* "...overall metrics such as the global error rate of their assay seems conspicuously absent"
* Comment from Jorge: "This needs to be provided in the response as well. A paragraph and a table devoted to a head-to-head comparison between the ‘high intensity’ assay and TEC-Seq, Guardant, CAPP-Seq, SafeSeqS would be absolutely required to address this comment. Please provide this in the simplest possible manner. My suggestion is after Response to Reviewers’ Table 6, state that after taking the steps we have taken, **the estimated error rate of the high intensity would be xxxxx, whereas for TEC-Seq, Guardant, CAPP-Seq, SafeSeqS, using similar metrics, the estimated global error rate would xxxx, xxx, xxx, respectively.** This is absolutely essential."

### **Response:**

Several groups have explored the space of high accuracy error corrected sequencing. Integrated Digital Error Suppression (iDES) (Newman et al, 2016 PMID: 27018799) computed a per-base error rate which optimally balanced error suppression with molecular depth as 2x10-5 The Safe-Sequencing System (Safe-SeqS) (Kinde et al 2011 PMID: 21586637) reported 0.9x10-5 supermutants (likely errors) per base pair. Both reports are similar to the per base error rate of 1x10-5 to 3x10-5 (depending on the base and error type, as reported in the methods section of the manuscript that describes the supplemental noise model [pages X-X]) reported herein. Additionally, Lanman (2015 PMID: 26474073) and Phallen (2017 PMID: 28814544 ) both point out that beyond per base error rates, effective filtering for false positives is necessary; each reports stringent filtering on small, highly curated panels to produce no false positive mutation calls in 1.56x106 bases attempted, and fewer than 1 false positive mutation call per 3x106 bases attempted, respectively, on younger individuals. This report included a panel that was more than ten-fold larger than the reports noted above, with 1.5 variant calls per age-matched control sample in approximately 1x106 bases per experiment.

(Can we also point out that 1 sample is close to the size of their entire reported study?)

**References: (4 examples in the above paragraph)**

1. Source for per base error rate establishing technological basis (Newman, Kinde):

a) computed the per-base error rate which optimally trades off error-suppression for molecular depth as 2x10^-5 - figure 2, Newman et al.

b) 0.9x10-5 (table 2, Kinde et al)

2) false positive rate for variant calling, (Lanman & Phallen) the primary metric they report

a) 1 false positive in 1.56x10^6 - Figure 3, Lanman - Note they claim in text (and abstract) that it is a real variant for 0 false positives. This study evaluates only 20 samples who are young.

b) Although conventional sequencing of these samples would have resulted in thousands of putative alterations among the regions analyzed, the TEC-Seq analyses significantly reduced the sequencing error rate to fewer than one false positive (call) per 3 million bases sequenced - page 3 of Phallen

i) I note that Phallen et al appear to have mis-computed the per base error rate in the text (off by a factor of 3 or more) and done so in a way that is incompatible with our numbers (they over-estimate effective accuracy by not pooling across positions).