Received: 22 February 2022 | Revised: 27 April 2022 | Accepted: 1 May 2022

DOI: 10.1111/cge.14147

ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

Genetic clinicians' confidence in BOADICEA comprehensive breast cancer risk estimates and counselees' psychosocial outcomes: A prospective study

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Funding information
European Union Horizon 2020 research and innovation programme, Grant/Award Number: 634935

Abstract

Counseling for familial breast cancer focuses on communicating the gene test result (GENE) to counselees, but risk prediction models have become more complex by including non-genetic risk factors (NGRF) and polygenic risk scores (PRS). We examined genetic clinicians' confidence in counseling and counselees' psychosocial outcomes, using the BOADICEA risk prediction tool with different categories of risk factors as input. A prospective observational study in Dutch, French and German genetic clinics was performed including 22 clinicians, and 406 of 460 (88.3%) eligible cancer-unaffected women at high breast cancer risk assessed at pre-test and 350 (76.1%) at post-test. We performed multilevel analyses accounting for the clinician, and counselees' characteristics. Overall, risk estimates category by GENE versus GENE+ NGRF, or GENE+NGRF+PRS differed in 11% and 25% of counselees, respectively. In multilevel analyses, clinicians felt less confident in counseling when

the full model provided lower breast cancer risks than GENE (i.e., in 8% of cases). Older counselees expressed higher breast cancer risk perception and worries about the hereditary predisposition when the full model provided higher breast cancer risks than GENE only. Genetic clinicians appear confident with breast cancer risk comprehensive models, which seem only to affect perceptions of older counselees.

KEYWORDS

BOADICEA, breast cancer risk estimates, genetic-specific psychosocial difficulties, risk communication, self-confidence

1 | INTRODUCTION

Breast cancer is the most common cancer and cause of cancer death for women worldwide.[1] Major breast cancer risk factors are familial cancer history and presence of a genetic susceptibility.[2] Carriers of a pathogenic variant in *BRCA1*, *BRCA2*, and *PALB2*, or in *ATM*, *BARD1*, *CHEK2*, *RAD51C*, and *RAD51D* have a high- or moderate-risk of developing breast cancer, respectively.[3] National guidelines provide advice for secondary prevention by breast cancer screening, and primary prevention with risk-reducing surgery or medication based on breast cancer lifetime risk and presence of a pathogenic variant in one of the breast cancer genes.[4–6]

Recently, additional genetic and non-genetic risk factors (NGRF) have been incorporated in breast cancer risk prediction models.[7] The additional genetic factors include common low risk variants associated with breast cancer, as summarized in a polygenic risk score (PRS).[8] NGRF include individuals' hormonal, reproductive and lifestyle factors.[9] These models allow for more personalized clinical advice such as the optimal age range, frequency, and modality of screening (i.e., ultrasound, mammography, and/or magnetic resonance imaging).

One of the most comprehensive risk prediction models is the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA version 5) which incorporates the effects of truncating variants in *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *ATM*, a PRS based on 313 variants, pedigree-based family history, mammographic density and known NGRF.[10] BOADICEA version 5 improves the predictive performance of breast cancer risk estimations,[7,10,11] and is incorporated in a user-friendly web-based application (CanRisk.org) to operationalize BOADICEA for clinical use.[12]

In an international survey, genetic clinicians who considered hormonal breast cancer risk factors as important, judged the previous BOADICEA version 3[13] of lower clinical utility.[14] Moreover, those who communicated numerical risk more frequently than others were also concerned about communicating estimates of BOADICEA version 3 to counselees. BOADICEA version 5[10] would in principle better respond to their expectations and result in more confidence in communicating breast cancer risk and clinical recommendations. However, a feasibility study of a CanRisk prototype among clinicians highlighted apprehension of applying the CanRisk tool in genetic consultations and of its impact on counselees.[15]

Integration of NGRF and the PRS into breast cancer risk assessment can result in an increased or decreased estimate compared with the estimate accounting for family history and the gene test result only[11,16] and communicating these risks may be even more complex and challenging for clinicians.[17] This may affect clinicians' confidence and communication with counselees, and pose a challenge for established risk communication procedures. However, it seems that after in-depth communication on the PRS during consultation, counselees' perceptions align with the level of PRS identified: compared with women at high breast cancer risk who were communicated a low PRS, those with a high PRS reported greater perceived risk.[18]

To provide insight into needs for communication improvement, we examined genetic clinicians' confidence in counseling (i.e., communication of breast cancer risk estimates and clinical recommendations) in relation to change (i.e., lower or higher vs. same) in risk estimates category by BOADICEA calculation. BOADICEA estimates were calculated using either the family history (FH) and the gene test result (henceforth termed BASIC) or FH + GENE + NGRF (henceforth termed FGN), or FH + GENE + NGRF + PRS (henceforth termed FULL).

Counselees' perceptions of breast cancer risk and genetic-psychosocial difficulties after testing might be affected by clinicians' communication and cancer risk perception be correlated to counselees' distress.[19] Therefore, we also assessed the relationship between change in BOADICEA estimates by different calculations (i.e., BASIC vs. FGN or FULL) and counselees' perceptions of breast cancer risk and genetic-psychosocial difficulties after testing.

As standard practice of clinical recommendations after breast cancer genetic testing is based on age, family history and the genetic test result, we also explored whether these relationships between change in BOADICEA estimates category and clinicians' or counselees' outcomes were different according to counselees' age and genetic test result received.

2 | METHODS

2.1 | Study design

This prospective observational study was undertaken within the "Breast Cancer Risk after Diagnostic Gene Sequencing" (BRIDGES) consortium (https://bridges-research.eu). Figure 1 indicates the assessment time points and main inclusion criteria by country setting.

The protocol was approved in France by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS: Consultative committee for information

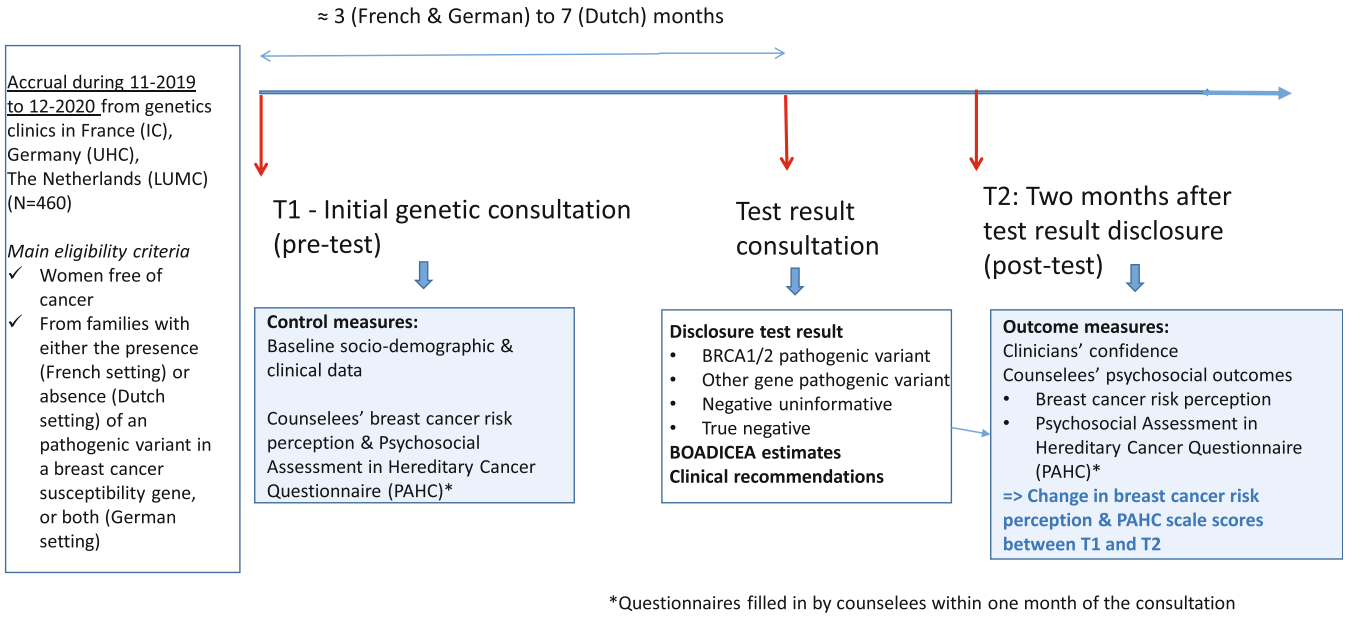

FIGURE 1 Design of the prospective cohort study [Colour figure can be viewed at wileyonlinelibrary.com]

management in health research—N° 16.314) and the Comité de Protection des Personnes Ile-de-France V (CPP—N° 18.12.28.38743 CAT2), in Germany by the Ethics Committee of the University Hospital of Cologne (N° 16-098) and in The Netherlands by the Medical Ethics Committee of the Leiden University Medical Centre (N° P19.010; NL68501.058,18).

2.2 | Study participants

All clinicians dedicated to genetic testing result disclosure in the genetic clinics of Curie Institute (France), University Hospital of Cologne (Germany) and Leiden University Medical Centre (The Netherlands) participated in the study (see Table S1 for details on demographic and professional characteristics).

From November 2019 to December 2020, women free of cancer, aged 18 years, or above were consecutively approached on the day of the initial (pre-test) visit in the French and German centers or, through a document accompanying the letter given to the index case and addressed to family members in the Dutch sample.

In the French center, women were recruited if a pathogenic variant in *BRCA1*, *BRCA2* or *PALB2* had been already identified in the family. They were invited to undergo predictive testing targeted on the pathogenic variant identified in the family. The Dutch cohort comprised first-degree female relatives of women affected with breast cancer who tested negative for a pathogenic variant in *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, or *PALB2*. The German cohort included women from families where a pathogenic variant had or had not been identified.

In the context of BRIDGES research, all women underwent testing with a multigene panel including *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *ATM*, *RAD51C*, *RAD51D*, *BRIP1* (TruRisk® v3.1.1).[20]

Women diagnosed with a breast cancer or any other cancer, or a major psychiatric disorder were not included.

Counselees who agreed to participate were invited to complete the study questionnaires at home (online or on paper) within 2 weeks after the pre-test consultation (French and German setting) or after providing informed consent for the Hereditary Breast and Ovarian cancer study Netherlands (HEBON) (Dutch setting) (T1) and again within 2 months after the post-test consultation (T2). When necessary, one reminder call was made to counselees. Questionnaires not completed within 1 month afterwards were considered missing.

Clinicians completed questionnaires within 1 week after test result disclosure.

2.3 | Breast cancer genetic testing and counseling

Breast cancer genetic testing and counseling were based on national guidelines.[4–6] Pre-test and post-test face-to-face consultations were provided in the French and German settings, and a post-test web-consultation in the Dutch setting. The test result disclosure consultation was provided by one of 9, 11, and 2 dedicated genetic clinicians in the French, German, and Dutch setting, respectively.

Predictive breast cancer risks were estimated using BOADICEA version 5[10] integrated in the CanRisk application.[15] Three calculations of breast cancer lifetime risk estimates were performed: one, termed BASIC, including birth year, family history, and the result of the gene panel test (1); a second adding to BASIC the NGRF (i.e., age at menarche, age of menopause, number of children, age of first live birth, oral contraception, hormone replacement therapy, body mass index, alcohol, height), and termed FGN (2), and a third incorporating FGN and the PRS, termed FULL (3). With BOADICEA FGN or FULL, breast

cancer risk classification could remain the same, or shift to a lower or a higher category.

In the three country settings, risk was discussed among the clinical team and was communicated to counselees with clinical recommendations based on team formal conclusions. Regardless of the genetic test result, risk from BOADICEA FULL was communicated in addition to risk from BOADICEA BASIC, although in the French setting only when the FULL model provided higher risk estimates. Risk from BOADICEA FNG was not communicated.

In the French setting, a lifetime breast cancer risk was mainly communicated in words with percentages above 30% considered high, between 20% and 30%, moderate, or below 20%, similar to the general population. In the German setting, a 10-year breast cancer risk was only communicated and in the Dutch setting both a lifetime and a 10-year risk were provided.

Clinical management recommendations were based on the woman's age, her multigene panel test result (i.e., presence of a pathogenic variant or, uninformative or true negative, depending on the absence or presence of the pathogenic variant identified in the family, respectively), estimates from BOADICEA, and clinical guidelines of the specific country. Due to the research setting, the woman received the clinical recommendation based on BOADICEA BASIC estimates if BOADICEA FULL provided a lower risk estimate than the BASIC version, representing the current standard procedure (Table S2 details the specific clinical recommendations by level of breast cancer risk estimates and genetic test result in the three country settings).

2.4 | Questionnaires and data collection

Sociodemographic and clinical data were collected from counselees or medical records.

Outcome variables were assessed with the following questionnaires.

Genetic clinicians' confidence in counseling was assessed at T2 using a study-specific three-item questionnaire addressing confidence in: (1) estimating breast cancer risk, (2) communicating breast cancer risk, and (3) communicating clinical recommendation for breast cancer risk, on an eight-point scale from 0 (not confident at all) to 7 (very confident). As internal consistency (Cronbach's alpha) for the three items was 0.94, a single variable was created. As this variable was not normally distributed, for multivariate analyses, a Box-Cox transformation was applied, leading to scores ranging from −0.5 to 24.0, with a high score corresponding to a high level of confidence.

Counselees' perceived lifetime risks of breast cancer were assessed in words and in figures each by one item. As responses to these items were highly correlated ($r = 0.82$), a single variable was created and an average standardized score was derived, with scores ranging from −2.11 to 1.97. Breast cancer risk perception was not collected in the Dutch sample.

Counselees' genetic-specific psychosocial difficulties were assessed using the 26-item "Psychosocial Aspects of Hereditary Cancer" (PAHC) questionnaire originally developed in Dutch[21] and cross-culturally validated in French and German.[22] To allow comparisons between country samples, the original six scales validated in Dutch were used. These address difficulties related to the hereditary predisposition, practical issues, familial issues, emotions, living with cancer and children-related issues. Cronbach's alphas were acceptable, close to 0.70 at T1 and T2, except for the PAHC "Practical issues" scale which was then omitted for multivariate analyses. PAHC scale scores range from 0 to 100 with a higher score corresponding to a higher difficulties.

As shown in Figure 1, counselees' questionnaires were completed at both T1 and T2 (Table S3 provides questionnaires' descriptive scores and internal consistencies).

2.5 | Statistical analyses

The effect of a change (i.e., lower or higher vs. same risk category) in BOADICEA estimates when comparing the BASIC with the FGN (1) or FULL (2) BOADICEA versions was tested on the following outcome variables, using multivariate mixed linear models: (1) clinicians' confidence in counseling, (2) counselees' perceptions of lifetime breast cancer risk, and (3) genetic-specific psychosocial difficulty (five PAHC scales).

For testing for effects of change in estimates by BOADICEA model (FULL or FGN vs. BASIC) on genetic clinicians' confidence, covariates in the null model comprised the intercept, random effect of clinicians on the intercept, counselees' education level and whether a pathogenic variant had been identified in the family.

For testing these effects on counselees' perceptions of breast cancer risk and psychosocial difficulties at T2, covariates in the null model comprised the intercept, the random effect of clinicians on the intercept, counselees' education level, whether a pathogenic variant had been identified in the family, the psychosocial outcome score at T1, and time lapse between T1 and T2.

First, we considered the best explanatory statistical model based on the Bayesian Information Criterion (BIC). The null model was compared with: (1) a model comprising the effect of change in BOADICEA estimates, (2) a model adding the effect of age (or the genetic test result), and (3) a model adding the interaction between age (or the genetic test result) and change in BOADICEA estimates.

We also considered the likelihood ratio test (LRT) statistically significant at p-values < 0.05 of each effect tested, that is, the change in breast cancer risk estimates by BOADICEA version, age or the gene test result, and their interaction with change in breast cancer risk estimates by BOADICEA version.

Whereas the BIC indicates which among several statistical models with parsimonious number of tested effects best predicts an outcome, the LRT specifies whether an additional variable has a significant effect at a certain level of significance.

Beta coefficients derived from statistical models were used to calculate means and 95% confidence interval (CI) for each outcome variable.

The effect of inter-clinicians' variability on outcomes was assessed by intra-class correlation coefficients (ICC).

TABLE 1 Counselees' sociodemographic and clinical characteristics ($N = 460$)

Country samples	Sample 1—FR ($N = 200$)	Sample 2—GE ($N = 222$)	Sample 3—NL ($N = 38$)
Age (years) Mean (*SD*)**	39.3 (13.3)[a]	41.0 (9.9)	45.4 (7.8)
Median (range)	36 (21–80)	41 (21–71)	46 (35–59)
Having children Yes *n* (%)***	97 (48.5)	140 (63.1)	29 (76.3)
Respondent counselees at T1 ($N = 403$)	**$N = 163$**	**$N = 206$**	**$N = 37$**
Education level n (%)***			
Compulsory education or below	4 (2.5)	8 (3.9)	1 (2.7)
Secondary or technical/vocational education	37 (23.1)	117 (56.8)	15 (40.5)
Higher education or above	119 (74.4)	81 (39.3)	21 (56.8)
Marital status *n* (%)*			
Married/partnered	97 (59.9)	146 (70.9)	-
Others (widowed, separated/divorced, single/never married)	65 (40.1)	60 (29.1)	-
Respondent counselees at T1 and T2	**Sample 1—FR ($N = 118$)**	**Sample 2—GE ($N = 199$)**	**Sample 3—NE ($N = 33$)**
Pathogenic variant identified in the family *n* (%) ***	118 (100)	47 (23.6)	0 (0)
Time lapse between pre- and post-test consultations (days)***			
Mean (*SD*)	108.0 (17.0)	96.7 (33.3)	219.8 (50.8)
Median (range)	106.0 (84–199)	90.0 (37–238)	228.0 (117–359)
Genetic test result *n* (%) ***			
Number of counselees with a pathogenic variant	33 (28.0)	31 (15.6)	-
Number of counselees with an uninformative result (families with no pathogenic variant identified)	-	143 (71.9)	33 (100)
Number of counselees with a negative result (families with pathogenic variant identified)	85 (72.0)	25 (12.6)	-
BOADICEA Lifetime risk—BASIC			
Mean (*SD*)	27.6 (27.0)	23.4 (17.7)	20.7 (4.4)
Median (range)	13.9 (3.0–86.5)	18.6 (4.4–94.0)	21.5 (13.3–32.3)
BOADICEA Lifetime risk—BASIC with NGRF			
Mean (*SD*)	27.7 (26.8)	22.5 (17.9)	21.0 (5.5)
Median (range)	14.5 (2.1–87.4)	18.0 (3.0–96.1)	21.7 (10.9–35.0)
BOADICEA Lifetime risk—FULL (BASIC with NGRF and PRS)			
Mean (*SD*)*	28.6 (27.5)	23.4 (18.5)	20.0 (7.7)
Median (range)	16.5 (2.4–91.2)	19.5 (2.0–98.6)	18.8 (8.6–37.7)

Note: Missing data on counselees' self-reported data: 0 (Sample 2 and 3), 1 to 3 (Sample 1).
Abbreviations: FR, France; GE, Germany; NGRF, Non-genetic risk factors; NL, Netherlands; PRS, polygenic risk score; T1, within 1 month after the pre-test consultation; T2, within 3 months after the post-test consultation.
[a]$p < 0.05$ for respondents versus non-respondents. Respondents in sample 1 are older than non-respondents at T1 (mean age = 40.4 compared with 34.5). No other difference between respondents and non-respondents at T1 and, at T1 and T2.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for differences between country samples.

Statistical analyses were performed with R software (R Core Team, 2020).

3 | RESULTS

Among 460 counselees consecutively approached, 163 and 118 (81.5% and 59%) in France, 206 and 199 (92.8% and 89.6%) in Germany, 37 and 33 (97.4% and 86.8%) in The Netherlands completed questionnaires at pre- (T1) and post-test (T2) (Table 1). Eligible counselees and non-participants at T1 and T2 did not significantly differ by age, having children or the test result, except that in the French sample at T1, respondents were slightly older compared with non-respondents.

Overall, a pathogenic variant (mostly *BRCA1* or *BRCA2*), an uninformative or a true negative result (i.e., absence of the pathogenic

TABLE 2 Number (%) of counselees by differences in estimates according to BOADICEA model version, genetic test result and country sample ($N = 350$)

BOADICEA BASIC with NGRF compared with BOADICEA BASIC	Same risk	Lower risk	Higher risk
Sample 1—FR	112 (94.9)	1 (0.8)	5 (4.2)
Pathogenic variant (33)	32 (97.0)	1 (3.0)	0 (0)
Uninformative result (0)	-	-	-
Negative result (85)	80 (94.1)	0 (0)	5 (5.9)
Sample 2—GE	172 (86.4)	14 (7.0)	13 (6.5)
Pathogenic variant (31)	28 (90.3)	2 (6.5)	1 (3.2)
Uninformative result (143)	120 (83.9)	12 (8.4)	11 (7.7)
Negative result (25)	24 (96.0)	0 (0)	1 (4.0)
Sample 3—NL	26 (78.8)	4 (12.1)	3 (9.1)
Pathogenic variant (0)	0 (0)	0 (0)	0 (0)
Uninformative result (33)	26 (78.8)	4 (12.1)	3 (9.1)
Negative result (0)	-	-	-
BOADICEA FULL (BASIC with NGRF and PRS) compared with BOADICEA BASIC	**Same risk**	**Lower risk**	**Higher risk**
Sample 1—FR	102 (86.4)	2 (1.7)	14 (11.9)
Pathogenic variant (33)	32 (97)	1 (3)	0 (0)
Uninformative result (0)	-	-	-
Negative result (85)	70 (82.4)	1 (1.2)	14 (16.5)
Sample 2—GE	141 (71.6)	16 (8.1)	40 (20.3)
Pathogenic variant (31)	26 (86.7)	3 (10)	1 (3.3)
Uninformative result (143)	95 (66.9)	11 (7.7)	36 (25.4)
Negative result (25)	20 (80)	2 (8)	3 (12)
Sample 3—NL	18 (54.5)	9 (27.3)	6 (18.2)
Pathogenic variant (0)	0 (0)	0 (0)	0 (0)
Uninformative result (33)	18 (54.5)	9 (27.3)	6 (18.2)
Negative result (0)	-	-	-

Note: Entries are number (%). - = non-applicable. BOADICEA lifetime breast cancer risk thresholds: low = <20%; moderate = 20%–30%; high= > 30%. Same, lower, higher when counselee changes categories according to BOADICEA version lifetime risk estimates. In GE sample, two missing data correspond to women from non-European descent for whom the PRS was not computed.

variant identified in the family) was disclosed to 64 (18.3%), 176 (50.3%), and 110 (31.4%) respondents, respectively. Details of the multigene panel test results of counselees' respondents are provided in Table S4.

Depending on country, BOADICEA lifetime breast cancer risk mean estimates by BASIC, FGN and FULL version ranged from 20.7 to 27.6, 21.0 to 27.7, and 20.0 to 28.6, respectively (Table 1).

Among counselees, breast cancer lifetime risk categories were similar between BOADICEA BASIC and FGN versions for 78.8% to 94.9% of them and BOADICEA BASIC and FULL versions for 54.5% to 86.4% of them (Table 2).

A change from standard breast cancer risk clinical recommendation after estimating breast cancer risk with BOADICEA FULL compared with BASIC version was reported by clinicians in 20.0%, 20.2%, and 12.1% of counselees in the French, German and Dutch settings, respectively (Table S5).

3.1 | Effect of change in breast cancer risk estimates by BOADICEA version on genetic clinicians' confidence in counseling

All 22 clinicians dedicated to counseling after breast cancer genetic testing across clinics participated in the study. Overall mean (*SD*) level of confidence was high across settings, ranging from 17.0 (1.24) to 21.3 (4.06) on the −0.5 to 24.0 scale range of Box-Cox transformed variable (Table S5).

Of the various statistical models that were fitted with genetic clinicians' confidence as an outcome, the null model (i.e., including counselees' education level and whether a pathogenic variant had been identified in the family) had the lowest BIC, indicating that the addition of effect variables did not further explain observed data.

Based on the LRT, a change in risk estimates between BOADICEA BASIC and FULL versions was significantly associated with genetic

TABLE 3 Clinicians' confidence predicted means (95% confidence interval) according to differences in estimates between the BOADICEA BASIC and BOADICEA FULL (incorporating NGRF and PRS) in multivariate mixed linear model

	Clinicians confidence in counseling	
	Predictors' B and 95% CI	**Predicted mean and 95% CI**
BAODICEA FULL (BASIC with NGRF and PRS) versus BOADICEA BASIC		
Same risk	REF	19.6 (18.2–21.1)
Lower risk	−2.52 (−4.24–−0.81)**	17.1 (15.0–19.2)
Higher risk	−0.38 (−1.47–0.71)	19.2 (17.5–20.9)

Note: Clinicians' confidence overall score distribution presented a ceiling effect so a Box-Cox transformation was applied, leading to an overall score range = −0.5–24.0. The null statistical model with the intercept, random effect of clinicians on the intercept, counselee's education level and presence of a pathogenic variant in the family is compared with: (1) the first model including the effect of change in BOADICEA estimates by incorporated breast cancer risk factors, (2) the second model adding the effect of age (or the genetic test result), and (3) the third model adding the interaction between change in BOADICEA estimates and age (or the genetic test result). Statistical significance tests take 'Same risk' as the reference category.
**p-value = 0.01.

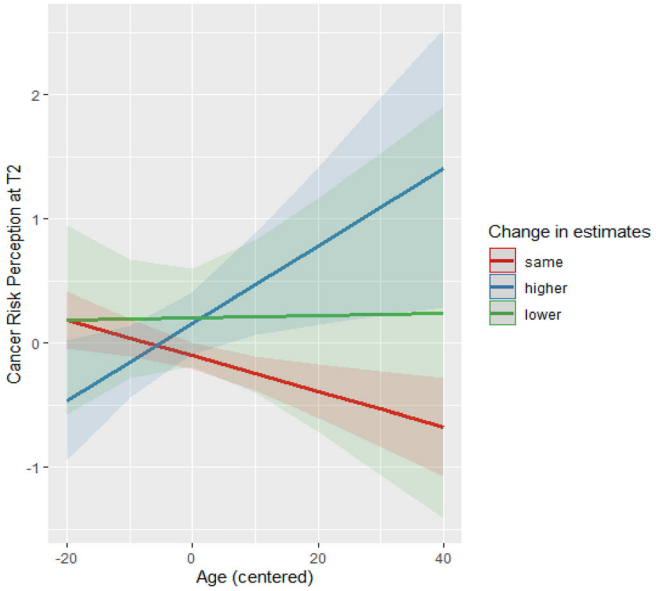

FIGURE 2 Predicted values in counselees' breast cancer risk perception by change between BOADICEA BASIC and FULL estimates and according to age. To avoid multicollinearity in models with interaction, continuous variables are centered so values of age represent the deviation from the mean (i.e., −20 means someone who is 20 years younger than the average age of the participants; 40 means someone who is 40 years older than the average age) [Colour figure can be viewed at wileyonlinelibrary.com]

clinicians' confidence: when estimates from BOADICEA FULL were lower than in the BASIC version, clinicians' level of confidence was found to be lower (Predicted mean [95% confidence interval of values predicted by the model] on Box-Cox transformed variable = 17.1 [15.0–19.2] vs. 19.6 [18.2–21.1], p-value = 0.02) (Table 3 and Table S6).

There was no association between clinicians' level of confidence and change in breast cancer risk estimates when comparing estimates from BOADICEA FGN and BASIC versions.

Between clinicians, we observed a large variability of their confidence in counseling with their counselees (ICC of 0.28 to 0.30).

3.2 | Effect of change in breast cancer risk estimates by BOADICEA version on counselees' perceptions of breast cancer risk and genetic-specific psychosocial difficulties

Of the various statistical models that were fitted with counselees' breast cancer risk perceptions and psychosocial difficulties at T2 as outcomes, the lowest BIC was with the null model (i.e., including counselees' education level, whether a pathogenic variant had been identified in the family, the outcome measured at T1, and time lapse between T1 and T2), except for breast cancer risk perception which was best explained by the statistical model including the multigene panel test result.

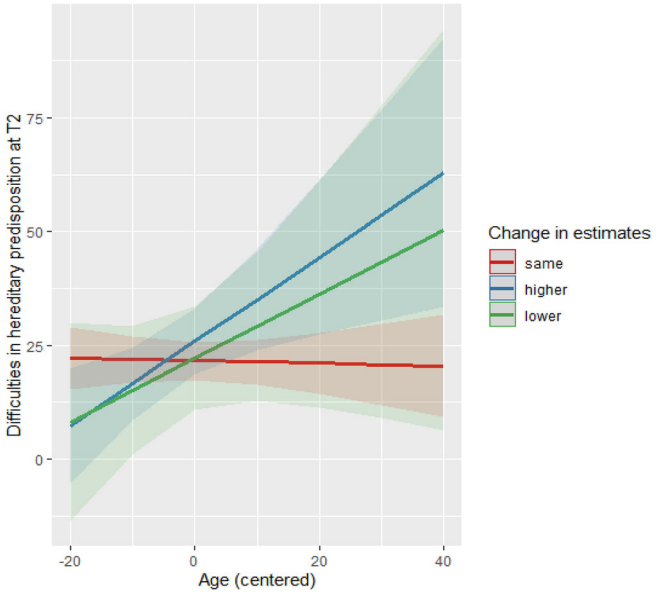

FIGURE 3 Predicted values in counselees' difficulties in hereditary predisposition by change between BOADICEA BASIC and FULL estimates and according to age. To avoid multicollinearity in models with interaction, continuous variables are centered so values of age represent the deviation from the mean (i.e., −20 means someone who is 20 years younger than the average age of the participants; 40 means someone who is 40 years older than the average age) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Counselees' predicted means (95% confidence interval) in psychosocial outcomes at T2 according differences in estimates between the BOADICEA BASIC and BOADICEA FULL (BASIC + NGRF and PRS) in multivariate mixed linear model

Breast cancer risk perception at T2	Predictors' B and 95% CI	Predicted mean and 95% CI
BAODICEA FULL (BASIC with NGRF and PRS) versus BOADICEA BASIC		
Same risk (any age)	REF	−0.05 (−0.27–0.17)
Age 30		0.10 (−0.14–0.35)
Age 60		−0.33 (−0.61–−0.05)
Lower risk (any age)	0.02 (−0.02–−0.05)	0.25 (−0.18–0.69)
Age 30		0.24 (−0.30–0.79)
Age 60		0.27 (−0.65–1.19)
Higher risk (any age)	0.05 (0.02–0.07)**	0.20 (−0.11–0.52)
Age 30		−0.13 (−0.49–0.23)
Age 60		0.81 (−0.16–1.46)
PAHC hereditary predisposition difficulties at T2		
BAODICEA FULL (BASIC with NGRF and PRS) versus BOADICEA BASIC		
Same risk (any age)	REF	17.17 (10.75–23.60)
Age 30		17.45 (10.26–24.64)
Age 60		16.65 (8.83–24.45)
Lower risk (any age)	0.73 (−0.32–1.79)	17.43 (5.35–29.52)
Age 30		10.20 (−5.70–26.09)
Age 60		31.32 (7.34–55.30)
Higher risk (any age)	0.95 (0.26–1.65)**	20.91 (12.41–29.40)
Age 30		11.37 (1.50–21.24)
Age 60		39.20 (22.45–55.95)

Note: Breast cancer lifetime risk perception was measured in words and in figures by two items; as responses to these items were highly correlated ($r = 0.82$), a single variable was created and an average standardized score derived, with an overall score range = −2.11–1.97. The "Psychosocial Aspects in Hereditary Cancer (PAHC)" hereditary predisposition scale score range = 0–100. The null statistical model with the intercept, random effect of clinicians on the intercept, counselee's education level, presence of a pathogenic variant in the family, psychosocial outcome at T1, and time lapse between T1 and T2 is compared with: (1) the first model adding the effect of change in BOADICEA estimates by breast cancer risk factors incorporated, (2) the second model adding age (or the genetic test result), and (3) the third model adding the interaction between change in BOADICEA estimates and, age or the genetic test result.
**p-value = 0.01.

Based on the LRT, perceptions of breast cancer risk and difficulties about the hereditary predisposition were significantly affected by changes in risk estimates between BOADICEA FULL and BASIC versions, according to counselees' age ($p = 0.003$ and $p = 0.01$, respectively): older counselees perceived higher breast cancer risk and more difficulties with the hereditary predisposition when estimates from BOADICEA FULL were higher than those from the BASIC version, as opposed to when estimates from BOADICEA FULL and BASIC were the same. In younger counselees, there was no effect of change in BOADICEA estimates on these outcomes (Figures 2 and 3, Tables S7 and S8).

Figures 2 and 3 depict predicted values in counselees' perceived breast cancer risk and difficulties with the hereditary predisposition, according to whether estimates from BOADICEA FULL are the same, higher or lower than from BOADICEA BASIC, and according to counselees' increased age.

Table 4 provides values of predicted means and values of 95% confidence interval for counselees' psychosocial outcomes in women aged 30 or 60 years old particularly.

There was no significant effect of changes in BOADICEA estimates and their interactions with age or the multigene panel test result on other PAHC psychosocial difficulties (Tables S9, S10, and S11).

Little inter-clinicians' variability on counselees' outcomes was observed suggesting that counselees presented similar perceptions of breast cancer risk or difficulties, regardless of the clinician and holding other potential effects constant.

4 | DISCUSSION

This observational prospective study examined the effect of changes in breast cancer risk estimates when incorporating NGRF alone or together with the PRS, on genetic clinicians' and counselees' experiences of post-test counseling in three European genetic clinics. Prior validation studies regarding the incorporation of NGRF and the PRS to family history and gene test result into breast cancer risk prediction models have been published.[7,11,16] However, to our knowledge, this study is novel in providing insight into genetic clinicians' beginning experience with using multifactorial predictive models of breast cancer risk. BOADICEA estimates integrating the PRS had not been calculated in the study clinics before. It adds to the quantitative study[18] that describes counselees' responses to receiving breast cancer risk estimates from a breast cancer PRS.

Overall, clinicians felt highly confident in communicating breast cancer risk and clinical recommendations. However, they felt less confident when BOADICEA estimates incorporating NGRF and the PRS were lower compared with estimates provided with the BOADICEA BASIC version. This was expected due to their limited experience with BOADICEA, and considering that their clinical experience is based mostly on the family history and gene test result only. Accordingly, in the high breast cancer risk context, clinicians may be reluctant to "de-escalate" clinical recommendations and so may feel ill at ease with lower estimates compared with standard estimations. With current risk thresholds, change in breast cancer risk estimates between BOADICEA FULL and BASIC affected on average ≈ 25% of counselees including 8% receiving lower risk estimates; it had the greatest impact among patients with an uninformative test result (Table 2). Clinicians in this study reported a modification of clinical recommendation in ≈ 17% of counselees (Table S5). This is in line with the absence of downgrading clinical advice in the less frequent scenario where counselees received lower breast cancer risk estimates.

We expected an indirect effect of change in BOADICEA estimates on genetic-specific counselees' psychosocial outcomes through

clinicians' communication of breast cancer risk and clinical advice. Changes in BOADICEA estimates affected counselees' breast cancer risk perception and difficulties with the hereditary predisposition (e.g., coping with the test result).

With increasing age, perception of breast cancer risk and difficulties with the hereditary predisposition or familial issues correlated with higher estimates computed by BOADICEA FULL. This suggests an adequate breast cancer risk perception in line with objective estimates, which has also been observed after receiving results from *BRCA1* or *BRCA2* gene testing.[23] This observation was specific to increasing age. In contrast, in younger counselees, there was no difference on these psychological outcomes whether estimates from the different BOADICEA calculations remained the same or changed. At younger ages, breast cancer 10-year risks are lower, especially when the multigene panel test result is negative or non-informative (which it was in the majority of these cases) and most counselees were communicated a 10-year breast cancer risk (i.e., all counselees in the Dutch and German setting). In the French setting, breast cancer risk was communicated over the lifetime but with caution, informing that it must be recalculated in the next 10 years. Changes in BOADICEA estimates did not influence other counselees' psychosocial difficulties (e.g., familial issues, emotions, or living with cancer), which suggests that these later difficulties might be less affected by the communication of BOADICEA estimates during the consultation.

These results apply to a limited number of clinicians, counselees' willingness to be tested, approached in only one genetic clinic per country, including one with a small sample and a questionnaire missing in one setting. Major factors such as counselees' education level, the clinician who saw the counselee or the presence of a pathogenic variant in the family that could bias results were accounted for in statistical models. However, the number of control variables is limited and this was at the cost of several variables in statistical models, small sample sizes by cross-tabulated variables (e.g., few counselees with a pathogenic variant and a lower risk from BOADICEA FULL compared to BASIC), and small effect sizes. Based on the BIC, which penalizes the number of variables included in the statistical model, the effect change in BOADICEA estimates did not improve the statistical fit to the data. Therefore, this study needs to be replicated with a larger cohort.

Among its strengths, our study included all genetic clinicians involved in counseling after breast cancer risk testing in the genetic clinics, a high response rate among counselees, and small differences between respondents and non-respondents. It was performed in three European country settings, reflecting different genetic counseling practices. This study is relevant considering the rapidly evolving knowledge on breast cancer risk prediction models and their application in routine practice.

5 | CONCLUSION

Our findings suggest that genetic clinicians, although generally confident in counseling for breast cancer risk, feel less confident when comprehensive BOADICEA risk modeling (integrating NGRF and the PRS to family history and the gene panel test result) discloses lower risks than the BASIC version. Counselees' breast cancer risk perception and psychosocial difficulties seem to reflect counseling based on age, family history or the genetic test result, except for older counselees when BOADICEA FULL versions disclose higher risk estimates than the BASIC version.

AUTHOR CONTRIBUTIONS

Anne Brédart, Jean-Luc Kop, Peter Devilee, Dominique Stoppa-Lyonnet, Rita Schmutzler, and Sylvie Dolbeault designed the project. Anne Brédart, Anja Tüchler, Christi J. van Asperen, Antoine De Pauw, Kerstin Rhiem, Kerstin Rhiem, Dominique Stoppa-Lyonnet, Rita Schmutzler, and Sylvie Dolbeault collected data. Anne Brédart, Jean-Luc Kop, Anja Tüchler, Kerstin Rhiem, Dominique Stoppa-Lyonnet, Peter Devilee, Rita Schmutzler, and Sylvie Dolbeault analyzed, interpreted data, and drafted the work. All authors revised and provided final approval of the version to be published.

ACKNOWLEDGMENT

We are grateful to all participants, clinicians and counselees, who provided their time to complete the questionnaires.

FUNDING INFORMATION

This project has received funding from the European Union Horizon 2020 research and innovation programme under grant agreement No 634935 (BRIDGES). In France, at Institut Curie, this work was partly financed within the designated integrated cancer research site (SiRIC) under agreement INCa-DGOS-Inserm_12554.

CONFLICT OF INTEREST

Dominique Stoppa-Lyonnet declares the following conflict of interest: AstraZeneca is funding the French COVAR study coordinated by the Institut Curie and aiming to the classification of *BRCA1/2* Variants of Unknown Significance. The Department of Genetics of the Institut Curie is performing genotyping (PRS) of MammoRisk®, Predilife. Dominique Stoppa-Lyonnet and the Institut Curie have received honorarium for her participation in education meetings organized by AstraZeneca or Tesaro®. Rita Schmutzler declares the following conflict of interest: grants or contracts received from AstraZeneca, Amgen. Payment or honoraria received from AstraZeneca, JanssenCilag, Pfizer. Participation on a Data Safety Monitoring board for AstraZeneca; MSD, GSK, Clovis Oncology Pfizer. Peter Devilee reports grants from EU Horizon2020 programme during the conduct of the study. All other authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14147.

DATA AVAILABILITY STATEMENT

The study database is hosted at Institut Curie (France). It may be available after main publication for BRIDGES research program performed (in 2023).

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Lilyquist J, Ruddy KJ, Vachon CM, Couch FJ. Common genetic variation and breast cancer risk-past, present, and future. *Cancer Epidemiol Biomark Prev*. 2018;27:380-394.
3. Dorling L, Carvalho S, Allen J, et al. Breast cancer risk genes - association analysis in more than 113,000 women. *N Engl J Med*. 2021;384:428-439.
4. Moretta J, Berthet P, Bonadona V, et al. The French genetic and cancer consortium guidelines for multigene panel analysis in hereditary breast and ovarian cancer predisposition. *Bull Cancer*. 2018;105:907-917.
5. Kreienberg R, Albert U-S, Follmann M, Kopp IB, Kühn T, Wöckel A. Interdisciplinary GoR level III guidelines for the diagnosis, therapy and follow-up care of breast cancer. *Geburtshilfe Frauenheilkd*. 2013;73:556-583.
6. FSM. Richtlijn Borstkanker - Screening buiten het bevolkingsonderzoek. 2021.
7. Li SX, Milne RL, Nguyen-Dumont T, et al. Prospective evaluation of the addition of polygenic risk scores to breast cancer risk models. *JNCI Cancer Spectr*. 2021;5:pkab021.
8. Yanes T, Young MA, Meiser B, James PA. Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field. *Breast Cancer Res*. 2020;22:21.
9. Lammert J, Grill S, Kiechle M. Modifiable lifestyle factors: opportunities for (hereditary) breast cancer prevention - a narrative review. *Breast Care*. 2018;13:109-114.
10. Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and non-genetic risk factors. *Genet Med*. 2019;21:1462.
11. Lakeman IMM, Rodriguez-Girondo M, Lee A, et al. Validation of the BOADICEA model and a 313-variant polygenic risk score for breast cancer risk prediction in a Dutch prospective cohort. *Genet Med*. 2020;22:1803-1811.
12. Carver T, Hartley S, Lee A, et al. CanRisk tool-a web interface for the prediction of breast and ovarian cancer risk and the likelihood of carrying genetic pathogenic variants. *Cancer Epidemiol Biomark Prev*. 2021;30:469-473.
13. Lee AJ, Cunningham AP, Tischkowitz M, et al. Incorporating truncating variants in PALB2, CHEK2, and ATM into the BOADICEA breast cancer risk model. *Genet Med*. 2016;18:1190-1198.
14. Bredart A, Kop JL, Antoniou AC, et al. Use of the BOADICEA web application in clinical practice: appraisals by clinicians from various countries. *Familial Cancer*. 2018;17:31-41.
15. Archer S, Babb de Villiers C, Scheibl F, et al. Evaluating clinician acceptability of the prototype CanRisk tool for predicting risk of breast and ovarian cancer: a multi-methods study. *PLoS One*. 2020;15:e0229999.
16. Hurson AN, Pal Choudhury P, Gao C, et al. Prospective evaluation of a breast-cancer risk model integrating classical risk factors and polygenic risk in 15 cohorts from six countries. *Int J Epidemiol*. 2021;50:1897-1911.
17. Meiser B, Woodward P, Gleeson M, et al. Pilot study of an online training program to increase genetic literacy and communication skills in oncology healthcare professionals discussing BRCA1/2 genetic testing with breast and ovarian cancer patients. *Familial Cancer*. 2021;21:1-10.
18. Yanes T, Meiser B, Kaur R, et al. Breast cancer polygenic risk scores: a 12-month prospective study of patient reported outcomes and risk management behavior. *Genet Med*. 2021;23:2316-2323.
19. Eijzenga W, Bleiker EM, Hahn DE, et al. Prevalence and detection of psychosocial problems in cancer genetic counseling. *Familial Cancer*. 2015;14:629-636.
20. Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175:217-228.
21. Eijzenga W, Bleiker EM, Hahn DE, et al. Psychosocial aspects of hereditary cancer (PAHC) questionnaire: development and testing of a screening questionnaire for use in clinical cancer genetics. *Psychooncology*. 2014;23:862-869.
22. Bredart A, Anota A, Dick J, et al. The "psychosocial aspects in hereditary cancer" questionnaire in women attending breast cancer genetic clinics: psychometric validation across French-, German- and Spanish-language versions. *Eur J Cancer Care*. 2020;29:e13173.
23. Nelson HD, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. preventive services task force recommendation. *Ann Intern Med*. 2014;160:255-266.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Brédart A, De Pauw A, Tüchler A, et al. Genetic clinicians' confidence in BOADICEA comprehensive breast cancer risk estimates and counselees' psychosocial outcomes: A prospective study. *Clinical Genetics*. 2022;102(1):30-39. doi:10.1111/cge.14147