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**CanVIG-UK review of *BARD1*:** Until specific *BARD1* VCEP guidelines are available, consensus to use relevant recommendations from the ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for **ATM Version 1.5.0** (available at: <https://clinicalgenome.org/affiliation/50039/>, PDF attached below). Additional points of specification are given below where applicable.

**Please defer to the ATM VCEP guidelines for evidence combination rules.**

**Additional Note:** This guidance is intended for use in classification of the recurrent variant *BARD1* c.1935\_1954dup (p.Glu652fs) and canonical truncating variants only:

- Nonsense, frameshift, canonical splice site [ $\pm 1$  or  $\pm 2$  intronic positions] variants predicted to result in an out-of-frame transcript subject to nonsense-mediated decay (NMD)
- Initiation codon variants
- Intragenic deletions/duplications predicted to cause an out-of-frame transcript subject to NMD

**Summary: Evidence towards Pathogenicity**

| Evidence element | Evidence strengths allowed |             |             |             | Use as per VCEP | Additional clarifications/thresholds/data-sources                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------|----------------------------|-------------|-------------|-------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PVS1             | <b>_VSTR</b>               | <b>_STR</b> | <b>_MOD</b> | <b>_SUP</b> | X               | <p><b>From CanVIG-UK:</b><br/>For <i>BARD1</i>, follow Tayoun <i>et al.</i> 2018<sup>1</sup> guidance until boundaries specified by the VCEP.</p> <p>Follow <i>ATM</i> VCEP guidance for PVS1(RNA), see below:</p> <ul style="list-style-type: none"> <li>• PVS1_Visible(RNA) shall be used for observed splice defects, whether from canonical +/-1,2 positions or other spliceogenic regions (including mid-exonic missense/synonymous variants that cause splice defects) with baseline weight as per the below decision tree. Weight can be further modified based on the quality of the RNA study including consideration of concepts such as: <ul style="list-style-type: none"> <li>○ Starting material (where patient material is preferable to in vitro minigene)</li> </ul> </li> </ul> |

|     |  |      |      |      |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|--|------|------|------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |  |      |      |      |   | <ul style="list-style-type: none"> <li>○ Use of NMD inhibitors where translation does occur such as cell lines</li> <li>○ Primer design (to make sure it's comprehensive to capture possible multicassette events)</li> <li>○ Method of quantification <ul style="list-style-type: none"> <li>▪ where e.g. capillary electrophoresis is preferable to estimation by gel band density</li> <li>▪ where SNP analysis is most preferred (where analysis of exonic SNPs and their relative presence in aberrant and WT transcripts is informative)</li> </ul> </li> <li>○ Quantification (where complete effects should have increased weight over incomplete effects)</li> </ul> <p>In the event that RNA data are available and they reflect a substantial variant-specific impact, do not use both PVS1(RNA) and PP3 or BP4. However, in the event that RNA data are available and they reflect no variant-specific impacts, PP3 or BP4 may be applied in conjunction with BP7(RNA).</p> |
| PS1 |  | _STR | _MOD | _SUP | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PS2 |  |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PS3 |  | _STR | _MOD | _SUP | ✓ | <b>From CanVIG-UK:</b><br>For reference, please note that pre-publication functional data for <i>BARD1</i> is available <sup>1</sup> , and will be formally reviewed by CanVIG-UK in due course.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| PS4 |  | _STR |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PM1 |  |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PM2 |  |      |      | _SUP | ✓ | <b>From VCEP:</b><br>Per correspondence regarding <i>ATM</i> VCEP guidelines 06/08/2026: <ul style="list-style-type: none"> <li>• If AF is <math>\leq 0.001\%</math> (regardless of n) apply PM2_sup</li> <li>• If AF is <math>&gt; 0.001\%</math> but only n=1 in one population, apply PM2_sup.</li> <li>• Otherwise if AF is <math>&gt; 0.001\%</math>, do not apply PM2_sup, even if there is only one ancestry group with the variant and ancestry AF is <math>\leq 0.001\%</math></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| PM3 |  |      |      |      | X | <b>From CanVIG-UK:</b><br>No syndromic phenotype, do not use                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| PM4 |  |      | _MOD |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PM5 |  |      |      | _SUP | X | <b>From CanVIG-UK:</b><br>PM5_PTC may be applied at Supporting for non-splicing protein truncating variants which have already attained PVS1 at full strength, are predicted to undergo nonsense-mediated decay, AND are upstream of the most C-terminal known pathogenic protein truncating variant for that gene. As a gene-specific NMD boundary is not yet established; assume NMD is predicted unless in the final exon or the last 50 base pairs of the penultimate exon.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PM6 |  |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PP1 |  |      |      |      | X | <b>From VCEP:</b><br>No syndromic phenotype, do not use                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| PP2 |  |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PP3 |  |      |      | _SUP | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PP4 |  |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| PP5 |  |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

### Summary: Evidence towards Benignity

|         |     |      |      |      |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------|-----|------|------|------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BA1/BS1 | _SA | _STR |      |      | X | <b>From CanVIG-UK:</b><br>BA1: 0.000325 (0.0325%)<br>BS1: 0.0000325 (0.00325%)<br><br>The MTAF (maximum tolerated allele frequency) has been calculated using cardiodb using the calculate AF function with a breast cancer phenotype: prevalence 1 in 8; genetic heterogeneity 0.0013; allelic heterogeneity 1 (BA1) 0.1 (BS1); penetrance 0.25.<br>It is permissible to use the GrpMAX FAF on gnomAD against the MTAF cutoffs for BA1/BS1. See consensus guidelines for further details on GrpMAX FAF, and the use of cardiodb for calculating the maximum allele count / filtering allele frequency. |
|         |     |      |      |      |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BS2     |     |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BS3     |     |      | _MOD | _SUP | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|         |     |      |      |      |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BS4     |     |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BP1     |     |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BP2     |     | _STR | _MOD | _SUP | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BP3     |     |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BP4     |     |      |      | _SUP | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BP5     |     |      |      |      | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| BP7     |     | _STR | _MOD | _SUP | ✓ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

### Version History/Amendments

| Revised version | Date       | Section | Update                                         | Amended by | Approved by |
|-----------------|------------|---------|------------------------------------------------|------------|-------------|
| 1.0             | 26/08/2026 | --      | Initial Version                                | --         | CStAG       |
| 1.1             | 05/10/2026 | BA1/BS1 | Amended typing error (breast cancer phenotype) | Allen      | Allen       |

### References

1. Woo I, Casadei S, Snyder MW, et al. Saturation genome editing of *BARD1* resolves VUS and provides insight into BRCA1-BARD1 tumor suppression. Preprint. *medRxiv*. 2025;2025.11.03.25339440. Published 2025 Nov 6. doi:10.1101/2025.11.03.25339440