**Sequenza**

i) I wonder why the authors did not modify the thresholding for max ploidy in Sequenza in clear evidence of the model fitting to tetraploid normal genomes. I believe the default ploidy sequentially increments from 1 to 7 (step 0.1). Perhaps a more stringent thresholding on ploidy and copy number (default range 0 to 20) from sequenza would make the results more comparable to output from the other tools considered in this paper, and also yield better fit in correlation to ASCAT predictions of ploidy?

ii) It was interesting to to see the variance in pearson correlation for the different algorithms with ASCAT. The ABSOLUTE paper points out the bias in underestimating cancer cell fraction when using ASCAT. With that in mind, the low correlation from both ABSOLUTE and absCN-seq with ASCAT, in ploidy, might make one wonder why the authors did not consider additional methods for assessing tumour ploidy (using ‘spiked in’ tumour - matched normal pairs, for ex.). Another thing that comes forth is that while Sequenza, ABSOLUTE, and ASCAT are all SNP array based methods ( atleast partially), absCN-seq depends more so on coverage ratio, and furthermore, using the somatic CNV frequency to estimate tumour purity - the distinctly different cellularity and ploidy estimates from absCN-seq, as compared to the other methods, are hence quite interesting. I wonder if the methodologies for prediction of purity/ploidy may be a bias (in which case, I reiterate my point about the methodological justification of using ASCAT to assess ‘true state’).

**RAPTR-SV**

i) I am not sure why the authors went with a 20x coverage genome to demonstrate the application of their method on a ‘non-model organism’. A worthier comparison set should have atleast 60x coverage, in my opinion, especially since there is considerable pre-processing and chastity filtering of reads - leaves very few Break Point (BP) and non-BP reads in any given (split and/or discordant reads) set, to draw a conclusion about an INDEL from! Also, I do not fathorm the motivation for using a ‘non-model organism’ (also, what really defines a non-model organism? The only main drawbacks of using bulls as model organisms, that spring to my mind, are mechanistic rather than with any genetic/genomic underpinnings. What then, did the authors hope to unearth by trying to identify INDELs in this ‘non-model’ organism?). Particularly suspicious that they use this dataset, especially when the only subsequent mention of its results is in the last few lines of the paper as an initial comparison to Delly (with smaller INDELs being identified by RAPTR-SV than by Delly - wonder if that has anything to do with the low coverage!)

ii) The authors include a step for the removal of discordant read pairs that span gaps in the assembly. Won’t a thresholding on Phred Base Probability (which is also done) discount such discordant read pairs anyways? An additional gap filtration seems excessively stringent given that - one might be losing novel indels as a result of the en-masse filtration.

**BreakSeek**

i) Formula (1), page 4, models the indel reads’ distribution with an identical variance as the normal reads in the INDEL region. This does not seem suitably justified. The variance in fragment length will be influenced by the 2 break points (in event of a deletion) or by the adjusted wide interval spanning an insertion. Won’t it be statistically robust to model the read length variance for the indel reads separately from the normal reads?

ii) In the section about resolution of PEM and BP signals’ effects on deletion calling, the authors calim that majority of the Pindel/SOAPindel calls has no PEM support -  it is not clear where they demonstrate that this indeed is the case? It is also odd that they assess the validity of a deletion call by (as part of the 3 criteria) looking at the concordance between reported deletion size (by a tool) and expected size by their own EM algorithm.