

MolDX: NRAS Genetic Testing

Noridian Healthcare Solutions, LLC

Close

This LCD will be updated when it finalizes to include CPT 81479 for billing of this service.

Proposed

Please Note: This is a Proposed LCD.

Proposed LCDs are works in progress and not necessarily a reflection of the current policies or practices. Proposed LCDs in an approval status display on the CMS MCD for public review.

Contractor Information

Proposed

Contractor Name Noridian Healthcare Solutions, LLC

Contract Number 01112

Contract Type A and B MAC

Associated Contract Numbers (A and B MAC - 01182 - J - E) Noridian Healthcare Solutions, LLC, (A and B MAC - 01212 - J - E) Noridian Healthcare Solutions, LLC, (A and B MAC - 01312 - J - E) Noridian Healthcare Solutions, LLC

Proposed LCD Information



Source LCD ID N/A

Proposed LCD ID DL36335

Original ICD-9 LCD ID N/A

Proposed LCD Version 3

Proposed LCD Title MolDX: NRAS Genetic Testing

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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

CMS National Coverage Policy

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.

Jurisdiction California - Northern

Super MAC Jurisdiction J - E

Coverage Guidance



Indications:

Coverage Indications, Limitations and/or Medical Necessity

This is limited coverage policy for genetic testing of tumor tissue for somatic mutations in the NRAS gene (81404). Noridian will cover NRAS testing for metastatic colorectal cancer, per NCCN guidelines (Version 3.2014).

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 3.2014) 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, Noridian 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, 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.

Genotypephenotype 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.

Proposed Process Information



**Associated
Information
Sources of
Information and**

**Basis for
Decision**

1. Akslen LA, Angelini S, Straume O, et al. BRAF and NRAS mutations are frequent in nodular melanoma but are not associated with tumor cell proliferation or patient survival. *J Invest Dermatol.* 2005 Aug;125(2):312-7.
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3. Benson AB, et al. NCCN Clinical Practice Guidelines in Oncology™: colon cancer. National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf . Version 2. 2014. Accessed November 22, 2013.
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Open Meetings	Meeting Date	Meeting Information	State
	10/01/2015	The open public meeting will be held at the following location: Embassy Suites Flamingo Ballroom 4315 Swenson St. Las Vegas, NV 89119	American Samoa, California - Entire State, Guam, Hawaii, Northern Mariana Islands, California - Northern, California - Southern

Part B	Meeting Date	Meeting Information	State
MAC Contractor Advisory Committee (CAC) Meetings	10/09/2015	The Pacific Club Card Room 1451 Queen Emma St Honolulu, HI 96813	American Samoa, Guam, Hawaii, Northern Mariana Islands
	10/21/2015	DoubleTree by Hilton San Francisco Airport Tiburon/Sausalito Room 835 Airport Boulevard Burlingame, CA 94010	California - Entire State, California - Northern, California - Southern
	10/22/2015	Clark County Medical Association/NV State Medical Association 2590 E Russell Rd Las Vegas, NV 89120	Nevada

Comment

Period 10/01/2015

Start Date

Comment

Period 12/07/2015

End Date

Released

to Final Not yet released.

LCD Date

Reason for Creation of Uniform LCDs...

Proposed Creation of Uniform LCDs With Other MAC Jurisdiction

LCD

Noridian Healthcare Solutions, LLC JE Part B Contractor Medical Director(s)

Proposed Attention: Draft LCD Comments

LCD PO Box 6783

Contact Fargo, North Dakota 58108-6783

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Coding Information



Bill Type Codes 999x Not Applicable

Revenue Codes

Group 1: Paragraph

Group 1: Codes

CPT/HCPCS Codes

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)

Does the CPT 30% Coding Rule Apply?

No

ICD-10 Codes that Support Medical Necessity

Group 1: Paragraph

Group 1: Codes

Note: Performance is optimized by using code ranges.

C78.5

Secondary malignant neoplasm of large intestine and rectum

ICD-10 Codes that DO NOT Support Medical Necessity

Group 1: Paragraph

Group 1: Codes

Note: Performance is optimized by using code ranges.

Additional ICD-10 Information

Associated Documents

Proposed

Attachments	There are no attachments for this LCD.
Related Local Coverage Documents	This LCD version has no Related Local Coverage Documents.
Related National Coverage Documents	This LCD version has no Related National Coverage Documents.
All Versions	Version 3 - Updated on 08/06/2015 12:20:41, by Christine.Burnside@noridian.com, with effective dates N/A - N/A (Approved). Version 2 - Updated on 08/05/2015 19:27:44, by Ronda.Sears@noridian.com, with effective dates N/A - N/A. Version 1 - Updated on 08/05/2015 19:19:26, by Ronda.Sears@noridian.com, with effective dates N/A - N/A.