Johnathan Lancaster, MD PhD
Myriad Genetic Laboratories, Inc.
320 Wakara Way, Salt Lake City, UT 84108
801-505-5090
jlancaster@myriad.com
June 8, 2016
NCCN Guidelines Panel: Non-small Cell Lung Cancer

On behalf of Myriad Genetic Laboratories, I respectfully request the NCCN Non-Small Cell Lung Cancer Committee to review the enclosed data for inclusion of the 46-gene molecular prognostic score as an additional high-risk factor when defining high-risk patients with pathologic stage IB (T2a, N0) or IIA (T2b, N0) lung adenocarcinoma (ADC).

Specific Changes: Under NSCL-3 version 4.2016, footnote P "examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy." We recommend the following statement to be listed as an additional high-risk factor: ***For lung ADC, a high-risk 46-gene molecular prognostic score determined by a CLIA-certified RNA expression-based assay.***

Rationale: The results and associated methodologies of the current high-risk factors when considering the use of chemotherapy for pT2a/bN0 lung ADC are mainly prognostic in nature, qualitative, subjective, and highly variable in routine clinical practice – therefore making standardization challenging, expensive and vulnerable to interobserver variability.[1,2] A well-established, cost-effective,[3] and validated CLIA-certified 46-gene RNA expression assay provides a quantitative molecular prognostic score (mPS) that adds independent information not incorporated in the conventional clinicopathological factors used for defining high-risk patients with stage I or II lung ADC.[2-7] Furthermore, patients with potentially curable early stage disease and physicians can benefit from a proven molecular measure of disease aggressiveness similar to other gene assays demonstrating value in the multidisciplinary management of breast and prostate cancers.[8,9]

In addition to the previously published analytical, clinical and cost-utility validations,[3-7] new data distinct from prior studies was published highlighting a well-annotated cohort from MSKCC.[2] This large data set (n=1200) has been referenced and published numerous times; most recently used to guide the IASLC/ATS/ERS and WHO classifications of patients with lung ADC.[10-12] Results from this unique validation conclude that mPS is an independent prognostic marker in multivariable analyses irrespective of all clinical, surgical, pathological, histological and molecular factors of high-risk (HR=1.77; P=0.006).[2] The following key points represent the value of the aforementioned assay:

- 5-year lung cancer-specific survival differed between low-risk and high-risk mPS groups (96% vs 84%; P<0.001) including the identification of patients with high or low risk scores regardless of tumors greater than or less than 4 cm.

- mPS addresses two major limitations of the IASLC/ATS/ERS - WHO grading system: interobserver variability associated with determining predominant subtype and stratifying risk for patients with intermediate-grade (40-70% of lung ADC). In patients with intermediate-grade acinar or papillary predominant subtypes, high mPS was associated with worse 5-year lung cancer-specific survival (P<0.001 and 0.015 respectively), compared with low mPS.
- Increasing mPS is strongly associated (P<0.001) with increasing solid component subtype: objective measure of an otherwise subjective variable.
- mPS; pronounced prognostic discrimination in patients with both less than and greater than 5% micropapillary subtype with limited/wedge resection (P<0.007 and 0.001, respectively).
- mPS predicts mortality risk independently of KRAS and EGFR mutation status (P=0.002)

In light of the arguably subjective and difficult to standardize universally high-risk factors and the conflicting data on the cutoff for tumor size, physicians need additional means to assess risk and treatment options for this early stage patient population. This validated CLIA-certified RNA expression-based signature of cell cycle progression genes is significantly and independently associated with lung cancer prognosis in multiple published large patient cohorts (n=2,272). The 46-gene mPS provides a reproducible, quantitative measure of tumor aggressiveness to be used as a complement to the existing high risk factors and as a means of identifying patients with less aggressive disease – thus helping physicians successfully tailor treatment decisions for patients with stage I or II lung ADC who are at the highest and lowest risk of mortality following curative-intent surgical resection.

Sincerely,

Johnathan Lancaster, MD PhD
Chief Medical Officer

References:

1. Bunn PA, Kim, E. Improving the care of patients with stage IB non-small-cell lung cancer: role of prognostic signatures and use of cell cycle progression biomarkers. *Clinical Lung Cancer* 2015; 16:245-251.
2. Eguchi T, Kadota K, Chaft J, et al. Cell cycle progression score is a marker for five-year lung cancer-specific mortality risk in patients with resected stage I lung adenocarcinoma. *Oncotarget*, 2016, 10.18632/oncotarget.9129.
3. Stenehjem DD, Bellows, BK, Yager KM, et al. Cost-utility of a prognostic test guiding adjuvant chemotherapy decisions in early-stage non-small cell lung cancer. *Oncologist* 2016; 21:196-204.
4. Wistuba II, Behrens C, Lombardi F, et al. Validation of a proliferation-based expression signature as prognostic marker in early stage lung adenocarcinoma. *Clin Cancer Res* 2013; 19:6261-6271
5. Bueno R, Hughes E, Wagner S, et al. Validation of a molecular and pathological model for five-year mortality risk in patients with early stage lung adenocarcinoma. *J Thorac Oncol* 2015; 10:67-73
6. Rakha E, Pajares MJ, Llie M, et al. Stratification of resectable lung adenocarcinoma by molecular and pathological risk estimators. *Eur J Cancer* 2015; 51:1897-1903.
7. Warf MB, Fosso PG, Hughes E, et al: Analytical validation of a proliferation-based molecular signature used as a prognostic marker in early stage lung adenocarcinoma. *Biomark Med* 2015; 9: 901-10
8. Gradishar WJ, Anderson BO, et al. Breast Cancer Version 2.2016. *NCCN Clinical Practice Guidelines in Oncology.* https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
9. Mohler JL, Armstrong AJ, et al. Prostate Cancer Version 3.2016. *NCCN Clinical Practice Guidelines in Oncology.* https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
10. Yoshizawa A, Motoi N, Riely GJ, Sima CS, Gerald WL, Kris MG, Park BJ, Rusch VW and Travis WD. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Mod Pathol* 2011; 24:653-664.
11. Ujiie H, Kadota K, Chaft JE, Buitrago D, Sima CS, Lee MC, Huang J, Travis WD, Rizk NP, Rudin CM, Jones DR and Adusumilli PS. Solid predominant histologic subtype in resected stage I lung adenocarcinoma is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival. *J Clin Oncol* 2015; 33:2877-2884.
12. Nitadori J, Bograd AJ, Kadota K, Sima CS, Rizk NP, Morales EA, Rusch VW, Travis WD and Adusumilli PS. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. *J Natl Cancer Inst* 2013; 105:1212-1220.