Protocol

Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC)

(20445)

Medical Benefit		**Effective Date**: 07/01/14	**Next Review Date**: 05/15
Preauthorization	No	**Review Dates**: 05/09, 05/10, 05/11, 05/12, 05/13, 05/14	

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. ***Preauthorization is not required.*** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Description

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (TK) frequently overexpressed and activated in non-small cell lung cancer (NSCLC). Mutations in two regions of the *EGFR* gene (exons 18-24)—small deletions in exon 19, and a point mutation in exon 21 (L858R)—appear to predict tumor response to tyrosine kinase inhibitors (TKIs) such as erlotinib. This Protocol summarizes the evidence for using EGFR mutations to decide which patients with advanced NSCLC should be considered for erlotinib therapy and which are better suited for alternative therapies.

Background

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease. (1) When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of eight to 11 months and a one-year survival of 30% to 45%. (2, 3)

Laboratory and animal experiments have shown that therapeutic blockade of the EGFR pathway could be used to halt tumor growth in solid tumors that express EGFR. (4) These observations led to the development of two main classes of anti-EGFR agents for use in various types of cancer: small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies that block EGFR-ligand interaction. (5)

Three orally administered EGFR-selective small molecule TKIs have been identified for use in treating NSCLC: gefitinib (Iressa®, AstraZeneca), erlotinib (Tarceva®, OSI Pharmaceuticals), and afatinib (Gilotrif™, Boehringer Ingelheim). Only erlotinib and afatinib are approved by the U.S. Food and Drug Administration (FDA); gefitinib may be continued in patients already receiving gefitinib in the U.S.

FDA Status

Erlotinib received initial FDA approval in 2004 for second-line treatment of patients with advanced NSCLC. In 2013, erlotinib indications were expanded to include first-line treatment of patients with metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations. (6) A companion diagnostic test, the cobas® *EGFR* Mutation Test, was coapproved for this indication. Afatinib was FDA-approved in July 2013 for first-line treatment of patients with metastatic NSCLC with *EGFR* exon 19 deletions or L858R mutations. (7) A companion diagnostic test, the therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, was coapproved for this indication.

Both tests are polymerase chain reaction (PCR) assays. FDA-approved product labels for both erlotinib and afatinib indicate that *EGFR* mutations must be "detected by an FDA-approved test" but do not specify which test must be used.

Policy (Formerly Corporate Medical Guideline)

Except as noted below, analysis of two types of somatic mutation within the EGRF gene—small deletions in exon 19 and a point mutation in exon 21 (L858R) may be considered **medically necessary** to predict treatment response to erlotinib or afatinib in patients with advanced lung adenocarcinoma or in whom and adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of two types of somatic mutation within the EGRF gene – small deletions in exon 19 and a point mutation in exon 21 (L858R) is considered **investigational** for patients with advanced NSCLC of squamous cell-type.

Analysis for other mutations within exons 18-24, or other applications related to NSCLC is considered **investigational**.

Policy Guideline

The test is intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutations in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor gene are considered good candidates for treatment with erlotinib and afatinib. Patients found to be wild type are unlikely to respond to erlotinib or afatinib; other treatment options should be considered.

Current (2014) guidelines from the National Comprehensive Cancer Network recommend *EGFR* mutation testing:

- for patients with advanced lung cancer, nonsquamous cell type; or
- when biopsy specimens are small and histology is mixed.

Current (2014) guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend:

- *EGFR* mutation testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history);
- In the setting of fully excised lung cancer specimens, *EGFR* mutation testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and
- In the setting of more limited lung cancer specimens (e.g., biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, *EGFR* testing may be performed in cases showing squamous cell histology. Clinical criteria (e.g., young age, lack of smoking history) may be useful to select a subset of these samples for testing.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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