MOLECULAR REPORT PHYSICIAN GUIDE

CONFIDENTIAL

PATIENT		SPECIMEN		HEALTHCARE PROVIDER
Name:	**Jane Doe**	Specimen Type:	**Saliva**	Dr. John Doe, M.D.
Date of Birth:	**09/09/1999**	Date Received:	**06/12/2017**	233 E. Erie St., #506
Gender:	**Male**	Completion of Testing:	**07/24/2017**	Chicago, IL 60611
Accession #:	**XXX-17-111111**			Phone: 312-838-2400
Test Type:	**Cancer Predisposition**			Fax: 312-838-2404

Ordering Physician: Dr. Thomas Pitts, M.D.

Result: Negative – No pathogenic variants were identified

Additional Findings: No variants of clinical significance were identified

PERSONAL/FAMILY HISTORY SUMMARY AND MANAGEMENT INFORMATION

FAMILY MEMBER	DIAGNOSIS/CANCER	AGE
Father	Pancreatic, Colon	80, 70
Sister	Breast	55
Brother	Prostate	49

FAMILY MEMBER	DIAGNOSIS/CANCER	AGE

Genes tested: APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, ELAC2, EPCAM, HRAS, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RET, SMAD4, STK11, TP53.

** Patient personal/family history was provided by the healthcare provider on the requisition form.

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OVERVIEW OF RESULTS

Patient tested negative for any pathogenic mutations on our genetic testing panel. Patient should speak to a genetic counselor about their results, and consult with their physician to create an appropriate medical management plan.

- Patient risk may still be increased depending on other circumstances such as personal or family history of cancer, or rare genomic alterations not identified by this test. Medical management should be handled in a context that considers relevant factors such as lifestyle, smoking, personal/family history and other factors that may impact cancer risk.
- While the results of the patient's genetic test do not indicate any genetic link to an increased risk of cancer, this test result does not preclude a cancer diagnosis in the future. Regular visits with a healthcare provider can help ensure proper care, and detect a potential cancer earlier.

UNDERSTANDING A NEGATIVE TEST RESULT

Patient test results should be understood in the context of family history of cancer and genetic testing results of family members. For patients with one or more family members with a known mutation at a specified locus, a "true-negative" indicates that the running mutation has not been passed to the patient.

For patients whose family members have not been tested, it is recommended that affected relatives get tested to determine if there is a hereditary cause for their cancer.

For a patient whose family members have not been tested (or in cases where family members have tested negative) the negative test result indicates that the patient does not have a mutation in any of the regions tested, but may have increased cancer risk due to factors, either genetic or otherwise.

Result	**Description**
Negative - When familial cancer is known	The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member. Patient's cancer risk is roughly the same as the general population
Negative - Cause of familial cancer unclear	The person is not a carrier of a known cancer-predisposing gene, and the carrier status of other family members is either also negative or unknown. Patient's cancer risk is based on family history. Testing family members can help further clarify risk

ADDITIONAL FINDINGS

Other Variants: Variants of clinical significance are reported. Variants identified as benign or likely benign polymorphisms are not reported. Evidence indicates that these variants do not impact cancer risk.

Current medical opinion recommends against using findings of variants that are not clinically significant to modify patient medical management. Medical management decisions should be made based on personal and family history and any other clinically significant findings.

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SUMMARY & METHODOLOGY

TARGET GENES: 31 germline cancer genes

This cancer screening panel is a full risk sequencing of germline mutations involved in familial cancer predisposition. The panel interrogates 31 germline key-cancer predisposition genes, targeting mutational hotspots associated with both common and rare familial cancer syndromes. All translated exons and immediately adjacent intronic regions are sequenced. Single nucleotide polymorphisms, duplications, insertions, deletions, and variants of uncertain significance can be detected. Sequencing analysis on the other genes included in the panel described above are consistent with intron variant and synonymous variant polymorphisms and are considered benign.[1-5]

Genomic DNA from **Jane Doe's** submitted specimen, was enriched for the complete coding regions and splice site junctions of the genes described in the panel. The products were sequenced on two different massive parallel sequencing platforms; Miniseq Illumina platform (clonal bridge amplification/ reversible dye terminator) and Ion Torrent Platform (Ion sphere particles- Chef System/S5XL). The sequences were aligned to reference sequences based on Human Genome build GRCh37/UCSChg19. BRCA-1/BRCA2 concurrent deletion/duplication testing was performed by Multiple Ligation Probe Amplification (MLPA). Fragment analysis and comparative analysis were performed by Coffalyser DB software, v.140701 (MRC-Holland). Sequencing bio-informatics pipelines were analyzed by Illumina VariantStudio v.3.0 and Torrent Suite Software v.4.0.2., respectively. Discrepancies between platforms, if any, were resolved by selective incorporation of chain-terminating dideoxynucleotides (Sanger Sequencing) targeting with specific FWD/REV primer 5' M13 tailed and HPLC purified. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Genetic data are stored under Variant call format (VCF).[6,7] AMD follows internal policies and ACMG recommendations for variants reporting.[8] Benign and likely benign variants, if present, are not included in this report, but are available upon request.

COMMENTS & CONCLUSION

Most human cancers are "sporadic" because there is no identifiable inherited gene mutation involved. Those cancers develop as a result of environmental factors such as carcinogenic cigarette smoke that randomly induce mutations in cells, leading to uncontrolled growth. Such factors are encountered throughout life and act over a long period of time.

Familial cancers, on the other hand, tend to occur because it is a specific gene with a defined inheritance pattern. Thus, one is born with a preexisting risk factor for cancer, acting as "one strike". Years later another event triggers the cancer growth. Most of classic familial cancer syndrome involves a tumor suppressor gene with the "two hit" hypothesis. A person inherits one copy of the gene mutated (first hit), but still has another functional copy of this gene on the other chromosome. Sometime later, a mutation wipes out the normal copy (second hit), and growth control is lost. This allows a clone of neoplastic cells to arise and multiple organs can be affected. Thus, familial cancers often involve more than one organ, and affected individuals can have more than one cancer.

This cancer screening is a multiple gene panel that includes the most frequent tumor suppressor genes involved in inheritance of genetic factors increasing cancer risk.

Conclusion: This test results are negative for pathogenic variants on the gene panel described above.

Dr. Sam Smith, Laboratory Director

This report was electronically signed

Disclaimer: The accompanying Technical Specifications summary describes the analysis, method, performance characteristics, nomenclature, and interpretive criteria of this test. This test result does not exclude the possibility of other predisposing mutations that have been reported in individuals with increased risk. There are infrequent genetic abnormalities in long homopolymers or highly homologous regions that this test may not detect. This result, however, rules out the majority of abnormalities believed to be responsible for hereditary cancer susceptibility due to mutations on the gene panel described. The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued, and may change as new scientific information becomes available. The interpretation of this test may be impacted if the patient has a hematologic malignancy or an allogeneic bone marrow transplant. This test may be considered investigational by some states. This test and its performance characteristics were determined by the laboratory. It has not been reviewed by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

ENDNOTES AND FURTHER RESEARCH INFORMATION

(1) Flicek et al. Nucleic Acids Research 2013 41 Database issue: D48-D55 doi: 10.1093/nar/gks1236 (2) Helga Thorvaldsdóttir, James T. Robinson, Jill P. Mesirov. Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. Briefings in Bioinformatics 2012. (3) Genome Res. 2009 Jul; 19(7):1316-23. doi: 10.1101/gr.080531.108. Epub 2009 Jun 4. (4) Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, Sirotkin K. dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 2001 Jan 1; 29(1):308-11.
(5) Fokkema IF, Taschner PE, Schaafsma GC, Celli J, Laros JF, den Dunnen JT (2011). LOVD v.2.0: the next generation in gene variant databases. Hum Mutat. 2011 May; 32(5):557-63.World 2011. (10) GenomeWeb DNA Electronics Licenses IP to Ion Torrent. August 2010. (11) 2013 Annual Clinical Genetics Meeting. American College of Medical Genetics and Genomics. Green R, Berg JS, Grody WW et al. (6) Bio-IT World, Davies, K. Powering Preventative Medicine. Bio-IT World 2011. (7) GenomeWeb DNA Electronics Licenses IP to Ion Torrent. August 2010. (8) 2013 Annual Clinical Genetics Meeting. American College of Medical Genetics and Genomics. Green R, Berg JS, Grody WW et al.

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This cancer-risk predisposition test was ordered on your behalf in consult with your health care provider due to factors such as personal and/or family history of cancer which indicated that you may have a change in your DNA (called a "mutation") that increases your risk of one or more kinds of cancer.

Result: Negative – No changes found that are linked to increased cancer risk.

TESTING FAMILY MEMBERS

To fully understand the implications of your test, it is helpful to know whether family members (particularly those who have had cancer), have a mutation that is linked to increased cancer risk. Speak to family members (particularly those who have had cancer, as well as older relatives who have not had cancer) about getting tested.

NEXT STEPS

- Communicate with your doctor to help determine next steps.
- Speak to a genetic counselor can help you better understand your risks and options. A genetic counselor can help you understand the ramifications of your test results, and how to communicate with family members you may want to speak to about genetic cancer risk. Your doctor can help you find a genetic counselor or you can search at www.NSGC.org to find a counselor in your area, or one who provides counseling over the phone.
- Speak to family members about your shared cancer history and discuss the idea of genetic testing with them.

Though recommendations in this report are suggested and many are recommended by authoritative organizations, the best course of action is to speak to your physician and relevant specialists to determine your next steps. It is beneficial to find out as much as you can about your family history of cancer and bring that information with you for any discussions, as that information will play a role in helping identify the best course of action.

ADDITIONAL RESOURCES AND SUPPORT

National Society of Genetic Counselors	http://www.nsgc.org/
Genetic Information Nondiscrimination Act	http://www.ginahelp.org/

This document provides an overview of the results for your genetic test for cancer risk. Your doctor has received a more comprehensive report which he/she can share with you. You can also request a full report by sending a request in writing.