Incorporating truncating variants in \textit{PALB2}, \textit{CHEK2}, and \textit{ATM} into the BOADICEA breast cancer risk model

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\textbf{Purpose:} The proliferation of gene panel testing precipitates the need for a breast cancer (BC) risk model that incorporates the effects of mutations in several genes and family history (FH). We extended the BOADICEA model to incorporate the effects of truncating variants in \textit{PALB2}, \textit{CHEK2}, and \textit{ATM}.

\textbf{Methods:} The BC incidence was modeled via the explicit effects of truncating variants in \textit{BRCA1/2, PALB2, CHEK2}, and \textit{ATM} and other unobserved genetic effects using segregation analysis methods.

\textbf{Results:} The predicted average BC risk by age 80 for an \textit{ATM} mutation carrier is 28\%, 30\% for \textit{CHEK2}, 50\% for \textit{PALB2}, and 74\% for \textit{BRCA1} and \textit{BRCA2}. However, the BC risks are predicted to increase with FH burden. In families with mutations, predicted risks for mutation-negative members depend on both FH and the specific mutation. The reduction in BC risk after negative predictive testing is greatest when a \textit{BRCA1} mutation is identified in the family, but for women whose relatives carry a \textit{CHEK2} or \textit{ATM} mutation, the risks decrease slightly.

\textbf{Conclusions:} The model may be a valuable tool for counseling women who have undergone gene panel testing for providing consistent risks and harmonizing their clinical management. A Web application can be used to obtain BC risks in clinical practice (http://ccge.medschl.cam.ac.uk/boadicea/).

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\section*{INTRODUCTION}

Breast cancer (BC) exhibits strong familial aggregation, such that the risk of the disease increases with increasing number of affected relatives. First-degree relatives of women diagnosed with BC are at approximately twice the risk of developing BC than women in the general population.\textsuperscript{1} Many BC-susceptibility variants have been identified to date. Approximately 15–20\% of this excess familial risk is explained by rare, high-penetrance mutations in \textit{BRCA1} and \textit{BRCA2}.\textsuperscript{2,3} Other rare, intermediate risk variants (e.g., \textit{PALB2, CHEK2}, and \textit{ATM}) are estimated to account for \textasciitilde5\% of the BC familial aggregation,\textsuperscript{4,6} and the common, low-risk alleles account for a further 14\% of familial risk.\textsuperscript{7,8}

To provide comprehensive genetic counseling for BC, it is important to have risk-prediction models that take into account the effects of all the known susceptibility variants and also account for the residual familial aggregation. Some existing genetic risk-prediction algorithms incorporate the effects of \textit{BRCA1} and \textit{BRCA2} mutations, including BRCAPRO,\textsuperscript{9} IBIS,\textsuperscript{10} and BOADICEA.\textsuperscript{2,11} BOADICEA accounts for the residual familial aggregation of BC in terms of a polygenic component that models the multiplicative effects of a large number of variants, with each making a small contribution to the familial risk.\textsuperscript{3}

Next-generation sequencing technologies that enable simultaneous sequencing of multiple genes through gene panels\textsuperscript{12,13} have now entered clinical practice. However, the clinical utility of results from such genetic testing remains limited because none of the currently available risk-prediction models incorporate the simultaneous effects of rare intermediate-risk variants and other risk factors, particularly explicit family history. As a result, providing risk estimates for women who carry these mutations, and their relatives, is problematic.\textsuperscript{6}

In this article, we describe an extension to the BOADICEA model to incorporate the effects of intermediate risk variants for BC, specifically loss-of-function mutations in the three genes for which the evidence for association is clearest and the risk estimates are most precise: \textit{PALB2, CHEK2}, and \textit{ATM}. The resulting model allows for consistent BC risk prediction in unaffected women on the basis of their genetic testing and their family history.

\section*{MATERIALS AND METHODS}

\textbf{BC incidence in BOADICEA}

We build on the existing BOADICEA model.\textsuperscript{2,3,11} Briefly, in this model the BC incidence, $\lambda_i(t)$, for individual $i$ at age $t$ is assumed
Rare variants in the BOADICEA breast cancer risk model | LEE et al

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### Table 1: Mutation frequency and relative risk for loss-of-function variants in PALB2, CHEK2, and ATM

| Allele frequency | PALB2 | CHEK2 | ATM |
|------------------|-------|-------|-----|
| 0.057 %          | 0.26% | 0.19 %|

The relative risk values for PALB2 are taken from ref. 20. The mutation frequency for PALB2 is taken from a private communication from Easton and Pharoah based on data from unaffected individuals from the United Kingdom. Relative risk values for CHEK2 and ATM are from ref. 6 and are not age specific. The allele frequency for CHEK2 is from ref. 28, and the allele frequency for ATM from ref. 29.

### Original Research Article

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carriers. A higher RR for familial BC for ATM carriers has also been found, although data are more limited.

**PALB2 characteristics**
Because of the small number of case–control studies for PALB2 or ATM, we used alternative family-based data. Age-dependent RRs of female BC for carriers of loss-of-function variants in PALB2 were taken from a large collaborative family-based study. With the exception of specific Nordic founder mutations, data on mutation frequencies in the general population are sparse. We assumed a mutation allele frequency of 0.057% based on data from targeted sequencing of 8,705 UK controls (unpublished data). This is close to the average estimate across published estimates.

**CHEK2 characteristics**
Most existing data pertain to the CHEK2 1100delC variant, which is the most common truncating variant in northern European populations. CHEK2 1100delC has been evaluated in many case–control studies. As a result, we based the CHEK2 estimates on the CHEK2 1100delC carrier estimates from a meta-analysis. We assumed that the allele frequency of the 1100delC mutations was 0.26%, which is the combined frequency across unselected population controls of European ancestry. There is some evidence that the RRs for BC in CHEK2 1100delC carriers decline with age. However, because age-specific estimates are currently imprecise, we used a single RR across all ages.

**ATM characteristics**
We obtained estimates for truncating mutations in ATM from a combined analysis of three estimates from cohort studies of relatives of ataxia-telangiectasia (A-T) patients. The great majority of A-T patients carry two truncating ATM mutations, and relatives of A-T patients are therefore known to have a high probability of being carriers of an ATM mutation. We assumed that the allele frequency of truncating variants in ATM was 0.19%, based on data from UK controls. As for CHEK2, there is some evidence of a decline in RR with age, but, lacking precise estimates, we used a single estimate across all ages.

**RRs for other cancers**
In addition to the risks of female BC, BOADICEA takes into account the associations of BRCA1 and BRCA2 mutations with the risks of male breast, ovarian, pancreatic, and prostate cancers. Several studies have investigated associations of the truncating variants in PALB2, ATM, and CHEK2 1100delC with the risks of these cancers (and others). However, none of the
studies provided convincing evidence of association for any of these cancers, and accurate penetrance estimates are currently lacking for those cancers that may have associations. Therefore, for the purpose of the current implementation, we assumed that these mutations are not associated with risks of other cancers.

Incorporating breast tumor pathology characteristics

Previous studies have described the incorporation into BOADICEA of differences in tumor pathology subtypes between BRCA1, BRCA2, and noncarrier BCs. Specifically, BOADICEA includes information on tumor estrogen receptor (ER) status, triple negative (estrogen-, progesterone-, and HER2-negative) (TN) status, and the expression of basal cytokeratin markers CK5/6 and CK14.

BCs in CHEK2 1100delC mutation carriers have been found to be ER-positive in a greater proportion compared with tumors in non-CHEK2 mutation carriers (88 vs. 78% in the general population). Reliable data pertaining to the TN and basal cytokeratin receptor status are not currently available. Therefore, in the current implementation, we only incorporated differences by BC ER status for CHEK2 1100delC carriers. Age-specific distributions were not available.

Published data on the prevalence of tumor subtypes in PALB2-associated BCs are sparse; although some differences from the general population have been reported, these are based on small numbers. Currently, there are no available data pertaining to tumor pathology subtype distributions for carriers of ATM truncating mutations. We therefore assumed that tumor subtype distributions for PALB2 and ATM mutation carriers are the same as those for the general population.

Mutation screening sensitivity

We have introduced separate mutation test screening sensitivities for PALB2, CHEK2, and ATM to allow for the fact that some risk-conferring variants in these genes may be missed by current methods. In the BOADICEA Web Application (BWA), we assumed default values of 90% for PALB2 and ATM truncating variants and of 100% for the CHEK2 1100delC variant. However, these values can be customized by users. The specificity of mutation testing was assumed to be 100%.

RESULTS

Figure 1a and Supplementary Figure S1 shows the implied average cumulative BC risks predicted by BOADICEA by mutation status on the basis of the assumed RRs for an unaffected female 20 years of age. The predicted average breast risk by age 80 years was 28.2% for an ATM mutation carrier, 29.9% for CHEK2, 50.1% for PALB2, 73.5% for BRCA1, and 73.8% for BRCA2.

Table 2. The variance explained by PALB2, CHEK2, and ATM and the percentage of the overall polygenic variance explained by all three combined

| Age  | PALB2 variance | CHEK2 variance | ATM variance | Total polygenic variance (%) |
|------|---------------|----------------|--------------|------------------------------|
| 25   | 0.0691        | 0.0201         | 0.0121       | 3.04                         |
| 30   | 0.0668        | 0.0201         | 0.0121       | 3.26                         |
| 35   | 0.0611        | 0.0201         | 0.0121       | 3.40                         |
| 40   | 0.0519        | 0.0199         | 0.0112       | 3.43                         |
| 45   | 0.0403        | 0.0197         | 0.0119       | 3.35                         |
| 50   | 0.0294        | 0.0193         | 0.0116       | 3.26                         |
| 55   | 0.0216        | 0.0188         | 0.0114       | 3.34                         |
| 60   | 0.0165        | 0.0182         | 0.0111       | 3.66                         |
| 65   | 0.013         | 0.0176         | 0.0108       | 4.34                         |
| 70   | 0.0105        | 0.017          | 0.0104       | 5.77                         |
| 75   | 0.0085        | 0.0164         | 0.0101       | 9.77                         |

Figure 2 shows the mutation carrier probabilities predicted by BOADICEA for a female with unknown family history as a function of her age at cancer diagnosis, and for a 30-year-old female diagnosed with BC (whose mother has had BC) as a function of her mother’s age at diagnosis (also shown in Supplementary Tables S1 and S2 online). The mutation carrier probabilities for ATM and CHEK2 did not show a marked change with age at diagnosis (reflecting the assumption of a constant RR), but the mutation carrier probabilities for PALB2 decreased with age, although less markedly than for BRCA1/2. The mutation carrier probabilities were higher for women with a family history, but the effect was more marked for BRCA1/2 and PALB2 than for CHEK2 or ATM.

Predicted cancer risks for mutation carriers are family history–specific

In our model, the residual polygenic component was assumed to act multiplicatively with PALB2, CHEK2, and ATM mutations on BC risk. As a result, the risks for mutation carriers will vary by family history. Figure 1 shows the predicted cumulative BC risk for a 20-year-old woman by her mutation status. In (a), the woman is assumed to have unknown family history. In (b), the woman is assumed to have a mother affected with BC at age 40. In (c), the woman has a mother and sister who are cancer-free at ages 70 years and 50 years, respectively. These clearly show that predicted BC risks increased with an increasing number of affected relatives and depend on the phenotypes of unaffected family members. For example, although the average BC risks by age 80 years for CHEK2 and ATM mutation carriers were lower than 30% (a common criterion for “high” risk, e.g., the NICE guideline), the BC risk exceeded this threshold when a mutation carrier had a family history of BC (e.g., 42.6% for ATM and 44.7% for CHEK2 with an affected mother).
Comparing Figure 1a and 1c, we see that the risk for a woman with no history of BC is lower than the average BC risk.

The effect of negative predictive testing

The extended BOADICEA model can also be used to predict risks in families in which mutations are identified but other family members test negative. This is demonstrated for a number of family history scenarios in Figure 3, which depend on the mutation status of the proband and her mother. The predicted risks for mutation-negative family members depend on both the family history and the specific mutation identified. Thus, for families with a history of BC, namely, Figure 3c, e, and g, the reduction in BC risk after negative predictive testing is greatest when a BRCA1 mutation was identified in the family, with the risks being close to (although still somewhat greater than) the population risk. This effect was most noticeable for women with a strong family history. The reduction for women whose mother carried a BRCA2 or PALB2 mutation is less marked, whereas for women whose mother carried a CHEK2 or an ATM mutation, the risks decreased only slightly with a negative predictive test, even with a strong family history. For a woman with no history (Figure 3a), her risk based on the family history alone (i.e., in an untested family) was slightly lower than that of the population risk. After negative predictive testing, her predicted risk decreased further. The biggest decrease was observed when a BRCA1 mutation was identified in the mother.

Updates to the BWA

We have now updated the BWA (http://cge.medschl.cam.ac.uk/boadicea/) to accommodate these extensions to the BOADICEA model. The BWA enables users to either build a pedigree online or upload pedigrees. When users build an input pedigree online, the program now enables users to specify PALB2, CHEK2, and ATM genetic test results. Similarly, we have extended the BOADICEA import/export format (described in Appendix A of the BWA v4 user guide: https://pluto.srl.cam.ac.uk/bd4/v4/docs/BWA_v4_user_guide.pdf) so that users can include this information in their files.

DISCUSSION

Cost-effective sequencing technologies have brought multi-gene panel testing into mainstream clinical care.6,13,35 Although several established BC-susceptibility genes are included in these panels, their clinical utility is limited by the lack of risk-prediction models that consider the effects of mutations in these genes and other risk factors, particularly family history. Here, we present an extended BOADICEA model that incorporates the effects of rare protein truncating variants in PALB2, CHEK2, and ATM. This is the first BC risk model to include the explicit effects of susceptibility genes other than BRCA1 and BRCA2, and it can be used to provide comprehensive risk counseling on the basis of family history and mutation screening of the five genes. The model can also be used to predict risks of developing BC and the likelihood of carrying truncating mutations in any of the five genes.

The extended BOADICEA model is based on a number of assumptions. To ensure that the model is computationally efficient, we used a single “major” locus with six alleles representing the truncating variants in the five genes and a wild-type allele. In comparison with a model consisting of five separate loci each with two alleles, this should be a reasonable approximation because all the variants are rare. However, it is possible that the effects will be greater in families segregating more than one rare variant. It also represents a substantial reduction in the number of genotypes (36 vs. 1024), and in execution time; we measured execution time and found it was reduced by a factor of 21,000. These simplifications will become more critical as the number of susceptibility genes included in the model increases. A previous study identified six other genes for which the association with BC was well established (TP53, PTEN, STK11, CDH1, NF1, and NBN), and this list is likely to increase with time.
Figure 3  BOADICEA breast cancer (BC) risk for negative testing by family history. The predicted risk of BC by her mother’s mutation status and for different family histories for a 20-year-old woman in the United Kingdom born in 1975. The predicted risk is shown for four different family histories. The graphs (b), (d), (f) and (h) correspond to risks for the pedigrees (a), (c), (e) and (g), respectively. The figures show the predicted risks for a proband (arrow) in families without any mutation testing in the five genes, i.e., this corresponds to the predicted risk on the basis of family history information alone (black curves). The rest of the curves correspond to the cases where the proband is assumed to be negative for the mutation identified in the family. To enable direct comparisons, the proband is assumed to be 20 years old in all examples.
Without robust data on risks to carriers of two or more truncating variants (in different genes), we assumed that dual mutation carriers develop BC according to incidences for the higher penetrance gene. Recent evidence suggests that gene–gene interaction between CHEK2, ATM, BRCA1, and BRCA2 may not be multiplicative (indeed, a multiplicative model would be implausible for BRCA1 and BRCA2 because it would predict an extremely high risk at very young ages). This may reflect the biological relationships between the proteins encoded by the genes. The proteins encoded by all five genes play roles in DNA repair, and loss-of-function mutations in these genes are predicted to impair DNA repair. Our implementation would be consistent with a model in which if the pathway is disrupted by one mutation, then further disruption by a lower penetrance mutation would not increase risk.

Although there is strong evidence that mutations in PALB2, CHEK2, and ATM confer increased risk of BC in females, there are currently no precise risk estimates for the other cancers considered by BOADICEA (male breast, ovarian, pancreatic, or prostate) or other cancers. However, several studies have provided tentative evidence of associations. Because of the lack of precise cancer risk estimates, we have assumed no association between truncating variants in PALB2, CHEK2, and ATM (i.e., RR = 1). If there are true associations between the PALB2, CHEK2, and ATM truncating variants and other cancer risks, then we expect that PALB2, CHEK2, and ATM mutation carrier probabilities may potentially be underestimated in families where other cancers occur. However, if accurate risk estimates become available, then they can easily be included in our implementation.

BOADICEA allows cancer tumor characteristics to be taken into account, as we have done previously for BRCA1 and BRCA2 (refs. 2,11,36). The provision of subtype-specific risks can be useful for genetic counseling and may guide chemoprevention. However, data on the additional genes are currently sparse. In this model, we incorporated a higher probability of ER-positive tumors in CHEK2 1100delC carriers relative to noncarriers. Some studies have suggested differences in the tumor characteristics from PALB2 mutation carriers and noncarriers, but larger studies are required to establish such differences.

We considered only the effects of truncating variants in PALB2, ATM, and the CHEK2 1100delC variant, for which robust BC risk estimates are available. In doing this, we are making the usual simplification that all truncating variants in these genes confer similar risks. Although there is no evidence to contradict this, it may change as further data accumulate. Also, there is evidence that missense variants in CHEK2 and ATM confer elevated BC risks, but that the risks that they confer can differ from the risks associated with truncating variants. For example, the ATM c.7271T>G missense variant has been reported to confer a higher risk than truncating variants, but the confidence intervals associated with this estimate are currently wide. It has been suggested that other rare, evolutionarily unlikely missense variants in ATM are also associated with increased BC risks. Future extensions of BOADICEA can accommodate such differences on the basis of more precise cancer risk estimates. In CHEK2, the missense variant Ile157Thr has been associated with a lower risk than the 1100delC variant. This variant has been incorporated into a polygenic risk score on the basis of common genetic variants, which we expect to incorporate into BOADICEA in the future. The model could also be applicable for other truncating variants in CHEK2, under the assumption that they confer risks similar to those of the 1100delC variant. However, the available data are scarce and some modification of the mutation frequencies may be required.

Under the BOADICEA model, women testing negative for known familial mutations (true negatives) and who have family history are predicted to be at higher risk for BC than the general population. The level of risk depends on both family history and the specific mutation identified. So far, epidemiological studies have reported estimates for “true negatives” only for families with BRCA1 and BRCA2 mutations, but the estimated RRs (compared with the population risks) vary widely. Moreover, all the reported estimates are associated with wide confidence intervals because the studies have been based on small sample sizes. The reported estimates are summarized in Table S3. To provide a direct comparison with the predicted risks by BOADICEA, we have included the implied RRs for the true negative women in Figure 3 relative to the population. These are all in line with the published estimates for true negatives. Therefore, the predictions by BOADICEA are consistent with published data. It is worth noting that if the true RRs for the true negatives in families with BRCA1 and BRCA2 mutations are in line with those predicted by BOADICEA, then very large prospective studies of true negatives would be necessary to demonstrate significant associations.

The current model is a synthetic model based on segregation analyses of families in the United Kingdom together with risk estimates derived from studies of European populations. We have previously implemented procedures for extrapolating the model to populations with different baseline incidence rates based on the assumption that the RRs conferred by the genetic variants in the model are independent of the population. Thus, the model should be broadly applicable to developed populations of European ancestry, but its applicability to populations with lower incidence rates and populations of non-European ancestry has yet to be evaluated. The implementation also allows the allele frequencies to be adjusted. This may be particularly relevant for CHEK2; in European populations, the founder 1100delC variant accounts for the majority of carriers of truncating variants and its frequency varies across populations.

The extended BOADICEA model presented here has addressed a major gap in BC risk prediction by including the effects of truncating variants in PALB2, CHEK2, and ATM that are included in widely used commercial gene panels. The model could be a valuable tool in the counseling process of women who have undergone gene panel testing, because it provides consistent BC risks and thus harmonizes the clinical
management of at-risk individuals. Future studies should aim to validate this model in large prospective cohorts with mutation screening information and to evaluate the impact of the risk predictions on decision making.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

The authors declare no conflicts of interest.

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