Patient/Client:
Jane Doe

DOB: May 25, 1977
ID: 37883127
Sex assigned at birth: Female

Specimen: Saliva
Barcode: 01234500540938
Report date: Oct 9, 2023
Specimen collected Sep 26, 2023
Specimen received: Sep 30, 2023

Ordering provider:
Jenny Jones, MD
NPI: 1234567890

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

Pathogenic variants (also called mutations) in the *BRCA1* gene are associated with an increased risk of developing breast, ovarian, pancreatic, and prostate cancer.

This result does not mean that you have a diagnosis of cancer or that you will definitely develop cancer in your lifetime. The level of risk depends on many factors including your age, history of hormone treatment, past surgeries, family medical history, and other factors. As additional information is gathered across more populations, risk estimates and associated health impacts may change.

It is important to speak with a healthcare provider, including a genetic counselor, about this test result and what it means for you. Your healthcare provider can help interpret this result in the context of other important factors, such as your personal medical history, your family history, or other tests you have had.

Genes with pathogenic variants

Pathogenic variants are changes in the DNA sequence of a gene that affects its ability to function.

Gene	Variant	Classification
BRCA1	c.181T>G (p.Cys61Gly) Alternative name(s): g.41258504A>C, BIC: C61G, 300T>G Zygosity: Heterozygous Transcript: ENST00000357654	Pathogenic

Supporting evidence

***BRCA1* c.181T>G (p.Cys61Gly):** This missense variant replaces a conserved cysteine with glycine at codon 61 in the RING domain of the BRCA1 protein. Functional studies have shown that this variant disrupts the oligomerization properties of BRCA1 (PMID: 9525870), abolishes interaction with BARD1 and ubiquitin-ligase activity associated with BRCA1 (PMID: 11278247, 11320250), inhibits BARD1-dependent repression of BRCA1 transcriptional activity (PMID:18243530), abolishes homology-directed DNA repair activity (PMID: 20103620), and renders the mutant protein unable to complement BRCA1-null mouse or human haploid cells (PMID: 2386711, 30209399). This variant is a common cause of breast and ovarian cancer in individuals of Eastern European ancestry (PMID: 10447273, 10788334, 11102977, 20345474, 205007347, 20569256, 29492181) and has been shown to be a founder mutation in the Polish population by haplotype analysis (PMID: 19594371). This variant has been identified in 8/250754 chromosomes in the general population by the Genome Aggregation Database (gnomAD). Based on the available evidence, this variant is classified as Pathogenic.

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Genes analyzed

The genes below were analyzed as part of this test. Unless specified above, no pathogenic or likely pathogenic genetic variants associated with an increased personal risk of disease were identified.

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

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, copy number variants, insertions and inversions, and to infer diplotypes. Reported variants may be confirmed by alternate technologies, including Sanger sequencing, MLPA, aCGH or probe-based genotyping. Analysis, variant calling and reporting focus on the complete coding sequence and adjacent intronic sequence of the primary transcript(s) indicated below, unless otherwise indicated in the Limitations section. Greater than 99% of the panel regions indicated below (see “Genes” section) are covered at ≥50X, and our minimum acceptance criteria for coverage is >99.9% at ≥20X. For *PMS2* exons 12-15, the reference genome has been modified to align all sequence reads derived from *PMS2* and the *PMS2CL* pseudogene to *PMS2*, and candidate variants are identified using variant calling algorithms that have been modified to expect 4 alleles. The exact location of relevant candidate variants is determined by long-range PCR using primer sequences that are specific to *PMS2* and *PMS2CL*, followed by individual nested PCR and Sanger sequencing of the relevant regions of *PMS2* and *PMS2CL*.

This test was developed and its performance characteristics determined by Color Health, Inc. (“Color”), which maintains 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 is intended for clinical purposes. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this laboratory developed test to go through premarket FDA review. The test should not be regarded as investigational or for research. This test has received the European Conformity (CE) mark in compliance with the EU legislation.

Identified variants are described using the recommended HGVS nomenclature, relative to the reported transcript. Exons are numbered beginning with the first exon of the reported transcript, which can be non-coding. Variants are classified according to the standards and guidelines for sequence variant interpretation established by the American College of Medical Genetics and Genomics (ACMG) and described using recommended classification nomenclature: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign (PMID:25741868). Variants are classified in the context of the following disease phenotypes: breast cancer, ovarian cancer, uterine cancer, colorectal cancer, melanoma, pancreatic cancer, stomach cancer, and prostate cancer. For a complete list of gene-phenotype associations please visit: color.com/learn/color-genes. All classifications are evaluated by a board certified medical geneticist or pathologist.

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Pathogenic and likely pathogenic variants that can directly impact an individual's personal risk of hereditary disease are reported, with supporting evidence and comprehensive variant details provided. The presence of VUS(s) is always reported with specific variant details and supporting evidence available upon request. Likely benign and benign variants are not reported.

Genes

APC (257430), *ATM* (278616), *BAP1* (460680), *BARD1* (260947), *BMPR1A* (372037), *BRCA1* (357654), *BRCA2* (544455), *BRIP1* (259008), *CDH1* (261769), *CDK4** (257904), *CDKN2A* (p14ARF, 304494), *CDKN2A* (p16INK4a, 579755), *CHEK2* (328354), *EPCAM** (263735), *GREM1** (300177), *MITF** (394351), *MLH1* (231790), *MSH2* (233146), *MSH6* (234420), *MUTYH** (450313), *PALB2* (261584), *PMS2** (265849), *POLD1** (440232), *POLE** (320574), *PTEN* (371953), *RAD51C* (337432), *RAD51D* (345365), *SMAD4* (342988), *STK11* (326873), *TP53* (269305)

Numbers represent Ensembl transcript IDs (e.g. ENST00000357654).

** Only specific locations are analyzed (see Limitations).*

Limitations

* *CDK4*: analysis is limited to chr12:g.58145429-58145431 (codon 24). *EPCAM*: analysis is limited to deletions that minimally encompass the 3' end of the gene including exons 8 and/or 9. *GREM1*: analysis is limited to duplications that overlap the upstream regulatory region. *MITF*: analysis is limited to chr3:g.70014091 (including c.952G>A). *MUTYH*: Single heterozygous pathogenic variants, likely pathogenic variants, and variants of uncertain significance are not reported. *PMS2*: variants of uncertain significance are not reported for exons 12-15. Analysis excludes three variants commonly observed in the pseudogene *PMS2CL*: c.2182_2184delinsG, c.2243_2246delAGAA and deletion of exons 13-14 (chr7:g.6015768_6018727del). *POLD1*: analysis is limited to chr19:g.50909713 (including c.1433G>A). *POLE*: analysis is limited to chr12:g.133250250 (including c.1270C>G).

Color only reports results within the reportable range (specified above) for the genes that are on the ordered test(s). Variants that may also impact regions outside of the reportable range (e.g., copy number variants encompassing multiple genes) will only be interpreted and reported in reference to the impact within the reportable range– interpretation for regions outside the reportable range is generally not provided.

This test is not optimized to detect chromosomal aneuploidies. As such, if detected, chromosomal aneuploidies (including sex chromosomal aneuploidies) will not be reported. This test also does not reliably detect mosaicism or complex rearrangements such as translocations and gene conversions. However, if a variant is detected below the typical range for heterozygous germline variants, it may be reported as a secondary finding if confirmed by an alternative technology. Sensitivity to detect specific types of variants may be reduced. This includes: deletions and insertions in the range of 40-250bp, copy number variants that do not overlap more than 250bp of contiguous coding sequence, variants in regions of low/high GC content, and variants in the vicinity of homopolymers and simple sequence repeats. Inversions including at least one coding exon will be detected only if the breakpoints are covered by the Color test. Phase determination between multiple variants co-occurring in the same gene is generally not possible.

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.

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Disclaimers

Color makes no representation or guarantee that the sequencing process is free of error and under no circumstances will Color be liable for any such error. 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 uncommon, may occur due to sample mix-up, DNA contamination, or other laboratory operational errors (including, without limitation, equipment or reagent failure, or upstream supplier 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.

All classifications are based on review, interpretation, and/or analysis of evidence available at the time of reporting, including, without limitation, medical literature and scientific databases, and may change as new evidence becomes available.

In the absence of an identified pathogenic or likely pathogenic mutation, standard risk models may be employed to determine risk estimates 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 or incomplete personal or family history is provided. "Elevated risk" is not a diagnosis and does not guarantee that a person will develop the disease.

Reviewed By

Name, Credentials

Date