Melanoma is an aggressive cancer with an estimated 87,110 cases and 9,730 deaths in 2017. The lifetime risk of developing melanoma in the United States is 1 in 34 for men and 1 in 54 for women. However, many melanomas are curable if they are detected early and diagnosed accurately. 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. Melanoma can be difficult to diagnose, yet accurate and early diagnosis of melanocytic lesions is vital to improved patient outcomes. Histopathologic examination has long been the standard for melanoma diagnosis, and while it is adequate for most cases, evidence suggests that at least 15% of lesions are diagnostically challenging by histopathology. Even experienced dermatopathologists disagree in some cases, and, depending on the type of lesions evaluated, diagnostic discordance ranges from 15-38%. In these equivocal cases, patients often receive indeterminate or inaccurate diagnoses, leading to inappropriate treatment. For example, patients may receive unnecessary re-excisions, sentinel lymph node biopsies, and protracted clinical follow-up if a diagnostically challenging benign lesion is reported as indeterminate. Alternatively, a diagnostically challenging melanoma may be mistakenly diagnosed as a benign nevus, resulting in progression to late-stage melanoma.

Myriad myPath Melanoma, a 23-gene expression signature, has been developed as an objective and accurate method for differentiating malignant melanoma from benign nevi that overcomes some of the limitations of aCGH and FISH.

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, accurate, and reproducible assay that improves the
accuracy of histopathology alone, resulting in a more definitive diagnosis and more optimal patient care. No additional biopsies or special tissue processing are necessary for the test. myPath Melanoma is performed on five standard tissue sections from the existing biopsy, making it amenable for use in small lesions (unlike aCGH) 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’. Scores between -16.7 and -2.1 are reported as ‘likely benign’, scores between -2.0 and -0.1 are reported as ‘indeterminate’, and scores between 0.0 and +11.1 are reported as ‘likely malignant’. The ‘indeterminate’ reporting range (approximately 10% of results) was introduced in order to maximize sensitivity and mitigate potential misclassification of low-scoring malignant melanomas.

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 assessed the robustness and precision of the test as run in the laboratory, including RNA yield, RNA stability, dynamic range, precision, linear range and stability of extracted RNA. These studies indicate this signature is robust and reproducible for formalin-fixed paraffin-embedded melanocytic lesions.
**CLINICAL VALIDITY**

The myPath Melanoma assay was developed in a training cohort of 464 melanocytic lesions. MyPath Melanoma scores were subsequently validated in three cohorts distinct from the training cohort. The current standard in diagnosing melanocytic lesions is histopathologic diagnosis. However, given the known limitations of histopathology, previous studies have suggested that the examination of cases by multiple pathologists improves the accuracy and reliability of this standard. In line with this practice, myPath Melanoma was initially developed and evaluated using consensus histopathologic diagnosis as a reference standard. The assay was additionally evaluated in comparison to the more objective standard of documented clinical outcomes.

The three clinical validation studies included over 1,300 melanocytic neoplasms (almost 200 of which were lesions with diagnoses proven by clinical outcomes) and demonstrated overall diagnostic accuracy of >90%, with diagnostic accuracy being defined as sensitivity (proportion of correctly identified positive/malignant cases) and specificity (proportion of correctly identified negative/benign cases) compared to the standard. Collectively, these validation data demonstrate the ability of myPath Melanoma to differentiate melanoma from benign nevi in a broad range of subtypes, by providing independent and additional diagnostic information compared to clinical and pathologic features.

**CLINICAL UTILITY AND IMPACT ON PATIENT CARE**

Clinical utility studies quantifying the impact of myPath Melanoma demonstrate an increase in definitive diagnoses and changes in patient treatment following testing. In a prospective study, use of the test led to a 42.7% reduction in the number of cases classified as indeterminate (those for which dermatopathologists could not make a definitive distinction between benign or malignant). In a second prospective study, the actual treatment received by the patient was changed from the pre-test recommendation in 71.4% of cases that were diagnostically challenging; including an 80.5% decrease in re-excisions in cases initially recommended for excision that received a benign test result.
SUMMARY

This issue of indeterminate diagnoses in melanocytic lesions is a problem that leads to inappropriate and inaccurate patient treatment. myPath Melanoma is an objective diagnostic tool that provides additional information and avoids the variability inherent in other adjuncts to histopathology.

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 impact both pathologists and dermatologists in making informed diagnoses and treatment decisions.

REFERENCES