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

Background

Biallelic constitutional (likely) pathogenic variants in *ATM* cause Ataxia Telangiectasia (A-T). 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)[1]. 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[2,3]. Current published data demonstrate differential cancer risks associated with truncating variants (OR ≥2.0) compared to most missense variants (OR<2.0)[4] 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). 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[6] 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, 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[7].

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 propose the following strategies for analysis and reporting of variants in different contexts.

Where analysis is recommended, variants should be interpreted and classified using ATM VCEP guidelines and CanVIG gene-specific recommendations[8],[9, 10].

A. Variants detected during diagnostic testing through NHS labs under indications related to cancer predisposition

We propose that interpretation and reporting of variants is restricted to:

1. Truncating variants, as defined as:
    a. nonsense, frameshift, canonical splice site [±1 or ±2 intronic positions] variants predicted to result in a 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[11].

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

2. Exception variants:
   At present, *ATM* NM_000051.3: c.7271T>G is the only exception to the truncating definition above that should be analysed and reported under these referral types. Other variants may be added to the exception variant reporting list in the future. See section "Exception Variant Reporting" below for detail.

No other variants require evaluation.

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 the variant should be reported as an exception variant.

Exception variant reporting

At present, only the *ATM* NM_000051.3: c.7271T>G 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 offered if:

1. The variant is classified as likely pathogenic/pathogenic

AND

2. There is evidence suggesting a loss of function equivalent to that of a truncating variant (e.g. by influencing kinase activity, data related to radiosensitivity/phosphorylation)

   OR

   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 functionally important residues as per VCEP guidance (where there is no/minimal leakiness)

   OR

   There is consistent and significant case: control data from BRIDGES, UK Biobank and CARRIERS[12,13] demonstrating BC associated OR - >2.0, with lower confidence interval >1.5.

Where an NHS laboratory team determines a variant to meet criteria for reporting, relevant evidence **should be submitted to CanVIG** so that the evidence for the variant can be shared with members and approved (or not) by CStAG for addition to the list of exception variants and ratified thereafter by UKCGG.

This list will be periodically updated, and an alert will be circulated via CanVIG when updated. This will happen no more frequently than annually. This list is available here**.**

Exception variant reporting should be undertaken **prospectively** only. We do not recommend retrospective testing/reanalysis for exception variants where patients have already had diagnostic *ATM* testing.

In terms of clinical management, carriers of variants fulfilling these criteria can be managed in the same way as those carriers of truncating variants, with information regarding family history and clinical context considered alongside genotype.

C. Other likely pathogenic/pathogenic variants ascertained via A-T testing or other non-cancer indications

Where variants have been ascertained through non-cancer pathways (e.g. A-T testing**)** that would not be otherwise be reported as part of a diagnostic screen for cancer predisposing variants, carrier mothers of affected children can be offered moderate risk screening, unless otherwise indicated based on family history. We would not advocate for cascade testing of other relatives (unless there is a history of consanguinity/otherwise indicated for A-T risk).

Variants only ascertained through non-cancer indications (i.e. in absence of personal/family history of cancer) will not routinely be considered for listing as exception variants for reporting through cancer panels.

Review

Given locoregional variability in lab processes, we welcome your feedback (terri.mcveigh@nhs.net) on implementation of this approach and will review this statement in June 2025. Please continue to upload information and queries related to *ATM* variants ascertained in your laboratories to CanVar-UK.

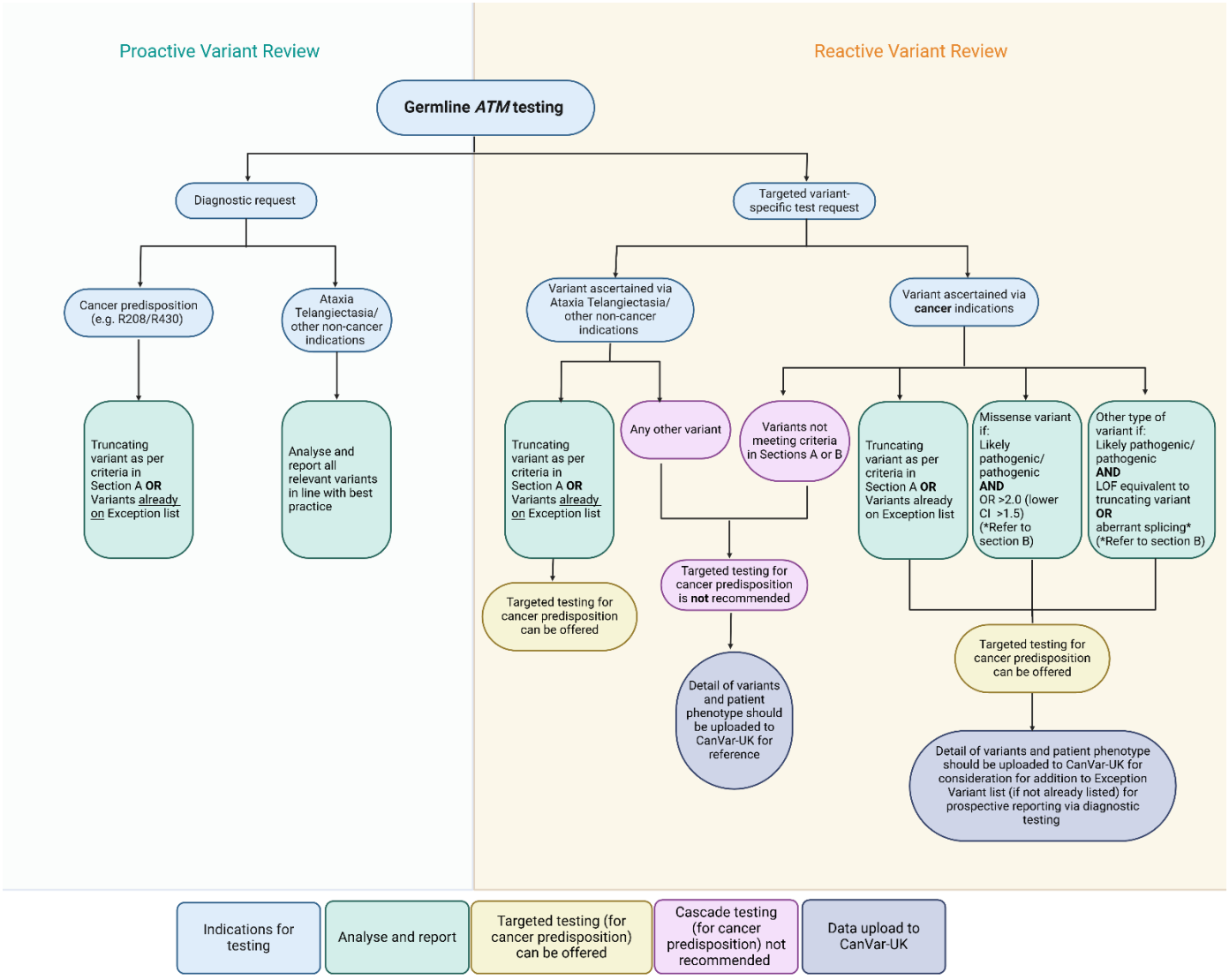

Figure 1: Recommended practice for analysis and reporting of ATM variants (larger version available to download from website)

References

[1] nhsgms-panelapp.genomicsengland.co.uk/entities/ATM

[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] 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.
[5] 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.
[6] 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.
[7] Breast screening: very high risk women surveillance protocols - GOV.UK (www.gov.uk)
[8] Richardson ME, Holdren M, Brannan T, et al. Specifications of the ACMG/AMP variant curation guidelines for the analysis of germline ATM sequence variants. Am J Hum Genet. 2024 Sep 17:S0002-9297(24)00332-X. doi: 10.1016/j.ajhg.2024.08.022. Epub ahead of print. PMID: 39317201.
[9] ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ATM Version 1.1
[10] CanVIG Gene Guidance | CanGene-CanVar (cangene-canvaruk.org)
[11] 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.
[12] 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.
[13] 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.