Cancer Risk Genetic Test Report

NovoFocus™ CR

Content

Patient and Order Details

PATIENT	SPECIMEN	PHYSICAN
Name: ****** **Patient NRIC/FIN/ID:** ****** **Gender:** Female **Data of Birth:** Jan.01.1981 **Nationality:** China **Diagnosis:** Unkown	**Specimen I.D.:** NKHS180158503-5A **Specimen Type/Size:** Blood **Specimen Collection Date:** 2019/06/26 **Specimen Received Date:** 2019/06/28	**Ordering Physician:** Not Given **Institution:** Organization Name

Test Indication (Personal / Family History Summary)

Personal History: Unkown

Family Member	Cancer/Clinical Diagnosis	Age at Diagnosis
Unkown	Unkown	Unkown
Unkown	Unkown	Unkown
Unkown	Unkown	Unkown

Results Summary

Interpretation: Positive.

Interpretation: Negative.

Gene	Variant	Classification	Zygosity
NF1	NM_000267.3 c.499_502delTGTT (p.Cys167GlnfsX10)	Pathogenic	Heterozygote
ATM	NM_000051.3 c.8814_8824del11 (p.Met2938IlefsX14)	Pathogenic	Heterozygote
MUTYH	NM_001128425.1 c.925-2A>G	Likely pathogenic	Heterozygote

The genetic test contains 106 hereditary cancer risk genes, and it is found that NF1 pathogenic variant , ATM pathogenic variant and MUTYH likely pathogenic variant, so your risk of developing cancer is higher than the general population.

This individual is heterozygous for a pathogenic variant in the NF1 gene, consistent with Neurofibromatosis type 1(NF1) syndrome. NF1 syndrome is associated with an increased risk of pheochromocytoma (1-13%), malignant peripheral nerve sheath tumors (6-16%), optic nerve gliomas (15%), breast cancer in women, gastrointestinal stromal tumors (GIST) and childhood leukemias.

This individual is also heterozygous for a pathogenic variant in ATM. Associated risks include an increased risk for breast cancer in women, and for colon, pancreatic, prostate, and other cancers in both women and men.

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Recommendations

- Genetic counseling is recommended to discuss the implications of these results.
- Surveillance and treatment recommendations for Neurofibromatosis type 1 are summarized in Evans et al. (2017) and the Neurofibromatosis 1 article in GeneReviews (Friedman 2018). In addition, the "NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian" include management recommendations for individuals with pathogenic variants in NF1.
- The "NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian" include management recommendations for individuals with pathogenic variants in ATM.
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- First degree relatives have up to a 50% chance of also having the pathogenic variant(s) identified in this individual. Targeted testing for the pathogenic variant(s) is available for at-risk relatives.
- For individuals and family members of reproductive age, assessment of the reproductive risk associated with

being a carrier of an ATM pathogenic variant is recommended.

- If you would like to discuss these results in further detail, please consult your healthcare provider or genetic counselor.

Summary of genomic alterations

No clinically significant mutation can be found.

Summary of genomic alterations found in patient specimen

No	Gene	Chr.	Exon /Intron	Transcript	cDNA_Change AA_Change	Zygosity	Allele Frequency (1000 Genomes)	Mutation type	Classification
1	NF1	Chr17	exon	NM_000267.3	c.499_502delTGTT p.Cys167Glnfs X10	Het	***	Frameshift	Pathogenic
2	ATM	***	***	NM_000051.3	c.8814_8824del11 p.Met2938Ilefs X14	Het	***	Frameshift	Pathogenic
3	MUTYH	Chr 1	intron10	NM_001128425.1	c.925-2A>G	Het	0.00299521	Splicing	Likely pathogenic
4	KIF1B	Chr 1	exon22	NM_015074.3	c.2173G>A p.V725M	Het	0.000199681	Missense	Uncertain significance
5	XPA	Chr 9	exon5	NM_000380.3	c.571C>G p.L191V	Het	0.000199681	Missense	Uncertain significance
6	TP53	Chr 17	exon3	NM_000546.5	c.91G>A p.V31I	Het	0.00179712	Missense	Uncertain significance
7	HOXB13	Chr 17	exon2	NM_006361.5	c.832G>T p.V278L	Het	0.000998403	Missense	Uncertain significance
8	ERCC2	Chr 19	exon10	NM_000400.3	NM_ c.921C>G p.N307K	Het	-	Missense	Uncertain significance
9	MSH2	Chr 2	exon7	***	c.1255C>A p.Q419K	Het	0.000798722	Missense	Likely Benign
10	EXT2	Chr 11	exon5	***	c.995G>A p.R332H	Het	0.000798722	Missense	Likely Benign
11	MSH6	Chr 2	exon10	***	c.4068_4071dupGATT	Het	-	Frameshift	Likely Benign

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No	Gene	Chr.	Exon /Intron	Transcript	cDNA_Change AA_Change	Zygosity	Allele Frequency (1000 Genomes)	Mutation type	Classification
					p.K1358 Dfs*2				
12	MSH2	Chr 2	exon12	***	c.1886A>G p.Q629R	Het	0.00219649	Missense	Benign
13	FANCD 2	Chr 3	exon23	***	c.2141C>T p.P714L	Het	-	Missense	Benign
14	PRSS1	Chr 7	exon4	***	c.508A>G p.K170E	Het	0.00159744	Missense	Benign
15	MSH3	Chr 5	exon1	***	c.181_189 dupGCAGCGC CC p.P63_P64insA AP	Hom	-	Frameshift	Benign

Note:

1. Analyze the gene variation by detecting the full exon of the gene in the list and intron regions near exon. Analysis and classify the variation by using the latest scientific research progress. As new scientific advances emerge, the classification and interpretation of some variations may change, and we will keep them up to date.
2. According to the guidelines of the American College of Medical Genetics and Genomics (ACMG), genetic mutations carried by individuals can be divided into the following five categories:
   a. Pathogenic variant: There is abundant evidence that this is a high-risk pathogenic mutation.
   b. Likely pathogenic variant: There is some evidence that this is a high-risk pathogenic mutation.
   c. Uncertain significance variant: There is not enough evidence to classify the mutation into categories a, b, d or e.
   d. Likely benign variant: There is some evidence that this is not a pathogenic mutation.
   e. Benign variant: There is abundant evidence that this is not a pathogenic mutation.
3. "-": No information available from the medical literature or database.
4. Heterozygosis (Het): A condition in which two alleles at the same locus have different genotypes.
5. Homozygous (Hom): A condition in which two alleles at the same locus have the same genotype.
6. Nonsense mutation: When a change in a base causes a codon representing an amino acid to mutate into a termination codon, thereby causing premature termination of peptide chain synthesis.
7. Missense mutation: When the codon encoding one amino acid is replaced by a base, it becomes the codon encoding another amino acid, thus changing the amino acid type and sequence of the polypeptide chain.
8. Synonymous mutation: Nucleotide variations that do not cause amino acid changes.
9. Frameshift mutation: In a normal DNA molecule, the increase or decrease of one or a few adjacent nucleotides causes a series of aberrant changes in the code that follow this position.
10. If you are carrying a variety of mutation types, please refer to the risk management measures corresponding to the most pathogenic mutation..
11. This table lists only the detailed information of the low frequency of 1000 genomes.

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Analyzed and reported by:

Checked and approved by:

Detailed Test Results

NM_000267.3(NF1):c.499_502delTGTT (p.Cys167GlnfsX10)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
NF1	NM_000267.3	c.499_502delTGTT	p.Cys167GlnfsX10	Heterozygote	PATHOGENIC

Clinical and Variant Interpretation

Variant description: This deletion of 4 nucleotides in NF1 is denoted c.499_502delTGTT at the cDNA level and p.Cys167GlnfsX10 (C167QfsX10) at the protein level. The normal sequence, with the deleted bases in brackets, is TGTT[delTGTT]CAGA. The deletion causes a frameshift which changes a Cysteine to a Glutamine at codon 167, and creates a premature stop codon at position 10 of the new reading frame.

Gene description: Tumor suppressor gene NF1(neurofibromin 1) encoded protein appears to function as a negative regulator of the Ras signal transduction pathway, which promotes cell growth and differentiation. Defects in this gene are responsible for tumorigenesis as a result of the tumor inhibition function of NF1 protein is impaired and cell growth is uncontrolled. Mutations of NF1 gene are associated with many diseases including neurofibromatosis, monocytic leukemia, Watson syndrome, melanoma, lung cancer, colorectal cancer, etc.

Variant analysis: This variant is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. This variant, previously published as NF1 495delTTGT, has been observed in multiple individuals with a clinical diagnosis of Neurofibromatosis Type 1 (Osborn 1999, Ars 2003, Lee 2006, Bendova 2007, Brinckmann 2007, Wimmer 2007, Sabbagh 2013, Schaefer 2013, Uusitalo 2014). Pasmant et al. (2011) identified this variant in an individual whose malignant peripheral nerve sheath tumor displayed loss of heterozygosity.Therefore, in view of the current research progress, we consider this variant to be a pathogenic variant.

NM_000051.3(ATM): c.8814_8824del11 (p.Met2938IlefsX14)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
ATM	NM_000051.3	c.8814_8824del11	p.Met2938IlefsX14	Heterozygote	PATHOGENIC

Clinical and Variant Interpretation

Variant description: This deletion of 11 nucleotides in ATM is denoted c.8814_8824del11 at the cDNA level and p.Met2938IlefsX14(M2938IfsX14) at the protein level. The surrounding sequence is TGAT[del11]AGGA. The deletion causes a frameshift, which changes a Methionine to an Isoleucine at codon 2938, and creates a premature stop codon at position 14 of the new reading frame.

Gene description: The protein encoded by ATM(ATM serine/threonine kinase) gene belongs to the PI3/PI4-kinase family. This protein is an important cell cycle checkpoint kinase that phosphorylates many checkpoint proteins such as p53, CHK2, H2AX, MDM2, BRCA1 and so on, upon DNA stress. ATM encoded protein is an integration point of different signal transduction pathways which are crucial for cellular homeostasis. Mutations of ATM in cells bring about accumulation of DNA damage and genomic instability, leading to tumorigenesis. Mutations of ATM gene are associated with many cancers including endometrial cancer, bowel cancer, stomach cancer, etc.

	Variant analysis: This variant is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. ATM c.8814_8824del11 has been observed in individuals with a personal history of Ataxia-Telangiectasia (Gilad 1998, Sandoval 1999, Cavalieri 2008, Prodosmo 2013). Therefore, in view of the current research progress, we consider this variant to be a pathogenic variant.

NM_001128425.1(MUTYH):c.934-2A>G

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
MUTYH	NM_001128425.1	c.934-2A>G	--	Heterozygote	Uncertain Significance

Clinical and Variant Interpretation	**Variant description**: This variant is denoted MUTYH c.934-2A>G or IVS10-2A>G and consists of an A>G nucleotide substitution at the -2 position of intron 10 of the MUTYH gene. Using an alternate transcript, this variant has been reported as MUTYH c.892-2A>G. This variant destroys a canonical splice acceptor site and is predicted to cause abnormal gene splicing, leading to an abnormal message that is subject to nonsense-mediated mRNA decay or to an abnormal protein product.This variant is of a heterozygous type. **Gene description**: MUTYH is located at 1p34.1 and encodes 546 amino acids. Associated with hereditary polyposis, it is an autosomal recessive gene. The MUTYH protein is a specific adenine transglucosylase located in the nucleus and mitochondria and involved in base excision repair. If the MUTYH protein is inactivated, it will easily lead to the transversion of G:C-->A:T during replication, thereby promoting tumorigenesis. In patients with familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (AFAP), if no APC gene mutation was detected, MUTYH mutations were detected with a 33% and 57% chance, respectively. The two most common variants in 70%-86% of MAP patients are p.Y179C and p.G396D (originally named Y165C and G382D). MUTYH heterozygous variants increase the risk of breast cancer by 1.9 times. **Variant analysis:** The mutation is known as variation (rs77542170) and the frequency in the ExAC population is 0.00102. The mutation was recorded as a causative mutation in the ClinVar database (variation ID: 41766). It has been reported in the literature that mutations in this splice site produce abnormal mRNA transcripts, which in turn leads to truncation of the MUTYH protein and loss of nuclear localization of the protein [PMID: 15180946]. Since the wild-type MUTYH protein is mainly localized in the nucleus, this data indicates that this splicing variation disrupts protein function [PMID: 16199547]. The mutation has been reported to be a heterozygous mutation in several individuals with colorectal adenoma, colorectal cancer [PMID: 15890374, 17703316] and/or breast cancer [PMID: 15890374, 17703316, 26824983], but the mutation has not been determined. Whether it is the cause of the disease. Therefore, in view of the current research progress, we consider this variant to be an likely pathogenic variant. Since the variation is heterozygous, your first-degree relatives are 50% likely to carry the mutation. It is recommended that your relatives participate in further testing to determine genetic risk.

NM_015074.3(KIF1B):c.2173G>A(p.V725M)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
KIF1B	NM_015074.3	c.2173G>A	p.V725M	Heterozygote	Uncertain Significance

Clinical and Variant Interpretation	**Variant description**: The mutation is that the 2173th nucleotide located in exon 22 is mutated from G to A, resulting in the mutation of the 725th amino acid in the corresponding protein sequence from proline to methionine. This mutation belongs to a heterozygous missense mutation. **Gene description**: KIF1B, located at 1p36.22, encodes 1816 amino acids, which encodes a motor protein that transports mitochondria and synaptic vesicle precursors, which are involved in vesicle-mediated transport and megakaryocyte development pathways. This genetic variant can lead to progressive neurogenic dystrophy. This gene is also closely related to pheochromocytoma. **Variant analysis:** The variation is known as variation (rs189631845) and in the ExAC population is 0.0000247. This variation was not included in the ClinVar database. The algorithm developed for predicting the effect of missense mutations on protein structure and function (SIFT, polyphen2, MutationAssessor) suggests that this mutation does not destroy the structure or function of the protein. Therefore, in view of the current research progress, we consider this variant to be uncertain significance variant.

NM_000380.3(XPA):c.571C>G(p.L191V)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
XPA	NM_000380.3	c.571C>G	p.L191V	Heterozygote	Uncertain Significance

Clinical and Variant Interpretation	**Variant description**: The mutation at position 571 of exon 5 is mutated from C to G, resulting in the mutation of 191th amino acid in the corresponding protein sequence from leucine to proline, which is a heterozygous missense mutation. **Gene description**: XPA is located at 9q22.33 and encodes 273 amino acids. This gene is a zinc finger protein involved in DNA excision repair and is part of the NER (nucleic acid excision repair) complex. It is responsible for repairing photochemical products induced by UV radiation. The encoded protein can be involved in the pathway of nucleotide excision repair and transcription-coupled nucleotide excision repair (TC-NER). The variation of XPA is closely related to the complementation group A of the xeroderma pigmentosum. The diseases involved also include Xpa-related xeroderma pigmentosum. **Variant analysis:** The variation is a known variation (rs562768588) and the frequency in the ExAC population is 0.00016. This variation is recorded as an uncertain significance mutation (Variation ID: 135458) in the ClinVar database. The algorithm developed for predicting the effect of missense mutations on protein structure and function (SIFT, polyphen2, MutationAssessor) suggests that the mutation does not destroy the structure or function of the protein. Therefore, in view of the current research progress, we consider this variant to be an uncertain significance variant.

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NM_000546.5(TP53):c.91G>A(p.V31I)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
TP53	NM_000546.5	c.91G>A	p.V31I	Heterozygote	Uncertain Significance

Clinical and Variant Interpretation	**Variant description**: The 91th nucleotide of the mutation located in exon 3 was mutated from G to A, resulting in the mutation of the 31st amino acid in the corresponding protein sequence from proline to isoleucine. This mutation belongs to a heterozygous missense mutation. **Gene description**: Located at 17p13.1, encoding 393 amino acids, TP53 is a tumor suppressor gene that is a negative regulator of cell growth cycle and is involved in important biological functions such as cell cycle regulation, DNA repair, cell differentiation, and apoptosis. , its mutation will lead to Li-Fraumeni syndrome (LFS) and Li-Fraumeni like syndrome (LFL). It is autosomal dominant. TP53 variant carriers are 50% cancer risk by the age of 30 and have a lifetime cancer risk of up to 90%. LFS and LFL characterization includes: soft tissue and osteosarcoma, breast cancer, brain cancer, and adrenocortical cancer. The study found that a small percentage of female breast cancer patients had TP53 mutations without BRCA1 and BRCA2 mutations. Other cancers, such as pancreatic cancer, may also occur when carrying TP53 mutations. The incidence rate is relatively low, accounting for about 80% of children's adrenocortical carcinoma; 2%-10% in juvenile brain cancer patients; 2%-3% in osteosarcoma patients; The proportion in hereditary breast cancer is less than 1%. **Variant analysis:** The variation is known variation (rs201753350) and the frequency in the ExAC population is 0.00026. This variation is recorded as an uncertain significance mutation or possibly benign in the ClinVar database (Variation ID: 127827). The algorithm developed for predicting the effect of missense mutations on protein structure and function (SIFT, polyphen2, MutationAssessor) suggests that the mutation does not destroy the structure or function of the protein. This mutation is outside the p53 transactivation domain. In functional studies, this variant showed moderately reduced cell proliferation inhibitory activity and transcriptional activity against p21 (CDKN1A) and MDM2 compared to wt-tp53 [PMID: 17690113]. This mutation has been reported in several cancer patients, but there is no evidence of causality [PMID: 1565143, 20436704, 17690113, 27545002]. Therefore, in view of the current research progress, we consider this variant to be an uncertain significance variant.

NM_006361.5(HOXB13):c.832G>T(p.V278L)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
HOXB13	NM_006361.5	c.832G>T	p.V278L	Heterozygote	Uncertain Significance

Clinical and Variant Interpretation	**Variant description**: The mutation at position 832 on exon 2 was mutated from G to T, resulting in the mutation of the 278th amino acid in the corresponding protein sequence from valine to leucine. This mutation belongs to a heterozygous missense mutation. **Gene description**: THOXB13, located at 17q21.32, encodes 284 amino acids and encodes a transcription factor that belongs to the homeobox gene family. HOXB13 plays a role in fetal skin development and skin regeneration. This gene is closely related to prostate cancer.

	Variant analysis: The variation is a known variation (rs200997384) and the frequency in the ExAC population is 0.00024. This variation is recorded as an uncertain significance mutation (Variation ID: 128038) in the ClinVar database. This mutation is located in the androgen receptor (AR) binding domain [PMID: 19917249]. The algorithm developed for predicting the effect of missense mutations on protein structure and function (SIFT, polyphen2, MutationAssessor) suggests that the mutation does not destroy the structure or function of the protein. This mutation was not observed in any breast or prostate cancer cases, but was observed in the control groups of two different studies [PMID: 22718234, 27424772]. After multiple comparisons, this mutation was not found to be statistically significantly associated with prostate cancer [PMID: 23555315]. Therefore, in view of the current research progress, we consider this variant to be an uncertain significance variant.

NM_000400.3(ERCC2):c.921C>G(p.N307K)

Gene	Transcript	cDNA Change	AA_Change	Zygosity	Classification
ERCC2	NM_000400.3	c.921C>G	p.N307K	Heterozygote	Uncertain Significance

Clinical and Variant Interpretation	**Variant description**: The mutation at position 921 on exon 10 was mutated from C to G, resulting in the mutation of amino acid 307 in the corresponding protein sequence from asparagine to lysine. This mutation belongs to a heterozygous missense mutation. **Gene description**: ERCC2 is located at 19q13.32 and encodes 760 amino acids. ERCC2 acts as a tumor suppressor gene and encodes a DNA repair factor. The protein encoded by the ORF is involved in the cleavage of the transcribed nucleotides and is a member of the basal transcription factor BTF2/TFIIH, which is dependent on ATP. The melting enzyme activity belongs to the RAD3/XPD melting enzyme family. Diseases associated with ERCC2 include lung cancer, colorectal cancer, and esophageal cancer. **Variant analysis:** The mutation is a known variation (rs781205093), no population frequency. The mutation is not included in the ClinVar database. Algorithm developed to predict the effect of missense mutations on protein structure and function (SIFT, polyphen2, MutationAssessor). Both suggest that the mutation may disrupt the structure or function of the protein. Therefore, in view of the current research progress, we consider this variant to be an uncertain significance variant.

Please note that low penetrance and late age-of-onset variants that are associated with disease may be present at a low frequency in large population studies.

Test Details

Accreditations

This test was conducted in a College of American Pathologists (CAP) accredited facility for next-generation sequencing (CAP Number: 9043632, AU-ID: 1759306). Its performance characteristics was determined in compliance to all applicable standards for the accreditation. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Methodology

For the screening of genetic cancer susceptibility, the next-generation sequencing technology is used to deeply sequence the genes known to be associated with the risk of hereditary cancer, to pinpoint the genetic variation, and to annotate the currently known mutations in conjunction with the latest research progress. This provides a comprehensive assessment of your risk of developing hereditary cancer and provides recommendations for living and medical examinations.The method can detect mutations including exon regions of genetic cancer-related genes and intron regions (including point mutations, small fragment insertions) near exon, excluding genomic structural variations (e.g. Large fragment and Loss of heterozygosity, replication and inversion rearrangement, large fragment and heterozygous insertion mutation (such as ALU-mediated insertion) and mutations in gene regulatory regions or deep intron regions.

Gene list

AIP	ALK	APC	ATM	AXIN2	BAP1	BARD1
BLM	BMPR1A	BRCA1	BRCA2	BRIP1	BUB1	BUB1B
BUB3	CDC73	CDH1	CDK4	CDKN1B	CDKN2A	CEBPA
CHEK2	CYLD	DDB2	DICER1	DIS3L2	EGFR	ELAC2
EPCAM	ERCC2	ERCC3	ERCC4	ERCC5	EXT1	EXT2
FANCA	FANCB	FANCC	FANCD2	FANCE	FANCF	FANCG
FANCI	FANCL	FANCM	FH	FLCN	GATA2	HNF1A
HOXB13	KIF1B	KIT	MAX	MEN1	MET	MITF
MLH1	MLH3	MRE11	MSH2	MSH3	MSH6	MUTYH
NBN	NF1	NF2	NSD1	NTRK1	PALB2	PALLD
PDGFRA	PHOX2B	PMS1	PMS2	PRKAR1A	PRSS1	PTCH1
PTEN	RAD50	RAD51C	RAD51D	RB1	RET	RHBDF2
RNASEL	RUNX1	SDHA	SDHAF2	SDHB	SDHC	SDHD

SETD2	SLX4	SMAD4	SMARCB1	SRD5A2	STK11	SUFU
TMEM127	TP53	TSC1	TSC2	VHL	WT1	XPA
XPC						

Interpretation of genetic information

The genetic information interpretation rules refer to the relevant guidelines of the American College of Medical Genetics and Genomics (ACMG). The report focuses on mutation points that are currently clearly associated with the disease or that may be associated with the disease. The report will not include synonymous variations, non-splicing mutations in intron regions and common benign polymorphic variants unless relevant pathogenicity has been reported.. Relevant interpretations are based on our current understanding of disease and disease genes. The annotations for the mutations are referenced to public databases such as dbSNP, 1000Genome, HapMap and HGMD. It is recommended that the clinician or relevant medical professional perform a clinical phenotypic association with the subject based on the test results. As scientific research progresses, the classification and interpretation of partial variations may change and we will remain updated. If you have questions or if there are related diseases in your family members, please contact the inspection unit. The test results are laboratory test data, which are only used for the purpose of mutation screening, and do not represent the final diagnosis results, and be for clinical reference only.

Statement on interpretation of variation

The results of the mutation interpretation are based on the current cutting-edge scientific research and the variation information in the international public database. The public database contains the variation information of various populations. Therefore, the final pathogenic interpretation needs to be combined with the patient's clinical manifestations, family history, and a unique database of local populations. If the mutated information submitted in the public database is inaccurate or does not match, it does not rule out that the interpretation result will be wrong. Hereditary tumors are complex polygenic diseases. If the test results do not match the clinical manifestations, other tests can be considered for verification. The test results in the report provide reference for further clinical testing, prevention and monitoring of the subject.

Risk management measures for cancer

Risk of developing cancer

Since you have not detected a mutation in your disease, the risk of cancer is consistent with the general population, but your risk of developing cancer may increase for the following reasons:

- Other non-genetic factors (eg: environment).
- Other hereditary cancer syndromes.
- There are mutations that cannot be detected due to current detection techniques.

Note: Data from European and American people, for reference only.

In the light of you have a likely pathogenic variant in the MUTYH gene, your risk of developing cancer is significantly higher than the general population and it needs to be taken seriously. However, you don't need to be overly nervous. You can check the disease regularly and take other appropriate measures to prevent it. At the same time, you can achieve three early clinical measures: early detection, early diagnosis, early treatment, then you will have a high chance to prevent cancer from developing or curing.

The list of disease risks caused by MUTYH mutations is as follows:

Homozygous mutation			
Cancer	**Age（year）**	**Risk of developing cancer**	**Risk of the general population**
Colorectal cancer	To 80	43%-100%	3.4%
Small Intestine Cancer	To 80	4%	0.2%
Heterozygous mutation			
Cancer	**Age（year）**	**Risk of developing cancer**	**Risk of the general population**
Colorectal cancer	To 80	3.4%-10%	3.4%

Management Options for Risk Reduction

Your genetic test results show that your disease risk is consistent with the general population. In general, you do not need special precautions and measures. However, it is still recommended that you manage your risk based on your family history and medical history.

- Your healthcare provider can develop the medical management options that are right for you.
- Your health care provider can help you decide if you or your family need further genetic testing.

You can check your tumor regularly, maintain regular exercise, and maintain a balanced diet. At the same time, you need to do early clinical measures: early detection, early diagnosis, early treatment, then you will have a high probability To prevent or cure the disease.

Cancer risk management measures related to MUTYH mutation

There are a few things you can do to reduce your cancer risk. Discuss with your health care provider or clinician before deciding on a suitable plan.

Homozygous mutation			
Cancer	**Measure**	**Age**	**Frequency**
Colorectal cancer	Colonoscopy	25-30 years	3-5/yeat
	Colorectal surgery assessment and consultation	Density and distribution according to adenoma	uncertain
Small Intestine Cancer	Upper gastrointestinal endoscopy	30-35years	3-5/yeat
Heterozygous mutation			
Cancer	**Measure**	**Age**	**Frequency**
Colorectal cancer	Colorectal cancer screening	50years	According to individual circumstances

Note: The above risk management recommendations are derived from the NCCN guidelines and leading-edge scientific research. Specific risk management measures should be carefully selected in conjunction with their own quality of life requirements and family history.

What Does this Result Mean for Family Members?

● In most cases, your family members do not need to have a tumor genetic test, because no pathogenic or potentially pathogenic variants are detected in you.

● In some cases, it is recommended that relatives diagnosed with the tumor receive genetic testing in order to find more information about your family's genetic risk.

If you have any questions about your genetic test results, please contact the hotline and website.

Genetic variants are hereditary and the pathogenic variant are detected in your genes, so:

● Your family members (parents, children, brothers, and sisters) have a 50% chance of having the same variation.

● Your distant relatives (cousin, uncle, aunt etc.) may also have the same variation.

● In general, mutations will only be found in the parent (father or mother) with a family history of cancer.

● Relatives interested in genetic testing need to know your specific mutations. The cost of a single site detection is much less than the full cost of testing.

● If your relatives:

★ The pathogenic variant is detected, his/her risk of developing cancer will increase and you can benefit from proper medical management.

★ The pathogenic variant is not detected. His/her risk of developing cancer is the same as the general population. He/she can follow the general population screening guidelines.

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