# Oncology Genetic Test Report

Breast High/Moderate Risk Panel

| PHYSICIAN | PATIENT | SAMPLE |
|---|---|---|
| **Dr. J. M. Hibbert**<br><br>Springfield General<br>734 Evergreen Terrace,<br>Springfield, 90210<br>Acct # 4567 | Krabappel, Edna<br>DOB: 01-Jan-1970 Sex: F<br>Ethnicity: Caucasian<br>Patient ID: KSD-965<br>82 Evergreen Terrace,<br>Springfield, 90211<br>Acct # 4567 | Specimen ID: 456745287<br>Date of Report: 30/Mar/19<br>Date Collected: 22/Mar/19<br>Date Received: 23/Mar/19<br>Patient ID: KSD-965<br>Source: BLOOD IN EDTA<br>NORTH AMERICA EST |

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**Genes Evaluated:** ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53

Test Indication:

Personal history of breast cancer. Family history of breast and other cancer. No reported history of genetic testing.

## Result Summary: POSITIVE

Gene: ATM Results: c.7327C>T (p.Arg2443Ter) Classification: PATHOGENIC
Zygosity: HETEROZYGOUS

This individual is heterozygous for a pathogenic mutation in ATM, consistent with an increased risk for cancer.

No additional variants of clinical or unknown signicance were detected by sequencing or deletion/duplication analysis.

## Recommendations

•Genetic counseling is recommended to discuss the implications of these test results.

•Breast MRI screening is recommended in addition to mammographic screening for any woman with at least a 20% lifetime risk for breast cancer (Saslow 2007, NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian v.2.2015).

•For individuals and family members of reproductive age, assessment of the reproductive risk associated with being a carrier of an ATM mutation is recommended.

•The first degree relatives of this patient have a 50% chance of also testing positive for the ATM mutation identified.

•If you would like to discuss these results in further detail, please call one of our genetic counselors.

•To learn more information about these results, please visit: www.oncogenedx.com/atm-gene-positive-results

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## Comment On Results

Gene: ATM Results: c.7327C>T (p.Arg2443Ter) Classification: PATHOGENIC
cDNA RefSeq: NM_000051.3

Interpretation: This mutation is denoted ATM c.7327C>T at the cDNA level and p.Arg2443Ter (R2443X) at the protein level. The substitution creates a nonsense mutation, which changes an Arginine to a premature stop codon (CGA>TGA) in exon 50, and is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. This mutation has been reported in the compound heterozygous state in two individuals with Ataxia-telangiectasia (Sandoval 1999) and is considered pathogenic.

The presence of one mutation in the ATM gene has been shown to increase a woman's lifetime risk to develop breast cancer. Two studies independently estimated that female heterozygous ATM mutation carriers have approximately a two-fold increase risk for breast cancer (RR = 2.2-2.4) (Thompson 2005, Renwick 2006, Tavtigian 2009). Thompson et al. (2005) studied 1160 ATM mutation carriers and concluded that female heterozygous ATM mutation carriers who are less than 50 years of age had a significantly increased risk for breast cancer (RR = 4.9) compared to women over 50 years of age where a statistically significant risk could not be identified. One study suggests an increased risk for colon cancer, but the confidence intervals are wide (Thompson 2005). An association with pancreatic cancer has also been proposed. A recent study of 166 unrelated familial pancreatic cancer patients revealed that 2.4% carried an ATM mutation, and of families with 3 or more cases of pancreatic cancer, 4.6% carried an ATM mutation (Roberts 2012).

Ataxia-telangiectasia (A-T), an autosomal recessive condition, is caused by two mutations (one affecting each allele) in the ATM gene. This multisystem disorder is characterized by progressive neurodegeneration, telangiectasias, immunodeficiency, and increased cancer risks. If an ATM mutation carrier's partner is also heterozygous for an ATM mutation, the risk to have a child with A-T is 25% for each pregnancy.

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## Methods

Genomic DNA from the submitted specimen was enriched for the complete coding region and splice site junctions of the genes on the panel using custom Sure Select targeted capture. The products were sequenced on either an Illumina MiSeq or HiSeq instrument with 2x150 or 2x100 paired-end reads, respectively. The sequence was aligned to reference sequences based on human genome build GRCh37/UCSC hg19. Capillary sequencing was used to confirm all variants with clinical or unknown significance and to analyze regions with inadequate coverage by Next Generation sequencing. Concurrent deletion/duplication testing was performed for all of the genes on the panel using either exon-level array CGH or MLPA. Confirmation of copy number changes was performed by MLPA, qPCR, or repeat aCGH analysis. If present, apparently homozygous variants were conrmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. The genes evaluated by this test are listed on the first page of the report.

Technical Limitations: Neither sequencing nor exon-level aCGH can reliably detect mosaicism and cannot detect chromosomal aberrations. Deletions involving more than 20bp and insertions involving more than 10bp are not reliably detected by the sequencing methodology, and deletions or duplications of less than 250bp are not reliably detected by array CGH. Some genes have inherent sequence properties that yield suboptimal data in certain regions and pathogenic variants in those regions may not be reliably identied. For instance, sequence and deletion/duplication analysis of CHEK2 is complicated by the presence of pseudogenes or homologous sequences that involve multiple exons of CHEK2. In the absence of mRNA/cDNA studies, we cannot completely exclude the possibility of undetectable clinically signicant variants in certain regions of CHEK2. False negatives may occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. Additionally, rare false negatives may occur when testing for a specic variant identied at a laboratory other than GeneDx if a familial positive control is not provided. The ability to detect genetic variants and naming conventions can differ among laboratories.

This test was performed at GeneDx, 207 Perry Parkway, Gaithersburg, MD 20877. Interpretation of the data was performed at either GeneDx or BioReference Laboratories, 481 Edward H. Ross Drive, Elmwood Park, NJ 07407.