**Division of Pulmonary,
Critical Care, Allergy
and Sleep Medicine**
96 Jonathan Lucas Street
CSB 816; MSC 630
Charleston, SC 29425
www.musc.edu/pulmonary

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To: submissions@nccn.org
Re: Submission Request – Non-Small Cell Lung Cancer
Submitted by:

Gerard A. Silvestri MD, MS, FCCP
Hillebrand Professor of Thoracic Oncology
Division of Pulmonary and Critical Care Medicine
Medical University of South Carolina
96 Jonathan Lucas St.
Room 812 CSB, Charleston, SC, 29425-0630
Phone: 843 792-3167
Email: silvestri@musc.edu

Date of request: 1/27/21
NCCN Guidelines Panel: Non-Small Cell Lung Cancer

I respectfully request the NCCN – Non-Small Cell Lung Cancer Panel to review the enclosed data for inclusion of the Integrated Classifier in the CLINICAL PRESENTATION AND RISK ASSESSMENT for Incidental finding of nodule suspicious for lung cancer.

Specific Changes: Recommend revisions to DIAG-1, RISK ASSESSMENT, addition of a third category Biomarker factor*, between Patient factors and Radiologic factors, with "●Integrated Classifier blood test should be considered" in the new category, and the corresponding asterix footnote reading, *A blood test, the integrated classifier (Nodify XL2®, Biodesix Inc), is an option to help guide active surveillance decisions in patients with newly discovered solid lung nodules 8-30 mm in diameter and a pretest probability of cancer at ≤50%.

FDA Clearance: FDA clearance is not required for this assay because the assay is performed at a laboratory at Biodesix. The assays performed by the Biodesix laboratories are regulated and certified under the Clinical Laboratory Improvement Amendments (CLIA), and the College of American Pathologists (CAP). Additional regulatory approval is supported by noting that the Integrated Classifier has received CMS MolDx approval.

Rationale: This assay was developed with over 1,500 patient samples and now clinical experience confirms a predicted cancer risk classification change of 55% of 2,014 tested nodule patients (12) to very low risk so healthcare providers can recommend active surveillance with confidence.

The following articles are submitted in support of this recommendation.

Development, validation, analytical validation, regulatory:

1. Li XJ, Hayward C, Fong PY, et al. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. Sci Transl Med 2013; 5:207ra142

2. Li X, Lee LW, Hayward C, et al. An integrated quantification method to increase the precision, robustness, and resolution of protein measurement in human plasma samples. Clinical proteomics 2015;12:3.

3. Vachani A, Pass HI, Rom WN, et al. Validation of a multiprotein plasma classifier to identify benign lung nodules. J Thorac Onc 2015;10:629-637.

4. Kearney P, Hunsucker SW, Li XJ, Porter A, Springmeyer S, Mazzone P. An integrated risk predictor for pulmonary nodules. *PLoS One.* 2017;12(5):e0177635

5. CMS MolDx WPS L37216. [MolDX: BDX-XL2 Local Coverage Determinations (noridianmedicare.com)](noridianmedicare.com). Accessed 12/20/2020.

Clinical validation, extended analyses:

6. 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

7. Tanner NT, Springmeyer SC, Porter A, Jett J, Mazzone P, Vachani A, Silvestri G. 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. DOI: https://doi.org/10.1016/j.chest.2020.10.069

Clinical utility publications

8. Vachani A, Hammoud Z, Springmeyer S, et al. Clinical Utility of a Plasma Protein Classifier for Indeterminate Lung Nodules. Lung 2015; 193:1023-1027

9. Pritchett M, Sigal BW, Bowling MR, et al. First Look at the Distribution of Risk of Malignancy Pre and Post-Test Using a Blood-Based Biomarker in Patients with Pulmonary Nodules in a Real-World Observational Study. Am J Respir Crit Care Med. 2020;201:A4465

10. Pohl K, Springmeyer S, Jett J, Silvestri G. Lung Nodule Integrated Classifier Biomarker: First Data with Real-World Clinical Use*. Chest*, 2020 - https://doi.org/10.1016/j.chest.2020.08.1324

Telemedicine and COVID-19

11. Springmeyer SC, Jett J, Bhadra K, Kheir F, Majid A. Managing Lung Nodules Using Telemedicine and Molecular Biomarkers During the COVID-19 Pandemic. *Chest*. 2020 Oct;158(4):1794-1795. doi: 10.1016/j.chest.2020.05.574

Sincerely,

Gerard A. Silvestri MD, MS, FCCP
Hillebrand Professor of Thoracic Oncology
Division of Pulmonary and Critical Care Medicine
Medical University of South Carolina