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Updated Testing Sensitivities and Variants of Uncertain Significance in CanRisk

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Abstract

Background: The CanRisk platform provides breast, ovarian and prostate cancer risk predictions on the basis of multiple risk factors including germline variants in nine cancer susceptibility genes. Predictions are dependent on assumptions about the sensitivity of genetic testing and how variants of uncertain significance (VUS) are handled. **Methods:** We propose updated default sensitivities to reflect current testing protocols, using data from large population studies. These sensitivities are based on the assumption that structural variants are typically identified for all genes and that negative tests imply that potentially pathogenic VUS are absent. **Results:** Revised sensitivities result in lower predicted cancer risks for individuals who test negative for pathogenic variants.

Conclusions: These new default settings have been incorporated into CanRisk and better reflect current clinical usage. Caution is required, however, in using the tool for counselling individuals with potentially pathogenic VUS.

Background

The BOADICEA and CanRisk-Prostate algorithms model the risks of breast, ovarian and prostate cancer using data on multiple risk factors, including pathogenic germline variants, common genetic variants, hormonal, reproductive and lifestyle risk factors, and family history¹⁻³. These models are available through the CanRisk platform⁴.

Collectively, these models consider data on pathogenic variants (PVs) in 9 genes¹: *ATM*, *BARD1*, *BRIP1*, *BRCA1*, *BRCA2*, *CHEK2*, *RAD51C*, *RAD51D* and *PALB2*. For each of these genes, an individual is assumed to either carry a pathogenic variant (PV) or not. In the current version, all PVs in a gene are associated with the same disease risks (i.e. the risk classification is binary)². The CanRisk tool allows data to be recorded, for each gene, whether testing was done, whether it was a variant search (termed “Mutation search” on the tool) or a predictive test (termed “Direct Gene test” on the tool), and whether the result was positive (“Mut Present”) or negative (“Mut Absent”).

The models allow for the fact that genetic testing will miss some variants, by incorporating a genetic testing sensitivity: the probability that a PV affecting the gene will be detected and reported as such. These sensitivities apply to index individuals undergoing variant screening – the sensitivity of testing for a specific variant in relatives of carriers, using a direct gene test, is always assumed to be 1.

Variants that could be missed can be classified into:

- (a) Variants that the testing was designed to detect, but were missed for technical reasons.
- (b) Variants that were detected but not recognised as PVs.
- (c) Variants that the testing was not designed to detect.

The sensitivity of a variant search test is often thought of (and reported) in terms of the “technical sensitivity”, that is the probability that a test will detect a variant it is designed to detect. The technical has increased over time as technology has advanced and for current gene panel sequencing is generally considered to be extremely high (close to 1) in accredited clinical laboratories³. However, this only relates to variants in category (a), whereas what matters for the risk modelling is the *overall* sensitivity, taking into account all three categories above.

A recent consensus report on the use of CanRisk highlighted revisiting the testing sensitivities as an important area for future work⁵. Here we describe a new approach to defining these sensitivities, provide update defaults to be incorporated into CanRisk and discuss the implications.

¹ The prostate model also includes the coding variant *HOX13B* p.Gly84Glu. As this is a single SNP variant that can be assumed to be genotyped without error, it is not relevant here.

² This is a slight oversimplification. The algorithm considers PVs in different genes as different alleles of the same gene. This substantially improves efficiency but does lead to approximations related to carrying two PVs, though this is rare and not directly relevant here (see (1)).

³ The sensitivity may however be lower in research testing in large epidemiological studies, where some target sequence may be missed. See e.g. Dorling et al(7).

Methods

The overall sensitivity (s) is given by

$$s = (1 - c)(1 - v)s_T$$

Where s_T is the technical sensitivity, v is the probability that a variant is detected but not considered a PV and c is the probability that a PV is “cryptic” and not targeted by the test.

Variants in category (b) are *Variants of Uncertain Significance* (VUS). These could include some missense variants, splice variants or in-frame insertions/deletions. Such variants make a significant contribution to the burden of potential risk variants in several genes, including *BRCA1*, *BRCA2* and *ATM*⁶. Variants in category (c) could include large rearrangements (unless the testing specifically includes them), or other more cryptic variants.

Mathematically, the sensitivity s enters the cancer risk model calculations in the situation in which an individual is tested but found negative (i.e. the observation is “No PV”). The residual probability that an individual is a carrier of a pathogenic variant (and already calculated by the models) is given by:

$$\begin{aligned} P(G = 1|Data, No PV) &= \frac{P(No PV|G = 1)P(G = 1|Data)}{P(No PV|G = 1)P(G = 1|Data) + P(No PV|G = 0)P(G = 0|Data)} \\ &= \frac{(1 - s)P(G = 1|Data)}{(1 - s)P(G = 1|Data) + P(G = 0|Data)} \end{aligned}$$

Where G is the true genotype (0 or 1, for non-carrier or carrier respectively) for the gene of interest and *Data* refers to all other data being considered (family history, risk factors etc). Alternatively stated, the odds of no pathogenic variant before testing $P(G = 1|Data)/P(G = 0|Data)$ is multiplied by $(1 - s)$. Naturally, when a pathogenic variant is detected, $P(G = 1|Data, PV) = 1$ and the sensitivity is irrelevant.

Current default sensitivities

The appropriate sensitivities clearly depend on what testing was done and the assumed frequencies of the different types of variants. The sensitivities (and allele frequencies) can be adjusted, but CanRisk sets some defaults. For the current version of the models⁷ implemented in CanRisk v.4.0, these were derived using the following broad assumptions:

- (i) The technical sensitivity is 1.
- (ii) Large rearrangements would be detected for *BRCA1* and *BRCA2* (on the assumption that an additional technology such as MLPA was used if necessary), but not the other genes.
- (iii) A proportion of missense variants in *BRCA1* and *BRCA2*, but not other genes, are pathogenic but not currently recorded as such (i.e. are reported as VUS).
- (iv) No other “cryptic” pathogenic variants exist (i.e. $c = 0$).

The details of how the relevant sensitivities have been calculated are given in Lee *et al*⁷. The key information for (iii) is the estimated proportion of pathogenic variants that are reported VUS. These were derived as described in Dorling *et al*.⁸ (Table 1). We note that although the technical sensitivity is assumed to be 1, the overall sensitivity is much lower; this can lead to situations, particularly

where the family history of cancer is extensive, in which the residual carrier probability is still high even after a negative test. This can lead to complications in the genetic counselling process.⁵

Revised proposal

A feature of the current scheme is that the incomplete sensitivity of *BRCA1* and *BRCA2* testing, in particular, is driven by VUS. This is because the current platform records tests as positive or negative, and VUS are considered to be negative tests. This is logically consistent but ignores information on whether a potentially pathogenic VUS was actually detected, information that is available to the clinician. In the majority of cases, potentially pathogenic VUS can be excluded. In this case, the appropriate observation is not “No PV” but “No PV or potentially pathogenic VUS”.

The carrier probability calculation in this case then takes the form:

$$\begin{aligned}
 P(G = 1|Data, NoVariant) &= \frac{P(NoVariant|G = 1)P(G = 1|NoVariant)}{P(NoVariant|G = 1)P(G = 1|Data) + P(NoVariant|G = 0)P(G = 0|Data)} \\
 &= \frac{(1 - (1 - c)s_T)P(G = 1|Data)}{(1 - (1 - c)s_T)P(G = 1|Data) + P(G = 0|Data)}
 \end{aligned}$$

Where “NoVariant” implies no PV and no potentially pathogenic VUS. Thus, the odds of being a carrier, in the situation in which no variant is detected, are multiplied by $(1 - (1 - c)s_T)$ rather than $1 - s = 1 - (1 - c)(1 - v)s_T$. The effective sensitivity is therefore $(1 - c)s_T$. This makes a considerable difference if the proportion of PVs that are VUS is substantial.

Following discussions with clinical geneticists in the UK Cancer Genetics Group, there was a consensus that it would be better to treat a negative test in CanRisk as implying no potentially pathogenic variant or potentially pathogenic VUS. This would more accurately reflect current clinical practice, in which patients with a negative test result are informed that the test did not identify any clinically actionable variants. It was also suggested to update the assumed default testing scheme has been updated to bring it into line with more usual practice, in which all genes are tested according to the same protocol. The revised assumptions are therefore:

- A single testing protocol for all genes, covering single nucleotide variants (SNVs), indels, and large rearrangements.
- technical sensitivity of 0.99 for SNVs and indels, and 0.95 for large rearrangements, for all genes.
- As before, there are no other cryptic variants.

The resulting effective sensitivities for each gene then depend on the proportion of PVs that are large rearrangements versus SNVs and indels. The proportion of PVs that are large rearrangements were determined as described in Dorling *et al.*⁸

The assumed technical sensitivities are clearly difficult to estimate with any precision and may vary according to the methodology⁹. There is general consensus that the technical sensitivity should be very close to 1 for SNVs and indels but lower for rearrangements (with insertions in particular known to be occasionally missed). We sought the views of the regional Genomics Laboratories in the UK. The 3 laboratories that responded all indicated a sensitivity of at least 99% for indels and 95% for large rearrangements, based on their own quality control assessment (for all genes in CanRisk except for *BARD1*, which is not on the current NHS Inherited Breast and Ovarian Cancer Panel R208). The

values 0.99 and 0.95 that we have assumed are therefore probably conservative (and hence may overestimate to the residual probability of carrying a PV, but the differences are likely to be very small).

The assumption of “no cryptic PVs” is impossible to evaluate directly since there is no gold standard for detecting them. For most genes, this issue is largely theoretical: the effects of any such undetected variants will be effectively absorbed into the unexplained polygenic component of breast, ovarian, prostate cancer susceptibility. In principle, cryptic variants in *BRCA1* and *BRCA2*, where the risks of breast and ovarian cancer are high, could affect the risk calculations. However, the frequency of such variants is presumably very low, given that PVs have historically been identified in the large majority of multiple case breast-ovarian cancer families¹⁰. Therefore, remaining cryptic variants can be regarded as absorbed within the large rearrangements that are missed by testing.

Results

The revised sensitivities are given in Table 1. As expected, these are markedly higher for all genes. The revised higher sensitivities can have a marked impact of the residual carrier probabilities, and corresponding cancer risks, in the context of a negative test (indicated as “Mut-absent” in the CanRisk tool). Consider for example the pedigree in Figure 1, of a 40-year woman with a family history of both breast and ovarian cancer. The estimated probability that this woman carries a PV in any of the 9 risk genes is ~20.5% (17.5% due to *BRCA1* and *BRCA2*) if she is untested. After a negative test for all genes, the residual PV carrier probability becomes ~6.5% using the current sensitivities but reduces to 0.34% with the new revised sensitivities (Table 2). Most of the reduction is due to the higher *BRCA1* and *BRCA2* sensitivity, though there is a marked reduction in the residual carrier probabilities for all other genes (due to implied testing for large rearrangements). There is a corresponding reduction in the cancer risk estimates, which is particularly marked for ovarian cancer: for example, the lifetime ovarian cancer risk is 8.6% with no testing, 3.1% with a negative test and the current sensitivities, and 0.3% with a negative test and the new sensitivities (Table 3).

Discussion

This updated scheme for defining testing sensitivities provides estimates that are more in line with current gene panel testing practice and based on the more usual interpretation of the term “negative test”. This can lead to a marked reduction in the predicted residual cancer risk for individuals who test negative. The revised sensitivities in Table 1 are now used as the default sensitivities in CanRisk (from version v.4.-1 onwards). Users still have the option to modify the assumed genetic testing sensitivities, either by entering custom values or by adjusting them according to the considerations described above, using the “Advanced Options” menu.

It is important to note, however, that this change comes with the caveat that a negative test implies not only that no PV was detected but also that *no suspicious VUS was present*. As a consequence of the revised sensitivities, CanRisk does not make any risk predictions in the case where a suspicious VUS that might be pathogenic is present. The CanRisk documentation has been updated to reflect this. CanRisk could be adapted to incorporate risk prediction in the context of VUS, but this will depend on knowledge of the probability that the variant is in fact pathogenic. We aim to incorporate this in a future CanRisk release.

Finally, note that the current model does not currently allow for variants which are risk associated but with lower risks – notably missense variants in *CHEK2*⁶ or atypical risk variants in *BRCA1* or *BRCA2* such as *BRCA1* c.5096G>A^{11,12} (or, similarly, for variants that have higher risks than typical PTVs, which may apply to a subset of variants in *ATM*¹³). We aim to update the models and the CanRisk platform to allow for such atypical risk variants.

Authors' contributions

DfE, JU-S, SA, MT and ACA conceived the research and obtained funding. TC and LF developed the CanRisk tool and incorporated the revised estimates. HH, KS, OT and MT provided information on the use of CanRisk and laboratory testing protocols. All authors read and approved the final manuscript.

Data availability

All estimates and results presented here are based on previously published results.

Competing interests

TC, LF, ACA and DfE are listed as creators of the BOADICEA model, which has been licensed by Cambridge Enterprise (University of Cambridge). MT is the Editor-in-Chief of *BJC Reports*; he was not involved in any aspect of the handling of this manuscript or any editorial decisions. The remaining authors declare no conflicts of interest.

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Table 1. Current and proposed new default gene testing sensitivities for CanRisk.

Gene	Assumed proportion of large rearrangements ¹	Assumed proportion of PVs that are VUS ²	Current Sensitivity (CanRisk v.4.0)	New Sensitivity (CanRisk v.4.1onwards)
<i>ATM</i>	0.06	-	0.94	0.99
<i>BARD1</i>	0.11	-	0.89	0.99
<i>BRCA1</i>	0.15	0.090	0.89	0.98
<i>BRCA2</i>	0.02	0.034	0.96	0.99
<i>BRIP1</i>	0.05	-	0.95	0.99
<i>CHEK2*</i>	0.16	-	0.98	0.99
<i>RAD51C</i>	0.22	-	0.78	0.98
<i>RAD51D</i>	0.14	-	0.86	0.98
<i>PALB2</i>	0.08	-	0.92	0.99

¹See Dorling *et al.*⁸

²Derived from Dorling *et al.*⁶

³For *CHEK2*, ~74% of carriers in Europeans carry the 1100delC variant⁸. The estimated proportion of large rearrangements among non-1100delC carriers is ~0.16, hence the overall proportion is ~0.04.

Table 2. Predicted carrier probabilities for the proband in the example pedigree in Figure 1.

Gene	Carrier probabilities		
	No testing	Proband tested negative	
		current sensitivities (CanRisk v.4.0)	new sensitivities (CanRisk v.4.1)
<i>BRCA1</i>	9.26%	2.31%	0.18%
<i>BRCA2</i>	8.23%	1.99%	0.11%
<i>PALB2</i>	0.40%	0.25%	0.01%
<i>CHEK2</i>	0.85%	0.73%	0.01%
<i>ATM</i>	0.38%	0.33%	0.01%
<i>BARD1</i>	0.09%	0.08%	0.00%
<i>RAD51D</i>	0.50%	0.29%	0.01%
<i>RAD51C</i>	0.55%	0.35%	0.01%
<i>BRIP1</i>	0.23%	0.19%	0.00%

Table 3. Predicted cancer risks for the proband in the pedigree in Figure 1.

	10-year breast cancer risk	Lifetime breast cancer risk	10-year ovarian cancer risk	Lifetime ovarian cancer risk
No testing	5.9%	24.1%	1.0%	8.6%
Proband negative (current -CanRisk v.4.0)	2.9%	16%	0.4%	3.1%
Proband negative (new – CanRisk v4.1)	2.6%	15.2%	0.1%	0.3%

Figure 1. Example pedigree (fictitious) of a woman (indicated with arrow) with a family history of breast and ovarian cancer, undergoing genetic testing. Circles indicate females, squares indicate males. Orange circle indicates a breast cancer case; dark green circle indicates an ovarian cancer case. For each individual, numbers before the y indicate age at death or current age. Years after the y indicate year of birth.

