A comprehensive diagnostic offering workflow increases the rate of actionable results of the 23- and 35-gene expression profile tests for use as ancillary diagnostic tools for difficult-to-diagnose melanocytic lesions

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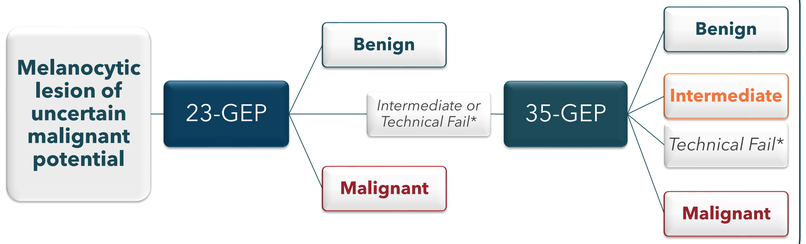
Background

- Diagnostic discordance in suspicious 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; myPath Melanoma**) and **35-GEP** (**DiffDx-Melanoma**) 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 likely benign, intermediate, or malignant.[5-7]
- The 23-GEP has shown accuracy metrics of over 90% sensitivity in multiple clinical studies that included patient outcomes.[8-10] However, the 23-GEP historically has resulted in ~23% of cases receiving either a technical failure or an intermediate result, which can be perceived as **nonactionable**.[6,11-13]
- The 35-GEP test can address this shortcoming and showed both an increased sensitivity in the first validation cohort and a decreased nonactionable rate of 8.5%.[7]
- Clinical utility has been demonstrated with benign and malignant GEP test results;[11,14] therefore, those test results are defined as **actionable**.

Objective

- Today, both the 23- and 35-GEP are offered from a single laboratory as part of a **comprehensive diagnostic offering** (**CDO**) 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 to the 35-GEP (**Figure 1**).
- Here we report test result metrics from this clinical workflow.

Figure 1. Clinical workflow of the comprehensive diagnostic offering



*Does not generate a test report. Cases with Intermediate or Technical Fail results from the 23-GEP undergo testing with the 35-GEP. **GEP**, gene expression profile.

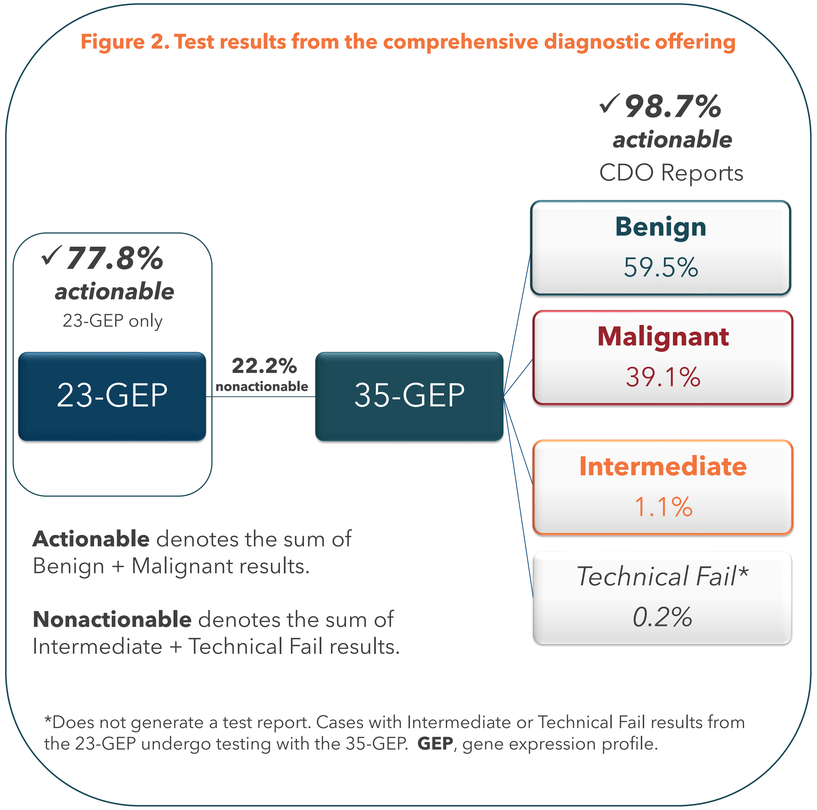
Methods

- The study included clinical cases submitted to Castle Biosciences for CDO testing with results reported since implementation of the workflow between June 3 and August 31, 2021.
- All cases not receiving a benign or malignant result from the 23-GEP were run on the 35-GEP, except for pediatric cases (<18 years), which were only run on the 23-GEP and excluded from this analysis.
- Technical fail includes samples with insufficient quantity of RNA and/or control or discriminant gene amplification failure based on the requirements for each test.

Results

- The median age for the patient population receiving CDO test results was 49.0 years (range, 18.1-95.5), and 59.2% of patients were female.
- The 23-GEP test gave an actionable result of benign or malignant in 77.8% of cases, which is comparable to past reporting in ambiguous cases for this test[6,11] (**Figure 2**).
- Nonactionable classifications of the 23-GEP test were 22.2% (12.9% intermediate and 9.4% technical failure). These cases then underwent testing with the 35-GEP test, and an additional 20.9% of originally submitted cases received an actionable result. Only 1.1% of cases received a final intermediate test result (i.e., from both tests); the technical failure rate for the CDO was 0.2% (**Figure 2**).
- This clinical workflow increased the rate of an actionable report from 77.8% to 98.7% when compared with 23-GEP testing alone (**Figure 2**).

Figure 2. Test results from the comprehensive diagnostic offering



Actionable denotes the sum of Benign + Malignant results.

Nonactionable denotes the sum of Intermediate + Technical Fail results.

*Does not generate a test report. Cases with Intermediate or Technical Fail results from the 23-GEP undergo testing with the 35-GEP. **GEP**, gene expression profile.

Conclusions

- Combining the 23-GEP and 35-GEP tests into a single workflow leverages the strengths of both assays.
- The CDO workflow for histopathologically ambiguous melanocytic lesions has substantially improved reporting of **clinically actionable results** from a historic rate of ~77% for the 23-GEP alone to over 98%.
- Eligible cases with a malignant result from the CDO can also be subsequently run on the 31-GEP prognostic test (Decision Dx-Melanoma), without requiring extra tissue, to predict the likelihood of recurrence and sentinel lymph node biopsy positivity.

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Acknowledgments & Disclosures

- This study was sponsored by Castle Biosciences, Inc.
- All authors are employees and shareholders of Castle Biosciences, Inc.

Presented at the 2021 Fall Clinical Dermatology Conference in Las Vegas, NV; October 21-24, 2021.

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