



Blood-based biomarker testing to aid in the early diagnosis of lung cancer

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Lung cancer is the number one cause of cancer deaths in both men and women in the United States. The overall 5-year survival is 22% [1]. This poor overall survival is primarily due to the fact that lung cancer is not diagnosed until the patient has symptoms such as coughing up blood, shortness of breath, chest pain and/or weight loss. Symptomatic lung cancer is usually advanced stage disease with limited chance of curable treatment. The best chance for curative treatment is to detect and diagnose lung cancer while it is clinically silent or asymptomatic and most likely to be early stage.

The best chance to detect and diagnose early stage lung cancer is through low dose computed tomography (LDCT) chest screening in high risk individuals and/or by evaluation of asymptomatic non-calcified indeterminate pulmonary nodules (IPNs). High risk individuals eligible for LDCT chest screening are defined by the United States Preventative Services Task Force (USPSTF) based on age and smoking history: 55-80 years old with 30 pack-years of smoking history and quit smoking less than 15 years ago. A pack-year is defined as one pack per day for a year. The criteria were established in 2013, but there is currently a draft recommendation under review to expand the criteria to younger patients with less smoking history [2]. Although lung cancer screening programs have shown great potential to improve early diagnosis, they are still new, and adoption is low so in this article we will focus on IPNs.

An IPN is defined as a nodule (spot, lesion) in the lung that is less than 30 mm in diameter (1 inch = 25 mm). It is estimated that over 1.5 million adult Americans will have an IPN identified each year [3]. These nodules are usually detected incidentally by x-rays or scans done for other reasons such as chest trauma, evaluation for blood clots in the lungs, or for evaluation of heart disease. Some IPNs are due to lung cancer when it is often early stage disease and curable with surgery. The challenge is that the majority of IPNs are benign (not cancer), so the dilemma for physicians is to determine which IPNs are malignant (cancerous) and should be removed surgically and which are benign and need not be biopsied or removed. In current practice, approximately 25-35% of all operations performed for IPNs turn out to be benign nodules, such as scar tissue or residual tissue from a prior respiratory infection [4]. These patients have undergone surgery and the associated risk of complications for a benign IPN that did not need to be removed. How can we do better?

Blood-based biomarker tests offer a non-invasive way to help identify patients with IPNs at higher risk of cancer or conversely those at lower risk. The Nodify Lung™ blood-based testing strategy combines two tests to stratify risk and inform next steps for diagnosis. The Nodify CDT™ test helps identify those with high risk of malignancy by measuring a panel of seven autoantibodies. Autoantibodies are produced by the immune system in response to changes or abnormalities in tissue and have long been studied as a potential marker for disease – in the case of the Nodify CDT test, the autoantibodies are against lung cancer associated antigens. The test can be used in patients with IPNs between 8 mm and 30 mm with intermediate risk of lung cancer (5%-65%) as estimated by the attending physician or by the Mayo/Swensen nodule risk calculator [5].

The test has a high specificity or relatively few false positive test results, meaning that a positive result often indicates the presence of lung cancer [6]. The Nodify CDT test results are combined with the initial risk to calculate a personalized risk of lung cancer. A “Moderate Level” or “High Level” of the autoantibodies increases the likelihood of malignancy and moves many of the patients with intermediate risk IPNs into the high-risk category where the probability of malignancy is >65%. Medical guidelines suggest that patients in this high-risk category should undergo more intensive evaluation such as PET scan (positron emission tomography), biopsy and/or possible surgery [7]. The Nodify CDT blood test does not detect all lung cancers, so if the test results come back as “No Significant Levels of Autoantibodies Detected” then these IPNs have to be followed carefully as clinically indicated.

The second part of the testing strategy is the Nodify XL2™ test to help identify lower risk IPNs. It is based on two blood proteins that are associated with cancer or

inflammation combined with five other clinical factors based on a patient's medical history and the size, shape, and location of the IPN on the imaging scan. This test is used in patients with IPNs between 8 mm and 30 mm with intermediate risk of lung cancer in the range of 5-50%. The test has a high sensitivity for benign nodules or relatively few false negative test results. A "Likely Benign" or "Reduced Risk" test result decreases the likelihood of malignancy and moves many patients into the very low risk category where the probability of cancer is less than 5%. Medical guidelines suggest that patients in this category can have their nodules watched by serial CT chest scans over time instead of proceeding with a biopsy and/or surgery [7]. Benign nodules will shrink/disappear or stay the same size, whereas the small number of cancers will be seen to enlarge over time. Only those enlarging nodules will then have further evaluation. Clinical research with the test indicates that testing may reduce unnecessary biopsies and surgeries on benign nodules by 40% [8].

Both tests have undergone extensive research over the past 10 years and have multiple peer-reviewed publications and international conference presentations. Nodify Lung testing was recently made available to physicians in the US to help triage patients with new IPNs based on their risk classification. The results are available within a week so there is not a long delay before a robust discussion about the next steps. A quick result is important since this is an anxious time for patients. The tests require only a standard blood draw, which can be performed in a physician's office, local laboratory, or even at the patient's home by a certified mobile phlebotomist (specialists in drawing blood). With increased use of telemedicine, the tests can be performed through virtual physician appointments to discuss the test results and next steps in the diagnostic plan.

Ultimately, the goal of Nodify Lung testing is to help identify patients with a high risk of lung cancer that should be evaluated sooner, while reducing the number of invasive procedures on those patients with benign IPNs. Incorporating biomarkers into the risk assessment of an IPN helps ensure that each patient receives a more accurate and personalized care plan based on all available information.

Contributors:



Our mission is to improve every patient's lung cancer care by empowering physicians with swift, comprehensive, and actionable insights.

James Jett, M.D. has served as our Co-Chief Medical Officer since October 2019. Dr. Jett joined Biodesix after the acquisition of Oncimmune LLC where he served as Chief Medical Officer since 2016. Dr. Jett is a board-certified physician in Pulmonary Medicine and served in pulmonary medicine and on the consulting staff of Mayo Clinic in Rochester, Minnesota for 28 years before moving to join the faculty as a professor of medicine at National Jewish Health in Denver, Colorado from 2010 to 2015. His research interests have focused on screening, diagnosis, and treatment of lung cancer. From 2006 to 2012, Dr. Jett served as the Editor-in-Chief of the Journal of Thoracic Oncology and from 2008 to 2017 as the Co-Editor of the Lung Cancer Section of the premier medical electronic textbook Up-To-Date. Dr. Jett has held professional memberships with numerous organizations such as the American Thoracic Society, International Association for the Study of Lung Cancer, American Society of Clinical Oncology, North Central Cancer Treatment Group, and the American College of Chest Physicians. Dr. Jett received his doctorate degree from the University of Missouri in Columbia, Missouri and he completed his internal medicine and pulmonary medicine training at the Mayo Clinic. Dr. Jett's academic honors include the 2013 IASLC Merit Award, Clinical Educator Award from the ATS Assembly on Clinics Problems, 2014; selection for the 2015 Edition of Who's Who in America; and the Lifetime Achievement Award from the ATS Assembly on Thoracic Oncology, 2015.

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Center in 1984, where he served as President and Director of Clinical Research at the Virginia Mason Research Center, and co-developed programs in Lung Volume Reduction Surgery and Thoracic Oncology. His research interests have included diagnostic and therapeutic uses of fiberoptic bronchoscopy and bronchoalveolar lavage, treatment of severe emphysema, and early diagnosis of pulmonary nodules and lung cancer. Dr. Springmeyer has held many professional membership and leadership positions including the American Thoracic Society; Board Member and Chair of Council of Chapter Representatives, Washington Thoracic Society; President and Board Member, American College of Chest Physician; Fellow, and the American Association of Bronchology and Interventional Pulmonology. Dr. Springmeyer received his doctorate degree from the University of Utah, and he completed his training at the University of Washington.

References

- [1] American Lung Association, "State of Lung Cancer," 2019.
- [2] Boyles S, "USPSTF: Extend Eligibility for CT Lung Cancer Screening," *MedPage Today*, p. <https://www.medpagetoday.com/hematologyoncology/lungcancer/87444>, 7th July 2020.
- [3] Gould M, et al, "Recent Trends in the Identification of Incidental Pulmonary Nodules," *American Journal of Respiratory and Critical Care Medicine*, vol. 192, no. 10, pp. 1208-1214, 2015.
- [4] Tanner N, et al, "Management of Pulmonary Nodules by Community Pulmonologists," *CHEST*, vol. 148, no. 6, pp. 1405-1414, 2015.
- [5] Swensen S, et al, "The Probability of Malignancy in Solitary Pulmonary Nodules," *Arch Internal Med*, vol. 157, pp. 849-855, 1997.
- [6] Chapman C, et al, "EarlyCDT-Lung test: improved clinical utility through additional autoantibody assays," *Tumor Biology*, vol. 33, no. 5, pp. 1319-1326, 2012.
- [7] Gould M, et al, "Evaluation of Individuals with Pulmonary Nodules: When is it Lung Cancer?," *CHEST*, vol. 143, no. 5, pp. e93S-e120S, 2013.
- [8] Silvestri G, 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*, vol. 154, no. 3, pp. 491-500, 2018.