Performance of a 35-Gene Expression Profile Test in Suspicious Pigmented Lesions of the Head and Neck

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SYNOPSIS

•The accurate diagnosis of melanocytic neoplasms is a significant clinical challenge in dermatopathology; while histopathologic assessment is frequently sufficient, high rates of diagnostic discordance are reported.[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

Melanoma *in situ* and invasive melanoma of the head and neck require special consideration in regard to excision, surgical staging, and treatment regimens, often making diagnostic timing and accuracy critical for this subset of lesions.[8] Our objective is to demonstrate accuracy of the 35-GEP within lesions located on the head and neck.

METHODS

•Lesions on the head and neck in the ≥18 yo population were analyzed from the cohort published in Estrada *et al*.; samples are described in **Table 1**.

•Clinically diagnosed melanomas tested with the 31-GEP (prognostic melanoma test available from Castle Biosciences Inc.) were included in this study. Benign samples were acquired from 7 centers. Benign samples were reviewed and included in the study if 2/3 or 3/3 diagnoses were concordant.

•The 35-GEP utilizes dual algorithms based on neural networks to provide a result of benign, intermediate-risk or malignant.[7]

RESULTS

Table 1. Demographic information

	Melanoma N=50	Benign nevi N=55
Age, median (range)	73 (31-92)	51 (18-90)
Sex, % male	84	36
Breslow thickness, mm (range)	1.1 (0.2-4.0)	NA
T stage, % (n)		
T0	14 (7)	-
T1a	22 (11)	-
T1b	26 (13)	-
T2a	12 (6)	-
T2b	8 (4)	-
T3a	12 (6)	-
T3b	4 (2)	-
Unknown	2 (1)	-
Ulceration % (n)		
Present	14 (7)	-
Absent	70 (35)	-
Not addressed	16 (8)	100 (55)
Sub-location on head/neck, % (n)		
Cheek	24 (12)	24 (13)
Ear	8 (4)	5.5 (3)
Forehead	8 (4)	9 (5)
Lip	0 (0)	4 (2)
Neck	26 (13)	16 (9)
Nose	8 (4)	5 (3)
Scalp	20 (10)	31 (17)
Other	6 (3)	5.5 (3)

Table 2. Performance of the 35-GEP in different subtypes of nevi and melanoma of the head and neck

	35-GEP Result		
≥18 yo population	**Benign, n**	**Intermediate-risk, n**	**Malignant, n**
Melanomas	***1***	***1***	***48***
Desmoplastic	0	0	4
Lentiginous	0	0	2
Lentigo maligna	0	0	15
In situ	0	0	7
Nevoid	0	0	3
Nodular	1	0	9
Spitzoid	0	1	0
Superficial spreading	0	0	8
Nevi	***53***	***2***	***0***
Blue	14	1	0
Common nevi			
Compound	3	0	0
Intradermal	17	0	0
Junctional	1	0	0
Not specified	10	0	0
Dysplastic			
Compound	4[a]	0	0
Junctional	2[b]	0	0
Spitz	2	1	0

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

Table 3. 35-GEP accuracy metrics in a subset of lesions located on the head and neck

	N=105	
	35-GEP	**95% CI**
Sensitivity	97.96%	89-100%
Specificity	100%	93-100%
PPV	100%	93-100%
NPV	98.15%	90-100%
Intermediate-risk result	2.86%	

Samples that received the intermediate-risk result were excluded from the calculation. The PPV and NPV were calculated with an assumption that the cohort presented here is a random sample of the population. PPV – positive predictive value; NPV – negative predictive value; CI – confidence interval.

CONCLUSIONS

•The 35-GEP test is intended to refine diagnoses of melanocytic neoplasms by providing clinicians with an objective ancillary tool with high accuracy.

•The test provides a narrow intermediate-risk zone of 2.86% in lesions on the head and neck.

•The most common melanoma subtype was lentigo maligna melanoma and the 35-GEP performed well in this subtype. The most common benign subtype was intradermal nevus and the 35-GEP also performed well in this subtype.

•A test with these accuracy metrics has been shown to alleviate uncertainty in difficult-to-diagnose lesions leading to recommendations for decreased unnecessary procedures while appropriately identifying at-risk patients.[9]

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REFERENCES

1. Elmore *et al. BMJ*. 2017;357:j2813
2. Shoo *et al. J Am Acad Dermatol.* 2010;62(5):751-756
3. Patrawala *et al. J Am Acad Dermatol.* 2016;74(1):75-80
4. Farmer *et al. Hum Pathol*. 1996;27(6):528-531
5. Gonzalez *et al. J Am Acad Dermatol.* 2017;77(3):543-548
6. Piepkorn *et al. JAMA Netw Open*. 2019;2(10):e1912597
7. Estrada *et al. SKIN J Cutan Med.* 2020;4(6):506-522
8. Kienstra et. al. *Cancer Control*. 2005;12(4):242-247
9. Farberg et. al. *SKIN J Cutan Med*. 2020;4(6):523-533