UKCGG/CStAG statement on reporting practice for variants in *ATM v.2.2*

Summary of Recommendations

- 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** (cancer indications) analysis and reporting: Laboratory teams are expected to restrict interpretation and reporting to canonical PTVs and *ATM* c.7271T>G
- 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
    - Canonical PTVs, *ATM* c.7271T>G **AND**
    - 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 <u>exception variant criteria</u>:
        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 <u>**not**</u> be undertaken if case:control evidence is available and demonstrates associated cancer OR <2, but may be considered for variants meeting criterion 2(a) OR 2(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:
    - 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
    - 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.

Background

Biallelic constitutional (likely) pathogenic variants in *ATM* cause Ataxia Telangiectasia (A-T). Certain monoallelic constitutional (likely) pathogenic variants in *ATM* are associated with increased risks of certain cancers.

At present, testing of *ATM* is available for patients with A-T associated phenotypes (R295, R15, R29, R54, R56, R57, R326) as well as for patients with strong personal and/or family history of breast cancer (R208) or prostate cancer (R430)[2]. All clinically actionable variants (likely pathogenic/pathogenic or suspicious variants of uncertain significance) are analysed and reported when *ATM* testing is requested under indications related to A-T.

However, 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. 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[3,4]. Current published data demonstrate differential cancer risks associated with truncating variants (OR ≥2.0) compared to most missense variants (OR<2.0)[3] in *ATM*. Variants in *ATM* are most strongly associated with ER-positive cancers, which are typically associated with favourable prognosis, and data is lacking as to whether surveillance or risk-reducing surgery influences overall survival[5].

At present, when *ATM* testing is undertaken for indications related to cancer predisposition, interpretation and reporting of variants are restricted to truncating variants and the high-risk

missense variant (c.7271T>G). **Where analysis is recommended, variants should be interpreted and classified using *ATM* VCEP guidelines and CanVIG gene-specific recommendations[6,7, 8].**

The decision, to restrict reporting to certain *ATM* variants when testing is undertaken via R208/R430 panels (or any other panels related to cancer predisposition on which *ATM* is included in the future) was made following discussions at National Cancer Leads and Cancer Variant Interpretation-UK (CanVIG) Steering and Advisory Group (CStAG) meetings, for the reasons mentioned here above.

Other considerations include:

1. Disproportionate time and resources required by laboratory teams related to interpretation and reporting of missense variants compared to clinical utility
2. Risk estimates generated by CanRisk[9] are currently based on risks associated with truncating variants in *ATM*, although there are plans to incorporate data related to missense variants in this model in the future

We acknowledge that, although missense variants as a combined group are associated with a low-moderate risk breast cancer risk (OR<2.0), some individual missense *ATM* variants may be associated with higher cancer risks, comparable to those associated with truncating variants. An example includes *ATM* c.7271T>G p.(Val2424Gly), which is reported to be associated with high breast cancer risks, and for women in whom this variant is identified, very high-risk breast screening is recommended[10].

Reporting of missense variants is routine when *ATM* testing is undertaken under indications related to A-T, or when *ATM* testing is undertaken in non-NHS laboratories. Such variants may also be identified through whole genome sequencing undertaken for either rare disease or cancer indications. Missense variants in *ATM* of likely germline origin may also be identified during testing of tumour-derived DNA. Furthermore, there is variability in understanding and application of the term “truncating” to classify variant types, 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 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 this guidance, which supersedes version 1 of the statement.

Strategy for interpretation and reporting of variants in *ATM* (figure 1)

When making decisions regarding *ATM* variant interpretation and reporting, it is important to consider the context in which a variant has been ascertained **(cancer or non-cancer)** and 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 under indications related to cancer predisposition

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 *ATM* testing under cancer indications:

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. *ATM* NM_000051.3: c.7271T>G p.(Val2424Gly). 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 *ATM* NM_000051.3: c.7271T>G p.(Val2424Gly) missense variant is included as an exception to the approach to analyse and report truncating variants for diagnostic cancer predisposition indications.

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 OR >2.0, with lower confidence interval >1.5[5,11]

   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 OR <2, but may be considered for variants meeting criterion 2(i) OR 2(ii) 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 *ATM* testing. 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 the classification of a variant is based on evidence unrelated to cancer risk, and that cancer risk is uncertain.

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

> *Please note, this variant is classified as (likely) pathogenic in the context of ataxia telangiectasia, however the evidence for ATM-related cancers is very limited. The associated cancer risk uncertain and therefore the patient should be managed appropriately, based on their personal and family history.*

Clinical management of patients in whom such variants are identified should be guided by personal and family cancer history. 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.

Though very few participants favoured reporting of all (likely) pathogenic *ATM* variants when testing was undertaken for cancer predisposition, consensus could not be reached regarding tight restriction of reporting to canonical PTVs and *ATM* c.7271T>G, either in the diagnostic setting (proactive variant review) or targeted testing (reactive review).

Likely reflecting an awareness of the challenges in arbitration and maintenance of a whitelist of exception variants, only a minority of attendees favoured maintaining this on a formal basis, while a larger proportion supported maintaining an informal list via CanVar-UK.

Table 1: Results of polls at CanVIG meeting 13/06/2025

	Diagnostic cancer panel testing (proactive)	**Targeted testing (reactive)**
Only truncating variants and *ATM* c.7271T>G be reported	29/63 (46%)	22/59 (37%)
All (likely) pathogenic variants should be reported	6/63 (5%)	2/59 (3%)
A formal whitelist of exception variants should be maintained by a single nominated laboratory	11/63 (17%)	9/59 (15%)
An informal whitelist of exception variants should be maintained as a collective community effort via CanVar-UK	20/63 (32%)	26/59 (44%)

Conclusion

When *ATM* diagnostic testing is undertaken under a cancer indication, laboratory teams are not expected to report variants other than canonical PTVs and c.7271T>G p.(Val2424Gly). 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.

References

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[3] 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.

[4] 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.

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[7] ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ATM Version 1.1

[8] CanVIG Gene Guidance | CanGene-CanVar (cangene-canvaruk.org)

[9] 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.

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Figure 1 Strategy for interpretation and reporting of variants in *ATM* v2.2