Over half of patients with non-small cell lung cancer (NSCLC) present with advanced and therefore incurable disease, and treatment in this setting has generally been with platinum-based chemotherapy. More recently, the identification of specific, targetable oncogenic “driver” mutations in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

### Related Policies
- KRAS Mutation Analysis in Non-Small-Cell Lung Cancer

### Policy
Except as noted below, analysis of 2 types of somatic mutation within the EGFR 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 an adenocarcinoma component cannot be excluded (see Policy Guidelines).

Analysis of 2 types of somatic mutation within the EGFR 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 EGFR mutations within exons 18 to 24, or other applications related to NSCLC, is considered investigational.

Analysis of somatic mutations of the KRAS gene is considered investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC.

Testing for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered investigational.

### Policy Guidelines
These tests are 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. Current (2014) guidelines from the National Comprehensive Cancer Network (NCCN) 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.

Effective in 2013, there is a specific CPT code for testing for common variants of EGFR:

- 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)

Prior to the creation of code 81235, no specific CPT codes were available, and this laboratory test would likely have been coded using a series of nonspecific genetic testing codes. One laboratory website listed the following group of CPT codes for this testing: 83907, 83900(x2), 83901(x18), 83891, 83896(x29), 83898(x6), 88381, 83914(x29), 83912-26.

If testing is done by immunohistochemical assay, CPT code 88342 would likely be reported. If testing is done by fluorescence in situ hybridization (FISH), CPT code 88365 would likely be reported.

Testing for mutations in the other genes listed above would be reported with the unlisted molecular pathology code 81479 unless a more specific code exists such as 81275 for KRAS, 81404/81405 for RET or 81406 for BRAF.

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as
investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### Rationale

#### Background

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiotherapy, 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 8 to 11 months and a 1-year survival of 30% to 45%.\(^2,3\) More recently, the identification of specific, targetable oncogenic “driver” mutations in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. Testing for EGFR mutations in clinical decision making for the treatment of NSCLC is routine. The use of testing for other mutations to direct targeted therapy is not well established and continues to evolve.

**EGFR**

The EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small molecule TKIs). These targeted therapies dampen signal transduction through pathways downstream to the EGF receptor, such as the RAS/RAF/MAPK cascade. RAS proteins are G-proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Mutations in 2 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 TKIs such as erlotinib.

The prevalence of EGFR mutations in NSCLC varies by population, with the highest prevalence in non-smoking Asian women, with adenocarcinoma, in whom EGFR mutations have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.

**KRAS**

The KRAS gene (which encodes RAS proteins) can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EGFR receptor. Mutations in the KRAS gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

**ROS**

ROS1 codes for a receptor TK of the insulin receptor family, and chromosomal rearrangements result in fusion genes. The prevalence of ROS1 fusions in NSCLC varies from 0.9% to 3.7%.\(^4\) Patients with ROS1 fusions are typically never smokers with adenocarcinoma.
RET
RET (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported. RET fusions occur in 0.6% to 2% of NSCLCs and in 1.2% to 2% of adenocarcinomas.

MET
MET amplification is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR-TKIs.

BRAF
RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the BRAF gene is the most frequently mutated in NSCLC, in approximately 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the mutations in NSCLC are non-V600E mutations. Most BRAF mutations occur more frequently in smokers.

HER2
HER2 is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. HER2 is expressed in approximately 25% of NSCLC. HER2 mutations are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.

Targeted Therapies
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), although originally FDA approved, in 2004, a phase 3 trial that suggested gefitinib was not associated with a survival benefit. In May 2005, FDA revised gefitinib labeling further limiting its use to patients who had previously benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib.

For the treatment of KRAS-mutated NSCLC, EGFR TKIs and anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Cetuximab may be used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy. Panitumumab is not generally used in NSCLC.

Proposed targeted therapies for the remaining genetic alterations in NSCLC that are addressed in this policy are trastuzumab and afatinib for HER2 mutations, crizotinib for MET amplification, and ROS1 rearrangement, vemurafenib and dabrafenib for BRAF mutations and cabozantinib for RET rearrangements.

Regulatory 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. 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 which test must be used.

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 Act (CLIA). To date, FDA has chosen not to require any regulatory review of this test.

**Rationale**

**EGFR**

Two publications\(^7\),\(^8\) 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 tyrosine kinase (TK) domain of the epidermal growth factor receptor (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 TEC Assessment on this topic was first published in November 2007.\(^9\)\(^9\) 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 non-small cell lung cancer (NSCLC). This Assessment was updated in 2010,\(^10\) with revised conclusions indicating that EGFR mutation testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.\(^10\)

A 2013 meta-analysis\(^11\) 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 tyrosine kinase inhibitors (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\(^12\)-\(^20\) 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,\(^21\)-\(^23\) objective radiologic response was 40% to 70%, median PFS was 8 to 14 months, and median overall survival (OS) was 16 to 29 months. In patients with wild-type tumors,\(^24\) 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 NSCLCa

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>No. Mutated/No. Tested (%)</th>
<th>Objective Radiologic Response (%)</th>
<th>Median PFS (95% CI), mo</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutation positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackman et al (2009)</td>
<td>84 enrolled</td>
<td>70</td>
<td>13</td>
<td>28.7</td>
</tr>
<tr>
<td>Rosell et al (2009)</td>
<td>350/2105 (16.6)</td>
<td>70</td>
<td>14 (11.3 to 16.7)</td>
<td>27 (24.9 to 33.1)</td>
</tr>
<tr>
<td>Sun et al (2010)</td>
<td>144/164 (32)</td>
<td>40</td>
<td>8</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>EGFR mutation negative (wild type)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshioka et al (2010)</td>
<td>30 enrolled</td>
<td>3.3</td>
<td>2.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

CI: confidence interval; OS: overall survival; PFS: progression-free survival.

*a All patients had stage IIIA/IV NSCLC.

In 2011, 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) versus 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.

In 2011, 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% versus 33%.
in first-line trials and 47% versus 28.5% in second-line trials. TKIs 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 2010 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.

PFS 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.

OS 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)

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

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, “The efficacy of EGFR tyrosine kinase inhibitors 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
EGFR 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 epidermal growth factor receptor 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,36 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.37 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**

In 2009, Rosell et al22 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 al38 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 history appeared to be the strongest discriminator, results varied across studies; for example, Eberhard et al17 observed EGFR mutations in 6.4% of patients with SCCs and Rosell et al22 in 11.5% of patients with large cell carcinomas. (Both of these studies had small sample sizes.)

For patients with SCC, guidelines from the National Comprehensive Cancer Network (NCCN)39 indicate that the low incidence of EGFR mutations in SCC does not justify routine testing of all tumor specimens.39 This conclusion is based on the Sanger Institute’s Catalogue of Somatic Mutations in Cancer (COSMIC)40 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.39 This recommendation was based on a case series of 13 patients with squamous or pseudosquamous histology.41 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.42 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, e.g., tumors with pure squamous cell histology with no immunohistoc hemey evidence of adenocarcinoma differentiation (e.g., thyroid transcription factor 1 [TTF-1] or mucin positive). (Evidence grade A, excellent quality evidence)*
When lung cancer specimens are limited (e.g., biopsy, cytology) and an adenocarcinoma component cannot be completely excluded, EGFR testing may be performed in cases showing squamous cell histology; clinical criteria (e.g., 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 criterion 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.

Ongoing and Unpublished Clinical Trials

A search of online ClinicalTrials.gov in September 2014 found several phase 3 trials in patients with NSCLC and EGFR mutations, assessing several different TKIs and clinical scenarios, including a TKI versus chemotherapy, a TKI +/- chemotherapy, use of TKIs in first versus subsequent lines of therapy and use of TKIs in the neoadjuvant setting.

Section Summary

Several RCTs, nonconcurrent prospective studies, and single-arm enrichment studies demonstrate that detection of epidermal growth factor receptor (EGFR) gene mutations identifies patients with 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 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.
EGFR 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.

**KRAS**

**KRAS and EGFR Tyrosine Kinase Inhibitors**

Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from post hoc analyses of 2 phase 3 trials of TKIs in patients with wild-type (nonmutated) versus KRAS-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and 2 meta-analyses.

Pao et al (2005) were the first to suggest that patients with KRAS-mutated lung tumors were nonresponsive to treatment with EGFR tyrosine kinase inhibitors (TKIs). Thirty-six patients with bronchioloalveolar carcinoma underwent KRAS mutation analysis; 9 (25%) were found to harbor KRAS mutations. Response was by a single radiologist, who was blinded to patient outcome, using RECIST (Response Evaluation Criteria in Solid Tumors). None of 9 patients with KRAS-mutated tumors responded to erlotinib (p=0.553).

Zhu et al (2008) performed a post hoc subgroup analysis of KRAS mutations in patients with advanced NSCLC who had failed standard chemotherapy and had been previously randomized to receive erlotinib or placebo. The original Phase 3 trial (National Cancer Institute of Canada Clinical Trials Group Study BR.21; 2005) was the first to demonstrate a significant survival advantage with the use of an EGFR TKI in previously treated NSCLC patients. In post hoc analysis, 206 (28%) of the original 731 tumors were tested for KRAS mutations, which were identified in 30 patients (15%). Among the 206 tested patients, 118 (57%) were assessable for response to erlotinib. Of 98 patients with wild-type KRAS, 10 (10.2%) responded to erlotinib; of 20 patients with mutated KRAS, 1 patient (5.0%) responded (HR [erlotinib vs placebo] in patients with mutated KRAS, 1.67; 95% CI, 0.62 to 4.50; p=0.31; HR in wild-type patients, 0.69; 95% CI, 0.49 to 0.97; p=0.03). In Cox regression, the interaction between KRAS mutation status and treatment was not statistically significant (p=0.09).

Eberhard et al (2005) performed a post hoc subgroup analysis of KRAS mutations in previously untreated patients with advanced NSCLC who had been randomly assigned to receive chemotherapy with or without erlotinib. Of the original 1079 patients, tumor DNA from 274 patients (25%) was sequenced for KRAS mutations. Baseline demographics between patients with available tumor DNA and those without were balanced. KRAS mutations were detected in 55 of 274 patients (21%). Response rate for patients with wild-type KRAS was 26%, regardless of treatment received. In patients with KRAS-mutated tumors, response rate was 8% for those receiving chemotherapy with erlotinib and 23% for those receiving chemotherapy alone (p=0.16; 95% CI for difference: -5% to 35%); median OS was 4.4 months (95% CI, 3.4 to 12.9) in patients who received erlotinib and 13.5 months (95% CI, 11.1 to 15.9) in those who received chemotherapy alone (p=0.019).

In a 2007 Phase 2, multicenter, open-label study, Jackman et al evaluated treatment response to erlotinib in chemotherapy-naive patients 70 years of age or older who had advanced NSCLC. Of 80 patients eligible for treatment, 41 (51%) had KRAS mutation analysis; 6 patients (15%) were mutation-positive, none of whom responded to erlotinib. Five (14%) of 35 patients with wild-type KRAS had a partial response.

In a 2008 phase 2 trial, Miller et al assessed response to erlotinib in 101 patients with lung bronchioloalveolar carcinoma (n=12) or adenocarcinoma, bronchioloalveolar subtype.
Eighteen patients (18%) had KRAS-mutated tumors, and none of them responded to erlotinib (95% CI, 0% to 19%; p<0.01). In patients without a KRAS mutation, response rate was 32%. Median OS in patients with KRAS-mutated tumor was 13 months versus 21 months in patients with KRAS wild-type tumor (p=0.30).

In a 2006 Phase 2 trial, Giaccone et al studied response to erlotinib in 53 chemotherapy-naive patients with advanced NSCLC. Histologic material was available to assess KRAS mutational status from 29 patients, 10 of whom (34%) had mutations. All 10 were nonresponders to erlotinib (p=0.125).

In 2009, Boldrini et al reported on the association between KRAS and EGFR mutation status and several clinical variables in 411 patients with lung adenocarcinoma, and presented a subgroup analysis of tumor response in patients treated with erlotinib or gefitinib. KRAS mutations were observed in 17.9% of all patients. The subset analysis comprised 21 women with stage IV disease who received a TKI as second- or third-line therapy and were assessed for radiographic tumor response using RECIST. Mean age of this subpopulation at the time of diagnosis was 60.8 years (range 40-86). Nineteen (90%) of 21 women were KRAS wild-type, and of those, 8 (42%) showed partial response, 4 (21%) had stable disease, and 7 (37%) had progressive disease. Two patients with KRAS mutations had progressive disease.

Schneider et al (2008) reported on the relationship between clinical benefit and putative tumor markers in a subgroup of patients participating in a global open-label, single-arm study of erlotinib in advanced NSCLC, involving 7043 patients in 52 countries (the TRUST study). The subgroup in this publication was from German centers and comprised 311 patients with stage III/IV disease who were treated with erlotinib because they had failed or were not medically suitable for standard first-line chemotherapy. Tumor response was assessed using RECIST. Seventeen patients (15%) had KRAS mutations, and none had a response to erlotinib; 2 patients had stable disease. The impact of KRAS mutation status on OS (p=0.06) and PFS (p not reported) was of borderline statistical significance. The authors concluded that current data did not support selection of patients for treatment with erlotinib on the basis of tumor molecular characteristics and that further studies were needed to determine definitively whether patients with KRAS mutations can derive survival benefit from erlotinib.

Two meta-analyses on the relationship between KRAS mutations and response to EGFR TKI therapy are outlined next. Data were insufficient to make a determination about an association between KRAS mutation status and PFS or OS in these meta-analyses.

Linardou et al (2008) performed a meta-analysis of 17 studies with 1008 patients, 165 (16.4%) of whom had a KRAS mutation. Eligible studies reported response (complete or partial) stratified by KRAS mutational status. Primary end points were sensitivity and specificity of KRAS testing, defined as KRAS mutation carriers showing no response to erlotinib (stable disease or progressive disease) and KRAS wild-type patients showing a response, respectively. Sensitivity and specificity were assessed overall and in subgroups defined by TKI received (gefitinib and/or erlotinib), response criteria (RECIST or World Health Organization), possible selection bias, and previous chemotherapy, if any. There was no significant difference in sensitivity or specificity across subgroups. The presence of a KRAS mutation was associated with a lack of response to TKIs (sensitivity: 0.21; 95% CI, 0.16 to 0.28; specificity: 0.94; 95% CI, 0.89 to 0.97; positive likelihood ratio: 3.52; negative likelihood ratio: 0.84). (For the analysis, likelihood ratios were calculated by using pooled estimates for sensitivity and specificity.) The authors concluded that KRAS mutations conferred a high level of resistance to anti-EGFR therapies; however, this conclusion is tentative due to limitations of the study, such as lack of individual patient data.
Prospective validation is needed. Furthermore, incomplete reporting of survival data precluded meaningful assessment of the effect of KRAS mutation on survival. Other limitations included heterogeneity of response end points, treatment regimens, and patient selection criteria, and the retrospective design of included studies.

Mao et al (2010) performed a meta-analysis of 22 studies in 1470 patients with NSCLC (1335 [91%] evaluable for response), 231 (17%) of whom had KRAS mutations. Studies were heterogeneous in patient populations (smoking history, tumor histology, stage, ethnicity, treatment received) and response criteria. The primary end point was objective response rate, defined as the sum of complete and partial response. Objective response rates for patients with mutated KRAS and wild-type KRAS were 3% and 26%, respectively. Incomplete reporting of survival data precluded meaningful assessment of the effect of KRAS status on survival in NSCLC patients treated with EGFR TKIs. Data for PFS and OS stratified by KRAS status were available in 8 studies. Median PFS in KRAS-mutated and wild-type patients was 3.0 months and 3.9 months, respectively. Median OS in KRAS-mutated and wild-type patients was 4.7 months and 10.7 months, respectively. However, only 2 studies presented hazard ratios with 95% confidence intervals for PFS and OS, and therefore, pooled analysis to derive an overall HR was not performed.

Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single institution in China. Patients with mutated KRAS were random matched on tumor, node, metastasis (TNM) stage, time of first visit within 1 year, and histology, to both EGFR mutation-positive and KRAS/EGFR wild-type patients. Seventy patients (4%) received EGFR TKI therapy. In this group, median PFS was 11.8 and 2.0 months in patients with EGFR and KRAS mutations, respectively, and 1.9 months in wild-type patients; in comparison with wild-type patients, PFS was statistically longer in patients with EGFR mutations (p < 0.001) but no different in patients with KRAS mutations (p = 0.48). The authors observed that “the presence of an EGFR mutation, but not a KRAS mutation, was predictive of responsiveness to EGFR TKI treatment.”

Fiala et al (2013) reported on a retrospective analysis of patients with squamous cell NSCLC who underwent EGFR, KRAS, and PIK3CA (phosphatidylinositol-3-kinase catalytic subunit-alpha) mutation testing. Of 215 patients tested, 16 (7.4%) had mutated KRAS. Of 174 tested patients who were treated with an EGFR TKI (erlotinib or gefitinib), median PFS in KRAS-mutated patients was 1.3 months versus 2.0 months in KRAS wild-type patients (n=160 [92%]); the difference was not statistically significant (Kaplan-Meier [KM] log-rank test, p = 0.120). Median OS in this treated group was 5.7 months in KRAS-mutated patients versus 8.2 months in KRAS wild-type patients, a statistically significant difference (KM log-rank test, p = 0.039). The authors concluded that KRAS mutation status may have a negative prognostic role but a predictive role was not confirmed. “Patients with squamous cell NSCLC harboring these mutations could benefit from targeted treatment and should not be excluded from treatment with EGFR TKIs.”

Two reviews published in 2013 concluded that, in comparison with KRAS mutation testing, EGFR mutation status is the preferred predictive marker for response to EGFR TKIs in patients with NSCLC.59, 60

**KRAS and Anti-EGFR Monoclonal Antibodies**

Two Phase 3 trials, BMS-099 and FLEX, investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC. Subsequently, investigations of KRAS mutation status and cetuximab treatment were performed for both trials.

In the multicenter Phase 3 BMS099 trial (2010), 676 chemotherapy-naïve patients with stage IIIIB/IV NSCLC were assigned to taxane and carboplatin with or without
cetuximab. The primary end point was PFS; secondary end points were overall response rate, OS, quality of life, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. There was a trend in OS favoring cetuximab; however, this was not statistically significant. A post hoc correlative analysis of this trial was conducted to identify molecular markers for the selection of patients most likely to benefit from cetuximab. Of the original 676 enrolled patients, 202 (29.9%) had tumor samples available for KRAS testing. KRAS mutations were present in 35 patients (17%). Among patients with wild-type KRAS, OS was similar between the cetuximab-containing arm (n=85) and the chemotherapy alone arm (n=82) (HR=0.93; 95% CI, 0.67 to 1.30; \( p=0.68 \); median survival, 9.7 and 9.9 months, respectively). Among patients with KRAS mutations, OS was similar between the cetuximab-containing arm (n=13) and the chemotherapy-alone arm (n=22) (HR=0.91; 95% CI, 0.45 to 2.07; \( p=0.93 \); median survival, 16.8 and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions between the presence of KRAS mutations and outcomes evaluated; treatment differences favoring the addition of cetuximab in the KRAS-mutated subgroup were consistent with those observed in the wild-type KRAS subgroup and in the overall study population. The authors concluded that the results do not support an association between KRAS mutation and lack of cetuximab benefit similar to that observed in patients with KRAS-mutated metastatic colorectal cancer. However, results should be interpreted with caution due to small subgroup sample sizes and retrospective nature of the analysis.

In this open-label, randomized, Phase 3 FLEX trial, 1125 chemotherapy-naive patients with stage III/IV, NSCLC were randomly assigned to receive either chemotherapy (cisplatin and vinorelbine) plus cetuximab (n=557) or chemotherapy alone (n=568). The primary end point was OS. Patients who received chemotherapy plus cetuximab survived longer than those who received chemotherapy only (median OS, 11.3 months vs 10.1 months, respectively; HR for death, 0.87; 95% CI, 0.76 to 1.00; \( p=0.04 \)). Subsequently, KRAS mutation testing was performed on archival tumor tissue of 395 (35%) of 1125 patients. KRAS mutations were detected in 75 tumors (19%). Among patients with mutated KRAS, OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (median OS, 8.9 months vs 11.1 months, respectively; HR=1.00; 95% CI, 0.60 to 1.66; \( p=1.0 \)). Among patients with wild-type KRAS, OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (median OS, 11.4 months vs 10.3 months, respectively; HR=0.96; 95% CI, 0.75 to 1.23; \( p=0.74 \)). PFS also was similar in cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR=0.97; 95% CI, 0.76 to 1.24) and wild-type (HR=0.84; 95% CI, 0.50 to 1.40) KRAS. Response rates in the cetuximab-containing arm in patients with KRAS-mutated and wild-type tumors were 36.8% and 37.3%, respectively (\( p=0.96 \)). Overall, there was no indication that KRAS mutation status was predictive of cetuximab effect in NSCLC.

**Ongoing and Unpublished Clinical Trials**

A phase 3 trial is currently recruiting patients to assess PFS and secondarily OS with dacomitinib, another selective TKI, compared with erlotinib for the treatment of advanced NSCLC in patients who have received 1 or more prior anti-cancer therapies. (NC1013605554) KRAS mutation status will be collected at baseline. Estimated enrollment is 800, with an estimated study completion date of September 2014.
Section summary

**KRAS and EGFR Tyrosine Kinase Inhibitors**

Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from post hoc analysis of 2 phase 3 trials that compared TKI efficacy in patients with wild-type (nonmutated) versus KRAS-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and 2 meta-analyses. Although studies have shown that KRAS mutations in patients with NSCLC confer a high level of resistance to TKIs, data are insufficient to assess any association between KRAS mutation status and survival in these patients.

**KRAS and Anti-EGFR Monoclonal Antibodies**

A lack of response to EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and use of these drugs is largely restricted to patients with wild-type KRAS. The expectation that KRAS mutation status also would be an important predictive marker for cetuximab response in NSCLC has not been shown. In 2 randomized trials with post hoc analyses of KRAS mutation status and use of cetuximab with chemotherapy, KRAS mutations did not identify patients who would not benefit from anti-EGFR antibodies, as outcomes with cetuximab were similar regardless of KRAS mutation status.

**ROS**

Bergethon et al conducted a retrospective analysis of the clinical characteristics and treatment outcomes of patients with NSCLC with a ROS1 rearrangement. The authors screened 1073 patients from multiple institutions for ROS1 rearrangements using a FISH assay and correlated ROS1 status with clinical characteristics, OS, and when available, ALK rearrangement status. Clinical data were extracted from medical record review. In vitro studies with human NSCLC cell lines were also conducted to assess the responsiveness of cells with ROS1 rearrangements to crizotinib. Of the tumors that were screened, 18 (1.7%) had ROS1 rearrangements, and 31 (2.9%) had ALK rearrangements. All of the ROS1-positive tumors were adenocarcinomas. The patients with ROS1 rearrangements were significantly younger (median age 49.8 years) and more likely to be never-smokers, when compared with the ROS1-negative group (each p < .001). There was no survival difference observed between the ROS1-positive and negative groups. The in vitro studies showed evidence of sensitivity to crizotinib. Finally, the authors reported the clinical response of 1 patient in their study with a ROS1 rearrangement. The patient was enrolled as part of an expanded phase I cohort, in an open-label, multicenter trial of crizotinib. The patient had no EGFR mutation or ALK rearrangement. After treatment failure with erlotinib, the patient was treated with crizotinib and had near complete resolution of tumor without evidence of recurrence at 6 months.

Kim et al reported clinical outcomes in 208 never-smokers with NSCLC adenocarcinoma, according to ROS1-rearrangement status. ALK rearrangements and EGFR mutations were concurrently analyzed. The patients had clinical stages ranging from I-IV, but most were stage IV (41.3%). Of the 208 tumors, 3.4% (n=7) were ROS1 rearranged. ROS1 rearrangement was mutually exclusive from ALK rearrangement, but 1 of 7 ROS1-positive patients had a concurrent EGFR mutation. Patients with ROS1 rearrangement had a higher objective response rate and longer median PFS on pemetrexed than those without a rearrangement. In patients with ROS1 rearrangement, PFS with EGFR-TKIs was shorter than those patients without the rearrangement. None of the ROS1-positive patients received ALK inhibitors (e.g., crizotinib), which is the proposed targeted therapy for patients with NSCLC and this genetic alteration.
**RET**

In a phase 2 prospective trial for patients with RET fusion-positive tumors, preliminary data on 3 patients treated with cabozantinib showed a partial response in 2 patients, and 1 with stable disease approaching 8 months.67

**MET**

A phase 2 trial of MET-positive NSCLC, in which patients were treated with an anti-MET antibody plus erlotinib, showed improved PFS and OS.68

**BRAF**

Rare case reports have documented a response to vemurafenib in patients with NSCLC and a BRAF mutation.69-71

**HER2**

Mazières et al reported on a retrospective review of a consecutive series of patients with NSCLC who were tested for a HER2 mutation, and the authors assessed clinicopathologic characteristics and patient outcomes according to mutation status.72 A HER2 mutation was identified in 65 of 3800 (1.7%) patients, and was mutually exclusive of other driver mutations (EGFR, ALK, BRAF), with the exception of 1 case in which both a HER2 and KRAS mutation were identified. The patient population in which a HER2 mutation was found had a median age of 60 years (range, 31-86), 69% were women, and 52% were never-smokers. All of the tumors were adenocarcinomas, and 50% were stage IV (n=33). The patients with stage IV disease received conventional chemotherapy, and of these, 16 patients also received HER2-targeted therapy as additional lines of therapy (for a total of 22 individual anti-HER2 treatments that were evaluable). Four patients had progressive disease, 7 had disease stabilization, and 11 with partial response. PFS for patients with HER2 therapies was 5.1 months.

**Summary of Evidence**

Over half of patients with non-small cell lung cancer (NSCLC) present with advanced and therefore incurable disease, and treatment in this setting has generally been with platinum-based chemotherapy. More recently, the identification of specific, targetable oncogenic “driver” mutations in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

In NSCLC, the first successful example of targeted therapy involved mutations in the epidermal growth factor receptor (EGFR) gene, in which lung tumors harboring specific activating mutations in the EGFR kinase domain showed a high sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Phase 3 studies comparing EGFR-TKIs with chemotherapy in patients with EGFR-mutated NSCLC have shown that TKIs are superior to chemotherapy in terms of tumor response rate and progression free survival, with a reduction in toxicity and improvement in quality of life.

Currently, routine testing of NSCLC for EGFR mutations is recommended in patients with non-squamous NSCLC, because TKIs are recommended if the tumor has an EGFR mutation.

Therefore, EGFR 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. KRAS mutations may be prognostic in NSCLC and may predict a lack of response to TKIs, but the impact of testing for these mutations on clinical management is unknown.
Studies have not shown that KRAS mutations identify a population that may benefit from the use of anti-EGFR monoclonal antibodies. Therefore, analysis of somatic mutations of the KRAS gene is considered investigational as a technique to predict treatment non-response to anti-EGFR therapy with the TKIs erlotinib and the anti-EGFR monoclonal antibody cetuximab in NSCLC.

Other, potentially targetable oncogenic mutations have been characterized in lung adenocarcinomas, including in the genes ROS, RET, MET, BRAF and HER2. The data on the use of targeted therapies in NSCLC with a mutation in 1 of these genes is preliminary, in that much of the demonstrated sensitivity of tumor to the various drugs has been in vitro or in animal studies, and published data on patient tumor response and survival outcomes are extremely limited, consisting of case reports and small case series. Therefore, testing for genetic alterations in the genes ROS, RET, MET, BRAF and HER2, for targeted therapy in patients with NSCLC, is considered investigational.

**Supplemental Information**

### Practice Guidelines and Position Statements

**National Comprehensive Cancer Network (NCCN) Guidelines**

NCCN guidelines for the treatment of NSCLC recommend the following:

EGFR mutation testing is recommended (category 1) in patients with non-squamous NSCLC (i.e., adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified, because erlotinib or afatinib (category 1 for both) is recommended for patients who are positive for EGFR mutations. 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 squamous cell carcinoma, 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 adenocarcinoma.

NCCN states that "KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy."

NCCN does not give specific recommendations for testing for genetic alterations in the genes ROS, RET, MET, BRAF or HER2 in NSCLC, however, they state that the following targeted agents are now recommended for patients with specific genetic alterations: afatinib, cabozantinib, crizotinib, dabrafenib, erlotinib, gefitinib, trastuzumab and vemurafenib (category 2A).

**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 tyrosine kinase inhibitor 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 an 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.”

**U.S. Preventive Services Task Force Recommendations**

Mutation testing for targeted therapy in NSCLC is not a preventive service.

**Medicare National Coverage**

There is no national coverage determination (NCD) for mutation testing in NSCLC. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


9. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Epidermal growth factor receptor (EGFR) mutations and tyrosine kinase inhibitor
therapy in advanced non-small-cell lung cancer. TEC Assessments 2007; Volume 22, Tab 6. PMID
10. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC).
Epidermal growth factor receptor (EGFR) mutations and tyrosine kinase inhibitor therapy in advanced non-small-cell lung cancer. TEC Assessments 2010; Volume 25, Tab 6. PMID
23. Sun J M, Won YW, Kim ST, et al. The different efficacy of gefitinib or erlotinib according to epidermal growth factor receptor exon 19 and exon 21 mutations in


52. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar

**Documentation Required for Clinical Review**

- History and physical and/or consultation notes including:
  - Diagnosis and cancer stage
  - Previous treatment plan(s) and response(s)
  - Current treatment plan
  - Clinical justification for analysis testing

**Post Service**
- Analysis testing results

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when policy criteria are met. Services are considered investigational when the policy criteria
are not met or when the code describes application of a product in the position statement that is investigational.

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<td>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)</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<td>11/26/2014</td>
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<td>Medical Policy Committee</td>
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Definitions of Decision Determinations

**Medically Necessary**: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental**: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation**: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).
For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.