

## RATIONALE

- Usual interstitial pneumonia (UIP) is a fibrotic lung injury pattern associated with chronic fibrosing interstitial lung diseases with poor prognosis and few effective treatments.
- During clinical evaluation, UIP is often missed by high resolution CT scan (HRCT) alone.
- The Envisia Genomic Classifier (EGC) is a molecular test for UIP in transbronchial biopsies (TBBx) which was prospectively validated and showed utility in the multidisciplinary review and diagnosis of IPF patients.

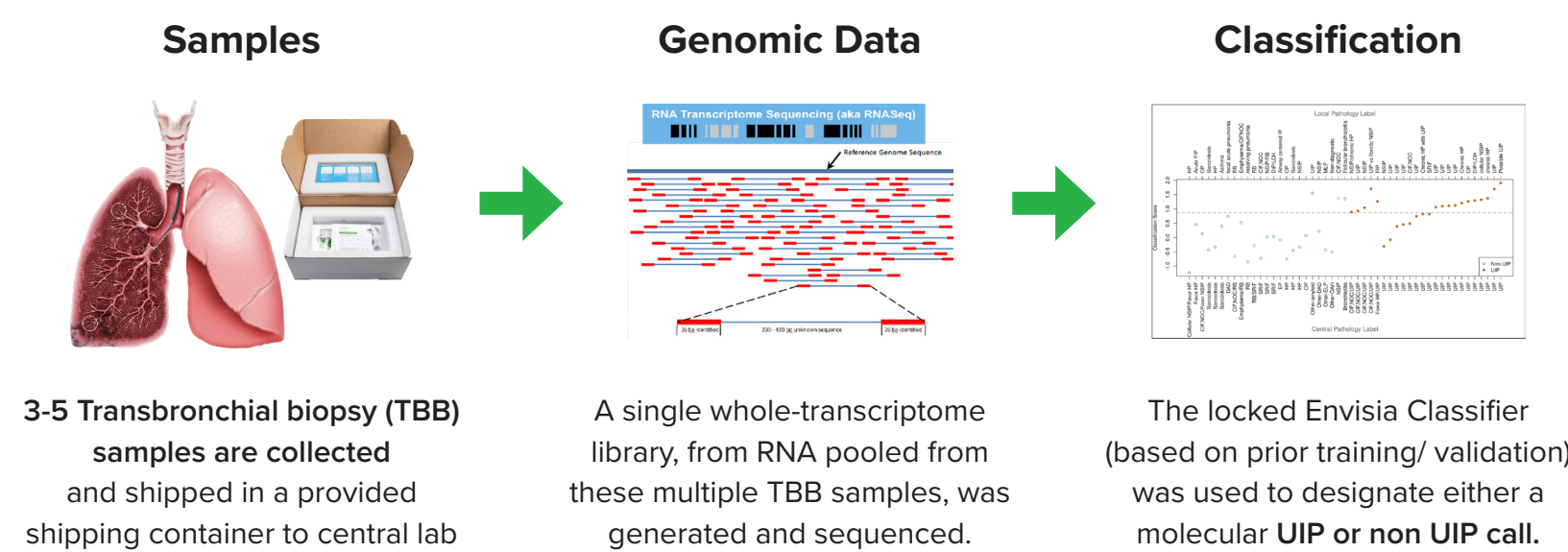
## OBJECTIVE

We evaluated the performance of the Envisia classifier in a second prospective clinical validation cohort when used in conjunction with local radiology to improve the diagnostic yield and accuracy of a UIP pattern as determined by reference pathology (truth labels).

## METHODS

- Patients were allocated for this independent clinical validation from the BRAVE (Bronchial Sample Collection for a Novel Genomic Test) cohort.
- Histopathology diagnoses were used to derive UIP or non-UIP reference standard truth labels for each subject.
- Whole-transcriptome RNA-sequencing was performed on TBBx samples in the Veracyte CLIA certified reference laboratory.
- The test's previously validated and locked machine learning algorithm was used to classify each subject as UIP or non-UIP.
- After exclusions for non-diagnostic histopathology and process errors, 96 subjects remained for blinded testing against reference truth.

### Sample Collection, Processing and Prediction from the Envisia Classifier



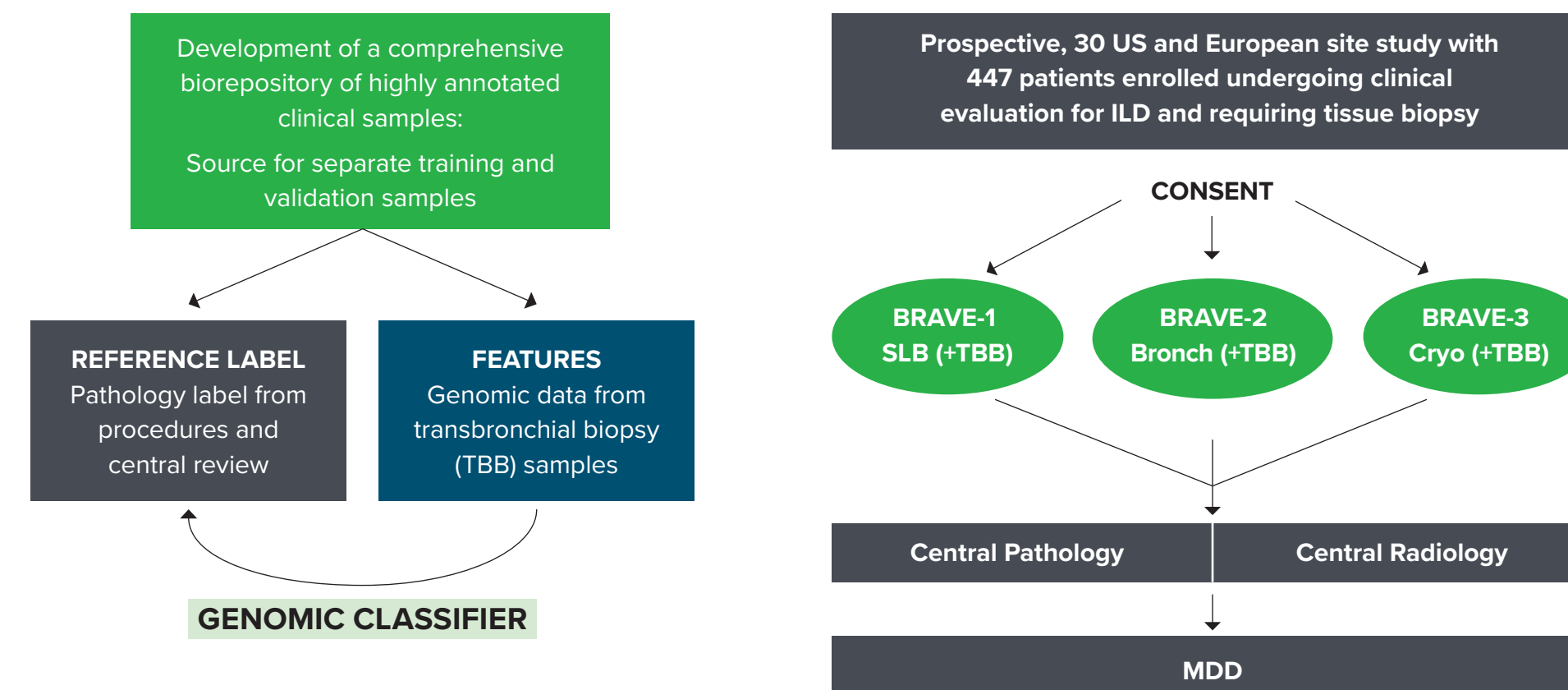
- HRCT features identified by study sites (local radiology) were used to diagnose the CT pattern according to Fleischner Society criteria:<sup>3</sup>
  - Typical UIP
  - Probable UIP
  - Indeterminate for UIP
  - Features consistent with a non-IPF diagnosis
- 85 patients with local radiology diagnoses and classifier test results were scored for accuracy and yield in detecting a UIP pattern against reference pathology.

### Review of Local HRCT Scan Reports

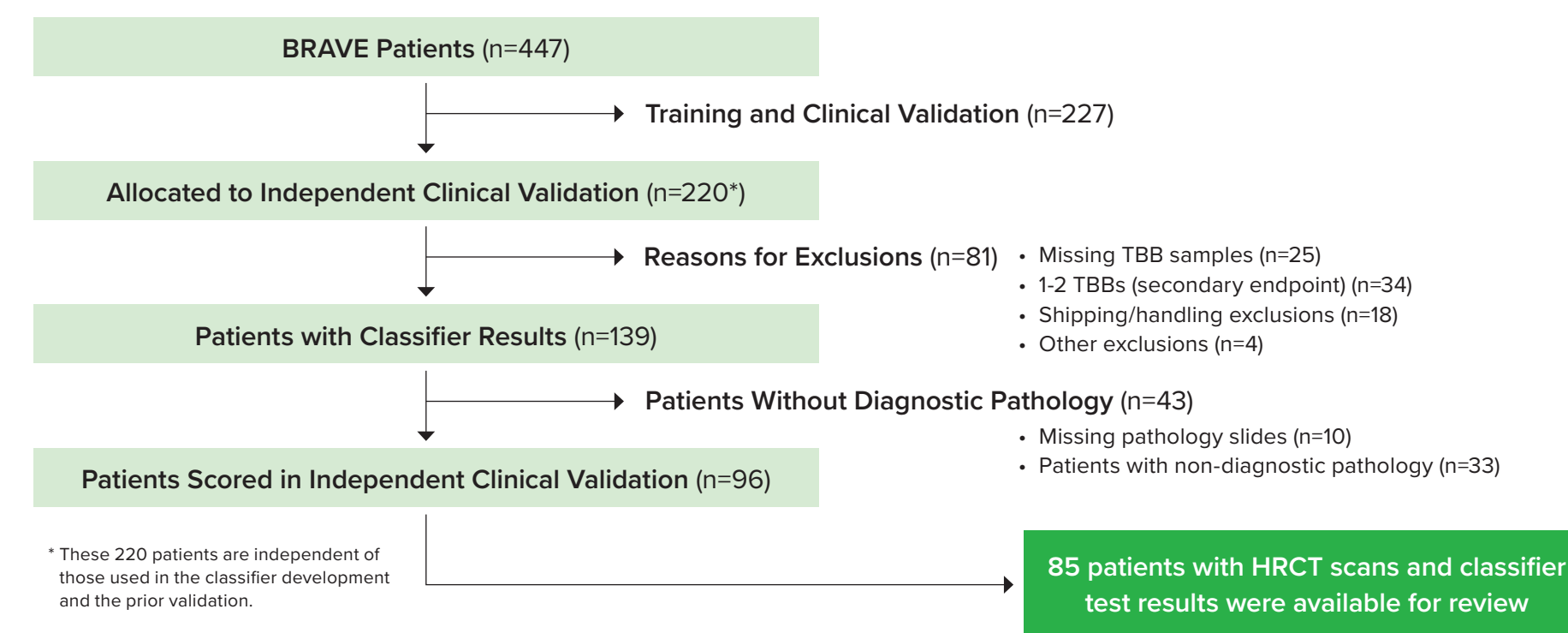
- Local HRCT scan reports were systematically interpreted according to the Fleischner Society criteria by two independent reviewers in a prospectively designed protocol for HRCT review.
- Reviewers were blinded to the clinical information of the patient, the results of the Envisia Classifier and the histopathological diagnosis associated with each HRCT scan report.
- These two interpretations for each HRCT report were independently documented and subsequently compared. If there was discordance between the two reviews, the two reviewers conferred until an agreement was reached.
- If there was persistent disagreement between the two reviewers regarding the interpretation of the HRCT report, a third reviewer would have served as a tie breaker. There were no cases that required interpretation by a third reviewer.

## METHODS (CONT'D.)

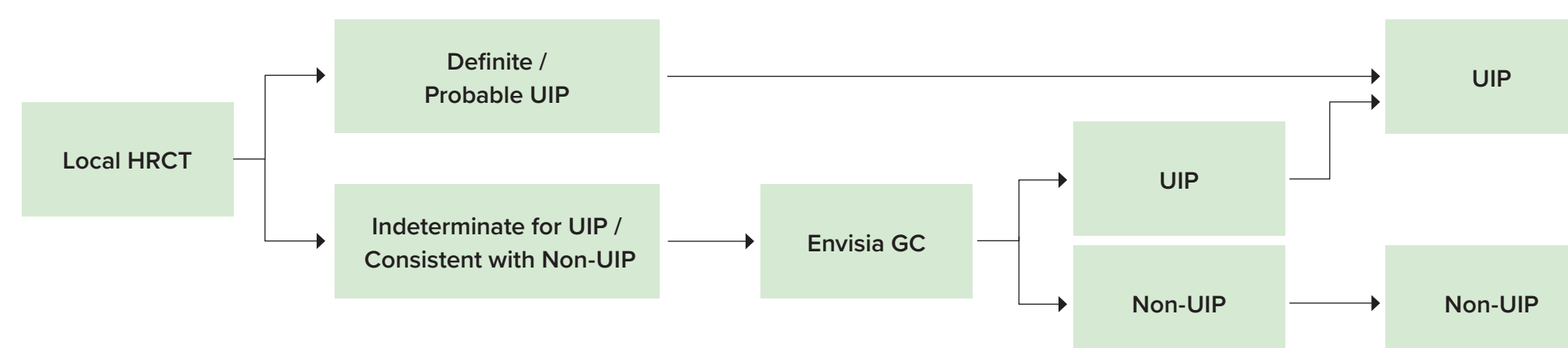
**FIGURE 1.** BRAVE: The Clinical Studies Supporting Algorithm Development Validation, and Clinical Utility of the Envisia Genomic Classifier



**FIGURE 2.** Derivation of Envisia Genomic Classifier Validation Cohort



**FIGURE 3.** Algorithm for UIP Determination by Local HRCT in Combination with Envisia Classifier



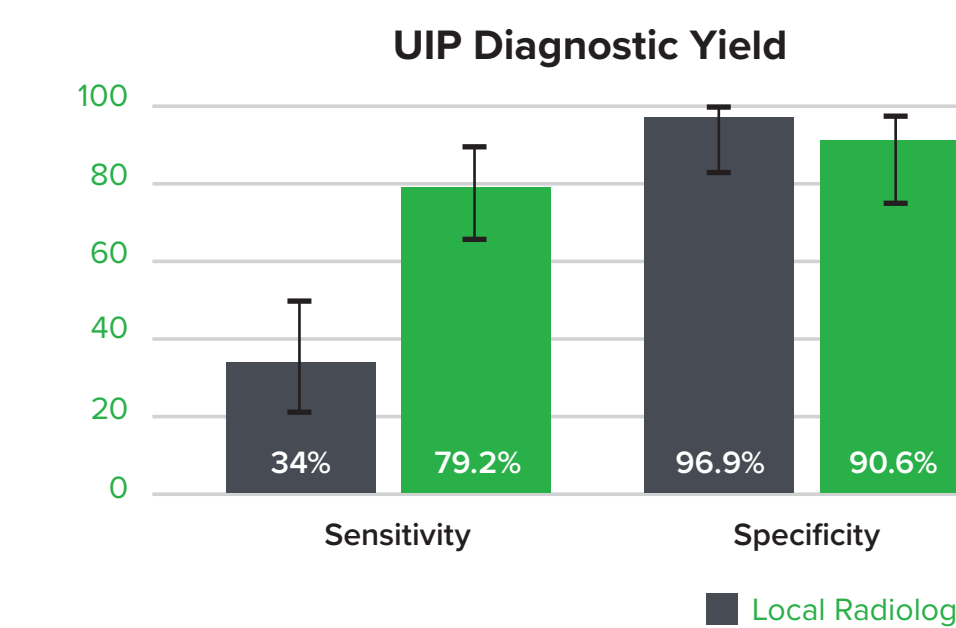
## RESULTS

### Diagnostic Yield of Local Radiology Compared to Local Radiology with Envisia

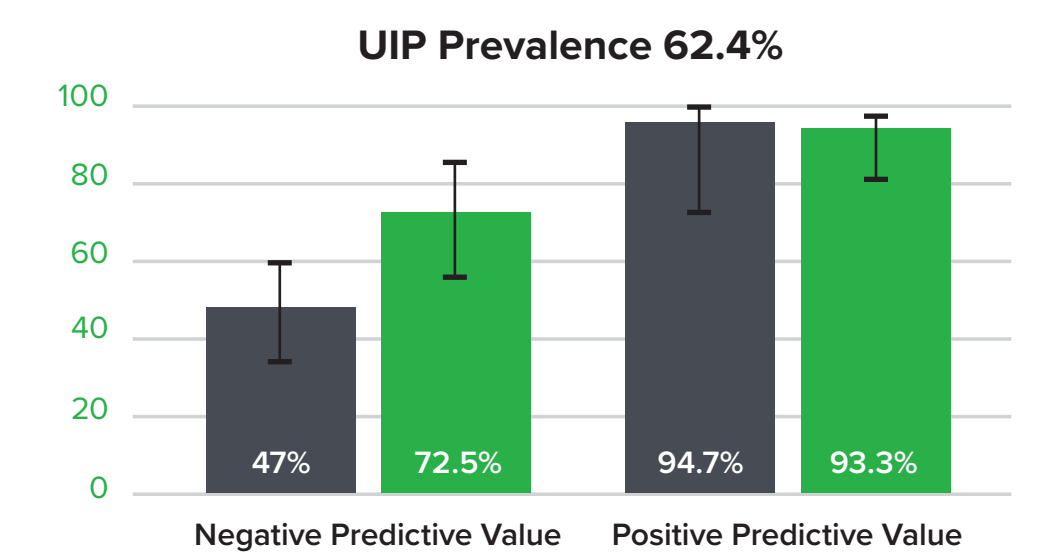
Local Radiology Result	Pathology reference standard	
	UIP (N=53)	Non-UIP (N=32)
Definite/Probable UIP	18	1
Indeterminate for UIP/ Consistent with non-IPF	35	31
<b>Sensitivity</b>	34.0% [21.5–48.3]	
<b>Specificity</b>	96.9% [83.8–100]	
<b>NPV</b>	47.0% [34.6–59.7]	
<b>PPV</b>	94.7% [74.0–99.9]	
<b>UIP Prevalence</b>	62.4%	

Local Radiology Result + Envisia Classifier	Pathology reference standard	
	UIP (N=53)	Non-UIP (N=32)
Definite/Probable UIP or Envisia Classifier UIP	42	3
Indeterminate for UIP/ Consistent with non-IPF and Envisia Classifier non-UIP	11	29
<b>Sensitivity</b>	79.2% [65.9–89.2]	
<b>Specificity</b>	90.6% [75.0–98.0]	
<b>NPV</b>	72.5% [56.1–85.4]	
<b>PPV</b>	93.3% [81.7–98.6]	
<b>UIP Prevalence</b>	62.4%	

**FIGURE 3A.** The Addition of the Envisia Classifier to Local HRCT Detects UIP with Improved Sensitivity While Minimally Affecting Specificity



**FIGURE 3B.** The Addition of the Envisia Classifier to Local HRCT Increases NPV While Maintaining PPV >90%



## CONCLUSIONS

- In this prospective multi-center clinical validation study, the diagnostic accuracy and yield for a UIP pattern was substantially improved when the Envisia Classifier was used as a complement to local radiology.
- The Envisia Classifier in combination with HRCT enhanced the sensitivity and improved the NPV of UIP diagnosis without significantly affecting the specificity or PPV.
- The recognition of a UIP pattern by the Envisia Classifier on TBBx combined with HRCT and clinical factors in a multidisciplinary discussion may assist clinicians in making an ILD (especially IPF) diagnosis without the need for any additional biopsies (eg. SLB).

## References

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## Disclosures

- Veracyte, Inc is the sponsor of this study.
- Dr Amy Case is a member of Boehringer-Ingelheim and Genentech: Speaker's bureau.
- Dr Ganesh Raghu is a consultant for Veracyte, Inc.