ACT Risk™

GENETIC TEST FOR HEREDITARY CANCERS

This material is intended for healthcare professionals only.

ACT GENOMICS®

ACT Risk™

Covers 67 genes associated With 9 hereditary cancer types And 11 cancer syndromes

It focuses on 9 major types of hereditary cancers—including breast, colorectal, melanoma, pancreatic, and neuroendocrine tumors—commonly found in Asian populations. The analysis leverages international genomic databases (e.g., GnomAD, 1000 Genomes, ClinVar, COSMIC), Taiwan Biobank, and ACT Genomics' proprietary database of Asian ethnic variants. This test enables early detection of inherited cancer risk, supporting timely implementation of risk mitigation and management strategies.

GENES TESTED	HEREDITARY CANCERS										HEREDITARY CANCER SYNDROMES										
	Breast	Ovarian	Colorectal	Endometrial	Melanoma	Pancreatic	Gastric	Prostate	Neuroendocrine	Others	Hereditary Breast and Ovarian Cancer Syndrome	Hereditary Diffuse Gastric Cancer	Lynch Syndrome	Juvenile Polyposis Syndrome	Peutz-Jeghers Syndrome	Familial Adenomatous Polyposis	MUTYH-associated Polyposis	Li-Fraumeni Syndrome	Cowden Syndrome	Melanoma-Pancreatic Cancer Syndrome	von Hippel-Lindau
APC			●			●	●			●						●					
BRCA1	●	●				●		●			●										
BRCA2	●	●			●	●		●			●										
CDH1	●						●					●									
CHEK2	●		●					●													
EPCAM		●	●	●		●	●						●								
MLH1	●	●	●	●		●	●	●					●								
MSH2		●	●	●			●	●					●								
MSH6		●	●	●			●	●					●								
MUTYH			●														●				
PALB2	●	●				●		●													
PMS2			●	●									●								
PTEN	●		●	●						●									●		
RAD50	●	●																			
RAD51C	●	●						●													
RAD51D	●	●						●													
TP53	●		●	●	●	●	●	●		●								●			
VHL									●												●
ALK										●											
ATM	●	●				●		●													
ATR								●													
AXIN2			●																		
BARD1	●																				
BLM			●																		
BMPR1A			●				●							●							
BRIP1	●	●						●													
CDK4					●																
CDKN2A					●	●														●	
CFTR						●															
ENG									●												
EPAS1									●												
FAM175A								●													
FANCC	●	●																			
FH									●												
FLCN										●											
GALNT12			●																		
GEN1								●													
GREM1			●																		
MAX									●												
MC1R					●																
MDH2									●												
MEN1									●												
MET										●											
MRE11	●	●						●													
MSH3			●																		
NBN	●	●						●													
NF1	●									●											
NF2										●											
NTHL1			●																		
POLD1			●																		
POLE			●																		
PRSS1						●															
RB1										●											
RET									●	●											
SCG5			●																		
SDHA							●		●	●											
SDHB							●		●	●											
SDHC							●		●	●											
SDHD							●		●	●											
SDHAF2									●												
SMAD4			●				●		●					●							
SPINK1						●															
STK11	●	●	●	●		●	●			●					●						
TMEM127									●												
TSC1										●											
TSC2										●											
XRCC2	●	●																			

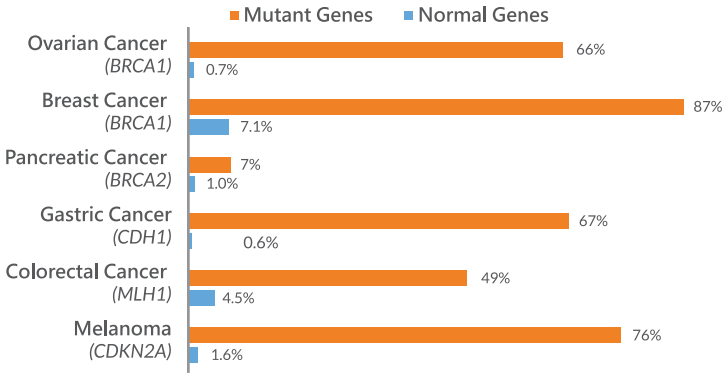
* Genes listed in the yellow box include LGR testing
* The list was made in accordance with the NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, Colorectal and databases such as GnomAD, 1000 Cenome, ClinVar, COSMIC, Taiwan Biobank, and the ACTGenomic's ethnicity-related genetic variant database.
* This list of genes is for reference only, and ACT Genomics reserves the right to change and modify the list.

The benefits of genetic testing, more personalized care options

When multiple cases of cancer occur within a family, it is important to evaluate the possibility of a shared inherited risk factor, such as pathogenic mutations in cancer-associated genes.

What are Hereditary Cancers?

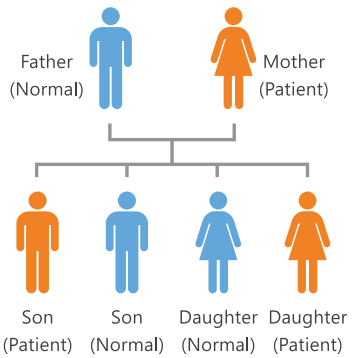
Approximately 5–10% of cancers are caused by inherited genetic mutations.[1] In addition to *BRCA1/2* mutations, which are widely known to increase the risk of breast, ovarian, pancreatic and prostate cancer, mutations in many other hereditary cancer-related genes also increase the lifetime risk of cancer by up to 90 times in comparison with the general population (Figure 1).[2–5]



<Figure 1> Cancer Gene Mutations Increase the Risks of Cancer.

Although hereditary cancers constitute a small proportion of all cancer cases, they should not be overlooked. Many of the cancer-stricken families carry susceptibility or predisposing genes which are passed down in the family across multiple generations. Based on the penetrance rate, these genes can be classified as either high penetrance, moderate penetrance, or low penetrance.[6] Patients with moderate-to-high penetrance genes have a significantly higher risk of developing cancer. Therefore, in accordance with the recommendations of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guideline, cancer screening, monitoring, and intervention need to be performed early. Indeed, a study in 2017 found that the incidence of colorectal cancer could be reduced if patients with these susceptibility gene (e.g., *MLH1*, *MSH2*, *MSH6*, *PMS2*) mutations underwent regular colonoscopy and polyps removal, which were found to decrease the mortality rate by a staggering 65%.[7]

Understanding The Hereditary Patterns of Cancer Is Essential For Assessing Familial Cancer Risk.

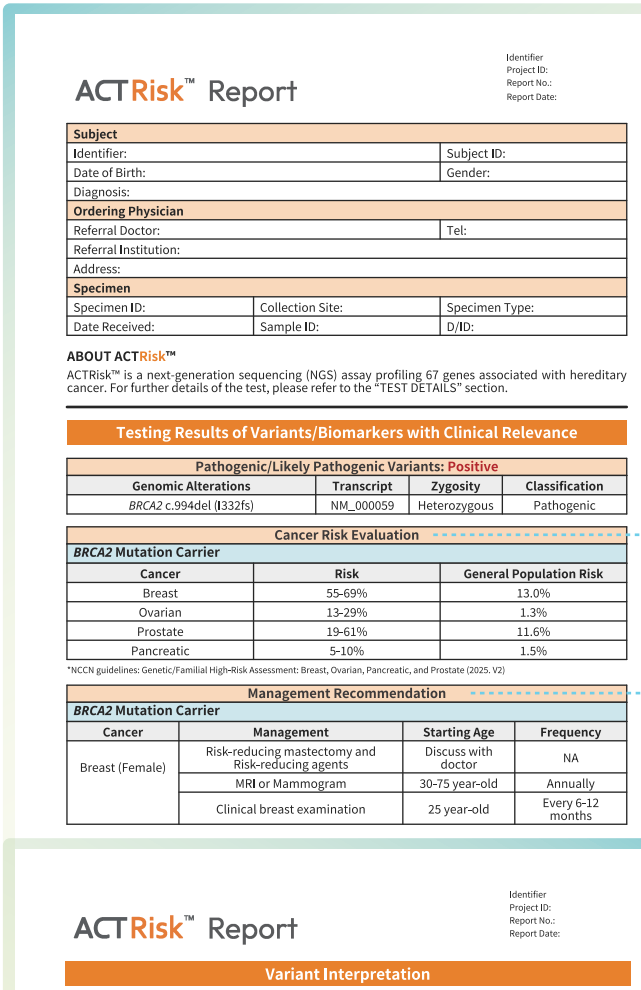


<Figure 2> Autosomal Dominant Inheritance of *BRCA1* Gene

Patients with a hereditary cancer usually have a family history of cancer. Therefore, it is important to consider both the paternal and maternal lines of inheritance. Using hereditary breast and ovarian cancer syndrome (HBOCS) as an example, *BRCA1* mutations are inherited in an autosomal dominant fashion (Figure 2). As such, each of the siblings or children would have a 50% chance of carrying the mutant *BRCA1* gene from the parent, which predisposes them to the development of hereditary cancers. Therefore, the occurrence rate of these cancers in the affected family would be comparatively higher than others. The onset of these cancers may also be earlier compared to the average age of onset of the respective cancers. Since each hereditary cancer has different characteristics, it is highly recommended that genetic counselling is conducted by a trained professional before and after the tests.

1. NIH, Genetic Testing for Inherited Cancer Susceptibility Syndromes
2. Kuchenbaecker, KB, et al. JAMA. 2017;317(23):2402–2416.
3. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Colorectal
4. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast and Ovarian
5. NCCN Guidelines: Gastric Cancer
6. Semin Oncol. 2016 Oct;43(5):528-535
7. Emma Steel, et al. Hered Cancer Clin Pract. 2017;15:1

ACT Risk™ Report



ACT Risk™ Report

Identifier
Project ID:
Report No.:
Report Date:

Subject		
Identifier:		Subject ID:
Date of Birth:		Gender:
Diagnosis:		
Ordering Physician		
Referral Doctor:		Tel:
Referral Institution:		
Address:		
Specimen		
Specimen ID:	Collection Site:	Specimen Type:
Date Received:	Sample ID:	D/ID:

ABOUT ACTRisk™

ACTRisk™ is a next-generation sequencing (NGS) assay profiling 67 genes associated with hereditary cancer. For further details of the test, please refer to the "TEST DETAILS" section.

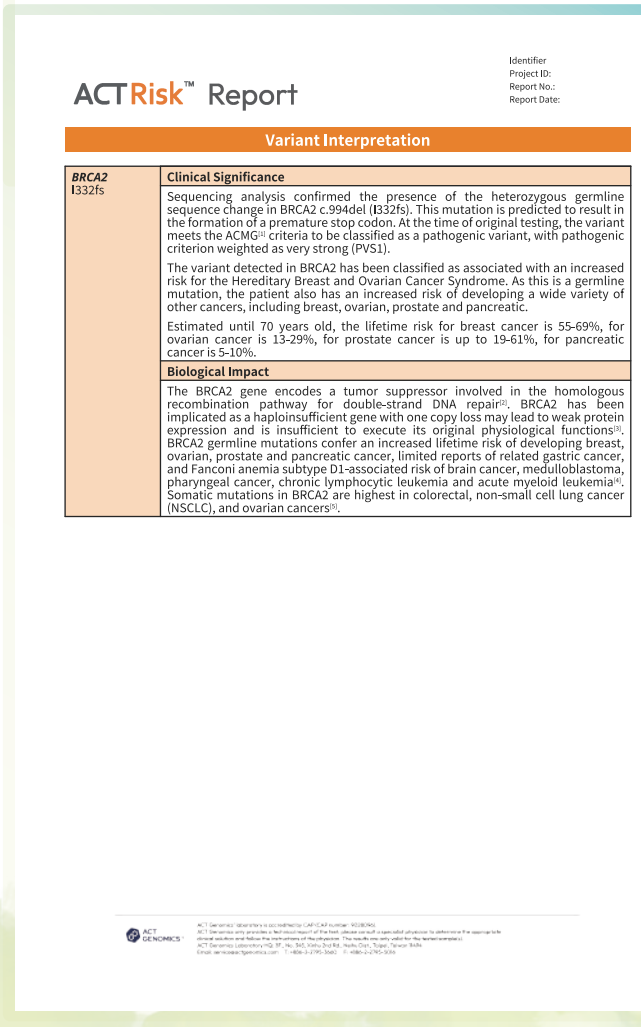
Testing Results of Variants/Biomarkers with Clinical Relevance

Pathogenic/Likely Pathogenic Variants: Positive			
Genomic Alterations	**Transcript**	**Zygosity**	**Classification**
BRCA2 c.994del (I332fs)	NM_000059	Heterozygous	Pathogenic

Cancer Risk Evaluation		
***BRCA2* Mutation Carrier**		
Cancer	**Risk**	**General Population Risk**
Breast	55-69%	13.0%
Ovarian	13-29%	1.3%
Prostate	19-61%	11.6%
Pancreatic	5-10%	1.5%

*NCCN guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (2025. V2)

Management Recommendation			
***BRCA2* Mutation Carrier**			
Cancer	**Management**	**Starting Age**	**Frequency**
Breast (Female)	Risk-reducing mastectomy and Risk-reducing agents	Discuss with doctor	NA
	MRI or Mammogram	30-75 year-old	Annually
	Clinical breast examination	25 year-old	Every 6-12 months



ACT Risk™ Report

Identifier
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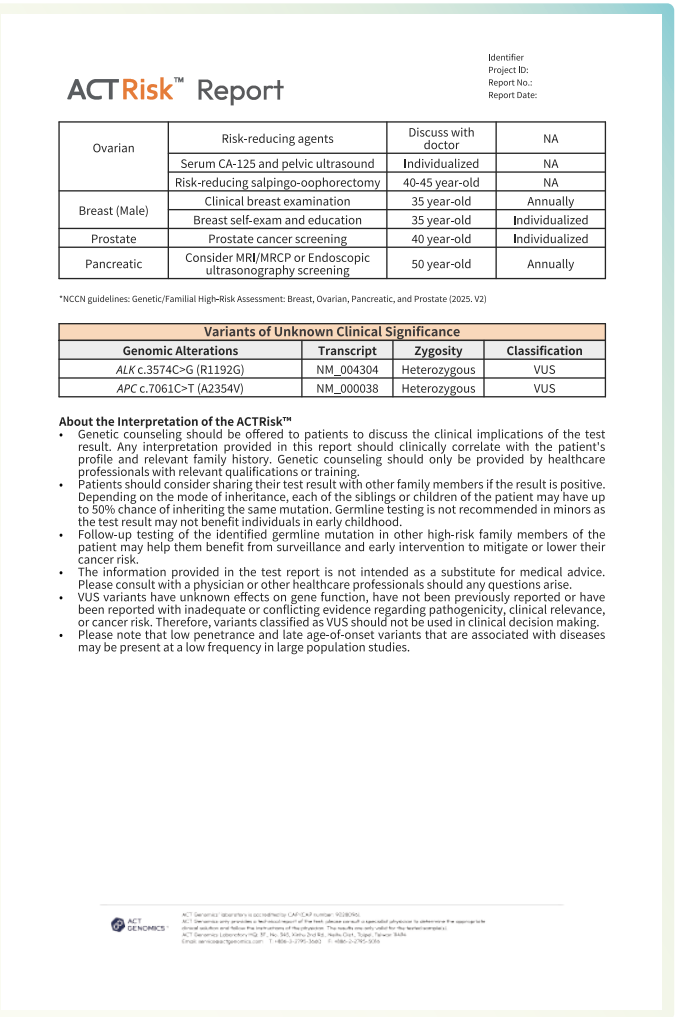
Report Date:

Variant Interpretation

BRCA2 I332fs	**Clinical Significance**
	Sequencing analysis confirmed the presence of the heterozygous germline sequence change in BRCA2 c.994del (I332fs). This mutation is predicted to result in the formation of a premature stop codon. At the time of original testing, the variant meets the ACMG[1] criteria to be classified as a pathogenic variant, with pathogenic criterion weighted as very strong (PVS1). The variant detected in BRCA2 has been classified as associated with an increased risk for the Hereditary Breast and Ovarian Cancer Syndrome. As this is a germline mutation, the patient also has an increased risk of developing a wide variety of other cancers, including breast, ovarian, prostate and pancreatic. Estimated until 70 years old, the lifetime risk for breast cancer is 55-69%, for ovarian cancer is 13-29%, for prostate cancer is up to 19-61%, for pancreatic cancer is 5-10%.
	Biological Impact
	The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[2]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[3]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[4]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[5].



ACT Risk™ Report

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Ovarian	Risk-reducing agents	Discuss with doctor	NA
	Serum CA-125 and pelvic ultrasound	Individualized	NA
	Risk-reducing salpingo-oophorectomy	40-45 year-old	NA
Breast (Male)	Clinical breast examination	35 year-old	Annually
	Breast self-exam and education	35 year-old	Individualized
Prostate	Prostate cancer screening	40 year-old	Individualized
Pancreatic	Consider MRI/MRCP or Endoscopic ultrasonography screening	50 year-old	Annually

*NCCN guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (2025. V2)

Variants of Unknown Clinical Significance			
Genomic Alterations	**Transcript**	**Zygosity**	**Classification**
ALK c.3574C>G (R1192G)	NM_004304	Heterozygous	VUS
APC c.7061C>T (A2354V)	NM_000038	Heterozygous	VUS

About the Interpretation of the ACTRisk™

- Genetic counseling should be offered to patients to discuss the clinical implications of the test result. Any interpretation provided in this report should clinically correlate with the patient's profile and relevant family history. Genetic counseling should only be provided by healthcare professionals with relevant qualifications or training.
- Patients should consider sharing their test result with other family members if the result is positive. Depending on the mode of inheritance, each of the siblings or children of the patient may have up to 50% chance of inheriting the same mutation. Germline testing is not recommended in minors as the test result may not benefit individuals in early childhood.
- Follow-up testing of the identified germline mutation in other high-risk family members of the patient may help them benefit from surveillance and early intervention to mitigate or lower their cancer risk.
- The information provided in the test report is not intended as a substitute for medical advice. Please consult with a physician or other healthcare professionals should any questions arise.
- VUS variants have unknown effects on gene function, have not been previously reported or have been reported with inadequate or conflicting evidence regarding pathogenicity, clinical relevance, or cancer risk. Therefore, variants classified as VUS should not be used in clinical decision making.
- Please note that low penetrance and late age-of-onset variants that are associated with diseases may be present at a low frequency in large population studies.

SNV & INDELs

A single nucleotide variants (SNV), insertion or deletion mutation is a type of genetic mutation where sequences of nucleotides are changed/ inserted/deleted from the reference genome. (e.g. activating mutation in oncogenes or truncating mutation in tumor suppressor genes)

LGR

Large Genomic Rearrangements (LGR) is a DNA segment in exon-level with large genomic rearrangements in comparison with a reference genome. (i.e. duplication, heterozygous deletion and homozygous deletion)

CANCER RISK & MANAGEMENT RECOMMENDATION

Cancer risk mitigation and management would be recommended based on clinical practice guidelines. Overall recommendations for cancer hereditary information for test subject's and physician's reference.

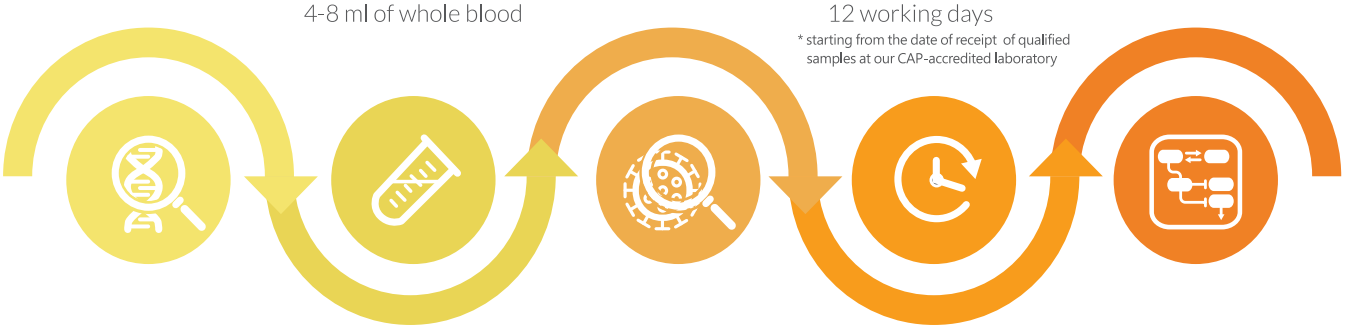
Disclaimer:

- The visuals above are for illustrative purposes only and may differ from the actual report
- ACT Genomics only provides a technical report and not a professional interpretation report.
- Be sure to consult and seek the advice of a specialist physician to determine the appropriate clinical solution for you.

ACT Risk™ Specifications

Sample Type
4-8 ml of whole blood

Turnaround Time
12 working days
* starting from the date of receipt of qualified samples at our CAP-accredited laboratory



Number of Genes Tested
67 hereditary cancer-related genes

Types of Mutant Genes Analyzed
-Single nucleotide variants (SNVs)
-Small insertions and deletions (small InDels)
-Specific exon-intron splicing site mutation of selected genes
-Large Genomic Rearrangements (LGR)of 18 genes, including *BRCA1/2* and MMR genes.

Databases Used
-International databases such as GnomAD, 1000 Genome, ClinVar and COSMIC
-Taiwan Biobank
-ACT Genomics' in-house ethnographic database supported by published evidence

Who should consider the test?

Multiple family members who have cancer

A family member who has multiple cancers, an early-onset cancer, or a rare cancer

Anyone who is concerned about carrying a hereditary cancer gene

Hallmarks of ACT Risk™

Information on 67 types of Hereditary Cancer Genes
The test requires only a single blood draw and provides a comprehensive analysis of 9 major hereditary cancers and 11 genes associated with cancer syndromes, using whole exome sequencing (WES).

Comprehensive Information from International Databases
International databases including GnomAD, 1000 Genomes, ClinVar, and COSMIC, as well as Taiwan Biobank and ACT Genomics' proprietary Asian population genetic database.

High Sensitivity
NGS offers high sensitivity, enabling accurate detection of inherited genetic mutations relevant to hereditary cancer risk.

Detailed Cancer Risk & Clinical Management Report
Provides cancer risk information based on the latest international clinical research literature and National Comprehensive Cancer Network (NCCN) guidelines for corresponding clinical management, offering comprehensive and easily understandable insights.

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

ACT Risk™

ACT GENOMICS®

ACT Genomics Co.,Ltd.
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