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Clinical Interpretation of Pathogenic *ATM* and *CHEK2* Variants on Multigene Panel Tests: Navigating Moderate Risk

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Abstract

Comprehensive genomic cancer risk assessment (GCRA) helps patients, family members, and providers make informed choices about cancer screening, surgical and chemotherapeutic risk reduction, and genetically targeted cancer therapies. The increasing availability of multigene panel tests for clinical applications allows testing of well-defined high-risk genes, as well as moderate-risk genes, for which the penetrance and spectrum of cancer risk are less well characterized. Moderate-risk genes are defined as genes that, when altered by a pathogenic variant, confer a two to five-fold relative risk of cancer. Two such genes included on many comprehensive cancer panels are the DNA repair genes *ATM* and *CHEK2*, best known for moderately increased risk of breast cancer development. However, the impact of screening and preventative interventions and spectrum of cancer risk beyond breast cancer associated with *ATM* and/or *CHEK2* variants remain less well characterized. We convened a large, multidisciplinary, cross-sectional panel of GCRA clinicians to review challenging, peer-submitted cases of patients identified with *ATM* or *CHEK2* variants. This paper summarizes the inter-professional case discussion and recommendations generated during the session, the level of concordance with respect to recommendations between

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Supplementary Material

Supplement 1. Cancer Genetics and Genomics Conference syllabus. Supplement 2. Participant survey

the academic and community clinician participants for each case, and potential barriers to implementing recommended care in various practice settings.

Keywords

Cancer genetics; *ATM*; *CHEK2*; moderate-risk gene; panel test; genomic cancer risk assessment (GCRA)

Introduction & Background

The clinical utility of genomic cancer risk assessment (GCRA) using single gene germline testing for cancer predisposition is well established [1–6]. Comprehensive GCRA helps patients, family members, and providers make informed choices about cancer screening, surgical and chemoprophylactic risk reduction, and genetically targeted cancer therapies. Historically, genetic testing evaluated for high-penetrance cancer predisposition genes such as *BRCA1* and *BRCA2*. The advent of high-throughput next generation sequencing (NGS) and competitive marketing by multiple commercial vendors is driving down costs thereby increasing the availability of multigene panel tests for clinical applications. In addition to bundling well-defined high-risk genes, many panels also include a growing number of low and moderate-risk genes for which the penetrance and spectrum of cancer risk are less well characterized.

Moderate-risk genes are defined as genes that, when altered by a pathogenic variant, confer a two to five-fold relative risk (RR) of cancer [7]. Historically, the high cost of sequencing and a lower cancer incidence among carriers of moderate-risk pathogenic variants limited the identification of carriers for enrollment in retrospective and case-control studies. NGS and multigene panel testing are driving the identification of many more carriers of pathogenic variants in moderate-risk genes. The application of GCRA in carriers of moderate-risk genes is now common practice among many providers, however, prospective data and consensus management guidelines to help patients and providers make informed decisions are limited.

Among the moderate-risk genes appearing on commercial multigene cancer panels are the DNA repair genes **ataxia-telangiectasia mutated (*ATM*)** and **checkpoint serine-threonine kinase 2 (*CHEK2*)**. *ATM* is located on chromosome 11 and encodes a serine threonine kinase that is activated in response to DNA double-strand breaks. ATM participates in DNA repair by phosphorylating downstream proteins involved in cell cycle checkpoint control, apoptosis, and DNA repair [8]. Pathogenic bi-allelic variants in *ATM* result in ataxia-telangiectasia (A-T), which is characterized by progressive cerebellar degeneration, oculocutaneous telangiectasia, immunological deficiency, radiosensitivity, and an increased risk of cancer [9–11]. Heterozygous carriers of pathogenic *ATM* variants do not display characteristic clinical features of autosomal recessive A-T, but do share an increased predisposition to cancer [10, 11]. The carrier frequency of *ATM* pathogenic variants is estimated at 0.5-1% in the general population [9]. Retrospective reviews undertaken to better quantify the relative risk of specific cancers in heterozygous carriers of pathogenic *ATM* variants demonstrate an increased risk of breast cancer (RR=2.8), but were unable to

quantify postulated increased risk for colon, prostate, and pancreatic cancer[12, 13]. Consequently, the National Comprehensive Cancer Network (NCCN) consensus statements do not include recommendations for colorectal, prostate, or pancreatic cancer screening in patients with pathogenic *ATM* variants[14]. Further research is needed to better quantify the risk of cancer development and utility of increased screening in patients with inherited pathogenic *ATM* variants.

CHEK2 is located on chromosome 22 and also encodes a serine threonine kinase involved in the DNA damage response. CHEK2 is phosphorylated in response to double-strand DNA breaks, DNA alkylation, or replicative stress, and once phosphorylated, CHEK2 activates downstream targets including p53 to mediate cycle arrest and apoptosis [15, 16]. Germline *CHEK2* sequence variants were first identified in Li-Fraumeni Syndrome families that do not carry *TP53* pathogenic variants [15, 17]. While different studies have reported possible association with increased risk for breast, colon, and prostate cancer, precise relative risk estimates are limited to breast cancer; accordingly, at the time of the study, NCCN screening recommendations for *CHEK2* carriers were limited to breast cancer screening [7, 18–20]. Notably, truncating and pathogenic missense variants in *CHEK2* confer a RR of 3.0 (90% CI 2.6-3.5) and 1.58 (95% CI 1.42-1.75) respectively [21]. *CHEK2* variant c. 1100delC (p.Thr367Metfs), a truncating variant, is the best-characterized *CHEK2* pathogenic variant, seen in up to 1-2% of the general population [15, 17, 22].

An ever-increasing number of patients are being identified with pathogenic variants in moderate-risk genes, including, *ATM* and *CHEK2*. Recent work by Couch *et al.* evaluating pathogenic variants in 41,611 eligible consecutive white women with breast cancer referred for hereditary cancer genetic testing demonstrated that 6.18% of women harbored a pathogenic variant, excluding the high-risk genes *BRCA1* and *BRCA2* and low-risk founder *CHEK2* variants c.470C>T (p.Ile157Thr) and c.1283C>T (p.Ser428Phe); among the most commonly mutated genes were *ATM* (1.06%) and *CHEK2* (1.73%) [23]. Similarly, in a retrospective review of 337 patients who met NCCN criteria for HBOC assessment and underwent multigene panel evaluation, 25 (7.4%) patients had a pathogenic non-*BRCA* variant, and variants in *CHEK2* and *ATM* each accounted for 15% of the total pathogenic variants identified [24]. Despite the inclusion of moderate-risk cancer genes on multigene panels and the frequency of pathogenic variants in these genes, there are currently only limited data to estimate the risk of cancer development in this patient population. There are few, if any, prospective studies of surveillance or risk reduction interventions to guide cancer risk management in these patients and management recommendations are often based on expert opinion. Further, genetic counselors and physicians often have limited clinical experience with the management of patients with pathogenic variants in moderate-risk genes. Tung *et al.* have proposed a general counseling framework for clinicians providing care to individuals with moderate-penetrance variants associated with an increased risk of cancer development [21].

Given the limited data regarding risk of cancer development and appropriate surveillance and risk reduction interventions in patients with *ATM* and *CHEK2* variants, we hypothesized that there is heterogeneity among GCRA practitioners in the clinical management of *ATM* and *CHEK2* patients. We convened a large, multidisciplinary, cross-

sectional (academic and community oncology practices across the United States) panel of GCRA clinicians to review challenging, peer-submitted cases of patients identified with *ATM* or *CHEK2* pathogenic variants. The review was integrated in a session at an annual cancer genomics conference, "*New Frontiers in Diagnosis, Screening, and Management of Inherited Cancer Syndromes*", co-hosted by The University of Chicago and The City of Hope on April 8-9, 2016, in Chicago, IL (Supplement 1). Our aims were to share clinical experiences with reported variants in *ATM* and *CHEK2* genes, identify provider knowledge gaps and areas of uncertainty, and survey whether patients get uniform access to recommended screening and prevention measures. This paper summarizes the inter-professional case discussion and recommendations generated during the session, the level of concordance with recommendations between the academic and community clinician participants for each case, and potential barriers to implementing recommended care in various practice settings.

Methods

Participants/Procedure

Participants included 104 conference attendees, comprised of physicians and allied health care professionals from diverse oncology practice settings across the United States (US) and internationally, including clinicians who participate in the nationwide, National Cancer Institute (NCI)-supported program, *Clinical Cancer Genomics Community of Practice* (CCGCoP), for GCRA training and practice support [25, 26]. Prior to the conference, participants were invited to submit cases from their clinical oncology practices with complex or challenging results, with a particular emphasis on pathogenic variants in *ATM* or *CHEK2* yielded from clinical multigene panel tests.

The panel was comprised of five cancer genomics thought leaders representing different academic settings and disciplines. The session was co-moderated by a cancer genomics physician and a cancer risk genetic counselor. Presenters were invited to share each anonymized case, which included a brief clinical synopsis, pedigree, results of genetic testing, and specific management questions. The panel and participants discussed challenges related to each case and panelists generated recommendations in real-time that incorporated existing evidence from the literature, applied clinical judgment related to screening and risk management, and emphasized best practices in genetic counseling and patient and family communications. NCCN guidelines were cited when applicable, using the versions in effect at the time of the conference, NCCN Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2015, and Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2016 (detailed in Table 1). During the session, participants contributed to the oral case discussion and also documented their perceptions, interpretations, and feedback related to each case using a survey. Three cancer genomics clinician researchers documented key points and recommendations that were raised by the presenters or generated from panel discussion on each case.

Instrumentation

Participant demographic information including terminal degree, type of clinical practice, and geographic location of practice was collected on the conference registration form.

Case Submission Form

Case submissions were elicited from conference registrants one month prior to the conference via email, and included a de-identified pedigree, any relevant genetic testing results, and a brief description of specific challenges or questions related to the case.

Participant Feedback Survey

Participants completed a paper and pencil survey comprised of yes/no questions and open-ended prompts eliciting prior GCRA experiences, feedback on each case presented, and participant's perceived learning value of the session (Supplement 2).

Data Analysis

Documentation outlining expert panel recommendations performed by three cancer genomics clinician researchers were compiled, compared for consistency, and summarized to reflect expert panel discussion and recommendations for each case. Quantitative and qualitative survey data from session participants were entered into Microsoft Excel 2013 spreadsheets and audited for accuracy [27]. Given the limited number of international participants and variation in screening practices by country, only participant data from clinicians practicing in the US was analyzed. Descriptive statistics were computed for demographic, yes/no, and rating scale items. Coding and thematic analyses of open-ended responses were conducted by two clinical researchers through a series of iterations, and frequencies of responses coded under each theme were tallied. Quantitative and qualitative outcomes were triangulated to increase the depth and validity of the findings [28]. Members of the expert panel and session moderators reviewed final panel and participant recommendations for relevance and accuracy.

Results

As summarized in Table 2, 104 (47%) of 219 clinicians who attended the conference participated in the case working session. Of these, 99 clinicians (95%) practiced within the US and were included in final data analysis. Eighty-one (82%) reported that they provide GCRA services as all or part of their practices, primarily in community hospital (52%) or private practice (29%) settings, and roughly half (51%) are active members of the CCGCoP.

Of nine GCRA cases presented, the three *ATM* and two *CHEK2* cases summarized below were selected to represent the key clinical challenges, discussion points, and recommendations generated during the case working session.

ATM

Cases one through three include patients with an inherited *ATM* variant.

Case 1: *ATM* Carrier Seeking Risk-Reducing Mastectomy—A 34-year-old unaffected female was referred for GCRA due to a family history of breast cancer and a known pathogenic *ATM* variant, c.1564_1565delGA (p.Glu522ILefs), that was previously identified in her sister, who was diagnosed with breast cancer at age 49. Family history (Figure 1) was also notable for breast cancer in the consultand's mother at age 60 and maternal aunt at age 69, and for a maternal great-aunt with an unspecified female cancer as an adult. Her paternal family included cancer of unknown primary in a first cousin at age 50. Single-site testing for the pathogenic *ATM* variant, c.1564_1565delGA (p.Glu522ILefs), in the consultand was positive.

Presenting Problem/Questions: 1) What are the recommended breast cancer screening recommendations for the unaffected 34-year old consultand? 2) How does one address the question of risk reducing mastectomy (RRM) for this patient? 3) Do test results change management for the consultand given an empiric lifetime breast cancer risk estimate of 23% by the Claus model [29]?

Panel Recommendations: Screening for the consultand should include annual mammogram and breast MRI starting 10 years younger than the age of breast cancer diagnosis in the consultand's sister [7]. With regard to breast cancer prevention, the panel advised that the consultand's Gail score be calculated when she reaches 35 years of age, and tamoxifen may be considered if her 5-year risk of breast cancer development is greater than 1.67% [30]. RRM was not recommended given moderate lifetime breast cancer risk in carriers of a pathogenic *ATM* variant, however, the panel concurred that discussion of RRM may be appropriate depending on the consultand's breast cancer risk-tolerance. The panel noted that risk management was not meaningfully altered by the *ATM* carrier status, given that MRI surveillance, in addition to mammogram, is recommended for women with a lifetime risk of breast cancer that exceeds 20% based on empiric risk models[29, 31]. The panel also emphasized the importance of testing other family members to identify other at-risk individuals and to determine on which side of the family the *ATM* variant segregated. The participants noted that, in their clinical practices, identification of *ATM* variants within families was often discordant with their expectations, (i.e., not segregating with the reported breast cancers). This reflects reported observations that the attributable risk and negative predictive value for *ATM* carriers is limited, emphasizing the importance of residual empiric risk based on family history. That is, unlike families with an inherited high-risk variant, testing negative for a known familial moderate-risk variant is not thought to reduce the individual's risk to that of the general population.

Participant Feedback: Forty-seven (51%) participants noted that they had seen similar cases in their GCRA practices. Eighty-five (98%) fully or mostly concurred with the recommendations.

Case 2: Pancreatic Cancer Risk for *ATM* Carriers – True or Unrelated?—An 80-year-old female of Czech and Polish ancestry with a personal history of estrogen receptor positive (ER+), progesterone receptor positive (PR+), and Her2/neu negative invasive ductal carcinoma of the right breast diagnosed at age 65 was seen for GCRA. Family history

(Figure 2) was significant for a brother who recently died from pancreatic cancer at age 81, and a sister who died of renal cell carcinoma at age 54. The proband's son died of pancreatic cancer at age 53, and her 57-year-old daughter was diagnosed with early stage uterine cancer at age 52. A hereditary cancer panel evaluating 49 genes was ordered. Between the time of testing and result disclosure, the patient was diagnosed with metastatic pancreatic adenocarcinoma. Results from the panel revealed a pathogenic *ATM* variant, c.3850delA (p.Thr1284GInfs). Three of the patient's adult children subsequently tested positive for the *ATM* variant and inquired regarding their own cancer screening recommendations.

Presenting Problem/Questions

1. How should one counsel regarding pancreatic cancer screening in patients with ann *ATM* variant, and in this family in particular?
2. How are recommendations influenced by *ATM* carrier status?

Panel Recommendations: Although there is evidence that pancreatic cancer risk is moderately increased (~5% lifetime) in *ATM* carriers, there are currently no NCCN guidelines for pancreatic cancer screening in *ATM* carriers [32]. Therefore, the panel advised that family history should guide the approach to pancreatic cancer screening for this family. A working definition of familial pancreatic cancer is a consultand with a pair of first-degree relatives affected by pancreatic cancer or a total of three family members affected by pancreatic cancer [33]. Given that the consultand's children met criteria for familial pancreatic cancer, the panel recommended consideration of annual pancreatic cancer screening with alternating endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) [34, 35]. These recommendations were independent of *ATM* carrier status. The panel also emphasized that screening may be considered in a consultand with an *ATM* variant and a single first-degree relative affected by pancreatic cancer depending on their risk-tolerance, after appropriate counseling regarding the risks and limitations of pancreatic cancer screening.

Participant Feedback: Twenty (21%) participants noted that they had seen similar cases in their GCRA practices. All participants agreed with the panel's recommendations. Nineteen (25%) participants stated that their patients would not have access to all recommended pancreatic cancer screening due to lack of insurance coverage or availability of an EUS-qualified gastroenterologist. This raised the ethical issue of equity.

Case 3: Is radiation treatment contra-indicated in a carrier of homozygous *ATM* variants of uncertain significance?—

A 48-year-old woman of Northern European ancestry, recently diagnosed with clinical stage II ER+, PR+, Her2/neu+ invasive breast cancer with nodal involvement, was referred for GCRA. Family history (Figure 3) included a diagnosis of melanoma at age 50 in the proband's father and lung cancer in a paternal uncle, who was a smoker. Testing with an eight gene, breast cancer focused panel was performed. The proband was found to be homozygous for a variant of uncertain significance (VUS) in the *ATM* gene, c.4258C>T (p.Leu1420Phe), previously reported in both heterozygous and homozygous states. Per the report generated by the commercial genetic testing laboratory, this *ATM* VUS is not associated with A-T in the homozygous

state. However, in a large case-control study of breast cancer patients, *ATM* c.4258C>T (p.Leu1420Phe) conferred a statistically significant increased risk of breast cancer when in the homozygous state (OR 5.31 CI=1.35-20.87) [36]. Increased breast cancer risk has not been observed in heterozygous carriers of this VUS [37].

Presenting Problem/Questions: 1) Should the *ATM* VUS affect breast cancer treatment, specifically radiation therapy, in this proband? 2) What is the significance of this result for other family members?

Panel Recommendations: The panel advised that given the evidence that homozygous carriers of the *ATM* c.4258C>T (p.Leu1420Phe) VUS do not have a phenotype consistent with A-T, concern about radiosensitivity should not influence breast cancer treatment, and the proband should receive standard-of-care therapy for her malignancy. The panel also advised that there is insufficient evidence to recommend against radiation therapy for heterozygous *ATM* carriers if it is indicated based on cancer diagnosis; this information was not included in NCCN guidelines at the time of the conference, but has since been incorporated [38, 39]. With regard to other family members, genetic testing may also be considered to evaluate for homozygous carriers, specifically siblings who would each have a 1/4 chance of being homozygous for the *ATM* variant.. The panel emphasized that the proband should be encouraged to enroll in a research registry to aid in further characterizing the *ATM* VUS. Of note, a second case with a proband who is homozygous for the *ATM* c. 4258C>T (p.Leu1420Phe) variant was submitted to the conference organizers from a separate clinical practice, reflecting the commonality of this alteration.

Participant Feedback: Seven (9%) participants noted that they had seen similar cases in their GCRA practices. All participants agreed with the panel's recommendation. Participants who shared a similar experience expressed frustration with limited data in this context and emphasized the importance of encouraging patient participation in research.

CHEK2

Cases four and five represent challenges related to test results that revealed inherited pathogenic variants in the *CHEK2* gene.

Case 4: Prioritizing Genetic Testing in Time Sensitive Situations—A 54-year-old Caucasian female with a personal history of ductal carcinoma in situ at age 44, treated with lumpectomy, and a new diagnosis of invasive ductal carcinoma at age 54, was referred for GCRA prior to cancer treatment. The proband's mother was diagnosed with liver cancer at age 81; the proband had no knowledge of other cancers on either side of her family (Figure 4). Testing was initiated to evaluate *BRCA1* and *BRCA2*, to ensure rapid results due to an upcoming surgical date, with reflex to a 21 gene breast/ovarian cancer panel. Findings included a pathogenic variant in *CHEK2*, c.1100delC (p.Thr367Metfs), a VUS in *ATM*, c. 6067G>A (p.Gly2023Arg), and a VUS in *BRIP1*, c.577G>A (p.Val193Ile); since the time of original testing, the *BRIP1* VUS was reclassified as benign[40].

Presenting problem/questions: 1) What are the recommendations for breast cancer screening and management in *CHEK2* carriers? 2) How should one approach selection of the appropriate gene panel in a time-limited situation? 3) Is there a potential for gene-gene interactions between the pathogenic *CHEK2* variant and *ATM* VUS or *BRIP1* VUS?

Panel Recommendations: The panel advised that, as per NCCN guidelines, evidence is insufficient to recommend consideration of RRM in *CHEK2* carriers, and that management should be based on family history, treatment of the patient's current cancer, and future cancer risk-tolerance given the limited data available to guide decision making. The panel reinforced NCCN guideline recommendations for annual mammogram and annual breast MRI in females with an inherited *CHEK2* variant (Table 1). The panel also commented on the challenges of choosing the appropriate breast cancer specific gene panel, in particular, whether one should choose a high-risk breast cancer panel with reflex to moderate-risk genes if testing is initially ordered to guide surgical management recommendations. The panel concurred that a proximal surgery date may necessitate sending an abbreviated panel with rapid turnaround time to help decide between mastectomy and breast conserving surgeries. Regarding the question of potential significance of the findings of both a *CHEK2* pathogenic variant and VUSs in *ATM* and *BRIP1*, the panel stated that there is no evidence for interaction of variants. The VUSs should be interpreted as uninformative and unless reclassified as pathogenic have no bearing on treatment or screening recommendations for the proband, nor should they be used to discern risk in family members. The panel emphasized that practices providing GCRA should have a follow-up model in place that performs regular review of the literature and updates carriers if a VUS is re-classified as pathogenic. Of note, two additional cases were submitted which discussed the question of gene-gene interaction, highlighting the frequency of identifying more than one variant on panel testing.

Participant Feedback: Thirty-four (45%) participants noted that they had seen similar cases in their GCRA practices. Fifty-seven (95%) fully or mostly concurred with the recommendations.

Case 5: Spectrum of Screening for *CHEK2* Carriers—A 31-year-old female recently diagnosed with invasive breast cancer was referred for GCRA. The proband's father was diagnosed with prostate cancer at age 43 and died of recurrence at age 65 (Figure 5). Her paternal aunt died of colon cancer at age 60 and a paternal uncle was diagnosed with prostate cancer at age 40. The patient was tested using a high-moderate-risk cancer panel, which detected a pathogenic *CHEK2* variant, c.470C>T (p.Ile157Thr).

Presenting Problem/questions: 1) What spectrum of cancers should one screen for in *CHEK2* carriers? How does family history influence screening recommendations?

Expert Panel Recommendations: Pending completion of breast cancer treatment, the panel recommended that the proband undergo annual mammogram and breast MRI of remaining breast tissue. It was acknowledged that there is emerging evidence that breast cancer risk associated with the *CHEK2* missense variant, c.470C>T (p.Ile157Thr) is less than that reported for the truncating variants; however, our current approach is to include MRI in

screening recommendations for all carriers of a pathogenic *CHEK2* variant, as we do not have sufficient data to make refined genotype/phenotype distinctions. For colonoscopy screening, the panel recommended colonoscopy every 5 years starting at age 40, though the association of colon cancer risk and this specific *CHEK2* variant is not established. At the time of the study, specific recommendations for colon cancer screening in *CHEK2* carriers were not included in NCCN guidelines, however, current guidelines are consistent with this recommendation (Table 1)[14, 41]. An association between *CHEK2* variants and prostate cancer incidence are cited in the literature, but no screening guidelines are provided in NCCN [19, 20]. It was recommended that segregation analysis could be performed on the paternal uncle with prostate cancer to see whether the variant segregated with disease as this could be helpful for counseling the proband's brothers; cancer site in a proband with a *CHEK2* variant may influence the relative risk of specific cancers for his/her first-degree relatives [20]. Although the NCCN does not outline specific screening guidelines for prostate cancer in *CHEK2* carriers, the panel recommended that annual PSA should be considered starting at age 40 based on family history. Finally, it is important to emphasize that mutations do not act in isolation and more research is needed to understand gene environment interactions in cancer development in *CHEK2* carriers as well as other cancer predisposition genes.

Participant Feedback: Twenty-five (38%) participants noted that they had seen similar cases in their GCRA practices. Of the 12 (23%) participants who challenged the recommendations discussed, most questioned the merits of colon and prostate cancer screening in *CHEK2* carriers. Participants indicated that their patients likely would not have access to recommended colonoscopies before age 50 in the absence of a significant family history of colorectal cancer.

Discussion

The increasing utilization of multigene panels evaluating high and moderate-risk genes has broadened the scope of GCRA while generating new challenges for clinical practitioners and affected families. This manuscript reviews recommendations for the management of patients with *ATM* and *CHEK2* pathogenic variants, two frequently implicated moderate-risk genes included on many commercial testing panels, generated by a multidisciplinary, cross-sectional panel of GCRA clinicians at an annual genomic conference. Pathogenic variants in *ATM* and *CHEK2* are associated with a moderately increased risk of breast cancer, RR 2.8 and 1.58-3.0, respectively [21]. However, the impact of screening and preventative interventions and spectrum of cancer risk beyond breast cancer associated with *ATM* and/or *CHEK2* variants remain less well characterized. We reviewed 5 clinical cases involving *ATM* or *CHEK2* encountered in the GCRA setting to help outline the current body of literature and also highlight expert recommendations for patient management. Key themes that surfaced during this discussion included: application of RRM in carriers of moderate-risk genes, accessibility of recommended screening and preventative services, and the influence of moderate-risk genes in the setting of a strong family history.

Application of RRM in carriers of moderate-risk genes

Discussion of the option of RRM is recommended in carriers of high-risk breast cancer genes such as *BRCA1* or *BRCA2* or individuals with a strong family history of breast cancer when genomic analysis does not reveal mutations in any of the known inherited cancer predisposition genes [7, 42–45]. This guideline is meant to balance the potential medical and psychological morbidities of RRM with up to a 90% decrease in the risk of developing breast cancer [46–49]. Important psychological considerations when pursuing RRM include the impact on a woman's perceived quality of life, sexuality, and body image; investigations into whether there is a negative psychological impact on high-risk women following RRM are mixed [43]. Alternatively, the question of whether RRM, an invasive surgical intervention, is warranted as a preventative measure for a female carrier of a moderate-risk gene remains to be determined given concerns about over diagnosis and over treatment in healthy individuals. Specifically, NCCN guidelines outline that there is insufficient evidence to recommend RRM in carriers of *ATM* or *CHEK2* variants based on associated relative risk of breast cancer [7]. However, panelists agreed that RRM may be discussed in *ATM* and *CHEK2* carriers in the context of personal and family history, patient risk-tolerance, psychological and surgical morbidity, and alternative methods of risk reduction, such as chemoprevention and close surveillance. Ultimately, consideration of RRM is an individualized decision between the patient, her GCRA team, and her surgeon; and in the future, there are also likely to be increasing challenges by 3rd Party Payors. Prospective studies to define the risk reduction benefit of RRM in carriers of moderate-risk genes are not available to guide medical management. As such, more studies, with longer follow up, are needed to help GCRA practitioners educate patients when considering irreversible surgical intervention.

Accessibility of screening and preventative services

Performing heightened breast cancer screening measures such as breast MRI in carriers of variants in moderate-risk genes is outlined in current NCCN guidelines, although studies to support medical benefit and justify cost of intensive surveillance are lacking [7]. The panel participants stated that they observe heightened breast screening guidelines and shared the opinion that these guidelines facilitate obtaining insurance coverage for heightened screening although benefits are not as well defined. Additional surveillance studies advocated by experts, including pancreatic and colorectal cancer surveillance in *ATM* carriers and prostate cancer screening in *CHEK2* carriers, raised a greater challenge for some panel participants. These interventions also lack a body of literature to support their implementation currently and are not recommended in NCCN. Barriers to these screening procedures include lack of insurance coverage and lack of access to trained specialists, particularly in the field of pancreatic cancer screening with EUS. This challenge raises the issue of equity of access to care in GCRA based on patient financial means or proximity to a specialized/major medical center. Over time, data from the Precision Medicine Initiative "All of Us" as well as ongoing registries and complementary consortia will help characterize the RR of additional cancers in *ATM* and *CHEK2* carriers and lead to incorporation of additional cancer screening into national guidelines; although, one must use caution when interpreting registry data as this may not reflect true population risk estimates [50].. Until

then, GCRA practitioners must consider cost effective ways to manage *ATM* and *CHEK2* carriers, when national guidelines remain at the level of Expert Opinion.

Influence of moderate-risk genes in the setting of a strong family history

In some clinical situations, a patient undergoing GCRA may meet a level of risk that warrants heightened screening and chemoprophylaxis based on cancer risk models derived from family and personal history of breast cancer, prompting the question of whether genetic testing for moderate-risk genes adds value to the evaluation [29, 51, 52]. In this setting, genetic testing for moderate-risk genes may be warranted to help identify additional cancer risks. Further, identification of a moderate-risk gene may prompt cascade testing and segregation analysis to establish whether the variant is causative of the family cancer history, beneficial for patient counseling and future research. Unlike in the case of a high-risk gene, a family member who is a “true negative” and did not inherit a moderate-risk variant, does not eliminate his/her familial cancer risk. This interpretation of negative testing for moderate-risk genes emphasizes the importance of residual empiric risk based on family history. A pathogenic variant in a moderate-risk gene such as *ATM* or *CHEK2* can only be interpreted as a part of the explanation in a family history of breast cancer.

The aforementioned themes highlight the need for additional research to better characterize cancer-specific relative risk, genotype-phenotype associations, influence of personal and family history, and impact of heightened surveillance and preventative measures in the evaluation and management of *ATM* and *CHEK2* carriers. In the future, risk modifiers, such as the Polygenic Risk Scores, may also be incorporated to improve and better personalize risk stratification for *ATM* and *CHEK2* mutation carriers[53]. Additional topics and challenges exist in the field of moderate-risk genes, which are beyond the scope of this manuscript. Research is ongoing to refine our understanding of moderate-risk genes and their utility in GCRA. Panel-based discussions and surveys of GCRA practitioners are incredibly useful as we aim to understand the current state of GCRA across the US, so that we may continue to refine our approach to the management of moderate-risk genes and welcome an era where comprehensive GCRA is widely available to the general public.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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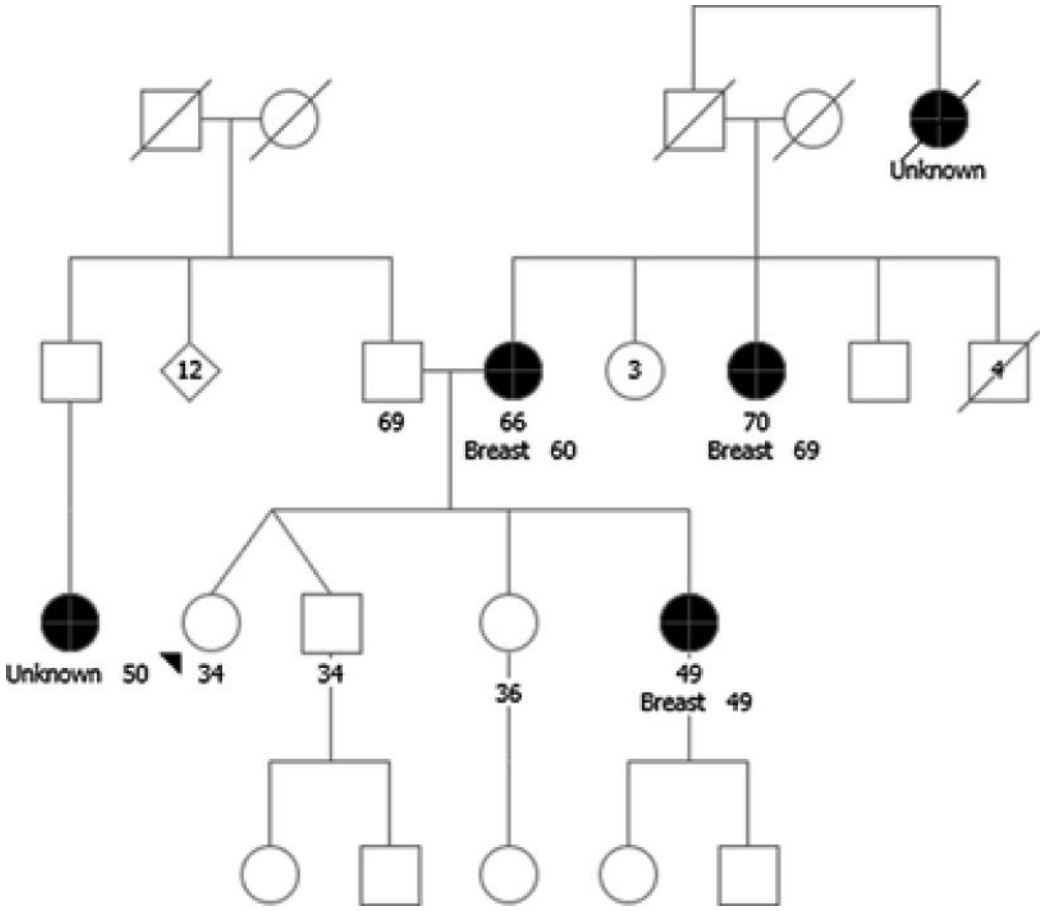

Fig. 1.

Case 1: *ATM* Carrier Seeking Risk-Reducing Mastectomy. Unknown, cancer of unknown type. Breast, breast cancer. Please see associated vignette for more details

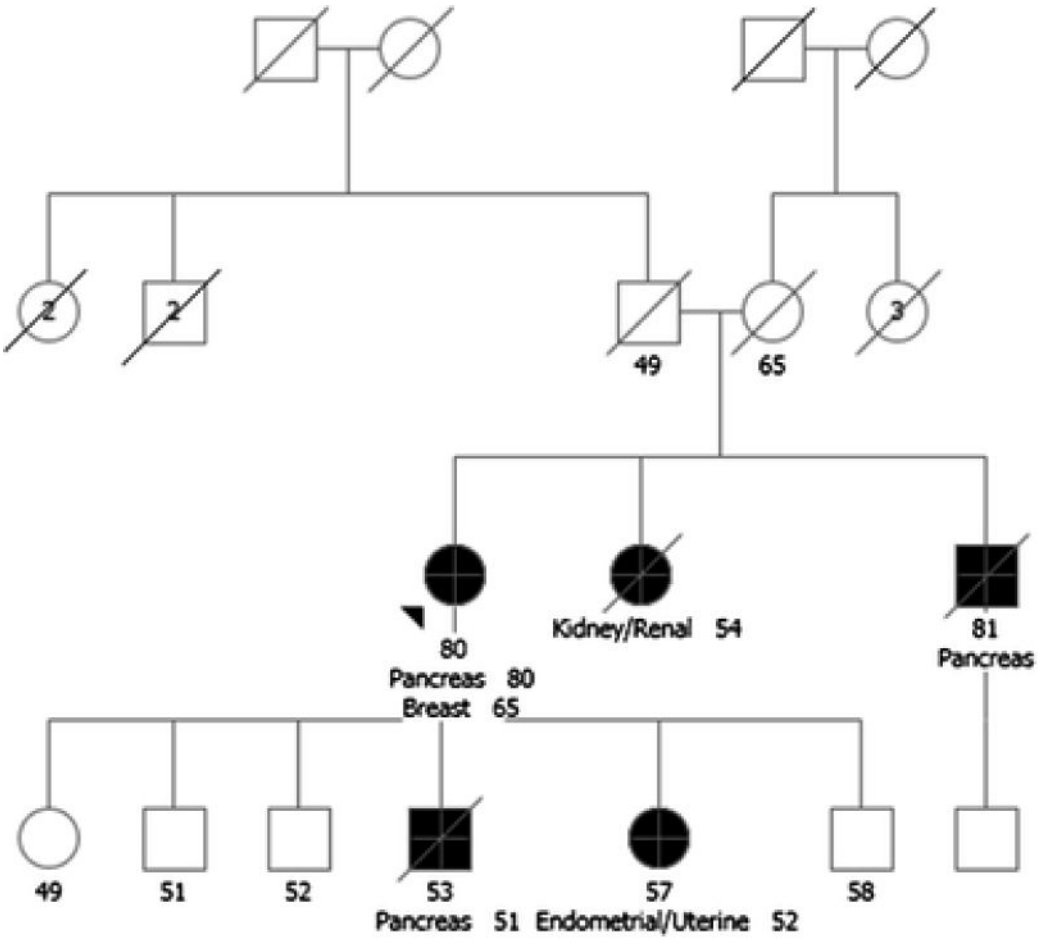

Fig. 2.

Case 2: Pancreatic Cancer Risk for *ATM* Carriers – True or Unrelated? Pancreas, pancreas cancer; Endometrial, endometrial cancer; Kidney, kidney cancer; Breast, breast cancer. Please see associated vignette for more details

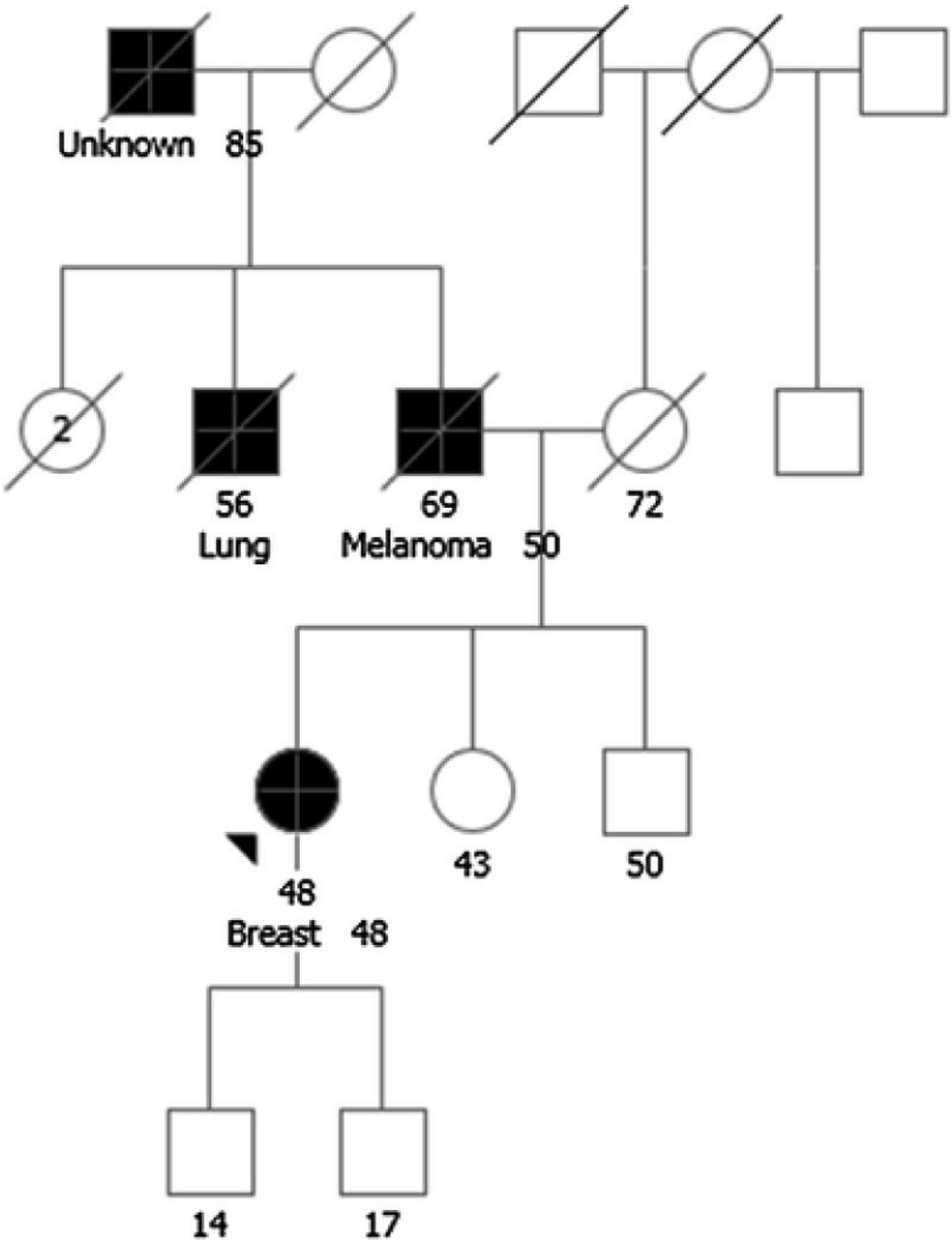

Fig. 3.

Case 3: Is radiation treatment contra-indicated in a carrier of homozygous *ATM* variants of uncertain significance? Lung, lung cancer; Breast, breast cancer. Please see associated vignette for more details.

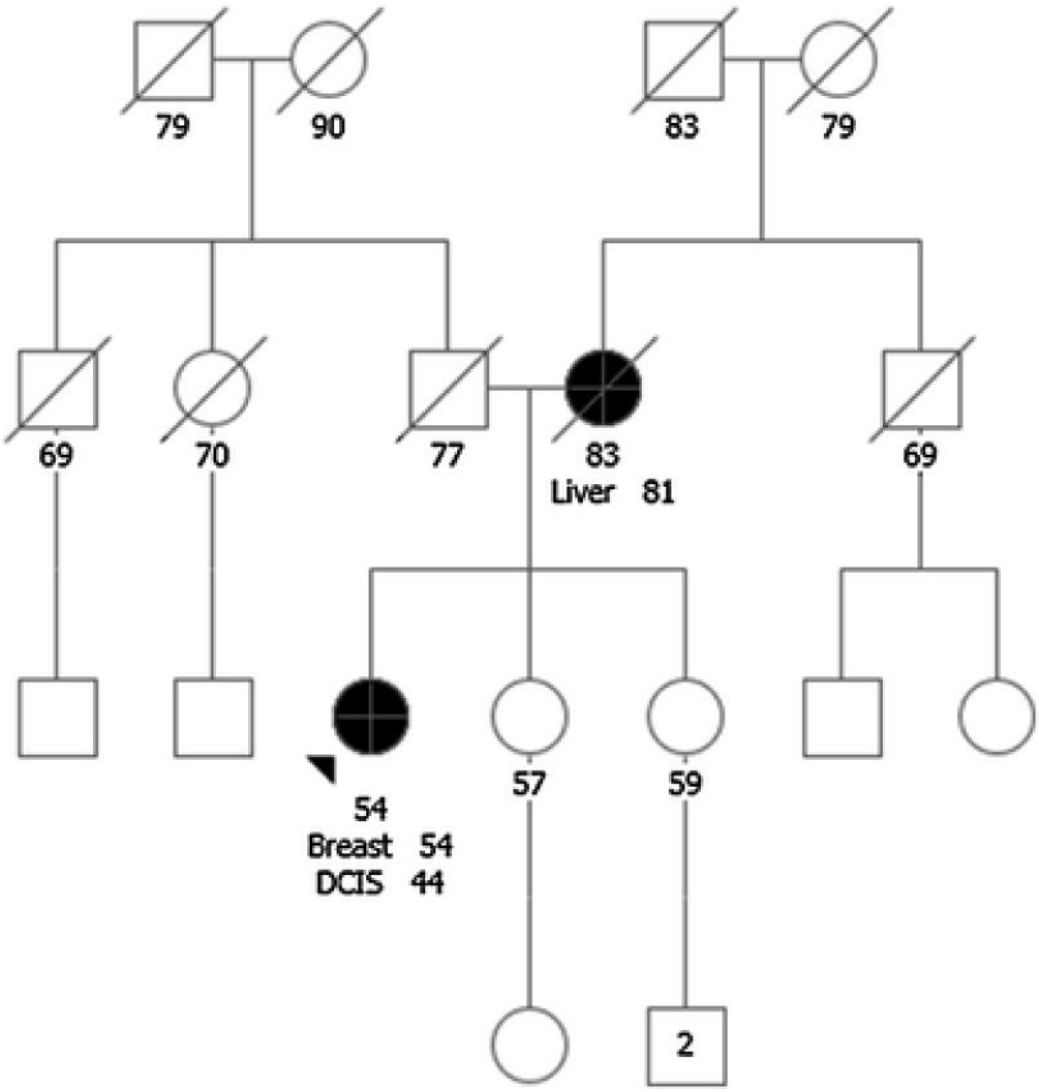

Fig 4.

Case 4: Prioritizing Genetic Testing in Time Sensitive Situations. Breast, breast cancer; DCIS, ductal carcinoma in situ; Liver, liver cancer. Please see associated vignette for more details

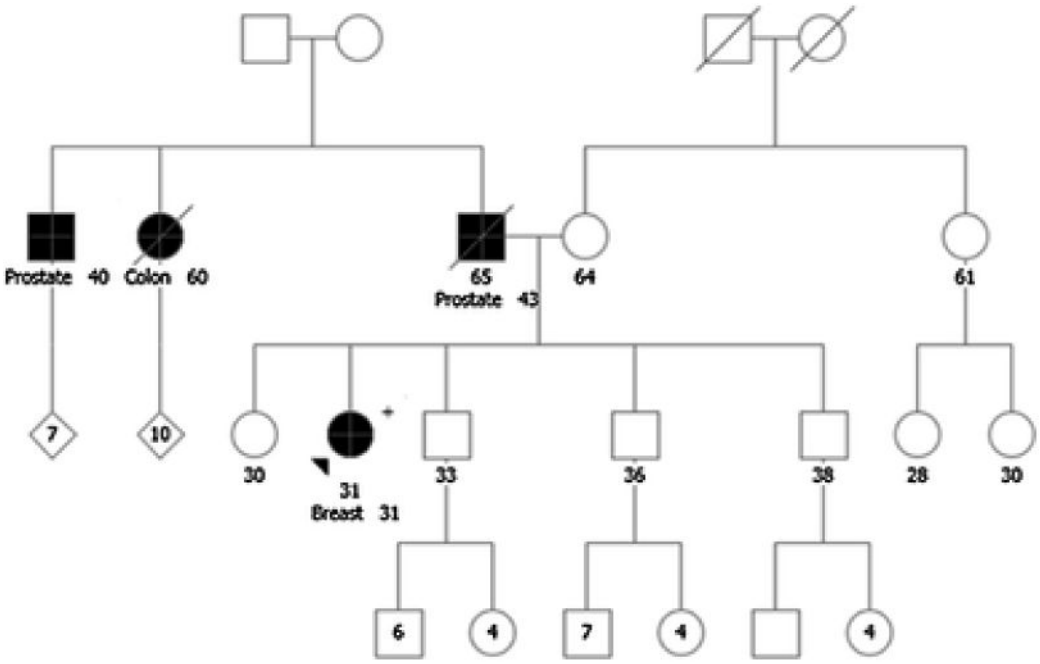

Fig. 5.

Case 5: Spectrum of Screening for *CHEK2* Carriers. Colon, colorectal cancer; Prostate, prostate cancer; Breast, breast cancer. Please see associated vignette for more details

Table 1

NCCN Guidelines in publication at time of survey study (NCCN Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2015), (NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2016)

Gene	Breast Cancer	Colon Cancer
ATM	**Screening:** Annual mammogram and consider breast MRI starting at age 40 **RRM:** Consider based on family history	Not addressed
CHEK2	**Screening:** Annual mammogram and consider breast MRI starting at age 40 **RRM:** Consider based on family history	**Not addressed**

Table 2

Demographics of Participants in *ATM/CHEK2* Case Working Session

Participant Characteristics	**N (%)**
Terminal degree	
MD	32 (32%)
RN/APN	34 (34%)
GC	25 (25%)
PhD	1 (1%)
Other	7 (7%)
Practice Setting	
Private Practice	29 (29%)
Community Hospital	51 (52%)
Academic Medical Institution	11 (11%)
Other	4 (4%)
Omitted	4 (4%)
Participants currently delivering GCRA services as partor all of their practices	
Yes	81 (82%)
No	14 (14%)
Omitted	4 (4%)
City of Hope Clinical Cancer Genomics Community of Practice members (CCGCoP)	
Yes	50 (51%)
No	48 (48%)
Omitted	1 (1%)