Questions on Li, Ruan and Durbin (2008) *Genome Research* 18:1851-8.

Mapping short DNA sequencing reads and calling variants using mapping quality scores.

1. What where the practical challenges that prompted this paper? How did emerging sequencing technologies in 2008 differ from previous techniques?

2. The paper refers to the Smith-Waterman algorithm for sequence alignment. What are some of the differences between the Smith-Waterman algorithm and the newly proposed methods?

3. The proposed methods rely on several seeds for each alignment. What are these seeds? Why are multiple seeds used?

4. What is a *unique* alignment? What are the weaknesses of relying on *unique* alignments?

5. The authors define the concept of mapping quality. What are some of the sources of error that are captured in these mapping qualities? What sources of error are not captured in the mapping quality?

6. The authors explain that only ~85% of the genome can be re-sequenced with 36-bp reads. Why is that? What are some of the options they suggest to enable a greater fraction of the genome to re-sequenced?

7. When evaluating the quality of a read mapper, the authors suggest considering both the fraction of reads that are mapped and the fraction of reads that are incorrectly mapped. How would you tune these quantities using their algorithm?

8. How would you compare the performance of two mapping algorithms that produce mapping qualities?

9. In passing, the authors mention that the fraction of false-positive variants will be larger when re-sequencing tumor samples. Why is that?

10. The authors create an index of reads and then walk through the genome sequence, looking for matches against this index. What would be the advantages and disadvantages of indexing the genome instead?

11. Can you think of refinements or modifications to the proposed algorithm that would improve performance with more modern technologies (which generate reads that are more numerous, longer and with improved base quality)?

12. What struck you most about the paper?