INTERVENTIONAL PULMONOLOGY

Transbronchial Lung Cryobiopsy is Safe and Effective for Diagnosing Acutely Ill Hospitalized Patients with New Diffuse Parenchymal Lung Disease

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Abstract

Introduction Transbronchial lung cryobiopsy (TBLC) is an accepted alternative to surgical lung biopsy (SLB) for diagnosing diffuse parenchymal lung disease (DPLD) that is less invasive and results in comparable diagnostic yields. Performing lung biopsies on hospitalized patients, however, has increased risk due to the patient's underlying disease severity. Data evaluating the safety and efficacy of TBLC in hospitalized patients are limited. We present a comparison of TBLC for hospitalized and outpatients and provide the safety and diagnostic yields in these populations.

Methods Demographic data, pulmonary function values, chest imaging pattern, procedural information, and diagnosis were recorded from enrolled patients. Complications from the procedure were the primary outcomes and diagnostic yield was the secondary outcome.

Results 77 patients ($n = 22$ hospitalized vs $n = 55$ outpatient) underwent TBLC during the study period. Comparing adverse events between hospitalized and outpatients revealed no statistically significant differences in pneumothorax (9%, $n = 2$ vs 5%, $n = 3$), tube thoracostomy placement (5%, $n = 1$ vs 2%, $n = 1$), grade 2 bleeding (9%, $n = 2$ vs 0%, $n = 0$), escalation in level of care (5%, $n = 1$ vs 0%, $n = 0$), 30-day mortality (9%, $n = 2$ vs 2%, $n = 1$), and 60-day mortality (9%, $n = 2$ vs 4%, $n = 2$) ($p > 0.05$ for all). No deaths were attributed to the procedure. 95% of cases received a multidisciplinary conference diagnosis (hospitalized 100%, $n = 22$ vs outpatients 93%, $n = 51$, $p = 0.32$).

Conclusion Our experience supports that TBLC may be a safe and effective modality for acutely ill-hospitalized patients with DPLD. Further efforts to enhance procedural safety and to determine the impact of an expedited tissue diagnosis on patient outcomes are needed.

Keywords Diffuse parenchymal lung disease · Interstitial lung disease · Transbronchial lung cryobiopsy · Respiratory failure

Abbreviations

ASA	American Society of Anesthesiologists
DPLD	Diffuse parenchymal lung disease
REBUS	Radial endobronchial ultrasound
IP	Interventional pulmonology
IPF	Idiopathic pulmonary fibrosis
HRCT	High-resolution CT chest
MDC	Multidisciplinary conference
SLB	Surgical lung biopsy
TBLC	Transbronchial lung cryobiopsy
UIP	Usual interstitial pneumonia

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Introduction

Diagnosing diffuse parenchymal lung disease (DPLD) remains challenging. A multidisciplinary conference (MDC) is recommended to evaluate patient factors, radiographic findings, and often histopathological data [1]. Guidelines recommend obtaining a tissue biopsy for suspected DPLD when there is diagnostic uncertainty based on non-invasive

data alone [1]. Options available for obtaining a tissue sample include transbronchial lung cryobiopsy (TBLC) and surgical lung biopsy (SLB), which has traditionally been the standard method. When TBLC is used in conjunction with an MDC, it represents a reasonable alternative to SLB with comparable accuracy, decreased morbidity, and potential cost savings [2–5].

While lung biopsy is generally considered safe and effective, studies have suggested that hospitalized patients who undergo this procedure might be at higher risk of complications compared to non-hospitalized patients. Performing SLB on hospitalized patients with suspected DPLD results in high rates of complication with significant morbidity and mortality rates as high as 16% [6–9].

There are limited data evaluating whether TBLC is a safe and effective modality to obtain a tissue sample for hospitalized patients with suspected DPLD. A prior study revealed that hospitalized patients undergoing TBLC have an objectively higher level of acuity compared to outpatients in terms of supplemental oxygen requirement, comorbidities requiring steroid, immunosuppressive or antibiotic treatment, and American Society of Anesthesiologists (ASA) scores [10]. To help determine whether TBLC is safe and effective for acutely ill-hospitalized patients with suspected DPLD we present a comparison of TBLC procedures performed at our institution for hospitalized and outpatients and provide the safety and diagnostic yields in these populations.

Methods

Study Cohort

All patients consecutively presenting to our interventional pulmonology (IP) clinic or inpatient consult service for evaluation of newly discovered DPLD by high-resolution CT chest (HRCT) from November 2019 through May 2021 were consented for TBLC and enrolled. Patients with DPLD that were already on treatment (immunosuppressive or antifibrotic therapy prescribed specifically for lung disease), were unable to stop anti-platelet or anti-thrombotic medications, or had a platelet value $< 50 \times 10^9$/L were excluded. Pulmonary hypertension was evaluated prior to procedure by transthoracic echocardiogram, if indicated. Decision to proceed with biopsy was made in collaboration with the MDC when able. The study was approved by the institutional review board of the Medical College of Wisconsin PRO00036023.

Demographic data, pulmonary function test (PFT) values, chest imaging pattern, which was determined as per established criteria [1], medications, comorbidities, and supplemental oxygen need were extracted from the medical record. Procedural information, including biopsy location, number of lobes biopsied, total biopsies performed, and final MDC diagnosis, were recorded. Complications from the procedure, including pneumothorax, bleeding severity, worsening respiratory status, change in level of care, and 30-day and 60-day mortality, were the primary outcomes. Diagnostic yield from the procedure was the secondary outcome.

Procedure Description

All procedures were performed under general anesthesia with neuromuscular blockade and positive end expiratory pressure of 5–10 cm H_2O through an 8.5-mm endotracheal tube. A flexible bronchoscope (Olympus BF-1TH190, inner diameter 2.8 mm or Olympus BF-XT190, inner diameter 3.2 mm, Olympus America, Center Valley, PA, USA) was used for airway inspection. Bronchoalveolar lavage was then performed to evaluate for infectious process as per guideline recommendations [11].

Based on imaging review, the bronchoscope was then directed to targeted abnormal areas. 3 ml of phenylephrine (1:100,000 dilution from a stock 100mcg/ml concentration) was instilled into each identified airway segment and allowed to dwell for ~ 3 min to promote vasoconstriction and to mitigate bleeding risk. Under fluoroscopic guidance, a transbronchial forceps biopsy was performed to evaluate for bleeding tendency in the periphery of the lung beyond the area visualized. Additional biopsies were performed for microbiology studies and the Envisia Genomic Classifier, if clinically indicated.

A disposable (1.7 mm, 31 cases, CO_2 as the cryogen) or reusable (1.9 mm, 46 cases, N_2O as the cryogen) cryoprobe (Erbe Medizintechnik GmbH, Tübingen, Germany) was used for all procedures. Prior to biopsy, the cryoprobe was tested in room-temperature saline to determine optimal activation time. The cryoprobe was then inserted through the working channel, directed under fluoroscopic guidance to the target area, advanced until resistance was met, and then pulled back to within 0.5–1.0 cm of the pleura.

While the patient was apneic, the cryoprobe was activated under fluoroscopic guidance and the bronchoscope and cryoprobe were removed en bloc. After the specimen was thawed in room-temperature saline, the cryoprobe was removed from the working channel. The bronchoscope was then reinserted to evaluate for bleeding with ventilation resumed. Once biopsies were complete and airway hemostasis was confirmed, a post-procedure chest x-ray was performed immediately after the procedure to evaluate for pneumothorax. For 9 patients (8 outpatient and 1 inpatient), TBLC was performed with cone-beam CT guidance as previously described [12].

Statistical Analysis

Categorical variables were expressed as a number and percentage and comparisons were done with the Chi-square test or the Fisher's exact test. Continuous variables were expressed as mean with standard deviation or as median with interquartile range and comparison were done with the student's t test. All p-values were two-sided and $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SAS version 9.4 (SAS Institute).

Results

77 patients ($n = 22$ hospitalized vs $n = 55$ outpatient) underwent TBLC during the study period. There were no significant differences in age, sex, race/ethnicity, smoking status, PFTs, or chest imaging pattern between the groups (Table 1). However, inpatients had a statistically significant increased ASA score (3.3 ± 0.48) compared to outpatients (3.0 ± 0.51) ($p = 0.0062$). Additionally, inpatients had more total comorbidities on average than outpatients (2.9 ± 1.6 vs 1.9 ± 1.2) ($p = 0.0070$) and were more likely to carry certain comorbidities, including history of malignancy (68% $n = 15$ vs 24% $n = 13$) ($p = 0.0002$) or history of transplant (31% $n = 7$ vs 4% $n = 2$) ($p = 0.0017$) (Table 2). Hospitalized patients were more likely to be receiving treatment with steroids for non-pulmonary disease (45% $n = 10$ vs 18% $n = 10$) ($p = 0.0137$), were more likely to be receiving immunosuppressive medication (36% $n = 8$ vs 13% $n = 7$) ($p = 0.0266$), and were more likely to require supplemental oxygen (55% $n = 12$ vs 18% $n = 10$). Admission diagnoses for hospitalized patients included hypoxic respiratory failure ($n = 11$), COVID-19 pneumonia ($n = 2$), dyspnea ($n = 2$), interstitial lung disease ($n = 2$), altered mental status ($n = 1$), cholecystitis ($n = 1$), pneumonia ($n = 1$), pulmonary nodules ($n = 1$), and severe sepsis ($n = 1$).

TBLC was done in a single lobe in 39 (51%) patients, while 38 (49%) had two lobes sampled (Table 3). The average number of biopsies per procedure was 4.4 ± 1.5. The right lower lobe was most frequently biopsied at 53% followed by the right upper lobe 30%, the left lower lobe at 9%, and the left upper lobe at 8%.

Complications from the procedure were similar in both groups (Table 4). Pneumothorax occurred in 6% ($n = 5$) of patients ($n = 2$, 9% inpatient vs $n = 3$, 5% outpatient) ($p = 0.6202$). Chest tube placement was required in 3% ($n = 2$) of patients ($n = 1$, 5% inpatient vs $n = 1$, 2% outpatient) ($p = 0.4925$). All chest tubes were removed within 24 h. Grade 2 bleeding, as per consensus definition [13], occurred in 3% ($n = 2$) of patients, both of whom were inpatients ($n = 2$, 9% inpatient), and of which one, although hemodynamically stable, was transferred to the intensive

care unit for closer monitoring as per the primary care team's decision ($n = 1$, 2% of patients, 5% of inpatients, transfer in level of care). For all other patients, only grade 1 bleeding occurred, which did not require any intervention aside from brief suctioning with observation until hemostasis was confirmed. All cause 30-day and 60-day mortality were similar between the two groups and no deaths were directly attributable to the procedure. For the inpatient mortalities, one patient died ten days after the procedure, which was one week after discharge from the hospital, due to out of hospital cardiac arrest with ventricular fibrillation on initial

Table 1 Patient Characteristics

	Outpatient	Inpatient	Total	p value
Age (mean ± SD)	64 ± 13	61 ± 10	63 ± 12	0.3191
Sex (n, %)	55	22	77	0.1494
Female	30(55%)	8(36%)	38(49%)	
Male	25(45%)	14(64%)	39(51%)	
Race (n, %)				0.3126
Caucasian	43(78%)	16(72%)	59(77%)	
Black	7(13%)	3(14%)	10(13%)	
Hispanic	2(4%)	3(14%)	5(6%)	
Asian	3(5%)	0(0%)	3(4%)	
BMI (mean ± SD)	31 ± 8	30 ± 7	31 ± 8	0.4618
BMI < 30 (n, %)	29(53%)	13(59%)	42(55%)	
BMI > 30 (n, %)	26(47%)	9(41%)	35(45%)	
Smoking Status (n, %)				0.9106
Current	2(4%)	1(4%)	3(4%)	
Former	28(51%)	12(55%)	40(52%)	
Never	25(45%)	9(41%)	34(44%)	
ASA Score (mean ± SD)	3.0 ± 0.51	3.3 ± 0.48	3.1 ± 0.52	**0.0062**
PFTs (mean ± SD)				
FEV1% predicted	71 ± 20	69 ± 19	71 ± 20	0.8154
FVC % predicted	68 ± 17	66 ± 19	68 ± 17	0.6194
TLC % predicted	79 ± 22	83 ± 19	80 ± 22	0.5372
DLCO % predicted	60 ± 19	62 ± 29	60 ± 21	0.8626
HRCT Pattern (n, %)				0.5565
Alternative	35(64%)	19(85%)	54(70%)	
Probable UIP	4(7%)	1(5%)	5(7%)	
Indeterminant for UIP	3(6%)	1(5%)	4(5%)	
NSIP	5(9%)	0(0%)	5(7%)	
HP	7(12%)	1(5%)	8(10%)	
Pneumonitis	1(2%)	0(0%)	1(1%)	

Bold value indicates statistical significance (p < 0.05)

Data are expressed as number (%) or mean ± standard deviation

ASA American Society of Anesthesiologists, *DLCO* diffusing capacity for carbon monoxide, *FEV1* forced expiratory volume in 1 second, *FVC* forced vital capacity, *HP* hypersensitivity pneumonitis, *HRCT* high-resolution CT chest, *NSIP* nonspecific interstitial pneumonitis, *SD* standard deviation, *TLC* total lung capacity, *UIP* usual interstitial pneumonia

Table 2 Comorbidities and medications

	Outpatient n (%)	Inpatient n (%)	Total n (%)	p value
Comorbidities				
Hypertension	32(58%)	16(73%)	48(62%)	0.234
GERD	24(44%)	7(32%)	31(40%)	0.3394
Malignancy	13(24%)	15(68%)	28(36%)	**0.0002**
Diabetes	15(27%)	8(36%)	23(30%)	0.4311
Cardiac (CAD or CHF)	9(16%)	6(27%)	15(19%)	0.3421
[a]Post-Transplant	2(4%)	7(31%)	9(12%)	**0.0017**
OSA	11(20%)	4(18%)	15(19%)	1
Any Comorbidity	48(87%)	20(91%)	68(88%)	1
Comorbidity Count (mean ± SD)	1.9 ± 1.2	2.9 ± 1.6	2.2 ± 1.4	**0.00701**
Medications				
Aspirin	15(27%)	7(32%)	22(29%)	0.69
P2Y12	6(11%)	0(0%)	6(8%)	0.1745
Anticoagulation	8(15%)	3(14%)	11(14%)	1
Steroids	10(18%)	10(45%)	20(26%)	**0.0137**
[b]Immunosuppressives	7(13%)[1]	8(36%)[2]	15(19%)[1]	**0.02661**
Oxygen Requirement				**0.0013**
Room Air	45(82%)	10(45%)	55(71%)	
Nasal Cannula	10(18%)	9(41%)	19(25%)	
HFNC	0(0%)	3(14%)	3(4%)	

Bold values indicate statistical significance (p < 0.05)

Data are expressed as number (%)

CAD coronary artery disease, *CHF* congestive heart failure, *GERD* gastroesophageal reflux disease, *HFNC* high-flow nasal cannula, *OSA* obstructive sleep apnea, *SD* standard deviation

[a]Post-transplant organs include bone marrow ($n=5$), liver ($n=2$), and kidney ($n=2$)

[b]Immunosuppressives include chemotherapy ($n=7$), immunomodulatory ($n=4$), and anti-rejection medications ($n=6$). 2 patients were on multiple classes of immunosuppressive medications

Table 3 Procedural characteristics

	Outpatient n (%)	Inpatient n (%)	Total n (%)
Biopsy Information			
One Lobe	27(49%)	12(55%)	39(51%)
Two Lobes	28(51%)	10(45%)	38(49%)
Total Biopsies (mean ± SD)	4.5 ± 1.5	4.3 ± 1.5	4.4 ± 1.5
Location			
Left Upper Lobe	7(8%)	3(9%)	9(8%)
Left Lower Lobe	6(7%)	3(9%)	10(9%)
Right Upper Lobe	27(33%)	8(26%)	35(30%)
Right Lower Lobe	43(52%)	18(56%)	61(53%)

Data are expressed as number (%) or mean ± standard deviation

SD standard deviation

Table 4 Adverse events

	Outpatient n (%)	Inpatient n (%)	Total n (%)	p value
Pneumothorax	3(5)	2(9)	5(6)	0.6202
Chest Tube	1(2)	1(5)	2(3)	0.4925
Grade II Bleeding	0(0)	2(9)	2(3)	0.0789
Transfer in Level of Care	0(0)	1(5)	1(1)	1
All Cause 30-day Mortality	1(2)	2(9)	3(4)	0.1947
All Cause 60-day Mortality	2(4)	2(9)	4(5)	0.5735

Data are expressed as number (%)

rhythm. The other patient died on hospice due to refractory hypoxemic respiratory failure due to ARDS from COVID-19 pneumonia 29 days after the procedure.

A final MDC diagnosis was obtained in 95% ($n=73$) of patients (inpatient 100% $n=22$ vs outpatients 93% $n=51$) ($p=0.32$) (Table 5). The most common diagnosis was chronic hypersensitivity pneumonitis (26%, $n=20$),

Table 5 Biopsy results

	Outpatient n (%)	Inpatient n (%)	Total n (%)	p value
MDC Diagnosis	51(93)	22(100)	73(95	
Chronic HP	19(35)	1(5)	20(26)	
CTD-ILD	10(18)	3(14)	13(17)	
Organizing Pneumonia	2(4)	5(23)	7(9	
Drug-Induced Pneumonitis	2(4)	3(14)	5(7)	
Granulomatous Pneumonitis	4(7)	0(0)	4(5)	
Unclassifiable ILD	4(7)	0(0)	4(5)	
CFILD	0(0)	2(9)	2(3)	
IPF	3(5)	1(5)	4(5)	
Vaping-Induced Lung Injury	1(2)	1(5)	2(3)	
Lung Adenocarcinoma	1(2)	1(5)	2(3)	
Bronchiolitis	1(2)	1(5)	2(3)	
Emphysema	2(4)	0(0)	2(3)	
[a]Other	6(10)	4(15)	10(11)	0.3200

CFILD chronic fibrosing interstitial lung disease, *CTD-ILD* connective tissue disease-related interstitial lung disease, *HP* hypersensitivity pneumonitis, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis

[a]Other includes bronchiolitis ($n = 1$), CMV pneumonitis ($n = 1$), combined pulmonary fibrosis and emphysema ($n = 1$), granulomatous and lymphocytic interstitial lung disease ($n = 1$), graft versus host disease ($n = 1$), interstitial pneumonia with autoimmune features ($n = 1$), myelofibrosis ($n = 1$), plastic bronchitis ($n = 1$), pneumonia ($n = 1$), and respiratory bronchiolitis interstitial lung disease ($n = 1$)

followed by connective tissue disease-related interstitial lung disease (17%, $n = 13$), organizing pneumonia (9%, $n = 7$), and drug-induced pneumonitis (7%, $n = 5$). Four (5%) patients (all outpatients) were determined to have unclassifiable DPLD and did not receive a definitive diagnosis.

Discussion

While the utility of TBLC in establishing a diagnosis for patients with DPLD is well established, concerns remain regarding potential complications, including pneumothorax and bleeding. Debate also centers upon optimal patient selection. We present our analysis comparing complication rates in outpatients and inpatients to better assess the safety profile of TBLC in different patient populations. Although inpatients had an objectively higher degree of clinical acuity, as indicated by statistically significant differences in comorbidities (history of malignancy, history of transplant, supplemental oxygen requirement), and ASA scores (Tables 1

and 2), rates of complications and the ability to obtain a diagnosis were similar.

Despite various procedural techniques employed to mitigate against complications developing, ensuring safety during TBLC remains a challenge due to the increased risk of pneumothorax and bleeding compared to conventional forceps biopsy. Recent meta-analyses of TLBC procedures reported pneumothorax rates of 9.5–12% and moderate to severe, or grade 2 bleeding, of 4.9–39% [14, 15]. Our study revealed a comparable incidence of pneumothorax (6%, $n = 5$, of patients; 9%, $n = 2$, inpatients; 5%, $n = 3$, outpatients) and grade 2 bleeding (3%, $n = 2$, of patients; 9%, $n = 2$, inpatients; 0%, $n = 0$ outpatients) compared to prior studies with no differences seen in the more acutely ill inpatient group (Table 4). These results are also comparable to the prior study comparing inpatients to outpatients, in which no statistically significant difference in complication rates was found [10].

Best practice recommendations based on expert guidelines exist for TBLC. These include using a large diameter endotracheal tube and fluoroscopic guidance [16, 17], given the high rate of pneumothoraxes in cases performed without fluoroscopy [18]. Similarly, radial EBUS has been used to visualize vascular structures prior to obtaining the sample, but this approach does not allow for real time guidance during the actual biopsy [19]. Use of a two-scope technique has been employed to re-enter the airway more rapidly in order to visualize and to potentially control bleeding, but does not decrease the incidence of complications [20, 21]. Comparable results are found when using prophylactic endobronchial blockers or balloons [22, 23], although the severity of bleeding may decrease. Recent data using vasoconstricting medications and cone-beam computed tomography guidance, however, are promising in reducing complications [12, 24, 25]. Additional studies layering these different modalities together, and in comparison, will be informative to further improve patient safety.

While SLB remains the gold standard approach for obtaining a tissue diagnosis for DPLD, there is an accepted role for TBLC in this process [26]. This value stems from the advantages of TBLC over SLB as a more cost-effective option [3] and its lower complication rates [5, 14, 15]. SLB performed nonelectively on acutely ill-hospitalized patients may lead to a mortality ranging from 6.3 to 16% [6–9]. In contrast, elective SLB carries a 30-day mortality of 1.5–2.4% [9, 27, 28]. Our study aimed to investigate whether there was an increased risk of complications among acutely ill-hospitalized patients who underwent TBLC, as is the case for SLB. Our results showed no statistically significant differences in complication rates when performing TBLC for sicker patients (Table 4). Additionally, a final MDC diagnosis was obtained in 95% of patients undergoing TBLC, suggesting that this procedure may facilitate patient care

(Table 5). Along with the prior study [10], this data support the safety and utility of TBLC in both inpatients and outpatients.

Final MDC discussion resulted in chronic hypersensitivity pneumonitis (26%, *n* = 20) as the most common diagnosis, followed by connective tissue disease-related interstitial lung disease (17%, *n* = 13), organizing pneumonia (9%, *n* = 7), and drug-induced pneumonitis (7%, *n* = 5). Few cases of IPF were reported (5%, *n* = 4). This finding may be attributable to the increase confidence in radiographic interpretation of chest imaging in determining a definite UIP pattern, thus negating biopsy of these patients, as recommended by guidelines [29]. It is also possible that an increased incidence of pneumothorax may occur when performing TBLC on patients with a definite UIP pattern on imaging given the peripheral honeycombing and subpleural disease, which is the optimal location of the cryoprobe for TBLC. It will be of interest to determine if the incidence of pneumothoraces and diagnosed cases of IPF from TBLC decreases overtime with further refinement in patient selection.

With the development of more data supporting the safety of TBLC on inpatients, it will be important to determine the overall impact of an expedited tissue diagnosis on patient care. Patients with new respiratory symptoms, abnormal PFTs, and/or abnormal chest imaging suggestive of DPLD often wait a prolonged time prior to obtaining a diagnosis and to establishing a treatment plan [30, 31]. The potential impact on patient outcomes, including preservation of lung function as measured by PFTs and lung structure as depicted by HRCT, may be positively impacted by performing TBLC while hospitalized to expedite management and is an area of future study. Additionally, TBLC may play a role in evaluating patients with known DPLD admitted for an exacerbation or concern for disease progression. Understanding if the histology shows a change from an inflammatory state responsive to further immunosuppression to a fibrotic state requiring anti-fibrotic therapy may impact further treatment.

Our study has limitations. These include the smaller sample size of inpatients compared to outpatients and the inability to control for the clinical status, inpatient versus outpatient, of this observational uncontrolled study. However, a strength of our study is its inclusive nature of all patients undergoing TBLC during the study period. We were able to obtain objective data to demonstrate that while inpatients were of higher illness acuity (Tables 1, 2), TBLC may be a safe procedure with minimal complications (Table 4) and is also effective in obtaining a diagnosis (Table 5).

TBLC is an accepted option for obtaining a tissue sample for patients with DPLD given its comparable accuracy and increased safety profile compared to SLB. Our study suggests that TBLC may be a safe and effective modality in acutely ill-hospitalized patients and outpatients. Our results support considering TBLC in the evaluation of patients who are hospitalized with an acute pulmonary process where a tissue diagnosis may guide management. Efforts to further optimize the procedure to enhance safety and to determine the impact of an expedited tissue diagnosis on patient outcomes are needed.

Declarations

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