Author’s response to reviews

Title: Hereditary gynaecologic cancers in Nepal: A proposed model of care to serve high risk populations in developing countries

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Thank you to the peer reviewers and the editor for constructive comments on our paper. We have highlighted yellow texts for the changes made based on the reviewer's comments. The red texts are the edits made by us in terms of making grammatical corrections and/or restructuring into simpler sentences. Our responses as below:

Comment 1-
Some idea of what the QALY value that can be afforded in Nepal would help to underpin the argument made for introduction of genetic testing in Nepal.

Response 1
We searched the literature locally and internationally in English, however we could not find any relevant studies related to Quality adjusted life years (QALY) in genetic testing.

Comment 2-
Whether all endometrial cancers (diagnosed at any age) or only those diagnosed under 60 or 70 should be tested for Lynch Syndrome - and the need for reflex methylation testing for those tumours with loss of MLH1, to relieve the downstream burden gene testing and counselling.
Response 2

There is current debate as to whether all endometrial cancers should undergo MMR immunohistochemistry, irrespective of age at diagnosis, or only those diagnosed under age 60 or 70. However, as methylation of MLH1 as a cause of deficient expression becomes more common at older ages, there is a greater need for reflex methylation studies without an age limit for immunohistochemistry. This needs to be balanced against the potential to miss women with Lynch Syndrome diagnosed at older ages.

(Included in Page-6)

Comment 3-

I think that it would be important that such an enthusiastic gynaecological oncology group is linked in to these resources. [I can assist in that introduction - for example, there is a Nepalese Country Node of the Human Variome Project]

Response 3

Regarding genetics in Kathmandu. I looked at the HVP website and Nepal is linked but has not submitted any data. We contacted Kathmandu Centre for Genomics and research laboratory and it was confirmed that BRCA or Lynch Syndrome genes are not performed in Nepal.

Molecular genetics services are gradually being introduced into Nepal, but at this time, testing for hereditary cancer predisposition genes is not available.

(Included in Page 21)

Comment 4

There is little mention of any culturally-specific issues relating to informed consent. When would such consent be done in the context of a service in Nepal? At tumour testing? After methylation testing (is negative)? Before germline testing?
Response 4

This would include key aspects of providing culturally appropriate informed consent prior to germline testing

(Included in page- 20)

Comment 5

The paper gives no hint, even from case series or anecdotal experience, that there is burden of hereditary gynaecological cancers- though doubtless there is.

Response 5

There are hospital annual reports which shows evidence of ovarian and breast cancers are in increasing trend. As there are no practice of BRCA/Lynch gene testing, the proportion of genetic origin remains unknown.