**Genetic Testing for Cutaneous Malignant Melanoma**

**Effective:** March 1, 2018

**Next Review:** February 2019  
**Last Review:** February 2018

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**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.

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**DESCRIPTION**

Genetic markers for cutaneous malignant melanoma (CMM) are being evaluated in those with a family history of the disease and to estimate risk for those who do not have family history of CMM.

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**MEDICAL POLICY CRITERIA**

Genetic testing for variants associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered **investigational**.

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

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**CROSS REFERENCES**

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20  
2. Gene Expression Profiling for Melanoma, Genetic Testing, Policy No. 29

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**BACKGROUND**

A genetic predisposition to cutaneous malignant melanoma is suspected in specific clinical
situations:

- Melanoma has been diagnosed in multiple family members;
- Multiple primary melanomas are identified in a single patient; and
- 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. While some of the familial risk may be related to shared environmental factors, four main genes involved in CMM susceptibility have now been identified:

- **CDKN2A**, located on chromosome 9p21, encodes proteins that act as tumor suppressors. Mutations at this site can alter the tumor suppressor function.
- **CDK4** is an oncogene located on chromosome 12q13 and has been identified in about six families worldwide.
- A third gene, not fully characterized, maps to chromosome 1p22.
- **BAP1**, which is located on 3p21, encodes a protein that acts as a tumor suppressor.[1-3]

The incidence of **CDKN2A** disease-associated variants 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** disease-associated variants. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas.[4] However, the incidence of **CDKN2A** mutations increases with a positive family history; **CDKN2A** disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20–40% in kindreds with three or more affected first-degree relatives.[5] Variant detection rates in the **CDKN2A** gene are generally estimated as 20–25% in hereditary CMM but can vary between 2% and 50%, depending on the family history and population studied.

Hereditary CMM has been described as a family in which either two first-degree relatives are diagnosed with melanoma or a family with three melanoma patients, irrespective of the degree of relationship.[6] Others have defined hereditary CMM as having at least three (first-, second-, or third-degree) affected members or two affected family members in which at least one was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative, or one member had multiple primary melanomas.[7]

Other malignancies associated with hereditary CMM, specifically those associated with **CDKN2A** variants, have been described. The most pronounced associated malignancy is pancreatic cancer, followed by 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 **BRCA2** gene variants have been described in families with melanoma and breast cancer, gastrointestinal cancer, pancreatic cancer, or prostate cancer.

Hereditary forms of 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 since 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} variants, there were family members with multiple atypical nevi who were non-carriers of the \textit{CDKN2A} familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from non-carriers of CMM susceptibility in these families.

Both germline and somatic variants of \textit{BAP1} have been reported to have varying degrees of penetrance and has been described in an autosomal-dominant pattern within three families of European descent.\textsuperscript{[3,8]} \textit{BAP1} as a germline variant increases CMM susceptibility; however, the complete tumor spectrum associated with germline \textit{BAP1} variants is not known.\textsuperscript{[1]} The information provided by the presence of a germline \textit{BAP1} variant is not clinically actionable at this time.

Some common allele(s) are associated with increased susceptibility to CMM but have low penetrance. One such gene 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 of which are risk factors for CMM. Variants in \textit{MC1R} also modify the CMM risk in families with \textit{CDKN2A} variants.\textsuperscript{[9]}

**EVIDENCE SUMMARY**

Human Genome Variation Society (HGVS) nomenclature\textsuperscript{[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.

Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

**ANALYTIC VALIDITY**

No published data on the analytic validity of genetic testing for variants associated with cutaneous malignant 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 variants. For example, variants in the \textit{CDKN2A} gene can occur along its entire length, and some of these variants represent benign variants. Interpretation will improve as more data accumulate regarding the clinical significance
of individual variants in families with a known hereditary pattern of melanoma. However, the penetrance of a given variant will also affect its clinical significance, particularly because the penetrance of CDKN2A variants may vary with ethnicity and geographic location.\cite{4,5} For example, exposure to sun and other environmental factors, as well as behavior and ethnicity may contribute to penetrance. Bishop et al estimated that the calculated risk of developing melanoma before age 80 years in carriers of CDKN2A variants ranged from 58% in Europe to 91% in Australia.\cite{11}

Interpretation of a negative test is another issue. CDKN2A variants 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.\cite{4} For example, in a 2012 review Ward noted that 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 risk.”\cite{12} In a 2011 meta-analysis of 145 genome-wide association studies, eight independent, genetic loci were identified as being associated with a statistically significant risk of cutaneous melanoma, including six with strong epidemiologic credibility (MC1R, TYR, TYRP1, SLC45A2, ASIP/PIGU/MYH7B, CDKN2A/MTAP).\cite{13} 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.\cite{14}

In 2016, Di Lorenzo published a study on 400 patients with cutaneous melanoma who were observed in a six-year period at an Italian university.\cite{15} Forty-eight patients have met the criteria of the Italian Society of Human Genetics (SIGU) for the diagnosis of familial melanoma and were screened for CDKN2A and CDK4 variants. Genetic testing revealed that none of the families carried variants in the CDK4 gene and only one patient harbored the rare CDKN2A p.R87W variant. The study did not identify a high variant rate of CDKN2A in patients affected by familial melanoma or multiple melanoma. This difference could be attributed to different factors, including the genetic heterogeneity of the Sicilian population. It is likely that, as in the Australian people, the inheritance of familial melanoma in this island of the Mediterranean Sea is due to intermediate/low-penetrance susceptibility genes, which, together with environmental factors (as latitude and sun exposure), could determine the occurrence of melanoma.

In 2013, Puntervoll published a description of the phenotype of individuals with CDK4 variants in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls).\cite{16} The incidence of atypical nevi was higher in those with CDK4 variants (70% in melanoma patients; 75% in unaffected individuals) than in those without CDK4 variants (27%; p<0.001). The distribution of eye color or hair color was not statistically different between CDK4 variant-positive individuals (with or without melanoma) and variant-negative family members. The authors concluded that “it is not possible to distinguish CDK4 melanoma families from those with CDKN2A variant based on phenotype.” Therefore, the clinical significance of this genetic distinction is currently unclear.

In 2012, Cust classified 565 patients with invasive cutaneous melanoma diagnosed between 18 to 39 years of age, 518 sibling controls, and 409 unrelated controls into MC1R categories defined by presence of high risk or other alleles.\cite{17} Compared with sibling controls, two 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 R151C high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other $MC1R$ alleles (not considered high risk) and odds of developing melanoma in unadjusted or adjusted analyses. In 2010, Psaty published an article on identifying individuals at high risk for melanoma and emphasized the use of family history.[18]

A 2016 study by Wendt evaluated $MC1R$ variants and melanoma risk in a hospital-based case-control study that included 991 melanoma patients and 800 controls.[19] $MC1R$ variants were associated with a higher risk of melanoma after adjustment for age, sex, and ultraviolet radiation exposure ($\geq 2$ variants, OR, 2.13 [95% CI, 1.66-2.75], $P < .001$; $P$ for trend <.001).

In 2017, Borroni published an Italian case series of 92 consecutive, unrelated patients with familial atypical mole/multiple melanoma syndrome (FAMMM) that were offered genetic counseling and testing for $CDKN2A$ and $CDK4$ variants.[20] FAMMM is characterized by primary cutaneous melanoma in at least two relatives and/or two or more primary cutaneous melanomas in the same patient. Genetic testing was extended to family members of patients with identified variants. $CDKN2A$ variants were found in 19 of the 92 unrelated patients (20.6%) and in 14 healthy relatives. Of these relatives with variants, 11 later underwent excision of dysplastic nevi.

In 2012, two studies further examined the association of $MC1R$ variants and melanoma in southern European populations.[21,22] Ibarrola-Villava conducted a case-control study in three sample populations from France, Italy, and Spain.[21] Susceptibility genotypes in three genes involved in pigmentation processes were examined in 1639 melanoma patients (15% familial) and 1342 controls. $MC1R$ 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—TYR, which encodes a tyrosinase, and SLC45 A2, which encodes a melanosome enzyme—were also studied. In univariate logistic regression analysis, $MC1R$ red hair color variants were significantly associated with the odds of developing melanoma in a dose-dependent fashion: OR for one allele: 2.2 (95% CI, 1.9 to 2.6); OR for two 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 $MC1R$ 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 studied 49 $CDKN2A$- variant positive and 390 $CDKN2A$- variant negative Italian patients with cutaneous melanoma.[22] $MC1R$ variants were associated with increased odds of melanoma only in $CDKN2A$- variant-negative patients in a dose-dependent fashion: OR for one high-risk allele: 1.5 (95% CI, 1.1 to 2.0); OR for two high-risk alleles, 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, effects of $MC1R$ variants were statistically significant in most $CDKN2A$ variant-negative subgroups and few variant-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 variant-positive (OR=71.2; 95% CI, 23.0 to 221.0) and variant-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=one first-degree relative with >10 nevi and /or atypical nevi) increased the odds of melanoma in variant-positive cases only (OR=2.44; 95% CI, 1.3 to 4.5). This finding underscores the significance of nongenetic factors (e.g., sun exposure, and history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

In 2010, Kanetsky conducted a study to describe associations of \( MC1R \) (melanocortin one receptor gene) variants and melanoma in a U.S. population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure.[23] 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 \( MC1R \) variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of two low-risk, or any high-risk \( MC1R \) 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 \( MC1R \) 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.

In 2009, Yang conducted a study to identify modifier genes for CMM in CMM-prone families with or without \( CDKN2A \) variants.[24] Investigators genotyped 537 individuals (107 CMM) from 28 families (19 \( CDKN2A \)-positive, nine \( CDKN2A \)-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 \( CDKN2A \) variant-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 \( CDKN2A \) variants.

CLINICAL UTILITY

In 2003 and 2010 the American Society of Clinical Oncology issued policy statements on genetic and genomic testing for cancer susceptibility.[25,26] Both statements recommended that, outside of a research setting, genetic testing for cancer susceptibility should be offered only when the following three 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 \( CDKN2A \) variants 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 \( CDKN2A \) would alter these management recommendations. The following clinical situations can be considered.
Affected Individual with a Positive Family History

If an affected individual tests positive for a CDKN2A variant, they 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 CDKN2A mutation. A positive result will establish a familial variant, 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 variant), it is very difficult to interpret the clinical significance of a variant, as described. The likelihood of clinical significance is increased if the identified variant 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 variant 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 variants in families at high risk of melanoma, and risk of melanoma in those harboring these variants. Other studies have focused on the association between CDKN2A and pancreatic cancer.[27-29] 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.[30]

In 2018, Stump reported changes in sun protection and stress levels following genetic counseling and test reporting for the CDKN2A/p16 variant.[31] Participants included 18 minors from melanoma-prone families, with a mean age of 12.4. Nine were carriers and nine were noncarriers. Compared to baseline, at one year post-disclosure, all subjects self-reported significantly fewer sunburns. In addition, a greater proportion reported sun protection adherence. There were no significant differences between genotypes. Depressive symptoms and cancer worry declined and anxiety symptoms, which began low, remained unchanged post-disclosure. In interviews, all mothers of the subjects indicated that genetic testing was beneficial. Reasons included that it promoted risk awareness (90.9%) and sun protection (81.8%) without making their children scared (89.9%). Independent practice of sun protection by their children was reported by 45.4% of mothers.

In 2013, Aspinwall reported outcomes for 37 patients (62%) of this cohort who were available for two-year follow-up.[32,33] Anxiety, depression, and cancer-specific worry declined over two 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 2012, Branstrom examined a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with increased risk of melanoma.[34] 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.

In a 2011 retrospective case-control study, van der Rhee sought to determine whether a surveillance program of families with a Dutch founder variant in CDKN2A (the p16-Leiden variant) allowed for earlier identification of melanomas.[35] 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 variant 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 a 2008 study, Aspinwall found short-term change in behavior among a small group of patients without melanoma who were positive for the CDKN2A variant.[36] In this prospective study of 59 members of a CDKN2A variant-positive pedigree, behavioral assessments were made at baseline, immediately after CDKN2A test reporting and counseling, and at one month follow-up (42 participants). Across multiple measures, test reporting caused CDKN2A disease-associated variant 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 one month.

Two similar behavioral studies were published in 2016. Levin examined behavior patterns in families in Norway in which a CDKN2A variant was identified.[37] This authors reported that 66% (95/144) of variant carriers' first-degree relatives contacted the researchers within the study period, 98% (126/128) of all relatives who came for genetic counseling requested genetic testing, and 93% (66/71) of those with variants wanted referral for yearly skin examinations. Wu studied the impact of melanoma genetic test reporting and counseling on the frequency of discussion about preventive behaviors between 24 counseled adults and their children and grandchildren.[38] Conversations about preventive behaviors were assessed before testing and at one and six months after testing, using open-ended questions. The authors reported that these discussions declined after test reporting, with a faster decline in variant non-carriers, and that there was a large gap between the number of participants who intended to have preventive behavior discussions and the number that reported having had such discussions at follow-up.

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK[39]

In 2018, the National Comprehensive Cancer Network (NCCN) updated their clinical guidelines on melanoma which say, “Consider referral to a genetics counselor for p16/CDKN2A mutation
testing in the presence of 3 or more invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family. Testing for other genes that can harbor melanoma-predisposing mutations (eg, CDK4, TERT, MITF, and BAP1) may be warranted.”

**MELANOMA GENETICS CONSORTIUM**[^5]

Genetic testing for CDKN2A variants is currently available; however, the Melanoma Genetics Consortium (GenoMEL) recommends offering testing to patients only in the context of research protocols because clinical utility is uncertain.

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY**[^26]

In 2010, the American Society of Clinical Oncology (ASCO) updated its policy statement on genetic and genomic testing for cancer susceptibility. ASCO recommends that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

**SUMMARY**

There is not enough research to show that genetic testing for cutaneous melanoma can improve health outcomes, including for people with melanoma or a family history of melanoma. There are no clinical guidelines based on research that specifically recommend this type of testing. Therefore, genetic testing for variants associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.

**REFERENCES**


37. Levin, T., Maehle, L. Uptake of genetic counseling, genetic testing and surveillance in hereditary malignant melanoma (CDKN2A) in Norway. *Fam Cancer.* 2016 Nov 01. PMID: 27804060


### CODES

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