

# Serum proteomic cancer risk classification of indeterminate pulmonary nodules

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Policy contains: Biomarker; BDX-XL2; EarlyCDT; indeterminate pulmonary nodule; Nodify CDT; Nodify XL2; proteomics.

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## Coverage policy

The following serum-based proteomic tests are investigational/not clinically proven and, therefore, not medically necessary for classifying the risk of malignancy of indeterminate pulmonary nodules:

- Nodify XL2<sup>®</sup> assay, also referred to as BDX-XL2, (Biodesix, Boulder, Colorado; formerly Xpresys Lung 2<sup>®</sup> [XL2], Integrated Diagnostics, Seattle, Washington).
- Nodify CDT<sup>®</sup> (Biodesix, Boulder, Colorado), also called EarlyCDT Lung<sup>®</sup> (Oncimmune Holdings, Nottingham, United Kingdom).

### Limitations

No limitations were identified during the writing of this policy.

### Alternative covered services

Guideline-directed care for indeterminate pulmonary nodules, including, but not limited to (Gould, 2013; MacMahon, 2017):

- Computed tomography.
- Functional imaging (e.g., positron emission tomography).
- Surgical biopsy, including video-assisted thoracoscopic surgery.
- Nonsurgical biopsy (e.g., transthoracic needle biopsy or endobronchial biopsy).

## Background

Current management of pulmonary nodules identified on chest computed tomography relies on establishing the probability (risk) of malignancy as defined by the American College of Chest Physicians' framework (Gould, 2013). The probability of malignancy is estimated clinically or with a validated quantitative risk model. The predominant imaging factors influencing risk are nodule size and morphology, but clinical risk factors such as smoking history, carcinogenic exposure, emphysema, fibrosis, upper lobe location, family history, age, and gender are also important considerations. Typically, nodules with a high probability of malignancy (greater than 65%) are managed aggressively, and those considered low risk (0% to 5%) are managed conservatively.

Approximately half of the pulmonary nodules identified by chest computed tomography comprise intermediate-risk nodules (5% to 65%) and often have features of both high-risk and low-risk disease (Gould, 2013). They require further diagnostic evaluation with additional imaging or invasive procedures to distinguish malignant nodules in need of more aggressive intervention from those with benign disease that can be monitored safely. However, even minimally invasive procedures carry significant complications and downstream medical costs to patients (Huo, 2019).

Novel biomarkers have been proposed to further stratify intermediate-risk pulmonary nodules (Codreanu, 2017). Blood-based biomarkers offer a minimally invasive tool in the early detection of lung cancer and monitoring of both screened and incidentally discovered lung nodules. In oncology, plasma-based proteomic biomarkers apply the study of proteins and their interactions in a cancer cell by proteomic technologies (Cheung, 2017). Commonly used proteomic techniques include two-dimensional polyacrylamide gel electrophoresis, mass spectrometry, and protein arrays.

Several proteomic tests for lung nodule classification are emerging (Birse, 2017; Codreanu, 2017; Daly, 2013; Mehan, 2014). Most are in developmental or technical validity stages and lack the advanced clinical validation that would support clinical utility. Two proteomic tests are commercially available, and the current versions of these tests are the subject of this policy.

The Nodify XL2 assay incorporates the ratio of two plasma proteins associated with lung cancer and cancer immune response — LG3BP and C163A — with five clinical risk factors (age, smoking status, nodule diameter, shape, and location) to identify patients with likely benign lung nodules — a “rule-out [malignancy] test.” A higher ratio suggests a higher probability of cancer. The assay has undergone several technical refinements and validation studies (Li, 2013; Vachani, 2015a, 2015b; Kearney, 2017). The current version is intended for patients at least 40 years of age with an 8- to 30-millimeter nodule, and  $\leq 50\%$  pretest risk of malignancy based on the Mayo Clinic model solitary pulmonary nodule calculator; no history of non-lung cancer within five years, and no lung cancer history (Biodesix, 2023).

EarlyCDT Lung measures a panel of seven autoantibodies to tumor-associated antigens known to be elevated for all types of lung cancer and from the earliest stage of the disease. It estimates the probability of malignancy across histologies and stages, stratified into four risk categories (Lam, 2011; Chapman, 2012; Massion, 2017). In 2019, Oncimmune partnered with Biodesix to advance EarlyCDT Lung into the United States, now marketed as Nodify CDT (Laboratory Network, 2019). Eligibility criteria for the tests are at least 40 years of age, an 8- to 30-millimeter nodule, a  $\leq 65\%$  pretest risk of malignancy based on the Mayo Clinic model solitary pulmonary nodule calculator, and no previous diagnosis of cancer (Biodesix, 2023).

The U.S. Food and Drug Administration has not required any regulatory review of either Nodify XL2 assay or EarlyCDT Lung as of this writing.

## Findings

We identified no clinical practice guidelines that address blood biomarkers for lung nodule classification. The National Institute for Health and Care Excellence issued guidance in February 2022, concluding that not enough evidence exists to recommend use of EarlyCDT Lung to assess risk of cancer in solid pulmonary nodules (National Institute for Health and Care Excellence, 2022).

According to American Thoracic Society guidance, to determine if a proteomic biomarker is ready to support lung nodule evaluation, the evidence must progress from the discovery and analytic validation phases to clinical validation phases in independent, intended-use populations; and then to evidence of clinical utility (Mazzone, 2017). A proteomic biomarker will have clinical utility if it shifts a patient from an indeterminate category to another clinical decision threshold, and either mitigates the use of unnecessary medical procedures without delaying a cancer diagnosis (i.e., a “rule-out” test), or expedites therapy for early lung cancer through earlier detection without substantially increasing the number of procedures performed on patients with benign nodules (i.e., a “rule-in” test). The pretest probability of malignancy for each patient must be known, as it will influence both positive and negative predictive values essential for determining the risk of malignancy based on the biomarker result.

The current evidence consists of industry-sponsored observational studies describing the diagnostic performance (clinical validity) of the Nodify XL2 and Nodify CDT in clinical populations with incidentally detected indeterminate lung nodules on computed tomography. Nodify CDT has also been examined as a screening test. Clinical utility studies of both tests are ongoing as of this writing.

### Nodify XL2

The evidence for the XL2 consists of initial results from the observational, multisite Pulmonary Nodule Plasma Proteomic Classifier validation study (PANOPTIC; ClinicalTrials.gov identifier NCT01752114; Silvestri, 2018) and a follow-up study (Tanner, 2021). The trial comprised 178 patients (149 with confirmed benign nodules and 29 with confirmed malignant nodules) age 40 years or older with an 8- to 30-millimeter lung nodule incidentally detected on computed tomography (i.e., not screen-detected), and with a  $\leq 50\%$  probability of cancer as assessed by the Mayo Clinic model for solitary pulmonary nodules.

Diagnosis was confirmed using histopathology or serial radiography for one year. The prevalence of malignancy in the study population was estimated to be 16%, and 59% of malignancies were adenocarcinoma. The sensitivity, specificity, and negative predictive value of the XL2 were 97% (95% confidence interval, 82% to 100%), 44% (36% to 52%), and 98% (92% to 100%), respectively. Comparison of the area under the receiver-operating characteristic curves showed that XL2 performed better than positron emission tomography, Veterans Affairs and Mayo Clinic validated lung nodule risk models, and physician cancer probability estimates ( $P \leq .001$ ). Using these estimates, the investigators hypothesized that a likely benign XL2 test could reduce the number of invasive procedures in those with benign nodules by 36% (an absolute risk reduction of 10.1% for all patients with benign nodules), although 3% of malignant nodules would have been misclassified as benign.

To comply with guideline recommendations of a two-year follow-up period (Gould, 2013), Tanner (2021) reported a follow-up analysis of the PANOPTIC trial extended to a second year and to those with multiple pulmonary nodules. Data for 161 patients of the original 178 (90%) were available for analysis. All nodules designated as benign at year one remained benign (e.g., stable or resolved) at year two with no change in pathologic diagnoses or nodule size by computed tomography. Fifty-seven percent of 178 patients had an average of three nodules (with a range of one to 10) on computed tomography. There was no significant difference in XL2 performance between those with multiple nodules compared with those with one nodule ( $P = .164$ ). The authors of both studies called for prospective clinical utility studies to confirm these findings.

These estimates of diagnostic performance should be interpreted cautiously. The XL2 applies likelihood ratios to estimate the post-test probability of malignancy using a single cutpoint that converts the test result from a continuous variable to a binary variable, rather than using likelihood ratios with multilevel cutoffs that better reflect a continuous variable test result (Ost, 2022). As a result, the negative likelihood ratio reported in the XL2 will tend to underestimate risk of malignancy in this population. In addition, they applied 16% prevalence of malignancy for the overall study population to determine the post-test probability of malignancy, which may not reflect the probability of cancer in the individual patient being tested.

Two clinical studies are examining the clinical utility of the Nodify XL2 for its ability to reduce unnecessary invasive procedures on benign lung nodules while not significantly increasing the number of malignant lung nodules routed to computed tomography surveillance. Patient enrollment criteria are similar to the criteria in the PANOPTIC trial:

- A Registry to Evaluate the Performance of the BDX-XL2 Test (ORACLE; ClinicalTrials.gov identifier NCT03766958) is an observational study comparing patient management using the XL2 test to a historical control obtained from chart review. The study began in 2018, and the estimated completion date is December, 2023.
- The Nodify XL2 classifier clinical utility study in low- to moderate-risk lung nodules (ALTITUDE; ClinicalTrials.gov identifier: NCT04171492) is a prospective, multicenter randomized controlled trial. The study began in 2020, and the estimated completion date is December, 2024.

### Nodify CDT

Nodify CDT is intended as an adjunct to standard care for early detection of lung cancer and for risk classification of indeterminate pulmonary nodules. The current evidence focuses on describing diagnostic performance (Jett, 2014; Massion, 2017) and potential cost-effectiveness (Edelsberg, 2018; Sutton, 2020) in clinical populations with incidentally detected indeterminate lung nodules on computed tomography.

The evidence suggests EarlyCDT Lung may improve diagnostic performance. The study limitations included lack of clear inclusion and exclusion criteria, no direct comparative evidence with current standard care, and a short follow-up period of six months, which do not permit sufficient evidence to guide clinical implementation.

- Jett (2014) examined the clinical outcomes and test results of 1,613 patients from multiple sites in the United States deemed at high risk for lung cancer by their physician. At six-month follow-up, 61 patients (4%) were diagnosed with lung cancer of mixed histologies, 25 of whom tested positive by EarlyCDT Lung (sensitivity = 41%). A positive EarlyCDT Lung test was associated with a 5.4-fold increase in lung cancer incidence versus a negative test.
- In a subgroup of 296 patients, for whom a nodule ranging from 4 millimeters to 20 millimeters in largest diameter was identified within six months of molecular testing, the prevalence of malignancy in the study population was 25% (Massion, 2017). When treating both computed tomography and EarlyCDT Lung as binary tests, adding EarlyCDT Lung to three independent risk models improved diagnostic performance with high specificity (> 92%) and positive predictive value (> 70%).

A cost-effectiveness analysis from a U.S. perspective modeled computed tomography surveillance with and without EarlyCDT Lung for the initial diagnosis of incidentally detected, intermediate-risk (5% to 60%) lung nodules measuring 8 millimeters to 30 millimeters in diameter (Edelsberg, 2018). The base population of 1,000 patients had a prevalence of malignancy of 9.5% and would be scheduled for computed tomography surveillance alone under current practices. Costs were calculated in 2016 U.S. dollars. With EarlyCDT Lung, assuming a sensitivity and specificity of 41% and 93%, respectively, the cost per quality-adjusted life year gained was \$24,330. When sensitivity and specificity were set at 28% and 98%, respectively, the cost per quality-adjusted life year gained was \$24,833. The cost-effectiveness of EarlyCDT Lung was insensitive to all cost parameters,

except for the cost of the test. A similar analysis, taken from the United Kingdom perspective, produced similar results (Sutton, 2020).

EarlyCDT Lung has been studied as an initial test in a lung cancer screening program prior to computed tomography, with mixed results. In a high-risk cohort (n = 246 patients) referred from their general practitioner on suspicion of lung cancer, the overall test sensitivity was 33% for lung cancer and 31% for primary lung cancer and lung metastases combined (Borg, 2021). In a subgroup of patients that met current tomographic screening criteria (age 55 to 80 years and a minimum of 30 tobacco pack years), the sensitivity was 37%. The molecular test performed best in elderly patients with late-stage lung cancer and a heavy smoking history, and was insufficiently sensitive to be used as an inclusion criterion in a lung cancer screening program.

In the German Lung Cancer Screening Intervention Trial, the EarlyCDT Lung test was insufficiently sensitive (13.0%, 95% confidence interval 4.9% to 26.3%) for detecting early-stage lung cancer in a computed tomography screening population (n = 180 patients) (González Maldonado, 2021).

In the Early Diagnosis of Lung Cancer Scotland trial (Sullivan, 2021), 12,208 participants at risk of developing lung cancer were randomized to receive either the EarlyCDT Lung test and, if test-positive, low-dose CT scanning every six months for up to two years; or to receive standard clinical care (for symptomatic presentation only). At two years, there were 127 lung cancers in the study population (1.0% prevalence). In the intervention arm, 33 out of 56 (58.9%) lung cancers were diagnosed at stage 3/4 compared with 52 out of 71 (73.2%) in the control arm. The hazard ratio for stage 3/4 presentation was 0.64 (95% confidence interval 0.41 – 0.99). The authors stated that while there were nonsignificant differences in lung cancer and all-cause mortality after two years, a stage shift toward earlier-stage lung cancer diagnosis in the EarlyCDT Lung arm warrants further investigation.

One U.S. study of EarlyCDT Lung has recently been completed: “Lung cancer screening study with low-dose CT scan and blood biomarker” (ClinicalTrials.gov identifier: NCT01700257). No results have been published as of this writing (ClinicalTrials.gov, 2020).

In 2022, no additional references to the policy were warranted.

In 2023, we added a review stating that EarlyCDT was limited by low sensitivity, especially for advanced lung cancer, warranting more development; and Nodify XL2 performed best in cases with pretest cancer probability of < 50% (Ostrin, 2020).

We added a study of persons with pulmonary nodules (n = 394), randomized to subjects with Nodify XL2 and controls. The Nodify group were 74% less likely to undergo an invasive procedure; two of the six authors are employed by Biodesix, Inc. (Pritchett, 2023).

We added a randomized controlled trial (n = 12,208) of psychological outcomes of lung cancer screening using the EarlyCDT blood test plus computed tomography. Those testing positive (compared to negative) had lower positive affect, greater impact of worries, screening distress, worry about tests, and more frequent lung cancer worry. Compared to the control group, those testing negative had a lower negative affect, higher positive affect, less impact of worries, and less-frequent cancer worry. Differences were small and short-lived (Hancox, 2023).

## References

On September 28, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “proteomics” (MeSH), “solitary pulmonary nodule” (MeSH), “biomarkers, tumor” (MeSH), “proteomic,” “BDX-XL2,” “Nodify,” “EarlyCDT,” “NodifyCDT,” and “solitary pulmonary nodule.” We included the best available evidence according to established evidence

hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Biodesix. Nodify Lung. <https://www.biodesix.com/our-tests/nodify-lung>. Published 2023.

Birse CE, Tomic JL, Pass HI, Rom WN, Lagier RJ. Clinical validation of a blood-based classifier for diagnostic evaluation of asymptomatic individuals with pulmonary nodules. *Clin Proteomics*. 2017;14:25. Doi: 10.1186/s12014-017-9158-9.

Borg M, Wen SWC, Nederby L, et al. Performance of the EarlyCDT® lung test in detection of lung cancer and pulmonary metastases in a high-risk cohort. *Lung Cancer*. 2021;158:85-90. Doi: 10.1016/j.lungcan.2021.06.010.

Chapman CJ, Healey GF, Murray A, et al. EarlyCDT®-Lung test: Improved clinical utility through additional autoantibody assays. *Tumour Biol*. 2012;33(5):1319-1326. Doi: 10.1007/s13277-012-0379-2.

Cheung CHY, Juan HF. Quantitative proteomics in lung cancer. *J Biomed Sci*. 2017;24(1):37. Doi: 10.1186/s12929-017-0343-y.

ClinicalTrials.gov. Lung cancer screening study with low-dose CT scan and blood biomarker. ClinicalTrials.gov identifier: NCT01700257.

<https://www.clinicaltrials.gov/ct2/show/NCT01700257?term=Early+CDT&draw=4&rank=1>. Last update posted December 31, 2020.

Codreanu SG, Hoeksema MD, Slebos RJC, et al. Identification of proteomic features to distinguish benign pulmonary nodules from lung adenocarcinoma. *J Proteome Res*. 2017;16(9):3266-3276. Doi: 10.1021/acs.jproteome.7b00245.

Daly S, Rinewalt D, Fhied C, et al. Development and validation of a plasma biomarker panel for discerning clinical significance of indeterminate pulmonary nodules. *J Thorac Oncol*. 2013;8(1):31-36. Doi: 10.1097/JTO.0b013e31827627f8.

Edelsberg J, Weycker D, Atwood M, Hamilton-Fairley G, Jett JR. Cost-effectiveness of an autoantibody test (EarlyCDT Lung) as an aid to early diagnosis of lung cancer in patients with incidentally detected pulmonary nodules. *PLoS One*. 2018;13(5):e0197826. Doi: 10.1371/journal.pone.0197826.

González Maldonado S, Johnson T, Motsch E, Delorme S, Kaaks R. Can autoantibody tests enhance lung cancer screening? — An evaluation of EarlyCDT® Lung in context of the German lung cancer screening intervention trial (LUSI). *Transl Lung Cancer Res*. 2021;10(1):233-242. Doi: 10.21037/tlcr-20-727.

Gould MK, Donington J, Lynch WR, et al. 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;143(5 Suppl):e93S-e120S. Doi: 10.1378/chest.12-2351.

Hancox J, Ayling K, Bedford L, Vedhara K. Psychological impact of lung cancer screening using a novel antibody blood test followed by imaging: the ECLS randomized controlled trial. *J Public Health Oxf*. 2023;45(2):e275-e284. Doi: 10.1093/pubmed/fdac032.

Huo J, Xu Y, Sheu T, Volk RJ, Shih YT. Complication rates and downstream medical costs associated with invasive diagnostic procedures for lung abnormalities in the community setting. *JAMA Intern Med*. 2019;179(3):324-332. Doi: 10.1001/jamainternmed.2018.6277.

Jett JR, Peek LJ, Fredericks L, et al. Audit of the autoantibody test, EarlyCDT-Lung, in 1600 patients: An evaluation of its performance in routine clinical practice. *Lung Cancer*. 2014;83(1):51-55. Doi: 10.1016/j.lungcan.2013.10.008.



Kearney P, Hunsucker SW, Li XJ, et al. An integrated risk predictor for pulmonary nodules. *PLoS One*. 2017;12(5):e0177635. Doi: 10.1371/journal.pone.0177635.

Laboratory Network. Newsletter. Oncimmune and Biodesix form strategic partnership to unlock full potential of EarlyCDT Lung in US. <https://www.biospace.com/article/-oncimmune-and-biodesix-form-strategic-partnership-to-unlock-full-potential-of-earlycdt-lung-in-us/>. Published June 28, 2019.

Lam S, Boyle P, Healey GF, et al. EarlyCDT Lung: An immunobiomarker test as an aid to early detection of lung cancer. *Cancer Prev Res (Phila)*. 2011;4(7):1126-1134. Doi: 10.1158/1940-6207.Capr-10-0328.

Li XJ, Hayward C, Fong PY, et al. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. *Sci Transl Med*. 2013;5(207):207ra142. Doi: 10.1126/scitranslmed.3007013.

MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. *Radiology*. 2017;284(1):228-243. Doi: 10.1148/radiol.2017161659.

Massion PP, Healey GF, Peek LJ, et al. Autoantibody signature enhances the positive predictive power of computed tomography and nodule-based risk models for detection of lung cancer. *J Thorac Oncol*. 2017;12(3):578-584. Doi: 10.1016/j.jtho.2016.08.143.

Mazzone PJ, Sears CR, Arenberg DA, et al. Evaluating molecular biomarkers for the early detection of lung cancer: When is a biomarker ready for clinical use? An official American Thoracic Society policy statement. *Am J Respir Crit Care Med*. 2017;196(7):e15-e29. Doi: 10.1164/rccm.201708-1678ST.

Mehan MR, Williams SA, Siegfried JM, et al. Validation of a blood protein signature for non-small cell lung cancer. *Clin Proteomics*. 2014;11(1):32. Doi: 10.1186/1559-0275-11-32.

National Institute for Health and Care Excellence. EarlyCDT Lung for lung cancer risk classification of solid pulmonary nodules. <https://www.nice.org.uk/guidance/dg46/chapter/3-Committee-discussion>. Published February 23, 2022.

Ost DE. Interpretation and application of the likelihood ratio to clinical practice in thoracic oncology. *J Bronchology Interv Pulmonol*. 2022;29(1):62-70. Doi: 10.1097/lbr.0000000000000788.

Ostrin EJ, Sidransky D, Spira A, Hanash SM. Biomarkers for lung cancer screening and detection. *Cancer Epidemiol Biomarkers Prev*. 2020;29(12):2411-2415. Doi: 10.1158/1055-9965.EPI-20-0865.

Pritchett MA, Sigal B, Bowling MR, Kurman JS, Pitcher T, Springmeyer SC. Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: Results from the ORACLE study. *PLoS One*. 2023;18(7):e0287409.

Silvestri GA, Tanner NT, Kearney P, et al. Assessment of plasma proteomics biomarker's ability to distinguish benign from malignant lung nodules: Results of the panoptic (Pulmonary Nodule Plasma Proteomic Classifier) trial. *Chest*. 2018;154(3):491-500. Doi: 10.1016/j.chest.2018.02.012.

Sullivan FM, Mair FS, Anderson W, et al. Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. *Eur Respir J*. 2021;57(1). Doi: 10.1183/13993003.00670-2020.

Sutton AJ, Sagoo GS, Jackson L, et al. Cost-effectiveness of a new autoantibody test added to computed tomography (CT) compared to CT surveillance alone in the diagnosis of lung cancer amongst patients with indeterminate pulmonary nodules. *PLoS One*. 2020;15(9):e0237492. Doi: 10.1371/journal.pone.0237492.

Tanner NT, Springmeyer SC, Porter A, et al. Assessment of integrated classifier's ability to distinguish benign from malignant lung nodules: Extended analyses and 2-year follow-up results of the panoptic (pulmonary nodule plasma proteomic classifier) trial. *Chest*. 2021;159(3):1283-1287. Doi: 10.1016/j.chest.2020.10.069.

Vachani A, Hammoud Z, Springmeyer S, et al. Clinical utility of a plasma protein classifier for indeterminate lung nodules. *Lung*. 2015;193(6):1023-1027. Doi: 10.1007/s00408-015-9800-0.(a)

Vachani A, Pass HI, Rom WN, et al. Validation of a multiprotein plasma classifier to identify benign lung nodules. *J Thorac Oncol*. 2015;10(4):629-637. Doi: 10.1097/jto.0000000000000447.(b)

## Policy updates

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