

## **Reviewer's report**

**Title:** Penetrance of HNPCC-related cancers in a retrospective cohort of 12 large Newfoundland families carrying a MSH2 founder mutation: an evaluation using modified segregation models

**Version:** 1 **Date:** 3 August 2009

**Reviewer:** David Goldgar

### **Reviewer's report:**

#### Major Compulsory Revisions

On page 3, the authors state that individuals with an HNPCC cancer who were first degree relatives of a known carrier, were presumed to be carriers. This clearly is incorrect, particularly since some of the HNPCC cancers are not as specific to the syndrome (e.g., ovarian) as colon and endometrial. In any case, this would clearly result in an upward bias the penetrance estimates. It is not clear to me at all why the authors would do this; obviously the carrier probability for unknown carriers should be a calculated conditional on the other genotypes and phenotypes in the pedigree and their phenotype, and the current values of the parameters being estimated.

The discussion of the ascertainment correction was a bit difficult to follow. Perhaps an example would help. More importantly, the authors do not compare this with the (at least in my experience) usual way of correcting for ascertainment in these large pedigrees, that is, conditioning on the genotype of the proband and the phenotypes of all individuals in the ascertainment set (which conservatively could be the entire pedigree). In the case of the large Newfoundland pedigrees that have been expanded over the years, it may be possible to correct only for the original pedigree that was first noted/published, which would increase power.

#### Discretionary Revisions.

I thought that there were perhaps too many figures, given the relatively straightforward data that is to be communicated, but I will leave that decision to the editor and the authors.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests