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Psychosocial problems in women attending French, German and Spanish genetics clinics before and after targeted or multigene testing results: an observational prospective study

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ABSTRACT

Objectives and setting Advances in multigene panel testing for cancer susceptibility has increased the complexity of counselling, requiring particular attention to counselees' psychosocial needs. Changes in psychosocial problems before and after genetic testing were prospectively compared between genetic test results in women tested for breast or ovarian cancer genetic susceptibility in French, German and Spanish clinics.

Participants and measures Among 752 counselees consecutively approached, 646 (86%) were assessed after the initial genetic consultation (T1), including 510 (68%) affected with breast cancer, of which 460 (61%) were assessed again after receiving the test result (T2), using questionnaires addressing genetic-specific psychosocial problems (Psychosocial Aspects of Hereditary Cancer (PAHC)-six scales). Sociodemographic and clinical data were also collected.

Results Seventy-nine (17.2%), 19 (4.1%), 259 (56.3%), 44 (9.6%) and 59 (12.8%) women received a *BRCA1/2*, another high/moderate-risk pathogenic variant (PV), negative uninformative, true negative (TN) or variant of uncertain significance result (VUS), respectively. On multiple regression analyses, compared with women receiving another result, those with a VUS decreased more in psychosocial problems related to hereditary predisposition (eg, *coping with the test result*) (ß=−0.11, p<0.05) and familial/social issues (eg, *risk communication*) (ß=−0.13, p<0.05), almost independently from their problems before testing. Women with a PV presented no change in hereditary predisposition problems and, so as women with a TN result, a non-significant increase in familial/social issues. Other PAHC scales (ie, emotions, familial cancer, personal cancer and children-related issues) were not affected by genetic testing.

Conclusions In women tested for breast or ovarian cancer genetic risk in European genetics clinics, psychosocial problems were mostly unaffected by genetic testing. Apart from women receiving a VUS result, those with another test result presented unchanged needs in counselling in particular about hereditary predisposition and familial/social issues.

Strengths and limitations of this study

- ► The Psychosocial Aspects of Hereditary Cancer questionnaire proved useful for monitoring further counselling needs after multigene or targeted hereditary breast or ovarian cancer testing.
- ► The study was performed in cancer genetics practices from three European countries.
- ► The study findings are valid to women opting for genetic testing and test disclosure,who were mainly affected with breast cancer and could not be compared with an appropriate control group.
- ► Only one genetics clinic per country precludes comparisons of psychosocial difficulties between countries.
- ► Further research should address the variability between clinicians in communication style.

INTRODUCTION

A hereditary predisposition explains approximately 10% of all breast cancers (BC).[1] With next-generation DNA sequencing and the discovery of new cancer susceptibility genes, the simultaneous analysis of multiple genes, so-called multigene panel testing, is implemented in clinical practice.[2] In addition to the highly penetrant hereditary breast or ovarian cancer (HBOC) predisposition genes such as *BRCA1*, *BRCA2* and *PALB2*, multigene panels also involve BC (eg, *ATM* and *CHEK2*),[3] ovarian cancer (OC) (eg, *BRIP1*, *RAD51C* or *RAD51D*) [4] moderate-risk genes and other hereditary syndrome high-penetrant BC susceptibility genes (eg, *TP53*, *PTEN*, *CDH1* or *STK11*). Multigene testing is generally primarily proposed to a woman in the family who developed BC or OC (index case). If a pathogenic variant is found, blood

relatives are currently proposed for targeted genetic testing.

Individuals undergoing genetic testing for cancer risk ask help to appraise and manage their risk of developing cancer, inform their family about cancer genetic predisposition, clarify their children's risk and, when affected by cancer, gain information about why they developed the disease.[5 6] They experience counselling needs for specific problems related to the hereditary predisposition, familial and personal cancer, familial and social issues and children-related issues within the cancer genetic context,[7] which may elicit request for psychological help.[8]

Different national guidelines in Europe recommend genetic counselling before and after genetic testing for breast or ovarian cancer risk.[9–12] This healthcare discipline is defined as 'the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease',[13] and so it aims at responding to counselees' specific psychosocial problems.[14]

Genetic counselling provides a large quantity of information involving genetic and statistic concepts, which may be ambiguous and imprecise.[15 16] With multigene panel testing, this complexity is increased especially because of the addition of moderate-risk genes and the identification of an increased number of variants of uncertain significance (VUS).[17] Both have unclear clinical recommendations.[16 18] Prolonged clinical distress is uncommon after single-gene testing for HBOC susceptibility.[19] However, an inconclusive result such as a VUS may elicit misunderstanding,[20 21] uncertainty[21 22] and decisional conflicts about clinical management,[23] potentially leading to increased distress,[24] miscommunication between family members[25] and inadequate cancer risk management decisions.[21 26 27] On receiving a pathogenic moderate-penetrance gene variant, counselees may experience higher distress and uncertainty compared with a negative, VUS and even a pathogenic high-penetrance variant.[28]

Few studies have addressed psychosocial outcomes after multigene testing for cancer risk.[28–30] This observational prospective study assessed the effect of HBOC testing on specific psychosocial problems in women attending different European genetics clinics (ie, in France, Germany and Spain). Specifically estimating the effect of genetic testing, we assessed changes in these problems before and after test disclosure. The outcome measure consists in a recently validated questionnaire purported to monitor a comprehensive range of psychosocial problem specifically relevant to the cancer genetics context.[31] Indeed, counselees may experience a wide range of psychosocial problems, which unaddressed may exacerbate their distress[32] and so pointing to these problems according to the test result might target specific counselling needs.[33] We hypothesised a lower decrease before and after testing in psychosocial problems of women receiving a high/moderate-risk pathogenic variant[28 30 34 35] or VUS result[21 36] compared with women receiving a negative test result. We also estimated the effect of psychosocial problems before testing on the relationship between the genetic result and psychosocial problems after testing to further clarify remaining counselling needs, as initial worries often predict subsequent difficulties.[6 19 28 30]

METHODS

Patient and public involvement

Counselees were involved in the study by providing feedback on the content, format and burden of the survey. Questionnaires were revised according to counselees' feedback. They will be involved in plans for dissemination of the study. The study results will be publicly available through the website of 'Breast Cancer Risk after Diagnostic Gene Sequencing' research programme (https://bridges-research.eu).

Study design and setting

An observational prospective study[37] was undertaken within the clinical translation work package of 'Breast Cancer Risk after Diagnostic Gene Sequencing' research programme (https://bridges-research.eu). The study design is showed in figure 1. Accrual took place from November 2016 to April 2018 in the genetics clinics of Institute Curie (France), University Hospital of Cologne (Germany) or Catalan Institute of Oncology (Spain).

BC gene testing and counselling

BC gene testing and counselling were specific by setting and based on specific guidelines in each country (Groupe Génétique et Cancer in France[12 38]; German Consortium for Hereditary Breast and Ovarian Cancer-German Gynaecological Oncology Group in Germany[10]; and 'Oncoguia' guidelines in Spain.[11]

Genetic counselling was considered important, before and after testing,[9 10 38] and to be performed according to principles of patient-centred communication.[10]

Across guidelines, gene panel testing was mainly performed in women affected with BC (index cases). A 12-gene, 34-gene and 9-gene panel was tested in France (Paris), Germany (Cologne) and Spain (Barcelona), respectively. Targeted testing was proposed to relatives of pathogenic variant carriers.

Genetic counselling was provided in face-to-face consultations: in the French setting, pretest consultation was provided by one of five genetic counsellors with a biology background and the result disclosure by one of five medical geneticists; in the German setting, pretest and post-test consultations were provided by one of ten physicians, including a medical geneticist and nine gynaecologists and in the Spanish setting, by one of four genetic counsellors with a background in biology for one of them or nursing for the three others.

The pretest consultation lasted up to 1 hour. Women were informed about hereditary cancer risks and the genetic testing process. Information most systematically provided at that time comprised the probability that the

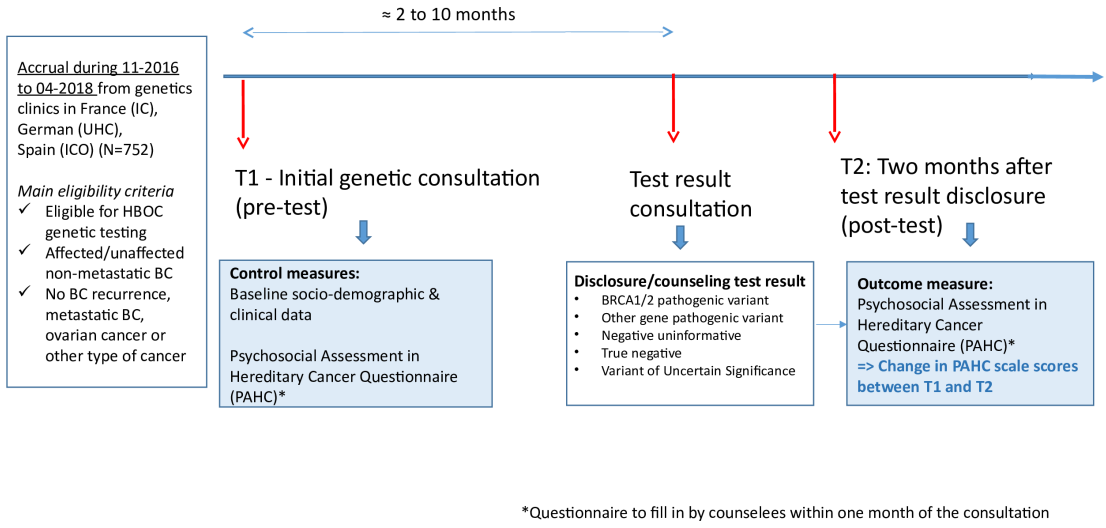

Figure 1 Design of the prospective cohort study. BC, breast cancer; HBOC, hereditary breast or ovarian cancer; IC, Institute Curie; ICO, Barcelona Institute of Oncology; UHC, University Hospital Cologne.

woman be carrier of a pathogenic mutation and cancer risks (breast or ovarian) according to the test result.

The duration of the post-test consultation ranged from 15 min in case of a negative result to 1 hour for a pathogenic variant. Information on cancer risks and medical management was validated in multidisciplinary team meetings. Women were systematically informed about their cancer risk in words and, depending on the test result and the country setting, also in percentage (ie, systematically in women receiving a pathogenic variant in the German setting, most frequently in these women in the French and Spanish settings, never in percentage in case of negative uninformative in the Spanish setting), using 'Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm' (BOADICEA) estimates[39] in the French and German settings.

Women receiving an uninformative test result were generally told that no pathogenic variant was found, which does not preclude a possible yet unknown genetic predisposition explaining the family history of cancer. When a VUS was identified, women were told that this result does not allow for concluding that a causal variant was found; however, clinicians would keep the woman informed if this variant was reclassified as pathogenic in the future. Women receiving a true negative result were informed that their risk of breast or ovarian cancer was the same as the general population.

A psychological consultation was systematically proposed at the pretest and post-test consultations but only available on-site in the French and German settings. Further details on genetic counselling[40] in the three settings are provided in online supplementary material S1.

Study participants

Seven hundred and fifty-two women aged above 18 years, eligible for BC risk testing according to national criteria, unaffected or affected with a non-metastatic BC were consecutively approached, including 258, 324 and 170 in the French, German and Spanish genetics clinics, respectively. Women with a BC recurrence, a personal history of OC or a major psychiatric disorder were not included.

In each setting, women accepting to participate in the study received a set of questionnaires to fill in at home and return within 1 month after the initial (pre-test) consultation (T1) and then 2 months after the genetic test result disclosure (post-test) consultation (T2).

Study variables and sources of measurement

Sociodemographic characteristics were collected from counselees after the initial consultation. Women were also asked whether they had lost family member(s) due to breast or ovarian cancer and if they had received psychological help after the receipt of the test result.

Clinical data were collected from medical records. BC risk estimates were computed at T1 and just before the test result disclosure using the BOADICEA web application (BWA v3, University of Cambridge, Cambridge, UK)[39] (data only available for IC, Paris and UHC, Cologne).

Possible gene panel testing results included: (1) a pathogenic variant on *BRCA1/2* or (2) other high/moderate-risk gene, or (3) a non-informative result (no pathogenic variant in index person) or (4) a VUS. Possible targeted gene testing included either a high/moderate-risk pathogenic variant or true negative result (no pathogenic variant in predictive tested healthy woman).

Outcomes consist in the genetic-specific psychosocial problems that were assessed at T1 and T2 using the 26-item 'Psychosocial Aspects of Hereditary Cancer' (PAHC) questionnaire[31] translated according to standard guidelines[41] and comprehensively assessed for psychometric performance (Brédart *et al*, The 'Psychosocial Aspects in Hereditary Cancer' questionnaire in women attending BC genetic clinics: reliability, validity, responsiveness and interpretability across French, German and Spanish versions. Under review). A six-factor PAHC model

Table 1 Sociodemographic and clinical characteristics of study participants by country setting

	French participants (n=213)	German participants (n=300)	Spanish participants (n=133)
Age (years)			
Mean (SD)	48.0 (11.9)	47.4 (10.7)	47.9 (12.0)
Median (range)	48.0 (21–78)	48.2 (18–77)	48.0 (19–80)
Education level, n (%)****			
Compulsory education or below	6 (2.8)	37 (12.4)	45 (34.1)
Secondary or technical/vocational education	60 (28.4)	167 (56.0)	44 (33.3)
Higher education or above	145 (68.7)	94 (31.5)	43 (32.6)
Marital status, n (%)			
Married/partnered	149 (70.3)	212 (71.4)	102 (77.3)
Others (widowed, separated/ divorced, single/never married)	63 (29.7)	85 (28.6)	30 (22.7)
Having children, n (%) (yes)	170 (79.8)	213 (71.0)	103 (77.4)
Personal breast cancer, n (%) (yes)			
Overall women****	171 (80.3)	254 (84.7)	85 (63.9)
Women with gene panel test†	168 (93.9)	242 (98.8)	82 (97.6)
Women with targeted test†	3 (8.8)	12 (22.2)	3 (6.1)
Time since breast cancer diagnostic (months)*			
Mean (SD)	39.1 (62.3)	27.7 (65.4)	41.4 (70.3)
Median (range)	13.3 (0.36–342.3)	4.0 (-0.99–490.5)	7.8 (0.69–390.8)
Having lost a family member due to breast/ovarian cancer, n (%)(yes)	86 (42.8)	128 (44.4)	60 (46.9)
BOADICEA breast cancer first or contralateral risk estimates			
Mean (SD)	19.6 (11.9)	18.1 (9.2)	/
Median (range)	17.7 (0.8–82.9)	16.6 (0.7–81.1)	/

BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm.

Participants at T2	French participants (n=172)	German participants (n=220)	Spanish participants (n=68)
Psychological help since test result receipt, n (%) (yes)*‡	20 (11.6)	32 (15.3)	7 (10.3)
Psychological help since test result receipt among counselees' referred by genetics clinician, n (%)§	11 (61.1)	19 (65.5)	3 (42.9)

one BOADICEA BC risk estimates missing in French sample as not computed for bilateral breast cancer; other missing data (≤12) due to women self-report omissions.
Significant difference between country setting: *p<0.05, ****p<0.0001.
†Total n for gene panel and targeted testing are 179 and 34, 245 and 54, 84 and 49, in France, Germany and Spain, respectively.
‡Missing data: n=11 and 1 in German and Spanish participants.
§Missing data: n=2 and 3 for French and German participants.

yielded acceptable confirmatory factor analysis goodness-of-fit indexes ($\chi 2/df=3.64$, root mean square error of approximation (RMSEA)=0.061 (90% CI 0.057 to 0.066), Comparative Fit Index (CFI)=0.91, Tucker Lewis Index (TLI)=0.90), providing scales about concerns about hereditary predisposition (HP) (eg, *coping about the DNA test result*), family and social issues (FSI) (eg, *contacting family members about genetic testing*), emotions (E) (eg, *insecure about the future*), familial cancer (FC) (eg, *worry that a family member would have cancer*), personal cancer (PC) (eg, *worry about chance of getting cancer (again)*) and children-related issues (CRI) (eg, *guilt about passing the genetic alteration*). These PAHC scales demonstrated expected conceptual differences with distress and satisfaction with counselling. Different interindividual levels of psychosocial difficulties were evidenced (p values <0.05). We also assessed the PAHC ability to respond to change (ie, intra-individual improvement or deterioration) in perceived difficulties and computed a minimal clinically important difference threshold in PAHC scores comparing these

scores with self-reported needs for additional counselling (ie, resolution or development of further counselling needs before and after testing), which yielded a 10% change threshold on the PAHC score 1–100 score range. Internal consistencies for these scales administered at T1 and T2 were adequate with Cronbach's alphas of 0.84 and 0.84 for HP, 0.72 and 0.81 for FSI, 0.87 and 0.89 for E, 0.79 and 0.83 for FC, 0.71 and 0.65 for PC, and 0.73 and 0.74 for CRI.

Psychosocial covariates included generic distress (ie, anxiety and depression) measured at T2 by the Hospital Anxiety and Depression Scale (HADS), available in French,[42] German[43] and Spanish[44] versions. Scores range from 0 to 42; a cut-off of 12 versus 13 has been proposed to identify possible cases of distress.[42 45] Additionally, counselee's perceived lifetime risks of developing (new or recurrence) BC was measured at T2 in words and in figures. As responses to these items were highly correlated (r=0.86), a single variable was created. Taking the 'Don't know' response apart, other response categories of both items were coded from 0 ('not concerned') to 6 ('major risk' or 'over 80%'), and an average score was derived. The later variable was then recoded as 0 ('don't know'; 'not concerned'), 1 ('low risk' below 2.5), 2 ('moderate risk' between score 2.5 and 3.5) and 3 ('high risk' above 3.5).

To address potential questionnaire non-responses, when necessary, a reminder call was made 2 weeks after the date of expected questionnaire receptions. Questionnaires not received within 1 month after the initial visit and within 3 months after the post-test genetic visit were considered missing. A sample size of 500 counselees was targeted in order to compare groups of at least 50 counselees by main genetic test results (ie, positive, negative or VUS) and allow for multivariate analyses. Questionnaire completion online was possible through CleanWeb technology.

Statistical analyses

Statistical analyses were performed with R software.[46] Sociodemographic and clinical characteristics were described using mean (SD) or median (range) for continuous variables and the number (percentage) for categorical variables. Respondents were defined as having provided one response at least to the sociodemographic and PAHC questionnaires. For each multi-item scale, missing data were replaced by the mean value of the scale when at least half of the items on that scale had been completed.

We used the *F*-test (analysis of variance) for continuous data and the χ^2 test for categorical data to compare respondents and non-respondents at T1 (for age, parental and disease status), respondents by country settings and differences in PAHC mean scale scores by test result and country. Respondents and non-respondents at T2 were compared using logistic regression, accounting for country, age, education, marital and parental status, loss of a relative due to BC or OC, BC status, genetic test type, BC (new) risk perception, distress and genetic-specific problems at T1. Paired Student t-test was used to compare PAHC mean scale scores over assessment times and by countries, with Bonferroni correction.

Multiple regression analyses were performed on PAHC scale scores at T2 as the dependent variables, and in order to estimate the effect of the test result (ie, the change before and after testing may reflect the effect of genetic testing), we controlled for PAHC scores at T1. In addition, for each regression model, we also controlled for possible risk or protective factors of psychosocial problems,[47 48] including country, sociodemographic (age, education level, marital and parental status) and clinical factors (BC diagnostic status, reported loss of family member(s) due to BC or OC), the type of genetic test (targeted or panel), BC risk perception and distress after the test result disclosure, the length of time between the pretest and post-test consultations and psychological help receipt after test disclosure. We also tested the interaction between PAHC scale scores at T1 and the test result on PAHC scale scores at T2.

Multiple regression analyses were performed[49] in which, in all models, covariates were introduced in a first block, the test result in a second block and the interaction terms in a third block. As the effect of the type of genetic test was confounded with the comparison of true negative (only identified in counselees' undergoing targeted testing) and negative uninformative, these results were lumped together. Similarly, as the effect of a pathogenic variants on another high/moderate-risk gene was confounded with country (among 19 of these, 18 were identified in the German sample), all pathogenic gene variant results were grouped. The reference category was the negative results (true and uninformative) to which we compared either pathogenic variants or VUS results. There was no concern about multicollinearity given that all variables displayed a VIF (variance inflation factor) inferior to an acceptable value of 4.4.[50]

RESULTS

Description of the samples

Among 752 counselees consecutively approached, 213 and 172 (82.6% and 66.7%) in France, 300 and 220 (92.6% and 67.9%) in Germany and 133 and 68 (78.2% and 40.0%) in Spain, respectively, completed the questionnaires after pretest (T1) and post-test (T2).

Table 1 displays sociodemographic and clinical characteristics of the French, German and Spanish respondents. Less than 12 missing data were observed in women self-reported information. Their mean ages (SD) were of 48.0 (11.9), 47.4 (10.7) and 47.9 (12.0) years, and 171 (80.3%), 254 (84.7) and 85 (63.9) of them were affected with BC, respectively. Based on the BOADICEA BC risk estimation model,[39] the mean (SD) per cent of BC lifetime risk estimates by age 80 years before testing was 19.6 (11.9) and 18.1 (9.2) in France and Germany, respectively (data not available in Spain).

Country samples differed significantly in terms of level of education (p<0.0001) and BC diagnosis status (p<0.0001). At T1, there was no significant difference between respondents and non-respondents on age, having children, BC diagnosis and, for the French and German samples, on BOADICEA estimates. At T2, respondents and non-respondents differed on BC diagnosis and country samples such that women affected with BC and from the German relative to the Spanish setting were more frequently respondents (p<0.05).

Seventy-nine (17.2%), 19 (4.1%), 259 (56.3%), 44 (9.6%) and 59 (12.8%) women received a pathogenic *BRCA1/2* or high/moderate-risk variant other than *BRCA1/2*, uninformative, true negative or VUS result. The median length of time between the initial and test disclosure consultations was shorter in Germany (56 days) compared with France (183 days) and Spain (98 days) (online supplementary material S2).

After testing, 20 (11.6), 32, (15.3) and 7 (10.3) counselees had received psychological help, respectively (p<0.05 for comparison between countries), and among them 11 (61.1%), 19 (65.5%) and 3 (42.9%) had been referred by a genetics clinician, in the French, German and Spanish setting, respectively.

Change in genetic-specific psychosocial problems over assessment time

On the PAHC questionnaire, the level of missing data per item was below 5% in all three countries. At both assessment times, mean scores of psychosocial problems were lowest in the 'Familial/Social Issues' domain across countries, ranging from 11.9 in Spain to 16.6 in Germany. After testing, psychosocial problem mean scores were highest in the 'familial cancer' domain in France (65.8) and Spain (79.0) and in 'personal cancer' (55.0) in Germany (table 2).

Over assessment times, an overall statistically significant decrease was observed in the following concerns: 'hereditary predisposition' (p<0.001), 'personal cancer' (p<0.05) and 'children-related issues' (p<0.001). This decrease was also statistically significant for 'hereditary predisposition' in France (p<0.01) and Germany (p<0.001) and for 'children-related issues' only in Germany (p<0.001). No statistically significant decrease appeared in psychosocial problems related to 'familial and social issues', 'emotion' and 'familial cancer'.

Among scales displaying a statistical difference over time, this decrease was clinically significant (according to the validated 10% change threshold in PAHC scale scores) only in concerns about 'hereditary predisposition' (10.7) and 'children-related issues' (11.8) in the German sample.

Mean change in genetic-specific psychosocial problems by genetic test results and country

Bivariate analyses were performed comparing test results on mean changes in levels of psychosocial problems before and after testing (table 3). A statistically significant difference between test results appeared on change in hereditary predisposition and familial/social issues (p<0.01).

Only women receiving a true negative (TN) or a VUS result presented a clinically significant decrease in hereditary predisposition concerns; although increasing in women receiving a pathogenic variant (PV) or TN result, changes in familial/social difficulties did not reach clinical significance.

A statistically significant difference between countries was also observed on familial/social issues' (p<0.05). PAHC scores at T2 only by test result and country are provided in online supplementary material S3, and details of table 3 are provided in online supplementary material S4.

Multiple regression analyses

In multiple regression analysis (table 4), across models including covariates, the genetic test result and the interaction between the test result and PAHC scale scores at

Table 2 Bivariate analyses of genetic-specific psychosocial difficulties mean (SD) score over assessment times, overall and for each country

	French participants		German participants		Spanish participants	
Psychosocial difficulties (PAHC scales) Mean (SD)	**T1 n=213**	**T2 n=172**	**T1 n=300**	**T2 n=220**	**T1 n=133**	**T2 n=68**
Hereditary predisposition***	29.1 (20.2)	22.4 (20.4) **	**33.7 (24.1)**	**23.0 (24.9) *****	45.4 (26.6)	35.7 (27.5)
Familial and social issues	15.9 (17.3)	15.8 (16.7)	16.6 (16.7)	14.6 (20.4)	11.9 (16.0)	15.1 (20.3)
Emotions	30.0 (23.1)	30.6 (24.1)	33.8 (24.3)	30.4 (22.8)	29.3 (23.3)	27.1 (24.0)
Familial cancer	67.7 (25.0)	65.8 (27.5)	51.9 (24.3)	50.3 (25.9)	80.0 (18.8)	79.0 (21.4)
Personal cancer*	57.7 (27.0)	54.6 (28.5)	58.5 (28.6)	55.0 (27.2)	53.6 (31.8)	48.8 (29.8)
Children-related issues***	47.6 (26.7)	41.7 (27.7)	**43.2 (26.9)**	**31.4 (25.4) *****	60.3 (25.3)	54.8 (25.5)

T1=assessment after the initial genetic consultation; T2=assessment 2 months after the receipt of genetic test result. PAHC score range: (0–100). Statistically significant difference between assessment times (with Bonferroni correction): *p<0.05; **p<0.01; ***p<0.001 and in bold clinically significant differences (over 10% change threshold in PAHC scale scores), overall and for each country setting.
PAHC, Psychosocial Aspects of Hereditary Cancer.

Table 3 Bivariate analyses of mean (SD) differences between T2 and T1 in genetic-specific psychosocial difficulties between test results

	PAHC 1 Hereditary predisposition	PAHC 2 Familial and social issues	PAHC 3 Emotions	PAHC 4 Familial cancer	PAHC 5 Personal cancer	PAHC 6 Children-related issues
Genetic test result						
BRCA1/2 pathogenic variant (n=79)	−3.5 (23.1)	4.9 (17.7)	−0.1 (18.1)	−0.1 (19.6)	0.9 (22.2)	−2.7 (19.0)
Other high/moderate-risk pathogenic variant (n=19)	−2.5 (22.7)	6.0 (28.3)	−3.2 (20.2)	−6.1 (25.3)	−8.8 (20.3)	−3.7 (21.7)
Negative (uninformative) (n=259)	−7.3 (23.2)	−0.2 (17.1)	−1.9 (20.8)	−2.5 (19.8)	−3.3 (25.0)	−7.2 (23.0)
Negative (true) (n=44)	−12.9 (24.6)	4.3 (17.2)	−4.0 (15.4)	1.4 (20.5)	−11.6 (29.7)	−11.7 (24.3)
VUS (n=59)	−18.3 (29.8)	−6.5 (20.7)	−0.7 (25.8)	−3.0 (21.9)	−5.5 (21.3)	−11.9 (23.6)
Country						
France (n=172)	−5.7 (19.7)	1.7 (17.8)	0.5 (18.8)	−3.2 (21.9)	−2.7 (27.3)	−4.8 (23.0)
Germany (n=220)	−10.3 (26.6)	−1.5 (18.9)	−2.8 (21.5)	−1.4 (19.7)	−4.4 (20.6)	−10.0 (22.6)
Spain (n=68)	−9.5 (28.0)	4.5 (18.4)	−34 (21.1)	−0.6 (18.9)	−5.2 (29.5)	−5.5 (21.0)

Notes: T1=assessment after initial genetic consultation; T2=assessment 2 months after receipt of genetic test result. PAHC: score range=0–100, a difference of ~10 of the scale range is clinically significant. Overall statistically significant difference between test results on respondents at T1 and at T2: HP and FSI=**p<0.01 and between countries: FSI=**p<0.05.
PAHC, Psychosocial Aspects of Hereditary Cancer; VUS, variants of uncertain significance.

T1, the percentage of explained variance (adjusted R^2) in domains of psychosocial problems at T2 ranged from 28% (hereditary predisposition) to 60% (emotion) (all p<0.001).

Only adding the test result to covariates in these models improved the prediction of psychosocial problems in 'hereditary predisposition' (p<0.01) and 'familial and social issues' (p<0.05). Compared with a negative test result (true negative and uninformative), receiving a VUS was associated to lower problems in 'hereditary predisposition' (ß=−0.11, p<0.05). Addition of the combined effect of the test result and PAHC scale scores at T1 tended to be significant for scores in 'hereditary predisposition' (F (2,381)=2.9, p<0.06) and was significant for 'familial and social issues' (F (2,365)=3.7, p<0.05). The effect of scores at T1 on scores at T2 was weaker for a VUS than other genetic test results (figures showing the interactions in online supplementary material S5).

Among covariates, compared with Germany, counselees in Spain presented higher levels of problems in 'hereditary predisposition' (ß=0.14, p<0.01), 'familial cancer' (ß=0.11, p<0.05) and 'children-related issues' (ß=0.21, p<0.001). Distress and PAHC scores at T1 significantly predicted all problems (ß ranging from 0.13, p<0.01, for distress and 'children-related issues' to 0.61, p<0.001, for T1 PAHC scores and 'familial cancer'). Being affected with BC was associated to higher problems in 'personal cancer' (ß=0.18, p<0.05). Compared with women who reported not knowing their risk of BC, those who presented a low risk perception presented lower 'familial cancer' and 'personal cancer' scores (ß=−0.10, p<0.05). The receipt of psychological help after testing was associated to higher problems in the 'emotions' domain (ß=0.09, p<0.01).

Other covariates did not significantly predict psychosocial problems.

DISCUSSION

In this study, we assessed changes in a comprehensive range of specific psychosocial problems before and after genetic testing, in women undergoing gene panel or targeted testing for HBOC syndrome in three European country genetics clinics and compared these changes according to the test result received and the problem levels before testing. Information on the extent to which genetic testing presents gaps in responding to counselees' psychosocial needs[14] and focus for improved counselling could thus be provided.

Psychosocial problems only decreased in the domains of hereditary predisposition, personal cancer and children-related issues but this decrease was clinically significant only in German participants and for hereditary predisposition and children-related domains. Problems remained high, especially in the domains of personal and familial cancer and children-related issues (mean level above 33 corresponding to Eijzenga *et al*[31] cut-off score converted on a 0–100 scale indicating need of clinical attention). These problems

Table 4 Multivariable analyses: effect of the genetic test result on scores of genetic-specific psychosocial difficulties at T2 controlled for scores at T1

	PAHC 1 Hereditary predisposition ß	PAHC 2 Familial and social issues ß	PAHC 3 Emotions ß	PAHC 4 Familial cancer ß	PAHC 5 Personal cancer ß	PAHC 6 Children-related issues ß
Country						
Spain versus Germany	0.14**	0.08	0.01	0.11*	0.03	0.21***
France versus Germany	0.04	0.05	0.02	0.01	−0.00	0.15 (0.063)
Age (years)	−0.01	−0.02	0.01	0.03	−0.06	0.06
Education level						
Secondary education versus compulsory or below	−0.06	−0.08	−0.01	−0.01	−0.02	0.03
Superior education versus compulsory or below	−0.09	−0.07	0.07	−0.02	−0.00	−0.04
Marital status (married/partnered vs others)	0.00	−0.06	0.04	0.01	−0.03	−0.03
Having children (yes)	−0.03	−0.02	0.02	0.01	−0.00	−0.07
Having lost a family member due to breast/ovarian cancer (yes)	0.03	0.02	0.01	0.05	−0.05	0.00
Personal breast cancer (yes)	−0.06	−0.10	−0.07	−0.06	0.18*	0.04
Type of genetic test (gene panel vs targeted test)	0.06	0.11	0.06	−0.05	0.04	0.01
Breast cancer risk perception at T2						
Don't know vs						
Low	−0.01	−0.05	−0.07	−0.10*	−0.10*	−0.10 (0.092)
Moderate	0.00	−0.06	−0.02	0.00	−0.03	0.00
High	0.02	0.06	0.06	−0.01	0.05	0.01
Generic distress (HADS) at T2	0.28***	0.21***	0.54***	0.23***	0.29***	0.13**
Psychological help at T2	−0.05	0.03	0.09**	0.01	0.06	0.03
Length of time between initial and genetic test disclosure consultations	−0.02	−0.00	−0.05	0.07	−0.00	0.00
PAHC score at T1	0.39***	0.45***	0.30***	0.61***	0.41***	0.57***
Block 1 (control variables): *F*(df); R^2; adjusted R^2	9.2 (17,385); 0.29; 0.26	9.5 (17,369); 0.30; 0.27	36.1 (17,379); 0.62; 0.60	32.0 (17,386); 0.59; 0.57	26.1 (17,383); 0.54; 0.52	15.1 (17,282); 0.48; 0.44
Genetic test result						
High/moderate-risk pathogenic variant	0.07	0.06	−0.01	−0.03	−0.01	0.06
VUS	−0.11*	−0.08	0.02	−0.03	−0.04	−0.04
Block 2 (+genetic test result): *F*(df); R^2; adjusted R^2	9.1 (19,383); .031; 0.28	9.0 (19,367); 0.32; 0.28	32.2 (19,377); 0.62; 0.60	28.7 (19,384); 0.59; 0.57	23.3 (19,381); 0.54; 0.51	13.7 (19,280); 0.48; 0.46
Difference between block 1 and block 2: *F*(df); p	5.7 (2,383); 0.004	3.7 (2,367); 0.026	0.30 (2,377); 0.74	0.64 (2,384); 0.53	0.37 (2,381); 0.69	1.20 (2,280); 0.29

Continued

Table 4 Continued

	PAHC 1 Hereditary predisposition β	PAHC 2 Familial and social issues β	PAHC 3 Emotions β	PAHC 4 Familial cancer β	PAHC 5 Personal cancer β	PAHC 6 Children-related issues β
Interaction						
High/moderate-risk pathogenic variant × PAHC score at T1	0.02	0.01	−0.02	−0.07 (0.082)	0.00	−0.05
VUS × PAHC score at T1	−0.11*	−0.13*	−0.06 (0.076)	0.01	0.05	−0.02
Block 3 (+genetic test result and PAHC scale interaction): *F*(df); R^2; adjusted R^2	8.6 (21,381);0.32; 0.28	8.6 (21,365); 0.33; 0.29	29.4 (21,378); 62; 0.60	26.2 (21,382); 0.59; 0.57	21.1 (21,379); 0.54; 0.51	12.4 (21,278); 0.48; 0.44
Difference between block 2 and block 3: *F*(df); p	2.9 (2,381); 0.055	3.7 (2,365); 0.027	1.6 (2,375); 0.20	1.71 (2,382); 0.18	0.66 (2,379); 0.52	0.46 (2,278); 0.63

T1=assessment after the initial genetic consultation; T2=assessment 2 months after the receipt of genetic test result.
*p<0.05, **p<0.01, ***p<0.001.
HADS, Hospital Anxiety and Depression Scale; PAHC, Psychosocial Aspects of Hereditary Cance; VUS, variant uncertain significance.

concern pain about the (possible) loss of family members, fear of developing (new or recurrence) cancer or increased cancer risk in children, which were also highly prevalent in women from HBOC syndrome in other country settings.[32 51]

In multivariate analyses, the genetic test result was associated to psychosocial problems only in domains of hereditary predisposition and familial and social issues. These study findings and the high level of problems underline the overall impact of undergoing HBOC genetic testing, whatever the actual test result communicated.[52] Two months after the test result disclosure, women carrying a pathogenic variant or an uninformative test result revealed little change in problems related to 'hereditary predisposition' and so remaining needs in aspects such as clinical decision making.

We acknowledge the following limitations in this study. Samples comprised women opting for genetic testing and test result disclosure and who were mainly affected with BC, reflecting current population of counselees in the participating centres (respondents did not differ on key available characteristics). Recruiting counselees from only one genetics clinic per country did not allow differentiating between the potential effect of the country and genetics clinic. We could not systematically record which clinician met which counselee and so the variability between clinicians was not controlled. The communication content was validated during multidisciplinary team meetings in the different settings; however, variability may have occurred in subtle aspects such as clinicians' communication style.[53] As the rates of pathogenic variants on moderate-risk genes was small and almost only present in German participants, we could not adequately contrast this type of test result with others. Finally, as the outcome measure was specifically designed for individuals undergoing genetic counselling in order to highlight further counselling needs after testing, we could not compare levels of difficulties in our samples with an appropriate control group.

Unexpectedly,[36] women receiving a VUS result decreased in problems related to hereditary predisposition, almost independently from their levels of problems before testing. The effect of the test result may partly reflect the information provided during counselling. Lower problems in women receiving a VUS result compared with non-carriers suggests a particular attention to the content of counselling in the case of this particular genetic test result. A VUS result raises uncertainty about clinical management.[22] In these study settings, the message conveyed by the communication of a VUS seemed more reassuring than that of an uninformative negative test result. Recommendations for managing VUS have recently been issued, advising that counselees may be recontacted if a VUS is reclassified into 'clinically actionable' or 'definitively non-pathogenic'.[18] Adherence to these guidelines may avoid detrimental between-clinicians discordant messages.[54] This information imparted to counselees may have led them to put their concerns and expectations on hold while non-carriers, mostly individuals receiving an uninformative result in these

samples, remained uncertain about their cancer risk status (eg, how to explain one's BC diagnostic) and its medical consequences.

Problems in familial and social issues were relatively low and significantly different across test results: in women carriers of a PV and those receiving a TN result, these problems increased (non-significantly), which may be explained by the need to inform relatives after learning one's test result. This may be challenging, especially to those tested positively[55] or elicit feelings of guilt in non-carriers towards family members who might receive a pathogenic result,[7] therefore causing need for additional counselling for familial or social support and communication.[56 57]

Distress was strongly related to all domains of psychosocial problems 2 months after the receipt of the test result,[32 48] highlighting the many facets underlying distress that may be targeted for counselling. The role of genetic clinicians, psychologists or psychosocial workers with regard to psychosocial problems specific to the genetic context is not clearly delineated.[58] The effect of genetic testing on psychosocial problems related to hereditary predisposition concerns suggests that genetic clinicians played a main role in that domain. A recent study observed that genetic counsellors define their role regarding psychosocial problems as short term, referring counselees to mental health services when they perceive limited social support or significant anxiety related to a high-risk status or recent cancer diagnosis.[58] Psychological care after the test result receipt was associated to higher negative emotions, suggesting that more distressed counselees received psychological care or that this was ineffective in reducing negative emotions 2 months after the receipt of test result. Less than 15% of counselees received psychological care after testing, and among these, about 40%–60% of them had been referred by genetics clinicians depending on the country setting. This study suggests the need to improve access and uptake of psychosocial counselling in women undergoing genetic testing for cancer susceptibility.[8 59]

As expected due to possible dissimilarities in cultural values and expectations[60] and genetic counselling modalities,[61] significant differences in some genetic-specific problems were observed between countries. Concerning genetic counselling, variations between study settings in terms of clinicians' background, risk communication precision (eg, in figures in addition to words) and psychological care availability may partly explain these differences. Aspects of the genetic counselling consultation such as the content of risk communication and approach to facilitate coping and decision making in relation to resolution of psychosocial problems require further research.[62]

CONCLUSIONS

In women tested for breast or ovarian cancer genetic risk in one of three European cancer genetics clinics, specific psychosocial problems were mostly unaffected by genetic testing. Apart from women who received a VUS, those with another test results presented unchanged needs in counselling in particular about hereditary predisposition and familial/social issues.

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