Hereditary Cancer

Cancer occurs when normal cells begin to grow uncontrollably, forming a malignant tumor. Approximately 1 in 3 people will develop cancer in their lifetime. While the majority of cancer is sporadic (non-hereditary), approximately 5-10% of cancers occur because an individual was born with a harmful change in a gene that increased their risk to develop cancer. These harmful changes are also known as pathogenic variants and can be identified through genetic testing.

Genes and Lifetime Risks

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk Genes</td>
<td>• Well-studied</td>
</tr>
<tr>
<td></td>
<td>• Greater than 4-fold risk of developing one or more cancers</td>
</tr>
<tr>
<td></td>
<td>• Can cause a moderate risk for other cancers</td>
</tr>
<tr>
<td></td>
<td>• Cancer and/or tumors may develop at young ages and there is a risk for multiple diagnoses</td>
</tr>
<tr>
<td></td>
<td>• National or expert opinion guidelines for screening and prevention are established</td>
</tr>
<tr>
<td>Moderate-Risk Genes</td>
<td>• Well-studied</td>
</tr>
<tr>
<td></td>
<td>• Approximately 2- to 4-fold risk of developing one or more cancers</td>
</tr>
<tr>
<td></td>
<td>• May increase risk for other cancers</td>
</tr>
<tr>
<td></td>
<td>• Cancer and/or tumors may develop at young ages and there is a risk for multiple diagnoses</td>
</tr>
<tr>
<td></td>
<td>• Limited guidelines for screening and prevention</td>
</tr>
<tr>
<td>Newer-Risk Genes</td>
<td>• Not as well-studied</td>
</tr>
<tr>
<td></td>
<td>• Precise lifetime risks and tumor spectrum not yet determined</td>
</tr>
<tr>
<td></td>
<td>• Guidelines for screening and prevention are limited or not available</td>
</tr>
</tbody>
</table>
Table 1 reviews genes associated with an increased risk of cancer in the presence of a pathogenic variant and provides information on which cancers and/or tumors are associated with these genes. Specific lifetime risk estimates are provided when available and are based on published medical literature. Of note, there are other genes associated with rare cancers and/or tumors that may not be included in the chart below.

Table 1: Lifetime Cancer and/or Tumor Risks for Genes Associated with Hereditary Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Cancer and/or Tumor Risks*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Risk Genes</strong></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>Colorectal (up to 93%), Small bowel (4-12%), Gastric, Thyroid, Pancreatic, Brain, Liver, Desmoid tumors, Gastrointestinal polyps</td>
</tr>
<tr>
<td>BMPR1A, SMAD4</td>
<td>Colorectal (40-50%), Gastric (up to 21% if gastric polyps), Small bowel, Pancreatic, Gastrointestinal polyps</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Female breast (57-87%), Ovarian (24-54%), Prostate, Male breast, Pancreatic, Fallopian tube, Primary peritoneal, Endometrial</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Female breast (41-84%), Prostate (up to 34%), Ovarian (11-27%), Pancreatic (5-7%), Male breast (4-7%), Melanoma, Fallopian tube, Primary peritoneal, Endometrial</td>
</tr>
<tr>
<td>CDH1</td>
<td>Gastric (40-83%), Female breast (39-52%), Colorectal</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Melanoma (28-76%), Pancreatic (14%)</td>
</tr>
<tr>
<td>EPCAM, MLH1, MSH2, MSH6, PMS2</td>
<td>Colorectal (11-80%), Endometrial (12-61%), Ovarian (1-24%), Gastric (&lt;1-20%), Urinary tract (1-10%), Pancreatic, Biliary tract, Small bowel, Brain, Sebaceous tumors, Prostate</td>
</tr>
<tr>
<td>FH</td>
<td>Renal (10-18%), Paraganglioma/Pheochromocytoma, Leiomyomas-skin and uterine</td>
</tr>
<tr>
<td>FLCN</td>
<td>Renal (6-41%)</td>
</tr>
<tr>
<td>MUTYH*</td>
<td>Colorectal (up to 80%), Small bowel (up to 4%), Endometrial, Gastrointestinal polyps</td>
</tr>
<tr>
<td>PALB2</td>
<td>Female breast (25-58%), Male breast, Pancreatic, Ovarian</td>
</tr>
<tr>
<td>PTEN</td>
<td>Female breast (25-85%), Thyroid (3-38%), Endometrial (5-28%), Colorectal, Renal, Melanoma, Gastrointestinal polyps</td>
</tr>
<tr>
<td>SDHB</td>
<td>Paraganglioma/Pheochromocytoma (77%), Renal, Gastrointestinal stromal tumor (GIST)</td>
</tr>
<tr>
<td>SDHD</td>
<td>Paraganglioma/Pheochromocytoma (up to 86%), Renal, Gastrointestinal stromal tumor (GIST), Thyroid</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Cancer and/or Tumor Risks*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Risk Genes</strong></td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>Female breast (45-54%), Colorectal (39%), Pancreatic (11-36%), Gastric (29%), Ovarian tumors (21%), Lung (15-17%), Small bowel (13%), Cervical (10%), Testicular tumors (9%), Endometrial (9%), Gastrointestinal polyps</td>
</tr>
<tr>
<td>TP53</td>
<td>Female breast, Sarcoma-bone and soft tissue, Brain, Hematologic malignancies, Adrenocortical carcinoma, among others. Overall risk for cancer: nearly 100% in females, 73% in males</td>
</tr>
<tr>
<td>TSC1, TSC2</td>
<td>Renal cancer (5%) and tumors, Benign central nervous system tumors, Hamartomatous tumors</td>
</tr>
<tr>
<td>VHL</td>
<td>Renal (up to 69%), Pancreatic neuroendocrine tumors (up to 17%), Hemangioblastomas, Pheochromocytomas</td>
</tr>
<tr>
<td><strong>Moderate-Risk Genes</strong></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>Female breast, Colorectal, Pancreatic, Prostate</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Ovarian</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Female breast, Male breast, Colorectal, Gastric, Prostate, Thyroid, Endometrial, Ovarian</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Ovarian, Female breast</td>
</tr>
<tr>
<td>RAD51D</td>
<td>Ovarian, Female breast</td>
</tr>
<tr>
<td><strong>Newer-Risk Genes</strong></td>
<td></td>
</tr>
<tr>
<td>AXIN2</td>
<td>Colorectal, Colon polyps</td>
</tr>
<tr>
<td>BAP1</td>
<td>Renal, Melanoma, Mesothelioma</td>
</tr>
<tr>
<td>BARD1</td>
<td>Female breast, Ovarian</td>
</tr>
<tr>
<td>CDK4</td>
<td>Melanoma, Non-melanoma skin cancer, Pancreatic</td>
</tr>
<tr>
<td>FANCC</td>
<td>Female breast</td>
</tr>
<tr>
<td>HOXB13</td>
<td>Prostate</td>
</tr>
<tr>
<td>MET</td>
<td>Renal</td>
</tr>
<tr>
<td>MITF</td>
<td>Renal, Melanoma</td>
</tr>
<tr>
<td>NBN</td>
<td>Female breast, Melanoma, Non-Hodgkin lymphoma, Prostate</td>
</tr>
<tr>
<td>POLD1</td>
<td>Colorectal, Endometrial, Colon polyps</td>
</tr>
<tr>
<td>POLE</td>
<td>Colorectal, Gastrointestinal polyps</td>
</tr>
<tr>
<td>SCG5/ GREM1</td>
<td>Colorectal, Colon polyps</td>
</tr>
<tr>
<td>SDHC</td>
<td>Paraganglioma/Pheochromocytoma, Renal, Gastrointestinal stromal tumor (GIST)</td>
</tr>
<tr>
<td>XRCC2</td>
<td>Female breast</td>
</tr>
</tbody>
</table>

*Most commonly associated cancers/tumors listed; lifetime risks provided when available. Risks relate to carriers of a single pathogenic variant with the exception of MUTYH.*
Influencing Factors on Cancer and/or Tumor Risk

The lifetime risks of cancer in the presence of certain variants are provided in Table 1 when available and are estimates based on the currently available research. 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 tumor. 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 (such as asbestos exposure) or lifestyle factors (such as obesity, smoking, or diet).

For some genes, the parent from which a person inherits a pathogenic variant impacts the risk of disease (this is called imprinting). For example, in the case of SDHD, patients who inherit the pathogenic variant from their father have been found to have a higher risk to develop certain tumors, specifically paraganglioma and pheochromocytoma.
Identifying Patients at Risk for Hereditary Cancer

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

- Certain cancers diagnosed at a young age, such as breast or colorectal cancer
- Multiple cancers in one person, either of the same origin (such as two separate colorectal cancers) or of different origins (such as breast cancer and ovarian cancer)
- Diagnosis of certain rare cancers, such as ovarian or male breast cancer, at any age
- Multiple relatives diagnosed with the same or related cancers on the same side of the family and spanning multiple generations
- 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 some of the test options available for individuals at risk for a hereditary cancer syndrome.

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Genes Included</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comprehensive Cancer Panel</strong></td>
<td>APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SGR/GREM1, SMAD4, STK11, TP53, VHL, XRCC2</td>
<td>3 weeks</td>
</tr>
<tr>
<td><strong>High/Moderate Risk Panel</strong></td>
<td>APC, ATM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL</td>
<td>3 weeks</td>
</tr>
<tr>
<td><strong>Breast/Ovarian Cancer Panel</strong></td>
<td>ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, TP53, XRCC2</td>
<td>3 weeks</td>
</tr>
<tr>
<td><strong>Breast Cancer High/Moderate Risk Panel</strong></td>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, TP53</td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Lynch/Colorectal Cancer Panel</strong></td>
<td>APC, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2</td>
<td>3 weeks</td>
</tr>
<tr>
<td><strong>Colorectal Cancer Panel</strong></td>
<td>APC, ATM, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PHOX2B, PMS2, POLD1, POLE, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SGR/GREM1, SMAD4, STK11, TP53, VHL, WT1, XRCC2</td>
<td>3 weeks</td>
</tr>
<tr>
<td><strong>OncoGeneDx Custom Panel</strong></td>
<td>ALK, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDK4, CDKN2, CHEK2, DICER1, EPCAM, FANCC, FH, FLCN, HOXB13, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PHOX2B, PMS2, POLD1, POLE, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SGR/GREM1, SMAD4, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, WT1, XRCC2</td>
<td>3 weeks</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, targeted testing of certain variants based on ethnicity, and testing of select genes, such as BRCA1 and BRCA2. There are also testing panels for other tumor types, and these panels include Pancreatic Cancer, Paraganglioma/Pheochromocytoma, Pediatric Tumors and Renal Cancer. For a complete list of available testing options, please visit our website at www.genedx.com/oncology-genetics.

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 and/or exon array testing.

**Sample Submission**

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

Additionally, all test requisition forms are available for download from the GeneDx website: 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: wecare@genedx.com
Genetic Testing Process

Patient Identification
- Discussion of personal and family history
- Explanation of genetic testing options

Sample Submission
- The patient’s sample and necessary paperwork are sent to the laboratory

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

Genetic Test Results
- Contains information on the results of the genetic test and available medical management options
- The final report is sent to the ordering healthcare provider

Post-Test Discussion
- The healthcare provider and the patient discuss the test results, medical management options, and implications for family members

GUIDE FOR HEREDITARY CANCER
Genetic Test Results

Nearly all test results fall into one of four categories: positive (pathogenic variant), likely pathogenic variant, negative and 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 to 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. 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 that of 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 across the country can be found at: www.nsgc.org

Test results are available within three 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 Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Medical Management Guidelines</th>
</tr>
</thead>
</table>
| **APC**       | • Frequent colonoscopy starting at an early age; if adenomas are identified, increase the interval of colonoscopy  
• If the patient undergoes colectomy, continued endoscopic evaluation post-colectomy  
• Prophylactic colectomy is not always needed in AFAP. Colectomy is generally recommended for individuals who have adenomas that cannot be managed through colonoscopy  
• Upper endoscopy with duodenoscopy and visualization of the ampulla of Vater  
• Consider hepatoblastoma (childhood liver cancer) screening, including liver palpation, bio-chemical screening and abdominal ultrasound  
• Physical examination, including abdominal palpation and thyroid examination  
• One or more management recommendations may begin in childhood or adolescence |
| **ATM**       | • Increased breast awareness, including breast self-examination  
• Clinical breast examination  
• Breast MRI and mammogram starting at an early age  
• Consider breast cancer risk-reduction strategies, including the option of prophylactic mastectomy |
| **BMPR1A**, **SMAD4** | For both genes  
• Frequent colonoscopy starting at an early age  
• Upper endoscopy  
• One or more management recommendations may begin in childhood or adolescence  
For **SMAD4** only  
• Screen for vascular lesions associated with hereditary hemorrhagic telangiectasia (HHT) |
| **BRCA1, BRCA2** | • Increased breast awareness, including breast self-examination for both men and women  
• Clinical breast examination for both men and women  
• Breast MRI and mammography starting at an early age  
• Consider prophylactic mastectomy  
• Bilateral salpingo-oophorectomy (BSO)  
• Consider transvaginal ultrasound of ovaries and CA-125 blood tests for women who have not had a BSO  
• Consider the use of risk-reducing medications (such as tamoxifen, raloxifene and oral contraceptives)  
• Consider prostate cancer screening starting at an early age  
• Consider pancreatic cancer screening and full body skin examination dependent on family history |
<p>| <strong>BRIP1</strong>     | • Consider bilateral salpingo-oophorectomy |</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Medical Management Guidelines</th>
</tr>
</thead>
</table>
| **CDH1**<sup>2,3</sup> | - Increased breast awareness, including breast self-examination  
- Clinical breast examination  
- Breast MRI and mammography starting at an early age  
- Consider prophylactic mastectomy  
- Consider the use of risk-reducing medications (such as tamoxifen or raloxifene)  
- Prophylactic gastrectomy  
- In the absence of gastrectomy, upper endoscopy  
- Consider colonoscopy starting at an early age, dependent on family history |
| **CDKN2A**<sup>4-7</sup> | - Frequent total body dermatological examination, including serial photography of atypical nevi (moles) and self-examination  
- Consider pancreatic cancer screening dependent on family history  
- One or more management recommendations may begin in childhood or adolescence |
| **CHEK2**<sup>1,2</sup> | - Increased breast awareness, including breast self-examination  
- Clinical breast examination  
- Breast MRI and mammogram starting at an early age  
- Consider breast cancer risk-reduction strategies  
- Periodic colonoscopy starting at an early age* |
| **EPCAM**<sup>1</sup>, **MLH1**<sup>1</sup>, **MSH2**<sup>1</sup>, **MSH6**<sup>1</sup>, **PMS2**<sup>1</sup> | - 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 periodic upper endoscopy with extended duodenoscopy  
- Consider urinalysis to screen for urinary tract cancers  
- Consider physical examination with neurological examination |
| **FH**<sup>8,9</sup> | - MRI of the kidneys  
- Gynecologic examination and baseline pelvic imaging  
- Dermatological examination  
- One or more management recommendations may begin in childhood or adolescence |
| **FLCN**<sup>10</sup> | - MRI of the kidneys  
- High-resolution CT of the lungs  
- Dermatological examination |
| **MUTYH**<sup>1</sup> | **For 2 pathogenic variants**  
- Frequent colonoscopy starting at an early age  
- Consider upper endoscopy with duodenoscopy  
- Colectomy is generally recommended for individuals who have adenomas that cannot be managed through colonoscopy  
- Physical examination  
**For 1 pathogenic variant**  
- Consider periodic colonoscopy starting at an early age* |

* Given limited data to support these guidelines, caution should be used when making recommendations.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Medical Management Guidelines</th>
</tr>
</thead>
</table>
| NBN         | • Increased breast awareness, including breast self-examination  
• Clinical breast examination  
• Breast MRI and mammogram starting at an early age  
• Consider breast cancer risk-reduction strategies |
| PALB2^2,4   | • Increased breast awareness, including breast self-examination  
• Clinical breast examination  
• Breast MRI and mammogram starting at an early age  
• Consider breast cancer risk-reduction strategies, including the option of prophylactic mastectomy  
• Consider pancreatic cancer screening dependent on family history |
| POLD1^1     | • 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* |
| POLE^1      | • 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^2      | • Increased breast awareness, including breast self-examination  
• 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^2    | • Consider bilateral salpingo-oophorectomy |
| RAD51D^2    | • Consider bilateral salpingo-oophorectomy |
| SCG5/GREM1^1| • 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* |
| SDHB^11,12  | • Blood or urine analysis to screen for paragangliomas and pheochromocytomas  
• MRI or CT of the abdomen, thorax, and pelvis  
• One or more management recommendations may begin in childhood or adolescence |
| SDHC^11,12, SDHD^11,12 | • Blood or urine analysis to screen for paragangliomas and pheochromocytomas  
• MRI or CT of the skull base, neck, and body  
• 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.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Medical Management Guidelines</th>
</tr>
</thead>
</table>
| **STK11**<sup>1,2</sup> | • Clinical breast examination  
• Breast MRI and mammography starting at an early age  
• Pelvic exam with Pap smear and consideration of transvaginal ultrasound  
• Periodic colonoscopy starting at an early age  
• Upper endoscopy and small bowel visualization  
• Pancreatic cancer screening  
• Testicular examination  
• Physical examination  
• One or more management recommendations may begin in childhood or adolescence |
| **TP53**<sup>2</sup> | • Increased breast awareness, including breast self-examination  
• 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 |
| **TSC1**<sup>3</sup>,  
**TSC2**<sup>2</sup> | • Baseline brain MRI with follow up as needed  
• Baseline electroencephalograph (EEG) with follow up as needed  
• Evaluation for associated neuropsychiatric disorders  
• Abdominal MRI  
• Renal function assessment  
• Periodic pulmonary function testing and high-resolution chest CT  
• Periodic electrocardiogram  
• Echocardiogram  
• Dermatologic, dental and ophthalmologic examinations  
• One or more management recommendations may begin in childhood or adolescence |
| **VHL**<sup>4</sup> | • Imaging (such as ultrasounds, MRIs) to evaluate the kidneys, adrenal glands, and pancreas  
• Blood pressure monitoring  
• Blood or urine analysis to screen for pheochromocytomas  
• MRI of brain/spine  
• Physical, hearing and ophthalmologic examinations  
• Pregnant women affected with VHL require additional monitoring  
• One or more management recommendations may begin in childhood or adolescence |

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 \( \text{ATM}, \text{BRCA2}, \text{BRIP1}, \text{FANCC}, \text{FH}, \text{MUTYH}, \text{NBN}, \text{PALB2}, \text{POLE}, \text{RAD51C}, \text{SDHA}, \text{SDHB}, \text{SDHD}, \text{SMARCA4}, \text{SMARCB1}, \text{XRCC2} \) and the Lynch syndrome genes (\( \text{EPCAM}, \text{MLH1}, \text{MSH2}, \text{MSH6} \) and \( \text{PMS2} \)).\(^{18-22}\) 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 across the country can be found at: www.nsgc.org
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 provide 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/billing

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

Resources for Patients

American Cancer Society: www.cancer.org
GeneDx: www.oncogenedx.com
National Cancer Institute: www.cancer.gov
National Society of Genetic Counselors: www.nsgc.org
References


Select references on medical management provided.
For additional details, please visit www.genedx.com/oncology-genetics
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 whole exome sequencing 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 30 geneticists and 100 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.