Subtype performance of the ancillary diagnostic 23- and 35-gene expression profiles (GEP) for difficult-to-diagnose melanocytic lesions

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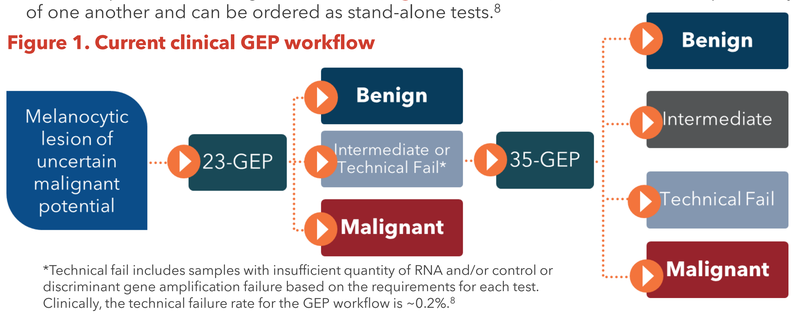
Background

- Diagnostic discordance in cutaneous melanocytic lesions is well documented and particularly prevalent among difficult-to-diagnose cases, for which histopathology may be insufficient for a definitive diagnosis.[1-4]
- The **23-gene expression profile** (**GEP**) and **35-GEP** tests are clinically available, objective ancillary tools that facilitate diagnosis of melanocytic lesions with ambiguous histopathology. The tests use proprietary algorithms to produce results of: **suggestive of benign neoplasm**; **intermediate** (**cannot rule out malignancy**); or **suggestive of malignant neoplasm**.[5-7]
- The GEP tests have demonstrated accuracy metrics of 90.4 – 94.9% sensitivity and 92.5 – 96.2% specificity for the 23-GEP, and 94.7 – 99.1% sensitivity and 89.5 – 94.3% specificity for the 35-GEP.[5-7]
- Today, both the 23- and 35-GEP tests are offered from a single laboratory. Under the current laboratory workflow, unless preferred otherwise by the ordering clinician, clinical samples are processed first through the 23-GEP test, and if a technical failure or intermediate result is received, processed through the 35-GEP (**Figure 1**). However, both are run independently of one another and can be ordered as stand-alone tests.[8]

Figure 1. Current clinical GEP workflow



*Technical fail includes samples with insufficient quantity of RNA and/or control or discriminant gene amplification failure based on the requirements for each test. Clinically, the technical failure rate for the GEP workflow is ~0.2%.[8]

Here, the performance of the 23- and 35-GEP tests using the clinical workflow was tested on unequivocal cases from a variety of subtypes

Methods

- Melanocytic lesions and associated de-identified clinical data from patients ≥18 years of age were included in this study. Samples were acquired under an IRB-approved protocol, including those previously submitted for clinical testing for the 31-GEP melanoma prognostic test. Samples were independently reviewed (blinded to the original diagnosis) by at least 3 total dermatopathologists for adjudication and included if they received at least 2 out of 3 diagnostic concordance with choices of benign, malignant, or uncertain malignant potential (UMP) (**Table 1**). Subtype in this analysis was determined by the submitting dermatopathologist. All cases not receiving a benign or malignant result from the 23-GEP were run on the 35-GEP.

Results

Table 1. GEP workflow overall performance accuracy metrics

Performance Cohort, n=350		
		95% Confidence interval
Sensitivity	96.0%	92.0% – 99.0%
Specificity	87.8%	80.8% – 93.8%
Positive predictive value	89.0%	83.8% – 94.1%
Negative predictive value	95.6%	91.1% – 98.9%
Intermediate result	*1.5%*	

Table 2. GEP workflow test result by lesion subtype (as indicated by submitting dermatopathologist)

	Final GEP workflow result		
Subtype*	**Benign, n**	**Intermediate, n**	**Malignant, n**
***Melanomas* (n=245)**			
Acral lentiginous			15
Common			15
Desmoplastic			20
Lentigo maligna	1		30
Melanoma *in situ*			16
Nodular	4		77
Not specified	1		4
Spitzoid	3		17
Superficial spreading	1		41
***Benign nevi* (n=100)**			
Blue	28	1	1
Compound	9		3
Compound dysplastic	26[A]	1	3[B]
Deep penetrating	1		
Intradermal	1		1
Junctional dysplastic	13[C]	1[D]	4[E]
Spitz	7		

*5 samples did not have adequate subtype information. Dysplastic nevi had different degrees of atypia: A: 13 mild, 2 moderate; B: 2 mild, 1 moderate; C: 6 mild, 4 moderate; D: 1 moderate; E: 3 mild, 1 moderate.

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Results

Table 3. GEP workflow performance accuracy metrics by lesion subtype

Subtype*	n	Sensitivity	Specificity
Melanomas			
Acral lentiginous	15	100%	
Common	15	100%	
Desmoplastic	20	100%	
Lentigo maligna	31	96.8%	
Melanoma *in situ*	16	100%	
Nodular	81	95.1%	
Spitzoid	20	85%	
Superficial spreading	42	97.6%	
Benign nevi			
Blue	30		93.3%
Compound dysplastic	30		86.7%
Junctional dysplastic	18		72.2%

*Only subtypes with n ≥15 are shown.

Conclusions

- The 23- and 35-GEP test workflow results in high accuracy across a large spectrum of subtypes of melanocytic neoplasms.

References

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