



Universiteit
Leiden
The Netherlands

Germline variants in the mismatch repair genes: Detection and phenotype

Suerink, M.

Citation

Suerink, M. (2021, March 3). *Germline variants in the mismatch repair genes: Detection and phenotype*. Retrieved from <https://hdl.handle.net/1887/3147165>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3147165>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/3147165> holds various files of this Leiden University dissertation.

Author: Suerink, M.

Title: Germline variants in the mismatch repair genes: Detection and phenotype

Issue date: 2021-03-03



Well documented high-grade serous ovarian cancers should not be tested for mismatch repair deficiency

Manuscript in preparation

Manon Suerink, Marthe de Jonge,
Christi van Asperen, Tjalling Bosse, Maartje Nielsen

ABSTRACT

High-grade serous ovarian cancer (HGSOC) is the most common histological subtype of ovarian cancer. Prevalence of cancer predisposition syndrome in this specific subtype is high (up to 24%, mainly *BRCA1* and *BRCA2* pathogenic variants). Whether mismatch repair (MMR) deficiency and Lynch syndrome are associated with HGSOC is still a topic of discussion.

Immunohistochemical staining of the MMR proteins was performed in 54 HGSOC to determine MMR deficiency status. Histopathological review was performed on all included cases to confirm histological subtype. Furthermore, a systematic PubMed search was performed to identify and evaluate recent literature on this topic.

All analysed HGSOC in our case series were MMR proficient. This observation was further strengthened by literature, where we found a prevalence of MMR deficiency and Lynch syndrome of 0–0.4%, with the notable exception of one outlier (15.2% MMR deficiency). However, the cases included in the latter study did not undergo central pathology review according to current standards.

There was no association in our cohort between HGSOC and MMR deficiency. This finding is corroborated by a review of recent literature, indicating that well documented HGSOC should not be tested for MMR deficiency.

INTRODUCTION

Ranking 7th in the list of most common cancers in females, ovarian cancer is not one of the most frequent types of cancer.¹ However, if ovarian cancer develops, mortality rates are high (<45% 5-year survival).² A substantial proportion (up to 24%) of ovarian cancers is caused by genetic predisposition syndromes, most commonly mutations in *BRCA1* and *BRCA2*.³ Another genetic predisposition for ovarian cancer is Lynch syndrome, caused by heterozygous pathogenic variants in one of four mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6* or *PMS2*).⁴

Lynch syndrome-associated cancers are characterized by MMR deficiency, which can either be demonstrated by expression loss of the MMR proteins through immunohistochemical (IHC) staining or by determining microsatellite instability (MSI) status of the tumour.⁵ These two techniques can be used as a pre-screening method to identify patients with a high chance of having Lynch syndrome. If MMR deficiency is present in the tumour, Lynch syndrome can be demonstrated (or ruled out) by subsequent sequencing of the MMR genes in DNA isolated from non-neoplastic tissue. It should be noted that the majority of MMR deficiency tumours (around two-thirds in colorectal and endometrial cancer) is caused by epigenetic silencing of both *MLH1* alleles or two somatic mutations in one of the MMR genes as a sporadic, non-hereditary event.^{5,6}

Identifying women with a higher risk of developing ovarian cancer is pursued so they can be offered prophylactic bilateral salpingectomy.^{7,8} It is therefore recommended that all women with high-grade serous ovarian cancer (HGSOC) are offered molecular testing of the *BRCA*-genes.^{9,10} Universal screening for Lynch syndrome in ovarian cancers is more controversial. Although prevalence of MMR deficiency in unselected ovarian cancer was around 10% in a systematic review published in 2011 by Murphy and Wentzensen, there was high heterogeneity between included studies.¹¹ Furthermore, after this review new classification guidelines have been published in 2014, which have increased reproducibility of histopathological subtyping in ovarian cancer. This is particularly relevant since it has been suggested that, similar to Lynch syndrome-associated endometrial cancer, there is a predominance of endometrioid and clear-cell histological subtypes in Lynch syndrome-associated ovarian cancer.¹² Some therefore recommend universal testing for Lynch syndrome of only these histological subtypes of ovarian cancer.¹²⁻¹⁴

Nonetheless, some controversy remains on whether these recommendations can be justified based on currently available literature.^{15,16} In a systematic review, 22% of Lynch syndrome-associated ovarian cancers are reported to be of serous histology⁴

and 25% of ovarian cancers from a Dutch cohort of ovarian cancers in patients with Lynch syndrome was reported to be of high-grade serous histology.¹⁷ Additionally, in the aforementioned systematic review of Murphy and Wentzensen, prevalence of MSI for serous ovarian cancers was 7.9%.¹¹ No distinction was made yet between low-grade and high-grade ovarian cancers in this review.

Some say the reasons for finding MMR deficiency in serous ovarian cancer and, vice versa, serous ovarian cancers in Lynch syndrome patients are 1) misclassification of histological subtypes and 2) the occurrence of incidental serous tumours in patients with Lynch syndrome.^{14,15} Misclassification of histological subtypes is not uncommon in ovarian cancer, particularly if histological sub classification is not up to current standards (i.e. supported by biomarker analysis such as immunohistochemical analysis of TP53 and WT1).^{14,18,19} This is particularly relevant in (research) cohorts that include historical cases. Central pathology review by a dedicated gynaecology pathologist to confirm histological subtyping, preferably by applying the world health organisation guidelines of 2014 and supported by biomarker analysis, is therefore important in such cohorts.

We present a series of centrally reviewed HGSOCs (n=54), which were immunohistochemically stained for the MMR-proteins. Additionally, recent literature was searched for unselected HGSOC cohorts that were screened for MMR deficiency and/or Lynch syndrome.

METHODS

LUMC case series

Our cohort consists of prospectively included ovarian cancer patients from seven hospitals in the Netherlands and was described before as the COBRA cohort by de Jonge *et al.*²⁰ Sixty-six women with ovarian cancer consented to the study and were included without any preselection criteria (such as family history), 54 of these women had HGSOC. Immunohistochemical staining of formalin-fixed paraffin embedded (FFPE) sections was performed as described before²¹ to determine MMR deficiency status. MMR deficiency was defined as absent nuclear staining of at least one of the MMR proteins. A two-antibody approach to immunohistochemical staining was applied (staining PMS2 and MSH6 as a first step, followed by reflex staining of the protein within the same heterodimer if either PMS2 or MSH6 showed aberrant staining).²²

Histopathology slides from all cases were centrally revised by an expert gynaecopathologist (TB) according to the most recent (2014) World Health Organization classification system.

The study was approved by the medical ethics committee of the LUMC (reference number: P16.009).

Literature review

PubMed was searched for publications that report on unselected (i.e. no preselection was made based on family history or other criteria that increase mutation detection rates) serous ovarian cancer cohorts in which screening for MMR deficiency and/or Lynch syndrome was carried out. Data from publications that report on the prevalence of MMR deficiency in serous ovarian cancer and that were published after the release of the latest WHO guidelines in 2014 extracted and summarised. Furthermore, because histological subtyping is prone to interobserver variation, it was assessed whether central pathology review was performed on the cohorts in included publications.

Additionally, data from all publications that report on DNA panel sequencing to detect germline MMR variants were extracted.

The PubMed-search-strategy can be found in the supplementary materials and resulted in 265 hits on April 1st 2020. Titles of publications were screened for relevance. Subsequently, abstracts and, if necessary, content of possibly relevant manuscripts were read to decide whether they contained relevant data.

5

RESULTS

LUMC case series

Immunohistochemical staining was performed on all 54 HGSOs (mean age at diagnosis: 65.2 years, age range 46 – 89 years). None of the analysed samples showed expression loss of any of the MMR proteins.

Literature review

Our literature search identified three relevant publications that screened serous ovarian cancers for MMR deficiency, either through immunohistochemical staining of the MMR proteins or through microsatellite instability analysis. Two of these publications performed central pathology review to confirm the diagnosis of HGSO. Prevalence of MMR deficiency varied was 0% in two studies and 15.2% in the one study that did not perform central pathology review (table 1). This latter study also did

Chapter 5

not differentiate between high-grade and low-grade serous ovarian cancer. Our own cohort was included in the table as well (0% MMR deficiency).

Furthermore, three publications were identified that report on the prevalence of Lynch syndrome as analysed by germline gene panel analysis in a cohort of serous ovarian cancers. All three publications were published before or around the time of the release of the WHO guidelines for histological subtyping. Only one of these publications mentions central pathology review. Two out of three studies did not specify whether their serous ovarian cancer cases were high-grade or low-grade. Regardless, the prevalence of Lynch syndrome is very low in all three publications (0 – 0.4%, table 2). In addition a publication by Chui et al.¹² was identified as being of relevance. In this publication 20 ovarian cancers from Lynch syndrome patients are revised. After expert review, none of the twenty cases was of serous histology. Before review there was one serous carcinoma and two carcinomas of mixed histology with also a serous component, two of these tumours were classified as endometrioid and in one mixed tumour there was no serous component after revision, although it was still classified as a mixed type.¹²

Table 1. Mismatch repair (MMR) deficiency as determined through immunohistochemical staining or microsatellite instability analysis in serous ovarian cancer.

Publication	High-grade serous versus serous not specified	Central pathology review	Method of pathology review	Method of MMR deficiency analysis	Number of included cases	MMR deficient
					n	n (%)
Rambau (2016) ²⁹	High-grade	Yes	Biomarker expression analysis using IHC, panel not clearly specified	Immunohistochemistry on tissue microarrays	149	0 (0)
Leskela (2020) ³⁰	High-grade	Yes	According to 2014 WHO guidelines (including IHC of WT1, PR, p53, and Napsin A)	Immunohistochemistry on tissue microarrays	124	0 (0)
This manuscript	High-grade	Yes	According to 2014 WHO guidelines	Immunohistochemistry on whole sections	54	0 (0)
Akbari (2017) ²⁵	Not specified	No		MSI analysis (5 marker panel as recommended by the National Cancer Institute)	389	59 (15.2)
Subtotal with central pathology review					327	0 (0)
Total					716	59 (8.2)

Table 2. Prevalence of Lynch syndrome as determined through sequencing of germline DNA in patients with serous ovarian cancer. MMR = mismatch repair.

Publication	Central pathology review	High-grade serous versus serous not specified	Method of central review	No. of cases	Germline MMR-mutation (DNA sequencing)					Total with Lynch syndrome
					MLH1	PMS2	MSH2	MSH6	Not specified	
				n	n	n	n	n	n	n (%)
Walsh (2011) ³¹	No	Serous not further specified		242	0	0	0	0	-	0 (0.0)
Pal (2012) ³²	No	Serous not further specified		933	-	-	-	-	2	2 (0.2)
Norquist (2014) ³³	Yes	High-grade serous	centrally reviewed by gynecologic pathologists, unsure cases were resolved by consensus	1118	0	4	0	1	-	5 (0.4)
Total				2293						7 (0.3)

DISCUSSION

In our cohort of centrally revised HGSOCs, no cases with MMR deficiency were identified. Furthermore, the prevalence of MMR deficiency in recently published serous ovarian cancer cohorts that underwent central pathology review was extremely low (0 – 0.4%, Table 1 and 2).

There are several good arguments in favour of implementing universal MMR deficiency screening in ovarian cancer. First of all, a Lynch syndrome diagnosis benefits the patient and her family as it offers them the opportunity to begin colonoscopy surveillance and/or undergo preventive surgery of the uterus and ovaries. Furthermore, MMR deficiency, regardless of whether it has a sporadic or hereditary cause, is relevant for treatment (immunotherapy)^{23,24} and prognosis (MMR deficient tumours have been associated with better survival).¹⁷ Additionally, MMR deficiency status might aid in histological subtyping (e.g. when discerning HGSOC from high-grade endometrioid ovarian cancer). Nonetheless, health funding should be spent wisely and efficiently and screening for MMR deficiency should be reserved for those histological subtypes with a reasonable a priori chance of a relevant outcome. Furthermore, it is of interest for patients who already have a Lynch syndrome diagnosis to know whether they have an increased risk of HGSOC, since this subtype has a relatively poor prognosis. It is therefore important to establish whether or not an association exists between MMR deficiency/Lynch syndrome and HGSOC.

Our cohort with centrally revised, HGSOCs adds further evidence to the existing literature that the link between MMR deficiency and HGSOC is weak at best. These results corroborate guidelines that suggest not to perform universal MMR deficiency screening in HGSOC.¹²⁻¹⁴ Recent literature on MMR deficiency prevalence in unselected serous ovarian cohorts, as summarized in table 1 and 2, supports these guidelines as well. Only one recent publication reports a high prevalence of MMR deficiency in serous ovarian cancer. Considering that the results of this study are such an extreme outlier, we believe that these results are incorrect due to lack of central pathology review, possibly in combination with other factors that cannot be derived from the manuscript.²⁵ The fact that no differentiation is made between high-grade and low-grade tumours within this study strongly suggests that the 2014 WHO guidelines for histological subtyping are not followed.

An additional argument against a link between HGSOC and Lynch syndrome is the lack of serous tubal intraepithelial carcinomas (STICs) in prophylactic gynaecologic specimens from Lynch syndrome patients.²⁶ As the majority of HGSOC originate in the fallopian tubes, presence of a precursor lesions in the form of STICs would be

expected in individuals with an increased risk of HGSOC (as observed in *BRCA1/2*-mutation carriers).^{27,28}

The most important source of caution regarding subtype specific MMR deficiency screening are publications of case series with ovarian cancer patients from Lynch syndrome families where serous ovarian cancer is quite prevalent.^{4,15} This is likely explained by the fact that high-grade endometrioid ovarian cancer and HGSOC can be hard to discern and, thus, histological misclassification. Another explanation could be the coincidental occurrence of sporadic serous ovarian cancer within a Lynch syndrome patient (in a minority of cases).^{14,15}

As mentioned above, Chui *et al.*¹² already published evidence suggesting that misclassification of histological subtypes is at least part of the explanation. Unfortunately, their cohort is the only publication to thoroughly revise a cohort of Lynch syndrome-associated ovarian cancers. Future research efforts should therefore focus on gathering larger cohorts of ovarian cancers from molecularly confirmed Lynch syndrome patients and perform histological subtyping according to current standards. If there are truly HGSOC cases in Lynch syndrome patients, then these should be analysed for signs of MMR deficiency (*i.e.* loss of MMR staining, presence of MSI and/or a second, somatic hit of the affected MMR protein) to see whether tumour development was a consequence of the germline mutation.

Based on our finding of 0% MMR deficiency in centrally revised HGSOC, the low prevalence of MMR deficiency in well-characterised HGSOC cohorts as published in literature and the argumentation as provided in the discussion, an association between HGSOC and MMR deficiency/Lynch syndrome is unlikely. These findings stress the relevance of careful histological subtyping for pathologists and imply that universal MMR deficiency testing is not required in HGSOC. Clinical geneticists can refrain from requesting MMR deficiency analysis in well-documented (recently diagnosed) HGSOC. In older cases histopathological review should be considered.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;68(6):394-424.
2. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. *Best Practice & Research: Clinical Obstetrics & Gynaecology*. 2017;41:3-14.
3. Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, Roeb W, Agnew KJ, Stray SM, Wickramanayake A, Norquist B, Pennington KP, Garcia RL, King MC, Swisher EM. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108(44):18032-18037.
4. Helder-Woolderink JM, Blok EA, Vasen HFA, Hollema H, Mourits MJ, De Bock GH. Ovarian cancer in Lynch syndrome; a systematic review. *European Journal of Cancer*. 2016;55:65-73.
5. Cerretelli G, Ager A, Arends MJ, Frayling IM. Molecular pathology of Lynch syndrome. *Journal of Pathology*. 2020;250(5):518-531.
6. Haraldsdottir S, Hampel H, Tomsic J, Frankel WL, Pearlman R, de la Chapelle A, Pritchard CC. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. *Gastroenterology*. 2014;147(6):1308-1316 e1301.
7. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. *American Journal of Surgery*. 2016;212(4):660-669.
8. Kohlmann W, Gruber SB. Lynch Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R))*. Seattle (WA)1993.
9. Vergote I, Banerjee S, Gerdes AM, van Asperen C, Marth C, Vaz F, Ray-Coquard I, Stoppa-Lyonnet D, Gonzalez-Martin A, Sehouli J, Colombo N. Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients. *European Journal of Cancer*. 2016;69:127-134.
10. Lancaster JM, Powell CB, Chen LM, Richardson DL, Committee SGOCP. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecologic Oncology*. 2015;136(1):3-7.
11. Murphy MA, Wentzensen N. Frequency of mismatch repair deficiency in ovarian cancer: a systematic review This article is a US Government work and, as such, is in the public domain of the United States of America. *International Journal of Cancer*. 2011;129(8):1914-1922.
12. Chui MH, Ryan P, Radigan J, Ferguson SE, Pollett A, Aronson M, Semotiuk K, Holter S, Sy K, Kwon JS, Soma A, Singh N, Gallinger S, Shaw P, Arseneau J, Foulkes WD, Gilks CB, Clarke BA. The histomorphology of Lynch syndrome-associated ovarian carcinomas: toward a subtype-specific screening strategy. *American Journal of Surgical Pathology*. 2014;38(9):1173-1181.
13. Zeimet AG, Mori H, Petru E, Polterauer S, Reinthaller A, Schauer C, Scholl-Firon T, Singer C, Wimmer K, Zschocke J, Marth C. AGO Austria recommendation on screening and diagnosis of Lynch syndrome (LS). *Archives of Gynecology and Obstetrics*. 2017;296(1):123-127.
14. Chui MH, Gilks CB, Cooper K, Clarke BA. Identifying Lynch syndrome in patients with ovarian carcinoma: the significance of tumor subtype. *Advances in Anatomic Pathology*. 2013;20(6):378-386.
15. Benusiglio PR, Coulet F. Serous ovarian carcinoma in patients with Lynch syndrome: Caution is warranted. *Gynecol Oncol Rep*. 2018;26:69-70.
16. Ryan N, Wall J, Crosbie EJ, Arends M, Bosse T, Arif S, Faruqi A, Frayling I, Ganesan R, Hock YL, McMahon R, Manchanda R, McCluggage WG, Mukonoweshuro P, van Schalkwyk G, Side L, Smith JH, Tanchel B, Evans DG, Gilks CB, Singh N. Lynch syndrome screening in gynaecological cancers: results of an international survey with recommendations for uniform reporting terminology for mismatch repair immunohistochemistry results. *Histopathology*. 2019;75(6):813-824.

17. Woolderink JM, De Bock GH, de Hullu JA, Hollema H, Zweemer RP, Slangen BFM, Gaarenstroom KN, van Beurden M, van Doorn HC, Sijmons RH, Vasen HFA, Mourits MJE. Characteristics of Lynch syndrome associated ovarian cancer. *Gynecologic Oncology*. 2018;150(2):324-330.
18. Kobel M, Kalloger SE, Lee S, Duggan MA, Kelemen LE, Prentice L, Kalli KR, Fridley BL, Visscher DW, Keeney GL, Vierkant RA, Cunningham JM, Chow C, Ness RB, Moysich K, Edwards R, Modugno F, Bunker C, Wozniak EL, Benjamin E, Gayther SA, Gentry-Maharaj A, Menon U, Gilks CB, Huntsman DG, Ramus SJ, Goode EL, Ovarian Tumor Tissue Analysis c. Biomarker-based ovarian carcinoma typing: a histologic investigation in the ovarian tumor tissue analysis consortium. *Cancer Epidemiology, Biomarkers and Prevention*. 2013;22(10):1677-1686.
19. Leskela S, Romero I, Cristobal E, Perez-Mies B, Rosa-Rosa JM, Gutierrez-Pecharroman A, Santon A, Gonzalez BO, Lopez-Reig R, Hardisson D, Vera-Sempere F, Illueca C, Vieites B, Lopez-Guerrero JA, Palacios J, Poveda A. The Frequency and Prognostic Significance of the Histologic Type in Early-stage Ovarian Carcinoma: A Reclassification Study by the Spanish Group for Ovarian Cancer Research (GEICO). *American Journal of Surgical Pathology*. 2020;44(2):149-161.
20. de Jonge MM, Ruano D, van Eijk R, van der Stoep N, Nielsen M, Wijnen JT, Ter Haar NT, Baalbergen A, Bos M, Kagie MJ, Vreeswijk MPG, Gaarenstroom KN, Kroep JR, Smit V, Bosse T, van Wezel T, van Asperen CJ. Validation and Implementation of BRCA1/2 Variant Screening in Ovarian Tumor Tissue. *Journal of Molecular Diagnostics*. 2018;20(5):600-611.
21. Stelloo E, Jansen AML, Osse EM, Nout RA, Creutzberg CL, Ruano D, Church DN, Morreau H, Smit V, van Wezel T, Bosse T. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. *Annals of Oncology*. 2017;28(1):96-102.
22. Mojtahed A, Schrijver I, Ford JM, Longacre TA, Pai RK. A two-antibody mismatch repair protein immunohistochemistry screening approach for colorectal carcinomas, skin sebaceous tumors, and gynecologic tract carcinomas. *Modern Pathology*. 2011;24(7):1004-1014.
23. Naboush A, Roman CA, Shapira I. Immune checkpoint inhibitors in malignancies with mismatch repair deficiency: a review of the state of the current knowledge. *Journal of Investigative Medicine*. 2017;65(4):754-758.
24. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA, Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409-413.
25. Akbari MR, Zhang S, Cragun D, Lee JH, Coppola D, McLaughlin J, Risch HA, Rosen B, Shaw P, Sellers TA, Schildkraut J, Narod SA, Pal T. Correlation between germline mutations in MMR genes and microsatellite instability in ovarian cancer specimens. *Familial Cancer*. 2017;16(3):351-355.
26. Downes MR, Allo G, McCluggage WG, Sy K, Ferguson SE, Aronson M, Pollett A, Gallinger S, Bilbily E, Shaw P, Clarke BA. Review of findings in prophylactic gynaecological specimens in Lynch syndrome with literature review and recommendations for grossing. *Histopathology*. 2014;65(2):228-239.
27. Shaw PA. Hereditary Carcinomas of the Ovary, Fallopian Tube, and Peritoneum. *Surgical Pathology Clinics*. 2011;4(1):461-478.
28. Visvanathan K, Shaw P, May BJ, Bahadiri-Talbott A, Kaushiva A, Risch H, Narod S, Wang TL, Parkash V, Vang R, Levine DA, Soslow R, Kurman R, Shih IM. Fallopian Tube Lesions in Women at High Risk for Ovarian Cancer: A Multicenter Study. *Cancer Prevention Research (Philadelphia, Pa)*. 2018;11(11):697-706.
29. Rambau PF, Duggan MA, Ghatage P, Warfa K, Steed H, Perrier R, Kelemen LE, Kobel M. Significant frequency of MSH2/MSH6 abnormality in ovarian endometrioid carcinoma

- supports histotype-specific Lynch syndrome screening in ovarian carcinomas. *Histopathology*. 2016;69(2):288-297.
30. Leskela S, Romero I, Cristobal E, Perez-Mies B, Rosa-Rosa JM, Gutierrez-Pecharroman A, Caniego-Casas T, Santon A, Ojeda B, Lopez-Reig R, Palacios-Berraquero ML, Garcia A, Ibarra J, Hakim S, Guarch R, Lopez-Guerrero JA, Poveda A, Palacios J. Mismatch Repair Deficiency in Ovarian Carcinoma: Frequency, Causes, and Consequences. *American Journal of Surgical Pathology*. 2020;44(5):649-656.
 31. Walsh CS, Blum A, Walts A, Alsabeh R, Tran H, Koeffler HP, Karlan BY. Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening. *Gynecologic Oncology*. 2010;116(3):516-521.
 32. Pal T, Akbari MR, Sun P, Lee JH, Fulp J, Thompson Z, Coppola D, Nicosia S, Sellers TA, McLaughlin J, Risch HA, Rosen B, Shaw P, Schildkraut J, Narod SA. Frequency of mutations in mismatch repair genes in a population-based study of women with ovarian cancer. *British Journal of Cancer*. 2012;107(10):1783-1790.
 33. Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, Bernardis SS, Casadei S, Yi Q, Burger RA, Chan JK, Davidson SA, Mannel RS, DiSilvestro PA, Lankes HA, Ramirez NC, King MC, Swisher EM, Birrer MJ. Inherited Mutations in Women With Ovarian Carcinoma. *JAMA Oncol*. 2016;2(4):482-490.

SUPPLEMENTAL INFORMATION

Pubmed Search strategy:

("Colorectal Neoplasms, Hereditary Nonpolyposis"[mesh] OR "Hereditary Nonpolyposis Colorectal Carcinoma"[ti] OR "Hereditary Nonpolyposis Colorectal Cancer"[ti] OR "Lynch syndrome"[ti] OR "Lynch"[ti] OR "Lynch syndrome I (site-specific colonic cancer)" [Supplementary Concept] OR "MLH1 protein, human" [Supplementary Concept] OR "MLH1"[ti] OR "MSH2"[ti] OR "MLH 1"[ti] OR "MSH 2"[ti] OR "PMS2"[ti] OR "MSH6"[ti] OR "MSH 6"[ti] OR "LS"[ti] OR "HNPCC"[ti] OR "MutL Proteins"[mesh] OR "MutL"[ti] OR "MutS Homolog 2 Protein"[mesh] OR "MutS"[ti] OR "MMR genes"[ti] OR "MMR gene"[ti]) AND ("Early Detection of Cancer"[Mesh] OR "screening"[tw] OR "screened"[tw] OR "detecting"[tw] OR "detection"[tw] OR "detected"[tw] OR "identification"[tw] OR "identifying"[tw] OR "identified"[tw] OR "identify"[tw] OR "IHC"[tiab] OR "Immunohistochemistry"[tw] OR "immunocytochemistry"[tw] OR "immunofluorescence"[tw] OR "mismatch repair proteins"[tw] OR "MMR"[tiab] OR "Microsatellite Instability"[Mesh] OR "microsatellite instability"[tw] OR "MSI"[tiab] OR "panel"[tw] OR "panels"[tw] OR "Genetic Testing"[Mesh] OR "Genetic Testing"[tw] OR "Genetic Test"[tw] OR "Genetic Tests"[tw] OR "Microsatellite Repeats"[Mesh] OR "Microsatellite Repeat"[tw] OR "Microsatellite Repeats"[tw] OR "histology"[tw] OR "histological"[tw] OR "Histology"[Mesh]) AND ("Ovarian Neoplasms"[Mesh] OR (("Neoplasms"[Mesh:NoExp] OR "Neoplasm"[tw] OR "Neoplasms"[tw] OR "tumor"[tw] OR "tumors"[tw] OR "tumour"[tw] OR "tumours"[tw] OR "cancer"[tw] OR "cancers"[tw] OR "Carcinoma"[Mesh:NoExp] OR "carcinoma"[tw] OR "carcinomas"[tw]) AND ("Ovary"[Mesh] OR "Ovary"[tw] OR "ovaries"[tw] OR "ovarian"[tw])))) AND ("2011"[Date - Publication] : "3000"[Date - Publication]) AND English[Language]

Well documented high-grade serous ovarian cancers should not be tested for mismatch repair deficiency

5