Author’s response to reviews

Title: Psychosocial impact of prognostic genetic testing in uveal melanoma patients: A controlled prospective clinical observational study

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Author’s response to reviews:

Dear Ladies and Gentlemen,

thank you very much for considering our research article for publication in your scientific journal and your detailed review on this matter. As requested, we made slight alterations according to your recommendations as follows:

Technical Comments
Editor Comments:
The use of the abbreviations IG and OG in the manuscript and tables does not really save on word count and is confusing, since those who opt for prognostic testing are not receiving an intervention per se and you also discuss the use of psychological interventions in your manuscript as an outcome.

Authors’ Adjustments:
As recommended, we changed the term Intervention Group to Test Group (TG) in the whole manuscript, as well as in the attached figures.

Reviewer 1: Gabriella Pravettoni
Reviewer’s comment:
No limits are reported in the summary. High results heterogeneity is an obstacle when relying on a small sample and this should be mentioned. The research is an effective exploration of a very relevant topic and further research would be helpful to compare results in different contexts (diseases, comorbidities, clinical history...). Investigating psychological constructs highly benefit from qualitative measures that could help to better understand mental representation of the choice from the patient perspective (motivations, understanding of consequences...). Trait measures (e.g. risk propensity, health literacy and numeracy) could provide more information on how the choice was made by patients and how they could mediate the emotional impact of the results report.

Authors’ Adjustments:
As recommended, we added the aforementioned points in our summary at the end of the manuscript. We discussed the problem of sample size and made recommendations for future research, e.g. qualitative approaches, examination of specific traits (risk propensity etc.) and the examination of this topic in other contexts.

Reviewer 2: Elizabeth Bancroft

Abstract

Reviewer:
The abstract is problematic, the objectives outlined do not match those listed within the manuscript itself. For example the abstract states an outcome being utilization of psycho-oncological services; this needs harmonization within the manuscript.

Authors’ Adjustments:
Thank you very much on your comment to harmonize the objectives mentioned in the manuscript with those in the abstract. To harmonize the objectives mentioned in the manuscript with those in the abstract we added information on the topic concerning the utilization of psycho-oncological services, as recommended. In the abstract, as well as in the manuscript itself, we now explicitly distinguish between two objectives concerning psycho-oncological services:
1) The need for interventions over time (esp. after prognostication) and
2) characteristics of patients who mainly utilize these interventions.
We now depict these objectives equally in the abstract (section ‘Objectives of the study’) and in the ‘result’ section to avoid misunderstandings.

Reviewer:
The design and methods in the abstract do not give an indication of the time period of the study and the groups are not well defined; the results do not give an indication of the direction of the reported statistically significant differences. For example, it is stated that certain factors can predict the patient's choice for prognostic testing, but it is not clear whether the factors listed predict for increased or decreased uptake.

Authors’ Adjustments:
In the section ‘Design and Methods’, we included the time period of the study course (12months) and a more detailed definition of groups (‘Patients consenting to prognostication formed the test group, while those who refused constituted the observational group), according to the reviewer’s proposal. Due to limited word count (350), we unfortunately had to eliminate the second part of the following sentence: ‘We applied binary logistic regression analysis, multiple linear regressions and a mixed model to
examine different trajectories of psychosocial impact over time, to reveal group differences and to assess risk factors for prolonged psychological distress’) and change the first sentence of the Discussion.

As recommended, one result depicted in the abstract needed further specification. We altered the last sentence as follows: Female sex, higher general distress and higher anxiety were associated with the use of interventions. The other results were left unchanged, since the direction of the reported significant differences was already outlined distinctly (‘Treatment method (enucleation > brachytherapy), lower social support and higher general distress could significantly predict patient’s choice for prognostic testing. […] perceived risk of metastases was significantly increased in patients with poor prognosis, while it decreased in those with good prognosis. […] significant decrease over time appeared in […]]. Mental quality of life increased over time. […] the utilization of psycho-oncological interventions increased significantly. […]’).

Background

Reviewer:
The description of prognostication would benefit from being addressed sooner than lines 48-49 as this is a key component of this study. You need to make this really easy for a non-expert audience to understand.

Authors’ Adjustments:
Thank you for your advice to address prognostication sooner in the introduction in order to simplify the text for non-experts. But we considered it advisable to first address the matter at hand, namely the medical condition of uveal melanoma, its prevalence and fatal consequences (first seven lines), before leading over to the description of prognostication.

Reviewer:
My main concern with the manuscript as written is that you have used comparisons in the background and discussion to the wider genetic counselling literature looking at the psychosocial impact of germline genetic testing for hereditary cancer predisposition gene mutations such as BRCA1/2. The type of testing under evaluation in this study is very different as it is somatic tumour prognostic testing for a cancer that a person is living with. I would recommend removing the comparisons made in lines 48 to 57, as well as corresponding sections in the discussion, and finding more appropriate literature for comparison with your cohort. There are examples of somatic genetic testing for risk of recurrence / prognostic factors in other tumour types (eg breast cancer) that would make a much better comparison set than trying to compare the impact of germline and somatic testing, which have hugely different implications for the family and individual, including risk of other primary cancers. It would be helpful to define the somatic prognostic testing better in the introduction as advised above.

Authors’ Adjustments:
Thank you very much for this elaborated comment on different types of genetic testing. However, research on the psychosocial impact of uveal melanoma is sparse, so we used some literature on other types of cancer (breast cancer) to discuss our results if the phenomenon has not yet been surveyed in the framework of uveal melanoma. We explicitly pointed out that there is a difference between prognostic testing in breast cancer and uveal melanoma (e.g. ‘Breast cancer genes 1 and 2 (BRCA1/2) mutations may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer. The psychological impact of genetic risk counseling in hereditary breast cancer is not exactly applicable to prognostic testing in UM. However, there are similarities in emotional response and coping behavior of
patients after receiving results of genetic risk testing or prognostic testing’, line 52-55; and ‘Although prognostic testing in breast cancer, as mentioned in the introduction, is not exactly comparable to uveal melanoma, the following studies on resilience and quality of life should be mentioned’, line 331-333). Since coping mechanisms and psychological responses of patients affected by cancer are similar, we left cases in which transferability of results is given e.g. anxiety, perceived cancer risk, interpretation of results etc.

To avoid further misunderstands, we discarded literature on colorectal cancer completely.

If the reviewer still wishes to eliminate the literature on BRCA1/2, we are willing to delete those studies from the manuscript without further hesitation.

Objectives of the study

Reviewer:
You state that your hypotheses have been published elsewhere, but if relevant to your research questions presented here they should be included here.

Authors’ Adjustments:
To avoid misunderstanding, we discarded the sentence, that hypotheses are displayed elsewhere in detail. The detailed descriptions of the topics already contain all relevant information necessary for the uninformed reader.

Study Population

Reviewer:
You state that participants were "assigned" to the intervention group, but elsewhere state this is a patient-driven choice. The wording needs to be clarified.

Authors’ Adjustments:
As recommended, we replaced the expression ‘assigned to the intervention group’ with ‘if genetic testing was requested by the patient’ to stress the voluntariness of prognostic testing. Equally we changed the term ‘were allocated to” to ‘comprised’ in line 157.

Measurement Points and instruments

Reviewer:
Psycho-oncological interventions are referred to but not defined within the manuscript

Authors’ Adjustment:
We added further information on the psycho-oncological interventions, as requested (e.g. ‘These interventions took place as inpatient or outpatient treatment with an approximate duration of 50 minutes each and were conducted by a clinical psychologist specialized in psycho-oncology. The interventions contained elements of resource activation, relaxation techniques (breathing exercises and imaginations) and containment of disease-related affects.’).

Results

Reviewer:
Where you are stating there are statistically significant differences, it would be helpful to indicate the direction of the difference in the text.

Authors’ Adjustments:
We specified significant results by indicating the direction of the effects (e.g. ‘Patients who agreed to
testing were significantly younger than those who refused’ etc.).

Reviewer:
Your figures on separate pages lack legends - although these do appear within the text. All abbreviations should be defined.

Authors’ Adjustments:
As suggested, we added the definition of abbreviations to the figures’ and tables’ legends in the text and the attachment (e.g. ‘Figure 3, Unadjusted means of Perceived Risk over time per group. OG = Observational Group, TG = Test Group, D3 = Disomy 3, M3 = Monosomy 3’).

Reviewer:
Your supplementary files would benefit from the scale ranges being included so that the reader understands the context of the scores - or this could be included in the methods section when listing the scales.

Authors’ Adjustments:
We added another column in table 1 in section ‘Measurement points and instruments’ depicting relevant information on the utilized scales (number of items, scale ranges etc.), facilitating the interpretation of the graphs in the result section.

Further Adjustments:
We further discarded the variable ‘attitudes towards testing’ from table 1 in the section ‘measurement points and instruments’ since we did not use it for further calculations and therefore depicts unnecessary information for the reader.

We also added another affiliation of one of the co-authors, since he changed his work place since the first submission.

We also changed the tense in the abstract from present into past tense to adjust the tense to the rest of the article. We also made some revisions concerning grammar and vocabulary as recommend. If further alterations need to be made, please do not hesitate to let us know.

As far as the comment on statistical revision is concerned: We already had an external statistician revise our analyses. If further questions on the analyses or on any other matter arise, please do not hesitate to contact us.

Sincerely,

Marietta Lieb