Measuring the effects of genetic testing: studies on thrombophilia, sickle cell trait, recurrent miscarriage and male subfertility
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Chapter 2

Evaluating the psychological effects of genetic testing in symptomatic patients

*a systematic review*

Fleur Vansenne, Patrick M.M. Bossuyt, Corianne A.J.M. de Borgie

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ABSTRACT

Most research on the effects of genetic testing is performed in individuals at increased risk for a specific disease (pre-symptomatic subjects) but not in patients already affected by disease. If results of these studies in pre-symptomatic subjects can be applied to patients is unclear. We performed a systematic review to evaluate the effects of genetic testing in patients and describe the methodological instruments used. 2611 Articles were retrieved and 16 studies included. Studies reported great variety in designs, methods and patient outcomes. In total 2868 participants enrolled of which 62% were patients. Patients appeared to have a lower perceived general health and higher levels of anxiety and depression than pre-symptomatic subjects before genetic testing. In the long term no psychological impairment was shown. We conclude that patients differ from pre-symptomatic subjects and may be more vulnerable to negative effects of genetic testing. Conclusions from earlier research on pre-symptomatic genetic testing cannot be generalized to patients, more standardized research is needed.

INTRODUCTION

Since the Human Genome Project progressively more genetic factors have been discovered that are risk factors in the development of disease.\(^1\) This has resulted in the growing use of tests to identify these genetic factors in patients affected by certain diseases or conditions. To support decision making in health care regarding the increasingly available genetic tests, the additional value of genetic testing should be clearly demonstrated.\(^2\) In general, the clinical utility of these genetic tests is rarely evaluated before they are introduced in clinical care.\(^3\) Consequently evidence of the clinical effectiveness of genetic testing in symptomatic patients is often lacking. We often do not know the positive or the negative effects of genetic testing, from the health professional and from the patient’s perspective.

Research on the psychological effects of genetic testing has been primarily performed within pre-symptomatic subjects. These are subjects at increased risk but yet unaffected, identified in high-risk populations or as members of affected families.\(^4\) Testing pre-symptomatic persons allows for extensive genetic counseling, where benefits, limitations, risks of testing and coping strategies can be discussed. In daily clinical practice, genetic testing in symptomatic patients often leaves no time for this kind of extensive counseling. Conclusions based on research in pre-symptomatic subjects can therefore not automatically be generalized to symptomatic patients. At this moment, the psychological effects of genetic testing in symptomatic patients are largely unknown. A number of studies is available, but numbers are small, the results apparently conflicting, and conclusions variable. We therefore performed a systematic review of the published studies, relying on a systematic search of the literature and standardized data extraction.

METHODS

Search strategy

Potential eligible articles were systematically searched for in the MEDLINE (1966 to October 2008), EMBASE (1985 to October 2008) and PsychInfo databases (1806 to October 2008). We did not use language restrictions. The following search terms were used, both as MESH terms and free text (unless noted otherwise). Patients: no specific search terms. Intervention: “genetic testing”, “genetic screening”, disease, diagnosis Comparison: no specific search terms.
Outcomes: “psychology”; anxiety; anxieteries; nervousness; stresses; distress; psychological; “impact”; psychosocial; worry; worrying; “stress, psychological”; anguish; “mental suffering”; distress; emotion; “Stress”; depressive; “Depression”; worries; “risk perception”.

Bibliographies of relevant articles were scanned for additional articles. Recent overview articles and relevant reports were also studied. In addition we searched the Health Technology Assessment (HTA)-database and the Database of Abstracts of Reviews of Effects (DARE).

Selection

Identified publications were assessed for eligibility by reading title and abstract. They were included if they described (a) a prospective study, (b) evaluating a genetic test, (c) in at least 20 patients and, (d) using one or more validated psychological instruments. Psychological instruments were considered validated if they had been satisfactorily tested previously in the population for which they had been designed. Full copies of potentially eligible manuscripts were obtained. After reading the full text, articles were evaluated for eligibility and only included if they met all inclusion criteria.

One reviewer (FV) assessed the title and abstract of references identified by the search strategy. The full reports of all potentially eligible studies were then evaluated independently by two reviewers (FV and CdB). Any disagreements were resolved in discussions. Data from selected articles were extracted and evaluated by one reviewer (FV).

Because we anticipated substantial heterogeneity, no attempt at formal meta-analysis was made. Our primary goal was to summarize the effects of the genetic test in symptomatic patients. Secondary, we summarized study design features, such as outcome parameters and study population, and methods, such as instruments and moments of evaluation.

RESULTS

In total, 2,611 manuscripts were retrieved and assessed for eligibility by reading title and abstract (See figure 1). Many manuscripts retrieved from EMBASE and PsycINFO were reports of qualitative or observational studies and therefore did not meet our selection criteria. In total 48 studies were potentially eligible. When the full text was obtained 32 studies could not be included, most often because no symptomatic patients had been included in the study. A set of 16 studies met our inclusion criteria and were assessed completely (table 1). The study reports had been published between 2000 and 2008. They had been conducted in the United States (n=8), the Netherlands (n=3), Italy (n=2), the United Kingdom (n=1), Norway (n=1) and Canada (n=1). Included studies were classified according to the disease for which patients were tested. We present the characteristics of the included studies related to genetic testing for hereditary cancers in table 1A, and for all other diseases in table 1B.

Study groups

In the 16 studies, a total of 2,868 participants had been included, of which 1,775 (62%) were patients. In five studies all participants were symptomatic patients. The other studies compared patients undergoing symptomatic genetic testing with high-risk subjects undergoing pre-symptomatic genetic testing. The percentage of symptomatic patients per study varied from 15% to 68%.

In more than two-thirds of the studies (n=11) all participants were female. They either have (had) breast and/or ovarian cancer or were at high risk for these diseases. The other studies included patients and pre-symptomatic subjects with colon cancer, a combination of breast, ovarian or colon cancer, hemochromatosis, thrombosis and familial hypercholesterolemia. In these studies the percentage males varied between 8% and 44%.

Participants had been enrolled in the studies through specialized (cancer) clinics, clinical genetics departments, or at their own initiative. Socio-demographics were comparable between studies (except for gender). The majority of participants were Caucasian (85-100%), with a mean age of 50, married (70 to 87%), with children (66-98%) and at least college level education.
Evaluating the psychological effects of genetic testing in patients: a systematic review

Chapter 02

Evaluation of the effects of genetic testing

Timing of Assessment

The number of points in time at which the effects of genetic testing were measured varied from 1 (n=1), 2 (n=6), 3 (n=8) to 4 (n=1). The actual timing relative to testing varied greatly and we therefore defined five time frames (table 2). Two-thirds of the studies (n=11) reported a measurement before the first meeting with the physician about the genetic test (baseline). Most studies (n=10) reported a (short) follow-up period after disclosure of the genetic test result (median 2.0 months, IQR 1-6 months). Only 6 studies reported a measurement (more than) 1 year after disclosure of the genetic test result.

Evaluation of the effects of genetic testing

Effects of genetic testing

In eight studies that evaluated genetic testing for hereditary cancer no differential effects of disclosure of the genetic test result on psychological well-being were found. Gritz et al. and Condello et al. described that mean scores on depression and anxiety scales remained stable over time and within normal limits for cancer-affected participants, regardless whether a mutation was found (positive result) or not. In the study of Gritz et al. the mean score on the STAI-State in women with a mutation was 32.2 (SD 8.2) at baseline, and 36.2 (SD 11.5) at 12 months follow-up. For women without a mutation these scores were 31.9 (SD 9.3) and 32.1 (SD 9.4) respectively (p-values not reported). These scores were all within normal ranges. Both studies found an association between anxiety and depression scores at baseline and at follow-up, where higher scores at baseline were linked to higher scores at follow-up, with no influence of mutation status.16,19

Figure 1: Flowchart search strategy: selection and inclusion

Figure 1: Flowchart search strategy: selection and inclusion

Evaluation study design genetic testing

Measurements

Included papers reported a great variety in instruments and outcome parameters used to describe the effects of genetic testing (See tables 1 and 2). The instruments can be grouped into two categories: Quality of Life (both generic and disease-specific) and psychological well-being (anxiety, depression, disease-specific distress, post-traumatic stress). To measure Quality of Life seven different instruments had been used. Anxiety was measured by three different instruments, of which two were used in four different versions. Depression was measured by three different instruments. To determine disease-specific stress the Impact of Event Scale (IES) was often used, (sometimes only a subscale). The IES was anchored to the occurrence or recurrence of the underlying disease, which was cancer in all studies. One study also used the Multidimensional Impact of Cancer Risk Assessment (MICRA) to determine disease-specific stress.23
Table 1: Characteristics of included studies: patients with cancer, study design and results of evaluation of genetic testing.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population (n)</th>
<th>Subject of evaluation</th>
<th>Design</th>
<th>Used instruments Psychological wellbeing (anxiety, depression, other)</th>
<th>Used instruments QoL (generic(G), disease specific (DS))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood</td>
<td>2000</td>
<td>♀ patients with B/Ov with positive family history B/Ov (n=35)</td>
<td>test before/after test BRCA+ vs. BRCA-</td>
<td>HSCL-25 (G)</td>
<td>IES (O)</td>
<td></td>
</tr>
<tr>
<td>Tercyak</td>
<td>2001</td>
<td>♀ patients with B/Ov (n=55) High risk ♀ with positive family history B/Ov (n=52)</td>
<td>test before/after test BRCA+ vs. BRCA-</td>
<td>STAI-State (A)</td>
<td>MBSS (O)</td>
<td></td>
</tr>
<tr>
<td>Schwartz</td>
<td>2002</td>
<td>♀ patients with B/Ov (n=186) High risk ♀ from family with known BRCA mutation (n=93)</td>
<td>test before/after test BRCA+ vs. BRCA-</td>
<td>HSCL-25 (G)</td>
<td>IES (O)</td>
<td></td>
</tr>
<tr>
<td>Loader</td>
<td>2004</td>
<td>♀ patients with B/Ov (n=87) High risk ♀ with positive family history B/Ov (n=87)</td>
<td>test before/after test B/Ov vs no B/Ov BRCA+ vs. BRCA-</td>
<td>SF-36 (G)</td>
<td>BDI (D)</td>
<td></td>
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<tr>
<td>Reichelt</td>
<td>2004</td>
<td>Families with known BRCA1 mutation: ♀ patients with B/Ov (n=43) ♀ without B/Ov (n=244)</td>
<td>test before/after test BRCA+ vs. BRCA-</td>
<td>GHQ-28 (G)</td>
<td>HADS (A/D)</td>
<td></td>
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<tr>
<td>Van-Roosmalen</td>
<td>2004</td>
<td>♀ patients with B/Ov (n=192) ♀ with positive family history B/Ov (n=176)</td>
<td>test before test B/Ov and no B/Ov before/after positive test result</td>
<td>STAI-State (A)</td>
<td>CESD (D)</td>
<td></td>
</tr>
<tr>
<td>Schwartz</td>
<td>2004</td>
<td>♀ patients with B, recently diagnosed, with positive family history (n=194)</td>
<td>test BRCA+ vs. BRCA-</td>
<td>FACT-GQ (DS)</td>
<td>STAI-State (A)</td>
<td></td>
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<tr>
<td>Gritz</td>
<td>2005</td>
<td>Patients with C (n=89) ♀/♀ with positive family history C (n=66)</td>
<td>test MSH2/MLH1+ vs. MSH2/MLH1- Before / after test result</td>
<td>QLI (G)</td>
<td>STAI-State (A)</td>
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<tr>
<td>Loader</td>
<td>2005</td>
<td>patients with C, with positive family history B/Ov (n=36)</td>
<td>test MSH2/MLH1+ vs. MSH2/MLH1-</td>
<td>IES-Intrusion (O)</td>
<td>SSQ (O)</td>
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<td>♀ patients with B/Ov (n=105) ♀ with positive family history B/Ov (n=133)</td>
<td>uninformative test result vs BRCA+ and BRCA-</td>
<td>uninformative test result</td>
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<tr>
<td>Condello</td>
<td>2007</td>
<td>♀ patients with B/Ov (n=25) ♀ with positive family history B/Ov (n=12)</td>
<td>test B/Ov vs. no B/Ov before / after test result</td>
<td>HAD (A/D)</td>
<td>FACES III (O)</td>
<td></td>
</tr>
<tr>
<td>Tercyak</td>
<td>2007</td>
<td>♀ patients with B, recently diagnosed, with positive family history (n=149)</td>
<td>test BRCA+ vs. BRCA-</td>
<td>C282Y mutation and 5569A polymorphism in HFE gene vs no mutations</td>
<td>SF-36 (G)</td>
<td>STAI (A)</td>
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<tr>
<td>Marteau</td>
<td>2004</td>
<td>Patients with clinical diagnosis or family history of HC (n=117)</td>
<td>test genetic testing</td>
<td>genetic testing vs. no genetic testing</td>
<td>HADS part (A/D)</td>
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<td>Legnani</td>
<td>2006</td>
<td>Patients with thrombophilic disease (n=63) Healthy relatives of patients (n=22)</td>
<td>test thrombophilic vs. thrombophilic -</td>
<td>CBA-H</td>
<td>A-scale (A)</td>
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Table 1: Characteristics of included studies: patients, study design and used instruments for evaluation of genetic testing.

Used abbreviations:

Abbreviations of used instruments:
Table 2 Moments of evaluation, before and after the genetic test, per study.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Before 1st genetic consultation, before disclosure</th>
<th>After 1st genetic consultation, before disclosure</th>
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<th>&gt; 6 weeks after disclosure genetic test result</th>
<th>&gt; 1 year after disclosure genetic test result</th>
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<td>Legnani</td>
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</tbody>
</table>

Tercyak et al. found in both his studies a significant increase in distress in patients with hereditary breast and ovarian cancer after receiving a positive genetic test result, compared to their baseline scores and to patients with a negative genetic test result (scores not reported). Van Roosmalen et al. described an increase in distress from baseline in women with an uninformative test result, i.e. a negative test result in the absence of a known mutation in the family, whereas scores in women with a positive test result remained stable over time.

The studies that evaluated genetic testing for other diseases than hereditary cancer found no negative psychological consequences of disclosure of the test result. Marteau et al. found no effects of mutation status on well-being, compared to baseline scores. Power and Adams, and Legnani et al. described a decrease in anxiety after receiving a positive test result, while anxiety levels remaining stable in participants receiving a negative test result (no scores reported).

Nine studies used the IES to measure disease-related distress before and after genetic testing. In an attempt to compare the results of the different studies, we present in figure 2 the mean IES total stress scores and the standard error of the mean after disclosure of the genetic test result in symptomatic patients. This was possible in only five studies, since some studies only used a subscale of the IES or did not report the scores. Van Dijk et al. presented IES-scores in two affected groups, those with and without a mutation found. In each study, all total scores were within normal limits and there were no significant differences in mean scores between studies.

Patients vs. pre-symptomatic subjects

A few studies have reported differences between patients and pre-symptomatic subjects, mostly at baseline. Van Roosmalen et al. showed that women with breast and/or ovarian cancer had significantly higher scores on depression and cancer related distress and a lower score on general health at baseline compared to pre-symptomatic women. The mean scores on the CESD at baseline were 10.0 (SD 8.6) for affected women and 7.6 (SD 8.0) for unaffected women (p=0.01). After receiving a positive test result they found high anxiety and depression scores in affected and healthy pre-symptomatic women, resulting in comparable scores in these two groups after disclosure. In a sub-analysis Van Roosmalen et al. found that this worse well-being at baseline applied especially to women who had been diagnosed with cancer less than one month after the genetic test result for hereditary breast and ovarian cancer, regardless of mutation status (scores not reported). Van Dijk et al. described an increase in distress from baseline in women with an uninformative test result, i.e. a negative test result in the absence of a known mutation in the family, whereas scores in women with a positive test result remained stable over time.
Loader et al. and Reichelt et al. also reported more distress and worse well-being in cancer patients compared to pre-symptomatic subjects at baseline. In the study of Legnani et al. more depressive feelings were observed in patients compared to healthy controls at baseline (scores not reported). On the other hand, Schwartz et al., Van Dijk et al. and Gritz et al. reported no significant differences in psychological well-being between cancer patients and pre-symptomatic subjects at baseline.

**Other outcomes**

Five studies studied the effects of genetic testing on behaviour and evaluated changes in behaviour before and after genetic testing. These studies looked at risk-reducing behaviour, the willingness to take medication, and the choice for (preventive) surgical treatment. Loader et al. reported that participants were more adherent to surveillance measures for colon and endometrial cancer 12 months after disclosure as the number of cases of cancer in the family increased, as well as with more worries about cancer. The result of the genetic test for hereditary colon cancer had no influence on this adherence. Schwartz et al. reported that the result of the genetic test for hereditary breast and ovarian cancer had a strong influence on the choice for surgical treatment options in women with recently diagnosed breast cancer. Women with a positive genetic test result opted significantly more often for extensive surgery, such as a bilateral mastectomy, compared to women who had received a negative genetic test result (48% versus 24% respectively). In the study of Tercyak et al. the same surgery for the same condition was evaluated, here 54% of women with a positive genetic test result opted for contralateral mastectomy compared to 25% of women with a uninformative genetic test result. Behaviour was also influenced by the genetic test result in the study by Loader et al. After receiving a positive genetic test result for hereditary breast and ovarian cancer 89% of the women who had completed childbearing had a prophylactic oophorectomy within 4 years after disclosure, compared to none of the women with cancer and a negative genetic test result.

In the study of Marteau et al. patients with familial hypercholesterolemia and a positive genetic test result express less strong beliefs in the efficacy of diet in reducing their cholesterol level six months after disclosure, and stronger beliefs in the efficacy of cholestero-lowering medication, compared to patients with a negative genetic test result and patients who had not been genetically tested. This did not lead to changes in risk-reducing behaviour in the positive test result group, compared to baseline. Neither were there changes in risk-reducing behaviour in the negative result group six months after disclosure.

Figure 2 Mean (plus SEM) total stress score on the IES-questionnaire after disclosure of the genetic test result compared between studies.

Range of IES total scores between 0-75. Score 0-8 subclinical range, 9-25 mild range, 26-43 moderate range, 44 or more severe range.

Abbreviations: IES: Impact of Event Scale, SEM: standard error of the mean, B+: breast cancer, BRCA+: mutation present in gene involved in hereditary breast and ovarian cancer, uninf.: uninformative test result.
DISCUSSION

This systematic review of research on psychological effects of genetic testing in symptomatic patients revealed a great variety in outcomes. Overall, disclosure of the result of the genetic test does not seem to have negative effects on long term well-being, in terms of anxiety, depression or disease-specific distress. In the short term, just after disclosure of the genetic test result, an effect on well being is sometimes observed, in terms of an increase in depressive feelings and anxiety or distress.\textsuperscript{10,14,23} In general, these effects are in concordance with studies on the psychological effects of pre-symptomatic genetic testing.\textsuperscript{18,25}

Health-related behaviour seems to be influenced by the genetic test result, especially in hereditary cancer syndromes, where more often (preventive) strategies such as surveillance or surgery exist.\textsuperscript{12,15,17,21,23} Some researchers reported differences between symptomatic patients and pre-symptomatic subjects, with patients reporting a lower general health, more feelings of depression, and more disease-specific distress before the genetic testing process.\textsuperscript{10,14} In others this was not found.\textsuperscript{15,17,21}

We observed a great variety in study design (outcome parameters and population) and methods (measurements and moments) making formal meta-analysis hazardous. Only 16 of all retrieved manuscripts met all our inclusion criteria. Most of the published studies on the effects of genetic testing are qualitative or only include pre-symptomatic subjects.

Genetic testing in symptomatic patients differs from testing pre-symptomatic subjects. Unlike pre-symptomatic subjects, patients have been diagnosed with an underlying disease, and this will already affect their well-being. Patients reported a lower well-being before genetic testing than pre-symptomatic subjects in some studies. The genetic test has an additional effect on well-being, which might make patients more vulnerable than pre-symptomatic subjects. The difference between the measurement of the psychological impact of a disease and the psychological impact of a genetic test was not always taken into consideration in the 16 studies we found. An illustrative example is the use of the Impact of Event Scale (IES), which has been used in nine studies to measure trauma-related psychological distress. All studies reported the use of the IES to measure disease-related stress, whereas the scores on the instrument are used to interpret the effect of genetic testing. The effect of the underlying disease should be taken into account in measuring the effect of genetic testing, as the two events are not identical.\textsuperscript{26}

There is a difference between patients and pre-symptomatic subjects in the way they are confronted with genetic testing, where patients are often tested within their diagnostic work-up, without receiving pre-test counseling, and they are sometimes even unaware of the fact that a genetic test is performed, where pre-symptomatic patients are most often self-referred.\textsuperscript{27}

In the past, authors have already suggested that extensive pre-test counseling might lead to a (self-) selection in pre-symptomatic subjects where participants who feel that they may not be able to cope with the genetic test result do not proceed with the testing procedure.\textsuperscript{24,29} Others even suggested that self selection has already taken place before genetic counseling in self-referrals. There is evidence that substantial numbers of pre-symptomatic subjects never present at clinical genetics departments, especially for genetic testing for untreatable conditions, such as Huntington's disease.\textsuperscript{30} These self-selection mechanisms could lead to more favourable psychological outcomes in pre-symptomatic subjects after testing.\textsuperscript{28,29} Several authors have indicated that pre-symptomatic subjects who seek genetic testing are generally well-educated and of high social economic status.\textsuperscript{23,29,31,32} The psychological effects of genetic testing in a clinic-based sample may therefore have very different, and potentially worse, outcomes.\textsuperscript{11}

Additionally, we assume that genetic testing in symptomatic patients has different effects for different conditions. Most research identified in this review was done on hereditary cancer syndromes, as is most research on the effects of genetic testing. Generalization of earlier results to other conditions where genetic tests are performed is therefore not correct.\textsuperscript{7,33,34}

Behavioural changes were reported in all studies that looked at the behaviour of patients after disclosure of the results of genetic testing, but these changes could not always be traced back to the genetic test result. The association between receiving genetic risk-information and patients’ willingness to change behaviour is unclear, but could be strong, since genetic information has an effect on different perspectives of life because of its hereditary character. This relationship is not necessarily a positive one, an illustrative example is the so-called ‘certificate of health’ effects in screening programs, where receiving a negative test result may make people more resistant to general health recommendations because they interpret the test result from screening as showing that they are immune to the effects of unhealthy lifestyles.\textsuperscript{39} Health-related behaviour is an important outcome parameter in genetic evaluation studies and should be taken into consideration.\textsuperscript{36}
Our review showed that in the long-term there seem to be no negative consequences on psychological well-being in symptomatic patients after disclosure of a genetic test result, but studies differ greatly in study methodology, are hard to compare, and most included small numbers of patients. More uniformity is needed in studies evaluating genetic testing, in design (outcome parameters and population) and in methods (measurements and moments) if we want to study and compare outcome, to enlarge the evidence base for making rational and informed decisions about genetic testing in symptomatic patients.

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