Validation of the Melanoma Diagnostic Score (MDS)

- Expression of Gene Component #1 was the most effective differentiating feature in the forward selection model. (P-value = 1.2x10^-10).
- The model was improved by adding Gene Component #2 (P-value = 3.9x10^-10) and the average expression from the Gene Component #3 gene group (P-value = 7.2x10^-10) (Figure 2A).
- The three components in this model had distinct expression profiles that were not highly correlated with each other (Figure 2B).
- Incorporating additional gene groups or other individual genes to the model did not increase the diagnostic performance.

**Figure 3.** Final Gene Expression Signature.

The final MDS signature consists of 23 genes (Figure 3).
- Component #1 regulates melanocyte differentiation.
- Component #2 is a group of 5 genes that have multiple functions including some immune regulation.
- Component #3 represents 6 genes involved in immune signaling.
- 8 housekeeper genes are necessary for normalization of gene expression.
- Performance of the gene signature was clinically validated in a cohort of 437 lesions (Figure 1).
- The final MDS distribution ranged from -16.7 to +11.1 (Figure 4).
- Scores from -16.7 to -0.1 are reported as benign.
- Scores from 0 to +11.1 are reported as malignant.
- Using a predefined threshold of zero and a bimodal score distribution, the MDS discriminated melanoma from nevi with 90% sensitivity and 91% specificity (P-value<1x10^-16; AUC = 96% (Figure 1).

**Figure 4.** Distribution of diagnostic scores in the clinical validation cohort.

**Figure 5.** ROC curve of diagnostic scores in the clinical validation cohort.

**RESULTS**

- A 23-gene signature has been clinically validated to differentiate melanoma and nevi with a sensitivity of 90% and a specificity of 91%.
- Expression of genes regulating melanocyte differentiation and immune responses appear to represent critical differences between benign and malignant melanocytic lesions.
- The gene signature provides diagnostic information independent of histopathology and has been shown to modify physician behavior in approximately a third of cases.
- A 33.2% change in management recommendations was observed in a retrospective case review study (Rock et al; USCAP Annual Meeting 2014).
- Preliminary results of an ongoing prospective study suggest these results, with a 35.1% change in management recommendations observed to date.
- In order to provide a better interpretation of the diagnostic score, an indeterminate zone could be introduced.
- The performance, objectivity, reliability, and minimal tissue requirements of this diagnostic test make it well-suited for clinical use as an adjunct to histopathology.

**CONCLUSIONS**

- The performance, objectivity, reliability, and minimal tissue requirements of this diagnostic test make it well-suited for clinical use as an adjunct to histopathology.