Phosphorus Diagnostics

ONCOLOGY

PERFORMED AT PHOSPHORUS DIAGNOSTICS,
3 REGENT STREET, LIVINGSTON, NJ 07039

ORDERING PRACTICE

Practice Code: 100
Sample Cardiology Clinic
374 Broadway
New York, NY 10001
Physician: Dr. Sample

JANE DOE

DOB: 1973-02-19
Gender: Female
Ethnicity: European
Procedure ID: 87000
Kit Barcode: 201612092248585
Specimen: Blood, #10000
Specimen Collected: 2016-01-12
Specimen Received: 2016-01-13
Specimen Analyzed: 2016-01-21
Report Generated: 2016-02-03

TEST INFORMATION

Panel: Pan Cancer Panel
Indication: Diagnostic for Patient History

SUMMARY OF RESULTS

Positive: Pathogenic Variant Identified

GENE	LOCATION	VARIANT	INHERITANCE	ZYGOSITY	CLASSIFICATION
APC	Exon 5; Chrom 5	c.448A>T (p.Lys150Ter)	Autosomal Dominant	Heterozygous	**PATHOGENIC**
VHL	Exon 1; Chrom 3	c.47A>C (p.Glu16Ala)	Unknown	Heterozygous	UNCERTAIN SIGNIFICANCE

INTERPRETATION

This patient is heterozygous for the c.448A>T (p.Lys150Ter) pathogenic variant in the *APC* gene.

This result indicates that this patient may be affected with, or may be predisposed to developing, familial adenomatous polyposis.

This patient is also heterozygous for the c.47A>C (p.Glu16Ala) variant of unknown clinical significance in the *VHL* gene. The contribution of this variant to the patient's phenotype is unknown.

RECOMMENDATIONS

Clinical follow-up with a oncologist or medical geneticist is recommended to discuss medical management.

Genetic counseling is recommended for this patient.

Genetic testing may be useful in identifying family members at risk for disease. Genetic counseling is recommended for all individuals undergoing genetic testing.

VARIANT INFORMATION

PATHOGENIC

APC c.448A>T (p.Lys150Ter)

This variant leads to a premature termination at codon 105, which is expected to result in an absent or significantly disrupted protein product. Variants resulting in truncations have been previously reported in familial adenomatous polyposis. This mutation does not appear in large population databases, indicating it is not a common variant.
This variant has been shown to segregate with disease in one family with FAP (PMID: 12702160). Therefore, this variant is classified as pathogenic.

GENE INFORMATION: *APC*

APC encodes a tumor suppressor protein that antagonizes the WNT signaling pathway. Mutations in *APC* are associated with autosomal dominant familial adenomatous polyposis (MIM:17500), including the subtypes Gardner syndrome, Turcot syndrome, and attenuated FAP. Approximately 90% of individuals with familial adenomatous polyposis have a mutation in *APC*.

CANCER RISKS: *APC*

Individuals with one pathogenic *APC* variant have a 70%-100% risk of developing colorectal cancer in their lifetime (PMID: 18063416, 19822006, 1673441). They also have elevated risks for duodenal and gastric cancers (PMID: 18237868), and may also be at increased risk for pancreatic cancer (PMID: 18612695), and, rarely, other cancers (PMID: 18612695).

UNCERTAIN SIGNIFICANCE

VHL c.47A>C (p.Glu16Ala)

This variant repclaces a glutamic acid with alanine at codon 16. This variant has not been reported in the literature, and does not appear in population databases. In silico analyses (SIFT/PolyPhen) are not concordant. In summary, this is a novel missense change that may or may not impact protein function. Therefore, this variant is classified as a variant of uncertain significance.

GENE INFORMATION: *VHL*

VHL encodes a tumor suppressor protein and functions in numerous cellular pathways. Mutations in *VHL* lead to autosomal recessive erythrocytosis (MIM:263400), and autosomal dominant von Hippel-Lindau syndrome (MIM:193300). Von Hippel-Lindau syndrome leads to an increased risk for cancer of the nervous system, kidney, pancreas, and endocrine system.

CLIA #31D2123554

METHODS

SEQUENCING

Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization based protocol and sequenced using Illumina technology. Reads are aligned to the reference sequence (Grch37, standard genome build hg19), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript. Exonic deletions and duplications are called using a copy number variation (CNV) algorithm. The CNV algorithm calculates a statistical likelihood of each copy number state by comparing the depth of sequencing coverage at targeted exons to a baseline depth measure in control samples. A confidence threshold is used for each assertion of copy number state for each exon where the sequence data met a minimum quality standard of ≥ 20x depth of unique properly paired reads. This algorithm detects most intragenic deletions and duplications, although rare single-exon events may be missed. The analytical sensitivity and specificity of this assay is >99% and >99%, respectively. All reportable variants are confirmed by orthogonal technologies as part of our ongoing quality management process. Unless otherwise indicated, all targeted regions were sequenced with ≥ 20x depth of coverage. Regions with a read depth below this are supplemented with orthogonal testing, if they contain previously reported pathogenic variants. The assay targets all coding regions of the indicated transcript, 10 base pairs of flanking intronic sequence, and specific intronic and intragenic genomic regions demonstrated to be causative of disease. However, for some genes only targeted loci are analyzed.

Phosphorus can be contacted via phone at 1-855-746-7423 or by email at support@phosphorus.com

LIMITATIONS

Although this test is highly accurate, no genetic test is 100% sensitive. This analysis is designed to detect pathogenic variants within the coding regions of genes included in the current panel that are associated with specific forms of hereditary cancer. Hence this analysis will not detect novel sequence variants in the promoter region and other non-coding regions, as well as it does not assay untranslated exons. Also, the sensitivity to detect insertions and deletions larger than 15 base pairs but smaller than a full exon may be reduced. Some exons of a few individual genes have inherent sequence properties that yield suboptimal data, and pathogenic variants in those regions may not be reliably identified. Low-level mosaicism will not be detected. Moreover, this analysis does not detect every pathogenic variant associated with this disease because of genes not included in the current panel or unknown to be associated with the disease at this time. It also does not test for all known genetic diseases. Errors in testing (both false positives and false negatives) may also occur for reasons that include, but are not limited to specimen issues (e.g. inaccurately marked samples causing sample mix-up, DNA quality and quantity not meeting minimum requirements), rare genetic variants interfering with analysis, assay technical limitations, biological factors (e.g. recent blood transfusions, circulating hematolymphoid neoplasm, or history of bone marrow transplantation), and other technical issues.

This analysis is intended to detect germ-line genetic variants, and is not intended for the detection of somatic genetic variants.

If a pathogenic variant is detected, the patient may be a carrier of, affected with, predisposed to, or at risk for certain disease(s) or condition(s) associated with that variant. If no pathogenic variant is found, the patient may be at reduced risk of being a carrier of, affected with, predisposed to, or at risk for the disease(s) or condition(s) tested for in the current panel. However, further testing may be necessary, since negative test results may reduce, but do not eliminate, the chance that the patient is a carrier of, affected with, predisposed to, or at risk of having said disease(s) or condition(s). In addition, other pathogenic variant(s) or factors that are not included in our services may impact an individual's risk of or predisposition to certain disease(s) or condition(s). Thus, this report does not provide definitive conclusions regarding risk of, predisposition to, or diagnosis of certain disease(s) or condition(s). Variants classified as likely benign or benign are not included in this report, but are available upon request. The possibility that these variants contribute to disease cannot be excluded.

As new information becomes available, variant classification may evolve over time.

Providers are encouraged to contact support@phosphorus.com to obtain updated information.

DISCLAIMER

This report reflects the analysis of an extracted DNA sample; and it does not constitute medical advice. Any questions or concerns regarding the contents of this report or any prevention, cure, mitigation, or treatment of a medical condition or disease should be directed to a qualified oncologist, medical geneticist, or genetic counselor.

This test was developed and its performance characteristics determined by Phosphorus Diagnostics, LLC. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test results are to be used for clinical purposes and should not be regarded as investigational or for research.

VARIANT CLASSIFICATION

All variants that are identified in the sequenced genes and determined to be pathogenic, likely pathogenic, of uncertain significance are reported. Variants determined to be likely benign or benign are not reported, but are available upon request. Variants are classified in accordance with ACMG guidelines (PMID: 25741868).

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GENES ASSAYED

AIP	NM_003977
AKT1	NM_001014431
ALK	NM_004304
APC	NM_000038
ATM	NM_000051
AXIN2	NM_004655
BAP1	NM_004656
BARD1	NM_000465
BLM	NM_000057
BMPR1A	NM_004329
BRCA1	NM_007300
BRCA2	NM_000059
BRIP1	NM_032043
BUB1B	NM_001211
CASR	NM_001178065
CDC73	NM_024529
CDH1	NM_004360
CDK4	NM_000075
CDKN1B	NM_004064
CDKN1C	NM_000076
CDK2A	NM_000077
CEBPA	NM_004364
CEP57	NM_014679
CFTR	NM_000492
CHEK2	NM_001005735
CTRC	NM_007272
DICER1	NM_030621
DIS3L2	NM_152383
DKC1	NM_001363
EGFR	NM_005228
ENG	NM_001114753
EPCAM	NM_002354
ERCC4	NM_005236
EZH2	NM_004456
FAM175A	NM_139076
FANCA	NM_000135
FANCB	NM_152633
FANCC	NM_000136
FANCD2	NM_033084
FANCE	NM_021922
FANCF	NM_022725
FANCG	NM_004629
FANCI	NM_001113378
FANCL	NM_001114636
FANCM	NM_020937
FH	NM_000143
FLCN	NM_144997
GALNT12	NM_024642
GATA2	NM_032638
GPC3	NM_001164617
GREM1	NM_013372
HOXB13	NM_006361
HRAS	NM_001130442
KIF1B	NM_015074
KIT	NM_000222
MAX	NM_002382
MEN1	NM_000244
MET	NM_001127500
MITF	NM_198159
MLH1	NM_000249
MLH3	NM_001040108
MRE11A	NM_005591
MSH2	NM_000251
MSH6	NM_000179
MUTYH	NM_001128425
NBN	NM_002485
NF1	NM_001042492
NF2	NM_000268
PALB2	NM_024675
PALLD	NM_001166108
PDGFRA	NM_006206
PHOX2B	NM_003924
PIK3CA	NM_006218
PMS2	NM_000535
POLD1	NM_001256849
POLE	NM_006231
POT1	NM_015450
PRKAR1A	NM_212471
PRSS1	NM_002769
PTCH1	NM_000264
PTCH2	NM_003738
PTEN	NM_000314
RAD50	NM_005732
RAD51C	NM_058216
RAD51D	NM_133629
RB1	NM_000321
RECQL4	NM_004260
RET	NM_020975
RINT1	NM_021930
RUNX1	NM_001754
SDHA	NM_004168
SDHAF2	NM_017841
SDHB	NM_003000
SDHC	NM_003001
SDHD	NM_003002
SLX4	NM_032444
SMAD4	NM_005359
SMARCA4	NM_001128849
SMARCB1	NM_003073
SMARCE1	NM_003079
SPINK1	NM_003122
STK11	NM_000455
SUFU	NM_016169
TERC	NR_001566
TERT	NM_198253
TINF2	NM_001099274
TMEM127	NM_001193304
TP53	NM_001276760
TSC1	NM_000368
TSC2	NM_000548
VHL	NM_000551
WRN	NM_000553
WT1	NM_024426
XRCC2	NM_005431

PANEL INFORMATION: PAN CANCER PANEL

The Pan Cancer Panel is a comprehensive next-generation sequencing (NGS) panel that analyzes genes associated with increased risks for hereditary breast, colon, gastric, uterine, ovarian, brain, nervous system, renal, urinary tract, prostate, pancreatic, and other cancer.

Breast cancer occurs frequently in the general population, with the average woman's lifetime risk of developing breast cancer being approximately 12% (SEERP). Although the majority of breast cancer is not related to heritable factors, in approximately 5-10% cases breast cancer is caused by a specific genetic change. Women who carry these genetic changes may be at significantly increased risk of developing breast cancer in their lifetime. The majority of hereditary breast cancer is caused by mutations in the BRCA1 and BRCA2 genes, which can lead to lifetime breast cancer risks of 46-87% (7907678,12677558, 20301425), and other, rarer genes can cause similar or higher breast cancer risks. Frequently, changes in genes that result in increased risks for breast also predispose individuals to increased risks for other cancers.

Colorectal cancer occurs frequently in the general population, with the average person's lifetime risk of developing colorectal cancer being approximately 5% (SEERP). Although the majority of colorectal cancer is not related to heritable factors, in approximately 5-10% cases colorectal cancer is caused by a specific genetic change (24714764). Individuals who carry these genetic changes may be at significantly increased risk of developing colorectal cancer in their lifetime. The majority of hereditary colorectal cancer is caused by mutations in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes, which can lead to lifetime colorectal cancer risks of up to 82%, and other, rarer genes are also associated with an increased risk for malignancy (20301390).

Ovarian cancer affects approximately 1% of women during their lifetime, and uterine cancer affects approximately 2% of women (SEERP). Although the majority of ovarian and uterine cancer is not related to heritable factors, approximately 5% of uterine cancer (8781735) and at least 10-15% of ovarian cancer is caused by a specific genetic change (16284991). Individuals who carry these genetic changes may be at significantly increased risk of developing ovarian and uterine cancer in their lifetime. The majority of hereditary uterine is caused by mutations in the EPCAM, MLH1, MSH2, PMS2, and MSH6 genes, related to Lynch syndrome, while the majority of hereditary ovarian cancer is caused by mutations in the BRCA1/2 genes related to hereditary breast and ovarian cancer syndrome. Individuals who carry disease causing changes in these genes, and other, rarer genes, are at increased lifetime risks for uterine cancer (up to 60%) and ovarian cancer (up to 63%) (20301390, 20301425).

Pancreatic cancer affects approximately 1.5% of individuals in their lifetime (SEERP). Although the majority of pancreatic cancer is not related to heritable factors, in approximately 5-10% cases pancreatic cancer may be hereditary (19260742). Individuals who carry disease causing genetic changes may be at significantly increased risk of developing pancreatic cancer in their lifetime. For example, individuals with a pathogenic BRCA1/2 mutation have up to 7% lifetime risk for pancreatic cancer ((20301425), while individuals with STK11 or CDKN2A mutations have up to 36% and 17% lifetime risks for pancreatic cancer, respectively (20051941,10956390).

Thyroid cancer affects approximately 1.2% of individuals in their lifetime (SEERP). Although the majority of thyroid cancer is not related to heritable factors, approximately 25% of medullary thyroid cancer and 5-15% of non-medullary thyroid cancer is related to heritable factors (21455198).). Individuals who carry disease causing genetic changes may be at significantly increased risk of developing thyroid cancer in their lifetime. For example, individuals with a pathogenic RET mutation have >95% lifetime risk to develop medullary thyroid cancer (20301434).

Brain and nervous system cancer affects approximately .6% of individuals in their lifetime (SEERP). Although the majority of brain and nervous system cancer cases are not related to heritable factors, approximately 5% of central nervous system cancers are associated with underlying genetic conditions (24535705). Individuals who carry disease causing genetic changes may be at significantly increased risk of developing brain or nervous system cancer in their lifetime; for example, individuals with pathogenic *VHL* changes have a 60-80% risk to develop hemangioblastoma (21955200).

Renal cancer affects approximately 1.6% of individuals in their lifetime, and bladder cancer affects approximately 2.6% of individuals in their lifetime (SEERP). Although the majority of renal and urinary tract cancer cases are not related to heritable factors, approximately 3-5% of renal cell carcinoma is due to genetic changes (19584731). Individuals who carry disease causing genetic changes may be at significantly increased risk of developing renal or urinary tract cancer in their lifetime. For example, individuals with a pathogenic *VHL* mutation have up to a 70% risk for renal cancer (20301636).

Frequently, changes in genes that result in increased risks for one type of cancer also predispose individuals to increased risks for other malignancies.

INHERITANCE

Hereditary pancreatic cancer is typically inherited in an autosomal dominant manner, although several of the genes on this panel are associated with recessive genetic conditions:

- *MLH1*, *MSH2*, *PMS2*, and *MSH6* are associated with constitutional mismatch repair deficiency
- *ATM* is associated with ataxia telangiectasia
- *BRCA2*, *BRIP1*, *FANCC*, *PALB2*, and *RAD51C* are associated with Fanconi anemia
- *MUTYH* is associated with *MUTYH*-associated polyposis
- *NBN* is associated with Nijmegen breakage syndrome
- *BLM* is associated with Bloom syndrome

INCLUDED DISORDERS

This panel includes genes associated with:

- Hereditary breast and ovarian cancer syndrome
- Familial adenomatous polyposis
- Lynch syndrome (hereditary non-polyposis colon cancer)
- Peutz-Jeghers syndrome
- Li-Fraumeni syndrome
- von-Hippel-Lindau syndrome
- Hereditary diffuse gastric cancer
- Cowden syndrome
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Tuberous sclerosis complex
- Multiple endocrine neoplasia type I
- Multiple endocrine neoplasia type II
- Ataxia telanglectasia
- Bloom syndrome
- Reinoblastoma
- Simpson-Golabi-Behmel syndrome
- Nevoid basal cell carcinoma
- Juvenile polyposis syndrome
- Nijmegen breakage syndrome
- MUTYH-associated polyposis

SIGNED BY

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