23-gene expression profile (GEP) testing for diagnosis of cutaneous melanocytic lesions in a Medicare-eligible population

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Background

- The incidence of cutaneous melanoma, which is typically diagnosed via histopathological evaluation, increases with age.[1]
- The **23-GEP** test is an objective, clinically available ancillary tool that facilitates the diagnosis of melanocytic lesions with ambiguous histopathology. The test uses a proprietary algorithm to report results of **suggestive of benign neoplasm, suggestive of malignant neoplasm, or intermediate** (**cannot rule out malignancy**).[2-6]
- The 23-GEP test has demonstrated 90.0 – 91.5% sensitivity and 91.0 – 92.5% specificity in lesions classified by histopathological majority review,[2,3] 93.8 – 96.8% sensitivity and 87.3 – 96.2% specificity in lesions with known outcomes,[4,5] and 90.4% sensitivity and 95.5% specificity in equivocal lesions with known outcomes.[6]
- The higher incidence of melanoma in older individuals is reflected in diagnostically ambiguous cases submitted for 23-GEP testing. The clinical stratification of 23-GEP test results demonstrate a higher proportion of malignant results in older patients, with a ~20% malignant rate at age 30, ~40% at age 60, and ~55 – 70% for patients over age 80.[7]
- Here, we present the accuracy of 23-GEP testing in a Medicare-eligible population as well as a meta-analysis of patients ≥65 years old from the first two validation studies.[2,3]

Methods

- Melanocytic lesions and associated de-identified clinical data from patients ≥65 years old were included in this IRB-approved study (65+ performance cohort).
- Lesion inclusion for the 65+ performance cohort was dependent upon the level of diagnostic concordance. Case histopathology was independently reviewed by 2–4 dermatopathologists (from a pool of 11) and designated as benign, malignant, or uncertain malignant potential (UMP). Independent reviews and the original clinical diagnosis were utilized to determine inclusion. Lesions were included in the study if they were fully concordant (benign, n=141; malignant, n=132) or if a majority could be established despite lack of full concordance (**Figure 1A**) (i.e., minority UMP diagnoses).
- Lesions with opposing diagnoses were excluded from both the 65+ performance and the meta-analysis (**Figure 1B**).
- Accuracy metrics and two-tailed 95% confidence intervals (CIs) were calculated without intermediate results (**Table 1** and **Table 2**) and using resampling x10,000 iterations to establish a balanced number of benign versus malignant samples (**Table 2**).

References

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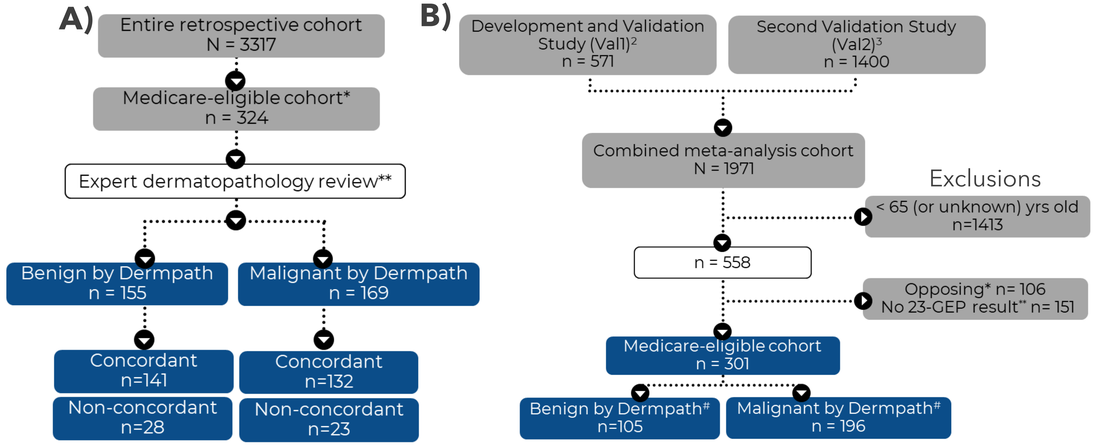
Acknowledgments & Disclosures

JAP and KM have served as expert dermatopathological reviewers for Castle Biosciences, Inc. SIE has served as a consultant and expert dermatopathological reviewer for Castle Biosciences, Inc. JJS, BHR, MDB, JHR, and MSG are employees and shareholders of Castle Biosciences, Inc. This study was supported by Castle Biosciences, Inc.

Results

Figure 1. Consort Diagrams A) 65+ performance cohort. B) Meta-analysis cohort.



*≥ 65 years old with 23-GEP result **Blinded dermatopathology review by 2-4 independent reviewers in addition to clinical diagnosis.

*Opposing: both benign and malignant designations **Discriminant gene(s) or housekeeping control gene(s) failure to amplify within acceptable parameters. #2 or 3 dermatopathologist reviewers gave the same diagnosis of benign or malignant, allowing for 1 out of 3 UMP designations from Val2 cases (UMP was not an option in the Val1 study).

Table 1. 23-GEP accuracy metrics in the current study

65+ Performance Cohort, n=324		95% CI
Sensitivity	**92.4%**	88.1%-96.3%
Specificity	**89.4%**	84.2%-94.2%
Positive predictive value	**90.6%**	85.9%-95.0%
Negative predictive value	**91.4%**	86.3%-95.7%
Intermediate result	*7.7% (n=25)*	

Table 2. 23-GEP accuracy metrics pooled from previous studies

Meta-analysis Cohort, n=301		95% CI
Sensitivity	**94.1%**	88.5%-98.0%
Specificity	**87.5%**	80.6%-93.3%
Positive predictive value	**89.0%**	82.6%-93.3%
Negative predictive value	**93.6%**	88.5%-97.8%
Intermediate result	*2.7% (n=8)*	

The 65+ performance cohort and the meta-analysis cohort accuracy metrics are statistically similar and do not differ significantly from previously published studies where all ages were included.

Guidelines

Table 3. The 23-GEP test use guidelines as a diagnostic aid for ambiguous melanocytic lesions.

Organization	Recommendation
National Comprehensive Cancer Network (NCCN)[8]	The NCCN guidelines direct physicians to consider the use of molecular testing, including GEP, in melanocytic lesions that are equivocal by histopathology.
American Society of Dermatopathology (ASDP): Appropriate Use Criteria (AUC) for Ancillary Diagnostic Testing [9]	The ASDP's AUC committee has designated six key clinical scenarios in dermatopathology as "majority usually appropriate" for ancillary diagnostic GEP testing.
American Academy of Dermatology (AAD) Guidelines of Care for the Management of Primary Cutaneous Melanoma[10]	The AAD supports the use of ancillary diagnostic molecular techniques (e.g., GEP, CGH, FISH) for equivocal melanocytic neoplasms.
Skin Cancer Prevention Working Group (SCPWG)[11]	The SCPWG advocates for the use of GEP tests to distinguish between benign and malignant melanocytic lesions.
Centers for Medicare and Medicaid Services (CMS)[12]	Designated as covered test in L39375: MolDX: Molecular Assays for the Diagnosis of Cutaneous Melanoma

Conclusions

- The 23-GEP accuracy metrics in Medicare-eligible individuals are similar to previous studies which included all ages.
- The high accuracy and clinical utility of the 23-GEP test demonstrated across multiple prior studies are applicable to the Medicare-eligible population.
- These data further validate the use of 23-GEP in the Medicare-eligible population and support its position in national guidelines.

Presented at the College of American Pathologists (CAP) Annual Meeting; October 7-10, 2023. Chicago, IL

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