UKCGG/CStAG statement on reporting practice for variants in “moderate risk” breast* cancer susceptibility genes

Summary of Recommendations

- This document relates to interpretation and reporting of variants in genes associated with “moderate risk” breast cancer susceptibility. Such genes include *CHEK2*, for which testing is currently available under R208 and R430 indications. It is anticipated that current NHS panels will expand in the future to include additional genes, such as *BARD1*. An exception to this guidance is *ATM*, which requires special consideration given allelic rare disease associations. For *ATM*-specific guidance, please refer to UKCGG/CStAG statement on reporting practice for variants in *ATM* v.2.2 (08/10/2025).
- This document supersedes UKCGG statement on reporting practice for missense variants in *CHEK2* (03/04/2024).
- *This document does not pertain to reporting of variants in genes associated with ovarian cancer susceptibility (*RAD51C, RAD51D, BRIP1*), which require different consideration given relative lack of available large-scale data demonstrating any difference in **ovarian** cancer risks between truncating and non-truncating variants.
- Canonical protein truncating variants (PTVs) are defined as:
    a) Nonsense, frameshift, canonical splice site [±1 or ±2 intronic positions] variants predicted to result in an out-of-frame transcript subject to nonsense-mediated decay (NMD)
    b) Initiation codon variants
    c) Intragenic deletions/duplications predicted to cause an out-of-frame transcript subject to NMD[1].
- For **diagnostic** analysis and reporting: Laboratory teams are expected to restrict interpretation and reporting to canonical PTVs and *CHEK2* c.349A>G p.(Arg117Gly)
- Laboratory teams are **not** expected to prospectively report through diagnostic referrals or to retrospectively interrogate data from previous testing for additional variants deemed reportable.
- For referrals for **targeted variant-specific analysis and reporting**: we recommend reporting of
    1. Canonical PTVs
    2. *CHEK2* c.349A>G p.(Arg117Gly) **AND**
    3. Other (likely) pathogenic variants for which there is consistent and significant case: control data from BRIDGES, UK Biobank and CARRIERS, demonstrating BC associated OR >2.0, with

lower confidence interval >1.5, if variants meet ONE of the following exception variant criteria:

a. *Functionally null*: There is functional evidence suggesting a loss of function equivalent to that of a truncating variant (e.g. loss of kinase activity with supporting radiosensitivity and/or phosphorylation data)
b. *Aberrant splicing*: The variant has been empirically shown to affect splicing, resulting in an out-of-frame transcript subject to NMD **OR** in-frame transcript with the removal of critically important functional residues as per VCEP guidance (where there is no/minimal leakiness), i.e. PVS1_vstr(RNA) is applicable

- Targeted variant-specific analysis and reporting of variants should **not** be undertaken if case:control evidence is available and demonstrates associated cancer risk OR <2, but may be considered for variants meeting criterion 3(a) OR 3(b) if no case:control data is available.
- Where exception variants are reported, wording of reports **must** include information regarding lines of evidence used for variant classification and should explicitly mention if there is a paucity of data regarding cancer association for a particular variant. Reports should include statement to indicate that cascade testing should only be offered if considered appropriate, depending on clinical utility.
- For variants where robust data regarding a cancer association does not exist, clinical teams should:
    1. Exercise caution in assuming a risk equivalent to canonical PTVs, particularly if risk estimation tools (CanRisk) are employed and management should be guided by the patients clinical and family history
    2. Consider clinical utility of cascade testing of relatives if information on genotype will not change clinical management
- Evidence related to any variants deemed “reportable” as exception variants should be entered onto CanVar-UK.
- **It is not feasible for UKCGG/CStAG to maintain a formal whitelist of exception variants**

Background

With respect to variants in genes associated with cancer predisposition, analysis and reporting of variants are restricted to those associated with at least intermediate penetrance (generally accepted as odds ratio in excess of 2) and where identification of the variant has clinical utility, contextualised to the background incidence of the cancer in question. For this reason, NHS-funded constitutional testing of certain cancer susceptibility genes (e.g. *EGFR, MC1R*) is not currently offered or

recommended, and for genes in which associated penetrance depends on variant type, restricting of variant analysis and reporting is recommended[2,3].

NHS-funded *CHEK2* testing is available under certain cancer indications (R208 Familial Breast Cancer and R430 Familial Prostate Cancer). It is anticipated that other "moderate risk" breast cancer predisposition genes will be added to relevant NHS panels as further data becomes available. This document relates to interpretation and reporting of variants in such genes, if there is data suggesting different effect sizes associated with truncating and non-truncating variants.

Associated cancer risks

Published evidence demonstrates that missense variants as a combined group in *CHEK2, BARD1* and other "moderate risk" breast cancer susceptibility genes are associated with a low-moderate cancer risk compared to higher risks conferred by truncating variants[2]. There is some evidence to suggest that certain functionally impaired variants may confer risks similar to those of PTVs[4]. **However, for most rare non-truncating variants, data for variant-specific risks are scant.**

Data are available for certain recurrent variants, including *CHEK2* c.349A>G p.(Arg117Gly). Across multiple studies, this variant has been demonstrated to confer cancer risk OR comparable to that of *CHEK2* truncating variants [iCOG Study; OR = 2.26, (95% CI: 1.29 - 3.95); BRIDGES OR =2.69, (95% CI 1.46–4.94) and UK Biobank (unpublished analysis of 21/19,719 female BC patients and 93/219,405 female non-BC controls); OR 2.51 (95% CI: 1.50-4.21). Furthermore, various different assays have consistently demonstrated that this variant is associated with loss of function[5,6,7,8]. Given the evidence for this variant, we recommend that this variant is analysed and reported on the relevant diagnostic panel and that testing in family member can be offered where clinically appropriate.

Variants in certain moderate risk breast cancer susceptibility genes also confer increased risks of ovarian cancer (e.g. *RAD51C, RAD51D*). Although it may be inferred that variants conferring low-moderate risk of breast cancer may be likely to have an equivalent effect size with respect to ovarian cancer risk, but, at present, there is a paucity of data specifically evaluating differential (if any) ovarian cancer risks between variant types. Although data is lacking as to whether breast cancer surveillance or risk-reducing breast surgery influences overall survival in carriers of variants associated with moderate risk[9], there is strong and consistent evidence demonstrating effective and cost-effective interventions to prevent ovarian cancer by risk-reducing surgery in women with a relatively low absolute ovarian cancer risk (in excess of 5%)[10,11,12].

Variant reporting practice

When testing is undertaken interpretation and reporting of variants are restricted to truncating variants. **Where analysis is recommended, variants should be interpreted and classified using CanVIG gene-specific recommendations[13].**

The decision to interpret and report only truncating variants in *CHEK2*, *ATM* (and any other moderate risk genes for which there is evidence of differential breast cancer risks between variant classes) was made following discussions with relevant key stakeholders, including National Cancer Genetics Leads, UK Cancer Genetics Group council and CanVIG membership, based on the following considerations:

1. Disproportionate laboratory time and resource in interpretation and reporting of missense variants compared to clinical utility
2. Published data demonstrates that for most missense variants, the magnitude of associated breast cancer risk falls below an odds ratio (OR) of 2.
3. Risk estimates generated by CanRisk[14] are currently based on risks associated with truncating variants in the genes included in the model, although there are plans to incorporate data related to missense variants in the future

Other countries and commercial laboratories do interpret and report missense variants in these genes such that laboratory and clinical teams may receive referrals for targeted testing in at-risk relatives. Non-truncating variants may also be identified through whole genome sequencing undertaken for either rare disease or cancer indications or during testing of tumour-derived DNA.

Furthermore, there is variability in understanding and application of the term “truncating” to classify variant types in the literature, leading to inconsistency in reporting (e.g. non-canonical splicing variants) by some, but not all, laboratories.

UKCGG acknowledge that this discrepancy in reporting practice has resulted in challenges in clinical practice. To address this, and to rationalise allocation of limited resources, we proposed strategies for restricted analysis and reporting of variants in *ATM* in different contexts (UKCGG/CStAG statement on reporting practice for variants in *ATM* v.1 31/10/2024). **Following a pilot period in which this statement was enacted, a dedicated CanVIG meeting was held to discuss challenges and determine preferred practice of the community. The discussions at that meeting informed an update to guidance for reporting of variants in *ATM* (v2 29/70/2025, v2.2 08/10/2025)[15] and in other “moderate risk” breast cancer susceptibility genes.**

Strategy for interpretation and reporting of variants in moderate risk breast cancer susceptibility genes (figure 1)

When making decisions regarding variant interpretation and reporting, it is important to consider whether testing has been requested on a diagnostic basis **(proactive testing)**, or following detection of a variant in another laboratory, sample (tumour) or family member **(reactive testing)**.

A. Variants detected during diagnostic testing through NHS labs

As part of routine clinical practice, we recommend that interpretation and reporting of variants is restricted to (likely) pathogenic variants in the categories here below. **Only variants as per these definitions require review and classification during diagnostic testing for cancer predisposition. Assessment regarding truncating effect is not required for other variant types.**

Variants that should be reported through diagnostic *CHEK2* testing:

1. Canonical protein truncating variants, as defined as:
    a) nonsense, frameshift, canonical splice site [±1 or ±2 intronic positions] variants predicted to result in an out-of-frame transcript subject to nonsense-mediated decay (NMD)
    b) initiation codon variants
    c) Intragenic deletions/duplications predicted to cause an out-of-frame transcript subject to NMD[1].
2. NM_007194.4(CHEK2):c.349A>G (p.Arg117Gly). This is the only exception to the truncating definition above that should be analysed and reported under diagnostic (cancer) referrals.

Laboratory teams are not expected to undertake evaluation of other missense variants or variants of other types during diagnostic testing under cancer indications.

B. Referrals related to variants detected during somatic testing, via cancer predisposition testing by non-NHS laboratories, or via historic testing prior to implementation of this statement

Referrals for targeted testing of variants meeting the criteria set out in section A can proceed. Referrals may be received related to variants other than those types listed in section A, ascertained through different cancer-related pathways such tumour testing or from a non-NHS laboratory, that would not otherwise have been reported as part of a diagnostic test for indications related to cancer predisposition in NHS laboratories. In this instance, a review of the variant is required to determine if targeted germline testing can be offered for the variant in question as an exception variant.

Exception variant criteria

At present, only the NM_007194.4(CHEK2):c.349A>G (p.Arg117Gly) missense variant is included as an exception to the approach to analyse and report truncating variants.

Testing of other variants not fulfilling the truncating criteria outlined above may be considered **IF**:

1. The variant is classified as likely pathogenic/pathogenic

   AND

2. There is consistent and significant case: control data from BRIDGES, UK Biobank and CARRIERS, demonstrating BC associated cancer risk OR >2.0, with lower confidence interval >1.5[9,16]

   AND

3. Variant meets ONE of the following exception variant criteria:
   a. *Functionally null*: There is functional evidence suggesting a loss of function equivalent to that of a truncating variant (e.g. loss of kinase activity with supporting radiosensitivity and/or phosphorylation data)
   b. *Aberrant splicing*: The variant has been empirically shown to affect splicing, resulting in an out-of-frame transcript subject to NMD **OR** in-frame transcript with the removal of critically important functional residues as per VCEP guidance (where there is no/minimal leakiness), i.e. PVS1_vstr(RNA) is applicable

Targeted variant-specific analysis and reporting of variants should **not** be undertaken if case:control evidence is available and demonstrates associated cancer risk OR <2, but may be considered for variants meeting criterion 3(a) OR 3(b) if case:control data do not exist. Where such variants are reported, wording of reports **must** include information regarding lines of evidence used for variant classification and should explicitly mention if there is a paucity of data regarding cancer association.

Where an NHS laboratory team determines a variant to meet exception criteria for targeted testing for cancer susceptibility, relevant evidence **should be submitted to CanVar-UK** so that the evidence for the variant can be shared with members.

We **do not** recommend retrospective testing/reanalysis for exception variants where patients have already had diagnostic testing of the gene in question. Laboratory teams are **not** expected to routinely undertake interpretation and reporting of exception variants for prospective diagnostic referrals.

Wording of reports where exception variants identified

Where laboratory teams evaluate and choose to report (likely) pathogenic variants other than truncating variants meeting the exception criteria (both as defined above) for which robust evidence demonstrating associated cancer risk OR >2.0 (lower CI >1.5) does not exist, the report **must** explicitly state that such data is lacking.

Figure 1: Exemplar wording for use when variants are reported for which case:control evidence demonstrating cancer risk is not available

> *Data regarding cancer risk OR associated with this variant is not yet available. Clinical teams should consider personal and family history, lifestyle and reproductive factors in addition to genotype, and should exercise caution when using CanRisk to generate lifetime cancer risks.*

Clinical management of patients in whom such variants are identified should be guided by personal and family cancer history in addition to genotype. Clinical teams should also inform probands that cascade testing for unaffected relatives **may not be indicated** if result will not change clinical management. However, if clinically appropriate, predictive testing *may* be offered to relatives, after consideration of clinical utility and impact of result on clinical management. Cancer risk estimates from currently available tools (such as CanRisk) are based on higher-risk variants, so caution is advised if applying these tools for risk estimation in carriers of variants for which data regarding equivalent risk does not exist.

Challenges in variant-restricted reporting

At the time of the original proposal for exception variant reporting, we suggested that a list of exception variants be maintained on a prospective basis by UKCGG/CanVIG, and that variants would be added to such a list if deemed appropriate by UKCGG and CStAG.

A CanVIG meeting focused on exception variant reporting was held on 13th June 2025, at which variants flagged for consideration as exception variants were discussed. It became apparent that consensus regarding reporting would not easily be achieved for those variants for which robust case-control evidence suggesting cancer risk OR>2 does not exist. It also became apparent that the practicalities and workload associated with maintaining an exception list would be impractical and unfeasible for members of council of UKCGG or CStAG to enact in their voluntary roles.

An informal poll was undertaken during the meeting to determine the preferred practice of the community regarding reporting of exception variants.

Conclusion

When diagnostic testing of moderate risk breast cancer susceptibility genes is undertaken under a cancer indication, laboratory teams are not expected to report variants other than canonical PTVs and NM_007194.4(CHEK2):c.349A>G (p.Arg117Gly). Where a decision has been made that a variant of another type should be reported, careful wording of the report is required. Clinical teams should consider other clinical factors in providing estimates of cancer risk and in determining management of patients in whom "other" variant have been reported and should consider clinical utility before offering predictive genetic testing to unaffected relatives. It is not feasible to maintain a formal whitelist of exception variants, but laboratory teams are encouraged to communicate rationale for reporting of non-standard variants via CanVar-UK.

*Note: variants in "moderate risk" ovarian cancer susceptibility genes

This document purposefully relates to variants associated with a breast cancer predominant cancer risk. When diagnostic testing of moderate risk genes associated with ovarian (+/- breast) cancer susceptibility is undertaken, laboratory teams are not expected to routinely report variants other than canonical PTVs. However, referrals related to targeted testing for non-PTVs require special consideration, and it may not always be possible or appropriate to apply the flow proposed here above for *ovarian* cancer susceptibility genes. Interpretation of associated OR should consider population incidence of a particular cancer type, and relative rarity of ovarian cancer compared to breast cancer is such that an OR ~2 may not necessarily equate to an absolute risk at which risk-reducing intervention would be considered appropriate. Furthermore, there is a relative paucity of robust case:control data related to ovarian cancer-specific OR associated with different variant types in these genes. On the other hand, risk-reducing ovarian surgery is cost-effective and associated with a survival advantage even at relatively low absolute ovarian cancer risks[17]. It is important, therefore, that professional judgement be applied in interpretation and reporting of, and onward clinical action related to, variants in such genes, informed by the patient and familial phenotype and other co-existing risk factors. As with all variants associated with a moderate cancer risk, clinical teams should consider all relevant factors, in addition to genotype, when providing advice to carriers and non-carriers.

References

[1] Abou Tayoun AN, Pesaran T, DiStefano MT, et al. Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion. Hum Mutat. 2018 Nov;39(11):1517-1524. doi: 10.1002/humu.23626. Epub 2018 Sep 7. PMID: 30192042; PMCID: PMC6185798.

[2] Dorling L, Carvalho S, Allen J, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021;384(5):428-439.

[3] McVeigh TP, Lalloo F, Frayling IM, et al. Challenges in developing and implementing international best practice guidance for intermediate-risk variants in cancer susceptibility genes: *APC* c.3920T>A p.(Ile1307Lys) as an exemplar. J Med Genet. 2024 Jul 19;61(8):810-812. doi: 10.1136/jmg-2024-109900.

[4] Stolarova L, Kleiblova P, Zemankova P, et al. ENIGMA CHEK2gether Project: A Comprehensive Study Identifies Functionally Impaired CHEK2 Germline Missense Variants Associated with Increased Breast Cancer Risk. Clin Cancer Res. 2023 Aug 15;29(16):3037-3050. doi: 10.1158/1078-0432.CCR-23-0212. PMID: 37449874; PMCID: PMC10425727.

[5] Roeb W, Higgins J, King MC. Response to DNA damage of CHEK2 missense mutations in familial breast cancer. Hum Mol Genet. 2012 Jun 15;21(12):2738-44. doi: 10.1093/hmg/dds101. Epub 2012 Mar 13. PMID: 22419737; PMCID: PMC3363333.

[6] Chrisanthar R, Knappskog S, Løkkevik E, et al. CHEK2 mutations affecting kinase activity together with mutations in TP53 indicate a functional pathway associated with resistance to epirubicin in primary breast cancer. PLoS One. 2008 Aug 26;3(8):e3062. doi: 10.1371/journal.pone.0003062. PMID: 18725978; PMCID: PMC2518116.

[7] Delimitsou A, Fostira F, Kalfakakou D, et al. Functional characterization of CHEK2 variants in a Saccharomyces cerevisiae system. Hum Mutat. 2019 May;40(5):631-648. doi: 10.1002/humu.23728. Epub 2019 Mar 9. PMID: 30851065.

[8] Sodha N, Mantoni TS, Tavtigian SV, et al. Rare germ line CHEK2 variants identified in breast cancer families encode proteins that show impaired activation. Cancer Res. 2006 Sep 15;66(18):8966-70. doi: 10.1158/0008-5472.CAN-06-1990. PMID: 16982735.

[9] Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021 Feb 4;384(5):440-451. doi: 10.1056/NEJMoa2005936. Epub 2021 Jan 20. PMID: 33471974.

[10] Manchanda R, Legood R, Antoniou AC, Gordeev VS, Menon U. Specifying the ovarian cancer risk threshold of 'premenopausal risk-reducing salpingo-oophorectomy' for ovarian cancer prevention: a cost-effectiveness analysis. J Med Genet. 2016 Sep;53(9):591-9. doi: 10.1136/jmedgenet-2016-103800. Epub 2016 Jun 27. PMID: 27354448.

[11] Manchanda R, Gaba F, Talaulikar V, Pundir J, Gessler S, Davies M, Menon U; Royal College of Obstetricians and Gynaecologists. Risk-Reducing Salpingo-Oophorectomy and the Use of Hormone Replacement Therapy Below the Age of Natural Menopause: Scientific Impact Paper No. 66 October 2021: Scientific Impact Paper No. 66. BJOG. 2022 Jan;129(1):e16-e34. doi: 10.1111/1471-0528.16896. Epub 2021 Oct 20. PMID: 34672090; PMCID: PMC7614764.

[12] Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. Gynecol Oncol. 2015 Dec;139(3):487-94. doi: 10.1016/j.ygyno.2015.10.001. Epub 2015 Oct 5. PMID: 26436478.

[13] CanVIG-UK Consensus Specifications | CanGene-CanVar

[14] Lee AJ, Cunningham AP, Tischkowitz M, et al. Incorporating truncating variants in PALB2, CHEK2, and ATM into the BOADICEA breast cancer risk model. Genet Med. 2016 Dec;18(12):1190-1198. doi: 10.1038/gim.2016.31. Epub 2016 Apr 14. PMID: 27464310; PMCID: PMC5086091.

[15] Exceptional variants/gene-specific variant reporting - Cancer Genetics Group

[16] Rowlands CF, Allen S, Balmaña J, et al. Population-based germline breast cancer gene association studies and meta-analysis to inform wider mainstream testing. Ann Oncol. 2024 Oct;35(10):892-901. doi: 10.1016/j.annonc.2024.07.244.

[17] Wei X, Oxley S, Sideris M, Kalra A, Sun L, Yang L, Legood R, Manchanda R. Cost-Effectiveness of Risk-Reducing Surgery for Breast and Ovarian Cancer Prevention: A Systematic Review. Cancers (Basel). 2022 Dec 12;14(24):6117. doi: 10.3390/cancers14246117. PMID: 36551605; PMCID: PMC9776851.

Figure 1: Strategy for interpretation and reporting of variants in moderate risk breast cancer susceptibility genes