Performance of a diagnostic 35-gene expression profile test (GEP) on difficult-to-diagnose melanocytic lesions

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SYNOPSIS

- The accurate diagnosis of melanocytic neoplasms and characterization of their malignant potential remain significant clinical challenges in dermatopathology.[1-4]
- Visual assessment of hematoxylin and eosin (H&E) stained lesions is inherently subjective and relies on expert interpretation and integration of a wide spectrum of architectural and cytologic features that are weighted differently based on the presumed subtype of melanocytic neoplasm and heavily influenced by the pathologists' personal experience and training.[5]
- Difficult-to-diagnose lesions are commonly sent for second opinions to expert dermatopathologists who have more experience with challenging cases; however, the nature of many lesions remains ambiguous with discordant rates of diagnoses ranging from 25-43%.[1,6]
- The 35-gene expression profile (GEP) test has reported accuracy metrics of 99.1% sensitivity, 96.2% specificity, 96.1% positive predictive value (PPV) and 99.1% negative predictive value (NPV) within the clinically available ≥18-year-old (yo) population (n=474).[7]

OBJECTIVE

To demonstrate use in the intent-to-use difficult-to-diagnose melanocytic lesion population, which includes diagnostically discordant lesions and lesions designated as unknown malignant potential (UMP), cases were analyzed using the 35-GEP test. Accuracy metrics are not provided as a definitive diagnosis for comparison was not achieved.

METHODS

- Samples were acquired from 7 centers. Samples were reviewed by 2 to 3 independent dermatopathologists and used in the study if diagnoses included benign and malignant designations or if diagnoses included more than one unknown malignant potential (UMP) designation.
- Difficult-to-diagnose lesions in the ≥18 yo population which were excluded from analysis from the cohort published in Estrada *et al*. were analyzed with 35-GEP; samples are described in **Table 1**.
- The 35-GEP utilizes dual algorithms based on neural networks to provide a result of benign, intermediate-risk or malignant.[7] Accuracy metrics cannot be calculated as the true diagnosis was unable to be captured.

RESULTS

Table 1. Demographic information

	Difficult-to-diagnose lesions N=65
Age, median (range)	46 (18-87)
Sex, % male	44.6
Location on body, % (n)	
Abdomen/Chest	6.1 (4)
Acral	3.1 (2)
Back	43.1 (28)
Extremities	32.3 (21)
Head/Neck	13.9 (9)
Other	1.5 (1)

Table 2. 35-GEP results in difficult-to-diagnose lesions

	35-GEP Result		
	Benign, n	**Intermediate, n**	**Malignant, n**
Lesions, % (n)	77% (50)	3% (2)	20% (13)

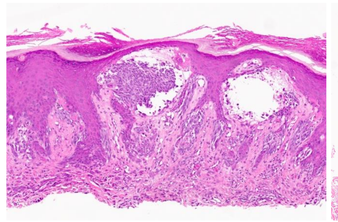
Table 3. Subtype of melanocytic proliferation as determined by submitting dermatopathologist

	35-GEP Result		
≥18 yo population	**Benign, n**	**Intermediate, n**	**Malignant, n**
Blue	4	0	1
Compound	4	0	1
Deep Penetrating	6	0	2
Dysplastic			
Compound	20[a]	0	1[b]
Junctional	11[c]	1	0
Spitz	5	1	8

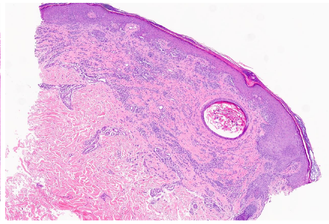
Dysplastic nevi had different degrees of atypia: a – severe (n=5), moderate (n=8), mild (n=3); b – severe (n=1); c – severe (n=5), moderate (n=3), mild (n=3).

Figure 1. Representative H&E images

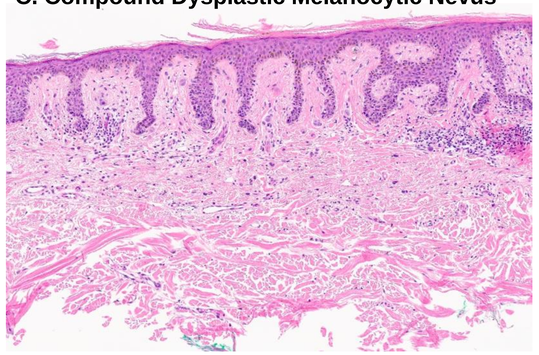
A. Irritated Atypical Spitz



B. Atypical Compound Melanocytic Lesion



C. Compound Dysplastic Melanocytic Nevus



D. Compound Melanocytic Nevus

A. 3 out of 3 UMP concordance, 35-GEP result of intermediate. **B**. 3 out of 3 UMP concordance, 35-GEP result of malignant. **C**. 1 benign and 2 UMP reviews, 35-GEP result of benign. **D**. 3 out of 3 UMP concordance, 35-GEP result of benign.

CONCLUSIONS

- The 35-GEP test is intended to refine diagnoses of melanocytic neoplasms by providing clinicians with an objective ancillary tool with high accuracy.[7]
- In a cohort of 65 difficult-to-diagnose melanocytic lesions, the test provided a result in 100% of lesions, (i.e. no technical failures).
- The 35-GEP test provided an actionable result in 97% of these difficult-to-diagnose lesions, as only 2 cases received an intermediate 35-GEP results.
- Due to the high level of histopathological diagnostic discordance accuracy metrics are not presented.
- Lesion subtypes are presented, however, due to discordance of lesion subtype, only the submitting dermatopathologists' subtype is shown.
- Representative images demonstrate UMPs by histopathological diagnosis that were provided a 35-GEP result.
- A test with these published accuracy metrics in lesions with diagnostic concordance has been shown to alleviate uncertainty in difficult-to-diagnose lesions leading to recommendations for decreased unnecessary procedures while appropriately identifying at-risk patients.[8]

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