

BRCA1/BRCA2: CanVIG-UK Gene-Specific Guidance



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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
<p>PS4: Case-control: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls</p>	<p>NHSD case control data can be used for case-control analysis:</p> <ul style="list-style-type: none"> • Controls should represent appropriate ethnicity and sex matching (i.e. female individuals from UKBiobank should be used if the case series consists predominantly of females, as with the current NHSD 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 • Current data/denominator counts for base substitutions are available at CanVar-UK • For non-base-substitutions i.e. deletions/duplications/insertions, NHSD counts can be accessed from CanVIG-UK <p>If there are insufficient data to perform case-control analyses, PS4 can be applied:</p> <ul style="list-style-type: none"> • 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 pattern of diagnoses consistent with a hereditary breast and ovarian cancer syndrome.
<p>PM2: Absent from controls (or at extremely</p>	<p>Female controls of any/all ethnicities from gnomAD v4.1 (or the non-UKBiobank partition of gnomAD v4.1 if using UKBiobank for</p>

low frequency if recessive) in ESP, 1000GP, or ExAC		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)	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: red; color: white; padding: 2px;">_VSTR</div> <div style="background-color: red; color: white; padding: 2px;">_STR</div> <div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div> </div>	<p>Please refer to the ENIGMA <i>BRCA1</i> and <i>BRCA2</i> VCEP look-up table (Specifications Table 4) for the latest advice on application of PVS1 and PM5_PTC for variants across <i>BRCA1</i> and <i>BRCA2</i>.</p> <p>For reference, ENIGMA has compiled the below list of splice variants for which the variant transcript may be functional and for which PVS1 is applied at reduced strength or is not applicable.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Gene</th> <th>Region</th> <th>Position</th> <th>Strength</th> </tr> </thead> <tbody> <tr><td rowspan="24">BRCA1</td><td rowspan="4">intron 1</td><td>c.-20+1</td><td>N/A</td></tr> <tr><td>c.-20+2</td><td>N/A</td></tr> <tr><td>c.-19-1</td><td>N/A</td></tr> <tr><td>c.-19-2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 5</td><td>c.301+1</td><td>Sup</td></tr> <tr><td>c.301+2</td><td>Sup</td></tr> <tr><td rowspan="2">intron 6</td><td>c.442-1</td><td>Sup</td></tr> <tr><td>c.442-2</td><td>Sup</td></tr> <tr><td rowspan="2">intron 7</td><td>c.548-1</td><td>N/A</td></tr> <tr><td>c.548-2</td><td>N/A</td></tr> <tr><td rowspan="4">intron 8</td><td>c.593+1</td><td>N/A</td></tr> <tr><td>c.593+2</td><td>N/A</td></tr> <tr><td>c.594-1</td><td>N/A</td></tr> <tr><td>c.594-2</td><td>N/A</td></tr> <tr><td rowspan="4">intron 9</td><td>c.670+1</td><td>N/A</td></tr> <tr><td>c.670+2</td><td>N/A</td></tr> <tr><td>c.671-1</td><td>Mod</td></tr> <tr><td>c.671-2</td><td>Mod</td></tr> <tr><td rowspan="3">intron 10</td><td>c.4096+1</td><td>Mod</td></tr> <tr><td>c.4096+2</td><td>Mod</td></tr> <tr><td>c.4097-1G>C, G>T</td><td>Sup</td></tr> <tr><td rowspan="3">intron 11</td><td>c.4186-1</td><td>Sup</td></tr> <tr><td>c.4186-2A>C, A>T</td><td>Sup</td></tr> <tr><td>c.4358-1</td><td>Sup</td></tr> <tr><td rowspan="2">intron 12</td><td>c.4358-2A>C, A>T</td><td>Sup</td></tr> <tr><td>c.5193+2T>C</td><td>N/A</td></tr> <tr><td rowspan="24">BRCA2</td><td rowspan="2">intron 1</td><td>c.-40+1</td><td>N/A</td></tr> <tr><td>c.-40+2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 2</td><td>c.68-1</td><td>Sup</td></tr> <tr><td>c.68-2</td><td>Sup</td></tr> <tr><td rowspan="2">intron 3</td><td>c.317-1</td><td>N/A</td></tr> <tr><td>c.317-2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 4</td><td>c.425+1</td><td>N/A</td></tr> <tr><td>c.425+2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 6</td><td>c.517-1G>C, G>T</td><td>N/A</td></tr> <tr><td>c.517-2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 7</td><td>c.631+1</td><td>N/A</td></tr> <tr><td>c.631+2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 9</td><td>c.794-1G>C, G>T</td><td>N/A</td></tr> <tr><td>c.794-2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 10</td><td>c.1909+1</td><td>N/A</td></tr> <tr><td>c.1909+2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 11</td><td>c.6842-1</td><td>N/A</td></tr> <tr><td>c.6842-2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 12</td><td>c.6937+1</td><td>N/A</td></tr> <tr><td>c.6937+2</td><td>N/A</td></tr> <tr><td rowspan="2">intron 17</td><td>c.7976+2C>T</td><td>N/A</td></tr> <tr><td>c.8488-1</td><td>Sup</td></tr> <tr><td rowspan="2">intron 19</td><td>c.8488-2</td><td>Sup</td></tr> <tr><td>c.8953+2T>C</td><td>N/A</td></tr> <tr><td rowspan="2">intron 23</td><td>c.9118-1G>A</td><td>Sup</td></tr> <tr><td>c.9257-1G>C, G>T</td><td>Sup</td></tr> <tr><td rowspan="2">intron 24</td><td>c.9257-2</td><td>Sup</td></tr> </tbody> </table> <p>Adapted from ENIGMA, 2017¹ and ENIGMA VCEP Guidelines v1.1.0</p>	Gene	Region	Position	Strength	BRCA1	intron 1	c.-20+1	N/A	c.-20+2	N/A	c.-19-1	N/A	c.-19-2	N/A	intron 5	c.301+1	Sup	c.301+2	Sup	intron 6	c.442-1	Sup	c.442-2	Sup	intron 7	c.548-1	N/A	c.548-2	N/A	intron 8	c.593+1	N/A	c.593+2	N/A	c.594-1	N/A	c.594-2	N/A	intron 9	c.670+1	N/A	c.670+2	N/A	c.671-1	Mod	c.671-2	Mod	intron 10	c.4096+1	Mod	c.4096+2	Mod	c.4097-1G>C, G>T	Sup	intron 11	c.4186-1	Sup	c.4186-2A>C, A>T	Sup	c.4358-1	Sup	intron 12	c.4358-2A>C, A>T	Sup	c.5193+2T>C	N/A	BRCA2	intron 1	c.-40+1	N/A	c.-40+2	N/A	intron 2	c.68-1	Sup	c.68-2	Sup	intron 3	c.317-1	N/A	c.317-2	N/A	intron 4	c.425+1	N/A	c.425+2	N/A	intron 6	c.517-1G>C, G>T	N/A	c.517-2	N/A	intron 7	c.631+1	N/A	c.631+2	N/A	intron 9	c.794-1G>C, G>T	N/A	c.794-2	N/A	intron 10	c.1909+1	N/A	c.1909+2	N/A	intron 11	c.6842-1	N/A	c.6842-2	N/A	intron 12	c.6937+1	N/A	c.6937+2	N/A	intron 17	c.7976+2C>T	N/A	c.8488-1	Sup	intron 19	c.8488-2	Sup	c.8953+2T>C	N/A	intron 23	c.9118-1G>A	Sup	c.9257-1G>C, G>T	Sup	intron 24	c.9257-2	Sup
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	PS1: Same amino acid change as an established variant	<div style="background-color: red; color: white; padding: 2px;">_STR</div>	Within forthcoming ACMG guidance, it is anticipated that these elements will all be incorporated within PP3 and only awarded to variants within key domains.																																																																																																																																						
PM4: Protein-length-changing variant	<div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div>	In the interim, we recommend:																																																																																																																																							
PP3: In silico: Multiple lines of computational evidence support a deleterious effect on the gene or gene product	<div style="background-color: green; padding: 2px;">_SUP</div>	<ul style="list-style-type: none"> Use of PM1_sup and/or PM4_sup for any variant within BRCA1 RING (αα 2-101), BRCT (αα 1650-1857) COILED-COIL DOMAIN (αα 1391-1424), BRCA2 DNA-binding domain (αα 2481-3186), and BRCA2 PALB2 binding domain (aa 10-40). 																																																																																																																																							
PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic seen before	<div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div>	<ul style="list-style-type: none"> Use of PM1_mod or PM4_mod for a variant at specific residues³: 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 DBD: 2607, 2626, 2627, 2663, 2722, 2723, 2748, 3052, 3124 																																																																																																																																							
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	<div style="background-color: red; color: white; padding: 2px;">_STR</div> <div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div>	<ul style="list-style-type: none"> 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 																																																																																																																																							

functional domain (e.g. active site of an enzyme) without benign variation		
PS3: Functional: Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: red; color: white; padding: 2px;">_VSTR</div> <div style="background-color: red; color: white; padding: 2px;">_STR</div> <div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div> </div>	<p>BRCA1 Strong: Findlay et al, 2018⁴; Bouwman et al, 2020⁵; Starita et al, 2018¹⁵ Supporting: Fernandes et al, 2019⁶; Petitalot et al, 2019⁷</p> <p>BRCA2: Strong: *Guidugli et al, 2018⁸; *Hart et al, 2019⁹; *Richardson et al, 2021¹⁰; Ikegami et al, 2020¹⁷; *Hu et al, 2022¹⁸; *Hu et al, 2024¹⁹, Biswas et al, 2020²⁰ Moderate: Mesman et al, 2019¹⁶ *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.</p> <p><u>Additional Notes:</u> 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.</p>
PP1: Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: red; color: white; padding: 2px;">_VSTR</div> <div style="background-color: red; color: white; padding: 2px;">_STR</div> <div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div> </div>	<p>Segregation evidence from multifactorial analysis data is incorporated within the combined scores described in the PP4/BP5 recommendations.</p> <p>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’</p>
PS2/PM6: De novo (maternity and paternity confirmed/unconfirmed) in a patient with the disease and no family history	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: red; color: white; padding: 2px;">_STR</div> <div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div> </div>	
PM3: in trans with a pathogenic variant	<div style="display: flex; flex-direction: column; gap: 2px;"> <div style="background-color: red; color: white; padding: 2px;">_STR</div> <div style="background-color: yellow; padding: 2px;">_MOD</div> <div style="background-color: green; padding: 2px;">_SUP</div> </div>	<p>Frequency data regarding co-occurrence in trans is incorporated within the combined scores described in the PP4/BP5 recommendations.</p> <p>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:</p> <ul style="list-style-type: none"> • Clinical: diagnosis of childhood cancer or skeletal/structural/developmental abnormalities • Molecular/Cellular: aberration on mitomycin-induced chromosomal breakage +/- depletion of BRCA2 in lymphocytes <p>Both clinical and molecular/cellular aberrations must be present for a case to contribute to evidence Evidence cannot exceed ‘Strong’</p> <p>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.</p>

<p>PP4: Phenotypic specificity (Patient's phenotype or family history is highly specific for a disease with a single genetic aetiology)</p>	<p>_VSTR _STR _MOD _SUP</p>	<p>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.</p> <p>Suitable analyses:</p> <ul style="list-style-type: none"> • Easton et al, 2007¹¹ • Vallée et al, 2012¹² • Parsons et al, 2020¹³ • Caputo et al, 2021¹⁴ <p>Evidence is presented as either a Likelihood Ratio (LR) or Log Likelihood Ratio (LLR).</p> <p>If evidence is supplied as an LR: Use the table below to directly convert the LR to the applicable Evidence Strength.</p> <p>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).</p> <p>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.</p> <table border="1" data-bbox="667 1137 1474 1391"> <thead> <tr> <th>Likelihood Ratio</th> <th>Evidence (Exponent) Points</th> <th>Evidence Strength towards pathogenicity</th> </tr> </thead> <tbody> <tr> <td>2.08 – 4.30</td> <td>1</td> <td>SUP</td> </tr> <tr> <td>4.31 – 18.70</td> <td>2</td> <td>MOD</td> </tr> <tr> <td>18.71 – 350.40</td> <td>4</td> <td>STR</td> </tr> <tr> <td>≥ 350.41</td> <td>8</td> <td>VSTR</td> </tr> </tbody> </table> <p>Explanatory Notes:</p> <ul style="list-style-type: none"> • Where multiple potentially valid LR/LLRs are available for a variant, the value from the most recent publication 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) 	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
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															

Evidence towards Benignity

<p>BA1/BS1: Allele frequency is “too high” in ExAC or gnomAD for disorder</p>	<p>_SA _STR</p>	<p>BA1: MTAf = 0.001 (0.1%) BS1: MTAf = 0.0001 (0.01%)</p> <p>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.</p>
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		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 full penetrance expected at an early age	_STR _SUP																
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	_SUP	Can be used for missense variants with no predicted splicing effect (as per main CanVIG-UK consensus specification) at non-conserved residues outside of <i>BRCA1</i> RING (aa 2-101), BRCT (aa 1650-1857) COILED-COIL DOMAIN (aa 1391-1424) and <i>BRCA2</i> DNA-binding domain (aa 2481-3186) and <i>BRCA2 PALB2</i> binding domain (aa 10-40)															
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 <i>in vitro</i> or <i>in vivo</i> 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 <table border="1" data-bbox="662 1809 1452 2056"> <thead> <tr> <th>Likelihood Ratio</th> <th>Evidence (Exponent) Points</th> <th>Evidence Strength towards benignity</th> </tr> </thead> <tbody> <tr> <td>0.48 – 0.23</td> <td>-1</td> <td>SUP</td> </tr> <tr> <td>0.22 – 0.05</td> <td>-2</td> <td>MOD</td> </tr> <tr> <td>0.049 – 0.00285</td> <td>-4</td> <td>STR</td> </tr> <tr> <td><0.00284</td> <td>-8</td> <td>VSTR</td> </tr> </tbody> </table>	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
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Recommendations for the management of conflicting functional assay results See table below for management of discrepancy for BRCA1 variants between Findlay et al, 2018⁴ and Bouwman et al, 2020⁵ 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 \pm 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 ENIGMA 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 <i>et al</i> 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

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