Reviewer's report

Title: High-resolution characterization of sequence signatures due to non-random cleavage of cell-free DNA

Version: 1 Date: 14 March 2015

Reviewer: David Pisetsky

Reviewer's report:

Major compulsory revision

The authors should expand on the biology of the system especially as the sequences come from women who are pregnant. Importantly, they should address whether there are sex differences in the generation of extracellular DNA and whether pregnancy affects these mechanisms. Given the effects of sex hormones which can act on cell involved in DNA clearance, this issue should be addressed.

The source of extracellular DNA is not clear and there could be differences in the processes leading to release of fetal vs. maternal DNA which could account for any difference in properties. It would be useful for the authors to consider whether the DNA is arising from apoptosis or necrosis or some process of the placenta.

A number of different nuclease could affect the properties of DNA. These are both intra and extracellular proteins. This issue should be discussed in the context of properties of DNA in the blood. Again, there could be maternal-fetal differences.

A recent by Chan et al discussed related issues in lupus and indicated that disease-specific properties could influence DNA. The authors may want to cite this paper but also limit the conclusions of their study to the more specific setting of pregnancy.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

No competing interests.