Clinical Policy Title: Molecular targeted therapy

Clinical Policy Number: 05.01.05

Effective Date:   October 1, 2016
Initial Review Date:  June 15, 2016
Most Recent Review Date:  May 1, 2018
Next Review Date:  May 2019

Related policies:

CP# 05.01.04   Molecular analysis for targeted therapy of lung cancer

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Coverage policy


- Analysis of two types of somatic mutations within the Epidermal Growth Factor Receptor (EGFR) gene, small deletions in exon 19 and a point mutation in exon 21 (L858R) may be considered medically necessary to predict an improved response to afatinib or erlotinib in patients with advanced lung adenocarcinoma, or in whom an adenocarcinoma component cannot be excluded.
- Analysis of somatic rearrangement mutations of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.
- Analysis of somatic rearrangement mutations of the K-ras (KRAS) and N-ras (NRAS) genes may be considered medically necessary to predict treatment response to cetuximab in patients with metastatic colorectal cancer, anal cancer, and small bowel adenocarcinoma.
Limitations:

Other molecular analyses related to targeted therapy for lung cancer are considered investigational, including:

- Small deletions in exon 19 and a point mutation in exon 21 (L858R), which are types of somatic mutations within the EGFR gene, for patients with advanced squamous cell lung cancer. EGFR testing would be considered investigational for advanced non-small cell lung cancer (NSCLC) if mutation-directed therapy is being considered.
- Other EGFR mutations within exons 18 – 24 or other applications related to NSCLC.
- Other somatic rearrangement mutations of the ALK gene.
- Somatic mutations of the Kirsten rat sarcoma (KRAS) gene to predict the efficacy of anti-EGFR monoclonal antibody cetuximab in NSCLC.
- Genetic alterations in the genes ROS, ROT, MET, BRAF and HER2 for targeted therapy in patients with NSCLC.
- All other uses of genetic testing for lung cancer are considered investigational and, therefore, medically unnecessary.

Alternative covered services:

- Standard chemotherapy.

Background

Molecular tumor profiling is becoming increasingly important in the management of patients with advanced cancer. Hotspot-based assays are most commonly used in clinical practice. These range from polymerase chain reaction (PCR)-based assays of a single point mutation (e.g., BRAF V600E mutation testing in melanoma) to more extensive PCR- or mass spectrometry-based platforms assessing multiple point mutations across several genes (such as SNaPshot® or Sequenom®).

Targeted next-generation sequencing (NGS) sequences the entire coding region of a large number of genes with clinical cancer relevance. Although less comprehensive than whole genome and whole exome sequencing (WGS/WES), targeted NGS does provide a comprehensive analysis of genes with potential therapeutic and prognostic importance, a quick turnaround time (two to three weeks in most cases), and a standardized analytics methodology.

Genomic testing for patients with rare cancers, tumors in children, metastatic cancer of unknown primary, primary brain cancer, triple negative breast cancer, and metastatic cancer have become valuable diagnostic adjuncts in the oncologist’s toolbox. Unfortunately, there is no material medical evidence to support use of many of these tests, and it is mainly on potential and comprehensive range (rather than proof of efficacy) that they have entered mainstream evaluation and management. The
popular thinking is that by enabling physicians to select the appropriate therapy immediately and avoid drugs that are not likely to be effective, these tests can save time, money, and lives.

Lung cancer is one of the most common cancers in which molecular targeted therapy has come to the fore. In 2015, an estimated 221,200 Americans were diagnosed with the disease. Lung cancer has historically had high mortality rates; an estimated 158,040 Americans die annually from the disease, the most of any cancer type. The five-year survival rate from the disease is and remains low, rising only from 12.2 percent to 18.4 percent between 1975–1977 and 2005–2011.

Part of the difficulty in treating lung cancer is that 40 percent of new cases have metastasized to other parts of the body at diagnosis. For these patients, chemotherapy is the only treatment option, but the five-year survival rate for these patients is just 4 percent, according to the National Cancer Institute (NCI). Because up to 40 percent of lung cancer cases have metastasized by the time of diagnosis, improved treatments for advanced lung cancer are needed.

Recent developments have identified several drugs (afatinib, crizotinib, and erlotinib) that can target therapy to cancer cells (which traditional chemotherapy does not do) for NSCLC. These drugs are much better tolerated by lung cancer patients and have been approved by the U.S. Food and Drug Administration (FDA) for first- and second-line treatments.

Classifying molecular arrangements helps predict what patients with advanced lung adenocarcinoma will likely have extended progression-free survival (PFS) and fewer side effects to these targeted therapies than traditional chemotherapy. In particular, small deletions in exon 19 and a point mutation in exon 21 (L858R) predict an improved response to afatinib or erlotinib. Those patients with somatic rearrangements of the ALK gene will likely have improved outcomes when treated with crizotinib.

However, and despite the empiric emergence of these therapies in the clinical realm, there is not a great deal of medical evidence regarding molecularly targeted therapy to support its routine use for most patients. For example, one recent popularly promoted test (GPS Cancer®) has not yet completed a clinical validation study. Patients who enroll in the proposed Qualitative Integrative Lifelong Trial (QUILT) will receive therapies chosen on the basis of their GPS Cancer® test results, and will be stratified across their anatomical tumor types as well as by their stage of cancer. They will then be placed into various arms of a clinical trial testing targeted therapies or immunotherapies against standard of care.

The QUILT trial is somewhat similar to the NCI Molecular Analysis for Therapy Choice (MATCH) basket trial, a next-generation sequencing-based test to stratify patients into clinical trials of targeted therapies. A basket trial includes patients with any solid tumor or lymphoma with one of many genomic abnormalities known to drive cancer. Patients are matched with a targeted agent that has shown promise against their abnormality, regardless of what tissue-type of cancer they have. One efficiency of basket trials is that showing efficacy does not require many patients.

The NCI-MATCH trial is using a targeted panel and is focusing on single targeted agents added to
standard therapy. Although more patients than expected have enrolled into the NCI-MATCH, not many matches have yet been made. Patients can be enrolled at 2,400 clinical sites throughout the country, all members of NCI’s National Clinical Trials Network or National Community Oncology Research Program. Pharmaceutical companies are donating the drugs. Starting in 2016, another trial, Pediatric MATCH, will enroll children with cancer. NCI-MATCH — essentially a group of phase II trials — is not designed with an eye toward drug approval.

QUILT is different in study design in that it will sequence patients’ entire genomes and transcriptomes; thus, it has the theoretical advantage of being a comprehensive test, as opposed to a smaller panel or one that focuses only on deoxyribonucleic acid (DNA). This is an important consideration in tumor diagnosis and treatment because of the heterogeneous nature of cancer. Basket trials and others designed around genomic alterations are expected to evolve as investigators gain more data and experience with their challenges.

Recurrent "driver" mutations at specific gene loci define clinically relevant molecular subsets of cancers amenable to using a targeted NGS assay and targeted ribonucleic acid (RNA) sequencing. Two examples of this genre of tests include Foundation Medicine's FoundationOne® and FoundationOne Heme® tests. FoundationOne® has been previously described in detail and clinically validated (Frampton, 2013). Foundation ran more than 32,000 tests in 2015; however, reimbursement for the test in the health insurance marketplace is sporadic.

Molecular Health also offers an NGS-based tumor profiling test, recently rebranded as Engineus®, that evaluates more than 600 genes. NGS is a powerful tool to identify tumor-specific genetic changes. Caris Life Sciences offers tumor profiling using a variety of technologies including immunohistochemistry, NGS, and fluorescent in situ histology (FISH). Caris has described several techniques that highlight the frequency of actionable targets in various cancer types including glioblastoma, ovarian, bladder, and triple-negative breast cancer. Caris recently launched a network to create guidelines for tumor profiling.

According to the National Comprehensive Cancer Network (NCCN 2018), patients with HER2-negative metastatic breast cancer may benefit from BRCA1 and BRCA2 testing. The OlympiAD trial using the BRACAnalysis CDx test demonstrated that olaparib significantly reduced the risk of disease progression or death in patients with germline BRCA-mutated HER2-negative metastatic breast cancer.

Many unanswered questions remain regarding full integration and clinical implementation of these technologies. As molecularly targeted therapeutic agents with increasing clinical efficacy are developed targeting a variety of cell signaling pathways, comprehensive genetic profiling with targeted NGS will likely continue to increase in importance.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
• Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
• The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on March 19, 2018. Search terms were “molecular therapy,” (MeSH), “lung cancer,” “genomic testing,” “cancer therapy,” “ALK,” and “EFGR.”

We included:
• **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
• **Guidelines based on systematic reviews.**
• **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Sohal (2015) evaluated molecular targeted therapy across 250 adult patients with multiple advanced and incurable solid tumors using a large NGS panel (FoundationOne®). There were 15 tumor types, with the most common diagnoses being colorectal (25 percent), breast (18 percent), and lung (13 percent) cancers. Tumor sequencing was feasible in 223 (89 percent) cases, and identified a potentially actionable alteration in 141 (63 percent) cases. A specific therapeutic recommendation was made in 109 (49 percent) cases; only 24 (11 percent) patients received a targeted therapy. The most common reason for not receiving a targeted therapy was the unavailability of open clinical trials.

Frampton (2013) was one of the first to advance the notion that as more clinically relevant cancer genes are identified, comprehensive diagnostic approaches are needed to match patients to therapies. Working with the FoundationOne® researchers, the group took on the challenge of optimization and analytical validation of assays that interrogate millions of bases of cancer genomes altered by multiple mechanisms. They described a test based on massively parallel DNA sequencing to characterize base substitutions, short insertions and deletions (indels), copy number alterations, and selected fusions across 287 cancer-related genes from routine formalin-fixed and paraffin-embedded (FFPE) clinical specimens. Test sensitivity achieved was 95 – 99 across alteration types, with high specificity (positive predictive value > 99 percent). The authors went on to apply the test to 2,221 clinical cases and identified clinically actionable alterations in 76 percent of tumors, three times the number of actionable alterations detected by then-current diagnostic tests.

Johnson (2014) retrospectively assessed demographics, NGS results, and therapies received for patients undergoing targeted NGS (exonic sequencing of 236 genes and selective intronic sequencing from 19 genes) between April 2012 and August 2013. Samples from 103 patients were tested; most frequently
breast carcinoma (26 percent), head and neck cancers (23 percent), and melanoma (10 percent). Most patients (83 percent) were found to harbor potentially actionable genetic alterations, involving cell-cycle regulation (44 percent), phosphatidylinositol 3-kinase-AKT (31 percent), and mitogen-activated protein kinase (19 percent) pathways. With median follow-up of 4.1 months, 21 percent received genotype-directed treatments, most in clinical trials (61 percent), leading to significant benefit in several cases. The most common reasons for not receiving genotype-directed therapy were selection of standard therapy (35 percent) and clinical deterioration (13 percent). The authors concluded that as time goes on, NGS results will be used to guide therapy in an increasing proportion of patients.

The authors surmised that a targeted NGS approach has potential value in several ways. First, additional potentially active therapies can be identified, enabling clinical trial enrollment for patients without available treatment options and pinpointing trials for patients likely to benefit. Conversely, even “negative” sequencing information may be clinically useful to direct patients toward non-genotype-directed clinical trials (i.e., immunotherapy, chemotherapy) or even no additional treatment. Second, novel genetic findings can be found (e.g., a BRAF fusion in melanoma), which leads to preclinical studies and new clinical trials. Third, targeted NGS can help define prognostic and pathologic characteristics of molecular cohorts within and across tumor types, facilitating the development of further basket trials. Finally, targeted NGS sequencing can be used as an initial sequencing strategy to investigate unexpected responses in clinical trials for both clinical and research purposes, analogous to previously published approaches with WGS.

A prospective study (Meric-Bernstam 2015) of 2,000 consecutive patients with advanced cancer who underwent genomic testing using either an 11-gene (251 patients) or a 46- or 50-gene (1,749 patients) multiplex platform found 789 patients (39 percent) had at least one mutation in potentially actionable genes; and 83 patients (11 percent) with potentially actionable mutations went on genotype-matched trials targeting these alterations. Of 230 patients with PIK3CA/AKT1/PTEN/BRAF mutations that returned for therapy, 116 (50 percent) received a genotype-matched drug. Forty patients (17 percent) were treated on a genotype-selected trial requiring a mutation for eligibility, 16 (7 percent) were treated on a genotype-relevant trial targeting a genomic alteration without biomarker selection, and 40 (17 percent) received a genotype-relevant drug off trial. Challenges to trial accrual included patient preference of non-investigational treatment or local treatment, poor performance status or other reasons for trial ineligibility, lack of trials or slots, and insurance denial.

The authors concluded that broad implementation of multiplex hotspot testing is feasible; however, only a small portion of patients with actionable alterations were actually enrolled onto genotype-matched trials. Increased awareness of therapeutic implications and access to novel therapeutics are needed to optimally leverage results from broad-based genomic testing. Reddy (2015) evaluated 60 male and 5,000 female breast cancer samples to identify differences and commonalities between the two diseases. The authors looked for patterns within the male breast cancer (MBC) cohort that might show relationships with known breast cancer subtypes (e.g., HER2-positive) and were able to identify possible therapies in 98 percent of MBC cases based on protein expression and gene copy number. HER2 overexpression and amplification were lower in MBC samples than in female breast cancer (FBC);
however, the investigators noted that when HER2 aberrations are identified in MBC patients, use of HER2-targeted therapies may be efficacious. In total, 80 percent of MBC cases tested positive for high levels of Ki-67, a protein associated with aggressive disease.

The authors concluded that this study in MBC reflects an expanding range of potential treatment options for this rare cancer and underscores the importance of examining the individual molecular profile of a patient's cancerous tissue to more clearly delineate the most appropriate therapy. Moreover, the differences observed in gene mutation, amplification and protein expression profiles suggest that the standard of care in FBC patients may not necessarily be the best treatment option for male breast cancer patients.

A study of 423 women with breast cancer (Andre 2014) found sequencing was feasible in about 70 percent of cases, and showed that 195 (46 percent) specimens had actionable alterations; however, only 43 (10 percent) patients received a therapy.

The poor survival rates for patients with lung cancer (especially those with metastases), difficulties tolerating chemotherapy regimens, and improved knowledge of genetic abnormalities in lung cancer patients has led to development and approval of a series of drugs that target cancerous cells.

A prospective clinical study of 1,500 patients with advanced lung cancer (Kris 2014) sequenced tumors for 10 common alterations for whom targeted therapies were available for off-label or investigational use. Full genotyping was feasible in about half (n = 733, 48 percent) and an actionable target was found in 466 (30 percent) cases. Of these, 275 (18 percent) patients received a targeted therapy. The median overall survival (OS) was 2.1 – 2.4 years when a targeted therapy could not be administered; when a drug targeting a detected actionable alteration was given, the median OS was 3.5 years (P <.001).

The Lux-trial program of the Boehringer Ingelheim pharmaceutical company (Ingelheim am Rhein, Germany) comprises more than 10 trials worldwide, including lung (LUX-lung) and other cancers. Begun in the mid-2000s, the program incorporates a LUX-Lung component, focusing on targeted therapies for lung cancer. The initial results of LUX-Lung 1 were released in December 2010.

The first targeted lung cancer therapy to earn FDA approval was gefitinib (Iressa®). FDA approval in May 2003 for gefitinib was as monotherapy for patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies — a third-line treatment. In June 2005, the FDA withdrew approval for gefitinib use in new NSCLC patients based on lack of evidence that it extended life. On July 13, 2015, the FDA granted approval for use of gefitinib as a first-line treatment for NSCLC.

The next drug to receive FDA approval for locally advanced or metastatic NSCLC was erlotinib (Tarceva®). On April 16, 2010, the FDA granted approval of the drug for such patients whose disease had not progressed after four cycles of platinum-based first-line chemotherapy. On May 14, 2013, the FDA granted approval for erlotinib (Tarceva®) as a first-line treatment for patients with metastatic NSCLC.
whose tumors have EGFR exon 19 deletions and exon 21 (L858R) substitution mutations. This approval marked the first for targeted therapy for advanced NSCLC cases.

The FDA action was based on clinical trials, principally a study of erlotinib versus platinum-based doublet chemotherapy (n = 174). Results showed consistently greater outcomes for the erlotinib group. Median PFS was 10.4 months versus 5.2 months; median OS was 22.9 months versus 19.5 months, which was not significant; and the objective response rate (ORR) was 65 percent for the erlotinib arm versus 16 percent for the chemotherapy arm (Khozin 2014).

On July 12, 2013, the FDA added afatinib (Gilotrif®) as a first-line treatment for metastatic NSCLC patients whose EGFR exon 19 deletions or exon 21 (L858R) substitution mutations have been detected. The FDA relied on a LUX-Lung 3 Phase III Study with 345 patients that showed afatinib patients lived about as long as those on chemotherapy, with fewer side effects. Afatinib had a higher PFS than pemetrexed and cisplatin chemotherapy (11.1 months versus 6.9 months). Those patients with EGFR mutations had an even higher median PFS — of 13.6 months (Sequist 2013).

On the same day afatinib was granted FDA status as a first-line treatment for NSCLC, the FDA approved the diagnostic test Therascreen® to help doctors determine whether a lung cancer patient’s tumor has the EGFR mutation.

On November 20, 2013, the FDA approved crizotinib (Xalkori®) to be used as a first-line treatment for NSCLC patients whose malignancies are ALK-positive. The action was based largely on a clinical trial of 343 patients receiving oral crizotinib versus IV chemotherapy (pemetrexed plus cisplatin or carboplatin). The crizotinib group had a greater ORR than the chemotherapy group (74 percent versus 45 percent) and a longer median PFS (10.9 months versus 7 months). However, the one-year survival rate was 16 percent for the crizotinib group, which was actually less than the 21 percent survival rate for chemotherapy patients (Solomon 2014).

As targeted therapy advances through preclinical and clinical trials (and in oncologic practice) it is likely that a series of meta-analyses and systematic reviews covering dozens of trials will eventually emerge to support this genre of testing and treatment. Already, some of those trials reviewing the accuracy of metastatic tests show a strong ability to predict which patients have tumors amenable to targeted therapy (Chen 2014, Dahabrh 2010, Qiu 2015). A small number of meta-analyses focused on efficacy have already shown that targeted therapy based on molecular analysis in advanced-stage NSCLC patients has resulted in longer PFS, greater response rates and fewer adverse effects (Hotta 2015, Lee 2013, Liang 2014).

On the other hand, overall survival rates have yet to show superior results that are distinguishable from traditional chemotherapy, and survival at five years after therapy (especially with lung cancer) remains rare. The challenge of refining molecular analysis in genetic material of patients with advanced cancer to improve efficacy of targeted therapy remains a high priority for future research.
Policy updates:

The 2017 American Society of Clinical Oncology guideline on systemic therapy for patients with stage IV NSCLC revised recommendations include the following:

- Regarding first-line treatment for patients with non-squamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, EGFR/ALK /ROS1), if the patient has high programmed death ligand 1 (PD-L1) expression, pembrolizumab should be used alone; if the patient has low PD-L1 expression, clinicians should offer standard chemotherapy. All other clinical scenarios follow 2015 recommendations.

- Regarding second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy, if NSCLC tumor is positive for PD-L1 expression, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab; if tumor has negative or unknown PD-L1 expression, clinicians should use nivolumab or atezolizumab.

All immune checkpoint therapy is recommended alone plus in the absence of contraindications:

- For patients who received a prior first-line immune checkpoint inhibitor, clinicians should offer standard chemotherapy.

- For patients who cannot receive immune checkpoint inhibitor after chemotherapy, docetaxel is recommended; in patients with nonsquamous NSCLC, pemetrexed is recommended.

In patients with a sensitizing EGFR mutation, disease progression after first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy, and T790M mutation, osimertinib is recommended; if NSCLC lacks the T790M mutation, then chemotherapy is recommended. Patients with ROS1 gene rearrangement without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

A systematic review (Koleva-Kolarova 2017) assessed the clinical effectiveness of non-hormonal targeted therapies (TTs) looking for improvements in median progression-free survival (PFS) and OS in receptor-positive metastatic breast cancer. Thirty-eight studies (n = 17,192 patients) demonstrated in the aggregate that TTs added 3.3 months to the median PFS (0.7-9.6; hormone receptors [HRs] 0.74, 95% confidence interval [CI] 0.71-0.77) of receptor-positive metastatic breast cancer patients and prolonged their median OS by 3.5 months [0-4.7; HRs 0.90, 95% CI 0.82-0.98]. The highest increase in median PFS of 3.6 months was found in HER2-/HR+ patients, while the highest increase in median OS of 7.2 months was observed in HER2+/HR mixed-status patients. First-line TTs were most effective in increasing the median PFS in the HR+/HER2- group by 2.0 months, and in the HER2+/HR mixed group by adding 4.7 months to the median OS. Second-line TTs were most effective for HER2-/HR+ patients by adding 2.6 months to their PFS, and for HER2+/HR mixed patients by adding 3.1 months to their median OS. The authors concluded that, although small, the gain in months of median PFS and median OS was significant, and suggested applying a personalized approach to maximize the benefits of targeted therapy.

Summary of clinical evidence:
## Citation | Content, Methods, Recommendations
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Hanna (2017) Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. **Key points:**
- ASCO guideline on systemic therapy for patients with stage IV NSCLC revised recommendations include the following:
  - Regarding first-line treatment for patients with non-squamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, EGFR/ALK /ROS1), if the patient has high programmed death ligand 1 (PD-L1) expression, pembrolizumab should be used alone; if the patient has low PD-L1 expression, clinicians should offer standard chemotherapy. All other clinical scenarios follow 2015 recommendations.
  - Regarding second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy, if NSCLC tumor is positive for PD-L1 expression, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab; if tumor has negative or unknown PD-L1 expression, clinicians should use nivolumab or atezolizumab.
- All immune checkpoint therapy is recommended alone plus in the absence of contraindications.
  - For patients who received a prior first-line immune checkpoint inhibitor, clinicians should offer standard chemotherapy.
  - For patients who cannot receive immune checkpoint inhibitor after chemotherapy, docetaxel is recommended; in patients with nonsquamous NSCLC, pemetrexed is recommended. In patients with a sensitizing EGFR mutation, disease progression after first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy, and T790M mutation, osimertinib is recommended; if NSCLC lacks the T790M mutation, then chemotherapy is recommended.
- Patients with ROS1 gene rearrangement without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

Koleva-Kolarova (2017) Increased life expectancy as a result of non-hormonal targeted therapies for HER2 or hormone receptor positive metastatic breast cancer: A systematic review and meta-analysis. **Key points:**
- A systematic review inclusive of 38 studies (n = 17,192 patients) demonstrated in the aggregate that TTs added 3.3 months to the median PFS (0.7-9.6; HRs 0.74, 95% CI 0.71-0.77) of receptor-positive metastatic breast cancer patients and prolonged their median OS by 3.5 months (0-4.7; HRs 0.90, 95% CI 0.82-0.98).
- The highest increase in median PFS of 3.6 months was found in HER2-/HR+ patients, while the highest increase in median OS of 7.2 months was observed in HER2+/HR mixed-status patients.
- First-line TTs were most effective in increasing the median PFS in the HR+/HER2- group by 2.0 months, and in the HER2+/HR mixed group by adding 4.7 months to the median OS.
- Second-line TTs were most effective for HER2-/HR+ patients by adding 2.6 months to their PFS, and for HER2+/HR mixed patients by adding 3.1 months to their median OS.
- The authors concluded that, although small, the gain in months of median PFS and median OS was significant, and suggested applying a personalized approach to maximize the benefits of targeted therapy.

Frampton (2013) Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA **Key points:**
- RCT of 2,221 subjects across 287 cancer-related genes who underwent massively parallel DNA sequencing (FoundationOne®) and identified clinically actionable alterations in 76% of tumors.
- Most of the mutations were base substitutions, short insertions and deletions.
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| sequencing                            | (indels), copy number alterations, and selected fusions.  
  - Test sensitivity achieved was 95% – 99%.  
  - Test specificity > 99%. |
| Sohal (2015)                          | **Key points:**  
  - A prospective study in 250 patients with colorectal (25%), breast (18%), lung (13%), and pancreatobiliary (13%) cancers.  
  - Tumors were sequenced using FoundationOne®.  
  - Of 223 evaluable samples, 49% (n = 109) of patients were recommended a specific therapy, but only 11% (n = 24) received such therapy.  
  - Lack of clinical trial access (n = 49) and clinical deterioration (n = 29) were the most common barriers to treatment. |
| Meric-Bernstam (2015)                 | **Key points:**  
  - Prospective study of 2,000 consecutive patients with advanced cancer who underwent testing using either an 11-gene (251 patients) or a 46- or 50-gene (1,749 patients) multiplex platform.  
  - Seven hundred eighty-nine patients (39%) had at least one mutation in potentially actionable genes.  
  - Eighty-three patients (11%) with potentially actionable mutations went on genotype-matched trials targeting these alterations.  
  - The authors concluded increased awareness of therapeutic implications and access to novel therapeutics are needed to optimally leverage results from broad-based genomic testing. |
| Johnson (2014).                       | **Key points:**  
  - Assessed demographics, NGS results, and therapies received for patients undergoing targeted NGS between April 2012 and August 2013.  
  - Samples from 103 patients were tested; most frequently breast carcinoma (26%), head and neck cancers (23%), and melanoma (10%).  
  - Most patients (83%) were found to harbor potentially actionable genetic alterations, involving cell-cycle regulation (44%), phosphatidylinositol 3-kinase-AKT (31%), and mitogen-activated protein kinase (19%) pathways.  
  - The most common reasons for not receiving genotype-directed therapy were selection of standard therapy (35%) and clinical deterioration (13%).  
  - The authors concluded that as time goes on, NGS results will be used to guide therapy in an increasing proportion of patients. |
| Kris (2014)                           | **Key points:**  
  - Clinical trial of 1,500 patients with advanced lung cancer.  
  - Authors sequenced tumors for 10 common alterations.  
  - An actionable target was found in 466 (30%); 275 (18%) patients received a targeted therapy and the remaining subjects received either no therapy or standard therapy.  
  - The median (OS) was 3.5 years (P < .001) longer when a targeted therapy could be administered. |
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<td>Andre (2014)</td>
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<td>Comparative genomic</td>
<td>- A study of 423 women with breast cancer found sequencing was feasible</td>
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<td>Molecular profiling</td>
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<td>- Identified potential therapies in 98% of MBC cases.</td>
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<td>- In total, 80% of MBC cases tested positive for high levels of Ki-67,</td>
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<td>a protein associated with aggressive disease.</td>
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<td>Survival benefits in</td>
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<td>mutation in NSCLC</td>
<td></td>
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<tr>
<td>Chen Z (2014)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Are immunohistochemical</td>
<td>- Fifteen trials; looked at efficacy of anti E746-E750 antibody.</td>
</tr>
<tr>
<td>methods adequate to</td>
<td>- Immunohistochemistry alone is sufficient for detecting EGFR mutations.</td>
</tr>
<tr>
<td>detect EGFR mutations</td>
<td>- Molecular-based analyses needed if anti E746-E750 results are negative.</td>
</tr>
<tr>
<td>Liang (2014)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Do TKI inhibitors</td>
<td>- Twenty Phase II and III controlled trials, 10,834 participants.</td>
</tr>
<tr>
<td>improve outcomes for</td>
<td>- Increases in PFS and ORR for patients qualifying for targeted therapy.</td>
</tr>
<tr>
<td>patients with certain</td>
<td>- No increase in OS and disease control rates.</td>
</tr>
<tr>
<td>mutations</td>
<td></td>
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<tr>
<td>Lee (2013)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Does EGFR inhibitor</td>
<td>- Twenty-three trials, 14,570 participants.</td>
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<tr>
<td>raise progression</td>
<td>- EGFR/tyrosine-kinase inhibitor (TKI) therapy extends PFS, but not OS.</td>
</tr>
<tr>
<td>free-survival and</td>
<td></td>
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<tr>
<td>overall survival (PFS</td>
<td></td>
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<tr>
<td>and OS)</td>
<td></td>
</tr>
<tr>
<td>Dahabreh (2010)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Are certain EGFR</td>
<td>- Fifty-nine trials, 3,101 participants eligible for EGFR mutation.</td>
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<tr>
<td>mutations predictors</td>
<td></td>
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<tr>
<td>of responses to</td>
<td></td>
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<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------</td>
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<tr>
<td>TKI targeted therapy</td>
<td>• EGFR mutations accurately predicted response to single-agent TKI therapy.</td>
</tr>
</tbody>
</table>

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


Jardim DL, Conley A, Subbiah V. Comprehensive characterization of malignant phyllodes tumor by whole
genomic and proteomic analysis: biological implications for targeted therapy opportunities. *Orphanet J Rare Dis.* 2013;8:112.


Mullard A. NCI-MATCH trial pushes cancer umbrella trial paradigm. *Nat Rev Drug Discov.*


Reddy B, Westcott G. Molecular profiling is not the future: it is now! Future Oncol. 2015;11(10):1459-61.


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tr>
<td>81235</td>
<td>EGFR (epidural growth factor receptor) (eg, non-small cell lung cancer), gene analysis</td>
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<tr>
<td>81245</td>
<td>FLT3 (fms-related tyrosine kinase 3), gene analysis</td>
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<tr>
<td>88342</td>
<td>Anaplastic lymphoma kinase</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<td>C17.0-C17.9</td>
<td>Malignant neoplasm, small bowel</td>
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<tr>
<td>C19</td>
<td>Malignant neoplasm, colorectal</td>
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</tr>
<tr>
<td>C21.0-C21.8</td>
<td>Malignant neoplasm, anus</td>
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<tr>
<td>C34.00-C34.92</td>
<td>Malignant lung neoplasm</td>
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<table>
<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comment</th>
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