

Local Coverage Determination (LCD): MoIDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer (L38327)

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|------------------------------------|---------------|-----------------|--------------|---|
| Noridian Healthcare Solutions, LLC | A and B MAC | 01111 - MAC A | J - E | California - Entire State |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01112 - MAC B | J - E | California - Northern |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01182 - MAC B | J - E | California - Southern |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01211 - MAC A | J - E | American Samoa Guam Hawaii Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01212 - MAC B | J - E | American Samoa Guam Hawaii Northern Mariana Islands |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01311 - MAC A | J - E | Nevada |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01312 - MAC B | J - E | Nevada |
| Noridian Healthcare Solutions, LLC | A and B MAC | 01911 - MAC A | J - E | American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands |

LCD Information

Document Information

LCD ID

L38327

Original Effective Date

For services performed on or after 08/24/2020

LCD Title

MoIDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer

Revision Effective Date

N/A

Proposed LCD in Comment Period

N/A

Revision Ending Date

N/A

Source Proposed LCD

DL38327

Retirement Date

N/A

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Notice Period Start Date

07/09/2020

Notice Period End Date

08/23/2020

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CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are considered to be reasonable and necessary.

42 Code of Federal Regulations (CFR) 410.32(a). Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This policy concerns the use of molecular diagnostic laboratory tests (tests of DNA, RNA, and / or proteins) as a predictive classifier for non-small cell lung cancer (NSCLC).

Molecular classifiers are considered reasonable and necessary when a beneficiary meets all of the following criteria:

1. The patient has a non-squamous NSCLC with a tumor size < 5cm, and there are no positive lymph nodes (*i.e.* American Joint Committee on Cancer Eighth Edition Stages I and IIa)
2. The patient is sufficiently healthy to tolerate chemotherapy
3. Adjuvant platinum-containing chemotherapy is being considered for the patient
4. The test is ordered by a physician who is treating the patient for NSCLC (generally a medical oncologist, surgeon, or radiation oncologist) to help in the decision of whether or not to recommend adjuvant chemotherapy.

Summary of Evidence

Non-Small Cell Lung Cancer (NSCLC) is a deadly cancer with estimated incidence of 41.2 per 100,000 people and an incidence in those 65 years of age and older of 238.1 per 100,000 people.¹ While mortality rates have improved since 1975, the 5-year relative survival is estimated to be only 24.2% for all stages of disease (SEER Summary Stages) and only 60.1% for localized disease, the least advanced stage of disease.¹

Consensus guidelines recommend surgical resection for medically operable NSCLC due to research finding that this mode of therapy gives the greatest chance of cancer survival.² As with many cancers, adjuvant chemotherapy is a possible treatment following resection, and a meta-analysis pooling a number of high quality studies showed that the cisplatin adjuvant treatment tends to improve survival in patients with NSCLC with the benefit being more pronounced in those who have a higher risk disease based on a prior version of AJCC staging criteria.³ Notably, within this meta-analysis adjuvant chemotherapy was not found to improve overall or disease free survival among those with early stage NSCLC, particularly Stage IA NSCLC. Risk grouping based on AJCC staging criteria has remained the basis of identifying groups of patients with NSCLC for selection of treatment intensity,² and AJCC staging criteria have evolved in recent years.

Consensus guidelines from the National Comprehensive Cancer Care Network for the management of NSCLC recommend consideration of chemotherapy for patients with Stage IB and Stage IIA cancer based on the most recent (eight edition) AJCC staging information.² For Stage IA cancer, chemotherapy is not a recommendation. For Stages

IB and IIA cancer adjuvant chemotherapy is recommended to be considered, particularly for patients with additional high risk clinical or pathological factors. For medically operable higher stage disease, adjuvant chemotherapy, in addition to possible radiation, is recommended without further qualification. Notably, in 2017 the American Joint Committee on Cancer released the eighth edition of staging information for NSCLC, which redefined T1a tumors as no longer being tumors < 2 cm, but specifically tumors < 1 cm. The importance of this is that each centimeter of size is associated with increased risk, and tumors smaller than 1 cm have a lower risk than those of 1-2 cm.⁴

While clear clinical and pathologic staging approaches have been developed to risk stratify patients and clear treatment guidelines based risk strata have been published to guide management based on risk strata, disease recurrence is common. One large retrospective study of patterns of disease recurrence in early stage patients undertaken at a single large academic center.⁵ The study reviewed the records of patients who underwent surgery for T1 and T2 and N0 and N1 NSCLC patients and looked for evidence of recurrence in the medical record. Records of 975 patients were reviewed, the majority of whom had Stage IA (45%) or Stage IB (39%) disease. Nearly all patients (96%) had negative surgical margins. Adjuvant chemotherapy was used in 7% and radiation treatment was used in 3%. The rate of local recurrence in this cohort was 23%, and the rate of distant recurrence was 34%, suggesting that disease recurrence is common even among patients with localized margin-negative disease classified as low risk based on available clinical and pathologic data. More recent data from the Surveillance, Epidemiology, and End Results database, shows that even among those patients with localized disease, 5 year survival rates are at around 60%.¹

Molecular Risk Stratification

The frequent recurrence of NSCLC following resection in patients classified as low risk based on clinical and pathologic data motivated the development of a molecular classifier that might be able to more accurately identify which patients are likely to have disease recurrence or metastatic disease.

The Razor 14-Gene Lung Cancer Assay is quantitative PCR analysis designed to be used on formalin-fixed, paraffin embedded lung cancer tissue. The test relies on an algorithmic interpretation of the quantitative PCR data on RNA from 11 cancer-related target genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1).

A study by Kratz and colleagues briefly describes the development of the test and describes clinical validation of the test's predictive ability in two additional cohorts.⁶ The test and algorithmic interpretation were developed using a training cohort of 361 non-squamous resected samples at a single academic medical center. The test was then validated in samples from 433 patients with Stage I disease from hospitals in the Kaiser Permanente Northern California system by Kaiser Permanente Division of Research (KPDOR). Another large scale validation was done on a cohort of 1006 Chinese patients treated at institutions participating in the China Clinical Trials Consortium (CCTC). In the validation components the biopsy samples were sent to a laboratory and data was analyzed by researchers who were blinded to patient outcomes. A risk class of low, intermediate, or high risk was assigned to each biopsy prior to outcome data being released. The investigators studied overall survival in relation to risk score as the primary outcome, and lung-cancer specific mortality in relation to the risk score as a secondary outcome. In the KPDOR Cohort the mean age was 66.6 years with a median of 106 months of survivor follow-up. The 5-year mortality rate (time post-resection) was 43%. The majority of cases (77%) were adenocarcinoma. The KPDOR cohort was strictly Stage I cancers, of which 68% were Stage IA. In the CCTC cohort the mean age was 58.3 years with a median of 53.4 months of survivor follow-up. The 5-year mortality rate (time post-resection) was 42%. The majority of cases (88%) were adenocarcinoma. This cohort contained patients with Stages I, II, and III disease; 47% had stage I disease (24% stage IA and 23% Stage IIA), 22% had stage II disease (7% had Stage IIA disease and 15% had Stage IIB disease), and 26% had stage III disease.

In summary, this initial clinical validation study showed that there were significant differences in overall and cancer-specific survival between molecular classifier risk strata, even among AJCC Stage I patients in the KPDOR cohort. The estimated 5 overall year survival based on molecular risk group for all patients in the KPDOR cohort was 71.4% in the low-risk group, 58.3% in the intermediate-risk group, and 49.2% in the high-risk group. The estimated 5 year lung-cancer specific survival based on molecular risk group for all patients in the KPDOR cohort was 84.6% in the low-risk group, 70.3% in the intermediate-risk group, and 63.3% in the high-risk group. The estimated 5 overall year survival based on molecular risk group for all patients in the CCTC cohort was 74.1% in the low-risk group, 57.4% in the intermediate-risk group, and 44.6% in the high-risk group.

A subsequent study evaluated the ability of the Razor 14-Gene Lung Cancer Assay to identify high risk disease particularly in small node-negative disease from the above cohorts.⁷ In 2012 (prior to the publication of the new AJCC staging information), the authors addressed the issue of whether the assay accurately risk stratifies patients with small tumors, including a subset analysis of tumors < 1 cm. While this group was only 26 patients, they found that risk stratification based on the assay was associated with statistically significant differences in 5 year survival.⁸

Following the development of the assay and retrospective validation studies, the ability of the test to differentiate early recurrence was prospectively studied in a study of 52 patients with non-squamous NSCLC.⁹ The average age was 62 years, with a mean tumor size of 3.23 cm. The study was mostly Stage I patients; 25 Stage IA, 15 Stage IB, 7 Stage IIA, 2 Stage IIB, and 2 Stage IIIA. The median disease-free interval was 10.3 months, and the median lung-cancer specific survival was 10.3 months. Overall mortality was 8%. No recurrences or lung-cancer specific deaths were observed in the low or intermediate risk groups. The recurrence rate was 29% in the high risk group with a lung-cancer specific mortality of 14% in this group.

A more recent observational prospective study using the Razor 14-Gene Lung Cancer Assay in a slightly larger single institution cohort has recently been published.⁷ In this study, 100 consecutive patients with stages IA, IB, and IIA disease treated with a surgical resection between 2011 and 2015 received molecular testing for risk stratification. The sample had a median age of 67.5 years and was composed of 58 Stage IA patients, 32 Stage IB patients, and 10 Stage IIA patients. The treating clinicians were made aware of the results of the molecular classification results, though the decision of whether or not a patient received adjuvant chemotherapy was individualized to the patient. There were 52 patients stratified as molecular low risk, and 48 stratified as molecular high risk, which for this study included both intermediate and high risk classifications. No patients with molecular low risk disease were given adjuvant treatment. The 5-year disease free survival was 93.8% among those with molecular low risk disease and 91.7% among those with molecular high risk disease treated with adjuvant chemotherapy. For those with molecular high risk disease not treated, 5 year disease-free survival was 48.9%.

A study on physician use of the test obtained data from 58 physicians who treated 120 Stage I or II NSCLC patients.¹⁰ The study showed that physicians tended to change management recommendations with regard to the use of chemotherapy ($p < 0.001$ for all patients). There was no significant change between pre- and post-test recommendations for low risk molecular disease ($p = 0.999$) or intermediate risk molecular disease ($p = 0.146$). There was a significant change particularly in the high molecular risk group ($p < 0.001$) with a recommendation to treat 26 of 54 patients with chemotherapy based on pretest information and 44 of 54 patients with chemotherapy based on post-test information.

Analysis of Evidence (Rationale for Determination)

Level of Evidence

Quality: Moderate
Strength: Limited
Weight: Limited

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury¹¹ where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process for Evaluating Genetic Tests.¹² The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

For patients with medically operable NSCLC, surgical resection is a well-accepted treatment, possibly in conjunction with adjuvant chemotherapy with a platinum-based combination and / or radiation in patients with higher risk disease. In consensus guidelines for patients in the lowest risk disease classification, observation only is recommended following surgery. For patients with higher risk disease chemotherapy possibly with radiation is recommended. Current NCCN guidelines rely on clinical and pathologic risk stratification tools, primarily the AJCC schema; molecular markers of risk are not considered in these treatment guidelines. Moreover, evidence shows that even among patients with low risk disease based on clinical and pathologic features, recurrence is common, and that outcomes for those who are likely to have recurrence can be improved in lung cancer with the use of platinum-containing chemotherapy regimens. However, since platinum-containing chemotherapy regimens do not improve survival and may negatively impact survival among lower risk patients, accurate discrimination of those with low from those with high risk disease is critical to successfully improving the outcomes of patients with the use of this treatment. As such, a molecular classifier that can accurately predict who will have disease recurrence or metastatic disease among patients already considered low risk for these outcomes by clinical and pathologic criteria could be used as a decision tool to improve outcomes by helping to determine who is an appropriate candidate for platinum-containing adjuvant treatment so as to improve survival.

Observational evidence has shown that molecular risk stratification with the Razor 14-Gene Lung Cancer Assay enhances risk-stratification among patients with tumors considered low risk based on clinical and pathologic criteria. Since treatment intensity, particularly the decision as to whether or not to pursue adjuvant chemotherapy is based on risk grouping, the information provided by the test provides incremental information that can inform physician management so as to improve outcomes. Furthermore, early observational prospective evidence suggests that adjuvant chemotherapy given to patients who do not have a low molecular risk improves disease-free survival to be similar to those with molecular low risk disease.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A57329 - Billing and Coding: MoIDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer

A58271 - Response to Comments: MoIDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer

LCD(s)

DL38327 - MoIDX: Razor 14-Gene Lung Cancer Assay

Related National Coverage Documents

N/A

Public Version(s)

Keywords

N/A