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Genetic testing for hereditary cancer predisposition: *BRCA1/2*, Lynch syndrome, and beyond

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Abstract

Obstetrician/gynecologists and gynecologic oncologists serve an integral role in the care of women at increased hereditary risk of cancer. Their contribution includes initial identification of high risk patients, screening procedures like bimanual exam, trans-vaginal ultrasound and endometrial biopsy, prophylaxis via TAH and/or BSO, and chemoprevention. Further, gynecologists also serve a central role in the management of the secondary repercussions of efforts to mitigate increased cancer risks, including vasomotor symptoms, sexual function, bone health, cardiovascular disease, and mental health. The past several years has seen multiple new high and moderate penetrance genes introduced into the clinical care of women at increased risk of gynecologic malignancy. Awareness of these new genes and the availability of new multigene panel tests is critical for providers on the front-line of women's health.

Keywords

Genetic risk; *BRCA1/2*; Lynch syndrome; Panel tests

Introduction

Over twenty years have elapsed since the cloning of the *BRCA1* and *BRCA2* genes (*BRCA1/2*), key discoveries that fostered the appreciation of germ-line genetic analysis in high risk individuals and the introduction of genetic risk assessment into the routine care of women at risk for breast cancer (BC) and ovarian cancer (OC)[1]. Guided by expert recommendations from the National Comprehensive Cancer Network (NCCN), the US Preventive Services Task Force (USPSTF), and others, testing that was initially reserved for only the highest risk patients evaluated in a tertiary care setting has expanded into the

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Conflicts of interest

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practices of specialists and primary care physicians, including obstetrician/gynecologists and gynecologic oncologists [1–3]. Research has provided a clearer understanding of the risks of cancer associated with mutations in *BRCA1/2* [4, 5], the mismatch repair (MMR) genes of Lynch syndrome (LS) including *MLH1*, *MSH2*, *MSH6* and *PMS2* [6], and in other genes, and has supported the development of evidence-based practices and guidelines toward cancer prevention employing surgical prophylaxis, intensive screening, and chemoprevention [1, 2, 7]. Further, a multitude of behavioral health research has provided a clearer understanding of how perceptions of cancer risk impact health behaviors, communication, and family functioning. Among the achievements in the past 25 years of genetic risk assessment includes a much expanded understanding of ovarian cancer genetics, the introduction of universal colorectal cancer (CRC) and endometrial cancer (EC) tumor screening for LS at many centers, and the characterization of new genes that contribute to women's cancer risks (see Table 1).

Recently, the transition to next-generation sequencing (NGS) platforms has begun to reshape the field of cancer genetics and has broadened the clinician's options for quantifying cancer risk. The increased speed and lower cost associated with NGS-based DNA sequencing has led to the rapid clinical availability of multi-gene panels for risk assessment. In tandem with the landmark Supreme Court decision overturning patent protection for *BRCA1/2* testing, the past 2 years have seen an explosion of new gene panel options for diverse indications. A selection of currently available (as of October 1 2015) panel tests relevant to gynecologic malignancies may be seen in Table 2. Current commercial panels test a selection of genes and are often focused on a particular tumor or population, but may also assess risks across a number of cancer genes, tumor types, or syndromes (e.g. a panel of 12 genes associated with hereditary OC). Other advancements in clinical genetics are also impacting women's health. For example, universal LS screening of all cases of EC is helping to refine our understanding of the prevalence of LS and penetrance of the LS genes.

Among the goals of this manuscript is to broaden the awareness of genes and syndromes that may impact the care of women, and to summarize current data on prevention options and their consequences. Further, we will present clinical scenarios wherein both the benefits and drawbacks of panel testing may be appreciated. Ultimately, our hope is that women's health practitioners will gain a greater awareness of their central importance in identifying and mitigating hereditary cancer risks in women. With this knowledge, the growing complexity of cancer risk assessment will also be appreciated, as well as the importance of seeking support from genetics professionals to ensure that patients are aware of the risks and understand the results and implications of their testing.

Cancer syndromes with gynecologic manifestations

Genetic testing for hereditary cancer risk makes feasible cancer prevention through intensive screening, surgical prophylaxis, and chemoprevention. Identifying causative genetic mutations allows women to get an estimate of their lifetime risks for OC and EC in an effort to support informed decisions about managing cancer risks and subsequent lifestyle decisions such as childbearing. Another advantage of risk assessment is the decrease in the anxiety for those women in a family with a known genetic predisposition to a gynecologic

cancer but who are, upon testing, found to be “true negative” or non-carriers of a familial gene.

Common cancer syndromes with gynecologic cancer risks: Hereditary Breast-Ovarian Cancer (HBOC) and Lynch syndrome (LS)

Evidence for an autosomal-dominant inherited trait predisposing women to both BC and OC was first reported by Lynch et al in the 1970s. This predisposition would later be known as hereditary breast-ovarian cancer (HBOC) [8]. Around the same time, hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome (LS) was also described as an inherited predisposition to CRC and other cancers, including EC and OC [9, 10]. Today, experts appreciate that mutations in the tumor suppressor genes *BRCA1* and *BRCA2*, associated with HBOC, and mutations in the mismatch repair genes associated with LS (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) are very common, found in approximately 1/500 and 1/300 individuals, respectively. Indeed, these two syndromes underlie a substantial portion of BC (10%), OC (10–15%), CRC (3–5%), and EC (2–3%) in the population.

Both *BRCA1* and *BRCA2* gene mutations are associated with an increased risk of breast and OC. *BRCA1* mutation carriers are at high risk of early-onset BC and especially the triple negative BC subtype. Other cancer risks associated with *BRCA1/2* mutations include second breast cancer, male breast cancer (*BRCA2*), pancreatic and prostate cancers, and melanoma [4, 5]. The cumulative life-time risks of ovarian cancer associated with these genes differs based on multiple factors, such as the disease penetrance of each gene, population and study methodology, or ascertainment bias [11]. The risk of *BRCA1*-associated OC is higher than that associated with *BRCA2* mutations, as studies have shown that in high-risk *BRCA1/2* families the OC risk by age 70 in *BRCA1* carriers is 44–63% and in *BRCA2* carriers 27–31% [12]. *BRCA1*-associated OCs occur an average of 5–10 years prior to sporadic OCs, *BRCA2*-associated OCs occur, on average, at the same age as sporadic OCs [11].

Carriers of LS mutations are at risk of numerous cancers such as CRC, EC and OC, and other cancers including stomach, small bowel and genitourinary tumors (e.g. renal pelvis), brain cancer (Turcot syndrome), and skin manifestations (Muir-Torre syndrome). Cancer risks have some variability across the LS genes—*MLH1* and *MSH2* are most strongly associated with early-onset CRC and EC, while *MSH2* has more extra-colonic manifestations. *MSH6* mutations are somewhat rarer and associated with later onset CRCs and a higher risk of EC. Finally, data appear to suggest germ-line *PMS2* mutations may be less penetrant than the other LS genes [6, 7, 13].

Until recently, the consensus opinion has been that 10–15% of unselected OC have a genetic predisposition, but data now clearly indicate that HBOC and LS underlie at least 20%. *BRCA1/2* mutations are responsible for the majority of epithelial OC associated with HBOC [14]. Women with LS are at 5–15% lifetime risk of OC, compared to the 1.4% risk in the general population [15]. Another 5% (total 25% of all OC) are due to a pathogenic mutation in a gene other than the *BRCA1/2* or the LS genes [14, 16]. Several other genes associated with OC are known and are discussed below. In LS, EC incidence may be as high as that of CRC [10] and more than half of the affected women with LS usually present with a gynecologic malignancy (usually EC) as their index cancer [17]. The fraction of ECs

attributed to genetic predisposition is not as well-defined; however, 2–6% of EC can be linked to LS alone [18].

Rare syndromes with gynecologic manifestations: Peutz-Jeghers syndrome; Cowden syndrome (CS); Reed syndrome or Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC); Li-Fraumeni-syndrome (LFS); Polymerase Proofreading Associated Polyposis (PPAP)

A growing number of rare syndromes are associated with gynecologic cancers and manifestations. Mutations in the *STK11* gene, which is a tumor suppressor gene, comprise Peutz-Jeghers syndrome (PJS), a rare (1:20,000) autosomal dominant disease manifesting as muco-cutaneous pigmentation, gastrointestinal hamartomas, increased risk of breast, ovarian and cervical neoplasms. Ovarian tumors include benign sex cord tumors with annular tubules (SCTATs)[19], dysgerminomas, granulosa cell, Brenner, and Sertoli cell tumors. SCTATs differ in patients with PJS where they are often multifocal, bilateral, and small [19]. PJS is also associated with minimal deviation adenocarcinoma (MDA), previously known as adenoma malignum of the cervix, with an estimated 15–30% lifetime risk, and an earlier age of onset in PJS vs non-PJS patients (mean age 33 years vs 55 years, respectively).

PTEN hamartoma tumor syndrome or Cowden syndrome (CS) is due to an autosomal dominant mutation in the *PTEN* gene which increases the risk of cancer in multiple organ systems including cancers of the endometrium (estimated lifetime risk of 28%), breast and thyroid (follicular type)[20]. Patients with CS can also develop a mixed polyposis of the small and large intestines. Benign manifestations of CS include large head circumference (>57 cm), skin lesions (trichilemmomas, lipomas), uterine fibroids and thyroid disorders (multi-nodular goiter).

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) or Reed syndrome is caused by germ-line mutations in the fumarate hydratase (FH) gene, and is characterized by an increased risk of type 2 papillary renal cell carcinoma and uterine tumors (leiomyomas and leiomyosarcomas) [21]. The risk of leiomyosarcoma is less well defined in this group. Many carriers are also affected by painful cutaneous leiomyomas.

Patients with Li-Fraumeni syndrome (LFS) carry germ-line mutations in the *TP53* gene and are at risk of a number of cancers including OC and EC. LFS is also known as SBLA syndrome for sarcoma, breast, leukemia, and adrenal gland cancers. LFS tumors include soft tissue or osteosarcomas, brain tumors, premenopausal breast cancers, leukemias, adrenal cortical carcinomas, and bronchoalveolar lung carcinomas [22]. While classic LFS is highly penetrant (nearly all carriers develop cancer), emerging data suggest an attenuated Li-Fraumeni Like syndrome (LFLS) may also exist [22]. LFS-associated OC seems to have an earlier age of onset, with a median age of 39.5 years of age, compared with 64.3 years of age for sporadic OC.

Finally, Polymerase Proofreading Associated Polyposis (PPAP) syndrome is characterized by mutations in the exonuclease proofreading domain of two DNA polymerase tumor suppressor genes (*POLE* and *POLD1*). Recent research has described an increased risk of EC associated with *POLD1* mutations [23]. Mutation carriers also are at risk of early-onset

CRC and polyposis (small and large bowel). *POLD1* mutations are rare (<1%) among unselected EC [23]. Interestingly, while germ-line *POLE* mutations are not associated with EC risk, somatic *POLE* mutations have been shown to portend improved PFS in EC [24].

Genes in the Fanconi Anemia pathway associated with gynecologic cancers: RAD51C, RAD51D, BRIP1, MRE11

The Fanconi Anemia (FA) pathway is critical to homologous recombination and repair of double-strand DNA breaks. Pathogenic mutations in some genes in the FA pathway were initially linked to a moderate increase in the risk of BC [*CHEK2*, *BARD1*, *MRE11A*, *NBN* (*NBS1*), *RAD50*, *RAD51C*, *RAD51D*, *BRIP1* (*FANCF*)], while *PALB2* (*FANCD1*) has been associated with high risk of BC. Recent data indicate risk of OC is also increased with FA family mutations. *RAD51C* mutations were seen in 6/480 families (1.3%) with both BC and OC [25]. The lifetime risk of OC associated with *RAD51C* mutations is elevated up to 9% [26]. The relative risk of OC for carriers of *RAD51D* mutations is estimated at 6.3 (95% CI 2.9–13.9) [27]. Further, mutations in *BRIP1* have been associated with a relative risk of 11–14 for invasive epithelial OC and high-grade serous disease, respectively, with a lifetime risk of approximately 6%. Heikkinen et al. have reported increased risk of OC with mutations in the MRE complex genes, including *MRE11*, *NBS1*, and *RAD50* [28].

Management of genetic risk for gynecologic cancers: screening, surgical prophylaxis, and chemoprevention

Recognizing that a substantial portion of the deadliest adult cancers associated with an inherited genetic mutation are specific to women's reproductive organs, it is not surprising that the roles of the gynecologist and gynecologic oncologist are considered integral to all steps of hereditary cancer risk management. Their contribution includes initial identification of high risk patients, screening procedures like bimanual exam, trans-vaginal ultrasound and endometrial biopsy, prophylaxis via TAH and/or BSO, and chemoprevention. Further, gynecologists also serve a central role in the management of the secondary repercussions of efforts to mitigate increased cancer risks, including vasomotor symptoms, sexual function, bone health, cardiovascular disease, and mental health. In the following section, basic principles of cancer prevention, reproduction, and factors important to quality of life are reviewed for patients with hereditary risk of cancer.

Ovarian Cancer (OC)

Screening—OC is one part of a spectrum of pelvic high grade serous cancers which also include fallopian tube and primary peritoneal cancer. There is no proven effective screening for OC, which is often discovered at an advanced stage (57% Stage 4) when the survival rate is poor (75% at one year, 44% at 5 years [1]). Many studies have investigated methods, including transvaginal ultrasound and/or serum CA125 testing, to screen high risk women [29], but these studies have failed to identify OC at lower stages or show an improvement in overall survival [30]. In fact, harm was demonstrated in the form of increased surgical complication rates in women undergoing surgery after a false positive screening test [1, 30].

Surgical prophylaxis—One of the clear benefits of knowing a patient's mutation status is the option to use risk-reducing surgical prevention in the form of prophylaxis. Expert guidelines including the National Comprehensive Cancer Network (NCCN) support the option for prophylactic surgery, including risk reducing salpingo-oophorectomy (RRSO) and/or total abdominal hysterectomy (TAH), after childbearing in *BRCA1/2* and LS mutation carriers [1]. Women with other gynecologic issues, such as abnormal pap smears, fibroids or pelvic pain, may consider TAH along with RRSO. For women with *BRCA1/2* mutations, RRSO is recommended between ages 35–40 when childbearing is complete. The recommended age is due to early age of onset of OC in *BRCA1/2* carriers; without intervention, 3% of women with *BRCA1* mutations are diagnosed with OC by age 40 and 21% by age 50 [4, 31]. There are currently no specific guidelines for other genes associated with OC or EC (*RAD51C/RAD51D/TP53/POLD1*) in terms of targeted age recommendations for prophylactic surgery. Women who choose RRSO must consider the optimal time for this surgery, a decision that is often one made in conjunction with a gynecologist and can significantly impact childbearing, contraception, and management of vasomotor symptoms.

RRSO reduces the risk of OC by ~75–96%; however *BRCA1/2* mutation carriers still carry a persistent risk (3–4%) of primary peritoneal cancer after RRSO [32, 33]. The impact of RRSO on breast cancer risk reduction remains controversial at this time. However, Domchek et al.[34] estimated a beneficial effect of RRSO on mortality in *BRCA1/2* mutation carriers: the hazard ratio after RRSO was 0.40 for all-cause mortality, 0.44 for BC-specific mortality and 0.21 for OC mortality.

Approximately 2–17% of women having RRSO for prophylaxis may have an occult cancer at the time of surgery. Serous tubal in situ carcinoma (sTIC), a precancerous tubal lesion, has also been identified in this population and is frequently located in fimbriated end of the fallopian tube adjacent to the ovary. The existence of tubal precancerous lesions has further led to the theory of the fallopian tube as the origin for pelvic serous cancers, which may impact preventive options for *BRCA1/2* carriers. If ongoing studies can demonstrate that prophylactic salpingo-oophorectomy with delayed bilateral oophorectomy (PSDO) is as effective as RRSO prior to age 40, this option would permit high risk women to avoid surgical menopause and its negative impact on quality of life. However, this option would notably offer no benefit for reduction of BC or OC risk, and thus, prophylactic salpingectomy alone is discouraged by NCCN guidelines outside a clinical trial.

Chemoprevention—Oral contraceptive pills (OCPs) have been shown to decrease the risk of OC. Narod et al first published evidence supporting a 50% reduction in OC with long-term use of OCPs [35]. In fact, OCPs have a duration dependent benefit (i.e. the longer the use, the greater duration of risk reduction). Among the potential limitations of OCPs for OC prevention is a concern for increased BC risk, although studies to date have shown somewhat conflicting results. While no randomized controlled data exist, several retrospective analyses have associated an increased risk of BC with ever using OCPs and longer duration of use [36, 37].

Endometrial cancer (EC)

Screening—Women with hereditary risk for EC have the option of surveillance with trans-vaginal ultrasound and endometrial biopsy, though these options, per NCCN guidelines, are not supported by data [7]. Nonetheless, screening can be considered if a patient has not completed childbearing, or is not ready or able to have prophylactic surgery. Irregular or postmenopausal bleeding is an early, identifiable symptom for EC. Women at risk for EC should be counseled to report any abnormal uterine bleeding [7].

Surgical prophylaxis—Prophylactic hysterectomy and RRSO is 100% protective against EC and OC in patients with LS [38] and should be considered by women who have completed childbearing. One study of known mutation carriers [38] found that half of women choosing prophylactic surgery do so after the age of 40 (25% > 45 years of age, median age 41 years). The median age of EC and OC diagnosis in this study was 46 and 42 years, respectively, with 6% of EC and 17% of OC diagnosed < 35 years [38].

Chemoprevention—A recent meta-analysis of 36 studies including 27,000 women with EC demonstrated that OCPs have a long-term benefit for reducing risk for EC in average risk women [39]. For every 5 years of OCP use, EC risk is reduced by 24%, and 10–15 years of use decreases risk by ~ 50%, regardless of the formulation used. The reduction in risk continues for at least 30 years; however, OCP use is not protective against sarcomas or high grade ECs. A recent study has also reported reduced risk of EC in women with LS who took OCPs for 1 year or more. In fact, there was increased risk reduction of endometrial cancer with longer duration of oral contraceptives [40]. Finally, an international randomized study has reported that high-dose aspirin (600 mg/day for at least 2 years) lowers the risks of extra-colonic tumors in LS by ~30% [41]. While clearly very promising, expert guidelines have been hesitant to endorse these benefits without further validation in additional studies [7].

Reproductive and sexual health considerations

Fertility

Women considering prophylactic surgeries have important issues to consider regarding timing of pregnancy, increased cancer risks with advancing age, and fertility issues. Further, the wider availability of reproductive technologies such as pre-implantation genetic diagnosis (PGD) may add further complexity to reproductive decisions. Some evidence suggests that fertility may be compromised in *BRCA1/2* mutation carriers through a negative effect on ovarian reserve caused by early accelerated oocyte apoptosis and depletion [42], leading to premature menopause. Population studies have found earlier age of menopause in *BRCA1/2* carriers compared to the general population, though not all studies have identified an impact on fertility or parity [33, 43]. These studies are important to share with women with *BRCA1/2* mutations, as this information may impact childbearing decisions. Fertility preservation is an option for women at risk for GYN cancers considering definitive surgery, and may necessitate reproductive endocrinology and infertility (REI) referral. For mutation carriers who are considering RRSO, embryo or oocyte cryopreservation is an option to preserve fertility prior to RRSO. A clear association of

fertility drugs to OC has to date not been definitively established. Women who are considering prophylactic hysterectomy can also consider 3rd party reproduction (surrogate).

Pre-implantation genetic diagnosis (PGD)

Another reason for mutation carriers to consider REI referral is for the purpose of PGD. REI specialists are able to test an embryo for the known genetic mutation and select an unaffected embryo. However, some health care providers and patients may not consider PGD due to personal or religious beliefs. Patient attitudes regarding PGD have been studied by a national advocacy group for *BRCA1/2* carriers (FORCE). While an overall low level of awareness (20–32%) of the option for PGD was noted among conference participants, approximately one-third thought PGD was an acceptable option to reduce risks of a child inheriting a known mutation. Positive attitudes toward PGD were associated with greater awareness of PGD, desire for more children, and previous pre-natal genetic testing [44].

Menopause, sexual considerations, and quality-of-life after RRSO

Approximately 60–70% of women with a *BRCA1/2* mutation elect to have RRSO between the ages of 35–70 [45]. Those with OC in their family are more likely to opt for RRSO [46]. Once a mutation carrier decides to move forward with oophorectomy, she faces myriad short- and long-term effects of surgical menopause. These include hot flashes and mood changes in the short-term, and long-term effects of vaginal dryness and sexual dysfunction in addition to increased risk of bone loss and cardiac disease. The major side effects of surgical menopause following salpingo-oophorectomy are summarized in Table 3.

QOL after RRSO has been extensively studied. Common themes include fewer cancer related worries in RRSO patients but also more menopausal symptoms and sexual dysfunction. Prospective studies have shown that RRSO (vs screening) may decrease sexual frequency up to one year after surgery [47] and lead to sexual dysfunction for up to 5 years. Finch et al found that *BRCA1/2* mutation carriers who elected for RRSO but took hormone replacement therapy post-operatively had less hot flashes and vaginal dryness, but still experienced decreased sexual satisfaction [33]. Patients have reported the need for more information regarding the impact of surgery on their sexual health and the availability of sex therapy [48].

Evolution of cancer risk assessment: Universal Lynch syndrome screening and multi-gene panel testing

Family history and predictors of genetic risk of cancer

The cornerstone of cancer risk assessment remains the review of family history, the appreciation of physical findings related to genetic syndromes (e.g. café-au-lait spots, large head circumference), and the construction of a detailed pedigree that includes ages of cancer diagnosis, ages and causes of death, and documentation of complex familial relationships (e.g. consanguinity). Online tools are available to assist patients in the organization of family history [49]. Guidelines to guide identification of patients appropriate for risk assessment are available from a number of professional organizations including the American Congress of Obstetricians and Gynecologists (ACOG), the Society of Gynecology

Oncology (SGO), the American Society of Clinical Oncology (ASCO), and the US Preventive Services Task Force (USPSTF) [1, 2, 50, 51]. While a plethora of factors are known to predict genetic risk of cancer, an abbreviated list of high-risk characteristics that may be useful in the routine care of women are provided in Table 4.

Founder mutations and common/recurrent mutations

A patient's ancestry can also offer a clue to cancer risks. In 1997, Struwing et al reported that individuals of Ashkenazi Jewish (AJ) ancestry (Eastern/Western European origin) had a markedly increased risk (~2%) of carrying a mutation in *BRCA1* (187delAG, 5382insC) or *BRCA2* (6174delT). Founder mutations in *BRCA1/2*, the MMR genes of LS, and other genes have since been described in other ancestral groups. In addition, founder mutations have been described in other cancer risk genes, including the *CHEK2* 1100delC mutation, and in the MMR genes of LS such as the American founder mutation in *MSH2*. In past years, the low cost of identifying a finite set of common mutations for a particular group of patients offered the option of efficiently screening a population for recurrent mutations. Yet except for *BRCA1/2* founder testing in AJ patients, examples of ancestry-based screening for cancer risk on the population level do not exist. Further, with the emergence of NGS-based DNA sequencing, the cost disparity of testing for a few recurrent mutations versus sequencing many genes or even whole genomes has narrowed significantly, thus diminishing the value of this approach.

Universal Lynch syndrome screening

In 2008, investigators from Ohio State University established the feasibility of screening incident CRC tumors for LS using immunohistochemical (IHC) staining and microsatellite instability (MSI) testing. They found ~3% of CRC were associated with a germ-line LS mutation, and demonstrated the low sensitivity of the Revised Bethesda Guidelines (RBG) for detecting germ-line mutations (RBG missed 25% of mutations)[52]. A companion analysis showed cost-effectiveness of their screening approach [53]. Since then, universal LS screening employing IHC, MSI or both tests has been adopted at the majority of NCI-designated cancer centers nationwide as well as many community hospitals. Taken in perspective, universal LS screening is the first example of a routine genetic risk test used to screen a defined population of individuals (incident CRC) for a hereditary cancer risk, and serves as a model for the future development of new NGS-based screening tests for genetic cancer risk.

Many centers also screen all incident endometrial cancers for LS (prevalence ~2%), in line with the 2014 Society of Gynecologic Oncology recommendations that all women with EC receive personal/family history and/or molecular screening for LS [54]; however, optimal procedures for molecular screening remain unclear [55]. For instance, some institutions have opted for age delimited screening (e.g. only screening patients < 60 years). Others include immediate *MLH1* promotor methylation testing when tumors lack expression of *MLH1/PMS2* by IHC to reduce false positive screens. This is because somatic *MLH1* promotor methylation, a sporadic event in tumors, accounts for 80% of all positive tests where *MLH1/PMS2* are absent, and methylation testing will clarify most of these results. Ultimately, both IHC and MSI are acceptable modalities for screening, with IHC offering the additional

advantages of being accessible for laboratories that lack molecular expertise and providing information on which proteins or gene may be affected. At our center, a universal screening approach that begins with reflex IHC screening of all EC and CRC (both without age limitations), and incorporates reflex MSI testing for equivocal IHC results only (e.g. unclear or atypical staining or expression) and MLH1 methylation testing (as a send out) only when initiated by the genetics team, was developed by a multi-disciplinary team of experts and has been in place since 2011 [56]. Among the benefits of universal LS screening is the elimination of system-level, provider, and family-history derived biases that may negatively impact referral of high-risk patients for risk assessment, and evidence supporting the cost favorability of this approach [57–59]. Nonetheless, weaknesses with the universal screening approach also exist, including the more frequent detection of families with low-penetrance mutations, bringing to light the question of need for intensive screening in these families, the high false positive rate as mentioned above, and the challenges of patient follow-up after a positive screen result [13, 60, 61].

NGS-based panel testing

Beginning in the late 1980's automated fluorescence-based sequencing using methods first described by Sanger became standard for DNA sequencing. Through 2013, commercial laboratories offered DNA sequencing for 1 or 2 cancer risk genes per test (e.g. *APC* or *BRCA1/BRCA2*). With the introduction of NGS, single gene tests are being replaced by testing conducted simultaneously on multiple genes. The advantages and disadvantages of panel testing have been reviewed extensively [62]. While a provider may be clinically most focused on only a handful of genes, one relative advantage of the panel test is the ability to examine multiple common and rare causes of cancer risk at the time of first presentation for testing rather than requiring patients to return for additional testing and counseling for each next test performed. For example, a patient with OC in the past may have endured 3–4 counseling visits while *BRCA1/2* and the MMR genes of LS were tested, while now these genes as well as rarer OC genes (e.g. *TP53*) can be tested simultaneously. Among the foremost limitations to panel testing is the inclusion of genes on some panels for which screening and prevention guidelines are still maturing. This creates a clinical conundrum where patients may receive test results of a mutation in a gene for which expert recommendations are limited or non-existent, placing providers in a challenging position to develop a prevention plan. Even more difficult, patients may receive an indeterminate result, indicating that due to insufficient testing experience for a particular gene, a result was identified whose significance is unclear. For patients and providers, this presents a potentially frustrating situation in that risks cannot be quantified, leaving patients and relatives with even greater uncertainty than they may have had before testing [62]. Finally, it is important for patients and providers to recognize that diagnostic genetic testing is constantly evolving as technologies become more powerful and incorporate more clinically relevant genes. Therefore, an indeterminate evaluation for LS in 2001 where only *MLH1* and *MSH2* sequencing was performed may be clarified in 2015 with panel testing.

Clinical cases from the Department of Clinical Genetics, Fox Chase Cancer Center

Through these case presentations, our goal is to highlight current challenges that gynecologists and gynecologic oncologists may face related to universal LS screening and panel testing.

Case presentation #1: Universal Lynch syndrome screening

RN, a 59 year old woman, underwent a TAH with complete surgical staging for a Stage IA (FIGO grade 3, endometrioid histology) endometrial adenocarcinoma. Her past medical history included hypertension and obesity (BMI 33). Her pedigree is seen in Supplemental Figure 1. Her parents were unaffected by cancer (mother died at age 53 in an auto accident; father died at 68 of myocardial infarction), and she has one sister who had BC (diagnosed age 67) who had a daughter with OC at age 41 (*BRCA1/2* testing in this individual was negative for mutation), and a maternal uncle with CRC (diagnosed age 74). Her 5 adult children are in good health (age range 19–34). Her EC IHC showed inconsistent MLH1 staining and clear loss of PMS2. She was initially disinterested in genetic counseling because of her perceived weak family history and negative *BRCA1/2* testing in her niece with OC (“she already had the genetic test”), but decided to carry forward after a strong recommendation from her doctor. Initially, MLH1 methylation testing was chosen because of her somewhat older age (59) and risk factors for EC (obesity), but MLH1 promotor methylation was not identified. Germ-line testing was pursued, and ultimately a *PMS2* mutation was identified. She was counseled about risks, screening and prevention for CRC, stomach cancer, and OC. She elected to have a RRSO.

This case highlights several important issues related to universal screening. Most importantly, screening EC cases for LS has improved detection of patients with germ-line LS, especially *PMS2* mutations. These mutations may exhibit lower penetrance, and can be missed family history criteria that rely on multiple affected family members. This case also illustrates the difficulty encountered with false positive IHC screening in EC. This patient’s age and obesity led to initial MLH1 promotor methylation testing as cause for her IHC result. Methylation testing can be a time and cost-burden to patients, and is not available on site at many centers. Finally, this case illustrates the importance of provider recommendation to seek counseling. Despite a positive screening test, the patient’s perceived genetic risk was low—this is not surprising in families with less penetrant family histories. Data from Heald et al [61] have suggested that sustained provider efforts are needed to be certain high risk patients on LS screening (IHC+ or MSI-H) receive appropriate follow-up. This is particularly important with universal LS screening because these patients more often have low perceived risk of having a genetic risk in the family. Patients often misunderstand genetic testing for cancer risks and the relevance of the result on their own behaviors, which can impact perceptions of risk. Finally, one must also remember that the patient’s small family size (only one sibling) and early maternal death can make hereditary cancer risks difficult to interpret—thus context is critical to consider when patients report family history.

Case presentation #2: Panel testing with unexpected finding

BG is a 40 year old woman who presented for risk assessment because of a personal history of thyroid cancer at age 27, and colon polyps (age 38)(Supplemental Figure 2). Her family history was notable for her mother with OC at age 48 and BC (age 68). She had a maternal aunt with BC at age 50, a maternal grandmother with CRC (age 70) and a paternal great aunt with OC in her 40's. Thinking that the most obvious hereditary syndrome for this family was *BRCA1/2*, it was suggested that BG's mother, MB, who had both BC and OC cancer, would be the most informative person to initiate testing. MB was tested for *BRCA1/2* (including rare mutation testing via the *BRCA1/2* BART test), and no mutation was found. Because of the history of CRC, MB then went on to a multi-gene panel and was found to have a deleterious mutation in the *PTEN* gene. BG was tested for the same mutation and was found to also be positive, explaining her early onset thyroid cancer and colon polyps. Based on her genetic test results, management recommendations for BG would include primary and secondary prevention options for BC, thyroid cancer, EC, CRC and kidney cancer. Both mammography and breast MRI screening for breast cancer and colonoscopy screening for CRC are recommended starting in the 30's. Renal ultrasound screening and random endometrial biopsies may be considered, although data is lacking on their effectiveness. BG should also consider risk reducing mastectomy and hysterectomy [1]. In addition to BG, her siblings and maternal cousins could benefit from site-specific testing for the *PTEN* mutation found in the family.

Case presentation #3: Panel testing with moderate penetrance gene

DB is a 43 year-old woman who presented with worry about her risk of OC and BC cancer (Supplemental Figure 3). She has no prior medical conditions and reports a healthy lifestyle. Her mother was diagnosed with BC at age 66. She has 3 healthy maternal uncles and a maternal aunt who was diagnosed with BC at age 64, who has a 43 year old daughter who was recently diagnosed with thyroid cancer. DB's maternal grandmother died at age 27 from a lung related infection and her maternal grandmother's sister died at age 40 of OC. DB's primary concern was her risk of OC. She had no relationship with her father's family. Because of the family history, particularly her maternal aunt's OC, she met criteria for genetic testing. While her mother or maternal aunt would have been a better candidate for genetic testing because they had cancer, her mother was not interested in testing. Therefore, DB was counseled and tested. Because of the variety of cancers in her family, a multi-gene panel was suggested, which identified a mutation in *BRIP1*.

BRIP1 is associated with a moderately increased risk of cancer. *BRIP1* has been shown to directly interact with the BRCT domain of *BRCA1* [63]. As a member of the Fanconi Anemia pathway, *BRIP1* is linked to DNA repair. *BRIP1* mutations have been linked to BC (about 20–25% lifetime risk) and OC (7–10% lifetime risk). It remains inconclusive whether this mutation was transmitted through her maternal lineage, as no one on that side of the family has received testing subsequently. This case illustrates that there are HBOC and other families for which the multi-gene panel testing allows the identification of mutations that may explain the familial pattern of BC and OC, mutations which otherwise would not have been found in step-wise or syndrome-specific genetic testing approach. The case also illustrates some of the limitations of panel testing. Here, we remain moderately uncertain

whether the *BRIP1* mutation caused the BC and OC seen in the family. As genetic knowledge is still evolving, providers must be cautious in the interpretation of new genes, since many of the cancer risks associated with these genes are poorly defined. In this example, DB's concerns for OC risk were addressed, and since several reports now indicate a link between *BRIP1* and OC, she can consider risk reducing BSO. Panel testing and the *BRIP1* mutation helped in the implementation of a primary prevention plan for her risk of OC, and it also helped in designing a plan for early detection of BC through the use of screening breast MRI.

Summary

Clinical genetics is rapidly evolving. The identification of new genes associated with hereditary OC and EC is expanding our ability to explain a greater fraction of familial cancer cases and offer predictive testing in families to quantify cancer risks and alert at-risk members. Further, advancing testing technologies, namely NGS-based panel tests, allow for increasingly rapid, inexpensive, and comprehensive evaluation of cancer risks. Finally, the evolution of novel approaches to screen patients for genetic risk, including universal tumor screening for LS, are allowing more high risk individuals to be identified, informed about their cancer risks, and provided options for risk reduction. It is anticipated that with these new approaches will come the ability to identify all high risk individuals before they develop cancer when cancers can be prevented through screening, prophylaxis, and chemoprevention. Finally extensive research into managing the implementation and side effects of prevention has permitted high risk women to increasingly maintain quality of life while mitigating cancer risks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Obstetrician/gynecologists and gynecologic oncologists are in a unique position to identify women at increased hereditary risk of cancer

Obstetrician/gynecologists and gynecologic oncologists frequently provide preventive options to their high-risk patients such as screening, prophylactic surgery, and chemoprevention

Cancer risk assessment is evolving with to include new genes and new multi-gene panel tests for women's hereditary cancer risk

Gynecologic cancers and conditions relevant to women's health, associated risk genes and disease penetrance, and cancer prevention options

Table 1

Disease site	Histology	Syndrome	Gene	Cancer Penetrance	Prevention*	Screening*
Ovary	Adenocarcinoma	Hereditary Breast/Ovarian Cancer (HBOC)	BRCA1, BRCA2	16–54%	Surgical Risk reducing salpingo oophorectomy (RSO) Chemoprevention Oral contraceptives	Transvaginal ultrasound Tumor marker monitoring (CA-125)
		Lynch/Hereditary Non-Polyposis Colorectal Cancer (LS/HNPCC)	MLH1, MSH2, MSH6, PMS2	4–24%		
		Li Fraumeni	TP53	Not well defined		
		Moderate penetrance genes	RAD51C, RAD51D, BRIP1	Not well defined. Up to 10%		No guideline specific recommendations; insufficient evidence to recommend RRSO per NCCN [1]
Uterine Corpus	Sex cord stromal tumors	Peutz Jeghers (PJS)	STK11	21%	No guideline specific recommendations	
	Adenocarcinoma	Lynch/Hereditary Non-Polyposis Colorectal Cancer (LS/HNPCC)	MLH1, MSH2, MSH6, PMS2	15–60%	Prophylactic abdominal hysterectomy and salpingo-oophorectomy (TAHBSO)	Transvaginal ultrasound Endometrial biopsy
		Cowden	PTEN	May approach 28%	Prophylactic hysterectomy	
		Polymerase proofreading associated polyposis (PPAP)	POLD1	Not well defined	No guideline specific recommendations	
	Uterine leiomyoma	Hereditary Leiomyomatosis Renal Cell Cancer (HLRCC, Reed syndrome)	FH	Common	No guideline specific recommendations	
Cervix	Uterine Leiomyosarcoma	Cowden	PTEN			
	Adenoma malignum	Li Fraumeni	TP53	Not well defined		
		Peutz-Jeghers (PJS)	STK11	10%	No guideline specific recommendations	

* Providers should consult guidelines for recommendations on evidence-based screening in each syndrome

commercial panels and genes examined

[illegible]

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Actionable genes are defined as those with consensus guidelines for medical management of ovarian or uterine cancer risk, e.g. USPSTF, NCCN
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Some labs listed have additional comprehensive cancer panels with inclusion of supplementary genes related to colon, kidney, or other cancer risks.

Table 3

Short- and long-term side effects of surgical menopause

Side effect	Incidence	Treatment options	Details
Vasomotor symptoms	30–80% of general population in menopausal women	-Premenopausal women who undergo RRSO are candidates for HRT -Short term use of HRT can be used up to age of menopause in unaffected women without increasing risk of BC [64] -National societies support use of HRT in women with early menopause until age of natural menopause is reached -Other medications including anti-depressants (Effexor), gabapentin and clonidine can be used for symptom relief	-Premenopausal women with a history of BC are not candidates for HRT -Combination HRT for women with a uterus is required to prevent EC -some women will not feel comfortable using hormones regardless of severity of symptoms -Some antidepressants interfere with Tamoxifen
Vaginal dryness	28–35% report vaginal dryness [48]	-Vaginal estrogen (estrogen cream, vagifem tablets, vaginal ring) can be used for dryness and dyspareunia -Also newer oral option in Ospemifene (new selective estrogen receptor modulator shown to be safe in postmenopausal women but not studied in breast cancer patients) [65] -First line treatments include vaginal moisturizers and lubricants	-Vaginal estrogens can be considered even in women with BC
Sexual dysfunction/decreased libido	Up to 54% (mean 5 years after RRSO for BRCA carriers)	-Include as part of assessment before and after surgery and at each follow up visit; women cite need for provider to bring up the topic -Those with persistent lack of libido or sexual satisfaction should be referred to a sex therapist	-HRT does not reverse effect of impaired sexual function (loss of desire and less satisfaction) after BSO -there is no data on effectiveness or safety of androgen replacement -Low or absent desire is the most common sexual dysfunction in women and is often multifactorial [66].
Loss of bone density	50–50% osteoporosis; 7–12% osteopenia	-In women age 50–59, 54% osteopenia and 7% osteoporosis in BRCA+ patients after RRSO and avg. age of 50: 55.6% had osteopenia, 12.1% had osteoporosis [67] -Identifying women at risk for bone loss can allow for intervention before fracture/morbidity -DEXA 1–3 years after RRSO -Recommend calcium, vitamin D and weight-bearing exercises to all patients -Refer to specialist for any patient with levels consistent with osteoporosis	-Many carriers have multiple risks for loss of bone density including use of aromatase inhibitors for those with BC -Use of HRT immediately after RRSO can mitigate the risk of bone loss
Cardiovascular disease	-Early menopause due to BSO increases the risk of CVD 2–4 times compared to natural menopause at 50 [68]	-One study found women who had BSO <45 and did NOT take estrogen had increased risk of death from all causes -Health care providers may be under prescribing HRT in unaffected premenopausal women for QOL and cardioprotection; women who have RRSO prior to natural menopause are at increased risk of CVD, and this risk may be attenuated with estrogen replacement	-Cardiovascular disease is the main cause of morbidity and mortality in the United States -HRT in premenopausal women after BSO is protective [33, 69]
Metabolic syndrome	-Post-menopausal status has been found to increase risk for metabolic syndrome of 60%	-Metabolic syndrome is a group of metabolic disorders including glucose intolerance, insulin resistance, central obesity, dyslipidemia and HTN; metabolic syndrome increases risk of CVD -RRSO has been associated with a higher risk of metabolic syndrome [70]	-Study [70] had a cross-sectional design so cause and effect cannot be established but association of RRSO and metabolic syndrome was confirmed -Use of HRT did not have an impact on rates of metabolic syndrome

Abbreviations: HRT (hormone replacement therapy, BC (breast cancer), RRSO (risk reducing salpingo-oophorectomy), BSO (bilateral salpingo-oophorectomy), CVD (cardiovascular disease); EC (endometrial cancer); QOL (quality of life)

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Table 4

Personal and family history and clinical characteristics associated with an increased risk of a cancer syndrome that includes a gynecologic malignancy

Characteristic	Clinical benchmark/example
Historical	
Early-age of cancer onset	Breast cancer diagnosis < 40 years; other cancer diagnosis < 50 years
Diagnosis of > 1 type of cancer	Diagnosis of colon and endometrial cancer
Diagnosis of same cancer > 1 time	Diagnosis of right breast cancer at 45 and a second right breast cancer at 55
Bilateral cancer	Diagnosis of bilateral breast cancer
Rarer cancers	Dysplastic gangliocytoma of the cerebellum (Cowden syndrome) Small bowel cancers, bile duct/gallbladder cancers, renal pelvis cancers (Lynch)
Tumor histologic characteristics	
Distinct high-risk pathology	
Breast cancer	Triple negative breast cancer (associated with BRCA1 mutations)
Ovarian cancer	
BRCA1/2 associated	More likely serous or endometrioid or clear cell; high grade; stain strongly for TP53
Lynch-syndrome associated	More likely endometrioid or clear cell
Endometrial cancer	Endometrioid endometrial cancer (Lynch); Microsatellite instability (Lynch syndrome); Lower uterine segment tumors (~30% are Lynch syndrome)
Sex cord stromal tumors	Suggestive of Peutz-Jeghers along with other cancer history
Adenoma malignum of cervix	Suggestive of Peutz-Jeghers along with other cancer history
Ancestry/race/ethnicity	
High-risk ancestral group	Ashkenazi Jewish individuals and increased risk of BRCA1/2 mutations
Non-cancer history/exam findings	
Skin findings	
Sebaceous skin cancers	Feature of Lynch syndrome/Muir-Torre variant
Trichilemmomas	Feature of Cowden syndrome
Papillomatous papules	Feature of Cowden syndrome
Acral keratoses	Feature of Cowden syndrome
Painful cutaneous leiomyomatosis	Feature of hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)
Other features	
Fibroid uterus	Features of Cowden syndrome/Hereditary Leiomyomatosis and Renal Cell Cancer
Large head circumference	Feature of Cowden syndrome