Epidermal Growth Factor Receptor (EGFR) Mutation Analysis Excluding Non-Small Cell Lung Cancer

Medical Policy #: 02.04.55
Original Effective Date: June 2016
Reviewed: May 2022
Revised: May 2021

DESCRIPTION

***Note**: This policy addresses Epidermal Growth Factor Receptor (EGFR) mutation analysis for all indications **except** non-small cell lung cancer (NSCLC). EGFR mutation analysis for non-small cell lung cancer (NSCLC) see medical policies: 02.04.78 Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer and 02.04.79 Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy).*

Epidermal Growth Factor Receptor (EGFR) (also called HER1 gene or ERBB1 gene) is a gene that makes a protein that is involved in cell growth and cell survival. EGFR activating mutations are found in exons 18 to 21 of the EGFR gene, which is part of the gene coding for the tyrosine kinase domain of the EGFR protein. Targeted therapies directed to tumors harboring activating mutations within the EGFR tyrosine kinase

domain (exons 18-21) have demonstrated some success in treating a subset of patients with non-small cell lung cancer (NSCLC) (see medical policies referenced above). Because of its critical role in tumor aggressiveness, EGFR has been an attractive target for anticancer therapy in cancers other than non-small cell lung cancer (NSCLC).

The functional activation of EGFR via mutation or amplification/overexpression has been identified in many tumor types, including but not limited to head and neck, gastroesophageal, breast, genitourinary, cutaneous, and colorectal cancers, and has been associated with proliferation, invasion, and metastasis. Alterations in EGFR have also been linked to primary resistance and accelerated tumor growth (designated as hyperprogression) from immune checkpoint inhibitors. However, EGFR amplification and overexpression in tissue have not been well established as reliable biomarkers for anti-EGFR agents for anything other than non-small cell lung cancer (NSCLC). The potential reasons include heterogeneity between primary and metastatic lesions, dynamic changes in genomic alterations that may emerge along with therapeutic pressure or progression, presence of genomic coalterations associated with resistance, and potential differences in response to copy number gain due to aneuploidy versus focal EGFR amplification.

There are two main sample types used for EGFR mutation analysis either tumor tissue using Real Time PCR, Sanger Sequencing or Next Generation Sequencing (NGS) or circulating tumor DNA.

Based on review of the peer reviewed medical literature prior studies looking at the relationship between EGFR amplification and therapeutic response to EGFR inhibitors have shown inconsistent results for patients with a wide range of malignancies. While EGFR amplification/overexpression is associated with cancer aggressiveness, previous studies failed to demonstrate tissue-based assessment of EGFR overexpression to be a reliable biomarker to predict clinical outcomes after anti-EGFR therapies except in non-small cell lung cancer (NSCLC). Current NCCN guidelines for solid tumors do not recommend EGFR mutation analysis except for certain clinical situations for non-small cell lung cancer (NSCLC). To date, there are various anti-EGFR therapies that are U.S. Food and Drug Administration (FDA) approved, including erlotinib, gefitinib, afatinib, and osimertinib for non–small-cell lung cancer (NSCLC) with specific activating EGFR mutations, and cetuximab and panitumumab for colorectal cancer without KRAS or NRAS mutations.

Summary of Evidence

Because of its critical role in tumor aggressiveness, EGFR has been an attractive target for anticancer therapy in cancers other than non-small cell lung cancer (NSCLC) such as head and neck, gastroesophageal, breast, genitourinary, cutaneous, and colorectal cancers. Studies have failed to demonstrate that tissue-based or circulating tumor DNA assessment of EGFR overexpression to be a reliable biomarker to predict clinical outcomes after anti-EGFR therapies except in non-small cell lung cancer (NSCLC). Current NCCN guidelines do not recommend EGFR mutation analysis except for certain

clinical situations for non-small cell lung cancer (NSCLC). The evidence is insufficient to determine the effects of the technology on net health outcomes in cancer management except for non-small cell lung cancer (NSCLC), whether performed as an individual test or as part of an expanded panel test.

Practice Guideline and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines

Acute Lymphoblastic Leukemia Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of acute lymphoblastic leukemia.

Acute Myeloid Leukemia Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of acute myeloid leukemia.

Ampullary Adenocarcinoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of ampullary adenocarcinoma.

Anal Carcinoma Version 1.2021
Does not include guidelines related to testing for EGFR in the management of anal carcinoma.

Basal Cell Skin Cancer Version 3.2022
Does not include guidelines regarding testing for EGFR in the management of basal cell skin cancer.

B-Cell Lymphomas Version 3.2022
Does not include any guidelines regarding testing for EGFR in the management of B-cell lymphomas

Bladder Cancer Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of bladder cancer.

Bone Cancer Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of bone cancer.

Breast Cancer Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of breast cancer.

Central Nervous System Cancers Version 2.2021
Lung Cancer
Systemic treatment options for patients with brain metastases from NSCLC include immunotherapy agents and targeted therapies for cancer that is anaplastic lymphoma kinase (ALK) rearrangement-positive and EGFR mutation – positive.

Treatment for Limited Metastatic Lesions
In patients with systemic cancers with options for CNS-active systemic therapies (e.g., ALK or EGFR mutations in NSCLC; BRAF mutations in metastatic melanoma), upfront systemic therapy alone may be considered in carefully selected, asymptomatic patients.

Does not include guidelines regarding testing for EGFR in the management except when related to brain metastases from NSCLC.

Cervical Cancer Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of cervical cancer.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of chronic lymphocytic leukemia/small lymphocytic lymphoma.

Chronic Myeloid Leukemia Version 3.2022
Does not include guidelines regarding testing for EGFR in the management of chronic myeloid leukemia.

Colon Cancer Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of colon cancer.

Dermatofibrosarcoma Protuberans Version 1.2021
Does not include guidelines regarding testing for EGFR in the management of dermatofibrosarcoma protuberans.

Esophageal and Esophagogastric Junction Cancers Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of esophageal and esophagogastric junction cancers.

Gastric Cancer Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of gastric cancer.

Gastrointestinal Stromal Tumors (GISTs) Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of gastrointestinal stromal tumors (GISTs).

Gestational Trophoblastic Neoplasia Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of gestational trophoblastic neoplasia

Hairy Cell Leukemia Version 1.2022
Does not include any information regarding testing for EGFR in the management of hairy cell leukemia

Head and Neck Cancers Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of head and neck cancers.

Hepatobiliary Cancers Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of hepatobiliary cancers.

Histiocytic Neoplasms Version 2.2021
Does not include guidelines regarding testing for EGFR in the management of histiocytic neoplasms.

Hodgkin Lymphoma Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of Hodgkin lymphoma.

Kaposi Sarcoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of Kaposi Sarcoma.

Kidney Cancer Version 4.2022
Does not include guidelines regarding testing for EGFR in the management of kidney cancer

Malignant Pleural Mesothelioma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of malignant pleural mesothelioma.

Melanoma: Cutaneous Version 3.2022
Does not include guidelines regarding testing for EGFR in the management of cutaneous melanoma.

Melanoma: Uveal Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of uveal melanoma.

Merkel Cell Carcinoma Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of Merkel cell carcinoma.

Multiple Myeloma Version 5.2022
Does not include guidelines regarding testing for EGFR in the management of multiple myeloma.

Myelodysplastic Syndromes Version 3.2022
Does not include guidelines regarding testing for EGFR in the management of myelodysplastic syndromes.

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes.

Myeloproliferative Neoplasms Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of myeloproliferative neoplasms.

Neuroendocrine and Adrenal Tumors Version 4.2021
Does not include guidelines regarding testing for EGFR in the management of neuroendocrine and adrenal tumors.

Occult Primary Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of occult primary.

Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of ovarian cancer including fallopian tube cancer and primary peritoneal cancer.

Pancreatic Adenocarcinoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of pancreatic adenocarcinoma.

Pediatric Acute Lymphoblastic Leukemia Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of pediatric acute lymphoblastic leukemia.

Pediatric Aggressive Mature B-Cell Lymphomas Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of pediatric aggressive mature B-cell lymphomas.

Pediatric Hodgkin Lymphoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of pediatric Hodgkin lymphoma.

Penile Cancer Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of penile cancer.

Primary Cutaneous Lymphomas Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of primary cutaneous lymphomas.

Prostate Cancer Version 3.2022
Does not include guidelines regarding testing for EGFR in the management of prostate cancer.

Rectal Cancer Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of rectal cancer.

Small Bowel Adenocarcinoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of small bowel adenocarcinoma.

Small Cell Lung Cancer Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of small cell lung cancer.

Small Tissue Sarcoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of small tissue sarcoma.

Squamous Cell Skin Cancer Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of squamous cell skin cancer.

Systemic Light Chain Amyloidosis Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of systemic light chain amyloidosis.

Systemic Mastocytosis Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of systemic mastocytosis.

T-Cell Lymphomas Version 1.2022
Does not include any information regarding testing for EGFR in the management of T-cell lymphomas.

Testicular Cancer Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of testicular cancer.

Thymomas and Thymic Carcinomas Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of thymomas and thymic carcinomas.

Thyroid Carcinoma Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of thyroid carcinoma.

Uterine Neoplasms Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of uterine neoplasms.

Vulvar Cancer (Squamous Cell Carcinoma) Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of vulvar cancer.

Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2022
Does not include guidelines regarding testing for EGFR in the management of Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma.

Wilms Tumor (Nephroblastoma) Version 1.2022
Does not include guidelines regarding testing for EGFR in the management of Wilms tumor.

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA).

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) (liquid biopsy) for cancer management is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer LDTs must be licensed by CLIA for high complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

EGFR mutation analysis using Real Time PCR, Sanger Sequencing or Next Generation Sequencing (NGS) are commercially available and these tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA).

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies:

- 02.04.79 Circulating Tumor DNA for Management of Non-Small Cell Lung Cancer (Liquid Biopsy)
- 02.04.78 Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer

Epidermal Growth Factor Receptor (EGFR) mutation analysis is considered **investigational** for all indications except for non-small cell lung cancer (NSCLC) whether performed as an individual test or as part of an expanded panel test.

Note: *For Epidermal Growth Factor Receptor (EGFR) mutation analysis related to non-small cell lung cancer (NSCLC) see the above related medical policies.*

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81235 EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

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- National Comprehensive Cancer Network (NCCN) Acute Myeloid Leukemia 1.2022
- National Comprehensive Cancer Network (NCCN) Ampullary Adenocarcinoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Anal Carcinoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Basal Cell Skin Cancer Version 3.2022
- National Comprehensive Cancer Network (NCCN) B-cell Lymphomas Version 3.2022
- National Comprehensive Cancer Network (NCCN) Bladder Cancer Version 1.2022
- National Comprehensive Cancer Network (NCCN) Bone Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Breast Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Central Nervous System Cancers Version 2.2021
- National Comprehensive Cancer Network (NCCN) Cervical Cancer Version 1.2022
- National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2022
- National Comprehensive Cancer Network (NCCN) Chronic Myeloid Leukemia Version 3.2022
- National Comprehensive Cancer Network (NCCN) Colon Cancer Version 1.2022
- National Comprehensive Cancer Network (NCCN) Dermatofibrosarcoma Protuberans Version 2.2022

- National Comprehensive Cancer Network (NCCN) Esophageal and Esophagogastric Junction Cancers Version 2.2022
- National Comprehensive Cancer Network (NCCN) Gastric Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Gastrointestinal Stromal Tumors (GISTs) Version 1.2022
- National Comprehensive Cancer Network (NCCN) Gestational Trophoblastic Neoplasia Version 1.2022
- National Comprehensive Cancer Network (NCCN) Hairy Cell Leukemia Version 1.2022
- National Comprehensive Cancer Network (NCCN) Head and Neck Cancers Version 2.2022
- National Comprehensive Cancer Network (NCCN) Hepatobiliary Cancers Version 1.2022
- National Comprehensive Cancer Network (NCCN) Histiocytic Neoplasms Version 2.2021
- National Comprehensive Cancer Network (NCCN) Hodgkin Lymphoma Version 2.2022
- National Comprehensive Cancer Network (NCCN) Kaposi Sarcoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Kidney Cancer Version 4.2022
- National Comprehensive Cancer Network (NCCN) Malignant Pleural Mesothelioma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Melanoma Cutaneous Version 3.2022
- National Comprehensive Cancer Network (NCCN) Melanoma Uveal Version 2.2022
- National Comprehensive Cancer Network (NCCN) Merkel Cell Carcinoma Version 2.2022
- National Comprehensive Cancer Network (NCCN) Multiple Myeloma Version 5.2022
- National Comprehensive Cancer Network (NCCN) Myelodysplastic Syndromes Version 3.2022
- National Comprehensive Cancer Network (NCCN) Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 1.2022
- National Comprehensive Cancer Network (NCCN) Myeloproliferative Neoplasms Version 2.2022
- National Comprehensive Cancer Network (NCCN) Neuroendocrine and Adrenal Tumors Version 4.2021
- National Comprehensive Cancer Network (NCCN) Occult Primary Version 1.2022
- National Comprehensive Cancer Network (NCCN) Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2022
- National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma Version 1.2022

- National Comprehensive Cancer Network (NCCN) Pediatric Acute Lymphoblastic Leukemia Version 1.2022
- National Comprehensive Cancer Network (NCCN) Pediatric Aggressive Mature B-cell Lymphoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Pediatric Hodgkin Lymphoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Penile Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas Version 1.2022
- National Comprehensive Cancer Network (NCCN) Prostate Cancer Version 3.2022
- National Comprehensive Cancer Network (NCCN) Rectal Cancer Version 1.2022
- National Comprehensive Cancer Network (NCCN) Small Bowel Adenocarcinoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Small Cell Lung Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Small Tissue Sarcoma Version 2.2022
- National Comprehensive Cancer Network (NCCN) Squamous Cell Skin Cancer Version 1.2022
- National Comprehensive Cancer Network (NCCN) Systemic Light Chain Amyloidosis Version 1.2022
- National Comprehensive Cancer Network (NCCN) T-Cell Lymphomas Version 1.2022
- National Comprehensive Cancer Network (NCCN) Testicular Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Thymomas and Thymic Carcinomas Version 1.2022
- National Comprehensive Cancer Network (NCCN) Thyroid Carcinoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Uterine Neoplasms Version 1.2022
- National Comprehensive Cancer Network (NCCN) Vulvar Cancer (Squamous Cell Carcinoma) Version 1.2022
- National Comprehensive Cancer Network (NCCN) Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2022
- National Comprehensive Cancer Network (NCCN) Wilms Tumor (Nephroblastoma) Version 1.2022

POLICY HISTORY		
Date	**Reason**	**Action**
May 2022	Annual Review	Policy Renewed
May 2021	Annual Review	Policy Revised
May 2020	Annual Review	Policy Renewed
September 2019	Interim Review	Policy Revised
May 2019	Annual Review	Policy Revised
May 2018	Annual Review	Policy Revised
May 2017	Annual Review	Policy Revised
June 2016	New Policy	Policy Implemented

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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