

Local Coverage Determination (LCD): MoIDX: NRAS Genetic Testing (L35073)

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Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
Palmetto GBA	A and B and HHH	MAC 11202 - MAC B	J - M	South Carolina
Palmetto GBA	A and B and HHH	MAC 11302 - MAC B	J - M	Virginia
Palmetto GBA	A and B and HHH	MAC 11402 - MAC B	J - M	West Virginia
Palmetto GBA	A and B and HHH	MAC 11502 - MAC B	J - M	North Carolina

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LCD Information

Document Information

LCD ID L35073	Original Effective Date For services performed on or after 10/01/2015
Original ICD-9 LCD ID L34627	Revision Effective Date For services performed on or after 01/01/2016
LCD Title MoIDX: NRAS Genetic Testing	Revision Ending Date N/A
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CMS National Coverage Policy Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are considered to be reasonable and necessary.

Title XVIII of the Social Security Act, §1862(a)(1)(D). Allows coverage and payment for clinical care items and services provided with the concurrence of the Secretary and with respect to research and experimentation conducted by, or under contract with, the Medicare Payment Advisory Commission or the Secretary, which are not reasonable and necessary to carry out the purposes of section

Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

42 CFR 410.32(a). States diagnostic tests must be ordered by the physician treating the beneficiary.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§ 80.6, Requirements for Ordering and Following Orders for Diagnostic Tests.

CMS On-Line Manual, Publication 100-08, Medicare Benefit Policy Manual, Chapter 3, §§ 3.4.1.3, Diagnosis Code Requirements.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Indications:

This is a limited coverage policy for genetic testing of tumor tissue for somatic mutations in the NRAS gene (81404). MoIDX will cover NRAS testing for metastatic colorectal cancer, per NCCN guidelines (Version 1.2016).

All other NRAS testing is non-covered.

Background:

RAS oncogene is a superfamily of signal transduction proteins, which are proteins that communicate signals between the cells. DNA mutations in the RAS family genes turns the signals on permanently such that the cells divide nonstop, leading to cancer. Three of this family's proteins, HRAS, KRAS, and NRAS are important in tumors and encode 21kD proteins called p21s.

Previous studies have shown that targeting oncogenic NRAS-driven melanomas requires decrease in both pERK and pAKT downstream of RAS-effectors for efficacy, which could be achieved by either targeting both BRAF and CRAF or BRAF and PIK3CA simultaneously in NRAS mutant tumor cells.

Colorectal Cancer:

Multiple signaling pathways are involved in colorectal cancer pathogenesis. The epidermal growth factor receptor (EGFR) plays a key role in activation of these pathways and is commonly overexpressed in metastatic colorectal cancer (mCRC). Consequently, EGFR is a target of anticancer therapies. Two of these drugs, cetuximab and panitumumab, are monoclonal antibodies that block EGFR action. The 2013 NCCN Clinical Practice Guidelines for Colon Cancer describes a recent study by Douillard et al [2013] which reported that 17% of 641 patients from the PRIME trial without KRAS exon 2 mutations were found to have mutations in exons 3 and 4 of KRAS or mutations in exons 2, 3, and 4 of NRAS. A predefined retrospective analysis of a subset of these patients showed that progression free survival (PFS) and overall survival (OS) were decreased in those who received panitumumab plus FOLFOX compared to those who received FOLFOX alone. For this reason the FDA indication for panitumumab was recently updated to state that panitumumab is not indicated for the treatment of patients with NRAS mutation-positive disease in combination with oxaliplatin-based chemotherapy.

In chemotherapy-refractory patients, fewer than 10% of patients who harbor one of these mutations respond to EGFR immunotherapy. The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) both recommend KRAS mutation testing prior to prescribing EGFR antagonist therapy for patients with mCRC and state that alternative therapy should be prescribed when mutations are detected.

However, NCCN Colorectal Guidelines (Version 1.2016) recommend "All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS mutations (KRAS and NRAS). At the very least, exon 2 KRAS mutation status should be determined. Whenever possible, non-exon 2 KRAS mutation status and NRAS mutation status should also be determined. Patients with any known KRAS mutation (exon 2 or non-exon-2) or NRAS mutation should not be treated with either cetuximab or panitumumab." Consequently, MolDX is expanding coverage of NRAS to patients with metastatic colorectal cancer.

Metastatic Melanoma:

The NRAS gene encodes a protein that helps control cell division. Approximately 15% to 20% of melanomas harbor an oncogenic NRAS mutation. NRAS mutations can occur in all melanoma subtypes, but may be slightly more common in skin with chronic sun damage or in nodular melanomas. In addition, NRAS mutations are not found in tumors with BRAF mutations.

Several studies have been carried out to examine whether mutations in BRAF and NRAS confer different pathological features and clinical behavior. The effect of these mutations on clinical outcome remains uncertain with previous studies reporting conflicting results.

The NRAS protein is a GTPase which can lead to the activation of other proteins (such as AKT and MEK) that are also in pathways that help regulate cell division. In theory, drugs that inhibit AKT or MEK also have the potential to counteract the effects of NRAS mutations, although NRAS targeting therapies are still in clinical trials. In addition, pathways that help regulate cell division also include other proteins that could potentially be targeted such as PI3K and mTOR.

Melanomas can be tested for NRAS mutations with targeted sequencing. There are several manufacturers of targeted genetic tests that can detect NRAS mutations in melanoma tumor samples. The prognostic significance of NRAS mutations is still not well understood and further investigation of the histologic types of melanoma with specific NRAS mutations in a larger series is necessary to validate these apparent impacts on patient outcomes. In smaller subsets of cutaneous melanoma, other activating mutations have been described, including NRAS, c-KIT, and CDK4.

Other Cancers:

Other neoplastic diseases in which NRAS mutations have been reported in the primary literature include: myeloid leukemia, bladder cancer, liver cancer, and proliferative thyroid lesions.

Schulten et al [2-013] directly sequenced mutational hotspot regions encompassing codons 12, 13, and 61 of the RAS genes in 381 cases of thyroid lesions. In addition, the putative NRAS hotspot region encompassing codon 97 was sequenced in 36 thyroid lesions. Schulten and team found mutations in 16 out of 57 patients.

Kompier et al [2010] reports that although they have been reported, NRAS mutations are not common in bladder cancer.

Although NRAS mutations have been identified in the above tumor types, evidence in the primary literature is limited with regard to the clinical utility of NRAS mutation testing and its impact on management and survival. There is currently insufficient evidence to demonstrate clinical utility of NRAS testing in these tumor types.

NRAS Testing in relation to Noonan syndrome diagnosis:

Noonan syndrome is a common autosomal dominant condition with an incidence of 1/1,000 to 1/2,500 people. Unlike the somatic tumor mutations discussed above, Noonan syndrome may be caused by a germline mutation in the NRAS gene which would be present in every cell of the body. Noonan syndrome is characterized by a number of phenotypic findings including distinctive facial features, short stature, heart defects, cryptorchidism, lymphedema, and coagulation defects, among others. Several syndromes have features that overlap clinically with Noonan syndrome including cardiofaciocutaneous syndrome, Costello syndrome, LEOPARD syndrome and Noonan--like syndrome with loose anagen hair. The genetic etiologies of these conditions can also overlap with Noonan syndrome.

Several of these disorders have been referred to as neurocardiofacialcutaneous syndromes, RASopathies or Ras/MAPK pathway disorders and have a shared pathway of genetic function.

They are characterized by facial dysmorphism, cardiac disease, reduced growth, skeletal and ectodermal defects and variable cognitive deficits. They also share a predisposition to development of malignancies.

Overall, approximately 75% of individuals with Noonan syndrome will have an identifiable mutation with gene panel testing. To date, NRAS mutations have been found in four individual case reports which suggests that NRAS testing for Noonan syndrome is unlikely to yield positive results. The clinical features appear to be typical with no particular or distinctive phenotype observed suggesting that mutation testing targeted to select individuals is not feasible.

Genotype-phenotype correlations have emerged that can help to direct medical management for those affected with an associated condition, but not specifically for NRAS mutations. For instance, mutations in the SOS1 gene have been associated with an increased chance for ectodermal involvement, development of certain solid tumors, pulmonary stenosis, and atrial and ventricular septal defects; with an associated decreased prevalence of cognitive defects, short stature, and hypertrophic cardiomyopathy.

Medical management recommendations are available for many of the Noonan syndrome spectrum disorders. Overlapping features result in overlapping medical management recommendations, typically guided by clinical features.

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph: N/A

Group 1 Codes:

81311 NRAS (NEUROBLASTOMA RAS VIRAL [V-RAS] ONCOGENE HOMOLOG) (EG, COLORECTAL CARCINOMA), GENE ANALYSIS, VARIANTS IN EXON 2 (EG, CODONS 12 AND 13) AND EXON 3 (EG, CODON 61)
81479 UNLISTED MOLECULAR PATHOLOGY PROCEDURE

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph: N/A

Group 1 Codes:

ICD-10 Codes

Description

C78.5 Secondary malignant neoplasm of large intestine and rectum

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General Information

Associated Information

N/A

Sources of Information and Basis for Decision

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Revision History Information

Please note: Most Revision History entries effective on or before 01/24/2013 display with a Revision History Number of "R1" at the bottom of this table. However, there may be LCDs where these entries will display as a separate and distinct row.

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
01/01/2016	R7	Added 2016 CPT code 81311 and removed 81404	<ul style="list-style-type: none">• Revisions Due To CPT/HCPCS Code Changes
12/03/2015	R6	Annual validation review. Updated version for NCCN guidelines referenced in policy and replaced Palmetto with MoIDX.	<ul style="list-style-type: none">• Other (Annual validation)
10/01/2015	R5	CPT code 81479 added to policy	<ul style="list-style-type: none">• Revisions Due To ICD-10-CM Code Changes
10/01/2015	R4	Addition of MoIDX to LCD title	<ul style="list-style-type: none">• Other (per request of MAC's using MoIDX service)
10/01/2015	R3	Completed Annual Validation	<ul style="list-style-type: none">• Other (Annual Validation)
10/01/2015	R2	For the following CPT/HCPCS codes either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: 81404 descriptor was changed in Group 1	<ul style="list-style-type: none">• Revisions Due To CPT/HCPCS Code Changes
10/01/2015	R1	Changed policy from noncoverage to limited coverage, per NCCN Coloractal Guidelines. Also added ICD-10 C78.5 to Codes that Support Medical Necessity.	<ul style="list-style-type: none">• Other (NCCN Guidelines changed policy from noncovered to limited coverage.)

Associated Documents

Attachments N/A

Related Local Coverage Documents Article(s) [A54810 - Response to Comments: MoIDX: NRAS Genetic Testing](#)

Related National Coverage Documents N/A

Public Version(s) Updated on 12/23/2015 with effective dates 01/01/2016 - N/A [Updated on 11/24/2015 with effective dates 12/03/2015 - 12/31/2015](#) Updated on 09/11/2015 with effective dates 10/01/2015 - 12/02/2015 [Updated on 07/01/2015 with effective dates 10/01/2015 - N/A](#) Updated on 06/18/2015 with effective dates 10/01/2015 - N/A Updated on 12/19/2014 with effective dates 10/01/2015 - N/A Updated on 03/24/2014 with effective dates 10/01/2015 - N/A Updated on 03/05/2014 with effective dates 10/01/2015 - N/A [Back to Top](#)

Keywords

N/A Read the [LCD Disclaimer](#) [Back to Top](#)