INTRODUCTION
Gene Expression Test that Differentiates Melanoma from Benign Nevi

Melanoma comprises approximately 5% of all skin cancer cases, yet results in 75% of skin cancer deaths. Melanoma incidence has increased more than 50% over the last decade, and estimates suggest 96,480 new diagnoses and 7,230 deaths in 2019. Treatment costs associated with melanoma are also rising dramatically, and are estimated to total $3.3 billion annually.

Melanoma can be difficult to diagnose, particularly in its earliest stages, yet accurate and early diagnosis of melanocytic lesions is vital to optimal patient outcomes. The ten year survival rate for patients with stage I melanomas is 86-95%, compared with only 10-15% among patients with stage IV melanomas. Histopathologic examination has long been the standard for melanoma diagnosis, and while it is adequate for most cases, evidence demonstrates that approximately 15% of lesions are diagnostically uncertain by histopathology.

myPath MELANOMA TEST
myPath Melanoma measures the expression of 23 genes: 14 genes involved in melanoma pathogenesis and 9 housekeeper genes. The diagnostic gene signature has three separate components that detect expression of genes involved in cell differentiation, cell signaling, and the immune response within the tumor microenvironment. The assay has been clinically validated in three independent cohorts to differentiate malignant melanoma from benign nevi with a sensitivity of 90-94% and a specificity of 91-96%. myPath Melanoma is an objective and reproducible assay that improves the accuracy of histopathology alone, resulting in a more definitive diagnosis and optimal patient care. myPath Melanoma is performed on five standard tissue sections from the existing biopsy, making it amenable for use in small lesions and reasonable for integration into the routine clinical practice of dermatopathology.

Using an algorithm, the measurements of the three gene components are combined and reported as a single numerical score. That number (the myPath Melanoma ‘score’), is shown on a scale that depicts the distribution of scores observed in clinical validation. Physicians receive a report showing this single numerical score and the corresponding classification: ‘likely malignant’, ‘likely benign’, or ‘indeterminate’.

myPath Melanoma Benign Result

Myriad myPath® Melanoma Score: -7.3

-16 -14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10

Benign Indeterminate Malignant

myPath Melanoma Malignant Result

Myriad myPath® Melanoma Score: 8.7

-16 -14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10

Benign Indeterminate Malignant
INTENDED USE POPULATION

myPath Melanoma has been clinically validated to differentiate benign nevi from malignant melanoma. It is intended for use in patients whose melanocytic lesion is not clearly benign or malignant based on clinical and/or histopathological features alone.

ANALYTICAL VALIDITY

Warf et al. performed an analytical validation study assessing performance of the myPath Melanoma assay in a design consistent with Clinical Laboratory Improvement Amendments (CLIA) Guidelines. This study evaluated the test as run in the laboratory, including RNA yield, RNA stability, dynamic range, precision, linear range and stability of extracted RNA, and demonstrated that the myPath signature is robust and reproducible.

CLINICAL VALIDITY

myPath Melanoma is the most extensively researched and validated ancillary diagnostic test for melanoma. The assay was developed in a training cohort of 464 melanocytic lesions. myPath Melanoma scores were subsequently validated in three cohorts, including over 1,300 melanocytic neoplasms, distinct from the training cohort. Clinical validation studies utilized either histopathology or actual patient outcomes as reference standards. In melanoma, a complete representation of a test’s validity can be achieved only through validation against both histopathology and patient outcomes.

The current standard in diagnosing melanocytic lesions is histopathologic diagnosis. In line with this practice, myPath Melanoma was initially developed and evaluated using consensus histopathologic diagnosis as a reference standard. The first validation of myPath Melanoma demonstrated greater than 92% diagnostic accuracy by comparison to concordant histopathologic diagnoses (diagnoses arrived at independently by multiple expert dermatopathologists).

To further assess accuracy using a reference standard independent of histopathologic diagnosis and confirm genuine clinical utility, two additional validation studies were performed in which the test result was compared to the eventual clinical outcomes of tested patients. In a cohort of 182 melanocytic neoplasms collected from patients with documented outcomes (distant metastases for malignant melanomas and median 6+ year uneventful follow-up for benign nevi), the mypath Melanoma score differentiated malignant melanoma from benign nevi with a sensitivity of 93.8% and a specificity of 96.2%. In a subsequent study, clinical follow-up was obtained for 127 patients whose lesions were tested with myPath in the first validation study. Of the 65 whose lesions were diagnosed histopathologically as melanoma, the myPath test produced a malignant result in 61, for an overall sensitivity of 93.8%. Lesions from 14 of the 65 patients went on to develop metastatic melanoma during a median follow-up period of 48 months, all of which had been correctly identified as malignant by the myPath test. Of the 62 patients whose lesions had been diagnosed as benign by histopathology, none developed recurrence or metastases during a median 30 month follow-up period. The myPath test classified 48 of 62 (77.4%) as benign, 7 of 62 as malignant (11.3%), and the remaining 7 as indeterminate, for an overall specificity of 88.7%.
CLINICAL UTILITY AND IMPACT ON PATIENT CARE

The myPath Melanoma result directly impacts clinical management, and two clinical utility publications demonstrate a consistent increase in definitive diagnoses and changes in clinical decision-making and patient treatment following testing. myPath utilization results in a reduction in unnecessary and costly treatments.

The first clinical utility study quantified the influence of the mypath Melanoma score on both the final diagnoses and the treatment recommendations made by board-certified dermatopathologists for 218 prospectively-submitted diagnostically challenging (equivocal or uncertain) melanocytic neoplasms encountered during routine clinical practice. Comparison of pre-test and post-test diagnoses demonstrated a 43% decrease in indeterminate diagnoses with use of the myPath score, driven primarily by the diagnoses of benign nevi in what had previously been ambiguous cases. In addition, treatment recommendations provided by dermatopathologists changed for 49% of patients after receiving the myPath test result.\(^\text{12}\)

A second study assessed the relationship between test result and change in treatment as measured by pre-test pathologist recommendation and post-test actual treatment delivered to a patient by the dermatologist. A cohort of 77 patients with pretest diagnoses of “indeterminate” (equivocal, uncertain, ambiguous) were followed throughout their clinical course. The myPath test produced definitive scores for all 77 neoplasms, and after a follow-up period, the tested patients’ dermatologists disclosed the actual treatment carried out in each case. Treatment differed from the pretest recommendation in over 70% of cases, and an 80% reduction in re-excisions was realized among cases that received a myPath Benign result (n = 44).\(^\text{13}\)

<table>
<thead>
<tr>
<th>Cases receiving an Indeterminate Diagnoses</th>
<th>Pre-test treatment recommended by pathologist</th>
<th>Actual post-test treatment performed by dermatologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-excision</td>
<td>93%</td>
<td>79%</td>
</tr>
<tr>
<td>No re-excision</td>
<td>7%</td>
<td>21%</td>
</tr>
</tbody>
</table>

80% reduction in re-excisions
**SUMMARY**

myPath Melanoma is an objective and reproducible assay that improves the accuracy of diagnoses based on histopathology alone. The peer-reviewed, published data demonstrate that myPath Melanoma is well-validated and has an overall diagnostic accuracy of >90% in melanocytic lesions with ambiguous histopathology, based on consistent results across studies performed in three independent validation cohorts. myPath Melanoma provides additional information that has been proven to reduce indeterminate diagnoses, driving a reduction in overtreatment. myPath is gaining support, as multiple organizations, including The National Comprehensive Cancer Network (NCCN) and the American Academy of Dermatology (AAD) recommend the use of molecular testing or gene expression testing for histologically equivocal lesions, which reflects the intended use of the assay. Moreover, Medicare Administrative Contractor Palmetto GBA MolDX issued a final local coverage determination for myPath, effective April 2019.

**REFERENCES**