Second-round review for

"Characterization of direct and/or indirect genetic associations for multiple traits in longitudinal studies of disease progression"

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We thank the authors for addressing all the questions from reviewers, however, in my opinion, there are still some concerns after the revision.

The biggest remaining concern is the model novelty compared with joint model for one longitudinal and one time-to-event trait which is previously proposed in Ibrahim et al. (2010). Based on the response to the Question 2 of Reviewer 1, the model novelty lies in the proposal of correlated random effects $\boldsymbol{D}$ and frailty term $\boldsymbol{U}$ that address the dependency among longitudinal quantitative traits (QTs) and time-to-event traits. However, the revised paper still does not provide a convincing explanation on the importance of the cross-QT or cross-trait information. The numerical results do not show the comparison (at least in the main body) between the full model JM-cmp and the separate model JM-sep ignoring the trait dependencies. Hence, doubts arise for the necessity to address the dependency among multiple QTs or time-to-event traits. Also, Ibrahim et al. (2010) aiming to estimate β and γ in the joint model under the one longitudinal and one time-to-event trait case can be used to classified the pathway of SNP effects. Therefore, I do not think it is appropriate to say that "no comparable method has been proposed in the literature to classify direct and/or indirect SNP association...".

A new concern lies in the hypothesis testing procedures. Based on the description on Page 17 of current manuscript, authors use a two-stage procedures to estimate the indirect effect (ignoring nuisance parameter α) β and direct effect γ: firstly fit the longitudinal model between QT (y) and SNP (g) and obtain the estimated parameter $\hat{\beta}$ and smoothed trajectory $\hat{X}$, then fit the time-to-event model between the trait hazard (λ) and predictors $\hat{X}$ and g to obtain $\hat{\gamma}$. Hence, the estimates $\hat{\beta}$ and $\hat{\gamma}$ are correlated, as are their test statistics. However, the joint hypothesis test presented in Table 1 does not address the correlation between the test statistics, and thus the type-I-error for the joint hypothesis test will inflate. Table 2 also only presents the empirical powers for test without reports on type-I-error. The correlation between estimates $\hat{\beta}$ and $\hat{\gamma}$ brings concerns about theoretical validation of the hypothesis test and the applications of proposed method to other datasets. Also, it is necessary to explicitly claim the null and alternative hypotheses before the specific test procedures.

In addition to the novelty, the model formulation should be more improved to avoid redundancy and ambiguity. For examples, there is no necessity to display Equation 1 and the left hand side of Equation 2 should use regular letter $y_i(t)$; in line 286 of the revised manuscript, the bold letter $\boldsymbol{t}$ in term $\boldsymbol{\lambda}(\boldsymbol{t})$ should be a regular letter t.

Regarding the big concern in novelty, I believe there is still room for improvement in the revised

manuscript.

References

Ibrahim, J. G., Chu, H., and Chen, L. M. (2010). Basic concepts and methods for joint models of longitudinal and survival data. *Journal of Clinical Oncology*, 28(16):2796.