Ambry Genetics®

Reclassification - 03/07/2022

Ordered By Contact ID:1247706 Org ID:3001	Patient Name: **Sinnott, Andrew**
Medical Professional: Kennelly, Rory, MD	Accession #: **18-097488** Specimen #: BX671155S
Client: St. Vincent's University Hospital (05211)	AP2 Order #: 573270 Specimen: Blood EDTA (Purple top)
Additional Authorized Recipient:	Birthdate: 12/01/1967 Sex at Birth: M
Murphy, Donal N/A Winter, Des MD Frayling, Ian MD, FRCPC	MRN #: Collected: N/A
	Indication: Diagnostic Received: 07/05/2018

Reclassification Notice for MUTYH p.R495H

RECLASSIFICATION DETAILS

ALTERATION	NEW CLASSIFICATION
MUTYH p.R495H	Variant, Likely Benign

INTERPRETATION

Based on current available data, the *MUTYH p.R495H* alteration has been reclassified to the new classification listed above. Classification category definitions are as follows:

- **Pathogenic Mutation**: alterations with sufficient evidence to classify as pathogenic (capable of causing disease).Targeted testing of at-risk family members and appropriate changes in medical management (i.e. high risk surveillance) for pathogenic mutation carriers recommended.
- **Variant, Likely Pathogenic (VLP)**: alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk family members and appropriate changes in medical management (i.e. high risk surveillance) for VLP carriers recommended.
- **Variant, Unknown Significance (VUS)**: alterations with limited and/or conflicting evidence regarding pathogenicity. Medical management to be based on personal and family clinical histories, not VUS carrier status.
- **Variant, Likely Benign (VLB)**: alterations with strong evidence against pathogenicity Targeted testing of at-risk family members not recommended. Medical management to be based on personal and family clinical histories.
- **Benign**: alterations with sufficient evidence to classify as benign. Targeted testing of at-risk family members not recommended. Medical management to be based on personal and family clinical histories.

The **p.R495H** variant (also known as c.1484G>A), located in coding exon 15 of the *MUTYH* gene, results from a G to A substitution at nucleotide position 1484. The arginine at codon 495 is replaced by histidine, an amino acid with highly similar properties. In one functional study, this variant demonstrated DNA glycosylase activity similar to that of wild type MUTYH in a DNA cleavage activity assay and a supF forward mutation assay (Shinmura K et al. *Hum. Mutat.* 2016 Apr;37:350-3). This variant has been previously detected in a cohort of 381 unselected endometrial cancer patients who underwent multi-gene panel testing (Ring KL et al. *Mod Pathol*, 2016 11;29:1381-1389). This variant has also been identified in conjunction with different *MUTYH* founder mutations in probands with no reported history of polyposis (Ambry internal data). This amino acid position is highly conserved in available vertebrate species. In addition, the *in silico* prediction for this alteration is inconclusive. Based on the majority of available evidence to date, this variant is unlikely to be pathogenic.

This reclassification notice only applies to the above mentioned alteration. If any other alterations were identified in the patient's genetic testing, please refer to the original report.

Genetic counseling is a recommended option for all patients undergoing genetic testing.

NOTE: This reclassification notification is being sent to the ordering provider (OP) listed on this patient's original test requisition form. If this contact information is outdated, a reasonable attempt should be made to locate and contact the original OP, the patient, and/or the clinician currently overseeing this patient's care.

The mutY DNA glycosylase (*MUTYH*) gene (NM_001128425.1) encodes the adenine DNA glycosylase protein, which is involved in oxidative DNA damage repair by excising adenine bases from the DNA backbone at sites where adenine is inappropriately paired with guanine, cytosine, or 8-oxo-7,8-dihydroguanine. This protein is thought to play a role in signaling apoptosis by the introduction of single-strand breaks following

oxidative damage. *MUTYH* is located on chromosome 1p34.1 and contains 16 coding exons. Monoallelic pathogenic germline alterations in *MUTYH* have been detected in individuals diagnosed with female breast and colorectal cancers; however, data is limited and conflicting (Jones N et al. *Gastroenterology.* 2009 Aug;137(2):489-94; Win AK et al. *Int J Cancer.* 2011 Nov 1;129(9):2256-62; Rennert G et al. *Cancer.* 2012 Apr 15;118(8):1989-93; Fulk K et al. *Fam Cancer.* 2019 Apr;18(2):197-201). Lifetime cancer risk estimates for monoallelic pathogenic alteration carriers are not currently available. Biallelic pathogenic germline alterations in *MUTYH* cause autosomal recessive *MUTYH*-associated polyposis (MAP). Individuals who carry two *MUTYH* pathogenic germline alterations in *trans* (on different chromosomes) have an estimated lifetime colorectal cancer risk of up to 80% (Jenkins MA et al. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb;15(2):312-4). Parents who each carry a *MUTYH* pathogenic alteration have a 25% chance for a child with MAP in every pregnancy. These risks should be discussed with *MUTYH* pathogenic alteration carriers of reproductive age.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- APC & MUTYH seq and del/dup (Product Code 8726)
- CustomNext: Cancer® (Product Code 9510)