FirstCarolinaCare
INSURANCE COMPANY

MP 2.04.34 Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC)

Medical Policy

Section Medicine

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Description

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (TK) frequently overexpressed and activated in non-small cell lung cancer (NSCLC). Mutations in two regions of the EGFR gene (exons 18-24) -- small deletions in exon 19 and a point mutation in exon 21 (L858R) -- appear to predict tumor response to tyrosine kinase inhibitors (TKIs) such as erlotinib. This 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.

Policy

Except as noted below, analysis of two 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 in patients with advanced NSCLC.

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

Policy Guidelines

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. Patients found to be wild type are unlikely to respond to erlotinib; other treatment options should be considered.
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 the testing is done by immunohistochemical assay, CPT code 88342 would likely be reported. If the testing is done by fluorescence in situ hybridization (FISH), CPT code 88365 would likely be reported.

Rationale

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy and best supportive care. Unfortunately in up to 85% of cases the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease (1). When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30 to 45% (2,3).

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

Two orally administered EGFR-selective small molecules (quinazolinamine derivatives) have been identified for use in treating NSCLC: gefitinib (Iressa®, AstraZeneca) and erlotinib (Tarceva®, Genentech BioOncology). While both are available for use in Europe, Canada and Asia, only erlotinib is available for use in new patients in the U.S.

Two publications (6,7) 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 domain of the EGFR gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R). These can be detected by direct sequencing or polymerase chain reaction technologies.

A TEC Assessment on this topic was first published in November 2007 (8). The 2007 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 has recently been revised (9) with new conclusions indicating EGFR mutation testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.

Thirteen publications have been published providing data on EGFR mutations in tumor samples obtained from NSCLC patients in erlotinib treatment studies. Nine of these (10-18) were
nonconcurrent-prospective studies of patients treated with erlotinib and then studied for the presence or absence of mutations. Four (Table 1) were prospective one-arm enrichment studies of mutation-positive (3 studies) (19-21) or wild-type (1 study) (22) patients treated with erlotinib.

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

<table>
<thead>
<tr>
<th>Study (Yr)</th>
<th>No. Mutated. No. Tested (%)</th>
<th>Mutation Positive Objective Radiologic Response (%)</th>
<th>Median Progression-free Survival (mos.) [95% CI]</th>
<th>Median Overall Survival (mos.) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackman et al. (2009) Prospective 1-arm treatment EGFR-positive patients with erlotinib, chemotherapy naïve (19)</td>
<td>84 enrolled</td>
<td>70</td>
<td>13</td>
<td>28.7</td>
</tr>
<tr>
<td>Sun et al. (2010) Prospective 1-arm treatment EGFR-positive patients with erlotinib in treatment failures (21)</td>
<td>144/164 (32)</td>
<td>40</td>
<td>8</td>
<td>15.8</td>
</tr>
<tr>
<td>Yoshioka et al. (2010) Prospective 1-arm treatment EGFR wild-type patients with erlotinib in treatment failures (22)</td>
<td>30 enrolled</td>
<td>3.3</td>
<td>2.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

* all patients had stage IIIA/IV NSCLC

Abbreviation: CI, confidence interval
In a Phase 3 prospective clinical trial in China, Zhou et al. (23) reported the results of first-line treatment of patients with EGFR-mutation positive NSCLC randomized to treatment with erlotinib (n=83) versus standard chemotherapy (gemcitabine plus carboplatin) [n=82]). They observed a significant increase in progression-free survival (PFS) compared to treatment with chemotherapy (13.1 vs. 4.5 months; hazard ratio [HR] 0.16 (p<0.0001). Patients treated with erlotinib experienced fewer grade 3 and 4 toxic effects than those on chemotherapy. These results were duplicated in a European population in the 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 endpoint had been met. At the time the study was halted (Jan 26, 2011), median PFS was 9.7 (8.4-12.3) months versus 5.2 (4.5-5.8) in the erlotinib and standard chemotherapy groups, respectively, hazard ratio 0.37 (0.25-0.54); p<0.0001). (24) Six percent of patients on erlotinib had treatment-related severe adverse events compared to 20% of those receiving a standard chemotherapy regimen.

Petrelli et al. (25) reported a meta-analysis of 13 randomized trials of 1,260 patients receiving tyrosine kinase inhibitors (TKIs) for first-line, second-line, or maintenance therapy and compared outcomes to standard therapy. Overall, they noted that in patients with EGFR mutations, use of EGFR TKIs increased the chance of obtaining an objective response almost 2-fold when compared to chemotherapy. Response rates were 70% vs. 33% in first-line trials and 47% versus 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, overall they did not improve survival.

In a pooled analysis of studies, EGFR mutations appear to demonstrate improved patient outcomes for patients treated with erlotinib, as compared to standard chemotherapy (median PFS of 13.2 versus 5.9 months, respectively). (26) Patients with EGFR mutations appear to be ideal candidates for treatment with erlotinib. Identification of patients likely to respond or to fail to respond to erlotinib treatment leads to tailored choices of treatment likely to result in predictable and desirable outcomes.

Data comparing erlotinib results in EGFR mutation-positive versus wild-type patients have also been reported in 9 other studies totaling 630 patients (Table 2). In studies of treatment with erlotinib, objective radiologic response rates in patients with EGFR-mutation-positive tumors ranged from 0% to 83% (median 45%) compared to objective radiologic response rates in patients with wild-type tumors of between 0% and 18% (median 5.5%). In the 5 studies statistically evaluating results, patients with EGFR-mutation-positive tumors always demonstrated statistically significant increases in objective radiologic response.

Progression-free survival (PFS) in patients with EGFR-mutation-positive tumors ranged from 6.8 to 13.1 months (median 12.5) and in wild-type tumors ranged from 1.4 to 5 months (median 2.5) (Table 2). In all cases in which these data were reported, EGFR-mutation-positive tumors showed a trend or a statistically significant increase in PFS rate.

Overall survival (OS) in patients with EGFR-mutation-positive tumors ranged from 10 to 35 months (median 21) and in wild-type tumors ranged from 3 to 12 months (median 8.1) (Table 2). In all cases in which these data were reported, EGFR-mutation-positive tumors showed a trend or a statistically significant increase in survival rate.
In the 3 prospective studies of EGFR mutation-positive patients (Table 1), (19-21) objective radiologic response rates were 40% to 70%, PFS times were 8 to 14 months, and OS times were 16 to 29 months. This performance was distinctly different than that observed in wild-type patients (22) (Table 2) who exhibited an objective radiologic response of 3.3%, a PFS of 2.1 months, and an OS of 9.2 months.

Of note, EGFR mutations appear to provide prognostic, as well as predictive information about the behavior of tumors. In the study by Eberhard et al., (15) improved outcome parameters were observed in EGFR-positive patients compared to wild-type patients for the population as a whole (standard chemotherapy and standard chemotherapy with erlotinib) in all measurement categories with objective radiologic response of 38% versus 23% (p=0.01), time to progression of 8 months versus 5 months (p<0.001), and OS (not reached versus 10 months [p<0.001]).

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Overall Radiologic response Rate-Median (range) %</th>
<th>Progression-free Survival-Median (range) mos.</th>
<th>Overall Survival-Median (range) mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-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></td>
<td>2.8</td>
<td>12</td>
</tr>
</tbody>
</table>

Rosell et al. (20) reported mutations in 16.6% of the total patients studied but noted these were found more frequently in women (69.7%), in patients who had never smoked (66.6%), and in 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 frequency of mutations have also revealed a higher prevalence in East Asians when compared to other ethnicities (38% versus 15%, respectively). (18) An increased incidence of mutations is clearly seen in these special populations (women, patients with adenocarcinoma, nonsmokers, and/or Asians); however, it does appear that a substantial number of patients without these selected demographics still exhibit EGFR mutations and would benefit from erlotinib treatment.

In a comprehensive analysis of 14 studies involving 2,880 patients, Mitsudomi et al. (24) noted mutations were observed in 10% of men, 7% of non-Asian patients, and 7% of current or former smokers, but only 2% of patients with nonadenocarcinoma histologies. While histology appears to be the strongest discriminating factor, results are diverse across studies. Eberhard et al.(15) observed mutations in 6.4% of patients with squamous cell carcinomas (SCCs) and Rosell et al.(20) in 11.5% of patients with large cell carcinomas. Numbers in these studies were small.

The National Comprehensive Cancer Network (NCCN) (28) has recently recommended testing not be performed in SCCs because of the low incidence identified in the Catalogue of Somatic
Mutations in Cancer (COSMIC) maintained by the Sanger Institute. (26) This database of 1,873 samples of squamous cell lung cancers was noted to contain EGFR mutations in 2.7% of samples with an upper confidence interval (CI) for the true incidence of mutations reported to be 3.6% or less.

Park et al. (30) in a preselected set of Korean patients treated with gefitinib, reported EGFR mutations to be present in 3 out of 20 (15%) male smokers with SCC, a patient subgroup that based on demographics should have a low yield of EGFR mutations. Two of the 3 patients identified with the mutation exhibited a response to the drug versus a response in 1 of 17 wild-type patients. The PFS in patients with EGFR was 5.8 months, compared to 2.4 months in the wild-type group (not statistically significant, p=0.07, but suggesting a trend favoring a treatment response in patients with the mutation).

In vivo studies by Dobashi et al.(28) have recently been reported showing that in tumors in Japanese patients with both adenocarcinomas and SCCs, EGFR mutations are associated with downstream phosphorylation of EGFR and constitutive activation of the EGFR pathway.

Both of these studies appear to support the potential value of testing in patients with tumors of squamous cell histology, particularly in Asians. However, similar studies have not been reported in non-Asian populations or in populations treated with erlotinib.

Gene sequencing is generally considered an analytical gold standard. A rapid response report on EGFR-mutation analysis has recently been published by the Canadian Agency for Drugs and Technologies in Health. (32) Based on an analysis of 11 observational studies evaluating the use of PCR-based strategies to detect mutations in the EGFR gene, this report concluded PCR-based approaches are capable of identifying mutations in the EGFR gene with a sensitivity equivalent to that of direct sequencing.

Summary

Two randomized controlled trials, non-concurrent prospective studies, and single-arm enrichment studies demonstrate that the detection of epidermal growth factor receptor (EGFR) gene mutations identifies patients who are likely to benefit from use of erlotinib and who therefore represent ideal candidates for treatment with this drug. These observations have been made in a population composed primarily of tumors with adenocarcinoma histology. There is currently no evidence to indicate whether this behavior is also seen in patients with squamous cell histology.

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

EGFR mutational analysis may be considered medically necessary to predict treatment response to erlotinib in patients with advanced non-small cell lung cancer (NSCLC); however, EGFR mutational analysis is investigational in patients with NSCLC of squamous-cell type.

National Comprehensive Cancer Network (NCCN) Guidelines

The National Comprehensive Cancer Network (NCCN) in the V1.2013 guidelines on non-small-cell lung cancer (33) recommends EGFR mutational analysis in patients with advanced NSCLC.
It does suggest testing be deferred in patients with squamous cell carcinomas because of the low incidence of mutation in this histopathology type, except in never smokers and small biopsy specimens.

**ASCO Publication Recommendations**

In a 2011 publication, (34) the American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion on EGFR mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. It concludes patients with NSCLC being considered for first-line therapy with an EGFR tyrosine kinase inhibitor should have their tumor tested for EGFR mutations to determine whether an EGFR tyrosine kinase inhibitor or chemotherapy is the appropriate first-line therapy.

References:


23. Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL,


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81235</td>
<td>EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q) (new code 1/1/13)</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>ICD-9-CM does not have specific coding for non-small cell lung cancer. The following malignant neoplasm of lung codes would be used.</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>162.3 -162.9</td>
<td>Malignant neoplasm of lung code range</td>
<td></td>
</tr>
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<td>ICD-10-CM (effective 10/1/14)</td>
<td>ICD-10-CM does not have specific coding for non-small cell lung cancer. The following malignant neoplasm of lung codes would be used.</td>
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<td>C34.0 -C34.92</td>
<td>Malignant neoplasm of bronchus and lung</td>
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<td>ICD-10-PCS (effective 10/1/14)</td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.</td>
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</tbody>
</table>

**Type of Service**  Medicine

**Place of Service**  Reference laboratory

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Epidermal Growth Factor Receptor Mutation Analysis