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Reclassification - 08/26/2025

Ordered By	Contact ID:5903265 Org ID:8141	Patient Legal Name: **Last, First**	
Medical Professional:	Unknown, Unknown, MD	Accession #: **01-083300**	Specimen #:
Client:	MOCKORG44 (10829)	AP2 Order #: 2946803	Specimen: Adult Saliva (Oragene Kit)
		Birthdate: 01/01/9999	Sex assigned at birth: F
		MRN #:	Date of Last Full Report: 08/26/2025
		Indication: Diagnostic/Family History	
		Original Test: CancerNext®	

Reclassification Notice for BRCA2 p.P3051Q

RECLASSIFICATION DETAILS

VARIANT	NEW CLASSIFICATION
BRCA2 p.P3051Q	Variant, Likely Benign

PREVIOUSLY REPORTED VARIANTS

No additional variants were reported.

INTERPRETATION

Based on current available data, the *BRCA2* p.P3051Q alteration has been reclassified to the new classification listed above. Classification category definitions are as follows:

- **Pathogenic Mutation**: alterations with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at-risk family members and appropriate changes in medical management (i.e. high risk surveillance) for pathogenic mutation carriers recommended.
- **Variant, Likely Pathogenic (VLP)**: alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk family members and appropriate changes in medical management (i.e. high risk surveillance) for VLP carriers recommended.
- **Variant, Unknown Significance (VUS)**: alterations with limited and/or conflicting evidence regarding pathogenicity. Medical management to be based on personal and family clinical histories, not VUS carrier status.
- **Variant, Likely Benign (VLB)**: alterations with strong evidence against pathogenicity. Targeted testing of at-risk family members not recommended. Medical management to be based on personal and family clinical histories.
- **Variant, Benign**: alterations with sufficient evidence to classify as benign. Targeted testing of at-risk family members not recommended. Medical management to be based on personal and family clinical histories.

The **p.P3051Q** variant (also known as c.9152C>A), located in coding exon 23 of the *BRCA2* gene, results from a C to A substitution at nucleotide position 9152. The proline at codon 3051 is replaced by glutamine, an amino acid with similar properties. Two saturation genome editing-based studies, including a haploid cell-survival assay and a humanized mouse embryonic stem cell line drug-response and cell-survival assay, demonstrate that this nucleotide substitution is functional (Huang H et al. *Nature.* 2025 Feb;638(8050):528-537; Sahu S et al. *Nature.* 2025 Feb;638(8050):538-545). This amino acid position is highly conserved in available vertebrate species. In addition, the *in silico* prediction for this alteration is inconclusive. Based on the majority of available evidence to date, this variant is unlikely to be pathogenic.

The *BRCA2* gene (NM_000059.3) is located on chromosome 13q13.1, encodes the breast cancer type 2 susceptibility protein, and contains 26 coding exons. Pathogenic variants in this gene are known to cause *BRCA2*-related cancer predisposition, which is inherited in an autosomal dominant fashion, and *BRCA2*-related Fanconi anemia, which is inherited in an autosomal recessive fashion. *BRCA2*-related cancer predisposition is characterized by a significantly increased cumulative lifetime risk for female breast cancer (55-69%), male breast cancer (1.8-7.1%), epithelial ovarian cancer (13-29%), pancreatic cancer (5-10%), prostate cancer (19-61%), and melanoma. *BRCA2*-related cancer predisposition is also associated with a contralateral female breast cancer risk of up to 26% within 20 years of initial breast cancer diagnosis with no intervention; however, this risk is age-dependent and more significant with earlier age (prior to age 40) of first breast cancer diagnosis (Kuchenbaecker K et al. *JAMA.* 2017 Jun 20;317(23):2402-2416; Hu C et al. *J Natl Cancer Inst.* 2020 Dec 14;112(12):1231-124; Breast Cancer Association Consortium. *N Engl J Med.* 2021;384:428-439; Hu C et al. *N Engl J Med.* 2021 Feb 4; 384(5): 440–451; Tai Y et al. *J Natl Cancer Inst.* 2007 Dec 5;99(23):1811-4; Chen J et al. *JNCI Cancer Spectr.* 2020 Apr 23;4(4):pkaa029; Chaffee K et al. *Genet Med.* 2018 Jan;20(1):119-127; Hu C et al. *JAMA.* 2018 Jun 19;319(23):2401-2409). Penetrance in individuals with *BRCA2*-related cancer predisposition is incomplete and

variable expressivity is observed; therefore, cancer risks will differ based on individual and family history. Published evidence suggests that both germline and somatic alterations in the *BRCA2* gene predict sensitivity to chemotherapy agents that induce DNA damage and have been included in some indications for approved poly(ADP-ribose) polymerase (PARP) inhibitor therapies (Kim G et al. *Clin Cancer Res.* 2015 Oct 1;21(19):4257-61; Balasubramaniam S et al. *Clin. Cancer Res.*, 2017 Dec;23:7165-7170). Loss of function has been reported as the mechanism of disease for *BRCA2*-related cancer predisposition. *BRCA2*-related Fanconi anemia is characterized by progressive bone marrow failure, adult-onset aplastic anemia, pre- and postnatal growth deficiency, abnormal skin pigmentation, characteristic skeletal malformations, and impaired endocrine functioning. *BRCA2*-related Fanconi anemia can be established in a patient following cytogenetic testing of patient lymphocytes that demonstrate increased chromosomal breakage and radial forms following diepoxybutane and mitomycin C exposure (Mehta P et al. *Fanconi Anemia*. 2002 Feb 14 [updated 2021 Jun 3]. In: *GeneReview*s [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022). Individuals with *BRCA2*-related Fanconi anemia are at an increased risk of malignancies with highest risk of acute myelogenous leukemia, early-onset solid tumors including head and neck squamous cell carcinoma, and non-melanoma skin cancer (García-de-Teresa B et al. *Genes* (Basel). 2020 Dec 21;11(12):1528, 2020). Individuals of reproductive age are at 25% risk of having a child with Fanconi anemia with each pregnancy when both biological parents have a pathogenic variant in *BRCA2*. Biallelic loss of function, with at least one hypomorphic allele, has been reported as the mechanism of disease for *BRCA2*-related Fanconi anemia.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- BRCA1/2 seq and del/dup (Product Code 8838)
- CancerNext® (Product Code 8824)

Genetic counseling is a recommended option for all patients undergoing genetic testing.

NOTE: This reclassification notification is being sent to the ordering provider (OP) listed on this patient's original test requisition form. If this contact information is outdated, a reasonable attempt should be made to locate and contact the original OP, the patient, and/or the clinician currently overseeing this patient's care

Please refer to original report for additional details.