LUNG BIOPSY IN INTERSTITIAL LUNG DISEASE (ILD) AND THE IMPACT OF TRANSBRONCHIAL CRYOBIOPSY

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Professor of Pathology (Emeritus)
Mayo Clinic College of Medicine
FINANCIAL DISCLOSURES

NONE
ROLE OF BIOPSY IN THE Dx OF ILD

In some cases, no role.

In some cases, the pivotal role.

In most cases, part of the database that must be correlated with clinical and radiologic features.
INTERSTITIAL LUNG DISEASES (ILDs): Background

>100 recognized with a diversity of pathologic features...... that can be grouped as follows:

- Histologically unique (No Dx/Dx)- a few
- Histologically characteristic (small Dx/Dx)- a few more
- Patterns of injury (much larger Dx/Dx)- a lot!

Clinical and radiologic correlation is most important in the last group
HISTOLOGICALLY UNIQUE ILD’S:
Examples

Pulmonary Langerhans Cell Histiocytosis (PLCH)
Lymphangioleiomyomatosis (LAM)
Diffuse Alveolar Septal Amyloidosis
Infections (eg. pneumocystis)
Neoplasms (many types)
1. HISTOLOGICALLY UNIQUE ILD’S
   (No Dx/Dx)

Small specimens may be adequate for definitive diagnosis (eg. TBBx)
DIAGNOSTIC TBBx

Unique histology of Lymphangioleiomyomatosis/LAM

"cyst"

HMB45 +
2. ILD’S WITH CHARACTERISTIC HISTOLOGY (relatively small Dx/Dx)

Examples

- Sarcoidosis
- Pulmonary Alveolar Proteinosis
- Hypersensitivity pneumonitis

Correlation of Clinical, Radiologic, and Pathologic findings is important ...

...And a small Bx (eg TBBx) may still be adequate for diagnosis
Diagnosis: “TBBx consistent with (and indeed characteristic of) sarcoidosis”
TBBx

Diagnosis: “TBBx consistent with HP”
3. ILD’s WITH NON-SPECIFIC PATTERNS OF LUNG INJURY (and a larger Dx/Dx)

Acute Lung Injury: Diffuse Alveolar Damage (DAD), Organizing pneumonia (OP/BOOP pattern)
Chronic inflammation and interstitial fibrosis: seen in the chronic interstitial pneumonias, especially UIP and NSIP.

These cases have a larger differential diagnosis, and Clinical-Radiologic correlation is necessary for diagnosis.

In your material here I suspect acute lung injury is the most common pattern seen.
Diffuse alveolar damage (DAD)

Organizing pneumonia (OP)

Main Lesions to consider:
- Infection
- Connective tissue disease
- Drug reaction
- Allergic/hypersensitivity
- Idiopathic

*Many unsolved*
Inflammation and Fibrosis in chronic IP’s: UIP and NSIP (and Chr HP!)

UIP vs NSIP is the major clinical problem - surgical biopsy needed for diagnosis
NONDIAGNOSTIC TBBx’s

Abnormal but not diagnostic

A list of pathologic findings (ie. a descriptive diagnosis) is not a definitive clinicopathologic diagnosis.

From a case of PLCH

From a case of COP
**TBBx IN ILD**

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnostic Bx</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 1978</td>
<td>31%</td>
<td>Nonspec- 44% Normal/Inad- 25%</td>
</tr>
<tr>
<td>N=939 (rev’d by Churg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Poletti 1988</td>
<td>37%</td>
<td>Nonspec- 34%</td>
</tr>
<tr>
<td>N=801</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensminger 2006</td>
<td>38%</td>
<td>TBBx “helpful” in 76% Not “helpful” in 24%</td>
</tr>
<tr>
<td>N=603</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MAJOR POINT:** ~2/3’s of TBBx’s are Nondiagnostic!!
The Pathology Report

Make a specific diagnosis if possible
If you have to be descriptive try to include a differential
If a TBBx mention that it may “good” even if nondiagnostic
Lung Biopsies

TBBx  

CryoBx  

VATS Bx  

Approximate Comparison
PATHOLOGIC DIAGNOSIS OF INTERSTITIAL PNEUMONIAS

The current dogma: Surgical/VATS lung biopsies required to recognize patterns, esp. UIP, NSIP

Transbronchial occasionally useful with clinical-radiologic correlation (but not in UIP/IPF)

Transbronchial cryobiopsies may change the entire paradigm!

-Architectural features as seen on SLBx can be appreciated
Surgical Lung Biopsies: Brief History
(Traditional open SLBx and VATS Bx)

Several studies in the 1970’s showed that SLBx had the highest diagnosis rate of available biopsy techniques (> 90%)

SLBx acclaimed as “gold standard”

1990’s Video Assisted Thoracic Surgical (VATS) biopsies shown to be just as good as traditional open surgical biopsies

VATS Bx now used at most institutions
Cryobiopsy: Brief History

1960’s cryoprobe used for airway obstruction
Early 2000’s flexible cryoprobe developed
2009 cryoprobe used to retrieve peripheral lung tissue: CryoBx (Babiak A Hetzel J, et al.)

Pubmed:
2010-2012: 6 reports
2013-2015: 25 reports
2016-July 2017: 55 reports
Transbronchial cryobiopsy in IPF

- Honeycombing
- Patchy fibrosis
- Fibroblast foci

All criteria for UIP are fulfilled

Images courtesy Alberto Cavazza MD
Transbronchial Cryobiopsy

Proposed as an alternative to VATS biopsy for diagnosis of interstitial lung disease (ILD).

Mains concerns have been:
- Increased complications
- Lower diagnostic yield

There are **TWO** comparisons to consider:
- Cryo vs TBBx - risks vs rewards
- Cryo vs VATS - risks vs rewards

With the question: “Can cryobiopsy replace VATS biopsy in some patients with ILD?”
What is transbronchial cryobiopsy?
How is it done?

A cryoprobe is inserted through the bronchoscope into the alveolar tissue, cooled, and the tissue that sticks to it removed with the probe and placed in saline/fixative.

Can be repeated for multiple specimens.
The endoscopy room

The anesthesiologist  1 bronchoscopist  2 endoscopy nurses

Images courtesy S. Tomassetti MD
Different sizes of Cryoprobes

2.4 mm

1.9 mm
Cryobiopsy: the technique

Slide courtesy A. Cavazza MD
Cryobiopsy: Pathology Issues

Thaw into saline with **minimal manipulation**
Transfer to formalin with **minimal manipulation**
Gross evaluation (size, color, etc.)
Routine processing; H&E slides (Additional stains eg. EVG, as needed).
Cryobiopsy: Grossing Considerations

Even when the specimens are fixed they are too fragile to cut grossly; it distorts the histology; the specimens should go whole for paraffin embedding.

What to do?
- Preserve tissue for further study
- Cut multiple levels* from the block
- Additional stains as desired

*At least 2

Key Points: Minimize manipulation and maximize surface area on the slides to facilitate pattern recognition
Cryobiopsy: the specimens

Those are big specimens!!
Morphometrical analysis of transbronchial cryobiopsies

Sergej Griff\textsuperscript{1}, Wim Ammenwerth\textsuperscript{2}, Nicolas Schönfeld\textsuperscript{2}, Torsten T Bauer\textsuperscript{2}, Thomas Mairinger\textsuperscript{1}, Torsten-Gerriet Blum\textsuperscript{2}, Jens Kollmeier\textsuperscript{2} and Wolfram Grünig\textsuperscript{2}

Diagn Pathol 2011; 6: 53

![Specimen Size](image1)

**Specimen Size**

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean</th>
<th>MAX</th>
<th>Min</th>
<th>P1</th>
<th>p99</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryo</td>
<td>17.078</td>
<td>31.885</td>
<td>0.633</td>
<td>0.633</td>
<td>31.885</td>
<td>10.66</td>
</tr>
<tr>
<td>Forceps</td>
<td>3.799</td>
<td>15.713</td>
<td>0.366</td>
<td>0.366</td>
<td>15.713</td>
<td>4.027</td>
</tr>
</tbody>
</table>

Figure 2 Specimen Size, graph in μm\(^2\), statistical data in mm\(^2\).

![Alveolar Tissue](image2)

**Alveolar Tissue**

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean</th>
<th>MAX</th>
<th>Min</th>
<th>P1</th>
<th>p99</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryo</td>
<td>11.562</td>
<td>25.155</td>
<td>0.449</td>
<td>0.449</td>
<td>25.155</td>
<td>9.071</td>
</tr>
<tr>
<td>Forceps</td>
<td>1.891</td>
<td>5.972</td>
<td>0.430</td>
<td>0.430</td>
<td>5.972</td>
<td>1.580</td>
</tr>
</tbody>
</table>

Figure 3 Size of the alveolar part, graph in μm\(^2\), statistical data in mm\(^2\).
Cryobiopsy: Size of specimens

<table>
<thead>
<tr>
<th>STUDY</th>
<th># Patients</th>
<th>Mean Size (mm(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babiak 2009</td>
<td>41</td>
<td>15.1</td>
</tr>
<tr>
<td>Fruchter 2013 (Lung Tx)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Kropski 2013</td>
<td>25</td>
<td>64.2 (= 8 \times 8 \text{ mm}) !!</td>
</tr>
<tr>
<td>Casoni 2014</td>
<td>69</td>
<td>43.1</td>
</tr>
<tr>
<td>Pajares 2014</td>
<td>39</td>
<td>14.7</td>
</tr>
<tr>
<td>Griff 2014</td>
<td>52</td>
<td>30.4</td>
</tr>
<tr>
<td>Forli Study (in prep)</td>
<td>310</td>
<td>44.8</td>
</tr>
</tbody>
</table>

My Olympus 4X objective with wide field oculars give me a viewing field of 24 mm\(^2\) (~ 5 mm. in diameter)
Cryobiopsy vs SLBx

Cryobiopsy 0.5 cm in diameter  =  0.25 cm$^2$
SLBx  4 x 2 cm                  =  8.0 cm$^2$

→ SLBx has ~32X the surface area of a cryobiopsy

But...a SLBx 4X3X2 cm. (~25 cm$^3$) is < 0.5% of the total lung volume (~6000 cm$^3$)
BOTH need clinical-radiologic correlation for interpretation!!
Not all cryobiopsies are created equal. A poor cryobiopsy is no better than a forceps TBBx.

The experience of the institution and the operator is critical!
Suboptimal Cryobiopsies: Examples

-Too small
-2 mm.
-No better than a TBBX
-Bronchial wall only
Are there artifacts/technical issues?

Yes............ examples

“FS artifact” is not really prominent

IPOX stains work fine

The tissue is fine for molecular studies
Artifact: “Implanted” Bronchiolar Epith.
Other Tissues found in Cryobx’s

- Visceral Pleura
- Pulmonary Arteries
- Parietal Pleura/Skeletal Muscle

Pleura present in ~30% patients in Forli study
Clinical pneumothorax in 20%
Events complicating lung biopsy for ILDs

- Pneumothorax
- Prolonged air leak
- Post procedure chest pain
- Bleeding
- Transient Resp. Failure NOS
- Fever
- Pneumonia/Empyema
- Acute Ex / Death

Slide courtesy S. Tomassetti MD
Cryobiopsy has significantly less complications and shorter hospitalization compared to VATS (2003-2015 ILD Bx’s)

All adverse events, excluding PNX:
- Cryo 6/297 0.2%
- VATS 20/150 13%

Median time of Hospitalization, days:
- Cryo 2.6 (0-17)
- VATS 6.1 (3-48)

P<0.0001

Data from S Tomassetti, Forli, Italy
Mortality following CryoBx for ILD
Review of literature (Medline & Embase)

Review of
15 STUDIES FOR SAFETY ANALYSIS,
INCLUDING 994 PATIENTS: only one death reported

Mortality for cryobiopsy 0.1%

There is some concern that some complications may be unpublished/under-reported.
Mortality may be higher.

Ravaglia C et al, Respiration 2016
Slide courtesy S. Tomassetti MD
Mortality following SLB for ILD in the USA: 2000-2011 (9700 deaths!)

16% (7,796) deaths following non-elective operations (95% CI 7,361-8,230)

1.7% (1,695 deaths) following elective operations (95% CI 1,506-1,883)

Hutchinson JP et al, AJRCCM 2015
BOTTOM LINE: CRYOBIOPSY IS SAFE...

...IN EXPERIENCED HANDS
Questions You Should Have

How easy are they to interpret?
How accurate/reliable for Dx?
Comparison to TBBx?
Comparison to SLBx?
How confident can you feel with your Dx?
Transbronchial Cryobiopsy for ILD
Expectations of pathology (same as for TBBx and VATS)

Make a specific pathologic diagnosis
Identify distinctive findings (with a small D/D)
Recognize a pattern (larger D/D)
Nondiagnostic (Normal tissue, Scant tissue, nonspecific findings**)

Clinical-rad-path correlation (MDD)
Applies to TBBx, CryoBx, and VATS Bx
Reassess pathologic interpretation
VATS

Higher risks
Higher accuracy

~75%
Histologic Diagnosis

TBB

Lower risks
Lower accuracy

~35%
Histologic Diagnosis

Cryobiopsy

Lower risks
High accuracy

>95%
Histologic Diagnosis
How should one interpret cryobiopsies?

What do I see?

1. What am I missing? Is it nondiagnostic/inadequate? ie. approach as a TBBx

2. What is the pattern I see? ie. approach as a SLBx

Either 1 or 2 could be true; the issue is addressed in clinical and radiologic correlation (MDD)

SLBx has the same issues; clinical-radiologic correlation is also necessary

NSIP
How should one interpret cryobiopsies?

1. Look for specific/unique/diagnostic features as in any specimen:
   (Eg. Malignant cells, organisms, PLCH, LAM, dusts, etc.)

2. Assess pattern as you would in a SLBx
   Confidence level important with cryobiopsies

   4X Objective gives a field size of 0.55 cm. on my scope
   - Adequate to see a pattern and
   - That is about the size of a good cryobiopsy
How much do you need to see in SLBx to identify a pattern??
How much surface area do you need to see in a SLBx to identify a pattern?

UIP

Circles ≈ 5 mm.
Circle ≈ 5 mm.
Circle ≈ 5 mm.
Circle ≈ 5 mm.
Sarcoid

Circle ≈ 5 mm.
How much surface area do you need to see in a SLBx to identify a pattern??

**Conclusion**: A 5 mm. field is adequate to see pathologic patterns in many (but not all) cases.
Cryobiopsy is more likely to miss focal lesions than a VATS biopsy.
Pattern: UIP
(from Colby TV in Arch Pathol Lab Med 2016 Sep 2. Epub ahead of print)
What do you see??

Small abnormal specimen: NSIP vs nonspecific changes??

3 mm.
THE KEY ISSUE:
When does “nonspecific changes” become a recognizable pattern?

My **subjective** opinion is....
when the specimen is $\geq 5\text{mm}$ in size.

I point out that this opinion is completely arbitrary and based on no data!

This gives pretest bias toward cryobiopsies.
CryoBx and (good) Forceps Bx in the same patient
**TB Cryobiopsy vs. Forceps TBBx**

Randomized trial published in 2014*
77 pts randomized

<table>
<thead>
<tr>
<th>Technique</th>
<th>Specimen Size mm²</th>
<th>Histologic Dx</th>
<th>MMD Dx</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forceps TBBx</td>
<td>3.3 +/- 4.1</td>
<td>34%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>TB Cryobiopsy</td>
<td>14.7 +/- 11</td>
<td><strong>74%</strong></td>
<td><strong>51%</strong></td>
<td>1. Bleeding &gt; in Cryobx (NS) 2. PTX similar</td>
</tr>
</tbody>
</table>

Cryobiopsy clearly superior to traditional Forceps TBBx

(* Pajares et.al. Respirology 2014; 19: 900-906)
TBBx vs Cryobiopsy (same magnification)

Two features allow pattern recognition in cryobiopsies: size and lack of crush artifact
Should cryobiopsy be proven against SLBx which is the accepted gold standard?
- ie. VATS and Cryobiopsy in the same patient
- Probably not for practical, financial, and ethical reasons but there is a current study in Australia
- Not relevant; we know SLBx is better

But was SLBx ever proven as useful against a gold standard?? NO!! (It was by acclamation of experts)
Cryobiopsies in practice  
(Forli Study 3/11 – 1/15)

524 cryobiopsies in 310 patients with ILD and non-diagnostic clinical-radiologic findings

1-6 Bx’s per patient

Biopsies inadequate in 33 pts (10.6%)
(Normal tissue or minimal changes)

“Adequate” in 277 pts (89.4%)

In ~80% of cases a histologic diagnosis was made in this series.
Patients who underwent Bronchoscopic Lung Cryobiopsy between 2011 and 2014

N=310

8 cases excluded for various reasons

N=302

<table>
<thead>
<tr>
<th>HISTOLOGIC PATTERN</th>
<th>N= 302</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>116 (38%)</td>
</tr>
<tr>
<td>NSIP</td>
<td>34 (11%)</td>
</tr>
<tr>
<td>HP</td>
<td>17 (6%)</td>
</tr>
<tr>
<td>SR-ILD</td>
<td>24 (8%)</td>
</tr>
<tr>
<td>GRANULOMATOSIS</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>MALIGNANCIES</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>OTHER</td>
<td>29 (10%)</td>
</tr>
<tr>
<td>NON DIAGNOSTIC</td>
<td>17 (6%)</td>
</tr>
<tr>
<td>DISAGREEMENT</td>
<td>32 (10%)</td>
</tr>
</tbody>
</table>

Poletti V et al, unpublished
Weighted Kappa for first choice diagnosis (UIP vs nonUIP)

<table>
<thead>
<tr>
<th>Histologic pattern</th>
<th>AC-TC</th>
<th>TC-GR</th>
<th>GR-AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>0.67 (0.58-0.75)</td>
<td>0.74 (0.66-0.80)</td>
<td>0.64 (0.55-0.71)</td>
</tr>
<tr>
<td>NSIP</td>
<td>0.39 (0.28-0.52)</td>
<td>0.25 (0.16-0.38)</td>
<td>0.24 (0.14-0.38)</td>
</tr>
<tr>
<td>HP</td>
<td>0.26 (0.13-0.45)</td>
<td>0.30 (0.13-0.54)</td>
<td>0.31 (0.17-0.48)</td>
</tr>
<tr>
<td>SR-ILD</td>
<td>0.72 (0.50-0.87)</td>
<td>0.42 (0.29-0.58)</td>
<td>0.41 (0.27-0.56)</td>
</tr>
<tr>
<td>GRANULOMATOSIS</td>
<td>0.90 (0.68-0.98)</td>
<td>0.78 (0.56-0.92)</td>
<td>0.87 (0.65-0.97)</td>
</tr>
<tr>
<td>MALIGNANCIES</td>
<td>0.93 (0.64-1.00)</td>
<td>0.86 (0.56-0.97)</td>
<td>0.80 (0.51-0.95)</td>
</tr>
<tr>
<td>OTHER</td>
<td>0.62 (0.38-0.65)</td>
<td>0.38 (0.27-0.51)</td>
<td>0.40 (0.27-0.54)</td>
</tr>
<tr>
<td>NON DIAGNOSTIC</td>
<td>0.45 (0.29-0.61)</td>
<td>0.08 (0.01-0.28)</td>
<td>0.06 (0.01-0.23)</td>
</tr>
</tbody>
</table>
Transbronchial Cryobiopsy
Clinical management implications
Cryo had a meaningful impact on MDT in this study
Conclusions

Transbronchial cryobiopsy has a meaningful impact on the multidisciplinary diagnosis of ILDs, and may prove useful in the diagnosis of IPF, the most common chronic chronic ILD

Impact on the Pathologist ??
VATS

Higher risks
Higher accuracy

~95%
Histologic Diagnosis

Cryobiopsy

Lower risks
High accuracy

~75%
Histologic Diagnosis

TBB

Lower risks
Lower accuracy

~35%
Histologic Diagnosis
Transbronchial Lung Cryobiopsy for Interstitial Lung Disease Diagnosis

A Perspective From Members of the Pulmonary Pathology Society

Kirtee Raparia, MD; Dara L. Aisner, MD; Timothy Craig Allen, MD, JD; Mary Beth Beasley, MD; Alain Borczuk, MD; Philip T. Cagle, MD; Vera Capelozzi, MD, PhD; Sanja Dacic, MD, PhD; Lida P. Hariri, MD, PhD; Keith M. Kerr, BSc, MB, ChB, FRCPATH, FRCPE; Sylvie Lantuejoul, MD, PhD; Mari Mino-Kenudson, MD; Natasha Rekhtman, MD, PhD; Anja C. Roden, MD; Sinchita Roy-Chowdhuri, MD, PhD; Lynette Sholl, MD; Maxwell L. Smith, MD; Eric Thunnissen, MD, PhD; Ming Sound Tsao, MD; Yasushi Yatabe, MD, PhD

Transbronchial lung cryobiopsy involves using a cryoprobe rather than forceps to obtain a bronchoscopic biopsy. Recent studies have shown that transbronchial cryobiopsy provides a larger specimen than conventional transbronchial forceps biopsy, and that the interobserver agreement in the interpretation of cryobiopsy specimens is comparable to that of a surgical lung biopsy. This is encouraging, and transbronchial lung cryobiopsy clearly has a role in the workup and diagnosis of interstitial lung diseases. However, very few patients who have been studied underwent both transbronchial lung cryobiopsy and surgical lung biopsy, and the available data suggest that the diagnostic accuracy of cryobiopsy may not be similar to that of surgical lung biopsy. Further study is needed before transbronchial lung biopsy can be recommended as a replacement for surgical lung biopsy.

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From the Department of Pathology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois (Dr Raparia); the Department of Pathology, University of Colorado Cancer Center, Denver, Colorado (Dr Capelozzi); Washington University School of Medicine, St. Louis, Missouri (Dr Dacic); and the University of California San Francisco, San Francisco, California (Dr Tsao).

(Arch Pathol Lab Med. doi: 10.5858/arpa.2016-0258-SA)
Pathologists focus on histologic diagnosis rate
   (Bigger is better; jokes about needing autopsy)
Clinicians are concerned with patient management which includes:
   Histologic diagnosis rate
   Morbidity of the procedure
   Patient diagnosis (that includes correlation of path with clinical, radiologic, and other findings)
Procedure with best histologic diagnosis rate may not be in the patient’s best interest.
Consider FNA vs Resecting nearly all thyroid nodules
Some Comments

Cryobiopsy and SLBx in the same patient ??

Not relevant; we know VATS has higher yield.

The issue is patient management and the question:

Is cryobiopsy of value in pt management?

YES! ....at least in preliminary studies so far.

A randomized study could compare cryobiopsy versus VATS with MDD diagnosis and/or outcome as endpoints.....but consider...........
......YOU are the patient

You get the VATS arm:  **Total mortality- 1.7%**
>95% chance of diagnosis; 1.7% mortality

You get the CryoBx arm:  **Total mortality- 0.53%**
~75% chance of diagnosis; 0.1% mortality
25% patients then go to VATS (1.7% mortality)

You can play with the numbers but CryoBx is favorable until its mortality reaches 1.3%
LOOKING FORWARD

I suspect selection of biopsy type in ILD will be tailored to:

*Clinical setting AND Institutional capabilities*

**Examples:**
- TBBx (+/- BAL) in suspected sarcoid or infection
- Transbronchial cryobiopsy in:
  - High risk patients
  - Institutions without access to SLBx
- SLBx still will have indications