Performance of the 35-Gene Expression Profile (GEP) Test for Use as an Adjunctive Melanoma Diagnostic Tool in a New Independent Validation Cohort

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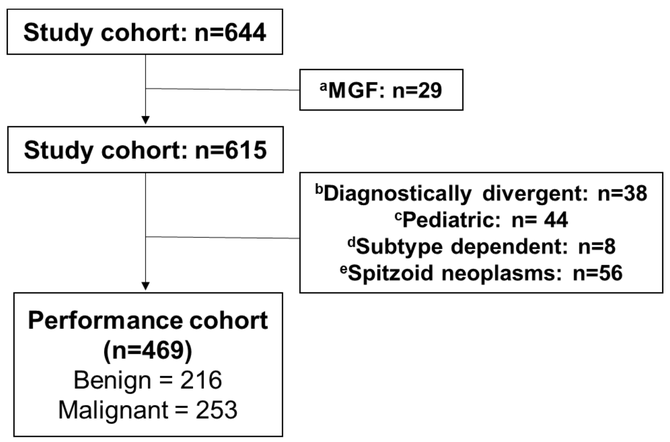
Background

- While histopathological examination is clear for many melanocytic neoplasms, high rates of diagnostic discordance are reported.[1-4]
- Certainty of diagnosis is needed, as the treatment pathways for benign vs. malignant melanocytic neoplasms diverge significantly.
- The **35-gene expression profile** (**GEP**) test is a clinically available objective ancillary tool that facilitates diagnosis of melanocytic lesions with ambiguous histopathology. The test uses a proprietary algorithm to produce results of likely benign, malignant or intermediate.[5,6]
- The 35-GEP test showed accuracy metrics of 99.1% sensitivity and 96.4% specificity in the first validation cohort (≥18-years-old, excluding spitzoid lesions).[5]
- The 23-GEP test has shown similar accuracy metrics[7-10] but has a high test failure rate and a high intermediate result rate.[8,11,12]
- Both the 35-GEP and the 23-GEP test are now offered through the same laboratory, enabling optimization of clinically actionable results.

Objective

- To describe the performance of the 35-GEP test in a novel cohort independent from those used to develop and initially validate the test[5] (**Figure 1**).

Figure 1. Performance Cohort



[a]MGF (multiple gene failure) rules: control genes were evaluated independently, and failure of any control gene resulted in sample exclusion. Triplicate gene expression data were aggregated and normalized using control probes.
[b]Diagnostically divergent: discordant between benign and malignant designations
[c]Pediatric: 17 years old or younger
[d]Subtype dependent: lesions without a majority subtype or equally split between subtype designation where algorithm inputs change the test result
[e]Spitzoid neoplasms: lesions with majority designation of Spitz nevi or spitzoid melanoma.

Methods

- Melanocytic lesions and associated de-identified clinical data from patients ≥18 years of age were obtained from eight laboratories and from lesions submitted for 31-GEP testing (a prognostic melanoma test) in this Institutional Review Board (IRB)-approved study. Lesions were independently reviewed by at least 2 dermatopathologists for diagnostic adjudication and included in the study if they received at least 2 out of 3 diagnostic concordance. Lesion subtype was determined by majority designation and listed as 'subtype discordant' if a majority was not reached.

Results

- Accuracy metrics demonstrate high performance of the 35-GEP test while maintaining a low intermediate result rate (**Table 1**).
- The 35-GEP demonstrates accurate performance across all subtypes reported, including those with subtype discordance (**Table 2**).
- The newly modified clinical testing workflow increased the rate of an actionable report from 77.8% to 98.7% when compared with 23-GEP testing alone (**Figure 2**, **Table 3**).

Table 1. 35-GEP Performance

	≥18 years old (n=469)	
	35-GEP	***95% CI***
Sensitivity	96.0%	93.6% - 98.4%
Specificity	92.2%	88.6% - 95.9%
PPV	93.8%	90.9% - 96.7%
NPV	95.0%	91.9% - 98.0%
Intermediate result	2.3%	

Samples that fall in the intermediate zone were excluded from the calculation.
PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

Table 2. 35-GEP Performance by Subtype

	35-GEP result, n		
	Benign	Intermediate	Malignant
Melanomas			
Acral lentiginous	1	0	25
Desmoplastic	0	0	9
Lentigo maligna	0	0	16
In situ	2	0	18
Nevoid	0	0	2
Nodular	3	0	62
Superficial spreading	1	0	71
Subtype discordant	3	1	39
Nevi			
Blue	33	1	5
Common			
Compound	34	2	0
Intradermal	41	0	1
Junctional	26	3	0
Dysplastic	35[a]	1[b]	7[c]
Subtype discordant	21	3	3

Dysplastic nevi had different degrees of atypia: a – mild (n=1), moderate (n=17) and severe (n=5); b – moderate (n=1); c – mild (n=1), moderate (n=4).

Figure 2. The Comprehensive Diagnostic Offering

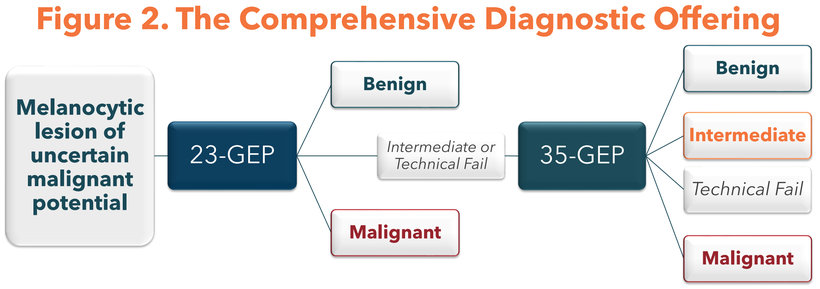


Table 3. Actionable Results from Clinical Testing with the Comprehensive Diagnostic Offering

	Actionable (%)	**Nonactionable** (%)
23-GEP only	77.8%	22.2%
Subsequent 35-GEP	20.8%	1.3%
Overall	**98.7%**	**1.3%**

Actionable is the sum of benign and malignant test results.
Nonactionable is the sum of intermediate and technical failure test results.

Conclusions

- The 35-GEP test is an accurate, objective ancillary tool that provides information that aids in the diagnosis of melanocytic lesions of uncertain malignant potential.
- This second independent cohort of the 35-GEP test confirms the accuracy metrics compared to the initial validation cohort and demonstrates high accuracy across a range of lesion subtypes.
- The 35-GEP test is now used in conjunction with the 23-GEP test. In clinical cases from June – August, 2021, test results of either benign or malignant were increased from 78% to 99% when the 35-GEP was utilized.
- Eligible cases with a malignant result from the 35-GEP can also be tested on the 31-GEP prognostic test without additional tissue, to predict the likelihood of recurrence and sentinel lymph node biopsy positivity.

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