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PATIENT INFORMATION

Name:	DOE, JANE	**Accession Number:**	CommTest1
Date of Birth:	02/16/1988	**Specimen Type:**	Oral saliva sample
Gender:		**Ordering Physician:**	Dr Physician
Race:			
Date Collected:	02/06/2018	**Date Received:**	02/08/2018

REVIEW STATUS: Final

TEST PERFORMED

OncoScreen. Sequence analysis was performed on this sample by means of targeted next-generation sequencing. See test details for more information.

CLINICALLY RELEVANT RESULTS SUMMARY: POSITIVE

Gene	Variants Detected	Classification	Zygosity
MUTYH	p.Y165C	Pathogenic	heterozygous

POSITIVE: Pathogenic/Likely Pathogenic

VUS: Variant of Unknown Significance

NEGATIVE: No clinically significant variants were detected

See Assay Limitations for More Information

CLINICALLY RELEVANT INTERPRETATIONS

MUTYH

p.Y165C
Pathogenic

Interpretation: This sequence change replaces tyrosine with cysteine at codon 179 of the MUTYH protein (p.Tyr179Cys). The tyrosine residue is highly conserved and there is a large physicochemical difference between tyrosine and cysteine. This variant is a known common cause of MUTYH-associated polyposis (PMID: 23035301). This variant has been reported to co-segregate with disease in individuals affected with colorectal cancer, familial adenomatous polyposis (FAP), and attenuated FAP (PMID: 12606733, 16557584, 17489848, 19793053, 21063410, 24444654). This variant is also known as c.494A>G (p.Tyr165Cys) in the literature. ClinVar contains an entry for this variant (Variation ID: 5293). MUTYH-related conditions are inherited in an autosomal recessive fashion. However, there is evidence that monoallelic pathogenic MUTYH variants including this particular variant are associated with increased risk of colon cancer (PMID: 16492921, 19394335, 21171015, 24444654). Experimental studies have shown that this missense change disrupts MUTYH protein function (PMID: 11818965, 18534194, 19953527, 20848659). For these reasons, this variant has been classified as Pathogenic. Genetic counseling and clinical correlation are recommended for all genetic testing. This assay does not test for structural variants which account for a percentage of pathogenic MUTYH genomic alterations. This assay does not test for all genes and variants related to a predisposition to cancer.

OTHER RESULTS- SEE ALSO "All Identified Variants: Detailed Information"

Interpretations of variants that are not under clinically relevant results are listed here. Variants for which no interpretation is available are listed in the "All Identified Variants: Detailed Information" section at the end of report.

No other identified variants warrant interpretive comments.

OTHER TEST RESULTS

Results from tests other than next-generation sequencing are listed here.

GENETIC COUNSELING

Regardless of genetic test results, clinical follow up for this individual and their family members may still be warranted. These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please visit: www.nsgc.org Or tagc.med.sc.edu/professional_organizations.asp.

Also, for your convenience, we are providing you with the contact information of **InformedDNA** for genetic counseling services:

Phone #: 1800-975-4819
Fax #: 1800-930-0961
E-mail: info@informedDNA.com
Online at: www.informeddna.com
Address: 877 Executive Center Dr. W. Suite 206, St. Petersburg, FL 33702

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TEST DETAILS

OncoScreen: Sequence analysis was performed on this sample by means of targeted next-generation sequencing of coding exons +/- 20bp of adjacent intronic nucleotides.

DNA was extracted from either saliva or peripheral blood sample for analysis. The technical component of the testing passed all established laboratory QC metrics, except for coverage of the targeted exons specified below under Coding Exon And Adjacent Intronic Nucleotides Coverage Metrics, where variants may not have been reliably detected.

Genes sequenced: *AIP*, *ALK*, *APC*, *ATM*, *BAP1*, *BLM*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *BUB1B*, *CDC73*, *CDH1*, *CDK4*, *CDKN1C*, *CDKN2A*, *CEBPA*, *CEP57*, *CHEK2*, *CYLD*, *DDB2*, *DICER1*, *DIS3L2*, *EGFR*, *EPCAM*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *EXT1*, *EXT2*, *EZH2*, *FANCA*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *FANCM*, *FH*, *FLCN*, *GATA2*, *GPC3*, *HNF1A*, *HRAS*, *KIT*, *MAX*, *MEN1*, *MET*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *NF1*, *NF2*, *NSD1*, *PALB2*, *PHOX2B*, *PMS1*, *PMS2*, *PRF1*, *PRKAR1A*, *PTCH1*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RECQL4*, *RET*, *RHBDF2*, *RUNX1*, *SBDS*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SLX4*, *SMAD4*, *SMARCB1*, *STK11*, *SUFU*, *TMEM127*, *TP53*, *TSC1*, *TSC2*, *VHL*, *WRN*, *WT1*, *XPA* and *XPC* were subjected to targeted next generation sequencing analysis.

Database Details: The versions/releases/builds/dates of the following databases were used to generate this report.

- Genomic Build:GRCh37.p13
- Genomic Anotation Sources:NCBI RefSeq v105
- ClinVar: 20150603
- dbSNP: 141
- NHLBI ESP: v.0.0.30
- dbNSFP: 3.0b2c
- ExAC: v0.3

Coding Exon and Adjacent Intronic Nucleotides Coverage Metrics:

Level 2 metrics is not available.

METHODOLOGY

Assay Methods: Genomic DNA is either provided or extracted from saliva or peripheral blood sample. Extracted DNA is used to identify relevant single nucleotide variants (SNV) and insertion/deletions (Indels). This assay does not detect genomic copy number variations and/or chromosomal structural rearrangements which account for a percentage of reported clinically significant alterations in the genes tested. Genomic libraries are prepared for targeted genomic regions and sequenced by next generation sequencing. The presence of genomic alteration within each of the genes is determined through bioinformatics analysis and comparison to databases. Adequate quality control metrics include a minimum of 50ng of genomic DNA, average mean sequencing depth of 20X coverage to give a limit of detection (LOD) of 20% for SNV and Indels.

Bioinformatics Methods: There are five informatics tools used. Novoalign is an alignment tool. Freebayes and Samtools (Mpileup) are variant callers used to identify substitutions. Pindel and GATK are a variant callers used to identify insertions, and deletions. Relevant versions and parameters used for each tool are detailed below:

1. Novoalign
Version 3-04_05Parameters: -o SAM -r none --hlimit 7 -t 20,4 -i 230 140 --matchreward 3 --softclip 9999 -l 30 -e 100 -H -c 12

2. Freebayes
Version v1.0.2-29Parameters: --min-alternate-count 10 --min-alternate-fraction 0.03 --min-coverage 10 --min-base-quality 20 --min-mapping-quality 30 --min-supporting-allele-qsum 20 --min-supporting-mapping-qsum 30 --min-alternate-qsum 40

3. Pindel
Version 0.2.5b8
sam2pindel:
Parameters: 270 sample 0 "Illumina-PairEnd"
pindel:
Parameters: -c ALL -r false -t false -l false -k false -T 5 -w 90

4. Samtools

Version 0.1.19
mpileup
Parameters: -ugBADSf
bcftools
Parameters: view -bcvg

5. GATK
Version 1.2
Parameters: -T UnifiedGenotyper -stand_call_conf 1.0 -stand_emit_conf 1.0 -dcov 5000 -G Standard -glm INDEL -nt 4
-T VariantFiltration --clusterWindowSize 15

Variants Reported
1. Pathogenic Variant: Alterations with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at risk family members for pathogenic mutation carriers is recommended. A pathogenic variant is always included in results reports and specific interpretation for each variant is provided in the context of patient specific demographics, personal and family history of cancer.
2. Likely Pathogenic Variant: Alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk family members. A likely pathogenic variant is always included in results reports. A likely pathogenic variant is always included in results reports and specific interpretation for each variant is provided in the context of patient specific demographics, personal and family history of cancer.
3. Variant of Unknown Significance (VUS): Alterations with limited and/or conflicting evidence regarding pathogenicity. Medical management is based on personal and family histories and not on the VUS carrier status. A VUS is typically not included in results reports unless a strong family history and/or strong tracking of such VUS with cancer in family members.

Assay Limitations: Assay failures may result from patient samples that render inadequate quantities and/or poor quality DNA, and specimens that do not generate sufficient sequencing coverage to allow accurate variant assessment.
Sequencing quality may be diminished in specific exon(s), and a pathogenic genomic alterations may be present in those exon(s), but not detected.
It is possible that pathogenic variants may not be reported by one or more of the tools because of the parameters used.
This assay does not detect genomic copy number variations and/or chromosomal structural rearrangements which account for a percentage of reported clinically significant alterations in the genes tested. Therefore, clinically significant alterations may be present and not detected by this assay. Clinical correlation and genetic counseling are

recommended for all genetic testing. This test does not test for all possible variants linked to cancer.

Data Analysis Group Version: 1.0.4 , Panel Version: 1.0.35

DISCLAIMER

This Report was generated using the materials and methods described above, which required the use of various reagents, protocols, instruments, software, databases, and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases, and/or other items may compromise the quality or accuracy of the Report.

The Report has been created based on, or incorporates references to, various scientific manuscripts, references, and other sources of information, including without limitation manuscripts, references, and other sources of information that were prepared by third parties that describe correlations between certain genetic mutations and particular diseases (and/or certain therapeutics that may be useful in ameliorating the effects of such diseases). Such information and correlations are subject to change over time in response to future scientific and medical findings. Alpha Genomix makes no representation or warranty of any kind, expressed or implied, regarding the accuracy of the information provided by or contained in such manuscripts, references, and other sources of information. If any of the information provided by or contained in such manuscripts, references, and other sources is later determined to be inaccurate, the accuracy and quality of the report may be adversely impacted. Alpha Genomix is not obligated to notify you of any impact that future scientific or medical research findings may have on the Report.The Report must always be interpreted and considered within the clinical context, and a physician should always consider the report along with all other pertinent information and data that a physician would prudently consider prior to providing a diagnosis to a patient or developing and implementing a plan of care for a patient. The report should never be considered or relied upon alone in making any diagnosis or prognosis. The manifestation of many diseases are caused by more than one gene variant, a single gene variant may be relevant to more than one disease, and certain relevant gene variants may not have been considered in the Report. In addition, many diseases are caused or influenced by modifier genes, epigenetic factors, environmental factors, and other variables that are not addressed by the Report (or that are otherwise unknown). As such, the relevance of the Report should be interpreted in the context of a patient's clinical manifestations. The Report provided by Alpha Genomix is provided on an "AS IS" basis. Alpha Genomix makes no representation or warranty of any kind, expressed or implied, regarding the Report. In no event shall Alpha Genomix be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the Report, your reliance on the Report, or any defect or inaccurate information included within the Report.

Medical knowledge annotation is constantly updated and reflects the current knowledge at the time.The test performance characteristics were determined by Alpha Genomix in collaboration with PierianDx. The Report was generated by Alpha Genomix as required by the CLIA 1988 regulations. The Report, and the tests used to generate the Report, have not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This laboratory is CLIA certified (CLIA ID number 26D2101152) to perform high complexity testing.