CyPath® Lung in Practice
From Uncertainty to Clarity and Confidence: Cases 5-7

Dr Gordon Downie, MD, PhD
Director, Titus Regional Hospital Lung Nodule Clinic and Interventional Pulmonology

BACKGROUND

The clinical burden of competent pulmonary nodule identification and definitive diagnosis is increasingly common. This is especially true in complex cases with conflicting results from diagnostic tests and procedures. Clinicians are tasked with in-depth difficult discussions with their patients when risk calculators, imaging, genetic and other adjuvant testing information points definitively either at benign or malignant process. Clinical presentations with unusual risk, imaging, age, functionality or newer adjuvant testing parameters make these discussions nearly impossible.[1,2,3,4]

The National Lung Screening Trial, which began in 2002 and was published in 2011, proved that low dose CT scanning of the chest (LDCT) reduced mortality from lung cancer.[5] This research has helped drive the development of dynamic technologies, including specialized imaging, biopsy devices, chemical assays and diagnostic algorithms, that have made the identification of pulmonary nodules dramatically more accurate.[6]

Additionally, pulmonary nodule clinics have proliferated across hospital systems, increasing the number of at-risk individuals who undergo lung cancer screening by imaging. CyPath® Lung testing has a unique position in this diagnostic process using flow cytometry with machine learning to recognize malignant cells in real time and therefore determine if a true lung cancer is likely or unlikely.[7] However, with these increased numbers of suspicious presentations, clinicians are encountering more “atypical presentations,” unusual growth patterns, nodular shapes similar to scarring or inflammation, low metabolic tumors and challenging locations or extremely poor functionality. [1, 2, 8] Taken together, conflicting clinical information pointing both toward and away from malignant processes is now a frequent situation.

Unusual presentations often increase clinical costs for surveillance of patients, and the more challenging location and/or poor functionality can increase the financial burden to our healthcare system.[9] Low dose CT scans, PET scans, genetic testing, nodule calculators and proteomic blood testing are all diagnostic tests that cannot determine in real time if the process is malignant and instead infer probabilities of malignancy.

Development of guided biopsy technologies including robotic-based bronchoscopy have given clinicians the ability to biopsy smaller and smaller processes.[10] However, it is not clear if population-based lung cancer probabilities justify the increased cost for these biopsies or if insurance coverage for this approach is sustainable.[4, 9] I present three cases employing noninvasive sputum flow cytometry analysis in addition to standard LDCT, PET scans and blood proteomic testing to help address clinical decisions in three “atypical” presentations in our pulmonary nodule clinic.

CyPath® Lung is a Laboratory Developed Test offered for sale by Precision Pathology Laboratory Services in accordance with the Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) Accreditation Program. CyPath® Lung received a Current Procedural Terminology (CPT) Propriety Laboratory Analysis (PLA) code 0406U specifically for its use and is reimbursed by Medicare and private insurance.

Case Study Mary: Stage IA NSCLC Detected in Patient With Low-Risk PET Result and Risk Calculator Score

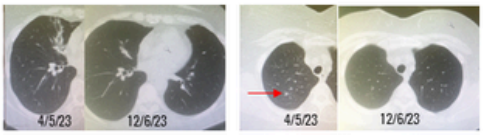
Patient Information and Initial Workup

- **Age:** 67 years old
- **Sex:** Female
- **Smoking status:** >50 pack-year history; currently smokes ½ PPD
- **Medical history:** Stage 3 COPD with frequent exacerbations; FEV1 = 45%
- **Family history:** Unremarkable
- **Status:** High risk because of smoking history and COPD
- **Presentation:** Symptoms of RML syndrome
- **LDCT scans:** 4/5/23 and 12/6/23
- **Surveillance:** 6-month follow-up recommended, but patient only agreed to 12-month LDCT

NOTE: Actual patient case, but name has been changed to ensure privacy.

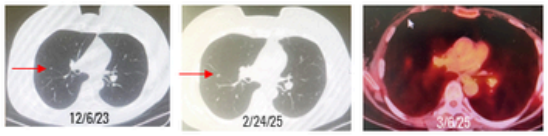
Imaging Results

RML and RUL scans: RML changes on 4/5/23 LDCT improved on 12/6/23 LDCT, consistent with RML syndrome. 4/5/23 RUL LDCT revealed 5-mm nodule with 1.9% Brock model risk that resolved on 12/6/23 LDCT.



RML scans RUL scans

Minor fissure scans: 12/6/23 LDCT scan revealed 3-mm nodule with 0.2% Brock model risk. 2/24/25 LDCT scan revealed 8-mm nodule with 4.6% Brock model risk. 3/6/25 PET scan with SUV of 1.1.



Changing non-calcified nodule in the minor fissure in the context of waxing and waning images in other parts of the lungs.

Additional Findings/Next Steps

- **Brock model risk:** 4.6%
- Bronchoscopy high risk and poor yield without robotic augmentation in a low-risk situation
- Risk calculator and PET suggested inflammation and not cancer, consistent with waxing and waning images

Outcome with CyPath® Lung

- **CyPath® Lung:** 3/4/25 test result: 0.83, likely lung cancer (NOTE: CyPath® Lung was not available at the time of the 2023 scans.)
- **Robotic wedge resection:** R0 resection on 6/5/25, but with close margin
- **Diagnosis:** Stage IA NSCLC; adenocarcinoma histology
- **Radiation oncology referral:** Opinion on close margin and possible need for radiation treatment
- **CyPath® Lung:** Detected lung cancer in high-risk patient with complex nodules when PET and risk models indicated low risk of malignancy

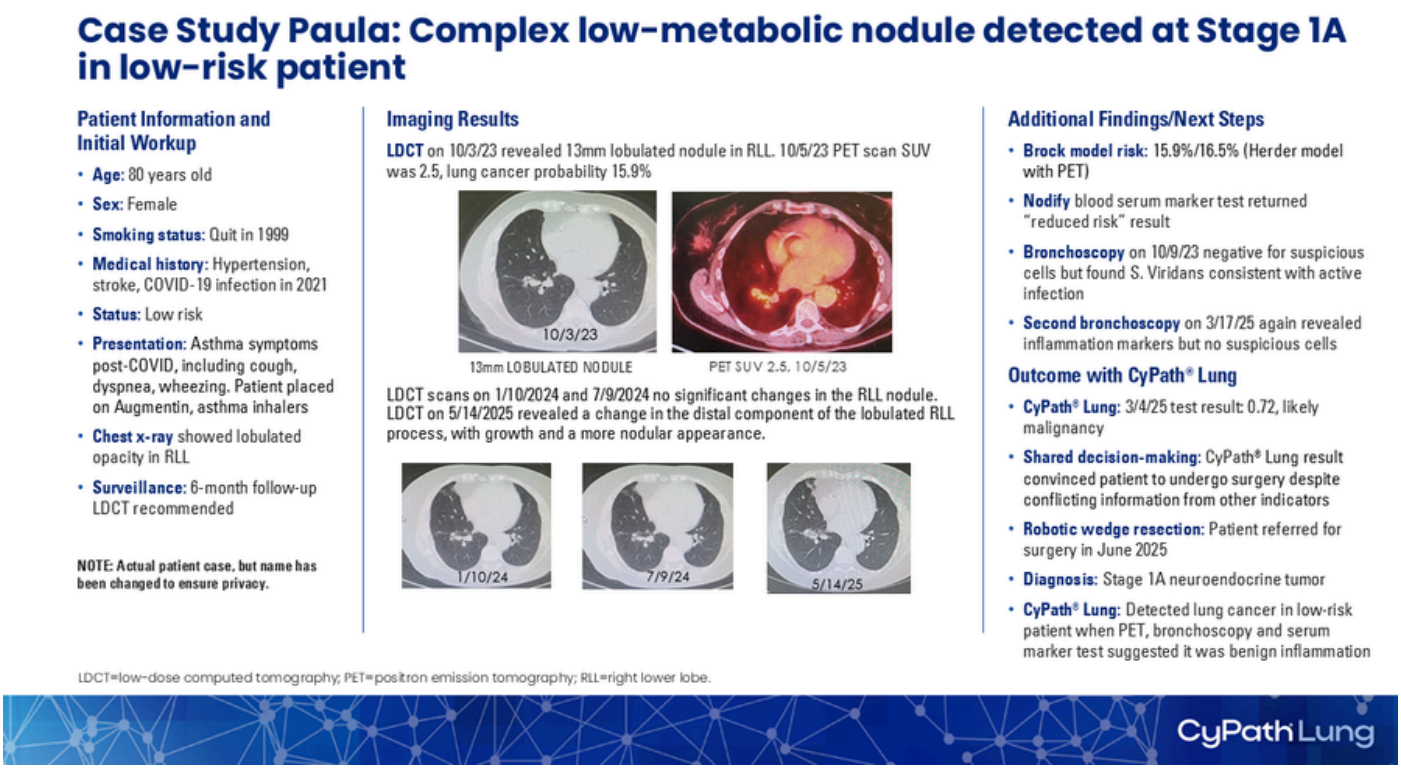
COPD=chronic obstructive pulmonary disease; LDCT=low-dose computed tomography; NSCLC=non-small cell lung cancer; PET=positron emission tomography; PPD=pack per day; RML=right middle lobe; RUL=right upper lobe.

Case 5: Stage 1A NSCLC Detected by CyPath® Lung in Patient with Low-Risk PET Result and Low-Risk Calculator Score

Case 5 is a complex atypical case highlighted by patient anxiety for any invasive procedures, waxing and waning imaging features, and a small nodule in a difficult location with a non-diagnostic PET scan. This patient is at high risk for lung cancer based on tobacco use which up until surgery was active. She has functionally significant COPD. However, her atypical presentation included bronchiectasis in the right middle lobe (RML) with ground glass opacities (GGO) and additional GGOs in other lung lobes.

The first two LDCT scans in 4/2023 and 12/2023 revealed a 5 mm nodule in the RUL which 100% resolved in the 12/2023 CT scan. Also, she presented with a significant RML process consistent with RML syndrome which dramatically improved by 12/2023, and the LUL process was a GGO with no PET uptake. Taken together the clinical presentation was consistent with waxing and waning inflammatory process. The new 3 mm nodule at the right minor fissure seen in 12/2023 could easily have been a new inflammatory feature, and the risk calculators gave cancer probabilities well below 5%. During the initial physician-patient interactions in 2023, the patient was definitive in wanting no invasive procedures based on her anxiety and the lack of robust convincing data points that suggested a cancer process rather than an inflammatory one. Society recommendations at this point recommend a six- to 12-month follow-up LDCT, and the patient opted for a 12-month follow-up LDCT. Patient anxiety delayed the LDCT until 2/24/2025 which revealed stable inflammatory areas, but the right minor fissure solid nodule had grown to 8-9 mm. A PET scan on 3/6/2025 had an SUV of 1.1, and her risk calculator probability had risen to 4.6%.

The physician-patient discussion revealed an impasse in opinion as the medical recommendation was for definitive treatment planning including thoracic surgical resection, whereas the patient wanted only serial LDCT scans. Patient agreed to a sputum analysis using the CyPath® Lung test which resulted in a high likelihood for cancer. Based on this result, the impasse was resolved, and the patient underwent a robotic wedge resection of the right minor fissure nodule which final pathology identified a Stage 1A adenocarcinoma.



Case 6: CyPath® Lung identifies Stage 1A neuroendocrine tumor after PET scan, bronchoscopies and a serum tumor marker test suggest non-cancerous inflammation

Case 6 is a complex atypical case in a low-risk, 80-year-old woman presenting with a low metabolic nodule by PET scan. The patient, who quit smoking in 1999, is low risk for lung cancer based on minimal tobacco use, no COPD and normal pulmonary function test (PFT). She developed pulmonary symptoms following a Covid-19 infection in 2021. Post Covid-19 she demonstrated a cough with occasional sputum production, wheezing and intermittent dyspnea.

She presented for an initial evaluation in 9/2023 at which time a chest X-ray in addition to her pulmonary symptom showed a lobulated opacity in the RLL. A LDCT scan 10/3/2023 revealed a lobulated process of 13 mm in the superior segment of the RLL. A PET scan on 10/5/2023 had an SUV of 2.5, suggesting a possible inflammatory process. Nodify blood testing was reported as "reduced risk" for malignancy, and the nodule calculator gave a cancer probability of 15.9%.

She underwent a recommended bronchoscopy on 10/09/2023. The result was negative for suspicious cells but culture positive for S. Viridans which was consistent with post-infectious injury bronchiectasis with an active infection. Patient was treated with Augmentin for three weeks and had a three-month follow-up LDCT scan. CyPath® Lung testing was not available during this initial diagnostic phase.

The subsequent LDCT scans on 1/10/2024 and 7/9/2024 revealed no significant changes in the RLL process. The patient's pulmonary symptom was minimal, well controlled on an inhaler regimen, and a continued LDCT every six months was recommended. The LDCT on 2/24/2025 demonstrated a change in the distal component of the lobulated RLL process, with growth and a more nodular appearance on the CT.

CyPath® Lung testing was performed on 3/04/2025 and suggested cancer was likely with a value of 0.72. A second bronchoscopy was performed on 3/17/2025 but again revealed markers of inflammation with no suspicious cells. The patient-physician conversation centered on her low-risk prolife, age of 80,

normal function with minimal pulmonary symptoms, and low SUV PET scan. However, given the changing aspect of the RLL process and the "likely cancer" CyPath® Lung test result, thoracic surgery was recommended.

The patient underwent robotic wedge resection of the superior segment RLL process on 6/25/2025 which final pathology was consistent with a Stage 1A neuroendocrine lung cancer.

Case Study Gloria: CyPath® Lung detects rare pulmonary mucinous adenocarcinoma at Stage 1A

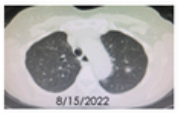
Patient Information and Initial Workup

- **Age:** 62 years old
- **Sex:** Female
- **Smoking status:** 100+ pack-year history
- **Medical history:** Stage 1 COPD (FEV1 109%)
- **Status:** High risk due to heavy smoking history and COPD
- **Presentation:** Chest X-ray with abnormal hyperinflation
- **Scans:** LDCT in August 2022, May 2023 and July 2024; PET in September 2022
- **Surveillance:** Patient missed recommended follow-up appointments

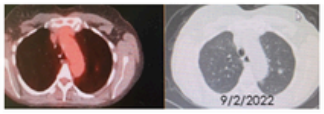
NOTE: Actual patient case, but name has been changed to ensure privacy.

Imaging Results

LDCT on 08/15/22 revealed 12mm LUL mixed solid nodule with GGO features, lung cancer probability of 16%. PET scan SUV was 1.19, lung cancer probability 3.5% under Herder model.

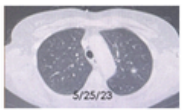


12 mm GGO LUL

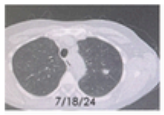


PET SUV 1.19

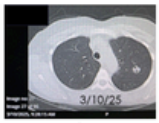
Missed 2 follow-up appointments; next LDCT scans were 5/25/23 and 10/18/2023 without significant changes. But 7/18/24 LDCT showed growth and less GGO characteristics. By 3/10/25 LDCT nodule had grown to 14mm with cystic changes.



No significant change



More solid, less GGO



Enlarged to 14mm, solid with cystic changes

Additional Findings/Next Steps

- **Brock model risk:** 16%/3.5% (Herder model with PET)
- **Nodify:** first blood serum marker test returned "reduced risk" result; second Nodify test came back as "indeterminate" with no circulating antibodies
- Patient refused invasive bronchoscopic biopsy
- **Follow-up PET:** denied by insurance in July 2024

Outcome with CyPath® Lung

- **CyPath® Lung:** 3/7/25 test result: 0.56, likely malignancy
- **Wedge resection:** Successful surgery on 6/11/25 with good margins, negative nodes
- **Diagnosis:** Stage 1A lung mucinous adenocarcinoma
- Patient quit smoking March 2025 and has returned to baseline pulmonary function
- **CyPath® Lung:** detected pulmonary mucinous adenocarcinoma in a high-risk individual whose previous tests and follow-up scans suggested a low probability of cancer

COPD=chronic obstructive pulmonary disease; LDCT=low-dose computed tomography; PET=positron emission tomography; LUL=left lower lobe; GGO=ground-glass opacity.

CyPath Lung

Case 7: Stage 1A pulmonary mucinous adenocarcinoma detected by CyPath® Lung in high-risk patient with inconclusive imaging and low-risk serum test results

Case 7 involves a complex atypical low-metabolic pulmonary nodule in a 62-year-old woman at high risk for lung cancer who is non-compliant with regard to follow-up appointments and treatment plans. The patient is high risk based on a greater than 100 pack-year smoking history, her age and COPD diagnosis. She initially presented in 10/2019 to address abnormal hyperinflated chest X-ray, without infiltrates or nodules, but associated with a cough with creamy sputum production, wheezing and intermittent dyspnea. LDCT scan for lung cancer surveillance and PFTs were recommended with a three-month follow-up.

She was lost to follow-up and did not have LDCT or return to office until 8/15/2022. The patient had continued to smoke. Her LDCT revealed a 12 mm LUL mixed solid with GGO features, and the nodule calculator gave a lung cancer probability of 16%. At the same time, the PET scan SUV was 1.19, and the Herder calculator model downgraded probability to 3.5 %.

Further adjuvant testing included a Nodify blood test with a reduced risk probability. CyPath® Lung was not available at this time. The patient flatly refused discussion of advanced bronchoscopic biopsy and opted for a six-month follow-up LDCT scan. She missed two follow-up appointments and did not return for her follow-up LDCT until 5/25/2023. Fortunately, her CT scans on 5/25/2023 and 10/18/2023 were without significant changes. She again missed an appointment but presented on 7/18/2024 with a LDCT demonstrating growth to 12 mm and less GGO characteristics. Her insurance denied a

repeat PET scan. Repeat Nodify testing changed to indeterminate but found no circulating antibodies to lung cancer.

The patient attempted her first CyPath® Lung test without our now-standard respiratory therapy guidance for optimal sputum collection. The result was an "unlikely cancer" score of 0.35. Patient again no showed until 3/4/2025 at which time a follow-up LDCT was scheduled and completed on 3/10/2025. The CT showed the nodule had grown to 14 mm and was mostly solid in appearance with some cystic changes.

A repeat CyPath® Lung with respiratory therapy guidance gave a score of 0.56, likely cancer. Based on the CyPath® Lung result, the patient agreed to a thoracic surgical resection of the LUL nodule. On 6/11/2025, the patient had a LUL lobectomy with a final pathology of Stage 1A invasive mucinous adenocarcinoma. She has subsequently quit tobacco use.

DISCUSSION

The clinical burden of assessing discovered pulmonary nodules, whether a serendipitous finding or part of a high-risk lung cancer screening program, commits the clinician to navigate the pitfalls of missing an early diagnosis of lung cancer or dealing with a serious complication from biopsy of a benign nodule. Further, atypical presentations with conflicting testing data make the patient-clinician conversation and decision making even more challenging.

Adjuvant lung cancer testing can complement LDCT and PET scans by helping to clarify indeterminate risk probabilities and guide clinical decision-making.[2] The three cases presented above involve atypical presentations which unfortunately are increasingly common when evaluating changing or newly discovered pulmonary nodules. In each case, non-diagnostic or conflicting results could have stalled a proactive diagnostic approach. CyPath® Lung provided real-time, actionable results that enabled physician–patient discussions to move forward and support the decision for definitive therapy.

Over the past 18 months, the CyPath® Lung sputum test has become an active component in our clinical assessment of newly discovered non-calcified pulmonary nodules. The three cases presented above had a quagmire of results, and CyPath® Lung was the central data point directing all three of my clinical discussions with each patient.

Cases 5 and 7 illustrate the powerful tool that CyPath® Lung brings to the evaluation of sub 10-15 mm non-calcified nodules. In each case, it was the CyPath® Lung test data point that allowed breakthrough discussions with both patients which resulted in definitive diagnostic and therapeutic intervention.

In our initial case presentation report, "CyPath® Lung in Practice: Cases 1-4," I presented cases with shared features that are commonly seen in lung nodule programs or pulmonary care clinics.[8] The cases presented here all had a preponderance of atypical features that dramatically increased the case complexity as well as how to approach the patient-physician discussions for both diagnostic testing and definitive treatment recommendations.

Atypical imaging results, including PET scans with low metabolic parameters and LDCTs with atypical shapes in difficult locations and long slow growth patterns, lead to indeterminate conclusions and complicate discussions about aggressive diagnostic and treatment options. Proteomic blood testing, which can be very useful in nodules 15 mm to 30 mm, was not helpful in these cases, indicating reduced risk probabilities or indeterminate findings.

Case 6 was an 80-year-old woman at low risk for lung cancer without significant symptoms and normal PFTs. The patient-physician discussions needed a compelling data point to overcome her reasonable trepidation about pursuing an invasive diagnostic or therapeutic intervention plan. CyPath® Lung testing was that defining data point that allowed us to decide together on her robotic thoracic surgical treatment.

Cases 5 and 7 shared patients with high anxiety levels which manifested in Case 5 as obstruction

to any invasive recommendations and in Case 7 as non-compliance with recommended follow-up studies and appointments. In all three cases, the CyPath® Lung data point was the critical real-time result that led directly to final diagnosis and definitive therapy.

CONCLUSION

No diagnostic test offers 100% specificity or sensitivity, and understanding the shortcomings and limitations of any new test is a learned journey. Presented here are three clinical scenarios that have significant atypical features, but which are becoming more frequent in lung nodule practices. We have found that adding CyPath® Lung testing to our algorithm has accelerated diagnosis, helped guide difficult clinical discussions and prevented unnecessary invasive procedures.

REFERENCES

1. Ludmila Guralnik, Radu Rozenberg, Alex Frenkel, Ora Israel and Zohar Keidar, Journal of Nuclear Medicine April 2015, 56 (4) 518-522; DOI: https://doi.org/10.2967/jnumed.113.131466

2. Ambrosini V, Nicolini S, Caroli P, Nanni C, Massaro A, Marzola MC, Rubello D, Fanti S. PET/CT imaging in different types of lung cancer: an overview. Eur J Radiol. 2012 May;81(5):988-1001. doi: 10.1016/j.ejrad.2011.03.020. Epub 2011 Mar 31. PMID: 21458181.

3. Kavidasan A, Syed N, Shetty P, Randhawa R, Bhattacharya M, et al. (2018) Atypical Presentations of Lung Cancer: A Case Series. J Oncol Res Ther: JONT-143. DOI: 10.29011/2574-710X. 000043

4. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, Wiener RS. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e93S-e120S. doi: 10.1378/chest.12-2351. PMID: 23649456; PMCID: PMC3749714.

5. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. doi:10.1056/NEJMoa1102873.

6. Weinberg, SE, & McDermont, S. Diagnostic evaluation of incidental pulmonary nodule. UpToDate in Medicine. 2025. Available at: www.uptodate.com.

7. Lemieux, ME, et al. Detection of early-stage lung cancer in sputum using automated flow cytometry and machine learning. Respir Res 24, 23 (2023).

8. Downie, G. "CyPath® Lung in Practice: Case 1-4" https://www.cypathlung.com/wp-content/uploads/2025/05/CyPath%C2%AE-Lung-in-Practice_Cases-1-4_CPL-25018.pdf.

9. Alduraibi AK. FDG avid solitary pulmonary nodule mimicking lung cancer. Radiology Case Reports. 2022 Apr;17(4):1047-1049. DOI: 10.1016/j.radcr.2022.01.038. PMID: 35145568; PMCID: PMC8818930.

10. Khan, F., Seaman, J., Hunter, T.D. et al. Diagnostic outcomes of robotic-assisted bronchoscopy for pulmonary lesions in a real-world multicenter community setting. BMC Pulm Med 23, 161 (2023). https://doi.org/10.1186/s12890-023-02465-w