17 Role of Genetics in Gynaecological Cancers

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17.1 Introduction

Advances in testing technologies, bioinformatics, falling costs, growing clinical applicability and increasing societal awareness has led to a surge in genetic testing for cancer susceptibility genes (CSGs). Over the years, genetic testing for gynaecological cancers has expanded rapidly, offering unprecedented insights into the heritability of certain cancer types, as well as new opportunities for diagnosis, treatment, and prevention. Understanding of key aspects of the genetics of gynaecological cancer and its applicability to clinical care has now become an essential part of clinical practice. In this chapter, we describe what a clinician working in women's health and oncology needs to know about genetics of gynaecological cancers, to offer optimal care to their patients.

Around 2.9 million women worldwide and ~88,000 UK women are diagnosed with ovarian cancer (OC), breast cancer (BC), endometrial cancer (EC), or colorectal cancer (CRC) every year. Around 1.05 million women worldwide and 25,000 women in the UK will die from these cancers each year [1–3]. These cancers account for ~50% cancers in women [3]. GLOBOCAN predicts these cancer cases will rise by 20–36% and deaths by 36–47% in UK women; while cases will increase by 27–53% and deaths by 49–69% in women worldwide over the next 20 years [2], leading to a huge increase in disease burden.

Studies from twins suggest that inheritable factors account for ~22% of ovarian cancer (OC), ~27% of breast cancer (BC) and ~35% of CRC risk [4]. Inheritable 'pathogenic and likely pathogenic variants' or 'mutations', here forth called 'Pathogenic variants' or 'PVs' in moderate to high penetrance CSGs account for around 15–20% OC [5, 6], 4% BC [7, 8], 3% EC [9] and 4% CRC [10, 11] with a majority being potentially preventable. See Table 17.1 for a list of relevant genes, associated cancer risks and corresponding risk management options.

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Table 17.1 Genes, relevant cancer risks and management options

	Cancer risks %				Risk management options				
GENE	BC	OC	CRC	EC	BC	OC	CRC	EC	Other
[a]*BRCA1/* [12]	−72	−44			RRM [13], CP (SERM), [14] [b]Screening (MRI, Mammogram) [15]	RRSO [16] RRESDO [17, 18]			Lifestyle Reproduction Contraception, PND, PGD
BRCA2	69	17							
[a]*PALB2* [19]	53	5							
[a]*RAD51C* [20]	21−	11−			[b]Screening (Mammogram) [15]				
RAD51D	20	13							
[c]*BRIP1* [21]		6							
[d]*MLH1* [22–24]		11	48	37		Hysterectomy and BSO [25]	Screening (Colonoscopy) [26]Surgical Prevention, CP (Aspirin) [27]	Hysterectomy [25] Annual USS, hysteroscopy and endometrial biopsy	
[d]*MSH2*		17	47	49					
[d]*MSH6*		11	20	41					
[d]*PMS2*[e]		3	10	13					

RRM Risk Reducing Mastectomy, *RRSO* Risk reducing Salpingo-oophrectomy, *RRESDO* Risk reducing early salpingectomy and delayed oophorectomy, *BSO* Bilateral Salpingo-oophorectomy, *Hyst* hysterectomy, *SERM* Selective Estrogen Receptor Modulators, *PGD* Pre-implantation Genetic Diagnosis, *PND* Prenatal Diagnosis, *CP* chemoprevention

[a]Breast and Ovarian cancer genes

[b]NHS High risk Breast Cancer Screening Programme

[c]Ovarian cancer gene

[d]MMR or Lynch Syndrome genes

[e]BSO is not recommended for *PMS2* as ovarian cancer risk is similar to population level risk

17.2 Cancer Syndromes

The common cancer syndromes encountered in gynaecological practice are associated with autosomal dominant gene mutations. These include Hereditary Breast and Ovarian Cancer (HBOC), Hereditary ovarian cancer (HOC) and Lynch Syndrome (LS). Other rarer conditions which contribute only a small proportion to the spectrum include Cowden's, Peutz-Jeghers and Li-Fraumeni syndromes. See Table 17.2 for a list of syndromes and associated cancers.

Hereditary Breast and Ovarian Cancer (HBOC) Includes families with multiple cases of breast and ovarian cancer. Important genes implicated include high penetrance *BRCA1*, *BRCA2*, *PALB2*, and moderate penetrance *RAD51C*, *RAD51D* genes.

Hereditary Ovarian Cancer (HOC) Includes families with multiple cases of ovarian cancer only. Important genes implicated include high penetrance *BRCA1*, *BRCA2*, *PALB2;* and moderate penetrance *RAD51C*, *RAD51D*, *BRIP1* genes.

Lynch Syndrome (LS) The tumour spectrum comprises a number of cancers of which colorectal cancer (CRC), EC, and OC are the commonest. Additionally, it includes gastric, small bowel, hepatobiliary, brain, ureteric and renal pelvic (upper urologic tract) cancers. LS is caused by a mutation in one of the MMR genes [23, 25]. MMR genes include *MLH1*, *MSH2*, *MSH6* and *PMS2*. Historically the Amsterdam criteria-2 (AC-2) were used to identify LS [28]. This follows a 3:2:1 rule and includes, (a) ≥3 relatives related by a first degree relationship with an LS cancer (described above), (b) These LS cancers should span ≥2 generations and (c) one (or more) of these cancers is <50 years [28]. Given the poor sensitivity of AC-2, Bethesda criteria were introduced and used at cancer diagnosis to determine which tumour samples should undergo molecular analysis via microsatellite instability (MSI) or immunohistochemistry (IHC) to identify MMR deficiency and enable subsequent triage for MMR gene testing. However, both AC-2 and Bethesda criteria miss a number of MMR PV carriers.

Cowden's Syndrome
Cowden's Syndrome is caused by PVs in the *PTEN* gene. These PVs are associated with a 10–28% risk of EC [29, 30]. However, the risk of OC is not increased. It is also associated with a 50% risk of BC and 3–10% risk of thyroid cancer.

Peutz-Jeghers Syndrome (PJS)
PJS is caused by PVs in the *STK11/LKB1* genes. PJS is characterised by polyps throughout the gastrointestinal tract and muco-cutaneous pigmentation. PJS is associated with an increased risk of adenoma malignum which is a rare cervical cancer. Additionally, benign sex cord stromal ovarian

Table 17.2 Relevant cancer syndromes

	HBOC	HOC	Lynch syndrome	Cowden's syndrome	Peutz-Jeghers syndrome
Genes	*BRCA1, BRCA2, RAD51C, RAD51D, PALB2*	*BRCA1, BRCA2, RAD51C, RAD51D, BRIP1*	MMR (*MLH1/MSH2/MSH6/PMS2*)	*PTEN*	*STK11/LKB1*
Cancers gynaecological	Ovary	Ovary	Ovary	Breast	Breast
	Breast		Endometrium	Endometrium	Cervix
Cancers other			Colon, gastric, ureteral, small bowel, ureteric, renal pelvic, biliary, pancreatic, glioblastoma	Colon, thyroid, benign hamartomas	Bowel hamartomas, gastric, pancreatic

tumours have been reported in PJS. Although EC and OC cases have been reported in some series these are uncommon [31, 32]. It is also associated with an increased risk of breast and gastrointestinal cancers. PJS-associated cervical cancer is difficult to screen for and preventive hysterectomy is not warranted.

Li-Fraumeni Syndrome (LFS) LFS is caused by germline *TP53* mutations, and is highly penetrant with up to 90% of carriers developing cancer by age 60 [33]. It is associated with young-onset sarcomas, breast cancer, colon cancer, adrenocortical carcinoma, leukaemia, lymphoma and childhood tumours. It does not increase the risk of ovarian, endometrial or cervical cancers.

17.3 Classes of Variants

Variants can be of 5 classes (see Table 17.3) [34]. Pathogenic and Likely pathogenic variants are clinically actionable (together called PVs). A small proportion of Variants of Uncertain Significance (VUS) may get reclassified as PVs in the future. However, currently no clinical intervention should be based on VUS alone.

17.4 Advantages of Genetic Testing

Effective preventive therapy options including risk reducing surgery, chemoprevention and screening are available to reduce PV carriers' cancer risks are available (see Table 17.1). Women can also make lifestyle, contraceptive and reproductive choices impacting cancer risk including pre-natal or preimplantation genetic diagnosis (PGD) to prevent transmission to their children [35].

Women at increased risk of ovarian cancer can opt for risk-reducing salpingo-oophorectomy (RRSO) which is the most effective option to reduce their OC risk once their family is complete [16, 36]. Traditionally it has been offered to *BRCA1/BRCA2* carriers and been shown to reduce OC incidence and mortality. There is a very small residual risk of primary peritoneal cancer. Additionally, 5% women may have STIC (serous tubular intraepithelial carcinoma) or early invasive cancer detected at histology, necessitating further investigations and surgical staging. RRSO has been found to be cost-effective above a 4–5% lifetime ovarian cancer risk threshold [37, 38]. At this level of OC risk it can add another 10 years to a woman's life who would have otherwise developed OC. This provides clinical utility for RRSO to be undertaken for the moderate penetrance genes too [39]. RRSO is now offered to women with moderate penetrance OC genes who are at intermediate (5–10%) risk of OC. Women undergoing premenopausal oophorectomy if not contraindicated, should be offered HRT until the average age of natural menopause (51 years) to minimize the detrimental consequences of early menopause. Women should be provided with evidence-based information, HRT advice, specialist counselling and long-term support to deal with

Table 17.3 Class of variants

Variant description	Variant class	Probability of being pathogenic	Clinical recommendations
Pathogenic	5	>0.99	Eligible for risk management options
Likely pathogenic	4	0.95–0.99	Eligible for risk management options
Variant of uncertain significance (VUS)	3	0.05–0.949	No clinical implication (on its own). Needs follow up. A small proportion may get reclassified as Class 4 or 5 in the future
Likely benign or likely not pathogenic	2	0.001–0.049	No clinical implication
Benign or not pathogenic	1	<0.001	No clinical implication

the health consequences of early menopause. Broad acceptance of the tubal hypothesis has led to risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) as a new OC prevention strategy for premenopausal women. This has high acceptability in premenopausal women concerned about the side effects of early surgical menopause [17, 40]. However, given the lack of long-term outcome data it is currently advocated in the context of a clinical trial [18]. Annual screening for ovarian cancer in a low-risk population has not shown a mortality benefit [41]. In high-risk women 4-monthly CA125 based screening using a longitudinal mathematical algorithm has been investigated and showed a significant stage shift [42], but these studies were not designed to assess survival or mortality. There is no national OC screening programme for high-risk women. Testing women with OC offers the opportunity for tailored chemotherapy treatment at first line (and relapse) settings, which can improve progression-free survival (see below) [43].

Women at increased risk of BC can opt for MRI/mammography screening and chemoprevention with selective estrogen receptor modulators (SERM) to reduce their BC risk [14]. Surgical prevention in the form of risk-reducing mastectomy (RRM) is the most effective option for reducing BC risk [13].

Options for LS/MMR carriers include prophylactic hysterectomy and bilateral salpingo-oophorectomy as the most effective intervention to prevent EC and OC. This is usually offered after the age of 40 years once a carrier's family is complete. Oophorectomy is not recommended in women with PMS2 PVs or Cowden's syndrome. Additionally 1–2 yearly colonoscopy for colorectal cancer screening and daily aspirin [27, 44] is advised to reduce CRC risk [26]. Although the evidence base for EC screening in high-risk women is limited, case series [45–48] show it can detect both precancer (complex atypical hyperplasia) and early cancer, although interval cancers may occur. EC screening may have a role to play in LS/Cowden's for women who wish to delay surgical prevention, and is usually undertaken from 35 years of age. EC screening options involve annual transvaginal ultrasound scanning (TVS) and endometrial sampling alone or outpatient hysteroscopy plus endometrial sampling (OHES). TVS alone without endometrial sampling is not effective.

17.5 Disadvantages of Genetic Testing

Some of the disadvantages described include some women feeling anxious or distressed after receiving a positive test result; feeling guilty about transmission to children and their risk; implications for family dynamics; marriageability (in some communities) and stigmatization (reported in a minority). Additionally, some women may receive an uncertain result called a variant of uncertain significance (VUS). Other issues to consider include potential implications for insurance/employment. In the US the GINA (Genetic Information Non-discrimination Act) and in the UK a code on genetic testing and insurance provides a moratorium between Department of Health and Association of British Insurers to protect against use of test results for setting insurance premiums (https://www.abi.org.uk/data-and-resources/tools-and-resources/genetics/code-on-genetic-testing-and-insurance/).

17.6 The Traditional Family History (FH) Based Approach to Genetic Testing

Traditionally, women carrying moderate to high penetrance PVs in CSGs have been identified by the FH based approach to genetic testing. This involves obtaining a detailed three generation FH, including both maternal and paternal sides of the family, ethnicity, types of cancer, ages of onset, ages of death, histology and any genetic testing undertaken. Results of any molecular testing

undertaken on tumour tissue and prophylactic surgical history should also be documented. Various FH models and clinical criteria have been used to predict probability of carrying a PV and to identify those who are at increased risk and should be offered genetic testing. This is dependent on knowledge and accuracy of FH. Commonly used models include the Manchester Scoring System (MSS), BOADICEA or CANRISK, Tyrer-Cuzick and BRCAPRO. In the UK *BRCA1/BRCA2* testing is offered to those who have an *apriori* ≥10% combined *BRCA1+BRCA2* probability. MSS is an easy-to-use table providing a score based on FH of BC, OC, prostate and pancreatic cancers on the same side of the family [49]. A combined score of 15 corresponds to the 10% testing threshold and a score of 20 to the 20% threshold. However, MSS cannot be used for Ashkenazi Jewish (AJ) families. Laxer clinical criteria are used for AJ families given the higher *BRCA* prevalence in this population [50].

Genetic testing may be diagnostic or predictive. A diagnostic genetic test is when the test is used to identify a PV in the family for the first time. This is often undertaken in an individual with cancer. Predictive genetic test is when the genetic test is used to identify a known PV in the family in another untested and usually unaffected family member.

17.7 Limitations to the Traditional FH Approach

FH or clinical criteria-based testing is moderately effective at identifying individuals with PVs but poor at ruling out the presence of one. This approach has involved testing affected individuals from high-risk families via high-risk cancer genetic clinics after face-to-face pre-test genetic counselling by geneticists/genetic counsellors. For this to be effective, it is important for individuals and their doctors to recognise the significance of their FH and act on it. However, a number of PV carriers are unaware of their FH or its significance, are not proactive in seeking advice, may lack a strong enough FH, or may not get referred and get excluded. This pathway has often been complex, varies regionally and internationally, and is associated with restricted uptake and underutilisation of genetic testing [51–53]. An analysis across Greater London shows that over 97% of *BRCA* carriers remain undetected despite 25 years of NHS testing [52].

Around 50% of BC/OC CSG carriers do not fulfil current clinical or FH-based criteria for genetic testing and are missed [5, 50, 54, 55]. Far greater numbers are missed through unselected population ascertainment. Bethesda and Amsterdam-II clinical criteria miss, 12–30% and 55–70% of MMR (Lynch Syndrome) carriers respectively [9, 56, 57]. Advances in testing technology and bioinformatics has now enabled large-scale delivery of high-throughput genetic testing. The limitations of the FH approach can be addressed by (a) unselected genetic testing at cancer diagnosis and (b) population testing. Unselected testing at cancer diagnosis improves genetic testing access and PV carrier identification in affected women. It has been implemented for OC [58] and CRC [59]; is now being implemented for EC [60]; and there have been calls for considering this for BC [54].

17.8 Unselected Genetic Testing at Ovarian Cancer Diagnosis

Around 11–18% of OC patients have germline *BRCA1/BRCA2* PV and another 6–9% have a somatic *BRCA1/BRCA2* PV in the tumour tissue alone which is not inherited [5, 61]. Thus two-thirds of PVs in tumour tissue originate from the germline, but one-third are somatic. *BRCA1/BRCA2* genes code proteins which are required in the homologous recombination repair (HRR) pathway of double stranded DNA breaks. PARP (poly ADP ribose polymerase) is an essential component of single-strand DNA repair. Inhibition of PARP leads to more double strand breaks and prevents HRR deficient (HRD) tumour cells from surviving chemotherapy

induced DNA damage [62]. HRD may occur due to a large number of genes mutations in the HRR pathway, including *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*. Tumours that are HRD deficient, regardless of the HRD deficiency is inherited or sporadic, are more susceptible to systemic therapy with 'PARP inhibitors' (PARPi) and platinum agents. This trait is referred to as "BRCAness". Approximately 50% of high grade serous OC are characterised by HRD and HRD assays are now being used in clinical practice [63]. Germline as well as somatic *BRCA* mutated OC have been shown to benefit from PARP-i therapy with improved progression free survival in both first line and recurrent settings [43, 62, 64–66]. This need to identify women who can benefit from first line PARPi therapy has given an impetus to genetic testing in all women with high grade epithelial non-mucinous OC. Testing on the basis of FH would miss around 50% of the germline PVs. A non-genetic cancer clinician driven 'mainstreaming approach' where counselling and genetic testing for all OC patients is undertaken by the medical oncologist/surgical oncologist/clinical nurse specialist is now part of standard NHS clinical practice [5, 67]. PV carrier identification enables cascade testing and primary cancer screening and prevention in unaffected relatives (see Table 17.1) along with secondary cancer prevention and access to novel drugs (e.g. PARP-inhibitors) or clinical trials to improve survival in affected carriers [43]. Parallel germline and somatic testing is recommended as ~10% of PVs are large genomic rearrangement (LGR) germline PVs and are missed by somatic testing. Germline testing for a panel of relevant OC genes can identify another 2–3% non-*BRCA* PVs whose family members can benefit from cascade testing and subsequent screening and prevention. It is important that only genes with well-established 'clinical utility' are tested for. We are against indiscriminate panel testing as in large commercial panels. A valid OC panel today could include *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2* and MMR genes. The lack of an effective OC screening strategy in low-risk women [41] further amplifies the need for identifying high risk women for precision prevention.

17.9 Unselected Genetic Testing at Endometrial Cancer Diagnosis

Given the number of LS cases missed by clinical criteria-based restricted access, the current recommendation is to test all EC tumours for MMR gene deficiency. This guideline was recently introduced into NHS practice by NICE in 2020 [60]. Tumours can be found to be MMR deficient by IHC or MSI. Both IHC and MSI show comparable sensitivity and high concordance. However, as IHC has been found to be more cost-effective and is easily accessible to pathologists, IHC is now used as first line to test endometrial cancer tissue for MLH1, MSH2, MSH6, and PMS2 gene expression. While 25–30% of ECs are found to be MMR deficient, only around 3% have LS [9]. If the EC tumour IHC shows somatic MSH2 or MSH6 deficiency (negative stain for MSH2/MSH6), germline testing for LS genes is indicated. If IHC shows MLH1 (often combined with PMS2) deficiency, MLH1 promotor hypermethylation testing needs to be performed first as the majority of these are due to sporadic silencing of the MLH1 gene by hypermethylation of the MLH1 promotor region within tumour cells and do not reflect the presence of LS [68]. A result of low hypermethylation (negative test) indicates requirement for germline testing, while a result of high hypermethylation (positive test) suggests a false positive result and excludes the need for germline MMR gene testing. Figure 17.1 depicts a recommended flow chart for IHC-based triage for MMR gene testing for LS. Figure 17.2 illustrates the numbers of LS patients that would be identified along with number of false positives if 1000 EC cases were tested [9, 69, 70]. All gynaecologists and gynaecological oncologists involved in the diagnosis and treatment of women with EC will need to be able to interpret these results as

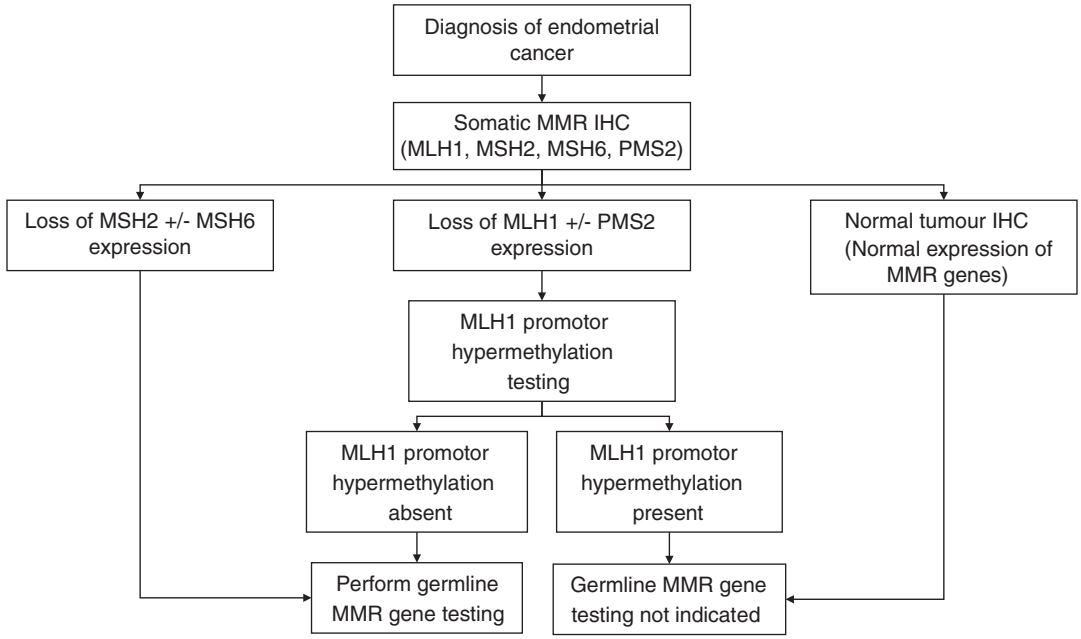

Fig. 17.1 Flow chart for IHC based triage for MMR gene testing for LS at diagnosis of endometrial cancer

well as counsel women and undertake genetic testing for LS. A similar mainstreaming approach has previously been implemented for OC cases across treatment pathways. Identified PV carriers need to be referred to clinical genetics and family members should be offered predictive testing. LS women with EC should be offered bowel screening (annual colonoscopy) and aspirin for chemoprevention. Unaffected family members can avail of screening or prevention options highlighted in Table 17.1.

17.10 Population Testing

The inadequacies and limitations of our current clinical approach to genetic testing, given the effective risk management/preventive options available for high-risk women, highlights the massive scale of missed opportunities for cancer prevention. Unselected unaffected population testing can overcome these limitations. The strongest evidence base for population testing comes from the Jewish population. Population-based *BRCA* testing in Ashkenazi Jews compared to FH/clinical criteria based *BRCA* testing is feasible, acceptable, safe, doesn't harm quality-of-life or psychological well-being, reduces long-term anxiety, identifies 150% additional *BRCA*-carriers [50, 71], can be delivered in a community setting [72, 73] and is extremely cost-effective [74, 75]. This supports changing paradigm to population-based *BRCA*-testing in the Jewish population [76, 77] and this approach has now very recently been implemented in Israel. It is important that other countries follow suit. Unselected germline testing in a non-Jewish general population has also been shown to be cost-effective, but this remains a matter of ongoing research [78–81].

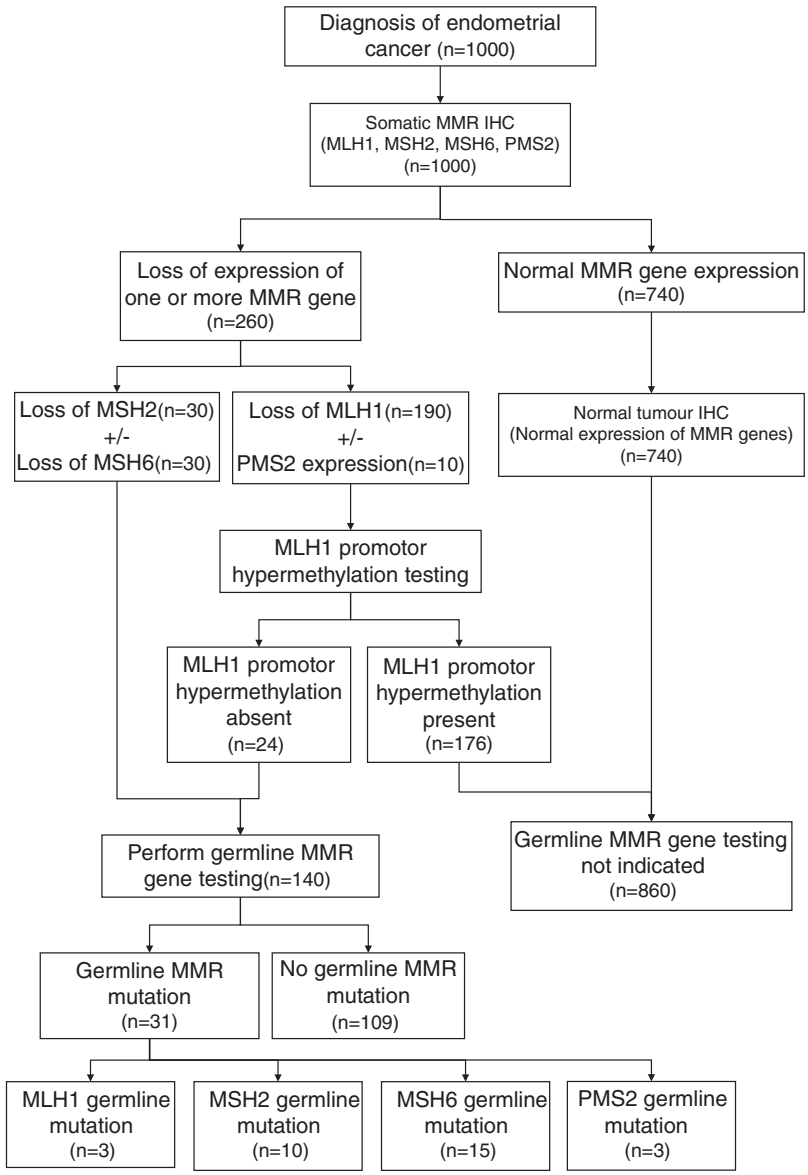

Fig. 17.2 Flow chart for number of LS patients identified if 1000 endometrial cancer cases were tested[9, 69]

17.11 Summary

Ovarian, breast, endometrial, and colorectal cancer cases are projected to rise over the next 20 years. 20% of ovarian cancers, 4% of breast cancers, 3% of endometrial cancers, and 4% of colorectal cancers are due to pathogenic variants in cancer susceptibility genes. CSG identification offers many opportunities to PV carriers including enhanced screening for early detection, prevention options including chemoprevention or risk-reducing surgery, along with pre-implantation genetic diagnosis to prevent variant transmission. Traditional genetic testing eligibility was based on family history and/or clinical criteria but is underutilised and misses 50% of PV carriers even with ideal usage. Unselected genetic testing is now recommended for all women with endometrial cancer following IHC triage. Unselected parallel panel germline and somatic genetic testing is now recommended for all women with high grade epithelial ovarian

cancer. Germline PVs and HRR deficient ovarian cancers are eligible for PARPi therapy. PV identification can enable secondary cancer prevention in cancer patients and cascade testing in family members to identify unaffected PV carriers who can benefit from precision prevention. Population-based *BRCA* genetic testing is now recommended for the Ashkenazi Jewish population.

Key Points

- Pathogenic variants in moderate to high penetrance cancer susceptibility genes of clinical utility account for around 15–20% OC, 4% BC, 3% EC and 4% CRC with a majority being potentially preventable.
- Family history-based clinical criteria for genetic testing miss >50% pathogenic variants in cancer susceptibility genes.
- Unselected genetic testing at cancer diagnosis is now recommended for all women with high grade epithelial ovarian cancer. Both germline and somatic testing should be undertaken in parallel to maximise variant identification. Germline PVs and HRR deficient tumours are eligible for PARPi therapy. Family members of germline PVs can undergo cascade testing for precision prevention.
- Unselected IHC testing at diagnosis and subsequent triage for MMR gene testing is now recommended for all women with endometrial cancer.
- Early recognition of cancer susceptibility gene carriers for *BRCA1/BRCA2*, *PALB2*, *RAD51C*, *RAD51D*, *BRIP1*, *MLH1*, *MSH2*, *MSH6* and *PMS2*, can offer women important opportunities for screening/early diagnosis and cancer prevention.
- RRSO is the most effective method of preventing ovarian cancer in women at increased risk of ovarian cancer. Hysterectomy and bilateral salpingo-oophorectomy is recommended in women with Lynch Syndrome. Early salpingectomy and delayed oophorectomy should currently only be offered in the context of a clinical trial.
- Population testing is now recommended for the Ashkenazi Jewish population and has recently been implemented in Israel.

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