Genetic Testing for Familial Cutaneous Malignant Melanoma

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I. Policy Description

Skin cancer is the most common form of cancer, arising from the metaplastic transformation from any of the cell types of the skin. Melanomas, which develop from the pigment-producing melanocytes, although much less prevalent than non-melanoma skin cancer, are increasing in incidence. Early and accurate diagnosis is essential, as late-stage melanoma is among the most fatal forms of skin cancer. This, however, presents a significant challenge due to the difficulty of interpreting the histopathology of melanoma and the resulting interobserver and intra-observer variability.

This policy covers testing to assess the genetic risk of familial cutaneous melanoma and diagnostic testing to differentiate melanocytic lesions with indeterminate histopathology.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

1) Genetic testing of the genes listed below (see Notes 1-3) for inherited forms of melanoma in an affected individual **MEETS COVERAGE CRITERIA** if the affected individual has two or more first-degree relatives with melanoma or the individual has three or more primary melanomas.
    a) *CDKN2a*
    b) *CDK4*
    c) *MC1R*
    d) *BAP1*
    e) *BRCA2*
    f) *MITF*
    g) *TERT*

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

2) Any other genetic testing for inherited forms of cutaneous melanoma **DOES NOT MEET COVERAGE CRITERIA**.

NOTE 1: For 5 or more genes being tested on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

NOTE 2: For panel testing of assessment of susceptibility to familial cutaneous malignant melanoma, please refer to M2066: Genetic Cancer Susceptibility Using Next Generation Sequencing.

NOTE 3: If there is a known familial variant in the patient history, those variant(s) should be tested for first.

III. Table of Terminology

Term	Definition
AAD	The American Academy of Dermatology
ACD	Adrenocortical dysplasia protein homolog
ACMG	American College of Medical Genetics and Genomics
AJCC-8	American Joint Committee on Cancer 8th edition
ATM	*Ataxia-telangiectasia mutated*
BAP1	*Breast cancer susceptibility gene-associated protein-1*
BRAF	*B-Raf proto-oncogene, serine/threonine kinase*
BRCA1	*Breast cancer susceptibility gene*
BRCA2	*Breast cancer susceptibility gene 2*
CDK4	*Cyclin-dependent kinase 4*
CDKN2A	*Cyclin-dependent kinase inhibitor 2a*
CGH	Comparative genomic hybridization
CHEK2	*Checkpoint kinase 2*
CLIA'88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
DNA	Deoxyribonucleic acid
EADO	European Association of Dermato-Oncology
EDF	European Dermatology Forum
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FAMMM	Familial atypical multiple mole-melanoma
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GEP	Gene expression profiling
KIT	*KIT proto-oncogene, receptor tyrosine kinase*
LDTs	Laboratory developed tests
LINC00518	*Long intergenic non-coding ribonucleic acid 518*
MAS	Melanoma-astrocytoma syndrome
MC1R	*Melanocortin-1 receptor*
MDM2	*Mouse double minute 2*
MEK	Mitogen-activated protein kinase /extracellular regulated kinase kinase
MITF	*Microphthalmia-associated transcription factor*
NBN	*Nibrin*

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NED	Without evidence of disease
NER	Nucleotide excision repair
NGS	Next generation sequencing
NPV	Negative predictive value
NSGC	National Society of Genetic Counselors
OS	Overall survival
p14ARF	Adenosine pyrophosphate -ribosylation factor tumor suppressor
p16	Cyclin-dependent kinase inhibitor 2A
p53	Tumor protein P53
PFS	Progression-free survival
PLA	Pigmented legion assay
PLA(−)	Pigmented legion assay negative
POT1	Protection of telomeres 1
PRAME	*Preferentially expressed antigen in melanoma*
PTEN	*Phosphatase and tensin homolog*
RB1	*Retinoblastoma protein*
SLNB	Sentinel lymph node biopsy
TERT	Telomerase Reverse Transcriptase
TMB	Tumor mutation burden
US	United States
USPSTF	U.S. Preventive Services Task Force
UV	Ultraviolet
WRN	*Werner's syndrome protein*
XP	Xeroderma pigmentosum
XPC	*Xeroderma pigmentosum group c*
XPD	*Xeroderma pigmentosum group d*

IV. Scientific Background

Cutaneous melanoma is one of the most aggressive forms of skin cancer due to its potential for metastasis with poor prognosis when not detected and treated at early stages. Unlike other solid tumors, melanoma affects young and middle-aged individuals with a median age at diagnosis of 57 (Leonardi et al., 2018). Melanoma incidence and mortality are on the rise, with the lifetime risk of developing cutaneous melanoma estimated to be 1 in 34 for women and 1 in 53 for men. But though complex and varied in nature, the main risk factors involved in the pathogenesis of cutaneous melanoma can be narrowed down to exposure to ultraviolet radiation, the accumulation of many common acquired melanocyte nevi, light skin phenotypes, and a family history of melanoma.

Ultraviolet (UV) light radiation from sun exposure is a major risk factor for melanoma skin cancer development, directly associated with an increased risk of melanoma. Skin type, number of congenital and acquired melanocytic nevi, genetic susceptibility, and a family history have also been associated with increased risk for melanoma. In addition to the total number of nevi, the size and type of nevi are also individually associated with an increased risk of melanoma, as approximately 25% of melanomas

originate from an existing nevus. Interestingly, a greater number of nevi with a 3mm diameter or larger was recently associated with melanoma death in males but not in females. Early and accurate identification of patients with increased risk of melanoma development is essential to enable risk-tailored surveillance, management of early staged patients with biologically aggressive tumors, and improvement of patient outcomes.

Genetic Testing for Familial Cutaneous Melanoma

A family history of melanoma is reported by about 10% of melanoma patients, and inherited germline mutations reportedly "increase melanoma risk from 4- to >1000-fold." Determining the genetic origin, however, is complicated, as a portion of familial melanoma can be attributed to shared sun exposure experiences in family members with susceptible skin types. The majority of familial cases lack identifiable germ-line mutations in either known susceptibility genes or in genes commonly mutated in sporadic melanoma. Uncommon, but high-risk, alleles have been found to contribute to the hereditary cancer phenotype that includes unilateral lineage, multi-generational, multiple primary lesions, and early onset of disease. Additional research has identified a relationship between telomere length and familial melanoma; patients with familial melanoma had longer telomeres compared to patients with sporadic melanoma. As such, genes such as *TERT*—which encodes for the catalytic subunit of telomerase—and POT1—a shelterin complex protein—have been implicated in the presence of multiple primary melanomas and early-onset melanoma in a subset of high-density families.

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and cyclin-dependent kinase 4 (*CDK4*) are the most commonly identified gene mutations in familial forms of melanoma, which can be defined as a family where either two first-degree relatives or three or more melanoma patients on the same side of the family are diagnosed with melanoma. Germline *CDKN2A* mutations have been identified in approximately 20-40% of familial melanoma cases where three or more family members are affected. *CDKN2A* encodes several proteins involved in cell cycle regulation, including p16, which inhibits *CDK4*, and p14ARF, which inhibits *MDM2* from regulating p53. Germline *CDKN2A* mutations in melanoma families are usually missense or nonsense changes that impair the function of the p16 protein, allowing for unchecked cell cycle progression; however, rare mutations in the p14ARF protein have also been reported and result in proteasomal degradation of p53 with subsequent accumulation of DNA damage. Overall survival is worse in those with a germline *CDKN2A* mutation than those with sporadic melanoma or familial melanoma with wild-type *CDKN2A* genes. Germline mutations also predisposed patients to an increased number of malignancies, such as pancreatic and lung cancer.

Mutations in *CDKN2A*/p16 are associated with familial atypical multiple mole-melanoma (FAMMM syndrome), which is characterized by numerous nevi (some atypical), a family history of melanoma, and an increased risk of pancreatic cancer. Carriers of a FAMMM mutation typically present with cancer at a younger age than non-carriers. Mutations in p14ARF are linked to Melanoma-Astrocytoma Syndrome (MAS), a variant of FAMMM characterized by both cutaneous melanomas and nervous system tumors. Inheritance of *CDKN2A* mutations are autosomal dominant, but these mutations have variable penetrance based on sun exposure patterns and coinheritance of other melanoma-associated variants, conferring a 76% lifetime risk of developing melanoma in the US. Mutations in *CDK4* are even less common, but were most often found affecting arginine 24, resulting in a CDK4 protein that is insensitive to inhibition by the p16 protein. No apparent differences exist in the phenotype (e.g., age at diagnosis, number of melanomas) of families carrying either *CDKN2A* or *CDK4* mutations. In aggregate, between 20-45% of familial melanomas are associated with germline mutations in *CDKN2A* or *CDK4*.

Other rare mutations have been associated with melanoma. Germline variations in the melanocortin-1 receptor (*MC1R*) gene alter the risk of melanoma in individuals with and without *CDKN2A* mutations. Germline variants in genes that encode for *BRCA1*-associated protein-1 (*BAP1*), telomerase reverse transcriptase (*TERT*), and microphthalmia-associated transcription factor (*MITF*) have also been added to the list of genes harboring familial melanoma-predisposing mutations. These are more often associated with "mixed cancer syndrome," where melanoma may appear in the context of a more general predisposition for malignancy. The *BAP1* tumor syndrome is associated with the appearance of cutaneous melanoma, uveal melanoma, and various internal malignancies. Mutations in the promoter region of *TERT*, the protein component of telomerase, and in various components of the shelterin complex have been associated with a higher incidence of melanoma and other internal malignancies. Mutations in *MITF* are associated with a higher nevus count, cutaneous malignant melanoma onset before 40 years of age, and non-blue eye color with no association to freckling, skin color, or hair color. Xeroderma pigmentosum (XP) is a rare disorder in which patients have a mutation in genes involved in nucleotide excision repair (NER). Patients with mutations in *XPC* and *XPD* have an increased risk of melanoma. Lastly, Cowden syndrome, a type of *PTEN* hamartoma tumor syndrome characterized by the appearance of trichilemmomas, papillomatous papules, mucosal lesions (papules) and palmar-plantar keratosis within the first three decades of life, is associated with a higher risk of melanoma.

Several proprietary gene panels exist for assessment of familial cutaneous melanoma. For example, the DermTech Pigmented Legion Assay (PLA) leverages their "Smart Sticker" technology to remove cellular material from the stratum corneum, the material of which is then analyzed for over-expression of *LINC00518* (*long intergenic non-coding RNA 518*) and *PRAME* (*preferentially expressed antigen in melanoma*), which may be incidental with genomic atypia associated with melanomas. Moreover, Invitae offers a 12-gene panel (9 primary genes plus 3 genes with "preliminary evidence for melanoma"), Fulgent offers a 14-gene panel, and GeneDx offers a 9-gene panel. These panels may include genes traditionally associated with familial melanoma itself (such as *CDKN2A*) as well as genes whose variants are not primarily associated with familial melanoma, but confer added risk regardless.

Clinical Utility and Validity of Genetic Testing for Familial Cutaneous Melanoma

The frequency of *CDKN2A* mutations in patients with a single primary melanoma or multiple primary melanoma were 1.2% and 2.9%, respectively; however, depending on selection criteria, mutation frequency rates of *CDKN2A* can range from 5% to 72% with a family history of melanoma considered the most important risk factor. The established rule of three is used when proposing genetic testing for primary melanomas; it is generally understood that when three or more melanomas or genetically related cancers are identified in the same patient, or in first- and second-degree relatives, the pretest probability is increased above 10% and the cost of genetic screening can be justified.

In a study on *CDK2NA* genetic testing conducted in Sweden between 2015 and 2020, 913 members across 403 families were identified with cutaneous melanoma. Pissa et al. (2021) found that melanoma cases found in families testing positive for pathogenic variants of *CDK2NA* boasted significantly higher mortality rates, such that families with the variants had 37.6% melanoma cases that died from melanoma as compared to the 10.0% without ($p<0.001$), independent of age, sex, and tumor stage. This significant melanoma-specific mortality associated with families with *CDK2NA* variants is motivation to identify and enroll carrier families in a preventive surveillance program. However, a potential confounding variable involves the diagnoses of pancreatic cancers in the subjects in the study; as pathogenic strains of CDK2NA are also associated with cancers other than melanomas, the 129 of the

913 members present a limitation to the specificity of the study as there did not appear to be a clear manner of segregating its influence.

Potjer et al. (2019) have determined that "Germline mutations in the major melanoma susceptibility gene *CDKN2A* explain genetic predisposition in only 10-40% of melanoma-prone families" and subsequently characterized 488 melanoma cases from non-*CDKN2A*/*CDK4* families to determine other important mutations in familial melanoma. The authors conclude that "multigene panel testing for familial melanoma is appropriate considering the additional 4% diagnostic yield in non-*CDKN2A*/*CDK4* families. Our study shows that *BAP1* and *MITF* are important genes to be included in such a diagnostic test."

Stolarova et al. (2020) analyzed 264 Czech melanoma patients with early onset, double primary tumors or family history by next generation sequencing NGS analysis of 217 genes, and they identified that "mutations in high-to-moderate melanoma risk genes and in other cancer syndrome genes were significantly associated with melanoma risk," with those genes including *CDKN2A, POT1,* and *ACD* for high-to-moderate melanoma risk, and *NBN, BRCA1/2, CHEK2, ATM, WRN,* and *RB1* for other cancer syndrome genes. An increased potential of carrying mutations was found in "patients with double primary melanoma, melanoma and other primary cancer, but not in patients with early age at onset." *CDK2NA* was the most frequently mutated gene among those with high-to-moderate risk, and in other studies reviewed by Stolarova et al. (2020), there was an increased risk for pancreatic cancer among families with *CDK2NA* mutation, and a more established family history.

Leachman et al. (2017) published an updated algorithm for the identification, testing, and management of hereditary melanoma; the rule of three has been incorporated into this algorithm as an indication for genetic testing in multiple melanomas. The researchers state that "Any patient or family that meets the updated rule of threes should be considered a candidate for genetic testing. If melanoma is the only cancer in a pedigree, then to meet the threshold of genetic testing, a pedigree should have three primary melanomas in first- or second-degree relatives in areas with a high melanoma incidence or two primary melanomas in a low-incidence area. This melanoma panel should include *BAP1*, *CDK4*, and *CDKN2A*. Genes for which risk has not been established but for which studies suggest an elevated risk include *MITF* and *POT1* and we recommend including these in the melanoma panel."

Gerami et al. (2017) tested the validity of a two-gene panel based on *LINC00518* and *PRAME* on differentiating melanoma from nonmelanoma in a multicenter study across 28 sites in the United States, Europe, and Australia. In a sample of 398 (87 melanomas and 311 nonmelanomas), it was found that this classification method was able to accurately identify melanomas from nonmelanomas with a sensitivity of 91% and a specificity of 69%. The real-world performance and utility of the proprietary two-gene assay PLA by DermTech was also retrospectively assessed by four US dermatology practices 3 to 6 months after the PLA. In this cohort of 381 patients, 51 tested positive and 330 tested negative, and from this dataset the authors found that the PLA had a high NPV of >99% and a high sensitivity of 91-95%, while also boasting high specificity (69-91%). However, it is unclear if the negative samples—as determined by the PLA—will remain so, as "we [the authors] cannot rule out that some PLA(−) lesions may not have been adequately reassessed in the follow-up period and we certainly recommend erring on the side of caution and surgically biopsying a lesion in question if additional risk factors, further clinical suspicion, or patient concern mandate such a step." However, the authors continue to assert that because 100% of the 51 resulted reported to be positive by the PLA were correctly identified and handled by surgical biopsy, at the least "these findings show that clinicians follow the guidance of the test", though only time will tell if the biopsies stand correct.

The clinical utility of genetic testing for hereditary melanoma families is debatable because *CDKN2A* status may not impact medical management in patients with melanoma. This was further confirmed by Tovar-Parra, Gutiérrez-Castañeda, Gil-Quiñones, Nova, and Pulido (2020), who found that *CDKN2A* polymorphisms p.G101W, p.R24P, p.M53I, and A148T, in a case-control study with 85 cases and 166 controls, were not associated with increased susceptibility to melanoma in the Colombian population, thereby demonstrating the lack of procedures that would need to be taken for those with this mutation. However, testing for *CDKN2A* mutations with genetic counseling was shown to be perceived as more informative and motivating to patients to adhere to prevention recommendations. Compared to no-test controls, participants who received test results (carriers and noncarriers) reported feeling significantly more informed and prepared to manage their risk, and carriers reported greater motivation to reduce sun exposure; all groups reported low negative emotions about melanoma risk. Parents reported high levels of preparedness to manage children's risk regardless of group. Carrier parents reported greater (but moderate) worry about their children's risk than no-test control parents.

Genetic testing for commonly known cutaneous melanoma mutations can be utilized to determine prognosis and overall survival. Aoude et al. (2020) found that "germline mutation status was the most significant biomarker for OS [overall survival]" and "survival outcomes for germline carriers are poor with the current standards of care." When using BRAF status and tumor mutation burden (TMB) for prognosis of cutaneous melanoma patients, "BRAF V600 wild-type patients had significantly longer PFS [progression-free survival] than the V600 mutant group (p = 0.0317) … For stage III/IV resected patients, TMB was also significantly associated with longer PFS (p = 0.0034)." The greater the number of recognizable mutations, the more targeted attacks against cancerous cells can be made and the better the prognosis.

V. Guidelines and Recommendations

National Comprehensive Cancer Network

The NCCN Guidelines for Cutaneous Melanoma recommend to "Consider the use of molecular testing for histologically equivocal lesions," either with comparative genomic hybridization (CGH) or fluorescence *in situ* hybridization (FISH) for detecting genetic mutations, though the former may be more sensitive and specific. The NCCN also states that "The use of gene expression profiling (GEP) testing according to specific AJCC-8 melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup."

On testing of primary lesions, the NCCN recommends that "mutational analysis for *BRAF* or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma who are without evidence of disease (NED), unless required to guide adjuvant or other systemic therapy or consideration of clinical trials". However, follow-up procedures for stage 0 *in situ*, IA-IIA NED, and IIB-IV NED melanomas now extends to "Pre-diagnostic genomic patch testing" as they "may also be helpful to guide biopsy decisions."

Moreover, the NCCN also recommended that a referral should be considered for genetic counseling "for p16/*CDKN2A* mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of

invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family" and "Testing for other genes that can harbor melanoma-predisposing mutations may be warranted."

Indications for genetic testing using emerging molecular technologies for diagnosis and prognostication, the NCCN recommended the following:

- "The panel does not recommend *BRAF* or NGS [next generation sequencing] testing for resected stage I-II cutaneous melanoma unless it will inform clinical trial participation.
- *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom *BRAF*-directed therapy may be an option.
- For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting. *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (e.g., larger NGS panels, *BRAF* non-V600 mutation) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial.
- If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., *KIT*, *BRAF* non-V600)."

The American Academy of Dermatology (AAD)

The AAD published guidelines for the care and management of primary cutaneous melanoma. It was stated that "There is insufficient evidence to recommend routine molecular profiling assessment for baseline prognostication. Evidence is lacking that molecular classification should be used to alter patient management outside of current guidelines (eg, NCCN and AAD). The criteria for and the utility of prognostic molecular testing, including GEP, in aiding clinical decision making (e.g., SLNB eligibility, surveillance intensity, and/or therapeutic choice) needs to be evaluated in the context of clinical study or trial." Further, a "C" recommendation was given regarding patient referral for genetic counseling "and possible germline genetic testing for select patients" with potential hereditary cutaneous melanoma.

Regarding patients with a family history of invasive cutaneous melanoma (at least three affected members on one side of the family), "Cancer risk counseling by a qualified genetic counselor is recommended."

European Society for Medical Oncology (ESMO)

The ESMO published 2019 guidelines for cutaneous melanoma diagnosis, treatment and follow-up. This article states that "Mutation testing for actionable mutations is mandatory in patients with resectable or unresectable stage III or stage IV [I, A], and is highly recommended in high-risk resected disease stage IIC but not for stage I or stage IIA-IIB. *BRAF* testing is mandatory [I, A]."

Regarding follow-up, long-term implications and survivorship, the ESMO has stated that "Patients must be aware that family members have an increased melanoma risk [III, B]. There is no recommendation for genetic testing."

European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC)

The EDF, EADO, and EORTC collaboratively released an interdisciplinary guideline on the diagnostics of melanoma. With regards to genetic testing of cutaneous melanoma, the guidelines suggest that genetic profiling of melanoma tissues using NGS may help in identifying the genetic alterations that are targetable by drugs. For specific stages and in relation to the *BRAF* V600 mutation, the guidelines recommend mutation testing for cancers stage III and higher. However, "mutational analysis for *BRAF* of the primary lesion is not recommended for patients with cutaneous melanoma but without evidence of the disease, unless required to guide consideration of clinical trials for adjuvant therapy."

"Mutational analysis is required to determine the BRAFV600 mutation status in patients with distant metastasis or non-resectable regional metastasis to identify those who are eligible to receive treatment with combined BRAF and MEK inhibitors, and in resected high-risk stage III melanoma patients in the adjuvant setting. BRAFV600 mutation testing should be performed on metastatic tissue, either distant or regional, or on primary tumor if sampling of the metastatic tissue is not feasible."

American Joint Committee on Cancer (AJCC)

The AJCC did not include any mention of molecular testing in the most recent 8th edition guidance on melanoma staging.

U.S. Preventive Services Task Force (USPSTF)

The USPSTF examined the utility of visual skin examination for the prevention of melanoma and found that "Only limited evidence was identified for skin cancer screening, particularly regarding potential benefit of skin cancer screening on melanoma mortality." The use of molecular tests in screening for melanoma is not mentioned.

National Cancer Institute

The NCI updated its PDQ cancer information summary on the genetics of skin cancer in June 2018; this was reaffirmed in 2020. It summarizes expert opinion on genetic testing: "Expert opinion regarding testing for germline pathogenic variants of *CDKN2A* follows two divergent schools of thought. Arguments for genetic testing include the value of identifying a cause of disease for the individual tested, the possibility of improved compliance with prevention protocols in individuals with an identified pathogenic variant, and the reassurance of a negative testing result in individuals in a family carrying a pathogenic variant. However, a negative test result in a family that does not have a known pathogenic variant is uninformative; the genetic cause of disease in these patients must still be identified. It should also be noted that members of families carrying a *CDKN2A* pathogenic variant who do not carry the variant themselves may remain at increased risk of melanoma. At this time, identification of a *CDKN2A* pathogenic variant does not affect the clinical management of the affected patient or family members. Close dermatologic follow-up of these people is indicated, regardless of genetic testing result, and pancreatic cancer screening has unclear utility."

In 2021, the NCI points to the NCCN for current guidance on identifying germline pathogenic variants in genes associated with hereditary melanoma: "the NCCN recommends that individuals with three or more invasive cutaneous melanomas or a combination of invasive melanoma, pancreatic cancer, and/or astrocytoma in an individual or family be referred for genetic counseling and discussion of genetic testing for *CDKN2A*. Recommendation for multigene (panel) testing is in the context of clinical and family history of melanoma with other cancers such as uveal melanoma, astrocytoma, mesothelioma, breast cancer, pancreatic cancer, and renal cancer."

American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors (NSGC)

Referral for cancer genetic consultation is recommended by the ACMG and the NSCG for the following types of melanomas:

- Hereditary melanoma for "any individual with a personal history of or first-degree relative with (i) three or more melanomas in the same person or (ii) three or more cases of melanoma and/or pancreatic cancer."

- Melanoma-astrocytoma syndrome for "any individual with a personal history of or first-degree relative with (i) melanoma and astrocytoma in the same person or (ii) one case of melanoma and one case of astrocytoma in two first-degree relatives."

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023
Updated Lines of Business	12/18/2023