# CLINICAL MANAGEMENT RECOMMENDATIONS

## Integrating Genomic Testing for Melanoma Into Your Practice

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### INTRODUCTION

Melanoma is the most dangerous form of skin cancer and mortality is dependent upon stage of diagnosis. Patients with a stage I melanoma will have a 97% 5-year survival rate versus a patient with a stage IV lesion will only have a 15% survival rate. Therefore, early detection is critical as management is heavily affected by prognosis. Given this relationship, accurate assessment of prognosis is critical for effectively managing melanoma. Traditionally, tumor depth and other clinical and histological factors have been used to help predict the likelihood of metastasis and have ultimately been used as a proxy for survival[1,2].

While the American Joint Committee on Cancer's (AJCC) clinicopathological factors are effective at accurately assessing tumor stage, the majority of deaths still occur in early stage disease[3]. Excluding stage IV patients, 80% of patients present with Stage I disease yet 41% of deaths still occur in this population. This is due to the fact that while the overall survival percentage is higher for thin melanomas, the absolute number of mortalities is greatest for thin tumors[4]. Furthermore, one study found pathological diagnostic discordance between thin invasive melanomas and melanoma in situ (MMIS) when reviewed by an expert dermatopathologist[5]. In addition, the factors that have been traditionally used for prognosis, including tumor thickness and ulceration status, are somewhat subjective. For all of these reasons, it has been suggested that adding molecular information to the AJCC melanoma staging system could contribute to improved prognostic accuracy in melanoma patients[6].

Recent advances in genomic technology have also led to earlier detection of melanoma and in some cases allowed the clinician to avoid an invasive biopsy altogether[7 8]. This clinical management guideline manuscript reviews how gene expression profiling (GEP) can be used to improve the diagnosis and prognosis of melanoma and will offer guidance on effective integration into clinical practice using patient vignettes.

### Using Genomics to Assess Prognosis

The 31-GEP test is a Clinical Laboratory Improvement Amendments (CLIA) approved test that uses formalin-fixed, paraffin-embedded tissue that requires no extra processing on behalf of the dermatologist or dermatopathologist. It identifies a genomic profile using a validated algorithm that identifies the likelihood of developing melanoma tumor recurrence or metastasis within 5 years. The test uses 28 genes and 3 control genes that are involved in many cellular processes associated with tumor progression and metastasis and assesses the net activity of the interplay between these genes[9]. The 31-GEP test was developed with the goal of assessing the risk of melanoma recurrence independent from clinicopathologic factors. Patients are risk stratified into Class 1A meaning low risk of melanoma recurrence, 1B/2A for moderate risk or Class 2B indicating a high risk of melanoma recurrence. Approximately 85% of patients fall within Class 1A (lowest risk category) or Class 2B (highest risk category).

Through a more accurate assessment of prognosis, 31-GEP can help guide management in the clinical setting. A patient with a low-risk result can be considered for lower frequency clinical follow up. A patient with a higher-risk result can be considered for closer monitoring and more aggressive intervention such as adjuvant therapy or advanced imaging.

The 31-GEP test has been validated in over 2,900 patients across 20 peer reviewed publications including validation/performance studies, prospective studies and clinical impact studies[10, 11,12]. Physicians, nurse practitioners and physician assistants have been shown to use the results from this test to make more risk appropriate changes in their clinical management[13,11].

The 31-GEP test can also guide decision making regarding sentinel lymph node biopsy (SLNB) in melanoma patients. As per the National Comprehensive Cancer Center (NCCN) guidelines, if the risk of SLNB positivity is less than 5%, SLNB should not be recommended to patients, but if the risk is calculated to be greater than 10% then it should be discussed and offered to the patient. Unfortunately the SLNB false negative rate is significant, with some studies estimating it be as high as 17%[14]. Moreover, the SLNB procedure itself has morbidity including poor wound healing, infection and lymphedema. Multiple studies have shown that the 31-GEP test is able identify lower SLNB positivity rates for Class 1A patients and higher positivity rates for Class 2B patients[15,16,17]. Vetto et. al. demonstrated that for patients 55 years or older, the 31-GEP test can identify a population with a low risk (<5%) of SLNB positivity and a high risk (>10%) of SLNB positivity[18]. When the test is applied to a T1-T2 SLNB eligible melanoma, a discussion regarding the potential avoidance of a SLNB procedure in a class 1A patient (< 5% risk of positivity) is possible. Conversely, the procedure could be offered to Class 2B patients (> 10% risk of positivity). This management approach has the potential to result in an increase in the yield of SLNB procedures, an avoidance of unnecessary surgical procedures in low-risk patients and a reduction in healthcare costs. Importantly, this test is also covered by Medicare.

## 31-GEP Test Clinical Examples

### Example 1

A 66-year-old female presents to your office for further management after a biopsy performed by a local family medicine physician. Results of the biopsy show

melanoma with Breslow thickness of 0.6 mm. There is no ulceration or mitoses present. The patient has no history of melanoma but does a have a history of a previously treated basal cell carcinoma and actinic keratosis. The patient asks you about her prognosis and if she needs any further treatment. To help guide this decision, you order the 31-GEP test on this patient's biopsy specimen. The result of this test is a class 2B which indicates she is at high risk for recurrence and metastasis. Based on this information you decide to alter your normal management regimen usually employed for a lesion of this thickness. You counsel the patient on the importance of being followed more frequently than you had originally planned and you also refer her to clinical oncology to evaluate the need for advanced imaging and adjuvant therapy. This example highlights a patient with traditionally low risk clinical tumor characteristics who has a high-risk tumor genetic profile and might therefore benefit from a more rigorous management regimen.

### Example 2

A 30-year-old Female patient presents to your office after her husband had noticed a changing pigmented lesion on her back. The patient has no past medical history and no history of skin cancer but did frequently use tanning beds throughout her college years. After taking a biopsy of the lesion, the report comes back a few days later with a 0.7 mm Breslow thickness melanoma extending to the base of the specimen. Since the actual Breslow thickness is unknown, you decide to order the 31-GEP test to help guide further management. The test shows a Class 1A result. Given this low-risk result, you can counsel the patient that she does not require more intensive monitoring and does not need any further imaging or adjuvant therapy. In this scenario, the 31-GEP test helps guide management by demonstrating that the patient was at a low risk for metastasis or recurrence, even though the true Breslow thickness could not be determined.

### Example 3

A 68-year-old Female patient returns to your office after having a biopsy proven melanoma detected in clinic the previous week. The patient's melanoma has a Breslow thickness of 1.1 mm, a mitotic rate of 1/mm$^2$, positive ulceration but no other high-risk features. As per AJCC staging criteria alone, this patient would qualify as stage T2b which would predict her likelihood of SLNB positivity to be >10%. Given that alone, you would discuss and offer the procedure to this patient. However, you decide to apply the 31-GEP test to the patient's already processed biopsy specimen. You receive a report which indicates the patient has a Class 1A result. Based on this new information, the predicted SLNB positivity rate is 2.9% and you can now confidently have an informed discussion with the patient on the low yield of the procedure.

### Example 4

A 63-year-old Male patient returns to your office after having a biopsy proven melanoma from his recent office visit. The patient's melanoma has a Breslow thickness of 0.7 mm and has no other high-risk features. As per the traditional staging criteria, this patient would qualify as stage T1a which would predict his SLNB positivity to be less than 5%. Therefore, you would not typically discuss and offer the procedure to this patient. However, you decide to apply the 31-GEP test to the patient's already processed biopsy specimen. You receive a report which indicates the patient has a

Class 2B result. Based on this new information, the predicted SLNB positivity rate is 15.1% and you can now confidently have an informed discussion about the procedure's benefits.

## Using Genomics to Assess Diagnosis

The 2-GEP test uses a noninvasive adhesive patch to sample a suspicious skin lesion to help classify pigmented lesions as melanoma or non-melanoma when dealing with clinically difficult cases[19]. This pigmented lesion assay analyzes two genes, LINC (long intergenic non-protein coding RNA 518) and PRAME (preferentially expressed antigen in melanoma). These two genes were chosen due to the fact that these were the best performing gene pairs, of an original 17 gene discriminatory set, when separating melanoma from non-melanoma lesions with high levels of accuracy[19]. LINC is a part of a cluster of regulatory RNA molecules involved in melanoma proliferation and PRAME promotes tumor progression by interfering with retinoic acid receptor (RAR) signaling.

The negative predictive value of the 2-GEP test was found to be greater than 99% in the real-world TRUST study. After analyzing over 5,000 patients, the 2-GEP test reduced biopsies by approximately 85%[20]. The test has been well validated with 14 peer-reviewed manuscripts demonstrating analytical validation, clinical validation and clinical utility. Clinicians have been shown to follow the test guidance in over 98% of cases[21,22]. Brouha et. al. demonstrated a close correlation between the genomic atypia and advanced histopathological atypia of melanoma, further validating the utility of the 2-GEP test as a non-invasive method to detect melanoma[8].

## 2-GEP Test Clinical Example

A 54-year-old male is being evaluated for a chief complaint of a "suspicious lesion". The patient has no personal history but does a have a family history of melanoma. He shows you a sharply demarcated, irregularly-shaped, 6 mm pigmented lesion on his left distal forearm which he thinks has been growing. However, clinical and dermoscopic exam reveals a mostly homogenous pigment pattern consistent with neighboring, smaller lesions. Given these equivocal findings, you decide to apply the 2-GEP test to evaluate the lesion for genomic atypia to help guide your decision to perform a biopsy. After applying the non-invasive skin patch and sending the specimen for analysis, you receive a report that LINC and PRAME were both detected. Given this additional information, you decide to perform a biopsy which resulted in a histopathological diagnosis of a 0.5mm, stage pT1a melanoma. The patient had a subsequent surgical excision with appropriate margins and has no signs of recurrence at his 6 month follow up and subsequent visits.

## Conclusion

Melanoma is a life-threatening neoplasm where early detection along with appropriately timed intervention has the ability to significantly improve outcomes. However, practice gaps still exist for the diagnosis and treatment of melanoma given the challenges in defining high-risk subsets of lower-risk patients who may die from this cancer. Furthermore, decisions to biopsy suspicious lesions are heavily dependent upon subjective visual exams. Integrating the non-invasive 31-GEP and 2-GEP tests into clinical practice for assessing melanoma

diagnosis and prognosis has been shown to enhance accuracy. For these reasons, gene expression profiling technology is becoming an important adjunct in clinical practice to the standard of care for melanoma management.

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