

# Local Coverage Determination (LCD): MoIDX: NRAS Genetic Testing (L36335)

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## Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

## LCD Information

## Document Information

LCD ID

Original Effective Date

L36335

For services performed on or after 07/05/2016

**LCD Title**

MoIDX: NRAS Genetic Testing

**Revision Effective Date**

For services performed on or after 12/01/2019

**Proposed LCD in Comment Period**

N/A

**Revision Ending Date**

N/A

**Source Proposed LCD**

DL36335

**Retirement Date**

N/A

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**Notice Period Start Date**

05/19/2016

**Notice Period End Date**

07/04/2016

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**CMS National Coverage Policy**

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

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.

## **Coverage Guidance**

### **Coverage Indications, Limitations, and/or Medical Necessity**

#### **Indications:**

This is limited coverage policy for genetic testing of tumor tissue for somatic mutations in the NRAS gene. Noridian will cover NRAS testing for metastatic colorectal cancer, per NCCN guidelines (Version 2.2016).

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 2.2016) recommend "All patients with metastatic colorectal cancer

should have tumor tissue genotyped for RAS mutations (KRAS and NRAS) and BRAF mutations. Patients with any known KRAS mutation (exon 2 or non- exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.” Evidence increasingly suggests that BRAF V600E mutation makes response to cetuximab highly unlikely, as a single agent, or in combination with cytotoxic chemotherapy. In light of the above, KRAS, NRAS and BRAF are covered for 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.

(Per NCCN Guidelines 3.2016- BRAF- targeted Therapies: “Approximately half of patients with metastatic cutaneous melanoma harbor an activating mutation of BRAF, an intracellular signaling kinase in the MAPK pathway. Most BRAF-activating mutations occurring in melanomas are at residue V600, usually V600E but occasionally V600K or other substitutions. BRAF inhibitors have been shown to have clinical activity in melanomas with BRAF V600 mutations. Inhibitors of MEK, a signaling molecule downstream of BRAF, may potentiate these effects. Recent efficacy and safety data from large randomized trials testing BRAF and MEK inhibitors have significantly impacted the recommended treatment options for patients with BRAF-mutation positive advanced melanoma.”)

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, cKIT, 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 [2013] 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.

### **Summary of Evidence**

N/A

### **Analysis of Evidence (Rationale for Determination)**

N/A

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## **General Information**

### **Associated Information**

## Sources of Information

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**Bibliography**

N/A

**Revision History Information**

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/01/2019	R5	<p>The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p>	<ul style="list-style-type: none"> <li>Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD. )</li> </ul>
12/01/2019	R4	<p>LCD is revised to move several CMS references to the companion billing and coding article.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p>	<ul style="list-style-type: none"> <li>Creation of Uniform LCDs With Other MAC Jurisdiction</li> </ul>
12/01/2019	R3	<p>As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p>	<ul style="list-style-type: none"> <li>Revisions Due To Code Removal</li> </ul>

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
01/19/2017	R2	Added the following ICD-10 codes under Group 1 that were left out of the C79.00-C79.9 range in error. C79.01, C79.02, C79.10,C79.11, C79.19, C79.2, C79.31, C79.32, C79.40, C79.49, C79.51, C79.52, C79.60, C79.61, C79.62, C79.70, C79.71, C79.72, C79.81, C79.82, C79.89, C79.9	<ul style="list-style-type: none"> <li>Revisions Due To ICD-10-CM Code Changes</li> </ul>
01/19/2017	R1	Added primary and secondary diagnoses codes under ICD-10 Codes that Support Medical Necessity:  Group 1: C77.0-C77.9 Secondary and unspecified malignant neoplasm of lymph nodes C78.00-C78.89 – Secondary malignant neoplasm of respiratory and digestive organs C79.00-C79.9 Secondary malignant of other and unspecified sites  Group 2: C18.0-C18.9 – Malignant neoplasm of colon C19 – Malignant neoplasm of recto-sigmoid junction C20 – Malignant neoplasm of rectum	<ul style="list-style-type: none"> <li>Revisions Due To ICD-10-CM Code Changes</li> </ul>

## Associated Documents

### Attachments

N/A

### Related Local Coverage Documents

Article(s)

A57486 - Billing and Coding: MoIDX: NRAS Genetic Testing

A55048 - Response to Comments: MoIDX: NRAS Genetic Testing

LCD(s)

DL36308

- (MCD Archive Site)DL36335

- (MCD Archive Site)

### Related National Coverage Documents

N/A

### Public Version(s)

Updated on 01/29/2020 with effective dates 12/01/2019 - N/A

Updated on 12/05/2019 with effective dates 12/01/2019 - N/A

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## **Keywords**

N/A