

# Hereditary Gynecologic Cancer Syndromes – A Narrative Review

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**Abstract:** Hereditary cancer syndromes are defined as syndromes, where the genetics of cancer are the result of low penetrant polymorphisms or of a single gene disorder inherited in a mendelian fashion. During the last decade, compelling evidence has accumulated that approximately 5–10% of all cancers could be attributed to hereditary cancer syndromes. A tremendous progress has been made over the last decade in the evaluation and management of these syndromes. However, hereditary syndromes associated with gynecologic malignancies still present significant challenge for oncogynecologists. Oncogynecologists tend to pay more attention to staging, histological type and treatment options of gynecological cancers than thinking of inherited cancers and taking a detailed family history. Moreover, physicians should also be familiar with screening strategies in patients with inherited gynecological cancers. Lynch syndrome and hereditary breast-ovarian cancer syndrome are the most common and widely discussed syndromes in medical literature. The aim of the present review article is to delineate and emphasize the majority of hereditary gynecological cancer syndromes, even these, which are rarely reported in oncogynecology. The following inherited cancers are briefly discussed: Lynch syndrome; “site-specific” ovarian cancer and hereditary breast–ovarian cancer syndrome; Cowden syndrome; Li-Fraumeni syndrome; Peutz-Jeghers syndrome; ataxia-telangiectasia; DICER1- syndrome; gonadal dysgenesis; tuberous sclerosis; multiple endocrine neoplasia type I, II; hereditary small cell carcinoma of the ovary, hypercalcemic type and hereditary undifferentiated uterine sarcoma; hereditary diffuse gastric cancer and MUTYH-associated polyposis. Epidemiology, pathogenesis, diagnosis, pathology and screening of these syndromes are discussed. General treatment recommendations are beyond the scope of this review.

**Keywords:** hereditary gynecologic cancer syndromes, pathogenesis, diagnosis, pathology, screening

## Introduction

Hereditary cancer syndromes (HCS) are defined as syndromes, where the genetics of cancer are the result of low penetrant polymorphisms or of a single gene disorder inherited in a mendelian fashion. Hereditary syndromes associated with gynecologic malignancies present significant challenge for oncogynecologists. Physicians tend to pay more attention to staging, histological type and treatment options of gynecological cancers than taking a detailed family history.<sup>1</sup> During the last decade, compelling evidence has accumulated that approximately 5–10% of all cancers can be attributed to hereditary cancer syndromes.<sup>2,3</sup> Concerning these conditions facilitates the opportunity to screen and identify individuals at higher risk of developing some types of cancers.<sup>3</sup> Moreover, identifying women with a hereditary pathogenic gene variant is essential in order to estimate the counseling strategies for cancer prevention, the future fertility, cancer surveillance and risk of transmitting pathogenic gene variants to their offspring. Additionally, other topics that should be discussed with patients are the potential initiation of hormone therapy after prophylactic surgery (bilateral salpingo-oophorectomy, mastectomy, hysterectomy) at-risk family members.<sup>1,3</sup> The most common hereditary gynecologic cancer syndromes (HGCSs) are hereditary breast–ovarian cancer syndrome and hereditary nonpolyposis colorectal cancer (HNPCC) syndrome.<sup>4</sup> They account approximately 10–18% of ovarian, tubal, peritoneal, and endometrial cancer cases.<sup>5</sup> Approximately 5% of uterine

cancers and 10% of ovarian cancers are due to HGCSs.<sup>6</sup> However, other HGCSs are rarely mentioned. The aim of the present review is to describe counseling strategies, pathogenesis, pathology and screening of the following HGCSs: hereditary nonpolyposis colorectal cancer syndrome; “site-specific” ovarian cancer and hereditary breast–ovarian cancer syndrome; Cowden syndrome; Li-Fraumeni syndrome; Peutz-Jeghers syndrome; ataxia-telangiectasia; DICER1- syndrome; gonadal dysgenesis; tuberous sclerosis; multiple endocrine neoplasia type I, II; hereditary small cell carcinoma of the ovary, hypercalcemic type and hereditary undifferentiated uterine sarcoma; hereditary diffuse gastric cancer and MUTYH-associated polyposis. General treatment recommendations are beyond the scope of this review. We only mentioned risk-reducing surgery as an option and described other author’s experience, because there are many controversies and further recommendations are debatable and could cause unnecessary overtreatment.

## Hereditary Gynecologic Cancer Syndromes

### Hereditary Nonpolyposis Colorectal Cancer Syndrome (HNPCC) -Lynch Syndrome Definition and Epidemiology

HNPCC syndrome, also known as Lynch syndrome (LS), is an autosomal dominant cancer predisposition characterized by increased risk and early occurrences of colorectal cancer. LS is also associated with elevated risk of cancers of the endometrium, ovary, breast, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin, pancreas, and prostate.<sup>7,8</sup> For patients with HNPCC syndrome, the lifetime risks of developing endometrial and ovarian cancer are approximately 30–71% and 4–24%, respectively.<sup>5,7,9</sup> Other studies estimated that approximately 60% of women with LS present initially with cancers of the female genital tract, of which 14% are associated with ovarian and 60% of endometrial cancer, respectively.<sup>10–12</sup> The syndrome accounts for at least 2% to 5% of all colorectal and endometrial cancers and increases the lifetime risk of colorectal cancer to as high as 60% to 85%.<sup>4,13</sup> Some studies reported higher risk of endometrial cancer development than colorectal cancer for patient with LS.<sup>4</sup> The average age of colorectal (mean age 41–44 years), ovarian, endometrial cancers (mean age 48–50 years) diagnosis in individuals with LS is younger than the general population – during the fourth decade.<sup>7,14,15</sup> One study estimated an incidence of endometrial cancer in LS among Japanese endometrial cancer patients of reproductive age ( $\leq 40$  years) being approximately 1.5%. However, authors also reported that 12.3% of the patients had variants of uncertain significance in MMR genes.<sup>16</sup> The risk of second, metachronous cancer occurrence in women with LS is 25% by 10 years after diagnosis of the primary cancer and 50% by 15 years after an initial cancer diagnosis.<sup>15</sup> Therefore, after the diagnosis of primary cancer associated with LS the patients should be adequately counseled and offered appropriate risk-reduction strategies (prophylactic surgery).<sup>4</sup> A woman with HNPCC who survives a colon cancer has an increased risk of developing an endometrial cancer.<sup>15</sup> The occurrence of breast cancer as part of Lynch syndrome is controversial. Some studies stated that breast cancer is not a part of LS, whereas others have suggested an epidemiologic association.<sup>7–17</sup>

### Pathogenesis

HNPCC is caused by mutations in the DNA mismatch repair (MMR) genes – MLH1, MSH2, MSH6 and less commonly PMS1, PMS2. These genes are responsible for repairing single base pair mismatches and mispaired loops of DNA during the process of DNA replication.<sup>1,13</sup> Some studies did not include mutations in the PMS1 as the cause of LS. It is reported that the cancer risk on LS depended on gene mutations and it is substantially lower for PMS2.<sup>18</sup> Dominguez-Valentin et al observed no difference in incidence of cancer between truncating and missense or aberrant splicing pathogenic variants in MLH1 and MSH2 carriers.<sup>19</sup> Mutation in the MMR genes causes microsatellite instability (MSI), where insertion of extra nucleotides in microsatellite repeats and leads to accumulation of gene mutations that affect proliferation and cell-cycle control.<sup>1,4,13</sup> The MSI is the hallmark of cancers associated with LS.<sup>5</sup> Rarely, the LS may occur due to inactivation of CHEK2 (cell cycle checkpoint kinase 2).<sup>20</sup> It should be stressed that MMR deficiency is not an absolute feature of LS, as most of MMR deficient endometrial cancers present with somatic inactivation of the MLH1 due to hypermethylation of the promoter region.<sup>18</sup> Cases, which are not caused by MLH1 hypermethylation or MMR gene mutation are considered sporadic via biallelic somatic MMR gene inactivation.<sup>18</sup> Figures 1 and 2 show the risk of LS-associated cancers depending on the MMR gene mutation.<sup>1,5,21,22</sup>

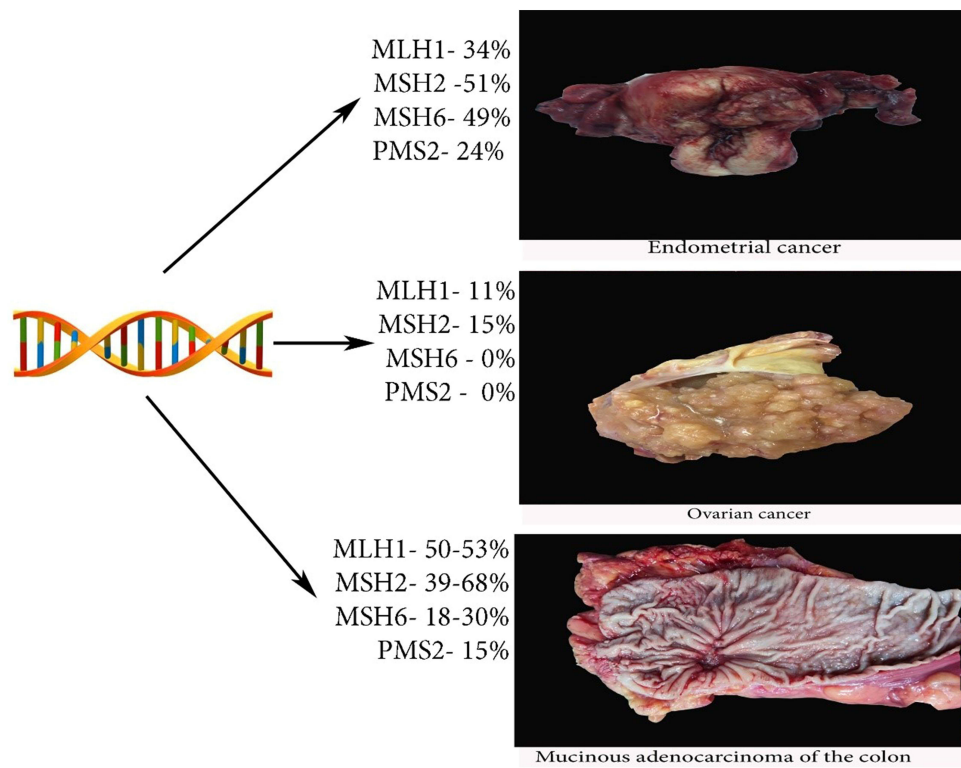


Figure 1 Risk of endometrial, ovarian and colon cancers in LS.

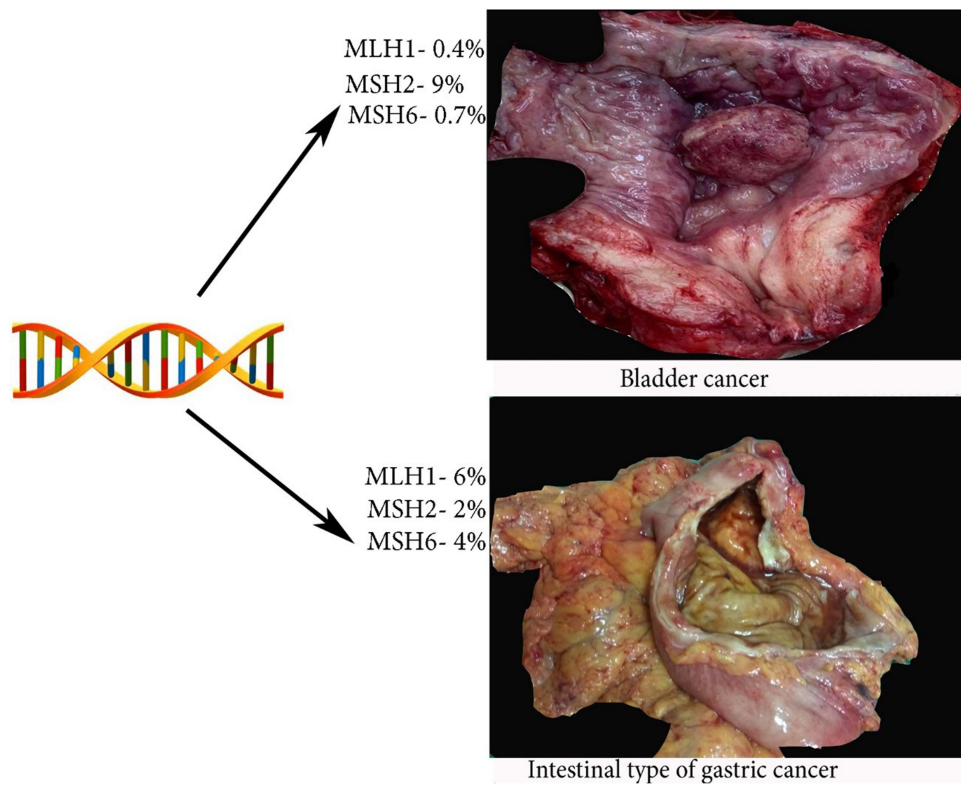


Figure 2 Risk of bladder and gastric cancer is LS.

## Diagnosis

The clinical criteria for the diagnosis of LS include revised Amsterdam II criteria and revised Bethesda criteria <sup>1,4,5,13,23–25</sup> (Table 1).

The purpose of the two criteria is to identify families eligible for further molecular analysis. As the specificity of the Amsterdam II criteria was high (98%), but the sensitivity low (22%), a Bethesda guideline was developed in 1997, and revised in 2004. The limitations of the Amsterdam criteria were that only 13% to 36% of families with molecularly confirmed HNPCC will meet these criteria. The revised Bethesda criteria has 82% specificity and 77% sensitivity and included endometrial cancer as sentinel cancer. <sup>4,5,26</sup> However, it has been estimated that screening by using these criteria could miss more than one-fourth of LS cases. Therefore, it is recommended screening for all patients with colorectal cancer, either by direct germline testing for mutation, MSI testing of tumor specimens via PCR or by initial tumor testing with immunohistochemistry (IHC) for MMR genes. <sup>5,23</sup>

Although it is controversial whether immunohistochemistry or molecular testing should be performed, it is stated that detection of mutated MMR genes by IHC is reliable (especially for endometrial cancer). Loss of PMS2 staining supposes PMS2 mutation, whereas loss of MSH6 staining is suggestive of MSH6 mutation. <sup>20</sup> Loss of MLH1 and PMS2 staining is likely to occur in MLH1 mutation, while loss of MSH2 and MSH6 staining may be observed in MSH2 mutation. <sup>20</sup> The benefit of IHC in LS is that the presence of MLH1, MSH2, MSH6, and PMS2 proteins rules out LS and further DNA-testing for MMR gene mutation is not necessary. <sup>23</sup> However, in cases of endometrial cancer related to LS, a MLH1 promoter methylation testing should be performed to rule out sporadic endometrial cancer, as MLH1 promoter hypermethylation is associated with sporadic cancers of the endometrium. <sup>27,28</sup> Buchanan et al investigated 702 patients with endometrial cancer diagnosed before 60 years of age by using tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing. Authors concluded that combination such a testing combination provided the highest positive predictive value for the identification of mutation carriers. <sup>27</sup> Other specific clinical characteristics that could be used to identify LS are the following: patients with colorectal cancer at young age, proximal colon location and the presence of synchronous or metachronous tumors. <sup>13,29</sup>

**Table 1** The Revised Amsterdam II and Bethesda Criteria

The Revised Amsterdam II Criteria	The Revised Bethesda Criteria Testing for Colorectal Tumors for Microsatellite Instability
At least three relatives must have an HNPCC-associated cancers (colorectal, endometrial, small bowel, ureter, or renal pelvic cancer) Cancers of the stomach, ovary, brain, bladder or skin are not included. All of the following criteria should be met	Patients with synchronous or metachronous endometrial or colorectal cancer diagnosed before age 50 years
One must be a first-degree relative of the other two	Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/ HNPCC-associated tumor, regardless of age
At least two successive generations should be affected	Patient < 60 years with colorectal cancer with MSI-H histology (presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern)
At least one of the HNPCC-associated cancers should be diagnosed at less than 50 years of age	Patients <50 years with endometrial or colorectal cancer and a first-degree relative with a Lynch/HNPCC-associated tumor
In cases of colorectal cancer -familial adenomatous polyposis should be excluded	Patient at any age with colorectal or endometrial cancer diagnosed with two or more first-degree or second-degree relatives with Lynch/ HNPCC- associated tumors, regardless of age
Histopathological verification of the tumors is necessary	

## Pathology

The histopathological features of colorectal cancer related to LS differ to colorectal cancer in general. Mucinous, poorly differentiated, diploid and signet-ring cancers are common in LS. HNPCC tumors are often associated with a prominent chronic inflammatory response (Crohn's-like reaction) (Figure 3). High numbers of tumour infiltrating lymphocytes are also observed. These features could serve as additional markers for LS recognition, although they are not specific.<sup>29,30</sup> It is believed that LS-related colorectal carcinomas arose from adenomas, which had a more rapid progression to carcinoma compared to those arising sporadically within the population.<sup>30</sup>

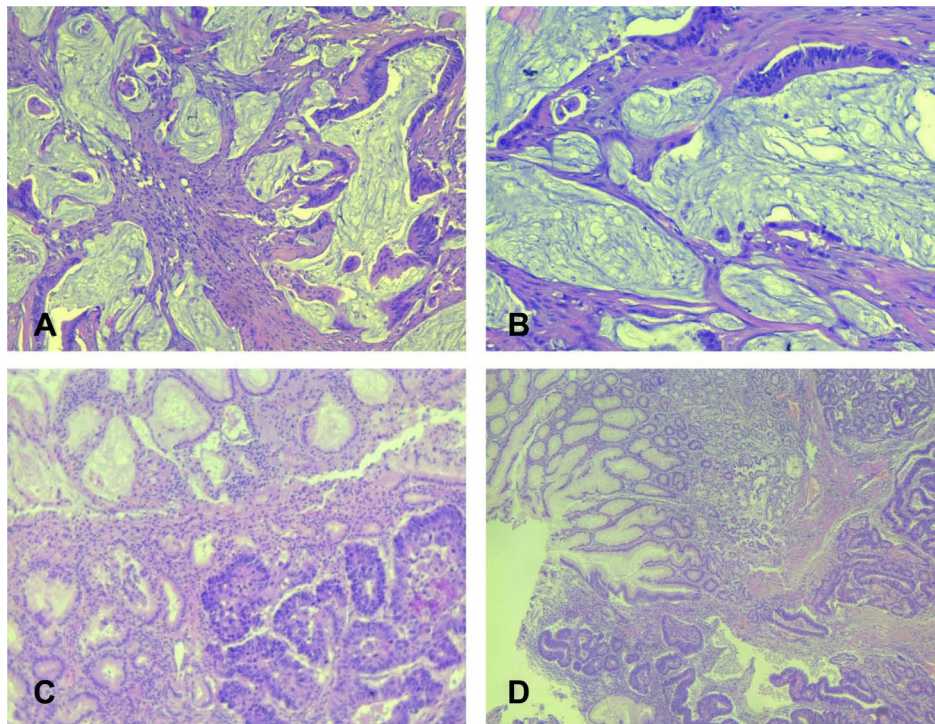
The histological features of endometrial cancer related to LS are non-specific – commonly of endometrial type, although non-endometrioid types are also observed – uterine papillary serous carcinoma, clear cell carcinoma, and uterine carcinosarcoma.<sup>2,29,31</sup> A non-endometrioid histology in LS is often observed in patient with MSH2 mutation. Moreover, compared to the sporadic endometrial cancer, the LS-EC shows tendency to develop in the lower uterine segment.<sup>30–32</sup> There are no differences of survival between LS-associated endometrial cancer (LS-EC) and the sporadic one.<sup>29</sup>

The histological features of ovarian carcinomas tend to be endometrioid, undifferentiated and clear cell.<sup>31,35</sup> Ryan et al identified 53 patients (proven MMR mutations) with LS-associated ovarian cancer. Authors reported that the endometrioid ovarian adenocarcinoma was the most common histology, followed by high-grade serous, clear cell and mixed. LS-associated ovarian cancer occurred at an earlier age (59 years) compared to the sporadic ovarian cancer.<sup>36</sup>

Gastric cancer is the second most common extracolonic malignancies. It is of an intestinal type related to *Helicobacter pylori*-associated chronic gastritis<sup>29</sup> (Figure 3).

The histology of LS-associated bladder and ureteral cancers do not differ from the sporadic ones.<sup>29</sup>

As mentioned above, although the presence of breast cancer in LS is controversial, Sheehan et al suggested that Lynch syndrome patients with PMS2 mutations might be at higher risk of developing breast cancer.<sup>37</sup> Walsh et al concluded that LS-associated breast cancer was often poorly differentiated with a high mitotic index, steroid hormone



**Figure 3** Histological features of mucinous colon adenocarcinoma and gastric carcinoma – intestinal type. (A and B) – mucinous colon adenocarcinoma. Strips of atypical tumor cells, and part of abortive glands floating in large extracellular mucin lakes comprising at least 50% of tumor area ((A) HEx200; (B) – HEx100). (C and D) – gastric cancer, intestinal type. Tumor is composed of confluent tubular structures consist of atypical cells with hyperchromatic nuclei similar to intestinal adenocarcinoma, which invade in submucosal gastric area. In upper part is antral mucosa with reactive mucinous foveolar hyperplasia ((C) - HEx100; (D) – HEx40).

receptor–negative with peritumoral lymphocytes and confluent necrosis. There is no predominance of lobular or ductal histological types, though Yee et al observed higher levels of MSI in lobular carcinomas (39%) than in infiltrating ductal cancers (13.5%).<sup>38,39</sup>

## Screening

Screening recommendations are more clear for colorectal cancer than for the gynecologic cancers (GCs), as less information is available regarding GCs.<sup>4,13</sup> Screening colonoscopy is the best screening method as it decreases the incidence of colorectal cancer and mortality in patients with Lynch syndrome.<sup>4,5</sup> Moreover, colonoscopy is a preferable method as patients with LS have proximal colon tumors that may be missed by more limited screening tools.<sup>40</sup> For patients with molecularly confirmed LS, colonoscopy should be performed every 1 to 2 years beginning at age 20 to 25 or 2–5 years before the earliest cancer diagnosis in a family member with a LS-associated colorectal cancer.<sup>4,5</sup> The colonoscopy is offered annually after the age 40.<sup>4</sup>

Screening for endometrial cancer includes combination of annual/biannual transvaginal ultrasound or endometrial biopsy starting at age 25–35, as well as evaluating abnormal vaginal bleeding.<sup>5,6,8</sup> However, evidence for endometrial cancer screening is less convincing, as ultrasound has a high false-positive rate and the efficiency of endometrial biopsy has not been evaluated.<sup>40</sup>

Although screening for ovarian cancer is controversial, pelvic examination, transvaginal ultrasound with serum Ca-125 levels should be conducted from an age of 30–35 years at 6 months or annually.<sup>23</sup>

Screening for breast cancer is the same as the population-based breast cancer screening recommendations.<sup>8</sup> Women with LS and childbearing plans should be screened before attempting to become pregnant.<sup>8</sup>

## Risk-Reducing Surgery

Risk reducing surgery is beyond the scope of this review, as there are many controversies in medical literature and further studies are needed in order to improve patients' outcome. For instance, some authors stated that as LS cancers are associated with younger age of onset, risk-reducing surgeries are recommended between the ages of 35–45, or when childbearing is complete.<sup>3</sup> Conversely, another study showed almost no benefit from risk-reducing surgery before 40 years of age and premenopausal bilateral salpingo-oophorectomy in MSH6 and PMS2 heterozygotes carriers was not associated with increased mortality.<sup>41</sup> Tzortzatos et al observed 41 women with LS who underwent risk-reducing surgery – 4 of them has occult complex atypical hyperplasia (2 patients) or endometrial cancer (two patients).<sup>42</sup> Duenas et al conducted the largest study published up to the date in a single-institution. Authors concluded that risk-reducing surgeries are effective in decreasing the rate of colorectal, endometrial and ovarian cancer. They compared risk reducing gynecological surgery vs surveillance in the gynecological cohort and showed that the cumulative, incidence at 75 years was 11.2% vs 46.3% for endometrial cancer and 0% vs 12.7% for ovarian cancer. Moreover, the mortality cumulative incidence was 0% vs 52.7%.<sup>43</sup> However, Seppala et al observed that uptake of risk-reducing gynecological surgery in LS aligned poorly regarding gene- and age-associated risk and did not correspond well with current clinical guidelines.<sup>44</sup>

## “Site-Specific” Ovarian Cancer and Hereditary Breast–Ovarian Cancer Syndrome Definition, Epidemiology and Pathogenesis

An approximately 23% of ovarian cancer is related to hereditary conditions.<sup>45</sup> “Site-specific” ovarian syndrome is a variant of hereditary breast-ovarian cancer syndrome (HBOCS) instead of a specific syndrome, as no gene has been identified, which increased susceptibility to ovarian cancer alone.<sup>46,47</sup> HBOCS is an autosomal dominant cancer syndrome, which is associated with an increased risk for female and male breast cancer, ovarian, tubal and primary peritoneal cancers.<sup>48,49</sup>

HBOCS is often associated with mutations in BRCA1, BRCA2 tumor suppressor genes, which are autosomal dominant with high penetrance.<sup>47</sup> BRCA1 and BRCA2 were identified in the mid 1990s, and both are responsible for the repair of DNA double-strand breaks via homologous recombination repair to maintain genomic stability.<sup>13,50</sup> BRCA1 and BRCA2 genes are located on chromosome 17q21 and chromosome 13q12.3, respectively.<sup>47</sup> In the general

population, the prevalence of these mutations is estimated at 1:300 to 1:500.<sup>31,48</sup> An increased risk of carrying BRCA germline pathogenic variants was described in the Ashkenazi Jewish population, which has a carrier risk of 2.5% (1:40).<sup>13</sup> Although these genes account for the majority of cancer cases of HBOCS (90–95%), recently other rare genes were identified such as CHEK2, RAD51C, RAD51D, BRIP1, PALB2, TP53 and BARD1.<sup>5,45</sup> Homozygous mutations did not occur in the BRCA1 gene, whereas rare diseases such as Fanconi's anemia and Wilms' tumor are related to homozygous BRCA2 mutation.<sup>47</sup> In the general population, about 10% ovarian cancer cases and 3–5% of breast cancer cases are associated with BRCA1 or BRCA2 gene mutations.<sup>9</sup> The risk for ovarian cancer occurrence varies between 39% and 63% for patients with BRCA1 mutation and 16.5–27% for BRCA2 mutation carriers, respectively. The risk of breast malignancy in individuals with BRCA1 and BRCA2 varies between 46–87% and 38–84%, respectively.<sup>48</sup> According to the World Health Organization (WHO), the incidence rate for breast cancer is 46% and 52% for BRCA1 and BRCA2 carriers, respectively.<sup>31</sup> The incidence rate for ovarian cancer is 12% and 6% for BRCA1 and BRCA2 carriers, respectively.<sup>31</sup> The mean age at ovarian cancer diagnosis for BRCA1, 2 carriers is younger than for patients with sporadic cancer (54–63 years).<sup>46</sup> The median age of ovarian cancer diagnosis for patients with BRCA1 carriers is 45 to 51 years and 57 to 63 years for BRCA2 carriers, respectively.<sup>13</sup> Recently, growing evidence suggests that the fallopian tube epithelia as an etiological site for the development of high-grade serous ovarian cancer.<sup>51</sup> Molecular and genetic data indicated that high-grade serous ovarian, tubal and peritoneal cancer had a similar origin and should be described collectively as HGSC.<sup>51</sup> Therefore, BRCA1, 2 mutations are also responsible for tubal and peritoneal cancer. Sakurada et al estimated the presence of BRCA mutations among 40 patients with primary fallopian tube cancer. The authors found that 26.7% of patients had BRCA mutations.<sup>52</sup>

Additionally, it should be stressed that approximately 10–20% of women with HBOCS 10–20% of HBOC, which underwent germline BRCA1/2 testing harboring variants of unknown significance. These variants are defined as an alteration of a DNA nucleotide sequence, which shows uncertain outcomes – corresponding protein loss or the possible risk of developing diseases. Fanale et al concluded that verifying new potentially pathogenic BRCA1/BRCA2 could urge for their re-classification.<sup>53</sup>

## Diagnosis

The diagnosis of BRCA1- and BRCA2-associated hereditary breast and ovarian cancer is estimated by finding a heterozygous germline pathogenic variant in BRCA1 or BRCA2 on molecular genetic testing.<sup>48</sup> Molecular testing includes BRCA1 and BRCA2 gene panel and a multigene panel.<sup>48</sup> Multigene panel is superior to only BRCA1/2 gene panel as it could estimate RAD51C, RAD51D, BRIP1, PALB2, BARD1, and the MMR gene mutations, which accounts for 4% of hereditary cancers.<sup>5</sup> The DNA recombinase RAD51 is one of the main proteins, which involves in DNA repair by homologous recombination. RAD51 include 5 paralogs (RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3). It was estimated that relative risk of ovarian and breast cancer for RAD51D mutation carriers was 6.30 and 1.32%, respectively. Meindl et al observed six monoallelic pathogenic mutations in RAD51C that conferred a high risk for ovarian and breast cancer. Rafnar et al concluded that BRIP1 behaved like a typical tumor suppressor gene in ovarian cancer.<sup>54–56</sup> Therefore, multigene panel could be considered as a definitive diagnostic method.<sup>5</sup> National comprehensive cancer network (NCCN) established the testing criteria for hereditary breast-ovarian cancer syndrome. In general, patients with personal history of breast or ovarian cancer at younger age or patients with family history (one or more than one close blood relatives with ovarian or breast cancer) should be tested. Moreover, patients with Ashkenazi Jewish ancestry, patients with relatives with male breast and prostatic cancer, triple negative breast cancer diagnosis at age <60 are also candidates for gene testing.<sup>57</sup> Additionally, patients who meet the diagnostic criteria, but are negative with previous limited testing, should be considered for further testing.<sup>57</sup> Generally, studies recommended BRCA testing for all patients with non-mucinous epithelial ovarian, tubal, and peritoneal cancers.<sup>5</sup> The percentage of identifying BRCA1 or BRCA2 for patients with a history of primary breast cancer who subsequently develop ovarian cancer is approximately 20%.<sup>6</sup> Sister, daughter or other relatives of women with positive BRCA mutations, should be considered for predictive testing and screening and preventive measures.<sup>6</sup>

## Pathology

Ovarian cancer associated with this syndrome has a distinct histologic subtype.<sup>5</sup> Currently, studies established that ovarian cancer associated with BRCA mutations arises subsequently in the tubal fimbria from occult serous tubal intraepithelial carcinoma.<sup>45</sup> High-grade serous adenocarcinomas with prominent intraepithelial lymphocytes, marked nuclear atypia and abundant mitoses are typical histological features of BRCA-associated ovarian cancer.<sup>48</sup> Some authors also include HBOCS with endometrioid ovarian adenocarcinoma.<sup>5,46</sup> Mucinous, borderline ovarian cancers and nonepithelial tumors are uncommon for this hereditary syndrome.<sup>46</sup>

BRCA1-related breast cancers tend to be bilateral and of medullar histology with high histological nuclear grade and high percentage of negative estrogen and progesterone receptors. HER2 overexpression is not common.<sup>48,50</sup> There is association between BRCA1 mutation and triple-negative breast cancer<sup>46–52</sup> (Figure 4).

Although some authors suggest the association between BRCA1 mutations and serous uterine cancer, more studies are needed to estimate the real risk.<sup>57</sup>

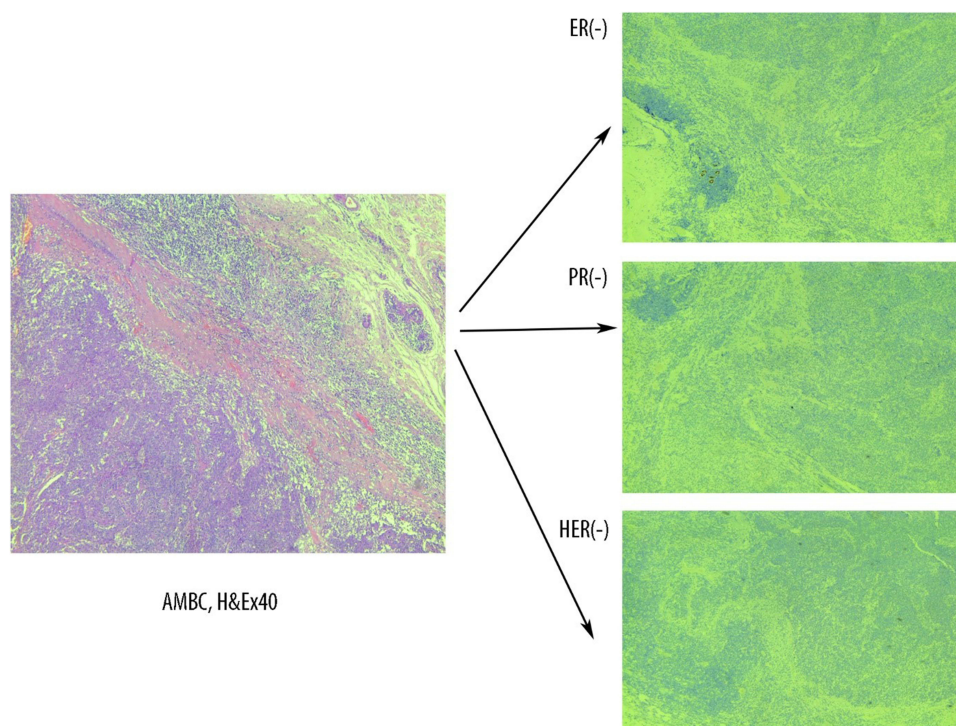
## Screening

Ovarian cancer screening for BRCA mutation carriers has no adequate positive or negative predictive value. Moreover, it does not decrease morbidity and mortality and false-positive rates in premenopausal women are high.<sup>4,13</sup> However, ovarian cancer screening for BRCA mutation carriers include transvaginal ultrasound combined with serum Ca-125 every 3 or 6 months starting either at age 35 or 5 to 10 years younger than the youngest affected member in the family.<sup>13,57</sup>

Breast cancer screening for BRCA carriers includes annual magnetic resonance imaging (MRI) with contrast starting at age 25 years.<sup>57</sup>

## Risk-Reducing Surgery

The same as the LS, risk-reducing surgery in HBOCS is associated with many controversies and debates. Risk-reducing salpingo-oophorectomy (RRSO) is recommended between 35 and 40 years or after completion of child bearing. Evans et al observed three cases of occult ovarian cancer at surgery among 160 BRCA1/2 carriers, who underwent bilateral sapling



**Figure 4** Triple negative atypical medullary breast cancer associated with BRCA1 mutation. AMBC – atypical medullary breast cancer. Absence of estrogen receptor (ER), progesterone receptor (PR) and HER2 immunohistochemistry expression.



oophorectomy.<sup>58</sup> RRSO for BRCA2 mutation carriers should be performed between 40 and 45 years, as the onset of ovarian cancer for women with BRCA2 mutation is 8–10 years later than in women with BRCA1 mutation.<sup>57</sup> Salpingectomy alone is not recommended.<sup>57</sup> However, Liu et al concluded that there are many uncertainties, and shared decision-making should be used for risk-reducing surgery related to HBOCS. Authors also observed benefit of risk-reducing surgery for pathogenic variants in BRCA1/2 as well as BRIP1 and RAD51C/D.<sup>59</sup> Moreover, Öfverholm et al found that overall mortality remained increased after risk-reducing surgery in BRCA1/2 carriers compared to the women in the general population.<sup>60</sup>

## Cowden Syndrome

### Definition, Epidemiology and Pathogenesis

Cowden syndrome (CS) is part of multiple hamartoma syndrome, which is caused by mutations in pentaerythritol tetranitrate (PTEN) gene, which has a role in the cell cycle regime. The gene is located in the long arm of the chromosome 10 and act as a tumor suppressor gene.<sup>1,5,61–67</sup> Mutations in the PTEN gene cause chromosomal instability and uncontrolled proliferation of cells, which result in characteristic hamartomas and malignancies.<sup>67</sup> Approximately 80% of patients with CS have mutations in the PTEN gene.<sup>65</sup> Somatic mutations in PTEN are one of the most commonly altered genes in EC.<sup>61</sup> Multiple hamartoma syndrome also includes Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome and proteus-like syndrome.<sup>66</sup> Bannayan-Riley-Ruvalcaba syndrome and CS have overlapping phenotypic features.<sup>64</sup> The incidence of Cowden syndrome is roughly 1 in 200,000. CS is an autosomal dominant disorder, which is associated with an increased risk of breast and endometrial cancer occurrence.<sup>62–64</sup> Other conditions related to the syndrome include epithelial (predominantly follicular) thyroid cancer, facial trichilemmomas (hamartomas of the infundibulum of the hair follicle), fibrocystic breast disease, gastrointestinal hamartoma and macrocephaly.<sup>62</sup> Mucocutaneous lesions (cutaneous papules, mucosal papillomas) are considered as pathognomonic finding.<sup>5</sup> Other authors described colonic polyps and esophageal glycogenic acanthosis as pathognomonic findings in CS.<sup>66</sup> The lifetime risk of breast cancer development for PTEN carriers varies 77% to 85%, whereas endometrial cancer occurs at the ages of 30–49 years, and the lifetime risk is 13–28%.<sup>31,62</sup> However, cases of endometrial cancer development associated with CS have been described in adolescent.<sup>63,64</sup> Some authors suggested formal evaluation (germline PTEN mutation analysis) for CS to be considered for adolescent patients with endometrial cancer.<sup>63</sup>

### Diagnosis, Testing and Screening

CS testing should be performed for individuals from a family with known PTEN mutation or with a personal history of Bannayan-Riley-Ruvalcaba syndrome.<sup>57</sup> Additionally, lack of PTEN expression by immunochemistry may help in diagnosis.<sup>61</sup> Early diagnosis of CS is essential in order to prevent the development of malignancies.<sup>65</sup> NCCN guidelines include major and minor testing criteria for CS. Individuals have two or more major criteria (one must be macrocephaly), three major criteria (without macrocephaly), one major and three or more minor criteria or 4 and more minor criteria are candidates for CS testing. Criteria are available on NCCN site.<sup>57</sup> Cases, which cover some, but not all diagnostic criteria are known as Cowden-like syndrome.<sup>31</sup>

Annual mammography or MRI with contrast should be considered for women with CS at age 30–35 years or 5–10 years before the earliest known family breast cancer.<sup>57,65</sup> MRI with contrast is the preferable imaging modality as is it more sensitive than mammography. Moreover, it can identify invasive breast cancer earlier compared to mammography.<sup>57,65</sup>

Although endometrial cancer screening has no proven benefit and the value of surveillance is limited, it is recommended endometrial sampling and transvaginal ultrasound every 1–2 years after the age of 30–35 years or 5 years before age of earliest endometrial cancer in the family.<sup>62,65</sup> Transvaginal ultrasound in premenopausal women is not recommended for screening.<sup>57</sup>

### Pathology

Low-grade endometrioid carcinomas and rarely serous endometrioid carcinoma are associated with CS.<sup>31,68</sup>

### Risk-Reducing Surgery

As there are many controversies, the risk-reducing bilateral mastectomy should be considered on an individual basis.<sup>61</sup> NCCN recommends prophylactic hysterectomy after childbearing and after careful discussion with patients.<sup>57</sup>

## Li–Fraumeni Syndrome

### Definition, Pathogenesis and Epidemiology

Li-Fraumeni Syndrome (LFS), also known as sarcoma, breast, leukemia, and adrenal gland (SBLA) cancer syndrome, is an autosomal-dominant hereditary cancer caused by germline loss-of-function mutations in TP53 (missense mutations).<sup>62,69–72</sup> The TP53 gene is located at the chromosome 17p13.1.<sup>69</sup> Gene mutations are more likely to be inherited or can arise early in embryogenesis, but 14% of patients harbor de novo TP53 mutations.<sup>62,69</sup> It is estimated that TP53 mutations occurred in approximately 70% of Li-Fraumeni syndrome and 40% of Li-Fraumeni-like families.<sup>69</sup> Mutations of that gene lead to an estimated 50-fold risk over the general population of developing several types of cancer.<sup>70</sup>

The incidence of LFS is approximately one in 20,000 people with predominance in female population.<sup>70</sup> Breast cancer is the most observed cancer and affects approximately 54% of women by the age of 70 years.<sup>62</sup> Roughly, 3–8% of women with breast cancer and that syndrome are diagnosed under 30 years.<sup>57</sup> Juvenile onset of cancers is often observed in LFS and more than half of cancers or soft-tissue sarcomas related to LFS occur before age 30.<sup>71</sup> The most common malignancies associated with LFS are soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, brain tumors, premenopausal breast, leukemia, bronchoalveolar lung cancer, colorectal, and gastric cancer. Soft tissue sarcoma, brain tumors, and adrenocortical carcinoma occur in young patient and sarcomas account 36.8% of all cancers in childhood.<sup>62,70</sup> Among them, the most common type are osteosarcomas (40.4%), sarcoma not otherwise specified (17%), rhabdomyosarcoma (16.5%), leiomyosarcoma (9.1%), and liposarcoma (4.9%).<sup>70</sup> The risk of developing malignancy is approximately 40% by age 20, and more than 90% by age 70. More than half of these patients will develop any type of second tumor.<sup>72</sup> Approximately 7–8% of patients will develop leiomyosarcoma of any site at a median age of 40 years.<sup>73</sup> Although there are cases of endometrial or ovarian cancer and LFS, even in adolescent, the link to the syndrome is not definitely established.<sup>71,74</sup>

### Diagnosis and Testing

Different authors had proposed many testing criteria for LFS through the years, but the most commonly used are the classic Li criteria and the Chompret criteria (Table 2).<sup>57,69,75</sup> Individuals who meet LFS testing criteria or patients with pathogenic variant verified on tumor genomic testing should undergo germline testing.<sup>57</sup> Additionally, an individual from a family with a known TP53 mutation should also be tested for LFS.<sup>57</sup>

### Screening

Screening for LFS associated breast cancer starts after age 20 years and includes annual breast MRI with contrast and mammogram with eventual tomosynthesis.<sup>57</sup> As preoperative diagnosis of uterine leiomyosarcoma has not been

**Table 2** Classic and Chompret Testing Criteria for Li-Fraumeni Syndrome

Classic Li- Fraumeni Criteria	Chompret Testing Criteria for Li-Fraumeni Syndrome
Individual with a sarcoma diagnosed before age 45 years	Individuals with a tumor belonging to LFS tumour spectrum (, premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma) before age 46 years and at least one first or second-degree relative with LFS tumour (other than breast cancer if probands has breast cancer) before age 56 years or with multiple tumours at any age
A first-degree relative diagnosed with any cancer before age 45 years	Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and initial of which occurred before age 46 years
A first- or second-degree relative diagnosed with any cancer before age 45 years or a sarcoma at any age	Individual with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset and irrespective of family history
	Individuals with breast cancer before age 31 years

established yet, screening is not possible. However, for PT53 mutation carriers annual whole-body MRI is recommended.<sup>57</sup>

### Pathology

Breast cancer associated with LFS tend to be mostly of ductal type and estrogen receptor positive with frequent HER2 co-expression. Prominent tumor infiltrating lymphocytes, nuclear atypia and high mitotic activity are observed.<sup>76</sup> A case of small cell carcinoma of the ovary, hypercalcemic type and concurrent pleomorphic liposarcoma of the cervix associated with LFS has been described in medical literature.<sup>77</sup>

### Risk-Reducing Surgery

As TP53 is frequently encountered in various cancers, it rarely has pathogenic variants in the germline.<sup>62</sup> As it is difficult to establish the diagnosis by tumor profiling, a prophylactic bilateral mastectomy should be discussed after accurate medical and family history of each patient.<sup>62</sup>

## Peutz-Jeghers Syndrome

### Definition and Epidemiology

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disease, which is characterized by gastrointestinal hamartomatous polyposis and mucocutaneous pigmentation in the oral mucosa, lips, wings of the nose, fingers and toes.<sup>78–80</sup> Mucocutaneous pigmentation occurs in approximately 95% of patients with PFS, but tend to disappear with age.<sup>62,78</sup> The syndrome is also associated with increased risk of malignancies of the gastrointestinal tract and extra-gastrointestinal organs with predominance of gynecologic ones (malignancies of breast, ovary, uterine cervix and endometrium).<sup>79</sup> However, increased risk of leukemia and renal, pulmonary, bone cancer has been observed.<sup>81</sup> The estimated incidence of the disease is 1 in 50,000–200,000 live births.<sup>79</sup> Despite the lung carcinoma, which is more common in men, there is no significant difference of developing malignant tumors according to sex.<sup>79</sup> However, females have earlier onset of malignant tumors than men.<sup>79</sup> The relative risk of ovarian, cervical and uterine cancers associated with this syndrome is 18–21%, 10% and 9%, respectively.<sup>71</sup> The estimated lifetime risk for breast cancer is approximately 24–54%.<sup>67</sup>

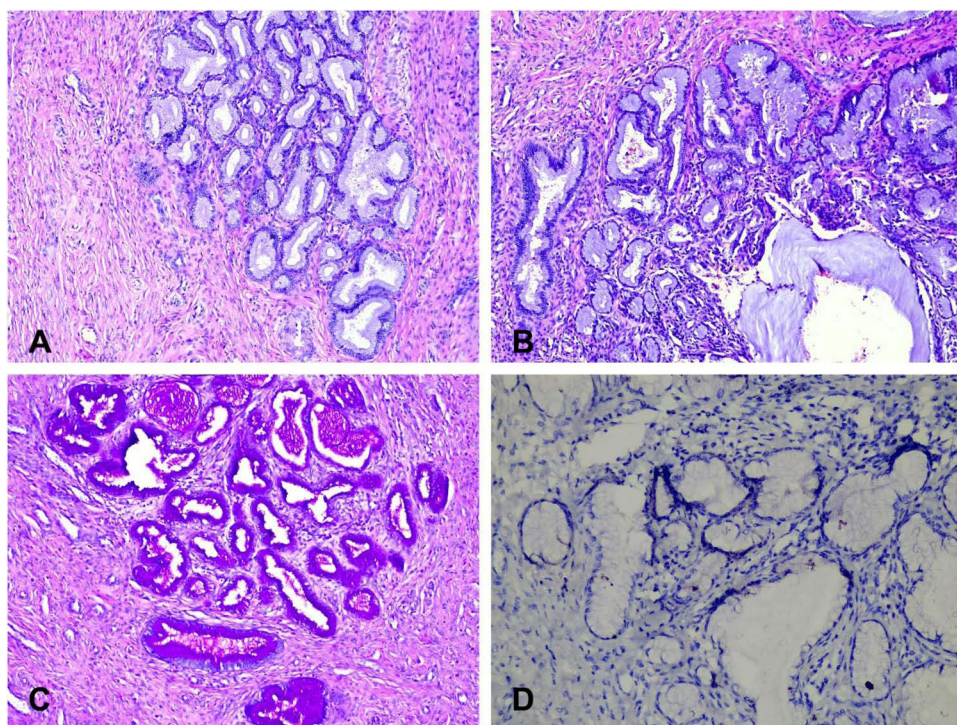
### Pathogenesis

PJS is caused by a germline mutation in the tumor suppressor serine/threonine kinase 11 gene (STK11), which was previously known as liver kinase B1 (LKB1).<sup>67,81</sup> The gene is located on chromosome 19p.13.3 and it is involved in cell cycle activities, mTOR (mammalian target of rapamycin) regulation, p53-dependent apoptosis and the regulation of vascular endothelial growth factor.<sup>67,80</sup> STK11 is found in approximately 94% of affected families and 25% of newly diagnosed cases are due to sporadic de novo mutations.<sup>67</sup>

### Pathology

PJS-associated gynecological cancers have characteristic histological types.<sup>71</sup> Ovarian tumors related to PJS are mainly the sex-cord tumors with annular tubules (SCTAT) with morphologic features between granulosa cell and Sertoli cell tumors. SCTAT are observed in 21% of women with an average age of diagnosis 28 years.<sup>62</sup> Other histological ovarian types that have been observed in this syndrome are Sertoli cell, mucinous, serous and mature teratoma.<sup>71</sup> SCTAT associated PJS have a lower risk of malignant transformation than the sporadic ones.<sup>71</sup> In the majority of cases, SCTAT with PJS was multifocal, bilateral, small and required microscopy to confirm the diagnosis, whereas SCATAT in general population are often unilateral and large.<sup>80</sup>

PJS-related cervical tumors include minimal deviation adenocarcinoma (MDA), lobular endocervical glandular hyperplasia (LEGH) and cervical gastric-type mucinous adenocarcinoma.<sup>31,62,82</sup> The risk of MDA occurrence in PJS patients is estimated to be 15–30%.<sup>79</sup> The average age of onset is 34–40 years, whereas that of MDA patients without PJS is 55 years.<sup>62,80</sup> Actually, MDA is an adenocarcinoma of the uterine cervix, which shows gastric-type differentiation.<sup>78</sup> LGEH has been identified adjacent to up to 50% of MDA and it is known as a precursor lesion of MDA.<sup>83</sup> MDA is a highly aggressive tumor with a dismal prognosis. Recurrences occur in the majority of patients within 2 years of diagnosis.<sup>77</sup> In Figure 5 is shown lobular endocervical glandular hyperplasia.



**Figure 5** Histology of lobular endocervical glandular hyperplasia. **(A)** – Lobular endocervical glandular hyperplasia (HE  $\times 100$ ). **(B)** – Glandular hyperplasia with lobular/acinar architecture composed of a central gland with cystic dilation, surrounded by smaller glands and cysts arranged in a floret-like pattern (HE  $\times 200$ ). **(C)** – Lobular endocervical glandular hyperplasia (PAS reaction  $\times 100$ ). PAS+ neutral mucin is observed in the cytoplasm of glandular cells. **(D)** – Lobular endocervical glandular hyperplasia (IHC-CEA  $\times 200$ ).

## Screening

It is possible for cervical cancer associated with PJS syndrome and include Pap smear and pelvic examination annually after 18–20 years of age. Screening for breast cancer related to PJS includes mammography and MRI annually after 30 years of age. Adolescent with suspected PJS should undergo annual physical examination for precocious puberty after 8 years of age.<sup>57</sup>

## Risk-Reducing Surgery

The benefits of RRS for gynecological cancers associated with Peutz-Jeghers syndrome have not been estimated.

## Ataxia-Telangiectasia

### Definition and Epidemiology

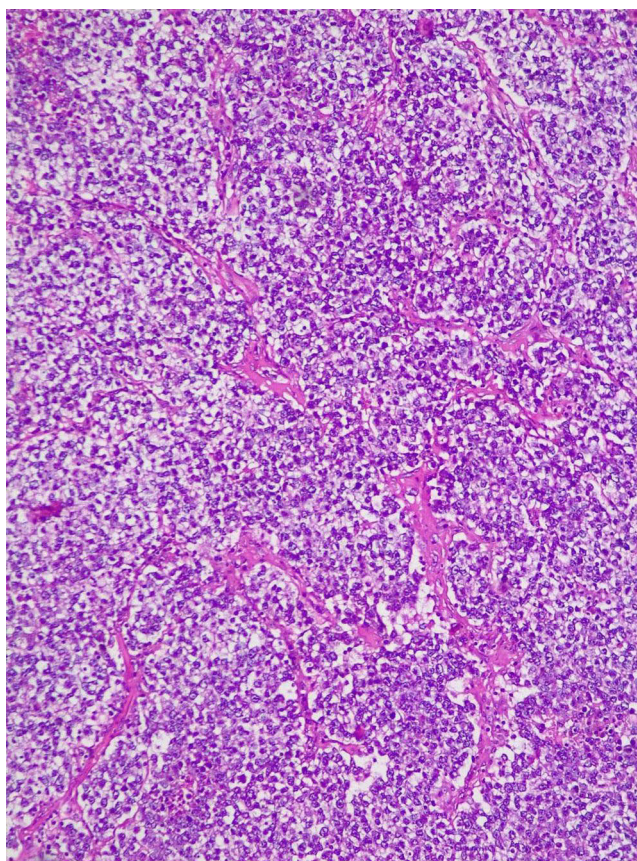
Ataxia-telangiectasia (AT) is an autosomal recessive hereditary disease, which include progressive cerebellar ataxia, oculomotor apraxia, choreoathetosis, sinopulmonary infections and oculocutaneous telangiectasia. The syndrome is also associated with radiosensitivity, primary immunodeficiency, sterility and high incidence of malignancies.<sup>31,84–86</sup> The overall incidence of the AT syndrome is estimated to be 1 case per 40,000–100,000 live births.<sup>31,87</sup>

### Pathogenesis

AT is caused by a punctual mutation in ATM gene localized in chromosome 11q22.3-23.1. This gene encodes a serine/threonine protein kinase that regulates the cell cycle and repair of DNA double-stranded breaks. Absence of ATM leads to genomic instability or DNA damage response, leading to carcinogenesis.<sup>31,84–86</sup>

### AT and Gynecological Malignancies

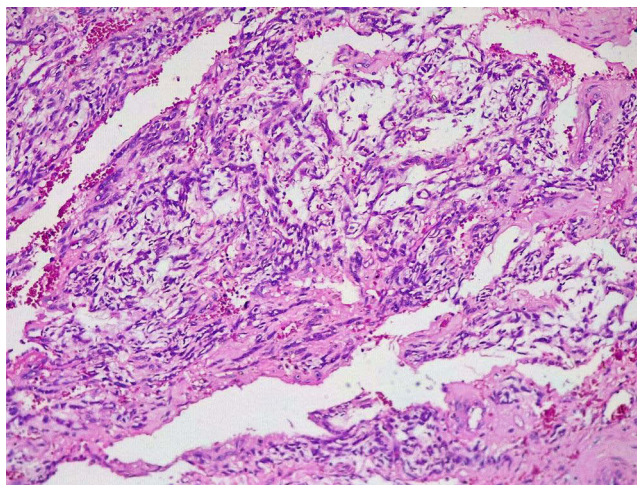
Patients with AT syndrome have an increased risk of developing leukemias and lymphomas.<sup>81</sup> According to the WHO, the ovary is the only gynecological site with neoplasms.<sup>31</sup> However, different studies showed association between uterine, breast cancer and AT syndrome.<sup>88,89</sup> Veiga- Fernandez et al reported for an increased risk (20–30%) for ATM



**Figure 6** Histology features of ovarian dysgerminoma. Sheets and nests of monotonous tumor cells separated by thin fibrous septa. Cells are polygonal with well-defined cell borders and abundant clear cytoplasm (HE x 10).

gene carriers for developing breast cancer.<sup>88</sup> Authors concluded that ATM carriers have a moderate-high risk of developing breast cancer.<sup>88</sup>

Ovarian tumors in AT syndrome patients are from non-epithelial origin – often dysgerminomas, and rarely gonadoblastomas and yolk sac tumors (Figures 6 and 7).<sup>31,84–86</sup>



**Figure 7** Histological features of ovarian yolk sac tumor. Mesenchyme-like pattern – tumor cells with variable atypia scattered in edematous and myxomatous connective tissue (HE x 10).

## Risk-Reducing Surgery

It is not reported as patients with AT syndrome have an average life expectancy of 25 years.<sup>31,87</sup>

## DICER1 Syndrome

### Definition and Epidemiology

DICER1 syndrome, first described in pulmonary blastoma, is a rare genetic autosomal dominant condition, which is associated with increased risk of neoplasms – pleuropulmonary blastoma, Wilms tumor, renal sarcoma, pineoblastoma, pituitary blastoma, thyroid cancers, embryonal rhabdomyosarcoma of the uterine cervix, gynandroblastomas and Sertoli-Leydig ovarian cell tumor.<sup>32,90–96</sup> It is estimated that approximately 1:2529–1:10,600 of people carry a pathogenic or likely pathogenic DICER1 variant.<sup>93,94</sup>

### Pathogenesis

The syndrome is associated with mutation in the DICER1 gene, which is located on chromosome 14q32.13.<sup>90</sup> The gene encodes an RNA endonuclease (Dicer), which is essential for processing microRNAs in the RNA interference pathway.<sup>31,90</sup> The children of DICER1 carriers have a 50% chance of inheriting the mutation as it is inherited as an autosomal dominant condition with decreased penetrance.<sup>93</sup> Mosaicism for missense variants in the five hotspot codons in the RNase IIIb domain (E1705, D1709, G1809, D1810 and E1813) have been found. That explains the possible presence of tumors in adolescence without a DICER1 germline mutation.<sup>91,92</sup>

### Testing

Genetic counseling and testing is recommended for individuals with a personal history of at least one major or two minor indications for testing. Additionally, individuals, which have one minor indication and a family history of a major or minor indication, are also candidates for testing. Some of the major and minor indications are shown in Table 3. The majority of indications for DICER1 genetic counseling and testing surveillance strategies are well described by Schultz et al.<sup>93</sup>

### DICER1 Syndrome and Gynecological Malignancies

As mentioned above, the gynecological neoplasms associated with DICER1 syndrome are embryonal rhabdomyosarcoma of the uterine cervix, gynandroblastomas and Sertoli-Leydig ovarian cell tumor.<sup>90–97</sup> Ovarian carcinoid tumor in a DICER1 carrier has also been described.<sup>97</sup> Most of Sertoli-Leydig ovarian tumors are unilateral and diagnosed at early stage (Stage I).<sup>98</sup> The majority of these tumors occur in adolescence. Young patients with gynandroblastomas and Sertoli-Leydig ovarian cell tumors often presented with virilization or amenorrhea.<sup>97</sup> Therefore, gynecologists should be aware of a DICER1 syndrome and such symptoms in adolescence.

**Table 3** Some of the Major and Minor Indications for DICER1 Genetic Counseling

Major	Minor
Individuals with PPB	Renal cysts
Lung cysts in childhood	Wilms tumor
Cystic nephroma	Multinodular goiter or differentiated thyroid cancer
Gynecological neoplasms – gynandroblastomas, Sertoli-Leydig ovarian cell tumor, embryonal rhabdomyosarcoma,	Poorly differentiated neuroendocrine tumor
Urogenital neuroendocrine tumors	Undifferentiated sarcoma
Pituitary blastoma	Macrocephaly
Pineoblastoma	Consider testing for any childhood cancer in constellation with any other minor criteria

## Surveillance Recommendations for Gynecological Malignancies

Patients and their parents should be familiar with possible gynecological syndromes due to DICER1-related tumours – hormonal symptoms including virilization, recurrent abdominal pain, and abdominal mass. That will provide an immediate imaging evaluation if clinically indicated. Schultz et al recommended pelvic and abdominal sonography every 6–12 months. Moreover, they stated that pelvic US should continue throughout adulthood. Surveillance imaging should continue until at least 40 years of age, although the ultimate time of imaging remains undetermined.<sup>93</sup>

## Gonadal Dysgenesis

### Definition and Epidemiology

Gonadal dysgenesis (GD) comprises a variety of sexual differentiation disorders with different somatic or genetic features.<sup>77,78</sup> The syndrome includes the following subtypes – 46, XY pure (complete) GD (Swyer syndrome); 46, XX complete GD; 45, X complete GD (Turner syndrome), partial GD and mixed GD (asymmetric or atypical GD – 45, X/46, XY mosaicism).<sup>23,77,78</sup> The syndrome affects one in 4500–5000 births.<sup>79</sup> GD is associated with an increased risk of gonadal tumor formation.<sup>77</sup>

### Gonadal Dysgenesis and Gynecological Cancers

Patients with GD are at increased risk of pure or mixed germ cell tumors.<sup>99–102</sup> The incidence of gonadal tumors in Swyer syndrome is approximately 30%, of which the majority are gonadoblastomas. Gonadoblastomas occur in 96% of patients with GD and tend to be bilateral. Gonadoblastomas are considered to be in situ germ cell neoplasms, which are associated with up to 50–60% risk of developing dysgerminoma.<sup>99,103</sup> Other germ cell tumors such as immature teratoma, seminomas, yolk sac tumors, embryonal carcinomas and choriocarcinoma can be encountered in patients with GD.<sup>99–103</sup> Approximately 6% of patients with Turner syndrome have a mosaic karyotype (partial fragments of the Y chromosome).<sup>99</sup> The majority of patients with Turner syndrome, who develop gonadal tumors are those with mosaic karyotype. In conclusion, gonadal tumors often occur in females with GD and Y-chromosome or Y-derived sequences in their genome.<sup>103</sup> GD-related tumors have the same histological features as their non-syndromic counterparts.<sup>31</sup>

### Pathogenesis

Genes DDX3Y and TSPY, which are localized on the proximal part of the short and long arms of the Y chromosome, are found in the majority of patients with gonadal dysgenesis and gonadoblastomas or germinoma.<sup>31,104</sup>

### Diagnosis

Preoperative diagnosis of GD and ovarian masses is mandatory as it can help surgeons to evaluate the necessity of gonadectomy before surgery.<sup>102</sup> Therefore, karyotyping or genetics testing should be evaluated in patients with amenorrhea, delayed pubertal development and pelvic masses.<sup>102,105</sup> Capito et al stated that in cases of ovarian tumour, delayed pubertal development, moderate  $\beta$ HCG level and elevated FSH level, Swyer syndrome and dysgerminoma should be suspected.<sup>105</sup> Authors concluded that preoperative karyotype analysis should be performed in such cases.<sup>105</sup>

### Risk-Reducing Surgery

The risk of GD-associated malignancies occurs in adolescence and increases with age in patients with Y chromosome or Y-derived sequences. The optimal protocol in the management of DSD is controversial.<sup>106</sup> According to some authors, prophylactic gonadectomy should be performed when the diagnosis of GD is established.<sup>99</sup> Currently, the majority of authors stated that the optimal timing of gonadectomy should be decided by multiple factors including the subgroup of disorder (gonadal dysgenesis, androgen insensitivity syndrome, androgen synthesis defects, etc), age and development of secondary sex characteristics.<sup>103</sup> Lui et al concluded that the optimal time for prophylactic gonadectomy is around age 16–18 when secondary sexual characteristics are developed. However, this step requires an accurate diagnostic evaluation in order to exclude premalignancy.<sup>103</sup> Abaci et al stated that safe and well-accepted guidelines for prophylactic gonadectomy in patients with GD are needed, as there are only a few prospective studies.<sup>106</sup>

## Tuberous Sclerosis

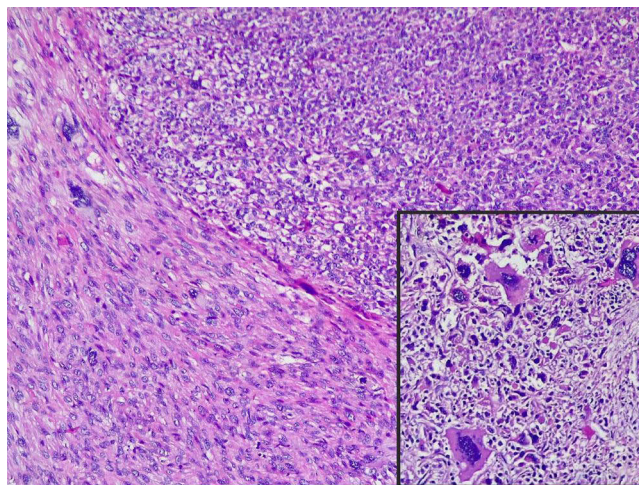
Tuberous sclerosis (TS) is an autosomal dominant neurocutaneous disorder, which is associated with the occurrence of benign congenital tumors in multiple organs. Neoplasms such as perivascular epithelioid cell differentiation (PEComa) including angiomyolipoma and lymphangiomyomatosis, can occur in association with TS. PEComas are an unusual group of rare mesenchymal neoplasms, composed of cells, which coexpress smooth muscle and melanocytic markers. These cells are also known as “perivascular epithelioid cells”. In the female genital tract, the most common location of PEComa is the uterine corpus, although other genital locations have been described (Figure 8).<sup>107–109</sup> Although association between TS and PEComa is controversial, many case reports described PEComa in TS (Figure 8).<sup>107–110</sup> Further larger studies are needed to prove the described association.

## Multiple Endocrine Neoplasia Type I and Type II

Multiple endocrine neoplasia Type I (MEN I) is an autosomal dominant inherited syndrome, which is associated with parathyroid, anterior pituitary and enteropancreatic endocrine cell tumors.<sup>111,112</sup> The MEN I gene is a tumor suppressor gene, which is located on chromosome 11q13. The MEN I gene encodes the protein menin.<sup>113,114</sup> Tumor occurrence in MEN I is explained by the “two hits” hypothesis where women affected by familial MEN I inherit one wild-type and one mutant allele. Tumor development is associated with later mutation of the remaining wild-type allele.<sup>113</sup> MEN II is an autosomal dominant inherited syndrome characterized by medullary thyroid carcinoma, with or without pheochromocytoma and hyperparathyroidism.<sup>111,112</sup> MEN II is divided into three subtypes: MEN IIA (Sipple’s syndrome), MEN IIB and familial medullary thyroid carcinoma. MEN II is caused by the rearranged during transfection (RET) gene mutations.<sup>115</sup> Numerous case studies reported the association between MEN I/II and ovarian carcinoids (Figure 9). Tamsen and Mazur reported a case of a woman with ovarian stromal carcinoid and MEN IIA. Authors concluded that MEN could be associated with ovarian carcinoids.<sup>116</sup> Spaulding et al described a case of ependymoma and carcinoid tumor arising from a mature cyst teratoma in a patient with MEN I. Authors discussed that MEN I could alert the pathogenesis of ovarian teratomas as they undergo new neoplastic transformation.<sup>113</sup> Recently, case reports of ovarian carcinoids and genetically confirmed cases of MEN I have been described.<sup>111,117</sup> However, large prospective studies are needed to prove the association and to establish adequate diagnosis, screening and management of such patients.

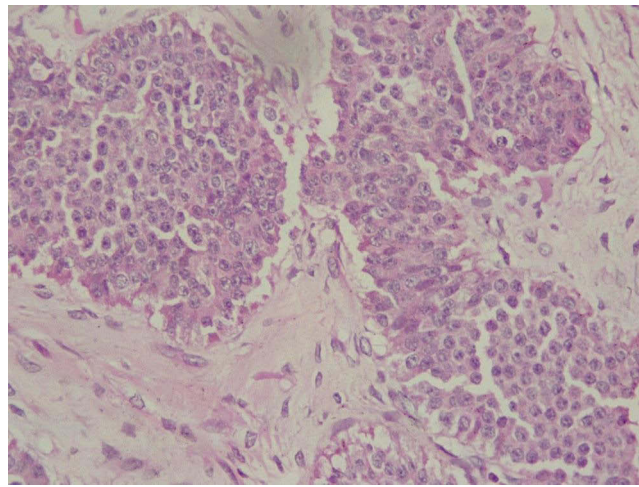
## Rhabdoid Tumour Predisposition Syndrome

Rhabdoid tumour predisposition syndrome is characterized by germline mutations involving the SMARCB1 gene or the SMARCA4 gene. SMARCB1 gene mutations are associated with renal rhabdoid tumor, whereas SMARCA4 gene mutations are related with manifestation of rare gynecological neoplasm.<sup>10</sup>



**Figure 8** Histological features of uterine PEComa. Upper right - solid nodules of epithelioid cells with eosinophilic-to-pale cytoplasm, well-defined cellular membranes and mild-to-moderate nuclear pleomorphism. Some cells displayed large bizarre nuclei /insertion/. Lower left - spindle-cell component (HE x 10, insertion HE X 40).





**Figure 9** Histological features of ovarian carcinoid. Round to oval tumor cells with pink cytoplasm and centrally located nuclei with salt-and-pepper chromatin, arranged in solid nests (HE  $\times$  10).

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) and undifferentiated uterine sarcoma (UUS) are rare and aggressive tumors of the female genital tract with a dismal prognosis.<sup>118,119</sup> The median age of diagnosis of SCCOHT is 24 years. The majority of patients with SCCHOT presented at advanced stage of the disease, but even if the tumor is diagnosed at stage I, the 5-year OS is 30–55%.<sup>120–124</sup> It has been reported that these tumors are oncogenically driven by somatic and/or germline mutations in SMARCA4.<sup>118,119</sup> That gene encodes the BRG1 protein, which participates in SWI/SNF chromatin remodeling and functions as a gene activator or repressor.<sup>120–124</sup> Connor et al described a case of a single family with an inherited germline SMARCA4 mutation. SCCOHT and UUS occurred in two different family members (a daughter and her mother).<sup>118</sup> Authors also made a literature review and found SMARCA4 inactivating genomic alterations in 48 cases of SCCOHT and 17 cases of UUS. Germline mutations of patients with SCCOHT and UUS were 38% and 11.8%, respectively.<sup>118</sup> Studies concluded that SCCOHT and USS are morphologically and genetically related and a germline link between these tumors is further established.<sup>118,120,121</sup> Witkowski et al and Pejovic et al described cases of SCCOHT in families affected by germline SMARCA4.<sup>122,124</sup> Therefore, genetic consultation should be offered for all patients with suspected SCCOHT and USS. If a germline SMARCA4 mutation is identified, genetic testing is recommended for all risk family members.<sup>118</sup>

There is no effective screening program for SMARCA4 carriers. Pejovic et al stated that serial pelvic ultrasound and serum calcium level measurements could be useful for patient with SCCOHT.<sup>124</sup> Additionally, there are limited data about risk-reducing surgery.<sup>118,122,123</sup> In medical literature, there are two case reports of risk-reducing surgery in patients diagnosed with SCCOHT and SMARCA4 mutation.<sup>122,124</sup> Pejovic et al reported a case of 13-year-old pubertal Caucasian girl with a family history of SCCOHT. Her mother and maternal aunt were diagnosed with SCCOHT prior to the identification of the SMARCA4 mutations and died soon after the diagnosis. The variant was maternally inherited as the patient was found to carry the same mutation. The patient underwent bilateral salpingo-oophorectomy at the age 13 after patient family consultation.<sup>123</sup> Berchuck et al described a case of a 33-year-old multipara patient, which had three female relative previously diagnosed with SCCOHT. After careful explanation and consulting with the patient, she underwent total laparoscopic hysterectomy with bilateral-salpingo-oophorectomy.<sup>123</sup> Authors concluded that prophylactic oophorectomy could prevent SCCOHT in carriers of germline SMARCA4 mutations.<sup>123</sup> Berchuck et al stated that patients who desire children might be best served by oocyte cryopreservation prior to prophylactic oophorectomy.<sup>123</sup> Further studies are needed to provide adequate risk reducing surgery guidelines.

## Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome, which is characterized by susceptibility to diffuse gastric cancer (DGC) and lobular breast cancer (LBC).<sup>125–127</sup> Its incidence is approximately

5–10 per 100,000 births.<sup>125</sup> HDGC is caused by inactivating germline mutations in the CDH1 tumour suppressor gene. It is the coding gene for E-cadherin and it is located on chromosome 16q22.1.<sup>125–127</sup> The majority of cases of DGC and LBC in CDH1 carriers occur before age 40 years.<sup>127</sup> The estimated cumulative risk of gastric and breast cancers in females by age 80 years is 56% and 42%, respectively.<sup>127</sup> CDH1 carriers with HDGC have lower 1- and 5-years survival rates compared to HDGC patients without germline CDH1 mutations. LBC could be the first manifestation of HDGC.<sup>126,128</sup> Benusiglio et al even recommended a revision of the definition of HDGC and proposed for consideration the term ‘Hereditary Diffuse Gastric and Lobular Breast Cancer’.<sup>128</sup> Corso et al observed that CDH1 germline mutations are mutually exclusive with BRCA1/2 alterations.<sup>129</sup>

## Testing

Blair et al proposed a panel of 3 family criteria and 9 individual criteria for genetic testing (Table 4).<sup>125</sup>

## Screening and Risk Reducing Surgery

Although prophylactic gastrectomy carries a 3–6% mortality rate and a 100% morbidity rate, it is recommended for CDH1 carriers in their 20 or 30s. If gastrectomy is contraindicated or the patient refuses surgery, an endoscopic surveillance should be considered as an option. Prophylactic gastrectomy is not recommended after 70 years of age.<sup>125–127</sup> Screening recommendation for breast cancer includes breast self-examinations after 20 years of age, clinical breast examinations every six month after 30 years of age and MRI breast examination annually starting at age 30. MRI is the preferable imaging modalities as the sensitivity of detecting lobular breast cancer by mammography is low.<sup>126,127</sup> Prophylactic bilateral mastectomy is not routinely recommended as there are very limited number of CDH1 mutation carriers who underwent prophylactic mastectomy.<sup>126,127</sup> However, after genetic counseling, this surgical procedure could be offered accordingly with the patient.<sup>129</sup> In cases of LBC in CDH1 mutation carriers, contralateral mastectomy could be considered.<sup>126,130</sup>

## MUTYH-Associated Polyposis

MUTYH-associated polyposis is an autosomal recessive condition, which is characterized by germline mutations in the mutY homolog (MUTYH) base excision repair gene. The gene is located on the short arm of chromosome 1 and encodes MYH glycosylase enzyme, which is associated with DNA damage repair. The cumulative risk of colorectal cancer is approximately 63% by age 60. Both monoallelic and biallelic MUTYH carriers are at increased risks of other cancer development, despite its autosomal recessive pattern.<sup>131</sup> Biallelic MUTYH mutations are inherited from both parents and occur in 0.01–0.04% of the Caucasian population. The estimated risk of ovarian cancer for biallelic MUTHYH mutation carriers is 14%.<sup>132</sup> Win et al estimated that biallelic MUTYH mutation carriers had a 17-fold increased risk of ovarian cancer, compared with the general population.<sup>132</sup> Monoallelic carriers do not demonstrate an elevated risk of ovarian cancer, but

**Table 4** Genetic Testing Criteria for HGC

Family Criteria	Individual Criteria
Two or more cases in family regardless of age and at least one diffuse gastric cancer	DGC before 50 years of age
One or more cases of DGC regardless of age, and one or more cases of LBC before 70 years of age	DGC in individuals of Maori ethnicity regardless of age
Two or more cases of LBC before 50 years of age	DGC in individuals with a personal or family history of cleft lip or cleft palate regardless of age
	History of DGC and LBS diagnosed before 70 year of age
	Bilateral LBC diagnosed before 70 years of age
	Gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals before 50 years of age

**Table 5** Hereditary Gynecologic Cancer Syndromes

Syndrome	Gene	Incidence	Cancers	Screening	Risk-Reducing Surgery
<i>Lynch syndrome</i>	MLH1, MSH2, MSH6, PMS2	1/660–2000	Colon, uterus, ovary, pancreas, gastrointestinal, kidney	CS – annually after 40 years of age; PE, US, Ca-125 – annually after 30–45 years of age	THBSO after completion of childbearing
<i>HBOCS</i>	BRCA1, BRCA2	1/300–600	Breast, ovary, fallopian tube, peritoneum, pancreas, skin(melanoma)	PE, US, Ca-125- every 6 months at age 35 MRI/mammogram – annually after 25 years of age	RRSO for BRCA1/2 BRCA1: 35–40 years BRCA2: 40–45 years Or after completion of childbearing; PBM after childbearing
<i>Cowden syndrome</i>	PTEN	1/200,000	Breast, uterus, thyroid	MRI/mammography-annually after 30–35 years of age; ES and US after 30–35 years of age	THBSO and PBM after the completion of childbearing
<i>Li-Fraumeni syndrome</i>	TP53	1/20,000	Breast, sarcoma, leukemia, adrenal gland, lung, stomach,	MRI/mammography after 20 years of age	Discuss PBM
<i>Peutz-Jeghers syndrome</i>	STK11	1/50,000–200,000	Breast, ovary, gastrointestinal, uterus, uterine cervix, lung, bone, leukemia	PAP smear and PE after 18–20 years of age; MRI/mammography after 30 years of age	Not estimated
<i>Ataxia-telangiectasia</i>	ATM	1/40,000–100,000	Leukemia, lymphomas, ovary, breast	Not estimated	Not estimated
<i>DICER1 syndrome</i>	DICER1	1/ 10,600	Lung, kidney, uterine cervix, ovary	Not estimated	Not estimated
<i>Gonadal dysgenesis</i>	46, XY; 45, X; 46 XX	1/ 4500–5000	Ovary	Not estimated	RRSO after 16–16 years of age
<i>Tuberous sclerosis</i>	TSC1; TSC2	1/6760–13,520			
<i>MEN Type I</i>	MEN 1	1/ 30,000	Parathyroid, pituitary, pancreas, small bowels, ovary	Not estimated	Not estimated
<i>MEN Type II</i>	RET	1/ 30,000	Thyroid, parathyroid, adrenal glands (PHEO) ovary	Not estimated	Not estimated
<i>HSCCOHT, HUUS</i>	SMARCA4	Unknown	Ovary, uterus	PE, Ca-125, serum calcium level - annually	Not estimated
<i>HDGC</i>	CDH1	5/10–100,000	Stomach, breast	CS – 25–30 years; MRI after 30 years of age	PG after 20–30 years of age; PBM- not recommended
<i>MUTYH-associated polyposis</i>	MUTYH	0.01–0.04% of the Caucasian population	Colon, rectum, ovary, uterus, breast	Not estimated	RRSO after 45–50 years of age

**Abbreviations:** HBOCS, hereditary breast-ovarian cancer syndrome; THBSO, total hysterectomy with bilateral salpingo-oophorectomy; MEN, multiple endocrine neoplasia; HSCCOHT, hereditary small cell carcinoma of the ovary, hypercalcemic type; HUUS, hereditary undifferentiated uterine carcinoma; HDGC, hereditary diffuse gastric cancer; PE, pelvic examination; US, ultrasonography; RRSO, risk-reducing bilateral salpingo-oophorectomy; ES, endometrial samplings; PG, prophylactic gastrectomy; PHEO, pheochromocytoma; PBM, prophylactic bilateral mastectomy; CS, colonoscopy.

according to some authors there is an increased risk of endometrial and breast cancer.<sup>131,132</sup> However, further studies are warranted to prove the association. The MUTYH mutated ovarian tumors are often of serous histology, but the MUTYH mutation and mechanism for oncogenesis demonstrated that multiple ovarian cancer histologies could be related to such a mutation.<sup>131–134</sup> More studies are needed to determine the optimal screening and risk-reducing surgery protocols.

The most important information of hereditary gynecologic cancer syndromes in the present article is summarized in Table 5.<sup>4–10,20–47,135–139</sup>

## Conclusion

Hereditary gynecologic cancer syndromes are a huge group of syndromes, where a tremendous progress has been made over the last decade in the evaluation and management. The availability and improvement of clinical genetic testing allows us to identify and consult patients and their families, which are at high risk of gynecologic cancer occurrence. Moreover, recommendations regarding epidemiology, pathology, screening and risk-reducing surgery have been developed for some gynecologic cancer syndromes. However, there also are many other questions that still need to be addressed regarding screening and risk-reducing surgery for some of the rarest inherited gynecologic cancers. Additionally, advances of molecular biology and genetic testing may improve treatment of these syndromes. Oncogynecologists should look beyond the horizon and start playing a greater role in the management of these high-risk patients. It must be underlined the importance of multidisciplinary management for such patients in order to achieve improvement of the quality of care and life.

## Data Sharing Statement

The authors declare that all related data are available concerning researchers by the corresponding author's email.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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