Abstract

Objective: To provide the physician with an overview of common genetic conditions that should be considered during a women’s annual gynaecological assessment to determine the patient’s risk or to initiate specific testing or referral to another subspecialty service, depending on personal or family history.

Options: This genetic information can be used for patient education and possible disease and/or mutation screening or diagnosis.

Outcomes: The use of this genetic information may allow improved risk-benefit assessment and management at the annual gynaecological examination.

Evidence: Studies published in English up to and including May 2010 were retrieved through searches of PubMed and the Cochrane Library, using appropriate controlled vocabulary (gynaecological diagnosis, genetic inheritance) and key words (genetic risk, genetic mutation, inheritance, family history, uterus, ovary, endometrial, vagina, colon, gastric, renal, breast, cardiac, thrombophilia, diabetes, epilepsy, leiomyomata uteri). Other literature sources were identified through searching the web sites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The levels of evidence are not adequate for evidence-based recommendations to be made.

Benefits, harms, and costs: This committee opinion will enhance the use of new genetic knowledge and its application to the annual gynaecological care of women. Risk management and diagnostic opportunities for genetic gynaecological conditions will be improved. A more complete understanding of genetic conditions may increase anxiety and psychological stress for women and their families.

Sponsors: Society of Obstetricians and Gynaecologists of Canada.

Recommendations

The levels of evidence are not adequate for evidence-based recommendations to be made.

INTRODUCTION

The objective of this committee opinion is to provide physicians with an overview of genetic conditions that should be considered during a woman’s annual gynaecological assessment. This will help to determine whether the patient has any specific genetic risk conditions so that specific testing can be initiated or referral made to another specialty service, depending on the patient’s personal or family history. New genes and other genetic factors are being rapidly identified, and a basic understanding of the common medical and surgical conditions that arise from them will help clinicians when they conduct systematic reviews at a woman’s annual or semi-annual gynaecological visit or when these conditions are discovered incidentally during other gynaecological investigations or surgeries.

This committee opinion reviews medical and surgical conditions with a genetic etiology that have gynaecological or obstetrical implications, and cancer and hereditary cancer syndromes that require annual follow-up.

MEDICAL OR SURGICAL CONDITIONS WITH A GENETIC ETIOLOGY THAT HAVE GYNAECOLOGICAL OR OBSTETRICAL IMPLICATIONS

Table 1 shows common medical and surgical conditions that have a multifactorial or single gene mode of inheritance that may be part of a woman’s personal or family history.

Diabetes Mellitus
The teratogenic risks associated with glucose imbalance in insulin-dependent diabetes were reviewed in a 2007 SOGC clinical practice guideline and in a 2002 review article.1,2

Maternal Cardiac Disease
Genetic cardiac disease can be considered as either congenital heart disease, with multifactorial, chromosomal, or genetic etiology, or coronary artery disease, with genetic and lifestyle risk factors.3 Congenital heart disease is typically identified in childhood, but with improved cardiac care, patients with congenital heart disease now live longer, frequently reaching child-bearing age. Chromosomal deletions (22q DiGeorge syndrome) and single gene disorders associated with congenital heart disease are summarized in Tables 2 and 3. Depending on the age of the patient and when the genetic association with the cardiac anomaly was recognized, testing for the specific gene mutation or chromosomal deletions may not have been completed when a patient presents for prenatal care.

Pre-conception counselling issues may be identified at an annual gynaecological visit. Patients should be made aware that if mutation/deletion is present in either parent, there is a risk it may be transmitted to the fetus. The availability of prenatal evaluation by invasive testing (amniocentesis, chorionic villus sampling) as indicated or by non-invasive screening/diagnosis by fetal echocardiography should be discussed with the prospective parents before pregnancy. Parents whose chromosome complement is “normal” according to test results (dependent on the cytogenetic/molecular level or detail of genetic testing) and who have an isolated congenital heart defect have an empiric increased risk of having a child with a congenital heart defect because of the multifactorial inheritance nature of the cardiac defect. This recurrence risk for isolated non-syndromic heart defects is estimated at 6.5% for an affected mother and 2.2% for an affected father.4 A fetal echocardiogram should be considered when either parent or a previous child was born with a congenital heart defect.

Factors related to screening and treatment of atherosclerotic heart disease are beyond the scope of this committee opinion, but if a strong family history is identified, the patient’s primary care physician and cardiology care provider should be notified that this is an area for evaluation and potentially for primary prevention

Epilepsy
Women with epilepsy have specific fertility and sexual issues that include a higher incidence of anovulatory cycles and infertility, ovarian cysts, and seizures related to changes in hormones of the hypothalamic pituitary axis (luteinizing hormone, prolactin).5 A woman with epilepsy may be up to 50% less likely to conceive spontaneously than a sibling without a seizure disorder. The exact etiology for this decreased fertility is unclear. Pre-conception counselling should be considered at a woman’s annual visits. For an epileptic woman who becomes pregnant, there are increased risks for birth defects secondary to the antiepileptic drugs she may be using. The teratology of prescription drugs was reviewed in a 2007 SOGC clinical practice guideline.6 Congenital malformations are estimated at 4% to 8% in

ABBREVIATIONS
AD autosomal dominant
AR autosomal recessive
CRC colorectal cancer
FAP familial adenomatous polyposis
HLRCC hereditary leiomyomatosis and renal cell cancer
HNPCC hereditary nonpolyposis colon cancer
MRKH Mayer-Rokitansky-Kuster-Hauser
MTHFR methylenetetrahydrofolate reductase
women with epilepsy and fetal antiepileptic drug exposure. The majority of defects are identified in the central nervous, orofacial, cardiovascular, and urogenital systems. Congenital anomaly screening in pregnancy should include a detailed ultrasound to identify structural defects in the fetus from 18 to 20 weeks, and possibly maternal serum alpha fetoprotein screening for open neural tube defects specifically. Joint SOGC-Motherisk guidelines indicate that women with epilepsy should supplement their diets with 5 mg of folic acid daily and a multivitamin to minimize the teratogenic component of the antiepileptic drugs.7 Monotherapy for epilepsy should be reviewed with the patient and her other physicians as a treatment option minimizing teratogenic risks.

### Uterine Leiomyomas

Uterine leiomyomas are the most common benign neoplasia developing within the uterus. It is not known whether a leiomyoma actually transforms into a malignant leiomyosarcoma, but the incidence of leiomyosarcoma is extremely low in premenopausal women when compared with the incidence in older postmenopausal women in whom they account for < 1% of uterine malignancies.8,9

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**Table 1. Common conditions with genetic contribution**

| Medical multifactorial | Atherosclerotic heart disease
| | Diabetes mellitus
| | Hypertension
| | Seizure disorders
| Oncology (indirect) multifactorial or single gene | Cancer (breast, ovarian, endometrial, colon)
| Genetic (single gene inheritance) | Bleeding disorder – hemophilia XL
| | – von Willebrand AD
| | Clotting disorder – antithrombin III AD
| | – protein C or S AD
| | – factor V Leiden AD
| Cystic fibrosis AR
| Familial hypercholesterolemia AD
| Fragile-X XL
| Glucose-6-phosphate dehydrogenase deficiency XL
| Hemoglobinopathies – sickle cell AR
| – thalassemia AR
| Huntington disease AD
| Marfan syndrome AD
| Muscular dystrophy XL
| Myotonic dystrophy AD
| Neural tube defect MF
| Neurofibromatosis AD
| Polycystic kidney AD/AR

**Table 2. Estimated 22q11 deletion frequency in congenital heart disease**

<table>
<thead>
<tr>
<th>Cardiac defect</th>
<th>Estimated deletion frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interrupted aortic arch</td>
<td>50 to 89</td>
</tr>
<tr>
<td>VSDs</td>
<td>10</td>
</tr>
<tr>
<td>With normal aortic arch*</td>
<td>3</td>
</tr>
<tr>
<td>With aortic arch anomaly†</td>
<td>45</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>34 to 41</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>8 to 35</td>
</tr>
<tr>
<td>Isolated aortic arch anomalies</td>
<td>24</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Transposition of the great arteries</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

VSD: ventricular septal defect.

*Left-sided aortic arch with normal branching pattern.

†Includes right aortic arch and/or abnormal branching pattern, cervical location, and/or discontinuous branch pulmonary arteries.

Table adapted with permission from Pierpont ME, Basson CT, Benson W, Gelb BD, Giglia TM, Goldmuntz E, et al.3
Genetic Considerations for a Woman’s Annual Gynaecological Examination

Genetic factors are now being identified. Somatic mutations and, less frequently, molecular alterations in the X chromosome must occur for the initiation and subsequent development of a myoma. The high prevalence of leiomyomas suggests that they result from stable mutations. Very specific genetic risks have been identified for HLRCC, which is inherited in an autosomal dominant fashion. Affected individuals demonstrate an increased risk for leiomyomas of the skin and uterus, as well as renal cancers. As leiomyomas have a prevalence of 30% in the female population (although this varies according to ethnicity), it is important for clinicians, gynaecologists, and other caregivers to be aware that HLRCC-associated kidney tumours are often biologically aggressive. Although screening for this mutation or for renal tumour in all women with leiomyomas is not recommended, clinicians should have a high index of suspicion when women present with hematuria suggestive of a renal tumour.

Thrombophilias

Thrombophilias can be inherited or acquired. The most common inherited disorders are mutations of factor V Leiden, prothrombin gene (G20210A mutation), and MTHFR mutation or homozygosity to MTHFR C677T, but the complete list of inherited disorders includes deficiencies in protein S, C, and Z or antithrombin III, homozygosity to 4G/4G mutation in PAI-1 gene, and polymorphisms in thrombomodulin gene. People of Caucasian heritage have a higher rate of genetic thrombophilias than other ethnic groups.

Several large studies have identified the association between thrombophilias and adverse pregnancy outcomes. Maternal problems are venous thromboembolism with deep vein thrombosis, pulmonary embolism, and cerebral vein thrombosis; peripheral and cerebral arterial thrombosis; and severe preeclampsia. Fetal and placental issues are thrombosis/infarction, placental abruption, recurrent miscarriage, fetal growth restriction, death, and stroke. In the presence of an inherited thrombophilia, the risk of developing preeclampsia has an estimated frequency of 4% to 27% with factor V Leiden, 0% to 11% with the prothrombin gene mutation, 1% to 25% with protein S deficiency, and 8% to 24% with the MTHFR variant. As some studies show the risk as being similar to baseline and others show a significantly increased risk, it remains unclear whether this association is significant.

Screening for inherited thrombophilias should be considered for women with a history of thromboembolism, including deep vein thrombosis. There have been few randomized trials, so definitive treatment and prophylaxis regimens have not been established. Within the genetic

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chromosome location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart defects</td>
<td></td>
</tr>
<tr>
<td>Familial congenital heart disease (ASD, atrioventricular block)</td>
<td>5q</td>
</tr>
<tr>
<td>D-TGA, DORV</td>
<td>2q</td>
</tr>
<tr>
<td>D-TGA</td>
<td>12q</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>8q</td>
</tr>
<tr>
<td></td>
<td>5q</td>
</tr>
<tr>
<td></td>
<td>20p</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>3p</td>
</tr>
<tr>
<td>ASD/VSD</td>
<td>8p</td>
</tr>
<tr>
<td></td>
<td>Xq</td>
</tr>
<tr>
<td>Heterotaxy</td>
<td>2q</td>
</tr>
<tr>
<td></td>
<td>3p</td>
</tr>
<tr>
<td></td>
<td>1q</td>
</tr>
<tr>
<td>Syndromes</td>
<td></td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>22q11</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>12q24</td>
</tr>
<tr>
<td>Alagille syndrome (PPS)</td>
<td>20p12</td>
</tr>
<tr>
<td>Char syndrome (PDA)</td>
<td>6p12</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>12q24</td>
</tr>
<tr>
<td></td>
<td>12p1.21</td>
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<tr>
<td></td>
<td>2p21</td>
</tr>
<tr>
<td>CHARGE association</td>
<td>8q12</td>
</tr>
<tr>
<td>Ellis-van Creveld syndrome</td>
<td>4p16</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>15q21.1</td>
</tr>
<tr>
<td>Marfan-like syndrome</td>
<td>3p22</td>
</tr>
<tr>
<td>Cardiofaciocutaneous syndrome</td>
<td>12p12.1</td>
</tr>
<tr>
<td></td>
<td>7q34</td>
</tr>
<tr>
<td></td>
<td>15q21</td>
</tr>
<tr>
<td></td>
<td>7q32</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>11p15.5</td>
</tr>
<tr>
<td>William syndrome/supravalvar aortic stenosis</td>
<td>7q11</td>
</tr>
</tbody>
</table>

ASD: atrial septal defect; D-TGA: D-transposition of great arteries; VSD: ventricular septal defect; DORV: double-outlet right ventricle; PPS: peripheral pulmonary stenosis; PDA: patent ductus arteriosus; CHARGE: coloboma, heart anomaly, choanal atresia, retardation, and genital and ear anomalies.

Table adapted with permission from Pierpont ME, Basson CT, Benson W, Gelb BD, Giglia TM, Goldmuntz E, et al.3
Table 4. Estimated number and lifetime risk of women who would develop or die of various types of cancer in 2007

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Lifetime risk of developing, 1 in</th>
<th>Lifetime risk of dying of, 1 in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Lung</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>Colorectal</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Endometrial</td>
<td>38</td>
<td>196</td>
</tr>
<tr>
<td>Skin</td>
<td>77</td>
<td>500</td>
</tr>
<tr>
<td>Ovarian</td>
<td>68</td>
<td>95</td>
</tr>
<tr>
<td>Cervical</td>
<td>135</td>
<td>385</td>
</tr>
</tbody>
</table>


thrombophilia group, most studies are observational with small, heterogeneous groups. A single RCT\textsuperscript{15} is available in which 160 women with at least 1 fetal loss after 10 weeks and heterozygosity for a single thrombophilia mutation (factor V Leiden, prothrombin G20210A mutation, protein S) were randomized to enoxparin 40 mg or low-dose ASA 100 mg daily. The enoxparin group had an increased live birth rate (86\% vs. 29\%), higher birth weight, and lower intrauterine growth restriction rates (10\% vs. 30\%) than the low-dose ASA group. Other thrombophilia treatment protocols are available.\textsuperscript{16,17} Referral to a treatment centre with expertise in the topic should be considered before anticoagulant treatment is initiated before or during pregnancy.

Pre-conception discussion with a woman with a thrombophilia and a past history of poor pregnancy outcome should include increased fetal surveillance starting at 24 weeks, with serial ultrasound (every 4 weeks) for fetal growth, umbilical artery Doppler, non-stress test and/or biophysical profile used as clinically required, and consideration of delivery by 39 weeks.\textsuperscript{11}

Contraception with estrogen-containing products is contraindicated unless long-term anticoagulation is used. Progestin-only products do not increase thromboembolic risks. Estrogen-containing hormone therapy may increase the risk of stroke and thromboembolic disease. Surgery on a woman with factor V Leiden requires thromboprophylaxis according to published protocols to decrease her thrombotic risk.\textsuperscript{18}

**Congenital Mullerian Anomalies**

Women with agenesis of the uterus and vagina but normal ovarian function and secondary sexual characteristics have Mayer-Rokitansky-Kuster-Hauser syndrome.\textsuperscript{19} A 2006 report of a cohort of 106 consecutive women with the MRKH syndrome reviewed other congenital anomalies associated with MRKH syndrome.\textsuperscript{18} Hypoplastic vagina was present in 61 women. Laterally displaced Mullerian remnants were present in 92 women, and 26\% of the remnants had a cavity with endometrial mucosa. Ovaries were extrapelvic in 16\%. Urinary tract abnormalities were present in 30\%, with unilateral renal agenesis (18\%), pelvic kidney (11\%), and horseshoe kidney (2\%) being the most common anomalies. The recognition of this wide variability of anatomical presentations is important for appropriate surveillance, diagnosis, and treatment of gynaecological problems in women with MRKH syndrome. A renal ultrasound is recommended to assess urinary tract anomalies, particularly before abdominal or pelvic surgery.

**RISK ASSESSMENT FOR CANCER AND HEREDITARY CANCER SYNDROMES (BACKGROUND, PERSONAL, FAMILY)**

Recent estimates of lifetime risk of a woman developing or dying from various types of cancer are shown in Table 4.\textsuperscript{20–22} Breast cancer occurs most frequently. It has a lifetime presentation risk of 1 in 8 and a death risk of 1 in 34 compared with cervical cancer, which has a presentation risk of 1 in 135 and a death risk of 1 in 385.

Despite these risks, a recent publication\textsuperscript{23} reported that a financially stable and well-educated population of women had very little knowledge or understanding of hereditary cancer risks. Cancers studied in this population included hereditary breast cancer, Lynch syndrome, and p16-related melanoma. Although approximately 11\% were identified as being at high-risk for at least 1 of the 3 syndromes (breast cancer 88.5\%, Lynch syndrome 6.1\%, p16-related melanoma 3.8\%), < 3\% had ever had genetic counselling or testing.

The discovery of genes responsible for hereditary cancer syndrome has led to specific recommendations for genetic testing for mutations in BRCA1 and BRCA2, responsible for hereditary breast and ovarian cancer, and the mismatch-repair genes responsible for the hereditary nonpolyposis colon cancer also known as Lynch syndrome.\textsuperscript{24} A 2007 commentary\textsuperscript{25} emphasized the need for more public education. A 2005 US Preventive Services Task Force recommendation\textsuperscript{26} indicates that women whose family history (first and second degree relatives) is indicative of deleterious mutations in BRCA1 or BRCA2 genes should be referred for genetic counselling and evaluation for these mutations. These women would benefit from obtaining information that would allow
informed choice about testing and further prophylactic treatment and risk-reduction surgery. This counselling should be done within a genetic oncology program by trained health care providers. There is increasing evidence to consider the benefits of chemoprevention or intensive screening in improving health outcomes in women who test positive for deleterious BRCA1 or BRCA2 mutations.\textsuperscript{27,28} However, there is fair evidence that risk-reduction surgery for these women significantly decreases breast and ovarian cancer incidence. In 2007, the American Cancer Society issued guidelines\textsuperscript{29} for offering screening breast MRI in women with a lifetime risk of breast cancer of 20% to $\geq 25\%$ (based on models of family history) using an annual breast MRI examination beginning at age 30. A more recent study\textsuperscript{30} indicates that although family history is a strong predictor of risk, it is not always required, as a cohort of women with apparently sporadic (no first or second degree relatives with breast or ovarian cancer) and early onset breast cancer had a 9.5\% incidence BRCA1 or BRCA2 mutation.

For women with BRCA1 or BRCA2 mutations, the risk of breast cancer is up to 87\% by the age of 70. Clinicians should ensure that women at risk are given tools to help them make the difficult decision about prophylactic salpingo-oophorectomy or bilateral mastectomy and the increased lifetime risks for BRCA-associated gynaecologic (ovarian, fallopian tube, and primary peritoneal) cancers.\textsuperscript{31} Recent reviews\textsuperscript{27,28} of ovarian cancer prevention in patients with BRCA1 or BRCA2 germ line mutations indicate that although chemoprevention (tamoxifen, raloxifene) and screening (twice yearly vaginal ultrasound and serum CA-125) both have a role, neither is efficacious enough to eliminate the need for risk reducing salpingo-oophorectomy in women with an inherited predisposition to ovarian cancer; therefore, risk reducing salpingo-oophorectomy will remain an important component of gynaecologic cancer risk reduction.

Although BRCA1 and BRCA2 account for the largest proportion of genetic susceptibility to breast cancer, other rare disorders make up approximately 10\% to 20\% of the genetic susceptibility. These include ataxia-telangiectasia (AR), oculocutaneous telangiectasia, cerebellar ataxia, variable immunodeficiency, lymphoid and epithelial cancers, Li-Fraumeni syndrome (AD), childhood bone or soft-tissue sarcomas, early onset breast cancer, acute leukemias, brain tumours, carcinoma of the lung or pancreas, melanoma, Cowden disease (AD), mucocutaneous lesions, thyroid, breast, hamartomatous polyps of the GI tract, macrocephaly, uterine leiomyomas), and very rare syndromes such as Gorlin syndrome (AD), Muir-Torre syndrome (AD), Peutz-Jeghers syndrome (AD), and partial androgen insensitivity syndrome (X-linked recessive).

For women with BRCA1 or BRCA2 mutations who have not undergone risk-reduction mastectomy, intensive breast screening with both annual mammogram and annual breast MRI beginning at age 25 years could be considered. American Cancer Society guidelines\textsuperscript{29} for breast cancer screening with MRI as an adjunct to mammography recommend that an annual MRI could also be used not only for the high-risk BRCA mutation carrier and first degree relative cohort but also for screening other high-risk breast cancer groups, such as women with a history of therapeutic radiation (e.g., for Hodgkin’s disease) to the chest between the ages of 10 and 30 years, women with Li-Fraumeni syndrome and first degree relatives, and women with Cowden or Bannayan-Riley-Ruvalcaba syndrome and first degree relatives.

In 2010, the Public Health Agency of Canada produced a “Decision Aid for Breast Cancer Screening in Canada.” It provides information on mammography to assist women aged $\geq 40$ in making decisions about screening. The document recommends that women aged 50 to 69 years who are at average risk should have screening mammograms every 2 years.\textsuperscript{32}

Endometrial cancers can also be a component of an inherited cancer susceptibility syndrome. For example, endometrial cancer is associated with HNPCC/Lynch syndrome. HNPCC is likely the most common hereditary cancer syndrome, causing about 1 in 20 cases of colorectal cancer.\textsuperscript{33} The mutation confers a lifetime risk of about 80\% that a carrier will develop CRC. Men with these mutations appear to have a greater risk of developing CRC than women. The mutation confers a 30\% to 60\% lifetime risk for endometrial cancer in female carriers. This is an inherited autosomal dominant mutation, and there are 4 known genes: hMLH1, hMSH2, hMSH6, PMS2.

Decision models for Lynch/HNPCC\textsuperscript{34} have compared 3 management strategies: (1) annual gynaecological examination alone; (2) annual examination with screening (ultrasound, endometrial biopsy, CA 125); and (3) hysterectomy with bilateral salpingo-oophorectomy. The third option may be considered for appropriately counselled women with Lynch/HNPCC to prevent gynaecologic cancers and their associated morbidities. The same research group has reported that this surgical approach is cost effective.\textsuperscript{35}

Recommendations for presymptomatic women with documented HNPCC/Lynch mutations include colonoscopic screening starting at age 25 and continuing as

<table>
<thead>
<tr>
<th>Topic</th>
<th>Guideline</th>
</tr>
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</table>
| Breast Cancer  | ACOG: Mammography should be performed every 1 to 2 years beginning at age 40 years and yearly beginning at age 50 years. All women should have an annual clinical breast examination as part of the physical examination. Despite a lack of definitive data for or against breast self-examination, it has the potential to detect palpable breast cancer and can be recommended.  
SOGC/GOC: Age 40 to 49, clinical breast examination by trained professional every 2 years; age 50 to 69, clinical breast examination by trained professional and mammogram every 2 years; > age 70, personal plan discussed with trained professional |
| Colorectal Cancer | ACOG: Beginning at age 50 years, 1 of 5 screening options should be selected:  
1. Yearly patient-collected FOBT or FIT,* or  
2. Flexible sigmoidoscopy every 5 years, or  
3. Yearly patient-collected FOBT or FIT* plus flexible sigmoidoscopy every 5 years, or  
4. Double-contrast barium enema every 5 years, or  
5. Colonoscopy every 10 years  
SOGC/GOC: Women at low risk > age 50 fecal occult blood every 2 years; Women at high risk (first degree relative affected with CRC, FAP, HNPCC, history of inflammatory bowel disease, benign polyps in colon or rectum) should discuss surveillance such as colonoscopy with trained gastrointestinal professional |
| Ovarian Cancer | ACOG and SOGC/GOC: Currently, there are no effective techniques for the routine screening of asymptomatic women at low risk for ovarian cancer. It appears that the best way to detect early ovarian cancer is for both the patient and her clinician to have a high index of suspicion of the diagnosis in the symptomatic woman, and both should be aware of the symptoms commonly associated with ovarian cancer. Persistent symptoms such as an increase in abdominal size, abdominal bloating, fatigue, abdominal pain, indigestion, inability to eat normally, urinary frequency, pelvic pain, constipation, back pain, urinary incontinence of recent onset, or unexplained weight loss should be evaluated, with ovarian cancer included in the differential diagnosis.  
Research in progress: combining CA125 and transvaginal ultrasound in a small study detected 34/38 ovarian cancers with 50% in stage I or II.  
FIT: fecal immunochemical testing; FOBT: fecal occult blood testing; CA125 blood test for cancer screening.  
*Both FOBT and FIT require 2 or 3 samples of stool collected by the patient at home and returned for analysis. A single stool sample for FOBT or FIT obtained by digital rectal examination is not adequate for the detection of CRC.  
Table adapted from Adams Hillard PJ and Berek JS, 20 Canadian Cancer Society. 46,47 |

Table 6. Primary and preventive care: periodic assessments in women who have a family history

<table>
<thead>
<tr>
<th>Age range</th>
<th>Periodic assessment (consider family history/risk)</th>
<th>Leading causes of death (genetic disease)</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 to 18 years</td>
<td>genetic testing/counselling congenital conditions</td>
<td>malignant neoplasms</td>
<td>2</td>
</tr>
<tr>
<td>19 to 39 years</td>
<td>genetic testing/counselling cardiovascular risk malignant neoplasms cardiac diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>40 to 64 years</td>
<td>CRC screening lipid/cholesterol profile diabetes breast cancer thyroid (TSH) malignant neoplasms cardiac diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>as above cardiac malignant neoplasms Alzheimer’s disease diabetes</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

TSH: thyroid stimulating hormone  
Table adapted from ACOG Committee Opinion No. 452. 45
frequently as once per year. Gyneaeological surveillance should start at age 30 (17% of endometrial cancers and 42% of ovarian cancers in these patients cohort are diagnosed by age 40). Women with Lynch syndrome do not have an increased risk for breast cancer, so they may benefit from estrogen-replacement therapy after oophorectomy to prevent or minimize the potential sequelae of surgically induced menopause.

Other genetic gastrointestinal cancers, including hamartomatous polyposis syndromes, gastric cancer, and CRC/familial adenomatous polyposis, are described in the Appendix.

Table 5 summarizes general approaches for cancer screening of breast, colon and ovary20,46,47 considering both Canadian and American sources.

Table 6 summarizes the primary and preventive care periodic assessments by female age groups.48

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APPENDIX. ADDITIONAL GASTROINTESTINAL CANCER INFORMATION

The hamartomatous polyposis syndromes are a heterogeneous group of disorders that share an autosomal-dominant pattern of inheritance and are characterized by hamartomatous polyps of the gastrointestinal tract. These syndromes include juvenile polyposis syndrome, Peutz-Jeghers syndrome, and PTEN hamartoma tumour syndrome. The frequency and location of the polyps vary considerably, as does the predisposition for the development of gastrointestinal and other malignancies. In addition, there are non-malignant manifestations, such as bleeding, intussusception, and bowel obstruction. Surveillance guidelines for these rare syndromes were published in 2007.

Gastric cancer is the second most common cause of cancer death worldwide. A germline mutation in the epithelial cadherin (CDH1) has an increased risk for diffuse gastric cancer and lobular breast cancer. A recent publication indicates the presence of a founder mutation from Newfoundland pedigrees. Published guidelines recommend providing genetic counselling to the family and beginning screening in the late teens or early 20s. The timing of prophylactic gastrectomy is an individual decision.

Colorectal cancer is the second leading cause of cancer death in North America. CRC evolves in an adenoma to carcinoma sequence during which a series of somatic alterations accumulate in the DNA of the tumour tissue. About 75% of these molecular changes are sporadic events, but the remaining 25% arise in individuals with a family history of colon cancer. HNPPC (etiology for 1 in 20 CRC) has been discussed previously. The other hereditary cancer (much rarer with 100 to thousands of polyps) is FAP, which is an autosomal dominant syndrome with germline mutations. Clinical onset is at a young age (12 to 15 years) with hundreds of adenomatous polyps in the colon and increased risk for gastric polyps, duodenal cancer, thyroid cancer, and desmoids tumours. There is an attenuated variety, AFAP, that has fewer than 100 adenomas with a proximal predominance and a later age of onset (55 years).

Cancer genetic risk assessment for hereditary colon cancer would include HNPPC and FAP. A recent mutation was identified specifically in the Ashkenazi Jewish population. A 2002 statement from American College of Medical Genetics and the American Society of Human Genetics presents guidelines for screening and tumour analysis. Identification of this colorectal family history should allow discussion with the patient about counselling, possible testing and referral to a hereditary cancer program through medical or provincial cancer agencies. Recently published results from a 2003 survey indicate only 23.5% of Canadian patients at risk for colon cancer reported receiving screening, but this dropped to 17.8% when only up-to-date screening was considered. Canadian recommendations are that screening involves geographic availability and patient discussion with the screening options of fecal occult blood testing every 2 years; flexible sigmoidoscopy every 5 years; double contrast barium enema every 5 years; colonoscopy every 10 years. The use of colonoscopy as a screening test for CRC has identified increased numbers of patients with polyps requiring follow-up. A recent review reports that most patients do not require intensive surveillance, as patients with 1 or 2 small (< 1 cm) adenomas can safely repeat colonoscopy after 5 to 10 years.