Endometrial Cancer Risk Among Germline *BRCA1/2* Pathogenic Variant Carriers: Review of Our Current Understanding and Next Steps

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ABSTRACT

PURPOSE To review the literature exploring endometrial cancer (EC) risk among surgical candidates with germline *BRCA1/2* pathogenic variants (PVs) to guide decisions around risk-reducing (rr) hysterectomy in this population.

DESIGN A comprehensive review was conducted of the current literature that influences clinical practice and informs expert consensus. We present our understanding of EC risk among *BRCA1/2* PV carriers, the risk-modifying factors specific to this patient population, and the available research technology that may guide clinical practice in the future. Limitations of the existing literature are outlined.

RESULTS Patients with *BRCA1/2* PVs, those with a personal history of tamoxifen use, those who desire long-term hormone replacement therapy, and/or have an elevated BMI are at higher risk of EC, primarily endometrioid EC and/or uterine papillary serous carcinoma, and may benefit from rr-hysterectomy. Although prescriptive clinical guidelines specific to *BRCA1/2* PV carriers could inform decisions around rr-hysterectomy, limitations of the current literature prevent more definitive guidance at this time. A large population-based study of a contemporary cohort of *BRCA1/2* PV carriers with lifetime follow-up compared with cancer-gene negative controls would advance this topic and facilitate care decisions.

CONCLUSION This review validates a potential role for rr-hysterectomy to address EC risk among surgical candidates with *BRCA1/2* PVs. Evidence-based clinical guidelines for rr-hysterectomy in *BRCA1/2* PV carriers are essential to ensure equitable access to this preventive measure, supporting insurance coverage for patients with either *BRCA1* or *BRCA2* PVs to pursue rr-hysterectomy. Overall, this review highlights the complexity of EC risk in *BRCA1/2* PV carriers and offers a comprehensive framework to shared decision making to inform rr-hysterectomy for *BRCA1/2* PV carriers.

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INTRODUCTION

Among women with *BRCA1/2* germline pathogenic variants (PVs), the lifetime risk of endometrial cancer (EC) is low but higher than that of the general population. Our current understanding of *BRCA1/2*-associated EC, including its pathogenesis, tumor biology, stage and age at presentation, and associated risk factors, remains limited. There are no discrete recommendations for risk-reducing hysterectomy (rr-hysterectomy) for females with *BRCA1/2* PVs. By contrast, the risk of EC is well established in women with Lynch syndrome and *PTEN* hamartoma tumor syndrome/Cowden syndrome for whom rr-hysterectomy is recommended when childbearing is complete.[1,11,12] In this article, we review the existing literature and its limitations, which preclude more definitive clinical guidelines for rr-hysterectomy in *BRCA1/2* PV carriers and outline the research necessary to fill this knowledge gap.

EC IN THE GENERAL POPULATION

Uterine cancer consists of uterine sarcoma and EC, which is further subdivided into endometrioid, serous, clear cell, carcinosarcoma (also known as malignant mixed Müllerian tumor),

and undifferentiated/dedifferentiated carcinoma. Few studies among *BRCA1/2* PV carriers include uterine sarcoma and most work is focused on EC.[2,3] In addition to these histologic subtypes, molecular subtypes of EC (ie, polymerase epsilon ultramutated, microsatellite instability hypermutated, copy-number low, copy-number high, and no specific molecular profile) are gaining greater recognition as specific features play increasing roles in treatment decisions.[4]

The median age for EC in the general population is 63 years, with >75% of cases diagnosed after age 55 years. Most patients are diagnosed with stage I endometrioid EC, which is localized in the uterus.[5] As endometrioid EC is an estrogen-sensitive cancer, risk factors include sources of elevated unopposed estrogen (eg, nulliparity, early menarche, late menopause, polycystic ovarian syndrome, and tamoxifen use).[6] A particularly aggressive subtype of EC, serous EC, also known as uterine papillary serous carcinoma (UPSC), accounts for <10% of all uterine cancer cases but over 40% of deaths.[7] UPSC and clear cell are estrogen-insensitive, more common among Black Americans, and associated with aggressive biology.[8] Although survival outcomes among Black Americans with UPSC are poor, tumor biology when characterized by microRNA profiling does not differ by race.[9] In recent years, the incidence and mortality of EC has risen in parallel to increasing rates of obesity in the United States.[10]

Noninvasive screening modalities currently do not exist for EC. Individuals with Lynch syndrome are recommended to receive annual endometrial biopsy and ultrasound starting at age 30-35 years.[6] Similarly, there is growing support to screen for EC starting at 35 years in patients with Cowden syndrome.[11] However, there are no screening recommendations for EC in the general population or among additional high-risk groups, such as women with elevated BMI or a *BRCA1/2* PV.[6,12] Moreover, irrespective of personal or familial gene mutations, family history plays a key role in modifying EC risk and warrants consideration if a screening protocol was established for those at risk.[13]

Among patients who are starting on tamoxifen for breast cancer (BC) treatment or prevention, there were efforts to explore EC screening with serial transvaginal ultrasounds.[14-16] Most studies found that patients with abnormal endometrium had abnormal vaginal bleeding, and therefore, the value of screening with transvaginal ultrasounds was low.[17] However, because of the higher rate of benign endometrial polyps among patients with postmenopausal BC (16%), the American College of Obstetricians and Gynecologists (ACOG) does recommend consideration of a baseline transvaginal ultrasound before initiating tamoxifen therapy among postmenopausal women.[17] Per ACOG guidelines, premenopausal women with no known increased risk of uterine cancer who are starting tamoxifen do not require additional monitoring beyond routine care.[17] By contrast, this screening practice is not supported by the National Comprehensive Cancer Network (NCCN) guidelines, which state that endometrial ultrasound and biopsy are not recommended in the absence of symptoms.[18]

If a patient does develop symptoms of EC, such as abnormal uterine bleeding, appropriate gynecologic care should be pursued. Diagnosis of EC typically consists of a transvaginal ultrasound, followed by hysteroscopy and endometrial biopsy.

LIMITATIONS OF THE CURRENT LITERATURE INFORMING RR-HYSTERECTOMY FOR *BRCA1/2* PV CARRIERS

In recent years, systematic reviews and meta-analyses exploring EC risk in *BRCA1/2* PV carriers have highlighted the shortcomings of previous work.[19-21] Most early studies focused on patients with EC who were subsequently identified as *BRCA1/2* PV carriers. Moreover, much of the data are from the 1990s, an era when this patient population was not offered high-risk screening and rr-interventions to manage their breast and ovarian cancer risk. Since many of these reports were not intended as genotype-phenotype correlation studies, histopathologic characteristics of the tumors, including EC subtype, were often unavailable. Therefore, these historic data sets may underrepresent the number of *BRCA1/2* PV carriers at risk of EC, particularly UPSC. Now that patients with *BRCA1/2* PVs have more effective management of their breast and ovarian cancer risks and improved life expectancy, their lifetime risk of EC may be higher than what historic data indicate.[22-24]

The longest prospective cohort study was performed by de Jonge et al.[25] This study followed 5,980 *BRCA1/2* PV carriers for a median of 22.5 years, from a median age ranging from 27.4-51.9 years,[25] which is younger than the average age of EC in the general population. Fifty-eight cases of EC were reported.[25] As expected in this cohort, the majority of EC occurred after age 40 years. To estimate the risk of developing EC by age 75 years, data were extrapolated using a competing risk analysis. The risk of overall EC was increased among all *BRCA1/2* PV carriers (hazard ratio [HR], 2.37; 95% CI, 1.53 to 3.69); in particular, overall EC risk was noted to be higher for *BRCA1* versus *BRCA2* PV carriers at 3.4% (95% CI, 2.46 to 4.8) versus 2.0% (95% CI, 1.09 to 3.30), respectively.[25] Using a competing risk analysis, the risk of developing UPSC by age 75 years was estimated to be 1.1% among all *BRCA1/2* PV carriers, with a higher risk for *BRCA1* (HR, 10.48; 95% CI, 2.95 to 37.20).[25]

Shu et al[2] performed a multicenter prospective cohort study to estimate risk of EC for 1,083 *BRCA1/2* PV carriers who received rr-bilateral salpingo-oophorectomy (rr-BSO) but did not pursue hysterectomy with a median follow-up of 5.1 years. A comparator group was not included. Eight cases of EC were reported.[2] In contrast to the study by de Jonge et al,[25] overall EC risk was not increased for *BRCA1/2* PV carriers (observed:expected [O:E] ratio, 1.9; 95% CI, 0.8 to 3.7).[2] However, similar to the study by de Jonge et al,[25] risk of UPSC was elevated for *BRCA1/2* PV carriers (O:E ratio, 14.8; 95% CI, 4.8 to 34.6), with increased risk for *BRCA1* PV carriers (O:E ratio, 22.2; 95% CI, 6.1 to 56.9).[2] Assuming a constant annual risk, the risk of developing UPSC by age 70 years was

estimated to be 2.6% or 4.7% assuming a relative risk compared with Surveillance, Epidemiology, and End Results data.[2]

A meta-analysis by Matanes et al[20] including 11 studies reported even lower rates of EC for *BRCA1/2* PV carriers, 0.58% (82/13,827), which likely reflects limitations of the included studies and not the actual prevalence. Although these estimates are informative, they reveal a need to better characterize the lifetime risk of EC in a prospective cohort of *BRCA1/2* PV carriers with long-term follow-up.

As broad population-based cancer genetic testing is not a routine practice, there is no comprehensive data set to compare EC rates in *BRCA1/2* PV carriers with cancer-gene negative controls. At a minimum, controls would ideally exclude other high-risk patients with Lynch or Cowden syndrome. In the study by de Jonge et al,[25] for example, standardized incidence ratios were calculated comparing cancer rates in *BRCA1/2* PV carriers with controls defined as noncarriers, but one third of controls had a previous history of BC, which is almost three-folds higher than expected for the general population (12%-13%). Consequently, 13.7% of controls had received tamoxifen.[25] We can glean information from the study by Heald et al,[26] where the incidence rates of hereditary EC susceptibility mutations were reported in women with uterine cancer, but this does not inform risk with *BRCA1/2* PVs. Previous work has also focused on somatic tumor testing to infer germline *BRCA1/2* status, and albeit informative to assess eligibility for therapies such as poly (ADP-ribose) polymerase inhibitors that target tumor cells with *BRCA1/2* PVs, these data do not provide an accurate estimate of EC risk in *BRCA1/2* PV carriers.[2,19]

Despite limitations of the existing literature (summarized in Table 1), insurance coverage for prophylactic hysterectomies has been restricted generally to *BRCA1* PV carriers in the United States. Historically, NCCN guidelines have emphasized the potential benefit of hysterectomy among *BRCA1* PV carriers because of increased risk of UPSC.[2,11] Further research is critical to inform evidence-based guidelines for prophylactic hysterectomy among *BRCA1* and *BRCA2* PV carriers to ensure equitable access to this potentially life-saving intervention.

BRCA1/2 PV carriers undergo several interventions that may influence the risk of EC. Many of the previous studies do not account for potential confounding factors, such as rr-BSO, type and formulary of hormone replacement therapy (HRT), obesity, tamoxifen, parity, and oral contraceptive use, each of which can affect EC risk. We will discuss four of these factors pertaining to *BRCA1/2* PV carriers.

rr-BSO and HRT

Women with germline *BRCA1/2* PV are recommended to undergo a rr-BSO after they complete childbearing and before menopause, typically at age 35-40 years for *BRCA1* PV carriers and 40-45 years for *BRCA2* PV carriers,[11] resulting in surgical menopause. HRT is recommended until age 50-51 years, the approximate age of natural menopause, for women in the general population who undergo surgical menopause and have no personal history of BC.[27] HRT raises estrogen levels with the goal of reducing risk of cardiovascular disease and osteoporosis, among other mordibidites.[28] In addition, vaginal estrogen therapy plays a critical role in the management of pelvic floor dysfunction and sexual health.[29,30] Although the data are limited, a small US-based study suggests that hysterectomy adversely affects pelvic floor function, irrespective of menopausal status.[31] While hysterectomy alone has not been shown to worsen sexual function, rr-BSO independently and when combined with hysterectomy adversely affects sexual health because of the induced hypoestrogenic state.[32,33]

Consequently, women with *BRCA1/2* PVs who undergo rr-BSO are more likely to start HRT at a younger age and for a longer duration than the general population, particularly *BRCA1* PV

TABLE 1. Limitation of the Existing Literature and Goals for Future Studies

Criteria	Existing Literature	Ideal Study
Comparator group/ controls	Non-BRCA status unknown for comparator group; Lynch syndrome and Cowden syndrome not routinely excluded	Cancer-gene negative controls (ie, patients who have been tested for multiple germline PVs and found to have no genetic mutations)
Recruitment period	Before implementation of comprehensive BRCA testing (recruitment starting in 1990s)	Recruitment of a contemporary cohort (after 2000)
Diagnosis of EC	Largest studies on the basis of registry data where cases cannot be confirmed with pathology reports and EC subtypes were not reported	Confirm the pathology findings and characterize the EC subtype
Follow-up	Follow-up does not extend to include median age at diagnosis of EC (>50 years)	Greater than 25 years of follow-up or until median age of 75 years
Controlling for confounders	Limited data reported on tamoxifen and HRT use, BMI, and personal history of BC	Consistent reporting of tamoxifen and HRT use (including duration and formulation), BMI, and personal history of BC
Reporting demographics	Variable reporting of age, race/ethnicity, and menopausal status	Consistent reporting of age, race/ethnicity, including Ashkenazi Jewish and African American/Black, and menopausal status

Abbreviations: BC, breast cancer; EC, endometrial cancer; HRT, hormone replacement therapy; PVs, pathogenic variants.

carriers. The impact of altered estrogen levels after these interventions on EC risk is unknown. Four single-arm studies in patients who have undergone rr-BSO, two of which are prospective studies, reported a low prevalence of EC (0.28%-0.74%) among women with a mean age of 45-50 years with 2-6 years of follow-up.[2,34-36] However, as previously noted, the follow-up remains insufficient relative to the age of onset of EC. None of the four studies report on HRT use.[2,34-36]

To our knowledge, only two studies that explored EC rates among women with *BRCA1*/2 PV report HRT use for all study participants. Segev et al[37] conducted a prospective cohort study of 4,893 women with a germline *BRCA1*/2 PV across 11 countries wherein participants completed questionnaires at baseline and every 2 years for a mean follow-up of 5.7 years. A subgroup analysis demonstrated no increased risk of EC among women with a history of HRT use. A subsequent case-control study that matched 83 EC cases to 1,027 controls confirmed no association between HRT use and EC.[38] Although the type of HRT was reported and stratified by estrogen plus progestin, estrogen-only, and progestin-only, the limited number of observed outcomes for each formulation precludes any substantive inference. An additional four studies describe HRT use in *BRCA1*/2 PV carriers diagnosed with EC, but no comparator group was included in these reports.[39-42]

It is also important to consider the impact of HRT duration and formulation not only for EC risk, but also on BC risk in *BRCA1*/2 PV carriers. Distinct from the general population, HRT after natural menopause and after rr-BSO for *BRCA1* PV carriers is not associated with increased BC risk.[43,44] In the general population, a meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer showed that a longer duration of any HRT and estrogen-progestin HRT (*v* estrogen-only) is associated with an increased risk of BC.[45] Among *BRCA1*/2 PV carriers with increased BC risk, these findings suggest that estrogen-only HRT is preferred in this setting, and, in fact, among *BRCA1* PV carriers who underwent surgical menopause after rr-BSO, the cumulative incidence of BC at 10 years of follow-up was 12% for those who used estrogen-only versus 22% for those who received estrogen plus progestin HRT ($P = .04$).[46] Most likely similar effects occur among women with *BRCA2* PVs as these tumors tend to be more hormonally driven and a shorter duration of HRT is required because of later onset of surgical menopause, but this has yet to be reported.

For patients with an intact uterus without the protective effects of progestin, the risks of endometrial hyperplasia and EC are significant, particularly with estrogen-only HRT administered >10 years.[47,48] Hence, estrogen-only HRT is contraindicated for patients with an intact uterus.[6] Although *BRCA1*/2 PV carriers are excluded, a phase IIB trial is underway evaluating the use of bazedoxifene and conjugated estrogen among women with a high risk of BC. Bazedoxifene is a selective estrogen receptor modulator (SERM) that acts as an estrogen-receptor agonist in bones but as an antagonist in the uterus and breast tissue. Therefore, this approach may offer an alternative form of HRT that better modulates BC risk in an individual with an intact uterus (ClinicalTrials.gov identifier: NCT04821141).[49] Future clinical studies of bazedoxifene and conjugated estrogen in the *BRCA1*/2 PV carrier population are necessary to minimize the risk of breast and gynecologic cancers.

Obesity

The risk of EC from HRT is influenced by body weight; women who are overweight or obese and receive HRT are at a greater risk of developing EC, specifically the endometrioid histology.[50] Independent of HRT, elevated BMI is a well-accepted risk factor for overall EC, including non–estrogen-dependent subtypes.[51-53] Only few studies have reported the BMI of patients with *BRCA1*/2 PVs diagnosed with EC, and these lack a comparator/control group.[38,40,54,55] Most studies did not discern a pattern in regard to BMI and EC risk.[38,40,55] One study by Lee et al[56] noted an elevated BMI in four of five cases of endometrioid EC.

As higher BMI is associated with higher perioperative risk, it bears consideration when recommending prophylactic hysterectomy.[57] Although vaginal and laparoscopic hysterectomies are preferred to an abdominal approach,[58] complication rates increase with higher BMI for any surgical technique.[59] An elevated BMI is also associated with pelvic floor dysfunction after hysterectomy in the general population.[60] Therefore, balancing the risk of future EC with operative risks and future quality of life becomes an important factor when considering the benefits of rr-hysterectomy among *BRCA1*/2 PV carriers with an elevated BMI.

Tamoxifen Use

As a SERM, tamoxifen can act as an antagonist or agonist depending on the tissue. Although tamoxifen blocks estrogen receptors (ER) in the breast tissue, it has an agonistic effect on the endometrium, increasing the risk of endometrial hyperplasia and EC. Consequently, tamoxifen use has been demonstrated to increase the risk of endometrioid EC, uterine sarcomas, and uterine carcinosarcomas.[61-63] There is growing evidence suggesting tamoxifen may increase EC risk through the phosphoinositol-3-kinase signaling pathway.[64]

EC risk bears consideration when prescribing tamoxifen.[65] Among *BRCA1*/2 PV carriers, tamoxifen is used for both BC treatment and prevention. In patients with a perceived ER-positive BC risk, there are now data to support a role for low-dose tamoxifen for prevention.[66] Beiner et al[40] conducted a prospective cohort study of 857 women with a *BRCA1*/2 PV, identifying six incident cases of EC after a mean follow-up of 3.3 years, and in four of the cases, tamoxifen use was ≥5 years. A subgroup analysis revealed an increased risk of EC with tamoxifen use. The authors postulated that the increased EC risk among all *BRCA1*/2 PV carriers can be primarily attributed to tamoxifen treatment for BC.[40] Similarly,

Segev et al[37] noted an increased EC risk with tamoxifen use among all *BRCA1/2* PV carriers and specifically among *BRCA1/2* PV carriers with a history of BC, concluding that tamoxifen use is the most relevant risk factor for developing EC. Further work confirmed an increased risk of EC with the use of tamoxifen for treatment and prevention of BC among *BRCA1* carriers; the odds ratio for EC was 3.66 for any use of tamoxifen and 7.19 for patients on tamoxifen with previous BC.[38] Other studies have reported tamoxifen use among *BRCA1/2* PV carriers diagnosed with EC, but these are descriptive studies, often with missing information on the dose and duration of use.[3,34,36,39,41,67]

Studies conducted among patients with BC irrespective of *BRCA1/2* PV status have not associated tamoxifen with a specific EC subtype.[61,68,69] Although endometrioid EC has historically been considered the most estrogen-sensitive,[70] in studies limited to *BRCA1/2* PV carriers, the association between endometrioid EC and tamoxifen has not been consistently reported. Shu et al[2] reported a higher risk of UPSC among tamoxifen-exposed women (3/273; O:E ratio, 24.4; 95% CI, 5.0 to 71.3). By contrast, other investigators noted that all cases of EC in the *BRCA1/2* PV population were of endometrioid subtype and associated with tamoxifen use.[40,54]

In *BRCA1/2* PV carriers diagnosed with an ER-positive BC who do not undergo hysterectomy, the use of an aromatase inhibitor (AI) may be preferable to tamoxifen, particularly in light of the recent SOFT-EST substudy demonstrating greater estrogen suppression with the AI exemestane compared with tamoxifen when used with triptorelin.[71,72] However, this is not always possible, given that patients with a higher BMI have higher levels of endogenous estrogen, such that achieving estrogen suppression with AI is more challenging, and therefore, these patients will often receive tamoxifen with ovarian suppression.[71] For this subpopulation, the benefits of ovarian function suppression will outweigh the risk of future EC, and therefore, tamoxifen should be continued but in light of existing evidence, and furthermore, obese *BRCA1/2* PV carriers diagnosed with ER-positive BC may warrant greater consideration for rr-hysterectomy. It is important to note that future studies would ideally stratify patients on the basis of menopausal status and include duration of tamoxifen use. Consistent reporting of duration and dose of tamoxifen is particularly relevant, given changing recommendations during the past decade for BC treatment and chemoprevention.[73]

Role of Hereditary Cancer Genetic Testing

Comprehensive hereditary cancer genetic testing, including rearrangement and deletion testing, is recommended for all individuals with a strong family history of BC as of 2005.[74] However, in the context of more advanced genetic technology in recent years, the genotype-phenotype correlation of *BRCA1/2* PV carriers requires improved calibration to better understand variations in tumor characteristics that are distinct to germline *BRCA1* and *BRCA2* PVs. Consequently, without greater understanding of EC tumor biology in *BRCA1/2* PV carriers, it is unclear how much the EC risk is attributable to other factors, namely those aforementioned, versus driven by homologous recombination deficiency.

There may be an emerging role for single-nucleotide polymorphism (SNP) and polygenic risk score (PRS) testing to predict risk and outcomes of nonendometrioid EC among *BRCA1/2* PV carriers.[75] However, the low incidence of EC compared with other cancer types with established PRS, such as BC, suggests that it will be challenging to stratify risk and calibrate these diagnostics, and therefore, lowers their utility in clinical practice.

The existing literature on SNPs for EC consists primarily of candidate-gene studies. The largest genome-wide association study (GWAS) consisted of 12,096 cases and 108,979 controls.[76] The authors noted that 350,000-400,000 cases would be needed for a GWAS to account for 80% of genetic variance in EC.[77] Even if a larger EC GWAS was performed, the findings would not be generalizable to the small subset of patients with a germline *BRCA1/2* PV.

Noninvasive biomarkers to help identify patients at risk of EC offer a more promising and feasible solution for clinical practice. This could include methylated DNA, circulating tumor DNA, circulating cell-free DNA, or serum protein biomarkers.[78,79] Serum human epididymis protein 4 (HE4) appears to be a promising biomarker, although current data are insufficient to introduce its use in clinical practice.[79,80] Circulating tumor markers, such as L1 cell adhesion molecule (L1CAM) and DJ-1, have been associated with nonendometrioid EC and may be of value in this setting as there is a higher prevalence of UPSC in *BRCA1* PV carriers.[81] Large validation studies are needed in this realm to determine which biomarker adds value to care.[79]

Tissue biomarkers and tumor genomic testing can inform risk stratification and prognostication of patients diagnosed with EC to allow for a more personalized treatment.[79,82] Future work is needed to better characterize the EC tumors that develop in *BRCA1/2* PV carriers. These findings can be compared with EC tumor characteristics of patients with Cowden or Lynch syndrome.

Organoid models offer an additional means of understanding tumor biology and cancer progression among *BRCA1/2* PV carriers. Similar to studies underway for Lynch syndrome,[83] organoid models derived from hyperplastic endometrium from *BRCA1/2* PV carriers at the time of hysterectomy can improve our understanding of precancerous changes, including potential biomarkers and genetic alterations in this select population, as well as identifying susceptibility to specific systemic therapies.[84]

In summary, despite mounting evidence indicating the EC risk in germline *BRCA1/2* PV carriers, there are insufficient data to indicate hysterectomy for all women with *BRCA1/2*

TABLE 2. Clinical Vignettes

Clinical Question	Clinical Management Recommendations
Case 1: A 40-year-old female premenopausal *BRCA2* PV carrier with +FamHx (sister diagnosed with low-grade EC at age 28 years), normal BMI, has completed her family, and is planning to undergo a rr-BSO with HRT	
Would her sister's *BRCA2* PV status influence management?	Knowing the sister's *BRCA2* status would likely inform care decisions in this setting
Would testing her sister's tumor for HRD-deficiency influence the clinical recommendation?	HRD testing is not clinically available even if the patient's relative consents to the testing and its role in informing care is unknown. This is a gap in our translational research efforts[a]
Should her sister's BMI at the time of her EC diagnosis influence decision making around rr-hysterectomy?	Since we do not know whether BMI influences EC risk in patients with *BRCA1/2* PVs, this factor should not inform rr-hysterectomy decisions, but it should be considered to assess the surgical risks if rr-hysterectomy cannot be performed laparoscopically or transvaginally because of higher BMI
If the patient hopes to avoid rr- mastectomy and has +FamHx of BC, would a rr-hystectomy be favored to allow for estrogen-only HRT?	If the patient desires treatment with estrogen-only HRT, there is need for shared decision making between the patient and her surgeon on the role of rr-hysterectomy in this context
Case 2: A 55-year-old female postmenopausal *BRCA2* PV carrier with no FamHx of HBOC, but +FamHx of EC (three sisters who live abroad and do not have access to germline genetic testing) and planning for a rr-BSO	
Would her sisters' germline genetic testing results influence decisions around rr-hysterectomy?	If one or more of her sisters with EC had the same *BRCA2* PV as our patient, this would likely alter our perspective on this patient's risk. Genomic testing laboratories that enable patient-initiated testing are available internationally and there is a discounted rate for cascade testing when there is a known germline pathogenic variant in a family. This should be encouraged if feasible in this context
Would knowing if her sisters' tumors were high-grade *v* low-grade EC affect her EC risk? Would testing her sisters' tumors for HRD deficiency influence the clinical recommendation?	There are no data to indicate that the tumor biology of her sisters' ECs would affect her risk; however, knowing this information may inform the discussion around rr-hysterectomy if the tumors are high-grade since there are no established screening protocols for early detection of *BRCA1/2* PV UPSC
Would her *BRCA2* PV status (*v BRCA1* PV) influence the recommendation for a rr-hysterectomy?	The *BRCA2* status may influence whether her health care insurance would offer coverage for a rr-hysterectomy considering current NCCN guidelines
Case 3: A 60-year-old female postmenopausal *BRCA1* PV carrier s/p rr-BSO and rr-mastectomy requiring urogynecologic surgery for stress urinary incontinence. No FamHx of EC, but +FamHx of BC (mother and maternal grandmother passed of metastatic BC at age <50 years)	
Would her *BRCA1* PV status (*v BRCA2* PV) influence the recommendation for a rr-hysterectomy?	Women with *BRCA1* PV have a slightly higher risk of EC than those with *BRCA2* PV, and this can be considered in a discussion around rr-hysterectomy
Does her need for an upcoming surgery influence the recommendation?	If rr-hysterectomy can be done at the time of her upcoming urogynecologic surgery, this may lower her perioperative risks rather than undergoing rr-hysterectomy as a separate surgery
Does her family history of cancer affect the recommendation for a rr-hysterectomy?	Her family history of metastatic BC and a shortened life-expectancy is consistent with the hereditary breast and ovarian cancer syndrome before high-risk screening

Abbreviations: EC, endometrial cancer; FamHx, family history; HBOC, hereditary breast and ovarian cancer; HRD, homologous recombination deficiency; HRT, hormone replacement therapy; MSI, microsatellite instable; NCCN, National Comprehensive Cancer Network; POLE, polymerase epsilon; PV, pathogenic variant; rr, risk-reducing; rr-BSO, risk-reducing bilateral salpingo-oophorectomy; UPSC, uterine papillary serous carcinoma.
[a]A multicenter effort recently characterized the molecular profile of 393 low-grade EC, classifying the tumors as POLE-altered, MSI, TP53-altered, and no specific profile; however, germline BRCA and HRD testing was not investigated in this cohort.[85]

PVs, given the low EC risk and the perioperative risks with surgical intervention. There are special clinical considerations specific to *BRCA1*/2 PV carriers that must inform the decision about hysterectomy (Table 2), necessitating clinical guidelines for this patient population. Patients with a personal history of BC, tamoxifen use, interest in long-term HRT, and/or elevated BMI are at higher risk of EC, primarily endometrioid EC and/or UPSC as per available evidence, and may benefit from rr-hysterectomy if their life expectancy is favorable. However, limitations of the current literature prevent more definitive clinical guidelines. A large population-based study of a contemporary cohort with a lifetime follow-up compared with cancer-gene negative controls would advance this topic and facilitate care decisions. As data evolve, decisions regarding rr-hysterectomy should be shared between patients and clinicians with expertise in the field. Moreover, since germline PVs in both *BRCA1* and *BRCA2* increase EC risk, national guidelines and insurers should support coverage for patients with either *BRCA1* or *BRCA2* PVs who elect to pursue hysterectomy to reduce their risk of EC. The current understanding of EC risk in *BRCA1*/2 PV carriers is sufficient to suggest that rr-hysterectomy may have a potential life-saving impact in this patient population. Therefore, concerted efforts are required to facilitate development of clinical guidelines to establish a standard of care to manage EC risk among *BRCA1*/2 PV carriers.

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