Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for mutations associated with familial cutaneous malignant melanoma (CMM) or associated with susceptibility to cutaneous malignant melanoma (CMM) to be investigational.*

Background/Overview
A genetic predisposition to CMM is suspected in specific clinical situations: (1) melanoma has been diagnosed in multiple family members; (2) multiple primary melanomas are identified in a single patient; and (3) in the case of early age of onset. A positive family history of melanoma is the most significant risk factor; it is estimated that approximately 10% of melanoma cases report a first- or second-degree relative with melanoma. Although some of the familial risk may be related to shared environmental factors, 3 main genes involved in CMM susceptibility have been identified. Cyclin-dependent kinase inhibitor 2A (CDKN2A), located on chromosome 9p21 encodes proteins that act as tumor suppressors. Mutations at this site can alter the tumor suppressor function. The second gene, cyclin-dependent kinase 4 (CDK4), is an oncogene located on chromosome 12q13 and has been identified in about 6 families worldwide. A third gene, not fully characterized, maps to chromosome 1p22.

The incidence of CDKN2A mutations in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a CDKN2A mutation. Mutations are also infrequent in those with an early age of onset or those with multiple primary melanomas. However, the incidence of CDKN2A mutations increases with a positive family history; CDKN2A mutations will be found in 5% of families with first-degree relatives, rising to 20% to 40% in kindreds with 3 or more affected first-degree relatives. Mutation detection rates in the CDKN2A gene are generally estimated as 20% to 25% in hereditary CMM but can vary between 2% and 50%, depending on the family history and population studied. Validated clinical risk prediction tools to assess the probability that an affected individual carries a germline CDKN2A mutation are available.

Familial CMM has been described as a family in which either 2 first-degree relatives are diagnosed with melanoma or a family with 3 melanoma patients, irrespective of the degree of relationship. Others have defined familial CMM as having at least 3 (first-, second-, or third-degree) affected members or 2 affected family members in which at least 1 was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative, or 1 member had multiple primary melanomas. No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.

Other malignancies associated with familial CMM, specifically those associated with CDKN2A mutations, have been described. The most pronounced associated malignancy is pancreatic cancer. Other associated...
malignancies include other gastrointestinal malignancies, breast cancer, brain cancer, lymphoproliferative malignancies, and lung cancer. It is also important to recognize that other cancer susceptibility genes may be involved in these families. In particular, germline \textit{BRCA2} gene mutations have been described in families with melanoma and breast cancer, gastrointestinal cancer, pancreatic cancer, or prostate cancer.

CMM can occur either with or without a family history of multiple dysplastic nevi. Families with both CMM and multiple dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome (FAMMM). This syndrome is difficult to define because there is no agreement on a standard phenotype, and dysplastic nevi occur in up to 50\% of the general population. Atypical or dysplastic nevi are associated with an increased risk for CMM. Initially, the phenotypes of atypical nevi and CMM were thought to cosegregate in FAMMM families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that in families with \textit{CDKN2A} mutations, there were family members with multiple atypical nevi who were noncarriers of the \textit{CDKN2A} familial mutation. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of CMM susceptibility in these families.

Some common allele(s) are associated with increased susceptibility to CMM but have low to moderate penetrance. One gene of moderate penetrance is the melanocortin 1 receptor gene (\textit{MC1R}). Variants in this gene are relatively common and have low penetrance for CMM. This gene is associated with fair complexion, freckles, and red hair, all risk factors for CMM. Variants in \textit{MC1R} also modify the CMM risk in families with \textit{CDKN2A} mutations.

\textit{Melaris}® (Myriad Genetics. Salt Lake City, UT) is a commercially available genetic test of the \textit{CDKN2A} gene.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). \textit{Melaris} and other \textit{CDKN2A} tests are LDTs and available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**

Validation of the clinical use of any diagnostic test focuses on 3 main principles: (1) analytic validity of the test; ie, the technical performance of the test; (2) clinical validity, ie, the diagnostic performance of the test, such as sensitivity, specificity, and positive and negative predictive values in different populations of patients and compared with the criterion standard; and (3) clinical utility of the test, ie, how the results of the diagnostic test will be used to improve patient management.
Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016

Analytic Validity
No published data on the analytic validity of genetic testing for mutations associated with familial cutaneous melanoma were identified.

Clinical Validity
Clinical validity is related to interpretation of the results of genetic analysis for the individual patient. One issue common to genetic testing for any type of cancer susceptibility is determining the clinical significance of individual mutations. For example, mutations in the CDKN2A gene can occur along its entire length, and some of these mutations represent harmless polymorphisms or noncoding mutations. Interpretation will improve as more data accumulate regarding the clinical significance of individual mutations in families with a known hereditary pattern of melanoma. However, the penetrance of a given mutation will also affect its clinical significance, particularly because the penetrance of CDKN2A mutations may vary with ethnicity and geographic location. For example, exposure to sun and other environmental factors, as well as behavior and ethnicity may contribute to penetrance. Bishop et al (2002) estimated that the calculated risk of developing melanoma before age 80 years in carriers of CDKN2A mutations ranged from 58% in Europe to 91% in Australia.

Interpretation of a negative test is another issue. CDKN2A mutations are found in less than half of those with strong family history of melanoma. Therefore, additional melanoma predisposition genes are likely to exist, and patients with a strong family history with normal test results must not be falsely reassured that they are not at increased risk. For example, in a 2011 meta-analysis of 145 genome-wide association studies, 8 independent, genetic loci were identified as being associated with a statistically significant risk of cutaneous melanoma, including 6 with strong epidemiologic credibility (MC1R, TYR, TYRP1, SLC45A2, ASIP/PIGU/MYH7B, CDKN2A/MTAP). Also, in a 2011 meta-analysis of 20 studies with data from 25 populations, red hair color variants on the MC1R gene were associated with the highest risk of melanoma, but non–red hair color variants also were associated with an increased risk of melanoma. In a 2012 review, Ward et al noted the genetics of melanoma are far from being understood, and “it is likely a large number of SNPs (single nucleotide polymorphisms), each with a small effect and low penetrance, in addition to the small number of large effect, high-penetrance SNPs, are responsible for CMM (cutaneous malignant melanoma) risk.”

In 2009, Yang et al conducted a study to identify modifier genes for CMM in CMM-prone families with or without CDKN2A mutations. Investigators genotyped 537 individuals (107 CMM) from 28 families (19 CDKN2A-positive, 9 CDKN2A-negative) for genes involved in DNA repair, apoptosis, and immune response. Their analyses identified some candidate genes, such as FAS, BCL7A, CASP14, TRAF6, WRN, IL9, IL10RB, TNFSF8, TNFRSF9, and JAK3, that were associated with CMM risk; after correction for multiple comparisons, IL9 remained significant. The effects of some genes were stronger in CDKN2A mutation-positive families (BCL7A, IL9), and some were stronger in CDKN2A-negative families (BCL2L1). The authors considered these findings supportive of the hypothesis that common genetic polymorphisms in DNA repair, apoptosis, and immune response pathways may modify the risk of CMM in CMM-prone families, with or without CDKN2A mutations.
In 2010, Kanetsky et al conducted a study to describe associations of \textit{MC1R} (melanocortin 1 receptor gene) variants and melanoma in a U.S. population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure. The study population included melanoma patients (n=960) and controls (n=396) who self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations of high- and low-risk \textit{MC1R} variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of 2 low-risk, or any high-risk \textit{MC1R} variant was associated with increased risk of melanoma (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.0 to 2.8; OR=2.2; 95% CI, 1.5 to 3.0, respectively). However, risk was noted to be stronger in or limited to people with protective phenotypes and limited sun exposure, such as those who tanned well after repeated sun exposure (OR=2.4), had dark hair (OR=2.4), or had dark eyes (OR=3.2). The authors concluded that these findings indicate \textit{MC1R} genotypes provide information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes or exposures alone. However, how this information impacts patient care and clinical outcomes is unknown.

Two subsequent studies in southern European populations examined further the association of \textit{MC1R} variants and melanoma. Ibarrola-Villava et al (2012) conducted a case control study in 3 sample populations from France, Italy, and Spain. Susceptibility genotypes in 3 genes involved in pigmentation processes were examined in 1639 melanoma patients (15% familial) and 1342 controls. \textit{MC1R} variants associated with red hair color were successfully genotyped in 85% of cases and 93% of controls. (Two other genes not associated with familial cutaneous melanoma—\textit{TYR}, which encodes a tyrosinase, and \textit{SLC45 A2}, which encodes a melanosomal enzyme—also were studied.) In univariate logistic regression analysis, \textit{MC1R} red hair color variants were significantly associated with the odds of developing melanoma in a dose-dependent fashion: OR for 1 allele: 2.2 (95% CI, 1.9 to 2.6); OR for 2 alleles: 5.0 (95% CI, 2.8 to 8.9). In analysis stratified by self-reported phenotype, these variants were statistically associated with increased odds of melanoma not only in individuals with fair phenotype (eye, hair and skin color) but also in those with dark/olive phenotype. The authors suggested that \textit{MC1R} genotyping to identify elevated risk in Southern European patients considered not at risk based on phenotype alone warranted further investigation. Effects on health outcomes are unknown.

Ghiorzo et al (2012) studied 49 \textit{CDKN2A}-mutation positive and 390 \textit{CDKN2A}-mutation negative Italian patients with cutaneous melanoma. \textit{MC1R} variants were associated with increased odds of melanoma only in \textit{CDKN2A}-mutation-negative patients in a dose-dependent fashion: OR for 1 high-risk allele: 1.5 (95% CI, 1.1 to 2.0); OR for 2 high-risk alleles, 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, effects of \textit{MC1R} variants were statistically significant in most \textit{CDKN2A} mutation-negative subgroups and few mutation-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, and total nevus count), sun exposure, and history of severe sunburn. In contrast, first-degree family history of cutaneous melanoma increased the odds of developing melanoma in both mutation-positive (OR=71.2; 95% CI, 23.0 to 221.0) and mutation-negative (OR=5.3; 95% CI, 2.0 to 14.3) patients, although uncertainty in the estimates of association was considerable. Family history of cutaneous nevi (at least 1 first-degree relative with >10 nevi and/or atypical nevi) increased the odds of melanoma in mutation-positive cases only (OR=2.44; 95% CI, 1.3 to 4.5). This finding underscores the significance of nongenetic factors (eg, sun exposure, and history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.
Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016

Cust et al (2012) classified 565 patients with invasive cutaneous melanoma diagnosed between 18 to 39 years of age, 518 sibling controls, and 409 unrelated controls into \textit{MC1R} categories defined by presence of high risk or other alleles. Compared with sibling controls, 2 \textit{MC1R} high-risk alleles (R151C, R160W) were associated with increased odds of developing melanoma (OR=1.7; 95% CI, 1.1 to 2.6; OR=2.0; 95% CI, 1.2 to 3.2, respectively), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared with unrelated controls, only the \textit{R151C} high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other \textit{MC1R} alleles (not considered high risk) and odds of developing melanoma in unadjusted or adjusted analyses. In 2010, Psaty et al published an article on identifying individuals at high risk for melanoma and emphasized the use of family history.

In 2013, Puntervoll et al published a description of the phenotype of individuals with \textit{CDK4} mutations in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls). The incidence of atypical nevi was higher in those with \textit{CDK4} mutations (70% in melanoma patients; 75% in unaffected individuals) than in those without \textit{CDK4} mutations (27%; p<0.001). The distribution of eye color or hair color was not statistically different between \textit{CDK4} mutation-positive individuals (with or without melanoma) and mutation-negative family members. The authors concluded that “it is not possible to distinguish \textit{CDK4} melanoma families from those with \textit{CDKN2A} mutation based on phenotype.” As noted previously, the clinical significance of this genetic distinction is currently unclear.

\textbf{Clinical Utility}

In 2003 and 2010, the American Society of Clinical Oncology issued policy statements on genetic and genomic testing for cancer susceptibility. Both statements recommended that, outside of a research setting, genetic testing for cancer susceptibility should be offered only when the following 3 criteria are met: (1) the individual being tested has a personal or family history suggestive of an underlying hereditary component; (2) the genetic test can be adequately interpreted; and (3) test results will guide diagnosis and management.

Although genetic testing for \textit{CDKN2A} mutations is recognized as an important research tool, its clinical use will depend on how results of genetic analysis can be used to improve patient management. Currently, management of patients considered high risk for malignant melanoma focuses on reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. Presently, it is unclear how genetic testing for \textit{CDKN2A} would alter these management recommendations. The following clinical situations can be considered.

\textbf{Affected Individual with a Positive Family History}

If an affected individual tests positive for a \textit{CDKN2A} mutation, he/she may be at increased risk for a second primary melanoma compared with the general population. However, limited and protected sun exposure and increased surveillance would be recommended to any patient with a malignant melanoma, regardless of the presence of a \textit{CDKN2A} mutation. However, a positive result will establish a mutation, thus permitting targeted testing for the rest of the family. Additionally, a positive mutation in an affected family member increases the likelihood of its clinical significance if detected in another family member. As described earlier, a negative test is not interpretable.
Unaffected Individual in a High-Risk Family

If the unaffected individual is the first to be tested in the family (i.e., no affected relative has been previously tested to define the target mutation), it is very difficult to interpret the clinical significance of a mutation, as described. The likelihood of clinical significance is increased if the identified mutation is the same as one reported in other families, although the issue of penetrance is a confounding factor. If the unaffected individual has the same mutation as an affected relative, then the patient is at high risk for melanoma. However, again it is unclear how this would affect the management of the patient. Increased sun protection and surveillance are recommended for any patient in a high-risk family.

Published data on genetic testing of the CDKN2A and CDK4 genes focus on the underlying genetics of hereditary melanoma, identification of mutations in families at high risk of melanoma, and risk of melanoma in those harboring these mutations. Other studies have focused on the association between CDKN2A and pancreatic cancer. One publication added the caution that differences in melanoma risk across geographic regions justify the need for studies in individual countries before counseling should be considered.

In a 2008 study, Aspinwall et al found short-term change in behavior among a small group of patients without melanoma who were positive for the CDKN2A mutation. In this prospective study of 59 members of a CDKN2A mutation-positive pedigree, behavioral assessments were made at baseline, immediately after CDKN2A test reporting and counseling, and at 1-month follow-up (42 participants). Across multiple measures, test reporting caused CDKN2A mutation carriers without a melanoma history to improve to the level of adherence reported by participants with a melanoma history. CDKN2A-positive participants without a melanoma history reported greater intention to obtain total body skin examinations, increased intentions and adherence to skin self-examination recommendations, and increased number of body sites examined at 1 month. In 2013, Aspinwall et al reported outcomes for 37 patients (62%) of this cohort who were available for 2-year follow-up. Anxiety, depression, and cancer-specific worry declined over 2 years, although baseline values were low and the declines are of uncertain clinical significance. Adherence to annual total body skin examinations and monthly skin self-examinations varied by carrier status; however, without a comparison group, it is not possible to attribute any change in adherence to knowledge of test results.

In a 2011 retrospective case-control study, van der Rhee et al sought to determine whether a surveillance program of families with a Dutch founder mutation in CDKN2A (the p16-Leiden mutation) allowed for earlier identification of melanomas. Characteristics of 40 melanomas identified in 35 unscreened patients (before heredity was diagnosed) were compared with 226 melanomas identified in 92 relatives of those 35 unscreened melanoma patients who were found to have the CDKN2A mutation and participated in a surveillance program over a 25-year period. Surveillance comprised a minimum of an annual total skin evaluation, which became more frequent if melanoma was diagnosed. Melanomas diagnosed during surveillance were found to have a significantly lower Breslow thickness (median thickness, 0.50 mm) than melanomas identified in unscreened patients (median thickness, 0.98 mm), signifying earlier identification with surveillance. However, only 53% of melanomas identified in the surveillance group were detected on regular screening appointments. Additionally, there was no correlation between length of screening intervals (for intervals <24 months) and melanoma tumor thickness at the time of diagnosis. The authors also noted
that despite understanding the importance of surveillance, patient noncompliance was still observed in the surveillance program, and almost half of patients were noncompliant when first diagnosed with melanoma.

In 2013, van der Rhee et al reported on a retrospective case-control study of 21 families with the p16-Leiden founder mutation. The purpose of the study was to investigate the yield of surveillance of first- and second-degree relatives of patients with melanoma (n=14 families) or with melanoma and pancreatic cancer (n=7 families). Overall, melanoma incidence rate was 9.9 per 1000 person-years (95% CI, 7.4 to 13.3) in first-degree relatives and 2.1 per 1000 person-years (95% CI, 1.2 to 3.8) in second-degree relatives. In comparison with the general population in the Netherlands, overall standardized morbidity ratio for melanoma was 101.0 (95% CI, 55.9 to 182.3) in first-degree relatives (observed, 45, expected, 0.76) and 12.9 (95% CI, 7.2 to 23.4) in second-degree relatives (observed, 11, expected, 0.53). Although the authors conclude that surveillance of second- (as well as first-) degree relatives from very high-risk melanoma families is justified based on these findings, it is unclear whether these findings apply to families without or with other CDKN2A mutations. Further, because increased sun protection and surveillance are recommended for any member of a high-risk family, clinical relevance of the finding is uncertain.

Branstrom et al (2012) examined a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with increased risk of melanoma. Fifty-three percent had been diagnosed with melanoma, and 12% had a positive susceptibility genetic test. The study indicated that a negative test might be associated with an erroneous perception of lower risk and fewer preventive measures.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00339222</td>
<td>Family Study of Melanoma in Italy</td>
<td>1600</td>
<td>NR</td>
</tr>
<tr>
<td>NCT00040352</td>
<td>Clinical, Laboratory, and Epidemiologic Characterization of Individuals and</td>
<td>3000</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Families at High Risk of Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00591500</td>
<td>A Model for Genetic Susceptibility: Melanoma</td>
<td>4082</td>
<td>Jul 2016</td>
</tr>
<tr>
<td>NCT00849407</td>
<td>Genetic Risk Factors and Acquired Oncogenic Mutations of Melanoma</td>
<td>2000</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT00450593</td>
<td>Studies of Familial Melanoma</td>
<td>5000</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**Summary of Evidence**
The evidence for genetic testing in patients who have melanoma and family history of this disease or unaffected individuals in a family at high risk of developing melanoma includes association studies between mutations in certain genes and the risk of developing cutaneous melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Data on the analytic validity of testing are lacking. Limitations with clinical validity include difficulties with mutation variant interpretations, variable penetrance of a given mutation, and residual risk with a negative mutation. Currently, management of
patients considered high risk for malignant melanoma focuses on reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. It is unclear how genetic testing for mutations associated with increased risk of melanoma would alter these management recommendations; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016


Policy History

Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016

09/06/2006 Medical Director review
09/20/2006 Medical Policy Committee approval
10/01/2008 Medical Director review
10/22/2008 Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009 Medical Policy Committee review
10/01/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010 Medical Policy Committee review
10/06/2011 Medical Policy Committee review
10/19/2011 Medical Policy Implementation Committee approval. Added “familial” to the policy title. Replaced “hereditary” with “familial” in the investigational statement and throughout the policy.
10/11/2012 Medical Policy Committee review
10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016 Medical Policy Committee review

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 11/2017

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81404</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>C43.0, C43.10-C43.12, C43.20-C43.22, C43.30-C43.39, C43.4, C43.51-C43.59, C43.60-C43.62, C43.70-C43.72, C43.8-C43.9, C44.00-C44.09, C44.101-C44.199, C44.201-C44.299, C44.300-C44.399, C44.40-C44.49, C44.500-C44.599, C44.601-C44.699, C44.701-C44.799, C44.80-C44.89, C44.90-C44.99, D03.0-D03.9</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.
Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
Current Effective Date: 11/16/2016

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.