Dr. Luque,

Thank you for your efforts as an editor for our recently submitted manuscript PONE-D-14-30128. The reviewer brings up several excellent points that were previously not addressed sufficiently. The two main technical issues from this review were the appropriateness of the non-functioning adenoma as a control, and the effects of age as a confounding covariate. We feel that both of these concerns are important, but addressable.

To the first point, we agree that this is an important caveat. On one hand, the non-secreting adenoma controls are technically a reasonable control, relative to “normal” controls. These samples are collected by the same surgeons using the same techniques and were processed identically. Furthermore these patients, even if not well age matched, do still have a pituitary tumor so are controlling for this factor. To the concern that the non-functioning adenoma is phenotypically altering the physiology of these patients we propose to both mention this as a potential issue and test this experimentally by comparing our data to publically available subcutaneous fat biopsy datasets from ‘normal’ patients.

To the age issue, we will re-analyse our data taking age into account as a principal covariate and examine the transcriptional changes in acromegaly patients at different age groups. On the let we show that for the mean gene, there is not only an age effect, as the reviewer hypothesized, but also evidence of an interaction between the age and the disease state for elderly (>60) patients. This is an exciting finding that will not only improve the robustness of our analysis by accounting for the age, but will also provide novel insights into the age-specific effects of growth hormone over production.



With these findings in mind, we would like to request an opportunity to complete these analyses to address these and the other reviewer suggestions in a new manuscript submission. We are confident that we can directly and rigorously address all the presented issues and provide a manuscript that is of high enough quality for publication.