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Cohort Comparison between Transbronchial Cryobiopsy and Surgical Lung Biopsy (SLB) in Patients Undergoing a Workup for Interstitial Lung Disease (ILD) from a Multi-center, Prospective Trial

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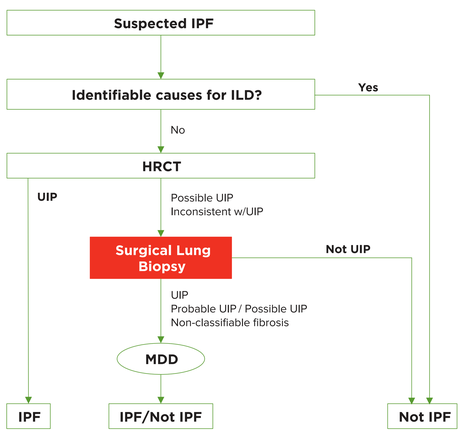
RATIONALE

Transbronchial cryobiopsy has been variably adopted for the workup of ILD in place of recommended SLB from the ATS/ERS/JRS/ALAT 2011 Guidelines (Figure 1) when HRCT is not definitive. Recent publications have suggested that the technology may provide a diagnostic yield of 50-80%. However, many clinical and performance questions remain unanswered including but not limited to criteria for patient selection, diagnostic accuracy and comparative effectiveness to SLB. The **BR**onchial Sample **A**nalysis for a No**V**el G**E**nomic Test (BRAVE) Study is a unique resource that can contribute further insights about the use and performance of cryobiopsies in patients undergoing evaluation for ILD.

FIGURE 1.
Surgical Lung Biopsy Recommended for IPF Diagnosis Without Confident HRCT UIP Pattern[1]



REFERENCES

1. Raghu G, et al. ATS/ERS IPF Guideline Update. *AJRCCM* 2013.

METHODS

The BRAVE Study is an IRB approved, prospective, multi-center study designed to collect comprehensive clinical data and biological materials from patients undergoing a work-up for an ILD. Under separate sub-protocols, sites may enroll patients in BRAVE-1 (surgical lung biopsies), BRAVE-2 (transbronchial biopsies), or BRAVE-3 (cryobiopsies) (Figure 2). Tissue samples collected across all BRAVE cohorts are reviewed by a central panel of 3 expert ILD pathologists who are blinded to local diagnosis and clinical data. Percent high concordance is derived from the frequency of diagnostic concordance amongst the first two pathologists reviewing the sample (Figure 3). The ATS/ERS/JRS/ALAT 2011 Guidelines for pathology criteria were adopted, with prospectively documented modifications to ensure consistency across reviewers.

FIGURE 2.
BRAVE Study Schema: 2012-2017

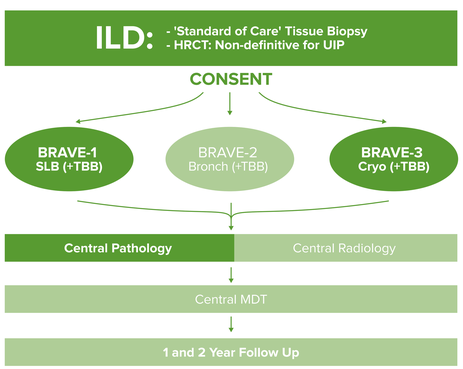


FIGURE 3.
Reference Standard "Truth" by Central Pathology

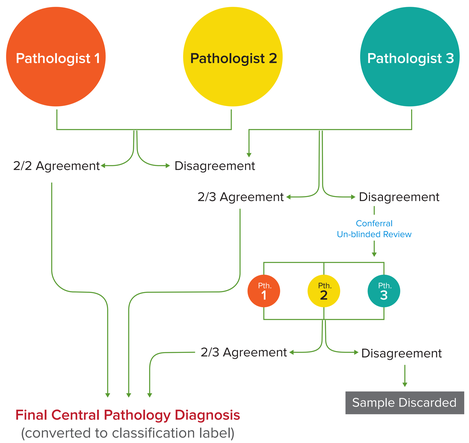


TABLE 1.
Objective of the BRAVE Studies

The purpose of the study is to collect transbronchial biopsy specimens, clinical data, and pathology slides for external review in order to optimize a molecular profiling diagnostic test in **BRAVE (Bronchial Sample Collection for a Novel Genomic Test)**. Three separate protocols that included those patients undergoing SLB **BRAVE-1**, TBB BRAVE-2, and Cryobiopsy BRAVE-3 for the diagnosis of an ILD.

Sample Collection Protocol for ILD: 2012-2017	BRAVE-1 Patients Undergoing Diagnostic Surgical Lung Biopsy	BRAVE-3 Patients Undergoing Diagnostic Cryobiopsy
Surgical Lung Biopsy (SLB)	1 Upper 1 Lower	N/A
Transbronchial Needle Biopsy (TBB)	2 Upper 3 Lower	2 Upper 3 Lower
Broncheo-alveolar Lavage (BAL)	1 Upper 1 Lower	1 Upper 1 Lower
Cryobiopsy	N/A	1 Upper or 1 Lower
Blood	✓	✓
Serum	✓	✓
Buccal	✓	✓

RESULTS

Table 2: Comparison of demographics, clinical diagnosis, and central pathological diagnosis between the two sub-protocol cohorts, BRAVE-1 and BRAVE-3.

The most commonly cited reason for a non-diagnostic sample in either cohort was technical inadequacy.

TABLE 2.
Comparison of BRAVE-1 and BRAVE-3 Cohorts

	SLB (BRAVE-1)	Cryobiopsy (BRAVE-3)	P-value
Enrolled patients	143	127	—
Mean age	62.7	62.9	0.92
Smokers / Non-smokers	56% / 44%	36% / 64%	**0.002**
Contributing sites	67%	55%	0.057
% samples - US sites	92% - 15 sites	76% - 5 sites	0.001
% samples - Non-US sites	8% - 2 sites	24% - 3 sites	0.001
Avg. samples / patient	2	1.5	—
Upper : lower lobe	1 : 2	1 : 2	—
Completed central pathology review	120	88	—
UIP on central radiology	18%	14%	0.474
Local clinical diagnosis of IPF	30%	25%	0.524
Histopathologic diagnoses:			
UIP	55%	18%	**<0.001**
Non-UIP	33%	27%	0.433
Fibrosis unclassifiable	8%	11%	0.621
Non-diagnostic	4%	41%	**<0.001**
% High concordance: 2 of 2 agreement	53%	47%	0.412

CONCLUSION

Differences between the two cohorts pivot largely on the percent of UIP and non-diagnostic calls by central pathologists despite relative parity across a broad range of cohort characteristics. Cryobiopsy is generally not as available as SLB, especially in the US, and has been differentially utilized more in Europe. While the percent high confidence pathology diagnoses between the two sample types is not significantly different, the challenge of technical sample adequacy as well as the learning curve of histopathology interpretation of the specimens acquired by cryobiopsy likely accounts for some of the disparity in diagnostic yield. Furthemore, obtaining adequate sub-pleural sampling may limit the ability of cryobiopsy to accurately sample UIP histology. Other diffuse parenchymal lung diseases had similar diagnostic yields. As the BRAVE Study has spanned nearly a five year period, and the experience with tranbronchial cryobiopsy has increased substantially over that interval, we look forward to being able to report on the changes in diagnostic yield over time. Our experience to date, however, is consistent with findings of others as outlined in Table 3 below. The accuracy of diagnoses in each respective cohort based on multi-disciplinary team determinations and longitudinal clinical follow-up will continue to be explored.

TABLE 3.
Transbronchial Cryobiopsy: Diagnostic Yield

Study	"Diagnostic Yield"
Kropski et al. *PLoS ONE* 2013;8:e78674	20/25 (80%)
Pajares et al. *Respirology* 2014;19:900	20/39 (52%)
Casoni et al. *PLoS ONE* 2014;9:e86716	36/69 (52%)
Hagmeyer et al. *Clin Respir J* 2015; epublished	23/32 (72%)
Overall Experience	**99/165 (60%)**

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