



Published in final edited form as:

Genet Med. 2023 October ; 25(10): 100870. doi:10.1016/j.gim.2023.100870.

ACMG PRACTICE RESOURCE: Management of individuals with germline pathogenic/likely pathogenic variants in *CHEK2*: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

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Conflict of Interest

Funding and support listed here did not support development of this document unless included in the acknowledgments section. H.H. is supported by the Cancer Research CRUK Catalyst Award, CanGene-CanVar, and has served on advisory boards for AstraZeneca. R.S. is supported by the German Cancer Aid and the Federal Ministry of Education and Research (BMBF), Germany. M.T. is supported by the National Institute for Health and Care Research (NIHR) Cambridge Biomedical Research Centre. D.R.S. is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute (NCI), Rockville, Maryland, and also performs contract clinical telehealth services for Genome Medical, Inc., in accordance with relevant NCI ethics policies. All other authors declare no conflicts of interest.

Additional Information

The online version of this article (<https://doi.org/10.1016/j.gim.2023.100870>) contains supplementary material, which is available to authorized users.

The Board of Directors of the American College of Medical Genetics and Genomics approved this practice resource on January 23, 2023.

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Abstract

Purpose: Although the role of *CHEK2* germline pathogenic variants in cancer predisposition is well known, resources for managing *CHEK2* heterozygotes in clinical practice are limited.

Methods: An international workgroup developed guidance on clinical management of *CHEK2* heterozygotes informed by peer-reviewed publications from PubMed.

Results: Although *CHEK2* is considered a moderate penetrance gene, cancer risks may be considered as a continuous variable, which are influenced by family history and other modifiers. Consequently, early cancer detection and prevention for *CHEK2* heterozygotes should be guided by personalized risk estimates. Such estimates may result in both downgrading lifetime breast cancer risks to those similar to the general population or upgrading lifetime risk to a level at which *CHEK2* heterozygotes are offered high-risk breast surveillance according to country-specific guidelines. Risk-reducing mastectomy should be guided by personalized risk estimates and shared decision making. Colorectal and prostate cancer surveillance should be considered based on

assessment of family history. For *CHEK2* heterozygotes who develop cancer, no specific targeted medical treatment is recommended at this time.

Conclusion: Systematic prospective data collection is needed to establish the spectrum of *CHEK2*-associated cancer risks and to determine yet-unanswered questions, such as the outcomes of surveillance, response to cancer treatment, and survival after cancer diagnosis.

Keywords

Cancer predisposition; Cancer risk; Cancer surveillance; *CHEK2*; Inherited cancer

Introduction

The *CHEK2* gene was originally identified in 1998 as a key effector kinase in cell cycle regulation, specifically through its role in the ATM-CHK2-p53 DNA damage response pathway.¹ Despite the initial discovery of the *CHEK2* variant NM_007194.4:c.1100del p.(Thr367fs) (henceforth described as *CHEK2* c.1100del) in multigene families, larger studies, most notably from the international *CHEK2* consortium, reported a high frequency of this variant (>1%) in healthy control individuals from The Netherlands and the United Kingdom.² In addition, a lack of segregation of c.1100del with affected individuals in breast cancer (BC) families is often observed, suggesting that the association of *CHEK2* with cancer predisposition may be more complex than initially thought. Although an early case series published in 1999 suggested that *CHEK2* may predispose to Li-Fraumeni syndrome,³ subsequent studies, including those based on the same families in the original case series, have strongly refuted this claim, and a large body of evidence has conclusively shown that variants in *CHEK2* are not associated with Li-Fraumeni syndrome.^{4,5}

Multiple studies have been published on the association of germline *CHEK2* variants with cancer predisposition, ranging from single case reports to large case-control analyses. Yet, there is a lack of clear guidance for the clinical management of women and men with a *CHEK2* germline pathogenic/likely pathogenic variants, collectively referred to here as “germline pathogenic variants” (GPVs). The dearth of clinical guidance has likely occurred because of the complexities in establishing the cancer spectrum and penetrance for *CHEK2* heterozygotes. Challenges in unraveling the role of *CHEK2* in cancer predisposition include (1) the high prevalence of common variants across primarily European populations (Supplementary Table 1), (2) early studies restricting analysis of *CHEK2* to the c.1100del variant and other common GPVs rather than full gene analysis, (3) varying estimates of penetrance depending on the study design and the population studied, (4) lack of characterization of rare missense variants, and (5) the significant role of family history and other modifiers in cancer risk estimates.

Although *CHEK2* is considered a moderate risk cancer predisposition gene, evidence suggests that cancer risks for heterozygotes lie on a continuous scale, ranging from population 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 *CHEK2* heterozygotes. Consequently,

disentangling the available data and information and translating this into recommendations for clinical practice has been both challenging and nuanced.

Rapid progress in genetic sequencing technologies has led to identification of an even greater number of *CHEK2* heterozygotes either through germline or tumor multigene panel testing and/or tumor genome/exome sequencing. As a result, there is an increasingly urgent clinical need for consistent, evidence-based, pragmatic guidelines for the management of *CHEK2* heterozygotes in clinical practice, specifically considering the clinical utility of personalized (rather than generalized) risk assessment and surveillance recommendations.

In this Clinical Practice Resource, we perform a review of the relevant literature, summarize *CHEK2*-associated cancer risks, present a framework for personalized risk assessment, provide expert guidance on the clinical management of *CHEK2* heterozygotes, and discuss knowledge gaps and the future work that is needed.

Materials and Methods

Detailed methods can be found in the Supplementary Materials (Supplemental Figure 1). Briefly, after proposal approval and review of potential or actual conflicts as per the relevant American College of Medical Genetics and Genomics (ACMG) policies, an international workgroup was identified, comprising members across North America, Europe, and Asia, including Australia, Singapore, the United States, Canada, the United Kingdom, Germany, and Spain, with expertise in clinical cancer genetics, genetic counseling, breast surgery, gynecologic surgery, and medical oncology. The workgroup developed a list of clinical areas in the management of *CHEK2* heterozygotes, performed a comprehensive literature review with specific questions in mind, which did not meet systematic review criteria (further details are in the Supplemental Methods, Supplemental Table 2, Supplemental Figure 1), and synthesized findings narratively. Older (pre-2015) reported disease-associated *CHEK2* variants were not reclassified according to more modern criteria.⁶

The workgroup met monthly via videoconference calls beginning in November 2020 and participated in email discussion and review throughout the process. Workgroup members independently drafted sections of the document commensurate with their area of expertise. 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.

CHEK2 variants

The first described variants in the *CHEK2* gene were the loss-of-function variant: c.1100del and the missense variant NM_007194.4:c.470T>C p.(Ile157Thr) (henceforth referred to as p.(Ile157Thr)).³ Both c.1100del and p.(Ile157Thr) are prevalent in Northern European cancer cases^{7–9} and are also present in the gnomAD founder subpopulation with frequencies of 0.87% and 2.5%, respectively (<https://gnomad.broadinstitute.org/>). Other

common variants have been reported across different geographical locations and ancestries (Supplemental Table 1).

In a recent analysis of 2508 *CHEK2* heterozygotes of self-reported “Caucasian” ancestry (2100 of 2508) identified through commercial multigene panel testing, a total of 2540 *CHEK2* GPVs (119 unique) were described (The term “Caucasian” is no longer used by the Journal but is used in the original article to which these studies refer. We have therefore not changed the term but recognizing it does not accurately describe the ancestry of the populations that were originally studied.¹⁰) The most commonly observed GPV, accounting for 85.6% (2173 of 2540) of the total identified, included (all NM_007194.4): c.1100del (30.8%); p.(Ile157Thr) (27.3%); c.1283C>T p.(Ser428Phe) (8.0%); c.1427C>T p.(Thr476Met) (5.3%); c.349A>G p.(Arg117-Gly) (4.6%); deletion exons 9–10 (3.4%); c.190G>A p.(Glu64Lys) (3.2%); and c.444+1G>A (3.0%).¹¹

Challenges in interpretation of *CHEK2* variants

Interdependence of pathogenicity and penetrance

Interpretation of variants in *CHEK2* poses challenges not only in determination of pathogenicity but also in terms of penetrance and clinical actionability. The lack of clear differentiation between pathogenicity and penetrance for specific *CHEK2* variants is problematic. For example, there is evidence that the common variant p.(Ile157Thr) adversely affects protein function and is therefore “deleterious;” yet, its penetrance is low and in isolation not at a level of clinical actionability, for which additional early cancer detection and prevention options above population level screening are typically indicated (see “Cancer risks for *CHEK2* heterozygotes” section).

Terminology for the classification and description of gene variants has evolved since the identification of the first *CHEK2* germline variant. Description of pathogenicity of sequence variants is now defined by published ACMG/Association for Molecular Pathology guidelines using specific, standard terminology: “Class 5 - pathogenic,” “Class 4 – likely pathogenic,” “Class 3 - uncertain significance,” “Class 2 - likely benign,” and “Class 1 - benign” with classification into these subgroups based on the probability of pathogenicity based on specific evidence-based criteria.⁶ In addition to variant classification, it is important that clinical validity (likelihood that the variant is related to the presenting cancer phenotype), as well as the clinical utility and actionability (ie, whether the result can be used to inform individual management) are taken into consideration.¹²

Prior studies have reported that variants in *CHEK2* are frequently found to have conflicting classifications by commercial laboratories because of differences in interpretation and interdependence of pathogenicity and penetrance.¹³ Although most GPVs in *CHEK2* in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) are frameshift, nonsense, or splicing variants, a small minority (<10%) are missense variants, such as NM_007194.4:c.433C>T p.(Arg145Trp) and p.(Arg117Gly). In contrast, the majority (>60%) with conflicting (pathogenic/likely pathogenic vs variant of uncertain significance [VUS]) or VUS interpretations of pathogenicity are missense variants, such as p.(Ile157Thr). Most major laboratories agree that the p.(Ile157Thr) variant has reduced penetrance for BC compared

with nonmissense *CHEK2* GPV, particularly the c.1100del variant (see “Cancer risks for *CHEK2* heterozygotes” section for additional details). ClinGen has developed guidance on terminology of reporting for low-penetrance variants.¹⁴ Yet, laboratories greatly vary in their reporting and interpretation of p.(Ile157Thr), as follows: (1) a “Special Interpretation” comment (with an asterisk to a “see below” comment for explanation), (2) “moderate risk variant,” (3) “pathogenic (low penetrance) variant,” or (4) “variant of uncertain significance (VUS).” Unfortunately, the downstream impact of inconsistent reporting can result in discrepant clinical management for both patients and relatives, highlighting the importance of using published recommendations. Particularly in the era of multigene panel testing, consistency is important to avoid confusion for health care professionals, patients, and families.¹²

Guidelines from the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) group set forth a framework for standardized reporting of germline cancer susceptibility variants, considering the complexity of pathogenicity and penetrance and associated clinical actionability. Their recommended framework assumed that only variants with 2-fold or greater risk would be reported because those conferring less than a 2-fold relative risk (RR) are in isolation, likely to be of minimal clinical significance.¹¹ Furthermore, clinical management recommendations should be determined considering the type of variant, in conjunction with the personal and/or family history of disease, and other known genetic and environmental risk factors.

Variant interpretation

Rare VUS, including missense variants and small in-frame deletions, account for approximately 50% of observed *CHEK2* variants identified through panel testing.¹¹ ACMG has made recommendations for variant interpretation and reporting according to a specified framework.⁶ However, interpretation of rare VUS is particularly challenging for *CHEK2*.

Classification of *CHEK2* VUS based on their location in specific domains has largely been unhelpful. Some groups have used various methodologies to help classify VUS in *CHEK2*, including yeast-based in vivo functional assays,¹⁵ complementation assays in human RPE1-*CHEK2* knockout cells,¹⁶ and DNA breakpoint assays for duplications.¹⁷ Another group has developed an integrated approach combining genomics, clinical study, radiography imaging, and protein informatics to classify a variant with conflicting interpretations.¹⁸ Most recently, a European group used a mouse embryonic stem cell-based system to quantitatively determine the functional impact of 50 missense VUS in human *CHEK2* and their association with BC and prostate cancer (PC). A correlation of loss of function with BC risk was demonstrated, suggesting that the assay may be a valuable tool to aid in clinical management.¹⁹

Variant registries (eg, ClinVar) are powerful tools to help standardize variant classification and guide clinical management. The ClinGen Hereditary Breast, Ovarian, and Pancreatic Cancer Variant Curation Expert Panel (<https://clinicalgenome.org/affiliation/50039/>) is currently working to define gene specifications of the ACMG/Association for Molecular Pathology rules for the classification of variants in *CHEK2*.

Variant interpretation relies on the integration of multiple sources of evidence, including, but not limited to, clinical data, functional assays, and population frequency.⁶ Newly published evidence or a change in how the available evidence is weighted or combined within a framework may result in an “upgrade” or “downgrade” of a variant. In some situations, reinterpretation of the evidence may result in reclassification and a change in clinical actionability. Reinterpretation is typically undertaken reactively (eg, in response to new published evidence or new diagnoses in a family), rather than proactively. It is recognized that proactive or regular variant reinterpretation is unlikely to be feasible for most laboratories and/or health care providers, and resources should be directed to reclassification scenarios in which a change in clinical management is most likely.^{20,21} In addition, ACMG and the European Society of Human Genetics have issued position statements with respect to the reinterpretation of genomic test results and subsequent recontact of individuals.^{20–22} Recently, published guidelines from CanVIG-UK present a detailed consensus framework for variant reclassification, setting out an approach to variant review, reissue of reports, recontact of individuals, and interlaboratory communication.²³ All groups recommend that clinicians should discuss the potential for reclassification with individuals who are undergoing genetic testing. Additionally, a number of groups are undertaking ongoing research, which considers the ethical, economic, legal, and clinical implications of variant reinterpretation.^{24–26}

Consistent with standard clinical practice,

- Reporting of CHEK2 variants should include clear language (standardized across laboratories) on variant pathogenicity and predicted penetrance, differentiating variants with reduced penetrance.
- Laboratories should consider implementing the ENIGMA recommendations when reporting out CHEK2 missense variants with RR < 2.
- As is the case for all VUS results, CHEK2 VUS should not be used to guide clinical management or for predictive genetic testing for family members.
- Clinicians should discuss the potential for reclassification of CHEK2 variants (especially VUS) with individuals.

Cancer risks for *CHEK2* heterozygotes

Breast cancer

Truncating variants—The first study to formally recognize *CHEK2* c.1100del as a female BC susceptibility variant derived the associated risk to be around 2-fold,² an estimate that has remained remarkably stable over the ensuing 2 decades, with the most recent study based on 548 BC cases and 248 healthy controls reporting an odds ratio (OR) of 2.66 (95% CI 2.27–3.11).²⁷ The same study generated an OR of 2.13 (95% CI 1.60–2.84) for the other protein truncating variants combined based on 156 cases and 70 controls. Another recent large study reported an OR of 2.47 (95% CI 2.02–3.05) for all GPVs (349 cases and 138 controls).²⁸ It is important to appreciate that these estimates are for European ancestry individuals, with varying OR reported for other populations (Supplemental Table 3). Furthermore, the OR declines with increasing age, with the risks being highest in women

younger than 40 years (OR 4.54, 95% CI 2.87–7.17) compared with women older than 60 years (OR 2.22, 95% CI 1.72–2.86).²⁷

Missense variants—The BC risk estimates for *CHEK2* heterozygotes with missense variants are, in general, lower than estimates for *CHEK2* truncating variants. A recent large study from the Breast Cancer Association Consortium (BCAC) BRIDGES project estimated an OR < 1.5 (OR 1.42, 95% CI 1.28–1.58; $P = 2.5 \times 10^{-11}$) for rare missense variants (defined as variants with a population frequency of <0.001) and found no correlation with the variant position in the gene.²⁷ A further study by the same group focusing on 1552 heterozygotes with 325 unique *CHEK2* missense variants used 5 in silico prediction models, functional protein domain, and overall frequency to predict the pathogenicity of individual missense variants and correlated this with BC risk. The study confirmed that, overall, missense variants are associated with lower risk than *CHEK2* truncating variants (OR 1.75, 95% CI 1.47–2.08) but that there could be significant variation in risk associated with specific missense variants depending on predicted pathogenicity from the in silico model, but not protein domain.²⁹

For at least some missense variants, there is evidence to suggest a BC risk similar to truncating variants. The common missense variant p.(Arg117Gly) was highlighted in a paper that studied RR of BC of specific rare variants in *CHEK2* and other BC genes via a multicenter case-control study comprising 42,671 cases and 42,164 controls. The study reported an association of p.(Arg117Gly) with BC (OR 2.26, 95% CI 1.29–3.95).³⁰ This was supported by a later BCAC study (OR 2.69, 95% CI 1.46–4.94),²⁹ suggesting that at least some missense variants are associated with clinically relevant BC risk. For missense variants less common than p.(Arg117Gly), an association is harder to establish and determining which variants are associated with clinically relevant cancer risk and which are not, presents a significant challenge. A recent article describing a new quantitative functional assay for *CHEK2* missense variants suggested that variants demonstrating a similar functional impact to p.(Arg117Gly) may confer the same level of cancer risk.¹⁹ Future studies may help support these findings and provide further evidence for specific missense variants for both BC and other cancers.

In another large study, ORs were reported for the common *CHEK2* missense variants p.(Ile157Thr) (OR 1.30, 95% CI 1.06–1.59; $P = .01$) and p.(Ser428Phe) (OR 1.26, 95% CI 0.76–2.12; $P = .37$).²⁸ The authors acknowledged that both of these variants have historically been considered pathogenic but highlighted that the observed OR did not reach currently accepted levels of clinical actionability ($RR > 2$)¹² and excluded them from the overall analyses of GPVs (Figure 1).

Another study recently re-evaluated *CHEK2* p.(Ser428Phe), a variant reported in 2005 to be associated with increased BC risk in Ashkenazi Jewish females.³¹ Using data obtained from multigene panels, an overall heterozygote rate of 486 of 341,531 (0.14%) was found in individuals diagnosed with any cancer type across all ethnicities, with 243 heterozygotes in 9980 individuals who self-identified as Ashkenazi Jews. The variant was not found to be more prevalent in cancer cases vs ancestry matched controls (OR 0.27, 95% CI 0.90–1.43; $P = .271$), and variant prevalence was not different in BC cases compared with controls (OR

1.23, 95% CI 0.90–1.74; $P = .176$), suggesting that this variant does not confer a clinically actionable BC risk.³²

Contralateral BC—Contralateral BC (CBC) risk was first reported in *CHEK2* c.1100del heterozygotes in a study from 2 Dutch cancer centers³³ (Supplemental Table 4). An association with CBC risk was suggested by an initial report of the population-based Women's Environmental Cancer and Radiation Epidemiology Study (WECARE) study, with an overall RR of 1.8 and a higher risk of 2.6 for those who received radiotherapy (RT) compared with those who did not, but did not reach statistical significance.³⁴ In a meta-analysis of 22 studies comprising >25,000 women with BC, of whom 459 were *CHEK2* heterozygotes, the hazard ratio (HR) for CBC was 2.8 and increased to 3.5 in women with estrogen receptor (ER)–positive BC.³⁵ A follow-up analysis of the WECARE study also reported an elevated but nonstatistically significant risk of CBC for *CHEK2* c.1100del heterozygotes.³⁶ This study was the only one to report on cumulative risks; 5- and 10-year CBC risk was 6.1% (95% CI 2.0–18.5) and 11.8% (95% CI 3.9–35.8) for all c.1100del heterozygotes. When considering RT treatment, the 5- and 10-year CBC risk was 2.2% (95% CI 0.3–18.0) and 4.3% (95% CI 0.5–35.5), respectively, for heterozygotes who did not receive RT and 8.4% (95% CI 2.5–28.0) and 16.0% (95% CI 4.8–53.5) for those who received RT.

Male BC—There have been conflicting findings in male BC (MBC), most likely because many of the studies have been small and in populations where c.1100del is not prevalent.^{2,37} This is exemplified by 2 studies showing that although *CHEK2* does not seem to make a significant contribution to risk in the Southern European population,³⁸ c.1100del was detected in 4 of 68 (5.9%) Finnish MBC cases (OR 4.47, 95% CI 1.15–13.18).³⁹ A large US study with MBC cases across several race/ethnicity groups (including 66% White, 10% Ashkenazi Jewish, 8% African American, 3% Asian, and 2% Hispanic) identified *CHEK2* heterozygotes in 16 of 581 (2.8%) cases (OR 2.4, 95% CI 1.4–3.9), half of whom had c.1100del (OR 3.8, 95% CI 1.7–7.8).⁴⁰ Notably, *CHEK2*-related MBC was diagnosed at an average age of 54 years, which is significantly younger than MBC caused by other genes ($P = .03$). A recent meta-analysis showed an increased risk for MBC for *CHEK2* heterozygotes (OR 3.13, 95% CI 1.94–5.07).⁴¹

Biallelic CHEK2 GPV—Because of the frequency of the c.1100del variant, homozygotes have been reported. Homozygotes may have a higher penetrance for both unilateral and bilateral BC.^{42–44} Two studies of c.1100del homozygotes in The Netherlands have showed that BC risk depends on the method of ascertainment. In the first study, homozygotes were identified in 8 of 2554 familial non-*BRCA1/2* BC cases, 4 of whom had bilateral BC.⁴³ The authors estimated that the risk of BC was approximately double that of heterozygotes. The second study identified 3 c.1100del *CHEK2* homozygotes in a cohort of 1435 sporadic BC patients from a hospital-based cohort (OR 3.4, 95% CI 0.4–32.6).⁴³ Both studies were limited by small size, and it is postulated that actual risks could be much higher than their estimates, given the high rate of bilateral cancers, and the very wide CIs.

More recently, in a series of individuals undergoing hereditary cancer panel testing through a commercial laboratory (excluding p.(Ile157Thr) and p.(Ser428Phe) from the analysis),

cancer risks were evaluated for monoallelic ($n = 6473$) and biallelic ($n = 31$, confirmed *in trans*) *CHEK2* heterozygotes.⁴⁵ Compared with monoallelic *CHEK2* heterozygotes (OR 2.02, 95% CI 1.90–2.15), biallelic *CHEK2* heterozygotes had a significantly higher risk for invasive BC (OR 8.69, 95% CI 3.69–20.47), were more likely to be diagnosed at or before age 50, and were more likely to have multiple primary BCs. Although biallelic *CHEK2* heterozygotes seemed to have a higher overall risk of cancer, a statistically significant excess of any individual cancer other than BC was not observed. Similar to previous studies, the CIs were wide but did not cross the range reported for those heterozygous for a pathogenic variant.

In contrast to the recessive phenotypes observed in the other BC predisposition genes, *PALB2*, *BRCA1*, *BRCA2*, and *ATM*, a recessive phenotype is not formally recognized for *CHEK2*. One publication reported a putatively novel cancer predisposition syndrome in which 2 unrelated individuals (1 with early-onset leukemia and 1 with multiple primary tumors), both homozygous for NM_007194.4:c.499G>A p.(Gly167Arg), had multiple complex chromosome translocations on peripheral blood samples.⁴⁶ However, the same pattern of chromosome translocation was not observed in an individual homozygous for a different missense variant, p.(Ser428Phe), and has not previously been reported in c.1100del homozygotes. More recently, 2 unrelated individuals with a similar syndrome were reported. Both had multiple cytogenetic anomalies on peripheral blood samples. One individual, affected with BC and multiple meningiomas, was homozygous for the NM_007194.4:c.793–1G>A variant, and the second individual, affected with papillary thyroid cancer and BC, had compound heterozygous variants of c.1100del and NM_007194.4:c.1312G>T p.(Asp438Tyr).⁴⁷ Further clarification is needed to understand if this novel DNA breakage phenotype is only conferred through homozygosity or compound heterozygosity for specific *CHEK2* variants and to investigate potential associated cancer risks or other phenotypic features.

Colorectal cancer

Truncating variants—An association of *CHEK2* c.1100del with colorectal cancer (CRC) was first proposed by the *CHEK2* consortium in multiplex families.⁴⁸ However, subsequent Scandinavian population-based studies did not confirm a statistically significant association^{49,50} (Supplemental Table 5). Further studies have also demonstrated nonsignificant CRC risks; however, many of these are limited to data from a single country.^{51–53}

Two meta-analyses of c.1100del reported a modestly increased CRC risk with OR of 2.11 (95% CI 1.41–3.16; $P = .0003$)⁵⁴ and OR of 1.88 (95% CI 1.29–2.73; $P = .001$).⁵⁵ The higher OR of 2.11 was later revised down with adjusted data to OR of 1.8 (95% CI 1.2–2.7), in agreement with the second metaanalysis.⁵⁶ As expected, the strength of association for CRC risk was greatest for familial CRC, compared with unselected or sporadic CRC, OR of 2.80 (95% CI 1.74–4.51; $P < .0001$).⁵⁴ Therefore, though the meta-analyses were supportive of an association of c.1100del with CRC risk, the risk falls at a low-to-moderate level of increased risk and likely in isolation below a level of clinical actionability. The results from the Scandinavian studies and meta-analyses are supported by a recently published

retrospective cohort study of individuals who underwent targeted panel or multigene panel testing in a single diagnostic laboratory over a 7-year period.⁴⁴ The authors did not find an association of *CHEK2* status with CRC and that individuals with *CHEK2* GPVs ($n = 3783$) had fewer cases of CRC, compared with individuals without a *CHEK2* GPV ($n = 33,034$) (OR 0.62, 95% CI 0.51–0.76; $P < .001$).

Missense variants—A statistically significant but weak association with CRC has been described for the p.(Ile157Thr) variant in 2 meta-analyses, with OR of 1.56 (95% CI 1.32–1.84; $P = 1.22 \times 10^{-7}$),⁵⁵ OR of 1.61 for unselected CRC (95% CI 1.40–1.87; $P < .001$) and OR of 1.97 for familial CRC (95% CI 1.41–2.74; $P < .001$).⁵⁷ In the recently published retrospective cohort study of individuals described above, an association for CRC was not found for heterozygotes of p.(Ile157Thr) (OR 0.8, 95% CI 0.61–1.04; $P = .09$), p.(Ser428Phe) (OR 0.26, 95% CI 0.1–0.55; $P < .001$), or p.(Thr476Met) (OR 0.86, 95% CI 0.49–1.41, $P = .64$), compared with individuals undergoing multigene panel testing without these variants.⁴⁴

Prostate cancer

Truncating variants—An association with PC was first described in 2003 with the identification of *CHEK2* variants in 15 of 400 (3.75%) individuals with sporadic PC and 11 of 298 (3.7%) individuals with familial PC at a single center (vs 6 of 423 [1.6%] controls) reaching statistical significance when p.(Ile157Thr) was excluded ($P = .008$).⁵⁸ Subsequent studies have also described an enriched number of *CHEK2* heterozygotes in PC.^{59–61} A study in Poland of 3 variants (c.1100del, c.444+1G>A, and p.(Ile157Thr)) in 140 Polish individuals with PC compared with 1921 controls reported an OR of 3.4 ($P = .004$) for unselected cases and OR of 9 for familial cases ($P = .0002$), excluding p.(Ile157Thr)⁶² (Supplemental Table 5).

A study using The Cancer Genome Atlas of inherited DNA repair genes of GPV in men with metastatic PC found a significantly increased frequency of *CHEK2* heterozygotes (excluding p.(Ile157Thr)) in 534 men with metastatic PC compared with men with clinically localized PC (RR 4.7, 95% CI 2.2–8.5; $P < .001$).⁵⁹

In a retrospective study of 703 individuals with lethal PC (defined as death due to metastatic cancer) and 1455 individuals with low-risk PC, a total of 15 *CHEK2* GPVs (excluding p.(Ile157Thr)) were identified. An association was not found for early-onset PC. Overall, the number of *CHEK2* heterozygotes was higher in lethal cases (2.28%) than in low-risk cases (1.65%), but the difference was not significant ($P = .31$). However, a statistically significant increase in the prevalence of *CHEK2* c.1100del heterozygotes was identified in individuals with lethal disease compared with individuals with low-risk PC (1.28% vs 0.16%; $P = .004$) with an estimated OR for lethal PC of 7.86.⁶³

A 2015 meta-analysis also confirmed a statistically significant increased risk of PC for c.1100del (OR 3.29, 95% CI 1.85–5.85; $P < .001$), but not for c.444+1G>A (OR 1.59, 95% CI 0.93–2.71; $P = .09$), suggesting that the increased risk may be limited to specific rather than all truncating variants.⁶⁴ A Danish population-based study observed a statistically

significant association of c.1100del with PC risk (HR 1.60, 95% CI 1.00–2.56; $P = .05$), though this was nonsignificant after Bonferroni correction.⁵⁰

Missense variants—Similar to risks for BC and CRC for missense GPVs, a lower PC risk has been described for p.(Ile157Thr) (OR < 2) compared with truncating variants. A meta-analysis showed an OR of 1.80 (95% CI 1.51–2.14; $P < .001$)⁶⁴ and a study from Poland showed OR of 1.7 ($P = .03$)⁶² (Supplemental Table 5).

Other cancers—A widely cited publication in 1999 claimed that variants in *CHEK2* were associated with Li-Fraumeni syndrome.³ However, it is very clear from the subsequent literature (and is the firm opinion of this workgroup) that GPVs in *CHEK2* do not cause Li-Fraumeni syndrome.^{4,5} Although *CHEK2* may have a role as a low-to-moderate risk multi-tumor predisposition gene,^{50,65} evidence of an association for cancers other than BC has been difficult to firmly establish (Supplemental Table 5).

A statistically significant association of *CHEK2* GPV with kidney cancer has been reported in 1 Danish prospective study (multifactorially adjusted HR 9.8, 95% CI 2.3–41.2) and 1 multicenter American study of individuals with advanced kidney cancer using Exome Aggregation Consortium controls (OR 3.0, 95% CI 1.3–5.8; $P = .003$).^{49,66} However, in a larger prospective Danish study, statistical significance (after Bonferroni correction) was not reached.⁵⁰ A retrospective study of multigene panel results from 844 individuals diagnosed with kidney cancer, aged 60 years or younger tested through a commercial laboratory, demonstrated that *CHEK2* GPVs were most commonly reported compared with other DNA damage response and repair genes with 19 of 844 (2.25%) *CHEK2* heterozygotes identified. Overall, *CHEK2* GPVs (with the exception of p.(Ile157Thr)) were found to be more common in the study group compared with Exome Aggregation Consortium, with recognition by the authors that the controls were not age or sex matched.⁶⁷ A further recent retrospective cohort study of 3783 *CHEK2* heterozygotes identified through multigene panel testing also suggests an association with kidney cancer (OR 2.57, 95% CI 1.75–3.68; $P < .001$) for *CHEK2* heterozygotes (excluding lower risk *CHEK2* variants: p.(Ile157Thr), p.(Ser428Phe), and p.(Thr476Met)).⁴⁴ Although current evidence suggests that *CHEK2* GPVs are likely associated with an increased risk of kidney cancer, the expert group felt that additional larger studies with appropriate controls are required to firmly establish an association and to inform clinical management (Supplemental Table 5).

A statistically significant increased risk of papillary thyroid cancer in *CHEK2* heterozygotes has been reported for both truncating variants and p.(Ile157Thr).^{68–70} However, these studies are limited to a single country (Poland). In a Danish population study, the incidence of thyroid cancer was marginally raised for *CHEK2* c.1100del heterozygotes (5 of 670 [0.9%] vs 99 of 86,303 [0.1%]). However, the age- and sex-adjusted HR did not reach statistical significance (HR 1.26, 95% CI 0.18–9.09; $P = .81$).⁵⁰ In a recent retrospective cohort study of 3783 *CHEK2* heterozygotes identified through multigene panel testing, an association with thyroid cancer was reached for *CHEK2* heterozygotes (excluding lower risk *CHEK2* variants: p.(Ile157Thr), p.(Ser428Phe), and p.(Thr476Met)) with OR of 1.63 (95% CI 1.26–2.08; $P < .001$). However, other groups suggest there is a low level of evidence to support an

increased risk of thyroid cancer in *CHEK2* heterozygotes.⁷¹ Consequently, the expert group considers that further larger studies are likely required to firmly establish any association.

The association of germline *CHEK2* variants with pancreatic cancer is also unclear. A low frequency of *CHEK2* GPV has been reported in small studies of familial and sporadic pancreatic cancer.^{72–74} In 2 studies from Poland, an association with *CHEK2* common variants was not described in 383 unselected individuals with pancreatic cancer compared with 4000 controls (OR 1.11; $P = .72$)⁷⁵; however, an association was reported when pancreatic cancer cases were selected on the basis of family history ($n = 105$) (OR 2.26; $P = .008$).⁷⁶ An association was reported by a European consortium for p.(Ile157Thr) that evaluated 2935 sporadic pancreatic cancer cases and 5626 controls (OR 1.74, 95% CI 1.15–2.63; $P = 8.57 \times 10^{-3}$), but the reported risk would be unlikely to change clinical management in isolation.⁷⁷ Further large case-control studies are needed to determine the risk of pancreatic cancer for *CHEK2* heterozygotes and inform clinical practice.

A risk of stomach cancer was reported for both *CHEK2* heterozygotes with truncating variants (OR 2.1; $P = .001$) and a lower risk for heterozygotes of p.(Ile157Thr) (OR 1.5; $P = .04$) in a study from Poland of 658 unselected individuals with gastric cancer and 8302 controls.⁷⁸ A statistically significant association was also reported by the prospective Copenhagen general population study with an age- and sex-adjusted HR of 5.76 (95% CI 2.12–15.6; $P = .001$), which remained significant after Bonferroni adjustment⁵⁰ but included only 89 individuals with gastric cancer with 4 c.1100del heterozygotes. The expert group felt that further large case-control studies across diverse populations are needed to fully characterize the risk of stomach cancer for *CHEK2* heterozygotes.

Overall, the opinion of this group is that further data are required to confirm clinically actionable associations with pancreatic, stomach, renal, and thyroid cancers. Many other associations for specific cancers have been suggested for *CHEK2* heterozygotes including, but not limited to, sarcoma,⁵⁰ hematological malignancies,^{79,80} melanoma,^{81,82} endometrial cancer,^{83,84} bladder cancer,⁸⁵ and testicular cancer,^{86,87} as well as a potential decreased risk of lung cancer^{88,89}; however, further data are required. At present, published data are not supportive of an association of *CHEK2* with ovarian cancer predisposition.^{16,90,91}

Evidence of an increased risk of pediatric cancers in *CHEK2* heterozygotes is limited. In general, *CHEK2* GPV were rarely observed, even in the largest cohorts. In 2 small studies, a statistically significant association of *CHEK2* variation with pediatric tumor risk was reported (Hodgkin lymphoma⁹²; neuroblastoma⁹³). However, multiple other studies have not observed any germline *CHEK2* GPV in individuals with a pediatric tumor.^{94–99} A study of exome sequencing in 5451 long-term childhood cancer survivors also did not show a statistically significant excess of *CHEK2* variation in any tumor type.¹⁰⁰ Furthermore, *CHEK2* GPVs do not seem to contribute to risk of subsequent neoplasm in childhood survivors of cancer.^{101,102} Therefore, though *CHEK2* GPVs are observed in a minority of children with a wide variety of cancers, at this time, there is limited evidence of a statistically significant association between *CHEK2* GPV and pediatric cancer risk. One small study demonstrated the clinical utility of companion tumor sequencing looking for loss of heterozygosity or a second coding sequence somatic hit in pediatric cancer tumors

with GPV in cancer predisposition genes.¹⁰³ Larger scale studies are needed to confirm or refute some of the proposed associations of *CHEK2* with pediatric cancer.

In summary, *CHEK2* is firmly established as a clinically relevant female BC predisposition gene with respect to truncating variants, with lower risks for missense variants. For CRC and PC, some studies are suggestive of an association with low-to-moderate risk for *CHEK2* truncating variants, whereas for other cancers, more data are required to confirm or refute an association. Companion tumor sequencing and/or somatic mutational signature analysis may help clarify whether a *CHEK2* GPV is implicated in tumorigenesis in specific cancers¹⁰⁴ (Figure 2).

- ACMG asserts that *CHEK2* heterozygosity is not associated with Li-Fraumeni syndrome.

For *CHEK2* heterozygotes with truncating variants:

- ACMG recognizes a definite association for BC predisposition.
- ACMG recognizes that there is an increased risk of contralateral BC; however, the magnitude of that risk is unclear.
- ACMG recognizes a likely low-moderate risk association for CRC predisposition.
- ACMG recognizes a likely moderate risk association for PC predisposition.
- ACMG considers that there is insufficient evidence to support a clear association for other cancers, including, but not limited to MBC, renal, thyroid, pancreatic, and pediatric cancers.

For *CHEK2* heterozygotes with missense variants:

- Studies of p.(Ile157Thr) and p.(Ser428Phe) heterozygotes show that cancer risk and penetrance are below the accepted levels of clinical actionability in isolation.
- Studies of p.(Arg117Gly) suggest that there is an association of BC risk, similar to truncating variants.
- Data on other *CHEK2* missense variants are limited but suggestive that for most variants, overall cancer risk and penetrance are lower than for truncating variants.

Personalized risk estimation: Polygenic risk score and modifiers of *CHEK2*-associated cancer risk

Polygenic risk scores—Risk modification from common germline variants in BC has been intensively studied using genome-wide association studies. Statistically significant disease-associated variants may be combined into a polygenic risk score (PRS). Studies of varying size have examined the effect of a PRS comprising 74¹⁰⁵ to more than a million individual variants¹⁰⁶; the largest study to date included 4286 *CHEK2* heterozygotes.¹⁰⁷ On a population level, the findings are consistent across studies that the risk from *CHEK2* heterozygosity and BC PRS are independent and combine multiplicatively. Combining the effect of the common and rare variants results in a distribution of risk in which

approximately 15% of individuals return to a population level of risk, whereas a similar sized group at the highest end of the distribution meets the definition of high risk (>30% lifetime risk).¹⁰⁸ The exact size of these groups varies in different studies depending on the performance of the specific PRS used.

There are known limitations using PRS in a clinical setting. Genetic associations of *etiological* significance are often interpreted as having *predictive* significance; it still needs to be proved that OR derived from PRS that are important etiologically are clinically useful in risk prediction.^{109,110} In addition, the genome-wide association studies used to identify PRS lacked diversity and are predominantly based on individuals of European ancestry. As a result, the potential clinical utility of PRS is limited to individuals of European ancestry.¹¹¹ Recognition of this ancestry-based health disparity and directed efforts to narrow this gap are underway.^{112–114}

There is very little information on the effect of the PRS for *CHEK2*-associated cancers other than BC, though a preliminary study in PC suggested a similar multiplicative interaction.¹¹⁵

Other modifiers—An individual's family history of BC influences personal BC risk in *CHEK2* heterozygotes as it does in the population.^{105–107,116} Larger studies have shown that there is some interaction between the risk associated with family history and that captured by the PRS or assigned to the *CHEK2* GPV.^{105,107} Adding family history information to a model of integrated risk can account for some attenuation and avoid overestimation.

Limited information is available on the role of personal BC risk factors (reproductive history, hormone use, body mass index, etc) specifically in *CHEK2* heterozygotes; however, the data available are consistent with these risk factors having an independent effect similar to that seen in the general population.¹⁰⁷

Personalized risk—An assessment that combines genetic, nongenetic, and epidemiological risk information provides a more accurate personal BC risk estimation for *CHEK2* heterozygotes than use of *CHEK2* genetic status in isolation. The combined assessment of genetic and nongenetic risk factors in determining early cancer detection and risk-reducing strategies for heterozygotes of GPV in cancer predisposition genes is known as a “personalized” risk assessment. Contrary to other BC predisposition genes, such as *BRCA1* or *BRCA2*, where the risk is largely conferred by heterozygosity for a pathogenic variant, there is substantial variance in distribution of risk for *CHEK2* heterozygotes. Consequently, a personalized assessment of BC risk may change the overall risk assessment and thus corresponding clinical management for a significant proportion of *CHEK2* heterozygotes, both in the direction of increased and decreased risk.

To date, within clinical genetics, personalized risk assessment has largely included evaluation of family history alone. However, particularly for BC risk assessment, new comprehensive tools such as CanRisk¹¹⁷ (<https://canrisk.org/>) can incorporate genetic information for *CHEK2* heterozygotes with truncating variants, family history, questionnaire-based factors, such as hormonal and lifestyle factors, and where available, PRS and mammographic density. Extension of the tool to include missense GPV and

development of similar tools for cancers other than BC are required to be able to provide fully comprehensive personalized assessments for *CHEK2* heterozygotes (Figures 3–5).

- ACMG encourages the use of personalized cancer risk estimates (eg, consideration of family history and/or use of tools such as CanRisk) for BC and clinical judgment for other cancers that incorporate personal and family history and variant-specific information to guide clinical management.
- ACMG considers that although PRS can support personalized risk assessment, knowledge of the clinical utility of PRS continues to accumulate, and at this time, use of PRS to influence clinical management should be limited to clinical trials.

Pathology of *CHEK2*-associated cancer

Nearly all the large clinicopathological studies of tumors arising in *CHEK2* heterozygotes have been conducted in women with BC. Tumors arising from other sites have only rarely been studied.

Two very large population-based control studies from 2021 provide the greatest insights into BC pathology in *CHEK2* and came to very similar conclusions. The BCAC²⁷ identified 704 *CHEK2* heterozygotes with truncating variants (78% comprising a single variant, c.1100del). *CHEK2* heterozygotes had almost equal risks of ductal carcinoma in situ, compared with invasive ductal carcinoma (OR of 2.2 and 2.5, respectively). In a case-only analysis, *CHEK2* heterozygotes were more likely to develop ER-positive than ER-negative invasive ductal carcinoma (OR 2.67 vs 1.64, respectively; $P = 9.1 \times 10^{-5}$), though the latter OR is still significant and seems to be driven by nontriple-negative ER-negative cases (OR 2.53, 95% CI 1.75–3.67).²⁷ These associations also held for rare missense variants in *CHEK2*. In a similarly designed study, 348 *CHEK2* heterozygotes were identified by Hu et al,²⁸ and similarly, the association was much stronger for ER-positive BC (OR of 2.60) than for ER-negative BC (OR of 1.40) or triple-negative BC (OR of 1.63); neither of the latter 2 OR were significant, perhaps because of the small effect size and smaller number of cases than in the BCAC study. When combined with other independent large academic^{118,119} and commercial laboratory studies,^{120,121} a clear picture emerges: *CHEK2* heterozygotes are more likely to have an ER-positive BC than a triple-negative BC. However, *CHEK2* heterozygotes can develop BC independently of their risk allele,^{122,123} and causality of a *CHEK2* GPV in a woman with BC should not be assumed.

An early study focused on the lower-penetrance *CHEK2* variant p.(Ile157Thr) (excluded from the above mentioned studies) found a remarkable excess of lobular BC.¹²⁴ This association was later confirmed and extended in a much larger study, which showed that p.(Ile157Thr) heterozygotes tend to have lobular, low-grade, ER-positive, and progesterone receptor-positive tumors that do not express p53¹²⁵; thus, they clearly differ from BC arising in *CHEK2* heterozygotes with truncating variants.¹²⁶ Other missense variants in *CHEK2* may also have this association with lobular BC.¹²⁷ Focusing solely on lobular BC in those diagnosed under the age of 60, Petridis et al¹²⁸ found that *CHEK2* heterozygosity was associated with lobular BC (OR 4.31), and the relationship was even more striking for

pure lobular carcinoma in situ (OR 9.90, 95% CI 3.42–28.66). Further studies are needed to confirm this association.

Other important pathological measures include the grade and stage of the breast tumor. A study from Finland found only 2 of 32 c.1100del heterozygotes harbored a grade 1 tumor, compared with 298 of 1087 controls (*CHEK2* wild type) and saw no effect on tumor size or stage.¹²⁹ However, these results were not replicated in a large BCAC study in which neither morphology nor grade differed between c.1100del cases and wild-type controls.¹³⁰ Genomic profiling of *CHEK2*-related BC has shown that loss of 1p may be a feature of these cancers.¹³¹

- ACMG recognizes that *CHEK2* heterozygotes who develop BC are more likely to develop ER-positive BC compared with ER-negative and triple-negative BC.

Outcomes of *CHEK2*-associated cancer

Outcome following BC in *CHEK2* heterozygotes has been the subject of several large studies. Huzarski et al¹³² tested 3592 women with nonmetastatic BC diagnosed at or below age 50 for 4 *CHEK2* variants ($n = 347$ for p.(Ile157Thr) and $n = 140$ for the 3 others). There was no significant effect on long-term outcome, compared with more than 3000 wild-type controls. This lack of effect could not be attributed to the inclusion of the generally less aggressive p.(Ile157Thr)-associated cancers. Based on the pathology, a difference in outcome might be expected between p.(Ile157Thr) and c.1100del. This was reported in a BCAC study of 590 p.(Ile157Thr) and 271 c.1100del heterozygotes from more than 26,801 women with BC. In an adjusted analysis, the authors noted a borderline significantly better BC-specific mortality outcome ($P = .058$) for p.(Ile157Thr) heterozygotes compared with c.1100del heterozygotes.¹²⁵ The point estimates for a poorer outcome associated with c.1100del were all greater than 1.0 but perhaps because of a lack of power, were not significant. Nearly all previous studies had found significantly adverse outcomes (measured variously as overall survival, BC-specific survival and incidence of CBC) for *CHEK2* c.1100del heterozygotes, with or without the administration of adjuvant chemotherapy and/or hormone therapy.^{35,133–136} In contrast, an early Finnish study, limited to c.1100del, had agreed with the Polish study in finding a negligible effect of c.1100del on survival.¹²⁹ On balance, when considering the generally favorable clinicopathological features of *CHEK2*-related BC, the outcomes seem to be poorer than expected. Again, the question of whether the variant in question is in fact contributing to the cancer is important.¹²³ A population-based study focused on *CHEK2* heterozygotes with cancer, second hits in the tumor, and outcome might help to refine the estimates of BC-specific survival following BC in *CHEK2* heterozygotes.

Studies on outcome for *CHEK2* heterozygotes affected by other cancers are limited. *CHEK2* heterozygotes were identified in 1.87% of 692 men with metastatic PC, compared with 0.4% in The Cancer Genome Atlas series of primary PC ($n = 499$), suggesting that *CHEK2* heterozygosity is associated with inferior PC outcomes.⁵⁹ The results of other studies, however, are varied, with some showing no effect of *CHEK2* heterozygosity on outcome,¹³⁷ others indicating worse outcomes for *CHEK2* c.1100del heterozygotes only,⁶³ and yet others

showing a reverse effect.¹³⁸ The role of *CHEK2* in outcome following a diagnosis of PC remains undetermined.

Therapeutic implications of *CHEK2* gene variation

CHEK2 has a role in cell cycle control after double-stranded DNA damage. However, unlike *BRCA1*-, *BRCA2*-, or *PALB2*-associated BC, most *CHEK2*-BC do not display genomic features of homologous recombination repair deficiency.¹³⁹ This observation suggests that tumors with *CHEK2* loss-of-function variants may not respond well to homologous recombination repair deficiency-targeted therapies, such as poly-adenosine diphosphate ribose polymerase inhibitors (PARPi), compared with *BRCA1*-, *BRCA2*-, or *PALB2*-deficient tumors and use at the current time is not recommended.¹⁴⁰

For *CHEK2* heterozygotes, there is some evidence of correlation with higher nodal involvement, CBC and worse survival outcomes compared with sporadic tumors.^{35,134,141} At the time of cancer diagnosis, in patients with early BC, this prognostic information may influence the primary therapeutic approach.

Sensitivity to standard chemotherapy for *CHEK2*-associated BC has been investigated in the neo-/adjuvant settings with inconclusive results.^{136,142,143} In the metastatic setting, a phase 2 clinical trial with the PARPi olaparib demonstrated no responses in 10 *CHEK2* heterozygotes.¹⁴⁴

Although elevated, nonstatistically significant risks of CBC have been observed for *CHEK2* heterozygotes treated with RT; thus, no definitive conclusions about the use of RT can be drawn.^{36,145}

In PC, de Bono et al¹⁴⁶ performed a randomized, open-label, phase 3 trial, evaluating the PARPi olaparib vs endocrine therapy in men with metastatic castration-resistant PC who had disease progression while receiving a new hormonal agent (eg, enzalutamide or abiraterone). In cohort B, 12 *CHEK2* heterozygotes without another known germline predisposition were included. Those treated with olaparib ($n = 7$) had a numerically longer median progression-free survival compared with the control arm ($n = 5$; 5.59 months vs 3.35 months), but this was not statistically significant.

In summary, there is insufficient evidence to recommend specific treatment for *CHEK2* heterozygotes affected with cancer. Management recommendations should be based on the usual clinical factors, prognostic information, and clinical judgment.

Despite the limited information on the benefits of *CHEK2*-guided tumor therapy, the likelihood that a *CHEK2* GPV identified in a tumor is also present in the germline is high. Previous publications have provided clear recommendations regarding germline testing after tumor sequencing for high-penetrance cancer predisposition genes but were more cautious about proceeding to germline testing for moderate penetrance genes, such as *CHEK2*.¹⁴⁷ In contrast, the National Comprehensive Cancer Network (NCCN) Genetics/Familial Breast, Ovarian, and Pancreatic guidelines suggest germline confirmation of tumor findings when of potential clinical significance to the individual or their family members.¹¹⁰ With greater inclusion of *CHEK2* on multigene panels and more clarity on clinical management,

particularly for BC, consideration of germline testing for *CHEK2* pathogenic variants identified in tumors may be appropriate where there is clinical utility for the individual or other family members. This is particularly important when considering *CHEK2* missense variants with a high population frequency (eg, the p.(Ile157Thr) variant) and questionable clinical significance based on cancer risks outlined in detail in this document. As noted above, the ENIGMA group has suggested that variants of limited clinical utility should not be routinely reported (or reported at all).¹¹ In the experience of this international work group, this guidance is observed in many countries, except for reports issued by laboratories in the United States, where lower risk variants such as *CHEK2* p.(Ile157Thr) are routinely reported.

- ACMG acknowledges that at this time there is insufficient evidence for *CHEK2* status to guide any specific targeted treatment.
- ACMG acknowledges that based on the limited clinical utility of some missense variants, they should not be routinely reported on tumor or germline tests.

Clinical management: Cancer surveillance and risk-reducing surgery

Breast cancer—As previously described in both the risk and the modifier section, though *CHEK2* has largely been considered a “moderate risk” BC gene, the distinction is blurred with risk being on a continuum, ranging from low (population) to moderate to high risk, influenced by the specific variant, type of variant (truncating vs missense), family history, non-*CHEK2* genetic background, and other factors. Although the average lifetime BC risk for a *CHEK2* heterozygote is approximately 25%, absolute risks can range from 15% to 40%, with risk for some heterozygotes crossing into population risk or risk observed for high-penetrance BC predisposition genes depending on modifiers as outlined above.^{49,148–150} It is important that rather than considering *CHEK2* status in isolation, the risk from the GPV needs to be considered in the context of other risk factors to enhance medical management.

With respect to breast surveillance, studies on the impact of early detection through surveillance are sparse, and long-term observations do not exist. The clinical validity and clinical utility as outlined in the Centers for Disease Control and Prevention’s ACCE model (“analytic validity, clinical validity, clinical utility and associated ethical, legal, and social implications”) are not yet sufficiently proven for non-*BRCA1* and non-*BRCA2* genetic testing and surveillance.¹⁵¹ In 1 small retrospective study of 78 asymptomatic women with non-*BRCA1/2* “deleterious mutations” (14 [18%] *CHEK2*), 25% underwent biopsy with most results being benign.¹⁵² Recognizing the difficulties of organizing studies comparing multiple approaches with BC surveillance for *CHEK2* heterozygotes because of the prohibitive sample sizes and follow-up times required, a recent comparative modeling analysis sought to address the gap in evidence.¹⁵³ This study integrated data from 12 population-based studies in the Cancer Risk Estimates Related to Susceptibility (CARRIERS) Consortium and estimates on performance for mammography and magnetic resonance imaging (MRI) from published literature to evaluate surveillance strategies consisting of annual mammography alone and with the addition of MRI starting at different ages for *CHEK2* heterozygotes. Overall, the analysis suggested that annual MRI

surveillance starting at 30 to 35 years followed by annual MRI and mammography at 40 years may reduce BC mortality by more than 50% for women with *CHEK2* GPV. Prospective, long-term data collection will be important to document and evaluate the effectiveness of surveillance in *CHEK2* heterozygotes to obtain reliable information on age-related positive and negative predictive values, as well as on prospective incidence rates.

The expert group considered that for *CHEK2* heterozygotes with most missense variants (p.(Arg117Gly) may confer higher risks, as noted above), because the published RR for BC is less than 2-fold (both for the common missense variants and rare missense variants), breast surveillance should not be based on *CHEK2* status, but rather on family history and/or other modifiers, consistent with current published guidelines on cancer predisposition genes from the ENIGMA group.¹¹

For *CHEK2* heterozygotes with truncating variants, personalized risk assessment should be considered to direct the level of BC surveillance. At a minimum, this would include assessment of family history of BC, but more comprehensive assessment could be undertaken to include other modifying factors with a tool such as CanRisk. Use of PRS is not currently considered standard of care but has the potential to be incorporated in the future. One challenge in the implementation of PRS in clinical practice is the broad heterogeneity of the scores arising from differences in the selection of variants and their validity.

The expert group recognized the differences in breast surveillance programs for women at both population and increased risk in different countries and suggests that country-specific recommendations be followed (Table 1).¹⁰⁷ Use of a risk assessment model, such as CanRisk, can generate a personalized risk figure, which can then be used alongside country-specific guidelines to direct surveillance according to level of risk.

At present and in agreement with NCCN, the group believed there was insufficient evidence to make specific recommendations for individuals who harbor biallelic *CHEK2* variants, though emerging evidence is supportive of BC risk equivalent to that seen for “high-risk” BC genes.⁴⁵

For some *CHEK2* heterozygotes, particularly those with a strong family history of BC, lifetime BC risk may be at a level at which considering bilateral risk-reducing mastectomy (RRM) would be appropriate in a shared decision-making approach. Again, a personalized risk assessment based on additional factors including family history is critical to offer the most appropriate clinical management. This aligns with the NCCN Genetic/Familial Breast, Ovarian, and Pancreatic Guidelines (NCCN 2.2022)¹¹⁰ and other international guidelines¹⁵⁴ that do not make general recommendations for RRM in *CHEK2* heterozygotes.

With respect to CBC risk, an expert panel convened by the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology recommended high-risk surveillance with an annual mammogram and MRI of remaining breast tissue for heterozygotes of moderate-penetrance genes without specifying an age limit.¹⁴⁰ Such intensified surveillance is in accordance with other recommendations by expert panels of health care professionals and guidelines, though age ranges vary.^{154,155}

Given the relevance of modifying factors, we would again recommend a personalized approach to direct ongoing breast surveillance to women who have a BC diagnosis.

With respect to risk-reducing contralateral mastectomy, a personalized risk assessment, which takes into consideration the age at BC diagnosis, and competing risks from a primary BC diagnosis should be undertaken. The current literature on management of *CHEK2* heterozygotes affected with BC suggests that there is widespread deviation of treatment from practice guidelines, including data to suggest overtreatment, and recommends that more data on long-term outcome and understanding of decision making are required.^{156,157}

Other cancers—For cancers other than BC, personalized risk assessments are more difficult to undertake in the absence of tools such as CanRisk. However, as in all families, personalized risk assessment can be made based on family history regardless of known GPV status. Furthermore, guidelines for surveillance and early detection may vary according to country; therefore, generalizable recommendations are difficult to make.

With respect to CRC, studies are at best supportive of a moderate association for *CHEK2* heterozygotes (see risk section). The working group believed that although an association with CRC is reported in some studies for both truncating and missense variants, the risk falls below a 2-fold RR (which we have previously defined as low increased risk). Therefore, for *CHEK2* heterozygotes with a family history of CRC, more frequent surveillance above population screening (eg, earlier and more frequent colonoscopy and/or fecal immunohistochemical testing [FIT]) may be appropriate (Table 1). In the absence of a family history, invasive and/or enhanced surveillance is likely not warranted. This approach is supported by a recent large retrospective cohort study of *CHEK2* heterozygotes, in which no association for CRC was found.⁴⁴ The authors suggested that intensive CRC screening of *CHEK2* heterozygotes may not be indicated and suggested that current guidelines should be refined. However, management advice does remain conflicting with another recent paper suggesting that individuals with *CHEK2* variants (c.1100del and p.(Ile157Thr)) have a similar CRC risk at age 40, compared with age 45 in the general population and propose that colonoscopy should begin at age 40 in individuals heterozygous for a pathogenic variant.¹⁵⁸ The NCCN Guidelines Version 2.2022 Genetic/Familial High-Risk Assessment: Colorectal¹⁵⁹ acknowledge the limited evidence but do suggest consideration of colonoscopy screening every 5 years, beginning at age 40 or 10 years before the age of the first-degree relative's CRC diagnosis. However, NCCN also comment that the data to support surveillance recommendations for *CHEK2* are evolving and caution should be used when implementing colonoscopy surveillance, given that new knowledge may emerge and suggest a shared decision-making approach is appropriate.

For PC, this working group thought that for *CHEK2* heterozygotes with truncating variants, it would be reasonable to discuss annual prostate-specific antigen surveillance in a shared decision-making process, especially in patients with a strong family history of PC (2 or more relatives) or history of young onset or metastatic cases.

There is no evidence for an increased risk for ovarian cancer in *CHEK2* heterozygotes. Consequently, risk-reducing salpingo-oophorectomy is not recommended based on *CHEK2* status; however, as always, it may be indicated based on family history.

This working group did not consider that the strength of association nor evidence on the prognosis of other cancers was currently robust enough to make clinical recommendations for early detection and prevention through surveillance. However, this guidance may change in the future as additional data are published. The group recognized the importance of education on modifiable risk factors for cancer, for example, smoking cessation, healthy diet, and awareness of signs and symptoms of cancer, and discussion of this in consultations is advised.

For *CHEK2* heterozygotes with truncating variants, ACMG advises the following:

- Personalized risk assessment using at least assessment of family history but ideally with a model such as CanRisk is important to consider when making BC surveillance recommendations.
- For women with BC, contralateral RRM should not routinely be offered but may be considered based on personalized risk assessment using a model such as CanRisk, the competing risk of first cancer prognosis, and shared medical decision making.
- For women without a prior diagnosis of BC, bilateral RRM should not routinely be offered but may be considered based on a personalized risk assessment using a model such as CanRisk and shared medical decision making.
- CRC and PC surveillance should be based on a personalized risk assessment, including family history and other risk factors.
- Education on modifiable risk factors for cancer is undertaken.

For *CHEK2* heterozygotes with missense variants, ACMG advises the following:

- In general, risk and penetrance are reduced compared with *CHEK2* truncating variants, and in isolation, they are unlikely to reach a level of clinical actionability, although some exceptions may exist, such as p.(Arg117Gly).
- BC, CRC, and PC surveillance should not be based on *CHEK2* status but rather on personalized risk assessment, including family history and other risk factors, and joint decision making is encouraged.
- Education on modifiable risk factors for cancer is undertaken.

Genetic counseling considerations

CHEK2 heterozygotes may be identified following targeted or multigene panel testing requested because of a personal cancer diagnosis of a *CHEK2*-associated cancer, unrelated personal diagnosis of cancers, or family history of cancer. At this time, *CHEK2* is not included as a gene on the ACMG Secondary Findings list for reporting following exome or genome sequencing,¹⁶⁰ largely because of the lack of clear strategies for clinical management when a variant is ascertained outside the context of a relevant family history.¹⁴⁷

There are challenges in counseling *CHEK2* heterozygotes including (1) evolving estimates of absolute risk for individuals with *CHEK2* findings²⁷ and (2) minimal evidence on the impact of surveillance and management recommendations for *CHEK2* heterozygotes.^{152,155} According to standard recognized practice, it is essential that *CHEK2* heterozygotes seek consultation with a health care professional with expertise and experience in cancer genetics who is familiar with the above challenges and who will be able to provide guidance should recommendations change in the future.

Confirmation that an individual has not inherited a familial *CHEK2* GPV may not reduce cancer risks to population level because predictive testing is more complex for *CHEK2* than for high-penetrance genes such as *TP53* or *BRCA1*. In this scenario, an individual risk calculation (particularly for BC) should be performed for these individuals with surveillance recommendations based on the remaining residual risk. Genetic counseling is recommended before and after testing for a familial *CHEK2* GPV so that appropriate clinical management can be advised in the absence or presence of a negative result. Predictive genetic testing for a familial *CHEK2* variant is not routinely recommended in childhood.¹⁶¹

CHEK2 heterozygotes may wish to discuss reproductive options with genetics health care professionals, including preimplantation and prenatal genetic testing options.^{162,163} Preimplantation genetic testing for monogenic disorders (PGT-M) involves consultation with reproductive endocrinology and in vitro fertilization. PGT-M includes in vitro fertilization with embryo biopsy at day 5, testing of the embryo with probes specific for the known familial mutation (KFM), and transfer of only those embryos that test negative. Although PGT-M for hereditary cancer syndromes with high penetrance and/or childhood onset are more routinely offered, PGT-M for moderate penetrance genes, such as *CHEK2*, is controversial, and, in general, not recommended, considering that cancer risks associated with *CHEK2* are not fully defined and because cancer risk is significantly modified by other factors.¹⁶⁴ Low levels of knowledge, moderate rates of acceptability, and a high need for information in the context of individuals with hereditary cancers have been reported,¹⁶⁵ and individual interest can vary.¹⁶⁶ Prenatal testing, involving chorionic villus testing or amniocentesis, is controversial, given the uncertainty, moderate cancer risks and modifying factors for *CHEK2* heterozygotes. Discussions with couples should be undertaken within the context of a clear counseling framework, given the considerable complexity and emotions involved.

Consistent with standard clinical practice,

- *CHEK2* heterozygotes should be referred to a genetics health care professional to discuss cancer risks, surveillance, and implications for other family members.
- Pre- and post-test genetic counseling should be undertaken when considering predictive genetic testing of *CHEK2*.
- Residual risk estimation (particularly for BC) and surveillance guidance should be provided for individuals with a negative result for a *CHEK2* familial variant to guide future surveillance.

Research gaps in clinical areas of need

There remains a paucity of data on *CHEK2* 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 prevalence of *CHEK2* heterozygotes in specific populations, lack of appropriately geographically matched control populations, insufficient numbers of individuals who have had comprehensive *CHEK2* analysis, 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,^{27,167} better estimation of cancer risk and development of comprehensive risk assessment models is required for other cancers, such as CRC and PC. Improved PRSs, risk models, and calculators validated across diverse populations are needed.

Prospective data collection is needed to help with the study of cancer risk and also determine the effectiveness of surveillance and risk-reducing surgery. With respect to the treatment of cancers in *CHEK2* heterozygotes, further 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 PRS is urgently needed, as are risk models and calculators validated across diverse populations.

Prospective collection of clinical data from *CHEK2* heterozygotes is urgently needed to

- Refine and improve cancer risk estimates
- Establish clear metrics on surveillance and treatment outcomes and survival
- Develop risk assessment tools
- Evaluate *CHEK2*-specific responses 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. We consider there to be strong evidence that *CHEK2* truncating variants are associated with a moderate risk of BC and evidence is supportive of a moderate risk of PC and low-moderate risk of CRC. However, cancer risks are strongly influenced by other factors, including family history, non-*CHEK2* 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 *CHEK2* in cancer predisposition is not complete, and further studies are needed to fully define the true spectrum of *CHEK2*-associated cancer risk as well as the effectiveness of early detection and risk-reducing interventions.

Given the many uncertainties, those at risk for *CHEK2*-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.

Note in Proof

Two recent, large studies refined risk estimates for CBC in *CHEK2* heterozygote women. The BRIDGES study analyzed 34,401 women of European ancestry with BC, including 676 CBCs (of which 38 were *CHEK2* heterozygotes) with a median follow-up of 10.9 years. Protein-truncating variants in *CHEK2* were associated with increased CBC risk [HR (95% CI): 2.25 (1.55–3.27)].¹⁶⁸ In the CARRIERS study, 15,104 women were prospectively followed after ipsilateral surgery for invasive breast cancer including 711 CBCs (of which 12 were *CHEK2* heterozygotes). *CHEK2* heterozygotes with BC were at significantly elevated risk [HR (95% CI): 2.0 (1.0–4.2)] of CBC. Among premenopausal women, the 10-year cumulative incidence of CBC was estimated to be 13% for *CHEK2* heterozygotes with breast cancer. Among post-menopausal *CHEK2* heterozygotes, the 10-year cumulative incidence of CBC was 4%.¹⁶⁹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Alicia Livinski of the National Institutes of Health Library and Jennifer Malinowski (ACMG) for expert help with the literature search and methodology. The content of this publication does not necessarily reflect the views or policies of the US Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

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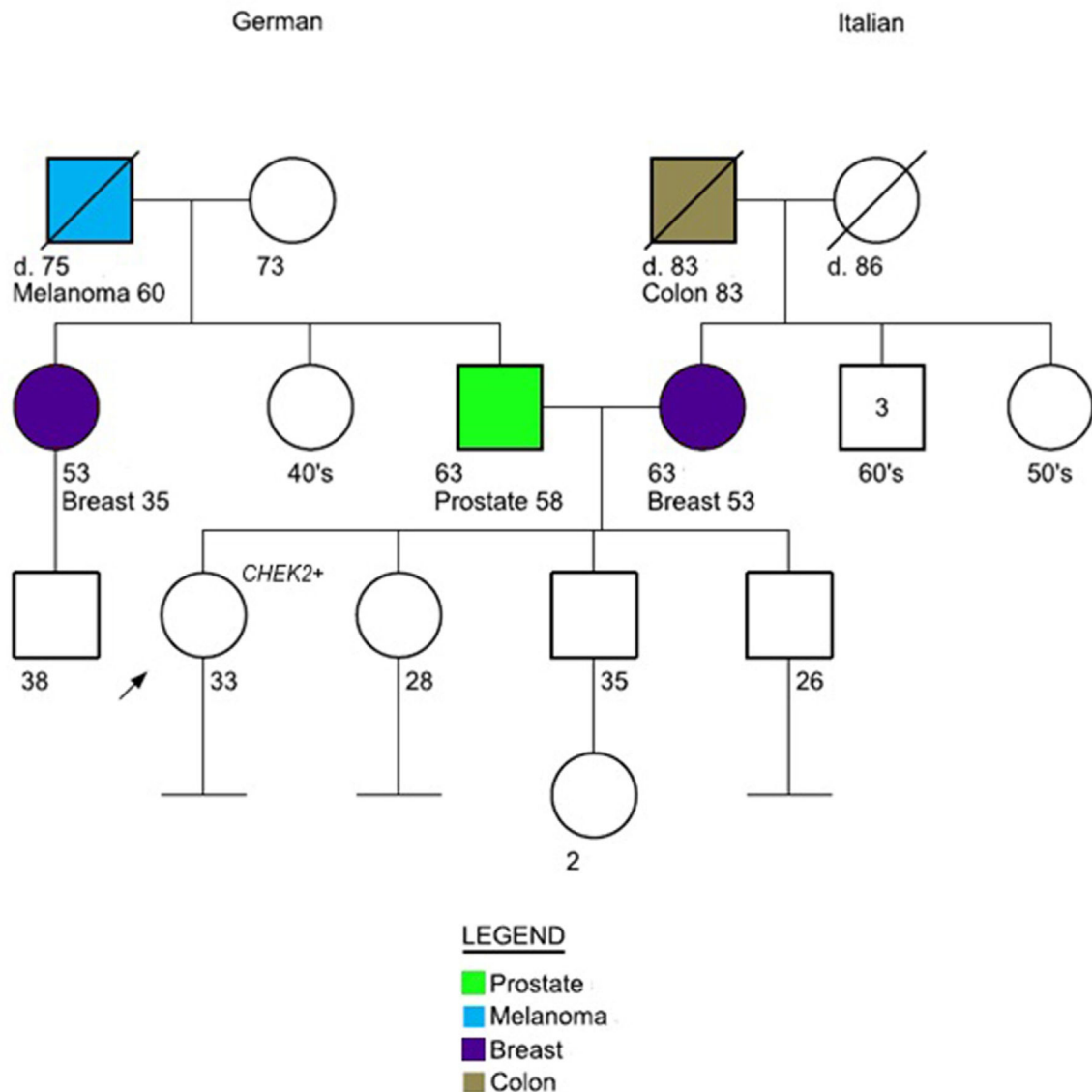


Figure 1. Cases illustrating *CHEK2* testing in practice.

CHEK2 case #1 is a 33-year-old woman who presented to the clinic with no personal history of cancer but had a history of breast cancer on both sides of the family. She was tested through a commercial laboratory, which identified the *CHEK2* p.(Ile157Thr) variant and reported it as a variant of uncertain significance. There are conflicting levels of pathogenicity on ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/RCV000144596/>, accessed March 2023). Discussion points are as follows. (1) this variant is reported by some diagnostic laboratories as “pathogenic (low penetrance),” “moderate risk variant,” or with a “Special Interpretation” note. In some countries, the *CHEK2* p.(Ile157Thr) variant is not even reported. (2) the difference between variant pathogenicity vs disease penetrance, is reflected in the differing terminology used by the various laboratories to interpret this variant. (3) in isolation, missense variants conferring less than 2-fold RR for BC and colorectal cancer (such as p.(Ile175Thr)) are not likely to result in a change in clinical

management. (4) breast cancer screening recommendations should be based primarily on country-specific guidance, family history, and other risk factors. (5) colorectal cancer screening recommendations should be based primarily on country-specific guidance, family history, and other risk factors.

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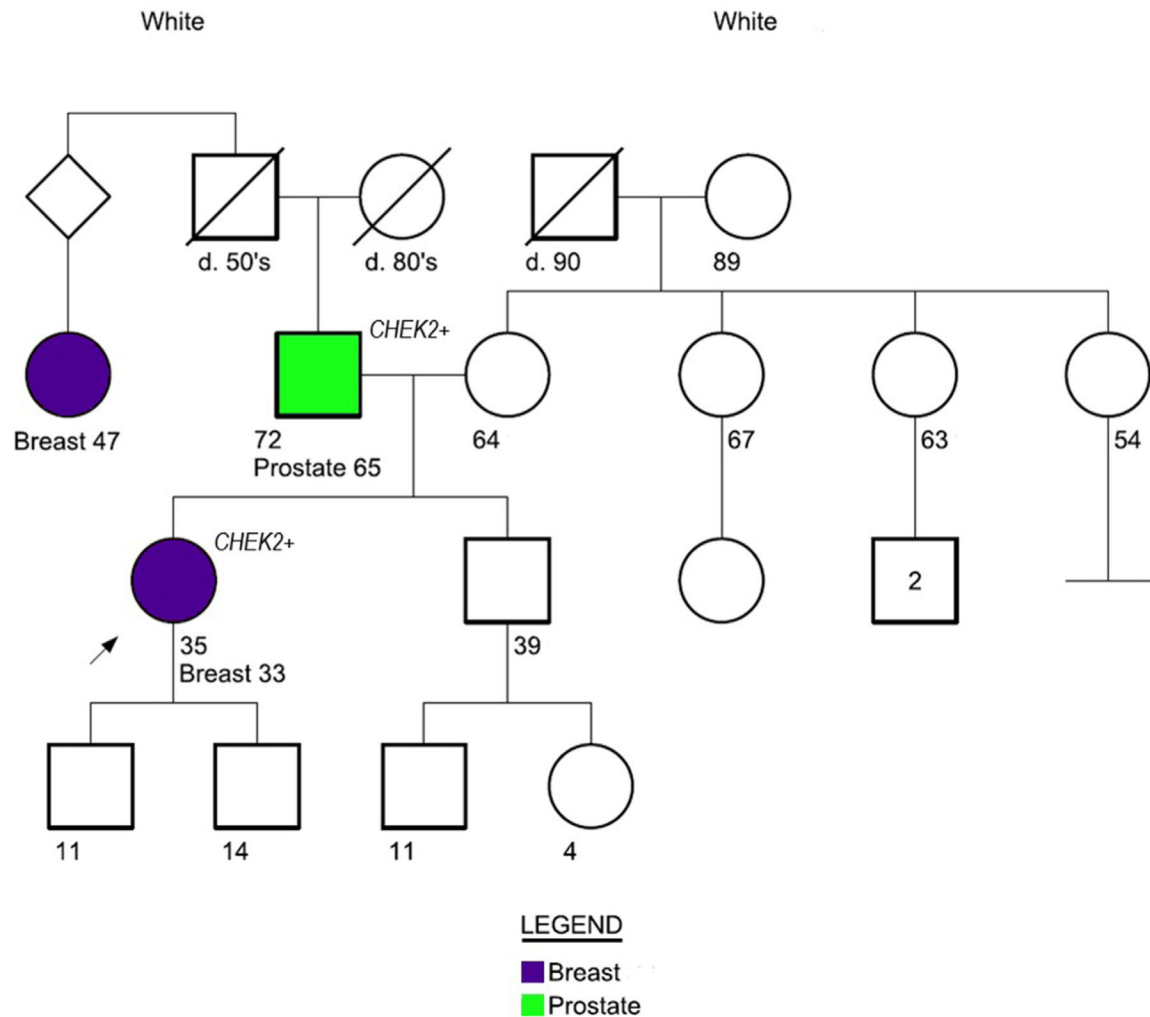


Figure 2. Cases illustrating *CHEK2* testing in practice.

CHEK2 case #2 is a 35-year-old female who was originally diagnosed at age 33 years with stage 2 breast cancer, at which time testing ordered by her oncologist included only *BRCA1/2*, with no P/LP variants identified. She was subsequently diagnosed with metastases to bone at age 35, at which time tumor testing was undertaken and identified a *CHEK2* c.1100del pathogenic variant. *BRCA1/2* testing was already covered through insurance, but additional germline testing for *CHEK2* was declined for coverage by her insurer. The individual's father subsequently proceeded with germline testing and was identified to have the same *CHEK2* c.1100del pathogenic variant. Discussion points are as follows. (1) the patient is young for a *CHEK2*-related breast cancer. (2) tumor sequencing may help clarify whether a *CHEK2* variant is implicated in tumorigenesis in specific cancers. (3) a known common variant, such as *CHEK2* c.1100del, uncovered in tumor sequencing can be presumed to be germline but still merits confirmation.

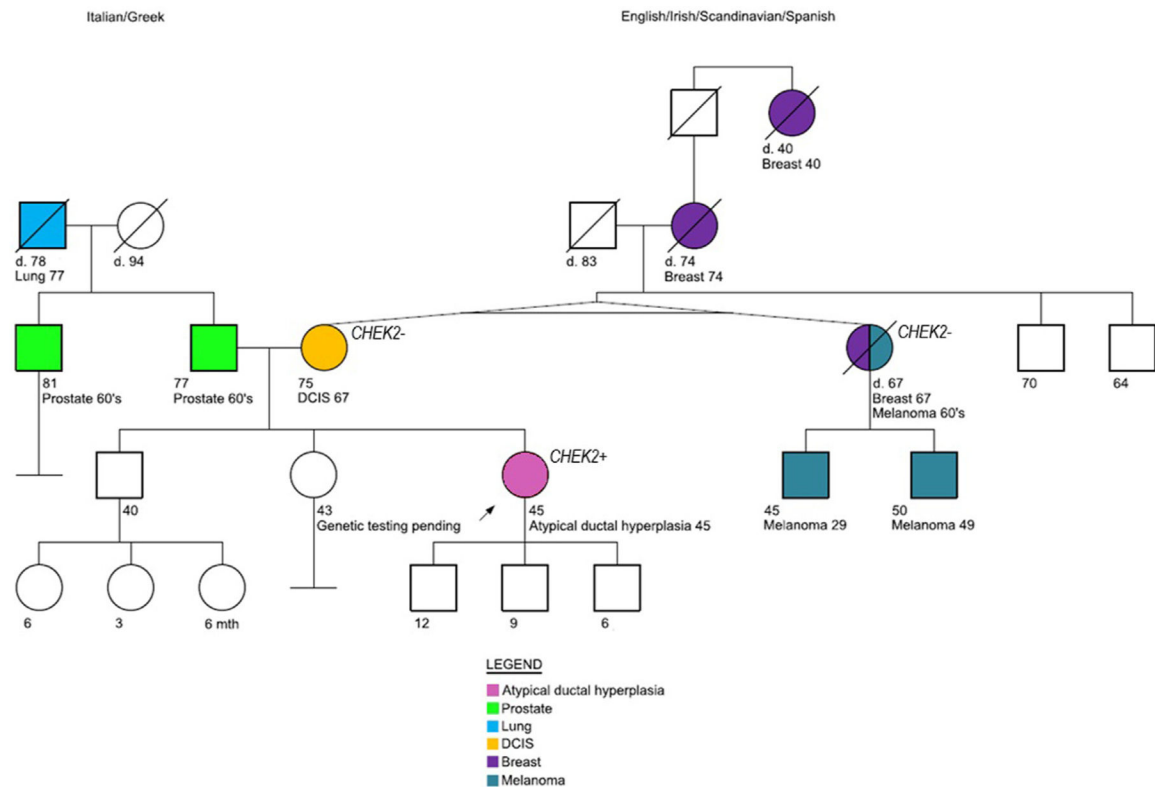


Figure 3. Cases illustrating *CHEK2* testing in practice.

CHEK2 case #3 is a 45-year-old woman who had atypical ductal hyperplasia in her left breast on a recent biopsy, which was subsequently confirmed on excisional biopsy to be low-grade DCIS. She had genetic testing because of a maternal family history of cancer. Mother had DCIS at age 67, at which time she was tested for *BRCA1* and *BRCA2*; no P/LP variants were identified. The mother's identical twin sister also had breast cancer at age 67 and was tested through multigene panels and was negative for any P/LP variants in *CHEK2*. She subsequently passed from metastatic disease. The patient was tested for inherited breast cancer because of her family history and found to have a *CHEK2* likely pathogenic splice-donor variant (c.1461+1G>T) (<https://www.ncbi.nlm.nih.gov/clinvar/122942210/>, accessed March 2023). Discussion points are as follows. (1) *CHEK2* likely pathogenic variant inherited from the side of the family without any history of breast cancer. (2) testing for her siblings, particularly her sister, would be recommended. Testing her brother, given the history of prostate cancer, may also be relevant. (3) the maternal family history of breast cancer would further increase patient's breast cancer risk. (4) breast cancer surveillance recommendations should be guided by CanRisk assessment. (5) breast cancer risk management should be recommended based on country-specific surveillance guidelines because the definition of "high" risk varies by country. (6) in the absence of a family history of colorectal cancer, colonoscopy surveillance should be offered in accordance with population-based guidelines. DCIS, ductal cancer in situ; P/LP, pathogenic/likely pathogenic.

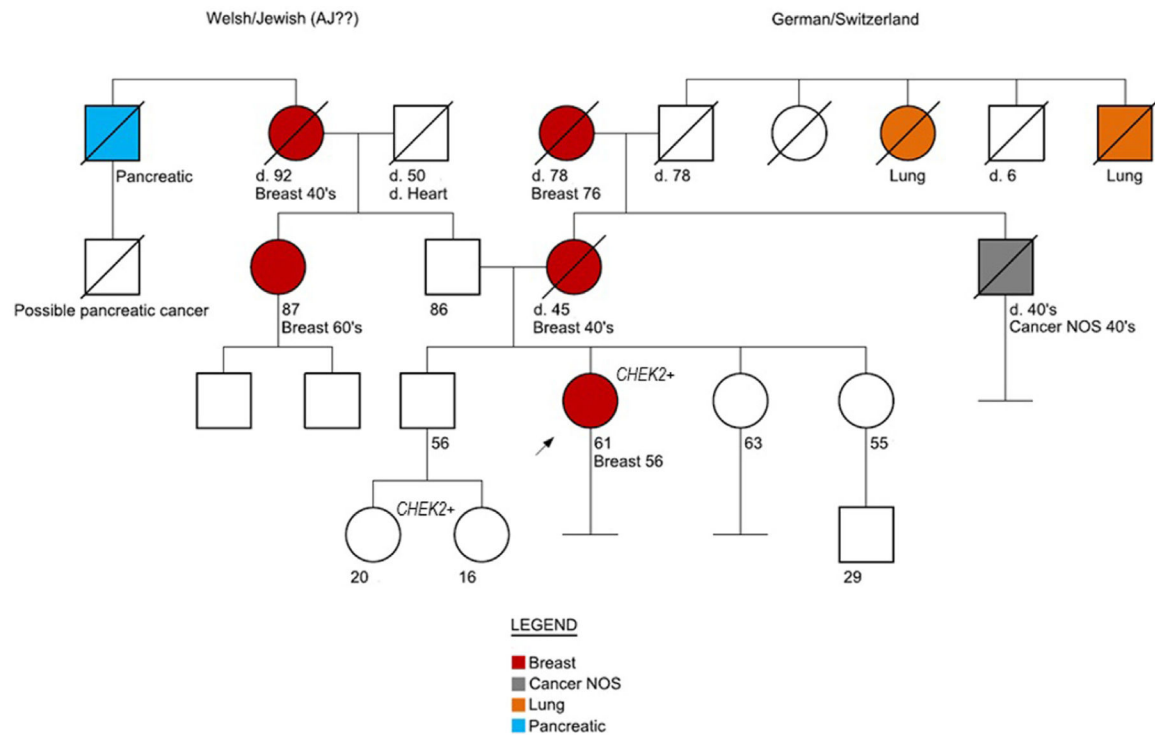


Figure 4. Cases illustrating *CHEK2* testing in practice.

CHEK2 case #4 is a 61-year-old female with breast cancer at age 56, which was treated with bilateral mastectomy. Genetic testing identified a *CHEK2* pathogenic variant c.1434del p. (Glu479fs) (<https://www.ncbi.nlm.nih.gov/clinvar/RCV000458226/>, accessed March 2023). A multigeneration family history of breast cancer was observed on both sides of the family; however, genetic testing was not undertaken among the extended family members, aside from the 20-year-old niece, who was found to harbor the *CHEK2* pathogenic variant. Discussion points are as follows. (1) per CanRisk, the niece has a >30% lifetime risk of breast cancer (Figure 5 or output 1). Country-specific surveillance guidelines should be followed for this level of risk. (2) this risk, however, can be modified in either direction by a polygenic risk score (see Figure 5 or outputs 2 and 3). (3) the use of polygenic risk scores is not standard of care at this time (pending additional validation and research) but may be helpful in development of personalized surveillance recommendations.

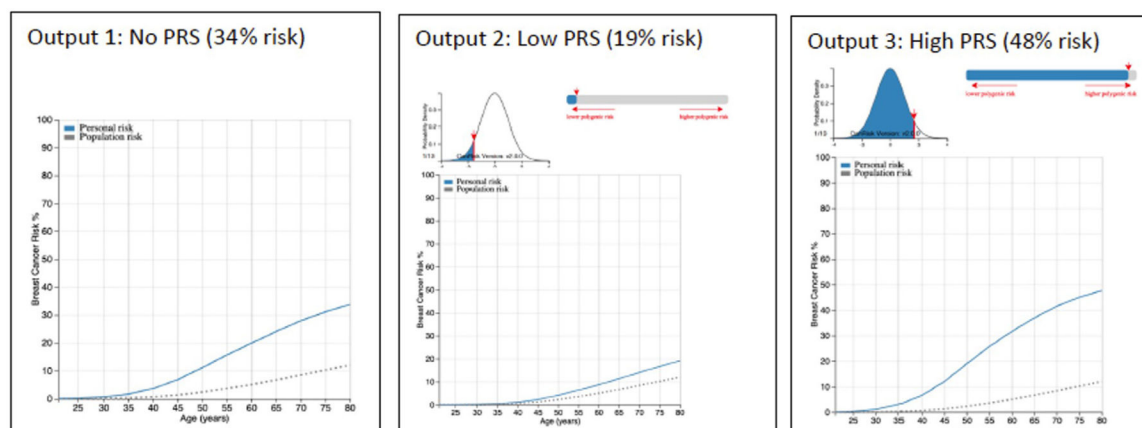


Figure 5.
CanRisk outputs focused on 20-year-old niece of proband, showing breast cancer risks to age 80.

Table 1

Summary of select *CHEK2*-associated cancers

Tumor Type	<i>CHEK2</i> Variant ^a	Association With Cancer Risk	Level of Increased Risk	Clinical Actionability and Management
Breast cancer	Truncating variants	Yes	Moderate (Biallelic [in <i>trans</i>] risk likely higher)	Yes, with personalized assessment Breast surveillance to be offered according to country-specific recommendation but is likely to at a minimum include annual mammogram from age 40 years and consideration of MRI ^b
Breast cancer	Missense variants, not including c.470T>C p.(Ile157Thr), and c.1283C>T p.(Ser428Phe)	Yes	Low-moderate	Not clinically actionable in isolation. Breast surveillance should be based on personalized assessment including family history as a minimum. Some exceptions may exist such as p.(Arg117Gly)
Breast cancer	Missense variants c.470T>C p.(Ile157Thr), and c.1283C>T p.(Ser428Phe)	Yes	Low	Not clinically actionable in isolation. Breast surveillance should be based on personalized assessment including family history as a minimum
Male breast cancer	Truncating variants	Yes	Moderate	Advice on self-examination and symptom awareness
Colorectal cancer	Truncating variants c.1100del p.(Thr367fs), data for other truncating variants unclear	Yes	Low-moderate	Not clinically actionable in isolation. Offer surveillance as per family history ^c
Colorectal cancer	Missense variants c.470T>C p.(Ile157Thr), and c.1283C>T p.(Ser428Phe) (other missense variants not studied)	Yes	Low	Not clinically actionable in isolation. Offer surveillance as per family history
Prostate cancer	Truncating	Yes	Moderate	Discuss PSA in shared decision-making process, particularly where family history
Prostate cancer	Missense	Unclear	Unclear	Unclear

CRC, colorectal cancer; *FIT*, fecal immunohistochemistry testing; *MRI*, magnetic resonance imaging; *NCCN*, National Comprehensive Cancer Network; *PSA*, prostate-specific antigen; *RR*, relative risk. Moderate risk is defined as a RR of 2 or greater. Low-moderate risk is defined as a RR of 1.5 to 2. Low risk is defined as a RR of 1 to 1.5. For more detailed information on studies reviewed by the group, see Supplemental Tables 3-5.

^aTranscript ID: NM_007194.4, Protein ID: NP_009125.1.

^bIn the United States, current NCCN guidelines advise annual mammogram beginning at age 40 with consideration of annual breast MRI (NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V1.2020). In the United Kingdom, breast surveillance is based on lifetime or 10-year risk with women at 17% or lower lifetime risk offered population level surveillance through the National Health Service Breast Screening Programme, women at 17 to 30% lifetime risk offered annual mammogram from 40 to 50 years followed by population level surveillance, women at >30% lifetime risk annual mammogram from 40 to 60 years, followed by population level surveillance and women at >40% lifetime risk annual MRI and mammogram from age 30 (<https://www.nice.org.uk/guidance/cg164>).

^cIn the United States, surveillance for individuals at moderate CRC risk may include consideration of colonoscopy every 5 years, from age 40 years; however, NCCN Guidelines Version 2.2022 Genetic/Familial High-Risk Assessment: Colorectal, recognize the CRC risk is not well established. In the United Kingdom, surveillance for individuals at moderate CRC risk includes a one-off colonoscopy at age 55 and FIT through the National Health Service Bowel Screening Programme.