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ACMG STATEMENT

Consideration of inherited cancer risk on a continuum: An international and multidisciplinary perspective: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

In the 1990s, the study of families with significant cancer burden across multiple generations led to the discovery of a number of cancer susceptibility genes (CSG), for example, *BRCA1* (HGNC:1100) and *BRCA2* (HGNC:1101), which are associated with increased lifetime risks of developing breast and ovarian cancer.[1,2] Consequently, heritable cancer risk was generally considered a binary or dichotomous event in clinical practice, based on the presence or absence

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of a germline pathogenic or likely pathogenic variant (GPV) in a known CSG. Since these initial discoveries, substantial evidence and clinical experience have led to modifications of this view. It is now clear that heritable cancer risk is more complex and presents on a continuum based on specific GPVs, in conjunction with interactions with additional genomic risk modifiers, and many hormonal, lifestyle, and other environmental risk factors. Each of these factors has a variable contribution to risk in an individual with a CSG GPV and can be dynamic over a lifetime. Ultimately, this leads to an increased risk of developing cancer over a lifetime (penetrance), which can present with the development of tumors in various organs (organ-specific penetrance) and varies with age (age-related penetrance). With data increasingly available from much broader and generalizable groups of individuals compared with the highly selected families originally used for CSG discovery,[3] clinical risk estimation for individuals with a GPV is becoming increasingly complex and requires a shift to considering risk on a continuum.

To date, penetrance estimates have been anchored to a CSG based on "typical" risks, generated through data utilizing a "phenotype-first" approach (ie, based on individuals ascertained through high-risk clinics with notable family or personal history of specific cancers). Although suited to gene discovery, this approach to ascertainment can lead to overestimation of penetrance and a biased view of organ-specific effects. Large-scale, population-based genomic studies now provide the ability to use a "genome-first" approach (or genomic ascertainment). Although this approach may potentially result in underestimation of penetrance, these population-based insights have enabled increasingly granular penetrance estimates with potential to provide more individualized risks to patients to support and enable appropriate clinical management decisions. This is particularly pertinent given that indications for genetic testing of CSGs have become increasingly permissive over time resulting in identification of ever-increasing numbers of individuals with a GPV in CSGs.[4,5] As a consequence of Bayes' theorem, diagnostic settings (eg, population-based screening vs clinic-based testing) need to be considered when estimating penetrance. The focus of this document is on concepts of CSG penetrance from diagnostic testing scenarios. Additionally, although not a focus of this document, there is a great need to develop frameworks and strategies for communicating risk on this dynamic continuum, in a manner that is comprehensible for both clinicians and patients. Moreover, refining thresholds for organ-specific cancer surveillance or risk-reducing interventions is critical to prevent overtreatment, as well as avoid missed opportunities for early cancer detection.

In this document, we consider the key concepts and considerations underpinning the paradigm shift in our understanding of inherited cancer risk (Box 1). We review our current understanding of factors and mechanisms influencing overall risk, the clinical complexities presented by our increased knowledge of risk, and how we might further refine our current understanding of risk estimation and approaches to resultant clinical management in the future. This is not a comprehensive review of the topic, and we have focused on breast cancer to illustrate relevant points, but the concepts are applicable to all CSGs. Also of note, although there are many exciting and emerging advances to refine cancer treatment based on CSG GPVs, this topic is beyond the scope of the current document.

Box 1. Key concepts in consideration of inherited cancer risk on a continuum

- Germline pathogenic variants (GPVs) in cancer susceptibility genes (CSGs) vary in their penetrance across organ sites and resultant influence on clinical management.
- Overall cancer risk in an individual with a GPV in a CSG can vary widely due to contributions from genetic factors such as the specific variant, wider genomic context (eg, common risk alleles comprising polygenic risk scores), and modifiable and non-modifiable factors, including but not limited to, family history, age, environment, lifestyle, and hormonal factors.
- Cancer risk perception for an individual can be influenced by factors such as personal context, experience of hereditary cancer risk, and subjective experience of risk.
- The threshold for clinical intervention to either reduce cancer risk or initiate cancer surveillance requires assimilation of all contributing risk factors, consideration of medical context (ie, other competing risks, such as comorbidities) and personalized counseling to enable individualized cancer risk management.

Fundamental components that underlie the risk continuum

For an individual with a GPV in a CSG, overall lifetime cancer risk is influenced by both the GPV and many other components, such that risk lies on a continuum (Figure 1). For each of these factors, the relative contribution to risk is variable and our understanding remains incomplete; thus, a fully comprehensive individualized risk assessment is not currently possible. Our understanding of risk factors and their relative contribution to cancer risk is evolving. For example, in breast cancer, the contributions of family cancer history, hormonal factors, or breast density are well established.[6-8] Emerging factors include the potential utility of polygenic risk scores (PRS) in refining risk estimates, which has the potential to alter clinical management particularly for individuals with a GPV in moderately penetrant CSGs (eg, such as *ATM* (HGNC:795) or *CHEK2* (HGNC:16627)).[9] Poorly characterized factors include most

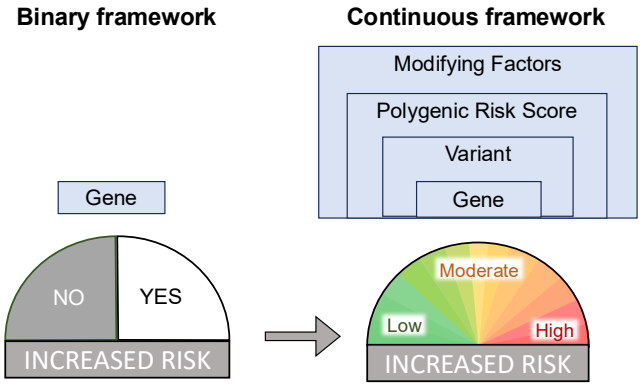


Figure 1 Conceptualizing cancer risk on a continuum. Diagram illustrating the shift in our understanding of cancer risk from a binary (or dichotomous) framework based on the presence or absence of a GPV in CSG, to a continuum based on an increased understanding of additional factors that can modify cancer risk in an individual.

genotype-phenotype correlations and the influence of wider genomic and epigenomic modifiers. The factors underlying the continuum of risk may be considered in 3 broad areas, genotype, genomic and epigenomic context, and other modifying factors.

Genotype

The presence or absence of a GPV in a known CSG can have a profound impact on an individual's lifetime risk of cancer. The overall risk for an individual is influenced by the CSG, some of which are associated with higher penetrance, whereas others are associated with intermediate penetrance. Using breast cancer as an example, *BRCA1* and *BRCA2* are typically considered to be "highly penetrant" breast CSGs, compared with *CHEK2* and *ATM,* which are typically considered to be intermediate- or moderate-penetrance genes. Furthermore, even within a given CSG, the specific GPV can influence penetrance.

The concept of pathogenicity underlies genotype interpretation with classification and seeks to determine the probability of a causal relationship of a variant to a phenotype (see Box 2[10-16] for a more detailed discussion on pathogenicity and penetrance). Once a probability of pathogenicity is determined, most commonly using the ACMG/AMP classification system, the variant can be assigned to 1 of 5 groups of varying likelihood of pathogenicity.[10] The highest level of pathogenicity (also known as class 5[17]) simply refers to the probability ($\geq$99%) that a given variant will cause a susceptibility disorder (ie, pathogenic). Although the evidence used to assess variant classification will be influenced by the typical penetrance for that gene in relation to cancer susceptibility alongside the population prevalence of the variant, no attempt is made to formally quantify the likelihood of the clinical disease phenotype developing using this classification system. As a result, 2 distinct pathogenic variants, in separate people, even if present in the same gene, can have widely differing levels of organ-specific penetrance dependent on the functional impact of those variants. For example, although both are pathogenic variants, loss-of-function *BRCA1* GPVs typically impart a 60% to 70% lifetime breast cancer risk when present in the heterozygous state (ie, high risk), whereas the hypomorphic *BRCA1* missense variant, NM_007294.4:c.5096G>Ap.(Arg1699Gln), commonly known as R1699Q, imparts a 24% lifetime breast cancer risk in the heterozygous state (ie, moderate risk) by age 70 years.[13,18,19] Analogously, pathogenic loss-of-function *ATM* variants typically impart a 20% to 25% lifetime breast cancer risk in the heterozygous state (ie, moderate risk),[20,21] whereas NM_000051.4:c.7271T>G p.(Val2424Gly), also known as V2424G, imparts a 43% lifetime breast cancer risk in the heterozygous state (ie, high risk) by age 70 years.[22]

Separating out pathogenicity and penetrance is an ongoing challenge, recognizing that Richards et al[10] only considered pathogenicity in their original ACMG classification system. The more recently developed ABC classification system first considers the functional impact of the variant followed by the clinical impact; however, it has not been widely adopted.[23,24] Frameworks to stratify risks will need to further refine the classification of GPVs to incorporate penetrance, which is needed to develop a refined assessment of clinically relevant risk.

Genomic and epigenomic context

Beyond GPVs in single CSGs, common genetic variants including single-nucleotide variants (SNVs), commonly referred to as single-nucleotide polymorphisms, and copy-number variants are present across the entire genome. Individually, each common variant is unlikely to have a significant impact on disease predisposition; yet, collectively, these variants can influence lifetime cancer risk.[25] Specifically, through the quantification of hundreds of these variants across the entire genome, a PRS, also known as a genomic risk score or "GRS," is generated, and can be used to generate and refine risk estimates in an organ-specific manner. Breast cancer PRS underscore the emerging importance of genome-wide context, particularly for moderate-penetrance breast CSGs, such as *ATM* and *CHEK2*, for which the modification of lifetime cancer risk based on PRS is more likely to result in changes to clinical recommendations.[9,26] For example, incorporation of PRS in a risk assessment model was reported to downgrade lifetime breast cancer risk to <20% in one-third of *CHEK2* heterozygotes and about half of *ATM* heterozygotes.[26] This finding is of clinical relevance, given that the threshold for breast MRI surveillance in the United States is a lifetime breast cancer risk of 20% or greater.[27] In contrast, PRS did not alter surveillance recommendations among *BRCA1*, *BRCA2*, and *PALB2* (HGNC:26144) heterozygotes highlighting the limited value of PRS in guiding clinical management in individuals with GPV in high-penetrance genes.[26] There remain limitations in the clinical prediction accuracy and utility of PRS in non-Northern European populations given the relative lack of genomic data.[28]

Box 2. Key definitions

Pathogenicity: The probability that there is a causal relationship of a variant to a phenotype. Variant classification through the ACMG/AMP guidelines assigns a probability of pathogenicity for an individual variant: pathogenic (P, >99%), likely pathogenic (LP, >90%), variant of uncertain significance (VUS, 10%-90%), likely benign (LB, <10%) and benign (B, <0.1%).[10] However, the classification of pathogenicity does not assess or quantify the penetrance or clinical severity (ie, expressivity) of that variant.

Penetrance: The probability that an individual with a given genotype expresses the phenotype.[a]

Complete penetrance is the situation in which all individuals with a given germline pathogenic variant (GPV) would develop a specific phenotype, whereas incomplete penetrance is the situation in which only a proportion of individuals with a GPV develop the phenotype.

Specifically, for cancer susceptibility genes (CSGs), penetrance refers to the age-dependent cumulative incidence of cancer over an individual's lifetime. This is often given in an organ-specific manner, eg, lifetime breast or ovarian cancer risk, and displays incomplete penetrance in nearly all CSGs, and referred to as "organ-specific penetrance" (ie, analogous to the concept of expressivity). The estimates are also largely derived from gene- rather than variant-specific estimates, given the rarity of most variants.

Relationship between risk and penetrance:

Whereas penetrance refers to the probability that an individual with a given genotype expresses the phenotype (ie, is linked to a specific gene or variant), risk is the probability for any individual to develop a specific disease (ie, cancer) over a certain period of time (eg, 5-year risk or lifetime risk). In clinical practice, the term "risk" is used to categorize the assessment of all risk factors (eg, genetics, lifestyle, and environmental factors) and is often linked to defined thresholds for clinical management.

Diagnostic testing vs genome-firsts screening: Another important consideration are the differences between diagnostic testing vs genomic screening (including secondary findings) scenarios. In the latter, the much lower prior probability of disease (vs diagnostic testing) means that, per Bayes' theorem, some instances of what appears to be nonpenetrance arise from the simple fact that, by definition, LP variants have a >90% (but not 100%) probability of pathogenicity. In other words, given that pathogenicity is <100% and the low prior probability (typically, akin to population risk of 1/400-1/50,000 for secondary findings genes) of disease, population screening will enrich for variants that are actually benign that are currently (and erroneously) classified with a high probability of pathogenicity (for further exploration of these emerging concepts, see Biesecker[11] and Katz et al[12]).

Hypomorphic variant ("hypomorph"): A variant that leads to reduced (but not complete loss) of gene activity. Operationally, a variant that displays reduced, but not loss of, function in functional assays (ie, refers to the functional impact). Presumably, the residual function contributes to reduced penetrance or altered expressivity of the associated phenotype, such as cancer.

Reduced penetrance pathogenic variant (RPPV): A variant that leads to reduced penetrance of the associated phenotype, when compared with the typical penetrance associated with pathogenic/likely pathogenic variants, which is still clinically relevant (ie, refers to the clinical impact). Clinically relevant is defined as associated with a substantial increase in risk in relation to the general population that justifies an intervention or distinct clinical management guidelines. Operationally, a variant that is associated with relative risks higher than the general population and lower than those associated with loss-of-function variants in case-control or segregation analysis.

Relationship between hypomorphs and RPPVs: All RPPVs are hypomorphic, but not all hypomorphs are RPPVs. For example, the *BRCA2* K3326* variant (NM_000059.4:c.9976A>T p.(Lys3326*)) is a hypomorph that is not an RPPV given that risks associated with it are not clinically relevant. Conversely, all *BRCA* RPPVs reported in a recent article were hypomorphic, with evidence of clinically relevant impact on function.[13]

Breast cancer risk categories (according to UK NICE guidelines): The classification of lifetime breast cancer risk varies considerably across and even within countries. For the purpose of this document, except where specified, we have defined moderate and high risk according to the National Institute for Clinical Excellence (NICE) guidelines.[14] The categories for lifetime breast cancer risk to age 80 years are defined as follows:

- Population: <17%
- Moderate: 17-29%
- High: ≥30%

Surveillance vs screening: Screening refers to population-based programs, eg, national breast screening programs based on age. Surveillance is focused on people at high risk of disease and is therefore distinct from screening in both scale (smaller) and intensity (greater), eg, MRI breast surveillance offered to women at increased breast cancer risk.[15]

[a]The formal definition of penetrance was made by Jurg Ott in his seminal book "Analysis of Human Genetic Linkage," in which penetrance was defined as "the conditional probability P(x|g) that an individual with a given genotype g expresses the phenotype x."[16] Importantly, and unstated in this definition, is the assumption that the genotype has a 100% probability of pathogenicity, a condition that has been established for only a small number of variants (eg, the Ashkenazi *BRCA1/2* founder variants and *CFTR* NM_000492.4:c.1521_1523del p.(Phe508del), commonly known as △F508).

Additionally, there exist SNVs that may not in themselves be classified as disease-associated that can modify cancer risk in the presence of a specific GPV. For example, the *TP53* (HGNC:11998) NM_000546.6:c.215C>G p.(Pro72Arg) variant and the *MDM2* (HGNC:6973) NM_002392.6:c.14+309T>G variant[29-31] both independently lead to increased TP53 degradation contributing to an earlier onset of tumorigenesis in *TP53* GPV heterozygotes. These effects appear to be specific to the underlying GPV with the same effect not observed in individuals with a GPV in other CSGs[32] and with a modest effect in the general population.[33]

Beyond genome-wide variants, there are examples of small effect variants clustering together in a haplotype that can potentially modify risk and expressivity of GPVs. For example, the *TP53* NM_000546.6:c.1010G>A p.(Arg337 His) variant, which is highly prevalent in Brazilian populations, may have differing penetrance and expressivity depending on the underlying haplotype.[34] Similarly, the *APC* (HGNC:583) NM_000038.6:c.3920T>A p.(Ile1307Lys) variant has been associated with an increased risk of colorectal cancer in individuals of Ashkenazi Jewish descent, whereas meta-analyses are not supportive of an association in other populations.[35]

Epigenomic modifications affect gene expression through specific changes that do not alter the DNA sequence. These modifications, such as DNA methylation, can play important roles in carcinogenesis and the development of drug resistance. The extent of these modifications, as well as the potential consequences of these complex alterations to lifetime cancer risk in individuals with GPV in CSGs, are not yet fully understood.[36-38]

Other modifying factors

There are a number of established and emerging factors that can influence overall lifetime cancer risk, which can be modifiable or nonmodifiable (Figure 2). Although a detailed discussion and comprehensive listing of these factors is beyond the scope of this effort, established factors include lifestyle (eg, alcohol and obesity), hormonal (eg, age at menarche/menopause), environmental (eg, UV radiation), and organ-specific factors (eg, breast density).[39,40] Categorizing these factors, and separating them from genomic context, is difficult. For example, genetic factors can influence the timing of menopause, and some of these factors can also influence an individual's cancer risk.[41] Similarly, obesity may have traditionally been considered a predominantly modifiable factor, but recent twin studies have demonstrated that genetic variation is a significant contributor to its etiology.[42,43]

Age is an established risk factor for most cancers. Most population cancer screening programs use age in isolation, rather than other factors, when establishing surveillance guidelines. In the context of a CSG, most genes show age-specific penetrance. For example, GPVs in *TP53* are associated with a significantly increased risk of cancer over a lifetime; however, there is a predisposition to some cancers in childhood (rhabdomyosarcoma, choroid plexus carcinoma, hypodiploid acute lymphoblastic leukemia, and adrenocortical cancer), and others are seen more commonly in adulthood (eg, breast cancer).[44,45]

Family history is also an independently established risk factor for most CSGs. Examples of the influence of family history on penetrance can be found across various CSGs. For example, the largest study to date in *RAD51C* (HGNC:9820) and *RAD51D* (HGNC:9823) heterozygotes demonstrated that both breast and ovarian cancer risk were significantly modified by family history.[46] For both genes, lifetime ovarian cancer risk exceeded 30% for heterozygotes with 2 first-degree relatives diagnosed with ovarian cancer, compared with a risk of approximately 10% for heterozygotes overall. The paraganglioma and pheochromocytoma susceptibility gene, *SDHA* (HGNC:10680), shows a significant family history risk modification[47,48] such that it is recommended that cascade testing is limited to first-degree relatives.[49] Interestingly, although family history is traditionally used clinically as a measure of inherited susceptibility, PRS can add an additional measure of genetic risk. Although there is some overlap in contribution, family history and the currently described PRS are largely independent and combine additively to an individual's cancer susceptibility.[50,51]

Genetic mechanisms underlying continuum of risk

Pathogenicity vs penetrance

The classification of pathogenicity reflects the disruption in gene function and, within the ACMG guidelines, are currently described as 5 categories based on the likelihood that a given variant is causative for a given phenotype. These guidelines have been adapted to provide more emphasis on a quantitative measure of the likelihood of pathogenicity.[52] We have already described the difficulty in uncoupling penetrance from pathogenicity in the "genotype" subsection above using well-characterized examples for *BRCA1* and *ATM*. These include examples of pathogenic variants, *BRCA1* R1699Q and *ATM* V2424G, in which the variant-specific penetrance differs from the "typical" penetrance estimates for pathogenic variants in these genes and thus can result in distinct clinical recommendations (Figure 3A). Examples beyond breast cancer susceptibility include low-penetrance *RET* (HGNC:9967) variants (eg, NM_020975.6:c.2410G>Ap.(Val804Met)) associated with multiple endocrine neoplasia type 2[53] and varying genotype-phenotype correlations seen in Von Hippel-Lindau syndrome.[54]

It also follows that laboratories have greatly varied in their reporting and classification of variants that are pathogenic based on functional assays and yet have reduced penetrance compared with the "typical" penetrance of the gene in question. For example, loss-of-function *CHEK2* variants generally impart a "moderate" lifetime breast

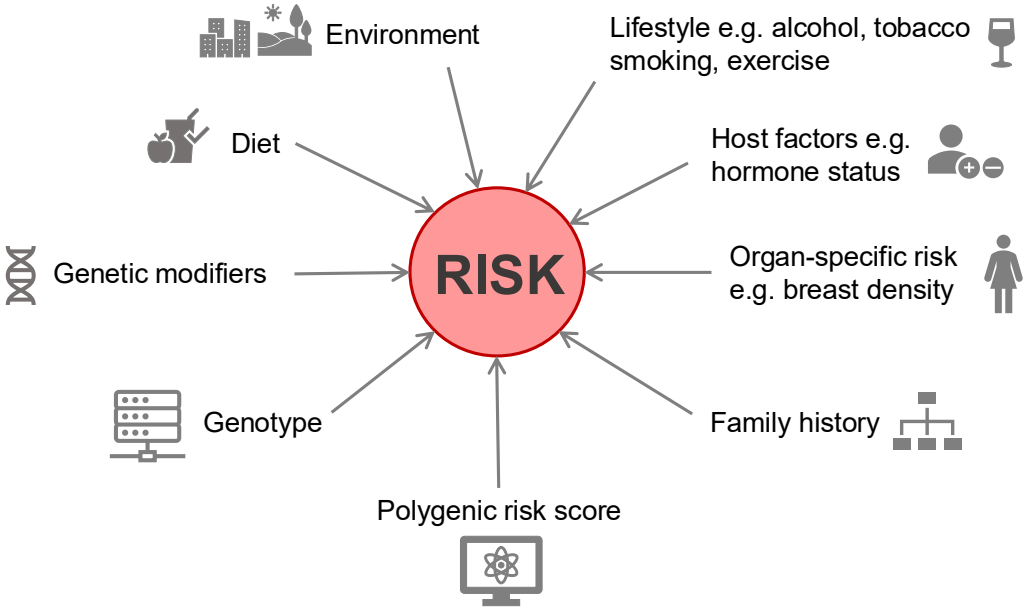


Figure 2 Examples of factors influencing individual cancer risk. A multitude of factors contribute to cancer risk.

cancer risk of 20% to 25%,[20,21] whereas the *CHEK2* NM_007194.4:c.470T>C p.(Ile157Thr), also known as *CHEK2* I157T, imparts a "low" lifetime risk of <20%.[55,56] In fact, the odds ratio of *CHEK2* I157T is comparable to an SNV identified by genome-wide association studies (GWAS) for breast cancer susceptibility variants (relative risk [RR] < 1.5) and not comparable to the risk conferred by most recognized loss-of-function *CHEK2* variants (RR > 2.0).[57] Consequently, *CHEK2* I157T is now largely accepted as a risk allele to be used within a PRS, rather than acting in isolation.[56,58] However, the discrepancy between pathogenicity and penetrance (ie, reduced compared with loss-of-function or truncating variants in *CHEK2*) contributes to a wide variation in reporting of this variant by clinical testing laboratories including: "Special Interpretation" comment (with an asterisk to a "see below" comment for explanation), "moderate risk," "pathogenic (low penetrance)," "hypomorphic," "reduced risk," "atypical risk," and "variant of uncertain significance (VUS)."

The current inconsistency in practice is partly because existing variant classification models are designed for highly or fully penetrant Mendelian variants, which rely on the dichotomous classification of pathogenic or benign.[10,59] However given that pathogenicity and penetrance are 2 separate factors, this can be problematic when considering clinical recommendations for variants that are considered to be pathogenic yet associated with lower than the "typical" penetrance for GPVs in the same gene (as described above through a few examples). To attempt to improve this, there have been efforts by various groups to help address the issue of reduced penetrance pathogenic variants (RPPVs) and the inconsistency in classifying and reporting these types of variants in clinical practice. Initially, the Evidence-based Network for the Interpretation of Germline Mutant Alleles 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 framework recommended that only variants with 2-fold or greater risk would be reported because those conferring less than a 2-fold RR are, in isolation, likely to have limited clinical utility.[60] More recently, ClinGen[61] and CanVIG-UK[62] developed guidance on terminology of reporting for RPPVs. In fact, RPPVs encompass the terminology set forth by ClinGen's "low penetrance" term, which is further qualified to reflect pathogenic or likely pathogenic classification.[61] There has been limited uptake of the ClinGen "low penetrance" terminology by laboratories, and the wider familial cancer community, based on the concern that this terminology may be misinterpreted to mean "low" risk in conjunction with the lack of precision of risk estimates for the majority of individual variants. Consequently, we assert that the uptake of "RPPV" terminology would be more acceptable to laboratories, and in line with CanVIG-UK guidance, because of increased specificity of language, compared with the existing ClinGen nomenclature. However, although these frameworks provide guidance for reporting practice and may reduce discordant classifications, associated recommendations for clinical practice are more challenging. Although there are some exceptions, such as for *BRCA1* R1699Q and *CHEK2* low-risk variants,[18,63] variant-level clinical guidance for RPPV is not yet widely available. The shift from a binary model of risk stratification to that of a risk continuum therefore requires the development of a clinically relevant risk stratification system that accounts for penetrance (Figure 3B).

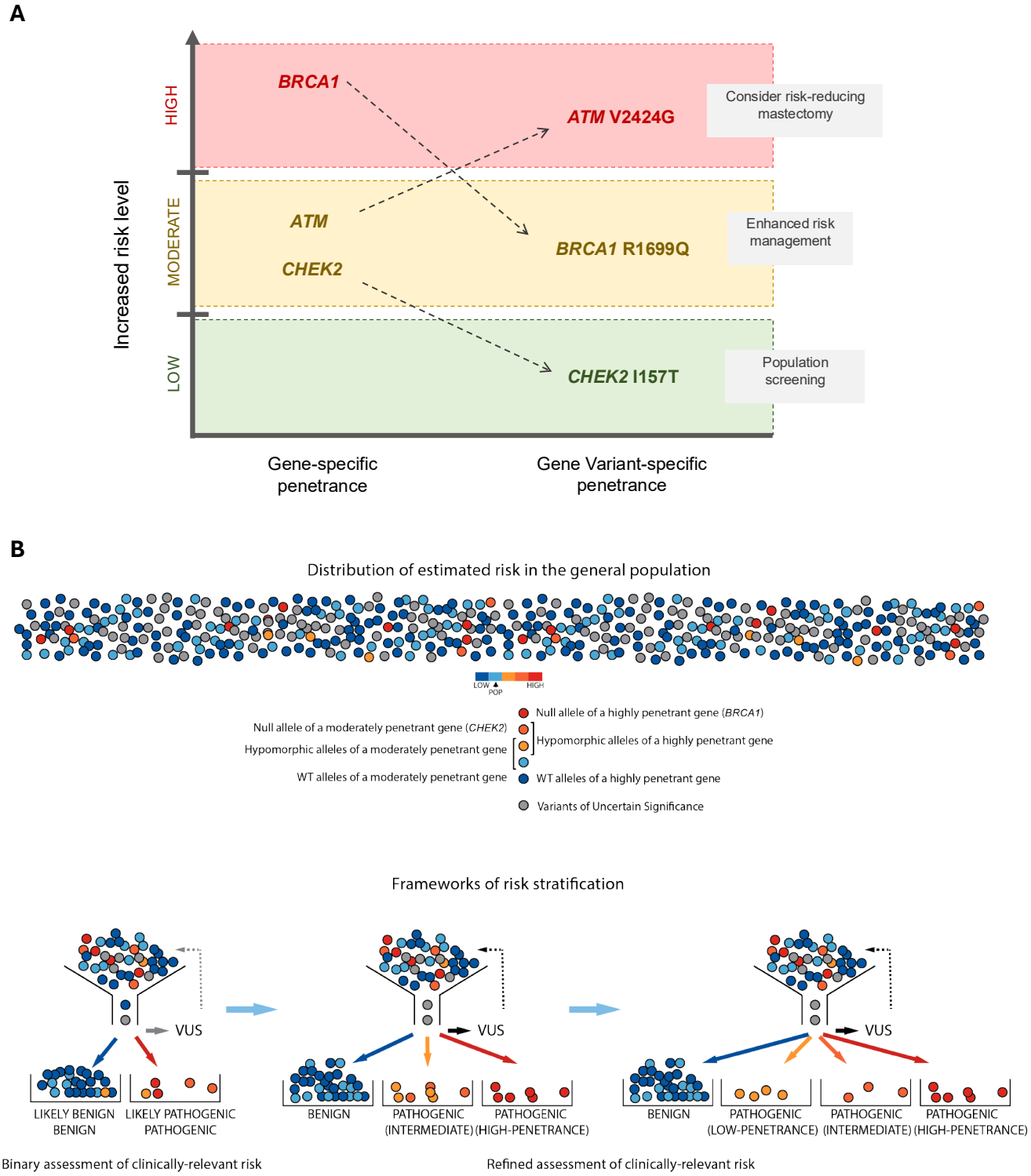


Figure 3 **Clinically relevant risk refinement.** A. Examples illustrate how specific genotypes in a CSG can deviate from "typical" gene-specific penetrance and impact clinical management. B. Schematic illustrating a framework of clinically relevant risk stratification for variants in CSGs to incorporate the penetrance of variants determined to be pathogenic. WT, wild type. Null refers to loss-of-function variants.

Given that the downstream impact of inconsistent reporting can result in discrepant clinical management for patients and relatives, consistency is important to avoid confusion for healthcare professionals, patients, and families. Consequently, the use of the published recommendations is particularly important in the era of multigene panel testing in which GPV in CSGs may be identified outside the context of a personal or family history of cancer.[60]

Clinical impact of modifying factors on penetrance

Until more sophisticated models are developed, clinical recommendations should consider the type of variant, in conjunction with the personal and/or family history of disease, and other known genomic and modifiable risk factors. In the future, we anticipate that PRS will increasingly be adopted in clinical cancer risk assessment as data on clinical validity and utility emerge. The application of these concepts in estimating risk are illustrated through examples in Figure 4A. These concepts allow for the estimation of risk for an individual, which ultimately determines clinical recommendations. The application of refined risk estimates incorporating modifying factors can lead to widely differing clinical recommendations in 2 individuals with pathogenic variants in the same genes, as illustrated by the 2 clinical case examples shown in Figure 4B.

Organ-specific penetrance

It is apparent from the spectrum of phenotypes resulting from variants in different CSGs that the presence of a GPV has a highly variable organ-specific penetrance. For example, GPVs in *CDH1* (HGNC:1748) lead to susceptibility to a very narrow spectrum of cancer types (diffuse gastric and lobular breast cancers), whereas GPVs in *TP53* lead to susceptibility to a wide spectrum of cancer types. The exact mechanism leading to this organ-specific effect, as well as the additional genetic and nongenetic modifiers that influence organ-specific cancer risk, are not well understood. Recent studies focused on epithelial cells from the grossly histologically normal breast tissue of individuals with GPVs in *BRCA1* or *BRCA2* found an enrichment for cancer-associated copy-number alterations compared with individuals with no GPV in a CSG.[64] Interestingly, this enrichment was seen in cells that had not undergone loss-of-heterozygosity at the *BRCA1* or *BRCA2* loci, although this was seen in rare instances of "cancer-like" single cells that displayed extreme aneuploidy. This finding challenges the notion of the Knudson 2-hit hypothesis as the sole cancer-initiating factor in individuals with a heterozygous GPV in a CSG. Furthermore, epigenomic characterization of breast tissue in a murine model of *BRCA1* haploinsufficiency has revealed a previously unappreciated procancer epigenetic state, suggesting that a heterozygous variant alone is sufficient for inducing a cancer-predisposed cellular state in at-risk tissues.[65] These studies support the concept of variant pathogenicity being associated with a cancer-predisposed cell state, which is determined by the underlying alteration in gene product function and not necessarily reliant upon loss of the wild-type allele to promote cancer initiation. The procancer predisposed state is likely cell-type specific and contributes to organ-specific cancer susceptibility, but further work is required to elucidate these mechanisms further.

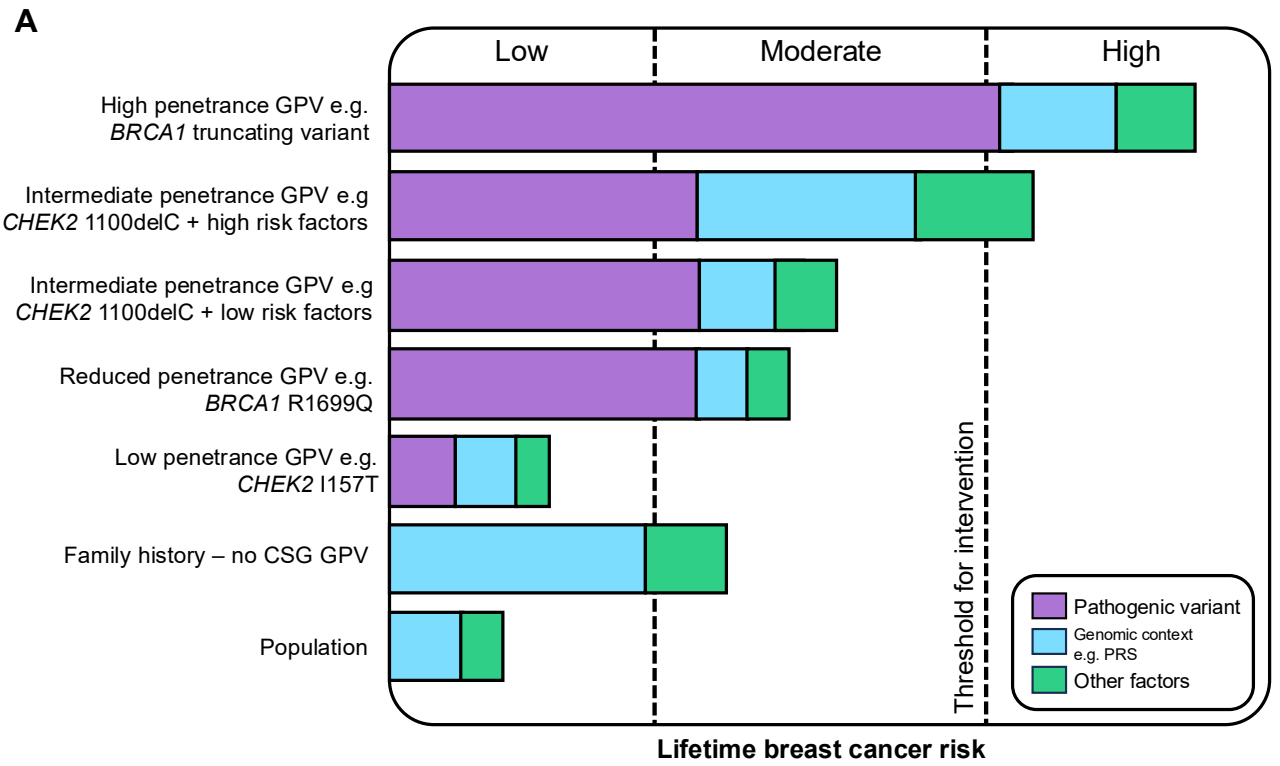
Pathogenicity and penetrance should be considered in the context of organ-specific effects given that a pathogenic variant in a gene may be highly penetrant for a specific cancer type and yet display moderate or low penetrance for another cancer type. For example, *PALB2* is considered to be a "high-penetrance" CSG for breast cancer, whereas the penetrance for ovarian cancer is only increased to clinically actionable thresholds in the presence of a family history of ovarian cancer and/or other risk factors.[66,67] In fact, when considering multifactorial risks, the combination of pathogenicity, age-dependent penetrance, and organ-specific penetrance can be modified by wider genomic context and environmental factors. Therefore, when considering clinical actionability and management, organ-specific penetrance for a given genotype should also include consideration of potential modifiers.

Clinical intervention thresholds based on a multifactorial risk continuum model

Once overall organ-specific risk has been assessed, it is important to consider the relevant clinical management. The risk thresholds for clinical actionability or intervention, eg, surveillance or risk-reducing interventions, vary by organ site. Factors affecting these organ-specific thresholds incorporate the absolute and relative organ-specific cancer risk compared with population risk and prevalence, organ-specific mortality rates, and the ability to detect and influence outcomes for specific cancers through currently available early detection (surveillance) or prevention (risk-reducing surgery or medication) strategies. In addition, the efficacy of interventions (eg, early detection rate through surveillance by cancer type) and possible consequences (eg, surgical menopause and psychological consequences of surgery) need to be considered. Other considerations include age distribution by organ site to guide age at initiation of interventions, as well as the natural history of cancer to guide frequency of surveillance. The key factors under consideration when determining the thresholds for intervention are summarized in Figure 5A.

Age-specific risks are particularly important to consider and warrant a specific mention. For example, although risk-reducing salpingo-oophorectomy (RRSO) is generally discussed at a lifetime ovarian cancer risk of 5% or greater, age-specific risks are important to consider, given the potential long-term sequelae of an early surgical menopause, including decreased bone density and increased risk of cardiovascular disease.[68] For some CSGs, such as *BRCA1* and *BRCA2*, age-specific penetrance is sufficiently high to justify premenopausal RRSO; however, for other CSGs, such as *RAD51C*, *RAD51D*, and *BRIP1* (HGNC:20473), the median age of ovarian cancer in women is older (ages 62, 57, and 65, respectively)[69] and supports consideration of RRSO closer to the age of 50. Importantly, even for these genes, timing of surgery may be influenced by family history of ovarian cancer and personal factors, such as menopausal symptoms.

Finally, thresholds are often clinical decisions based on expert consensus in the face of imprecise risk estimates or



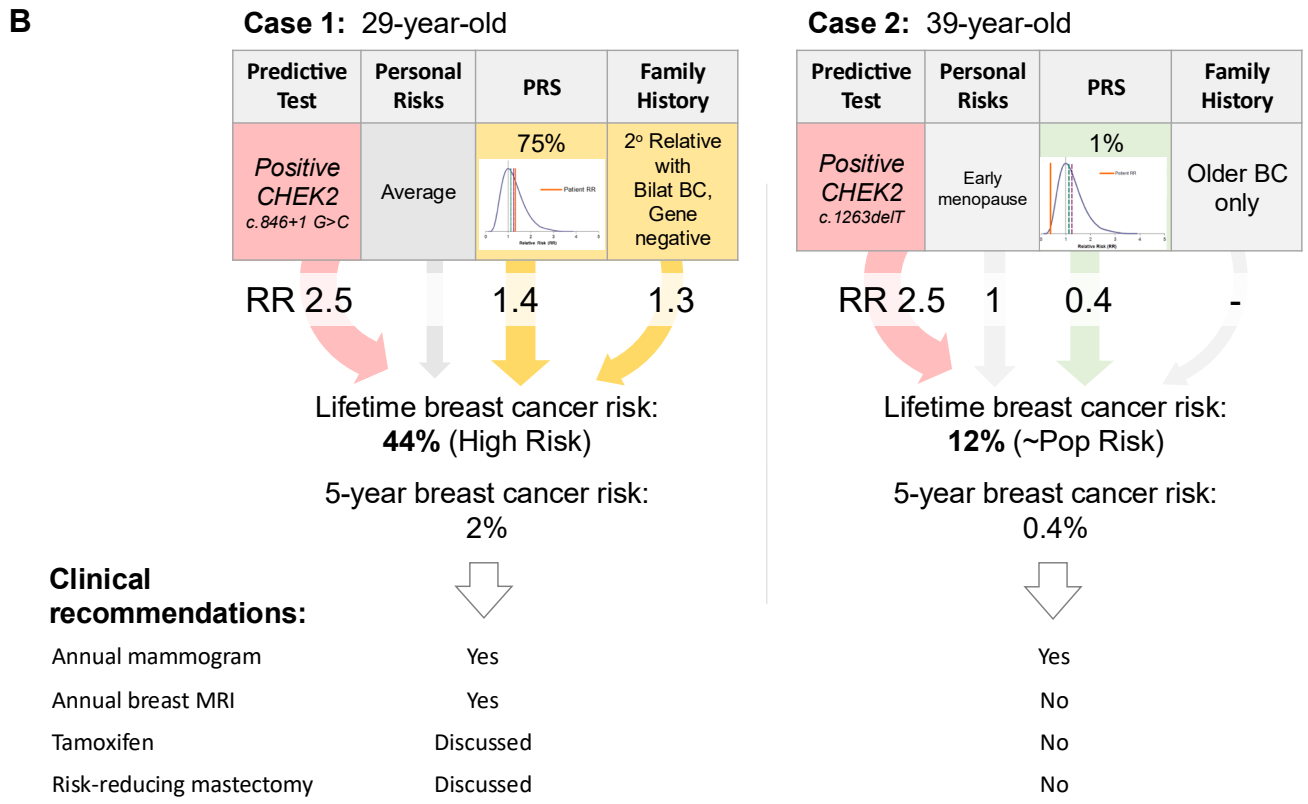
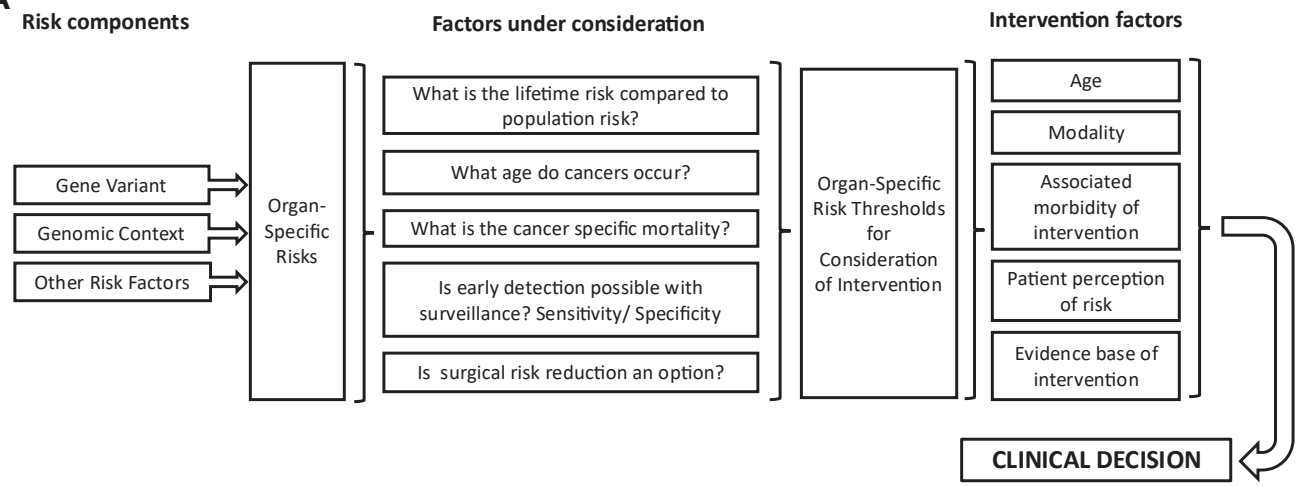


Figure 4 Examples of individualized cancer risk assessment based on genotype, genomic context, and other modifying factors. (A) Using hypothetical examples and (B) case-specific examples leading to differences in clinical management recommendations.

A



B

	Factors under consideration				Output / decision	
Organ site	**Population prevalence**	**Mortality**	**Early detection possible**	**Risk-reducing surgery available**	**Risk threshold for surveillance**	**Risk threshold for prophylactic surgery**
Breast	High	Low	Yes	Yes	>20%	>30-40%
Ovary	Low	High	No	Yes	N/A	>5%
Pancreas	Low	High	Maybe	No	>5%	N/A
Colorectal	Moderate	Moderate	Yes	No[a]	>10%	N/A[a]
Prostate	High	Low	Yes	No	>20%	N/A

Figure 5 Factors to guide organ-specific risk thresholds and recommended management modalities. A. Schematic summarizing the key considerations for clinical decision making regarding risk-reducing interventions. B. Table with a basic summary of factors and current risk thresholds for intervention at organ sites commonly associated with hereditary cancer risk. [a]Individuals with a GPV in *APC* should be counseled on risk-reducing surgical options based on their individual risk profile.

limited evidence, and vary across countries based on country-specific guidelines, resource allocation in publicly or privately funded health care systems, and policy-level factors (such as insurance coverage for interventions or nationally determined cost utility thresholds), which vary globally.[70] For example, in the United States, among those with inherited breast cancer predisposition and unaffected with breast cancer, the level of risk at which the option for risk-reducing mastectomy is considered is generally between 30% and 50% and varies across institutions.[71] In contrast, the United Kingdom has consensus-based guidelines of a risk threshold of 30% at which risk-reducing mastectomy may be considered.[14] As for inherited ovarian cancer predisposition, the level of risk at which RRSO is considered is approximately 5%, which reflects the lack of early detection options and the high mortality rates for ovarian malignancy.[71-73] Conversely, for inherited pancreatic cancer, the threshold for risk management is similarly in the 5% to 10% range, taking into account the high mortality rates; yet, risk-reducing surgery is not an option deemed appropriate given the significant associated risks and morbidity. Therefore, current pancreatic cancer risk management is focused on surveillance options for which data continue to emerge, and recommendations vary greatly across countries. Such organ-specific thresholds for cancer risk management, as outlined in Figure 5B, are important for healthcare professionals to explain and contextualize to their patients.

Ultimately, a focus on absolute risk estimates and thresholds poses challenges in guiding care. Rather, an alternate approach may be to include a range or confidence intervals (acknowledging some technical challenges with this approach) around each individualized risk assessment to demonstrate uncertainty in estimates, while also discussing the pros and cons of various options and using a shared decision-making approach.

Complexities in assessing and communicating risk in clinical practice

Considering risk as a continuum has clinical implications for cancer risk management in individuals with a GPV in a CSG. To date, clinical recommendations are generally gene

specific, resulting in recommendations based on "typical" penetrance, which could potentially result in under- or oversurveillance of individuals, and/or discussions of risk-reducing surgery, which may differ if a more individualized risk assessment was undertaken. We believe that it is increasingly important to consider the individual cancer risk for a person with a GPV in a CSG, taking into consideration the modifying risk factors outlined above, rather than risk anchored to generalized gene-specific penetrance.

At the present time, in addition to using clinical judgment and knowledge of relevant risk factors, a small number of clinical models are available that can help guide an individualized risk assessment. The CanRisk tool[74] can incorporate CSG GPV status, family history, breast density, PRS, and hormonal, lifestyle, and other risk factors, where available, to generate 5-year, 10-year, and lifetime risks of breast and ovarian cancer.[75] When using this web-based clinical tool, it is essential for users to understand that the risks generated by the model are affected by the extent and validity of the information entered for a given individual and that the model is based on specific data sets, eg, cancer risks for GPV in CSG are based on data derived from truncating variants; therefore, the model cannot be applied to any variants that deviate from "typical" penetrance estimates. Furthermore, future discoveries and/or new data on modifiers of risk may result in modifications and updates to the model that could result in a different CanRisk output and potentially alter clinical management recommendations.[76] Although the model generates a specific risk figure, a risk estimate will be associated with a degree of uncertainty reflecting the multifactorial nature and variable contribution of the input parameters. In addition, although we have focused on genetic testing in a diagnostic setting, for individuals ascertained outside traditional clinical pathways, eg, as a secondary finding, further caution is required (see Box 2) to provide a precise and clinically meaningful risk assessment.[5,77]

A consideration in the generation of specific risk estimate figures is the issue of "pseudo-precision," resulting in an illusion of certainty with individuals believing the quoted risk as the absolute truth. Therefore, although risk estimates from models are recommended where possible to help inform patient care, it is important for clinicians to explain their limitations and acknowledge the potential uncertainty, which can change as knowledge evolves. Furthermore, in addition to updates to assessment models, cancer risks can be dynamic over time because of changes in family history, lifestyle, or hormonal factors that could alter risk estimates, highlighting the need for repeat risk assessments to inform clinical management recommendations, and are particularly relevant when there are changes in family history. The time interval separating these reviews will be specific to each individual's risk factors, with significant influence from their underlying genotype. Recent UK guidelines have recommended best practice guidance for recontact and follow-up of individuals with GPV in CSGs, such that those deemed at "high" risk would be recontacted for review at time points associated with risk management interventions and informed to contact the relevant clinician in cases in which there are changes to the family history.[78]

Ultimately, although striving for individualized risk assessment is the end goal, there needs to be recognition that an accurate individualized risk estimate is not currently possible because of factors including, but not limited to, limitations in our data of recognized risk factors, uncertain or difficult-to-measure factors (such as environmental exposures), or lack of routine assessment of known risk factors (eg, such as mammographic density and family history, both recording and verifying). Consequently, it remains important for clinicians to explain the limitations of risk prediction tools with patients and use these tools as an adjunct when discussing breast cancer risk, potential lifestyle changes, and/or surveillance options. Another option may be to share confidence intervals associated with risk estimates, which incorporate uncertainty estimates and may mitigate the perception of high precision, while also encouraging shared decision making.

The importance of genetic counseling should also be strongly highlighted to help address these challenges. In addition to providing an individualized risk assessment, each individual's perception of risk will be influenced by personal factors, including experience of personal and family cancer diagnoses and treatment. Careful consideration of these factors to ensure that personalized counseling is delivered alongside individualized risk estimation is essential. Through this approach, at-risk individuals can be empowered to make informed decisions regarding risk management. Ideally, there is a need to develop tools to visually illustrate personalized risks by tissue type, incorporating risk thresholds, as illustrated in the individualized organ-specific malignancy risk profiles shown in Figure 6.[14,72] Visual representations of risk can be further developed to include components of risk including genotypes, genomic modifiers and modifiable risk factors, such as lifestyle. This can empower patients to identify ways in which they can manage or reduce their cancer risk.

Future models of risk assessment

Within the discipline of hereditary cancer predisposition, the clinical goal is to identify individuals at increased lifetime cancer risk, to enable early cancer detection, and to initiate appropriate risk-reducing interventions to improve outcomes for high-risk individuals and their wider families. The ability to provide a wholly "individualized" or "personalized" risk is a high aspiration borne from a desire to ensure that individuals can appropriately access interventions at relevant time points throughout their life.

However, despite improvements in our understanding of risk, there are limitations in our estimates of individualized risk both from the published literature available and current clinical prediction models as described. Importantly,

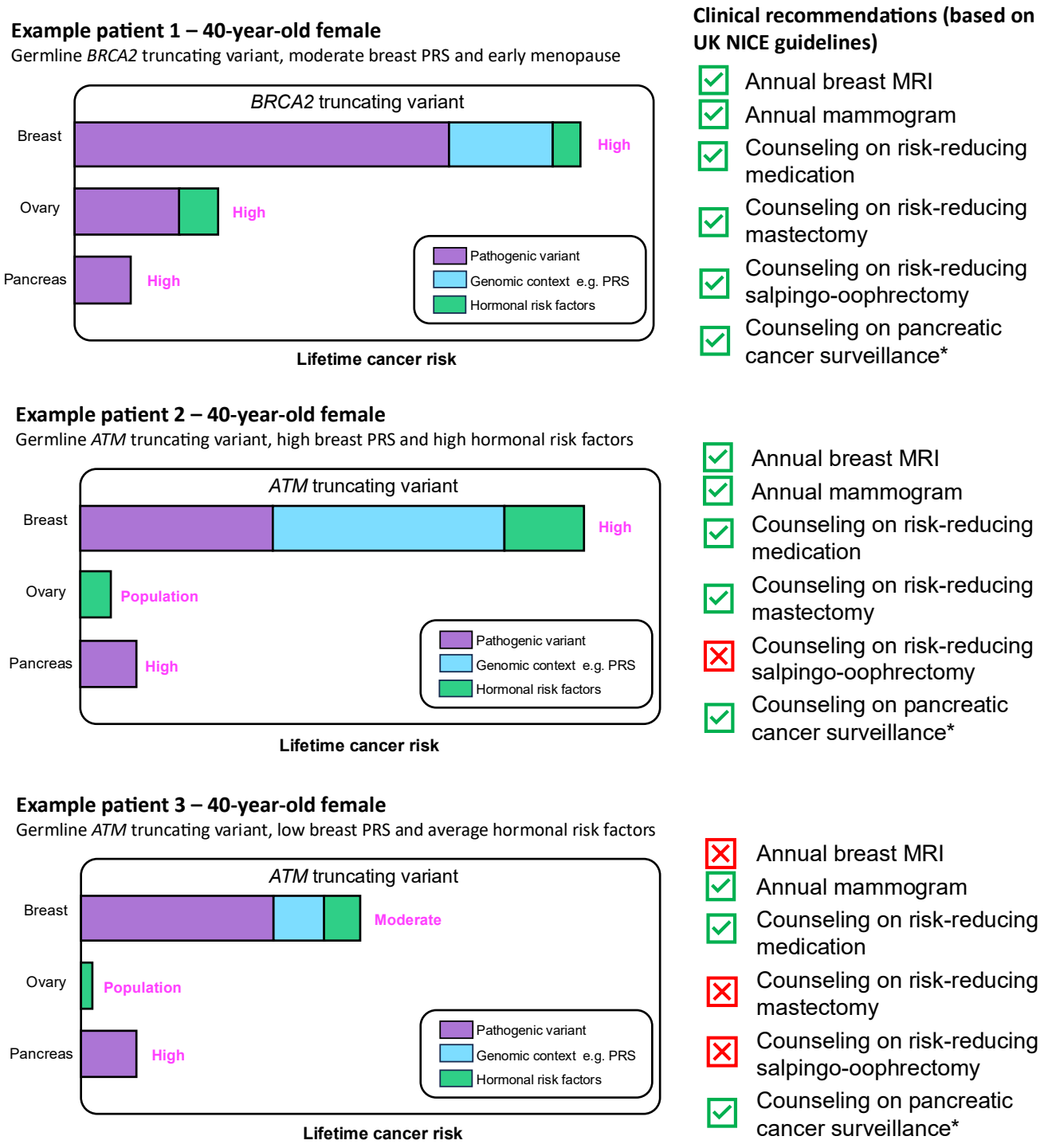


Figure 6 Visualizing components of individualized organ-specific cancer risk and their influence of clinical management recommendations. Example bar charts illustrate the potential components of organ-specific cancer risk and the associated impact on clinical recommendations, based on UK NICE guidelines.[14,72] *Current recommendations for pancreatic cancer surveillance vary by country and may only be offered in the context of a research study.

published risks estimated for a defined population are only the observed probability and thus cannot be directly applied to an individual even with those same risk factors.[79] Furthermore, discordant risks may be estimated from the same or different clinical models, depending on the various conditional probabilities and mathematical methods used in their development and/or the clinical information used in the model.

Although individual risk is not observable, clinical recommendations are based on published studies and clinical guidelines, alongside professional experience and judgment, within all disciplines of medicine. At present,

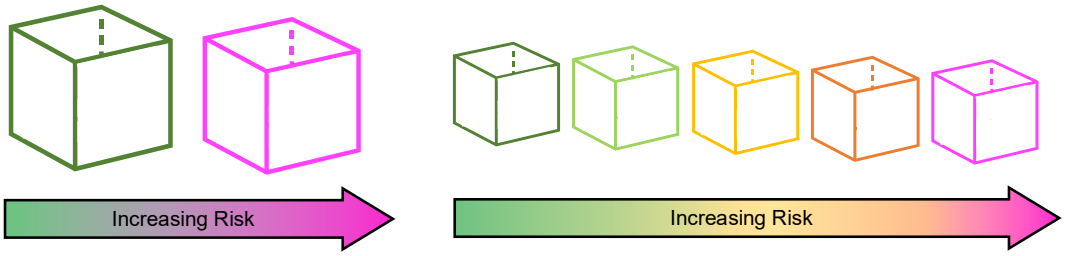


Figure 7 Conceptualizing risk refinement and precision over time. The development of hereditary cancer risk estimation will allow for increasingly granular risk estimations over time.

although our understanding of risk has greatly improved, as well as the known components of risk described above, there remain many unknowns. The working group believes that our understanding will become more refined over time, which underscores the need to develop a framework based on the continuum of risk.

Ultimately, our goal is the incorporation of variant-specific penetrance estimates into clinical risk assessments, where available, rather than gene-based or class-based (ie, loss of function, missense) aggregation of risks. If we consider dividing risk levels into ranges or "bins," we envision that the number of bins will gradually increase over time because we are able to reduce the size of the bins. This will ultimately allow a more granular and individualized clinical assessment (Figure 7). Although the group considers it important to move away from a binary approach to risk assessment, at the current time, a cautious approach to individualized assessment is required. We would suggest that, as with most areas of medicine and not unique to cancer genetics, consultations with patients should include a discussion of our current understanding and the potential for this to develop and change over time. We would encourage clear and open communication with patients, the use of visual resources, and openness about the uncertainties to ensure that clinicians and patients are empowered to make the best decisions based on the information currently available, often using a shared decision-making approach.

Proposed research directions

There remain key areas for future research to further refine cancer risk estimations. Larger longitudinal population-based studies from more diverse populations, prioritizing data from genomic ascertainment studies,[80] will reduce ascertainment bias, improve risk estimates for currently underrepresented groups, potentially increase the understanding of genotype-phenotype correlations, and identify additional genomic modifiers of penetrance. It will be of utmost importance that these large data sets are well curated, provide highly granular clinical detail, and are prospectively collected.

An additional priority will be leveraging large-scale electronic health records linked to genomic data through combination with machine learning approaches[81] to generate refined penetrance estimates for rare variants. Such integration of population-level clinical and genomic data offers a scalable path toward more accurate, individualized cancer risk prediction. Furthermore, variant classification and population-based study of genotype-phenotype correlations can be guided and validated through the use of in vitro studies, such as Multiplexed Assays of Variant Effect (MAVE),[82,83] in CSGs of interest that can guide assessments of pathogenicity.

The study of hereditary cancer risk through population-based studies can be further augmented through tumor and normal tissue studies to enable mechanistic insights into the molecular and cellular underpinning of cancer predisposition. A fundamental step in the acquisition of such data sets is the banking of fresh frozen tissue, which is amenable to the whole repertoire of genomic technologies and not just the limited toolkit available for formalin fixed tissue analysis. Further development of effective animal models and *in vitro* models of hereditary cancer predisposition will allow for experimental validation of putative targets and drivers of cancer susceptibility that are key to cancer biomarker discovery and the development of novel risk-reducing treatments.

Conclusion

The risk continuum for heritable cancer will become more complex as more information emerges. Unbiased population-level sequencing projects will enable the ongoing refinement of penetrance estimates and a comprehensive view of organ-specific risk. Focused investigation of the tissue-specific functional impact of risk factors, both individually and collectively, will provide information on genotype-phenotype correlations, genomic risk modifiers, and the role of the environment in modifying heritable risk.

Although improvement of our risk estimations is likely achievable, no model will ever perfectly predict an "individualized" risk given the intricate interactions of biology and the environment. Continuous review of risk, combined with effective and transparent counseling, will be required to ensure that patients, their families, and their clinicians are well informed and apply the most appropriate risk

management interventions. The challenges of variant classification and estimation of penetrance are not restricted to hereditary cancer genetics and have a wide applicability to all areas of medicine. It will be important that genomic medicine services are dynamic so as to respond to the ever-changing landscape of risk estimation and resulting management.

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Conflict of Interest

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Additional Information

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Supplemental Table 1. HGNC gene ID for genes referenced in manuscript

Gene Symbol	HGNC Gene ID
ATM	795
APC	583
BRCA1	1100
BRCA2	1101
BRIP1	20473
CDH1	1748
CFTR	1884
CHEK2	16627
MDM2	6973
PALB2	26144
RAD51C	9820
RAD51D	9823
RET	9967
SDHA	10680
TP53	11998

Supplemental Table 2: Full description for specific variants described in manuscript□

Gene Symbol	Genomic Description (GRCh37)	Genomic Description (GRCh38)	Coding DNA Description	Protein Description
ATM	NC_000011.9:g.108199929T>G	NC_000011.10:g.108329202T>G	NM_000051.4:c.7271T>G	NP_000042.3:p.(Val2424Gly)
APC	NC_000005.9:g.112175211T>A	NC_000005.10:g.112839514T>A	NM_000038.6:c.3920T>A	NP_000029.2:p.(Ile1307Lys)
BRCA1	NC_000017.10:g.41215947C>T	NC_000017.11:g.43063930C>T	NM_007294.4:c.5096G>A	NP_009225.1:p.(Arg1699Gln)
BRCA2	NC_000013.10:g.32972626A>T	NC_000013.11:g.32398489A>T	NM_000059.4:c.9976A>T	NP_000050.3:p.(Lys3326Ter)
CFTR	NC_000007.13:g.117199646_117199648delCTT	NC_000007.14:g.117559592_117559594delCTT	NM_000492.4:c.1521_1523del p.(Phe508del)	NP_000483.3:p.Phe508del
CHEK2	NC_000022.10:g.29091228del	NC_000022.11:g.28695240del	NM_007194.4:c.1263del	NP_009125.1:p.(Ser422ValfsTer15)
CHEK2	NC_000022.10:g.29105993C>G	NC_000022.11:g.28710005C>G	NM_007194.4:c.846+1G>C	NP_009125.1:p.?
CHEK2	NC_000022.10:g.29121087A>G	NC_000022.11:g.28725099A>G	NM_007194.4:c.470T>C	NP_009125.1:p.(Ile157Thr)
MDM2	NC_000012.11:g.69202580T>G	NC_000012.12:g.68808800T>G	NM_002392.6:c.14+309T>G	NP_002383.2:p.?
RET	NC_000010.10:g.43614996G>A	NC_000010.11:g.43119548G>A	NM_020975.6:c.2410G>A	NP_066124.1:p.(Val804Met)
TP53	NC_000017.10:g.7579472G>C	NC_000017.11:g.7676154G>C	NM_000546.6:c.215C>G	NP_000537.3:p.(Pro72Arg)
TP53	NC_000017.10:g.7574017C>T	NC_000017.11:g.7670699C>T	NM_000546.6:c.1010G>A	NP_000537.3:p.(Arg337His)