

## Cancer Risks for *PMS2*-Associated Lynch Syndrome

Sanne W. ten Broeke, Heleen M. van der Klift, Carli M.J. Tops, Stefan Aretz, Inge Bernstein, Daniel D. Buchanan, Albert de la Chapelle, Gabriel Capella, Mark Clendenning, Christoph Engel, Steven Gallinger, Encarna Gomez Garcia, Jane C. Figueiredo, Robert Haile, Heather L. Hampel, John L. Hopper, Noline Hoogerbrugge, Magnus von Knebel Doeberitz, Loic Le Marchand, Tom G.W. Letteboer, Mark A. Jenkins, Annika Lindblom, Noralane M. Lindor, Arjen R. Mensenkamp, Pål Møller, Polly A. Newcomb, Theo A.M. van Os, Rachel Pearlman, Marta Pineda, Nils Rahner, Egbert J.W. Redeker, Maran J.W. Olderode-Berends, Christophe Rosty, Hans K. Schackert, Rodney Scott, Leigha Senter, Liesbeth Spruijt, Verena Steinke-Lange, Manon Suerink, Stephen Thibodeau, Yvonne J. Vos, Anja Wagner, Ingrid Winship, Frederik J. Hes, Hans F.A. Vasen, Juul T. Wijnen, Maartje Nielsen, and Aung Ko Win

Author affiliations and support information (if applicable) appear at the end of this article.

Published at [jco.org](http://jco.org) on August 30, 2018.

The ideas and opinions expressed herein are those of the author(s), and endorsement by the State of Hawaii Department of Health, the National Cancer Institute, SEER Program, the State of California Department of Public Health, the Centers for Disease Control and Prevention, or their Contractors and Subcontractors is not intended nor should it be inferred. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Colon Cancer Family Registry, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the Colon Cancer Family Registry. Authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

M.N. and A.K.W. are joint last authors.

Corresponding author: Sanne W. ten Broeke, MD, Department of Clinical Genetics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, Netherlands; e-mail: [tenbroeke@lumc.nl](mailto:tenbroeke@lumc.nl).

© 2018 by American Society of Clinical Oncology

0732-183X/18/3629w-2961w/\$20.00

### ASSOCIATED CONTENT



Data Supplement  
DOI: <https://doi.org/10.1200/JCO.2018.78.4777>

DOI: <https://doi.org/10.1200/JCO.2018.78.4777>

### ABSTRACT

#### Purpose

Lynch syndrome due to pathogenic variants in the DNA mismatch repair genes *MLH1*, *MSH2*, and *MSH6* is predominantly associated with colorectal and endometrial cancer, although extracolonic cancers have been described within the Lynch tumor spectrum. However, the age-specific cumulative risk (penetrance) of these cancers is still poorly defined for *PMS2*-associated Lynch syndrome. Using a large data set from a worldwide collaboration, our aim was to determine accurate penetrance measures of cancers for carriers of heterozygous pathogenic *PMS2* variants.

#### Methods

A modified segregation analysis was conducted that incorporated both genotyped and non-genotyped relatives, with conditioning for ascertainment to estimates corrected for bias. Hazard ratios (HRs) and corresponding 95% CIs were estimated for each cancer site for mutation carriers compared with the general population, followed by estimation of penetrance.

#### Results

In total, 284 families consisting of 4,878 first- and second-degree family members were included in the analysis. *PMS2* mutation carriers were at increased risk for colorectal cancer (cumulative risk to age 80 years of 13% [95% CI, 7.9% to 22%] for males and 12% [95% CI, 6.7% to 21%] for females) and endometrial cancer (13% [95% CI, 7.0%–24%]), compared with the general population (6.6%, 4.7%, and 2.4%, respectively). There was no clear evidence of an increased risk of ovarian, gastric, hepatobiliary, bladder, renal, brain, breast, prostate, or small bowel cancer.

#### Conclusion

Heterozygous *PMS2* mutation carriers were at small increased risk for colorectal and endometrial cancer but not for any other Lynch syndrome-associated cancer. This finding justifies that *PMS2*-specific screening protocols could be restricted to colonoscopies. The role of risk-reducing hysterectomy and bilateral salpingo-oophorectomy for *PMS2* mutation carriers needs further discussion.

*J Clin Oncol* 36:2961-2968. © 2018 by American Society of Clinical Oncology

### INTRODUCTION

Lynch syndrome is most commonly associated with colorectal cancer and endometrial cancer. However, when first described in 1913, the observation of the co-occurrence of gastric cancer and endometrial cancer led to the initial identification of these families, underlining the apparently diverse phenotype.<sup>1</sup> The genetic background of Lynch syndrome is now known,

and it is caused by heterozygous germline mutations in one of the four mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, or *EPCAM* deletions. The broad Lynch syndrome-associated tumor spectrum includes not only colorectal cancer and endometrial cancer but also gastric, ovarian, small bowel, brain, urothelial cell, skin, pancreas, prostate, and biliary tract cancers.<sup>2,3</sup> The involvement of germline MMR mutations in the development of breast cancer is still a subject of debate.<sup>4-7</sup> Although the reported

cumulative risk (penetrance) to age 70 years for these non-colorectal, nonendometrial cancers in MMR gene mutation carriers is generally < 10%, mutation carriers still have a higher risk relative to the general population.<sup>3</sup> The Lynch syndrome-associated tumor phenotypes and their penetrance could depend on the type of MMR gene mutated or the specific variant.<sup>8,9</sup>

For heterozygous *PMS2* mutation carriers, accurate estimation of penetrance, especially for extracolonic cancers, has been hampered both by difficulties in variant analysis related to the existence of multiple pseudogenes and, perhaps more importantly, by problems in identifying *PMS2* mutation carriers because of a markedly lower penetrance.<sup>10-12</sup> Our previous study of penetrance for *PMS2* mutation carriers, using 98 *PMS2* families ascertained through family cancer clinics in several European countries, reported standardized incidence ratios for extracolonic cancers and found an increased *PMS2*-related risk of cancer of the small bowel, ovaries, renal pelvis and—most notably—of the breast.<sup>11</sup> Although that study presented the largest data set then available, we were unable to generate reliable estimates of penetrance for these cancers because of their infrequency. In addition, there was an ascertainment bias in this cohort because of the recruitment via family cancer clinics. Another study from Iceland reported significant increases in the risk of colorectal, endometrial, and ovarian cancer for two pathogenic *PMS2* founder variants.<sup>13</sup> This study and others have reported relatively high prevalence of *PMS2* variants in the population,<sup>13-15</sup> thus underlining the need for *PMS2*-specific cancer risks. In the current study, we have expanded the previous study database to 284 families, including several that were identified through a population-based ascertainment, with the aim of generating accurate penetrance estimates of colorectal, endometrial, and other cancers for patients with *PMS2*-associated Lynch syndrome.

## METHODS

### Data Collection

**European data set.** Pedigree data on families with a segregating pathogenic variant were originally collected between 2009 and 2012, as previously described.<sup>11</sup> These data were supplemented with *PMS2* families identified between 2012 and 2017. Briefly, data were collected in collaboration with the Netherlands Foundation for the Detection of Hereditary Tumors and with clinical genetic departments in the Netherlands, Norway, Germany, Sweden, Denmark, and Spain. Data collection from patient records included demographic data, family pedigrees, age and location of cancer diagnosis, polypectomy, and hysterectomy if applicable. When available, clinical and pathologic diagnoses were confirmed using patient records. Data collection and subsequent analysis protocols were approved by the local ethical review board (Leiden University Medical Center Ethics Review Board, protocol ID: P01.019).

**Ohio State data sets.** For the Ohio State data sets, the first set of patients included both population-based patients with colorectal and endometrial cancer from Columbus, Ohio, as described elsewhere,<sup>10,16-19</sup> and patients with cancer identified at family cancer clinics with absence of *PMS2* only on immunohistochemistry. The second set of patients from Ohio included only population-based patients with colorectal and endometrial cancer from 50 hospitals throughout the state of Ohio, as described previously.<sup>20</sup> All patients provided informed consent (Ohio State University Biomedical Sciences Institutional Review Board protocol IDs: 1999C0051, 1999C0245, and 2012C0123).

**Colon Cancer Family Registry data set.** The study cohort from the Colon Cancer Family Registry has been described in detail elsewhere.<sup>21-23</sup>

Between 1998 and 2012, the Colon Cancer Family Registry recruited families via population-based probands, recently diagnosed with colorectal cancer, in state or regional population cancer registries in the United States (Washington, California, Arizona, Minnesota, Colorado, New Hampshire, North Carolina, and Hawaii), Australia (Victoria), and Canada (Ontario). In addition, clinic-based probands were enrolled from multiple-case families referred to family cancer clinics in the United States (Mayo Clinic, Rochester, Minnesota and Cleveland Clinic, Cleveland, Ohio), Canada (Ontario), Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney, and Newcastle), and New Zealand (Auckland). Probands were asked for permission to contact their relatives to seek their enrollment in the Cancer Family Registry (detailed in Newcomb et al<sup>21</sup>). Informed consent was obtained from all study participants, and the study protocol was approved by the institutional research ethics review board at each registry. Information on demographics, personal characteristics, personal and detailed family history of cancer in first- and second-degree relatives, cancer-screening history, history of polyps, polypectomy, and other surgeries was obtained by questionnaires from all probands and participating relatives. Participants were followed approximately every 5 years after baseline to update this information. For the current study, each individual's lifetime cancer history was based on the most recent data (baseline or most recent follow-up). Reported cancer diagnoses and age at diagnosis were confirmed using pathology reports, medical records, cancer registry reports, and death certificates, where possible.

### Mutation Analysis and Clinical Variant Classification

Probands included in the cohorts were screened for point mutations as well as large genomic rearrangements in the *PMS2* gene (Data Supplement). Relatives of probands were tested for the specific family mutation. A detailed description of specific variants detected and their classification can be found in the Data Supplement.

### Statistical Analysis

For estimation of the hazard ratios (HRs) and age-specific cumulative risks (penetrance), we used a modified segregation analysis.<sup>24</sup> This analytical method is not subject to population stratification, can rigorously adjust for ascertainment, and uses data on all study participants, whether genotyped or not, thereby maximizing statistical power. Models were fitted by the method of maximum likelihood with the statistical package MENDEL 3.2.<sup>25</sup> Estimates were appropriately adjusted for the ascertainment of families using a combination of retrospective likelihood and ascertainment-corrected joint likelihood. A conditional likelihood was maximized, in which each pedigree's data were conditioned on the proband's *PMS2* mutation status, cancer history, and ages of cancer diagnoses (for population-based families) or on the proband's *PMS2* mutation status and the cancer history and ages of cancer diagnoses of all family members (for clinic-based families).

For the purposes of analysis, we restricted included individuals to the first- and second-degree relatives of the probands. Observation time started at birth and stopped at age at diagnosis of cancer for affected, and last known age or age at death for unaffected, family members. Because age information for each family member was required for the pedigree analysis, missing values were estimated using a defined protocol as follows. If an exact age was unknown but an age range was provided, age was estimated as the midpoint of that range. If age at diagnosis was unknown, it was assumed to be the same as age at death (if the relative was deceased) or the mean age at diagnosis for the specific cancer (if the relative was alive and older than the mean age at diagnosis). For relatives for whom last known age was unknown, ages were censored at the time they were last known to be alive (eg, at the age at a cancer diagnosis). In the absence of any age information, it was assumed that both parents of the proband were born in the same year, that years of birth differed by 25 years in each generation (eg, at birth of proband, parents were age 25 years and

grandparents were age 50 years), and the ages of the siblings were the same. As a sensitivity analysis, we conducted analyses with and without imputing missing age; the results did not differ materially, and therefore results from the nonimputed analysis were not shown in detail.

To calculate HRs, we used a likelihood-based approach in which age-specific incidence for *PMS2* mutation carriers was divided by that for noncarriers. Incidence rates for noncarriers were assumed to be the same as age-, sex-, and country-specific population incidence rates (Australia, Canada, United States, The Netherlands, Germany) for the period 1998 to 2002, as obtained from Cancer Incidence in Five Continents.<sup>26</sup> The period of 1998 to 2002 was selected for analysis because it was the closest available data set to the mean calendar year of cancer diagnoses in the sample. For each cancer, the age at cancer diagnosis was modeled as a random variable whose hazard was the relevant population incidence multiplied by a cancer-specific HR. For colorectal cancer, HRs for carriers were assumed to be continuous, piece-wise linear functions of age that are constant before age 40 years; linear in the intervals 40 to 50, 50 to 60, and 60 to 70 years; and constant after age 70 years. For all other cancer sites, HRs were assumed to be independent of age. HRs for colorectal cancer, endometrial cancer, and other cancers were estimated simultaneously to allow proper adjustment for colorectal cancer-based ascertainment schemes when estimating the risks of noncolorectal cancers and to increase power (by helping the model identify likely carriers from the placement of Lynch syndrome-associated cancers within each family). HRs were assumed to be independent of country of recruitment.

Age-specific cumulative risks (penetrance) of each cancer site for *PMS2* mutation carriers were calculated separately for males and females, using the formula:

$$1 - \exp\left(-\int_0^{80} \lambda(t) dt\right),$$

where  $\lambda(t)$  is the HR multiplied by the US population incidence.<sup>27</sup> Corresponding CIs were calculated using a parametric bootstrap. More specifically, 5,000 draws were taken from the multivariate normal distribution that the maximum likelihood estimates would be expected to follow under asymptotic likelihood theory. For each age, corresponding values of the cumulative risk were calculated, and the 95% CI for the cumulative risks to that age were taken to be the 2.5th and 97.5th percentile of this sample.

## RESULTS

The final analysis included 284 families (211 from the European, 19 from the Ohio State, and 54 from the CCFR data set), with 1,904 first- and 2,974 second-degree family members, in whom 513 were confirmed carriers (Table 1). The numbers and mean ages at diagnosis of each cancer site in first- and second-degree relatives are depicted in Table 2.

### Colorectal Cancer

*PMS2* mutation carriers were at increased risk of developing colorectal cancer, with an HR depending on age and sex of the mutation carrier: 6.51 (95% CI, 2.03 to 20.9) for males younger than 40 years; 1.70 (95% CI, 0.89 to 3.24) for males older than 70 years; 6.48 (95% CI, 2.24 to 18.8) for females younger than 40 years; and 2.23 (95% CI, 1.21 to 4.12) for females older than 70 years. Estimated cumulative risks of colorectal cancer to age 80 years for *PMS2* mutation carriers were approximately 13%

**Table 1.** Study Data Set Description

Individuals	No. of Family Members		
	Total	Male	Female
Probands (= No. of families)	284	149	136
FDR	1,904	953	951
SDR	2,974	1,487	1,487
Confirmed <i>PMS2</i> mutation carriers	513	209	304
FDR	339	128	211
SDR	174	81	93
Confirmed <i>PMS2</i> noncarriers	404	167	237
FDR	230	100	130
SDR	174	67	107

Abbreviations: FDR, first-degree relative; SDR, second-degree relative.

(95% CI, 7.9% to 22%) for male carriers and 12% (95% CI, 6.7% to 21%) for female carriers (general population 6.6% and 4.7%, respectively; Fig 1A).

### Gynecologic Cancers

*PMS2* mutation carriers were also at small increased risk of endometrial cancer, with an HR of 5.73 (95% CI, 2.98 to 11.0) and estimated cumulative risk to age 80 years of approximately 13% (95% CI, 7.0% to 24%), compared with females from the general population (2.4%; Fig 1B). There was no clear evidence of increase in the risk of ovarian cancer (HR, 1.52; 95% CI, 0.45 to 5.05; Fig 2).

### Other Cancers

There was no clear increase in risk of gastric, hepatobiliary, bladder, renal, brain, breast, or prostate cancer for *PMS2* mutation carriers (HR for each cancer shown in Fig 2). There were too few occurrences of small bowel cancer (n = 5) to generate an HR.

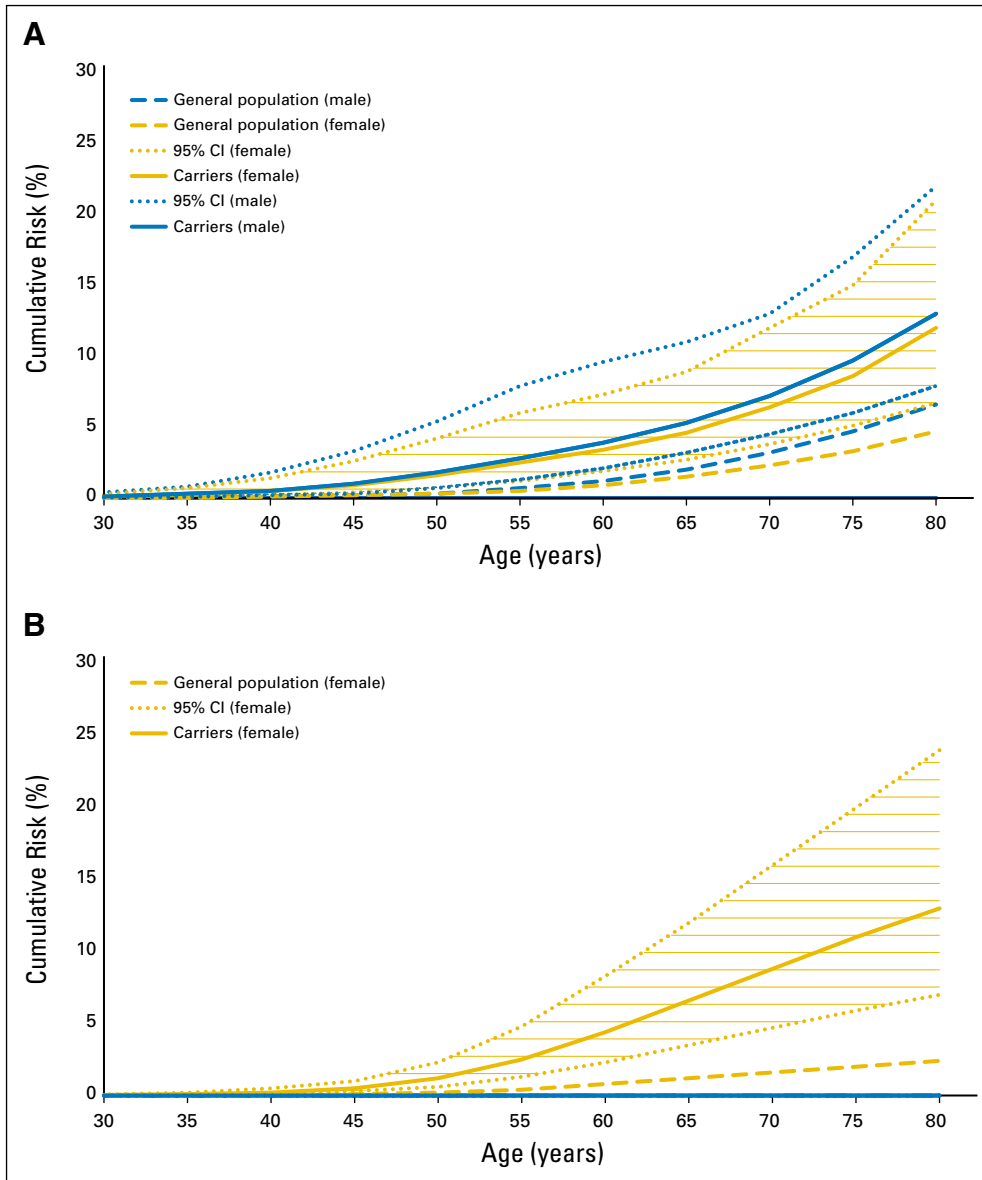
## DISCUSSION

On the basis of the results from this large, international study of heterozygous *PMS2* mutation carriers, the *PMS2*-associated Lynch

**Table 2.** No. and Mean Age at Diagnosis of Each Cancer Site in the FDRs and SDRs of Probands

Cancer	FDR (n = 1,904)		SDR (n = 2,974)	
	No.	Mean (SD) Age At Diagnosis (years)	No.	Mean (SD) Age at Diagnosis (years)
Colorectal	116	59.6 (14.7)	112	62.7 (3.0)
Endometrial	33	55.7 (9.04)	21	54.8 (13.7)
Ovarian	9	52.2 (14.8)	5	41.6 (22.8)
Brain	18	42.3 (26.9)	10	56.3 (26.0)
Hepatobiliary	5	56.2 (13.6)	3	60.7 (9.87)
Gastric	14	57.8 (8.72)	11	57.3 (11.0)
Bladder	7	71.7 (14.5)	5	70.0 (14.3)
Breast	47	58.1 (12.0)	50	59.2 (13.5)
Prostate	19	70.7 (12.2)	24	69.8 (14.1)
Renal	7	65.0 (13.7)	5	61.2 (10.8)
Small bowel	4	45.0 (9.6)	1	38

Abbreviations: FDR, first-degree relative; SD, standard deviation; SDR, second-degree relative.



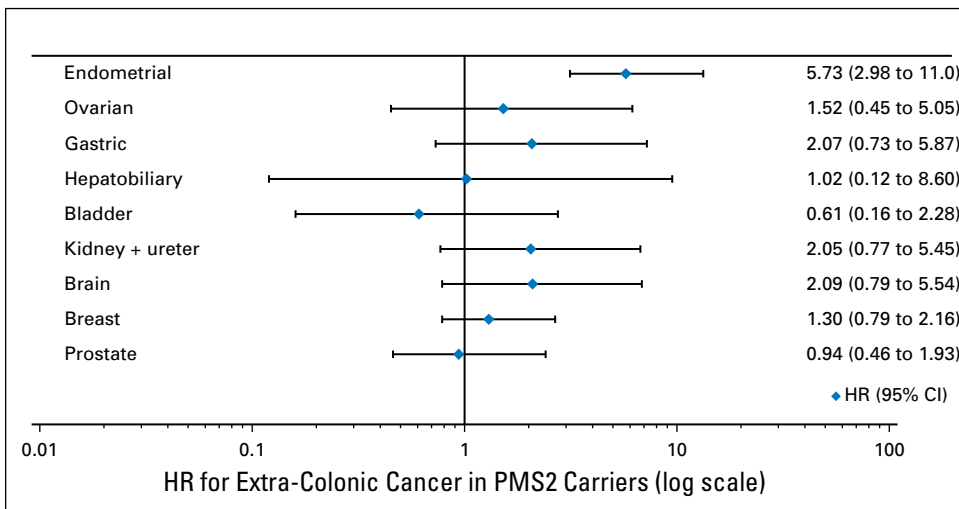
**Fig 1.** Cumulative risks (solid lines) and corresponding 95% CIs (dotted lines) of (A) colorectal cancer, and (B) endometrial cancer for heterozygous *PMS2* mutation carriers, and for the US general population (dashed lines). Blue and gold represent males and females, respectively.

syndrome spectrum seems to be restricted to colorectal and endometrial cancer only, underlining the distinct phenotype for *PMS2* mutation carriers. We have also shown that *PMS2* mutation carriers have much lower cancer risks compared with other MMR gene mutation carriers.

The previous two studies of *PMS2* mutation carriers have estimated cumulative risks to age 70 years of 11% to 20% for colorectal cancer and 12% to 15% for endometrial cancer.<sup>10,11</sup> Our current analysis has confirmed that *PMS2* carriers are at small increased risk of colorectal and endometrial cancer. These penetrance estimates are considerably lower than those for other MMR gene mutation carriers, which have been estimated at 35% to 55% for colorectal cancer and 10% to 45% for endometrial cancer.<sup>3</sup> A recent report from the Prospective Lynch Syndrome Database described cancer risk and survival for all patients with Lynch syndrome.<sup>7</sup> This report included 124 *PMS2* mutation carriers, with 524 observation years. The findings support our study data, in that endometrial cancer was the sole cancer type observed. Notably, colorectal cancer did not occur in

any of the *PMS2* mutation carriers undergoing regular colonoscopic screening. This, together with our penetrance estimates, could justify consideration of less-frequent colonoscopy screening for *PMS2* mutation carriers. This, together with our low penetrance estimates (Fig 1) could justify modification of the colonoscopy surveillance protocol, for example starting at age 35 to 40 years, every 2 to 3 years, similar to what has been proposed in the National Comprehensive Cancer Network guidelines.<sup>28</sup>

The Prospective Lynch Syndrome Database showed that endometrial cancer survival for all MMR pathogenic variant carriers was excellent, with a 10-year survival of 93% (95% CI, 85% to 97%). The reported survival for ovarian cancer in patients with Lynch syndrome was lower, at 74% (95% CI, 44% to 90%), but still better than that for sporadic ovarian cancer cases. Current surveillance guidelines advise that risk-reducing hysterectomy and bilateral salpingo-oophorectomy should be considered in women with Lynch syndrome, because transvaginal ultrasound with or without biopsy is ineffective in reducing risk of endometrial cancer



**Fig 2.** Hazard ratios (HRs) and corresponding 95% CIs of extracolonic cancers for *PMS2* mutation carriers.

and ovarian cancer and might not have a strong influence on survival.<sup>29</sup> The good survival rates for endometrial cancer, combined with the data presented in the current study showing no evidence of a clinically relevant increase in ovarian cancer risk for *PMS2* mutation carriers, raise questions about the justification of risk-reducing hysterectomy and bilateral salpingo-oophorectomy, which may be too rigorous in carriers of heterozygous pathogenic *PMS2* mutations.

In our previous study of patients with *PMS2*-associated Lynch syndrome, we found increased standardized incidence ratios (SIRs) for cancer of the small bowel, ovary, renal pelvis, and breast.<sup>11</sup> However, that study was limited by inclusion of confirmed mutation carriers identified through family cancer clinics and a limited number of cancer events. The first factor in particular could have been a potential source of ascertainment bias, because a strong family history of cancer and/or early-onset disease increases the likelihood of inclusion and *PMS2* testing. In that report, we did not adjust for this potential ascertainment bias when estimating SIRs for extracolonic cancers. Traditionally, a strong family history of colorectal and endometrial cancers prompted suspicion of Lynch syndrome, and consequently patients were tested for tumor MMR deficiency followed by MMR gene mutation testing. Currently, family histories of other cancers are increasingly being ascertained by clinical genetic centers for additional evaluation as possible Lynch syndrome. Therefore, it is important to take into account and adjust for ascertainment bias when estimating risks of cancers other than colorectal or endometrial cancer. Furthermore, pathogenic *PMS2* variants are relatively frequently observed using extensive gene panel testing for women with hereditary breast and ovarian cancer.<sup>30-33</sup> Nevertheless, we could not confirm an increased SIR for breast cancer in the current study (HR, 1.30; 95% CI, 0.79 to 2.16), and the discrepancy with earlier reports can probably be attributed to a high prevalence of *PMS2* (and *MSH6*) mutations in the general population. Conversely, the relative infrequency of *PMS2* variants among patients with Lynch syndrome can be explained by the milder phenotype, which makes ascertainment by family cancer clinics less likely.

The current study is the largest to date, to our knowledge, in estimation of cancer risks for heterozygous *PMS2* mutation

carriers. Previous studies have shown that analyses of retrospective data from clinic-based families (ie, ascertained because of family history of cancer) without (statistical) adjustment can lead to overestimation of cancer risks for mutation carriers.<sup>24,34,35</sup> In the current study, we used a high-level statistical approach to properly adjust for such ascertainment bias. The modified segregation method used data on all family members, regardless of whether they were genotyped, thereby maximizing statistical power while avoiding survival bias.

A potential limitation of the current study was the use of unverified cancer diagnoses that were self- or proband-reported, thus potentially affecting the accuracy of estimates. However, previous studies showed a high probability of agreement between proband-reported cancer status in first-degree relatives and the validated report (for example, 95.4% [95% CI, 92.6 to 98.3] for breast cancer, 83.3% [95% CI, 72.8 to 93.8] for ovarian cancer, and 79.3% [95% CI, 70.0 to 88.6] for prostate cancer).<sup>36</sup> Another possible limitation is that our analysis did not take into account a potential role for genetic or environmental modifiers of risk. The existence of such modifiers is plausible, because a high degree of variability in penetrance and phenotype has been observed,<sup>24</sup> and modifiers of cancer risk such as lifestyle, genetic modifiers, and phenotype-genotype correlations have been identified previously.<sup>37-40</sup> Our study estimated cancer risks of all variants combined; however, it is plausible that not all *PMS2* variants confer the same risk. A previous study in a selection of the currently analyzed cohort investigated genotype-phenotype correlations and found no difference in risk between the group of variants with retained versus loss of RNA expression.<sup>40</sup> However, this study did report that those carrying a variant with loss of RNA expression were diagnosed with colorectal cancer on average 9 years younger than those with retained expression. The influence of these modifiers is still not well understood, especially for *PMS2* mutation carriers, although efforts are currently ongoing to better define such factors and their potential role in modifying disease risk. Our study results highlight that studies of penetrance modifiers should take the specific MMR gene mutated into account.

In the current study, we analyzed the first data set, to our knowledge, large enough to generate the unbiased estimates for the



risk of each extracolonic cancer for *PMS2* mutation carriers. Our results show that *PMS2* carriers are only at small increased risk of colorectal and endometrial cancer. This underlines the importance of gene-specific genetic counseling of patients with Lynch syndrome and the development of appropriate clinical guidelines.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

#### AUTHOR CONTRIBUTIONS

**Conception and design:** Sanne W. ten Broeke, Frederik J. Hes, Juul T. Wijnen, Maartje Nielsen, Aung Ko Win

**Provision of study materials or patients:** Sanne W. ten Broeke, Carli M.J. Tops, Stefan Aretz, Inge Bernstein, Daniel D. Buchanan, Albert de la Chapelle, Gabriel Capella, Mark Clendenning, Christoph Engel, Steven Gallinger, Encarna Gomez Garcia, Jane C. Figueiredo, Robert Haile, Heather L. Hampel, John L. Hopper, Nicoline Hoogerbrugge, Magnus von Knebel Doeberitz, Loic Le Marchand, Tom G.W. Letteboer, Mark A.

Jenkins, Annika Lindblom, Noralane M. Lindor, Arjen R. Mensenkamp, Pål Møller, Polly A. Newcomb, Theo A.M. van Os, Rachel Pearlman, Marta Pineda, Nils Rahner, Egbert J.W. Redeker, Maran J.W. Olderode-Berends, Christophe Rosty, Hans K. Schackert, Rodney Scott, Leigha Senter, Liesbeth Spruijt, Verena Steinke-Lange, Manon Suerink, Stephen Thibodeau, Yvonne J. Vos, Anja Wagner, Ingrid Winship, Frederik J. Hes, Hans F.A. Vasen, Aung Ko Win

**Collection and assembly of data:** Sanne W. ten Broeke, Carli M.J. Tops, Stefan Aretz, Inge Bernstein, Daniel D. Buchanan, Albert de la Chapelle, Gabriel Capella, Mark Clendenning, Christoph Engel, Steven Gallinger, Encarna Gomez Garcia, Jane C. Figueiredo, Robert Haile, Heather L. Hampel, John L. Hopper, Nicoline Hoogerbrugge, Magnus von Knebel Doeberitz, Loic Le Marchand, Tom G.W. Letteboer, Mark A. Jenkins, Annika Lindblom, Noralane M. Lindor, Arjen R. Mensenkamp, Pål Møller, Polly A. Newcomb, Theo A.M. van Os, Rachel Pearlman, Marta Pineda, Nils Rahner, Egbert J.W. Redeker, Maran J.W. Olderode-Berends, Christophe Rosty, Hans K. Schackert, Rodney Scott, Leigha Senter, Liesbeth Spruijt, Verena Steinke-Lange, Manon Suerink, Stephen Thibodeau, Yvonne J. Vos, Anja Wagner, Ingrid Winship, Frederik J. Hes, Hans F.A. Vasen, Juul T. Wijnen, Maartje Nielsen, Aung Ko Win

**Data analysis and interpretation:** Sanne W. ten Broeke, Heleen M. van der Klift, Maartje Nielsen, Aung Ko Win

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

#### REFERENCES

- Lynch HT, Snyder CL, Shaw TG, et al: Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer* 15:181-194, 2015
- Umar A, Boland CR, Terdiman JP, et al: Revised Bethesda Guidelines for hereditary non-polyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 96:261-268, 2004
- Barrow E, Hill J, Evans DG: Cancer risk in Lynch syndrome. *Fam Cancer* 12:229-240, 2013
- Harkness EF, Barrow E, Newton K, et al: Lynch syndrome caused by MLH1 mutations is associated with an increased risk of breast cancer: A cohort study. *J Med Genet* 52:553-556, 2015
- Win AK, Lindor NM, Young JP, et al: Risks of primary extracolonic cancers following colorectal cancer in Lynch syndrome. *J Natl Cancer Inst* 104:1363-1372, 2012
- Scott RJ, McPhillips M, Meldrum CJ, et al: Hereditary nonpolyposis colorectal cancer in 95 families: Differences and similarities between mutation-positive and mutation-negative kindreds. *Am J Hum Genet* 68:118-127, 2001
- Møller P, Seppälä TT, Bernstein I, et al: Mallorca Group: Cancer risk and survival in *path\_MMR* carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 67:1306-1316, 2018
- Lindor NM, Petersen GM, Spurdle AB, et al: Pancreatic cancer and a novel MSH2 germline alteration. *Pancreas* 40:1138-1140, 2011
- Stuckless S, Parfrey PS, Woods MO, et al: The phenotypic expression of three MSH2 mutations in large Newfoundland families with Lynch syndrome. *Fam Cancer* 6:1-12, 2007
- Senter L, Clendenning M, Sotamaa K, et al: The clinical phenotype of Lynch syndrome due to germ-line *PMS2* mutations. *Gastroenterology* 135:419-428, 2008
- ten Broeke SW, Brohet RM, Tops CM, et al: Lynch syndrome caused by germline *PMS2* mutations: Delineating the cancer risk. *J Clin Oncol* 33:319-325, 2015
- Møller P, Seppälä T, Bernstein I, et al: Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: First report from the prospective Lynch syndrome database. *Gut* 66:464-472, 2017
- Haraldsdóttir S, Rafnar T, Frankel WL, et al: Comprehensive population-wide analysis of Lynch syndrome in Iceland reveals founder mutations in MSH6 and *PMS2*. *Nat Commun* 8:14755, 2017
- Espenschied CR, LaDuca H, Li S, et al: Multigene panel testing provides a new perspective on Lynch syndrome. *J Clin Oncol* 35:2568-2575, 2017
- Win AK, Jenkins MA, Dowty JG, et al: Prevalence and penetrance of major genes and polygenes for colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 26:404-412, 2017
- Hampel H, Frankel WL, Martin E, et al: Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol* 26:5783-5788, 2008
- Hampel H, Frankel WL, Martin E, et al: Screening for the Lynch syndrome (hereditary non-polyposis colorectal cancer). *N Engl J Med* 352:1851-1860, 2005
- Hampel H, Panescu J, Lockman J, et al: Comment on: Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Cancer Res* 67:9603, 2007
- Hampel H, Stephens JA, Pukkala E, et al: Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: Later age of onset. *Gastroenterology* 129:415-421, 2005
- Pearlman R, Frankel WL, Swanson B, et al: Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol* 3:464-471, 2017
- Newcomb PA, Baron J, Cotterchio M, et al: Colon Cancer Family Registry: An international resource for studies of the genetic epidemiology of colon cancer. *Cancer Epidemiol Biomarkers Prev* 16:2331-2343, 2007
- Jenkins MA, Win AK, Templeton AS, et al: Cohort profile: The Colon Cancer Family Registry Cohort (CCFRC). *Int J Epidemiol* 47:387-388i, 2018
- Colon CFR: Colon Cancer Family Registry Informatics Center. [www.coloncfr.org](http://www.coloncfr.org)
- Dowty JG, Win AK, Buchanan DD, et al: Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat* 34:490-497, 2013
- Lange K, Weeks D, Boehnke M: Programs for pedigree analysis: MENDEL, FISHER, and dGENE. *Genet Epidemiol* 5:471-472, 1988
- Ferlay J, Bray F, Steliarova-Foucher E, et al (eds): *Cancer Incidence in Five Continents: C15plus*. IARC CancerBase No. 9. Lyon, International Agency for Research on Cancer, 2014. <http://ci5.iarc.fr/Default.aspx>
- Win AK, Dowty JG, Cleary SP, et al: Risk of colorectal cancer for carriers of mutations in *MUTYH*, with and without a family history of cancer. *Gastroenterology* 146:1208-1211.e1-5, 2014
- Provenzale D, Gupta S, Ahnen DJ, et al: Genetic/familial high-risk assessment: Colorectal version 1.2016. NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 14:1010-1030, 2016
- Renkonen-Sinisalo L, Bützow R, Leminen A, et al: Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *Int J Cancer* 120:821-824, 2007
- Caminsky NG, Mucaki EJ, Perri AM, et al: Prioritizing variants in complete hereditary breast and ovarian cancer genes in patients lacking known BRCA mutations. *Hum Mutat* 37:640-652, 2016
- Desmond A, Kurian AW, Gabree M, et al: Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol* 1:943-951, 2015
- Castéra L, Krieger S, Rousselin A, et al: Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture

targeting multiple candidate genes. *Eur J Hum Genet* 22:1305-1313, 2014

33. Tung N, Battelli C, Allen B, et al: Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer* 121:25-33, 2015

34. Antoniou AC, Goldgar DE, Andrieu N, et al: A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. *Genet Epidemiol* 29:1-11, 2005

35. Vos JR, Oosterwijk JC, Aalfs CM, et al: Bias explains most of the parent-of-origin effect on breast cancer risk in BRCA1/2 mutation carriers. *Cancer Epidemiol Biomarkers Prev* 25:1251-1258, 2016

36. Ziogas A, Anton-Culver H: Validation of family history data in cancer family registries. *Am J Prev Med* 24:190-198, 2003

37. Talseth-Palmer BA, Wijnen JT, Brenne IS, et al: Combined analysis of three Lynch syndrome cohorts confirms the modifying effects of 8q23.3 and 11q23.1 in MLH1 mutation carriers. *Int J Cancer* 132:1556-1564, 2013

38. Win AK, Hopper JL, Buchanan DD, et al: Are the common genetic variants associated with colorectal cancer risk for DNA mismatch repair gene mutation carriers? *Eur J Cancer* 49:1578-1587, 2013

39. van Duijnhoven FJ, Botma A, Winkels R, et al: Do lifestyle factors influence colorectal cancer risk in Lynch syndrome? *Fam Cancer* 12:285-293, 2013

40. Suerink M, van der Klift HM, Ten Broeke SW, et al: The effect of genotypes and parent of origin on cancer risk and age of cancer development in PMS2 mutation carriers. *Genet Med* 18:405-409, 2016 [Erratum: *Genet Med* 18:108, 2016]

### Affiliations

**Sanne W. ten Broeke, Heleen M. van der Klift, Carli M.J. Tops, Manon Suerink, Frederik J. Hes, Hans F.A. Vasen, Juul T. Wijnen, and Maartje Nielsen**, Leiden University Medical Center, Leiden; **Encarna Gomez Garcia**, Maastricht University Medical Center, Maastricht; **Nicoline Hoogerbrugge, Arjen R. Mensenkamp, and Liesbeth Spruijt**, Radboud University Medical Center, Nijmegen; **Tom G.W. Letteboer**, University Medical Center, Utrecht; **Theo A.M. van Os and Egbert J.W. Redeker**, Academic Medical Center, Amsterdam; **Maran J.W. Olderode-Berends and Yvonne J. Vos**, University of Groningen; University Medical Center Groningen, Groningen; **Anja Wagner**, Erasmus Medical Center, Rotterdam, the Netherlands; **Stefan Aretz**, University of Bonn; University Hospital Bonn, Bonn; **Christoph Engel**, Leipzig University; Medizinisch Genetisches Zentrum Bayerstr, Leipzig; **Magnus von Knebel Doeberitz**, University of Heidelberg; German Cancer Research Center, Heidelberg; **Pål Møller**, University of Witten-Herdecke, Wuppertal; **Nils Rahner**, Heinrich-Heine-University, Düsseldorf; **Hans K. Schackert**, Technische Universität Dresden, Dresden; **Verena Steinke-Lange**, Medizinische Klinik und Poliklinik IV Campus Innenstadt, Klinikum der Universität München, Munich, Germany; **Pål Møller**, The Norwegian Radium Hospital; Oslo University Hospital, Oslo, Norway; **Inge Bernstein**, Hvidovre Hospital, Hvidovre, and Aalborg University Hospital, Aalborg, Denmark; **Daniel D. Buchanan, Mark Clendenning, John L. Hopper, Mark A. Jenkins, Christophe Rosty, Ingrid Winship, and Aung Ko Win**, The University of Melbourne; **Daniel D. Buchanan, Ingrid Winship, and Aung Ko Win**, Royal Melbourne Hospital, Parkville, Melbourne, Victoria; **Rodney Scott**, University of Newcastle, Newcastle, New South Wales, Australia; **Albert de la Chapelle, Heather L. Hampel, Rachel Pearlman, and Leigha Senter**, The Ohio State University Comprehensive Cancer Center, Columbus, OH; **Gabriel Capella and Marta Pineda**, Institut d'Investigació Biomèdica de Bellvitge, Barcelona, Spain; **Steven Gallinger**, Mount Sinai Hospital, Toronto, Ontario, Canada; **Jane C. Figueiredo and Robert Haile**, Cedars-Sinai Medical Center, Los Angeles, CA; **Loic Le Marchand**, University of Hawaii Cancer Center, Honolulu, HI; **Annika Lindblom**, Karolinska Institutet; Karolinska University Hospital, Stockholm, Sweden; **Noralane M. Lindor**, Mayo Clinic Arizona, Scottsdale, AZ; **Polly A. Newcomb**, Fred Hutchinson Cancer Research Center; University of Washington, Seattle, WA; and **Stephen Thibodeau**, Mayo Clinic, Rochester, MN.

### Support

Supported by Grant No. UL-2012-5515 from the Dutch Cancer Society and Grant No. UM1 CA167551 from the National Cancer Institute and through cooperative agreements with the following Colon Cancer Family Registry centers: Australasian Colorectal Cancer Family Registry Grants No. U01 CA074778 and U01/U24 CA097735; Mayo Clinic Cooperative Family Registry for Colon Cancer Studies Grant No. U01/U24 CA074800; Ontario Familial Colorectal Cancer Registry Grant No. U01/U24 CA074783; Seattle Colorectal Cancer Family Registry Grant No. U01/U24 CA074794; University of Hawaii Colorectal Cancer Family Registry Grant No. U01/U24 CA074806; and University of Southern California Consortium Colorectal Cancer Family Registry Grant No. U01/U24 CA074799. Seattle Colon Cancer Family Registry research was also supported by the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, which was funded by Control Nos. N01-CN-67009 (1996 to 2003) and N01-PC-35142 (2003 to 2010) and Contract No. HHSN2612013000121 (2010 to 2017) from the SEER Program of the National Cancer Institute, with additional support from the Fred Hutchinson Cancer Research Center. The Columbus-area Hereditary Non-Polyposis Colorectal Cancer study cohort in Ohio was supported by Grants No. NCI R01-CA67941 and CA16058. The Ohio Colorectal Cancer Prevention Initiative was supported by Pelotonia. The collection of cancer incidence data for the State of Hawaii used in this study was supported by the Hawaii Department of Health as part of the statewide cancer reporting program mandated by Hawaii Revised Statutes; the National Cancer Institute's SEER under Control Nos. N01-PC-67001 (1996 to 2003) and N01-PC-35137 (2003 to 2010) and Contract Nos. HHSN26120100037C (2010 to 2013) and HHSN261201300009I (2010 to current) awarded to the University of Hawaii. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's SEER Program under Contract No. HHSN261201000140C awarded to the Cancer Prevention Institute of California, Contract No. HHSN261201000035C awarded to the University of Southern California, and Contract No. HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement No. U58DP003862-01 awarded to the California Department of Public Health. Data from Sweden were collected with support of the Swedish Cancer Society and the Stockholm County Council (ALF project). This work was also supported by the Spanish Ministry of Economy and Competitiveness, cofunded by European Regional Development Fund (FEDER) funds—a way to build Europe— Grant No. SAF2015-68016-R (G.C.); Carlos III National Health Institute (CIBERONC); the Government of

Catalonia (Pla estratègic de recerca i innovació en salut and 2014SGR338); and the Scientific Foundation Asociación Española Contra el Cáncer. A.K.W. is a National Health and Medical Research Council (NHMRC) Career Development Fellow. M.A.J. is an NHMRC Senior Research Fellow. J.L.H. is an NHMRC Senior Principal Research Fellow. D.D.B. is an NHMRC Career Development Fellow and a University of Melbourne Research at Melbourne Accelerator Program (R@MAP) Senior Research Fellow. C.R. is a Jeremy Jass Pathology Fellow. M.N. is a Dutch Cancer Society Fellow.

**Prior Presentation**

Presented at the Biennial meeting of International Society for Gastrointestinal Hereditary Tumours (InSiGHT), Florence, Italy, July 8, 2017.



**Access the Latest Scientific Presentations With the 2018 Gastrointestinal Cancers Symposium Videos and Slides**

With the 2018 Gastrointestinal Cancers Symposium Videos and Slides, you can access practice-changing developments in gastrointestinal cancers care on any computer, tablet, or mobile device. Purchase the 2018 Gastrointestinal Cancers Symposium Slides separately or bundle the Videos and Slides and save at [shop.asco.org](http://shop.asco.org)

*ASCO members save 20%. Attendees of the Symposium receive the Videos and Slides for free.*



**ASCO** Education



**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Cancer Risks for *PMS2*-Associated Lynch Syndrome**

*The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [ascopubs.org/jco/site/ifc](http://ascopubs.org/jco/site/ifc).*

**Sanne W. ten Broeke**

No relationship to disclose

**Heleen M. van der Klift**

No relationship to disclose

**Carli M.J. Tops**

No relationship to disclose

**Stefan Aretz**

**Consulting or Advisory Role:** AstraZeneca

**Inge Bernstein**

No relationship to disclose

**Daniel D. Buchanan**

**Consulting or Advisory Role:** Merck Sharp & Dohme

**Albert de la Chapelle**

No relationship to disclose

**Gabriel Capella**

**Leadership:** VCN Biosciences

**Stock or Other Ownership:** VCN Biosciences

**Consulting or Advisory Role:** VCN Biosciences

**Research Funding:** VCN Biosciences (Inst)

**Mark Clendenning**

No relationship to disclose

**Christoph Engel**

No relationship to disclose

**Steven Gallinger**

No relationship to disclose

**Encarna Gomez Garcia**

No relationship to disclose

**Jane C. Figueiredo**

No relationship to disclose

**Robert Haile**

No relationship to disclose

**Heather L. Hampel**

**Stock or Other Ownership:** Genome Medical

**Consulting or Advisory Role:** BeaconLBS, InVitae, Genome Medical

**Research Funding:** Myriad Genetics (Inst)

**John L. Hopper**

No relationship to disclose

**Nicoline Hoogerbrugge**

No relationship to disclose

**Magnus von Knebel Doeberitz**

**Honoraria:** Merck Sharp & Dohme

**Research Funding:** NEC Europe, Merck Sharp & Dohme (Inst)

**Loic Le Marchand**

No relationship to disclose

**Tom G.W. Letteboer**

No relationship to disclose

**Mark A. Jenkins**

No relationship to disclose

**Annika Lindblom**

No relationship to disclose

**Noralane M. Lindor**

**Honoraria:** UpToDate (I)

**Patents, Royalties, Other Intellectual Property:** Royalties as editor for section in UpToDate (I)

**Travel, Accommodations, Expenses:** Intercept Pharmaceuticals (I)

**Arjen R. Mensenkamp**

No relationship to disclose

**Pål Møller**

No relationship to disclose

**Polly A. Newcomb**

No relationship to disclose

**Theo A.M. van Os**

No relationship to disclose

**Rachel Pearlman**

**Research Funding:** Myriad Genetics, InVitae

**Marta Pineda**

No relationship to disclose

**Nils Rahner**

No relationship to disclose

**Egbert J.W. Redeker**

No relationship to disclose

**Maran J.W. Olderode-Berends**

No relationship to disclose

**Christophe Rosty**

No relationship to disclose

**Hans K. Schackert**

No relationship to disclose

**Rodney Scott**

No relationship to disclose

**Leigha Senter**

**Honoraria:** Ambry Genetics

**Consulting or Advisory Role:** AstraZeneca

**Liesbeth Spruijt**

No relationship to disclose

**Verena Steinke-Lange**

**Consulting or Advisory Role:** AstraZeneca

**Manon Suerink**

No relationship to disclose

**Stephen Thibodeau**

No relationship to disclose

**Yvonne J. Vos**

No relationship to disclose

**Anja Wagner**

No relationship to disclose

**Ingrid Winship**

No relationship to disclose

**Frederik J. Hes**

No relationship to disclose

**Hans F.A. Vasen**

No relationship to disclose

**Juul T. Wijnen**

No relationship to disclose

**Maartje Nielsen**

No relationship to disclose

**Aung Ko Win**

No relationship to disclose

***Acknowledgment***

We thank all study participants of the Colon Cancer Family Registry and staff for their contributions to this project.