EML4-ALK (81479) Test Description

Biodesix, Inc. provides a blood-based genetic mutation analysis test measuring a patient's genetic profile in order to assist physicians in prescribing targeted therapies without the need for a tissue biopsy. With a minimal blood sample, Biodesix uses droplet digital polymerase chain reaction (ddPCR) methodology to measure echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (EML4-ALK) fusions resulting from genomic rearrangements. Physicians can order EML4-ALK (CPT code 81479) on its own or alongside other clinically actionable mutations. EML4-ALK is a clinically actionable mutation; identification of this via testing is considered standard of care in the treatment of patients with non-small cell lung cancer (NSCLC). Requiring only a simple blood draw, this minimally-invasive, pre-treatment test provides results in less than 72 hours, enabling physicians to make a timely and more-informed decision regarding their patients' therapy options.

Biodesix, Inc. performs all tests in its laboratory in Boulder, Colorado. The laboratory is accredited by CLIA (#06D2085730), New York State, and other states where required by law. Copies of certificates and licenses are available upon request. While there is an available CPT code for an EML4-ALK test (81401), it is specific to a single mutation or fusion. The Biodesix EML4-ALK test measures 4 fusions. If appropriately cross-walked based on Medicare pricing guidelines, the Biodesix EML4-ALK test should be priced at the rate of $190 x 4, or $760. Because of the similarity between the performance of the Biodesix EML4-ALK test and *EGFR* mutation testing for which Medicare reimbursement is $329.51 (CPT code 81235), Biodesix recommends that Medicare reimburse the EML4-ALK test at a minimum of the established Medicare rate for *EGFR* testing of $329.51.Currently, the most appropriate code for this test is 81479.

The ddPCR methodology performed by Biodesix has been validated in many peer-reviewed publications and journals since the late 1990's. A study about ddPCR by Vogelstein et al set the precedence for use of this methodology to identify predefined mutations by proving feasibility in identifying mutation of the *ras* oncogene.[i] Blood-based genotyping for the detection of actionable mutations using ddPCR continues to be at the forefront of blood-based mutation detection in advanced lung cancer, and patients with EML4-ALK positive tumors have targeted therapy options available to them that are FDA approved.[ii,iii]

To further prove the effectiveness of the ddPCR EML4-ALK test, Biodesix performed concordance analysis comparing results from tissue using FISH testing with results from the ddPCR technique. Results show 85% sensitivity, 100% specificity, and 95% concordance with FISH tissue testing.[iv] This high level of concordance demonstrates that blood-based testing through ddPCR is an accurate testing method for EML4-ALK. Importantly, blood-based testing can eliminate the need for additional biopsy to get sufficient tissue for FISH testing.

Targeted treatments for EML4-ALK patients have been approved by the Federal Drug Administration (FDA) after showing large improvements in tumor response and progression free survival compared to chemotherapy.

The Local Coverage Determination (LCD) L35396 *Biomarkers for Oncology* describes EML4-ALK and ROS1 mutations as indicated, predictive biomarkers for crizotinib therapy, and that testing for both biomarkers should provide adequate predictive information for patients with locally advanced or metastatic NSCLC. [v] EML4-ALK testing is considered medically necessary for those patients with a diagnosis of locally advanced or metastatic NSCLC that are tested on or after Dates of Service of October 1, 2015.

EML4-ALK targeted therapies can improve patient quality of life (QOL) and outcomes in those patients where the mutation is present. However, tissue based testing, which necessitates tissue biopsies, are a barrier to effectively and rapidly testing patients who may benefit from targeted treatments. The EML4-ALK test offered by Biodesix utilizes a simple blood draw and returns results in 72 hours, offering a non-invasive, timely, actionable result for physicians and their patients.

[i] Vogelstein, B., and K. W. Kinzler. "Digital PCR." Proceedings of the National Academy of Sciences 96.16 (1999): 9236-241.

[ii] Sacher AG, Paweletz C, Dahlberg SE, Alden RS, O'Connell A, Feeney N, Mach SL, Jänne PA, Oxnard GR. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol. [Published Online April 7th 2016]

[iii] Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small–cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27:4247-4253.

[iv] Foreman, T et al. Development of a Rapid Blood-based Test for EGFR Sensitizing and Resistance Mutations in NSCLC. Poster presented at AACR-NCI-EORTC International Conference on Molecular Targets
and Cancer Therapeutics, 2015, Nov 5-9; Boston, MA.

[v] Local Coverage Determination Biomarkers for Oncology (L35396) effective 10/01/2015 [12 Apr 2016]; Available from https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35396&ContrId=331&ver=22&ContrVer=1&Date=10%2f01%2f2015&DocID=L35396&SearchType=Advanced&bc=KAAAAAgAAAAAAA%3d%3d&

ROS-1 (81401) Test Description

Biodesix, Inc. provides a blood-based genetic mutation analysis test measuring a patient's genetic profile in order to assist physicians in prescribing targeted therapies without the need for a tissue biopsy. With a minimal blood sample, Biodesix uses droplet digital polymerase chain reaction (ddPCR) methodology to measure gene rearrangements that involve the Proto-oncogene 1 tyrosine-protein kinase (ROS-1). Physicians order ROS-1 utilizing CPT code 81401 on its own or alongside other clinically actionable mutations. ROS-1 is a clinically actionable variant in lung cancer and other tumor types. Identification of the fusion transcripts that result from ROS-1 rearrangements via testing is considered standard of care in the treatment of patients with non-small cell lung cancer (NSCLC) specifically. Requiring only a simple blood draw, this minimally-invasive, pre-treatment test provides results in less than 72 hours, enabling physicians to make a timely and more-informed decision regarding their patients' therapy options.

Biodesix, Inc. performs all tests in its laboratory in Boulder, Colorado. The laboratory is accredited by CAP, CLIA (#06D2085730), New York State, and other states where required by law. Copies of certificates and licenses are available upon request. There is no specific CPT code for a ROS-1 test using ddPCR methodology. Current CPT Code descriptions for ROS-1 are specific to the FISH methodology, and those laboratories utilizing FISH bill ROS-1 with CPT code 88271. The Biodesix ROS-1 test measure 8 fusions. Biodesix measures multiple fusions for ROS1 which is similar process for EML4-ALK. As a result, we base our pricing of ROS-1 on EML4-ALK. The FISH ALK CPT Code (81404) price is priced at $274.83. If appropriately cross-walked based on Medicare pricing guidelines, the Biodesix ROS-1 test would be appropriately priced at the rate of $274.83 x 8, or $2198.64. Because of the similarity between the performance of the Biodesix ROS-1 to *EGFR* mutation testing for which Medicare reimbursement is $331.82 (CPT code 81235), Biodesix recommends that Medicare reimburse the ROS-1 test at a minimum of the established Medicare rate for *EGFR* testing of $331.82.

The ddPCR methodology performed by Biodesix has been validated in many peer-reviewed publications and journals since the late 1990's. A study about ddPCR by Vogelstein et al set the precedence for use of this methodology to identify predefined mutations by proving feasibility in identifying mutation of the *ras* oncogene.[i] Blood-based genotyping for the detection of actionable mutations using ddPCR continues to be at the forefront of blood-based mutation detection in advanced lung cancer, and patients with ROS-1 positive tumors have targeted therapy options available to them that are FDA approved.[ii,iii]

To further prove the effectiveness of the ddPCR tests, Biodesix performs concordance analysis comparing results from tissue using FISH testing with results from the ddPCR technique. This was done for clinical validation for ALK which is the same workflow as for ROS-1. The clinical validation is published in Mellert et al. ROS-1 analytical validation studies demonstrate that the Lower Limit of Detection (LOD) for the ddPCR-based assay is 0.2% minor variant frequency.[iv] The high level of concordance for the EML4-ALK fusion transcript test demonstrates that blood-based testing through ddPCR is an accurate testing method for ROS-1. Importantly, blood-based testing can eliminate the need for additional biopsy to get sufficient tissue for FISH testing.

The Predictive and Prognostic Biomarkers section of the NCCN Guidelines® for NSCLC states that testing for ROS-1 gene rearrangements is recommended for patients with non-squamous or not otherwise specified disease so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as crizotinib.[v] Targeted treatments for ROS-1 patients have been approved by the Federal Drug Administration (FDA) after showing large improvements in tumor response and progression free survival compared to chemotherapy. Additionally, this section of the guidelines mentions the use of other methods that are being evaluated as acceptable methods by NCCN® standards.

ROS-1 targeted therapies can improve patient quality of life (QOL) and outcomes in those patients where these mutations are present. However, tissue based testing, which necessitates tissue biopsies, are a barrier to effectively and rapidly testing patients who may benefit from targeted treatments. The ROS-1 test offered by Biodesix utilizes a simple blood draw and returns results in 72 hours, offering a non-invasive, timely, actionable result for physicians and their patients.

[i] Vogelstein, B., and K. W. Kinzler. "Digital PCR." Proceedings of the National Academy of Sciences 96.16 (1999): 9236-241.

[ii] Sacher AG, Paweletz C, Dahlberg SE, Alden RS, O'Connell A, Feeney N, Mach SL, Jänne PA, Oxnard GR. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol. [Published Online April 7th 2016]

[iii] Roschild, S. "Targeted Therapies in Non-Small Cell Lung Cancer—Beyond EGFR and ALK" Cancers 2015, 7, 930-949; doi:10.3390/cancers7020816

[iv] Mellert H, Foreman T, Jackson L, et al. Development and Clinical Utility of a Blood-based Test Service for the Rapid Identification of Actionable Mutations in NSCLC. Journal of Molecular Diagnostics May 2017
Blood-based Test Service for the Rapid Identification of Actionable Mutations in NSCLC Journal of Molecular Diagnostics May 2017 (Online Apirl)

[v] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer, V5.2017 .N.C.C.N., Inc. 2016. All rights reserved. Accessed April 14, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

RET (81404) Test Description

Biodesix, Inc. provides a blood-based genetic mutation analysis test measuring a patient's genetic profile in order to assist physicians in prescribing targeted therapies without the need for a tissue biopsy. With a minimal blood sample, Biodesix uses droplet digital polymerase chain reaction (ddPCR) methodology to measure gene rearrangements that involve rearranged during transfection (RET) genes. Physicians can order RET testing utilizing the CPT code 81404 on its own or alongside other clinically actionable mutations. RET arrangements are known as clinically actionable variants measured in patients with lung cancer as well as some other tumor types. Identification of the fusion transcripts that result from RET rearrangements via testing is considered standard of care in the treatment of patients with non-small cell lung cancer (NSCLC) specifically. Requiring only a simple blood draw, this minimally-invasive, pre-treatment test provides results in less than 72 hours, enabling physicians to make a timely and more-informed decision regarding their patients' therapy options.

Biodesix, Inc. performs all tests in its laboratory in Boulder, Colorado. The laboratory is accredited by CAP, CLIA (#06D2085730), New York State, and other states where required by law. Copies of certificates and licenses are available upon request.

The ddPCR methodology performed by Biodesix has been validated in many peer-reviewed publications and journals since the late 1990's. A study about ddPCR by Vogelstein et al set the precedence for use of this methodology to identify predefined mutations by proving feasibility in identifying mutation of the *ras* oncogene.[i] Blood-based genotyping for the detection of actionable mutations using ddPCR continues to be at the forefront of blood-based mutation detection in advanced lung cancer, and patients with RET positive tumors (tumors that have RET rearrangements) have targeted therapy options that are under development for approval by the FDA. [ii,iii]

The Predictive and Prognostic Biomarkers section of the NCCN Guidelines® for NSCLC states that testing for RET gene rearrangements is recommended for patients with non-squamous or not otherwise specified disease so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as crizotinib.[iv] Targeted treatments for RET positive patients are under development for future approval by the Federal Drug Administration (FDA) after showing large improvements in tumor response and progression free survival compared to chemotherapy. Additionally, this section of the guidelines mentions the use of other methods that are being evaluated as acceptable methods by NCCN® standards. In addition to crizotinib, Cabozantinib for RET rearrangements is recommended based on data from a Phase II study. Another targeted therapy for RET includes Alectinib, a small molecule inhibitor that targets RET. Other targeted therapies are being developed according to the newest NCCN Guidelines including vandetabib.

RET targeted therapies can improve patient quality of life (QOL) and outcomes in those patients where either of these mutations are present. However, tissue based testing, which necessitates tissue biopsies, are a barrier to effectively and rapidly testing patients who may benefit from targeted treatments. The RET test offered by Biodesix utilizes a simple blood draw and returns results in 72 hours, offering a non-invasive, timely, actionable result for physicians and their patients.

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[i] Vogelstein, B., and K. W. Kinzler. "Digital PCR." Proceedings of the National Academy of Sciences 96.16 (1999): 9236-241.

[ii] Sacher AG, Paweletz C, Dahlberg SE, Alden RS, O'Connell A, Feeney N, Mach SL, Jänne PA, Oxnard GR. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. JAMA Oncol. [Published Online April 7th 2016]

[iii] Roschild, S. "Targeted Therapies in Non-Small Cell Lung Cancer—Beyond EGFR and ALK" Cancers 2015, 7, 930-949; doi:10.3390/cancers7020816

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