Hereditary Breast and Gynecologic Cancer

Breast Cancer
Breast cancer is the most common cancer found in women and approximately 1 out of every 8 (12%) women will be diagnosed with breast cancer in her lifetime. Although the disease occurs more frequently in women, breast cancer can also occur in men.

Gynecologic Cancer
Endometrial and ovarian cancers are the two gynecologic cancers most often associated with hereditary cancer syndromes. Endometrial cancer is the most common cancer found in the female reproductive system and approximately 1 out of every 36 (2.8%) women will be diagnosed with endometrial cancer in her lifetime. Ovarian cancer is the ninth most common cancer among females and approximately 1 out of every 70 (1.4%) women will be diagnosed with ovarian cancer in her lifetime.

Breast and gynecologic cancers occur when normal cells begin to grow uncontrollably, forming a malignant tumor. While the majority of breast and gynecologic cancer is sporadic and occurs by chance, approximately 5-10% of breast and endometrial cancers, and up to 25% of ovarian cancers, are hereditary. Hereditary cancers occur because an individual was born with a harmful change in a gene that increased his or her risk to develop cancer. These harmful changes are also known as pathogenic variants and can be identified through genetic testing.

The most common cause of hereditary breast and ovarian cancer are pathogenic variants in the BRCA1 and BRCA2 genes. Pathogenic variants in these genes are associated with a significant lifetime risk to develop breast, ovarian, and pancreatic cancer, among others. Endometrial cancer has also been reported in women with pathogenic variants in these genes. Pathogenic variants in the BRCA1 and BRCA2 genes occur in all ethnic groups however approximately 1 in 40 individuals with Ashkenazi Jewish ancestry carry one of three founder (common) variants. There are also other genes associated with hereditary breast and ovarian cancer for which testing is available.
The most common cause of hereditary endometrial cancer is Lynch syndrome (also known as Hereditary Nonpolyposis Colorectal Cancer syndrome). Lynch syndrome is primarily associated with an increased risk for endometrial and colorectal cancer; however it is also associated with ovarian, stomach, pancreatic and kidney cancers, among others. In some cases, there are screening tests that may be performed on endometrial and colorectal tumors to help identify those at risk for Lynch syndrome. These screening tests are known as microsatellite instability (MSI) and/or immunohistochemistry (IHC) and may assist in identifying those who would benefit from genetic testing. There are also other genes associated with hereditary endometrial cancer for which testing is available.

Genes and Lifetime Risks

Many genes have been associated with an increased risk of breast and gynecologic cancer. These genes can be categorized into three main groups: High-Risk, Moderate-Risk, and Newer-Risk.

High-Risk Genes

High-risk genes are well-studied, and pathogenic variants in these genes are associated with a significantly increased risk (greater than 4-fold risk when compared with the general population) to develop one or more cancers. These genes are often associated with well-defined hereditary cancer syndromes, which generally have published guidelines for screening and prevention. Patients with pathogenic variants in these genes may develop cancer and/or tumors at young ages or may have an increased risk for multiple cancer diagnoses in a lifetime.

High-risk genes associated with an increased risk of breast, ovarian and endometrial cancer include BRCA1, BRCA2 (BRCA-Related Breast and/or Ovarian Cancer syndrome); CDH1 (Hereditary Diffuse Gastric Cancer syndrome); EPCAM, MLH1, MSH2, MSH6, PMS2 (Lynch syndrome); biallelic pathogenic variants in MUTYH (MUTYH-Associated Polyposis or MAP); NF1 (Neurofibromatosis type 1 or NF1); PALB2; PTEN (PTEN Hamartoma Tumor syndrome, including Cowden syndrome); and TP53 (Li-Fraumeni syndrome). Figure 1 provides the lifetime risk of breast, ovarian and endometrial cancers when a pathogenic variant is identified in these high-risk genes.
Indicates Lifetime Breast Cancer Risk in General Population
Indicates Lifetime Ovarian Cancer Risk in General Population
Indicates Lifetime Endometrial Cancer Risk in General Population
Indicates Lifetime Risk Associated with a Pathogenic Variant(s)

BRCA1
39-59%

BRCA2
11-27%

CDH1
23-68%

EPCAM, MLH1, MSH2, MSH6, PMS2
Up to 24%

MUTYH
Increased**

NF1
Increased**

PALB2
Increased**

PTEN
5-28%

TP53
85%

* BRCA1, BRCA2, and PALB2 pathogenic variants are also associated with an increased risk for male breast cancer.
** Lifetime risks of cancer are known to be significantly increased above the general population risk although a precise lifetime risk is unknown.
Moderate-Risk Genes

Moderate-risk genes are often well-studied, and pathogenic variants in these genes are associated with a more modest risk (approximately a 2- to 4-fold risk when compared with the general population) to develop one or more cancers and/or tumors. Generally, there are limited guidelines for screening and surveillance. Similar to high-risk genes, patients with pathogenic variants in these genes may develop cancer and/or tumors at an early age and may develop multiple cancer diagnoses in a lifetime.

Newer-Risk Genes

In addition to high-risk and moderate-risk genes, other genes have been identified that are not as well-studied. Often the association with cancer and/or tumors may be newly discovered, or there may be limited data on the degree of cancer risk and/or full spectrum of tumors associated with genetic variants in these genes. Guidelines for screening and prevention are limited or not available.

Table 1 reviews the genes associated with an increased risk of breast, ovarian and/or endometrial cancers in the presence of a pathogenic variant and provides information on other cancers and/or tumors associated with these genes. Specific lifetime risk estimates are provided when available and are based on published medical literature.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Cancer and/or Tumor Risks*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>Female breast (55-87%), Ovarian (39-59%), Prostate, Male breast, Pancreatic, Fallopian tube, Primary peritoneal, Endometrial</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>Female breast (32.6-84%), Prostate (up to 34%), Ovarian (11-27%), Pancreatic (5-7%), Male breast (4-7.1%), Melanoma, Fallopian tube, Primary peritoneal, Endometrial</td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td>Gastric (44-80%), Female breast (23-68%), Colorectal</td>
</tr>
<tr>
<td><strong>EPCAM</strong></td>
<td>Colorectal (69-75%), Endometrial (12-55%), Ovarian, Gastric, Pancreatic, Biliary tract, Urinary tract, Small bowel, Brain, Sebaceous tumors, Prostate</td>
</tr>
<tr>
<td><strong>MLH1</strong></td>
<td>Colorectal (22-80%), Endometrial (31-61%), Ovarian (10-24%), Urinary tract (8-20%), Gastric (&lt;1-9%), Pancreatic, Biliary tract, Small bowel, Brain, Sebaceous tumors, Prostate</td>
</tr>
<tr>
<td><strong>MSH2</strong></td>
<td>Colorectal (22-80%) , Endometrial (22-54%), Ovarian (11-30%), Colorectal (11-24%), Gastric (6-20%), Urinary tract (1-3%), Pancreatic, Biliary tract, Small bowel, Brain, Sebaceous tumors, Prostate</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>Colorectal (20-44%), Endometrial (16-71%), Ovarian (1-11%), Gastric, Pancreatic, Biliary tract, Urinary tract, Small bowel, Brain, Sebaceous tumors, Prostate</td>
</tr>
<tr>
<td><strong>MUTYH</strong></td>
<td>Colorectal (up to 80%), Small bowel (up to 4%), Endometrial, Gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>Neurofibromas, Brain tumors (2-15%), Pheochromocytomas (1-13%), Sarcomas (6-13%), Female breast, Gastrointestinal stromal tumor (GIST)</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>Female breast (up to 58%), Male breast, Pancreatic, Ovarian</td>
</tr>
<tr>
<td><strong>PMS2</strong></td>
<td>Colorectal (11-20%), Endometrial (12-15%), Ovarian, Gastric, Pancreatic, Biliary tract, Urinary tract, Small bowel, Brain, Sebaceous tumors, Prostate</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Female breast (25-85%), Thyroid (3-38%), Endometrial (5-28%), Colorectal, Renal, Melanoma, Gastrointestinal polyps</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Female breast (85%), Sarcoma-bone and soft tissue, Brain, Hematologic malignancies, Adenocortical carcinoma, among others. Overall risk for cancer: up to 95% in females, 88% in males</td>
</tr>
</tbody>
</table>

**Moderate-Risk Genes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Cancer and/or Tumor Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATM</strong></td>
<td>Female breast (27-33%), Colorectal, Pancreatic, Prostate</td>
</tr>
<tr>
<td><strong>BRIP1</strong></td>
<td>Ovarian</td>
</tr>
<tr>
<td><strong>CHEK2</strong></td>
<td>Female breast, Male breast, Colorectal, Gastric, Prostate, Thyroid</td>
</tr>
<tr>
<td><strong>RAD51C</strong></td>
<td>Ovarian, Female breast</td>
</tr>
<tr>
<td><strong>RAD51D</strong></td>
<td>Ovarian, Female breast</td>
</tr>
</tbody>
</table>

**Newer-Risk Genes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Cancer and/or Tumor Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BARD1</strong></td>
<td>Female breast, Ovarian</td>
</tr>
<tr>
<td><strong>FANCC</strong></td>
<td>Female breast</td>
</tr>
<tr>
<td><strong>NBN</strong></td>
<td>Female breast, Non-Hodgkin lymphoma, Prostate</td>
</tr>
<tr>
<td><strong>POLD1</strong></td>
<td>Colorectal, Endometrial, Colon polyps</td>
</tr>
<tr>
<td><strong>RECQL</strong></td>
<td>Female breast</td>
</tr>
</tbody>
</table>

*Most commonly associated cancer/tumors listed; lifetime risks provided when available. Risks relate to carriers of a single pathogenic variant with the exception of MUTYH.

**Tumor spectrum is representative of Lynch syndrome; data are limited with regard to the association of certain cancers with pathogenic variants in MSH6, PMS2 and EPCAM.
Influencing Factors on Cancer and/or Tumor Risk

While individuals with pathogenic variants in these genes have increased risks of cancers and/or tumors compared to the general population, it is not a guarantee that a person will develop a cancer or tumors. In general, an individual’s risk to develop a specific cancer and/or tumor is dependent not only on genetic factors, but may also be influenced by environmental and lifestyle factors as well.

Breast Cancer Risk Factors

Several risk factors have been linked to breast cancer including lifestyle factors like diet, weight, exercise, smoking, and alcohol use. Other risk factors include age, a personal history of dense breast tissue, certain benign breast conditions, reproductive history, taking medications that contain hormones, and a family history of breast cancer, among others.

Ovarian Cancer Risk Factors

Several risk factors have been linked to ovarian cancer including lifestyle factors like diet and weight. Other risk factors include age, reproductive history, taking fertility or other medications that contain hormones, and a family history of ovarian cancer, among others.

Endometrial Cancer Risk Factors

Several risk factors have been linked to endometrial cancer including lifestyle factors like diet, weight and exercise. Other risk factors include age, reproductive history, taking Tamoxifen or other medications that contain hormones, being diagnosed with polycystic ovarian syndrome, and a family history of uterine cancer, among others.
Identifying Patients at Risk for Hereditary Breast and Gynecologic Cancer

Individuals with a personal and/or family history of the following may be at risk for hereditary breast, ovarian, and/or endometrial cancer. Family history includes first, second, and third-degree blood relatives (including parents, siblings, children, aunts/uncles, cousins, and grandparents).

- Breast or endometrial cancer diagnosed under 50 years of age
- Multiple cancers in one person, either of the same origin (such as two separate breast cancers) or of different origins (such as breast and ovarian cancer or endometrial and colon cancer)
- Ovarian cancer or male breast cancer at any age
- Multiple relatives diagnosed with the same or related cancers (including breast, ovarian, endometrial, pancreatic and/or prostate) on the same side of the family and spanning multiple generations
- Ashkenazi Jewish ancestry with a history of breast, ovarian or pancreatic cancer
- A known pathogenic variant in a blood relative

It is important to provide detailed information on the personal and family histories of cancer, including ages of diagnosis, pathology, and relationship between family members. This information can help determine if testing is appropriate and which test is medically necessary, as well as may impact insurance coverage.
# Test Options

Below are the tests available for individuals at risk for hereditary breast and gynecologic cancer.

## Breast and Ovarian Cancer Testing Options

<table>
<thead>
<tr>
<th>Test Option</th>
<th>TAT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1/BRCA2 Ashkenazi Founder Panel</strong></td>
<td>8-10 days</td>
<td>Targeted testing for three known founder variants in BRCA1 and BRCA2</td>
</tr>
<tr>
<td><strong>BRCA1/BRCA2 Sequencing and Deletion/Duplication</strong></td>
<td>8-10 days</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td><strong>Breast Cancer Management Panel</strong></td>
<td>2 weeks; RUSH</td>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, PALB2, PTEN, TP53</td>
</tr>
<tr>
<td><strong>Breast/Gyn Cancer Panel</strong></td>
<td>2 weeks</td>
<td>ATM, BARD1, BRCA1, BRCA2, BRI1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, PTEN, RAD51C, RAD51D, REQL, TP53</td>
</tr>
</tbody>
</table>

## Endometrial Cancer Testing Options

<table>
<thead>
<tr>
<th>Test Option</th>
<th>TAT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast/Gyn Cancer Panel</strong></td>
<td>2 weeks</td>
<td>ATM, BARD1, BRCA1, BRCA2, BRI1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, PTEN, RAD51C, RAD51D, REQL, TP53</td>
</tr>
<tr>
<td><strong>Lynch/Colorectal High Risk Panel</strong></td>
<td>2 weeks</td>
<td>APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2</td>
</tr>
</tbody>
</table>

## Panels for Multiple Cancer Types

<table>
<thead>
<tr>
<th>Test Option</th>
<th>TAT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comprehensive Common Cancer Panel</strong></td>
<td>2 weeks</td>
<td>APC, ATM, AXIN2, BAPI, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDKN2A, CHEK2, EPCAM, FANCC, FH, FLCN, HOXB13, MET, MITF, MLH1, MSH2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, POT1, PTEN,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAD51C, RAD51D, REQL, SCG5/GREM1, SDHB, SDHC, SDHD, SMAD4, STK11, TP53,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSC1, TSC2, VHL</td>
</tr>
<tr>
<td><strong>Common Cancer Management Panel</strong></td>
<td>2 weeks</td>
<td>APC, ATM, AXIN2, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPCAM, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POLD1, POLE, PTEN, RAD51C, RAD51D, SCG5/GREM1, SDHB, SDHC, SDHD, SMAD4,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STK11, TP53, TSC1, TSC2, VHL</td>
</tr>
<tr>
<td><strong>OncoGeneDx Custom Panel</strong></td>
<td>3 weeks</td>
<td>Create a customized cancer panel from a list of 64 cancer susceptibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>genes. For a complete list of available genes, please visit our website at</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="http://www.genedx.com/oncology">www.genedx.com/oncology</a></td>
</tr>
</tbody>
</table>
Additional testing options are available, including targeted variant testing for a previously identified pathogenic or likely pathogenic variant in a family member. For a complete list of available testing options, please visit our website at www.genedx.com/oncology. Appropriate test selection depends on the specific clinical history of a patient, including family history of cancer and/or previous personal or familial test results. Testing for most genes includes sequencing and deletion/duplication analysis via next-generation sequencing.

**Sample Submission**

Genetic testing can be performed on blood, oral rinse, buccal swab or extracted DNA samples. GeneDx test kits are available to ordering providers, and include sample collection items (such as collection tubes, mouthwash for oral rinse samples, and sponges for a buccal swab), the necessary sample submission paperwork, and a self-addressed return shipping label.

GeneDx is committed to providing an easy to use online platform to order genetic tests. Our online portal makes the ordering process simple and straightforward. Providers can now upload clinical information electronically, track the progress of an order, and receive results instantaneously through the portal. The portal can be accessed from our website www.genedx.com. Additionally, GeneDx forms can also be easily accessed for digital or print use at www.genedx.com/forms.

Please note that all testing must be performed under the guidance of a healthcare provider. For more information on the sample submission process, please visit our website: www.genedx.com/supplies or email us at: zebras@genedx.com
Your test was negative for any pathogenic (harmful) variants. You have undergone genetic testing to detect changes in the BRCA1 and BRCA2 genes, which are associated with an increased risk for breast, ovarian and other types of cancer. Your test was negative for any pathogenic variants.

At the laboratory, genetic testing for most genes includes next-generation sequencing and/or exon array analysis.

Contains information on the results of the genetic test and available medical management options.

The final report is sent to the ordering healthcare provider.

The health care provider and the patient discuss the test results, medical management options, and implications for family members.
Genetic Test Results

Nearly all test results fall into one of four categories: positive (pathogenic variant), likely pathogenic variant, negative and a variant of uncertain significance (VUS). Genetic counseling is recommended prior to and following genetic testing to understand the benefits and limitations of testing.

Positive Result

A positive result indicates a genetic variant (change) was identified in a specific gene and that variant is pathogenic (harmful). With a positive test result, the risk to develop a particular disease (in this case, cancer and/or tumors) is increased. The lifetime risk for cancer and/or tumors depends on which gene was identified as having the pathogenic variant.

Knowledge of a positive result provides valuable information to patients, healthcare providers, and family members as they develop a medical management plan. Results may direct treatment of a current cancer diagnosis or reduce the risk for or improve early detection of future cancers and/or tumors. A medical management plan may include enhanced screening or in some cases, risk-reducing surgery and/or medication. Furthermore, testing family members may be appropriate and can allow for more accurate predictions of their cancer and/or tumor risks.

Likely Pathogenic Variant Result

A likely pathogenic variant result indicates that there is a variant in a specific gene for which there is significant, but not conclusive, evidence of an increased risk to develop a particular disease (in this case, cancer and/or tumors). The lifetime risk for cancer and/or tumors depends on which gene was identified as having the likely pathogenic variant. With this type of result, a medical management plan may include similar options as described above for a positive result, including enhanced screening, risk-reducing options and testing of family members.
Negative Result

A negative result means that no reportable variants were identified. This result can have different implications depending on the specific circumstances related to the testing.

In many cases when no one in the family has previously been found to have a pathogenic variant, the reason for the patient’s personal or family history of cancer remains unknown. The result may be negative because there is a genetic predisposition in the family that the patient did not inherit or it may be that the cancers and/or tumors in the family are caused by something beyond the genes included on their test. The risk for future cancers and medical management recommendations should be based on personal and/or family history of cancer.

When an individual tests negative for a familial pathogenic variant that has already been identified in another family member, this is considered a true negative test result. In most cases, the risk for cancer is not expected to be greater than the general population. Sometimes this interpretation may be limited if the family member’s pathogenic variant was identified in a gene described as moderate-risk or newer-risk.

Depending upon the patient’s personal and family history of cancer, additional genetic testing may be indicated for the patient or a family member. Sometimes there are other genes that can explain the family history of cancer, or areas of a gene which were not examined with the initial test. A genetic specialist or other healthcare provider can determine if further genetic testing is appropriate.

Variant of Uncertain Significance (VUS) Result

A variant of uncertain significance (VUS) result means that a change in a specific gene was identified, however the effect of the variant cannot be clearly established. There may be conflicting or incomplete information in the medical literature about this variant and its association with an increased risk of cancers and/or tumors is unknown. In other words, it cannot be determined yet whether this variant is associated with an increased risk of cancer and/or tumors or it is a harmless (normal)
variant. In some cases, it may be helpful to test other family members through our Variant Testing Program to help clarify the risk. Over time, the VUS may become reclassified to either a “positive” or “negative” test result. The patient’s risk for future cancers and medical management recommendations should typically be based on personal and/or family history until the VUS is reclassified.

**Test Reports**

Test reports contain detailed information about a specific genetic result and, if available, medical management options. Additional support is available from our laboratory genetic counselors and local genetic providers within your area. Genetic counseling services can be found at [www.nsgc.org](http://www.nsgc.org) within the United States or [www.cagc-accg.ca](http://www.cagc-accg.ca) in Canada.

Test results are available within 2-3 weeks after a sample is received in the laboratory. Once complete, test results are sent to the ordering healthcare provider. The healthcare provider should share those results and discuss them in the context of the reported personal and family histories.

**Medical Management Based on Genetic Test Results**

Medical management options for early detection or risk reduction are available for many individuals found to have a pathogenic variant in a gene associated with hereditary cancer. The options may include enhanced screening, risk reducing surgery, and in some cases, risk reducing medication. Options for screening and risk reduction are based on national guidelines or consensus statements, when available, and are specific to the gene in which a pathogenic variant is identified.

Information on screening and risk reduction options are included in the report for a positive and likely pathogenic test result. A summary of medical management options are provided in [Table 2](#).
Table 2: Medical Management Options for Genes Associated with Hereditary Breast and Gynecologic Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Medical Management Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM*</td>
<td>- Breast awareness&lt;br&gt;- Clinical encounter, including clinical breast examination&lt;br&gt;- Breast MRI and mammogram&lt;br&gt;- Consider individualized prostate cancer screening based on personal and/or family history</td>
</tr>
<tr>
<td>BRCA1, BRCA2*</td>
<td>- Breast awareness, including breast self-examination for both men and women&lt;br&gt;- Clinical encounter, including clinical breast examination for both men and women&lt;br&gt;- Breast MRI and mammography starting at an early age&lt;br&gt;- Consider prophylactic mastectomy&lt;br&gt;- Bilateral Salpingo-Oophorectomy (BSO)&lt;br&gt;- Consider transvaginal ultrasound of ovaries and CA-125 blood tests for women who have not had a BSO&lt;br&gt;- Consider the use of risk-reducing medications (such as tamoxifen, raloxifene and oral contraceptives)&lt;br&gt;- Prostate cancer screening starting at an early age&lt;br&gt;- Consider pancreatic cancer screening and full body skin examination dependent on family history&lt;br&gt;&lt;br&gt;For BRCA2 only&lt;br&gt;- Consider individualized melanoma screening based on personal and/or family history</td>
</tr>
<tr>
<td>BRIP1*</td>
<td>- Consider bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>CDH1*</td>
<td>- Breast awareness&lt;br&gt;- Clinical encounter, including clinical breast examination&lt;br&gt;- Breast MRI and mammography starting at an early age&lt;br&gt;- Consider prophylactic mastectomy, not routinely recommended but may be reasonable for some women&lt;br&gt;- Consider the use of risk-reducing medications (such as tamoxifen or raloxifene)&lt;br&gt;- Prophylactic gastrectomy&lt;br&gt;- In the absence of gastrectomy, upper endoscopy&lt;br&gt;- Consider colonoscopy starting at an early age, dependent on family history</td>
</tr>
<tr>
<td>CHEK2*</td>
<td>- Breast awareness&lt;br&gt;- Clinical encounter, including clinical breast examination&lt;br&gt;- Breast MRI and mammogram&lt;br&gt;- Periodic colonoscopy starting at an early age*&lt;br&gt;- Consider individualized prostate cancer screening based on personal and/or family history</td>
</tr>
<tr>
<td>Gene</td>
<td>Medical Management Guidelines</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tbody>
</table>
| **EPCAM, MLH1, MSH2, MSH6, PMS2** | - Frequent colonoscopy (every 1-2 years in many cases) starting at an early age  
- Consider the option of prophylactic colectomy, particularly if surgery is required to address a colonic neoplasm or if frequent colonoscopy is not an optimal option for surveillance  
- Consider endometrial/ovarian cancer screening, which may include endometrial biopsy, transvaginal ultrasound and CA-125 blood tests  
- Consider prophylactic hysterectomy and bilateral salpingo-oophorectomy once a woman has completed childbearing  
- Consider the use of risk-reducing medications such as hormonal contraception  
- Consider periodic upper endoscopy with extended duodenoscopy  
- Consider urinalysis to screen for urinary tract cancers  
- Consider physical examination with neurological examination  
- Consider individualized prostate cancer screening based on personal and/or family history |
| **MUTYH** | For 2 pathogenic variants  
- Frequent colonoscopy starting at an early age  
- Baseline upper endoscopy with duodenoscopy  
- Colectomy is generally recommended for individuals who have adenomas that cannot be managed through colonoscopy  
- Physical examination  
For 1 pathogenic variants  
- Consider periodic colonoscopy starting at an early age, dependent on family history |
| **NBN** | - Breast awareness  
- Clinical encounter, including clinical breast examination  
- Breast MRI and mammogram  
- Consider individualized prostate cancer screening based on personal and/or family history |
| **NF1** | - Developmental assessment  
- Blood pressure monitoring  
- Monitoring of abnormalities of the central nervous system, skeletal system, or cardiovascular system by an appropriate specialist  
- Other studies (e.g., MRI) as indicated based on signs or symptoms  
- Physical and ophthalmologic examinations  
- Breast awareness  
- Clinical encounter, including clinical breast examination  
- Breast MRI and mammogram starting at an early age  
- One or more management recommendations may begin in childhood or adolescence |
<table>
<thead>
<tr>
<th>Gene</th>
<th>Medical Management Guidelines</th>
</tr>
</thead>
</table>
| **PALB2**  | • Breast awareness  
• Clinical encounter, including clinical breast examination  
• Breast MRI and mammogram starting at an early age  
• Consider pancreatic cancer screening dependent on family history                                           |
| **POLD1**  | • Frequent colonoscopy starting at an early age; if adenomas are identified, increase the interval of colonoscopy*  
• Colectomy may be appropriate for individuals who have adenomas that cannot be managed through colonoscopy* |
| **PTEN**   | • Breast awareness, including breast self-examination  
• Clinical encounter, including clinical breast examination  
• Breast MRI and mammography starting at an early age  
• Consider endometrial biopsy and/or transvaginal ultrasound; encourage patient education and prompt response to symptoms  
• Options of prophylactic mastectomy and hysterectomy can be discussed  
• Periodic colonoscopy starting at an early age  
• Thyroid ultrasound  
• Consider renal ultrasounds  
• Physical examination  
• Consider dermatological examination  
• One or more management recommendations may begin in childhood or adolescence |
| **RAD51C, RAD51D** | • Consider bilateral salpingo-oophorectomy                                                                                                                |
| **TP53**   | • Breast awareness, including breast self-examination  
• Clinical encounter, including clinical breast examination  
• Breast MRI and mammography starting at an early age  
• Consider prophylactic mastectomy  
• Consider periodic colonoscopy starting at an early age  
• Consider whole body MRI, including brain imaging  
• Comprehensive physical examination, including neurologic and skin examination starting at an early age  
• Use caution regarding radiation therapy for cancer  
• Additional surveillance based on family history of cancer  
• One or more management recommendations may begin in childhood or adolescence |

*Given limited data to support these guidelines, caution should be used when making recommendations.

For the details on the specific medical management options, including frequency of screening and ages to begin surveillance, please review the referenced guidelines or consensus statements.
Implications for Family Members

Regardless of the result, patients should share their test report with their blood relatives, who can then discuss the results with their healthcare providers. Sharing a copy of the test result with family members and healthcare providers will help to determine if additional testing is necessary and will ensure that the proper test is ordered for relatives, if indicated.

For most positive or likely pathogenic test results, first-degree relatives (including parents, siblings, and children) have a 50% chance to have the same variant. The risk for other family members to carry the variant depends on how closely related they are to the person with a positive or likely pathogenic test result. It is important to remember that for most of these genes, not all people who inherit a pathogenic or likely pathogenic variant will develop cancer and/or tumors, but the chance is increased above that of the general population.

In some cases, certain genes may also be associated with an autosomal recessive condition. This occurs when an individual inherits two pathogenic variants, one from each parent. For most autosomal recessive conditions, the two pathogenic variants occur within the same gene and affect both copies of that gene. The genes associated with autosomal recessive conditions include **ATM, BRCA2, BRIP1, FANCC, FH, MÜTYH, NBN, NTHL1, PALB2, POLE, RAD51C, SDHA, SDHB, SDHD, SMARCA4, SMARCBL1** and the Lynch syndrome genes (**EPCAM, MLH1, MSH2, MSH6 and PMS2**). When an individual has two variants in these genes, the cancer and/or tumor risks and the risks to family members are different than described above. In the case of a positive result, the report will provide additional information on the gene, inheritance and cancer and/or tumor risks.

Genetic Counseling

Prior to genetic testing, patients should speak to their healthcare provider and/or a genetic specialist about their personal and family history of cancer, allowing for cancer risk assessment. Healthcare providers should discuss the benefits and limitations of testing, as well as possible test results. These conversations help to determine if the patient meets clinical criteria for testing, facilitates appropriate test ordering and ensures that the patient has provided informed consent for genetic testing.
If a pathogenic variant has already been identified in a family member, testing of the specific variant is appropriate. If a pathogenic variant has never been identified, an affected family member with the highest likelihood for a positive result (such as having early-onset disease, bilateral disease or multiple primaries) is ideally the best person for initial testing within a family. If an affected family member is not available, testing of an unaffected family member can be considered, although a negative test result will not guarantee that the individual does not have an increased risk for cancer and/or tumors.

Once a patient makes the decision to undergo testing, post-test genetic counseling is recommended to understand the implications of the results, including discussion of cancer risks and appropriate medical management based on both the test results and the patient’s medical and family histories. Genetic counseling services can be found at www.nsgc.org within the United States or www.cagc-accg.ca in Canada.

**Insurance Coverage and Cost for Genetic Testing**

GeneDx accepts all commercial plans and is a Medicare provider. Additionally, GeneDx is a registered provider with several Medicaid plans. If a patient does not have health insurance or cannot afford to pay the cost of testing, GeneDx provides a financial assistance program to help ensure that all patients have access to medically necessary genetic testing.

For more information on the paperwork that is required by some insurance carriers, as well as additional details on patient billing or our financial assistance program, please visit our website: www.genedx.com and click on the “Billing” tab.
**Genetic Information Nondiscrimination Act**

The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects Americans from discrimination by health insurance companies and employers based on their genetic information. However, this law does not cover life insurance, disability insurance, or long-term care insurance. GINA’s employment protections do not extend to individuals in the U.S. military, federal employees, Veterans Health Administration and Indian Health Service. Some of these organizations may have internal policies to address genetic discrimination. For more information, please visit: [http://www.ginahelp.org/GINAhelp.pdf](http://www.ginahelp.org/GINAhelp.pdf)

**Resources**

**General**
- American Cancer Society
  [www.cancer.org](http://www.cancer.org)
- GeneDx
  [www.genedx.com/oncology](http://www.genedx.com/oncology)
- National Cancer Institute
  [www.cancer.gov](http://www.cancer.gov)

**Breast/Gyn Cancer**
- Bright Pink
  [www.brightpink.org](http://www.brightpink.org)
- Facing Our Risk of Cancer Empowered (FORCE)
  [www.facingourrisk.org](http://www.facingourrisk.org)
- Colon Cancer Alliance
  [www.ccalliance.org](http://www.ccalliance.org)
- Fight Colorectal Cancer
  [www.fightcolorectal.org](http://www.fightcolorectal.org)
- Hereditary Colon Cancer Takes Guts
  [www.hcctakesguts.org](http://www.hcctakesguts.org)
- Colon Cancer Alliance for Research and Education for Lynch Syndrome (CCARE)
  [www.fightlynch.org](http://www.fightlynch.org)

**Find a Genetic Counselor**
- Canadian Association of Genetic Counsellors
  [www.cagc-accg.ca](http://www.cagc-accg.ca)
- National Society of Genetic Counselors
  [www.nsgc.org](http://www.nsgc.org)
References

For a complete list of references by gene used for our educational and patient materials please visit our website at www.genedx.com/oncology and click on the “Resources” tab.

About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients diagnosed with rare disorders and the clinicians treating these conditions. Today, GeneDx has grown into a global industry leader in genomics, having provided testing to patients and their families in over 55 countries. Led by its world-renowned clinical genomics program, and an unparalleled comprehensive genetic testing menu, GeneDx has a continued expertise in rare and ultra-rare disorders. Additionally, GeneDx also offers a number of other genetic testing services, including: diagnostic testing for hereditary cancers, cardiac, mitochondrial, and neurological disorders, prenatal diagnostics, and targeted variant testing. At GeneDx, our technical services are backed by our unmatched scientific expertise and our superior customer support. Our growing staff includes more than 35 geneticists and 140 genetic counselors specializing in clinical genetics, molecular genetics, metabolic genetics, and cytogenetics who are just a phone call or email away to assist you with your questions and testing needs. We invite you to visit our website: www.genedx.com to learn more about us.