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THE CLINICAL IMPACT OF A GENE EXPRESSION SIGNATURE THAT DIFFERENTIATES BENIGN NEVI FROM MALIGNANT MELANOMA

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BACKGROUND
- Melanoma is among the most malignant of human cancers; however, many cases are curable if detected early
- Currently, histopathologic evaluation is considered the gold standard for the diagnosis of melanocytic lesions. But many studies demonstrate continued challenges when histopathology is used alone
  - Farmer et al. illustrated that within a panel of eight expert dermatopathologists, diagnostic discordance between two or more panel members was observed in 38% of cases
  - More sensitive and objective methods have been sought for distinguishing melanoma from nevi
- A 23-gene expression signature has been clinically validated to differentiate benign nevi from melanoma with a sensitivity of 90% and a specificity of 91%
- The primary objective of this study was to assess the impact of this new assay on decision-making and confidence among pathologists attempting to differentiate malignant and benign melanocytic tumors.

METHODS
Melanocytic Lesion Study Cohort
- Fifty melanocytic lesions were selected by a dermatopathologist from an archival set of 464 de-identified cases
  - The study cohort was enriched for lesions that are:
    - Known to be difficult to classify by histopathology alone
    - Known to have a high incidence of inter-observer variability and diagnostic discordance
    - Have conflicting histopathologic criteria
- A 23-gene expression assay was carried out by expert dermatopathologists
- Expression of the gene signature was analyzed in each of the 50 selected lesions
- A web-based Case Evaluation Tool was used to evaluate the diagnostic impact of the assay

RESULTS
- Table 1 summarizes the characteristics of the 50 lesions studied.
  - Initial, for only 30% of cases there was 100% concordance among all seven pathologists with regard to predicted biologic behavior.
- Ten of the fifty cases (20%) were either classified by the majority of pathologists as indeterminate or there was no majority consensus on diagnosis.
- When gene expression scores were provided, predicted biologic behavior was revised in 30% of cases (Figure 2).
- 9.4% of cases were upgraded to a more severe diagnosis (i.e. benign to malignant, benign to indeterminate, or indeterminate to malignant) 20.6% of cases were downgraded to a less severe diagnosis (i.e. malignant to benign, malignant to indeterminate, or indeterminate to benign).
- Diagnostic changes subsequently resulted in modified management recommendations for 33.2% of cases (Figure 2).
- A trend towards less invasive interventions was observed (i.e. standard excision with clear margins versus a wide excision).
- The pathologists’ average level of confidence increased by 16.4% for indeterminate cases reclassified as malignant (N=33) and 29.1% for cases reclassified as malignant (N=7)(Figure 3).
- The utility of the assay can be further demonstrated through the study of specific cases of interest from the study cohort (Figure 4).

CONCLUSIONS
- This study supports the clinical utility of a novel molecular assay capable of differentiating malignant melanoma from benign nevi.
- Changes in diagnosis, management recommendations, and pathologist confidence were observed when the gene expression score was available as part of a comprehensive case evaluation.
- The assay provides diagnostic information independent of histopathology.
- Further data regarding the clinical utility of this assay is currently being gathered through the prospective submission of diagnostically challenging melanocytic lesions by pathologists to a clinical laboratory for testing.

REFERENCES

Table 1. Characteristics of the 50 Melanocytic Lesions

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Age</td>
<td>Range</td>
<td>Median/Mean</td>
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<td>Biopsy Location</td>
<td>Trunk 14</td>
<td>Lower Extremity 6</td>
<td>Upper Extremity 3</td>
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<td>Gene Expression Score</td>
<td>Range</td>
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Figure 1. Web-based Case Evaluation Tool

Figure 2. Changes in Diagnoses and Management Recommendations after Review of Gene Expression Result

Figure 3. Pathologist Confidence Increases after Review of Gene Expression Result

Table 4. Case Studies

- Case 4: Seventy-year old female with pigmented lesion on the lower extremity
  - Initial Panel Diagnosis: Indeterminate
  - Score: Benign (2.75)
  - Second Panel Diagnosis: Benign

- Case 5: Forty-two year old female with pigmented lesion on the lower extremity
  - Initial Panel Diagnosis: 3 indeterminate / 3 malignant / 1 benign
  - Score: Benign (2.0)
  - Second Panel Diagnosis: Benign