SURETOX

SureGx

Hereditary Cancer Test

Sample Variant Report

495 Boulevard Suite 1A
Elmwood Park, NJ 07407
Phone: (201)791-7293
Fax: (201)866-425-4630
Director: Robert Rush, Ph.D.
Reviewed By: Vepkhia Pilauri, Ph.D.

CLIA #: 31D2063148

Client:	**Patient Name:** Variant Report	**Lab Acc#:** 1801267012 10:27AM
Phys.:	**DOB:** 05/21/1957 **Gender:** F **Specimen Type:** Oral Swab	**Collected:** 01/25/18 11:56AM **Accessioned:**01/26/18 11:05AM **Reported:** 02/08/18 12:58PM

Discover™ Hereditary Cancer Risk Assessment Report

Cancer Panel
BreastDiscover, OvarianDiscover, UterineDiscover, ColorectalDiscover, MelanomaDiscover, PancreaticDiscover, GastricDiscover, ProstaticDiscover, LungDiscover, CNSDiscover, KidneyDiscover,BladderDiscover.
Test Indication Information provided indicates that this individual has a personal and/or family history of cancer.

TEST RESULT SUMMARY:

Cancer Panel: Complete Cancer Panel			
Gene / Coordinate	**Variant**	**Classification**	**Zygosity**
BRCA1/ 41223094	c.4900A>G (p.Ser1634Gly)	POSITIVE	HOMOZYGOUS
MLH1 / 37090471	c.1299T>C (p.=)	UNSPECIFIED	HETEROZYGOUS

Recommendations

- Genetic counseling is recommended to discuss the implications of these results.
- In the absence of definitive pathogenic variant, this patient's risk for future cancers and medical management recommendations must be based on personal and family history of cancer.
- The clinical implications of the variant(s) of uncertain significance remain unclear. For that reason, predictive testing for variants of uncertain significance is not recommended for at-risk family members. However, targeted testing of certain family members may help to clarify the effect of such variants. Detailed review of the patient's clinical and family history information by our clinical genetics team is necessary for enrollment in our variant testing program.
- If you would like to discuss these results in further detail, please call one of our genetic counselors.
- GenomeConnect is an NIH initiative created to enable individuals and families with the same genetic variant or medical history to connect and share de-identified information. If you are interested in participating, please visit www.genomeconnect.org.

COMMENTS ON RESULTS:

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BRCA1/ 41223094	c.4900A>G (p.Ser1634Gly)	POSITIVE	HOMOZYGOUS

Interpretation:

Features characteristic of familial, versus sporadic, breast cancer are younger age at diagnosis, frequent bilateral disease, and frequent occurrence of disease among men Hall et al. (1990). According to the conclusions of the Breast Cancer Linkage Consortium (1997), the histology of breast cancers in women predisposed by reason of carrying BRCA1 and BRCA2 mutations differs from that in sporadic cases, and there are differences between breast cancers in carriers of BRCA1 and BRCA2 mutations. The findings were interpreted as suggesting that breast cancer due to BRCA1 has a different natural history from BRCA2 or apparently sporadic disease, which may have implications for screening and management. In studies of 103 women from 20 kindreds that were selected for the presence of 2 first-degree relatives with breast cancer and of 31 control women, Skolnick et al. (1990) found, by 4-quadrant fine-needle breast aspirates, evidence of proliferative breast disease in 35% of clinically normal female first-degree relatives of breast cancer cases and in 13% of controls. Genetic analysis suggested that genetic susceptibility caused both PBD, a precursor lesion, and breast cancer in these kindreds. The study supported the hypothesis that this susceptibility is responsible for a considerable proportion of breast cancer, including unilateral and postmenopausal breast cancer.

▼ REFERENCES

1. Antoniou, A., Pharoah, P. D. P., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., Loman, N., Olsson, H., Johannsson, O., Borg, A., Pasini, B., Radice, P., and 21 others. **Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies.** Am. J. Hum. Genet. 72: 1117-1130, 2003. Note: Erratum: Am. J. Hum. Genet. 73: 709 only, 2003. [PubMed: 12677558,images, related citations] [Full Text]
2. Antoniou, A. C., Spurdle, A. B., Sinilnikova, O. M., Healey, S., Pooley, K. A., Schmutzler, R. K., Versmold, B., Engel, C., Meindl, A., Arnold, N., Hofmann, W., Sutter, C., and 80 others.**Common breast cancer-predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers.** Am. J. Hum. Genet. 82: 937-948, 2008. [PubMed: 18355772, images, related citations] [Full Text]
3. Arason, A., Barkardottir, R. B., Egilsson, V. **Linkage analysis of chromosome 17q markers and breast-ovarian cancer in Icelandic families, and possible relationship to prostatic cancer.** Am. J. Hum. Genet. 52: 711-717, 1993. [PubMed: 8460636, related citations]

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Gene / Coordinate	Variant	Classification	Zygosity
MLH1 / 37090471	c.1299T>C (p.=)	UNSPECIFIED	HETEROZYGOUS

Interpretation:

Lynch syndrome is characterized by an increased risk for colorectal cancer (CRC) and cancers of the endometrium, stomach, ovary, small bowel, hepatobiliary tract, urinary tract, brain, and skin. In individuals with Lynch syndrome the following lifetime risks for cancer are seen: CRC: 52%-82% (mean age at diagnosis 44-61 years). Endometrial cancer in females: 25%-60% (mean age at diagnosis 48-62 years). Gastric cancer: 6% to 13% for gastric cancer (mean age at diagnosis 56 years). Ovarian cancer: 4%-12% (mean age at diagnosis 42.5 years; ~30% are diagnosed < age 40 years). The risk for other Lynch syndrome-related cancers is lower, though substantially increased over general population rates. [from GTR] Lynch syndrome, often called hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited disorder that increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin. Additionally, women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (the endometrium). People with Lynch syndrome may occasionally have noncancerous (benign) growths (polyps) in the colon, called colon polyps. In individuals with this disorder, colon polyps occur earlier but not in greater numbers than they do in the general population. https://ghr.nlm.nih.gov/condition/lynch-syndrome

Test Methods and Limitations

Developed by Illumina, this panel focuses on the coding exonic regions of genes annotated in HG19 reference genome. Genomic targets were identified based on information in the Human Gene Mutation Database (HGMD), the Online Mendelian Inheritance in Man (OMIM) catalog, GeneTests.org, Illumina TruSight sequencing panels and other commercially available sequencing panels. Combining data from these sources ensured that genes currently identified in clinical research settings as pathogenic were included in the panel.
Targeted regions for “Inherited Cancer Gene Panel” includes the exonic regions of the genes indicated below:

BreastDiscover:
ATM, BARD1, BRCA1, BRCA2, BRIP1, BUB1B, CDH1, CDKN1B, CHEK2, CYLD, ERCC4, FANCA, FANCE, NBN, NF1, NF2, PALB2, PTEN, SLX4, TP53, WRN

OvarianDiscover:
BARD1, BRCA1, BRCA2, BRIP1, CDC73, DDB2, DICER1, EPCAM, FANCM, MLH1, MSH2, MSH6, NF2, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53, WRN

UterineDiscover:
DDB2, EPCAM, ERCC3, ERCC4, EZH2, FH, HRAS, MLH1, MSH2, MSH6, NF2, PALB2, PMS2, PRF1, PTEN, RECQL4, STK11, TP53

ColorectalDiscover:
APC, BMPR1A, CDH1, CHEK2, CYLD, DDB2, DIS3L2, EPCAM, FANCA, FANCL, GNAS, KIT, MLH1, MSH6, MUTYH, PMS1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53, WRN

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MelanomaDiscover:
BAP1, BLM, BRCA2, CDK4, CDKN2A, DDB2, DICER1, ERCC3, ERCC5, EZH2, FANCB, FANCE, FANCL, GATA2, KIT, NF2, PTEN, TP53, XPA,XPC
PancreaticDiscover:
BRCA1, BRCA2, CDC73, CDKN1B, CHEK2, DICER1, FANCD2, FH, HNF1A, NBN, NF2, RAD50, TP53
GastricDiscover:
AIP, APC, BMPR1A, CDH1, EPCAM, FANCA, FANCB, KIT, MLH1, MSH2, MSH6, NF2, PRKAR1A, RAD50, RHBDF2, SMAD4, STK11, TP53
ProstaticDiscover:
BRCA1, BRCA2, CDC73, CDKN1B, CHEK2, DICER1, FANCD2, FH, HNF1A, NBN, NF2, RAD50, TP53
LungDiscover:
ALK, CYLD, EGFR, ERCC2, EXT1, EXT2, FANCA, FANCM, GATA2, GPC3, HRAS, NF2, PHOX2B, RHBDF2, WRN, XPA
CNSDiscover:
ALK, BLM, BUB1B, CDKN1B, CDKN1C, DIS3L2, EGFR, EXT1, EXT2, FANCC, FANCG, GPC3, MAX, NF1, NF2, PALB2, PDE4D, SDHA, SDHAF2, SDHB, SDHC, SDHD, SUFU, TMEM127, TSC1, TSC2, VHL, WT1
KidneyDiscover:
CASR, DIS3L2, EGFR, EPCAM, EXT2, FANCC, FANCD2, FANCM, FLCN, GPC3, MET, MLH1, MSH2, NF2, PMS2, PTEN, SDHB, SDHC, SDHD, SMARCB1, TP53, TSC1, TSC2, VHL
BladderDiscover:
DDB2, ERCC2, ERCC5, EZH2, FH, GNAS, HRAS, PRF1, RB1, RET, RUNX1

Other Clinical Comments:

A negative result may not correlate with lower risk due to the following reasons:
1. This report is based on the selected genes included in the test panel, and does not predict risks associated with other genes or unknown genes not included in the test.
2. Only the protein coding regions and splicing sites of these genes are included in the analysis and reported herein. Sequences outside the sequenced regions of these genes are not sequenced for genetic risk analysis.
3. Certain types of mutations other than single nucleotide changes or smaller deletions/ duplications may not be identified based on the current Next Generation Sequencing analysis technology used in this test.
4. A more complete limitation of the test can be found in Appendix A.

Sequencing and Variant Detection

Genomic DNA was extracted from clinical sample (oral swab), library preparation via Illumina protocols, capture-based enrichment of a targeted region was performed by solution-based hybridization which enriches for coding regions of targeted genes with specific probes. Multiple quality control steps were performed for sample and derivative quality evaluation. Sequencing was performed using the Illumina Next Generation Sequencing, with 100-151 bp reads, sequence QC metrics were required, and a minimum average coverage depth of 200X was required, Sequencing reads were aligned to the reference genome (UCSC hg19) by Local Run Manager enrichment module with GATK settings and validated by proprietary algorithm. The minimum sequence depth for all targeted regions was evaluated, further validation is recommended for exons with depth of coverage <50X. We recommend that variants of interest which do not meet the coverage minimum be confirmed clinically before treatment is undertaken.

Variant Analysis and Report Generation

Reported variants were filtered to include those present in the targeted coding exonic regions and adjacent splice sites. Resulting variants were analyzed and reported using the GCTK platform. To maintain the most up-to-date annotations, the database is updated regularly. As a result, variant classification and/or interpretation may change over time as more information becomes available.
The following databases and tools are included in the Illumina software platform:
1. Disease association: ClinVar
2. Population Frequencies: dbSNP (http://ncbi.nih.gov/SNP/), ensembl (www.wnsembl.org) , 1000 Genomes Project (www.1000genomes.org/), ExAC (http://exac.broadinstitute.org/).
3. Severity prediction: SIFT, MutationTaster, POLYPhen2
4. Conservation prediction: GERP++, PhyloP
5. Gene tolerance: RVIS score, according to published work 10.1371/journal.pgen.1003709

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Secondary/incidental Sequence Variant(s) based on ACMG guidelines are not in this report.
Not all mutations compared to the reference sequence have been listed on this report. Mutations were identified using the filters described below. These mutations were further reviewed by a medical geneticist, and only variations of clinical significance (primary findings) are included in this report.

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 generated based on, and incorporates references to various scientific 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. Suretox 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. Suretox 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 replied 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, environment 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. Medical knowledge annotation is constantly updated and reflects the current knowledge at the time.
The test performance characteristics were determined by Suretox. The Report was generated by Suretox 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), since FDA has determined that such clearance or approval is not necessary. This laboratory is CLIA certified to perform high complexity testing.