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The genetic prediction of risk for gynecologic cancers☆

Leslie M. Randall [a,*], Bhavana Pothuri [b]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California, Irvine, 101 The City Dr. South, Bldg 56, Room 262, Orange, CA 92868
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU Langone Medical Center, 240 E. 38th St., 19th floor, New York, NY 10016

HIGHLIGHTS

- Hereditary cancer syndromes are an important precision medicine opportunity.
- Homologous recombination mutations including BRCA contribute to ovarian cancer.
- DNA mismatch repair defects increase risk for both ovarian and uterine cancers.
- Risks can be significantly reduced with prophylactic surgery or surveillance.
- These mutations can predict response to novel molecular therapies.

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ABSTRACT

Salient to the intent of personalized medicine, hereditary cancer syndromes present significant opportunities in the treatment and prevention of some gynecologic cancers. Mutations in *BRCA1*, *BRCA2*, and DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2* are important causal agents in hereditary breast and ovarian cancer (HBOC) and Lynch syndromes. Though they only account for an estimated 10-18% of ovarian, tubal, peritoneal, and endometrial cancer cases, inherited cancers are imminently preventable if mutation carriers are identified in a timely manner. Population level screening is currently impractical due to low prevalence of disease, cost of testing, and ethical issues associated with testing, so diagnosis of these mutations is limited. Being affected by one of the heritable gynecologic malignancies is a logical entry point into the genetic counseling and testing pipeline for the patient and her family members. Thus, gynecologic cancer providers are uniquely positioned to diagnose germline mutations that can inform prognosis and treatment for their patients in addition to enabling prevention for patients' cancer-unaffected blood relatives, or "previvors". The purpose of this review is to describe our current perspective on testing for and implications of heritable cancer syndromes in the women with ovarian, tubal, peritoneal, and endometrial cancers.

1. Introduction

The diagnosis of hereditary cancer syndromes has, until recently, been reserved for women with ovarian or endometrial cancer who have extensive family history or early onset of disease suggestive of a causal mutation. A technologic explosion coupled with increasingly acceptable options for prevention and targeted chemotherapy are rapidly moving the hereditary cancer topic to the forefront of clinical practice. Genetic counseling and testing has been challenging due to significant risks of testing, in addition to increased resource utilization for quality genetics care. The benefits of testing for hereditary gynecologic cancers include more personalized prognosis-which is improved in BRCA mutation carriers compared to non-carriers, enhanced risk assessment for potentially synchronous cancers, and improved triage to targeted therapies like PARP inhibitors for BRCA carriers [1] and potentially immunotherapy for Lynch carriers [2]. The risks of testing are subject to clinician assumptions and include increased anxiety or depression from positive results, uncertainty over inconclusive results, financial costs of testing, and difficulty navigating the complex landscape of available testing modalities. Identification of women with inherited cancers has, however, not only opened doors for prevention, but has also unexpectedly contributed to our knowledge of the biology of these tumors.

2. Ovarian, tubal, and peritoneal cancers

Once thought to be different diseases, these three malignancies are more alike than not, especially when considering only tumors that result in the peritoneal carcinomatosis phenotype most often associated

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* Corresponding author.
E-mail addresses: lrandall@uci.edu (L.M. Randall), Bhavana.Pothuri@nyu.edu (B. Pothuri).

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with high grade serous or undifferentiated histologies. For the purpose of this review, ovarian, tubal, and peritoneal cancers will be collectively referred to as "ovarian cancers".

2.1. Hereditary breast and ovarian cancer (HBOC)

Families with pedigrees rich in breast and ovarian cancer cases have been the focus of intense research efforts for several decades. From these families, mutations in *BRCA1* and *BRCA2* have proven to be the most common cause of hereditary breast and ovarian cancers, increasing the relative risk for ovarian cancer to 40 times that of the general population [3]. *BRCA* genes encode proteins by the same name that contribute to the repair of double-stranded DNA breaks by homologous recombination (HR), a process in which the damaged DNA is replaced with the proper base pairs using the sister chromatid as a template [4]. Other protein co-factors in the HR process including *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *BARD1*, and the MMR genes have been implicated as potential etiologic agents in hereditary ovarian cancer [5]. Their genes are collectively referred to as HR deficiency (HRD) genes, and are also important when mutated in tumors themselves as somatic mutations. Moreover, somatic HRD was a key abnormality identified by the Cancer Genome Atlas analysis of high grade serous ovarian cancers [6].

2.2. BRCA1 and BRCA2

Now 25 years since *BRCA1* was localized to chromosome 17q21 [7], and 21 years since *BRCA2* was mapped to chromosome 13q12.3 [8], the discovery of these tumor suppressor genes has proven to be one of the most impactful in the history of gynecologic cancer. Germline mutations in *BRCA1* and *BRCA2* were identified by linkage analysis in families with clustering of breast cancer cases, with some visibility on associated ovarian cancer [3]. *BRCA* mutations can occur in women or men of any heritage, but specific high-frequency mutations, or founder mutations, occur mainly in Ashkenazi Jewish heritage (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) [9], but have also been identified in other races and ethnicities [10–14].

Our current estimation of breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers is derived from higher-risk, referral populations [10,15]. These studies demonstrate both reduced penetrance, meaning not all carriers will develop breast or ovarian cancer, and variable expressivity, meaning the cancer(s) that manifest among carriers can vary. In general, *BRCA1*-associated breast and ovarian cancer cases have a higher incidence than *BRCA2*, and breast cancer is more common than ovarian cancer, which in part is due to sporadic breast cancers in mutation carriers (Table 1). Due to variable expressivity, it is not possible to predict when an individual carrier will manifest ovarian cancer, therefore both *BRCA1* and *BRCA2* carriers are counseled the same with regard to age at which to pursue prevention options. As more diverse populations are tested, like ovarian cancer patients with no family history, our knowledge of penetrance and incidence is likely to expand.

2.3. Testing for BRCA1 and BRCA 2

Since at least 2014, multiple professional societies including the American College of Medical Genetics and Genomics (ACMG) [16], the American Society of Clinical Oncology (ASCO) [17], the National Cancer Comprehensive Network (NCCN) [18], the National Society of Genetic Counselors (NSGC) [16], and the Society of Gynecologic Oncology (SGO) [19] recommend genetic testing for all women with non-mucinous epithelial ovarian, tubal, and peritoneal cancers. Guidance regarding which test to perform, however, is not specific. The extent of testing ranges from screening founder populations for known founder mutations to sequencing *BRCA1* and *BRCA2*, and to performing panel testing of *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *BARD1*, and the MMR genes, which explain another 4% of hereditary cancers [5]. Other strategies include starting with low complexity and "reflex" to more complicated testing if initial testing does not diagnose a mutation. In general, the more genes tested, the more non-specific the results with increasing likelihood of encountering a "variant of uncertain significance", or a polymorphism that has not yet been classified as deleterious or benign. Most insurance carriers re-imburse for at least *BRCA1* and *BRCA2* testing, which typically runs $1000-3000 USD, but some might cover more complex panels with higher costs. Multiple vendors now offer *BRCA1* and *BRCA2* and panel testing, and in most cases, which test to order is the prerogative of the clinician, but at times, the third-party payor.

Genetic counselors are an excellent resource to determine which patients need which type of testing while providing invaluable counseling regarding the possibilities of false negative results and testing of family members or "cascade" testing. The availability of trained genetics professionals can vary, so efforts such as telemedicine genetic counseling are underway to improve access [20]. However, when trained genetic counselors are not accessible, it is better for the oncologist to provide counseling and testing than for the cancer-affected patient not to have testing at all. The content of counseling is not currently well-defined, but efforts are underway within the SGO to facilitate this education.

When deleterious mutations are identified, blood-relatives of the affected patient are eligible for genetic testing limited to the identified mutation. A negative result effectively classifies those at general population risk, and family members with positive results are triaged to risk-reducing strategies. There are no specific recommendations for when (at what age) to perform cascade testing. In general testing is not recommended for minors, but it should occur no later than 35 at which time risk-reducing surgery for ovarian cancer is recommended. Many might benefit from earlier testing, particularly when there is a family history of affected individuals under the age of 35.

2.4. Risk-reduction options

The most important aspect of hereditary cancer risk is that it can be significantly modified by prophylactic measures. For women with *BRCA1* and *BRCA2* mutations, the three options to mitigate risk are surveillance, chemoprevention, and risk-reducing surgery. Similar to average risk screening [21], high-risk surveillance of *BRCA* carriers with annual CA-125 and ultrasound has low impact on early detection, and carries the potential harms of unnecessary surgery [22]. A proposed improvement, the risk of ovarian cancer algorithm (ROCA), measures serial CA-125 values longitudinally to detect a velocity increase greater than that of established controls [23], prompting an imaging evaluation. A large prospective, randomized trial of annual ROCA in average risk women, escalated to every 6-12 weeks for abnormal results, reported a sensitivity and specificity of 85.8% (95% confidence interval 95% CI, 79% to 91%) and 99.8% (95% CI, 99.8% to 99.8%), respectively, at the expense of 5 surgeries per invasive cancer. However, only 42% of screen-detected cancers were Stage I or II and these included borderline tumors and other low risk histologies. [24] More research is needed to evaluate frequent, every 3-6 month, ROCA as a strategy for *BRCA* carriers. GOG 199 is one such trial that is currently maturing [25] which to date has reported only a multivariate association between abnormal ROCA and diagnosis of occult cancer at risk-reducing surgery ($p<0.01$) [26].

Chemoprevention is best achieved with combined oral contraceptives (COCs) in women without contraindications to this therapy. Meta-analysis of three case-control studies showed a significant risk reduction of ovarian cancer in *BRCA* mutation carriers with any past COC use (odds ratio [OR]: 0.57; 95% CI: 0.47-0.70) and significant trend by duration of COC use (OR: 0.95; 95% CI: 0.93-0.97; $p < 0.001$) [27].

Table 1
Cumulative incidence of breast and ovarian cancer in mutation carriers by age 70 [3,7]

	BRCA1	BRCA2
Breast cancer	55-78%	45-47%
Ovarian cancer	40%	11-17%

There are inconsistent reports of increased breast cancer risk with COC use in *BRCA* positive women, but no significant increase has been found in well-designed, comparative studies [28]. Therefore, the breast cancer risk, if any, is outweighed by significant benefit in younger carriers who wish to retain their ovaries.

In 2010, the Society of Gynecologic Oncology (SGO) issued a recommendation for removal of the fallopian tubes and ovaries (RR-BSO) at age 35 or after completed childbearing in *BRCA* mutation carriers [29]. At the time, this was based on compelling retrospective data reporting a significant risk reduction in ovarian, and serendipitously, breast cancer following this procedure (Tables 2 and 3) [30–33]. A large, non-randomized prospective cohort of 2,482 *BRCA* mutation carriers further supports an 86% risk reduction in ovarian cancer [hazard ratio (HR)= 0.14; (95% CI, 0.04-0.59)] and reduced risk of breast cancer [*BRCA1* HR 0.63 (95% CI, 0.41-0.96) and *BRCA2* HR 0.36 (95% CI, 0.16-0.82)] [34]. RR-BSO was also associated with a decrease in breast cancer–specific mortality [HR 0.44 (95% CI, 0.26-0.76)], and ovarian cancer–specific mortality [HR 0.21 (95% CI, 0.06-0.80)]. These data are consistent, powerful, and informative for carriers.

Premenopausal RR-BSO carries theoretic risks with regard to cardiovascular, bone, and sexual health. The paucity of data available, however, challenge these hypotheses. A prospective osteoporosis study of 212 women at least 5 years out from RR-BSO reported 22 fractures in 16 subjects, with an age-dependent standardized incidence rates (SIR) that were not higher than expected from the general population [SIR 5-44 years: 2.12 (95% CI 0.85-4.37)]; 45-64 years: 1.65 (95% CI 0.92-2.72)] Quality of life has been enhanced with RR-BSO in terms of reducing cancer worry, but dissatisfaction with sexual functioning has been a significant drawback and in one study was moderately to extremely compromised in 42.1%-53.7% of women [35,36]. Westin *et al* reported that most women in their cohort were satisfied with their choice of surgery, but difficulty with decision making was associated with lower satisfaction levels [37]. A final real deficit of the RR-BSO is the residual risk for peritoneal cancer following the procedure [38]. Though rare, it can be particularly psychologically distressing and, because no early diagnosis is available, it can negate the risk reduction benefit.

RR-BSO is an opportunity for early cancer diagnosis in approximately 3-8% of women undergoing the procedure [26,31,39]. The accuracy of occult cancer detection is dependent on the protocol reported by Powell, *et al*, that requires pathologists to submit the tubes and ovaries in their entirety plus serially section all specimens. This so-called SEE-FIM (Sectioning and Extensively Examining of the Fimbriated end) protocol [40] not only improved the sensitivity for occult cancer, but also changed our understanding of *BRCA*-related "ovarian" cancer.

2.5. The STIC that broke the ovary's back

With most cases diagnosed at an advanced stage, it had been long accepted that the ovary was the most common primary site in cases of peritoneal carcinomatosis, and that cancers arising from the fallopian tube or peritoneum were conversely very rare. Following the advent of the SEE-FIM protocol, most occult cancers diagnosed at RR-BSO were intraepithelial and were located in the distal, fimbriated portion of the tube [41]. The Crum group characterized these lesions as serous tubal intraepithelial carcinomas (STICs) and produced evidence that the majority of "ovarian" serous carcinomas have endosalpinx involvement or STIC [42]. This paradigm shift immediately begged the question of whether salpingectomies could be used as a pre-emptive procedure to menopause-inducing oophorectomy in pre-menopausal carriers [43]. Because GOG 199 did identify occult cancers limited to the ovary [26], it is premature to adopt salpingectomy alone for prevention. However, it might be an option in women who decline pre-menopausal oophorectomy. Prospective comparison trials are underway in the US (NCT01907789) and in Europe (NCT02321228) to study outcomes of delayed oophorectomy compared to standard RR-BSO.

3. Uterine Cancers

Known genetic predisposition to uterine cancer is predominantly composed of endometrial cancers in Lynch syndrome and Cowden's syndrome.

3.1. Lynch syndrome

Approximately 3-5% of uterine cancers are inherited, and Lynch syndrome accounts for the majority of hereditary uterine cancers, and is also the second most common cause of hereditary ovary cancer [44]. Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer [HNPCC], is a highly penetrant autosomal dominant inherited cancer susceptibility syndrome with a predilection to various cancers, most commonly colon and endometrial at an early age. Other cancers include those involving the ovary, gastric system, small bowel, hepatobiliary system, renal pelvis, ureter, as well as breast, brain and skin [45,46]. Although much attention has been shed on colon cancer since it is more common, it is reported that women with HNPCC have a lifetime risk of up 71% of developing endometrial cancer. This risk may equal or exceed a woman's risk of developing colon cancer which is 25-50%. In addition, women with Lynch syndrome have a lifetime risk of developing ovarian cancer of 4-24%.

The incidence of Lynch syndrome in patients presenting with endometrial cancer is approximately 2.3%, which is similar to the incidence in colon cancer [47,48]. However, in younger patients the incidence is much greater for both endometrial and colon cancer. In women less than 50 years of age, 5-9% of women with endometrial cancer, and 5-7% with colon cancer had a mismatch repair gene mutation. [49–51]. A retrospective review noted that endometrial cancer was the sentinel cancer in over 50% of cases, and preceded the colon cancer diagnosis by a median of 11 years. [52]

Lynch syndrome is characterized by mutations in the DNA mismatch repair genes (MMR), *MLH1*, *MSH2*, *MSH6*, *or PMS2*. [Table 4] The risk of cancer varies depending on the mutation. Women with *MLH1* have a 20-54% risk of developing endometrial cancer by age 70, while those with *MSH2* have a slightly lower risk of 21-49%. *MSH6* mutation carriers have a 16-71% risk, while those with *PMS2* mutations have a 15% risk of developing endometrial cancer. Similarly, for ovarian cancer in Lynch syndrome the lifetime risk of developing cancer varies by mutation. by age 70 is for *MLH1*, *MSH2* and *MSH6* is 4–20%, 7.5–24% and 0–13.5% respectively [53–55]. Deletions in the *EPCAM* gene may also result in Lynch syndrome by inactivation of *MSH2*.

Defects in the mismatch repair lead to genomic instability, which results in the development of Lynch associated cancers. The genomic instability effects both the coding and non-coding portions of the

Table 2
Sentinel studies reporting the incidence of ovarian cancer following RRSO. HR=hazard ratio to develop ovarian cancer

Author	Median F/U time (years)	RRSO − Cancer during F/U	RRSO + Cancer during F/U
Rebbeck 2002	8.8	58/292 (19.9%)	6/259 (2.3%) HR 0.04 (95% CI 0.01-0.16)
Kauff 2002	2.1	4/72 (5.6%)	0/98 (0%) HR 0.15 (95% CI 0.02-1.31)
Finch 2006	3.5	32/779 (4%)	7/1041 (0.6%)
Kauff 2008	3	12/283 (4.2%)	HR 0.15 (95% CI 0.04-0.56) BRCA 1 HR 0.28 (95% CI 0.08-0.92) all HBOC
Rebbeck 2009	Meta-analysis (varied) n=9072	(n=6739)	(n=2333) HR 0.21 (95% CI 0.12 to 0.39)

Table 3
Sentinel studies reporting the incidence of breast cancer following RRSO. HR=hazard ratio to develop ovarian cancer

	Median F/U time (years)	RRSO -	RRSO +
Rebbeck 2002	8.8	60/142 (42.3%)	21/99 (21.2%) HR 0.47 (95% CI 0.29-0.77)
Kauff 2002	2.1	8/72 (11%)	3/98 (3%) HR 0.32 (95% CI 0.08-1.2)
Kauff 2008	3	28/298 (9.5%)	19/303 (6.3%)
Rebbeck 2009	Meta-analysis (varied) n=9072	(n=6739)	(n=2333) HR 0.49 (95% CI 0.37 to 0.65)

genome including single and dinucleotide repeats, known as micro satellites. The addition or deletion of nucleotides results in microsatellite instability (MSI) which is a hallmark of Lynch associated cancers. MSI can also result from somatic changes in *MLH1* when the promoter region of *MLH* is hypermethylated. [56] This occurs in 20-30% of endometrial cancer cases, and 15-20% of colon cancers.

3.2. Testing for Lynch Syndrome

Identifying Lynch syndrome in patients with endometrial cancer is important as it quantifies their risk of developing other cancers and allows them to be effectively screened. In addition, it may also prevent the development of incidental cancers in family members through preventative surgery and screening measures. Prior to genetic testing, referral for research study of families with colorectal cancer was based on the **Amsterdam criteria** developed in 1990. [57] The Amsterdam II criteria were then developed to include other Lynch related cancers and Lynch syndrome should be suspected if all of the **Amsterdam II** criteria are met. (see Table 5) The specificity was high (98%) and the sensitivity was low (22%) with the Amsterdam II criteria, however, so the **Bethesda** guidelines were developed in 1997, and revised in 2004 to provide recommendations on which colorectal cancer patients should be considered for tumor testing of MSI. [58,59]. The sensitivity and specificity of the revised Bethesda criteria are 82% and 77%, respectively. The Bethesda criteria is not ideal for identifying which endometrial cancer patients should be referred for genetics, so a modification of the revised Bethesda criteria has been proposed. The **revised Bethesda criteria** includes endometrial cancer as sentinel cancer to identify individuals who should be referred for genetic assessment with any of the criteria listed in Table 6. [19]

Testing for Lynch syndrome can be done either by direct germline DNA testing for mismatch repair gene mutations, or by initial tumor testing with immunohistochemistry (IHC) for mismatch repair genes. Although the presence of a mutation is definitive, the absence of a gene mutation with germ line testing does not rule out Lynch syndrome. Therefore, it is recommended that the patient undergo initial tumor testing if feasible. (Fig. 1) This enables focused germ line testing, and identification of those who do not have Lynch syndrome. IHC of the four MMR proteins, MLH1, MSH2, MSH6, and PMS2 is relatively easy and inexpensive to perform. The presence of these proteins effectively rules out Lynch syndrome, except for the rare case where a deleterious missense mutation produces a full length protein that is non-functional. Therefore, if IHC does not show loss of expression, but clinical suspicion is high patients, may have MSI testing and should be referred for germ line genetic testing. MSI testing is performed with normal and tumor tissue from the same patient. Most laboratories utilize a panel of 5 microsatellite markers recommended by the National Cancer Institute. [60] Although MSI testing is utilized more commonly in colon cancer, it can also be utilized in endometrial cancer in this specific circumstance where no loss of IHC is noted with the MMR IHC, but clinical suspicion is high.

If MLH1, PMS2 or both proteins are absent on IHC, then testing for sporadic MLH promoter methylation is indicated. MLH1 and PMS2 exist as heterodimers and one or both can be absent on IHC, which can also lead to MSI. If tumor is tested positive for MLH1 hypermethylation, this rules out Lynch syndrome. [61] If *MLH1* is negative for methylation, referral for mismatch repair gene testing of *MLH1*, *PMS2*, or both is indicated. Approximately 20-30% of endometrial cancers and 15-20% of colon cancers have loss of MLH1 expression due to MLH1 promoter hypermethylation. [62,63] Similarly, *MSH2* and *MSH6* genes act as heterodimers in the cell, and loss of one or both proteins may be to a mutation in either gene, and germ line testing of *MSH2*, *MHS6*, or both is indicated. Due to the rapid development of massive parallel sequencing and gene panel testing, all these genes are being included, and there is less of a concern than when single site gene testing is performed. Given the reduction in costs over time , practioners are increasingly opting for lynch panel testing which includes other genes such as EPCAM.

When IHC tumor tests are abnormal, germ line testing will fail to identify a mutation in 10-15% of endometrial cancer patients with loss of MLH1 or PMS2, and 25-40% of endometrial cancer cases with loss of MSH2 or MSH6. In this setting, MSI testing and consultation with a genetics professional is indicated in determining subsequent management. Other causes of MMR deficiency, including the possibility of somatic methylation of MSH2, need to be considered. [64]

All women with endometrial or colon cancer should be assessed for Lynch syndrome utilizing one of the 3 strategies below. If feasible, tumor testing is the preferred choice.

1. Tumor testing of all endometrial or colon cancers presenting before the age of 60. [65] It is estimated that 5-13% of endometrial cancer cases before age 50 and 2-5 % of endometrial cancers diagnosed between 50 and 60 are attributed to lynch syndrome. This approach may increase specificity and decrease cost when compared to universal testing.
2. Tumor testing of all endometrial or colon cancers regardless of age. Universal testing is the most sensitive, but also least specific. Given 12-30% of Lynch syndrome associated endometrial and colon cancers do not meet the revised Bethesda criteria modified to include endometrial cancer, there is rationale for this approach. This approach is the most sensitive, but is also the least specific, and requires testing of three to four times as many patients.

Table 4
Lifetime risk of Lynch associated cancers in women based on MMR gene mutation.

	MLH1	MSH2	MSH6	PMS2
Endometrial cancer	20-54%	21-49%	16-71%	15%
Colon cancer	50-53 %	39-68%	18-30%	15%
Ovarian cancer	4–20%	7.5–24%	0–13.5%	
Upper urologic	0.4%	9%	0.7%	
Gastric	6%	2%	4%	
Small Bowel	6%	6%		
Biliary/pancreatic	4%	4%		
Brain tumors	1.7%	2.5%		

Table 5
Amsterdam 2 Criteria- All 3 criteria must be met.

1	Three or more relatives with histologically verified Lynch syndrome-associated cancers (CRC, cancer of the endometrium or small bowel, transitional cell carcinoma of the ureter or renal pelvis), one of whom is a first-degree relative of the other two and in whom familial adenomatous polyposis (FAP) has been excluded
2	Lynch syndrome-associated cancers involving at least two generations
3	One or more cancers were diagnosed before the age of 50 years

Table 6
Revised Bethesda criteria modified to include endometrial cancers- any on criteria triggers genetics referral.

1	Patients with endometrial or colorectal cancer diagnosed before age 50 years
2	Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/ HNPCC-associated tumor at any age
3	Patients with colorectal cancer with tumor-infiltrating lymphocytes, peritumoral lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern diagnosed before age 60 years
4	Patients with endometrial or colorectal cancer and a first-degree relative with a Lynch/HNPCC-associated tumor diagnosed before age 50 years
5	Patients with colorectal or endometrial cancer diagnosed at any age with two or more first-degree or second-degree relatives with Lynch/HNPCC- associated tumors, regardless of age

3. Clinical screening with a focused personal and family history with a 4 item checklist completed by patients [65] or the modified, revised Bethesda Criteria [60]

3.3. Screening for Lynch Syndrome

Screening for Lynch syndrome includes colonoscopy every 1-2 years beginning at age 20-25, or 2-5 years before the earliest cancer diagnosis in the family whichever is earlier. [66] Screening colonoscopy has been shown to reduce risk of colon cancer and mortality in patients with Lynch syndrome [67]. Screening recommendations for endometrial cancer include endometrial biopsy every 1 to 2 years, starting at the age of 30-35, as well as keeping a menstrual calendar and evaluating abnormal bleeding. Annual or biennial ultrasound had poor sensitivity in identifying endometrial cancers [68]. Utilizing endometrial biopsies at 1 to 3-year intervals resulted in the detection rate of endometrial hyperplasia or cancer of 5%. [69,70]. Although no consensus exists regarding use of ultrasound and CA-125 to detect ovarian cancer in Lynch syndrome, they are often incorporated into screening procedures for these patients.

3.4. Prevention and Counseling for Lynch syndrome patients

Chemoprevention includes use of oral contraceptives, which reduces endometrial cancer risk by 50% in the general population. [71] Although there is no specific data regarding efficacy in patients with Lynch syndrome, there is surrogate biomarker data to suggest oral contraceptives reduce proliferation in these patients. [72] For colorectal cancer, women taking 600 mg daily of aspirin for more than 2 years had a reduced incidence of colon cancer. Data on long term effect on mortality with such a strategy is lacking. [73] The CAPP3 study is evaluating whether lower doses of aspirin confer a similar benefit in patents with Lynch syndrome.

Risk reducing hysterectomy and BSO has been shown to significantly reduce the incidence of endometrial cancer from 33% to 0% at a mean follow-up of 7 years. Similarly, ovarian cancer incidence was reduced from 5.5% to 0% at a mean follow up of 11 years. [74] Given the risk of endometrial cancer in patients with Lynch increases from 2-5% at age 40 to 8-17% at age 50, and risk of ovary cancer increases from 1-2% at age 40 to 3-7% at age 50, risk reducing surgery should be discussed with the patient in their early to mid 40's. [55,75]

3.5. Cowden's syndrome

Cowden's syndrome is characterized by germline mutations in the phosphatase and tensin [*PTEN* gene] which is important in cell cycle control. [76] It is associated with a 19-28% risk of developing endometrial cancer by the age of 70. In addition, women who harbor *PTEN* mutations have up to a 50% risk of breast cancer and a 3-10% risk of thyroid cancer [77,78]. Patients with Cowden's syndrome also have the pathognomonic finding of mucocutaneous lesions, both cutaneous papules and mucosal papillomas which are almost always present by age 30.

3.6. Referral to genetics for endometrial cancer

Based on the American College of Medical Genetics (ACMG) recommendations, patients with endometrial cancer should be referred for genetic services if they meet the following criteria [16]:

- Endometrial cancer diagnosis at age <50
- Endometrial cancer diagnosis at age ≥50 if there is a first degree relative with colorectal or endometrial cancer at any age
- Synchronous or metachronous colorectal or endometrial cancer in the same person
- Endometrial cancer showing mismatch repair deficiency on tumor screening
- Endometrial cancer and 2 additional cases of any LS-associated cancer in the same person or in close relatives
- Epithelial endometrial cancer and two additional Cowden syndrome criteria in the same person

4. Conclusion

Hereditary cancers are at the heart of the precision medicine movement. Discovery of familial cancer genes has not only identified those eligible for life-saving prevention, but has also aided in the understanding of a piece of the tumor heterogeneity pie: tumor biology, biomarkers, and therapy targets in those affected. Despite all that has been

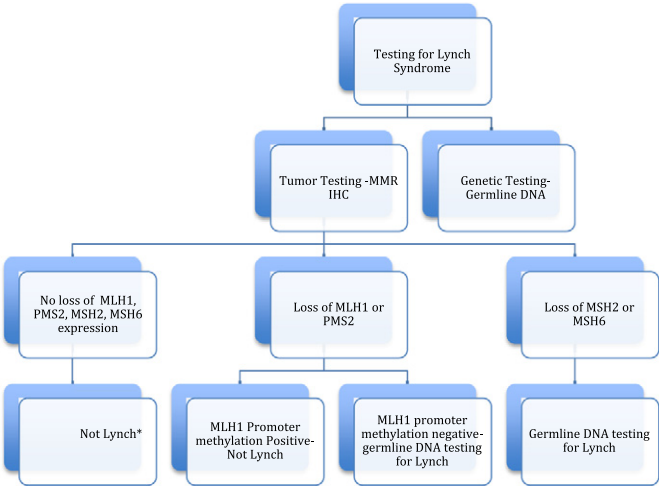

Fig. 1. * Except for the rare case of a deleterious missense mutation producing a full length non- functional protein. If IHC no loss of expression, but clinical suspicion high, MSI and germ line genetic testing is needed

accomplished, there is so much yet to do. The scope of this work will require a multidisciplinary approach that engages not only health professionals but also the organized patient advocacy groups to create a cultural shift that accommodates such a complex but crucial aspect of gynecologic cancer care.

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