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 (Linares, Zakaria, & Nizran, 2015). Melanomas, developing from the pigment producing melanocytes, although much less prevalent than non-melanoma skin cancer, are increasing in incidence (Holmes, 2014; Lee & Lian, 2018). Early and accurate diagnosis is essential as late-stage melanoma is among the most fatal forms of skin cancer (Cockerell et al., 2017). This, however, presents a significant challenge due to the difficulty of interpreting the histopathology of melanoma and the resulting interobserver and intraobserver variability (Elmore et al., 2017; Gerami et al., 2014). Gene expression tests have been developed to assess genetic predisposition and predict the biologic behavior of diagnostically challenging melanocytic neoplasms (Lee & Lian, 2018).

This policy covers testing to assess the genetic risk of familial cutaneous melanoma and diagnostic testing to differentiate melanocytic lesions with indeterminate histopathology. Genetic testing of melanoma tumors for therapy is addressed in M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy, and M2029 BRAF Gene Mutation Testing.

Scientific Background

Cutaneous melanoma is one of the most aggressive forms of skin cancer in its potential for metastasis (Leonardi et al., 2018) with poor prognosis when not detected and treated at early stages (Soura, Eliades, Shannon, Stratigos, & Tsao, 2016b). 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 (Chiaravalloti, Jinna, Kerr, Whalen, & Grant-Kels, 2018; Siegel, Miller, & Jemal, 2017) with the lifetime risk of developing cutaneous melanoma estimated to be 1 in 34 for women and 1 in 53 for men (Siegel et al., 2017).

Ultraviolet (UV) light radiation from sun exposure is a major risk factor for melanoma skin cancer development (Gilchrest, Eller, Geller, & Yaar, 1999; Holmes, 2014), directly associated with an increased risk of melanoma (Leonardi et al., 2018; Pennello, Devesa, & Gail, 2000). Skin type, number of congenital and acquired melanocytic nevi, genetic susceptibility and a family history have also been associated with increased risk for melanoma (Bauer & Garbe, 2003; Bevona, Goggins, Quinn, Fullerton, & Tsao, 2003; Hawkes, Truong, & Meyer, 2016). 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 (Gandini et al., 2005; Watt, Kotsis, & Chung, 2004). 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 (Zager et al., 2018), and improve patient outcomes (Cockerell et al., 2017).

Gene Expression Profiling for Diagnosis and Prognosis
Currently, patients presenting with a suspicious pigmented lesion undergo excisional biopsy which is then subjected to histopathologic examination by a pathologist (NCCN, 2018). The majority of melanocytic neoplasms can be accurately classified by this approach, however in some cases confidently differentiating benign melanocytic nevi from malignant melanoma can be extremely difficult or impossible despite additions to histopathologic assessment such as the evaluation of Breslow depth (Chiaravalloti et al., 2018; Lee & Lian, 2018). In these cases even diagnoses from expert pathologists can be discordant (Elmore et al., 2017; Farmer, Gonin, & Hanna, 1996; Gerami et al., 2014) and subject to diagnostic drift (Bush, Hunt, & Fraga, 2015). A number of diagnostic and prognostic genetic tests for melanoma have been developed as ancillary tests to assist in this differentiation and resultant risk stratification (Lee & Lian, 2018).

Clinical Validity and Utility of Gene Expression Profiling

myPath Melanoma (Myriad Genetics)

A 23-gene expression profile and algorithm that assigns various weights and thresholds of expression for each gene was developed (Clarke et al., 2015) to differentiate benign melanocytic nevi from malignant melanoma with a sensitivity of 89% and specificity of 93%, with validation (Clarke, Flake, et al., 2017) against an independent histopathologic evaluation by 3 experienced dermatopathologists giving a sensitivity of 91.5% and a specificity of 92.5%. This gene expression profile was developed into a commercial test as myPath Melanoma which gives a single score ranging where a negative number indicates a benign lesion and a positive number indicates melanoma with a reported sensitivity of 90-94% and specificity of 91-96% (Ko et al., 2017), and correlates closely with long term clinical outcome adding valuable adjunctive information to aid in the diagnosis of melanoma. An examination of the utility of this test (Cockerell et al., 2017) found that the results of this gene expression signature have a significant clinical impact with 71.4% (55/77) of cases changing from pretest recommendations to actual treatment. The majority of changes were consistent with the test result. There was an 80.5% (33/41) reduction in the number of biopsy site re-excisions performed for cases with a benign test result. However when more challenging samples were included (Minca et al., 2016) with 39 histopathologically unequivocal lesions (15 malignant, 24 benign) and 78 challenging lesions interpreted by expert consensus (27 favor malignant, 30 favor benign, and 21 ambiguous), it had somewhat lower sensitivity and specificity than FISH (FISH: 69% sensitivity, 91% specificity; myPath; 55% sensitivity, 88% specificity). In the unequivocal group, FISH and myPath score showed 97% and 83% agreement with the histopathologic diagnosis, respectively, with 93% and 62% sensitivity, 100% and 95% specificity, and 80% inter-test agreement. In the challenging group, FISH and the myPath score showed 70% and 64% agreement with the histopathologic interpretation, respectively, with 70% inter-test agreement. It also may have limited sensitivity in cases of desmoplastic melanoma, a rare fibrosing variant of melanoma (Clarke, Pimentel, Zalaznick, Wang, & Busam, 2017). The exclusion of melanocytic neoplasms that did not have a triple concordant diagnosis, and the lowered sensitivity and specificity when these sample types were included may significantly limit the applicability of this test in the most challenging diagnostic circumstances (Lee & Lian, 2018).

Pigmented Lesion Assay (DermTech)

To help support clinicians in their decision to biopsy, a noninvasive 2 gene expression assay of the LINC and PRAME genes has been developed for use on adhesive patch biopsies. It is reported (Gerami et al., 2017) to have a sensitivity of 91% and a specificity of 69% with a negative predictive value of over 99%. Using this assay, dermatologists improved their mean biopsy sensitivity from 95.0% to 98.6% (P = .01); specificity increased from 32.1% to 56.9% (P < .001). This result may increase the number of early melanomas biopsied and reduce the number of benign lesions biopsied, thereby improving patient outcomes and reducing health care costs. (Ferris et al., 2017). An application study of 381 patients (Ferris et al., 2018) found that the estimated real-world sensitivity was 95% and specificity was 91%. Overall, 93% of PLA results positive for both LINC00518 and PRAME were diagnosed
histopathologically as melanoma. The test altered clinical management of pigmented lesions and shows high clinical performance. However, it has not been tested in preexisting nevi, or a range of melanoma subtypes (Lee & Lian, 2018).

**DecisionDx Melanoma (Castle Bioscience)**

Even within easily identifiable early stage melanoma there is considerable variability in the risk of disease progression from 3 to 55% (Balch et al., 2009). A positive sentinel lymph node test result has high positive predictive value, but a negative one has very low negative predictive value. No proven survival benefit in performing a sentinel lymph node biopsy in T1 disease has been observed to date (Chiaravalloti et al., 2018). Gerami et al (2015) developed a 28-gene signature for the identification of high-risk cutaneous melanoma tumors to accurately predict metastasis risk in a multicenter cohort of primary cutaneous melanoma tumors by identifying genes that were upregulated in metastatic melanoma but not in primary melanoma. Metastatic risk was predicted with high accuracy in development (ROC = 0.93) and validation (ROC = 0.91) cohorts of primary cutaneous melanoma tumor tissue. The sensitivity was 100% and specificity of 78%. Kaplan–Meier analysis indicated that the 5-year disease-free survival (DFS) rates in the development set were 100% and 38% for predicted classes 1 and 2 cases, respectively (P < 0.0001). A second study (Gerami, Cook, Russell, et al., 2015) found that the gene expression profile was a more accurate predictor than sentinel lymph node biopsy independently, but also improved prognostication in combination with sentinel lymph node biopsy. A multi-center study (Zager et al., 2018) validated the prognostic accuracy in an independent cohort of cutaneous melanoma patients found that the gene expression profile was a significant predictor of recurrence free survival and distant metastasis free survival in univariate analysis (hazard ratio [HR] = 5.4 and 6.6, respectively, P < 0.001 for each), providing additional independent prognostic information to traditional staging to help estimate an individual’s risk for recurrence. A prospective evaluation of the gene expression profile’s performance in 322 patients enrolled in two clinical trials found that patient outcomes from the combined prospective cohort supports the gene expression profile’s ability to stratify early-stage CM patients into two groups with significantly different metastatic risk, that survival outcomes in this real-world cohort are consistent with previously published analyses with retrospective specimens, and that gene expression profile testing complements current clinicopathologic features and increases identification of high-risk patients (Hsueh et al., 2017). The clinical utility of the test in conjunction with sentinel lymph node biopsy can identify as many as 89% of the patients who will experience a distant metastasis, and over 70% of those patients who are SLNB-negative. This gene signature was developed and marketed commercially as the Decision Dx-Melanoma test. A follow up study (Cook et al., 2018) on the analytic validity of DecisionDx found inter assay concordance of 99% and inter instrument concordance of 95% with a technical success of 98%, demonstrating that DecisionDx-Melanoma demonstrates strong reproducibility between experiments and has high technical reliability on clinical samples. It may be a useful diagnostic and prognostic adjunct in the workup of thin to intermediate thickness melanomas, especially in counseling patients who are candidates for sentinel lymph node biopsy. However, this assay has not been tested on the full spectrum of histologic subtypes of melanoma, and it is unclear how these results should be integrated into current staging criteria (Lee & Lian, 2018).

**Genetic Testing for Familial Cutaneous Melanoma**

A family history of melanoma is reported by about 10% of melanoma patients (Soura et al., 2016b). 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 (Goldstein & Tucker, 2001). The majority of familial cases lack identifiable germ-line mutations in either known susceptibility genes or in genes that are commonly mutated in sporadic melanoma (Hawkes et al., 2016). 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 (Soura et al., 2016b).

Cyclin-dependent kinase inhibitor 2A (CDKN2A) and cyclin-dependent kinase 4 (CDK4) are the most commonly identified gene mutations in familial forms of melanoma. CDKN2A encodes
several proteins involved in cell cycle regulation including p16 which inhibits CDK4 (Hussussian et al., 1994; Koh, Enders, Dynlacht, & Harlow, 1995), and p14ARF which inhibits MDM2 from regulating p53 (Zhang, Xiong, & Yarbrough, 1998). 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, although rare mutations in the p14ARF protein have also been reported and result in proteasomal degradation of p53 with subsequent accumulation of DNA damage (Marzuka-Alcala, Gabree, & Tsao, 2014). 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 is associated with an increased risk of pancreatic cancer (Goldstein et al., 2007; Lynch & Krush, 1968). Mutations in p14ARF are linked to Melanoma-Astrocytoma Syndrome (MAS), a variant of FAMMM characterized by both cutaneous melanomas and nervous system tumors (Randerson-Moor et al., 2001). Inheritance of CDKN2A mutations is autosomal dominant, but variably penetrant based on sun expose patterns and coinheritance of other melanoma associated variants, conferring a 76% lifetime risk of developing melanoma in the US (Bishop et al., 2002; Cust et al., 2011). Mutations in CDK4 are even less common but were most often found were on arginine 24, resulting in a CDK4 protein that is insensitive to inhibition by the p16 protein. No apparent differences exist in the phenotype (eg, age at diagnosis, number of melanomas) of families carrying either CDKN2A or CDK4 mutations. In aggregate, somewhere between 20-45% of familial melanomas are actually associated with germline mutations in CDKN2A or CDK4 (Goldstein et al., 2007; Nelson & Tsao, 2009).

Other rare mutations have been associated with melanoma. Germline variations in the melanocortin-1-receptor MC1R gene, alter the risk of melanoma, both in individuals with CDKN2A mutations and in individuals without CDKN2A mutations (Marzuka-Alcala et al., 2014; Pasquali et al., 2015; Wendt et al., 2018). Germline variants in 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 melanoma-predisposing mutations (Soura, Eliades, Shannon, Stratigos, & Tsao, 2016a). These are more often “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 (Wiesner et al., 2011). 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 (Burke et al., 2013; Horn et al., 2013). Mutations in MITF are associated with reported an association with a higher nevus count, CMM onset before 40 years of age, and non-blue eye color with no association to freckling, skin color, or hair color (Bertolotto et al., 2011; Yokoyama et al., 2011). 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 (Paszkowska-Szczur et al., 2013). Lastly, Cowden syndrome, a type of PTEN hamartoma tumor syndromes, characterized by the appearance of trichilemmomas, papillomatous papules, mucosal lesions (papules) and palmar-plantar keratosis within the 3 first decades of life, is associated with a higher risk of presenting with melanoma (Bubien et al., 2013; Soura et al., 2016a).

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 melanomas were 1.2% and 2.9%, respectively (Berwick et al., 2006), however, depending on selection criteria mutation frequency rates of CDKN2A can range from 5% to 72% (Delaunay et al., 2017) with a family history positive for melanoma representing the most important risk factor. Using the established rule of 3 when proposing genetic testing, for primary melanomas, with 3 or more melanomas or genetically related cancers in the same patient or in first- and second-degree relatives increases the pretest probability above 10% to justify the cost of genetic screening.

Leachman et al published updated algorithm for identification, genetic testing, and management of hereditary melanoma incorporating the rule of three as an indication for
genetic testing in multiple melanomas. They 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” (Leachman et al., 2017).

The clinical utility of genetic testing for hereditary melanoma families is debatable because CDKN2A status may not impact medical management in patients with melanoma (Gabree, Patel, & Rodgers, 2014). However, testing for CDKN2A mutations with genetic counseling was shown to be perceived as more informative and motivating to adhere to prevention recommendations (Aspinwall et al., 2018). 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.

State and Federal Regulations, as applicable

The FDA has not approved any genetic expression profile test for diagnosis or prognosis of primary cutaneous melanoma. This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories. 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Policy Statement(s)

A. Guidelines and Recommendations
Gene Expression Profiling for Diagnosis and Prognosis

National Comprehensive Cancer Network

The NCCN Guidelines for Cutaneous Melanoma (NCCN, 2018) recommends: “Consider the use of molecular testing for histologically equivocal lesions.” However, “while there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low versus high risk for metastasis, routine (baseline) prognostic genetic testing of primary cutaneous melanomas (before or following sentinel lymph node biopsy) is not recommended outside of a clinical study. Newer prognostic techniques should not replace standard staging procedures.”

American Joint Committee on Cancer

The AJCC did not include any mention of molecular testing in the most recent 8th edition guidance on melanoma staging (Gershenwald et al., 2017).

US Preventive Services Task Force

The USPSTF (Wernli et al., 2016) examined the utility of visual skin examination for the prevention of melanoma. They found that “Only limited evidence was identified for skin cancer screening, particularly regarding potential benefit of skin cancer screening on melanoma mortality.” They do not mention any use of molecular tests in screening for melanoma.

American Society of Clinical Oncology (ASCO)/Society of Surgical Oncology (SSO)

The ASCO-SSO published guidelines(Wong et al., 2018) on the use of sentinel lymph node biopsy which did not address any adjunctive molecular techniques.

Genetic Testing for Familial Cutaneous Melanoma

National Comprehensive Cancer Network

The NCCN Guidelines for Cutaneous Melanoma (NCCN, 2018) recommend: “Consider referral to a genetic 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.”

National Cancer Institute

The NCI updated its PDQ cancer information summary on the genetics of skin cancer (NCI, 2002) in June 2018; 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.”

American College of Medical Genetics and Genomics and the National Society of Genetic Counselors
Referral for cancer genetic consultation is recommended by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors (Hampel, Bennett, Buchanan, Pearlman, & Wiesner, 2015) for the following:

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.”

### B. Indications and/or Limitations of Coverage

*Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request*

1. Genetic testing for inherited forms of melanoma is considered **EXPERIMENTAL AND INVESTIGATIONAL**. This includes, but is not limited to, testing of the *CDKN2A* and *CDK4* genes.

2. Genetic expression profiling testing for cutaneous melanoma is considered **EXPERIMENTAL AND INVESTIGATIONAL**.

3. Panel testing codes are considered **EXPERIMENTAL AND INVESTIGATIONAL**.

### Applicable CPT/HCPCS Procedure Codes

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 Gene: <strong>CDKN2A</strong> (cyclin-dependent kinase inhibitor 2A) (eg, CDKN2A-related cutaneous malignant melanoma, familial atypical mole-malignant melanoma syndrome), full gene sequence</td>
</tr>
<tr>
<td>81445</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
</tr>
<tr>
<td>81455</td>
<td>Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, ≥51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRB, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure Gene: <strong>CDK4</strong></td>
</tr>
<tr>
<td>0089U</td>
<td>Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)</td>
</tr>
<tr>
<td>0090U</td>
<td>Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant)</td>
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Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

**Evidence-based Scientific References**


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