Short Communication

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Melanoma Management

A clinical impact study of dermatologists' use of diagnostic gene expression profile testing to guide patient management

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Aim: Cutaneous melanocytic neoplasms with diagnostic and/or clinical ambiguity pose patient management challenges. **Methods:** Six randomized case scenarios with diagnostic/clinical uncertainty were described with/without a benign or malignant diagnostic gene expression profile (GEP) result. **Results:** Clinical impact was assessed by reporting the mean increase/decrease of management changes normalized to baseline (n = 32 dermatologists). Benign GEP results prompted clinicians to decrease surgical margins (84.2%). Malignant GEP results escalated surgical excision recommendations (100%). A majority (72.2%) reduced and nearly all (98.9%) increased follow-up frequency for benign or malignant GEP results, respectively. There was an overall increase in management plan confidence with GEP results. **Conclusion:** Diagnostic GEP tests help guide clinical decision-making in a variety of diagnostically ambiguous or clinicopathologically discordant scenarios.

Plain language summary: Dermatologists' use of diagnostic gene expression profiles for personalized patient care. When your doctor takes a piece of a mole, that mole is looked at under the microscope by a pathologist. The pathologist is responsible for figuring out if the mole is dangerous or not. Dangerous moles are removed with surgery to make sure all the dangerous tissue is gone. Moles without a health threat are left alone. Sometimes figuring out how dangerous a mole is is difficult. The pathologist may not provide the doctor with enough information for them to know how to treat your mole. There is a test that can provide information on whether your mole is unsafe. This test is called diagnostic gene expression profiling or GEP. In this study, GEP is used to help doctors figure out how to treat a mole and how often the patient should be seen in the office for skin checks. With GEP, important changes in patient treatment were identified. These include the need for an additional surgery, how much healthy tissue should be removed during surgery and how often the patient should be seen in the office. For suspicious moles where the pathology report is unclear, GEP can provide information that leads to more appropriate and personalized patient care.

Tweetable abstract: Ancillary diagnostic gene expression profile testing for ambiguous cutaneous melanocytic lesions helps optimize dermatologist recommendations for excision margin and follow-up.

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Suspicious pigmented skin lesions can often lead the treating clinician to perform a biopsy to determine if the lesion is malignant. The gold standard for determining the malignant potential of a suspicious pigmented lesion is histopathological analysis, which informs the final diagnosis and determines the management plan, often based on guideline criteria from the National Comprehensive Cancer Network (NCCN) and the American Academy of Dermatology (AAD) [1,2]. A diagnosis of primary cutaneous melanoma is recommended to be excised in accordance with tumor thickness (melanoma *in situ* [MIS] 0.5–1.0 cm margins, invasive melanoma ≥1 cm and ≤2 cm); recommended follow-up intervals are also dependent on tumor thickness and staging (MIS and Stage IA-IIA every 6–12 months, Stage IIB and higher every 3–6 months) [1,2]. A benign nevus without additional concerning factors can forgo excision or be completely removed with minimal margins (depending on clinicopathological correlation), and the patient may resume recommended routine skin checks every 12 months [3].

Borderline lesions pose not only a nomenclature issue [4–8] but also a patient care issue for dermatopathologists and dermatologists alike. Detailed, evidence-based guidelines are lacking on how to manage and treat these lesions [9–11]. In a conservative effort, borderline lesions, including but not limited to melanocytic tumor of uncertain malignant potential (MELTUMP), atypical intraepidermal melanocytic proliferation (AIMP), superficial atypical melanocytic proliferation of uncertain significance (SAMPUS), indeterminate, moderate and severely atypical nevi, etc. are often treated clinically as melanoma [10,12–14].

Gene expression profile (GEP) testing provides an objective result for the classification of borderline or ambiguous melanocytic lesions and is primarily intended for use during the diagnostic process [15–17]. The 23-GEP test has demonstrated 90.4–94.9% sensitivity and 88.7–96.2% specificity in a variety of studies, including cohorts with known long-term outcomes [15,16,18–20]. When GEP is used during the diagnostic process, unnecessary excisions can be avoided when a benign GEP result is received, and more aggressive treatment can be reserved for lesions receiving malignant GEP results [21–23]. In one report, patients that received a benign 23-GEP result and did not have an excision (88%) had no cases of recurrence over a mean of 38.5 months follow-up, indicating that incorporation of test results to de-escalate surgical intervention in these patients is appropriate [24]. Diagnostic GEP is included in numerous guidelines including the NCCN, American Society of Dermatopathology: Appropriate Use Criteria for Ancillary Diagnostic Testing (majority usually appropriate use for in 22 major clinical scenarios), AAD and the Skin Cancer Prevention Working group [1,2,25,26].

In addition to borderline/ambiguous lesions, there are other circumstances that can confound the management of a melanocytic lesion. For example, a diagnosis of benign nevus can be issued with contradictory language indicating excision is prudent, but may not come with suggested excision margins, leaving the treating clinician to subjectively interpret the result and make the final decision on a treatment plan. There can also be concerning language included in the pathology report that may make foregoing excision a difficult decision. Language such as atypical, uncertain, unusual or suspicious can contribute to this hesitancy and may prompt a treating clinician to escalate management regardless of the absence of a specific recommendation from the diagnosing pathologist to do so [5]. Finally, other considerations can impact the feasibility of an excision due to body site location, concerns of scarring or functionality, physical constraints, local tissue reconstruction limitations or the presence of patient comorbidities. All of these circumstances can be mutually challenging for both clinicians and patients [27]. These situations indicate a need for clarity for both borderline lesions and seemingly benign nevi with equivocal language in their diagnosis [28]. GEP may alleviate diagnostic and treatment ambiguity and has previously been demonstrated to impact patient management. When GEP results were utilized, the treating dermatologist often escalated or de-escalated care as appropriate [22,23].

Here, we describe how dermatologists with experience incorporating diagnostic GEP reported they would utilize the test results to guide personalized patient management through an online survey presenting scenarios based on randomized presentation of real-world cases with or without GEP results.

Materials & methods

Patient scenarios

Clinical and diagnostic information for eight patient scenarios (two for reference and six borderline/ambiguous) was provided to the study participants. Reference lesions of unequivocal Clark's nevus and melanoma were utilized as a means to exclude participants if responses did not align with guidelines; no participant was excluded. Diagnostic information (including the histopathological description) was taken from real-world pathology reports of

Table 1. Lesions scenarios are described below that encompass diagnoses and microscopic descriptions similar to verbiage found on a pathology report.

	Clinical impression	Diagnosis	Microscopic description and note	GEP
1	High clinical suspicion	Atypical intraepidermal melanocytic proliferation	Proliferation of atypical melanocytes confined to the epidermis: there is a proliferation of melanocytes arranged as solitary units at the dermoepidermal junction and above it. There is also a sparse mononuclear cell infiltrate with a few melanophages in the papillary dermis Note: These changes are quite suggestive of evolving melanoma *in situ*, although that diagnosis cannot be made with certainty in these sections. It would be advisable either to follow this lesion carefully or consider complete but conservative removal	None, benign, malignant
2	Comorbidities	Atypical intraepidermal melanocytic proliferation	Proliferation of atypical melanocytes confined to the epidermis: there is a proliferation of melanocytes arranged as solitary units at the dermoepidermal junction and above it. There is also a sparse mononuclear cell infiltrate with a few melanophagesin the papillary dermis Note: These changes are quite suggestive of evolving melanoma *in situ*, although that diagnosis cannot be made with certainty in these sections. It would be advisable either to follow this lesion carefully or consider complete but conservative removal	None, benign, malignant
3	Cosmetic site	Melanocytic neoplasm, atypical melanocytic proliferation	Sections reveal a proliferation of mildly atypical melanocytes arranged predominantly in nests at the lentiginous and focally bridging dermal-epidermal junction. Pagetoid spread is not seen. The junctional component of the lesion extends laterally beyond a central intradermal component which matures with depth and does not reveal significant cytologic atypia or mitoses. The papillary dermis is fibrotic. There is a superficial perivascular infiltrate of lymphocytes and melanophages	None, benign, malignant
4	Personal history of malignant melanoma	Melanocytic neoplasm, atypical melanocytic proliferation	Sections reveal a proliferation of mildly atypical melanocytes arranged predominantly in nests at the lentiginous and focally bridging dermal-epidermal junction. Pagetoid spread is not seen. The junctional component of the lesion extends laterally beyond a central intradermal component which matures with depth and does not reveal significant cytologic atypia or mitoses. The papillary dermis is fibrotic. There is a superficial perivascular infiltrate of lymphocytes and melanophages	None, benign, malignant
5	Cosmetic site	Dysplastic nevus with features of regression	There is prominent fibroplasia with telangiectases in the papillary dermis and abundant melanophages. A few small basophilic cells are present in nests suggesting residual nevus cells Note: The presence of nests of nevus cells associated with the fibrotic changes are features that are highly suggestive of regression of a dysplastic nevus. The changes are somewhat unusual and for that reason, it would be advisable to ensure that the lesion be completely excised, especially given that a more aggressive process may occasionally appear similar. A benign process is favored in these sections, however	None, benign, malignant
6	Personal history of malignant melanoma	Melanocytic neoplasm, deep penetrating	Sections show a domed segment of skin with an intradermal melanocytic proliferation that contains two populations of melanocytes. There is a palpation of small, bland appearing melanocytes with round to oval nuclei and relatively scant cytoplasm disposed of small nests. There is also a population of spindled and epithelioid melanocytes that have relatively monomorphic nuclei splayed between sclerotic collagen bundles. There is no epidermal component. No mitotic figures are evident. There is marked solar elastosis Note: Conservative excision is recommended to ensure the local eradication has been accomplished	None, benign, malignant

GEP: Gene expression profile.

melanocytic lesions. Clinical information was based on common clinical situations that may alter patient treatment. GEP test results were either not provided, benign, or malignant for each patient scenario in a randomized order, resulting in a total of 24 patient scenarios (Table 1). The scenario order was also randomized for each participant.

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Table 2. Questions for each scenario.

Question	Selection options
How would you treat the patient?	• No further treatment necessary • No further treatment necessary if lesion appears completely excised • Excise <5 mm margins (narrow but complete) • Excise ≥5 mm margins (but <1 cm) • Wide local excision (Excise ≥1 cm)
Which follow-up schedule would you recommend?	• Every 12 months • Every 6 months • Every 3 months • Every month
How confident are you in this management plan?	• 1 (not confident) • 2 (slightly confident) • 3 (somewhat confident) • 4 (fairly confident) • 5 (completely confident)

Participants were asked standardized questions for each patient scenario (Table 2).

Dermatologist study parameters

Board-certified dermatologists were invited for study participation based on prior use of GEP testing (minimum three encounters with GEP results). The objective of this study was to understand how diagnostic GEP results influence patient management of ambiguous lesions, which requires some education and practical use experience of a GEP test. The utilization of experienced GEP users was intended to provide accurate clinical use information which would not be possible in the absence of practical experience. Study questions were provided to participants via an anonymous online questionnaire in this Institutional Review Board (IRB)-approved study. Participants were asked demographic information questions as provided in (Supplementary Materials). Participants were required to complete the entire study in order to be included in the data analysis and to receive compensation for their time. The survey included a brief overview of the accuracy metrics of the 23- and 35-GEP where both reported similar accuracy metrics (Supplementary Materials). However, neither GEP test was specified in the survey scenarios. Only 'GEP result' of benign or malignant (or no GEP result) was provided. Survey data was collected anonymously via a webpage and analyzed using R software (version 4.2.1).

Data analysis

R software (version 4.2.1) was utilized for data analysis. The control for this analysis was comparison with case studies in the absence of GEP information, allowing for a difference in response to be assessed for cases that are otherwise identical. The order of cases randomized to control from order bias. Survey responses across ambiguous scenarios with benign or malignant GEP results compared with responses without GEP results were utilized to calculate the percentage of no change, increase or decrease change in patient management. Average percentages of change were then calculated across the vignettes. Average percentage no change and change (increase and decrease) are reported in a stacked bar graph (Figure 1) and described as overall percentage clinical impact. Average percentage change (Figure 2) was calculated by normalizing (scaling technique where data points are shifted and rescaled so they can be compared, i.e., set to 100%) the percentage change of the overall clinical impact score so the increase and decrease of that change can be compared. This descriptive analysis utilizes measures of central tendency (i.e., mean) for all figures. Data is reported as observation and descriptive as an independent summary of board-certified experienced test users.

Results

Study Information

Dermatologists were selected for participation based on their prior use (having ordered a GEP test at least three-times) of diagnostic GEP testing performed by Castle Biosciences. In total, 32 participants fully completed the online survey containing eight patient scenarios (two for reference and six borderline/ambiguous) where clinical and diagnostic information were provided. Each scenario was provided with either no GEP information, a GEP benign result, or a GEP malignant result, resulting in a total of 24 patient scenarios (borderline/ambiguous lesions listed in Table 1). Each patient scenario was followed by questions related to the treatment of the patient (Table 2). Participants were to assume the patient in question was 50 years old and female for each scenario and that the

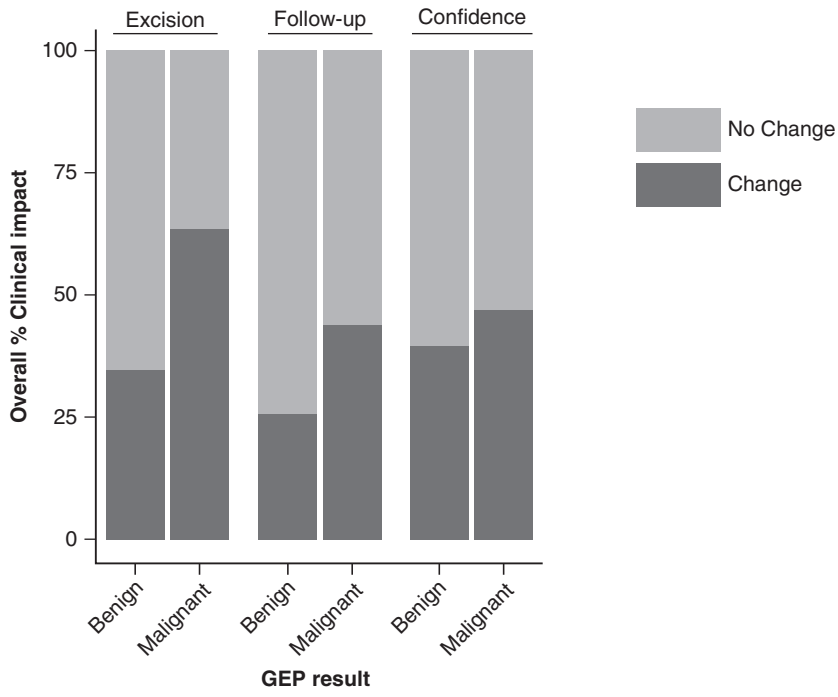

Figure 1. Change in survey respondent selection with gene expression profile results described as overall % clinical impact. Average percentage change and average percentage no change in comparison to no GEP results across ambiguous scenarios with either a benign or malignant GEP result is shown.
GEP: Gene expression profile.

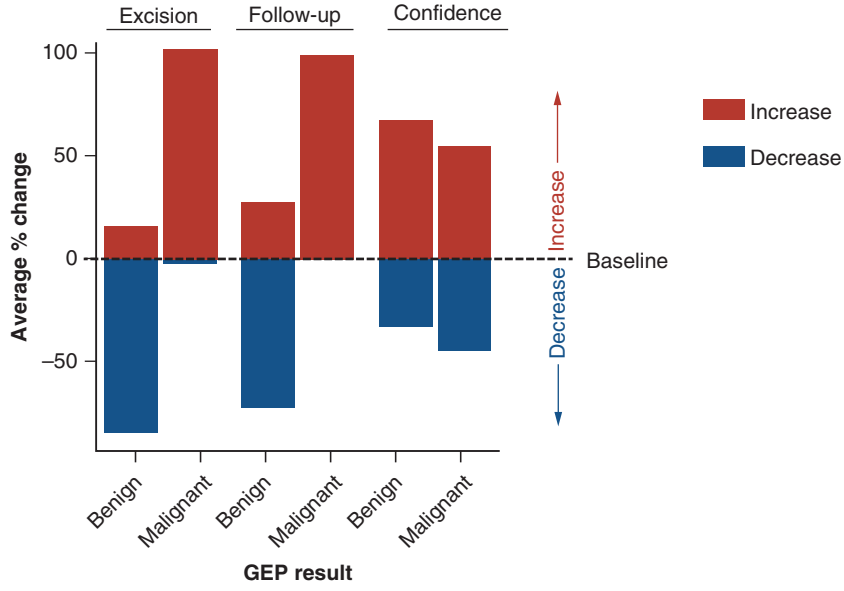

Figure 2. Clinical impact of gene expression profile results. Clinical impact is demonstrated as Average % change calculated from normalizing the overall percentage change to 100% thereby providing insight to increased or decreased escalation of patient management with GEP results across all scenarios. Treatment changes were aligned with GEP results the majority of the time.
GEP: Gene expression profile.

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location of the lesion was of no consequence unless specifically described in the scenario in an effort to keep age, sex and lesion location from affecting treatment considerations. Participants were also to assume that the margins were negative for each scenario. Overall, 47% of participants described their primary specialty as clinical dermatologist, and 44% described clinical dermatologist/dermatopathologist as their primary specialty. In their clinical practice, 44% indicated performing 10–50 biopsies of melanocytic lesions during the past month, and 31% indicated they performed >100 per month. Most study participants were in private practice with multiple locations.

Clinical impact of gene expression profile test results

Clinical impact was assessed by quantifying the directional shift in treatment in relation to the GEP result. The level of overall change compared with baseline (same case presented with no GEP results) for all six borderline/ambiguous scenarios is demonstrated in Figure 1. Clinical impact is shown as normalized increased or decreased change across all scenarios when either a benign or malignant result was presented for the ambiguous scenarios (Figure 2). GEP results altered surgical excision treatment recommendations across a variety of scenarios. When a malignant GEP result was provided, 100% of surgical excision recommendations were increased. Conversely, when a benign GEP result was provided, 84.2% of respondents decreased in their recommended surgical excision management. Similarly, follow-up cadence was influenced by GEP results. When a malignant GEP result was received, 98.9% of follow-up visit recommendations were increased in frequency. Alternatively, when a benign GEP result was given, 72.2% of respondents decreased their follow-up visit cadence suggestion. Generally, when GEP results were provided, overall clinician confidence increased (67.4% with benign results and 54.9% with malignant results); there was less pronounced clinical confidence when a malignant GEP result was received. Malignant GEP results prompted only a modest increase in recommendation for sentinel lymph node biopsy, perhaps in part due to lack of staging information.

Gene expression profile impacts surgical excision planning & follow-up cadence

Treatment recommendations from the participating dermatologists across the six ambiguous scenarios are shown (Figure 3). The vast majority of clinicians recommended to excise with 5–10 mm margins the two lesions with AIMP diagnoses (81% for lesion #1 and 62% for lesion #2, Table 1) when no GEP results were provided. When a malignant GEP result was provided, the recommendation to excise was further solidified with all respondents (100% for lesions #1 and #2) recommending some level of excision. When benign GEP results were provided, the number of recommendations for excision were decreased overall to 19% (lesion #1, Table 1), and 25% recommended no excision (lesion #2, Table 1). In the pair of lesions with atypical proliferation diagnoses (lesions #3 and #4), the majority of recommendations without GEP were to have no excision (72% for lesion #3 and 63% for lesion #4). When malignant GEP results were provided, the majority recommendation shifted to excision with 5–10 mm (96% for lesion #3 and 97% for lesion #4). Both the dysplastic nevus with regression and the deep penetrating nevus had the majority of clinicians recommending an excision with narrow but complete margins without GEP (62%, lesion #5; 78%, lesion #6, Table 1). When a benign GEP result was included, 50 and 16% of recommendations did not recommend an excision, respectively. Most recommendations with a malignant GEP result suggested more aggressive margins (60 and 84%, respectively, excise 5–10 mm or wide local excision (WLE).

Recommended follow-up frequency across the six ambiguous scenarios is presented in Figure 4. For the atypical proliferations, dysplastic nevus with regression and deep penetrating nevus, the baseline follow-up recommendation was every 6 to 12 months. With a GEP malignant result, the majority shifted to every 3 to 6 months. Benign GEP results closely mirrored the baseline. For the AIMP lesions, majority baseline follow-up was already at a heightened 3 to 6 months. With benign GEP results, some rates of recommendations for a 12-month follow-up were slightly increased (6% for lesion #1 and 16% for lesion #2). Malignant GEP results showed greater numbers of dermatologists electing a preferred 3-month follow-up cadence (66%, with high clinical concern or comorbidities present).

Discussion

Dermatologists can encounter situations where a borderline/ambiguous diagnosis or a diagnosis with uncertain terminology (e.g., benign lesion with recommendation to re-excise, possible evolving MIS/atypical lesion with clean but narrow biopsy margins with unclear re-excision need) may also be coupled with clinical features that make management plans difficult to determine. Communication efforts between the diagnosing pathologist and treating clinician can alleviate situations where the pathologist was unaware of clinical factors (including dermoscopy or

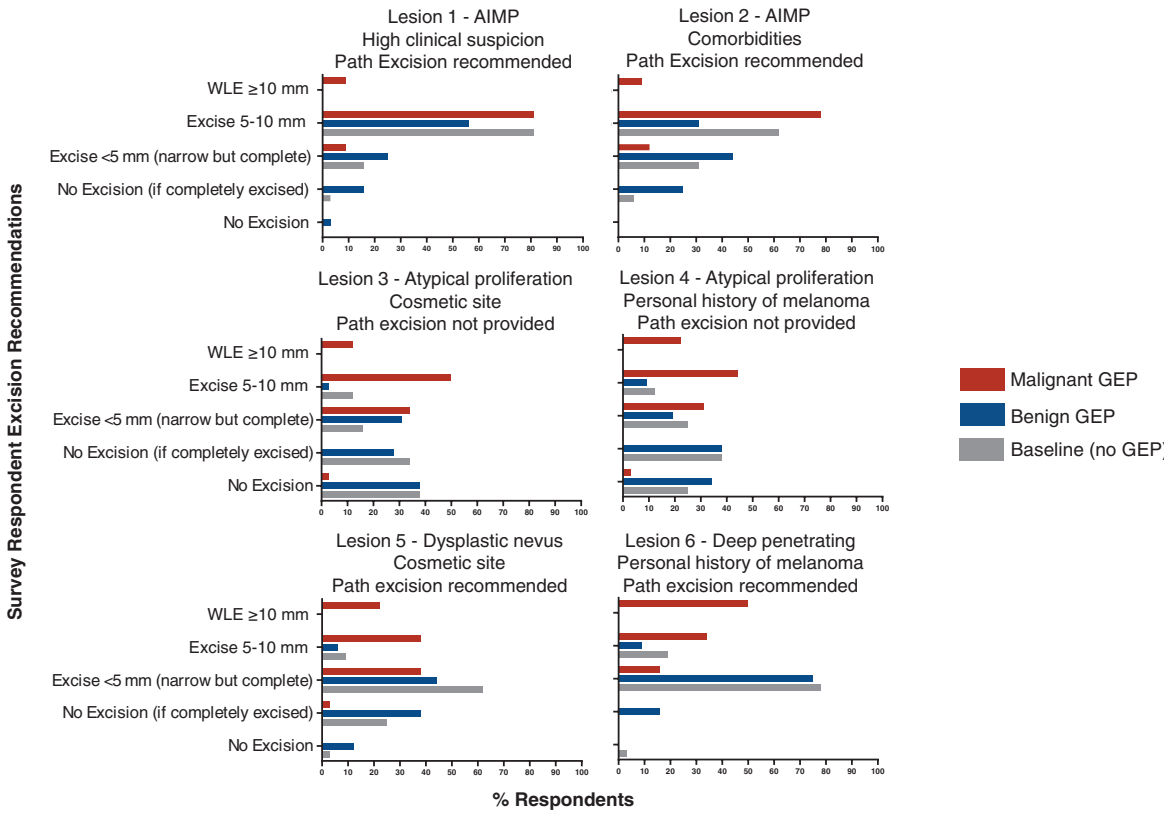

Figure 3. Gene expression profile results impact surgical excision recommendations, including margin decisions. y-axis, survey respondent excision recommendations. x-axis, percentage of respondents. Each bar graph represents responses for each ambiguous lesion. Respondent recommendations are stratified by GEP result. Malignant GEP results tended to skew excision responses to be more aggressive and benign GEP results tended to result in less aggressive excision recommendations.
AIMP: Atypical intraepidermal melanocytic proliferation; GEP: Gene expression profile; WLE: Wide local excision.

reflectance confocal microscopy virtual biopsy) that may have influenced the diagnosis. Pathologists can also assist in making sure the treating clinician is aware of the intent of the specific language in the pathology report, especially the microscopic description [29,30]. Regardless, diagnostic GEP results can help determine management plans if clinicopathological correlation is still not achieved [22,23]. Second opinions are a vital resource for further clarifying histopathologically ambiguous cases. However, second opinions do not always alleviate borderline lesion ambiguity; a recent study indicates that dermatopathologists may be incorrectly swayed to change their original diagnostic decision during the consultation process, further complicating this practice [31–33].

Here, we focused on specific borderline/ambiguous scenarios and provided a granular level of excision recommendations and follow-up cadence as recommended by an experienced group of clinicians to optimize patient management strategies. This descriptive study was not intended to provide management guidelines for the care of patients with ambiguous lesions, but rather intended to highlight difficulties in ambiguous lesion management and demonstrate granularity in the clinical utility of GEP to guide surgical excision and follow-up in patients with ambiguous lesions. Dermatologists were more likely to escalate or de-escalate management according to the provided GEP result, indicating that more patients would receive personalized management plans that better align with the malignant potential of the lesion. In addition, dermatologists were more confident in their management plans when GEP results were included in the mock pathology report. The study is limited by the fact that non-specific GEP test results were provided (i.e., 23-GEP or 35-GEP was not specified) in an effort to establish broad diagnostic GEP clinical utility and to allow focus on the various ambiguous scenarios. Additionally, the survey did not poll clinicians who do not use GEP testing in their current clinical practice.

Clinical utility of diagnostic GEP tests for guiding patient management has been demonstrated previously [21–23]. Reductions of 76.7–80.5% in the recommendation to excise have been reported with benign GEP results [21,23]. In

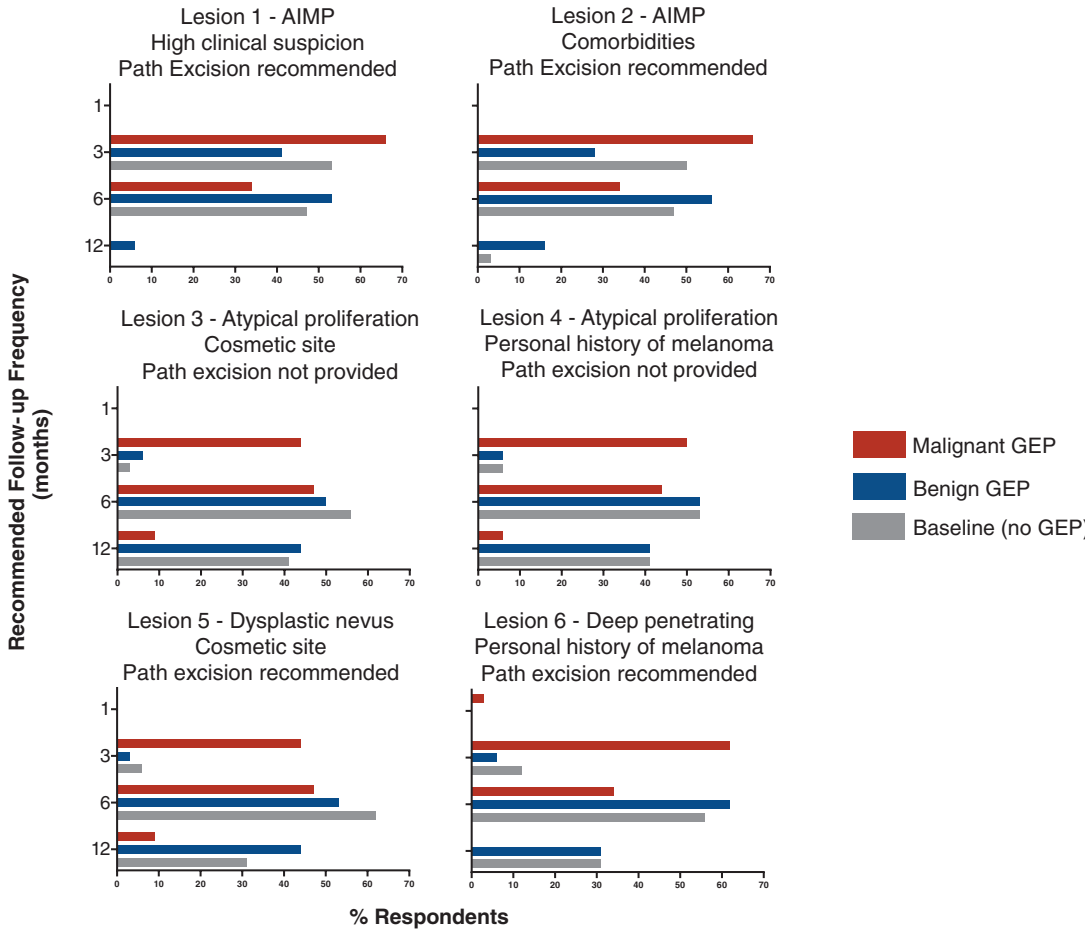

Figure 4. Gene expression profile results alter follow-up frequency. y-axis, survey respondent recommended follow-up frequency (months). x-axis, percentage of respondents. Each bar graph represents responses for each ambiguous lesion. Respondent recommendations are stratified by GEP result. Malignant GEP results typically influenced follow-up to be more frequent and benign GEP results typically resulted in less frequent follow-up. AIMP: Atypical intraepidermal melanocytic proliferation; GEP: Gene expression profile.

addition, 74.1% of dermatologists reduced office visit cadence when a benign GEP result was received [23]. Long term follow-up data has demonstrated it is safe to forego re-excision when a benign GEP result is received [24]. When a malignant GEP result was provided there was a 75% increase in excision recommendations and 95.2% of dermatologists increased their office visits recommendation cadence [21,23]. The data described here is corroborative of these studies and adds additional transparency to the various treatment recommendations with and without GEP results.

It is possible that the lesions described in this study's mock pathology language would have received different diagnoses and treatment recommendations depending on the specific dermatopathologist. Diagnostic discordance has been described in many studies and is more common in lesions with difficult histopathology [34–37], for which ancillary testing platforms have shown varying degrees of agreement [38–46]. Participants were not provided their recommendations with/without GEP in a directly comparative manner, but were presented in a randomized fashion. Counterintuitive responses using GEP (i.e., an escalation in excision margins when a benign GEP result was provided) may simply be due to the level of discordance in intraobserver reproducibility, as all scenarios were randomized to ensure treatment of each scenario as if it was an independent patient.

Conclusion

The addition of GEP testing to diagnostic scenarios with confounding clinical features and uncertainty in optimal management prompted important changes in recommendations regarding the need for excision, appropriate

margins, and follow-up-frequency. In addition to diagnostically ambiguous cases where the dermatopathologist includes ancillary diagnostic GEP testing, these data indicate that dermatologists utilize GEP results to help determine personalized management plans for patients with lesions of uncertain malignant potential.

Summary points

- Diagnostic gene expression profile (GEP) influences patient management when included for cases with an ambiguous pathology report.
- Changes in management when prompted by GEP are aligned with the GEP result, for which escalation was primarily reserved for malignant GEP results and de-escalation primarily reserved for benign GEP results.
- Regarding surgical treatment, when benign GEP results were provided, 29.7% of treatment recommendations were de-escalated.
- When malignant GEP results were provided, 63.5% of clinicians increased their surgical excision recommendations.
- Patient follow-up frequency was recommended to be reduced by 18.8% when a benign GEP result was included and conversely, follow-up frequency was increased by 43.2% when a malignant GEP result was provided.
- Clinician confidence in managing their patients was increased when either a benign or malignant GEP result was provided.
- GEP can add risk-aligned value to patient management in circumstances of ambiguous pathology reports.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/mmt-2023-0002

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: A Witkowski, AD Jarell, KL Ahmed, JJ Siegel, BH Russell, JH Rogers, MS Goldberg, NF Fernandes, J Ludzik and AS Farberg; data collection: KL Ahmed, JJ Siegel, BH Russell and JH Rogers; analysis and interpretation of results: A Witkowski, AD Jarell, KL Ahmed, JJ Siegel, BH Russell, JH Rogers, MS Goldberg, NF Fernandes, J Ludzik and AS Farberg; draft manuscript preparation: BH Russell and JH Rogers; and all authors reviewed the results and approved the final version of the manuscript.

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KL Ahmed, JJ Siegel, BH Russell, JH Rogers and MS Goldberg are employees and shareholders of Castle Biosciences, Inc. AS Farberg is an advisor for Castle Biosciences, Inc. A Witkowski, AD Jarell and NF Fernandes are speakers for Castle Biosciences, Inc. J Ludzik has no financial conflicts of interest to disclose. Survey respondents received compensation for their time spent completing the survey. Support for this study was provided by Castle Biosciences, Inc.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The survey study protocol was approved by the Western Institutional Review Board (WA, USA). All responses were collected anonymously.

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