



## Response to Wang et al.

We appreciate the comments by Wang et al.<sup>1</sup> on our paper entitled “*MSH6* and *PMS2* germ-line pathogenic variants implicated in Lynch syndrome are associated with breast cancer.”<sup>2</sup> We agree with many of the limitations outlined in their letter, and have previously discussed these limitations in our paper and in responses to ten Broeke et al.<sup>3</sup> and Evans et al.,<sup>4</sup> to which we refer the reader. As we have previously acknowledged in our paper, any research conducted in our sample based on testing within clinical settings may be a biased estimate of risk based on population samples. Wang et al. question the use of standardized incidence ratios (SIRs) in our study, and while we agree with some of the noted limitations of using a SIR, we do not believe that these limitations render our conclusions to be invalid as Wang et al. suggest. As stated in our paper and in our response to Evans et al., our findings for *MSH6* are similar to those of Couch et al., to which both Evans et al. and Wang et al. refer as an appropriate analytical method for examining this association.

Although we pooled data from over 50,000 women who had undergone multigene panel testing between 2013 and 2016, our estimates were based on only 423 women who had a single germline pathogenic variant in any of the four mismatch repair genes we examined. Thus, larger studies are needed to validate our findings. We agree that prospective validation, in particular using population-based cohorts, should be performed to minimize the ascertainment bias, and our findings need to be replicated in larger studies before clinical breast cancer management recommendations are adopted.

## DISCLOSURE

M.E.R. is an employee of GeneDx/BioReference Laboratories, Inc./OPKO Health, and has a salary as the only disclosure. W.K.C. is a former employee of BioReference Laboratories. B.D.S. has multiple disclosures, which include stock options and employment with GeneDx/BioReference Laboratories/OPKO Health. The other authors declare no conflicts of interest.

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