A CLINICALLY VALIDATED GENE EXPRESSION SCORE IMPACTS DIAGNOSIS AND MANAGEMENT RECOMMENDATIONS OF MELANOCYTIC LESIONS BY DERMATOPATHOLOGISTS

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BACKGROUND

- Many studies have documented suboptimal accuracy and reproducibility in the diagnosis of melanocytic lesions when histopathology is used alone.[1-3]
- Adjunctive methods that provide objective and reliable data have been sought to distinguish melanoma from nevi.
- A 23-gene expression signature has been clinically validated to differentiate benign nevi from malignant melanomas.[4]
  - A single Melanoma Diagnostic Score (MDS) calculated based upon the expression of the gene signature is reported to ordering pathologists and used as an adjunctive diagnostic tool (Table 1).
- In a retrospective case review study, the MDS modified pathologist behavior in approximately 1/3 of cases, with a 33.2% change in treatment recommendations observed.[5]
- The current study aims to verify the results of this retrospective study in a prospectively-collected cohort of difficult to diagnose cases.

Table 1. *MDS Reporting Ranges*

MDS			Result
-16.7	→	-2.1	Benign
-2.0	→	-0.1	Indeterminate
0	→	11.1	Malignant

STUDY DESIGN

Objective

Quantify the impact of a novel molecular diagnostic test on diagnosis and treatment recommendations made by dermatopathologists attempting to differentiate malignant and benign melanocytic tumors.

Endpoints

The percentage change in diagnosis and intended treatment recommendations.

Methods

- Representative sections of difficult to diagnose melanocytic lesions encountered during routine dermatopathology practice were submitted to a clinical laboratory for gene expression testing by qRT-PCR.
- The submitting dermatopathologist completed a pre-test questionnaire for each case recording the following:
  - Diagnosis *(benign, malignant, or indeterminate)*
  - Diagnostic confidence *(very unsure, unsure, somewhat unsure, neutral, somewhat confident, confident, very confident)*
  - Additional diagnostic workup
  - Treatment recommendations *(no further treatment necessary, no further treatment necessary if lesion is completely excised, close clinical surveillance of the biopsy site for possible recurrence, excision with a margin of normal skin, wide local excision, sentinel lymph node biopsy and/or other evaluation for evidence of metastasis, and "other")*

Methods -*Continued*-

- An MDS was calculated based upon measured gene expression, and the score was reported to the submitting dermatopathologist.
- After the result was reported, the dermatopathologist completed a post-test questionnaire with questions similar to those on the pre-test questionnaire.
- Changes between the pre- and post-test questionnaires were calculated for diagnostically challenging cases.
  - Diagnostically challenging cases were defined as those cases submitted with a pre-test diagnosis of indeterminate, or a pre-test diagnosis of benign or malignant where the dermatopathologist had lower diagnostic confidence *(very unsure, unsure, somewhat unsure, or neutral)*.
- For treatment recommendations, only the most severe, or invasive, recommendation selected on the survey was considered. Sentinel lymph node biopsy and/or other evaluation for evidence of metastasis was considered the most invasive and no further treatment necessary was considered the least invasive.

Table 2. *Demographic and Other Baseline Characteristics*

Characteristic	Statistic/Category	Total Population (N=1,695)	Diagnostically Challenging Subset (N=218)
Age (years)	n	1,635	204
	Mean	51.4	45.5
	SD	20.12	20.56
	Median	54.0	46.0
	Min, Max	3, 97	6, 88
Gender	Female	827 (48.8%)	118 (54.1%)
	Male	746 (44.0%)	91 (41.7%)
	Missing	122 (7.2%)	9 (4.1%)
Procedure Type	Shave biopsy	1346 (79.4%)	156 (71.6%)
	Punch biopsy	181 (10.7%)	25 (11.5%)
	Elliptical excision	152 (9.0%)	31 (14.2%)
	Biopsy	2 (0.1%)	2 (0.9%)
	Missing	14 (0.8%)	4 (1.8%)
Anatomical Site of Lesion	Back / Neck	529 (31.2%)	37 (17.0%)
	Extremities	478 (28.2%)	81 (37.2%)
	Face	125 (7.4%)	19 (8.7%)
	Abdomen	85 (5.0%)	10 (4.6%)
	Chest	90 (5.3%)	19 (8.7%)
	Acral	69 (4.1%)	12 (5.5%)
	Scalp	38 (2.2%)	4 (1.8%)
	Genital	5 (0.3%)	1 (0.5%)
	Other	275 (16.2%)	35 (16.1%)
	Missing	1 (0.1%)	0
Pre-test Diagnosis	Benign	928 (54.7%)	23 (10.6%)
	Malignant	592 (34.9%)	20 (9.2%)
	Indeterminate	175 (10.3%)	175 (80.3%)
myPath Score	n	1695	218
	Mean	-3.2	-3.9
	SD	5.53	5.06
	Median	-3.5	-4.2
	Min, Max	-16.3, 10.9	-15.2, 10.3
myPath Result	Benign	992 (58.5%)	134 (61.5%)
	Malignant	538 (31.7%)	60 (27.5%)
	Indeterminate	165 (9.7%)	24 (11.0%)

Note: Max= Maximum, Min= Minimum, SD= Standard Deviation

RESULTS

- Table 2 summarizes the baseline characteristics of the total population of cases eligible for study inclusion (N=1,695), as well as the diagnostically challenging subset of interest (N=218).
- Figure 1 outlines the diagnostic changes made when the MDS for diagnostically challenging cases was available to the dermatopathologists.
  - 80.3% of cases were initially recorded with a pre-test diagnosis of indeterminate. This was reduced to 37.6% after the MDS was reported.
- The change in indeterminate diagnoses along with a change in confidence for benign or malignant diagnoses resulted in an overall decrease in the number of diagnostically challenging cases identified within the total population after testing.
- Figure 2 details the changes in treatment recommendations made for diagnostically challenging cases according to the MDS result.
  - In 39.4% of cases receiving a benign MDS result, recommendations were downgraded to less invasive treatment.
  - In 45.8% of cases receiving a malignant MDS result, recommendations were upgraded to a more invasive treatment.

Figure 1. *Changes in Diagnosis After Review of the MDS*

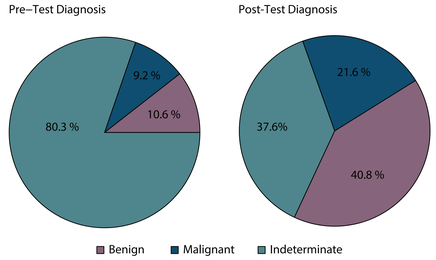
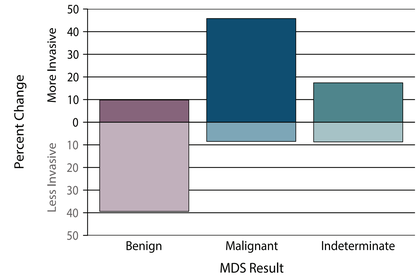


Figure 2. *Changes in Treatment Recommendations by MDS Result*



CONCLUSIONS

- This study provides prospective evidence of the clinical utility of a novel molecular assay capable of differentiating malignant melanoma from benign nevi.
- When the MDS was available as part of a comprehensive evaluation of diagnostically challenging cases, indeterminate diagnoses were reduced by 42.7% and changes in treatment recommendations were observed in 49.1% of cases.
- Integration of the MDS into current pathology practice has the potential to enhance patient care through more definitive diagnoses of melanocytic lesions and personalized medical treatment.
- Studies are underway to further characterize the larger cohort of cases that have undergone clinical gene expression testing.

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