BRCA1/BRCA2: CanVIG-UK Gene-Specific Guidance

Date: 05/02/2026 Version: 1.31

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For use in conjunction with CanVIG-UK Consensus Specification for Cancer susceptibility Genes of ACGS Best Practice Guidelines for Variant Classification. Evidence lines for which there are no gene-specific recommendations should be reviewed in context of CanVIG-UK Consensus Specification for Cancer Susceptibility Genes.

Evidence towards Pathogenicity

Evidence element and evidence strengths allowed		Thresholds/data-sources/applications specifically relevant to BRCA1/BRCA2
PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls	_VSTR _STR _MOD _SUP	NDRS case control data can be used for case-control analysis: • Controls should represent appropriate ethnicity and sex matching (i.e. female individuals from UK Biobank should be used if the case series consists predominantly of females, as with the current NDRS case series) • For unenriched cases, an OR threshold of >4 should be used based on the ENIGMA threshold for high-penetrance genes. However, as this is an enriched series, a dataset-specific enrichment factor should be used to calculate the odds ratio (OR) threshold where available. Otherwise, an OR threshold of >8 should be used • If there are ≤6 case observations, recommend to cap application of PS4 at Strong • Current data/denominator counts for base substitutions are available at CanVar-UK • For non-base-substitutions i.e. deletions/duplications/insertions, NDRS counts can be accessed from CanVIG-UK If there are insufficient data to perform case-control analyses, PS4 can be applied: • at PS4_sup if there are observations of the variant in ≥5 different families **and** the variant is seen in ≤ 1/50,000 individuals in UKBiobank

		• at PS4_mod if there are observations of the variant in ≥10 different families **and** the variant is absent from UKBiobank. • Families used must have a strong pattern of diagnoses consistent with a hereditary breast and ovarian cancer syndrome. Due to possible presence of unaffected individuals in the dataset with unknown family history, this does not include families from CIMBA[20].
PM2: Absent from controls (or at extremely low frequency if recessive) in ESP, 1000GP, or ExAC	_MOD _SUP	Female controls of any/all ethnicities from gnomAD v4.1 (or the non-UKBiobank partition of gnomAD v4.1 if using UKBiobank for PS4) should be used (due to low penetrance in male pathogenic variant carriers). If the variant is absent from non-UKBiobank female controls but is present in UKBiobank female controls, then PM2 may be applied at a maximum of supporting. Otherwise, the main CanVIG-UK consensus guidance should be followed.
PVS1: **Predicted null variant** (in a gene where LOF is a known mechanism of disease)	_VSTR _STR _MOD _SUP	Please refer to the ENIGMA *BRCA1* and *BRCA2* VCEP look-up table (Specifications Table 4: "Summary of codes applicable for variants considered against the *BRCA1* and *BRCA2* PVS1 decision trees") for the latest advice on application of PVS1 and PM5_PTC for variants across *BRCA1* and *BRCA2*.
PS1: Same amino acid change as an established variant	_STR	Within forthcoming ACMG guidance, it is anticipated that these elements will all be incorporated within PP3 and only awarded to variants within key domains. **In the interim, we recommend:** • Use of PM1_sup and/or PM4_sup for any variant within: ○ BRCA1 ▪ RING (αα 2-101) ▪ COILED-COIL DOMAIN (αα 1391-1424) ▪ BRCT (αα 1650-1857) ○ BRCA2 ▪ PALB2 binding domain (aa 10-40) ▪ DNA-binding domain (αα 2481-3186) • Use of PM1_mod or PM4_mod for a variant at specific residues[1]: ○ BRCA1 ▪ RING: 18, 22, 37, 39, 41, 44, 47, 61, 64, 71 ▪ BRCT: 1685, 1688, 1697, 1699, 1706, 1708, 1715, 1736, 1738, 1739, 1748, 1764, 1766, 1770, 1775, 1786, 1837, 1838, 1839, 1853 ○ BRCA2 ▪ DBD: 2607, 2626, 2627, 2663, 2722, 2723, 2748, 3052, 3124 • PM1 cannot be used where functional data are being used for PS3, as per main CanVIG-UK guidance • PP2 should not be used for BRCA1/BRCA2 • Use PM5_PTC as per the ENIGMA BRCA1 and BRCA2 VCEP guidelines • Use PM5, PS1, PP3 otherwise as per CanVIG-UK Consensus Specification
PM4: Protein-length-changing variant	_MOD _SUP	
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	_SUP	
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	_MOD _SUP	
PM1, PP2: Enrichment/constraint: **PP2**: Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease **PM1:** Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation	_STR _MOD _SUP	
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	_VSTR _STR _MOD _SUP	**<u>BRCA1</u>** **Strong:** Findlay et al, 2018[2]; Bouwman et al, 2020[3]; Starita et al, 2018[4] **Supporting:** Fernandes et al, 2019[5]; Petitalot et al, 2019[6] **<u>BRCA2:</u>** **Strong:** *Guidugli et al, 2018[7]; *Hart et al, 2019[8]; *Richardson et al, 2021[9]; Ikegami et al, 2020[10]; *Hu et al, 2022[11]; *Hu et al, 2024[12], Biswas et al, 2020[13]

		Moderate: Mesman et al, 2019[14] *Please note that results from these studies utilise the same assay, and as such results should not be used in combination to attain higher evidence scores for PS3 or BS3. Additional Notes: See the full list of CanVIG-UK reviewed functional assays and scores on the CanVIG-UK website. See the table at the bottom of this document for guidance on combining assay results.
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	_VSTR _STR _MOD _SUP	Segregation evidence from multifactorial analysis data is incorporated within the combined scores described in the PP4/BP5 recommendations. Meiosis counting approaches may be used in addition if this evidence comes from families not already included in the multifactorial analyses. **Evidence cannot exceed 'Very strong'**
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history	_STR _MOD _SUP	
PM3: in trans with a pathogenic variant	_STR _MOD _SUP	Frequency data regarding co-occurrence in trans is incorporated within the combined scores described in the PP4/BP5 recommendations. ***In addition***, the SVI recommendations for in trans Criterion (PM3) can be used for either BRCA1 or BRCA2 for individuals with a Fanconi anaemia phenotype if this evidence comes from families not already included in the multifactorial analyses used for PP4. Evidence towards a Fanconi phenotype comprise: • **Clinical:** diagnosis of childhood cancer or skeletal/structural/developmental abnormalities • **Molecular/Cellular:** aberration on mitomycin-induced chromosomal breakage +/- depletion of BRCA2 in lymphocytes Both clinical and molecular/cellular aberrations must be present for a case to contribute to evidence **Evidence cannot exceed 'Strong'** ***Note:*** Caution is required in inferring the pathogenicity for the monoallelic phenotype, as variants may be hypomorphic (e.g. a variant contributing and causing a Fanconi anaemia phenotype may be low penetrance for breast cancer). Where the majority of evidence for variant pathogenicity comes from observations of the variant in cases of Fanconi Anaemia, it may be appropriate to comment on this in the clinical report.
PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)	_VSTR _STR _MOD _SUP	Published multifactorial analysis data providing likelihood ratios (LR) or log likelihood ratios (LLR) encompassing multiple evidence types can be applied under PP4/BP5. The **combined score** should be used, representing the totality of evidence. Suitable analyses: • Easton et al, 2007[15] • Vallée et al, 2012[16] • Parsons et al, 2020[17] • Caputo et al, 2021[18] • Li et al, 2020[19] Evidence is presented as either a Likelihood Ratio (LR) or Log Likelihood Ratio (LLR).

If evidence is supplied as an LR: Use the table below to directly convert the LR to the applicable Evidence Strength.

If evidence is supplied as an LLR: First, convert the LLR to a Likelihood Ratio (LR) by finding the exponent of the LLR; conversion of an LLR to an LR can be done using the =EXP(LLR) function within Excel if a natural log has been used or the =10^LLR function in Excel if log to base 10 has been used. Once the LR is calculated, use the table below to directly convert the LR to the applicable Evidence Strength (LR of 7.38 = MOD).

Conversions from LR or LLR to Evidence (Exponent) points is also available for applicable variants at https://canvaruk.org/, where 'ACMG LLR' is equivalent to Evidence (Exponent) points.

Likelihood Ratio	Evidence (Exponent) Points	Evidence Strength towards pathogenicity
2.08 – 4.30	1	SUP
4.31 – 18.70	2	MOD
18.71 – 350.40	4	STR
≥ 350.41	8	VSTR

Explanatory Notes:

- Where multiple potentially valid combined LR/LLRs are available for a variant, evidence (exponent) points may be summed across the following studies, which have been confirmed to be independent: Parsons et al, 2020[17], Caputo et al, 2021[18], Li et al, 2020[19]. Otherwise, the value from the publication with the largest cohort of families should be used.
- Evidence (Exponent) Points are calculated by applying the logarithm of the LR to base 2.08. A calculated Evidence Point that is between two categories (eg 3 points) is assigned the weaker strength of the two categories it lies between (eg MOD for 3 points)

Evidence towards Benignity

BA1/BS1: Allele frequency is "too high" in ExAC or gnomAD for disorder	_SA _STR	**BA1: MTAF = 0.001 (0.1%)** **BS1: MTAF = 0.0001 (0.01%)** The MTAF (maximum tolerated allele frequency) has been calculated using cardiodb using the calculate AF function: prevalence 0.125; genetic heterogeneity 0.01; allelic heterogeneity 1 (BA1) 0.1 (BS1); penetrance 0.72 (BRCA1), 0.69 (BRCA2). See training resources from Miranda Durkie for further details. Female controls should be used when determining the maximum allele count / filtering allele frequency. See consensus guidelines for further details on Grpmax Filtering AF, and the use of cardiodb for calculating the maximum allele count / filtering allele frequency.
BS2: Observation in controls inconsistent with disease penetrance. Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with	_STR _SUP	

full penetrance expected at an early age		
BP4: In silico: Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)	_SUP	
BP1: Missense variant in a gene for which primarily truncating variants are known to cause disease	_STR	Per VCEP specifications: Can be used at Strong for missense, silent, and in-frame variants with no predicted splicing effect (SpliceAI ≤ 0.1) at residues outside of (potentially) clinically important functional domains: ○ BRCA1 ▪ RING (aa 2-101) ▪ COILED-COIL DOMAIN (aa 1391-1424) ▪ BRCT (aa 1650-1857) ○ BRCA2 ▪ PALB2 binding domain (aa 10-40) ▪ DNA-binding domain (aa 2481-3186)
BP7: Synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence	_SUP	
BP3: In-frame deletions/insertions in a repetitive region	_SUP	
BS3: Well-established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing	_STR _MOD _SUP	*see PS3
BS4: Non segregation with disease	_STR _SUP	*see PP1
BP2: Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis	_STR _SUP	*see PM3
BP5: Alternate molecular basis for disease	_VSTR _STR _MOD _SUP	*see PP4 for explanation

Likelihood Ratio	Evidence (Exponent) Points	Evidence Strength towards benignity
0.48 – 0.23	-1	SUP
0.22 – 0.05	-2	MOD
0.049 – 0.00285	-4	STR
<0.00284	-8	VSTR

Recommendations for the management of conflicting functional assay results See table below for management of discrepancy for BRCA1 variants between Findlay et al, 2018[2] and Bouwman et al, 2020[3] discordant assay results. For more general guidance regarding conflicting results from other functional assays, refer to the table in the main CanVIG-UK consensus specification.

Findlay Class	Findlay Score	Bouwman Platinum	Bouwman Olaparib	Bouwman DR-GFP	PS3_STR	BS3_STR
LOF	<-1.328	All deleterious/ likely deleterious (1 intermediate allowed)			✓	×

LOF	<-1.328	Any are neutral/likely neutral	×	×
INT (towards LOF)	-1.328 to -1.038	All deleterious/ likely deleterious	✓	×
INT (towards FUNC)	-1.038 to -0.748	All neutral/likely neutral	×	✓
INT	-1.328 to -0.78	Conflicting results or any intermediate	×	×
FUNC	>-0.748	All neutral/likely neutral (1 intermediate allowed)	×	✓
FUNC	>-0.748	Any are deleterious/likely deleterious	×	×

N.B: Bouwman et al, 2020 "not clear" refers to opposite categorisation ± the standard deviation of repeat experiments and should be treated as conflicting assay results. Where a variant is LOF on the Findlay et al assay and has an RNA score of <-2, this indicates that LOF is due to interference with splicing and therefore should not be treated as conflicting evidence if the variant is neutral on the Bouwman et al assay.

Version History/Amendments

Revised version	Date	Section	Update	Amended by	Approved by
1.12	***01/09/2021***	PP4	Guidance on use of LLRs from published epidemiological studies amended to account for the use of natural logs in the statistics presented	Garrett	Turnbull
1.12	***01/09/2021***	PM1	Addition of critical residues in the DNA binding domain of BRCA2. Critical residues in all listed functional domains updated to mirror draft 2021 ENIGMA guidance	Garrett	Turnbull
1.12	***01/09/2021***	BP1	Resolution of typo in BRCT region specification	Garrett	Turnbull
1.13	***15/10/2021***	PVS1	Clarification that PVS1 may not be applicable for some of the variants at ENGIMA specified positions	Garrett	Turnbull
1.14	***02/12/2021***	PS4	Terminology change to reflect transition of PHE to NHSD	Garrett	Turnbull
1.14	***02/12/2021***	PVS1	Addition of recommendations for variants within the first 100bp	Callaway	CStAG
1.15	***28/04/2022***	PM1/ PM4	Clarification that PM1_sup and PM4_sup may be used in combination but PM4 not to be used at moderate. Removal of mention that CanVIG-UK provide non-white ethnicity counts under PS4	Garrett	CStAG
1.16	***28/07/2022***	PP5	Removal of Lindor *et al* 2011 paper from recommended genetic epidemiology papers to use in calculating Evidence (Exponent) Points.	Allen	Turnbull
1.17	***27/09/2022***	PS4	Addition of PS4_mod application where ≥10 HBOC families observed.	Garrett	CStAG
1.18	***31/03/2023***	PP5/ BP6	Rewording of application details for clarity. Removal of reputable source evidence from PP5 per consensus specification. Addition of recommended analyses papers.	Allen	CStAG
1.18	***31/03/2023***	PVS1/ PM1/ PS3	Incorporation of functional assays, hotspot, and splice sites from upcoming ENIGMA recommendations.	Allen	CStAG
1.19	***26/05/2023***	PS4/PM2/ BA1/BS1	Update of databases to be used in-line with consensus specification.	Garrett	CStAG

1.19	***27/05/2023***	PS4	Update on case-counting approach where variant seen in multiple cases but also observed in control datasets.	Garrett	CStAG
1.19	***15/09/2023***	BA1/BS1	Clarification of MTAF usage and use of the filtering allele frequency.	Callaway	CStAG
1.19	***28/09/2023***	PP4/BP5	Moved multifactorial evidence from PP5/BP6 to PP4/BP5 in alignment with ENIGMA. PP5/BP6 evidence code removed.	CStAG	CStAG
1.19	***29/09/2023***	PM4	Added application at 'Moderate' for in-frame in/dels at specific residues.	Allen	CStAG
1.19	***29/09/2023***	PP1/PM3/ PP4/BP5	Recommendation to use the combined multifactorial score under PP4/BP5, rather than individual subcomponent scores	Garrett	CStAG
1.19	***29/09/2023***	PS4	Change of OR threshold from >10 to >8 for enriched case series where dataset-specific enrichment factors are not available (eg variant count releases from NHSD/NDRS)	CStAG	CStAG
1.19	***29/09/2023***	PVS1	Update of NMD boundary as per ENIGMA VCEP BRCA1 and BRCA2 guidelines	CStAG	CStAG
1.20	***24/01/2024***	PS3/BS3	Added Ikegami et al 2020 and Hu et al 2022 papers to functional study review list (PS3/BS3)	Allen	CStAG
1.20	***24/01/2024***	PVS1	Update to refer use of PVS1 to ENIGMA VCEP	Allen	CStAG
1.20	***30/04/2024***	PM2	Replaced ref to cancer-free gnomAD v2.1.1 and UKBiobank with gnomAD v4.1, clarified application of PM2 strength where data is in UKBiobank but absent from other gnomAD datasets.	Allen	CStAG
1.20	***30/04/2024***	PS3/BS3	Added statement to highlight assay result overlap for Couch lab assays	Allen	CStAG
1.20	***30/04/2024***	PS3/BS3	Updated functional assays scoring link	Allen	CStAG
1.20	***07/05/2024***	PM3	Typing error amendment – 'PP5' to 'PP4'	Allen	CStAG
1.21	***25/07/2024***	PVS1	Removed splice tables to refer only to the ENIGMA VCEP guidelines	Allen	CStAG
1.22	***28/01/2025***	PP4/BP5	Added Li *et al*., 2020 as reference for suitable studies	Allen	Turnbull
1.30	***12/08/2025***	PP4	Updated guidance around combining data when data are available from multiple studies	CStAG	CStAG
1.30	***12/08/2025***	PS4	Added caution for applying PS4 using the NDRS dataset when there are ≤6 case observations	CStAG	CStAG
1.31	***05/02/2026***	PS4	Added clarification on use of CIMBA data for case-counting	Allen	CStAG
1.31	***05/02/2026***	BP1	Updated guidelines to match ENIGMA BRCA1/BRCA2 VCEP specifications for BP1 (application at strong allowed, and allowed for in-frame variants outside a potentially clinically important functional domain)	Durkie/ Burghel/ Allen	CStAG
1.31	***05/02/2026***	PM1/PM4 /BP1	Re-formatted key domain/residues for clarity	CStAG	CStAG

References

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