

Sample Report

Hereditary Cancer Risk 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

SPECIMEN

Type: Saliva
Barcode: 223 234234 2343
Accession #: C-12345
Received: Apr 14, 2016

Report date: Apr 28, 2016



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

| GENE | MUTATION | CLASSIFICATION |
|--------------|---|----------------|
| <i>BRCA1</i> | c.181T>G (p.Cys61Gly) Alternate name(s): C61G, chr17.GRCh37:g.41258504A>C Transcript: ENST00000357654 Zygosity: Heterozygous | Pathogenic |

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.



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

LAB DIRECTOR

Sally Sample, MD

Date

* 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.

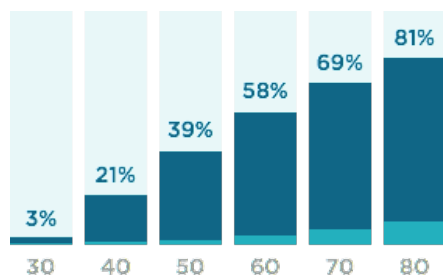
Risk and Family Information

RISK BY AGE

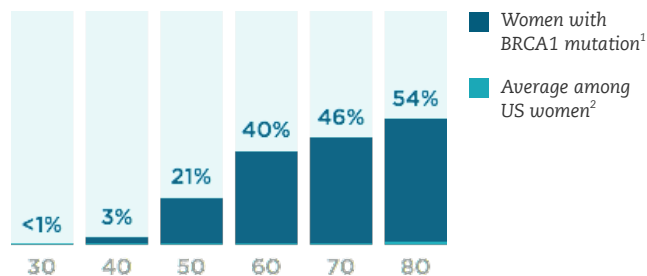
with a *BRCA1* mutation

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

BREAST CANCER



OVARIAN CANCER



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 | RISK BY AGE 80 WITH <i>BRCA1</i> MUTATION | AVG. US WOMAN ² |
|--|---|----------------------------|
| Pancreatic ³ | Elevated (3-5%) | < 1% |
| 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.

¹ King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and Ovarian Cancer Risks Due to Inherited Mutations in *BRCA1* and *BRCA2*. *Science*. October 2003; 302(5645):643-6.

² Surveillance, Epidemiology, and End Results Program (SEER). National Cancer Institute. <http://seer.cancer.gov/>. Accessed May 2015.

³ Mocci 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 Prevention*. May 2013; 22(5):803-11.



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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, prostate, and pancreatic 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.

| CANCER | RISK BY AGE 80 WITH <i>BRCA1</i> MUTATION | AVG. US MAN ² |
|----------------------------|---|--------------------------|
| Male breast ⁴⁻⁵ | 1.8% | < 0.1% |
| Prostate ⁵⁻⁶ | Elevated | 12% |
| Pancreatic ³ | Elevated (3-6%) | 1.1% |

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

⁴ Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male *BRCA1* and *BRCA2* mutation carriers. *Journal of the National Cancer Institute*. December 2007; 99(23):1811-4.

⁵ Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in *BRCA1* or *BRCA2*: a review of the literature. *Journal of Clinical Oncology*. February 2004; 22(4):735-42.

⁶ Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline *BRCA1* mutations increase prostate cancer risk. *British Journal of Cancer*. May 2012; 106(10):1697-701.

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).⁷ 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 CANCER⁸

- **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 (preferred) every year or mammogram if MRI is unavailable.
- **Between ages 30-75:** Mammogram and breast MRI screening 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 CANCER⁸

- 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 V.2.2015. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. Accessed Jun 1, 2015. 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.

⁸ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Guidelines Version 1.2016. Available at www.nccn.org. Published February 2016.

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 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)

of developing cancer. It is a very personal choice.

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.

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.



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TEST METHODOLOGY AND LIMITATIONS

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 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 insertions and deletions, and copy number variations located in the DNA coding sequences, nearby flanking regions (+/- 20bp) and known splice regions in the genes targeted by the Color panel. 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 client 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.

Genes

APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A(p14ARF), CDKN2A(p16INK4a), CHEK2, EPCAM*, GREM1*, MITF*, MLH1, MSH2, MSH6, MUTYH, NBN, 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 (+/- 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



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TEST METHODOLOGY AND LIMITATIONS

(Continued)

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 tested for duplications in the upstream regulatory region.

The test might have reduced sensitivity to detect insertions and deletions between approximately 40-250bp. While this test does detect large deletions and duplications, it is not designed to detect chromosomal aneuploidy or complex gene rearrangements such as translocations, large insertions, and inversions. It also does not reliably detect mosaicism.

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.

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.