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

Policy # 00289
Original Effective Date: 03/16/2011
Current Effective Date: 09/17/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC) is addressed separately in medical policy 00122.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider except as noted below, analysis of two types of somatic mutation within the epidermal growth factor receptor (EGFR) gene—small deletions in exon 19 and a point mutation in exon 21 (L858R) to predict treatment response to erlotinib or afatinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (See Background/Overview) to be **eligible for coverage.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers analysis of 2 types of somatic mutation within the epidermal growth factor receptor (EGFR) gene—small deletions in exon 19 and a point mutation in exon 21 (L858R) for patients with advanced non-small cell lung cancer (NSCLC) of squamous cell-type to be **investigational.***

Based on review of available data, the Company considers analysis for other mutations within exons 18-24, or other applications related to non-small cell lung cancer (NSCLC), to be **investigational.***

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

Background/Overview

Epidermal growth factor receptor is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. Mutations in 2 regions of the *EGFR* gene (exons 18-24) —small deletions in exon 19 and a point

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mutation in exon 21 (L858R)—appear to predict tumor response to tyrosine kinase inhibitors (TKIs) such as erlotinib. This policy 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.

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. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%.

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. These observations led to the development of 2 main classes of anti-EGFR agents for use in various types of cancer: small molecule TKIs and monoclonal antibodies that block EGFR-ligand interaction.

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.

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 (eg, 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 (eg, biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, *EGFR* testing may be performed in cases showing squamous cell histology. Clinical criteria (eg, young age, lack of smoking history) may be useful to select a subset of these samples for testing.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration
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. 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. 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

Rationale/Source

Two publications demonstrated that the underlying molecular mechanism underpinning dramatic responses in these favorably prognostic groups appeared to be the presence of activating somatic mutations in the TK domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R, indicating substitution of leucine by arginine at codon position 858). These can be detected by direct sequencing or PCR technologies.

A Technology Evaluation Center (TEC) Assessment on this topic was first published in November 2007. The Assessment concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of *EGFR* mutation testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC. This Assessment was updated in 2010, with revised conclusions indicating that *EGFR* mutation testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.

A 2013 meta-analysis of 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression free survival (PFS) in EGFR mutation-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy. (Comparisons were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively.) Among EGFR mutation-negative patients, PFS was improved with EGFR TKIs compared with placebo maintenance but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either mutation-positive or mutation-negative patients. Statistical heterogeneity was not reported for any outcome. The authors concluded that EGFR mutation testing is indicated to guide treatment selection in NSCLC patients.

Erlotinib

Thirteen publications provide data on *EGFR* mutations in tumor samples obtained from NSCLC patients in erlotinib treatment studies. Nine of these were nonconcurrent-prospective studies of treatment-naïve and previously-treated patients who received erlotinib and were then tested for the presence or absence of mutations; 4 (see Table 1) were prospective 1-arm enrichment studies of mutation-positive or wild-type patients treated with erlotinib. In 3 studies of *EGFR* mutation-positive patients, objective radiologic response

was 40% to 70%, median PFS was 8 to 14 months, and median OS was 16 to 29 months. In patients with wild-type tumors, objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months.

Table 1. Clinical Response in Prospective Studies of Erlotinib Therapy in Patients With *EGFR* Gene Mutation-Positive Advanced NSCLC[a]

Study (Year)	No. Mutated/ No. Tested (%)	Objective Radiologic Response (%)	Median PFS (95% CI), mo	Median OS (95% CI), mo
***EGFR*mutation positive**				
Jackman et al (2009) Prospective 1-arm treatment *EGFR*-positive patients with erlotinib, chemotherapy naïve	84 enrolled	70	13	28.7
Rosell et al (2009) Prospective 1-arm treatment *EGFR*-positive patients with erlotinib in treatment failure and chemotherapy naïve	350/2105 (16.6)	70	14 (11.3 to 16.7)	27 (24.9 to 33.1)
Sun et al (2010) Prospective 1-arm treatment *EGFR*-positive patients with erlotinib in treatment failures	144/164 (32)	40	8	15.8
***EGFR*mutation negative (wild type)**				
Yoshioka et al (2010) Prospective 1-arm treatment *EGFR* wild-type patients with erlotinib in treatment failures	30 enrolled	3.3	2.1	9.2

CI: confidence interval; OS: overall survival; PFS: progression-free survival.
[a] All patients had stage IIIA/IV NSCLC.

Zhou et al reported the results of a Phase 3 prospective clinical trial of first-line treatment of Chinese patients with *EGFR* mutation (exon 19 deletion or L858R)-positive NSCLC (87% adenocarcinoma)

randomized to treatment with erlotinib (n=83) or standard chemotherapy (gemcitabine plus carboplatin, n=82). PFS was significantly longer in patients who received erlotinib (13.1 vs 4.5 months; hazard ratio [HR], 0.16; p<0.001). Patients treated with erlotinib experienced fewer grade 3 and 4 toxic effects and more clinically relevant improvements in quality of life than those who received chemotherapy. These results were duplicated in a European population in the 2012 EURTAC trial (NCT00446225), a multicenter, open-label, randomized Phase 3 trial. Adult patients with *EGFR* mutations (exon 19 deletion or L858R mutation in exon 21) with NSCLC were randomized. Eighty-six received erlotinib, and 87 received standard chemotherapy. A planned interim analysis showed that the primary end point had been met. At the time the study was halted (Jan 26, 2011), median PFS was 9.7 months (95% confidence interval [CI], 8.4 to 12.3) vs 5.2 months (95% CI, 4.5 to 5.8) in the erlotinib and standard chemotherapy groups, respectively (HR=0.37; 95% CI, 0.25 to 0.54; p<0.001). Six percent of patients receiving erlotinib had treatment-related severe adverse events compared with 20% of those receiving a standard chemotherapy regimen.

Petrelli et al reported a meta-analysis of 13 randomized trials of 1260 patients with *EGFR* mutated NSCLC who received TKIs for first-line, second-line, or maintenance therapy, and compared outcomes with standard therapy. Overall, they noted that in patients, use of *EGFR* TKIs increased the chance of obtaining an objective response almost 2-fold when compared with chemotherapy. Response rates were 70% vs 33% in first-line trials and 47% vs 28.5% in second-line trials. Tyrosine kinase inhibitors reduced the hazard of progression by 70% in all trials and by 65% in first-line trials; however, they did not improve OS.

In a pooled analysis of patients with *EGFR* mutations (most commonly exon 19 deletions and L858R substitution mutations in exon 21), median PFS was 13.2 months in patients treated with erlotinib and 5.9 months in patients treated with standard chemotherapy (p<0.001). Patients with *EGFR* mutations appear to be ideal candidates for treatment with erlotinib. Identification of patients likely to respond or fail to respond to erlotinib leads to tailored choices of treatment likely to result in predictable and desirable outcomes.

Nine other studies totaling 630 patients have compared outcomes in *EGFR* mutation-positive and *EGFR* wild-type patients who were treated with erlotinib (see Table 2).

- Objective radiologic response rates ranged from 0% to 83% (median, 45%) in patients with *EGFR* mutation-positive tumors and from 0% to 18% (median, 5.5%) in patients with wild-type tumors. All 5 studies that statistically evaluated results demonstrated statistically significant increases in objective radiologic response among patients with *EGFR* mutation-positive tumors.
- Progression free survival ranged from 6.8 to 13.1 months (median, 12.5) in patients with *EGFR* mutation-positive tumors and from 1.4 to 5 months (median, 2.5) in patients with wild-type tumors. In all studies in which these data were reported, patients with *EGFR* mutation-positive tumors showed a trend or a statistically significant increase in PFS.
- Overall survival ranged from 10 to 35 months (median, 21) in patients with *EGFR* mutation-positive tumors and from 3 to 12 months (median, 8.1) in patients with wild-type tumors. In all cases in which these data were reported, *EGFR* mutation-positive tumors showed a trend or a statistically significant increase in OS.

Table 2. Outcomes in Patients According to *EGFR* Mutation Status in Response to Treatment With Erlotinib (9 studies of 630 patients)

Patients	Overall Radiologic Response (Range), %	Median PFS (Range), mo	Median OS (Range), mo
EGFR mutation-positive patients	45 (0-83)	12.5 (6.8-13.1)	21 (10-35)
Wild-type patients	5.5 (0-18)	2.5 (1.4-5)	8.1 (3-12)
Untested patients (intent to treat) – FDA label	Not reported	2.8	12

OS: overall survival; PFS: progression-free survival.

In a 2013 randomized controlled trial (RCT), Garassino et al in Italy compared the efficacy of erlotinib and docetaxel as second-line therapy in 219 *EGFR* wild-type patients with metastatic NSCLC who had received previous platinum-based therapy. Most patients (69%) had adenocarcinoma; 25% had squamous cell carcinoma (SCC). With a median follow-up of 33 months, median PFS was 2.9 months with docetaxel and 2.4 months with erlotinib (adjusted HR=0.71 95% CI, 0.53 to 0.95; p=0.02). Median OS was 8.2 months with docetaxel and 5.4 months with erlotinib (adjusted HR=0.73; 95% CI, 0.53 to 1.00; p=0.05). Grade 3 or higher skin adverse events occurred in 14% of the erlotinib group and did not occur in the docetaxel group. Grade 3 or higher neutropenia occurred only in the docetaxel group (20%). As stated in an accompanying editorial, "[T]he efficacy of *EGFR* TKIs is very limited for second-line treatment of wild-type *EGFR* NSCLC." A 2013 meta-analysis of 3 trials in patients with wild-type *EGFR* reported improved OS with erlotinib treatment in second and third line and maintenance settings. However, 75% of patients in the control arms in this analysis received placebo.

Epidermal growth factor receptor mutations may provide prognostic information (about disease recurrence and survival), as well as predictive information (about treatment response). In a 2005 study by Eberhard et al, improved outcomes were observed for *EGFR* mutation-positive patients compared with wild-type patients regardless of treatment (standard chemotherapy or standard chemotherapy plus erlotinib). Objective radiologic response was 38% versus 23% (p=0.01), median time to progression was 8 months versus 5 months (p<0.001), and median OS was not reached versus 10 months (p<0.001).

Afatinib
Unlike erlotinib (and gefitinib) that selectively inhibit *EGFR*, afatinib inhibits not only *EGFR* but also human EGFR 2 (*HER2*) and *HER4* and may have activity in patients with acquired resistance to TKIs (who often harbor a *T790M* mutation [substitution of threonine by methionine at codon 790] in *EGFR* exon 20). The efficacy and safety of afatinib was evaluated in the LUX-Lung series of studies.

LUX-Lung 3 was an RCT in 345 patients with stage IIIB or IV, *EGFR* mutation-positive, lung adenocarcinoma who were previously untreated for advanced disease. Seventy-two percent of patients were Asian, 26% were white, and 90% (308 patients) had common *EGFR* mutations (exon 19 deletion or

L858R substitution mutation in exon 21). Patients received either afatinib or chemotherapy (cisplatin plus pemetrexed). In stratified analysis of patients with common *EGFR* mutations, median PFS was 13.6 months for the afatinib group and 6.9 months for the chemotherapy group (HR=0.47; 95% CI, 0.34 to 0.65; p=0.001). Median PFS for the 10% of patients who had other *EGFR* mutations was not reported, but median PFS for the entire patient sample was 11.1 months in the afatinib group and 6.9 months in the chemotherapy group (HR=0.58; 95% CI, 0.43 to 0.78; p=0.001). Incidence of objective response in the entire patient sample was 56% in the afatinib group and 23% in the chemotherapy group (p=0.001). With a median follow-up of 16.4 months, median OS was not reached in any group; preliminary analysis indicated no difference in OS between the 2 treatment groups in the entire patient sample (HR=1.12; 95% CI, 0.73 to 1.73; p=0.60). Patients in the afatinib group reported greater improvements in dyspnea, cough, and global health status/quality of life than those in the chemotherapy group. Grade 3 or higher diarrhea, rash, and paronychia (nail infection) occurred in 14%, 16%, and 11% of afatinib-treated patients, respectively, and in no patients in the chemotherapy group. Grade 3 or higher mucositis (primarily stomatitis) occurred in 9% of the afatinib group and 0.9% of the chemotherapy group.

Three other published LUX-Lung studies evaluated patients with stage IIIB or IV lung adenocarcinoma who were previously treated for advanced disease, but each had design flaws that limit the interpretation of results.

- LUX-Lung 2 was a single-arm study of afatinib in 129 patients (87% Asian, 12% white) with *EGFR* mutation-positive disease. Patients had been treated with previous chemotherapy but not with EGFR-targeted therapy; approximately half of patients (enrolled after a protocol amendment) were chemotherapy-naïve. Objective responses (primarily partial responses) were observed in 66% of 106 patients with common *EGFR* mutations (exon 19 deletion or L858R) and in 39% of 23 patients with other *EGFR* mutations. Median PFS was 13.7 months in patients with common *EGFR* mutations and 3.7 months in patients with other *EGFR* mutations (p values not reported). Results for mutation-negative patients were not reported.
- LUX-Lung 1 and LUX-Lung 4 enrolled patients who had progressed on previous erlotinib, gefitinib, or both for advanced disease. Neither study prospectively genotyped patients. In the LUX-Lung 1 double-blind RCT, 96 of 585 enrolled patients (66% Asian, 33% white) were *EGFR* mutation-positive (76 common *EGFR* mutation-positive). In this group, median PFS was 3.3 months in the afatinib group and 1.0 month in the placebo group (HR=0.51; 95% CI, 0.31 to 0.85; p=0.009). In 45 mutation-negative patients, median PFS was 2.8 months in the afatinib group and 1.8 months in the placebo group, a statistically nonsignificant difference (p=0.22), possibly due to small group sizes. LUX-Lung 4 was a single-arm study of afatinib in 62 Japanese patients. Objective responses occurred in 2 of 36 patients with common *EGFR* mutations (5%) and in none of 8 patients with other *EGFR* mutations (p>0.05).

EGFR Mutation Frequency

Rosell et al reported *EGFR* mutations in 16.6% of the overall patient sample but noted an increased prevalence in women (69.7%), patients who never smoked (66.6%), and patients with adenocarcinomas (80.9%). Based on these findings, Rosell et al recommended *EGFR* mutation screening in women with lung cancer with nonsquamous cell tumors who have never smoked. Other reports on the mutation frequencies

have found higher prevalences among East Asians when compared with other ethnicities (38% vs 15%, respectively). Although there is a greater proportion of *EGFR* mutations in these special populations (women, never smokers, patients with adenocarcinoma, and/or Asians), many patients without these selected demographics still exhibit *EGFR* mutations and would benefit from erlotinib treatment.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al reported *EGFR* mutations in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies. Although histology appeared to be the strongest discriminator, results varied across studies; for example, Eberhard et al observed *EGFR* mutations in 6.4% of patients with SCCs and Rosell et al in 11.5% of patients with large cell carcinomas. (Both of these studies had small sample sizes.)

For patients with SCC, current guidelines from the National Comprehensive Cancer Network (NCCN) indicate that the low incidence of *EGFR* mutations in SCC "does not justify routine testing of all tumor specimens." This conclusion is based on the Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) that reported an observed *EGFR* mutation incidence of 2.7% in patients with SCC with an upper confidence limit for the true incidence of 3.6%. NCCN guidelines recommend consideration of mutation testing in never smokers with SCC or when biopsy specimens are small and histology is mixed. This recommendation was based on a case series of 13 patients with squamous or pseudosquamous histology. However, 7 patients (54%) were subsequently determined to have adenocarcinoma histology. All 6 remaining patients were never smokers, and all 6 had an exon 19 deletion or L858R substitution mutation in *EGFR.*

In 2013, the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology published joint evidence-based guidelines for molecular testing to select EGFR TKI therapy in patients with lung cancer. An *EGFR* mutation incidence of 0% to 5% in patients with SCC was reported. Recommendations for *EGFR* mutation testing in patients with SCC depend on tumor sample availability:

- For fully excised lung cancer specimens, *EGFR* testing is not recommended when an adenocarcinoma component is lacking, eg, tumors with pure squamous cell histology with no immunohistochemistry evidence of adenocarcinoma differentiation (eg, thyroid transcription factor 1 [TTF-1] or mucin positive). (Evidence grade A, excellent quality evidence)
- When lung cancer specimens are limited (eg, biopsy, cytology) and an adenocarcinoma component cannot be completely excluded, *EGFR* testing may be performed in cases showing squamous cell histology; clinical criteria (eg, lack of smoking history) may be useful to select a subset of these samples for testing. (Evidence grade A, excellent quality evidence)

Two studies may support the potential value of *EGFR* mutation testing in patients with SCC, particularly in Asian populations. However, similar studies have not been reported in non-Asian populations or in populations treated with erlotinib. A 2009 study by Park et al of preselected Korean patients treated with gefitinib reported *EGFR* mutations in 3 of 20 male smokers with SCC (15%), a patient subgroup expected to have a low prevalence of *EGFR* mutations based on demographics. Clinical response was observed in 2 of

3 mutation-positive patients and 1 of 17 wild-type patients; median PFS was 5.8 months in patients with mutated *EGFR* and 2.4 months in the wild-type group (p=0.07). In vivo analyses by Dobashi et al showed that in Japanese patients with both adenocarcinomas and SCCs, *EGFR* mutations were associated with downstream phosphorylation of *EGFR* and constitutive activation of the *EGFR* pathway.

In contrast, Fang et al (2013) reported *EGFR* mutations (all L858R) in 2% (3 patients) of 146 consecutively treated Chinese patients with early stage SCC. In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never smokers, 21% women), *EGFR* mutation prevalence (all exon 19 deletion or L858R) was 23.8%. Objective response occurred in 26.7% of 15 *EGFR* mutation-positive and 2.1% of 48 mutation-negative patients (p=0.002). Median PFS was 3.9 months and 1.9 months, respectively (p=0.19). Based on these findings, the authors concluded that routine *EGFR* mutation testing of all SCC specimens is not justified.

EGFR Mutation Testing
Gene sequencing is generally considered an analytic gold standard. In 2010, the Canadian Agency for Drugs and Technologies in Health published a rapid response report on *EGFR* mutation analysis. Based on 11 observational studies, the report authors concluded that PCR-based approaches identify *EGFR* mutations with a sensitivity equivalent to that of direct sequencing.

Summary
Several RCTs, nonconcurrent prospective studies, and single-arm enrichment studies demonstrate that detection of *EGFR* gene mutations identifies patients with non-small-cell lung cancer (NSCLC) who are likely to benefit from erlotinib or afatinib therapy and who are therefore ideal candidates for treatment with these drugs. These observations have been made in populations of patients with primarily adenocarcinomas. Currently, there is no little evidence to indicate that *EGFR* mutation testing can guide treatment selection in patients with squamous cell histology.

Patients who are found to have wild-type tumors are unlikely to respond to erlotinib or afatinib. These patients should be considered candidates for alternative therapies.

Epidermal growth factor receptor mutational analysis may be considered medically necessary to predict treatment response to erlotinib or afatinib in patients with advanced NSCLC; however, *EGFR* mutational analysis is investigational in patients with NSCLC of squamous cell type.

National Comprehensive Cancer Network (NCCN) Guidelines
The NCCN's current clinical practice guidelines for the treatment of NSCLC (version 2.2014, discussion update in progress) recommend *EGFR* mutational analysis in patients with advanced NSCLC, nonsquamous cell type. "Erlotinib is recommended as first-line therapy in patients with sensitizing *EGFR* mutations and should not be given as first-line therapy to patients negative for these *EGFR* mutations or with unknown *EGFR* status." Afatinib is recommended as first- or second-line therapy "for select patients with sensitizing *EGFR* mutations." In patients with SCC, *EGFR* mutation testing should be considered

"especially in" never smokers; when histology is assessed using small biopsy specimens (rather than surgically resected samples); or when histology is mixed adenosquamous.

American Society of Clinical Oncology Provisional Clinical Opinion
In 2011, the American Society of Clinical Oncology issued a provisional clinical opinion on *EGFR* mutation testing for patients with advanced NSCLC who are considering first-line *EGFR* TKI therapy. The authors concluded that such patients who have not previously received chemotherapy or an *EGFR* TKI should undergo *EGFR* mutation testing to determine whether chemotherapy or an *EGFR* TKI is appropriate first-line treatment.

College of American Pathologists Joint Guideline
In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR TKI therapy. Based on excellent quality evidence (category A), the guidelines recommend *EGFR* mutation testing in patients with lung adenocarcinoma regardless of clinical characteristics, such as smoking history. Guidelines for *EGFR* mutation testing in patients with SCC are reviewed in the Rationale section of the policy (see *EGFR* Mutation Frequency).

American College of Chest Physicians Guidelines
American College of Chest Physicians updated its evidence-based clinical practice guidelines on the treatment of stage IV NSCLC in 2013. Based on their review of the literature, guideline authors reported improved response rates, PFS, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with *EGFR* mutations, especially exon 19 deletion and L858R. ACCP recommends "testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line *EGFR* TKIs if mutation-positive."

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Coding

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

Policy # 00289
Original Effective Date: 03/16/2011
Current Effective Date: 09/17/2014

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81235, 88342, 88365
HCPCS	No codes
ICD-9 Diagnosis	162.0 thru 163.9, 231.2
ICD-9 Procedure	No codes

Policy History

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03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. New policy.
07/07/2011	Medical Policy Committee review
07/20/2011	Medical Policy Implementation Committee approval. Policy statement changed from investigational to eligible for coverage for two types of mutations in NSCLC that are not of squamous cell type.
06/28/2012	Medical Policy Committee review
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/23/2013	Coding updated
09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. Specified that non-small cell lung cancer is “of nonsquamous cell type” in the eligible for coverage statement.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Eligible for Coverage statement changed to include the drug afatinib. In the Eligible for Coverage section, replaced, “non-small cell lung cancer (NSCLC) of nonsquamous cell type” to “advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (See Background/Overview).”

Next Scheduled Review Date: 09/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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