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Citation for final published version:

Evans, D. G., Woodward, E. R., Lalloo, F., Møller, P., Sampson, J. , Burn, J., Moeslein, G. and Capella, G. 2018. Are women with pathogenic variants in PMS2 and MSH6 really at high lifetime risk of breast cancer? *Genetics in Medicine* 21 (8) , pp. 1878-1879. 10.1038/s41436-018-0401-1

Publishers page: <http://dx.doi.org/10.1038/s41436-018-0401-1>

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**Are women with pathogenic variants in *PMS2* and *MSH6* really at high lifetime risk of breast cancer?**

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**Conflict of interest:** None to declare

Word count 818

We read with some concern the recent article in Genetics in Medicine reporting a high lifetime risk of breast cancer in pathogenic variant (PV) carriers for *PMS2* and *MSH6* [1]. Although the reported odds ratios for breast cancer were given as: *MSH6* (2.11; 95%CI=1.56–2.86) and *PMS2* (2.92; 95% CI=2.17–3.92) the cumulative risks to age 60 were given as 31.1% (95%CI, 21.9–40.7) and 37.7% (95% CI, 27.5–47.8) respectively. These are equivalent to UK NICE defined high-lifetime risks. These two analyses are inaccurate given that the risk of breast cancer to the age of 60 years in the UK and USA is 5–6%. Therefore, if the risks from incidence ratios and Kaplan-Meier were equivalent, the odds ratios would be over 6-fold for *PMS2* and >5 fold for *MSH6*.

The most meaningful unbiased risks are likely to come from prospective analysis. The cumulative risk to age 70 years in 124 *PMS2* PV carriers was shown to be only 8.6% to age 70 years in the largest such analysis undertaken thus far [2]. A single case between 70–75 years gave a distorted non-significant increased risk. For *MSH6* the cumulative risk to age 75 years was 13.3% (95%CI=2.2–24.4) Odds ratio 1.4 (95% CI=0.2–2.6). As such the upper confidence interval at age 75 years for *MSH6* rules out the cumulative risks provided by the GeneDx study [1].

The huge discrepancy observed may be attributed to a number of issues including: (i) the lack of adjustment of the clear ascertainment bias in contrast with the majority of published reports of cumulative risk of breast cancer in patients with tumour suppressor gene variants; (ii) the absence of information on the proportion of women who were tested who had a breast cancer diagnosis. An earlier report from this group reported 5209/9276 (56.2%) of all referred samples had breast cancer [3]. If the proportion remains constant a huge bias is present that precludes any comparison of incidence ratios with the general population; (iii) the authors ‘compound the felony’ with the inappropriate use of Kaplan-Meier analyses for cumulative risks. Despite the fact the authors report an odds ratio of below one for *MLH1*, they then report a 15.5% (95%CI=5.5–30.2) risk of breast cancer by age 60 years. This is equivalent to a 3-fold excess risk. It is therefore highly likely that if the authors had carried out incidence ratios for those individuals testing negative for mis-match repair (MMR) and other PV, they would have demonstrated an increased risk with a cumulative risk to age 60 years of over 25%; and (iv) The authors have not reported whether the variants segregated with disease which would at least have provided some supportive data. Whilst the authors state that ‘the risks of other cancers, including breast are less clearly delineated’ this ignores most of the negative evidence available [2,4].

A more appropriate use of panel data to agnostically assess cancer risks would be to carry out a case control analysis. The largest analysis published thus far from Ambry Genetics (n= 65,057 women) [5] found an odds ratio below one for *PMS2* although a potential risk was seen for *MSH6* with an odds ratio of 1.93; (95%CI=1.16–3.27). Given the likely ratio of around 50% for those tested with breast cancer to those without, a form of internal case control for *PMS2* could be carried out within the available results. Interestingly for *PMS2* this was close to a 1:1 ratio with 35.5% having breast cancer and 34.7% without breast or another cancer. If one took the 0.13% prevalence of *PMS2* PV in the Ambry report as a control, then assuming the frequency of breast cancer cases was similar to the 56% in GeneDx first report, the reported incidence would be 44/28078 or 0.16% providing an odds ratio of only 1.2. As we were not provided with the proportion of breast cancers we cannot be certain of this figure but it is unlikely to have risen above an odds ratio of 2-fold. Even these case control series are limited by their use of control data.

Another important issue is that three of the panel tests provided by GeneDx exclude a real assessment of breast cancer genes and most of the *MSH2* and *MLH1* carriers (52% and 64%) were detected using the colorectal 16 gene panel or high-risk Lynch/colorectal 7 gene panel or endometrial 12 gene panel. This compared to only 18% of *PMS2* and 35% of *MSH6* ( $p < 0.0001$  for difference between gene duos). Ironically it may be because *PMS2* gives such lower overall risks of cancer that it has come out giving the highest risks of breast cancer in the GeneDx analysis paper [1].

It is crucially important that those discussing breast cancer risks with women with pathogenic *PMS2* and *MSH6* variants do not base their advice or management on the reported findings rather on the overall evidence available, in particular that coming from prospective observations in large numbers of cases.

### **Acknowledgements**

DGE and ERW are supported by the all Manchester NIHR Biomedical Research Centre (IS-BRC-1215-20007).

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