First international workshop of the *ATM* and Cancer Risk Group (4-5 December 2019)

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Abstract (n=190)

The first International Workshop of the *ATM* and Cancer Risk group focusing on the role of *Ataxia-Telangiectasia Mutated* (*ATM*) gene in cancer was held on December 4 and 5, 2019 at Institut Curie in Paris, France. It was motivated by the fact that germline *ATM* pathogenic variants have been found to be associated with different cancer types. However, due to the lack of precise age-, sex-, and site-specific risk estimates, no consensus on management guidelines for variant carriers exists, and the clinical utility of *ATM* variant testing is uncertain. The meeting brought together epidemiologists, geneticists, biologists and clinicians to review current knowledge and on-going challenges related to *ATM* and cancer risk. This report summarizes the meeting sessions content that covered the latest results in family-based and population-based studies, the importance of accurate variant classification, the effect of radiation exposures for *ATM* variant carriers, and the characteristics of ATM-deficient tumors.

The report concludes that *ATM* variant carriers outside of the context of Ataxia-Telangiectasia may benefit from effective cancer risk management and therapeutic strategies and that efforts to set up large-scale studies in the international framework to achieve this goal are necessary.

Introduction

The rare and severe disease Ataxia-Telangiectasia (A-T), which was first described in 1941 by the neurologist Denise Louis-Bar, is a complex phenotype that remains poorly understood. In its typical presentation, the disease begins in early childhood and combines cerebellar ataxia, oculomotor apraxia, dysarthria, cutaneous telangiectasia, immunodeficiency (B, T cells), premature aging [1], hypersensitivity to ionizing radiation and agents that cause DNA double-strand breaks [2-4], as well as a predisposition to malignancies [5-7]. The prognosis remains poor due to the high risk of cancer and the difficulties of treatment linked to high radio- and chemo-sensitivity of normal tissues and to the frequent severity of immune deficiency. A-T results from biallelic inactivating variants in the *Ataxia-Telangiectasia Mutated* (*ATM*) gene located at 11q22-23 [8]. *ATM* contains 62 coding exons and encodes a phosphoinositide 3-kinase-related kinase with more than 1,000 substrates that is involved in detecting DNA damage and activating the DNA damage checkpoints. ATM may also have cytoplasmic functions in oxidative stress regulation [9].

The worldwide prevalence of A-T is estimated to be between 1 in 40,000 and 1 in 300,000 live births [10-12]. From the late 1980s, epidemiological studies conducted in A-T families showed that heterozygous *ATM* pathogenic variant carriers (hereafter referred to as "HetATM") are also at increased risk of cancer [12-18], notably of breast cancer in female relatives [13,14]. Nowadays, however, HetATM are also identified outside of an A-T familial context through multigene panel testing; thus, the cancer risks associated with *ATM* variants are relevant to genetic counselling and cancer risk management of a much larger population. While the pathogenicity of rare variants found in clinically verified A-T patients can often be assumed, the assessment of variants found through sequencing studies outside of the A-T context are more challenging. Some variants lead to a loss of function of the gene product (nonsense or reading frameshift) and thus can usually be classified as pathogenic. However, missense variants are often observed and the determination of their pathogenicity is more problematic. Hence, *ATM* variant classification is an important part of determining clinical utility. Additionally, the characterization of specific pathological and genomic features associated with *ATM* inactivation in tumors could also help to identify HetATM without a severe personal or family history of cancers, and potentially inform therapeutic strategies in affected individuals.

Hence, a better understanding of the biological roles of *ATM*, plus the cancer spectrum associated with germline *ATM* deleterious variants (*i.e.* variants impacting a biological function of ATM), phenotype-genotype correlations, modifying factors of cancer risk and the genomic profile of ATM tumors should improve counselling to *ATM* variant carriers and inform recommendations on cancer screening and treatment. International collaborative efforts are needed to elucidate these questions and accelerate discoveries. This was the rationale for organizing the 2019 International Workshop of the *ATM* and Cancer Risk Group **(Supplemental Data 1)**. These topics, presented at the Workshop, are summarized in the following sections.

Cancer risk in Ataxia-Telangiectasia families

It has long been observed that A-T patients are predisposed to develop malignancies, particularly leukemia and lymphoma at a young age [7,5,6]. According to the French national registry of primary immune deficiencies, A-T patients have 35% increased risk of developing cancer before age 20, mainly T-cell prolymphocytic leukemia and lymphoma. They also have increased risk of developing carcinomas (breast, gastric, thyroid) later in life [5,6].

Relatives of A-T patients are themselves at increased risk of cancer [15-17]. In 1987, Swift *et al.* were the first to show that women related to a child with A-T had a higher risk of breast cancer than women from the general population [18]. Since ATM plays a central role in triggering appropriate responses to DNA damage [19,20] and cells of A-T patients are characterized by DNA damage response impairment after radiation exposure [2-4], it has been suggested that radiation exposure may also affect the DNA damage response and occurrence of cancers in HetATM.

Although A-T is a rare recessive disease, large numbers of HetATM can be identified or inferred among their relatives. Therefore, cohorts of A-T patients and their families who have been followed for several decades are highly informative to assess cancer risk of HetATM [21-26,17,27,14,13,28]. In these studies, estimated breast cancer relative risks ranged from 2 to about 5; the risk may vary depending on the location of the variant along the gene sequence [25]. Moreover, by studying cancer incidence and mortality in 1,160 relatives of 169 A-T patients from the United Kingdom (UK), Thompson *et al.* found an excess risk of cancer other than breast cancer in relatives, with suggestive increased risks of colorectal and stomach cancers [17]. More recently, by investigating cancer incidence in the 9,215 relatives of 135 French A-T index cases from the prospective cohort CoF-AT, Andrieu *et al.* confirmed the excess risk of breast cancer in HetATM and found an excess risk of leukemia, lymphoma and pancreatic cancer (Andrieu *et al.* personal communication). Much longer-term follow-up of these cohorts is now possible and meta-analyses of current data should provide more precise estimates of these risks.

Cancer risk of *ATM* variant carriers in Hereditary Breast and Ovarian Cancer Families

It is estimated that about 0.5% of the general population is HetATM [29,30]. Studies conducted in hereditary breast and ovarian cancer (HBOC) families or early onset breast cancer cases have estimated that *ATM* variants classified as pathogenic for A-T disease confer a 2 to 4-fold increase in breast cancer risk for variant carriers as compared to non-carriers [31,32,29,30]. Therefore, most published case-control and family-based studies described such *ATM* alleles as moderate-risk breast cancer susceptibility alleles although this risk may differ according to the type and localization of the variant [31-33,25,29,30]. *ATM* is now included in nearly all multigene panels used for HBOC genetic testing [34], and is among the most frequently altered genes in cases that test negative for *BRCA1* and *BRCA2* worldwide, with an *ATM* predicted pathogenic variant identified in up to 7.8% of them [35-41,33,29,30]. However, in most countries, results for *ATM* testing are not returned to patients because of imprecise risk estimates and a lack of management recommendations [34,42,43]. Nevertheless, the US National Comprehensive Cancer Network (NCCN) recommends annual mammographic screening starting at age 40 years for *ATM* pathogenic/likely pathogenic variant carriers, and an earlier screening with both mammography and magnetic resonance imaging (MRI) [44]. A recent study suggested that Ontario (Canada) adopt the same guidelines as NCCN for HetATM women [45]. In Australia, guidelines similar to those of *BRCA2* pathogenic variant carriers are applied only for heterozygous carriers of the founder missense variant *ATM* c.7271T>G (p.Val2424Gly), which has been estimated to confer a higher risk of breast cancer than the average risk for all other *ATM* pathogenic variants [46-49].

Interestingly, the original report of the c.7271T>G variant involved two British families, one of which, from Scotland, included three homozygous carriers with a mild form of A-T [46]. In subsequent studies reporting this variant, most carriers reported origins in the UK, consistent with a possible founder effect [50,47,46,51]. Indeed, this variant is extremely rare in the French and Spanish populations [33,52].

Several studies have been conducted to characterize *ATM* sequence variants and assess the breast cancer risk associated with them. A number of studies were presented at the workshop, their description and main findings are summarized in **Table 1**. While all studies show evidence of an increased risk in carriers, it is difficult to obtain a consensus breast cancer risk estimate because of the diversity of the population ascertainment, study design and *ATM* variant classification. Four national studies conducted in Norway, Macedonia, France and Germany included probands from HBOC families, while the US NCI-funded project CARRIERS analyzed sequencing data from 13 population-based studies [30]. As example, *ATM* LoF variants were found to be associated with breast cancer with an OR of 3.63 (95% CI: 2.67-4.94) in Germany, 1.8 (95% CI: 1.5-2.3) in CARRIERS and 17.4 (95% CI: 2.3-132) in France [33].

It should also be noted that breast cancer risk estimates in *ATM* families obtained in family-based studies may be biased if cancer risks are modified by other genetic or familial factors [53]. For example, a recent study demonstrated that the breast cancer risk in *ATM* variant carriers may be modified by a polygenic risk score based on common variants [54]; thus, risk prediction in *ATM* carriers will need to take into account the modifying effects of genetic and lifestyle factors [55]. Population-based studies avoid this bias but are challenging due to the low population frequency of variants, and thus requiring very large sample sizes to obtain precise estimates. With decreasing sequencing costs, this is now achievable, through studies such as those in the CARRIERS [30] and BRIDGES projects (https://bridges-research.eu) [29].

ATM variant carriers and risk of other cancers

Initial publications on relatives of A-T patients suggested an increased incidence of leukemias and lymphomas, and cancer of the stomach, pancreas, bladder and ovaries in HetATM [16,56], although subsequent studies have been inconclusive and controversial [15,28,24,17]. Outside of an A-T context, several family-based or population-based studies have investigated the role of *ATM* in the predisposition to a number of cancers, in particular pancreatic cancer, prostate cancer and melanoma.

- *Pancreatic cancer*

Sequencing analysis of 168 families with multiple pancreatic cancer cases identified germline *ATM* LoF variants in 6 families, suggesting a role for *ATM* in pancreatic cancer predisposition [57]. In subsequent independent studies, up to 3.4% of familial pancreatic cancer cases [58,59] and 0.9 to 4.2% of patients with pancreatic adenocarcinoma unselected for family history were found to carry an *ATM* LoF [60-62]. Furthermore, such variants were identified in 1.5% of patients with surgically resected intraductal papillary mucinous neoplasms, a pancreatic cancer precursor lesion [63].

- *Prostate cancer*

Alterations in a number of DNA repair genes have been examined in relation to prostate cancer risk in multiple, through relatively small studies until the workshop was held. In these series, an elevated frequency of predicted deleterious variants was observed in *ATM.* Notably, Nguyen-Dumont *et al.* recently conducted a case-case study comparing the prevalence of pathogenic/likely pathogenic germline variants in 787 men diagnosed with aggressive (defined as any stage 4, stage 3 and Gleason score ≥8 or death from prostate cancer) and 769 men with non-aggressive tumors. Although these

results did not reach statistical significance, more *ATM* pathogenic/likely pathogenic variant carriers were identified in men with aggressive than in men with non-aggressive prostate cancer (0.02% vs. 0.01%) [64]. More recently, the PRACTICAL (Prostate Cancer Analyses of Alterations in the Genome) consortium analyzed sequencing data from about 9,000 individuals. This larger study provided evidence that *ATM* pathogenic/likely pathogenic (as defined in ClinVar) variants are associated with a moderate prostate cancer risk for men of European ancestry (OR=4.4, 95% CI: 2.00-9.50). The study also showed that *ATM* variant carriers had a higher risk of early-onset disease (<65 years) but did not confirm that *ATM* variants predispose specifically to more aggressive phenotypes [65]. Germline testing of prostate cancer patients is however recommended for metastatic disease or family history suggestive of hereditary prostate cancer, with *BRCA2* considered a priority gene to screen in all settings, and *ATM* sequencing advised for consideration in testing to inform clinical trial eligibility and active surveillance decisions [66]. Indeed, PARP inhibitor treatment has been shown to be effective for prostate cancer in some small clinical trial studies on metastatic castrate-resistant prostate cancer in *ATM* variant carriers [67,68].

- *Cutaneous malignant melanoma*

Family and population studies have identified multiple high-, moderate-, and low-risk genes/loci implicated in melanoma susceptibility [69-72]. A single *ATM* SNP (c.146C>G; p.Ser49Cys) was reported to be associated with melanoma risk (hazard ratio: 4.8, 95% CI: 2.2-11) in a population study of >10,000 Danish individuals [73]. Subsequently, multiple GWAS, several led by the melanoma genetics consortium (GenoMEL), consistently found SNPs in/near *ATM* to be significantly associated with melanoma risk [74,75] including a recent large (36,760 cases; 375,188 controls) meta-analysis GWAS ($p=2.2x10^{-21}$ for rs1801516; c.5557G>A; p.Asp1853Asn) [69].

After GenoMEL groups reported potentially deleterious *ATM* variants in several melanoma-prone families [70,76], GenoMEL initiated a study to investigate whether *ATM* is a high/moderate-risk melanoma gene. Analyses of ATM data from 2,105 cases (873 from melanoma-prone families) and 1,446 controls suggested that *ATM* is likely to be a moderate-risk melanoma gene (Dalmasso *et al*., personal communication).

- *Cancer spectrum in heterozygous carriers*

Other studies have investigated the cancer spectrum in cohorts of HetATM outside of the context of Ataxia-Telangiectasia family members, but none of these studies were able to provide association measurements. Two ongoing prospective series involving familial cancer cases were presented at the workshop: the Hereditary Cancer Biobank of the Norwegian Radium Hospital (Oslo, Norway) and the Clinical Cancer Genetics Program at the University of Texas, MD Anderson Cancer Center (**Table 2**). In the Norwegian study, whole-genome sequencing was performed on 1,967 familial cancer cases with no pathogenic variants in *BRCA1, BRCA2, PTEN, TP53* or any of the DNA mismatch repair (MMR) genes, which were examined under standard diagnostics screening (Dominguez-Valentin et al., *in preparation)*. In the American study, *ATM* or multigene panel sequencing (which included *ATM*) was performed in 7,306 patients who underwent clinical testing, for hereditary cancer evaluation (Banu et al., *personal communication*). However, neither of these studies was sufficiently advanced to provide cancer risk assessments.

***ATM* variant classification**

- *Variant pathogenicity in A-T*

In about 80% of cases, variants responsible for A-T are protein-truncating leading to a loss of function of the protein, *i.e.* frameshift, nonsense, canonical splice sites and large genomic deletions (according to the distribution of variant in French ATM database maintained at Institut Curie, D. Stoppa-Lyonnet, personal communication). Attenuated forms of A-T have been described, and these forms are associated with one or both variants maintaining partial ATM function. In the UK for instance, a significant proportion of adult A-T patients have a milder form of A-T by virtue of the prevalence of a particular range of variants in the British Isles. Cells from these patients retain some ATM signaling/activity as shown by the ability of the expressed ATM to phosphorylate a range of ATM targets. These individuals comprise two groups; those with a missense variant producing ATM with reduced activity and those with a leaky splice site variant allowing expression of a low level of normal ATM resulting in reduced activity. The ATM signaling/activity assay allows determination of the pathogenicity of an *ATM* missense variant, as the variant on the other allele will usually result in loss of ATM expression. Although most missense variants will not express ATM with activity, some will, with reduced activity and all need to have their degrees of pathogenicity established. Otherwise, in the context of a heterozygous normal such a sequence change would remain designated as VUS. In a combined Dutch and UK cohort of such patients, individuals with a missense variant had milder neurological features and were more likely to remain ambulant than those with a leaky splice site variant. In contrast there was an indication that those carrying a missense variant were more likely to have a malignancy possibly as a result of a gain of function of the mutant *ATM* [77]. Remarkably, it was observed that breast cancer risk for A-T patients carrying a missense variant was particularly high [77,78].

- *Variant pathogenicity in hereditary cancers*

While *ATM* LoF variants may confer a sufficient cancer risk to affect clinical management recommendations, missense variants are more problematic and the majority would be considered as VUS. However, in the published studies focusing on breast cancer predisposition (independently of an A-T context), classification rules for missense substitutions vary according to the bioinformatics tool employed and/or the availability of functional assays to demonstrate the deleterious effect of the genetic alteration on the gene product function. Therefore, the frequency of so-called "*ATM* pathogenic or likely pathogenic" variants varies from 0.7% to 6.4% depending on variant classification, contributing to the difficulty in determining cancer risks for heterozygous carriers [35-41,33].

In Spain, a multidisciplinary group of molecular geneticists and researchers has initiated a collaborative effort to improve and standardize variant classification for hereditary cancer genes. It set up a database of *ATM* variants, with the initial collection of information from 769 individuals carrying 283 different *ATM* variants. Amid the 99 variants that appeared more than once, 35 had differences in classification among laboratories. Monthly team conferences are organized to review and adapt the American College of Medical Genetics and Genomics / Association for Molecular Pathology (ACMG/AMP) variant interpretation guidelines to *ATM*. The adapted criteria were used in the pilot classification of 50 representative variants carried by 254 index cases and a reduction in the number of VUS from 58% to 42% was observed [79].

In France, the ATM variant database lists all variants identified in A-T patients as well as variants characterized through multigene panel analyses of hereditary cancer cases tested at Institut Curie, which is the reference center for molecular

diagnosis of A-T. The database also centralizes associated clinical and family data of carriers to facilitate interpretation of variants [5].

Finally, a large American study, which was part of an ongoing collaboration with Ambry Genetics Laboratory (AGL) examined the characteristics of a set of 126,000 individuals tested for sequence variants in *ATM* in relation to their personal and family history of cancer. Preliminary analyses were restricted to 72,944 tested Caucasian/European individuals without pathogenic variants in other cancer predisposition genes (*BRCA1/2, PALB2, TP53, MMR* etc.) and who had provided information on personal/family history of cancer. Based on the AGL variant classification (largely equivalent to ClinVar), there were 774 individuals with a pathogenic *ATM* variant; 125 with a likely pathogenic variant; 2,727 with a VUS; and 69,318 with no reportable variant. Logistic Regression comparing the individuals with pathogenic *ATM* vs. those without a reportable variant was performed to determine the most important (statistically significant) personal and family history features for predicting the occurrence of a pathogenic *ATM* variant. This analysis identified a personal history of estrogen receptor positive (ER+) breast tumor diagnosed before age 50 (OR=1.9, $p<0.0001$) and a personal history of pancreatic cancer (OR=2.9; $p<0.0001$) as the strongest predictors, while a family history of pancreatic cancer was the best family history predictor. Other statistically significant personal history predictors were thyroid cancer, leukemia and prostate cancer diagnosed before age 60. Based on this logistic regression, and following approach previously used for *BRCA1/2* [80,81], likelihood ratios in favor of (or against) pathogenicity for each variant observed in the sample were calculated and these scores were used to assess the proportion of variants defined by various criteria (bioinformatic, domain etc.). For example, when considering all missense variants outside of the key functional domains (defined here as 3' of amino acid 1939) analysis indicated that the best fit to the data was that no variant in this group was pathogenic (proportion of pathogenic variants: upper 95% CI: 10%). Conversely the 80 variants assessed by the bioinformatics prediction tool BayesDel [82] having BayesDel scores greater than 0.30 and in functional domains, were all estimated to be pathogenic with a lower 95% CI of 70%.

Other efforts to optimize gene-specific *in silico* tools and *in vitro* assays aiming at predicting the impact of VUS at the functional and clinical levels are on-going worldwide, and a number of projects are led by Evidence-Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Clinical Working Group [83], as the clinical dilemma of variant classification which represent a key step for risk assessment, surveillance or treatment recommendations for carriers and family members.

ATM and radiation sensitivity

Since A-T patients are hypersensitive to ionizing radiation and agents that cause DNA double-strand breaks, the question on the role of an altered *ATM* product in the regulation of the cellular response to DNA damage induced by ionizing radiation arose. For HetATM, little is known about diagnostic radiation exposures and cancer risk, and so far, only therapeutic radiation has been investigated [84]. The population-based case-control study conducted by the WECARE Study Collaborative Group examined whether women who received radiation therapy as treatment for a first breast cancer are more likely to develop contralateral breast cancer if they carry an *ATM* pathogenic variant. Cases (n=708) were women with contralateral breast cancer and matched controls (n=1,399) had unilateral breast cancer; all were <55 years of age at diagnosis, and screened for variants in breast cancer-associated genes. This study showed that radiation therapy did not modify the association between known pathogenic *BRCA1/2* variants and contralateral breast cancer risk observed in

HetATM women; however, rare *ATM* missense variants were associated with an increased risk of radiation therapy-associated contralateral breast cancer (RR: 2.98, 95% CI: 1.31-6.80) [85]. In line with these results, a meta-analysis of 5,456 patients combining breast and prostate cancers evidenced a significant association between the common variant rs1801516 (p.Asp1853Asn) and increased risk of radiation-induced normal tissue toxicity [86].

To address the issue of whether breast cancer patients with *ATM* variants should be treated with standard radiotherapy regimes, or if treatment should be tailored due to increased radiosensitivity in specific patients, grant proposals have been submitted to analyze a cohort of >9,000 breast cancer patients with additional data on radiotoxicity after treatment (from 9 studies collated through REQUITE (EU) (https://www.requite.eu), NRG Oncology (US) (https://www.nrgoncology.org) and The Radiogenomics Consortium (UK) (https://epi.grants.cancer.gov/radiogenomics/)). *ATM* will be sequenced and identified variants assessed for risk of radiotherapy toxicity alongside variants in 34 other genes using the same sequencing panel as in the BRIDGES project (https://bridges-research.eu).

Profile of ATM-deficient tumors

Little is known about the morphology and molecular profiles of tumors developed by HetATM. So far, two studies [87,88] have carried out a genomic characterization of breast tumors developed by A-T patients or HetATM. Confirming previous observations [48], both studies have reported that ATM breast tumors mostly express estrogen receptors and do not show the triple-negative molecular subtype associated with BRCA1 breast tumors. Although both studies have investigated the genomic features of ATM breast tumors using different assays, some consistent findings have been highlighted. Loss-of-heterozygosity (LOH) of the wild-type allele appears as an important step in tumor development, as LOH at the *ATM* locus was observed in 67% and 79% of ATM tumors in the French study [87] and in the Australian/American study [88], respectively, with the latter study including mainly tumors from heterozygous carriers of the c.7271T>G variant. ATM breast tumors do not show the homologous recombination deficiency profile and the mutational signature associated with *BRCA1* and *BRCA2*, but show genomic alterations specific to luminal breast tumors (copy number losses at loci 16q, 17p and 22q; somatic variants in *PIK3CA* and *GATA3*). However, some genomic losses and regions of LOH appear to be specific to ATM breast tumors when compared with 'sporadic' breast tumors; these include loci 13q14.11-14.2 (*LHFP, FOXO1, LCP1, RB1*), 21p11.2-p11.1 (*TPTE, TEKT4P2, MIR3648-1, MIR3648-2, MIR3687-1, MIR3687-2*) and 22q11.23 (*GSTT1, GSTTP1, GSTTP2*). Additionally, the Australian/American study has also suggested that *ATM* germline variants and somatic variants in TP53 are mutually exclusive [88].

Taken together, these results show that ATM breast tumors do not resemble BRCA1 and BRCA2 breast tumors at the phenotypic and molecular levels. Germline *ATM* variants affecting the kinase activity of the protein have been associated with response to PARP inhibitors (PARPi) in patients with prostate tumor as previously mentioned [89] but this has not been demonstrated yet for breast cancer.

Regarding other tumors, whole genome and whole exome sequencing have been performed on pancreatic ductal adenocarcinoma. These approaches have identified somatic alterations and/or germline variants of *ATM* in 4-9% of such tumors [90-92]. Similar to breast cancer, pancreatic ductal adenocarcinomas with ATM loss do not show the homologous recombination deficiency profile. Histomorphologic analysis of pancreatic tumors from HetATM showed that histologic subtype was diverse with a statistically significant increase in colloid (mucinous non-cystic) carcinoma compared to unselected series of patients [93]. However, pancreatic precursor lesions, microscopic pancreatic epithelial neoplasms

and macroscopic intraductal papillary mucinous neoplasms were not more frequent than previously reported for patients with familial and sporadic pancreatic ductal adenocarcinoma [93].

Prospective cohorts of *ATM* variant carriers

For emerging rarely mutated cancer susceptibility genes, proof of evidence for clinical utility of targeted preventive strategies based on the respective genotypes are needed. However, prospective randomized studies are rarely feasible due to the limited numbers of variant carriers and therefore long follow up times. In Germany, the GC-HBOC has developed a concept of risk-adjusted preventive measures for rarely mutated risk genes. This concept is based on outcome evaluation by the use of a comprehensive registry that enables genotype/phenotype correlations and outcome analysis (HerediCaRe). This prospectively maintained registry comprises genetic test results, data on family history, breast cancer phenotype, therapies, disease course and associated carcinoma. It is intended to merge data from this specific registry with data from clinical cancer registries in order to obtain information on hard endpoints, such as mortality and morbidity. This allows the evaluation of age-related incidence rates and the efficacy of the surveillance program. Based on best current evidence available, a panel of experts of the GC-HBOC develops and consents recommendation for surveillance and preventive measures. Healthy and diseased HetATM women are currently invited to participate in an intensified surveillance program of the breast. This includes annual ultrasound and MRI of the breast from age 30 to 70 and biannual mammogram starting at 40. However, relatives with negative test results for *ATM* are not discharged from the program: surveillance is offered depending on risk calculations according to family history using e.g. CanRisk[CE]. This offer on predictive genetic testing and intensified surveillance is embedded in a non-directive counseling concept and in the near future, supported by decision aids for a preference-sensitive decision making

Along the same line in France, the prospective cohort CoF-AT which began in 2003 to follow women related to an A-T patient [23] was extended in 2018 to also include men, as well as female and male relatives of patients affected by a syndrome close to A-T (A-T like disorder, Nijmegen or Nijmegen-like disorders) and to cancer-prone families segregating an *ATM* variant or a variant altering a gene from the MRN complex, namely *MRE11A, RAD50* or *NBN* (CoF-AT2 Study). The main objectives of CoF-AT2 are to better estimate the risk of cancer taking into account other genetic and environmental/lifestyle factors such as exposure to radiations and potential genotype-phenotype correlations, to define the pathological characteristics of tumors developed by variant carriers, and to propose follow-up with a minimum of ten years, with early breast cancer screening action for women. Participating women are being offered an annual mammogram with a single view from age 40, with an additional mammary echography and then a biennial mammogram with two views from age 50. Epidemiological, familial and clinical data as cancer occurrence, together with biological samples (blood, tumors) of participants are collected, as well as mammograms to assess breast density. The cohort is multicentric, involving 43 clinics so far. To date, 580 subjects from 167 families have been enrolled, including 23 HBOC families and 12 pancreatic cancer-prone families.

International Consortium on *ATM* and Cancer: future plans

The workshop provided an opportunity to review what is known about *ATM* and its relationship to various cancers, to determine critical questions that need to be investigated, and to reiterate the need for collaborative efforts to set up large-scale genetic epidemiology studies.

Although retrospective studies are less complicated and may produce answers quickly, there are potential problems such as bias due to selection, survival or recall. In particular, selection of study participants through the family cancer clinics lead to cancer cases being oversampled for family history. In studies of *BRCA1* and *BRCA2* variant carriers, some methods have been developed to identify and reduce the impact of these problems [94] and will be useful for the analyses of *ATM* variant carrier cohorts. Population-based case-control studies can mitigate against some of these biases, but the studies need to be extremely large to provide reliable estimates. Moreover, prospective studies are essential to evaluate the full spectrum of disease outcomes. A drawback of prospective studies is the duration of the follow-up, which is needed to acquire sufficient power. International collaborations enabling meta-analyses of existing data are therefore needed to achieve sufficient statistical power.

The workshop initiative emanated from a desire to further examine the relationship between *ATM* and breast cancer, and thus, many of the attendees were scientists and clinicians with expertise in HBOC (cf. list of attendees in Notes section). More attendees with expertise in other cancers would have been beneficial to broaden the perspective. While the genetic epidemiology of *ATM* is also being actively pursued in disease-based consortia such as BCAC (http://bcac.ccge.medschl.cam.ac.uk/), BRIDGES, PRACTICAL and GENOMEL, workshop participants recognized the need for an *ATM*-specific interest group or consortium to study the full spectrum of health outcomes associated with *ATM* and to study the similarities and differences across cancer sites. Proposed objectives include: to better estimate the cancer risk associated with an *ATM* pathogenic variant by considering other genetic and environmental/lifestyle factors, genotype-phenotype correlations and other genetic heterogeneity; to better characterize pathological and molecular features of tumors developed by *ATM* variant carriers and to identify determinants of improved treatment and survival; and, finally, to improve *ATM* variant pathogenicity classification.

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Table 1. Contribution of *ATM* variants in breast cancer susceptibility in studies presented at the workshop.

Country	Study	Speaker	Population	Main findings	Reference
Norway	Hereditary Cancer Biobank	M. Dominguez Valentin (Oslo University Hospital)	1,967 familial cancer cases and negative for pathogenic variants in the *BRCA1/2, PTEN, TP53* or MMR genes.	11 LoF carriers were identified among 1967 cases. No reported OR associated with *ATM* variants.	Unpublished data
Macedonia	Macedonian Breast Cancer Association Study (MBCAS)	D. Plaseska-Karanfilska (Macedonian Academy of Sciences and Arts, Skopje)	390 probands from HBOC families, compared alleles frequencies to that of GnomAD and FLOSSIES public databases	7 LoF carriers among cases (1.8%), all were 40 years and less at breast cancer diagnosis: 4 also with a *BRCA1/2* pathogenic variant and 1 with an *EPCAM* pathogenic variant. Except for *BRCA1/ATM* double carrier, all had an ER+ breast tumor. 22 carriers (5,6%) of rare missense variants, classified as VUS according to the ACMG guidelines. No reported OR associated with *ATM* variants.	Unpublished data
France	GENE SISters (GENESIS)	F. Lesueur (U900-Institut Curie, Paris)	1,207 cases from HBOC families and negative for pathogenic BRCA1/2 variants & 1,199 unrelated controls	Focus on variants with MAF<0.005. 16 LoF carriers (1.3%) and 61 predicted deleterious missense variants (5.0%) among cases. LoF carriers had a higher risk than carriers of a rare missense (OR_{LoF}= 17.4 (2.3-132) vs. $OR_{missense}$=1.6 (1.0-2.3); P_{Het}=0.002). Mean age at diagnosis was 50.0 for LOF carriers and 50.9 for missense variants carriers. 85.5% of carriers (LoF + missense) had an ER+ breast tumor.	[33]
Germany	German consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)	N. Herold (University of Cologne)	5,589 cases from HBOC families & 2189 controls	81 LoF carriers among cases (1.5%), 71 unilateral, 10 bilateral. Associated OR=3.63, 95% CI: 2.67-4.94; median age at diagnosis for carriers was 45 years (range 27-80 years), 71.6% of carriers were under 50 years at diagnosis and 34.6% under age 40.	[95]
USA	CAnceR RIsk Estimates Related to Susceptibility (CARRIERS)	D. Goldgar (Hunstman Cancer Institute, Salt Lake City)	32,247 cases & 32,544 controls from 12 population-based cohort or case-control studies	mean age at diagnosis=62 years OR associated with pathogenic *ATM* variants (AGL variant classification; largely equivalent to ClinVar) = 1.8 (95% CI: 1.5 – 2.3); increased risk in women diagnosed with breast cancer before age 60 (OR=2.6, 95% CI: 1.9,3.6). No evidence of association between *ATM* variants and ER- breast tumour.	[30]

HBOC, Hereditary Breast and Ovarian Cancer; AGL, Ambry Genetic Laboratory; ER+, estrogen receptor positive tumor; ER-, estrogen negative tumor; MAF, minor allele frequency; OR, Odds ratio.

Table 2. Contribution of *ATM* variants in cancer (other than breast) susceptibility in studies presented at the workshop.

Country	Study	Speaker	Population	Main findings	Reference
Norway	Hereditary Cancer Biobank	M. Dominguez Valentin (Oslo University Hospital, Oslo)	1,967 familial cancer cases negative for pathogenic variants in the *BRCA1/2*, *PTEN*, *TP53* or MMR genes.	11 LoF carriers were identified among 1967 cases (12% colon cancer, 6% rectal cancer, 7% breast cancer, and 6% prostate cancer). Among LoF carriers, 4 had breast or ovarian cancer, 1 colon cancer, 1 testis cancer, 1 thyroid cancer and 4 were healthy members of cancer kindreds. 2 VUS were also identified (0.1%) No reported ORs associated with *ATM* variants.	Unpublished data
Texas, USA	Clinical Cancer Genetics Program	B. Arun (University of Texas MD Anderson Cancer Center, Houston)	7,306 patients for hereditary cancer evaluation: breast (68%), genitourinary (10%), pancreatic (5%), thyroid (2%), or ovarian (2%) cancer, melanoma (2%).	148 deleterious variant carriers (2.0%) were identified and 312 VUS carriers (4.7%). *ATM* carriers' distribution by cancer type was: leukemia 4%, pancreatic cancer 3.7%, gynecologic cancer 3.5%, gastrointestinal cancer 2.7%, genitourinary cancer 2.6%, thyroid cancer 1.7% and breast cancer 1.4%. 23% of the *ATM* variant carriers versus 18% of non-carriers had multiple primary cancers. Moreover, having a family history of breast, pancreatic, or gynecologic cancer, or lymphoma was more common in *ATM* variant carriers as compared to non-carriers. No reported ORs associated with *ATM* variants.	Unpublished data
United Kingdom (UK)		D.F Easton (University of Cambridge, Cambridge)	1,160 relatives of 169 A-T patients.	Excess risk of cancer other than breast cancer in relatives, with suggestive increased risks of colorectal and stomach cancers.	17
France	CoF-AT2 study	N. Andrieu (Inserm U900, Paris)	9,215 relatives of 135 French A-T index cases	Excess risks of leukemia, lymphoma and pancreatic cancer in HetATM	Unpublished data