A pathogenic mutation was identified in the BRCA1 gene.

Testing positive for a pathogenic mutation in the BRCA1 gene means your risks of developing breast and ovarian cancer are significantly greater than that of the average US woman. Your risk of pancreatic cancer is also increased by this mutation. This result does not mean that you have a diagnosis of cancer or that you will definitely develop cancer in your lifetime. Your actual risk may be different based on other genetic and non-genetic factors.

**DETAILS**

<table>
<thead>
<tr>
<th>GENE</th>
<th>MUTATION</th>
<th>CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>c.181T&gt;G (p.Cys61Gly)</td>
<td>Pathogenic</td>
</tr>
<tr>
<td></td>
<td>Alternate name(s): C61G, chr17.GRCh37:g.41258504A&gt;C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transcript: ENST00000357654</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zygosity: Heterozygous</td>
<td></td>
</tr>
</tbody>
</table>

**SUPPORTING EVIDENCE**

Variant is an established founder mutation in a population with the disease. Well-established in vitro or in vivo functional studies support a deleterious effect of the variant on the gene or gene product. Variant occurs in a critical amino acid of a well established protein functional domain. Computational and in silico lines of evidence consistently indicate that this variant is pathogenic. Reputable external databases consistently report variant as pathogenic. Variant is absent from or at extremely low frequency in population databases.
ADDITIONAL GENES ANALYZED

The genes below were analyzed, and no pathogenic or likely pathogenic genetic variants associated with an increased risk of breast, colorectal, melanoma, ovarian, pancreatic, prostate, stomach, or uterine cancers were identified:

- **APC, ATM, BAP1, BARD1, BMPRIA, BRCA2, BRIP1, CDH1, CDK4**, **CDKN2A (p16INK4a)**, **CHEK2, EPCAM**, **GREM1**, **MITF**, **MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2**, **POLD1**, **POLE**, **PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53**

**REVIEWED BY**

Tom Sample, MD, Pathologist

---

* Only positions known to impact cancer risk analyzed: **CDK4**: only chr12:g.58145429-58145431 (codon 24) analyzed. **EPCAM**: only large deletions and duplications including 3' end of the gene analyzed. **GREM1**: only duplications in the upstream regulatory region analyzed, **MITF**: only chr3:g.70014091 (including c.952G>A) analyzed, **POLD1**: only chr19:g.50909713 (including c.1433G>A) analyzed, **POLE**: only chr12:g.133250250 (including c.1270C>G) analyzed.

** PMS2: Exons 12-15 not analyzed.
Risk and Family Information

Risk among US women with a BRCA1 mutation to develop specific cancers by different ages in their life.

**INCREASED RISK FOR OTHER CANCERS**

In addition to increasing a woman’s risk for breast and ovarian cancers, mutations in the BRCA1 gene are known to increase the risk of developing pancreatic cancer.

<table>
<thead>
<tr>
<th>CANCER</th>
<th>RISK BY AGE 80 WITH BRCA1 MUTATION</th>
<th>AVG. US WOMAN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic³</td>
<td>Elevated (3-5%)</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

*Elevated: Risk is increased, but further research may clarify the exact risk figure.*

**FAMILY**

Consider sharing your results with relatives because:

- This mutation was most likely inherited from either your mother or your father. This would mean that one of your parents has the same mutation, and that your relatives on that side of the family may also have the same mutation. Fathers are just as likely to pass on a mutation as mothers.

- Each of your siblings has a 50% chance of having inherited this mutation. Brothers are just as likely to inherit it as sisters.

- Each of your children has a 50% chance of inheriting the same mutation. Men are just as likely as women to pass the mutation on to their children, and daughters and sons are equally likely to inherit it. Please keep in mind that children are not recommended to be tested for this mutation as it does not impact health or affect medical management in childhood.

---

FAMILY (Continued)

- If genetic testing indicates that a relative does not have the mutation (tests negative), that relative’s children are not at risk to inherit this mutation. These mutations do not skip generations.

How BRCA1 mutations affect men
If a man has a mutation in the BRCA1 gene, his chances of developing male breast, pancreatic, and prostate cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

<table>
<thead>
<tr>
<th>CANCER</th>
<th>RISK BY AGE 80 WITH BRCA1 MUTATION</th>
<th>AVG. US MAN(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male breast(^4,5)</td>
<td>1.8%</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Pancreatic(^6)</td>
<td>Elevated (3-6%)</td>
<td>1.1%</td>
</tr>
<tr>
<td>Prostate(^5,6)</td>
<td>Elevated</td>
<td>12%</td>
</tr>
</tbody>
</table>

Elevated: Risk is increased, but further research may clarify the exact risk figure.

---


Know Your Screening Guidelines

Below is a summary of screening guidelines from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) established by experts at the National Comprehensive Cancer Network (NCCN). They are for women who have a mutation in the BRCA1 gene. Your healthcare provider may use these NCCN Guidelines to help create a customized screening plan for you.

**BREAST AND OVARIAN CANCER**

- **Starting at age 18**: Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast self awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25**: Breast exam by your provider every 6-12 months.
- **Between ages 25-29 or individualized based on family history**: Breast MRI screening with contrast (preferred) every year or mammogram if MRI is unavailable.
- **Between ages 30-75**: Mammogram and breast MRI screening with contrast every year. Your provider may wish to alternate between these two screenings every 6 months.
- **Between ages 35-40, or after you are finished having children**: NCCN recommends a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) to lower the risk of developing breast and ovarian cancer. Ideally, this should involve a discussion with a gynecologic oncologist.
- **After age 75**: Your provider may discuss an individualized management plan with you.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts).
- Your provider may discuss the use of medications that might reduce the risk of developing breast or ovarian cancer.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.

**PANCREATIC CANCER**

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to BRCA1 mutation carriers. Please discuss your risk of pancreatic cancer with your healthcare provider.

---

7 Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V1.2017. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed September 20, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Common Questions

What does a positive result mean?
A positive result means that a mutation, or a genetic change, was identified in a specific gene that increases the lifetime chance of developing certain cancers. Your personal results contain more detailed risk information specific to the mutation identified in your genes. This result does not mean that you have cancer or that you will definitely develop cancer in your lifetime.

Who will see these test results?
Your results are available to you and the healthcare provider who ordered your test, as well as any additional providers you designated. Your results will not be sent by Color to your insurance company, employer, or any other healthcare provider without your explicit request.

Should I share my results with my healthcare provider?
Color recommends you share your results with your healthcare provider. Sharing your results allows your provider to guide you to appropriate resources and discuss tailored options for cancer screening and prevention.

Are there any protections against discrimination based on these results?
In 2008, a federal law called the Genetic Information Non-Discrimination Act (GINA) was passed. Under the terms of GINA, medical insurance companies and employers are prohibited from discriminating against individuals on the basis of genetic information. GINA defines genetic information as including not only genetic test results, but also family cancer history, and the fact that genetic testing occurred. The terms of GINA specify that insurance companies cannot raise rates, cancel a plan, or determine eligibility because of genetic testing. Employers also are prohibited from making hiring, firing, or promotion decisions based on genetic testing. The terms of GINA carry exceptions. For example, an exception might include employers with fewer than 15 employees and those with military insurance. Additionally, GINA does not extend to life, disability, or long-term insurance companies. Some states may have protections regarding discrimination from these types of insurance. Individuals may consider purchasing these policies prior to undergoing genetic testing.

CANCER RISKS

If there is no one in my family who had cancer, do I still have an increased risk?
Yes. This result means your chance of developing certain cancers over your lifetime is higher than that of an average person your age, regardless of your family history. We encourage you to speak with your healthcare provider and to schedule an appointment with a board-certified genetic counselor at Color.

How can I reduce my risk of developing cancer?
You and your healthcare provider can use this information to make a personalized screening and prevention plan. Following your plan may lower your chance of developing cancer or may increase the chance that any cancer detected will be diagnosed when it is at an earlier and more treatable stage. For more detailed information about some of the options that your healthcare provider could discuss with you, see the screening guidelines provided in your results. Please keep in mind that there is no right or wrong option when deciding on a plan to reduce your risk.
CANCER RISKS
(Continued)

Does this result mean that I need to have surgery?
You and your healthcare provider should discuss options for women with a BRCA1 mutation. Surgery may be one way to help reduce the risk of developing certain cancers. However, your age and other factors influence which risk-reduction strategy may be best for you at this time. Screening measures and risk-reducing medications other than surgery may also be available. If you have questions, speak with your healthcare provider.

SCREENING GUIDELINES FOR OTHER CANCERS

In addition to the screening guidelines provided related to cancers that are increased by a BRCA1 mutation, below are guidelines for women who have the same cancer risk as the average US woman. Your healthcare provider may use the American Cancer Society and NCCN Guidelines in addition to those listed in the Next Steps section of your report to help create a customized screening plan for you.

Colorectal cancer 9
- Between ages 50-75:
  - Colonoscopy every 10 years, or
  - Stool-based testing (high-sensitivity, guaiac-based, or immunochemical-based) every year, or
  - Stool-based DNA testing every 3 years, or
  - Flexible sigmoidoscopy every 5 years which may include guaiac- or immunochemical-based testing at year three, or
  - CT colonography every 5 years.
- These recommendations may change if you have polyps, colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

Melanoma 10
- To reduce the chance of developing skin cancers such as melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Stomach cancer
- Currently, there are no standard screening guidelines for stomach cancer. Please discuss any family history of stomach cancer with your healthcare provider.

Uterine cancer 11
- At the time of menopause: All women should be told about the risks and symptoms of

---


SCREENING GUIDELINES FOR OTHER CANCERS
(Continued)

endometrial cancer. Women should report any unexpected vaginal bleeding or spotting to their doctors.

• Some women, because of their history, may need to consider having a yearly uterine biopsy. Speak with a healthcare provider about your history.

General recommendations for all individuals

• Avoid all forms of tobacco
• Get to and stay at a healthy weight
• Get moving with regular physical activity
• Eat healthy with plenty of fruits and vegetables
• Limit how much alcohol you drink (if you drink at all)
• Protect your skin
• Know yourself, your family history, and your risks
• Get regular check-ups and cancer screening tests. A cancer-related check-up should include health counseling and, depending on a person's age and gender, exams for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some other diseases besides cancer.

ABOUT FAMILY

How did I get this mutation?

Both men and women can have and pass on mutations in the BRCA1 gene. You may have inherited the mutation from either your mother or your father. Based on this genetic analysis alone, it is not possible to determine how you inherited this mutation. In rare instances, a mutation could originate with you and would not be present in your mother or father. However, the great majority of BRCA1 mutations are passed from generation to generation. Please keep in mind that parents do not choose to pass a specific gene mutation to their children. Your risk of cancer is not affected by whether a mutation was passed to you from your father or your mother.

Should I talk with my relatives about my result?

You are encouraged to share these results with your relatives. It is normal to feel some anxiety about this. But knowing this information may help your relatives understand their own future risk of developing cancer, which may help them prevent a cancer or detect it early. However, keep in mind that not everyone wants to know their cancer genetic status and genetic testing is a personal decision. Talking about genetic test results and their impact on the family is an ongoing discussion rather than a one-time conversation.

Who specifically in my family should also get tested?

Mutations in the BRCA1 gene are inherited in a dominant fashion. This means that each of your siblings and children has a 50% chance of having inherited the same mutation. This mutation was likely inherited from one of your parents. If they choose to undergo testing, this can determine which side of your extended family is also at risk to have this BRCA1 mutation. It is typically recommended that an individual undergo genetic testing at an age at which it will impact their medical care (see Screening guidelines). Thus, for this mutation, genetic testing is

---

not generally recommended in minors (under the age of 18). Schedule a time to speak with a genetic counselor at Color for more detailed recommendations regarding testing your family members.
Methodology

The Color Test is designed to assess clinically relevant mutations in 30 genes associated with hereditary cancer risk. Genomic DNA is extracted from a saliva or peripheral blood sample using standard methods. Next Generation Sequencing libraries compatible with the Illumina platform are generated and enriched for the 30 genes via a custom designed Agilent SureSelect bait library. DNA fragments enriched from these genes are retrieved and analyzed using 2x150 paired end sequencing with an Illumina NextSeq 500 instrument. After alignment to reference genome GRCh37.p12 (hg19), low quality and duplicate reads are removed and variants are detected with GATK Haplotypecaller. This test detects single nucleotide substitutions, small deletions and insertions, copy number variations and inversions located in the DNA coding sequences, nearby flanking regions (+/- 20bp) and known splice regions in the genes targeted by the Color panel. The Color test has 100% coverage for all regions in our reportable range >20X. Our median coverage across our samples is >250X (can exceed 1000X) and our minimum acceptance criteria for depth is: >99% at >50X and 100% at 20X. Any exceptions to this are noted in the Limitations section.

Variants are classified according to the standards and guidelines for sequence variant interpretation of the American College of Medical Genetics and Genomics (ACMG). Variant classification categories include pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. All variants are evaluated by a board certified medical geneticist or pathologist. Identified likely benign and benign variants are not reported. The presence of a VUS is always reported, and the details are available upon request. All VUS and likely pathogenic variants are reviewed bi-annually for updates in the scientific literature. As part of the Color service, we will attempt to recontact the provider and/or the person that was tested if any reported variant’s classification changes.

Clinically actionable variants (i.e. likely pathogenic and pathogenic) are confirmed using an alternative technology (Sanger sequencing, aCGH or MLPA) in compliance with Color’s internal protocols and relevant ACMG guidelines. For SNVs and indels, a confidence model (color.com/variantconfidence) is used to identify high and low confidence variants. Low confidence variants, and structural variants (CNVs, insertions and inversions) are confirmed using an alternative technology. High confidence, clinically actionable variants that have been independently confirmed at least three times will not be submitted for further secondary confirmation. High confidence VUSs are reported without secondary confirmation.

This test was developed and its performance characteristics determined by Color Genomics, a clinical laboratory accredited by the College of American Pathologists (CAP) and certified under the Clinical Laboratory Improvement Amendments (CLIA) to perform high-complexity testing (CAP #8975161 - CLIA #05D2081492). This test has received the European Conformity (CE) mark in compliance with the EU legislation. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Genes

- **APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CDKN2B, CDKN2C, CHEK2, EPCAM, GREM1, MLH1, MLH3, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53**
TEST METHODOLOGY AND LIMITATIONS

(Continued)

* These genes are only analyzed at specific locations (see Limitations).

Limitations

This test aims to detect all clinically relevant variants within the genes analyzed (defined above). The majority of these genes are assessed for variants within all coding exons (+/- 20bp in the nearby flanking regions). Exons 12-15 of PMS2 and homopolymer regions outside of the coding regions cannot be reliably assessed with standard target enrichment protocols. For the CDK4, MITF, POLD1 and POLE genes, the elevated risk of cancer is associated with distinct functional genomic regions. The complete coding sequences of these genes are not reported, but instead only the following regions: CDK4 - chr12:g.58145429-58145431 (codon 24), MITF - chr3:g.70014091 (including c.952G>A), POLD1 - chr19:g.50909713 (including c.1433G>A) and POLE - chr12:g.133250250 (including c.1270C>G). In EPCAM, only large deletions and duplications including the 3’ end of the gene are reported. These are the only variants known to silence the MSH2 gene and therefore increase risk of associated cancer. GREM1 is only analyzed for duplications in the upstream regulatory region.

This test is not designed to detect chromosomal aneuploidy or complex rearrangements such as translocations. It also does not reliably detect mosaicism. The sensitivity to detect deletions and duplications in the range of 40-250bp, as well as those which deletion/duplication do not overlap more than 250bp of contiguous coding sequence, may be reduced. The presence of a large insertion may interfere with the chemistry used to target the genes of interest, which could decrease the detection sensitivity. In addition, the sequence and identity of a large insertion may not be completely resolved. Inversions including at least one coding exon will be detected only if the breakpoints are covered by the Color test. The sensitivity to detect variants in the vicinity of homopolymer regions may be reduced.

Color only reports findings within the genes that are on the panel. It is important to understand that there may be variants in those genes that current technology is not able to detect. Additionally, there may be genes associated with hereditary cancer risk whose clinical association has not yet been definitively established. The test may therefore not detect all variants associated with hereditary cancer risk. Additionally, in the unlikely event a variant is detected that is associated with a disorder or disease other than cancer, this information will be included in the report. Genetic counseling and/or physician consultation may be warranted to ensure complete understanding of your test results.

Environmental and other factors are thought to cause the majority of cancers. Consequently, tests that do not detect a pathogenic or likely pathogenic mutation do not eliminate an individual’s hereditary cancer risk and do not guarantee present or future health. In addition, the causes of cancer are multifactorial and can be influenced by both inherited and acquired genetic mutations, age, environment and various lifestyle choices. An individual’s risk of cancer is dependent upon each of these factors as well as family disease history. In very rare cases, such as circulating hematolymphoid neoplasm, allogeneic bone marrow transplant, or recent blood transfusion (within 7 days of testing), the results of germline DNA analysis may be complicated by somatic and/or donor mutations. DNA quality may be affected if a participant has received chemotherapy within the last 120 days.

Disclaimers

Color implements several safeguards to avoid technical errors, such as 2-dimensional barcoding...
and barcode scanning at several steps throughout the sequencing process. Color Genomics is not responsible for errors in specimen collection, transportation, and activation or other errors made prior to receipt at our laboratory. Due to the complexity of genetic testing, diagnostic errors, although rare, may occur due to sample mix-up, DNA contamination, or other laboratory operational errors. In addition, poor sample DNA quality and certain characteristics inherent to specific regions of an individual’s genomic DNA may limit the accuracy of results in those regions.

In the absence of an identified pathogenic or likely pathogenic mutation, several standard risk models may be employed to determine potential risk of breast cancer and guidelines displayed on this report. All risk estimation is approximate, sometimes cannot be specifically calculated, and is based on previously analyzed cohorts. Additionally, risk estimation may be incorrect if inaccurate personal or family history information is provided. An elevated risk of cancer is not a diagnosis and does not guarantee that a person will develop the disease.

Contact us free of charge at (844) 352-6567 with any questions.