PromicsEdge
By SelfDecode

ACMG SF v3.3 Clinical Predisposition Report

Report date: 23 February 2026

Client Information

Name:	ACMG BRCA
Age:	38
Sex:	Female
Height:	5ft 8" / 172cm
Weight:	143lb / 65kg

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About This Report

ACMG SF v3.3 Secondary Findings

This report analyzes your Whole Genome Sequencing (WGS) data using the **ACMG Secondary Findings (SF) list, version 3.2**. The ACMG SF list is developed by the **American College of Medical Genetics and Genomics**, and is internationally recognized as one of the most authoritative frameworks for returning medically actionable genetic information.

The ACMG recommends a curated list of gene–condition pairs that should be evaluated when sequencing is performed, even if not directly related to the reason for testing. These findings are known as **secondary findings** — genetic variants that may increase the likelihood of developing certain medical conditions, independent of your current symptoms or clinical indication.

The v3.3 list includes genes linked to:

✔ hereditary cancer syndromes
✔ cardiovascular conditions (including sudden cardiac death risk)
✔ metabolic conditions
✔ other clinically actionable genetic disorders

As described in the publication, this list is **maintained, evaluated, and updated regularly** by a working group of experts in medical genetics, genomics, cardiology, oncology, and bioinformatics . The purpose of the list is to identify genetic findings where **early detection, surveillance, or treatment may prevent or significantly reduce morbidity and mortality.**

What This Report Shows You

Your genome was analyzed specifically for **pathogenic or likely pathogenic variants** in the genes included in the ACMG SF v3.3 list. Variants classified as pathogenic or likely pathogenic according to ACMG criteria are returned. **Variants of Uncertain Significance (VUS) are not included**, per ACMG recommendations.

How to Interpret Your Results

Summary Table

You will first see a summary of all ACMG v3.3 conditions. For each condition, you can see:

Detected
You carry variants known to increase risk for the condition

Not Detected
No actionable variants were found in this gene

Inheritance Model
Explains how the condition is inherited genetically

Detailed Variant Pages (Only if a Risk Variants Are Found)

If a harmful variants are identified, you will receive a detailed explanation including:

ACMG clinical summary for the condition: Background, medical implications, intervention relevance	**Your specific variant(s):** SNP ID(s), genotype, pathogenicity classification	**Population frequency:** How common the variant is in large populations	**Risk interpretation:** Clarifies how likely the variant is to cause disease	**Inheritance explanation:** Whether 1 or 2 variants cause the condition

Interpretation:

AD (Autosomal dominant)	**Only 1 copy** of the mutated gene from one parent **is needed to cause the condition**.
SD (Semidominant)	**Only 1 copy** of the mutated gene from one parent **is needed to cause the condition**. **Those with 2 pathogenic mutations** (homozygotes or compound heterozygotes) **are more adversely affected** than those with one pathogenic mutation (heterozygotes).
AR (Autosomal recessive)	**2 copies**, one from each parent, **are needed to cause the condition**.
XL (X-Linked)	Males are affected. Females range from asymptomatic to affected, usually with a milder form of a condition

Inheritance pattern depends on the specific variant/mutation. Different variants can have a different inheritance pattern even in the same gene and for the same condition.

Mutations can differ in penetrance. A mutation can have **complete penetrance**. This means that everyone with the variant will develop the condition by a certain age. Mutations with **incomplete penetrance** cause the condition in some but not all people. This means that a certain percentage of people is expected to develop the condition in their lifetime.

Some conditions have **variable expressivity**. This means there is a broad spectrum of severity, even within the same family, with some individuals experiencing more severe issues early in life while others may have milder, later-onset symptoms.

Summary Overview

Detected Variants

Condition	Gene(s)	Inheritance	Status
Hereditary Breast and Ovarian Cancer	**BRCA1**	**AD**	⚠ **Detected**

Cancer

Condition	Gene(s)	Inheritance	Status
Familial Adenomatous Polyposis (FAP)	APC	AD	Not detected
Multiple Endocrine Neoplasia Type 2	RET	AD	Not detected
Hereditary Breast and Ovarian Cancer	**BRCA1**	**AD**	⚠ **Detected**
	BRCA2	AD	Not detected
	PALB2		
Hereditary Pheochromocytoma/Paraganglioma Syndrome	SDHA	AD	Not detected
	SDHB		
	SDHC		
	SDHD		
	SDHAF2		
	MAX		
	TMEM127		
Juvenile Polyposis Syndrome (JPS)	BMPR1A	AD	Not detected
	SMAD4		
Li-Fraumeni Syndrome (LFS)	TP53	AD	Not detected

Condition	Gene(s)	Inheritance	Status
Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)	MLH1	AD	Not detected
	MSH2		
	MSH6		
	PMS2		
	EPCAM		
Multiple Endocrine Neoplasia Type 1	MEN1	AD	Not detected
MUTYH-Associated Polyposis	MUTYH	AR	Not detected
NF2-related schwannomatosis	NF2	AD	Not detected
Peutz-Jeghers syndrome (PJS)	STK11	AD	Not detected
PTEN Hamartoma Tumor Syndromes	PTEN	AD	Not detected
Retinoblastoma	RB1	AD	Not detected
Tuberous sclerosis complex	TSC1	AD	Not detected
	TSC2		
Von Hippel-Lindau syndrome	VHL	AD	Not detected
WT1-related Wilms' tumor	WT1	AD	Not detected

Cardiovascular

Condition	Gene(s)	Inheritance	Status
Marfan Syndrome	FBN1	AD	Not detected
Loeys-Dietz Syndrome	TGFBR1	AD	Not detected
	TGFBR2		
	SMAD3		
Thoracic Aortic Disease	ACTA2	AD	Not detected
	MYH11		

Condition	Gene(s)	Inheritance	Status
Arrhythmogenic Right Ventricular Cardiomyopathy	PKP2	AD	Not detected
	DSP		
	DSC2		
	DSG2		
	TMEM43		
Catecholaminergic Polymorphic Ventricular Tachycardia	RYR2	AD	Not detected
	CASQ2	AR	Not detected
	TRDN		
Dilated Cardiomyopathy	TNNT2	AD	Not detected
	LMNA		
	FLNC		
	TTN		
	BAG3		
	DES		
	RBM20		
	TNNC1		
	PLN		
Hypertrophic Cardiomyopathy	MYH7	AD	Not detected
	MYBPC3		
	TNNI3		
	TPM1		
	MYL3		
	ACTC1		
	PRKAG2		
	MYL2		
Ehlers-Danlos Syndrome, Vascular Type	COL3A1	AD	Not detected

Condition	Gene(s)	Inheritance	Status
Familial Hypercholesterolemia	APOB	AD	Not detected
	PCSK9		
	LDLR	SD	Not detected
Long QT Syndrome Type 1	KCNQ1	AD	Not detected
Long QT Syndrome Type 2	KCNH2	AD	Not detected
Long QT Syndrome 3; Brugada Syndrome	SCN5A	AD	Not detected
Calmodulinopathy	CALM1	AD	Not detected
	CALM2		
	CALM3		

Metabolic

Condition	Gene(s)	Inheritance	Status
Biotinidase Deficiency	BTD	AR	Not detected
Fabry Disease	GLA	XL	Not detected
Ornithine Transcarbamylase Deficiency	OTC	XL	Not detected
Pompe Disease	GAA	AR	Not detected
Cerebrotendinous Xanthomatosis	CYP27A1	AR	Not detected
X-linked Adrenoleukodystrophy	ABCD1	XL	Not detected

Other

Condition	Gene(s)	Inheritance	Status
Hereditary Hemorrhagic Telangiectasia	ACVRL1	AD	Not detected
	ENG		
	SMAD4		
Hereditary Hemochromatosis	HFE	AR	Not detected

Condition	Gene(s)	Inheritance	Status
Malignant Hyperthermia	RYR1	AD	Not detected
	CACNA1S		
Maturity-Onset of Diabetes of the Young	HNF1A	AD	Not detected
RPE65-related retinopathy	RPE65	AR	Not detected
Wilson disease	ATP7B	AR	Not detected
Hereditary TTR (transthyretin) amyloidosis	TTR	AD	Not detected

Condition Details

Hereditary Breast and Ovarian Cancer

Category: Cancer | Genes: BRCA1, BRCA2, PALB2 (AD)

Hereditary Breast and Ovarian Cancer (HBOC) is a syndrome caused by pathogenic mutations in the ***BRCA1, BRCA2* and *PLAB2*** genes. Mutations in these genes **increase the risk of breast and ovarian cancer** in women, and increased risk of **breast and prostate cancer** in men.
About 45% to 65% of women with BRCA1 or BRCA2 mutations **will develop breast cancer during their lifetime**, and **11% to 40% will develop ovarian cancer**. Lifetime **risk of breast cancer for female *PALB2* carriers** is approximately **53%**.

An estimated 1 in 333 - 500 individuals in the general population have a disease-causing *BRCA1* or *BRCA2* mutation. That figure rises to about 1 in 40 in people of Ashkenazi Jewish ancestry.

Gene	SNP	Genotype	Inheritance	Chromosome	Position	Classification
BRCA1	17-43045709-A-G	0/1	AD	17	43045709	Likely Pathogenic
BRCA1	17-43045761-A-C	0/1	AD	17	43045761	Pathogenic

Screening & Surveillance

- **Breast Cancer:** *Imaging:* Annual breast MRI screenings are recommended starting at age 25 for *BRCA1/2* mutation carriers and age 30 for *PALB2* mutation carriers. Mammograms may be introduced at age 30, considering potential radiation sensitivity in BRCA mutation carriers. Breast imaging may begin 5 to 10 years before the youngest diagnosis of breast cancer in the family, but no later than age 30.
- **Ovarian Cancer:** *Transvaginal Ultrasound and CA-125 Testing:* Semi-annual screenings, including pelvic ultrasounds and blood tests for CA-125 levels, are often recommended, though their efficacy in early detection is limited.
- For men with *BRCA1/2* and *PALB2* pathogenic variants, clinical and self-breast examination is encouraged. Mammography is suggested at age 50 or 10 years prior to the earliest known breast cancer in the family. Prostate cancer screening is suggested starting at age 40 for those with *BRCA2* pathogenic or likely pathologic variants.
- Screening for pancreatic cancer: For those with a family history of pancreatic cancer in a first- or second-degree relative on the same side of the family as the pathogenic variant in *PALB2* or *BRCA1/2,* screening should begin 10 years before the earliest age of onset of pancreatic cancer in the family or at age 50, whichever comes first. Screening is performed with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS). Screening should be done at least annually.
- Annual full-body skin exams for melanoma is recommended.

Lifestyle Modifications

- **Diet and Exercise:** Engaging in regular physical activity and maintaining a balanced diet rich in fruits, vegetables, and whole grains can support general health. Regular exercise may modestly reduce breast cancer risk.
- **Maintain a healthy weight**: Weight gain can increase breast cancer risk.
- **Smoking Cessation:** Avoiding tobacco use is crucial, as smoking can increase the risk of various cancers.
- **Minimize UV exposure: Limit UV exposure to decrease the risk of melanoma.**
- **Limit alcohol consumption:** Moderate alcohol consumption has been linked to increased breast cancer risk.
- **Breastfeeding:** Breastfeeding, when possible, is encouraged – it may lower breast cancer risk in general, and for BRCA1 carriers specifically.

Medical Therapy

- **Chemoprevention:** *Tamoxifen:* This selective estrogen receptor modulator has been shown to reduce breast cancer risk in *BRCA1/2* mutation carriers and is considered for risk reduction. However, there is no data about efficacy of hormonal chemoprevention (tamoxifen or aromatase inhibitor) in *PALB2* carriers; moreover, studies have found that there is an increased risk of triple-negative breast cancer in *PALB2* carriers. Therefore, the benefits of this approach are unknown in *PALB2* carriers.
- **Targeted Therapy:** *PARP Inhibitors:* Medications like olaparib have been approved for treating certain BRCA-mutated breast and ovarian cancers, offering targeted therapeutic options. For example, **PARP inhibitors** (olaparib, talazoparib) significantly improve outcomes in metastatic BRCA-related breast and pancreatic cancers and are used as adjuvant therapy in some early breast cancers.

Surgery

- **Prophylactic Mastectomy:** Surgical removal of breast tissue can significantly reduce the risk of developing breast cancer in high-risk individuals.
- **Salpingo-Oophorectomy:** Removing the ovaries and fallopian tubes between age 35 and 40 for *BRCA1* and 40 and 45 for *BRCA2* carriers is strongly recommended, as it substantially lowers the risk of ovarian and fallopian tube cancers. An early age at diagnosis of ovarian cancer in the family may prompt consideration of such surgery at a younger age. For *PALB2* carriers, discuss risk-reducing bilateral salpingo-oophorectomy by age 45 to 50.

Family Planning & Genetic Counseling

- All individuals with BRCA1, BRCA2, or PALB2 mutations should receive genetic counseling regarding transmission risks. Each child of a carrier has a 50% chance to inherit the mutation.
- Preconception counseling is strongly advised. Options include PGD with IVF to select embryos without the mutation, as well as prenatal testing via CVS or amniocentesis.
- It is important to initiate these conversations early, as fertility planning may be altered by the recommended timing of prophylactic surgeries (e.g. BRCA1 women are urged to have children by ~35 and then remove ovaries). Women who undergo RRSO in their 30s should be offered fertility preservation (egg or embryo freezing) beforehand.

References

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4. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet