Short Communication

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Melanoma Management

Uveal melanoma patient attitudes towards prognostic testing using gene expression profiling

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Aim: This study explored uveal melanoma patient experiences and regret following molecular prognostic testing using a 15-gene expression profile (GEP) test. **Materials & methods:** A retrospective, cross-sectional survey study was conducted through an online questionnaire capturing patient-reported experiences with prognostic biopsy/molecular testing. **Results:** Of 177 respondents, 159 (90%) wanted prognostic information at diagnosis. Most 15-GEP-tested patients who shared their results (99%) reported gaining value from testing, as did patients tested with other methods. Patients who received prognostic testing experienced lower decision regret than those who opted out. Decision regret did not differ based on GEP class. **Conclusion:** Most uveal melanoma patients desire prognostic testing and gain value from the GEP, independent of a high- or low-risk result.

Plain language summary: Uveal melanoma is a rare but aggressive eye cancer, resulting in distant metastasis in nearly 50% of patients. Molecular prognostic testing is often employed to determine who is at high or low risk of developing metastatic disease. A prognostic 15-gene expression profiling (GEP) test is commonly used throughout the USA and parts of Canada. The goal of this survey was to assess patient experiences with the 15-GEP and other prognostic methods. Of the 177 patients who participated in the survey, the majority reported that they wanted prognostic information at the time of diagnosis. Of patients who underwent 15-GEP testing, nearly all reported gaining value from their test result, regardless of their individual risk profile. This study supports prior findings using other prognostic methods that patients prefer information about their risk of metastasis and reinforces the importance of discussing prognostic testing options with newly diagnosed uveal melanoma patients.

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Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with an incidence of approximately 2000 new cases per year in the USA [1]. Most patients (96%) present without evidence of metastatic disease at the time of diagnosis, and primary tumor control is achieved in a majority of cases. However, up to 50% of patients will ultimately develop distant metastasis, suggesting that undetectable disease spread (micro-metastasis) had occurred prior to the primary tumor diagnosis and treatment [2]. Therefore, metastatic risk is an important clinical challenge for physicians considering management decisions for UM patients.

Over the last several decades, great efforts have been made to understand the molecular landscape of UM and improve patient management through the incorporation of molecular prognostic testing methods [3–7]. By assessing the metastatic risk, these tests provide patients a tool to play an important and ever increasing role in the planning of their care. Prior work exploring the psychological impact of prognostic testing found that UM patients overwhelmingly want to know their prognosis, regardless of whether they receive a high-risk or low-risk result [8].

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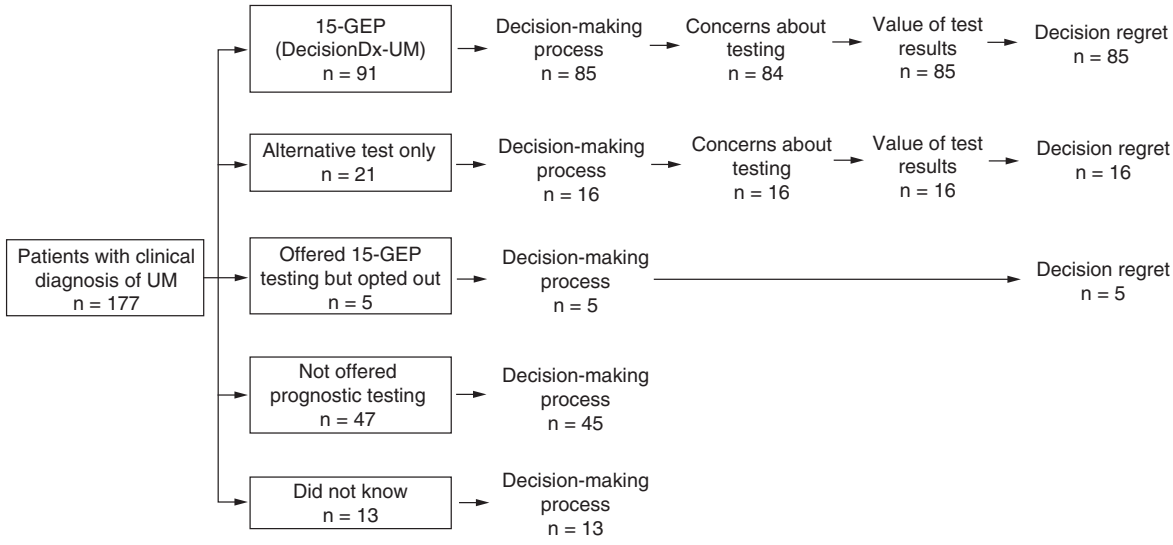

Figure 1. Survey study design. Flowchart overview of the survey structure and number of patients who responded to each series of questions.
15-GEP: 15-gene expression profile; DecisionDx-UM: DecisionDx-uveal melanoma test; UM: Uveal melanoma.

In the USA and western Canada, a prognostic 15-gene expression profile (15-GEP) test is commonly used to guide the systemic surveillance of UM patients. This test stratifies UM tumors into three molecular classes corresponding to either low- (Class 1A), intermediate- (Class 1B) or high-risk (Class 2) of metastasis [9,10]. The test has been shown to be a more accurate predictor of metastasis in multiple studies when compared with other clinical, pathologic and genetic risk factors including cytogenetic profiling [10–13]. As a result, the 15-GEP test has become the most commonly utilized method for molecular prognostication in the US.

The 15-GEP is included in both the American Joint Committee on Cancer (AJCC) and the National Comprehensive Cancer Network (NCCN) guidelines based on the test's high technical performance, consistent clinical validity and impactful changes to patient management decisions [9,10,13–26]. However, to our knowledge no studies have thoroughly explored the impact of prognostic testing specifically with the 15-GEP test on patient experiences. A retrospective chart review study conducted by Davanzo *et al.* [25] found that patients tested with the 15-GEP test were more likely to adhere to physicians' recommendations for follow-up and surveillance if they had a Class 2 (high-risk) result, suggesting that the test result positively impacts patient compliance. However, the perceived value of testing with the 15-GEP was not addressed. A cross-sectional survey study from Afshar *et al.* [27] reported that over 80% of Class 2 patients and over 90% of Class 1 patients gave a 'positive response' when asked if they were satisfied with the additional information provided by gene expression profiling, suggesting that patients do find value in prognostic testing with the 15-GEP. However, it is unclear how a 'positive response' was measured and what specifically patients gained from their test results [27].

The goal of this study was to understand patient experiences following testing with the 15-GEP test compared with patients with alternative or no prognostic testing.

Materials & methods

An online questionnaire was distributed by the Melanoma Research Foundation's CURE OM initiative in October 2020 that captured anonymized information regarding patient reported experiences following a clinical diagnosis of UM. All patients who were enrolled in their database were invited to participate in the survey, regardless of whether they had been offered prognostic testing at the time of diagnosis (see Supplementary Appendix A for the email invitation to participate that was distributed to patients). The study protocol was submitted to the Western Institutional Review Board ([IRB], WA, USA) and was formally exempted from the requirement for full IRB approval due to the anonymous nature of the survey data. Official documentation of this exemption is available upon request.

Patients were asked a branching series of questions (Figure 1) regarding the decision to undergo prognostic testing and the extent to which they felt decision regret using a validated Decision Regret Scale questionnaire [28].

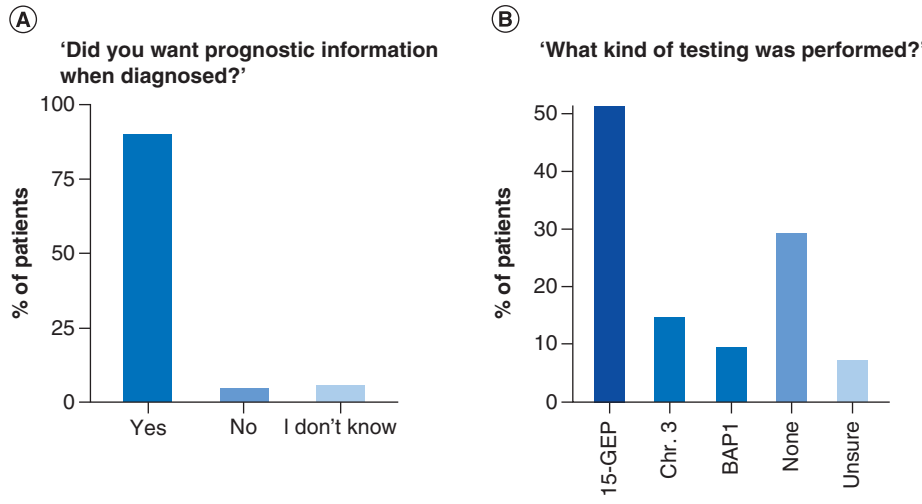

Figure 2. Desire for and use of prognostic testing in uveal melanoma patients. (A) Bar graph summarizing the proportion of patients who desired prognostic information at diagnosis compared with those who did not or were not sure. **(B)** Bar graph depicting the proportion of patients who reported having the 15-GEP, chromosome 3 testing, *BAP-1* sequencing, no testing or were unsure what type of testing was performed. Percentages do not add up to 100% due to the 18 patients who received more than one type of testing.
15-GEP: 15-gene expression profile.

Given the disparate number of respondents who opted in (n = 86) versus opted out (n = 5) of testing with the 15-GEP, power bias was tested using a bootstrap approach. Decision regret scores for groups of five patients from the 15-GEP tested group, ×10,000, were randomly resampled (with replacement) and the same Wilcoxon rank sum test was performed for each resampled group.

For the analysis of patients' responses regarding the value they found in prognostic testing, global Chi-square tests were performed to determine whether there were any differences between groups and response categories. If a difference was found, subanalyses were performed for the groups contributing most to the Chi-square statistic (i.e., 15-GEP with/without class result, any alternative testing). Responses were reported as percentages rounded to the nearest whole number.

Five statements were used to determine polarized or balanced decision-making by patients relative to an internal and/or external locus of influence. Choices were offered in a single question as 'select all that apply', allowing patients the freedom to indicate all sources of influence on their decision-making. The statements "My doctor or healthcare provider recommended it" and "A friend or family member recommended it" indicated an external locus. Internal locus statements were "I thought it would better inform my treatment options", "I wanted to better understand my future" and "I wanted to get all the information I could about my ocular melanoma". Patients who chose responses only reflecting internal or external sources were considered 'polarized', while those who chose at least one internal and external source were considered to have a 'balanced' sphere of influence. Significant differences in the frequencies of balanced and polarized spheres of influence between patient subgroups were determined by a Chi-square test. A summary of questions can be found in Supplementary Appendix B.

Results

Use of prognostic testing

A total of 177 consecutive respondents who were UM patients successfully completed and submitted the online survey. Of all survey respondents, 74% (130/177) were female, 25% (45/177) were male and 1% (2/177) preferred not to share their gender. When asked about the timing of their diagnosis, 66% (117/177) of patients reported being diagnosed with UM within 5 years of taking the survey, while 34% were diagnosed prior to 2015.

About 90% of respondents (159/177) reported wanting prognostic information at the time of diagnosis, while only 5% (8/177) did not want prognostic information and 6% (10/177) were not sure (Figure 2A). Of all respondents, 63% (112/177) reported that they received some type of prognostic testing (either one or multiple tests), while 29% (52/177) reported that no prognostic testing was performed and 7% (13/177) indicated that they did not know whether they had undergone prognostic testing or not. Just over half of the patients in the total cohort

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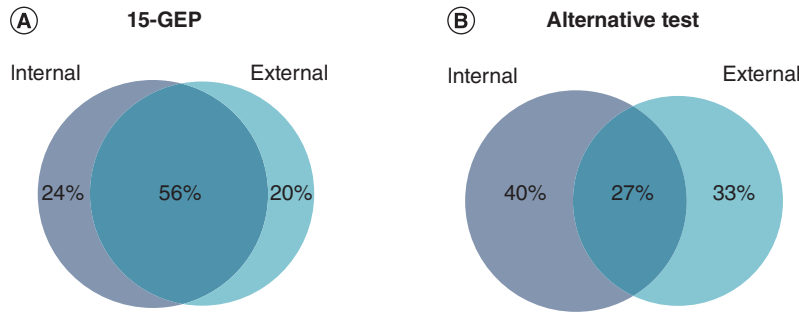

Figure 3. Internal versus external factors influencing patient decision to undergo prognostic testing. Venn diagrams depicting the proportion of internally and externally driven factors considered by patients prior to their decision to undergo either the 15-GEP test **(A)** or alternative tests **(B)**.
15-GEP: 15-gene expression profile.

(51%, 91/177) were tested with the 15-GEP, 15% (26/177) were tested with some type of chromosomal copy number analysis and 10% (17/177) had their tumor sequenced for somatic *BAP-1* mutations (Figures 1 & 2B). Of note, these groups include 18 patients that had more than one type of test performed (*BAP-1* + chromosome, n = 4; 15-GEP + chromosome, n = 3; GEP + *BAP-1*, n = 5; all 3 tests, n = 6).

Of the 81 patients who had 15-GEP testing with known test results, 35% (28/81) were Class 1A, 28% (23/81) were Class 1B and 37% (30/81) were Class 2, suggesting a representative population with regard to the proportion of low- and high-risk test results [10]. There were eight patients for which 15-GEP results were not captured (unanswered, n = 6; patient preferred not to share, n = 2) and two patients whose sample failed to generate a test result. Patients with other forms of prognostic testing were also asked to provide their test results. However, the heterogeneity across answers limited any meaningful statistical analyses from being performed in this group based on test results.

Interestingly, 29% of respondents (52/177) reported that no prognostic testing was performed (Figure 2B). Of these, the majority (90%, 47/52) did not remember prognostic testing being discussed or offered to them at the time of diagnosis, and 10% (5/52) indicated that they were offered molecular prognostic testing but declined (all five were offered the 15-GEP test).

Factors influencing patient decision to undergo prognostic testing

Patients were asked what factors influenced their decision to undergo prognostic testing, including factors that reflected an internal locus of decision-making and those that reflected an external locus of decision-making (see methods and Supplementary Appendix B). Patients offered 15-GEP testing more frequently reported a balanced decision making approach regarding the choice to undergo prognostic biopsy, incorporating both internal and external factors when weighing the decision (Figure 3A), compared with those who were offered prognostic testing other than the 15-GEP, who tended to be more polarized (Figure 3B; $X^2 = 4.37$, df = 1, p = 0.036).

Patient concerns about testing

Patients were asked about their main concerns while considering the decision to undergo prognostic biopsy. Many patients reported that they did not have any concerns (33/84 or 39% for 15-GEP, 9/16 or 56% for alternative tests; Figure 4). The cost of the test and/or biopsy procedure (14/84 or 17% for 15-GEP, 3/16 or 19% for alternative tests) and the potential negative impact that the results might have on their mental and emotional well-being (16/84 or 19% for 15-GEP, 3/16 or 19% for alternative tests) were common concerns regardless of which prognostic test was used. Patients receiving 15-GEP testing expressed concern about the potential risks of the biopsy procedure itself (18/84 or 21%) while this was not noted as a primary concern for patients with alternative testing only.

Value of test results to patients

To assess what value patients gain from their test results, patients were asked if they felt their test results were useful, and if so, what they felt they gained most from their results (Figure 5A). Of patients who underwent prognostic testing and shared their result, the majority (96/101 respondents, 95%) reported their test result was useful. In the subset of patients that underwent 15-GEP testing and shared their test results, the vast majority (80/81

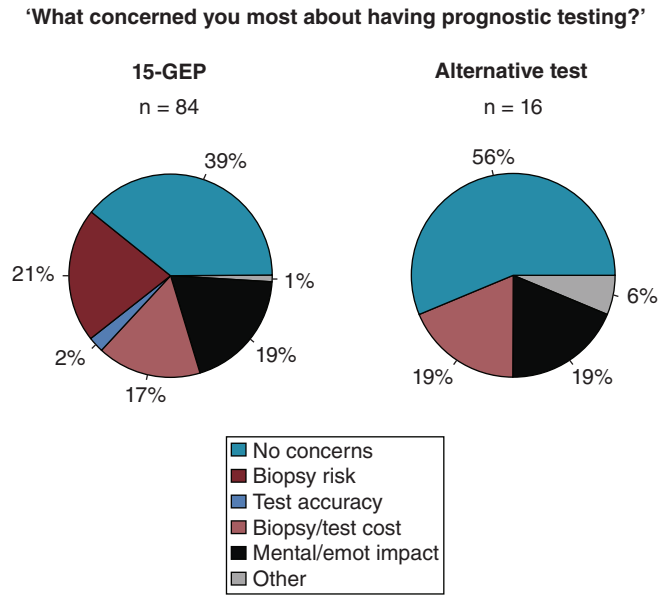

Figure 4. Patient concerns about prognostic testing. Pie charts summarizing 15-GEP tested (left) and alternatively tested (right) patients' main concerns when considering the decision to undergo prognostic biopsy.
15-GEP: 15-gene expression profile.

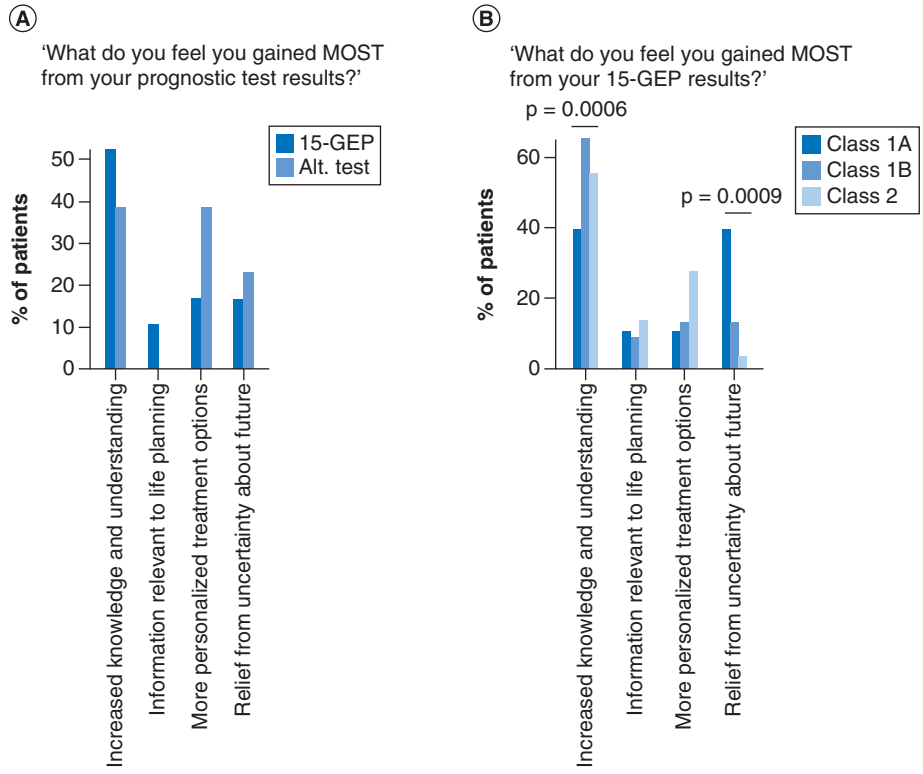

Figure 5. Value of prognostic testing results to patients. Bar graphs summarizing the value patients reported they gained the most from **(A)** 15-GEP test result compared with alternative test result (global $X^2 = 3.12$, df = 6, p = 0.37) and **(B)** a 15-GEP Class 1A (low-risk) result compared with a Class 1B (intermediate-risk) or Class 2 (high-risk) test result (global $X^2 = 14.99$, df = 3, p = 0.02).
15-GEP: 15-gene expression profile.

respondents, 99%) reported their test result was useful, with 52% (42/81) indicating their result was 'extremely useful'. Of all patients who responded to more detailed questions regarding the value of their test results, over half (52%, 44/85) of 15-GEP tested patients and 38% (5/13) of alternatively tested patients reported that their test result provided them with increased knowledge and understanding of their disease. Both the entire cohort who

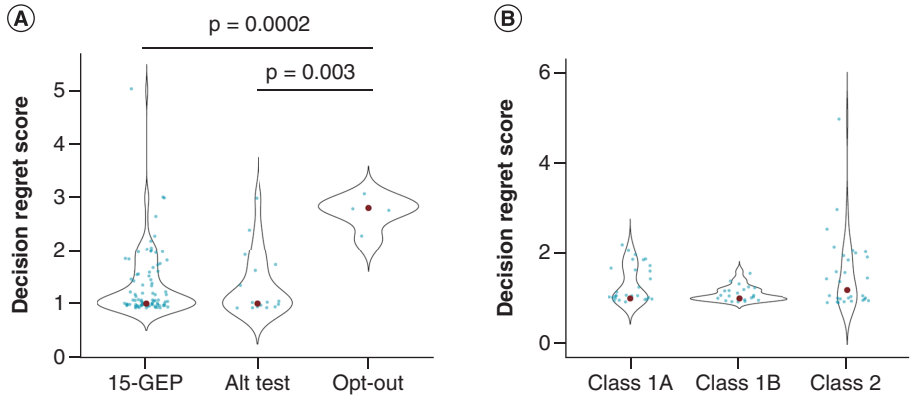

Figure 6. Decision regret regarding patients' choice to undergo or decline prognostic testing. Violin plots depicting Decision Regret Scale scores for **(A)** patients who were tested with 15-GEP, Alt. tests or those who opted out and **(B)** patients tested with the 15-GEP based on their test result, in other words, low-risk (Class 1A), intermediate-risk (Class 1B) or high-risk (Class 2).
15-GEP: 15-gene expression profile; Alt: Alternative; Opt-out: Opted out of testing.

underwent prognostic biopsy and the subset who specifically underwent 15-GEP testing also reported that their test result gave them a sense of relief from uncertainty about the future, more personalized treatment options and information relative to life planning. There were no significant differences in patients' responses depending on the type of prognostic test performed (Figure 5A).

When further analyzing the responses of 15-GEP tested patients by their class result, we found that patients who received a Class 1A (low-risk) result were >ten-times more likely than Class 2 (high-risk) patients to report gaining a 'sense of relief from uncertainty about the future' as a consequence of using the test (Figure 5B; $X^2 = 11$, df = 1, p = 0.0009). In contrast, a majority (16/29, 55%) of patients who received a Class 2 15-GEP result reported that their test result provided them 'increased knowledge and understanding' about their disease (Figure 5B; $X^2 = 17.48$, df = 3, p = 0.0006).

Decision regret after prognostic testing

Patients were asked a standard series of questions from a validated Decision Regret Scale questionnaire [28] to evaluate the extent to which they regretted their decision to undergo prognostic testing. The results indicate that patients who chose to have some kind of prognostic testing experienced less regret regarding their decision than patients who opted out of testing (Figure 6A; Kruskal–Wallis rank sum test, $X^2 = 14.07$, p = 0.0009; Wilcoxon rank sum tests as *post hoc* analysis; 15-GEP vs opt-out: W = 16, p = 0.0002; alternative test vs opt-out: W = 5.5, p = 0.003; 15-GEP vs alternative testing: W = 694, p = 0.89). Among patients who were tested with the 15-GEP there was no significant difference in decision regret levels between those receiving Class 1A, Class 1B or Class 2 results. (Figure 6B; Kruskal–Wallis rank sum test, $X^2 = 4.1$, p = 0.13).

Discussion

Most prior studies examining patient-reported experiences with prognostic testing for UM have been based on cytogenetic profiling of the primary tumor. Two studies from independent ocular oncology centers [8,29] were undertaken to examine prognostic testing with cytogenetics in patients diagnosed with UM. Researchers were specifically interested in patients' level of desire for prognostic information for the purpose of making personal life-planning decisions. The results were similar in both studies, with 97% of patients accepting an offer for prognostic testing. Interestingly, patients who received poorer prognoses reported gaining both a sense of control and the hope that regular monitoring would increase their chance of survival [8]. The single patient who declined prognostic testing was the only one who regretted their decision [8]. Our data reinforce this observation – that decision regret levels are highest for those who opt out of prognostic testing – in a larger, US-based patient cohort using a quantitative measure of decision regret.

Similarly, a previous prospective, single-institution, longitudinal study of 96 UM patients assessed depression, anxiety and decision regret prior to, 3 and 12 months after prognostic testing for chromosome 3 copy number [30].

Most patients (83–90%) reported no decision regret after undergoing the prognostic test, consistent with our results showing low overall decision regret for tested patients.

A more recent prospective observational study focusing on the impact of prognostic testing in UM patients found that use of cytogenetics for prognostic testing was not associated with poorer subsequent psychological well-being, but rather was associated with an improved accuracy of risk perception [31,32]. Similarly, our study revealed that high-risk test results do not cause patients psychological harm that would cause them to regret the decision to undergo prognostic testing. Nevertheless, there were differences in the specific types of perceived value of testing depending on whether the patient received a high- or low-risk result. High-risk patients were significantly more likely to value the increased knowledge they gained from their test result, while low-risk patients were more likely to value the sense of relief afforded to them by their test result.

Afshar *et al.* [27] recently reported that 62% of surveyed patients remembered receiving information on prognostic biopsy, which is similar to our findings (119/177 or 67%). However, in their cohort, only 23% of respondents reported the 15-GEP test being performed, while in our cohort over half of respondents reported having the 15-GEP test performed. It is surprising that such a high proportion of patients in our cohort did not remember being offered prognostic testing. It is possible that patients who were not offered the option of prognostic testing were more likely to respond to the survey. It is also possible that patients who reported that they had not been offered prognostic testing were in fact offered the option but have no recollection of it, as has been reported by others [33]. In our study, 34% of respondents were diagnosed with UM prior to 2015, so recall bias is a potential confounding factor to be considered which emphasizes the inherent challenges associated with collecting patient-reported data.

Cook *et al.* conducted an interview of 22 UM patients who had been offered cytogenetic prognostic testing to explore their decision-making process and reported that patients' choice did not reflect an autonomous decision but rather reflected trust in what their healthcare team offered to them. The authors proposed that emphasizing patient autonomy and active decision making is not necessary regarding this decision [33]. Interestingly, our findings suggest that patients in fact do play an active role in the decision-making process, and those who are offered the 15-GEP weighed both internal and external factors before making the final decision to undergo prognostic biopsy.

There was some evidence of sampling bias in our cohort, as the majority of respondents were female, though the gender distribution among the patients on the email distribution list who were eligible to complete the survey is unknown. This should be kept in mind when extrapolating results to the larger UM patient population which has a roughly equivalent gender distribution [1]. Also, it was not possible to calculate the response rate for this survey, since it was sent to a combined listserv including cutaneous melanoma patients, and not to a strictly UM patient group. However, for such a rare disease, this study had a reasonably large number of respondents (177) and the distribution of class risk assignments was similar to that seen in other patient populations [10]. Importantly, there were no significant differences in the ratio of Class 1 to Class 2 patients in the group of respondents diagnosed prior to 2015 compared with those diagnosed later, indicating that the 15-GEP tested patients diagnosed prior to 2015 were not biased toward receiving a favorable prognosis, as might be anticipated. An additional limitation of this study is that no detailed clinical data (e.g., tumor dimensions and stage at diagnosis or eventual disease progression) and limited demographic were collected in the survey. As a result, we are unable to assess if the tumor characteristics, metastatic status or age of this population are more broadly applicable, and whether these had a direct impact on patient attitudes.

One surprising finding was the proportion of patients (20%) who reported concerns regarding potential risks associated with the prognostic biopsy procedure. Given that the chance of serious biopsy related adverse events is low [34,35], there is clearly a need for physicians to educate patients on this procedure and ensure that their concerns are adequately addressed. Future clinical impact studies designed to understand how the physician's approach influences patient attitudes about the potential risks and benefits of prognostic biopsy/testing would be informative.

This study focused specifically on three common methods used for metastatic risk stratification in UM (15-GEP testing, chromosome 3 analysis and *BAP-1* sequencing) [36,37]. However, it is important to note that molecular prognostic testing, while widely available in the US and Canada, is not always easily accessible for patients. In the absence of molecular testing, a comprehensive evaluation of clinicopathologic features (such as tumor dimension, thickness and other staging factors) remains a valuable tool for assessing metastatic risk in newly diagnosed UM.

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Conclusion

In summary, patients with UM reported that they desired prognostic information at diagnosis, and usually accepted molecular prognostic testing when offered. Patients tested with the 15-GEP and other forms of prognostic testing indicated they valued their test results, regardless of whether their tumor was found to be at high- or low-risk for metastatic spread. Patients who underwent prognostic testing reported significantly lower levels of decision regret than those who opted out. As new therapeutic advancements continue to unfold for UM, prognostic testing provides important information to both patients and physicians and is becoming a valuable tool to guide risk appropriate metastatic surveillance as well as to identify those patients who would be most likely to benefit from enrollment into clinical trials. Psychological and quality of life concerns should be considered with great care, as UM patients face the worrying prospects of brachytherapy (or even enucleation) [38] and the overall high rate of eventual metastasis with limited treatment options.

Summary points

- A prognostic 15-gene expression profile test is widely used for risk stratification in uveal melanoma (UM).
- Other forms of prognostic testing available include chromosome 3 copy number analysis and *BAP-1* sequencing.
- Few previous studies in UM have explored patient attitudes toward prognostic testing.
- A total of 177 patients previously diagnosed with UM completed an online survey distributed by the Melanoma Research Foundation about their attitudes toward any prognostic testing they were offered or received.
- Patients who opted out of any kind of prognostic testing experienced elevated levels of decision regret.
- Patients who received a high-risk (Class 2) 15-gene expression profile result had similarly low decision regret when compared with those receiving intermediate- (Class 1B) or low-risk (Class 1A) results.
- Overall, most patients with uveal melanoma wanted prognostic testing at the time of diagnosis and did not regret their decision regardless of the results.

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-2022-0003

Author contributions

BK Williams, PG Hovland, SM Selig, K LiPira and KM Alsina conceptualized the study and designed the survey; L Johnston built the survey and led the data acquisition; JJ Siegel provided statistical support and data analysis; KM Alsina and JJ Siegel wrote the original draft of the manuscript; BK Williams, PG Hovland, SM Selig, K LiPira, A Sisco and L Johnston critically reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Financial & competing interests disclosure

BKW is a consultant for Castle Biosciences and sits on the Castle Biosciences Advisory Board; JJS and KMA are employees and shareholders of Castle Biosciences, Inc.; LJ, KL, SMS, and AS declare no relevant conflicts of interest to disclose; PGH is a consultant for Castle Biosciences and sits on the Castle Biosciences Advisory Board. Support for this study was provided by Castle Biosciences, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

This study was submitted for and formally exempted from Institutional Review Board approval due to the anonymous nature of the survey data. Signed, informed patient consent was waived due to the fully anonymous nature of the delivery of the survey data. A copy of this statement from the Institutional Review Board is available upon request.

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