DNA life

May 09, 2017

Hereditary Cancer Risk Test

PATIENT/CLIENT Milad Alexandre Mack Atala

DOB: Jun 06, 1968

Sex: Male

MRN: 1704011

Requisition #: 5575729

SPECIMEN

Report date: May 09, 2017

Type: Blood
Barcode: B-3540317
Collected: Apr 17, 2017
Received: Apr 20, 2017

No mutations were identified.

This means no pathogenic or likely pathogenic genetic variants associated with an increased risk of breast, colorectal, melanoma, ovarian, pancreatic, stomach, or uterine cancers were identified in any of the 30 genes analyzed.

This result does not eliminate your risk of developing cancer. Inherited mutations explain some cases of cancer, but most are not inherited and can not be explained by a single cause. Some non-genetic factors that can influence cancer risk include environment and lifestyle, as well as family history without a known genetic link. Your healthcare provider can help determine how your screening plan might be influenced by your health history and other factors.

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, 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*

* 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.

REVIEWED BY

Annette Meredith

May 09, 2017

Annette L. Meredith, Ph.D., M.S., FACMG, Medical Geneticist — Date

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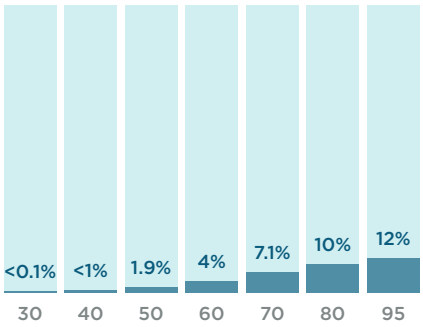
Risk and Family Information

AVERAGE RISK BY AGE

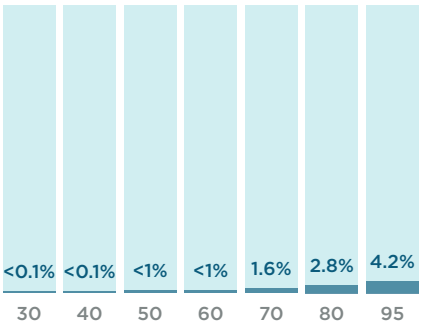
among US women

Average risk among US women to develop specific cancers by different ages in their lives. Breast and colorectal cancers are highlighted because they are more common.

BREAST CANCER



COLORECTAL CANCER



Average risk among US women[4]

OTHER CANCERS

TYPE	AGE 50[4]	AGE 95[4]
Uterine	<1%	2.8%
Melanoma	<1%	1.6%
Pancreatic	<0.1%	1.5%
Ovarian	<1%	1.3%
Stomach	<0.1%	<1%

FAMILY

Consider sharing your results with relatives who may also benefit from genetic testing. A few key points to remember:

- Your negative result significantly lowers the chance that you have an inherited mutation associated with hereditary cancer.
- It is still possible for your relatives to have a mutation that you did not inherit. They may benefit from their own genetic testing, especially those who have had cancer.
- If any of your relatives has a mutation, there is a 50% chance that their siblings and children also have the same mutation.
- A father and mother are equally likely to pass on a mutation. Sons and daughters are equally likely to inherit a mutation if one of their parents has it.
- If you learn that a relative of yours has a mutation, contact a Color genetic counselor to learn how that information may impact your risk assessment and interpretation of results.

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Know your screening guidelines [3]

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) and the American Cancer Society. These guidelines are 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® to help create a customized screening plan for you.

BREAST CANCER [1]

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-39:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 40:** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis.

COLORECTAL CANCER [2]

- **Between ages 50-75:** Screening options below.
  - 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 [7]

- 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.

OVARIAN CANCER [6]

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

PANCREATIC CANCER

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

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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[5]

- **At the time of menopause:** All women should be told about the risks and symptoms of 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[5]

- 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.

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Common Questions

GENERAL QUESTIONS

What does a negative test result mean?
A negative result means that no mutations, or genetic changes associated with an increased risk of the most common hereditary cancers, were identified in the genes that were analyzed. This result does not eliminate your risk of developing cancer. You may still be at increased risk of cancer due to other factors, mutations not detected by current technology, or mutations in other genes.

Does this result mean I'm not at risk of cancer?
No, the absence of mutations does not mean that you will not develop cancer. Cancer risk is also influenced by factors such as family history, environment, lifestyle, and random chance. In addition, not all of the genes related to hereditary cancer are known or included on the Color test. You should continue to follow the screening and prevention advice of your healthcare team, or schedule an appointment with a Color genetic counselor if you have questions.

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 healthcare 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 provider. Sharing your results allows your provider to guide you to appropriate resources and discuss tailored options for cancer screening and prevention.

What else can cause cancer besides gene mutations?
Most cancers are sporadic, meaning they do not seem to run in the family. Sporadic cancers are likely influenced by a combination of many factors, including age, sex, environment, and even random chance. Some families have more cancer than expected, but without a known genetic mutation or other single explanation. This is called familial cancer. Several risk factors have been associated with familial cancer, including family history, environmental exposures, and lifestyle factors.

What health history factors may influence my risk of breast cancer?
All women have some risk of developing breast cancer, even when they do not have a mutation in one of the genes analyzed by this test. There are many factors that can increase risk, including personal and family health history. Your healthcare provider can help determine how your screening plan might be influenced by your health history and other factors.

For breast cancer specifically, some factors known to influence risk include:

- History of cancer
- Family history of breast or ovarian cancer
- Ancestry (where a person is from in the world), including if they are of Ashkenazi Jewish descent
- Age at first period
- Age of first birth, if a woman has given birth
- One or more breast biopsies
- Breast biopsy showing atypical hyperplasia or lobular carcinoma in situ
- History of chest radiation therapy, mastectomy (removal of one's breast or breasts), or oophorectomy (removal of one's ovaries)

FAMILY IMPACT

What do my results mean to my relatives and do any of them need to consider genetic testing?
Though you do not carry a mutation associated with hereditary cancer, it is possible that your relatives have one that you did not inherit. The only way for them to know whether or not they have such a mutation is for them to undergo genetic testing. Genetic testing can be particularly informative for individuals in the family who have been diagnosed with cancer. Please schedule an appointment with a Color genetic counselor for specific recommendations about testing tailored to your family.

Should I talk with my relatives about my result?
You are encouraged to share these results with your relatives. Knowing this information may help them decide whether genetic testing is right for them. Relatives who have had cancer may especially find this information useful. However, keep in mind that not everyone wants to know their cancer genetic status and genetic testing is a personal decision.

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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 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 (SNV), small insertions and deletions (indels) in the DNA coding sequences, nearby flanking regions (+/- 20bp) and known splice regions in the genes targeted by the Color panel. In addition, copy number variations (CNVs), large insertions and inversions overlapping coding exons, are reported. The Color test has 100% coverage for all regions in our reportable range >20X. Our median coverage across our samples is >250X 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.

All clinically actionable variants (i.e. likely pathogenic and pathogenic) as well as all reported copy number variations, insertions and inversions are confirmed using an alternative technology (Sanger sequencing, aCGH or MLPA), in compliance with Color's internal protocols, ACMG guidelines in effect at the time of analysis, and applicable regulations. For SNVs and indels classified as VUS, a confidence model (color.com/variantconfidence) is used to identify high and low confidence variants. High confidence VUSs are reported without secondary confirmation. VUSs that are called with lower confidence are confirmed using an alternative technology.

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, 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 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 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.

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.