

Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer (NSCLC)

Effective: January 1, 2021

Next Review: November 2021

Last Review: December 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Targeted testing for specific gene variants, including *EGFR* and *BRAF* analysis, can be used to predict treatment response to targeted therapy in patients with advanced NSCLC.

MEDICAL POLICY CRITERIA

- I. Testing for *NTRK* and *RET* gene fusions and *ALK*, *KRAS*, *MET*, *PD-L1*, and *ROS1* variants may be considered **medically necessary** for selection of therapy.
- II. Testing for *EGFR* gene variants (in either tumor tissue or blood) may be considered **medically necessary** to select patients with advanced or metastatic (stage III or IV) non-small cell lung cancer (NSCLC) for treatment with FDA approved EGFR tyrosine kinase inhibitors as indicated. (See Policy Guidelines)
- III. Tumor testing for the *BRAF* variants may be considered **medically necessary** to select patients with advanced or metastatic (stage III or IV) NSCLC for treatment with BRAF- or MEK-inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]).

- IV. The Oncomine™ Dx Target test may be considered **medically necessary** to select patients with advanced or metastatic (stage III or IV) NSCLC for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®).
- V. The following analyses/tests are considered **investigational**:
- A. Testing for *EGFR* or *BRAF* variants for patients with NSCLC stage I or II
 - B. Testing for purposes other than treatment selection.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

The Oncomine™ Dx Target test was approved by the FDA as a companion diagnostic to aid in selecting NSCLC patients for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®). The test identifies tumors that have *EGFR* variants, *ROS1* fusions, and/or the *BRAF* V600E variant.

The FDA approved cobas® EGFR Mutation Test v2 is only intended to be used to aid in identifying patients with NSCLC whose tumors have defined *EGFR* mutations and for whom safety and efficacy of a drug have been established. This test may be run on either tumor or plasma samples.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
 - History and physical exam
 - Conventional testing and outcomes
 - Conservative treatment provided, if any

CROSS REFERENCES

1. [KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer](#), Genetic Testing, Policy No. 13
2. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
3. [BRAF Gene Mutation Testing To Select Melanoma or Glioma Patients for Targeted Therapy](#), Genetic Testing, Policy No. 41
4. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64
5. [Expanded Molecular Testing of Cancers to Select Targeted Therapies](#), Genetic Testing, Policy No. 83

6. [Circulating Tumor DNA and Circulating Tumor Cells for Management \(Liquid Biopsy\) of Solid Tumor Cancers](#), Laboratory, Policy No. 46
7. [Molecular Testing in the Management of Pulmonary Nodules](#), Laboratory, Policy No. 73
8. [Medication Policy Manual](#), Do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

TARGETED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. 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] Treatment of advanced NSCLC has generally been with platinum-based chemotherapy, with a median survival of 8 to 11 months and a one-year survival of 30% to 45%.^[2-3] More recently, the identification of specific, targetable oncogenic “driver” variants in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology.

EPIDERMAL GROWTH FACTOR RECEPTOR (*EGFR*)

EGFR is a receptor tyrosine kinase (TK) frequently overexpressed and activated in NSCLC. 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] The prevalence of *EGFR* variants in NSCLC varies by population, with the highest prevalence in non-smoking, Asian women, with adenocarcinoma, in whom *EGFR* variants have been reported to be up to 30-50%. The reported prevalence in the Caucasian population is approximately 10%.^[6]

Variants 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 first and second generation tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib and afatinib.^[7-8] In addition, a single point mutation in exon 20 (T790M) appears to predict tumor response to third generation TKIs such as osimertinib. These can be detected by direct sequencing or polymerase chain reaction (PCR) technologies.

Testing 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 EGFR gene are considered good candidates for treatment with first and second generation TKIs. Patients with the point mutation in exon 20 (T790M), which is indicative of acquired resistance to first and second generation TKIs, are considered good candidates for third generation TKIs. Patients found to be wild-type are unlikely to respond to TKIs, so other treatment options should be considered.

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 altered in NSCLC, in

approximately 1-3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants.^[9] Most *BRAF* variants occur more frequently in smokers.

KRAS

KRAS is a G-protein involved in the EGFR-related signal transmission. The *KRAS* gene, which encodes RAS proteins, can harbor oncogenic variants that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EFG receptor. Variants in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20-30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

REGULATORY STATUS

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, which was released on July 14, 2011,^[8] to address the “emergence of new technologies that can distinguish subsets of populations that respond differently to treatment.” As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices “when an appropriate scientific rationale supports such an approach.” In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

The Oncomine™ Dx Target test is an FDA approved companion diagnostic test for EGFR variants, ROS1 gene fusions, and the BRAF V600E variant, to aid in selection of the following targeted therapies:

- gefitinib (Iressa®)
- crizotinib (Xalcori®)
- dabrafenib (Tafinlar®) plus trametinib (Mekinist®).

The Oncomine™ Dx Target test is intended for patients with advanced or metastatic NSCLC.

There are two other U.S. Food and Drug Administration (FDA)-approved companion diagnostic tests for *EGFR* variant testing for NSCLC, intended to be used with select FDA approved *EGFR* tyrosine kinase inhibitors (TKIs):

- The cobas® *EGFR* Mutation Test v2 is a companion diagnostic test for the detection of exon 19 deletions and exon 20 and 21 (T790M and L858R, respectively) substitution variants in the *EGFR* gene in NSCLC tumor tissue. The FDA states:

“The test is intended to be used as an aid in selecting patients with NSCLC for whose tumors have defined *EGFR* variants and for whom safety and efficacy of a drug have been established as follows:

- Tarceva® (erlotinib) - Exon 19 deletions and L858R
- Tagrisso® (osimertinib) - T790M”

This test (v2) was approved 11/13/2015 as a result of an expansion of the original cobas® *EGFR* Mutation Test to cover testing for the T790M point mutation for use of osimertinib.

- The thescreen® *EGFR* Rotor Gene Q polymerase chain reaction (PCR) Kit is an automated molecular assay designed to detect the presence of *EGFR* exon 19 deletions and the exon 21 (L858R) substitution variant in NSCLC tumor tissue. The test is intended to be used to select patients with NSCLC for whom GILOTRIF® (afatinib) or IRESSA® (gefitinib) is indicated.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[10] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

The focus of the following review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

The clinical utility of testing for small deletions in exon 19 and a point mutation in exon 21 (L858R) in the *EGFR* gene to guide TKI treatment in patients with advanced NSCLC has been unequivocally demonstrated. Therefore, this review will focus on literature that has been published on the investigational indications described in this policy.

EGFR

Publications demonstrate that the underlying molecular mechanism underpinning dramatic responses in favorably prognostic groups of patients with advanced NSCLC appear to be the presence of activating somatic variants in the TK domain of the *EGFR* gene, notably small deletions in exon 19 and a point mutation in exon 21 (L858R).^[7-8] These activating somatic variants are also referred to as “sensitizing” variants because their presence strongly predicts sensitivity to TKIs. Four orally administered *EGFR*-selective small molecules (quinazolinamine derivatives) have been approved by the FDA for use in treating NSCLC patients with sensitizing variants: erlotinib (Tarceva®, Genentech BioOncology), afatinib (Gilotrif®, Boehringer Ingelheim Pharmaceuticals, Inc), gefitinib (Iressa®, AstraZeneca), and osimertinib (Tagrisso®, AstraZeneca).

There is sufficient evidence for the clinical utility of testing for small deletions in exon 19 and a point mutation in exon 21 (L858R) in the *EGFR* gene to guide TKI treatment in patients with advanced NSCLC. This evidence is published as numerous systematic reviews on monotherapies in general^[12-17], clinical trials and nonrandomized studies that have been published over the past decade for the use of genetic testing to inform treatment with erlotinib^[12-18-42], afatinib^[43-48], and gefitinib^[49-54].

Almost all patients who initially respond to an *EGFR*-TKI subsequently develop disease progression often due to acquired resistance. Publications demonstrate that the underlying molecular mechanism underpinning TKI acquired resistance is the generation of the somatic point mutation in exon 20 (T790M).^[55-58] This variant is also referred to as a “resistance” or

secondary variant, but can be overcome by a new class of TKIs (third generation). One orally administered EGFR-selective small molecule has been approved by the FDA for use in treating NSCLC patients with resistance variants: osimertinib (Tagrisso®, AstraZeneca).

The clinical utility of testing for the resistance variant T790M in the *EGFR* gene to guide treatment with third generation TKIs, such as osimertinib and rociletinib has been demonstrated in large clinical trials^[59-62], and preclinical studies.^[63]

BRAF

In June 2017, the FDA approved an additional indication for the use of dabrafenib and trametinib combination therapy in patients with NSCLC with *BRAF* V600E variant as detected by an FDA-approved test. The Oncomine™ Dx Target Test was approved as a companion diagnostic. The dabrafenib and trametinib product labels describe the results of an open-label, multicenter study of patients enrolled three cohorts: cohorts A and B had received at least one previous platinum-based chemotherapy regimen with demonstrated disease progression but no more than three prior systemic regimens; cohort C could not have received prior systemic therapy for metastatic disease.^[64 65] Trial results for cohorts A and B have also been published.^[66 67] Cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy. The response rate in the 57 previously treated patients in the study that were *BRAF*-positive by local lab test was 67% (95% CI 53% to 79%) compared with 73% (95% CI 50% to 89%) for the 22 patients that were also *BRAF*-positive by Oncomine™ Dx. The response rate in the 36 treatment-naive patients that were *BRAF*-positive by local lab test was 61% (95% CI 44% to 77%) compared with 61% (95% CI 39% to 80%) in the 23 patients that were also *BRAF*-positive by Oncomine™ Dx. Additionally, a "basket" study of vemurafenib in *BRAF* V600 variant–positive nonmelanoma cancers, including 20 patients with NSCLC, was published by Hyman (2015).^[68]

In summary, the response rate for dabrafenib monotherapy in 78 patients who had progressed on chemotherapy was 33% at 11 months median follow-up while the response rate for 19 patients (17 of which had progressed on chemotherapy) treated with vemurafenib monotherapy was 42% at eight weeks. Response rates for dabrafenib and trametinib combination therapy were higher than 60% in patients who had progressed on prior treatment and those that were treatment-naive. Toxicities were similar to those seen in melanoma patients taking BRAF or MEK inhibitors. Squamous cell carcinomas and other dermatological side effects occur.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)^[69]

NCCN guidelines for the treatment of metastatic NSCLC (v.3.2020 recommend *EGFR*, *ALK*, *ROS1*, *BRAF*, and PD-L1 testing for patients with non-squamous NSCLC (i.e., adenocarcinoma, large cell carcinoma) or NSCLC not otherwise specified. For patients with squamous cell carcinoma, the guidelines recommend PD-L1 testing, and considering *ROS1* and *BRAF* testing. There is a further recommendation to consider *EGFR* and *ALK* testing in never smokers, small biopsy specimens, or specimens with mixed histology.

According to these recommendations, molecular testing for all advanced or metastatic NSCLC should be conducted as a part of broad molecular profiling, which should include testing for *NRTK* gene fusion.

Regarding *KRAS*, the guidelines state:

Patients with *KRAS* mutations appear to have a shorter survival than patients with wild-type *KRAS*; therefore, *KRAS* mutations are prognostic biomarkers. *KRAS* mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs; it does not appear to affect chemotherapeutic efficacy. *KRAS* mutations do not generally overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* genetic variants. Therefore, selipratinib (Retevmo) testing may identify patients who may not benefit from further molecular testing. Targeted therapy is not currently available for patients with *KRAS* mutations.

COLLEGE OF AMERICAN PATHOLOGISTS, INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER, AND ASSOCIATION FOR MOLECULAR PATHOLOGY (CAP/IASLC/AMP)

The 2018 updated guidelines issued jointly by the CAP/IASLC/AMP recommend:^[70]

- *ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics. (Strong Recommendation)
- *ROS1* IHC may be used as a screening test in lung adenocarcinoma patients; however, positive *ROS1* IHC results should be confirmed by a molecular or cytogenetic method. (Expert Consensus Opinion)
- *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *ERBB2* (HER2) molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2* (HER2) mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)
- *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative. (Expert Consensus Opinion)

Regarding cell-free DNA (cfDNA) testing, the guidelines state:

- There is currently insufficient evidence to support the use of circulating cfDNA molecular methods for the diagnosis of primary lung adenocarcinoma. (No Recommendation)
- In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify EGFR mutations. (Recommendation)

- Physicians may use cfDNA methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKI; testing of the tumor sample is recommended if the plasma result is negative. (Expert Consensus Opinion)
- There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of EGFR T790M mutations at the time of EGFR TKI resistance. (No Recommendation)

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

In 2018, the American Society of Clinical Oncology (ASCO) endorsed the 2018 CAP/IASLC/AMP joint guidelines on molecular testing to select patients with lung cancer to determine treatment, with minor modifications. ASCO additionally recommends that *BRAF* testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.^[71]

SUMMARY

NTRK* AND *RET* GENE FUSIONS AND *ALK*, *KRAS*, *MET*, *PD-L1*, AND *ROS1

There is enough research to show that testing for *NTRK* and *RET* gene fusions and *ALK*, *KRAS*, *MET*, *PD-L1*, and *ROS1* variants can help to guide treatment for patients with non-small cell lung cancer (NSCLC). In addition, many clinical guidelines based on research recommend testing for patients with this disease. Therefore, *NTRK* gene fusions and *ALK*, *KRAS*, *PD-L1*, and *ROS1* genetic variant testing may be considered medically necessary for selection of therapy.

There is not enough research to show that for *NTRK* and *RET* gene fusions and *ALK*, *KRAS*, *MET*, *PD-L1*, and *ROS1* variants can improve health outcomes for patients when not used for treatment selection. Therefore, this testing is considered investigational when policy criteria are not met.

EGFR

There is enough research to show that testing for epidermal growth factor receptor (*EGFR*) variants can help to identify patients with advanced non-small cell lung cancer (NSCLC) who are likely to benefit from certain medications. In addition, many clinical guidelines based on research recommend testing for patients with this disease. Therefore, *EGFR* genetic variant testing may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that this testing improves health outcomes for patients who do not meet policy criteria, including patients with stage I or II NSCLC. Therefore, *EGFR* testing is considered investigational in these patients.

BRAF

There is enough research to show that tumor testing for the *BRAF* V600E variant can help to identify patients with advanced non-small cell lung cancer (NSCLC) who are likely to benefit from certain medications. In addition, clinical guidelines based on research recommend testing for this variant to guide treatment for select individuals with advanced NSCLC.

Therefore, tumor testing for *BRAF* variants may be considered medically necessary to select NSCLC patients for treatment with BRAF- or MEK-inhibitor therapy.

There is not enough research to show that this testing improves health outcomes for patients who do not meet policy criteria, including patients with stage I or II NSCLC. Therefore, *BRAF* testing is considered investigational in these patients.

ONCOMINE™ DX TARGET TEST

The Oncomine™ Dx Target Test is an FDA-approved companion diagnostic test to help identify non-small cell lung cancer (NSCLC) patients that may benefit from certain medications. The test identifies tumors that have variants in the *EGFR*, *ROS1*, and *BRAF* genes, which may respond to targeted treatments. This 23-gene test also includes testing for a number of genes that do not have clear evidence of clinical utility. While genetic test panels are generally considered to be investigational when there is not clinical utility for all genes in the panel, this test is the only FDA-approved companion diagnostic available to NSCLC patients to help with selection of certain targeted medications. Therefore, use of the Oncomine™ Dx Target test may be considered medically necessary to select patients with advanced or metastatic NSCLC for treatment with gefitinib (Iressa®), crizotinib (Xalcori®), or a combination of dabrafenib (Tafinlar®) and trametinib (Mekinist®).

There is not enough research to show that the use of the Oncomine™ Dx Target Test is useful for selecting therapy for patients without advanced or metastatic non-small cell lung cancer (NSCLC). Therefore, the use of this test is considered investigational for patients that do not meet policy criteria.

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72. BlueCross BlueShield Association Medical Policy Reference Manual "Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC)." Policy No. 2.04.45

CODES

Codes	Number	Description
CPT	0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
	81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
	81210	<i>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)</i>
	81235	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)
	81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) – which includes <i>RET</i> (ret proto-oncogene) (eg, multiple

Codes	Number	Description
		endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) – which includes <i>KRAS</i> (Kirsten rat sarcoma viral oncogene homolog) (eg, Noonan syndrome), full gene sequence; and <i>RET</i> (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) – which includes <i>BRAF</i> (B-Raf proto-oncogene, serine/threonine kinase) (eg, Noonan syndrome), full gene sequence
	81479	Unlisted molecular pathology procedure
	84999	Unlisted chemistry procedure
HCPCS	None	

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