

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.

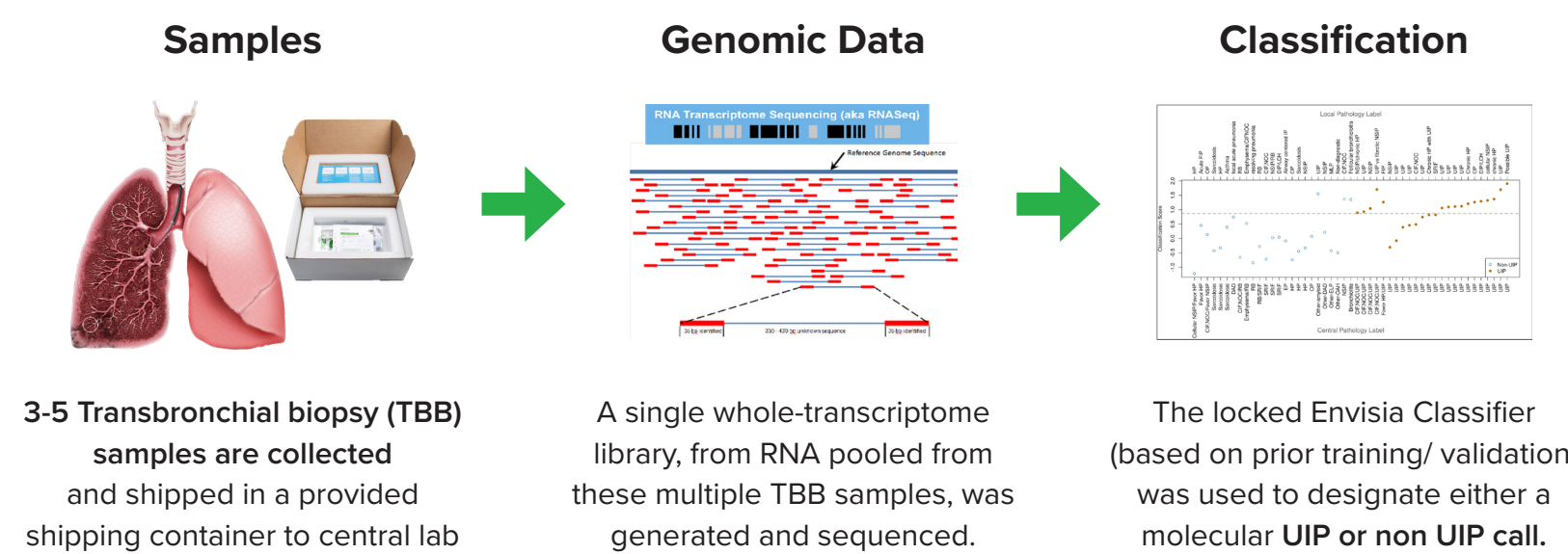
OBJECTIVE

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:³
 - 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

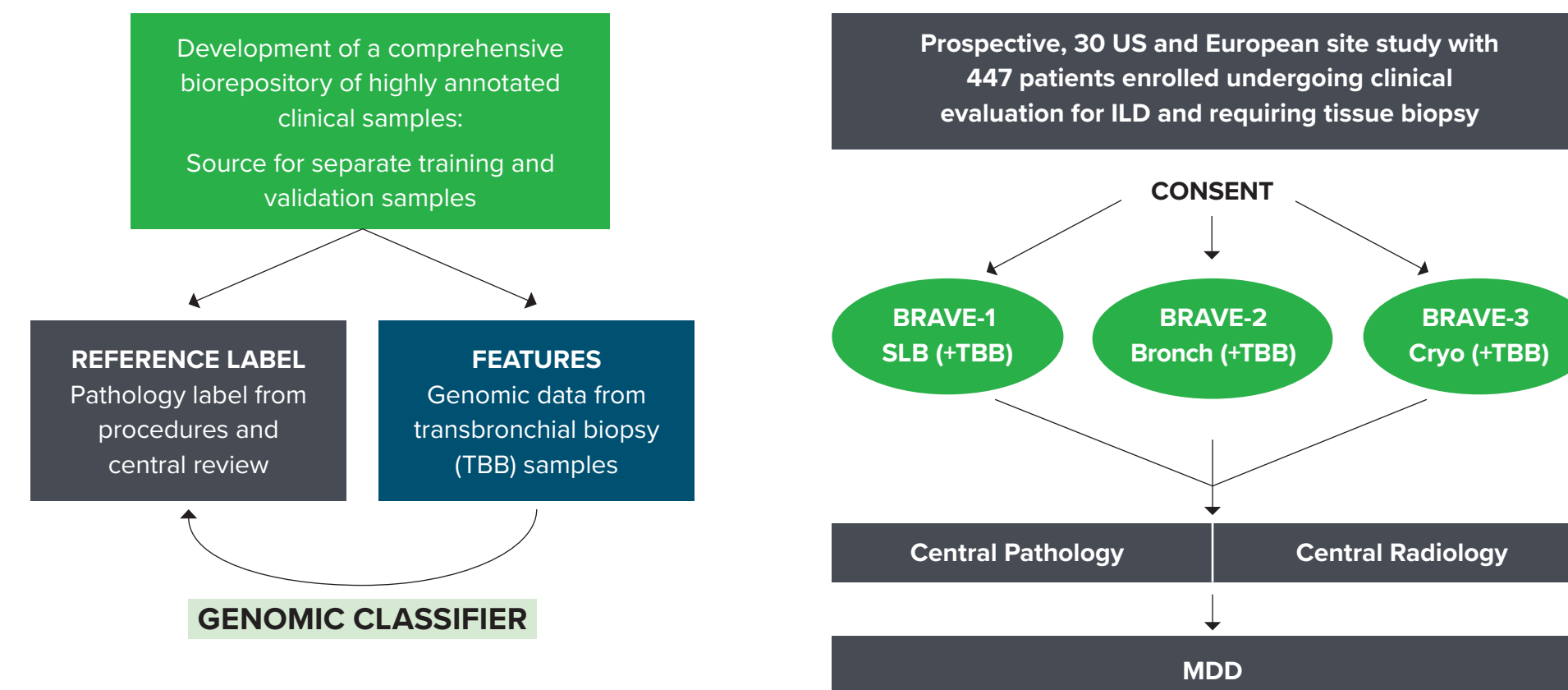


FIGURE 2. Derivation of Envisia Genomic Classifier Validation Cohort

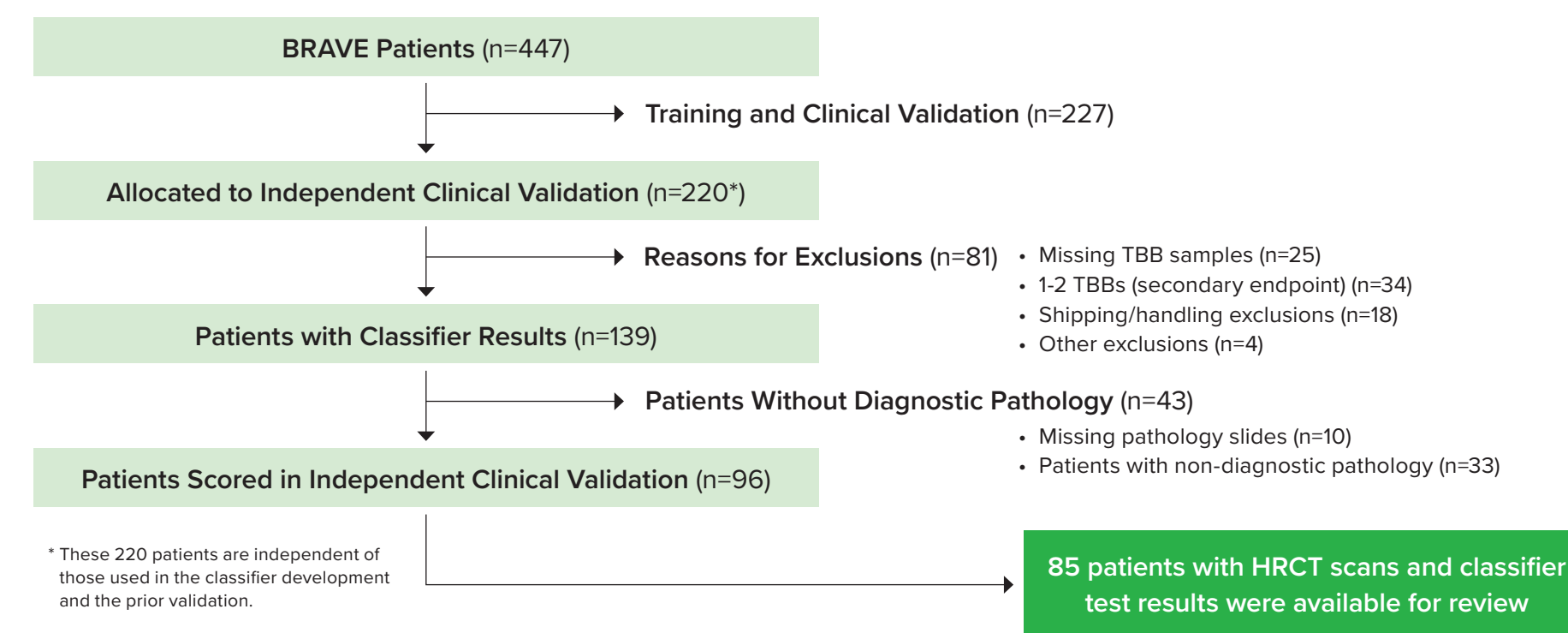
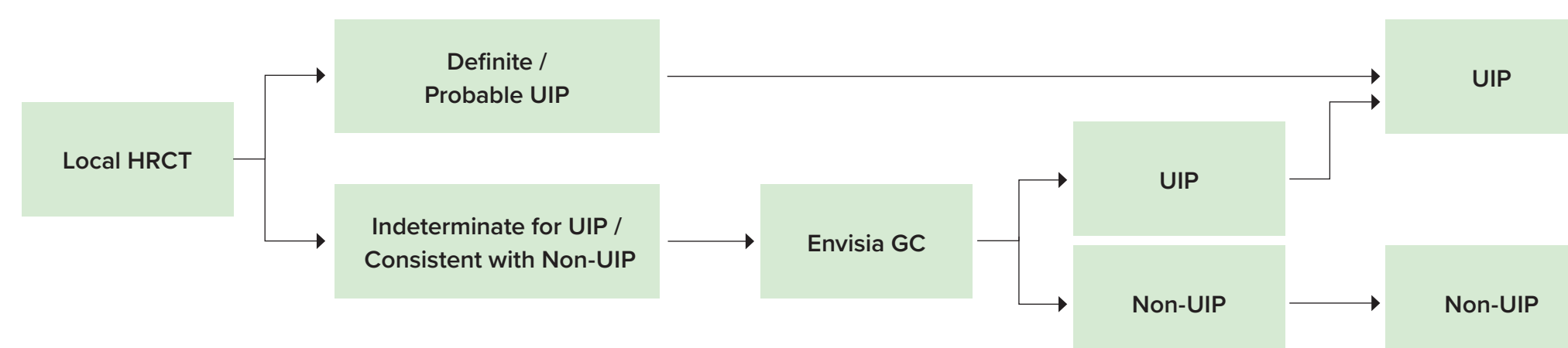


FIGURE 3. Algorithm for UIP Determination by Local HRCT in Combination with Envisia Classifier



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
Sensitivity	34.0% [21.5–48.3]	
Specificity	96.9% [83.8–100]	
NPV	47.0% [34.6–59.7]	
PPV	94.7% [74.0–99.9]	
UIP Prevalence	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
Sensitivity	79.2% [65.9–89.2]	
Specificity	90.6% [75.0–98.0]	
NPV	72.5% [56.1–85.4]	
PPV	93.3% [81.7–98.6]	
UIP Prevalence	62.4%	

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

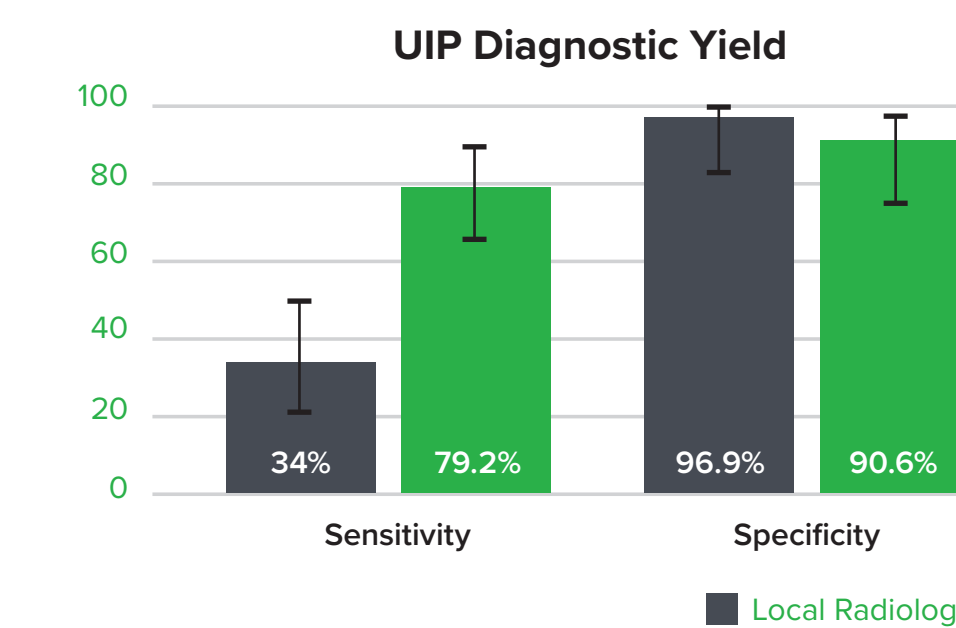
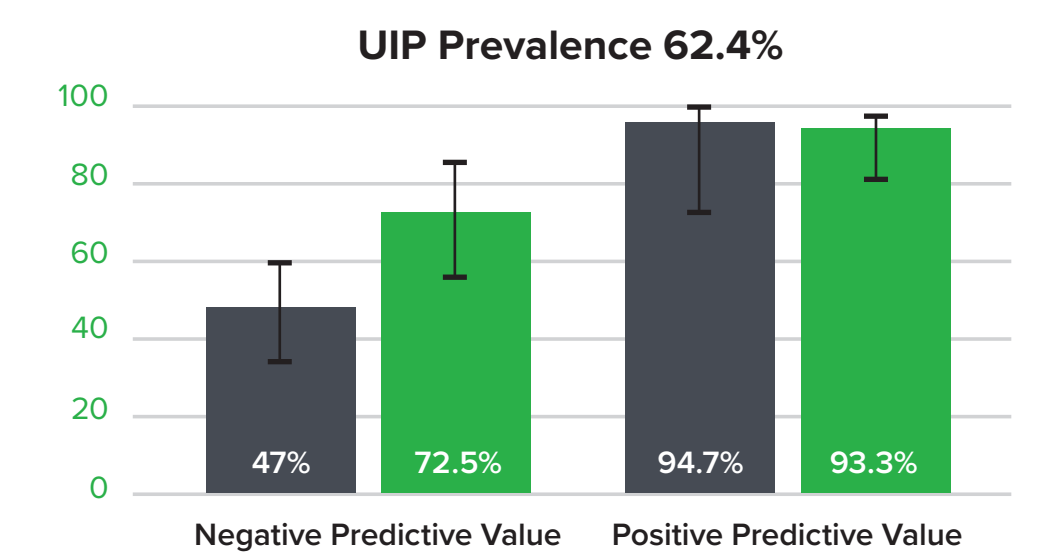


FIGURE 3B. The Addition of the Envisia Classifier to Local HRCT Increases NPV While Maintaining PPV >90%



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.