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**DISTRESS IN UNAFFECTED INDIVIDUALS WHO DECLINE, DELAY OR
REMAIN INELIGIBLE FOR GENETIC TESTING FOR HEREDITARY DISEASES:
A SYSTEMATIC REVIEW**

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ABSTRACT

Objective: Reviews on the psychosocial aspects of genetic testing for hereditary diseases typically focus on outcomes for carriers and non-carriers of genetic mutations. However, the majority of unaffected individuals from high-risk families do not undergo predictive testing. The aim of this review was to examine studies on psychosocial distress in unaffected individuals who delay, decline or remain ineligible for predictive genetic testing.

Method: Systematic searches of Medline, CINAHL, PsychINFO, PubMed and handsearching of related articles published between 1990 and 2012 identified 23 articles reporting 17 different studies that were reviewed and subjected to quality assessment.

Results: Findings suggest definitions of delaying and declining are not always straightforward and few studies have investigated psychological distress among individuals who remain ineligible for testing. Findings related to distress in delayers and decliners have been mixed, but there is evidence to suggest cancer-related distress is lower in those who decline genetic counselling *and* testing, compared with testers, and that those who remain ineligible for testing experience more anxiety than tested individuals. Psychological, personality and family history vulnerability factors were identified for decliners and individuals who are ineligible for testing.

Conclusions: The small number of studies and methodological limitations preclude definitive conclusions. Nevertheless, subgroups of those who remain untested appear to be at increased risk for psychological morbidity. As the majority of unaffected individuals do not undergo genetic testing, further research is needed to better understand the psychological impact of being denied the option of testing, declining and delaying testing.

Introduction

Despite early concerns over the potential for adverse psychological responses to genetic testing for disease risk [1], no systematic negative long-term psychological outcomes have been demonstrated [2, 3]. This may be attributable to the success of genetic counselling in facilitating adaptation to receiving genetic results as well as the benefits of reducing uncertainty regarding risk and providing information to guide screening, prevention or treatment decisions [4, 5]. However, little is known about the impact of *not* receiving genetic test results in the presence of a family history of disease.

Most unaffected individuals from families with a strong history of disease are ineligible for personal testing [6] as they are usually only tested after a mutation has been identified in an affected relative [7, 8]. For this reason, the majority of unaffected relatives are assumed to be at increased risk, but do not benefit from genetic counselling or the reduced uncertainty of knowing their *actual* risk. In addition, over a third of individuals who are eligible for testing choose not to be tested (decliners), or are undecided about testing or plan to be tested at a later date (delayers) [9-11].

The few studies of those who are ineligible for testing suggest anxiety may be higher in this group compared with identified mutation carriers and population controls [12, 13], and studies comparing those who decline to those who opt for testing have produced mixed results [14-17]; few, if any, studies focus on those individuals who delay genetic testing.

In light of the growing list of diseases for which a family history has been identified as a risk indicator, a systematic review of the psychological factors associated with delaying, declining or remaining ineligible for testing is timely. The aim of this systematic review was to answer the following questions: 1) What are the distress profiles of decliners and delayers? 2) What are the psychological outcomes for individuals who decline, delay or remain ineligible for testing? 3) What are the vulnerability factors for individuals who decline, delay or remain ineligible for testing?

Method

Search strategy

Searches were conducted in PsychINFO, Medline, CINAHL and PubMed between April 27, 2012 and May 8, 2012 and the results were limited to articles relating to adult humans that were published in English in a peer-reviewed journal since January 1, 1990. Search terms were developed, and adapted for each database, from the concepts of genetic testing, hereditary cancer, psychosocial factors and uncertainty, as well as additional terms such as 'absence of demonstrated mutation'.

Reference lists of eligible articles were examined to identify additional relevant studies. Reference lists of reviews identified through searches were screened, and articles citing included papers were identified through Web of Knowledge and assessed for eligibility.

Selection of eligible articles

Articles were eligible for inclusion in this review if they reported original research and included 1) participants at increased risk for disease based on family history, known genetic mutation or ethnic descent; 2) results for participants who were ineligible for testing (and had, therefore, not undergone the testing procedure), eligible but declined to learn results, and/or eligible but delayed testing; 3) at least ten participants in the group of interest [18];

and, 4) at least one measure of distress or explored coping with risk qualitatively. Articles were excluded if the study 1) assessed affected individuals only; 2) did not report results separately for affected and unaffected individuals (studies not reporting results separately but which controlled for personal cancer history or found no effect of affected status were included); 3) did not provide a clear description of the genetic testing statuses of the groups; 4) were review articles; or, 5) assessed only *intentions* to test. This last exclusion criterion was based on evidence that intention to undergo genetic testing is not necessarily indicative of behaviour [19, 20].

Information Extraction and Quality assessment

A data extraction sheet was used to record variables such as study participants, research question, study design, disease type, measures used, results and limitations relevant to the present review. The Quallsyst tool was used to document study quality, as it provides criteria for assessing a range of research designs [21]. All articles were independently assessed by LH and PB and discrepancies discussed until agreement was reached.

The studies relevant to the three review questions have been summarised under subheadings in Tables 1-3 and ordered according to quality of evidence, year of publication and alphabetically. Quality of evidence was ranked to reflect previously defined cut-offs [22] representing high (>80), moderate (70-80), adequate (50-70) and low (<50) quality.

Importantly, differences in disease characteristics and associated risk management and treatment options (see Appendix 1 for a summary) have the potential to influence testing decisions and psychological outcomes, and should be considered in reviewing the results. How these differences are likely to impact decisions and outcomes is beyond the scope of this paper and has been outlined elsewhere [23].

Results

The search yielded 1898 articles potentially eligible for review. Screening of titles, abstracts and exclusion of duplicate publications resulted in 91 articles being retrieved for full text screening. Application of inclusion/exclusion criteria and resolution of discrepancies reduced the number of articles for review to 17. Six additional articles were identified through reviews, citing articles and reference lists, resulting in 23 articles representing 17 different studies available for the review. Articles related to the same dataset or sample but reporting different data have been noted but reported separately. Articles presenting data relevant to more than one question of interest have been listed in all appropriate tables.

Definitional challenges

The distinction between declining and delaying testing was commonly acknowledged, but the classification of delayers and the concept of declining varied, reflecting the complexity of genetic test decision-making. Individuals who initially declined and either went on to undergo testing or indicated future testing as a possibility were variably grouped with testers and decliners, but never investigated independently. Decliners were sometimes separated into subgroups according to the stage at which they declined (e.g. pre- or post-counselling) or whether their testing decision was consistent with their pre-counselling test intention, and in one study it was not completely clear whether ‘declining’ was test decline or study participation decline. The authors of the current review chose to retain group classifications made by the study authors, but these complexities should be considered in the interpretation of the findings.

Research Question 1: Distress profiles of decliners and delayers

Eleven high quality articles presenting prospective data on this topic were identified (see Table 1). These articles assessed psychological distress prior to a decision about genetic testing being made, i.e. explored psychological predictors of decisions about testing. The majority of studies related to individuals at risk for familial breast and ovarian cancer (FBOC) with one each on hereditary non-polyposis colorectal cancer [HNPCC; 16] and Huntington's Disease [HD; 24]. Types of distress reported included depression, anxiety, cancer-related distress (most often represented by the intrusion subscale of the Impact of Event Scale [IES; 25]), general distress, subjective well-being and hopelessness. The stressor referred to in the IES varied; participants responded in relation to "cancer" [17], "threat of breast cancer" [26], or "having a family history of cancer" [27]. In two studies, the focus of the cancer-related distress measure was not reported [16, 28].

Depression and anxiety

Of eight studies comparing depression of decliners to testers, six reported no difference, one reported *higher* depression and one *lower* depression. Overall, contradictory findings may be attributable to differences in disease groups and/or measures used.

Based on the larger and more recent studies, decliners of FBOC testing report lower depression while decliners of HNPCC testing report higher depression compared with testers. Lerman et al [16] found that depression was associated with declining in those at risk for HNPCC, while all studies of individuals at risk of FBOC reported no difference or lower depression in decliners. For example, Reichelt et al [17] investigated unaffected women ($n = 301$) separately and found those who went on to decline BRCA1/2 testing had significantly *lower* levels of HADS-defined depressive symptoms, compared to testers ($M = 2.0$, $SD = 2.6$ vs $M = 1.3$, $SD = 1.8$, $p < .05$), although other potential confounders were uncontrolled. Lerman et al [27] found no difference between testers and decliners in depression, controlling for potential confounders. Five comparisons that found no difference for FBOC did not control for potential confounders including affected status [1, 27-30]. Notably, all studies using the Centre for Epidemiological Studies Depression Scale CES-D reported no difference or higher depression in decliners [1, 16, 27-30], while Reichelt et al [17] reported lower depression in decliners as assessed by the HADS.

Only two studies prospectively compared anxiety between testers and decliners and these show no difference between the groups. In women at risk of FBOC there were no differences between testers and decliners in anxiety in 301 unaffected women [17] or 126 women (46% affected) [28], however analyses did not control for potential confounders.

Cancer-related distress

We identified six studies that prospectively compared cancer-related distress in decliners and testers, with four reporting a lack of differences between the groups and two finding lower distress in decliners. However, the findings suggest that those who decline counselling *and* testing report lower levels of distress than testers and those who undergo counselling *and then* decline. For example, Lerman et al [27] found decliners ($n = 63$) at risk of FBOC who did not attend pre-notification education were more likely to report *lower* cancer-related distress (IES-intrusion score 0-1) than testers ($n = 86$), controlling for potential confounders. Similarly, Thompson et al found FBOC women who declined both counselling and testing reported the lowest levels of intrusion ($M = 5.5$, $SD = 2.2$) compared with those who declined after counselling ($M = 11.9$, $SD = 2.0$, $p < .05$) and those who were tested ($M = 9.5$, $SD = 1.5$, *n.s.*), with 'high' levels in 18%, 73% and 58% of individuals in each group, respectively, (X^2

(1, $n = 75$) = 11.2, $p = 0.004$) [26]. In contrast, decliners in four studies with no difference between groups all received counselling or education [16, 17, 19, 28]. Null findings were restricted either by uncontrolled analyses [16, 17, 28] or a small decliner group ($n = 12$) and unvalidated cancer-related distress measure [19].

General distress, hopelessness and well-being

Four studies found no differences between decliners and testers on general distress [17, 24, 28, 31], hopelessness [17] or subjective well-being [24]. These analyses did not control for potential confounders, although findings of Reichelt et al [17] relate to unaffected women only. The general distress measure used in one study was a composite score derived from a number of measures, some of which correlated with each other at only $r = .42$ [31], bringing into question its validity.

Research question 2: Psychological outcomes for individuals who decline, delay or remain ineligible for testing

Psychological outcomes – decliners (cross-sectional studies)

Six studies compared distress of testers and decliners in cross-sectional analyses, i.e. after a decision had been made regarding genetic testing, with three high, two moderate and one adequate quality (see Table 2a). Two studies related to FBOC, and one each to HNPCC, HD, Li-Fraumeni Syndrome (LFS) and familial melanoma (FM). Studies assessed anxiety, depression and cancer-related distress and, where the IES was used, the stressor was “having a family history of cancer” [27], “LFS” [4] or “familial melanoma” [32].

Depression and anxiety

There were no significant differences between testers and decliners in anxiety or depression, although the relevant studies suffered a number of methodological limitations. Using the HADS, Lodder et al and de Snoo et al found no differences between testers and decliners at risk of FBOC [33] or FM [32], yet both decliner groups were small ($n < 20$) and overall sample size was deemed inadequate. As a result, potential confounders were uncontrolled. In addition, de Snoo et al [32] did not report results of significance tests to support their finding. Decruyenaere et al [34] also found no difference between testers and decliners in anxiety in bivariate analyses that precluded controlling for identified demographic differences between groups.

Cancer-related distress

Five studies assessed cancer-related distress; two found *lower* levels of cancer-related distress in decliners, one found *no difference* and two found *higher* cancer-related distress in decliners. Taking study quality into consideration, the findings suggest decliners may experience less cancer-related distress than testers. Two large studies, of 302 individuals at risk of FBOC [35] and 258 individuals at risk of HNPCC [36], found lower levels of cancer-related distress in decliners compared with testers. However, in one study, timing of assessment for testers was unclear [35] and may have impacted distress levels, while in the other, declining participation in the study, presented as an opportunity to obtain “free genetic counselling, and the option of free genetic testing through a research study”, was the outcome variable of ‘test decline’ [36]. Therefore, test decline may have been confounded with study decline. In addition, a single item measured cancer-related distress, and age and education were uncontrolled, despite evidence of differences between groups on these variables [36] and well established correlations between these variables and cancer-related distress [37-40]. In spite of these limitations, we prioritised these findings on the basis of adequate sample size and the seriousness of the limitations in the other studies.

Psychological outcomes – decliners (longitudinal studies)

Six articles examined psychological outcomes of decliners in longitudinal studies that controlled for baseline levels (Table 2b). Direct comparison is limited by variations in measurement and conceptualisations of distress, and findings are complicated by methodological aspects. None of the studies reported *better* psychological outcomes for decliners. One study examined individuals with family histories of HD [24, 41], another study surveyed women at risk of FBOC [28, 31], and the samples in two articles on men and women at risk of FBOC may have overlapped [1, 30]. Compared with various groups, three of these studies reported *worse* outcomes for decliners, two reported *no difference* in outcomes for decliners, and one study reported *mixed findings* according to the comparison group and type of distress [28].

There is evidence of worse outcomes for decliners of HD testing across a range of outcomes, while there is stronger evidence of higher distress in decliners only in relation to cancer-related distress and only compared with non-carriers, in individuals at risk of FBOC. Among individuals at risk of FBOC, decliners and carriers reported more intrusive thoughts than those with uninformative negative and variant results three months after baseline [28], more intrusive thoughts than those with variant results six months after baseline [28] and smaller reductions in depression compared with non-carriers one month post-testing decision [30]. Despite the evidence of differences *between groups*, changes over time *within groups* of those at risk for FBOC were either unassessed [1, 30] or showed no effect of time [28], thus although decliners may not report the same benefits as non-carriers, it is unknown whether changes in depression for decliners reflected deteriorations in psychological functioning. Wiggins et al [24] compared individuals at risk of HD who either received results indicating an increased ($n = 37$) or decreased ($n = 58$) risk, or had ‘no change’ in risk due to declining ($n = 23$) or uninformative results ($n = 17$) (groups combined due to lack of significant demographic or psychological differences). The ‘no change’ group reported deteriorations in psychological functioning compared with baseline, compared with testers and across a range of outcomes.

Smith et al [28] did not find significant differences in overall distress, state anxiety or depression between testers and decliners, but the two other studies that reported *no effect* of study group on distress suffered from various limitations. FBOC decliners and testers did not report significantly different courses of distress over a six month period [30], however the composite distress measure may have been of questionable validity (refer to research question 1 results). No significant difference was found between the groups at risk for HD (increased-risk, decreased-risk, no change in risk, decliners) in rates of ‘adverse events’ [41], however the objective assessment of occurrence of an adverse event was not supplemented by the participant’s self-report and the small number of participants who had reported an adverse event precluded multivariate analyses.

Psychological outcomes - ineligible for testing

Two high quality studies of psychological outcomes in individuals who were ineligible for testing were identified in the literature [12, 13, 42, 43] (Table 2c). Overall, women at risk for FBOC who were ineligible for testing tended to report higher anxiety than mutation carriers, although findings for depression and cancer-related distress were mixed. Psychosocial distress (represented by scores on the General Health Questionnaire-28), mental quality of life, hopelessness, anxiety, depression, cancer-related distress (intrusion and avoidance related to ‘cancer risk’ and ‘being at risk of developing breast cancer’) were investigated.

In a series of cross-sectional comparisons, Geirdal et al compared women at risk for FBOC ($n = 176$) and HNPCC ($n = 63$) who were ineligible for testing to each other, BRCA1 mutation carriers ($n = 68$) and population controls [12, 42, 43]. Compared with mutation carriers, there were no significant differences in anxiety, depression, hopelessness, psychosocial distress, intrusion or avoidance for ineligible HNPCC women, however ineligible FBOC women reported *higher levels* of depression, psychosocial distress and mean anxiety, and *no significant differences* in prevalence of anxiety disorder, intrusion, avoidance and hopelessness [12, 42]. The combined FBOC/HNPCC group reported less depression, more anxiety, and comparable mental quality of life compared with population controls (Geirdal, et al., 2006; Geirdal, et al., 2005).

In a prospective study, Meiser et al [13] compared 90 women at risk of FBOC who underwent testing to 53 women who were ineligible for testing on anxiety, depression and cancer anxiety. Testers reported significant reductions in anxiety over time, controlling for potential confounders. Interestingly, there was an increase in state anxiety for women who were ineligible for testing from baseline ($M = 33.6$, $SD = 10.7$) to 12 months ($M = 39.0$, $SD = 12.2$). Although not reported, we estimated an effect size of 0.5, a moderate effect, using the baseline standard deviation [44] $[(39-33.6)/10.7]$, and used the group size to calculate $t = 3.39$, $p < 0.05$, demonstrating a significant increase in anxiety from baseline to 12 months for women who were ineligible for testing. Carriers tended to report higher cancer-related distress compared with the women who were ineligible for testing, however this may be due to differences in levels of familial cancer related events between participants with and without a known familial mutation. Depression levels did not differ between groups.

Note that Geirdal et al's ineligible women had undergone genetic counselling three months prior to participation, at which time they had been advised a mutation was assumed to be responsible for the family cancer history despite no mutation being identified [12]. In contrast, no risk information was available for ineligible women in the Meiser et al study [13].

Research question 3: Vulnerability factors for individuals who decline, delay or remain ineligible for testing

Four high quality articles identified factors increasing an individual's vulnerability to distress (Table 3). One prospective study assessed affected and unaffected American men and women at risk of FBOC who declined testing [1]. Geirdal et al reported cross-sectional data on unaffected women who were ineligible for testing from Norway in three articles with considerable sample overlap [42, 43, 45]. Two articles report cross-sectional data from a study of women at risk of FBOC and HNPCC. Due to a lack of significant differences between the risk groups, their data are combined in the analyses. One article reports the relationships between variables within the risk group [45], the other investigates relationships between variables and compares the risk group with population controls [43]. The third Norwegian article reports data from the FBOC group in the aforementioned study and compares them with a group of BRCA1 mutation carriers [42].

The four articles report that cancer-related distress (IES stressor "having cancer in the family" [1]), demographics, family history, personality and coping style are vulnerabilities for poorer mental quality of life, anxiety and depression. Evidence from these studies suggests that:

1. decliners who report high levels of cancer-related distress at baseline are more likely to develop clinically significant depressive symptoms than carriers and non-carriers [1];
2. among women at risk of FBOC who remain ineligible for testing, focus on emotions, venting of emotions and avoidance through behavioural disengagement are associated with increased prevalence of anxiety disorder [42];
3. among women at risk of FBOC and HNPCC who remain ineligible for testing:
 - persistence, the tendency to avoid harm, less self-directedness and less optimism are associated with higher levels of mental distress (combined anxiety and depression), and these traits demonstrate stronger associations with mental distress than demographic and cancer-related variables [45];
 - not having a partner is associated with increased risk of poorer mental quality of life [43];
 - higher levels of intrusion and avoidance are associated with poorer mental quality of life [43].

Discussion

We reviewed studies investigating distress in unaffected individuals at increased familial risk for disease who had not undergone genetic testing. These individuals comprise the majority of unaffected, at-risk family members and have been under-researched thus far. The majority of the identified studies have been conducted with members of hereditary cancer registries and involve individuals at risk for FBOC. At this time, research investigating distress in individuals who decline, delay or remain ineligible for Huntington's disease genetic testing is sparse and insufficient to allow a meaningful comparison with individuals at risk of hereditary cancer. The included studies, from seven different countries, are a mixture of longitudinal and cross-sectional studies with most of the relevant findings pertaining to decliners. This review identified few studies of individuals who were ineligible for testing and no studies reporting results for delayers as a group distinct from decliners. Past research has, justifiably, focused on the psychological well-being of individuals who undergo genetic testing, however this review points to a need to monitor distress levels in those who remain untested as well.

Those who declined to be involved in the genetic testing process altogether tended to report less cancer-related distress than testers. However, decliners have reported little confidence in their ability to cope with an unfavourable test result compared with testers [32, 36], implying the decision to decline involvement is made in the interest of avoiding distress. This indicates that test takers are likely to be self-selected [46], highlighting the importance of preserving autonomy in genetic testing decisions [41] and supporting the idea that anticipatory distress may lead to avoidance, while current distress may motivate a desire for genetic testing as a means to manage distress [26]. Some at-risk individuals perceive little value in finding out their result, particularly if they have no intentions of changing their risk management strategies regardless of the outcome [47], therefore the anticipated distress of a positive result justifies declining testing. Longer term psychological benefits of declining mutation testing remain unclear and further research is needed to elucidate the nature of these.

What is clear from this review is that not all decliners are the same. Some are passive decliners who are aware of the opportunity to undergo testing and choose not to approach genetic services. Such individuals often also decline to be involved in research studies [30], or are never invited to participate in research as a result of their non-attendance at familial cancer clinics. Consequently, the true denominator of potential testers is likely unknown.

Further, significantly more test decliners, compared with testers, withdraw from studies prior to completion [1]. Both issues may account for the small numbers of decliners, and the associated lack of statistical power, in many of the reviewed studies. Thus the findings from this review may not be generalizable to the population of individuals who choose not to undergo genetic testing.

Another group of decliners seek risk information from genetic services but do not seek genetic testing. Others commence the testing process by giving a blood sample but do not return for the testing results. Some of these decliners undergo testing at a later date or at least indicate interest in later testing [19, 34, 35]. The findings of this review support the assertion that one group consciously decides to remain untested while another group engages in an avoidant coping strategy and may not cope as well as the former group [34], confirming a need for 'delayers' to be considered separately.

Individuals with increased familial risk for disease who remain ineligible for genetic testing are an understudied group. The available evidence to date indicates that women who remain ineligible for testing for FBOC have higher levels of general anxiety than both women who have undergone testing and the general population. Whether general anxiety is directly related to genetic testing is unclear. Baum et al.'s model of stress and genetic testing [48] suggests that reducing uncertainty through genetic testing may be psychologically beneficial, thus the ongoing uncertainty of remaining ineligible for testing may be experienced as distressing. This model also proposes that being identified as a carrier may exacerbate distress related to the disease itself, and this might explain why carriers reported more cancer-related distress than women who were ineligible for testing. However, we know that stress related to non-familial cancer events is associated with increased anxiety in women at increased risk of FBOC and that stress specifically related to familial cancer events is associated with increased cancer-related distress rather than general anxiety [39]. Therefore, since familial cancer-related events are likely to be more common in families with identified mutations, any actual difference between the groups on this variable may have confounded results. Future studies comparing women with and without identified familial mutations should consider assessing this variable as a potential covariate.

The findings of this review indicate a need for support to be available for untested individuals. A number of demographic, psychosocial and family history factors have been associated with an increased risk of distress in untested individuals, consistent with research on those at risk for FBOC [39, 49] and HD [50]. Formal risk assessment and/or genetic counselling may not be sought in the absence of an identified mutation, but many of the high-risk individuals in the studies reviewed here were members of hereditary cancer registries and this membership may present opportunities to offer support. For example, additional support could be offered to those who decline testing following education or counselling, and to decliners who present with elevated cancer-related distress. Individuals who remain ineligible for testing may find the shared understanding of support groups helpful in relieving general anxiety. However, to date there is insufficient evidence to justify the cost-effectiveness of providing additional support. Further research is needed to establish what, if any, resources should be considered for use in these populations and how best to identify individuals whose distress levels warrant referral for additional support.

One limitation of this review was that our criteria excluded a number of potentially eligible qualitative studies of individuals who were ineligible for testing that did not report separate results for affected and unaffected individuals [e.g. 51, 52, 53]. Due to the nature of

qualitative inquiry, separate reporting of results for affected and unaffected individuals may not be appropriate. However, we deemed this exclusion criterion necessary since motivations for testing and distress responses to testing outcomes differ between affected and unaffected individuals [54]. Although this criterion was applied in the search process, we still reported results of bivariate analyses where affected status was uncontrolled. We did so because if test status was unrelated to distress in bivariate analyses these distress variables were often not included in multivariate analyses, particularly when these variables were not central to the study's aims. Future studies focused on the needs and functioning of unaffected individuals will expand our knowledge in this area. Most of the articles on women who were ineligible for testing included in this review used the same sample, limiting generalisability of these findings. Further, international variations in the procedures and rules governing risk assessment, genetic counselling and genetic testing complicate the generalisability of any study in this field [55].

The majority of unaffected high-risk individuals remain untested. The absence of research on delayers, mixed findings on decliners and our limited understanding of how individuals cope with being ineligible for testing indicate an urgent need to assess psychosocial functioning in these groups. Future studies could explore the experience of being ineligible for testing, how risk is understood within this context, what type of information, if any, is sought and the relationship between being ineligible for testing and psychological distress. Once these aspects are better understood, psychological functioning and risk factors for distress in individuals who are ineligible for testing should be assessed in settings that accurately reflect their experiences to improve generalisability of the findings.

Psychosocial support is routine for those seeking genetic testing. The results of this review indicate that individuals who do not undergo testing may also benefit from such support. Since one-on-one counselling resources are limited, this highlights the need for further research to identify those at highest risk for poorer psychological outcomes so that interventions can be targeted to individuals with the greatest need.

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Table 1. Distress profiles of decliners and delayers

Authors, year, country	Design and Method	Sample +ve = carrier -ve = non-carrier	Measures (-) indicates unvalidated measures	Control variables	Relevant Findings	Limitations
High quality						
Dougall, Smith, Somers et al., 2009, USA [#]	Design: Prospective Method: Baseline (post-counselling, pre-test decision) questionnaires, post-baseline test decision	<i>n</i> = 100 testers, 26 decliners FBOC women who were considering testing, recruited through a genetics program at a tertiary hospital, 46% affected	Distress (composite score calculated from GSI:SCL-90, IES, PSS, STAI, CES-D)		No difference between testers and decliners in distress at baseline.	Baseline comparison did not control for potential covariates Composite score of questionable validity - calculated from variables correlated with each other as low as 0.42.
Smith, Dougall, Posluszny et al., 2008, USA [#]	Design: Prospective Method: Baseline (post-counselling, pre-test decision) questionnaires, post-baseline test decision	<i>n</i> = 100 testers, 26 decliners FBOC women who were considering testing, recruited through a genetics program at a tertiary hospital, 46% affected	Overall distress (GSI:SCL-90) Cancer-related distress (IES) State anxiety (STAI) Depressive symptoms (CES-D)		No difference between testers and decliners in depression, anxiety or general distress at baseline.	Baseline comparison did not control for potential covariates
Kelly, Leventhal, Andrykowski et al., 2004, USA	Design: Prospective Method: Baseline (pre-counselling) questionnaire, post-counselling test decision	<i>n</i> = 94 testers (20+ve, 6-ve, 68 uninformative), 12 decliners FBOC Ashkenazi Jewish women who met pre-defined mutation-risk criteria, self- or physician-recruited, 50% affected	(-) Cancer-related distress (9 items adapted from POMS) Pre-counselling test intention (-10; 'absolutely will not' to 10; 'absolutely will') Self-reported provision of blood sample (yes/no) Receipt of test result (did/did not)	Age, education, income, affected status	No differences in cancer-related distress between decliners and testers who had no change in intentions to test. Pre-counselling trend for decliners to report higher cancer-related distress than testers who changed intentions to test (<i>p</i> = .07). Post-counselling trend for decliners to report higher cancer-related distress than testers who changed intentions to test (<i>p</i> = .07).	Unvalidated distress measure Decliner group small <i>n</i>
Reichelt, Heimdal, Moller & Dahl, 2004, Norway	Design: Prospective Method: Baseline (pre-counselling) questionnaire, post-counselling test decision	<i>n</i> = 287 testers, 58 decliners (not tested within 6mths of counselling) FBOC women from mutation-positive families registered with a hospital medical genetics unit, 15% affected	Anxiety and depression (HADS) General distress (GHQ-28) Hopelessness (BHS) Cancer-related distress - avoidance and intrusive thoughts related to 'cancer' (IES)		In unaffected women (<i>n</i> = 301), testers (<i>n</i> = 244) had a higher mean depression score than decliners (<i>n</i> = 57). No differences in anxiety, cancer-related distress, general distress or hopelessness.	Baseline comparison, although carried out separately for unaffected, did not control for other potential covariates
Thompson, Valdimarsdottir, Duteau-Buck et al., 2002, USA	Design: Prospective Method: Baseline (pre-counselling) questionnaire, post-counselling test decision	<i>n</i> = 40 testers (GC+GT+), 17 counselling decliners (GC-), 19 counselees who declined testing (GC+GT-) Unaffected African-American FBOC women enrolled in longitudinal study through a clinical genetics service	Cancer-related distress - intrusive thoughts related to 'the threat of breast cancer' (IES)	Unique contribution of variables assessed by logistic regression	Intrusive thoughts were independently associated with counselling/testing status. The GC- group reported less intrusive thoughts compared with GC+GT-. The GC+GT+ group did not report significantly different intrusive thoughts to either of the other groups.	

Table 1. (Continued)

Authors, year, country	Design and Method	Sample +ve = carrier -ve = non-carrier	Measures (-) indicates unvalidated measures	Control variables	Relevant Findings	Limitations
Biesecker, Ishibe, Hadley et al., 2000, USA	Design: Prospective Method: Baseline (pre-counselling) questionnaire, post-counselling test decision	<i>n</i> = 135 testers (includes "several" delayers), 37 decliners FBOC men and women enrolled in a familial cancer study at the National Cancer Institute, 8% affected	Depression (CES-D)		No difference between testers and decliners in depression at baseline.	Baseline comparison did not control for potential covariates Delayers (exact number unreported) not separated from testers
Lerman, Hughes, Trock et al., 1999, USA	Design: Prospective cohort study Method: Baseline (pre-education) phone interview, post-counselling decision to receive results	<i>n</i> = 84 testers (35+ve, 49-ve), 55 decliners HNPCC men and women from 4 extended HNPCC mutation-positive families, 19% affected	Depression (CES-D) Cancer-related distress - intrusive thoughts (IES)	Intra-family clustering, education, blood provision, marital	No difference between testers and decliners in cancer-related distress. Clinically significant levels of depressive symptoms (18% of sample) were associated with four-fold reduced uptake in women and two-fold reduced uptake in men.	Cancer-related distress comparison did not control for potential covariates
Lerman, Hughes, Lemon et al., 1998, USA [^]	Design: Prospective cohort study Method: Phone interview at baseline (pre-education), post-education test decision	<i>n</i> = 206 testers (97+ve, 109-ve), 121 decliners Affected and unaffected FBOC men and women from mutation-positive families registered at a hereditary cancer unit	Depression (CES-D)		No difference between testers and decliners in depression at baseline.	Baseline comparison did not control for potential covariates % affected not reported
Lerman, Schwartz, Lin, et al., 1997, USA ^{*^}	Design: Prospective Method: Baseline (post-notification of availability of testing/ pre-counselling) telephone interview, post-counselling decision to receive results	<i>n</i> = 86 testers, 63 decliners FBOC men and women from 11 families registered at a hereditary cancer unit, 17% affected	Outcome: Testing decision Predictors: Cancer-related distress - intrusive thoughts about 'having a family history of cancer' (IES) and general distress (CES-D)	Gender, objective risk (where affected = 100%), age, education, intra-family clustering	Those with lower IES scores (0-1) were more likely to decline than those with moderate (2-9) or higher (10+) scores. No difference between testers and decliners in depression (general distress) at baseline.	
Lerman, Narod, Schulman et al., 1996, USA ^{*^}	Design: Prospective cohort study Method: Baseline phone interview (pre-education and pre-test decision)	<i>n</i> = 115 testers (53+ve, 62-ve), 77 decliners FBOC men and women from 13 mutation-positive families registered at a hereditary cancer unit, 20% affected	Depression (CES-D)		No difference between testers and decliners in depression at baseline.	Baseline comparison did not control for potential covariates
Wiggins, Whyte, Huggins et al., 1992, Canada	Design: Prospective Method: Questionnaires at baseline (initial counselling), post-counselling test decision.	<i>n</i> = 95 testers (37 increased risk, 58 decreased risk), 40 'no change' (23 decliners, 17 uninformative result) Unaffected men and women at risk of HD participating in national genetic testing program	Psychological distress (GSI:SCL-90) Depression (BDI) Well-being (GWBS)		No differences between testers and decliners at baseline in psychological distress, depression or well-being.	

[#] * indicates studies with overlapping samples

[^] indicates studies which may have some overlap in samples

FBOC, Familial Breast/Ovarian Cancer; POMS, Profile of Mood States; HADS, Hospital Anxiety and Depression Scale; GHQ-28, General Health Questionnaire; BHS, Beck Hopelessness Scale; IES, Impact of Event Scale; GC, Genetic Counselling; GT, Genetic Testing; CES-D, Center for Epidemiological Studies Depression scale; HNPCC, Hereditary Non-Polyposis Colorectal Cancer; HD, Huntington's Disease; STAI, Spielberger State Trait Anxiety Inventory

Table 2a. Outcomes for decliners (cross-sectional)

Authors, year, country	Design and Method	Sample +ve = carrier -ve = non-carrier	Measures (-) indicates unvalidated measures	Control variables	Relevant Findings	Limitations
High quality						
Foster, Evans, Eeles et al., 2004, UK	Design: Cross-sectional Method: Baseline (at counselling, pre-test decision) questionnaire, compared to decliners CWS scores from separate questionnaire completed 12mths post-baseline	<i>n</i> = 275 testers, 27 decliners (including 5 delayers [tested post-participation]) Unaffected FBOC men and women from mutation-positive families who attended genetic centres for genetic counselling	Cancer worry (CWS)	Age	No demographic differences between decliners and delayers and testers. After controlling for age, decliners report less cancer worry than testers.	Delayers small <i>n</i> . Delayers not separated from decliners. Timing of assessments may have impacted distress levels.
Codori, Peteresen, Miglioretti et al., 1999, USA	Design: Cross-sectional Method: Self-report questionnaire for testers, phone interview for decliners	<i>n</i> = 77 testers, 181 decliners Unaffected men and women at risk of HNPCC participating in a colorectal cancer registry	Dependent variable: Testing decision Independent variable: frequency of cancer thoughts in past month (1 item, 4-point Likert scale)	Distance from hospital, intra-family clustering	More frequent cancer thoughts were significantly associated with study participation and, consequently, test uptake.	Test decline confounded with study decline. Age and education not controlled, despite differences. Single item to measure cancer-related distress
Decruyenaere, Evers-Kiebooms, Boogaerts et al., 1997, Belgium	Design: Cross-sectional Method: Self-report questionnaire	<i>n</i> = 63 testers, 14 decliners (applied for testing), 36 siblings (never applied for testing) Unaffected men and women at risk of HD who applied for testing at a genetics centre (and their siblings)	Anxiety (STAI)		Untested groups were pooled. No difference in anxiety between testers and decliners.	Bivariate statistical analyses precluded controlling for parity, which differed between tested and untested.
Moderate quality						
Lammens, Aaronson, Wagner et al., 2010, The Netherlands	Design: Cross-sectional Method: Self-report questionnaire and/or telephone interview	<i>n</i> = 52 testers (27+ve, 25-ve), 18 decliners/ delayers (4 had future testing intentions, 8 unsure about testing, 6 no intention to be tested) Men and women from 11 LFS mutation-positive families, 14% affected	Cancer-related distress - intrusive thoughts related to 'LFS' (IES) Cancer worry (CWS)	Age, gender	No differences in the number of decliners (17%), carriers (22%) and non-carriers (29%) reporting clinically significant levels of intrusive thoughts. No differences between groups in cancer worry.	Insufficient <i>n</i> . Unable to control for familial clustering.
Lodder, Frets, Trijsburg et al., 2003, The Netherlands	Design: Cross-sectional Method: Self-report questionnaire and/or telephone interview (decliners aware of possibility of testing >1yr earlier and did not apply for testing, testers assessed between blood sampling and result notification)	<i>n</i> = 85 testers, 13 decliners Decliners: women at risk of Testers: women who underwent testing between December 1995 and April 1998 FBOC participating in surveillance program at a cancer institute.	Anxiety and depression (HADS) (-) Cancer-related distress (9 items from IES)		No difference in cases of borderline-high anxiety and/or depression between decliners and testers. No difference in anxiety or depression between decliners and testers. 4/13 of the decliners reported at least 1 item in the cancer-related distress scale applied to them 'often'. The authors stated that "the others reported lower cancer-related distress levels", however no significance test was reported.	Affected status unreported but assumed to be unaffected. Timing of testers' assessment may have affected distress. Insufficient <i>n</i> . Evidence of between group demographic differences but small sample precluded multivariate analyses. Significance of between group differences in cancer-related distress not reported.

Table 2a. (Continued)

Adequate quality						
de Snoo, Riedijk, van Mil et al., 2008, The Netherlands	Design: Cross-sectional Method: Self-report questionnaire 0-6wks post-counselling/pre-testing	<i>n</i> = 75 testers, 19 decliners Men and women at risk of FM from 13 mutation-positive families associated with a tertiary medical centre skin screening clinic (Note: The melanoma mutation is also associated with a 17% pancreatic cancer risk)	Anxiety and depression (HADS) Cancer-related distress (IES) (-) DNA test expectancies (12 items, 5-point Likert scale) (-) Impact of pancreatic cancer information (3 items, 5-point Likert scale)	Gender, education	"Fears induced by the test result" and "worries" about melanoma and pancreatic cancer (from DNA test expectancies) were significantly associated with test decline. Both testers and decliners had low scores on the HADS, but no significance tests were reported. Did not report differences between testers and decliners for Impact of pancreatic cancer information, despite saying this was assessed.	Unclear whether psychological questionnaire before or at time of decline. Used unvalidated measures. Insufficient <i>n</i> and poor response rate (51%) "Given the relatively small sample size, only gender and educational level were entered as possible covariates" (p.793). Significance of between group differences in HADS scores not reported.

* indicates studies with overlapping samples

FBOC, Familial Breast/Ovarian Cancer; CWS, Cancer Worry Scale; HNPCC, Hereditary Non-Polyposis Colorectal Cancer; HD, Huntington's Disease; STAI, Spielberger State Trait Anxiety Inventory; LFS, Li-Fraumeni Syndrome; IES, Impact of Event Scale; HADS, Hospital Anxiety and Depression Scale; FM, Familial Melanoma

Table 2b. Outcomes for decliners (longitudinal)

Authors, year, country	Design and Method	Sample +ve = carrier -ve = non-carrier	Measures (-) indicates unvalidated measures	Control variables	Relevant Findings	Limitations
High quality						
Dougall, Smith, Somers et al., 2009, USA*	Design: Prospective Method: Questionnaires at baseline (post-counselling, pre-test decision), 1 week post-result or 3-4mths post-baseline for decliners (T2), 3mths post-T2, 6mths post-T2	<i>n</i> = 100 testers (positive, negative [uninformative], variant), 26 decliners FBOC women who were considering testing, recruited through a genetics program at a tertiary hospital, 46% affected	Distress (composite score calculated from GSI:SCL-90, IES, PSS, STAI, CES-D)	Age, income, use of psychiatric medication	No difference between testers and decliners in distress at any time point.	Composite distress score of questionable validity - calculated from variables correlated with each other as low as 0.42. Tested subgroup <i>ns</i> unreported
Smith, Dougall, Posluszny et al., 2008, USA*	Design: Prospective Method: Questionnaires at baseline (post-counselling, pre-test decision), 1 week post-result or 3-4mths post-baseline for decliners (T2), 3mths post-T2, 6mths post-T2	<i>n</i> = 100 testers (positive, negative [uninformative], variant), 26 decliners FBOC women who were considering testing, recruited through a genetics program at a tertiary hospital, 46% affected	Overall distress (GSI:SCL-90) Cancer-related distress (IES) State anxiety (STAI) Depressive symptoms (CES-D)	Age, income, education, use of psychiatric medication	No difference between groups in cancer-related distress at baseline or 1week post-result, but 3mths post-test those with uninformative/negative or variant results reported less intrusion than decliners and carriers. At 6mths decliners reported significantly more cancer-related distress than those with variant results.	Tested subgroup <i>ns</i> unreported
Lerman, Hughes, Lemon et al., 1998, USA^	Design: Prospective cohort study Method: Phone interview at baseline (pre-education), 1mth & 6mth follow-up	<i>n</i> = 206 testers (97+ve, 109-ve), 121 decliners FBOC men and women from mutation-positive families registered at a hereditary cancer unit	Cancer-related distress - intrusive thoughts about 'having cancer in the family' (IES) Depression (CES-D)	Baseline depression, gender, affected status, marital status	No difference between groups in depression at baseline. Significant difference in prevalence of depression at 1mth - 8% non-carriers, 14% carriers and 19% decliners. Multivariate analyses revealed that higher rates of depression at follow-up were only seen for decliners with elevated baseline cancer-related distress (see Table 3).	% affected not reported

Table 2b. (Continued)

Lerman, Narod, Schulman et al., 1996, USA [^]	Design: Prospective cohort study Method: Baseline (1-2mths pre-education) phone interview, 1mth follow-up phone interview (1mth post-testing decision/result notification)	<i>n</i> = 115 testers (53+ve, 62-ve), 77 decliners FBOC men and women from 13 mutation-positive families registered at a hereditary cancer unit, 19% affected	Depression (CES-D)	Intra-family clustering, affected status, baseline levels of outcome variables	For unaffected participants, there were greater reductions in depression for non-carriers compared with carriers and decliners at 1mth follow-up.
Wiggins, Whyte, Huggins et al., 1992, Canada [#]	Design: Prospective Method: Questionnaires at baseline (at initial counselling, pre-decision), 6mth and 12mth follow-up.	<i>n</i> = 95 testers (37 increased risk, 58 decreased risk), 40 'no change' (23 decliners, 17 uninformative result) Unaffected men and women at risk of HD participating in national genetic testing program	Psychological distress (GSI:SCL-90) Depression (BDI) Well-being (GWBS)	Difference scores used to minimise effect of baseline differences on outcomes	At 6mths, increase in well-being for the decreased risk group significantly different to reductions in well-being in 'no change' group. At 12mths, improvements in psychological distress in tested groups differed significantly from deterioration in 'no change' group. Reductions in well-being relative to baseline in 'no change' group at 6 and 12mths. At 12mths, depression had increased, compared to baseline, for 'no change' group compared to both tested groups.
Adequate quality					
Lawson, Wiggins, Green et al., 1996, Canada [#]	Design: Retrospective Method: Utilise data from Wiggins et al., 1992 study as well as questionnaire completed by clinicians and counsellors	<i>n</i> = 95 testers (37 increased risk, 58 decreased risk), 23 decliners, 17 uninformative result Men and women at risk of HD participating in national genetic testing program	Adverse event since baseline -whether clinical and/or quantitative criteria were met. Clinical = suicide attempt/plan, psychiatric hospitalisation, depression > 2mths, increase in substance use, breakdown of important relationships. Quantitative = clinically relevant changes in GSI and BDI	N/A	No significant difference between groups in number of adverse events. Baseline depression not controlled for. They did not use self-report of adverse events. Chi-square conducted where there were <5 cases in two cells.
* and [#] indicate studies with overlapping/same samples [^] indicates studies which may have some overlap in samples FBOC, Familial Breast/Ovarian Cancer; GSI:SCL-90, Global Severity Index of Symptom Checklist-90; IES, Impact of Event Scale; PSS, Perceived Stress Scale; STAI, Spielberger State Trait Anxiety Inventory; CES-D, Center for Epidemiological Studies Depression scale; BDI, Beck Depression Inventory; HD, Huntington's Disease; GWBS, General Well-Being Scale					

Table 2c. Outcomes for individuals who are ineligible for testing

Authors, year, country	Design and Method	Sample +ve = carrier -ve = non-carrier	Measures (-) indicates unvalidated measures	Control variables	Relevant Findings	Limitations
High quality						
Geirdal & Dahl, 2008b, Norway*	Design: Cross-sectional Method: Self-report questionnaires; 3mths post-counselling for ineligible for testing, 6wks post-result for carriers	<i>n</i> = 68 carriers, 174 ineligible for testing, Unaffected women at risk of FBOC who attended a hereditary cancer registry.	Anxiety and depression (HADS)	Education	Compared with the carriers, anxiety was higher in women who were ineligible for testing, but prevalence of disorder in both groups was 24%.	Cross-sectional design precludes controlling for pre-existing differences between groups. Did not control for differences between groups in familial cancer-related events.
Geirdal, Maehle, Heimdal et al., 2006, Norway*	Design: Cross-sectional Method: Self-report questionnaires 3mths post-counselling	<i>n</i> = 239 ineligible for testing, 1195 age-matched population controls. Women from families with no identified mutation who are at risk of FBOC (<i>n</i> = 176) or HNPCC (<i>n</i> = 63); members of a hereditary cancer registry. Risk groups combined due to lack of clinically significant differences.	Mental QoL (MCS: SF-12) Cancer-related distress - intrusion and avoidance related to 'cancer risk' (IES)	Age	No difference between women who were ineligible for testing and controls in prevalence of mental quality of life cases.	
Geirdal, Reichelt, Dahl et al., 2005, Norway*	Design: Cross-sectional Method: Self-report questionnaires 3mths post-counselling for ineligibles and 6wks post result for carriers	<i>n</i> = 68 carriers, 239 ineligible for testing, 10,000 age-matched population controls. Unaffected women at risk of FBOC (<i>n</i> = 176) or HNPCC (<i>n</i> = 63) who attended a hereditary cancer registry. Risk groups combined due to lack of clinically significant differences.	Anxiety and depression (HADS) Psychosocial distress (GHQ-28) Hopelessness (BHS) Cancer-related distress - intrusion and avoidance related to 'cancer risk' (IES)	Children, relatives with cancer, affected parent, marital status, education	No difference between carriers and ineligible for testing in cancer-related distress. Women ineligible for testing reported higher anxiety, more anxiety cases, and lower depression than controls. FBOC women ineligible for testing reported higher anxiety, depression and psychosocial distress, and more depression and psychosocial distress cases than carriers.	Cross-sectional design precludes controlling for pre-existing differences between groups. Did not control for differences between groups in familial cancer-related events.
Meiser, Butow, Friedlander et al., 2002, Australia	Design: Prospective Method: Questionnaires at baseline (pre-counselling for tested women), 7-10days post-notification (post-baseline for untested), 4mths & 12mths post-baseline	<i>n</i> = 90 testers (30+ve, 60-ve), 53 ineligible for testing controls Unaffected FBOC women who had approached a familial cancer clinic or outreach clinic	Cancer-related distress - intrusion and avoidance related to 'being at risk of developing breast cancer' (IES) Anxiety (STAI) Depression (BDI)	N/A	Carriers had higher cancer-related distress 7–10 days and 12mths post-notification compared to baseline and ineligible for testing, and a trend for higher cancer-related distress 4mths post-notification (<i>p</i> =0.054). Compared with ineligible for testing, carriers reported reductions in anxiety at 12mths and non-carriers reported reductions in anxiety at 7–10 days. Trend for lower state anxiety in non-carriers compared with ineligible for testing 4mths post-notification.	Did not control for differences between groups in familial cancer-related events

* indicates studies with overlapping samples

FBOC, Familial Breast/Ovarian Cancer; HADS, Hospital Anxiety and Depression Scale; HNPCC, Hereditary Non-Polyposis Colorectal Cancer; QoL, Quality of Life; MCS: SF-12, Mental Component Scale of the Short-Form 12 Health Survey; IES, Impact of Event Scale; GHQ-28, The General Health Questionnaire; BHS, Beck Hopelessness Scale; STAI, Spielberger State Trait Anxiety Inventory; BDI, Beck Depression Inventory

Table 3. Vulnerability factors for individuals who decline, delay or remain ineligible for testing

Authors, year, country	Design and Method	Sample +ve = carrier -ve = non-carrier	Measures (-) indicates unvalidated measures	Control variables	Relevant Findings	Limitations
High quality						
Geirdal & Dahl, 2008a, Norway*	Design: Cross-sectional Method: Self-report questionnaires 3mths post-counselling	<i>n</i> = 238 ineligible for testing Unaffected women from families with no identified mutation at risk of FBOC (<i>n</i> = 175) or HNPCC (<i>n</i> = 63); attendees of a hereditary cancer registry. Risk groups combined due to lack of clinically significant differences.	Personality traits (TCI) Optimism (LOT) Hopelessness (BHS) Mental distress (HADS) Cancer-related distress - intrusive thoughts related to 'the risk of developing breast cancer' (IES)	N/A	HADS - number of affected female relatives, harm avoidant and persistent temperamental traits, less self-directedness and less optimism associated with higher mental distress; harm avoidance strongest association. IES - cancer in a parent, harm avoidance, persistence and less optimism associated with cancer-related distress, optimism had strongest association.	
Geirdal & Dahl, 2008b, Norway*	Design: Cross-sectional Method: Self-report questionnaires; 3mths post-counselling for ineligible for testing, 6wks post-result for carriers	<i>n</i> = 174 ineligible for testing, 68 carriers Unaffected women at risk of FBOC who attended a hereditary cancer registry.	Coping strategies (COPE) Anxiety (HADS)	Education	'Focus on and venting of emotions', 'restraint coping' and 'behavioral disengagement' associated with increased prevalence of anxiety disorder in women who were ineligible for testing.	
Geirdal, Maehle, Heimdal et al., 2006, Norway*	Design: Cross-sectional Method: Self-report questionnaires 3mths post-counselling	<i>n</i> = 239 ineligible for testing, 1195 age-matched population controls Unaffected women from families with no identified mutation who are at risk of FBOC (<i>n</i> = 176) or HNPCC (<i>n</i> = 63); attendees of a hereditary cancer registry. Risk groups combined due to lack of clinically significant differences.	<u>Risk group:</u> Mental QoL (MCS: SF-12) Cancer-related distress - intrusion and avoidance related to 'cancer risk' (IES) <u>Controls:</u> Quality of life (SF-36)		Risk of poor mental QoL associated with being unpartnered for controls and women ineligible for testing. Poor mental QoL was associated with intrusion and avoidance in both groups.	
Lerman, Hughes, Lemon et al., 1998, USA	Design: Prospective cohort study Method: Baseline (pre-education) phone interview, 1mth & 6mth follow-up phone interviews	<i>n</i> = 206 testers (97+ve, 109-ve), 121 decliners FBOC men and women from mutation-positive families registered at a hereditary cancer unit	Low-moderate stress vs high stress; 0-10 vs 11-33, respectively scored for intrusive thoughts about 'having cancer in the family' (IES) Depression (CES-D)	Baseline depression, gender, affected status, marital status	For high stress, decliners 8x more likely to become depressed compared with non-carriers at 1mth follow-up. For unaffected high stress, higher rates of depression in decliners (44%) compared with carriers (24%) and non-carriers (16%) at 6mth follow-up.	% affected not reported

* indicates studies with overlapping samples

FBOC, Familial Breast/Ovarian Cancer; HNPCC, Hereditary Non-Polyposis Colorectal Cancer; TCI, The Temperament and Character Inventory; LOT, Life Orientation Test; BHS, Beck Hopelessness Scale; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Event Scale; COPE, Coping Orientation to Problems Experienced Scale; QoL, Quality of Life; MCS: SF-12, Mental Component Scale of the Short-Form 12 Health Survey; SF-36, Short-Form 36 Health Survey; CES-D, Center for Epidemiological Studies Depression scale

Appendix 1. Disease characteristics

Disease	Risk for mutation carriers	Prevention options	Screening options	Treatment options
Familial Breast/Ovarian Cancer (FBOC)	Up to 85% breast cancer risk and 60% ovarian cancer risk by age 70	Chemoprevention Prophylactic surgery - removal of breasts and/or ovaries	Mammogram Breast ultrasound MRI Transvaginal ultrasound (TVU) CA-125 blood test for ovarian cancer	Surgery Chemotherapy Radiation therapy Hormone therapy Targeted therapies
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)	80-85% Increased risk also for cancer of the uterus, stomach, small intestine, pancreas, kidney, ureter and ovary	Prophylactic surgery - removal of part or all of colon	Fecal occult blood test Colonoscopy Urine cytology TVU CA-125	Surgery Chemotherapy Radiation
Li-Fraumeni Syndrome (LFS) - high risk of various cancers from early childhood	Up to 90% lifetime risk, 20% risk before age 20	None (possible prophylactic mastectomy for female mutation carriers)	Unclear due to risk of cancer at multiple sites and possible increased sensitivity to radiation, but regular medical checks are carried out	Available but vary depending on type of cancer
Familial Melanoma (FM)	60-90% Possibility of concomitant increased pancreatic cancer risk (<20%)	Limitation of sun exposure	Skin examination	Surgery Chemotherapy Immunotherapy Radiation
Huntington's Disease (HD) - progressive neuropsychiatric disorder	100% - late onset	None	Physical and psychological screening to identify signs of disease onset	None, although treatments are available to manage and lessen symptoms