



## Sample Report

Hereditary Cancer Test

PATIENT/CLIENT

Jane Doe

DOB: May 25, 1977

ID: 123456

Sex: Female

Requisition #: 123456

## ORDERING PHYSICIAN

Dr. Jenny Jones  
Sample Medical Group  
123 Main St.  
Sample, CA

## PRIMARY CONTACT

Kelly Peters  
Sample Medical Group  
123 Main St.  
Sample, CA

## SPECIMEN

**Type:** Saliva  
**Barcode:** 223 234234 2343  
**Collected:** Sept 15, 2018  
**Received:** Sept 20, 2018

Report date: October 2, 2018



A pathogenic mutation was identified in the *BRCA1* gene.

Testing positive for a pathogenic variant (also called a mutation) in the *BRCA1* gene means your risks of developing breast and ovarian cancers are greater than that of the average US woman. Your risk of pancreatic cancer is also increased by this mutation.

There have been many studies that show that mutations in the *BRCA1* gene are linked to increased cancer risk. Research on this gene is ongoing. As additional information is gathered, risk estimates and associated cancers may change. If this happens, we will try to contact you.

## DETAILS

GENE	MUTATION	CLASSIFICATION
<i>BRCA1</i>	c.5266dupC (p.Gln1756Profs*74) <i>Alternate name(s): g.41209082dupG, BIC: 5382insC, 5385insC</i> <i>Transcript: ENST00000357654</i> <i>Zygosity: Heterozygous</i>	Pathogenic

## SUPPORTING EVIDENCE

Variant is an established founder mutation in a population with the disease. Truncating variant occurs in the gene where loss of function is a known mechanism of disease and is not located in the last or a commonly processed exon. Well-established in vitro or in vivo functional studies support a deleterious effect of the variant on the gene or gene product. Variant demonstrates significant disease association in appropriately sized case-control studies. The prevalence of the variant in affected individuals is increased compared to the prevalence in controls. Variant is absent from or extremely rare in population databases. Data from reputable databases support the classification of variant as pathogenic. Variant is absent from or extremely rare in control populations and occurs in 2 or more unrelated individuals with classically defined disease and without knowledge of another explanatory pathogenic variant. Variant demonstrates moderate cosegregation with disease in family members in a gene implicated in the disease.

## NOTES ABOUT YOUR RESULT

- Cancer risks and screening guidelines are typically based on studies of individuals with a family history of cancer. Medical management should be considered based on your personal and family history.



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- 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. Learn more below.

## GENES ANALYZED

## Additional genes analyzed

The genes below were analyzed, and no pathogenic or likely pathogenic variants associated with an increased risk of hereditary breast, colorectal, melanoma, ovarian, pancreatic, stomach, or uterine cancers were identified. Please see the test methodology and limitations section for additional information.

*APC, ATM, BAP1, BARD1, BMPR1A, BRCA2, BRIP1, CDH1, CDK4, CDKN2A (p14ARF), CDKN2A (p16INK4a), CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*

## REVIEWED BY

Tom Sample, MD, Pathologist

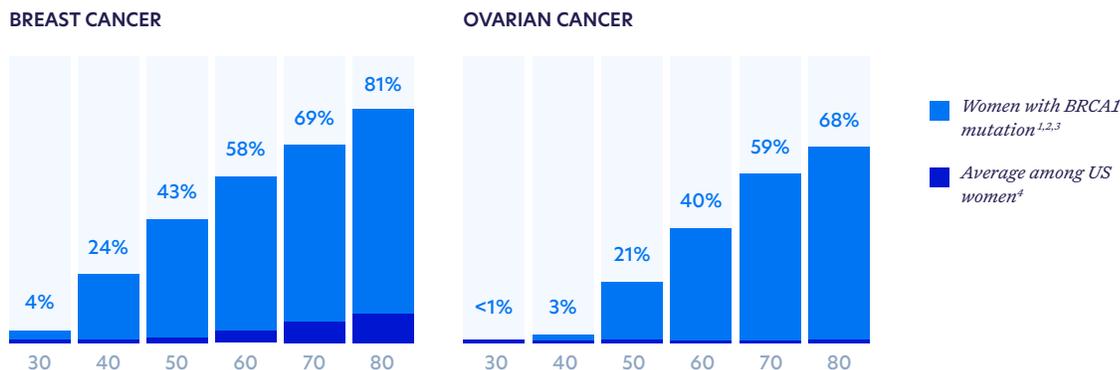
Date



### Risk and Family Information

#### RISK BY AGE WITH A BRCA1 MUTATION

Risk among US women with a *BRCA1* mutation to develop specific cancers by different ages in their lives. The risk listed represents the maximum risk at that age.



#### 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.

CANCER TYPE	RISK WITH BRCA1 MUTATION <sup>5</sup>	AVG. US WOMAN <sup>4</sup>
Pancreatic	Elevated (3-5%)	< 1%

*The risk of developing cancer by age 80. The specific chance of developing cancer has not been fully established and is based on data from one or more sources.*

#### ABOUT THE BRCA1 GENE

##### The BRCA1 gene

The *BRCA1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *BRCA1* is repairing damaged DNA before a cell divides to make more copies of itself. *BRCA1* works together with other genes such as *BARD1*, *PALB2*, and *BRCA2* to direct the repair of the DNA damage.

##### Impact of BRCA1 mutations

Like most genes, each person has two copies of the *BRCA1* gene: one inherited from each parent. A mutation in a single copy of the *BRCA1* gene inherited from either parent is known to increase risk of specific cancers (breast, ovarian, prostate, and pancreatic) over a lifetime.



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**FAMILY**

Consider sharing your results with relatives because:

- This *BRCA1* 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 mutations in the *BRCA1* gene, as they do not impact health or affect medical management in childhood.
- 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 cancers 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.

CANCER TYPE	AVG. US MAN <sup>4</sup>	WITH <i>BRCA1</i> MUTATION <sup>6,7,5,8</sup>
Male breast	<0.1%	1.8%
Pancreatic	1.1%	Elevated (3-6%)
Prostate	9.7%	Elevated

*The risk of developing cancer by age 80.*

*The specific chance of developing cancer has not been fully established and is based on data from one or more sources.*

## Know your *BRCA1* screening guidelines

These screening guidelines are for women who have a mutation in the *BRCA1* gene.

### BREAST AND OVARIAN<sup>9</sup>

- **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 awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25:** 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 every year. Your provider may discuss screening with tomosynthesis (3D mammogram) if MRI is unavailable.
- **Between ages 30-75:** Breast MRI screening with contrast and mammogram every year. Your provider may discuss screening with tomosynthesis and 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 cancers.
- **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 cancers.
- **Starting at age 30-35:** Your provider may discuss circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, but these techniques have not been shown to be effective in detecting early ovarian cancer.

### PANCREATIC<sup>9</sup>

- Currently, there are no pancreatic cancer screening guidelines specific to *BRCA1* mutation carriers. Your provider may discuss screening or referral to a specialist.

## Additional screening guidelines

In addition to the gene-specific information provided above, your healthcare provider may use the guidelines below for all US women to help create a customized screening plan for you.



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**COLORECTAL<sup>10</sup>**

- **Between ages 50-75:**
  - Colonoscopy every 10 years, or
  - Stool-based testing (high-sensitivity, guaiac-based, or immunochemical-based) every year, or
  - Stool-based FIT-DNA testing every 3 years, or
  - Flexible sigmoidoscopy every 5-10 years, or
  - CT colonography every 5 years.
- **After age 75:** Your provider may discuss an individualized management plan with you.
- These recommendations may change if you have polyps, colon cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

**UTERINE<sup>11</sup>**

- **At the time of menopause:** All women should be told about the risks and symptoms of uterine 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.

**MELANOMA<sup>12</sup>**

- To reduce the chance of developing 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**

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



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**GENERAL  
RECOMMENDATIONS  
FOR ALL INDIVIDUALS<sup>11</sup>**

- 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.



## Common Questions

### GENERAL 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 disorders. Your personal results contain more detailed risk information specific to the mutation identified in your genes, as well as information to share with your family members and healthcare provider.

#### What is a pathogenic mutation?

A pathogenic mutation is a variant in the DNA sequence of a gene that affects its ability to function. A pathogenic mutation is also referred to as a mutation in this report.

#### 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 consent.

#### 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 screening, prevention, and management.

#### Are there any protections against discrimination based on these results?

In 2008, a federal law called the Genetic Information Nondiscrimination Act (GINA) was passed to prohibit medical insurance companies and employers from discriminating against individuals on the basis of genetic information, including genetic test results, family cancer history, and even the fact that genetic testing occurred. GINA does not extend to life, disability, or long-term care insurance, which may be governed under state law. Protection against these and other types of discrimination may vary by state. Individuals may consider purchasing these policies prior to undergoing genetic testing. Federal and state laws regarding genetic discrimination change from time to time. We encourage you to keep informed of these important laws and regulations.

\*The statements made herein are for informational purposes only and do not constitute legal advice.

### CANCER RISKS

#### If there is no one in my family who had cancer, does a mutation in this gene still increase cancer risk?

Yes. Mutations in the genes analyzed are associated with an increased risk of developing certain cancers, regardless of 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 of developing cancer. It is a very personal choice.



## GENERAL QUESTIONS

(continued)

### If I've already had cancer, can I get it again?

All individuals who have been diagnosed with cancer have some chance of developing a new primary cancer or a recurrence of the original tumor in the future. This positive result does not significantly change the risk of developing a recurrence. We encourage you to speak with your healthcare provider to learn more about your chance of developing cancer in the future.

### Is genetic testing on tumors different than the Color Test?

Yes. The Color Test analyzes the genetic makeup you inherited from your mother and father, which can be found in your blood and all other cells of your body. The primary purpose of the Color Test is to find any potential inherited causes for your cancer in order to provide detailed information about your risk of developing other cancers in the future, as well as to give important information to your family members.

By contrast, the genetic testing on tumor tissue looks for DNA changes that occurred while the cancer was forming. These changes are only in the cancer cells, not in any other cells of your body, and were not inherited from your parents, nor can they be passed down to your children. The primary purpose of tumor genetic testing is to provide prognostic information and potential targeted treatments.

## FAMILY IMPACT

### How did I get this *BRCA1* 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 some instances, a mutation could originate with you and would not be present in your mother or father. If you have no family history of the disorder associated with the *BRCA1*, this may be why. However, the 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 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. Knowing this information may help your relatives understand their own future risk of developing the same disorder, which may help them prevent or detect it early. However, keep in mind that not everyone wants to know their risk to develop disorders 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.

## TEST METHODOLOGY AND LIMITATIONS

### Methodology

Genomic DNA is extracted from the submitted sample, enriched for select regions using a hybridization protocol, and sequenced using Illumina Next Generation Sequencing. Sequence data is aligned to a reference genome, and variants are identified using a suite of bioinformatic tools designed to detect single nucleotide variants, small insertions/deletions, and structural variants such as copy number variants, insertions and inversions. Reported variants may be confirmed by alternate technologies, including Sanger sequencing, MLPA or aCGH. Analysis, variant calling and reporting focus on the complete coding sequence and adjacent intronic sequence of the primary transcript(s), unless otherwise indicated.

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.

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 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. This test has received the European Conformity (CE) mark in compliance with the EU legislation.

### Genes

*APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4\*, CDKN2A(p14ARF), CDKN2A(p16INK4a), CHEK2, EPCAM\*, GREM1\*, MITF\*, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2\*, POLD1\*, POLE\*, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*

\* 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 (and adjacent intronic sequence). Exons 12-15 of PMS2 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; therefore, 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 since 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.



## TEST METHODOLOGY AND LIMITATIONS

(continued)

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 may be reduced in regions of low/high GC content, and in the vicinity of homopolymers and simple sequence repeats.

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 whose clinical association has not yet been definitively established. The test may therefore not detect all variants associated with hereditary cancer. Additionally, in the unlikely event a variant is detected that is associated with a disorder other than hereditary cancer, this information will not be included in the report. Genetic counseling and/or physician consultation may be warranted to ensure complete understanding of your test results.

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 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, standard risk models may be employed to determine potential risk of hereditary 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 is provided. An elevated risk for hereditary cancer is not a diagnosis and does not guarantee that a person will develop the disease.



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

- <sup>1</sup> King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302(5645):643-6. Pubmed Abstract
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- <sup>3</sup> Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017;317(23):2402-2416.
- <sup>4</sup> Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2013-2015. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.6. Accessed May 2018.
- <sup>5</sup> Mocchi E, Milne RL, Mendez-Villamil EY, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. *Cancer Epidemiology Biomarkers Prev*. May 2013;22(5):803-11. Pubmed Abstract
- <sup>6</sup> Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer*. May 2012;106(10):1697-701.
- <sup>7</sup> Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst*. December 2007;99(23):1811-4. Pubmed Abstract
- <sup>8</sup> Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. *J Clin Oncol*. February 2014;22(4):735-42.
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- <sup>12</sup> Skin Cancer Prevention and Early Detection. *The American Cancer Society*. Updated March 19, 2017. Accessed April 2, 2018. Available at [www.cancer.org](http://www.cancer.org)

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