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ACMG PRACTICE RESOURCE

Management of individuals with heterozygous germline pathogenic variants in *ATM*: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

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ABSTRACT

Purpose: *ATM* germline pathogenic variants (GPVs) are associated with a moderately increased risk of female breast cancer, pancreatic cancer, and prostate cancer. Resources for managing *ATM* heterozygotes in clinical practice are limited.

Methods: An international workgroup developed a clinical practice resource to guide management of *ATM* heterozygotes using peer-reviewed publications and expert opinion.

Results: Although *ATM* is a moderate (intermediate) penetrance gene, cancer risks may be considered as a continuous variable, influenced by family history and other modifiers. *ATM* GPV heterozygotes should generally be offered enhanced breast surveillance according to their personalized risk estimate and country-specific guidelines and, generally, risk-reducing mastectomy is not recommended. Prostate cancer surveillance should be considered. Pancreatic cancer surveillance should be considered based on assessment of family history, ideally as part of a clinical trial, with existence of country-specific guidelines. For *ATM* GPV

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heterozygotes who develop cancer, radiation therapy decisions should not be influenced by the genetic result. Although poly-adenosine diphosphate ribose polymerase inhibitors are licensed for use in metastatic castration-resistant prostate cancer and *ATM* GPVs, the evidence-base is currently weak.

Conclusion: Systematic prospective data collection is needed to establish the spectrum of *ATM*-associated cancer and determine the outlines of surveillance, response to cancer treatment, and survival.

Introduction

The *ATM* locus (HGNC:795) was originally mapped to 11q22-23 in 1988,[1] with subsequent discovery of the gene consisting of 66 exons and approximately 150 kb of genomic DNA in 1995.[2] The gene was identified characterizing individuals with Ataxia-Telangiectasia (AT), a childhood-onset autosomal recessive disorder characterized by progressive cerebellar ataxia, oculomotor apraxia, oculocutaneous telangiectasia, and immunological deficiency with frequent infections.[3-6] The ATM protein is a key regulator of cellular pathways that protect cells from malignant transformation which can result from exposure to genotoxic agents, such as ionizing radiation, which induce DNA double-strand breaks.

Although *ATM* heterozygotes do not have AT, an excess breast cancer (BC) risk among obligate heterozygous mothers of individuals with AT was first reported in the late 1970s,[7] subsequently confirmed across multiple studies. BC risk is elevated in the range of 2- to 3-fold for most *ATM* germline pathogenic/likely pathogenic variants, collectively referred to here as germline pathogenic variants (GPVs),[8-10] although risks may be higher for some selected missense variants.[11,12] *ATM* heterozygotes also have an increased risk of pancreatic, prostate, and gastric cancer.[10] Additionally, modest associations have been reported for cancers of the colorectum, ovaries, and melanoma,[10] but further larger studies are required to confirm cancer risks. Several hundred GPVs have been identified to date, most of which are truncating variants.[13,14]

The population frequency for heterozygous *ATM* GPVs can be estimated using the prevalence of AT in live births and the Hardy-Weinberg equilibrium or assessed directly through large-scale next-generation sequencing projects. Before the discovery of the *ATM* gene, Swift et al[15] estimated that the minimum heterozygote frequency of a gene causing AT in the United States would be 0.0034 (1/290), based on vigorous case finding. Schmitz et al[16] recently assessed the carrier frequencies of autosomal recessive conditions using Genome Aggregation Database genomes (gnomAD v3.1) in diverse populations.[17] The maximum gene heterozygote frequency for *ATM* was 0.00706 (1/142; Latino/Admixed American populations) with a gene heterozygote frequency of 0.00280 (1/357) in African/African American populations, 0.00230 (1/434) in Ashkenazi Jewish populations, 0.00270 (1/370) in East Asian populations, 0.00361 (1/277) for non-Finnish European populations, and 0.00083 (1/1204) in South Asian populations. These estimates are similar to the frequency of heterozygotes in controls in a recent population BC case-control study in the United States,[9] which found that *ATM* GPVs were present in 0.78% (253/32,247; 1/127) of case patients and 0.41% (134/32,544; 1/242) of controls.

Although the association of *ATM* GPVs with cancer predisposition has been reported across multiple studies, ranging from single-case reports to large case-control analyses, clear guidance for the clinical management of individuals assigned female or male at birth with an *ATM* GPV remains lacking. The dearth of clinical guidance has likely occurred because of the complexities in establishing the cancer spectrum and penetrance for *ATM* heterozygotes. Challenges in unravelling the role of *ATM* in cancer predisposition include (1) varying estimates of penetrance depending on the study design and the population studied, (2) uncertainties about the tumor spectrum and characteristics, (3) the role of family history and other modifiers in cancer risk estimates, (4) the difficulties of establishing robust genotype/phenotype associations, particularly for those missense variants that impart lower or higher risks than predicted truncating variants, and (5) widespread misinformation about the risks of therapeutic radiation among heterozygotes.

Although *ATM* is generally considered a moderate (also known as intermediate) risk cancer predisposition gene, the data indicate that cancer risks for heterozygotes lie on a continuous scale, ranging from population risk to high risk, influenced by the specific variant, family history, and modifying genetic and nongenetic risk factors. Given these uncertainties in risk, there is clinical caution regarding genetic testing and management of *ATM* heterozygotes. Consequently, disentangling the available data and information and translating this into guidance for clinical practice has been both challenging and nuanced, similar to other moderate-risk genes.[18]

Rapid progress in genetic sequencing technologies has led to identification of greater numbers of *ATM* heterozygotes either through germline or tumor multigene panel testing, tumor genome/exome sequencing, and/or carrier screening panels during pregnancy or preconception. As a result, there is an increasingly urgent clinical need for

consistent, evidence-based, pragmatic guidance for the management of *ATM* heterozygotes in clinical practice, specifically considering the clinical utility of personalized (rather than generalized) risk assessment and surveillance recommendations (ie, an estimated risk taking into consideration known risk factors based on current available evidence, rather than a risk based on genetic status alone).

Methods

An international workgroup with expertise in clinical cancer genetics, genetic counseling, gynecology, and medical oncology developed a list of clinical areas in the management of *ATM* heterozygotes and performed a comprehensive literature review with the assistance of a biomedical librarian (see Supplemental Methods). Section authors critically reviewed the search results and synthesized findings narratively; additional relevant publications were included based on author judgment and expertise. Before 2015, when the American College of Medical Genetics and Genomics (ACMG) variant classification guidelines were released,[19] disease-associated *ATM* variants were not classified according to more modern criteria; reclassification of older reported variants was not performed in this study. All reported disease-causing variations are referred to as GPVs.

Clinical management recommendations were derived by consensus from the literature resource and the collective expertise of the authors.

The workgroup met monthly via video conference calls beginning in October 2022 and participated in email discussion and review throughout the process. Workgroup members independently drafted sections of the document commensurate with their area of expertise and reviewed the entire manuscript. Clinical management recommendations were derived by consensus from the literature resource and the collective expertise of the authors. Working and final drafts were reviewed and approved by members of the Professional Practice and Guidelines Committee and the ACMG Board of Directors. As per ACMG policy, a mature draft of the manuscript was sent to ACMG membership for review and comment. The workgroup reviewed the comments and revisions were made to the final manuscript, which was then approved by the Professional Practice and Guidelines Committee and the ACMG Board of Directors.

Challenges in *ATM* variant interpretation

Challenges in *ATM* variant interpretation include genetic heterogeneity, lack of well-defined germline mutational hotspots, and cooccurrence of benign and pathogenic/likely pathogenic variants within the same gene domain and even within the same amino acid residue. However, perhaps the most difficult challenge when assessing the clinical impact of heterozygous *ATM* variants in cancer predisposition is moderate penetrance. This is illustrated when cosegregation analyses data support pathogenicity for a variant in a reduced penetrance gene by incorrectly assuming it is causative of an individual's phenotype (BC).[20]

Furthermore, current classification frameworks are mainly focused on variants in genes associated with early-onset, highly penetrant phenotypes not designed for moderate penetrance genes, such as *ATM*.[21] To address some of these challenges, the ClinGen Hereditary Breast and Ovarian Cancer Variant Expert Curation Panel and a Spanish *ATM* working group have made efforts to customize the widely used ACMG/Association of Molecular Pathology recommendations on variant classification,[19] resulting in specifications for the interpretation of sequencing variation in *ATM*.[22,23] These documents provide cutoff values for the use of case-control studies[24] and filtering allele frequencies for evidence of benignity and pathogenicity, in which *ATM*-specific prevalence (BC), allelic heterogeneity, genetic heterogeneity, and penetrance are considered.

Complex variations in penetrance among distinct types of variants have been described. The Gene Sisters (GENESIS) study directly compared truncating vs missense variants and found that heterozygotes for an *ATM* truncating variant had a significantly higher risk of developing BC than those with an *ATM* likely deleterious missense variant (OR = 17.4 vs OR = 1.6; p Het = 0.002),[25] recognizing that risks are higher for select higher-risk missense variants.[10-12,26-28] However, other evidence suggests that these associations are not straightforward as outlined in the next section. Of note, although some *ATM* GPVs are known to confer high and moderate cancer risk, there are currently no *ATM* GPVs submitted to ClinVar with a pathogenic, lower penetrance classification.[29]

The Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) group established guidelines outlining a standardized approach to report germline cancer susceptibility variants, considering factors such as pathogenicity, penetrance, and clinical actionability. Their proposed framework suggested reporting only variants with a 2-fold or higher risk because variants with less than a 2-fold relative risk (RR) are considered to have limited clinical relevance when considered in isolation.[30] Although these variants can be reported, clinical laboratories may choose not to report them, given that they do not have clinical utility. Additionally, recommendations for clinical management should be based on a comprehensive assessment of the specific variant, along with the individual's personal and/or family medical history, as well as other known genetic and environmental risk factors. Variants included in the current document are summarized in Supplemental Table 1.

Specific missense variants with higher cancer risk

Specific *ATM* variants predispose to higher risks than the average truncating variant in the range of 4- to 6-fold, most notably the NM_000051.4:c.7271T>G p.(Val2424Gly)

variant in the PIK domain),[10-12,26-28] which confers a BC risk of 52% by age 70[12] and 60% by age 80.[11] Although this high risk of BC was not replicated in a recent large case-control study,[31] other studies are supportive that this variant confers higher BC risks. Other similar variants have been reported, such as the Finnish founder GPV, NM_000051.4:c.7570G>C p.(Ala2524Pro) (OR = 8.5, 95% CI, 1.04-62.86, $P = .018$).[32]

Consistent with standard clinical practice, reporting of *ATM* variants should include clear language on variant pathogenicity and predicted penetrance.

Variants of uncertain significance

The combination of *ATM* being a large gene and being included in most hereditary cancer multigene panels has likely contributed to the great number of *ATM* variants of uncertain significance (VUS) identified by laboratories around the world. Illustratively, the University of Utah's ClinVar Miner web-based tool (https://clinvarminer.genetics.utah.edu/) lists *ATM* as the gene with the eighth-most variants with any review status submitted to ClinVar and the gene with the fifth-most variants classified as VUS. Furthermore, when variants with conflicting interpretations are excluded, VUS represent approximately half of total single-gene *ATM* variants reported ($n = 4333/8344$). In contrast to GPVs in *ATM*, for which most are truncating variants expected to cause loss of function, VUS in *ATM* are enriched for splice site, synonymous, intronic, and, especially, missense ($n = 3898/4333$) variants, for which functional and clinical significance is less evident.[33] Consequently, depending on the indication for testing, the chance of finding an *ATM* VUS may be higher than the chance of finding an *ATM* GPV.

To better understand the functional impact of these variants, various methods are effectively used to upgrade or downgrade VUS in *ATM*, including RNA analyses, AT (ATM null cell line) failure-to-rescue studies typically targeting phosphorylation, radiosensitivity assays, and variant prioritization algorithms.[34,35] Although some studies have used loss of heterozygosity (LOH) analyses to provide further evidence of pathogenicity for variants in cancer genes, the utility and reliability of these assays are still unclear. Indeed, although variant classification systems published by expert groups, such as ENIGMA and ClinGen Hereditary Breast and Ovarian Cancer Variant Expert Curation Panel's classification, provide a list of well-established functional assays for *ATM* variants, the results of LOH analyses have not yet been implemented as a reliable source of evidence. Similarly, the use of cosegregation analyses, a helpful tool in classification of VUS in other cancer genes, such as *BRCA1* (HGNC:1100) and *BRCA2* (HGNC:1101), is not recommended for intermediate penetrance genes, such as *ATM*.[23]

VUS in ATM should not be used to guide clinical management or for predictive genetic testing for family members, as is the case for all VUS results.

Variant reclassification

Variants in *ATM* can be reclassified (upgraded or downgraded) over time based on revised classification framework or new evidence, which may alter clinical actionability, which should be discussed between clinicians and patients at the time of testing. Several professional societies have published guidelines for re-contact of individuals, reclassification, and reissue of reports.[36-38]

Risk estimation: Cancer risks for *ATM* heterozygotes

Breast cancer

ATM was first identified as a female BC susceptibility gene over 35 years ago,[7] and 2 complementary studies in the mid-2000s derived the associated risk to be around 2-fold.[39,40] Risk estimates have remained stable over the ensuing 2 decades, with the most recent study (Breast Cancer Association Consortium [BCAC], and Breast Cancer Risk after Diagnostic Gene Sequencing [BRIDGES]) based on 294 cases and 150 controls giving an odds ratio (OR) for truncating variants of 2.10 (95% CI, 1.71-2.57).[8] Another large study (CARRIERS) published at the same time generated an OR of 1.82 (95% CI 1.46-2.27) for all GPVs (253 cases and 134 controls).[9] Given the size of these studies, a number of other important observations could be made. First, the risk is predominately for estrogen receptor (ER)-positive cancers, with ER-negative cancers having an OR of 1.01 (0.64-1.59)[8] and 1.04 (0.59-1.72).[9] Second, these estimates are for individuals of European descent, with a similar OR in the Asian population.[8] Third, the OR remains stable with increasing age, with the risks in women under 40 years of age (OR 1.77, 95% CI 0.87-3.44) similar to women over 60 (OR = 2.13, 95% CI, 1.61-3.28).[8]

Neither the BRIDGES[8] nor the CARRIERS[9] study observed an increased risk for contralateral BC for *ATM*, which was in contrast to the other canonical BC genes (*BRCA1*, *BRCA2*, *CHEK2* (HGNC:16627), and *PALB2* (HGNC:26144)).[41,42] The reasons for this are unclear and could be due to small numbers of observations in both studies. It is possible that as *ATM*-related BCs are predominately ER-positive, adjuvant hormone therapy for the primary cancer is particularly effective in preventing second BCs.

There is weak evidence of increased risk for male breast cancer (MBC) from *ATM* GPVs. A recent study identified *ATM* GPVs in 4/340 *BRCA1/2*-negative MBC cases and used Exome Aggregation Consortium (ExAC) controls to generate an OR of 3.36 (95% CI 0.89–8.96, $P = .04$).[43] An

earlier study of 102 Greek MBC cases identified 2 men with *ATM* GPVs,[44] and a US study identified *ATM* pathogenic variants in 6/586 MBC cases,[45] suggesting that around 1% to 2% of males with BC harbor GPVs in *ATM*.

Pancreatic cancer

A role for *ATM* in pancreatic cancer predisposition was proposed by detection of *ATM* GPVs in 2 families with familial pancreatic cancer using exome sequencing.[46] Further analysis of *ATM* identified 4 heterozygotes in 166 probands from families with 2 or more members with pancreatic cancer (2.4%).[47] An initial study of cancer risk in 1160 relatives of 169 patients in the United Kingdom with AT suggested that the risk of pancreatic cancer was increased in *ATM* heterozygotes (RR = 2.41; 95% CI, 0.34-17.1).[40] Although there were limitations to this early study with incomplete ascertainment of families and limited genotyping of family members, subsequent studies (included in a recent systematic review with information on 14,887 individuals affected with pancreatic cancer across 35 studies) reported a similar detection rate. The systematic review concluded that after *BRCA2* (2.9%), *ATM* had the highest frequency of GPVs (2.52%; 231 *ATM* heterozygotes in 9181 individuals with pancreatic cancer across 20 studies). As expected, the detection rate was slightly higher in cases selected for familial pancreatic cancer (32/1036, 3.09%).[48]

A recent multicenter cohort study of 2227 individuals from 130 pancreatic cancer families, predominantly of European ancestry from US and Canadian registries, included 155 *ATM* heterozygotes.[49] Among *ATM* heterozygotes, the average age at diagnosis of pancreatic cancer was 64 years (range 31-98), the cumulative risk of pancreatic cancer was estimated to be 1.1% (95% CI, 0.8%-1.3%) by age 50 years, 6.3% (95% CI, 3.9%-8.7%) by age 70 years, and 9.5% (95% CI, 5.0%-14.0%) by age 80 years, compared with 1.53% (95% CI, 0%-6.45%) risk by age 80 years in those without an *ATM* GPV. Overall, the relative risk of pancreatic cancer was 6.5 (95% CI, 4.5-9.5) in *ATM* heterozygotes compared with those without an *ATM* GPV. The authors recognized the potential for ascertainment bias, undertook proband correction, and noted that the risk estimates were not dissimilar from other studies undertaken on individuals with pancreatic cancer unselected for family history vs ExAC non-Cancer Genome Atlas reference controls (RR = 5.7, 95% CI, 4.4-7.3).[50] In contrast, a study utilizing data from a single commercial lab estimating pancreatic cancer risk using multivariable logistic regression models from multigene panel testing of 676,667 individuals, 2445 of whom had a personal diagnosis of pancreatic cancer and 52 *ATM* heterozygotes, reported a lower OR of 3.44 (95% CI, 2.58-4.60). This lower estimate may be attributable to adjustment of the data for clinical and demographic characteristics associated with cancer risk, including age, personal cancer history, family cancer history, and ancestry, as well as the fact that controls were clinically ascertained, compared with a population-based control set, as for the latter study.[51] A similar analysis of 627,742 patients referred for multigene panel hereditary cancer testing including 4607 *ATM* heterozygotes, 64 with pancreatic cancer, demonstrated an OR falling between the other studies of 4.21 (95% CI, 3.24-5.47),[10] and a recent phenome-wide association study of 214,020 participants demonstrated a similar OR of 4.44 (95% CI, 2.66-7.40).[52]

Prostate cancer

In individuals with prostate cancer, germline truncating variants in *ATM* were first identified in multicase prostate cancer families, with identification of *ATM* GPVs in 2/191 (1%) men from families with 3 or more cases of prostate cancer.[53] *ATM* has also been studied in the setting of early-onset, aggressive, and metastatic prostate cancer, although many of the initial studies were based on small-case series or in selected populations. In the metastatic setting, a retrospective study of 692 men from the United Kingdom and the United States, unselected for family history of cancer or age at diagnosis, identified 11 men with GPVs in *ATM* (1.6%), the second most frequently affected gene after *BRCA2* (5.3%).[54] Another study assessing the role of DNA repair genes in prostate cancer predisposition analyzed 787 men with aggressive disease and 770 with nonaggressive disease. For *ATM*, the proportion of GPVs was higher in the aggressive group (n = 14, 1.8%) vs the nonaggressive prostate cancer group (n = 5, 0.7%) (P = .06).[55]

Two recent large studies contributed further information on detection rates and overall association with prostate cancer risk. The Prostate Cancer Analyses of Alterations in the Genome (PRACTICAL) consortium undertook analysis of next-generation sequencing data from 13 PRACTICAL study groups comprising 5560 prostate cancer cases (including 65 *ATM* heterozygotes) and 3353 controls (including 8 *ATM* heterozygotes) of European ancestry and provided evidence that *ATM* GPVs (as defined in ClinVar) are associated with an increased lifetime prostate cancer (OR = 4.4, 95% CI, 2.00-9.50), as well as a higher risk of early-onset disease.[56] In the same year, a study comprising samples from 12 international studies comprising 5545 men with prostate cancer (2775 nonaggressive vs 2770 aggressive cases and including 47 *ATM* heterozygotes) investigated the role of GPVs in DNA repair genes in aggressive vs nonaggressive disease.[57] *ATM* had a statistically significant association with aggressive prostate cancer but with lower risk reported than the PRACTICAL study (OR = 1.88, 95% CI, 1.10-3.22). A recent international study confirmed the association with aggressive prostate cancer[58] in *ATM* heterozygotes.

A statistically significant association was not confirmed for young onset or familial cases. In the real-world setting, the previously described study by Hall et al[10] evaluating 627,742 patients referred for multigene panel hereditary cancer testing through a commercial laboratory, including 4607 *ATM* heterozygotes, 75 with prostate cancer, demonstrated a moderate association with prostate cancer predisposition (OR = 2.58, 95% CI, 1.93-3.44).

Gastric cancer

An early study of 1160 relatives of 169 AT patients in the United Kingdom suggested increased risks of colorectal and stomach cancers.[40] However, there has been conflicting information from further studies depending on the size of the study and population studied.

In the previously mentioned study by Hall et al[10] through a commercial laboratory data set, of 627,742 patients referred for multigene panel hereditary cancer testing, a moderate-risk association was reported for gastric cancer (OR = 2.97, 95% CI, 1.66-5.31), despite only 12 cases of gastric cancer overall in *ATM* heterozygotes. A recent large study of 10,426 patients with gastric cancer and 38,153 controls from BioBank Japan evaluating risk of gastric cancer with 27 potential gastric cancer predisposing genes, including 136 *ATM* heterozygotes, 76 with gastric cancer, found an association of *ATM* GPVs with a moderate-high risk of gastric cancer (OR = 5.50, 95% CI, 3.82-7.90).[59] A recent phenome-wide association study of 214,020 participants demonstrated an OR of 4.27 (95% CI, 2.35-7.44).[52]

Other cancers

An association of *ATM* GPVs has been suggested for other adult-onset cancers, but further larger studies are likely required to confirm cancer risks. Modest associations of *ATM* GPVs have recently been reported for colorectal cancer (OR = 1.49, 95% CI, 1.24-1.79), ovarian cancer (OR = 1.57, 95% CI, 1.35-1.83), and melanoma (OR = 1.46, 95% CI, 1.18-1.81).[10]

Personalized risk estimation: Polygenic risk score and modifiers of *ATM*-associated cancer risk

The moderate gene-specific risks associated with typical *ATM* GPVs points to a potentially important role of modifying factors in determining clinical implications at a personal level. A number of studies have examined whether genetic, personal, and lifestyle factors associated with cancer risks in the general population can influence the risk in individuals heterozygous for an *ATM* GPV to the extent that it would alter the clinical risk assessment and management recommendations. The largest of these studies have examined the combined effect of cancer-associated common genomic variants detected in genome-wide association studies in the form of a polygenic risk score (PRS) on the risk of BC and, to a lesser extent, prostate cancer. In the case of BC, the published data provide consistent evidence for a clinically important modifying effect that is similar to the magnitude of the effect of the BC PRS in the general population[60-64] and independent of other known risk factors, including family history. The degree to which combining PRS and gene-specific risks leads to reclassification of women into categories with different implications for clinical management varies in studies depending on the PRS used and the average risk estimate assigned to *ATM* GPVs. Lakeman et al,[63] using the well-described 313 BC PRS, reported that including this information altered the risk category of 18% of *ATM* GPV heterozygotes based on the 3 risk categories in the National Institute for Clinical Excellence guideline (https://www.nice.org.uk/Guidance/CG164). The study with the largest number of *ATM* heterozygotes ($n = 2666$),[62] which combined an 86 single-nucleotide variant PRS with personal risk factors and family history, as measured by the Tyrer-Cuzick model, reported that 31.5% had a final residual lifetime BC risk below 20%, whereas 9.7% were assessed with a residual risk of >50%. Overall, the data confirm a clinically significant contribution from the PRS that is important to consider for preventing inaccurate interpretation of *ATM*-associated BC risk at a personal level; however, currently, the literature is limited by a lack of prospective validation and being almost completely restricted to European populations.

The literature is even more limited in relation to the influence of polygenic risk on other cancers associated with *ATM* GPVs. Darst et al[65] described a significant modifying effect of a multiancestry PRS on prostate cancer risk in a group of men with GPVs in a range of prostate-cancer-associated genes, including *ATM*, whereas Xu et al[66] measured both *ATM* GPVs and a PRS as independently associated with prostate cancer risk in the UK Biobank. These findings are consistent with a simple multiplicative risk model, but the data remain preliminary. No similar studies have been published for pancreatic or other cancers. Consequently, it remains premature to use PRS to guide clinical care outside of research studies given existing uncertainties.

Personalized risk estimation: Other modifiers

Nongenetic factors may modify the risk of female BC associated with a heterozygous GPV in *ATM*. Therapeutic doses of radiation have been studied for possible increased toxicity and possible risk of a second primary BC. The concern is based on the findings of radiation sensitivity in individuals with AT (ie, with biallelic *ATM* GPVs). Although in vitro cellular assays,[67] a mouse model,[68] and an early case study[69] have suggested a possible increase in toxicity and/or cancer risk associated with germline heterozygosity for *ATM*, more recent clinical data suggest that adjuvant radiotherapy in BC treatment in women with a heterozygous *ATM* GPV is not contraindicated. In fact, radiation treatment has been demonstrated to reduce local relapse in this population.[70-72]

Multiple studies have evaluated short-term and long-term toxicity associated with radiotherapy among women with BC and an *ATM* pathogenic variant (PV).[71,73] These women do not appear to be at an increased risk for the development of toxicity (acute or late) after breast radiation. Furthermore, there is no evidence that adjuvant radiotherapy increases the risk of a second primary malignancy after BC treatment in *ATM* heterozygous women.[74]

Pathology of *ATM*-related tumors

Other than BC, there is a paucity of data on the specific pathological appearance of *ATM*-related tumors. Moreover, pathology of *ATM*-related tumors is complicated by an OR for all known cancer association among *ATM* heterozygotes in most studies of less than 5.0. Consequently, in a significant fraction of tumors occurring in *ATM* heterozygotes, the *ATM* PV is not causal for the cancer, which will dilute any real associations.

Breast cancer

In the large CARRIERS[8] and BRIDGES[9] studies (total ~80,000 affected women), a clear association between *ATM* GPVs and estrogen receptor (ER)-positive BC was observed (BRIDGES OR = 2.33, P = 9.1E−14, CARRIERS OR = 1.96, $P < .001$).[8,9] No association was seen for ER-negative BCs (OR = 1.01, P = .97 and OR = 1.04, P = .89, respectively).[8,9] In an extended BRIDGES study, the largest OR was seen for the high-grade, ER-positive, HER2-negative subgroup (OR = 4.99, 95% CI, 3.7-6.8), whereas for all HER2-positive groups and (as expected) triple-negative breast cancer (TNBC), no significant associations were seen.[75] Another study based on commercial laboratory testing (n = 56,480 tumors) found in contrast that, ER-positive, HER2+ BCs were most strongly associated with *ATM* GPVs (OR = 3.99), but none of the comparisons with other subgroups (except TNBC) were significant.[76] Although the sample sizes are much smaller, there is no compelling evidence that the overall effects of an *ATM* GPV on the core phenotype of BC differ in Black females.[77-79]

Through exome sequencing among BC patients, 24 arose in those with GPVs in *ATM*. As expected, all were ER positive and displayed little in the way of immune infiltration.[80] Nearly 80% of the tumors showed LOH of the wild-type allele, but none showed appreciable homologous recombination repair defects (HRD), as measured by mutational signature 3 activity. No *ATM*-related tumor contained a somatic PV in *TP53*. Other small studies have shown similar results.[81-83] Taken together, these findings demonstrate that *ATM*-related BCs are molecularly completely different to cancers causally related to the family of genes often associated with response to poly-adenosine diphosphate ribose polymerase inhibitors (PARPi) (eg, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*).

Pancreatic cancer

GPVs in *ATM* predisposes to pancreas adenocarcinoma.[84] Studies of *ATM*-related pancreas cancer have shown that LOH of the wild-type allele in most cases.[85,86] Park et al[86] reported a genome instability score (GIS)[87] of 11 (where a GIS ≥ 42 in breast and ovarian cancer equals HRD) among 33 patients. These data suggest that pancreatic cancer is likely to be less responsive than breast and ovarian cancer to therapies directed to HRD tumors. GPVs in genes shown to predispose to pancreatic cancer include *BRCA2*, *BRCA1*, and *ATM*[88] (see Outcomes of *ATM*-associated cancers section). As shown for BC, few *ATM* cases were *TP53*-mutated (n = 5, 11%), and none were clearly biallelic for *ATM* PVs.[86]

Prostate cancer

ATM protein can be detected by immunohistochemistry,[89] and loss of ATM protein is present in about 3% of primary prostate cancer but is much more frequent in grade 5 tumors (17/181, 9%) than among all other grades (8/650, 1%) ($P < .0001$) and is very sensitive for biallelic *ATM* inactivation. This finding is supported by germline genetic testing; only a very small percentage of all prostate cancer is associated with GPVs in cancer susceptibility genes,[90,91] but this percentage is often higher in men with advanced prostate cancer (associated with a higher Gleason score), especially those with metastatic castration-resistant prostate cancer (mCRPC). For *BRCA2*, the effect is very striking but is less so for *ATM*,[53,92-96] with the prevalence of *ATM* GPVs in most mCRPC studies being in the range of 1.6%-2.1%,[97] and is stable across population groups. As for pancreatic cancer, the HRD score for *ATM*-mutated prostate cancer appears to be lower than for *BRCA2*-mutated prostate cancer,[95,98] and it seems unlikely that *ATM*-related prostate cancer will respond to PARPi (see Therapeutic implications of *ATM* gene variation). Consequently, the main implication of finding an *ATM* GPV currently is that if prostate cancer does develop, it is likely to be more aggressive than for those without an *ATM* GPV.

Gastric adenocarcinoma

In the Cancer Genome Atlas study of more than 10,000 cancers, a significant association between gastric adenocarcinoma and *ATM* GPVs was observed.[99] In BioBank Japan, a highly significant association was also observed, which appears to be modulated by exposure to *H. pylori*.[59] Further work is required to establish the significance of this finding in non-Asian populations.

Outcomes of *ATM*-associated cancer

Breast cancer

A retrospective study of the records of 286 women with stage I-III BC with a median of 4.4 years of follow-up found that 25.6% harbored a GPV in a known BC gene (*ATM*; n = 8; 4%).[100] No significant differences were found in overall survival, locoregional recurrence, or disease-specific death between groups (patients with a GPV in *BRCA1/2* vs non-*BRCA1/2*). Acute and late toxicities were comparable across groups.

Prostate cancer

GPV *ATM* variants are often grouped with variants from other genes, making it difficult to discern *ATM*-specific outcomes. In a study of 692 men with metastatic prostate cancer (unselected for family history or age of onset), 82

(11.8%) harbored a GPV in a DNA repair gene, including 11 (1.6%) in *ATM*.[54] This incidence was higher than in men with localized prostate cancer. Of the 73 men with a Gleason score available (recognizing that higher Gleason scores are associated with worse outcomes), there was marginal evidence ($P = .04$) that a DNA repair gene GPV was associated with a Gleason score of 8 through 10 vs 7 or lower.

In a retrospective case study of 313 men who died of prostate cancer and 486 men with low-risk localized prostate cancer of European, African, and Chinese descent, 3 genes (*BRCA1, BRCA2, ATM*) were sequenced from germline DNA.[94] There were 19 GPVs in the 3 genes (6 *ATM*) in the lethal group and 7 GPVs (2 *ATM*) in the localized group. In the entire cohort, GPV status was not significantly associated with age at diagnosis. However, GPV status was significantly associated with more advanced prostate cancer at the time of diagnosis. Men with a GPV had a higher proportion of Gleason score >7 (71%) than those who did not (31%; $P = .00009$), as well as higher median prostate-specific antigen (PSA) levels (7.90 ng/ml) than those without an *ATM* GPV (6.20 ng/ml; $P = .048$). GPV status was significantly associated with progression of prostate cancer. Specifically, in men with lethal prostate cancer, GPV status differed significantly as a function of age at death. No GPVs were observed in 49 men dying from prostate cancer over the age of 80. Men with a GPV also died significantly sooner after diagnosis than men who did not harbor a GPV. In summary, GPV status of *ATM* and *BRCA1/2* distinguishes the risk for lethal and indolent prostate cancer and is associated with earlier age at death and shorter survival time.

A study of 172 men with mCRPC identified 9 men with a GPV in *BRCA1/2* ($n = 6$) or *ATM* ($n = 3$).[101] By numerous measures, outcomes to first-line next-generation hormonal therapy (abiraterone or enzalutamide) in men with a germline *BRCA1/2* or *ATM* GPV appeared better than in men who did not harbor such variation, but these conclusions are tempered by the small number of observations. A prospective multicenter study of 419 men with mCRPC found that 68 (16.2%) harbored a GPV in *ATM* ($n = 8$), *BRCA1* ($n = 4$), *BRCA2* ($n = 14$), or *PALB2* ($n = 0$), but there was no significant difference in cause-specific survival vs men who did not harbor GPVs in those genes.[102] In contrast, a study of 1160 Chinese men with prostate cancer found worse outcomes in men with a GPV in *ATM*, *BRCA2*, *PALB2*, or *MSH2* (HGNC:7325) (vs men without such variation) when treated with androgen deprivation therapy and abiraterone, but found similar benefit from docetaxel.[103] Separate analysis of the men with a GPV in *ATM* ($n = 19$) was not performed.

A meta-analysis of 11 studies (3944 progressors; 20,054 nonprogressors) found a significantly higher rate of individuals harboring a GPV in 1 of 5 genes (including *ATM*) in progressors vs nonprogressors.[104] The pooled odds for *ATM* was 1.93 (95% CI, 1.17-3.20); an *ATM* GPV was observed in 0.83% of 9465 progressors and 0.16% of 1882 nonprogressors.

A study of 557 metastatic prostate cancer patients sequenced *ATM* plus 10 other DNA damage repair genes[97] and found *ATM* GPVs in 11 (2%). The study summarized other recent large studies (range $n = 317$-867) sequencing germline variants in metastatic prostate cancer. *ATM* GPVs were consistently found in ~2% of these men, comparable to the frequencies observed for *CHEK2* and second only to *BRCA2* and associated with an earlier age of metastatic disease and death. Current evidence indicates that conventional therapies can be effective in metastatic cancer in men with *ATM* GPVs and should be considered before PARPi, which shows limited efficacy in this group.[105]

Pancreatic cancer

In a study of 464 individuals with high-risk pancreatic cancer undergoing surveillance,[106] 134 harbored a germline deleterious mutation in a pancreatic cancer risk gene (including 15 in *ATM*). The cumulative incidence of pancreatic cancer, high-grade dysplasia, and worrisome features on imaging was significantly higher in the germline mutation group than in the familial risk group. However, a subanalysis of individuals with an *ATM* variant showed no difference, but this was limited by a small number of events. In contrast, in a smaller study[107] of 133 people with metastatic pancreatic cancer, 15 (11%) harbored a deleterious germline mutation in a DNA damage repair gene (*ATM* [$n = 3$], *BRCA1/2*, *CDKN2A* [HGNC:1787], *CHEK2*, *ERCC4* [HGNC:3436], or *PALB2* [HGNC:26144]). Patients with a variant in a DNA damage repair gene had significantly improved overall survival compared with those who did not. Similarly, in a prospective study of 3078 patients with pancreatic adenocarcinoma with a median of 9.9 years of follow-up,[108] 175 harbored germline pathogenic variation in 1 of 8 homologous recombination repair (HRR) genes (including 65 in *ATM*, 2.1%). Patients with an HRR GPV were significantly younger, more likely to have metastatic disease at diagnosis and had a longer overall survival compared with patients without such variation. Notably, patients with an *ATM* GPV had significantly longer overall survival compared with patients without GPVs in any of the other 37 tested genes.

Clinical management: Cancer surveillance and risk-reducing surgery

Breast cancer

The variability in risk is reflected in differences in BC surveillance guidelines across various countries; in a recent European study, ages for initiating surveillance and for incorporating magnetic resonance imaging (MRI) into surveillance ranged from age 30 to 40.[109] A modeling analysis of *ATM* heterozygotes predicted a significant reduction in BC mortality using annual breast MRI starting at ages 30 to

35 years and annual mammography starting at age 40.[110] The importance of modifying factors in determining cancer risk underscores the importance of individualizing BC surveillance for *ATM* GPV heterozygotes using a risk assessment model, such as CanRisk, for truncating variants. Through CanRisk, the model-calculated risk along with country-specific guidelines may then be used to make final screening recommendations. Female *ATM* heterozygotes are generally offered an annual screening mammogram before or generally by age 40 and may additionally be offered an annual MRI depending on specific country thresholds and guidelines.

Guidelines across multiple countries, including the United States and Europe, all indicate insufficient evidence to routinely recommend risk-reducing mastectomy in unaffected female *ATM* heterozygotes (Supplemental Table 2). In cases warranted based on individualized BC estimates (eg, based on risk models that may include personal and family history, hormonal and lifestyle risk factors, breast density, and PRS), discussion of risk-reducing mastectomy should be part of a shared decision-making process and include a thorough discussion of surgical options and risks.

Although risks for contralateral BCs are not known to be increased, *ATM* GPV heterozygotes with a history of BC and remaining at-risk breast tissue may be offered individualized surveillance. In general, the data on *ATM*-related BC risk do not support routine consideration of risk-reducing mastectomy; however, the decision for an *ATM* heterozygote to undergo bilateral mastectomy at the time of diagnosis of unilateral BC should be a shared decision-making process based on individual estimated risk and BC characteristics (ie, age, tumor size, stage, grade, receptor status, laterality, and family history).

Additional cancer prevention options may be considered for those with very high-risk *ATM* variants, such as the c.7271T>G p.(Val2424Gly) variant, depending on specific country thresholds and guidelines.

Pancreatic cancer

The benefits of surveillance for pancreatic cancer remain unclear. A multicenter study using annual surveillance with endoscopic ultrasound and/or MRI/magnetic resonance cholangiopancreatography in 1461 individuals at increased risk identified 9 cancers during the study period, which equates to 2 cancers per 1000 individuals per year.[111] None of the cancers occurred in the 93 *ATM* heterozygotes. Of the 9 cancers, 7 were stage 1, and 8 were resectable. However, during the study period, 8 participants had pancreatic resections for concerning cystic lesions, 3 of which were high-grade pancreatic intraepithelial neoplasia, whereas 5 were low-grade dysplasia and therefore represent overdiagnosis. Another study of 336 high-risk individuals (including 1 *ATM* heterozygote) identified 10 cancers of which only 4 were resectable.[112] Seven out of 10 were heterozygotes for *CDKN2A*; therefore, one explanation may be that cancers in this group are more aggressive, but further studies are needed to confirm this.

Given the elevated risk for pancreatic cancer, *ATM* heterozygotes with a family history of pancreatic cancer in a first- or second-degree relative on the side of the family from which the GPV is known or thought to originate from may consider surveillance per the current international Cancer of the Pancreas Screening guidelines.[113] More recently, the American Society of Gastroenterology put forth guidelines focused on screening for pancreatic cancer in individuals at increased risk because of genetic susceptibility.[114] They included pancreatic cancer screening among individuals with heterozygous pathogenic variants in *ATM* who do not have a family history of pancreatic cancer, acknowledging that the quality of evidence is low. Pancreatic cancer screening regardless of family history was recently also included in the US-based NCCN Genetics/Familial Guidelines: Breast, Ovarian, Pancreatic, and Prostate Cancer.[115] Per current NCCN guidelines, those eligible should initiate surveillance at age 50 or 10 years younger than the initial familial exocrine pancreatic cancer diagnosis.[115]

Surveillance tests may include annual endoscopic ultrasound or MRI/magnetic resonance cholangiopancreatography; surveillance should be done in centers with appropriate expertise.[113] It is important to recognize that pancreatic cancer surveillance recommendations are mainly based on consensus rather than more rigorous evidence assessments, as additional data continue to be collected to determine the benefits from surveillance. Although surveillance for pancreatic cancer is encouraged in the context of a surveillance study in the United States, the position in the United Kingdom is that pancreatic cancer surveillance is not recommended outside of a research study because of the lack of data supporting efficacy.

Prostate cancer

Given the reported increased risk, it is reasonable to consider annual PSA testing beginning at age 40 (NCCN). A digital rectal exam may be useful to guide interpretation of PSA findings in *ATM* GPV heterozygote men.[116]

Ovarian cancer

There is no established method to detect ovarian cancer early[117]; therefore, the only means to reduce ovarian cancer risk is through risk-reducing salpingo-oophorectomy (RRSO). Female *ATM* heterozygotes do not usually meet the risk threshold to consider RRSO[118]; therefore, it is generally not recommended (NCCN). However, other factors such as family history, age of cancer diagnosis in family members, and other hormonal risk factors may be considered when making a decision about RRSO[119] in the context of shared decision making.

For ATM GPV heterozygotes ACMG advises the following:

- *BC surveillance recommendations should be based on an individualized risk assessment using a model such as CanRisk. Most ATM heterozygotes will meet the*

criteria for enhanced breast surveillance above population-based surveillance, and some will meet the criteria for breast MRI, based on country-specific guidelines/criteria. Note that CanRisk is not currently designed to incorporate risks associated with nontruncating variants, such as the higher risk variants (eg, c.7271T>G p.(Val2424Gly)), into the risk assessment and thus would underestimate risks and should not be used to generate risks for these variants.

- *Female ATM heterozygotes do not usually meet the risk threshold to offer bilateral risk-reducing mastectomy; thus, they should not be offered routinely but may be considered based on an individualized risk assessment using a model such as CanRisk and shared medical decision making.*
- *For females affected with BC, contralateral risk-reducing mastectomy should not be routinely offered but may be considered based on an individualized risk assessment using a model such as CanRisk and shared medical decision making.*
- *Pancreatic cancer surveillance should be considered but, ideally, as part of a clinical trial.*
- *It is reasonable to consider annual prostate cancer screening at age 40 with PSA testing.*
- *The data on ovarian cancer does not support routine risk-reducing salpingo-oophorectomy (RRSO). However, in the presence of a family history of ovarian cancer, or if gynecological surgery is planned for other reasons, shared decision-making RRSO including risks and benefits may be discussed.*

Therapeutic implications of *ATM* gene variation

In tumors with biallelic *ATM* inactivation, alteration of DNA damage checkpoints may indirectly compromise HRR. This has led to the investigation of targeted therapies, such as platinum-based chemotherapy and PARPi, in different tumor types.[120]

Most clinical research on targeted therapies in tumors with *ATM* GPVs occurred in patients with mCRPC who were enrolled in clinical trials after identification of any HRR mutation in tumor testing. Olaparib and talazoparib with enzalutamide have received FDA approval for patients with a GPV in any of the 12-HRR genes, including those with *ATM* GPVs. Nevertheless, there are conflicting data regarding the clinical benefit of PARPi, specifically in *ATM*-mutated tumors. Although the TOPARP-A and -B trials with olaparib showed enhanced antitumor activity,[121-123] this was not confirmed in the PROFOUND trial[124] nor in the phase-3 clinical trial TRITON-3 with rucaparib.[125] The combination of talazoparib with enzalutamide vs enzalutamide as first-line in patients with mCRPC was not statistically better in *ATM*-mutated patients. Overall, PARPi is likely to be ineffective in prostate tumors for which the driver lesion is an *ATM* GPV.[126]

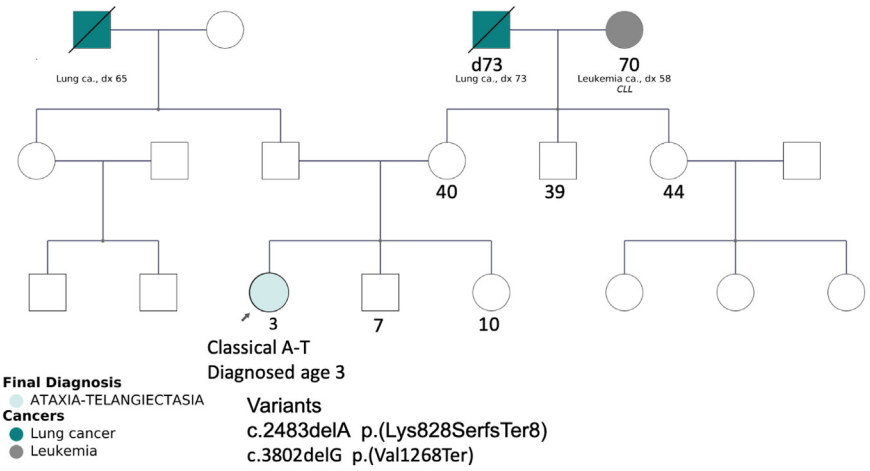

Figure 1 **AT proband.** A 3-year old child presented with gait unsteadiness. Examination findings included ataxia and oculocutaneous telangiectasia. Genetic testing identified 2 heterozygous truncating variants in the *ATM* gene: NM_000051.4:c.2483del p.(Lys828SerfsTer8) and NM_000051.4:c.3802del p.(Val1268Ter). Parental testing confirmed that these were in trans. Before the diagnosis of AT in the child, CanRisk calculated the 40-year-old mother's chance of developing breast cancer to age 80 as 11% based on the family history. As a heterozygote for a truncating *ATM* variant, her chance of developing breast cancer to age 80 was calculated as 21%. She was offered enhanced breast surveillance. Genetic testing was offered to her siblings and her partner's sister.
Discussion points are as follows:

- *ATM* GPVs can be ascertained through the diagnosis of an individual with AT.
- A family history of typical *ATM*-related cancers may be absent due to reduced penetrance.
- Parents are obligate *ATM* heterozygotes. Genetic counseling should include reproductive options and discussion of their cancer risks due to being *ATM* heterozygotes.
- Cascade testing of other adult family members is appropriate to guide their management.

Similarly, for patients with BC and an *ATM* GPV, there is limited evidence supporting the use of PARPi. In the TBCRC 048 trial, 8 patients with *ATM*-mutated metastatic BC (4 with GPVs) received olaparib, resulting in no observed responses.[127] Moreover, in the VIOLETTE trial, olaparib demonstrated restricted effectiveness in germline *ATM* heterozygotes with TNBC.

In colorectal and gastric cancers, different studies have highlighted *ATM* status as a prognostic factor. In the GOLD trial (a randomized, anonymized, placebo-controlled, multicenter Phase III trial that evaluated the safety and efficacy of olaparib in combination with paclitaxel for advanced gastric cancer), gastric cancer absent of staining for ATM protein by immunohistochemistry was linked to better outcomes than cancers for which staining was present, regardless of the treatment arm (paclitaxel or paclitaxel plus olaparib).[128] Another study involving metastatic colorectal cancer patients revealed a notably prolonged overall survival in tumors with an *ATM* GPV when compared with those with *ATM* wild-type status.[129]

In pancreatic ductal adenocarcinoma, anecdotal evidence is centered in the context of oxaliplatin-based chemotherapy, with partial or stable responses in *ATM*-mutated cases.[130,131] However, recent investigations revealed limited responses to olaparib in pancreatic ductal adenocarcinoma with *ATM* GPVs or immunohistochemistry-negative ATM.[132]

Among *ATM* heterozygotes, the literature does not support avoiding radiation therapy based on mutation status, including their avoidance or dose modification. Consequently, the current consensus is to offer radiation therapy when indicated, without taking *ATM* heterozygote status into account.

Novel drugs with potential synthetic lethality with *ATM*-deficient tumors, such as ataxia-telangiectasia and Rad3-related protein (ATR) inhibitors, are currently under investigation. Preclinical data demonstrated promising antitumor activity in *ATM*-deficient cells,[133-135] with several clinical trials currently ongoing.

In conclusion, despite there being very little evidence that PARPi work in patients with mCRPC and an *ATM* GPV,

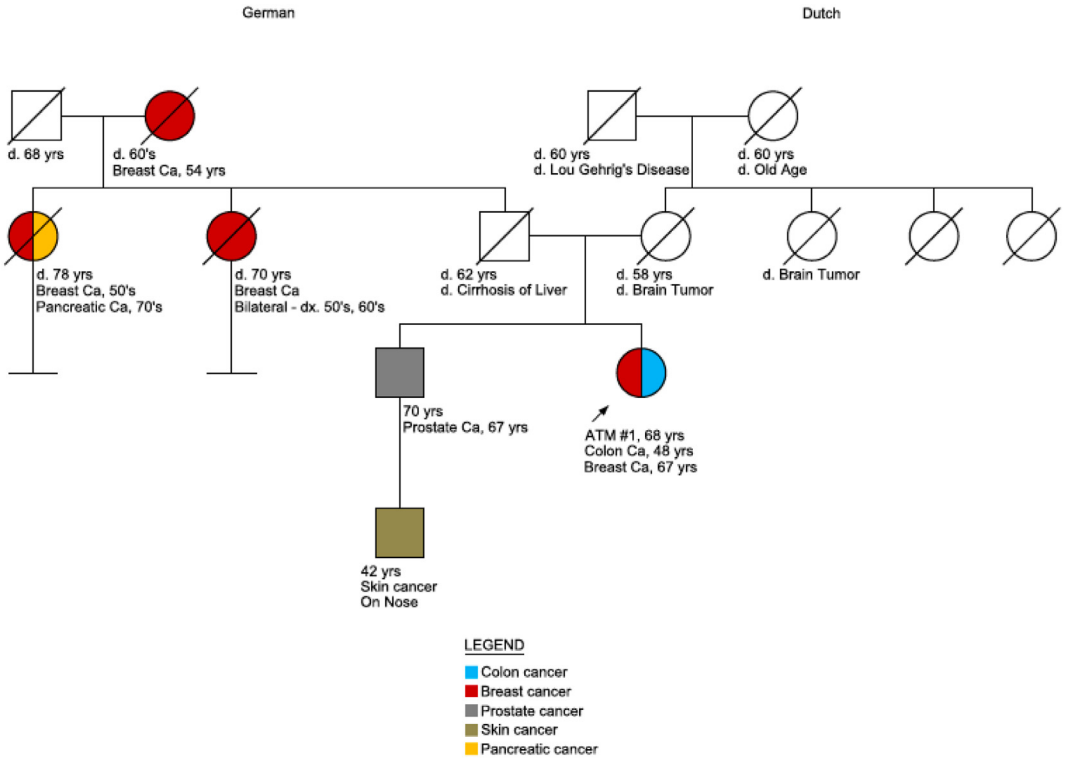

Figure 2 **Proband with higher penetrance *ATM* GPV.** A 67-year-old female with a recent diagnosis of breast cancer (hormone receptor positive) was treated with lumpectomy and chemotherapy. Because of her breast cancer diagnosis, she was offered multigene panel testing by her treating physician, through which she was identified to have an *ATM* GPV (c.7271T>G p.(Val2424Gly)). She was subsequently referred by her outside radiologist to the cancer genetic risk assessment service to discuss the implications of *ATM* GPV as it relates to radiation therapy. Of note, the patient also has a history of colon cancer diagnosed at age 48, and was treated with surgery and chemotherapy. Discussion points are as follows:

- The specific missense GPV is the higher penetrance *ATM* variant associated with up to a 60% lifetime risk of breast cancer.
- Reproductive implications: milder ataxia-telangiectasia phenotype associated with this GPV in the compound heterozygous or homozygous state GPV is missense in nature; thus, some protein is produced.
- Radiation therapy is not contraindicated based on *ATM* GPV.

olaparib as monotherapy and the combination of talazoparib with enzalutamide both have FDA approval under the label of any HRR tumor gene mutation. There is no evidence of clinical benefit for targeted therapies in other tumor types. When indicated, radiotherapy in patients with an *ATM* pathogenic variant should not be avoided.

AT

AT is an autosomal recessive multisystem neurodegenerative disorder affecting the central and peripheral nervous system, immune system, and respiratory system.[2] Individuals have a high risk of malignancy, particularly leukemia and lymphoma,[27,136-138] and a very high risk of BC at a young age.[27,138] There is increased radiosensitivity at both the cellular and clinical level.[139] Oculocutaneous telangiectasia and raised alpha-fetoprotein are helpful clues for making the clinical diagnosis.[140] Endocrine abnormalities, including hypogonadism, are common.[141] The incidence of AT has been estimated at between 1 in 300,000[142] and 1 in 100,000.[15]

Classical AT occurs in people who have biallelic *ATM* GPVs, which result in absent ATM protein or a mutant protein with no ATM kinase activity.[136] Other laboratory findings are increased chromosomal radiosensitivity[139] and increased chromosomal translocations in T-lymphocytes involving T cell receptor genes on chromosomes 7 and 14.[143] Classical AT usually presents with unsteadiness in early childhood, and children lose ambulation before their teenage years.[144] Neurological features include cerebellar ataxia, dysarthria, extrapyramidal features (such as dystonia or chorea), oculomotor apraxia, and peripheral neuropathy.[144] Individuals with classical AT have a predisposition to lymphoid tumors in childhood or as young adults and a predisposition to developing BC at a young age.[136] Immunodeficiency is caused by a reduced number of circulating T

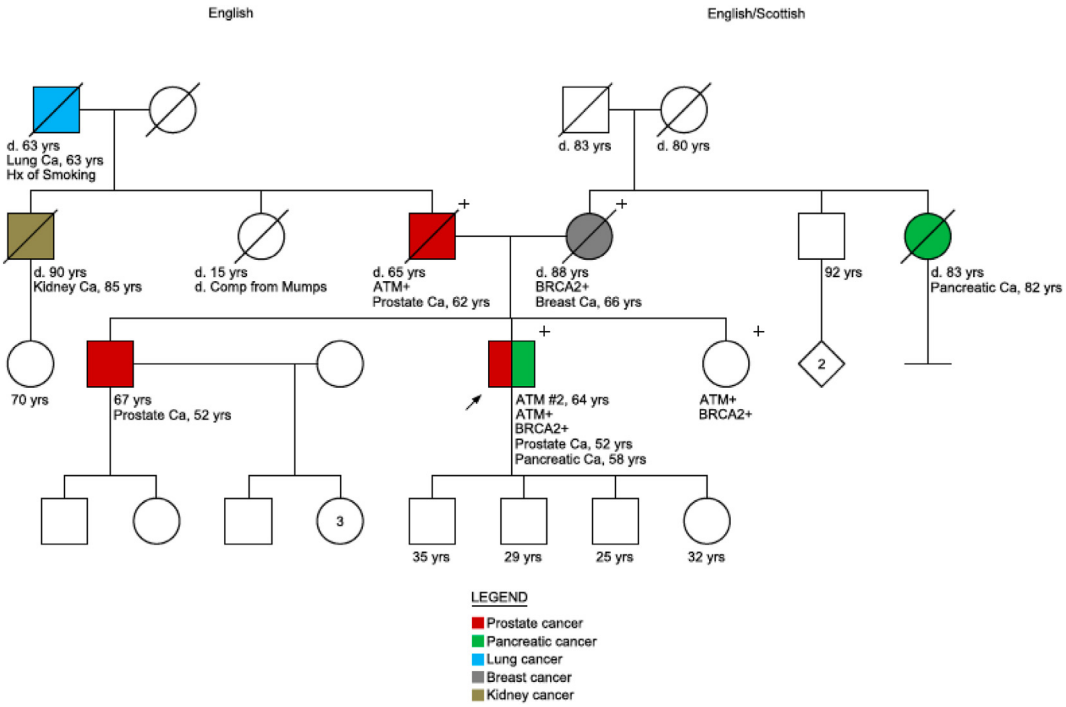

Figure 3 Proband with *ATM* GPV detected on tumor testing, with subsequent detection of an additional BRCA2 GPV. A 64-year-old male proband was originally diagnosed at age 52 with early-stage prostate cancer (Gleason 8) and treated with prostatectomy. At age 64, he presented with stage 4 disease, at which time tumor testing was performed and identified an *ATM* PV (NM_000051.4:c.8786+1G>A). Subsequent germline testing confirmed that the *ATM* PV was present in the germline (ie, it was a GPV), and additionally identified a *BRCA2* GPV (large rearrangement). Additional cancer history included that the patient was diagnosed at age 55 with stage I adenocarcinoma of the pancreas, which was treated with Whipple resection and chemotherapy. Testing in family members identified that his sister had both GPV in *ATM* and *BRCA2,* that the *BRCA2* GPV was maternally inherited, and the *ATM* GPV was paternally inherited.
Discussion points are as follows:

- In the proband's sister who has the GPVs in *BRCA2* and *ATM*, the breast cancer risks are not thought to be additive, but there are currently no data to support this. Consequently, cancer risk management recommendations would be that recommended for a *BRCA2* heterozygote, given the risks are much higher than that of an *ATM* heterozygote.
- Results of tumor testing must be confirmed in germline because ~10% of GPV are not identified through tumor testing because they are large rearrangements or other variants not detectable through sequencing.
- The family history of prostate cancer needs to be taken into account when considering prostate cancer risks, beyond the presence of the GPV.

cells and B cells, which frequently causes decreased or absent serum immunoglobulin A and immunoglobulin G2 levels.[145,146] Immunodeficiency can lead to recurrent sinopulmonary infections and bronchiectasis. Median survival in AT patients has been reported between 19 and 29.9 years and 19 and 25 years in 2 cohorts[147] and more recently as 26.9 years,[137] with a minority of patients surviving beyond 30 years.[145] The main causes of death are respiratory failure and malignancy.[146]

Individuals who have some retained ATM kinase activity are described as having variant AT.[148] There can be a low level of normal ATM protein due to leaky splice site variants, including a British founder variant NM_000051.4:c.5763-1050A>G.[28] Some missense variants, including the c.7271T>G p.(Val2424Gly) variant, result in a mutant protein with some retained ATM kinase activity.[28] Individuals with variant AT have a later age of onset, more slowly progressive neurological features, and are less likely to have respiratory and immune system involvement.[148] They have a lower risk of childhood cancers[136] than in classical AT. They have a longer life expectancy,[145] and their overall malignancy risk is elevated compared with the general population with both solid tumor and lymphoid malignancies reported.[148] In this group, individuals with missense *ATM* variants with retained kinase activity had a higher risk of cancer than those with leaky splice site variants,[148] as already outlined in the Risk estimation: Cancer risks for *ATM* heterozygotes section.

Genetic counseling considerations

ATM GPV heterozygotes may be identified after targeted or multigene panel testing requested because of a personal or family history of cancer, as part of screening for autosomal recessive and X-linked conditions during pregnancy and preconception,[149] or because of a family history of AT. Of note, although testing for *ATM* is widely available, this gene is not currently included as a gene on the ACMG Secondary Findings list for reporting after exome or genome sequencing.[150] Biological parents of an individual with AT are obligate heterozygotes. Other adult family members should be offered genetic counseling and testing to determine whether they are at risk. Predictive genetic testing for a familial heterozygous *ATM* variant is not routinely recommended in childhood, but testing of children who have a sibling with AT can be considered with appropriate genetic counseling if there is concern that they might be affected. See Figures 1 to 5 for examples of genetic counseling and management issues in pedigrees that harbor an *ATM* germline variant.

Genetic counseling of individuals with an *ATM* GPV should include a discussion of biallelic inheritance and implications to family planning with consideration of partner testing before planning a pregnancy. Assuming an *ATM* heterozygote frequency estimate of 1 in 200 (which varies by population, see the Introduction for more details), an *ATM* GPV heterozygote and an untested, unrelated partner

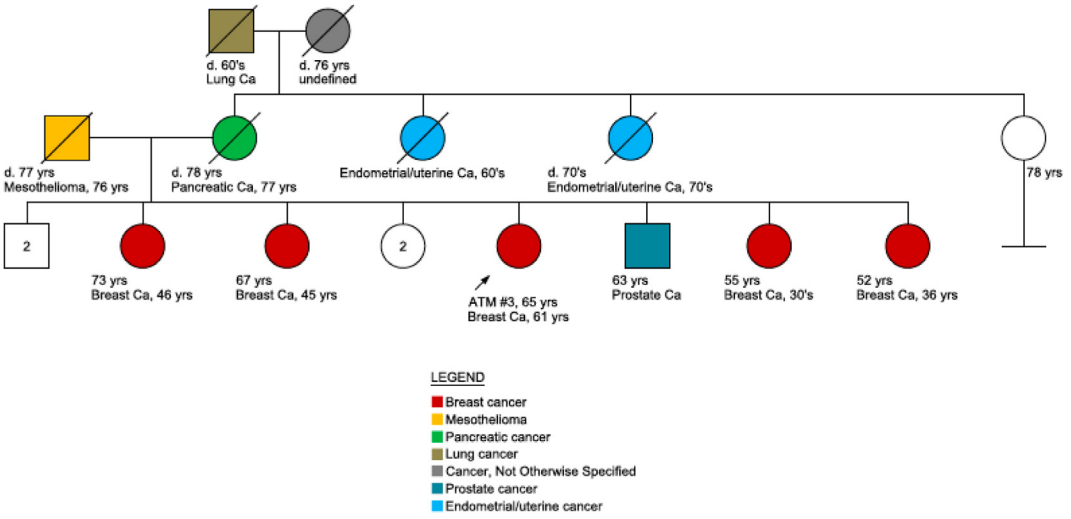

Figure 4 ***ATM* GPV in the context of strong family history of breast cancer, detected through update testing.** A 65-year-old female referred to genetics because of a personal history of breast cancer at age 61 was treated with lumpectomy and radiation and has a strong family history of breast cancer. Patient previously tested for *BRCA1/2* in 2007, with negative results. Patient was seeking genetic testing because her 56-year-old sister who was diagnosed with breast cancer in her 30s had recently undergone testing and was identified with a variant of uncertain significance (VUS) in the *PTEN* gene. Patient had multigene panel testing, including inherited breast cancer genes, and results identified a GPV in *ATM* (NM_000051.4:c.6239_6340del p.(Tyr2080Phefs*7)). During her disclosure appointment, the patient mentioned that she was meeting with a plastic surgeon to discuss options for risk reducing mastectomy with breast reconstruction.
Discussion points are as follows:

- Results do not fully explain striking family cancer history of breast cancer.
- Results of testing would likely not affect what is recommended for most family members with regard to breast surveillance.
- Despite the strong family history of breast cancer and the presence of the *ATM* GPV, the *PTEN* (HGNC:9588) VUS does not impact her clinical care nor would it be clinically indicated to specifically test family members for this VUS.

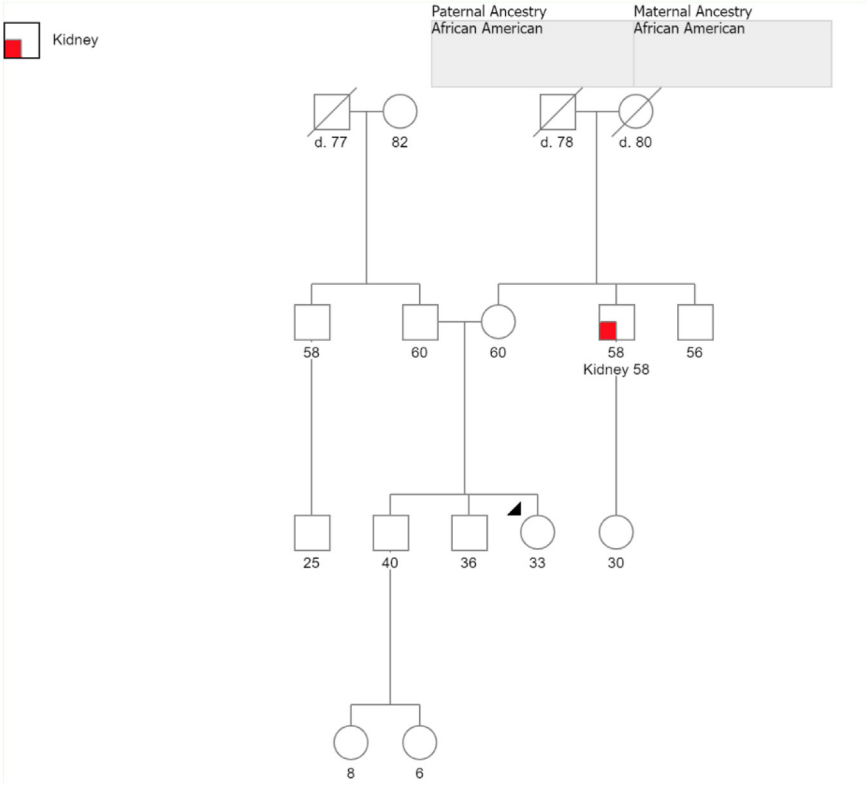

Figure 5 ***ATM* GPV incidentally detected in proband during carrier screening.** This 33-year-old cis-gender female had preconception carrier screening. She was found to have a heterozygous *ATM* GPV (NM_000051.4:c.3619G>T p.(Glu1207Ter)). Her partner subsequently had carrier testing and was not found to have any detectable *ATM* GPVs.
Discussion points are as follows:

- The risk of autosomal recessive AT in their future children is very low.
- Testing identified that the proband is at increased risk for female breast cancer and pancreatic cancer.
- The small family size, predominance of male family members, and absence of family history of relevant cancers further highlight the difficulty in providing accurate breast cancer risk assessment.

would have approximately a 1 in 800 chance of having an affected child with AT. Partner testing should be offered with appropriate genetic counseling, particularly if there is AT in the family or in the context of consanguinity. Partner testing could be done as a single-gene test or as part of an "expanded carrier screening" multigene panel. The ACMG practice resource about screening for autosomal recessive and X-linked conditions during pregnancy and preconception[149] proposes a tiered definition of carrier screening, in which *ATM* would fit into tier 4, which includes genes that are recommended to not be offered routinely but in specific circumstances, such as consanguineous pregnancies, and when family history suggests screening would be beneficial. Funding for partner testing varies across countries and health care systems, and some health care systems do not fund partner testing. For example, the National Health Service in England only funds partner testing when the carrier frequency of the condition is higher than 1 in 70 in the relevant population.[151]

Considerations for family planning, including preimplantation genetic testing and prenatal diagnosis through chorionic villus sampling or amniocentesis for the detection of biallelic variants, should be discussed with couples who both carry *ATM* GPVs. Prenatal diagnosis for detection of a single heterozygous *ATM* GPV in the fetus is controversial because it causes a moderate-risk adult-onset cancer predisposition syndrome. Although preimplantation genetic testing is offered for hereditary cancer syndromes with a high penetrance and/or childhood onset, preimplantation genetic testing to prevent transmission of a heterozygous *ATM* GPV is controversial because it is considered an adult-onset moderate penetrance gene (with a few exceptions).[152,153]

Consistent with standard clinical practice,

- *ATM heterozygotes should be referred to a genetics health care professional to discuss cancer risks, surveillance, and reproductive options, as well as implications for other family members.*
- *Pre- and posttest genetic counseling should be undertaken when considering predictive genetic testing for GPVs in ATM.*
- *Residual risk estimation (particularly for BC) and surveillance guidance should be provided for individuals who test negative for an ATM familial variant to guide future surveillance.*

- *Genetic counseling should include a discussion of biallelic inheritance, and partner testing may be offered for couples who are pregnant or planning a pregnancy.*

Research gaps in clinical areas of need

There remains a paucity of data on *ATM* heterozygotes compared with higher-risk cancer predisposition genes, such as *BRCA1* and *BRCA2,* both in terms of cancer risk and clinical outcomes. Furthermore, published data are conflicting and often difficult to interpret because of the varying prevalence of *ATM* heterozygotes across different populations, lack of appropriately geographically matched control populations, uncertainty of risk associated with rare missense variants, and the impact of risk modifying factors.

Although data from large case-control analyses have helped refine cancer risks for BC, and these risks are incorporated into the CanRisk model, allowing personalized BC risk estimation for truncating variants,[8,154] better estimation of cancer risk, particularly for missense variants, and development of comprehensive risk assessment models is required for other cancers, such as ovarian, pancreatic, and prostate cancer. Improved PRS, risk models, and calculators validated across diverse populations are needed.

Prospective data collection is needed to both help with the study of cancer risk but also determine the effectiveness of surveillance and risk-reducing surgery. With respect to treatment of cancers in *ATM* heterozygotes, additional studies are required to evaluate if these individuals may benefit from the same therapeutic agents used in *BRCA1* and *BRCA2* heterozygotes, which act in the same DNA repair pathways.

- *The development of improved polygenic risk scores is urgently needed, as are risk models and calculators validated across diverse populations.*
- *There is an urgent need for prospectively collected clinical data from ATM heterozygotes for the following:*
  - *Refine and improve cancer risk estimates*
  - *Establish clear metrics on surveillance and treatment outcomes and survival*
  - *Develop risk assessment tools*
  - *Evaluate ATM-specific response to established and novel therapies*

Conclusion

The statements made in this clinical practice resource are based on expert opinion using a comprehensive literature ascertainment approach. Specifically, regarding *ATM* heterozygotes, we consider there to be strong evidence that truncating variants are associated with a moderate risk of BC, and evidence is supportive of a moderate risk of pancreatic cancer, prostate cancer, and ovarian cancer. However, cancer risks are strongly influenced by other factors, including family history, non-*ATM* genetic background, and reproductive and lifestyle factors. Personalized rather than generalized advice on appropriate cancer risk management is required to offer the most appropriate medical management.

Evidence for the full role of *ATM* in cancer predisposition is not complete, and further studies are needed to fully define the true spectrum of *ATM*-associated cancer risk, as well as the effectiveness of early detection and risk-reducing interventions.

Given the many uncertainties, those at risk for *ATM*-related cancers and the health professionals who care for them are encouraged to contribute follow-up data to long-term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures.

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Conflict of Interest

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Additional Information

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Supplementary Information

Management of individuals with heterozygous germline pathogenic variants in *ATM*: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

Tuya Pal, MD, Katherine R. Schon, BM BCh, Esteban Astiazaran-Symonds, MD, Judith Balmaña, MD, PhD, William D. Foulkes, MBBS, PhD, Paul James, MD, PhD, Susan Klugman, MD, Alicia A. Livinski, MPH, MLS, Julie S. Mak, MS, Joanne Ngeow, MBBS, MPH, Nicoleta Voian, MD, MPH, Myra J. Wick, MD, PhD, Helen Hanson, MBBS, Douglas R. Stewart, MD, Marc Tischkowitz, MD PhD; on behalf of the ACMG Professional Practices and Guidelines Committee

GROUP	Component	ATM + cancer + mutation +	Keywords
1	ATM hets: cancer risk estimation	**ATM + cancer + mutation +**	Risk, likelihood, probability
2	ATM hets: cancer risk estimation	**ATM + breast, pancreatic, prostate cancer + mutation +**	Risk, likelihood, probability
3	Modifier: Polygenic Risk Score	**ATM + cancer + mutation +**	(polygenic*[tiab] OR PRS[tiab] OR PGS[tiab] OR SNP[tiab] OR "single nucleotide polymorphism"[tiab] OR SNV[tiab] OR "single nucleotide variant"[tiab] OR polygenic ingeritance[MeSH])
4	Modifier: other (hormonal, epi, etc, including radiation risks)	**ATM + cancer + mutation +**	Chemoprevention Chemosensitivity Radiation sensitivity Risk reduction ATM promoter hypermethylation
5	Generating personalized risks	**ATM + cancer + mutation +**	("risk model" OR "risk prediction" OR "multifactorial" OR "integrated risk" OR "personalized risk" OR "personal risk") **AND** ("genetic" OR "inherited" OR "familial" OR "hereditary")
6	Pathology	**ATM + cancer + mutation +**	tumor, grade, lymph node, stage, estrogen receptor, progesterone receptor, HER2, pathology, mutational signature, homologous recombination deficiency, loss of heterozygosity or biallelic inactivation, TP53, Methylation, monoallelic inactivation
7	Outcomes	**ATM + cancer + mutation +**	mortality
8	Clinical management: surveillance and risk-reducing surgery	**ATM + cancer + mutation +**	-Intensified surveillance -risk-reducing bilateral mastectomy -Risk-reducing contralateral mastectomy -radiation sensitivity
9	Therapeutic implications	**ATM + cancer + mutation +**	Chemotherapy / Targeted therapy / Immunotherapy /Precision medicine /Personalized medicine /Clinical trials / Radiotherapy / Radiation therapy

Final Search Strategies Used

Overall search on ATM

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract])) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR

corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 1

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract]) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract]))

AND (risk[Title/Abstract] OR risks[Title/Abstract] OR likelihood*[Title/Abstract] OR probability*[Title/Abstract] OR "Risk"[Major Mesh])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR

protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 2

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND ("Breast Neoplasms"[Mesh] OR "Pancreatic Neoplasms"[Mesh] OR "Prostatic Neoplasms"[Mesh] OR “breast cancer*”[Title/Abstract] OR “breast neoplasm*”[Title/Abstract] OR “mammary cancer*”[Title/Abstract] OR “breast tumor*”[Title/Abstract] OR “breast tumour*”[Title/Abstract] OR “breast carcinoma*”[Title/Abstract] OR “pancreatic neoplasm*”[Title/Abstract] OR “pancreatic cancer*”[Title/Abstract] OR “pancreas neoplasm*”[Title/Abstract] OR “pancreas cancer*”[Title/Abstract] OR “cancer of the pancreas”[Title/Abstract] OR “prostate cancer*”[Title/Abstract] OR “prostate neoplasm*”[Title/Abstract] OR “cancer of the prostate”[Title/Abstract] OR “prostatic neoplasm*”[Title/Abstract] OR “prostatic cancer*”[Title/Abstract] OR “prostate malignancy”[Title/Abstract:~2] OR “prostate tumor”[Title/Abstract:~2] OR “breast malignancy”[Title/Abstract:~2] OR “pancreatic tumor”[Title/Abstract:~2] OR “pancreas malignancy”[Title/Abstract:~2] OR “pancreatic malignancy”[Title/Abstract:~2])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract])) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract])

AND (risk[Title/Abstract] OR risks[Title/Abstract] OR likelihood*[Title/Abstract] OR probabilit*[Title/Abstract] OR "Risk"[Major Mesh])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR

protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 3

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((polygenic*[Title/Abstract] OR PRS[Title/Abstract] OR PGS[Title/Abstract] OR SNP[Title/Abstract] OR SNPs[Title/Abstract] OR "single nucleotide polymorphism"[Title/Abstract] OR SNV[Title/Abstract] OR "single nucleotide variant"[Title/Abstract] OR
“multigenic trait*”[Title/Abstract] OR “oligogenic trait*”[Title/Abstract] OR “complex trait*”[Title/Abstract] OR “multifactorial inheritance”[Title/Abstract] OR “complex inheritance”[Title/Abstract] OR "Multifactorial Inheritance"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh]) NOT (“Peak Radial Strain”[Title/Abstract] OR “Prognostic risk signature”[Title/Abstract] OR “prolyl-tRNA synthetase”[Title/Abstract] OR “Pierre Robin syndrome”[Title/Abstract] OR “prevalence ratios”[Title/Abstract] OR “Public regulated service”[Title/Abstract] OR “Plastic Reconstructive surgery”[Title/Abstract] OR prostaglandins[Title/Abstract] OR “public green space”[Title/Abstract]))

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR

"retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 4

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract])) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract])

AND (chemoprevent*[Title/Abstract] OR chemosensitivit*[Title/Abstract] OR “chemotherapy sensitiv*”[Title/Abstract] OR “radiation sensitivit*”[Title/Abstract] OR “risk reduction”[Title/Abstract:~2] OR “reduce risk”[Title/Abstract:~2] OR “reduce risks”[Title/Abstract:~2] OR “reduced risk” [Title/Abstract:~2] OR “reduced risks” [Title/Abstract:~2] OR “ATM promoter hypermethylation”[Title/Abstract:~2] OR "Chemoprevention"[Mesh])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR

corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title])

Group 5

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract])) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract])

AND (("risk model*"[Title/Abstract] OR "risk predict*"[Title/Abstract] OR “predicting risk”[Title/Abstract] OR multifactorial[Title/Abstract] OR "integrated risk*"[Title/Abstract] OR "personalized risk*"[Title/Abstract] OR "personal risk*"[Title/Abstract]) AND (genetic[Title/Abstract] OR genetics[Title/Abstract] OR inherit*[Title/Abstract] OR familial[Title/Abstract] OR hereditary[Title/Abstract]))

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR

"retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 6

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract])) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract])

AND (grade*[Title/Abstract] OR grading[Title/Abstract] OR “lymph node*”[Title/Abstract] OR stage*[Title/Abstract] OR staging[Title/Abstract] OR "Neoplasm Staging"[Mesh] OR “estrogen receptor*”[Title/Abstract] OR “progesterone receptor*”[Title/Abstract] OR HER2[Title/Abstract] OR pathology[Title/Abstract] OR “mutational signature*”[Title/Abstract] OR “mutation signature*”[Title/Abstract] OR “homologous recombination deficienc*”[Title/Abstract] OR “loss of heterozygosity”[Title/Abstract] OR “biallelic inactivation”[Title/Abstract] OR TP53[Title/Abstract] OR methylation[Title/Abstract] OR “monoallelic inactivation*”[Title/Abstract] OR "Receptors, Estrogen"[Mesh] OR "Receptors, Progesterone"[Mesh])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR

editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 7

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract]) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract]))

AND (mortality[Title/Abstract] OR mortalities[Title/Abstract] OR death[Title/Abstract] OR deaths[Title/Abstract] OR fatalit*[Title/Abstract] OR "Mortality"[Mesh])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR

protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 8

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human"[Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract]) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract]))

AND (surveillance[Title/Abstract] OR screening[Title/Abstract] OR screen[Title/Abstract] OR screens[Title/Abstract] OR screened[Title/Abstract] OR “risk manage*”[Title/Abstract] OR “managing risk*”[Title/Abstract] OR mastectom*[Title/Abstract] OR “radiation sensitivit*”[Title/Abstract])

AND (english[lang] AND medline[subset] AND ("1997"[Date - Publication] : "2023"[Date - Publication]))

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR

"retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Group 9

Database: PubMed
Platform: US National Library of Medicine
Date of search: March 6, 2023
Limits used: Publication year: 1997–2023; Language: English; Subset: MEDLINE

((ATM[Title/Abstract] OR "Ataxia Telangiectasia Mutated Protein*"[Title/Abstract] OR "Ataxia telangiectasia mutated"[Title/Abstract] OR "atm serine threonine kinase"[Title/Abstract] OR "ATM protein, human" [Supplementary Concept] OR "Ataxia Telangiectasia Mutated Proteins"[Mesh]) NOT ("Acute transverse myelitis"[Title/Abstract] OR atmosphere[Title/Abstract] OR “annals of translational medicine”[All Fields] OR “adipose tissue macrophage*”[Title/Abstract] OR “Ataxia-Telangiectasia”[Title/Abstract] OR “A-T”[Title/Abstract]))

AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR sarcoma*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract] OR lymphoma*[Title/Abstract] OR malignant[Title/Abstract] OR malignanc*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Cysts"[Mesh:NoExp] OR "Hamartoma"[Mesh] OR "Neoplasms by Histologic Type"[Mesh] OR "Neoplasms by Site"[Mesh] OR "Neoplasms, Experimental"[Mesh:NoExp] OR "Neoplasms, Hormone-Dependent"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Post-Traumatic"[Mesh] OR "Neoplasms, Radiation-Induced"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplastic Processes"[Mesh] OR "Neoplastic Syndromes, Hereditary"[Mesh] OR "Paraneoplastic Syndromes"[Mesh] OR "Precancerous Conditions"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Sarcoma"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Carcinoma"[Mesh])

AND ((mutation*[Title/Abstract] OR mutate*[Title/Abstract] OR mutating[Title/Abstract] OR variant*[Title/Abstract] OR variation*[Title/Abstract] OR polymorphism*[Title/Abstract] OR "Polymorphism, Genetic"[Mesh] OR SNP[Title/Abstract] OR heterozyg*[Title/Abstract] OR carrier[Title/Abstract] OR carriers[Title/Abstract] OR monoallelic[Title/Abstract]) NOT (“sinonasal polyposis”[Title/Abstract] OR “sinus node potential”[Title/Abstract] OR “sodium nitroprusside”[Title/Abstract] OR “special needs plan”[Title/Abstract] OR synaptophysin[Title/Abstract]))

AND (chemotherap*[Title/Abstract] OR “targeted therap*”[Title/Abstract] OR immunotherap*[Title/Abstract] OR “immunosuppression therap*”[Title/Abstract] OR “precision medicine”[Title/Abstract] OR “personalized medicine”[Title/Abstract] OR “clinical trial*”[Title/Abstract] OR radiotherap*[Title/Abstract] OR “radiation therap*”[Title/Abstract] OR "Molecular Targeted Therapy"[Mesh] OR "Radiotherapy"[Mesh] OR "Immunotherapy"[Mesh] OR "Precision Medicine"[Mesh] OR "Antineoplastic Protocols"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh])

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NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (mice[Title/Abstract] OR mouse[Title/Abstract] OR rat[Title/Abstract] OR rats[Title/Abstract] OR rodent*[Title/Abstract] OR rodentia*[Title/Abstract] OR animal*[Title/Abstract] OR Mice[Mesh] OR Rats[Mesh] OR Rodentia[Mesh] OR Muridae[Mesh])

NOT (letter[Publication Type] OR editorial[Publication Type] OR comment[Publication Type] OR news[Publication Type] OR "Congress"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR editorial[Title/Abstract] OR commentary[Title/Abstract] OR "conference abstract*"[Title/Abstract] OR "conference

proceeding*"[Title/Abstract] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "retraction of publication"[Title/Abstract] OR "retraction notice"[Title] OR "retracted publication"[Title/Abstract] OR "Published Erratum"[Publication Type] OR corrigenda[Title/Abstract] OR corrigendum[Title/Abstract] OR errata[Title/Abstract] OR erratum[Title/Abstract] OR protocol[Title] OR protocols[Title] OR “case report*”[Title/Abstract] OR “case series”[Title/Abstract] OR "Case Reports" [Publication Type])

Supplemental Table 1. *ATM* Variant Descriptions

Genomic description (GRCh37)	Genomic description (GRCh38)	Coding DNA description	Protein description
NC_000011.9:g.108199929T>G	NC_000011.10:g.108329202T>G	NM_000051.4:c.7271T>G	NP_000042.3:p.(Val2424Gly)
NC_000011.9:g.108155009del	NC_000011.10:g.108284282del	NM_000051.4:c.3802del	NP_000042.3:p.(Val1268Ter)
NC_000011.9:g.108137914del	NC_000011.10:g.108267187del	NM_000051.4:c.2483del	NP_000042.3:p.(Lys828SerfsTer8)
NC_000011.9:g.108179837A>G	NC_000011.10:g.108309110A>G	NM_000051.4:c.5763-1050A>G	NP_000042.3:p.?
NC_000011.9:g.108202225G>C	NC_000011.10:g.108331498G>C	NM_000051.4:c.7570G>C	NP_000042.3:p.(Ala2524Pro)
NC_000011.9:g.108224608G>A	NC_000011.10:g.108353881G>A	NM_000051.4:c.8786+1G>A	NP_000042.3:p.?
NC_000011.9:g.108188140_108188141del	NC_000011.10:g.108317413_108317414del	NM_000051.4:c.6239_6240del	NP_000042.3:p.(Tyr2080PhefsTer7)
NC_000011.9:g.108153479G>T	NC_000011.10:g.108282752G>T	NM_000051.4:c.3619G>T	NP_000042.3:p.(Glu1207Ter)

Supplemental Table 2. *ATM* Guidelines by Country

Country	Guideline	Breast	Breast (c.7271T>G)	Pancreatic	Prostate	Ovarian
United States	NCCN (Familial/Genetic High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer.V1.2025)	Start annual MRI age 30-35, mammogram age 40	Mentioned but no guidance provided	Start annual MRI/MRCP or EUS at age 50	Annual screening (PSA, digital rectal exam) starting age 40. Digital rectal exam (DRE) may be useful to guide interpretation of PSA findings.	Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history
United Kingdom	No current national guideline covering all aspects of ATM	Moderate risk breast screening 40-50 years or individualised asessment using CanRisk to determine surveillance according to NICE familial breast cancer guidelines (<17% population (three yearly mammogram from 50), 17-30% moderate risk (annual mammogram 40-49, then population), >30% high risk (annual mammogram 40-59yr, then population), or if >40% BRCA equivalent	Manage per BRCA guidelines (Annual MRI 30-50 years, annual mammogram from age 40 years)	no surveillance recommended, can offer EUROPAC research study if family history of pancreatic cancer	routine surveillance not currently recommened, consider if family history	risk-reducing salpingo oophorectomy (RRSO) not recommended; manage based on family history
Australia	EviQ guideline*	Moderate risk breast screening involving annual mammogram age 40-50, every second year from age 50 years. Consider MRI if dense breast tissue. Consider use of risk reducing medication.	Annual breast MRI screening 30-50 years with addition of annual mammogram from 40 years. Continuation of MRI for women with dense breast tissue beyond 50 years. Offer RRBM. Consider use of risk reducing medication.	No surveillance recommended - screening trials available.	No surveillance recommended	Not considered
Spain	SEOM (PMID:31889241)	Annual breast MRI age 40, according to pesonal and familial risk factors; annual mammogram age 40	not mentioned	consider annual MRI/MRCP or EUS at age 50 if family history of pancreatic cancer	not mentioned	potential increased risk. Insufficient evidence for RRSO

*https://www.eviq.org.au/cancer-genetics/adult/risk-management/1610-atm-monoallelic-pathogenic-variants-risk