NEOVARE™
PERSONALIZED DIAGNOSTICS
by siParadigm
Hereditary Cancer Risk Assessment Test

Name:
DOB: ID#:
Sex: Requisition #:

ORDERING PHYSICIAN		SPECIMEN	
Name:		Case#:	
Facility:		Collected:	Received:
Phone:		Final Report:	
Fax:		Specimen Type:	
Address:		Your #:	

POSITIVE RESULT (A MUTYH PATHOGENIC VARIANT IS IDENTIFIED), SEE INTERPRETATION

GENE	CLASSIFICATION	ZYGOSITY	VARIANT DETECTED	CANCER RISK
MUTYH	PATHOGENIC	HETEROZYGOUS	p.Gly396Asp	ELEVATED

INTERPRETATION

The protein encoded by the MUTYH gene plays important role in detecting and protecting against oxidative DNA damage. Pathogenic variants in one copy of the MUTYH gene can increase the risk of developing gastrointestinal polyps, colorectal cancer and possibly other cancer, particularly for individuals with a positive family history (PMID: 23035301).

Monoallelic pathogenic variants in the MUTYH gene have been reported with a small increase in colorectal cancer risk, and a twofold increased risk for carriers who have a family history of colorectal cancer (PMID:21171015).

There are published guidelines regarding risk-reducing options for individuals with pathogenic MUTYH variants (see the National Comprehensive Cancer Network at www.nccn.org).

Genetic counselors are available for healthcare providers to further discuss this result. Please call 844-NEOVARE (636-8273). To refer your patient for genetic counseling through Neovare, please call 844-NEOVARE (636-8273) or visit us at www.neovare.com

Sequence analysis identified a heterozygous genetic change in exon 13 of the *MUTYH* gene (Chr1:45797228, c.1187G>A, NM_001128425.1) with 45% allele frequency. This variant is a single base pair substitution, which is predicted to change glycine to aspartic acid (p.Gly396Asp, NP_001121897.1). 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: 11818965, 16557584, 17489848, 19793053). 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, 15931596) particularly

for individuals with a positive family history (PMID: 23035301). Based on the currently available information, we consider MUTYH p.Gly396Asp to be pathogenic. See the method and limitations section for test limitations.

INDICATION FOR TESTING

- Patient was diagnosed with prostate cancer and secondary malignant neoplasm of bone.

GENES ANALYZED

APC	*CDH1*	*MLH1*	*PALB2*	*RET*
ATM	*CDK4*	*MRE11A*	*PDGFRA*	*SDHA*
AXIN2	*CDKN2A*	*MSH2*	*PMS2*	*SDHB*
BAP1	*CHEK2*	*MSH3*	*POLD1*	*SDHC*
BARD1	*EPCAM*	*MSH6*	*POLE*	*SDHD*
BMPR1A	*HOXB13*	***MUTYH***	*PTEN*	*SMAD4*
BRIP1	*KIT*	*NBN*	*RAD50*	*STK11*
BRCA1	*MEN1*	*NF1*	*RAD51C*	*TP53*
BRCA2	*MITF*	*NTHL1*	*RAD51D*	*VHL*

SIGNED BY

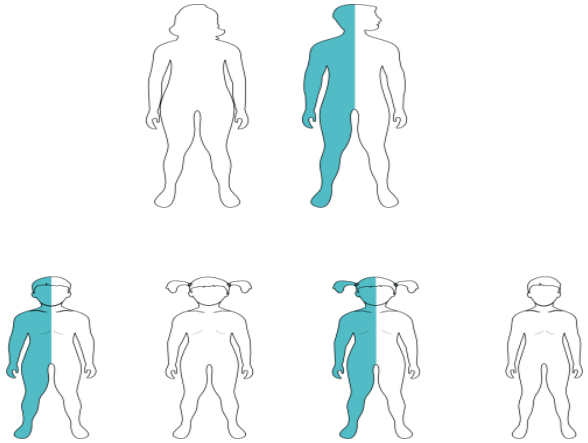
Sherif A. Nasr, MD, FCAP

DISCLAIMER

A positive genetic result does not guarantee that an individual will develop cancer. It means that the risk of developing cancer is expected to be higher than the average risk of the general population. There are also non-genetic risk factors not accounted for by this testing, including but not limited to age, lifestyle, and environmental factors as well as familial risk factors not currently known to have a genetic association. The information provided in this report should be interpreted in the context of the patient's medical history, family history, and other relevant clinical information. Genetic counseling is recommended. To better understand your risk, you can speak to one of our genetic counselors. See the method and limitations section for test limitations.

FAMILY MEMBERS

There is a 50/50 random chance to pass on a genetic variant in the *MUTYH* gene to each offspring. The image below shows that both men and women can carry and pass on these variants.



METHOD & LIMITATIONS

Genomic DNA was extracted from this patient's whole blood or saliva sample. Amplification of targeted regions was performed using hereditary custom panel of 651 amplicons that target 43 genes and Oncomine *BRCA1 & BRCA2* panel. Next generation sequencing was performed on the Ion S5 machine and analyzed with the Torrent Suite and Ion Reporter Software. GRCh37/Hg19 was used as reference for analysis, which

can be found @ http://www.ncbi.nlm.nih.gov/refseq/rsg/.

The mutation nomenclature is based on the convention recommended by the Human Genome Variation Society (http://www.hgvs.org/mutnomen/).

Limitations: This testing is validated to detect germline variants in the coding exons and parts of introns flanking each exon of the BRCA1 and BRCA2 genes in addition to coding exons of 43 additional genes. Genes covered are not all sequenced in their entirety. This technology cannot reliably detect variants at coverage below 100x. Accuracy of the call is determined by multiple factors, including but not limited to number of reads, ratio of variant call to normal allele and strand bias. Variants detected in genes with pseudogenes are confirmed by Sanger sequencing assays. This test is not designed to, and therefore cannot detect complex genetic events such as balanced chromosomal rearrangements and repeat expansions. Confirmation of the identities of pathogenic variants is performed by microarray technology and/or Sanger sequencing, if pertinent. Copy number variants are assessed for BRCA1 and BRCA2 using the Oncomine NGS BRCA1&2 panel and are reported based on the quality of the call. In some cases, confirmation by multiplex ligation-dependent probe amplification (MLPA) may be performed, if pertinent. Copy number variants are not tested for the other 43 genes. This test is designed to detect germline variants and is not intended to reliably detect somatic changes or low-level mosaicism. Individuals undergoing genetic testing should understand that rare diagnostic errors may occur. Possible sources of diagnostic errors include genotyping errors. Common examples of genotyping errors include: trace contamination of PCR, rare genetic variants which interfere with analysis, and mosaicism at levels below standard detection. This technology cannot reliably detect large insertions and deletions (>20bp), repeat expansions, or methylation status. All variants are classified according to the ACMG/AMP guidelines (PMID: 25741868). Variants classified as benign or likely benign are not reported. Sequencing results should be used in the context of available clinical information and should not be the sole basis for patient management and treatment. Interpretation of genetic variants is limited by the information available at the time of reporting and the clinical information provided with the sample. The classification and understanding of genetic variants may change over time as new information becomes available. Periodic review of the literature is recommended. Furthermore, negative results cannot eliminate the possibility of hereditary cancer.

CPT CODES

81162, 81408, 81405, 81292, 81298, 81314, 81317, 81321

ICD-10 CODES

C61 and C79.51.

End of report.