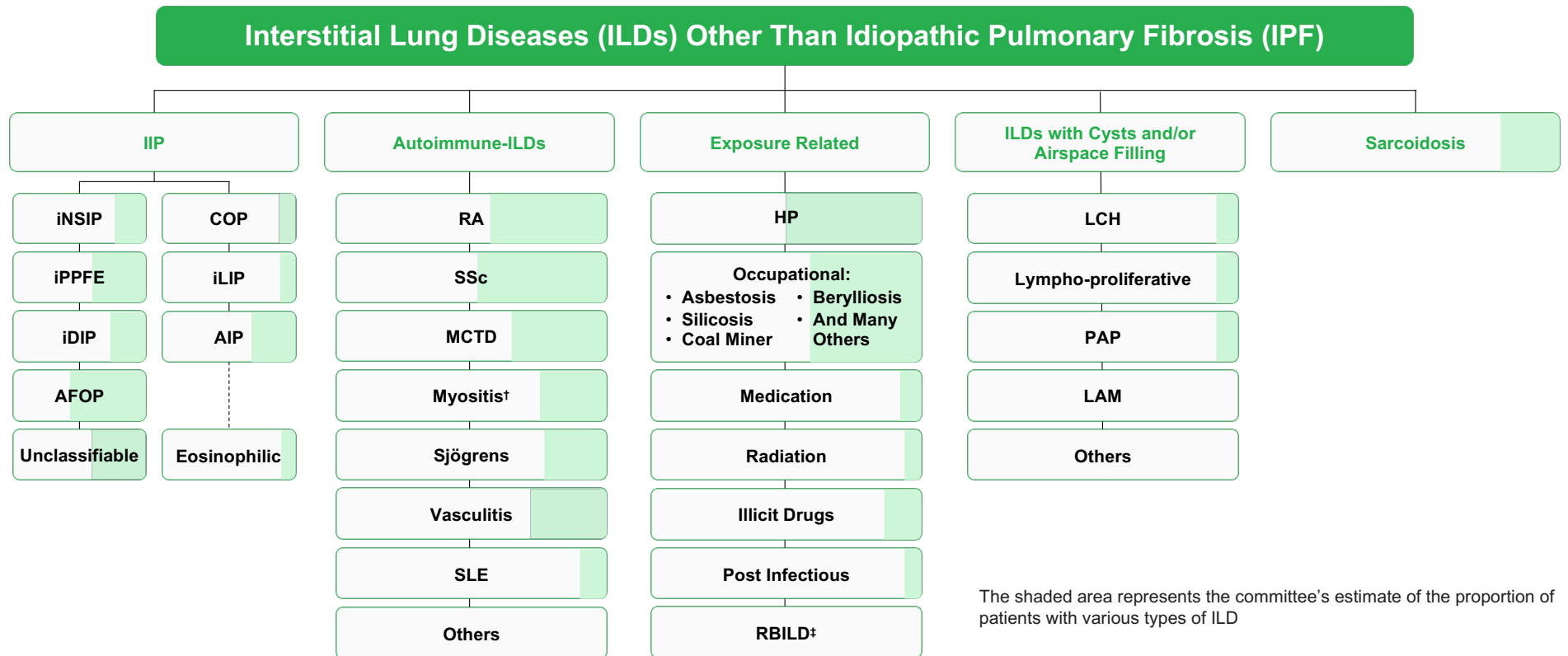
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as **at least two of the following three criteria occurring within the past year** with no alternative explanation:

1. **Worsening Respiratory Symptoms**

2. **Physiological Evidence of Disease Progression** (either of the following):
 - (a) Absolute decline in FVC $\geq 5\%$ predicted within 1yr of follow up
 - (b) Absolute decline in DL_{CO} (corrected for Hb) $\geq 10\%$ predicted within 1yr of follow up

3. **Radiological Evidence of Disease Progression** (one or more of the following):
 - (a) Increased extent or severity of traction bronchiectasis and bronchiolectasis
 - (b) New ground-glass opacity with traction bronchiectasis
 - (c) New fine reticulation
 - (d) Increased extent or increased coarseness of reticular abnormality
 - (e) New or increased honeycombing
 - (f) Increased lobar volume loss

ILDs Manifesting PPF: Shaded Area Represents Proportion of Patients



1. Raghu G, et al. *Am J Respir Crit Care Med*. Volume 205 Number 9 May 2022.

Case 1: 70-year-old Male

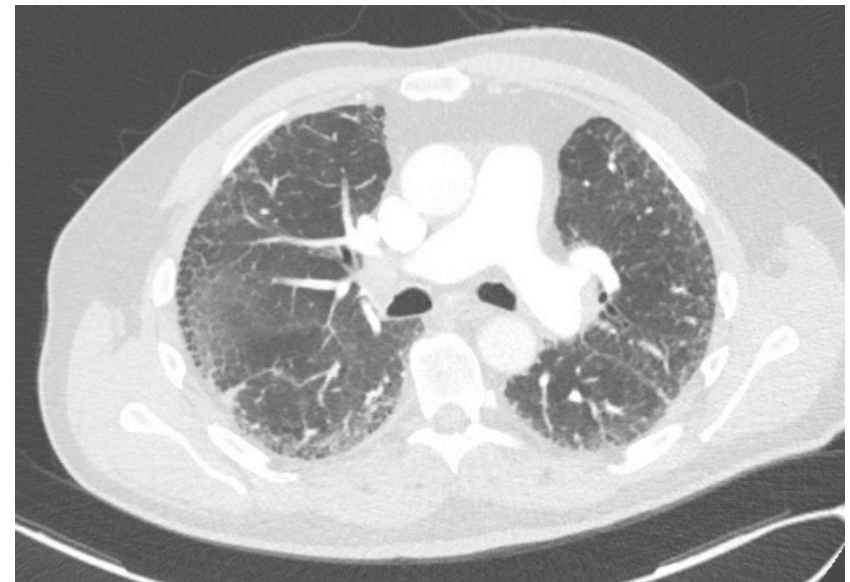
Patient Background & Exam

- 70-year-old Male c/o chronic cough >2 years
- Was admitted to the hospital for worsening shortness of breath. CXR showed interstitial infiltrates.
- Negative for any autoimmune features and HP panel
- + GERD
- Former smoker 1-2 PPD x 20 years, quit 20 years ago
- No Family History of Idiopathic Pulmonary Fibrosis (IPF)
- No birds, Jacuzzi, humidifiers

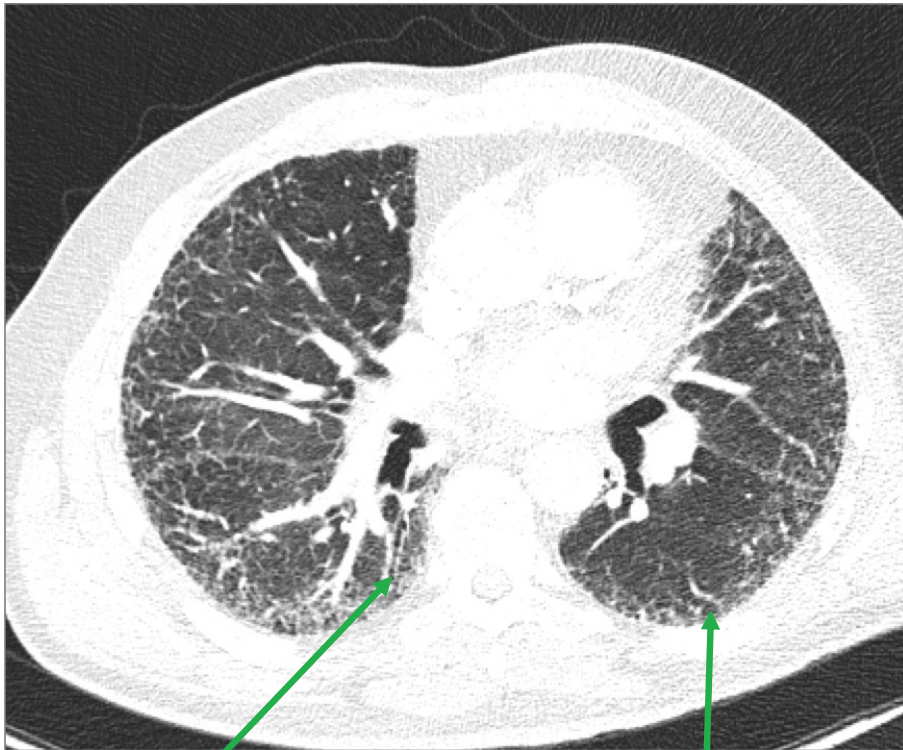
Pulmonary Function Test

| | |
|----------|-------------|
| FVC | 62% (3.02L) |
| FEV1 | 71% (2.43L) |
| FEV1/FVC | 0.83 |
| DLCO | 34% |

CT Scan

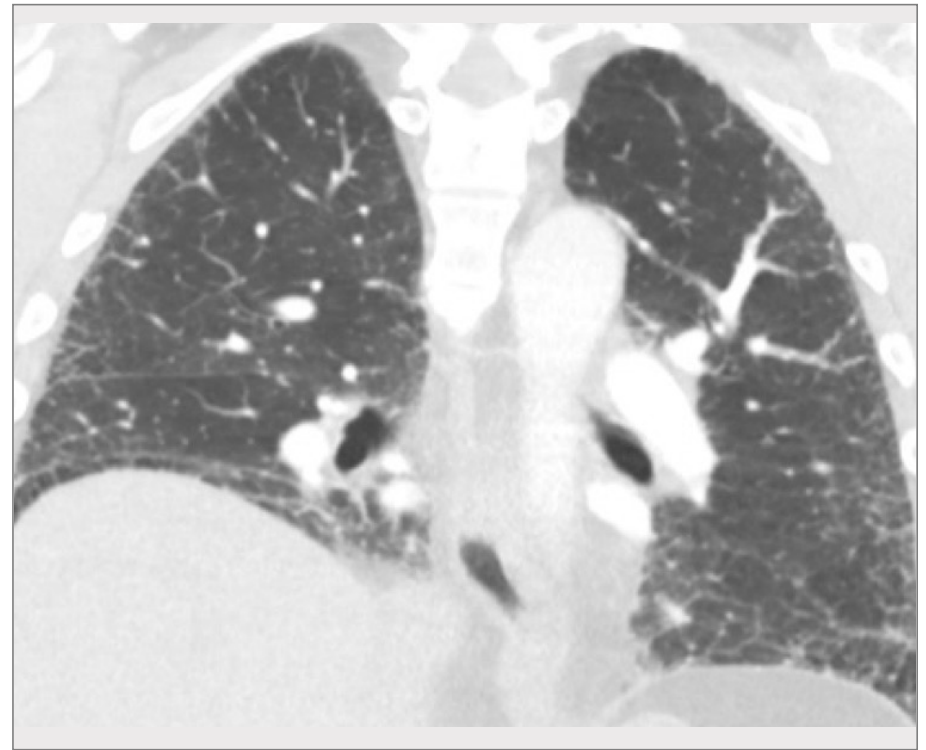


What Is The HRCT Pattern For This Patient?



Traction Bronchiectasis

Peripheral Reticulation



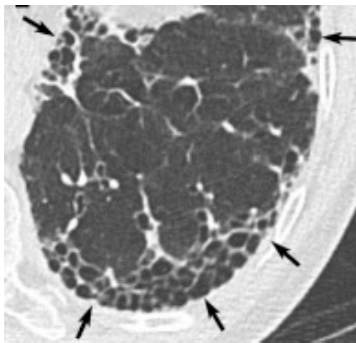


What is the HRCT Pattern for This Patient?

- A. UIP
- B. Probable UIP
- C. Indeterminate for UIP
- D. Alternative Diagnosis

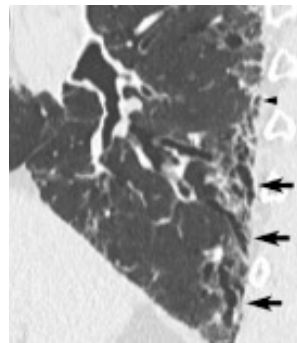
Likely Indeterminate for UIP

UIP Pattern



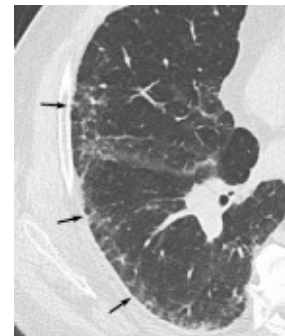
- Subpleural or basal predominant
- **Honeycombing** with or without peripheral traction bronchiectasis or bronchiolectasis
- **Reticular pattern, mild GGO**

Probable UIP Pattern



- Subpleural & basal predominant
- **No Honeycombing**
- **Reticular Pattern** with peripheral traction bronchiectasis or bronchiolectasis
- May have mild GGO

Indeterminate for UIP



- **Subtle Reticulation**
- May have mild GGO or distortion
- Lung fibrosis without any specific etiology

Alternative Diagnosis



- Examples may include:
 - Cysts
 - Predominant GGO
 - Mosaic attenuation
 - Nodules

Higher Diagnostic Confidence

Lower Diagnostic Confidence

Establishing a Confident Diagnosis May Be Challenging with Radiology and Clinical Factors Alone

DEPENDENT ON



Clinical exam & patient history

- Quality of interview and physical exam
- Time constraints with patient
- Level of experience



Quality & Technique of HRCT

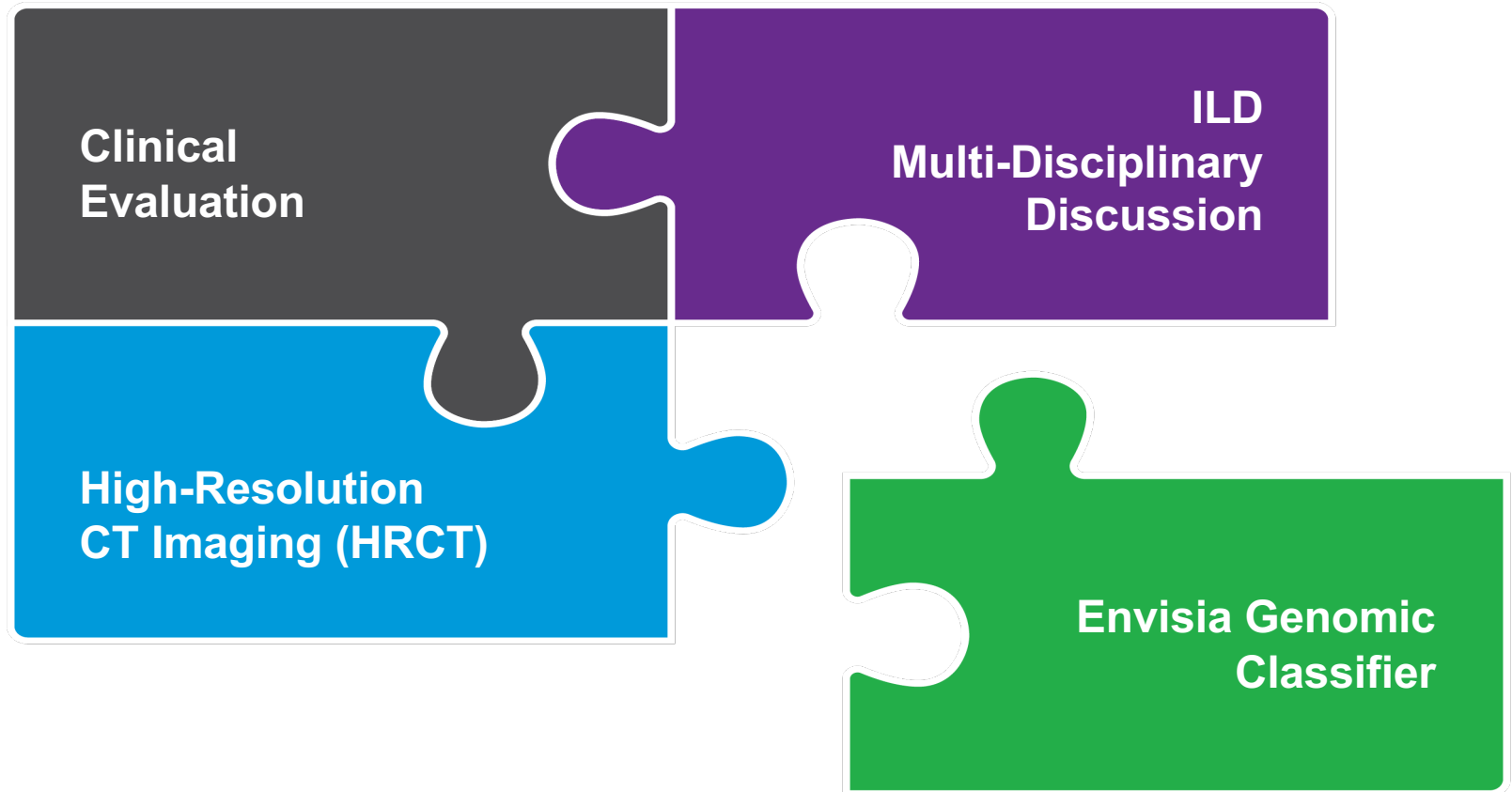
- Misses up to 60% of cases with UIP findings on histopathology^{10,11}
- Radiologist interpretation and access to thoracic radiologist experts may vary¹²

10 Chung et al. *CHEST* 2015; 147(2):450-459.

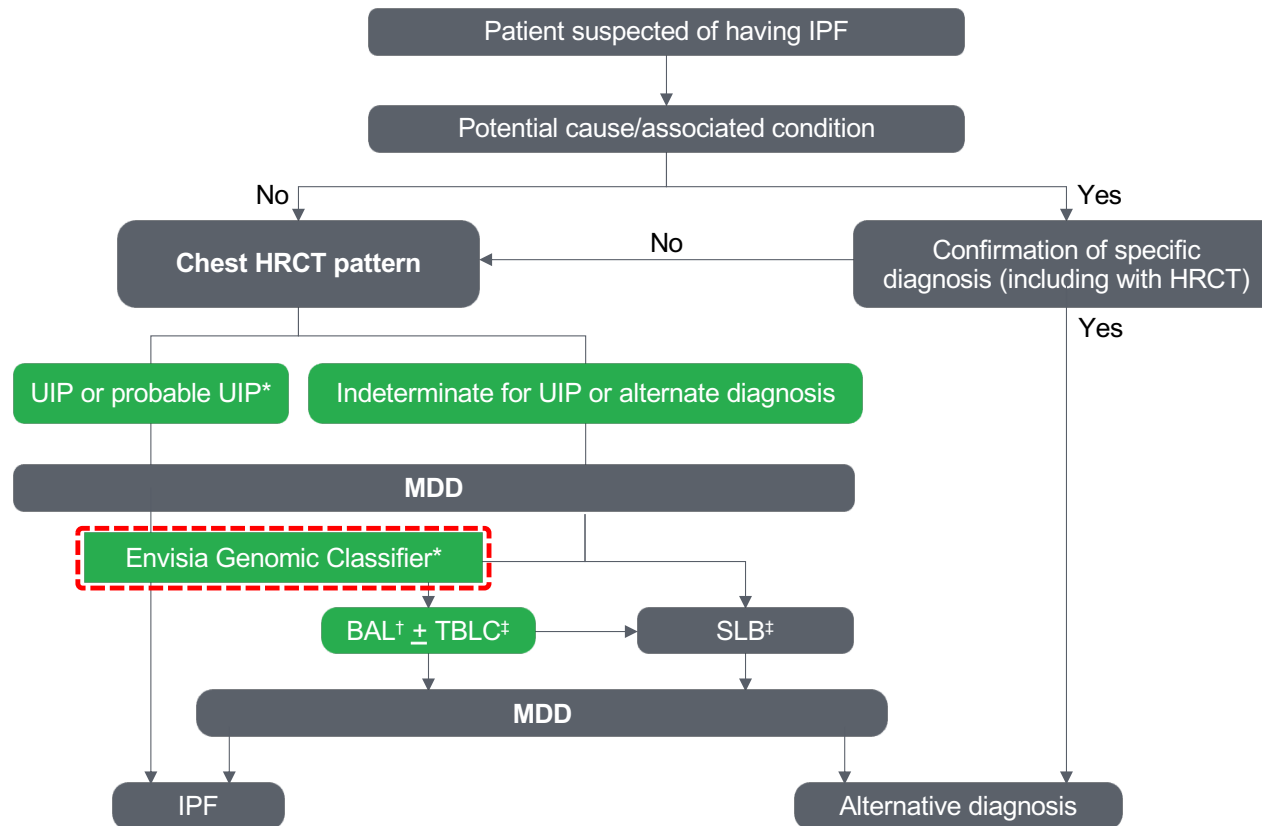
11. Raghu, et al. *Lancet Respiratory Medicine*, April 2019.

12. Walsh et al. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. *Thorax* 2016;71:45-51.

Envisia Classifier is Designed as a Complement to HRCT and Clinical Factors for a More Confident ILD Diagnosis



Future Diagnostic Algorithm with Integration of a Genomic Tool



* The Envisia Genomic Classifier test is available as part of Veracyte's CLIA-validated laboratory-developed test (LDT) service. This test has not been cleared or approved by the FDA.

* The Envisia test can be used in Probable UIP patients if the clinical context is not clear.

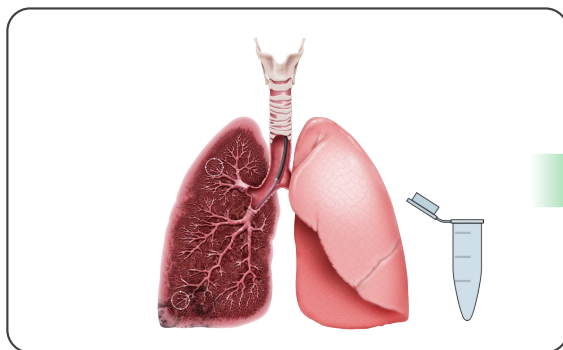


Envisia Genomic Classifier Overview

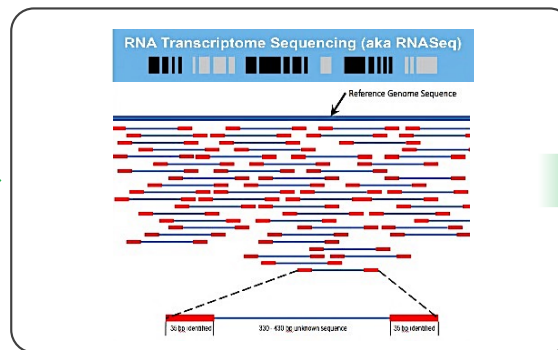
Fayeze Kheir, MD

Envisia Classifier Detects a Genomic Pattern of UIP Using Transbronchial Biopsy Samples

How Envisia Works:



3-5 transbronchial biopsy (TBB) samples are collected during a routine bronchoscopy



A single whole-transcriptome library from RNA pooled from TBB samples was generated and sequenced

A screenshot of an Envisia Patient Report. The report includes patient information, collection and received dates, facility name, requesting physician, and specimen type. The test result is positive for Usual Interstitial Pneumonia (UIP).

| PATIENT INFORMATION | | REPORT STATUS: FINAL | | PATIENT REPORT | |
|---|---|----------------------------|---------------------------------|-----------------------|--|
| PATIENT: John Doe | DOB: 21 Mar 1963 | GENDER: M | LAB ID: F-012-477 | MRN #: 127654 | |
| COLLECTION DATE: 05 May 2017 | FACILITY NAME: University Hospital of Anytown | RECEIVED DATE: 06 May 2017 | REQUESTING PHYSICIAN: Jane Demo | PHONE: (555) 555-5555 | |
| REPORT DATE: 17 May 2017 | REPORT CC: Donald Demo | | | PHONE: (555) 555-5555 | |
| Specimen Type, Location: Transbronchial biopsy (TBB) in the lung parenchyma | | | | | |
| TEST RESULT | | | | | |
| + POSITIVE for Usual Interstitial Pneumonia (UIP). | | | | | |

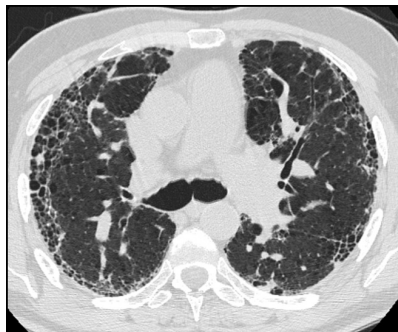
Locked Envisia classifier is used to designate either **positive** or **negative** molecular UIP

The Envisia Genomic Classifier test is available as part of Veracyte's CLIA-validated laboratory-developed test (LDT) service. This test has not been cleared or approved by the FDA.

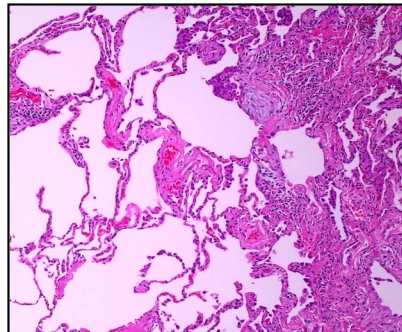
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UIP is a Critical Factor in Diagnosing IPF and Informing Prognosis

IPF is usually accompanied by a UIP pattern of injury but may also be associated with conditions that mimic IPF (e.g. HP, CTD-ILD)



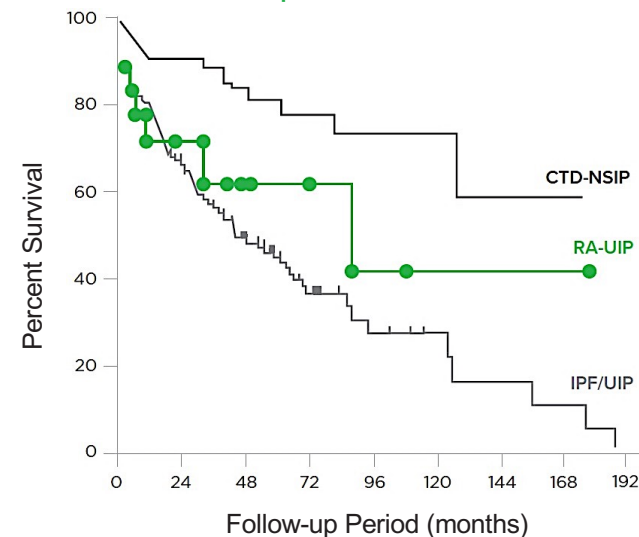
Radiographic UIP Pattern



Pathologic UIP Pattern

UIP is often associated with poor prognosis regardless of ILD sub-type¹³⁻¹⁵

Example from RA-ILD¹⁴



13. Kim et al. UIP in RA-ILD *Eur Respir J* 2010.

14. Kim et al. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. *Chest* 2009.

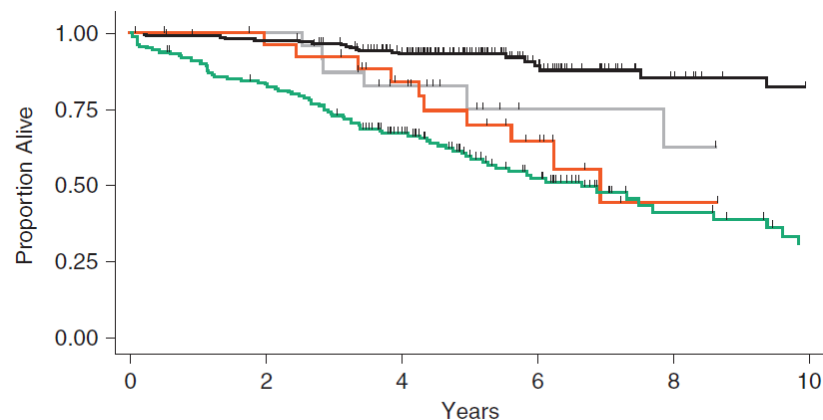
15. Wang et al. Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis. *Chest* 2017.

Impact of Lung Biopsy Information on Treatment Strategy of Patients with Interstitial Lung Diseases

Lung Biopsy (TBLC/SLB) Data

- In 34% of cases, LBx led to a reclassification of cases and increase in diagnostic confidence, resulting in a significant change in treatment strategy
- MDD Team
 - Less inclined to “wait and see” (15% to 4%) or to prescribe steroids (54% to 37%) and was more confident to treat with antifibrotics (23% to 44%) or immunosuppressive drugs (7% to 14%)

Lung Biopsy changes non IPF to IPF, or IPF to non IPF, and no change



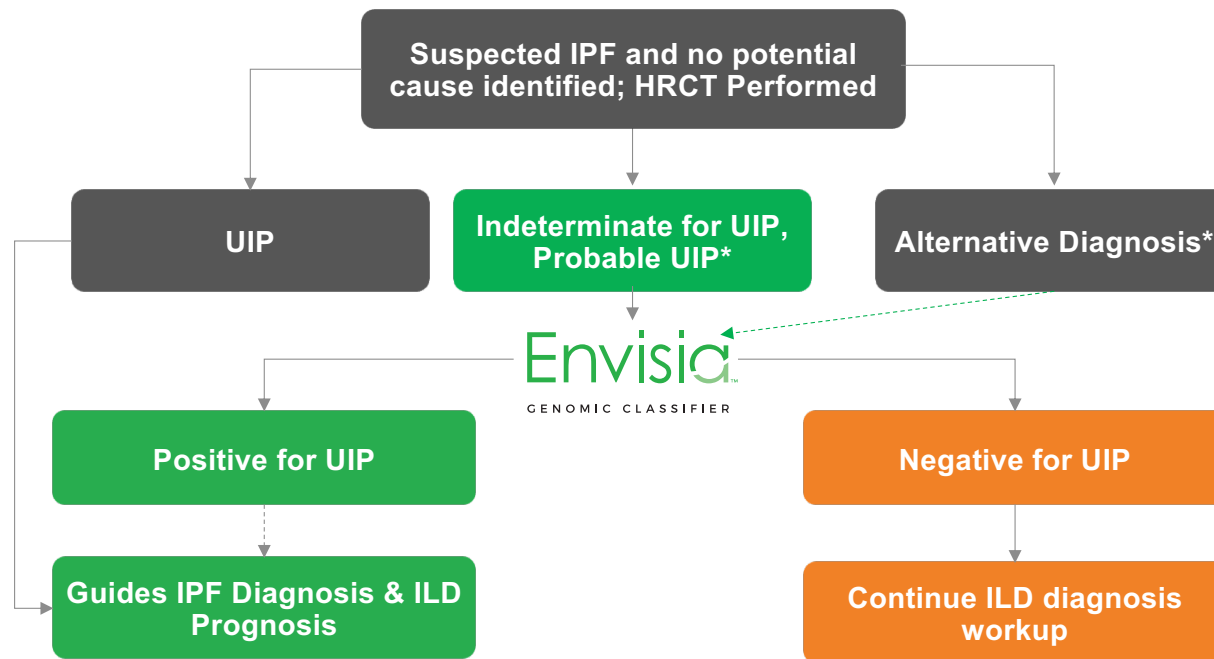
Critical information for treatment decisions



Tomassetti S, et al. *Ann Am Thorac Soc*. 2022 May;19(5):737-745.

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Envisia Classifier is Designed as a Complement to HRCT and Clinical Factors for a More Confident IPF Diagnosis and ILD Prognosis



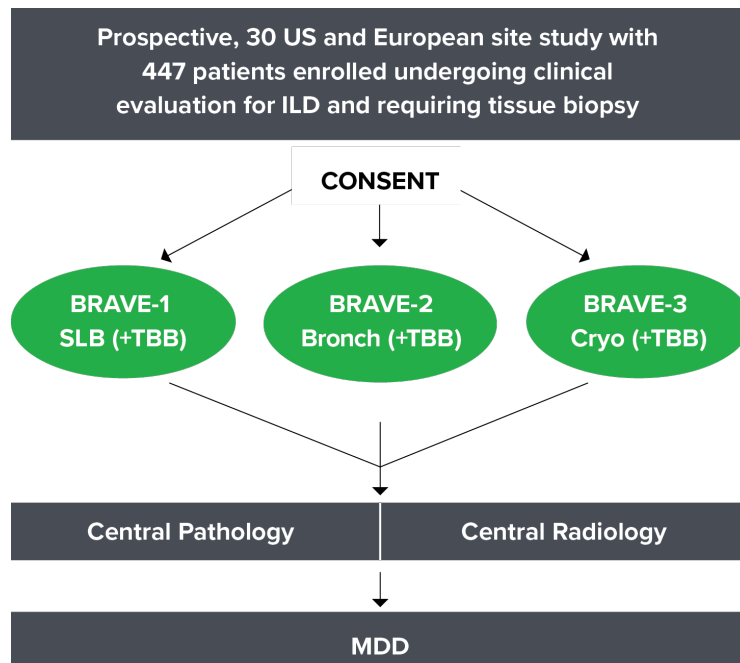
Envisia classifier does not confer a clinical diagnosis and must be interpreted in the context of other clinical factors such as demographics, clinical history, and HRCT findings.

* In patients for whom a confident IPF diagnosis cannot be made based on clinical factors and HRCT alone.

The Envisia Genomic Classifier test is available as part of Veracyte's CLIA-validated laboratory-developed test (LDT) service. This test has not been cleared or approved by the FDA.

BRAVE: Prospective Multi-Center Study for Development and Clinical Validation of Envisia Classifier

Study Design:



Classifier Development (n=90)

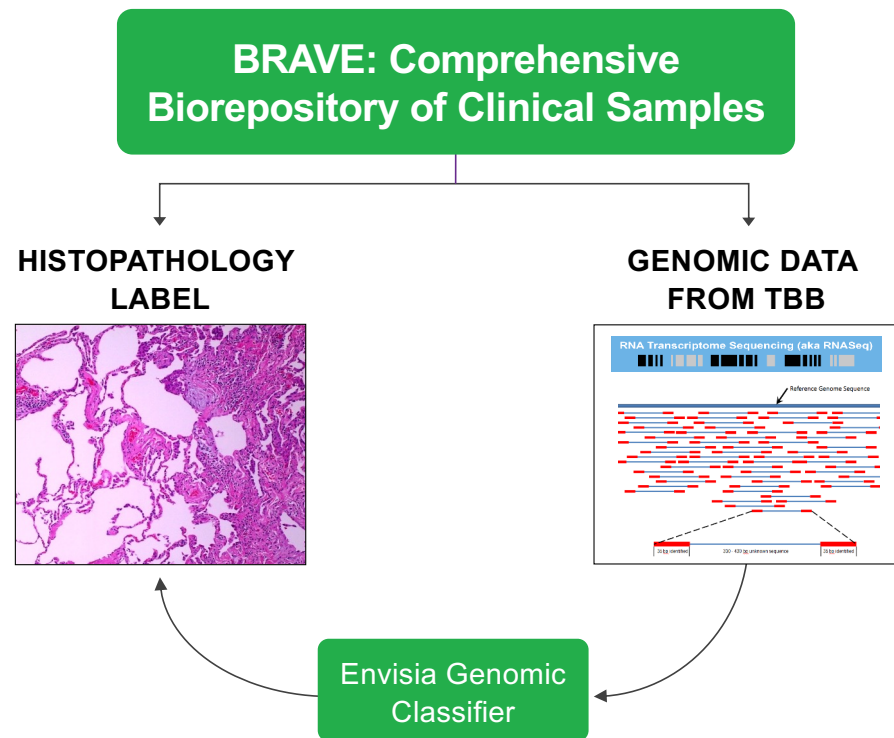
Two independent prospective Clinical Validation Studies

- Initial Validation Study (n=49)¹⁶
- Second Validation (n=96)¹⁷

16. Raghu, et al. *Lancet Respiratory Medicine*, April 2019.

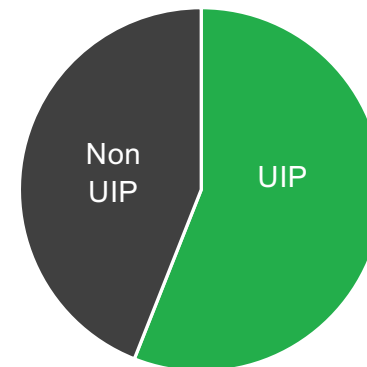
17. Richeldi L, et al. *American Journal of Respiratory and Critical Care Medicine*, July 2020.

Only Patients with a Confirmed Histopathology Label Were Used in the Development and Clinical Validation of Envisia Classifier



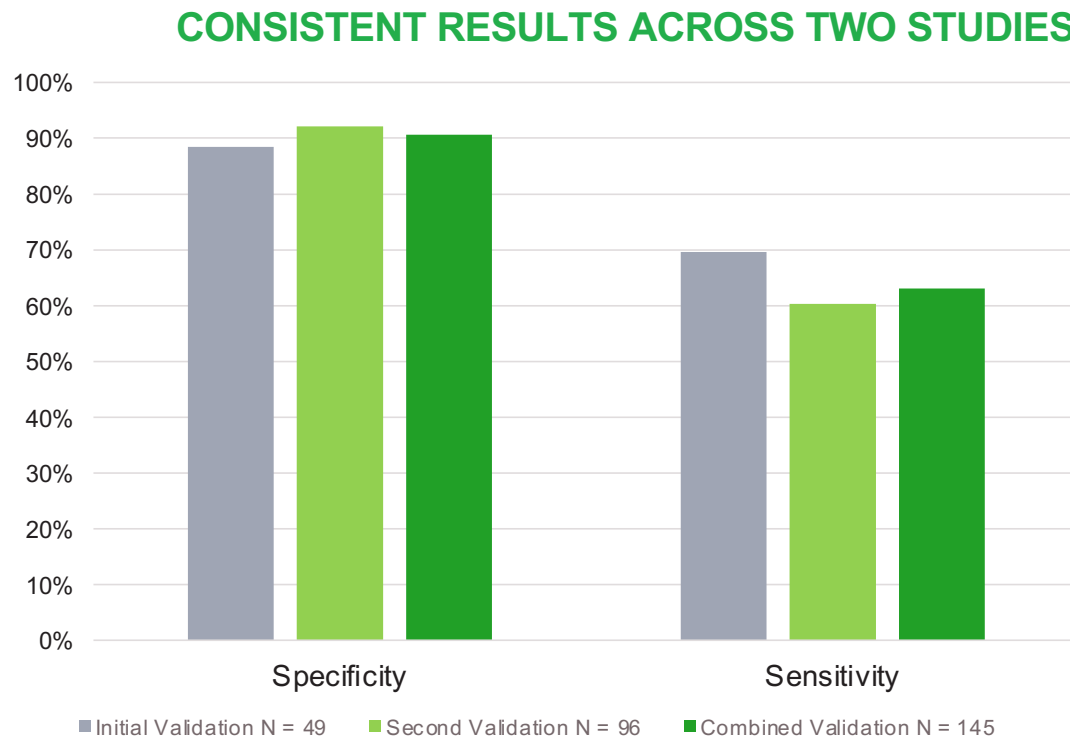
Diverse Set of ILD Patients Represented

HISTOPATHOLOGY LABELS



- Most common non-UIP diagnoses: RB, HP, Sarcoidosis, and NSIP
- Most common UIP diagnoses: IPF, Fibrotic HP, and CTD-ILD's

In Two Independent Prospective Clinical Validation Studies, Envisia Classifier Identified UIP with a Combined 91% Specificity Compared to Histopathology



COMBINED RESULTS



SPECIFICITY



SENSITIVITY

16. Raghu, et al. *Lancet Respiratory Medicine*, April 2019.

17. Richeldi L, et al. *American Journal of Respiratory and Critical Care Medicine*, July 2020.

Envisia Classifier Combined with HRCT Identified Twice as Many UIP Patients than HRCT Alone

Study Objective:

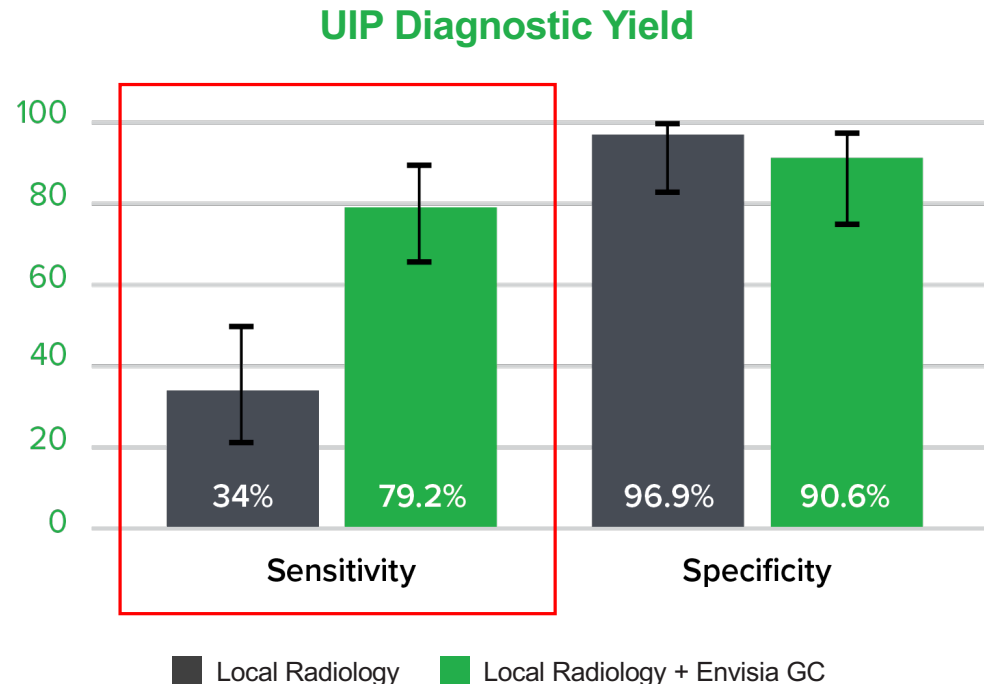
Assess performance of Envisia classifier when used in conjunction with local radiology compared to local radiology alone

Study Design:

Patients with local radiology diagnoses and Envisia classifier results were scored for accuracy and yield in detecting a UIP pattern against reference pathology (n=85)

Study Results:¹⁶

Addition of Envisia classifier to local HRCT detects UIP with improved sensitivity (34% HRCT alone vs. 79% HRCT+Envisia) while minimally affecting specificity



17. Richeldi L, et al. *American Journal of Respiratory and Critical Care Medicine*, July 2020.

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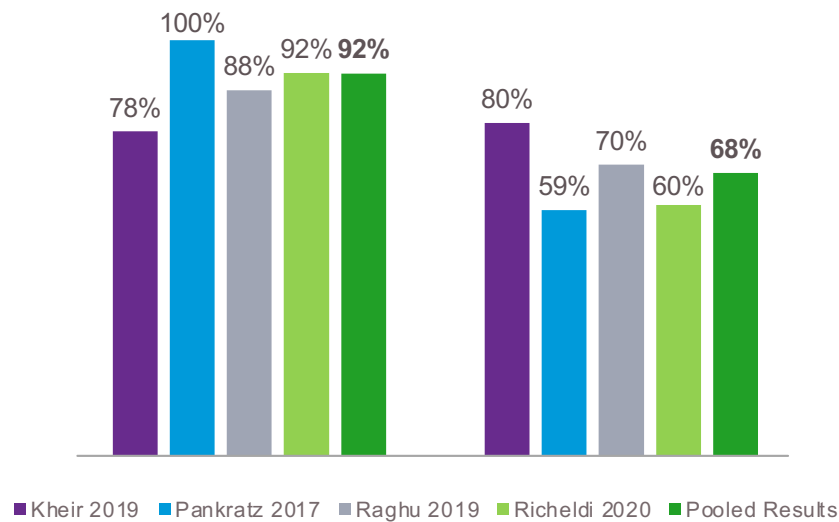


Systematic Review and Editorial in AnnalsATS May 2022

Fayez Kheir, MD

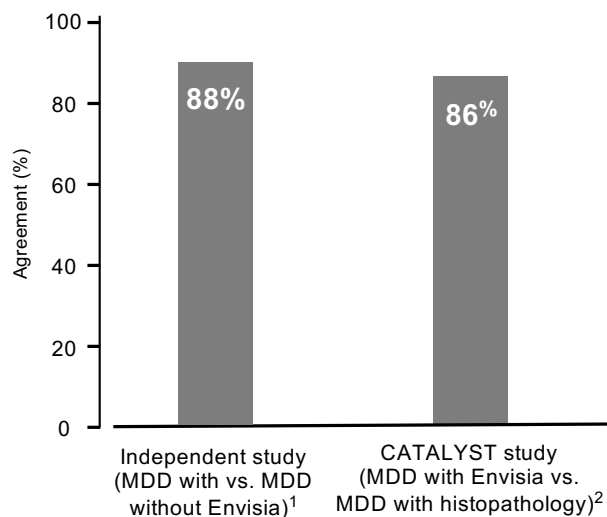
Use of a Genomic Classifier in patients with Interstitial Lung Disease A Systematic Review and Meta-Analysis

- Four relevant studies identified
- When aggregated by meta-analysis, Envisia testing identified UIP with **specificity of 92% and sensitivity of 68% across 195 total patients with ILD of unknown type**
 - Using histopathological diagnosis from samples obtained by SLB, TBLC, or MDD as the reference standard

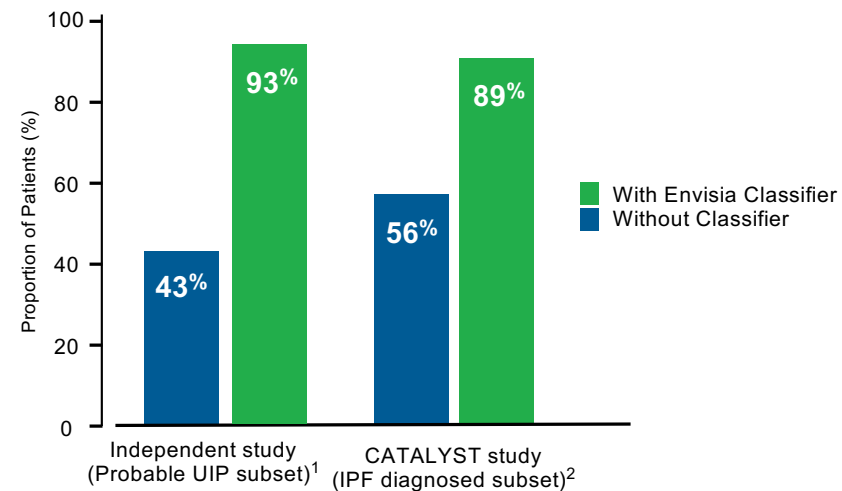


Agreement and Diagnostic Confidence in IPF Diagnosis Demonstrates Consistent Performance in Two Studies

Agreement in IPF vs. Non IPF Clinical Diagnosis



Confidence in IPF Diagnosis Increased with Addition of Envisia Classifier



1. Kheir et al. *CHEST*, May 2020.

2. Raghu, et al. *Lancet Respiratory Medicine*, April 2019.

3. Kheir, et al. *AnnalsATS*, May 2022.



Envisia Classifier Decision Impact Study

Mary Beth Scholand, MD

Clinical Utility of the Envisia Genomic Classifier in Patients with ILD: Decision Impact Survey Study Design

Study Design & Objective:

Prospective randomized Decision impact survey to determine impact of Envisia classifier on physicians' clinical decision making of patients undergoing ILD evaluation

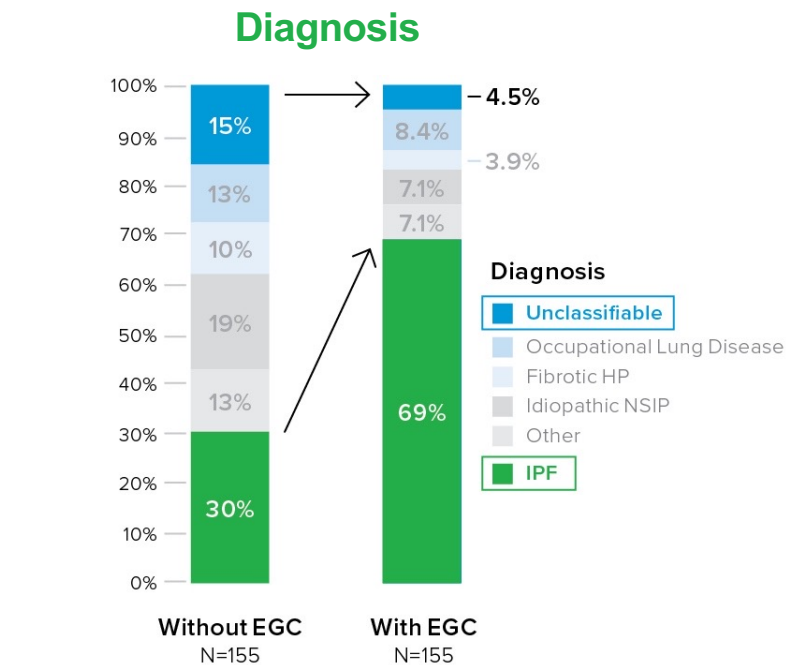
- 103 board certified Pulmonologists took survey with five cases randomly selected from 11 cases

Case Selection:

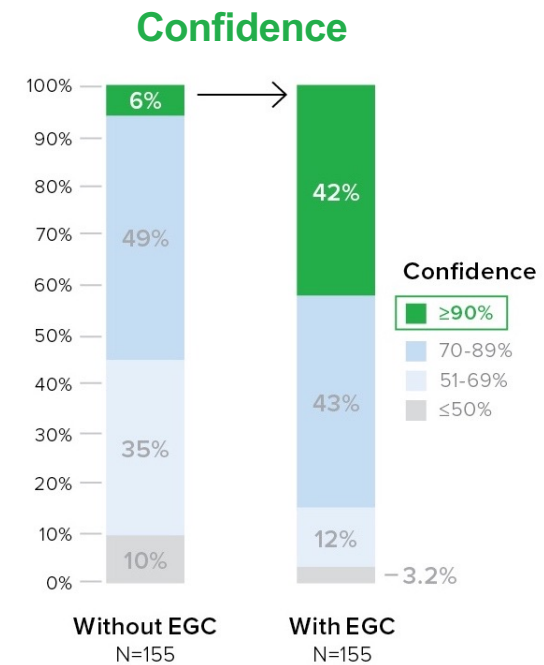
BRAVE study participants with:

- Undiagnosed ILD
- Envisia UIP+ result
- **Underwent a central MDD that resulted in final IPF diagnosis**

Results: The Number of and Confidence in IPF Diagnoses Increased with the Envisia Genomic Classifier



IPF Diagnosis with Envisia Increased >2X
(39% increase – p-value <0.001)



High Confidence (≥90%) Increased 7X
(36% increase – p-value <0.001)



Real World Case Studies

Moderator
Bill Bulman, MD

Let's Go Back to Our Patient – Case 1: 70-year-old Male

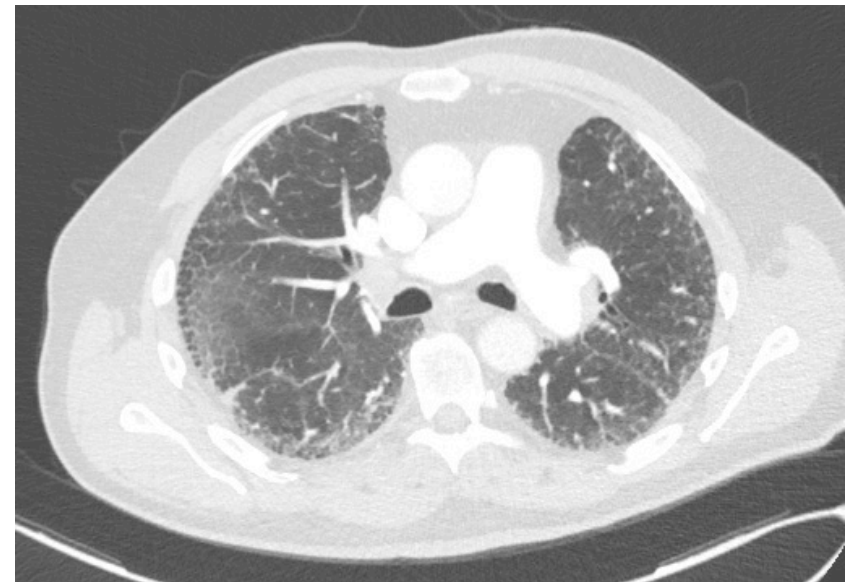
Patient Background & Exam

- 70-year-old Male c/o chronic cough >2 years
- Was admitted to the hospital for worsening shortness of breath. CXR showed interstitial infiltrates.
- Negative for any autoimmune features and HP panel
- + GERD
- Former smoker 1-2 PPD x 20 years, quit 20 years ago
- No Family History of Idiopathic Pulmonary Fibrosis (IPF)
- No birds, Jacuzzi, humidifiers

Pulmonary Function Test

| | |
|----------|-------------|
| FVC | 62% (3.02L) |
| FEV1 | 71% (2.43L) |
| FEV1/FVC | 0.83 |
| DLCO | 34% |

CT Scan



INDETERMINATE FOR UIP

What Would You Do Next?

- A. Bronchoalveolar Lavage Alone**
- B. BAL + Forceps Transbronchial Biopsy with Envisia**
- C. Cryobiopsy (with or without BAL)**
- D. Cryobiopsy (with Envisia)**
- E. VATS Lung Biopsy**
- F. Other**

Case 1: Differential Diagnosis and Test Results

Differential Diagnosis & Recommended Next Steps

- **Differential diagnosis:** HP, NSIP, IPF
- **Recommended next step:** BAL with TBB for Envisia

Test Results

- **Serology:** Negative
- **HP Panel:** Negative
- **Envisia Classifier:** Positive for UIP

Diagnosis and Treatment

- **Diagnosis:** IPF given that serology and HP panels were negative
- **Treatment Recommendation:** Antifibrotics

| BAL Results | Patient | Normal ² | IPF ² |
|-------------|---------|---------------------|------------------|
| Lymphocytes | 9% | 10-15% | 7-27% |
| Neutrophils | 13% | <=3% | 6-22% |
| Eosinophils | 4% | <=1% | 2-7% |
| Macrophages | 66% | >85% | 49-83% |

TEST RESULT

+ **POSITIVE** for Usual Interstitial Pneumonia (UIP).

RESULT INTERPRETATION

The performance of the classifier reflects concordance with the presence or absence of a UIP pattern determined by a central panel of pathologists specializing in interstitial lung disease (ILD). The assay is designed and optimized to be highly specific to reduce the likelihood of a false positive result.

In a combined analysis from two independent prospective, multicenter studies, 9% of patients who did not have a UIP pattern on histopathology had a positive result (false positive). 63% of patients with a UIP pattern on histopathology had a positive classifier result (true positive).^{1,2}

The Envisia Genomic Classifier does not confer a clinical diagnosis, and the result must be interpreted in the context of other clinical factors such as demographics, HRCT findings, clinical history and other diagnostic testing.

1. Raghu G, et al. *Lancet Respiratory Medicine*, April 2019

2. Richeldi L, et al. *American Journal of Respiratory and Critical Care Medicine*, July 2020

Test Methodology: RNA Sequencing

PERFORMANCE METRICS

Specificity

91%

Sensitivity

63%

16. Raghu G, et al. *Am J Respir Crit Care Med*. 2018;198:e44-e68.

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Case 2: 77-year-old Male

Patient Background & Exam

CC: SOB > 5 years, worsening in the past month

HPI:

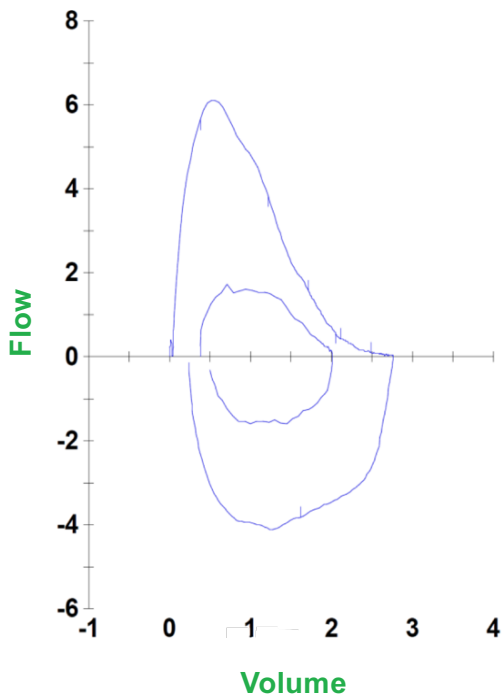
- 77 yo M with a PMHx of CAD s/p CABG and Afib
- No cough. No significant exposure to mold, birds, feathers, farming.
- No CTD symptoms such as joint swelling, rash, morning stiffness.
- No GERD
- **Smoking:** 1PPD x 18 years, quit 30 years ago
- **Occupational:** Worked in a steel mill for 10 years
- **Family History:** No pulmonary fibrosis

Physical Exam:

- **Lungs:** bibasilar crackles, right>left
- **Ext:** No clubbing

Case 2: PFT Lab Report & Serologies

PFT Lab Report



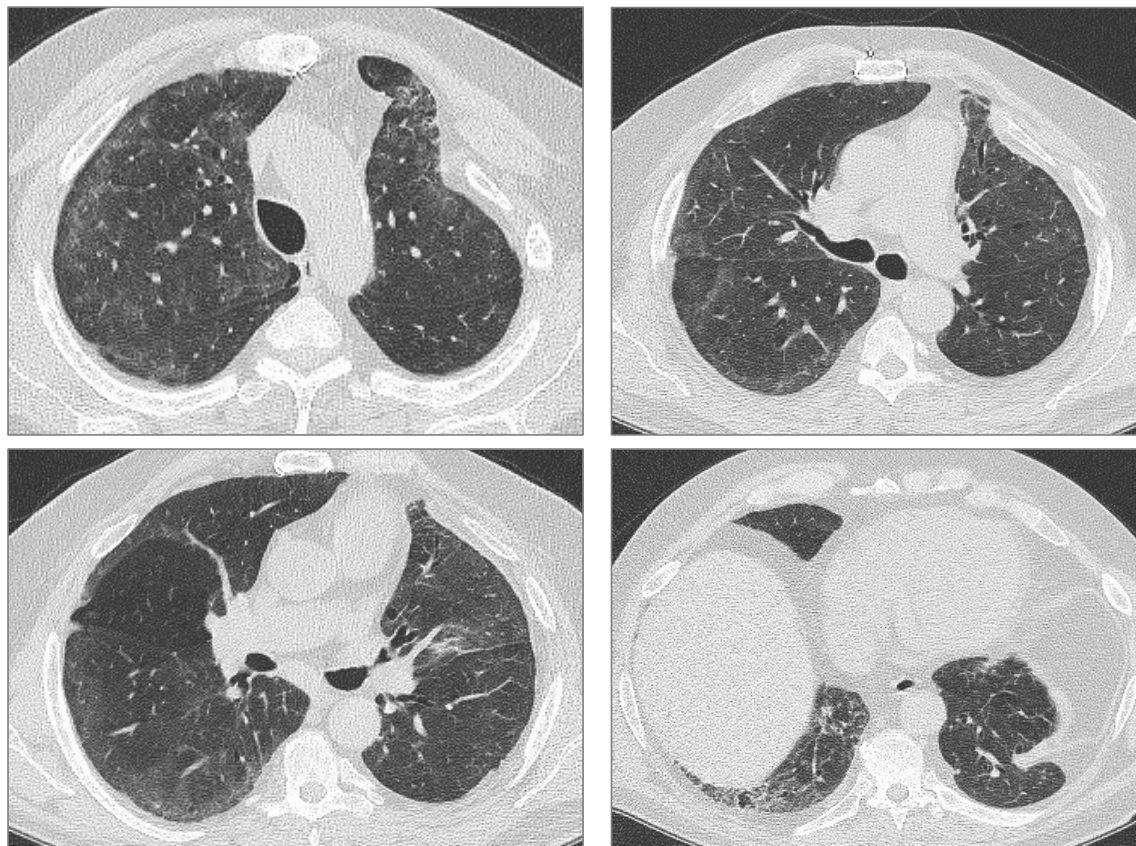
Pulmonary Function Test

| | |
|----------|-------------|
| FVC | 2.77 L, 78% |
| FEV1 | 60% |
| FEV1/FVC | 77% |
| DLCO | 9.7, 42% |

Serologies

- **ANA, ENA, RF, CCP, Myositis:** negative
- **HP Panel:** positive (Aureobasidium pullulans, Aureobasidium pullulans, Alternaria tenuis, Cladosporium herbarum, Penicillium notatum, Phoma spp, Trichoderma viride)

Case 2: HRCT



What Would You Do Next?

- A. Bronchoalveolar Lavage Alone**
- B. BAL + Forceps Transbronchial Biopsy with Envisia**
- C. Cryobiopsy (with or without BAL)**
- D. Cryobiopsy (with Envisia)**
- E. VATS Lung Biopsy**
- F. Other**

Case 2: Bronchoalveolar Lavage & Envisia Classifier Results


| BAL Results | Patient | Normal ² | IPF ² |
|-------------|---------|---------------------|------------------|
| Lymphocytes | 12% | 10-15% | 7-27% |
| Neutrophils | 4% | <=3% | 6-22% |
| Eosinophils | 1% | <=1% | 2-7% |
| Macrophages | 83% | >85% | 49-83% |



REPORT STATUS: FINAL
PAGES: 1 OF 1
CLIENT ID:
ENVISIA REQ:

PATIENT REPORT

TEST RESULT

 **NEGATIVE** for Usual Interstitial Pneumonia (UIP).

16. Raghu G, et al. *Am J Respir Crit Care Med*. 2018;198:e44-e68.



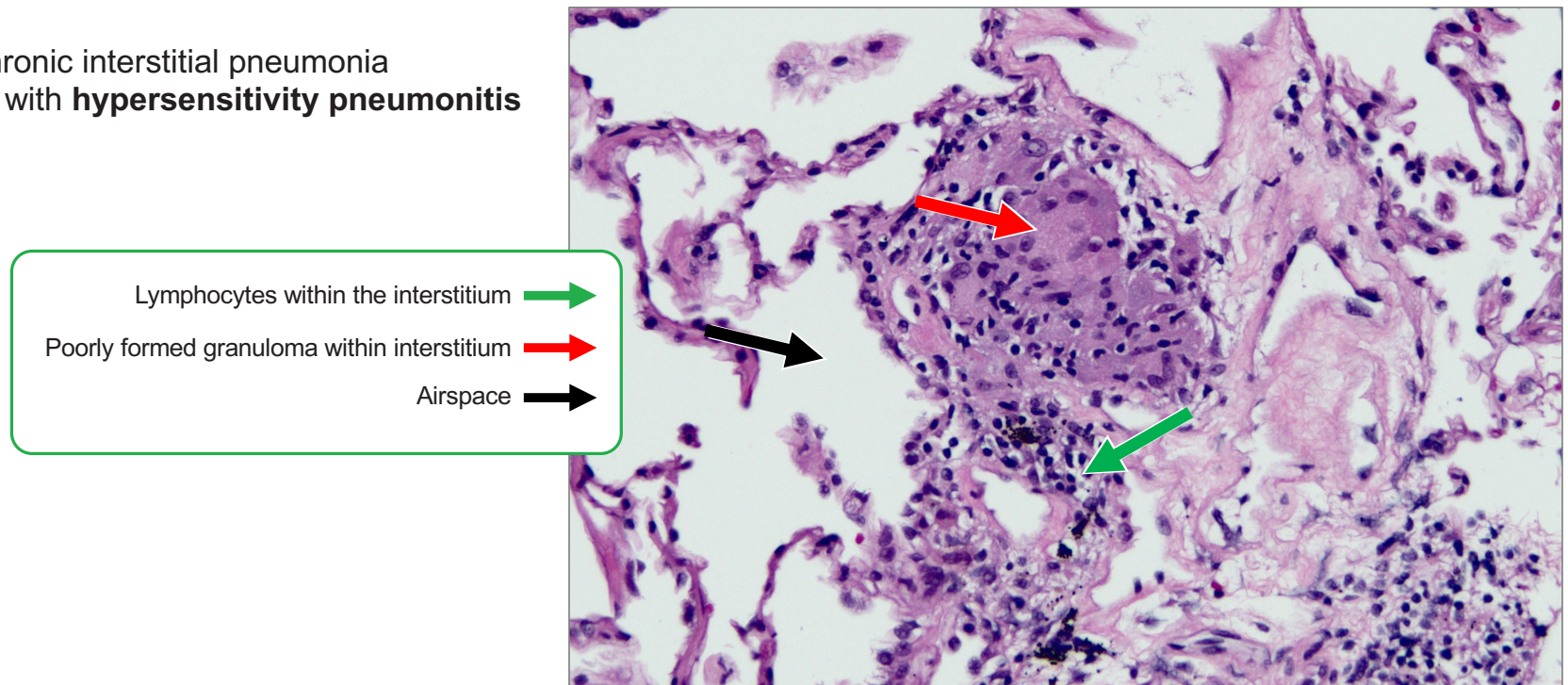
What Would be Your Leading Diagnosis For this Patient?

- A. Connective Tissue Disease (CTD)
- B. Non-Specific Interstitial Pneumonia (NSIP)
- C. Idiopathic Pulmonary Fibrosis (IPF)
- D. Hypersensitivity Pneumonitis (HP)

Case 2: Cryobiopsy Results & Final Diagnosis

Diagnosis

- Cellular chronic interstitial pneumonia consistent with **hypersensitivity pneumonitis**



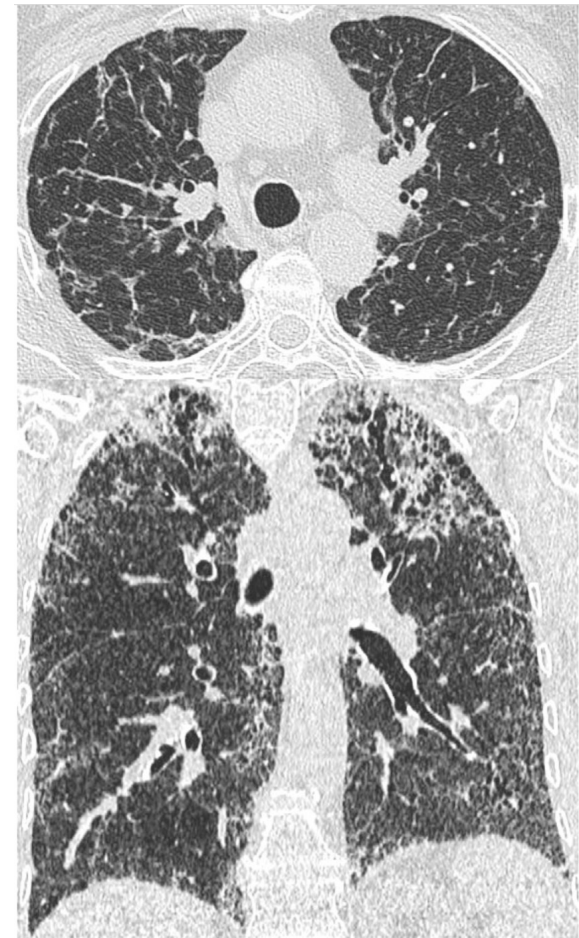
Case 3: 60-year-old Female – Unclassifiable with FVC Decline

Patient Background & Exam

- 60-year-old female defined as unclassifiable was initiated on immunosuppressive therapy
- At 6 months, patient shows >10% FVC decline
- Case brought back to MDD for discussion

| PFTs | Initial | Repeat at 6 months |
|----------|------------|--------------------|
| FVC | 2.01L, 45% | 1.65L, 34% |
| FEV1/FVC | 105% | 112% |
| DLCO | 10.3, 55% | 8.4, 39% |

**Would you consider this as Progressive
Pulmonary Fibrosing ILD?**



Discussion: Is There a Role for Envisia Genomic Classifier in Predicting Progressive Pulmonary Disease Earlier in the Disease Course



Summary: Who are the appropriate patients for Envisia Genomic Classifier?

Clinical Factors



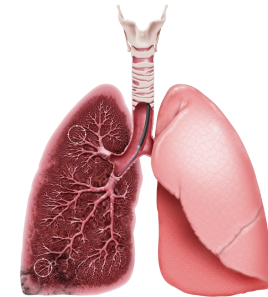
- No known causes identified (medication related, autoimmune disease, occupational, etc.)
- Suspected ILD

High Resolution CT



- Probable UIP or Indeterminate for UIP
- Alternative diagnosis if UIP is helpful for prognosis

Tolerability



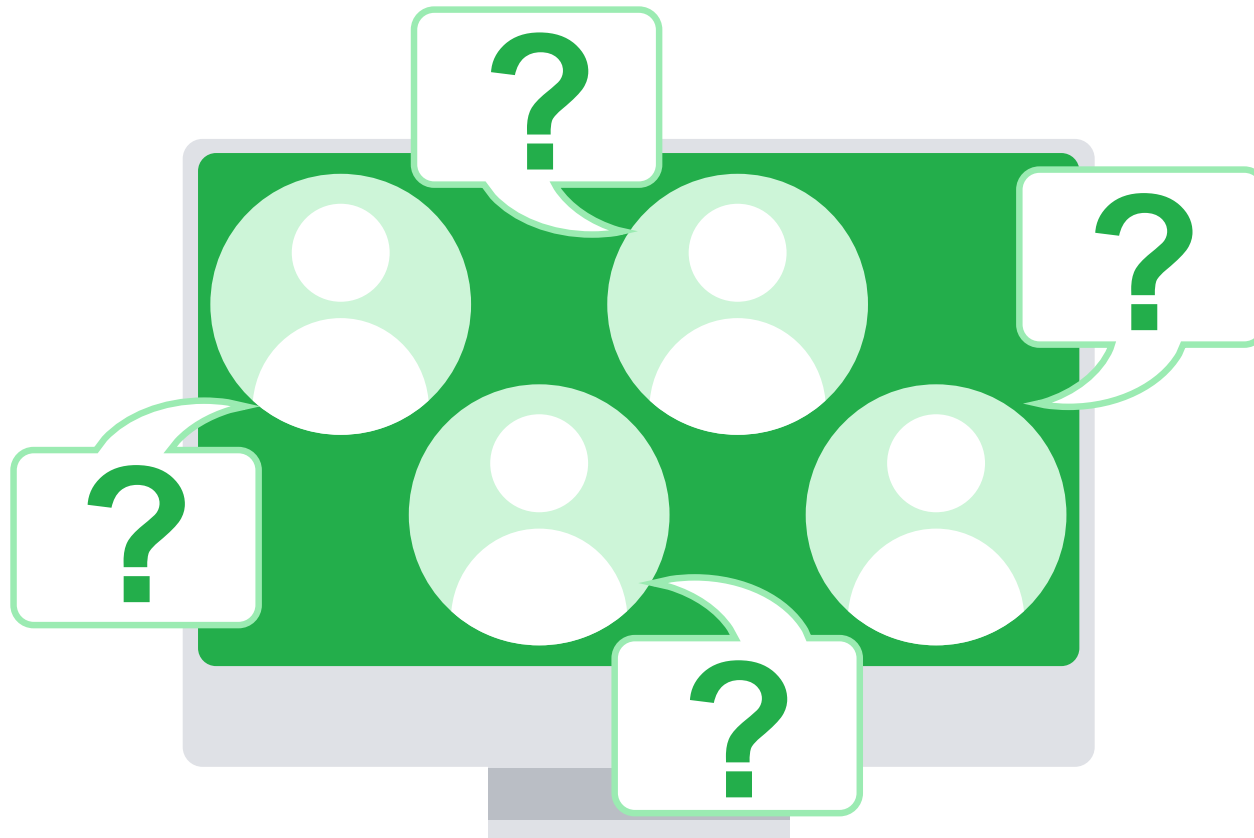
Candidate for standard TBB procedure (3-5 samples)

Envisia Classifier is Medicare Covered for Patients Meeting This Criteria

The Envisia Genomic Classifier test is available as part of Veracyte's CLIA-validated laboratory-developed test (LDT) service. This test has not been cleared or approved by the FDA.

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Questions? Please Submit Through Chat Function





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Appendix

Integrating the Envisia Genomic Classifier to Improve ILD Diagnostic and Prognostic Confidence

Helpful Tips for Attendees



- Please use Chrome or Firefox browser for best experience
- You will not be able to dial in for this virtual call
- You can listen to the presentation through your computer speakers



- Press F5 to refresh browser, if your screen freezes or the audio is not in sync
- Can also try running webinar in a different browser



- Use the Q&A box on the left-hand side of your screen
- Type your question in the open area and click “New Question” or “Submit”