Performance of a diagnostic 35-gene profile test (GEP) on difficult-to-diagnose melanocytic lesions

SYNOPSIS

The accurate diagnosis of melanocytic neoplasms and characterization of their malignant potential remain significant clinical challenges in dermatopathology.1

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.2

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%.1,3

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).4

RESULTS

Table 1. Demographic information

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Difficult-to-diagnose lesions</th>
<th>N=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>46 (18-87)</td>
<td></td>
</tr>
<tr>
<td>Sex, % male</td>
<td>44.6</td>
<td></td>
</tr>
<tr>
<td>Location on body, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen/Chest</td>
<td>6.1 (4)</td>
<td></td>
</tr>
<tr>
<td>Acral</td>
<td>3.1 (2)</td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td>43.1 (28)</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>32.3 (21)</td>
<td></td>
</tr>
<tr>
<td>Head/Neck</td>
<td>13.9 (9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.5 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. 35-GEP results in difficult-to-diagnose lesions

<table>
<thead>
<tr>
<th>Lesions, % (n)</th>
<th>Benign, n Intermediate, n Malignant, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free</td>
<td>77% (50)</td>
</tr>
</tbody>
</table>

Table 3. Subtype of melanocytic proliferation as determined by submitting dermatopathologist

<table>
<thead>
<tr>
<th>Blue</th>
<th>Compound</th>
<th>Deep Penetrating</th>
<th>Dysplastic Compound</th>
<th>Dysplastic Junctional</th>
<th>Spitz</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Dysplastic nevi had different degrees of atopia: a–severe (n=5), moderate (n=8), mild (n=3); b–severe (n=1); c–severe (n=5), moderate (n=3), mild (n=3).

Figure 1. Representative H&E images

A. Irritated Atypical Spitz
B. Atypical Compound Melanocytic Lesion
C. Compound Dysplastic Melanocytic Nevus
D. Compound Melanocytic Nevus

OBJECTIVE

To demonstrate use in the intent-to-use difficult-to-diagnose melanocytic lesion population, which includes diagnostically discordant lesions and lesions designated as unknown malignant potential (UMP), cases were analyzed using the 35-GEP test. Accuracy metrics are not provided as a definitive diagnosis for comparison was not achieved.

METHODS

•Samples were acquired from 7 centers. Samples were reviewed by 2 to 3 independent dermatopathologists and used in the study if diagnoses included benign and malignant designations or if diagnoses included more than one unknown malignant potential (UMP) designation.

•Difficult-to-diagnose lesions in the ≥18 yo population were excluded from analysis from the cohort published in Estrada et al. which were analyzed with 35-GEP; samples are described in Table 1.

•The 35-GEP utilizes dual algorithms based on neural networks to provide a result of benign, intermediate-risk or malignant.4 Accuracy metrics cannot be calculated as the true diagnosis was unable to be captured.

FUNDING & DISCLOSURES

Funding: This study was sponsored by Castle Biosciences, Inc. (CBI), which provided funding to contributing centers for tissue and clinical data retrieval. CBI is a CBI advisor and shareholder. HM, ND-S, NC, GH are CBI advisors. MSG, BHR and OZ are employees and shareholders of CBI.

CONCLUSIONS

•The 35-GEP test is intended to refine diagnoses of melanocytic neoplasms by providing clinicians with an objective ancillary tool with high accuracy.7

•In a cohort of 65 difficult-to-diagnose melanocytic lesions, the test provided a result in 100% of lesions, (i.e. no technical failures).7

•The 35-GEP test provided an actionable result in 97% of these difficult-to-diagnose lesions, as only 2 cases received an intermediate 35-GEP results.

•Due to the high level of histopathological diagnostic discordance accuracy metrics are not presented.

•Lesion subtypes are presented, however, due to discordance of lesion subtype, only the submitting dermatopathologists subtype is shown.

•Representative images demonstrate UMPs by histopathological diagnosis that were provided a 35-GEP result.

•A test with these published accuracy metrics in lesions with diagnostic concordance has been shown to alleviate uncertainty in difficult-to-diagnose lesions leading to recommendations for decreased unnecessary procedures while appropriately identifying at-risk patients.8

REFERENCES

1. Elmore et al. BMJ. 2017;357:j2813