January 5, 2016
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Dear Sir or Madam,

Re: Response to examiners' reports on PhD dissertation, student number 3062573.

I thank the examiners for their time, and helpful comments on my dissertation. I have made revisions to the dissertation where appropriate, which are documented in the following. In cases where revision was not practical, I have also included responses to the examiners' concerns.

Chapter 1
The examiners did not detail any specific concerns with this chapter.

Chapter 2
Examiner 1 asked whether a prognostic predictor could be suggested that uses fewer than the 361 gene expression measurements comprising the full PARSE score. This is certainly possible, and I have added a brief note to the dissertation that outlines how such a smaller predictor could be developed by using the data in Appendix D. I decided not to include such a smaller predictor in Chapter 2 of the dissertation, as this problem of identifying very small prognostic predictors is already directly addressed by Chapter 4.

Examiner 2 queried whether different survival-associated metagenes were found in different clinical subsets of the patient cohort. Unfortunately, the number of patients within each subset was too small to permit this particular analysis. However, for the two metagenes that were identified using the whole discovery cohort, metagene activity was verified to be independent of all measured clinico-pathological variables; this result is in the dissertation.

Examiner 2 asked for additional information on gene selection methods, and further discussion on the effect of this selection step on the metagenes identified; these have been added. Examiner 2 also queried why both metagenes found were associated with decreased survival. The analysis was not biased towards detecting metagenes associated with either better or worse survival, and with only two metagenes identified, it is my opinion that both of them being associated with poorer survival is coincidental.

Examiner 2 requested a comparison of the metagene activity scores to histopathological features, such as Ki-67 or E-cadherin staining. Unfortunately, these features

were only available for closely-matched tissue samples in a very small number of cases, making meaningful comparison impossible. This is certainly a valuable future direction for this work, particularly given its potential for clinical translation, and I have added a brief discussion of this point to the dissertation.

Chapter 3

Chapter 4
Examiner 1 asked whether any validation of this chapter's findings by IHC has been performed. This has not yet been done, but it is certainly an important next step to validate the utility of the Messina algorithm, as well as the specific prognostic classifiers described this chapter.

Chapter 5

General

All spelling and typographical errors have been corrected, and the chapter structure has been revised as suggested by Examiner 2.

Yours Faithfully,

Mark Pinese