MYRIAD myPath® Melanoma

EXECUTIVE SUMMARY

INTRODUCTION

Melanoma comprises just 1% of skin cancers, yet accounts for the vast majority of skin cancer deaths.[1] Early and accurate diagnosis is critical for long-term survival: the ten-year survival rate for patients diagnosed at stage I is about 86-95%, compared to just 10-15% among those diagnosed at stage IV.[2] However, melanoma can be difficult to diagnose, particularly in its earliest stages. The microscopic interpretation of tissue biopsies by pathologists (histopathology) has long been the standard for melanoma diagnosis, but histopathologic interpretation is subjective, and no single histological criterion definitively differentiates malignant melanomas from benign melanocytic nevi.[3] In fact, multiple studies suggest that approximately 15% of all biopsied melanocytic lesions may be ambiguous or diagnostically equivocal.[4-6] These diagnostically uncertain cases are often treated as malignant melanomas by default, driving unnecessary treatment and associated costs.

Myriad's myPath® Melanoma is a clinically validated test, designed for use as a diagnostic adjunct when the distinction between a benign nevus and a malignant melanoma cannot be made confidently by histopathology alone.

myPath effectively distinguishes between malignant melanoma and benign nevi with a sensitivity of **92 – 94%** and a specificity of **89 - 96%.***[7-9]

myPath testing results in a **57%** increase in definitive diagnoses in ambiguous cases.[10]

myPath demonstrates a **>80%** reduction in proposed treatment in indeterminate cases categorized as benign by myPath.[11]

TEST DESCRIPTION

myPath testing is obtained by submitting a tissue block or unstained slides with a completed myPath Test Request Form to Myriad. Using qRT-PCR methodology, the test measures the expression of 14 genes involved in cell differentiation, cell signaling, and immune response signaling, along with a set of 9 reference genes. A proprietary algorithm is applied that combines the measurements of gene expression, assigns a weight to each gene component, and establishes a threshold value. The result is a single numerical score that classifies a melanocytic lesion as one of the following:

- Likely benign
- Likely malignant
- Indeterminant

INTENDED USE

myPath Melanoma may be used as an adjunct to histopathology when the distinction between a benign nevus and a malignant melanoma cannot be made confidently by histopathology alone. Reasons that definitive diagnosis may not be achievable by histopathology include indeterminate/ambiguous histopathologic features, diagnostic disagreement among physicians, or indications that additional workup or consultation are necessary.

*Publications may reference percent negative agreement, a measure of diagnostic accuracy calculated identically as specificity.

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 critical laboratory parameters of the test's performance, including RNA yield, RNA stability, dynamic range, precision, and linearity, demonstrating that the myPath signature is robust and generates highly reproducible results. Complete results of the analytical validation of myPath Melanoma were published in the March 2015 issue of Biomarkers in Medicine.[12]

CLINICAL VALIDITY

myPath Melanoma is the most extensively researched and validated ancillary diagnostic test for melanoma, developed in a training cohort of 464 melanocytic lesions and subsequently validated in three separate cohorts comprised of more than 1,300 melanocytic neoplasms (distinct from the training cohort).[7-9,13] These clinical validation studies utilized both histopathologic interpretation by experts and actual patient outcomes as reference standards, and myPath demonstrated strong diagnostic accuracy against both reference standards.

Clarke et al. (2017) demonstrated greater than 92% diagnostic accuracy by comparison to concordant histopathologic diagnoses (arrived at independently by multiple expert dermatopathologists).[7]

Ko et al. (2017) demonstrated that the myPath score differentiated malignant melanoma from benign nevi with a sensitivity of 93.8% and a specificity of 96.2% in a cohort of 182 archived melanocytic neoplasms collected from patients with known outcomes.[8]

Ko et al. (2019) obtained clinical follow-up for 127 patients whose lesions were tested with myPath.

- Of the 65 lesions diagnosed histopathologically as melanoma, myPath produced a malignant result in 61, for an overall sensitivity of 93.8% by comparison to histopathologic diagnosis by experts. Given the known limitations of histopathologic diagnosis, myPath was also compared to actual clinical outcomes.
- All 14 lesions that later metastasized over a median follow-up period of 48 months were correctly identified as malignant by myPath. Thus, myPath sensitivity was 100% for metastasis-proven melanomas in this cohort.
- Of the 62 lesions diagnosed as benign by histopathology that did not recur or metastasize during a median 30-month follow-up period, myPath classified 48 of these (77.4%) as benign. This resulted in a specificity for myPath of 88.7% for this subset.[9]

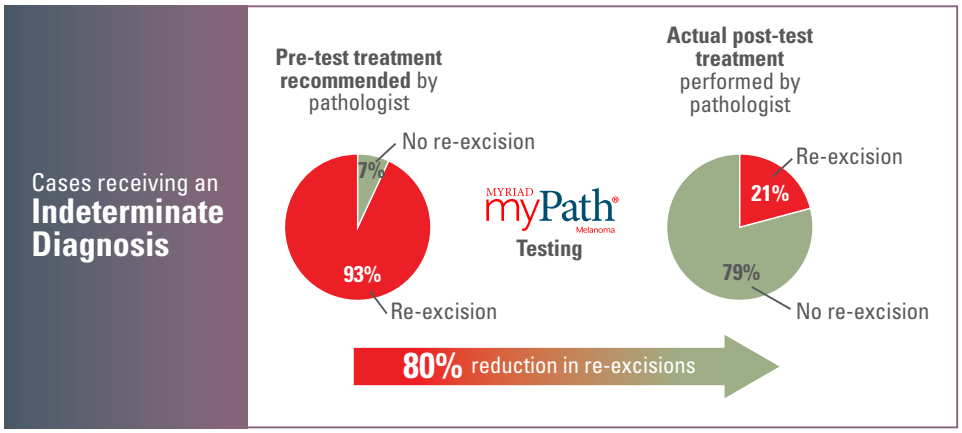
Clarke et al. (2020) evaluated myPath Melanoma by comparing test results with clinical outcomes in uncertain cases. Seven expert dermatopathologists blinded to test results and clinical outcomes quantified diagnostic certainty of each case, and 125 cases with known outcomes were defined as ambiguous or uncertain. myPath demonstrated 90.4% sensitivity in cases with proven metastases and 95.5% specificity in cases with no adverse events (>6 year median follow-up).[18]

CLINICAL UTILITY

The clinical utility of myPath® has been evaluated in separate studies that represent multiple aspects of diagnostic and treatment paradigms. Cockerell et al. (2016) examined 218 cases submitted for testing in the clinical setting. Use of myPath resulted in a 56.6% increase in definitive diagnoses for ambiguous cases.[10]

Cockerell et al. (2017) examined 77 ambiguous/indeterminant cases and compared referring dermatopathologist pre-test management recommendations with actual patient treatment received post-test at 6-12 month follow up. Use of myPath resulted in a 71.4% change from pre-test treatment recommendation to actual treatment performed, and an 80% reduction of re-excisions was realized among cases that received myPath Benign results.[11] (See Figure 1).

Figure 1: Reduction of treatment in myPath benign cases



Tschen et al. (2020) followed a critical subset of the Cockerell et al. (2016) study population, patients whose lesions were indeterminate by histopathology but were treated as benign with the aid of a benign myPath result. Of 25 patients with histologically ambiguous lesions classified as benign by myPath and subsequently treated as benign, none demonstrated disease progression, metastasis, or death. The absence of adverse events during clinical follow-up supports that myPath can identify benign lesions and safely guide clinical decision-making of patients whose biopsies are ambiguous or diagnostically uncertain by histopathology.[14]

These studies demonstrate that use of myPath increases the number of definitive diagnoses, decreases classification of lesions as 'indeterminate,' and produces substantial changes in patient treatment.

GUIDELINES & MEDICARE COVERAGE

- The National Comprehensive Cancer Network (NCCN) recommends molecular tests including gene expression assays for diagnostically equivocal lesions, in line with the intended use of myPath.[15]
- Medicare Administrative Contractor Palmetto GBA MolDX issued a final local coverage determination for myPath, effective April 2019.[16]
- An expert panel of physicians published appropriate use criteria in the official journal of the National Society for Cutaneous Medicine and provided the strongest level of recommendation, A-strength, for myPath in clinical scenarios that mirror the test's intended use.[17]

HEALTH ECONOMICS

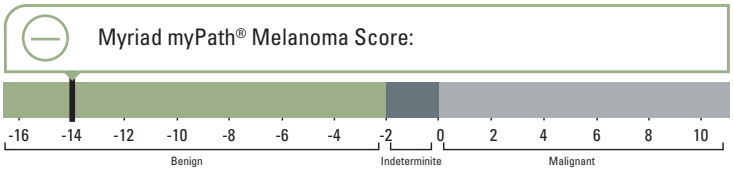
myPath Melanoma drives cost savings when compared to a paradigm in which no gene expression profiling of indeterminate lesions occurs. Savings are driven by a reduction of re-excisions in indeterminate cases categorized as myPath benign.[11] In a plan membership of one million, modeling indicates 272 indeterminate biopsies per year that would be appropriate for myPath testing. At $481 per tested member, total savings are estimated at $130,801 in the first year, compared to an arm where patients don't receive the test.[19]

TEST REPORT

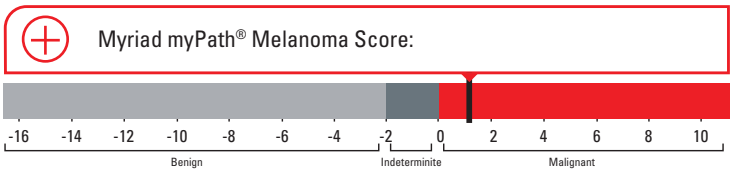
myPath test results are available to the ordering physician in approximately 5 – 7 days via the MyriadPro™ online portal. Physicians review and interpret myPath results in conjunction with other histopathological and clinical information to render a final diagnosis.

Sample test results:

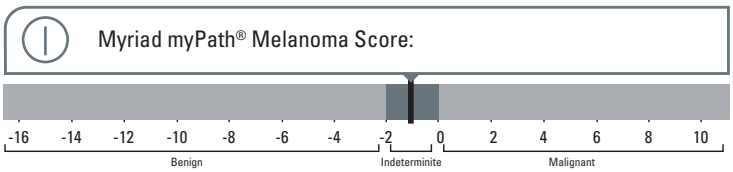
myPath Melanoma Benign Result



myPath Melanoma Malignant Result



myPath Melanoma Indeterminant Result



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myriad® WHEN DECISIONS MATTER