review

A systematic review of perceived risks, psychological and behavioral impacts of genetic testing

Jodi T. Heshka, MD, MSc[1], Crystal Palleschi, MSc[1], Heather Howley, MSc[1], Brenda Wilson, MRCP (UK), MFPHM (UK)[1], and Philip S. Wells, MD, FRCPC[1,2]

Genetic testing may enable early disease detection, targeted surveillance, and result in effective prevention strategies. Knowledge of genetic risk may also enable behavioral change. However, the impact of carrier status from the psychological, behavior, and perceived risk perspectives is not well understood. We conducted a systematic review to summarize the available literature on these elements. An extensive literature review was performed to identify studies that measured the perceived risk, psychological, and/or behavioral impacts of genetic testing on individuals. The search was not limited to specific diseases but excluded the impacts of testing for single gene disorders. A total of 35 articles and 30 studies were included. The studies evaluated hereditary nonpolyposis colorectal carcinoma, hereditary breast and ovarian cancer, and Alzheimer disease. For affective outcomes, the majority of the studies reported negative effects on carriers but these were short-lived. For behavioral outcomes, an increase in screening behavior of varying rates was demonstrated in carriers but the change in behaviors was less than expected. With respect to perceived risk, there were generally no differences between carriers and noncarriers by 12 months after genetic testing and over time risk perception decreased. Overall, predispositional genetic testing has no significant impact on psychological outcomes, little effect on behavior, and did not change perceived risk. It seems as though better patient education strategies are required. Our data would suggest better knowledge among carriers would not have significant psychological impacts and therefore, it is worth pursuing improved educational strategies. ***Genet Med* 2008:10(1):19–32.**

Key Words: *systematic review, genetic testing, perceived risk, behavioral outcomes, psychological outcomes*

The recent identification of various gene mutations associated with disease has made possible the use of mutation analysis to identify unaffected individuals at increased risk of specific conditions. Genetic testing thus has the potential to lower morbidity and mortality through early disease detection and targeted surveillance and prevention strategies. For some conditions, such as multiple endocrine neoplasia type 2 and Huntington disease, genetic testing is highly predictive. However, for multifactorial diseases such as colorectal cancer, breast and ovarian cancer, and Alzheimer disease (AD), genetic testing is less determinative and more "predispositional" in nature. In these cases, genetic risk prediction can help identify individuals at increased risk but, doing so may result in increased distress, anxiety, and stigmatization.

From the [1]Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada; and [2]Ottawa Health Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada.

Dr. Philip S. Wells, MD, The Ottawa Hospital, Suite F 649-1053 Carling Avenue, Ottawa, ON, Canada K1Y4E9. E-mail: pwells@ohri.ca.

Disclosure: The authors declare no conflict of interest.

Submitted for publication August 7, 2007.

Accepted for publication September 24, 2007.

DOI: 10.1097/GIM.0b013e31815f524f

The focus in genetics research has recently been the impact of testing on individuals and their families. To date, the majority of published research on complex disorders has focused on hereditary forms of colorectal, breast, and ovarian cancers, and Alzheimer disease although the latter is not currently used for clinical purposes. Colorectal cancer is one of the most common cancers in North America. The cumulative lifetime risk of colorectal cancer for the average individual is estimated to be around 5–6%.[1] Hereditary nonpolyposis colorectal carcinoma (HNPCC) is the most common hereditary colon cancer syndrome and is associated with one of five germline mutations (*hMSH2*, *hMLH1*, *PMS1*, *PMS2*, and *hMSH6*).[2–5] Mutations in these genes result in a lifetime colorectal cancer risk of approximately 80–85%.[6,7] Women with either a *BRCA1* or *BRCA2* gene mutation have a 56–87% and 10–60% lifetime risk of breast and ovarian cancer, respectively, compared with the general white population risks of 12.67 and 1.44%.[8] Increased risk of AD is associated with the apolipoprotein E4 allele. In comparison with other apolipoprotein E genotypes, the presence of this allele is associated with approximately a 3-fold increase in risk of AD; two copies of the allele increases risk 15- to 30-fold.[9]

As the genetic basis for complex multifactorial illnesses continues to be established, testing for relevant predispositional genes may become a legitimate element of clinical diagnosis and management of these illnesses. As this situation evolves, it

is important to examine the implications of genetic testing from the perspectives of patients and their families. A number of reviews investigating the impact of genetic counseling and testing have been published. For the most part, these reviews have focused on predictive testing, single mutations (e.g., *BRCA1/2*), genetic counseling alone, perceived risk, psychological impacts alone, or behavioral impacts alone. Few reviews have focused on predispositional testing or have examined the collective psychological and behavioral impacts of testing. The aim of this review is therefore to summarize recently published data describing the perceived risk, affective and behavioral impacts of undergoing predispositional genetic testing.

METHODS

Search strategy

Five electronic databases were searched using the OVID search interface: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, and PsycINFO. Each database search was conducted during the week of November 27, 2006, and all search results were limited to the years 2000–2006. A detailed search strategy was developed for use in MEDLINE and then adapted for each database. Search terms were based on the general categories of genetics and genetic testing, psychological factors and behavioral factors (Table 1). The reference lists of all relevant articles (including reviews) were examined for reports of additional studies, and retrieved by searching bibliographic databases and electronic journals. Also, the Science Citation Index (via Web of Science) was searched to find reports that had cited relevant studies. Key authors in this subject area were identified from these studies and used as additional search terms in the five electronic databases listed earlier.

Selection of eligible articles

Studies were included in this review if they (1) were published in a peer-reviewed journal in English; (2) included adult, human subjects; (3) evaluated the perceived risk, psychological, and/or behavioral impacts of genetic testing on individuals with a family history of any multifactorial adult onset genetic disorder; and (4) reported separate results for carriers and/or noncarriers. Studies were excluded if they (1) assessed only the intention to undergo genetic testing; (2) assessed the impacts of genetic counseling where subjects did not receive genetic test results; (3) assessed the impacts of genetic testing where subjects were already affected with the disorder in question (or where results were combined for affected and unaffected subjects); (4) assessed the impacts of testing for single gene disorders (e.g., Huntington disease); and (5) were studies of prenatal or childhood genetic testing.

Both randomized controlled trials and prospective studies were considered for this review, whereas qualitative studies and case reports were excluded. Outcomes of interest were perceived risk, affective (e.g., general distress, anxiety, depression, and disorder-specific worry), and behavioral (e.g., surveillance, screening uptake, lifestyle changes). With respect to perceived risk and affective outcomes, pre- and posttest data were required for inclusion. Posttest data alone for behavioral outcomes were sufficient for inclusion.

Reviews, editorials, letters to the editor, book reviews, and commentaries were excluded. A single reviewer independently screened the titles and abstracts of each remaining citation, and excluded studies based on the inclusion/exclusion criteria. If it was unclear whether the study met these criteria, the reviewer obtained the full text of the report for independent assessment. Two reviewers independently assessed the eligibility of all potentially eligible full-text studies, and any discrepancies were resolved through discussion and/or a third reviewer. All excluded studies and reasons for exclusion were documented.

Information extraction

Two reviewers independently abstracted data from all studies meeting the inclusion criteria using a piloted information extraction sheet. Discrepancies were resolved through discussion. Information was collected regarding study characteristics, study design, population, and outcomes (perceived risk, affective, behavioral). The reviewers were not blinded to the names of authors, journal, or institutions.

Quality assessment

A formal quality assessment was not performed, as the vast majority of studies were prospective, nonrandomized studies, and all well-validated quality assessment tools are intended for use with randomized controlled trials.

RESULTS

Study characteristics

A flow diagram of the search results is illustrated in Figure 1. The electronic database searches generated 1289 citations; from these abstracts, 139 reports were fully reviewed for eligibility. From these reports, a total of 35 articles and 30 studies met the inclusion criteria for the review (Table 2). In three instances, two separate studies were published using data collected from one large population.[11,12] However, because each study seemed to use different subsamples from the one larger population, or reported different outcome measures in each article, they were considered as separate studies.

In total, 16 studies assessed the impacts of genetic testing for hereditary breast and ovarian cancer (HBOC),[11–30] 11 for HNPCC,[31–41] one for both HBOC and HNPCC,[42] and two for AD.[43,44] In the studies on HBOC, the vast majority of participants were female. One study included both men and women[13] whereas another was specifically designed to assess the impact of genetic testing on behavior in men.[14] Studies on HNPCC and AD included both male and female participants. Affective outcomes measured in the studies included disorder-specific distress, general and state anxiety, depression, mood state, cancer worry, general distress, and psychiatric diagnosis. Table 3 summarizes the general and specific outcome measures of the studies included in this review. Behavioral outcomes included surveillance behaviors (e.g., mammography, breast exams,

Table 1
Review search strategy

MEDLINE/CENTRAL	EMBASE	CINAHL	PSYCINFO
1. genetic diseases, inborn/	1. exp human genetics/	1. genetics, medical/	1. genetic counseling/
2. genetics, medical/	2. genetic disorder/	2. Hereditary Diseases/	2. genetic disorders/
3. genetic screening/	3. exp genetic service/	3. genetic screening/	3. genetic testing/
4. exp genetic services/	4. genetic analysis/	4. genetic counseling/	4. genetic disorder$. tw.
5. genetic disorder$. tw.	5. genetic disorder$. tw.	5. genetic disorder$. tw.	5. genetic test$. tw.
6. genetic test$. tw.	6. genetic test$. tw.	6. genetic test$. tw.	6. genetic screen$. tw.
7. genetic screen$. tw.	7. genetic screen$. tw.	7. genetic screen$. tw.	7. genetic risk$. tw.
8. genetic risk$. tw.	8. genetic risk$. tw.	8. genetic risk$. tw.	8. genetic counsel$. tw.
9. genetic counsel$. tw.	9. genetic counsel$. tw.	9. genetic counsel$. tw.	9. PSYCHOLOGY/
10. psychology/	10. psychology/	10. PSYCHOLOGY/	10. DISTRESS/
11. adaptation, psychological/	11. mental stress/	11. ANXIETY/	11. ANXIETY/
12. stress, psychological/	12. anxiety/	12. DEPRESSION/	12. "DEPRESSION (EMOTION)"/or MAJOR DEPRESSION/
13. anxiety/	13. depression/	13. somatoform disorders/	13. SOMATIZATION
14. depression/	14. somatization/	14. "psychosocial aspects of illness"/	14. anxiety. tw.
15. somatization/	15. anxiety. tw.	15. anxiety. tw.	15. depression. tw.
16. anxiety. tw.	16. depression. tw.	16. depression. tw.	16. psychologic$ distress. tw.
17. depression. tw.	17. psychologic$ distress. tw.	17. psychologic$ distress. tw.	17. somatiz$. tw.
18. psychologic$ distress. tw.	18. risk management/	18. somatiz$. tw.	18. risk management/
19. somatiz$. tw.	19. risk reduction/	19. risk management/	19. health Behavior/
20. risk management/	20. health behavior/	20. health behavior/	20. coping behavior/
21. risk reduction behavior/	21. coping behavior/	21. behavioral changes/	21. risk perception/
22. health behavior/	22. health behavior$. tw.	22. adaptation, psychological/	22. health behavior$. tw.
23. health behavior$. tw.	23. perceived risk$. tw.	23. health behavior$. tw.	23. perceived risk$. tw.
24. perceived rsik$. tw.	24. perceived control$. tw.	24. perceived risk$. tw.	24. perceived control$. tw.
25. perceived control$. tw.	25. fatalis$. tw.	25. perceived control$. tw.	25. fatalis$. tw.
26. fatalis$. tw.	26. adult/	26. fatalis$. tw.	26. or/1–8
27. adult/	27. or/1–9	27. ADULT/	27. or/9–17
28. or/1–9	28. or/10–17	28. or/1–9	28. or/18–25
29. or/10–19	29. or/18–25	29. or/10–18	29. 26 and 27
30. or/20–26	30. 27 and 28	30. or/19–26	30. limit 29 to yr = "1999–2006"
31. 28 and 29	31. limit 30 to yr = "1999–2006"	31. 28 and 29	31. limit 30 to human
32. limit 31 to yr = "1999–2006"	32. limit 31 to human	32. limit 31 to yr = "1999–2006"	32. 26 and 28
33. limit 32 to humans	33. 32 and 26	33. 32 and 27	33. limit 32 to yr = "1999–2006"
34. 33 and 27	34. 27 and 29	34. 28 and 30	34. limit 33 to human
35. 28 and 30	35. limit 34 to yr = "1999–2006"	35. limit 34 to yr = "1999–2006"	35. 31 or 34
36. limit 35 to yr = "1999–2006"	36. limit 35 to human	36. 35 and 27	36. prenatal diagnosis/
37. limit 36 to humans	37. 36 and 26	37. 33 or 36	37. 35 not 36
38. 37 and 27	38. 33 or 37		
39. 34 or 38	39. prenatal diagnosis/		
40. prenatal diagnosis/	40. 38 not 39		
41. 39 not 40			

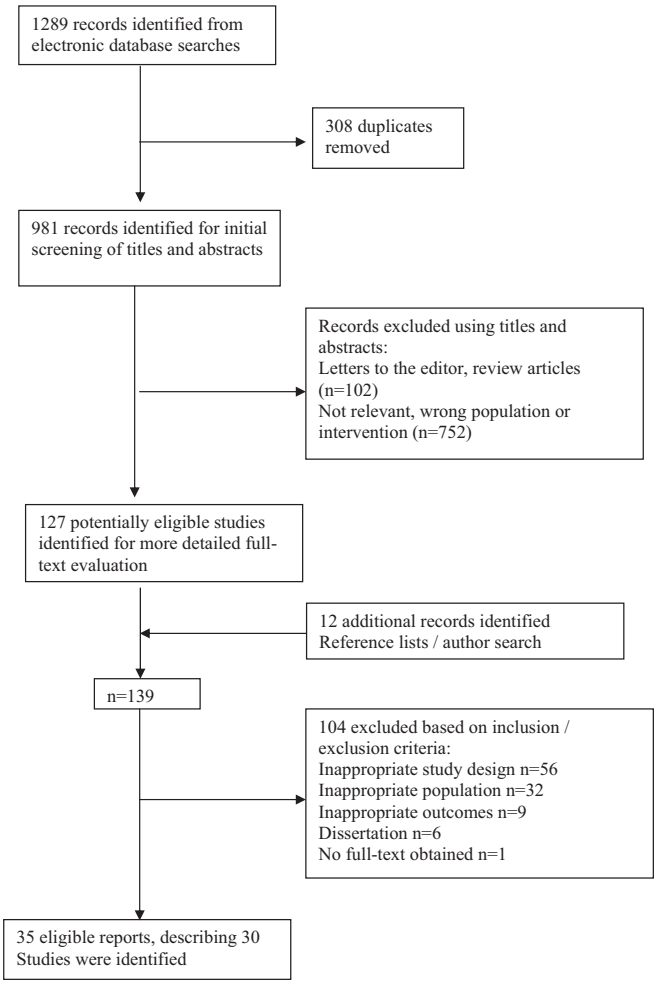

Fig. 1. QUOROM[10] flow diagram outlining the results of the literature search and the selection of studies for inclusion in the review.

transvaginal ultrasound, colonoscopy), prophylactic surgery (e.g., bilateral mastectomy or oophorectomy), and other preventive behaviors (e.g., chemotherapeutics, diet, exercise).

Affective outcomes

The studies assessing the impact of genetic testing for HBOC, HNPCC, and AD on affective outcomes pre- and posttesting in mutation carriers and noncarriers, and between carriers and noncarriers, are summarized in Table 4. General and specific distress, anxiety, depression, and worry were the outcome measures studies most frequently measured and will therefore be the focus of review.

General distress

Seven studies assessed general distress after genetic testing. The instruments used to assess general distress included the hospital anxiety and depression scale (HADS), the general health questionnaire-28, the Hopkins symptom checklist-25 or the symptom checklist-90. The majority of studies, irrespective of disease, found no effect of genetic testing for either carriers or noncarriers. Similarly, most studies found no difference between carriers and noncarriers after disclosure of test results. Two studies on HBOC[13,19] found that general distress was higher in carriers compared with noncarriers in the short term (i.e., 1 week to 4 months), whereas one study on HNPCC found that, while there was no change in distress for carriers in the long term (i.e., 12 months), noncarriers had lower general distress than carriers at 12 months follow-up.[33] An additional study found that not only did noncarriers have lower distress at 12 months, but so did carriers opting for surveillance strategies when compared with carriers opting for prophylactic mastectomy.[22] Neither of the studies on AD assessed the impact of genetic testing on general distress.

Specific distress

Sixteen studies examined the impact of genetic testing on cancer-specific distress, all using the impact of events scale. Eleven of these studies were on HBOC, four were on HNPCC, and one was on AD.

For HBOC, the majority of studies reported decreases in specific distress in the short term (i.e., 1 month) and the long term (i.e., 12 months) irrespective of carrier status. Two studies found no effect of genetic testing on specific distress in either carriers or noncarriers, or between groups.[21,28] A single study found that cancer-specific distress increased in carriers in the very short term (i.e., 2 weeks).[30] An equal number of studies ($n = 2$) found a decrease in specific distress in noncarriers compared with carriers or no difference between the two groups. A single study found specific distress increased in carriers compared with noncarriers at 1, 4, and 12 months.[13]

For HNPCC mutation carriers, studies found that genetic testing either had no effect on cancer-specific distress, or noted that distress increased in the short term (i.e., 2 weeks) and then returned to baseline levels. For noncarriers, specific distress either decreased after test result disclosure or did not change. In comparing carriers and noncarriers, noncarriers generally had lower cancer-specific distress than carriers. One study reported no difference between groups, but specific distress in this study was only assessed at 1 month after disclosure of genetic test results.[33]

Similarly, the single study assessing specific distress after genetic testing for AD reported no effect in carriers over time, but lower specific distress in noncarriers than carriers at all time points (6 weeks, 6 months, and 12 months).

Anxiety

Fifteen studies measured anxiety after genetic testing, most using the State-Trait Anxiety Inventory, two studies the HADS; one used the Beck Anxiety Inventory.[43]

For HBOC, 13 studies reported no difference between pretest and posttest anxiety levels among carriers at 12 months. One study found that anxiety had decreased 1 month posttest,[11] a second larger study found it had increased at 2 weeks,[30] and a third found increased levels of anxiety at 5 years when compared with 1 year.[21] Results were similar for noncarriers, with the majority of studies reporting no effect

Table 2
Summary of included studies ($n = 35$)

Authors	Condition	Country	Assessment timepoints	Outcomes
Aktan-Collan et al.[31]	HNPCC	Finland	Base, DS, 1 mo, 12 mo	Perceived risk; Affective State Anx, Worry
Andrews et al.[15]	HBOC	Australia	Base, 7–10 days, 1 mo, 12 mo	Affective: Spec dist, State Anx, Dep
Arver et al.[42]	HBOC, HNPCC	Sweden	Base, 1 wk, 2 mo, 6 mo, 12 mo	Affective: Anx, Dep
Botkin et al.[16]	HBOC	US	Base, 1–2 wk, 4–6 mo, 12 mo, 24 mo	Behavior: Surv, Surg
Claes et al.[32,33]	HNPCC	Belgium	Base, 12 mo	Perceived risk; Affective: Spec dist, State Anx; Behavior: Surv
Claes et al.[17]	HBOC	Belgium	Base, 12 mo	Perceived risk; Affective: Spec dist, State Anx
Collins et al.[34]	HNPCC	Australia	Base, 2 wk, 4 mo, 12 mo	Behavior: Surv, Surg
Gritz et al.[35]	HNPCC	US	Base, 2 wk, 6 mo, 12 mo	Perceived risk; Affective: State Anx, Dep, Worry
Hadley et al.[36]	HNPCC	US	Base, 6 mo, 12 mo	Behavior: Surv
Halbert et al.[37]	HNPCC	US	Base, 1 mo, 6 mo, 12 mo	Behavior: Surv
Johnson et al.[38]	HNPCC	US	Base, mean 12 mo (±3 mo)	Behavior: Surv
Kinney et al.[11,12]	HBOC	US	Base, 1 yr	Affective: Spec dist, Anx, Dep; Behavior: Surv and Surg
Lerman et al.[18]	HBOC	US	1 mo, 6 mo, 12 mo	Behavior: Surv and Surg
Liede et al.[14]	HBOC	Canada/US	Mean 2.2 yr posttest	Behavior: Surv
Lodder et al.[19]	HBOC	Netherlands	Base, 1–3 wk	Affective: Spec dist, Anx, Dep
Lodder/van Oostrom et al.[20–22]	HBOC	Netherlands	Base, 1–3 wk, 6 mo, 12 mo, 5 yr	Affective: Spec dist, Anx, Dep, Worry; Behavior: Surv and Surg
Lynch et al.[23]	HBOC	Canada/US	Base, mean 5.2 yr posttest	Affective: Gen dist, Worry, emotions, guilt; Behavior: Surv and Surg
Meijers-Heijboer et al.[24]	HBOC	Netherlands	Median 26 mo posttest	Behavior: Surg
Meiser et al.[25]	HBOC	Australia	Base, 7–10 days, 4 mo, 12 mo	Affective: Spec dist, State Anx, Dep
Meiser et al.[39]	HNPCC	Australia	Base, 7–10 days, 4 mo, 12 mo	Affective: Spec dist, State Anx, Dep
Metcalfe et al.[26]	HBOC	Canada/US	Mean 42.6 mo posttest	Behavior: Medication use, Surg
Murakami et al.[40]	HNPCC	Japan	Base, 1 mo	Affective: Presence/absence mental disorder
Peshkin et al.[27]	HBOC	US	Base, 1 mo, 6 mo, 12 mo	Behavior: Surv
Ponz de Leon et al.[41]	HNPCC	Italy	1–2 yr	Behavior: Surv
Reichelt et al.[28]	HBOC	Norway	Base, 6 wk	Affective: Anx, Dep, Gen distr, Hopelessness
Roberts et al.[43]	AD	US	Base, 6 wk, 6 mo, 1 yr	Affective: Anx; Behavior: General preventive behaviors
Romero et al.[44]	AD	US	Base, 1 mo, 4 mo, 10 mo	Affective: Mood state, emotional reactions
Schwartz et al.[29]	HBOC	US	Base, 6 mo	Perceived risk; Affective: Spec dist, Gen distr
van Roosmalen et al[30]	HBOC	Netherlands	Base, 2 wk	Affective: Spec dist, State Anx, Dep
Watson et al.[13]	HBOC	UK	Base, 1 mo, 4 mo, 12 mo	Perceived risk; Affective: Spec dist, Worry, Gen dist; Behavior: Surv, Surg

HBOC, hereditary breast and ovarian cancer; HNPCC, hereditary nonpolyposis colorectal cancer; AD, Alzheimer disease; DS, disclosure session; Spec dist, disorder-specific distress; Anx, anxiety; Dep, depression; Gen dist, general distress; Worry, cancer worry; Surv, surveillance; Surg, prophylactic surgery.

of testing on anxiety levels. Of studies comparing anxiety levels in carriers and noncarriers, all reported no difference between groups.

For HNPCC, anxiety levels were generally increased in carriers in the short term (i.e., at disclosure of test results and 2 weeks' posttest), but had returned to baseline levels or lower by 12 months. Anxiety levels in noncarriers were decreased at disclosure of test results or 1-month posttest, but, as with carriers, had returned to baseline levels or lower by 12 months. Comparisons between carriers and noncarriers demonstrated that carriers generally had higher levels of anxiety than noncarriers at disclosure of test results, but at subsequent time points anxiety levels were similar between groups.

A single study examined the impacts of genetic testing for both HBOC and HNPCC on anxiety.[42] Anxiety levels in both carriers and noncarriers decreased from pretest levels over the

Table 3
General and specific outcomes used in the included studies

General outcome	Specific outcome
Cognitive	Perceived risk
Affective	Disorder-specific distress or worry
	General or state anxiety
	Depression
	General distress
	General health status
	Psychiatric diagnosis
Behavioral	Surveillance behaviors
	Prophylactic surgery
	General preventive behaviors (i.e., diet, exercise, lifestyle)

course of 12 months and there were no differences between the two groups. Similarly, one study assessing anxiety after genetic testing for AD reported no differences between carriers and noncarriers at 6 weeks, 6 months, or 12 months.

Depression

Ten studies measured the impact of genetic testing for HBOC, HNPCC, and AD on depression using either the Center for Epidemiologic Studies Depression Scale or HADS. For all three diseases, the vast majority of studies reported no effect of genetic testing on depression scores in either carriers or noncarriers. Two studies, one on HBOC and the other on HNPCC, reported a brief increase in depression at 2 weeks posttest in carriers.[30,35] Also, one study on HNPCC reported decreased depression scores at 1 month,[44] whereas another found scores to be lower at 4 months.[25] There were no differences in depression scores between groups for HBOC, HNPCC, or AD at any time point beyond 2 weeks.

Worry

Three studies, one each on HBOC, HNPCC, and AD, assessed the impact of genetic testing on worry. The results of these three studies were conflicting: one reported increased worry in carriers and decreased worry in noncarriers at 2 weeks,[35] one found less worry in both carriers and noncarriers at 1 month,[44] whereas the third reported increased worry in carriers compared with noncarriers throughout the 12-month follow-up period.[13]

Behavioral outcomes

The studies assessing behavioral outcome measures are summarized in Table 5. Self-reported screening practices and prophylactic surgery were the main outcome measures.

Screening behavior

For HBOC, behaviors assessed included mammography, breast self-examination (BSE), and clinical breast examination (CBE) for breast cancer screening, and transvaginal ultrasound and cancer antigen (Ca)-125 measurement for ovarian cancer screening. Additionally, one study examined the impact of genetic testing on the use of prostate-specific antigen and digital rectal examination for screening purposes in men.

Mammography screening rates for the 12 months after disclosure of genetic test results ranged from 59 to 92% in *BRCA1/2* carriers and 30 to 53% in noncarriers. Most studies found that mammography rates increased in carriers postdisclosure in comparison with rates from the 12 months predisclosure. Although two studies reported increased 12-month rates in noncarriers as well,[16] most studies found that mammography use was higher in carriers than in noncarriers. Similarly, while the use of BSE and CBE increased in both carriers and noncarriers after genetic testing, a greater proportion of carriers used these modalities than noncarriers. Combined use of BSE and CBE ranged from 90 to 95% in carriers and 77 to 89% in noncarriers.

Use of transvaginal ultrasound and Ca-125 for ovarian cancer screening after genetic testing was also increased to a greater extent in carriers than in noncarriers, with rates of these tests ranging from 15 to 59% and 21 to 32% in carriers, and 5 to 8% and 5 to 6% in noncarriers, respectively.

For HNPCC, the main behavioral outcome measure was having a colonoscopy. As with breast and ovarian cancer screening, colonoscopy increased within the 12 months after genetic testing in carriers in comparison with noncarriers. Rates of colonoscopy ranged from 58 to 100% in carriers and 0 to 40.5% in noncarriers. However, one study found decreased use of sigmoidoscopy or colonoscopy in carriers at 12 months compared with baseline or pretest levels.[36]

Prophylactic surgery

Eight studies reported rates of prophylactic surgery for HBOC in carriers in the 12 months after genetic testing. Rates varied from 0 to 51% for mastectomies and 13 to 65% for oophorectomies. One additional study on HNPCC found that 9.5% of female carriers had had a hysterectomy in the 12 months postdisclosure.[34]

Use of chemotherapeutics and other health-related behaviors

Two studies found that 20–22.2% of female *BRCA1/2* carriers were using or had used chemotherapeutics (i.e., tamoxifen, raloxifene) to prevent breast cancer.[12,26] Also, two studies examined the impact of genetic testing on general health behaviors.[13,43] Although 43–52% of subjects tested for HBOC reported having made lifestyle changes believed to promote health and/or reduce cancer risk (e.g., change diet, exercise, quit smoking) since being tested, both carriers and noncarriers, and males and females, made similar changes. Conversely, apolipoprotein E4 carriers were reported to be more likely than noncarriers to report engagement in activities believed to potentially lower their risk of AD after disclosure of genetic test results.

Table 4
Studies examining affective outcomes of genetic testing

Authors	Study design	Sample size	Measurement timepoints	Outcome measures	Main findings
HBOC (*BRCA 1/2*)					
Andrews et al.[15]	Prospective	*N* = 4 C, 28 NC	Base, 7–10 days, 1 mo, 12 mo	Specific distress (IES)	C and NC: decrease in specific distress at 1 mo and 12 mo
				Anxiety (STAI)	no differences in state anxiety or depression
				Depression (BDI)	
Claes et al.[17]	Prospective	*N* = 34 C, 34 NC	Base, 12 mo	Specific distress (IES) anxiety (STAI)	C: decrease in ovarian cancer distress
					NC: decrease in breast and ovarian cancer distress
					ovarian cancer distress higher in C than NC
Kinney et al.[11]	Prospective	*N* = 19 C, 66 NC	Base, 1 mo, 4 mo, 12 mo	Specific distress (IES, 3-item scale)	C: lower anxiety at 1 mo only; lower specific distress at 4 mo only
				anxiety (STAI)	NC: lower depression at 1 mo only; lower anxiety at 1 mo only; lower specific distress at 1 mo and 4 mo
				Depression (CES-D)	
Lodder et al.[19]	Prospective	*N* = 25 C, 53 NC	Base, 1–3 wk	General distress (HADS)	General distress lower in NC than in C
				Specific distress (IES)	Specific distress lower in NC than in C
Lodder et al.[22]	Prospective	*N* = 26 C, 37 NC	Base, 6 mo, 12 mo	General distress (HADS)	General and specific distress lower in C opting for surveillance and NC than in C opting for mastectomy
				Specific distress (IES)	
van Oostrom et al.[21]	Prospective	*N* = 23 C, 42 NC	Base, 5 yr	General distress (HADS)	No differences in general or specific distress between C and NC
				Specific distress (IES, CWS)	C and NC: anxiety and depression higher at 5 yr compared to 1 yr
Meiser et al.[25]	Prospective	*N* = 22 C, 46 NC, 46 NT	Base, 7–10 days, 4 mo, 12 mo	Specific distress (IES)	C: specific distress higher at 7–10 days and 12 mo than in NT
				Anxiety (STAI)	NC: state anxiety lower at 7–10 days than in NT; depression lower at 4 mo than in NT
				Depression (HADS)	
Reichelt et al.[28]	Prospective	*N* = 80 C, 164 NC	Base, 6 wk	General distress (GHQ-28)	C and NC: no differences for any outcome measures over time or between C and NC
				Specific distress (IES)	
				Anxiety (HADS)	
				depression (HADS)	
				Hopelessness (BHS)	
Schwartz et al.[29]	Prospective	*N* = 78 C, 58 NC	Base, 6 mo	General distress (HSCL-25)	C: no differences in general or specific distress
				Specific distress (IES)	NC: decrease in general and specific distress
van Roosmalen et al.[30]	Prospective	*N* = 66 C	Base, 2 wk	Specific distress (IES)	C: increase in specific distress, anxiety and depression
				Anxiety (STAI)	
				Depression (CES-D)	

(*Continued*)

Table 4
Continued

Authors	Study design	Sample size	Measurement timepoints	Outcome measures	Main findings
Watson et al.[13]	Prospective	*N* = 91 C, 170 NC	Base, 1 mo, 4 mo, 12 mo	General distress (GHQ-28) Specific distress (IES) Worry (CWS)	General distress higher in female C than in female NC at 1 mo and 4 mo Specific distress higher in C than in NC at all time points Worry higher in C than in NC at all time points
HNPCC					
Aktan-Collan et al.[31]	Prospective	*N* = 84 C, 187 NC	Base, TDS, 1 mo, 12 mo	Anxiety (STAI) Fear of cancer/death (IAS) Attitudes to future (5-item scale)	C: higher anxiety at TDS only; more fear of cancer at all time points NC: lower anxiety at TDS only Anxiety higher in C than NC at TDS; more fear of cancer than NC at all time points
Claes et al.[33]	Prospective	*N* = 19 C, 21 NC	Base, 1 mo	Specific distress (IES) Anxiety (STAI)	C: no changes NC: decrease in anxiety Total group (C+NC) had lower anxiety at 1 mo; no differences in specific distress or state anxiety between groups at 1 mo
Claes et al.[32]	Prospective	*N* = 36 C, 36 NC	Base, 12 mo	General distress (SCL-90) Specific distress (IES) Anxiety (STAI)	C: decrease in anxiety for colorectal cancer NC: decrease in general and specific distress and anxiety Total group (C + NC) had lower specific distress and anxiety at 12 mo; higher specific distress in C than in NC at 12 mo
Gritz et al.[35]	Prospective	*N* = 19 C, 47 NC	Base, 2 wk, 6 mo, 12 mo	Specific distress (IES) Anxiety (STAI) Worry (3-item scale) Depression (CES-D)	C: higher specific distress, anxiety and depression than NC at 2 wk decrease in specific distress, anxiety and depression from 2 wk to 6 mo; increase in worry at 2 wk only NC: decrease in worry at 2 wk
Meiser et al.[39]	Prospective	*N* = 32 C, 82 NC	Base, 2 wk, 4 mo, 12 mo	Specific distress (IES) Anxiety (STAI) Depression (HADS)	C: higher specific distress at 2 wk only NC: lower specific distress at 2 wk, 4 mo and 12 mo Specific distress higher for C than NC at 2 wk and 12 mo; anxiety higher for C than NC at 2 wk only
Murakami et al.[40]	Prospective	*N* = 5C, 10 NC	Base, 1 mo	Major and minor clinical depression (DSM-III-R) Acute stress disorder or posttraumatic stress disorder (DSM-IV)	Single C met criteria for posttraumatic stress disorder
HBOC and HNPCC					
Arver et al.[42]	Prospective	*N* = 31 C, 56 NC	Base, 1 wk, 2 mo, 6 mo, 12 mo	Anxiety (HADS) Depression (HADS)	C: decrease in anxiety NC: decrease in anxiety No differences between C and NC

(*Continued*)

Table 4
Continued

Authors	Study design	Sample size	Measurement timepoints	Outcome measures	Main findings
AD (apoE3/E4 or apoE4/E4)					
Roberts et al.[43] (REVEAL study)	Randomized clinical trial	N = 46 C, 40 NC	Base, 6 wk, 6 mo, 12 mo	Specific distress (IES)	C: no changes
				Anxiety (BAI)	NC: lower specific distress than C at all time points
				Depression (CES-D)	No differences in anxiety or depression between C and NC
Romero et al.[44]	Prospective	N = 27 C, 49 NC	Base, 1 mo, 4 mo, 10 mo	Depression (GDS)	C: lower worry at 1 mo only
				Worry (POMS)	NC: lower depression and worry and higher relief at 1 mo only
				Relief (POMS)	

C, Carriers; NC, noncarriers; IES, Impact of Events Scale; STAI, State-Trait Anxiety Inventory; HADS, Hospital Anxiety and Depression Scale; BDI, Beck Depression Inventory; SCL-90, The Symptom Checklist; CES-D, The Center for Epidemiologic Studies Depression Scale; IAS, Illness Attitude Scale; POMS, Profile of Mood States; HSCL-25, Hopkins Symptom Checklist; GHQ-28, General Health Questionnaire; CWS, Cancer Worry Scale.

Perceived risk

The seven studies on HBOC and HNPCC that assessed risk perception after genetic testing are summarized in Table 6. Although one study reported that noncarriers had lower perceived risk of HBOC than carriers at 6 months,[29] there were generally no differences in risk perception of HBOC or HNPCC between carriers and noncarriers by 12 months after genetic testing. Two studies reported increased perceived risk in carriers in the short term (i.e., 1-month posttest),[13,31] but overall risk perception in carriers was either the same or lower than pretest levels at 12 months. Nearly all studies found that perceived risk of HBOC and HNPCC in carriers was lower 12 months posttest compared with before undergoing genetic testing.

DISCUSSION

Genetic testing has the potential to reduce morbidity and mortality by enabling early identification of individuals at increased risk for various heritable conditions, thereby allowing targeted surveillance and management. Research has only recently begun to examine the effects of predictive and predispositional genetic testing on individuals and their families. Many reviews have focused patients after detection of a single mutation (e.g., *BRCA1/2*), whereas others have focused only on psychological[45–47] or behavioral outcomes.[48] This review is the first, to our knowledge, to summarize the collective perceived risk, affective and behavioral impacts before and after predispositional genetic testing among unaffected individuals.

Reviews on the psychological impact of genetic testing have reported either no change in psychological outcomes among unaffected mutation carriers relative to baseline[45,46] or decreased anxiety and worry after genetic testing.[47] Meiser[45] noted that some studies have consistently shown short-term increases in anxiety among unaffected carriers. Results regarding depression have been mixed. We found that overall genetic testing had no impact of psychological outcomes such as general and specific distress, anxiety, or depression in either carriers or noncarriers. These results held true regardless of the measurement tools used or whether results were reported separately (e.g., anxiety, depression) or combined (as for the results of general distress that may have also included anxiety and depression). We also noted the trend in some studies for there to be short-term (i.e., up to 4 months) increases in some of these measures among carriers, although this trend disappeared with time. The impact of genetic testing on worry was less clear and only a few studies in our review assessed this outcome measure.

Few reviews have evaluated the impact of genetic testing on screening practices and rates of prophylactic surgery. Behavioral outcome data were mainly limited to breast, ovarian, and colorectal cancer screening, and prophylactic surgery. Wainberg and Husted[48] reported that rates of prophylactic mastectomy and oophorectomy among carriers varied between studies, but overall ranged from 0 to 54%, and 13 to 53%,

Table 5
Studies examining behavioral outcomes of genetic testing

Authors	Study design	Sample size	Measurement timepoints	Outcome measures	Main findings
HBOC (*BRCA 1/2*)					
Botkin et al.[16]	Prospective	*N* = 37 C, 92 NC	Base, 1–2 wk, 4–6 mo, 12 mo, 24 mo	Self-reported screening and surgery	Mammography: increased use at 12 mo, 24 mo in both C (62%, 57%) and NC (53%, 49%); no differences between groups
					BSE: increased use at 24 mo in C (83%) and NC (74%); no differences between groups
					CBE: increased use at 12 mo in C (95%) vs. NC (77%)
					TVUS: increased use at 12 mo in C (26%) vs. NC (5%)
					Ca-125: increased use at 12 mo, 24 mo in C (32%, 37%) vs. NC (5%, 5%)
					Mastectomy: none
					Oophorectomy: 46% of C by 24 mo
Kinney et al.[12]	Prospective	*N* = 10 C, 20 NC	Base, 12 mo	Self-reported screening, chemotherapeutics and surgery (25% of results compared with medical records)	Mammography: 71% in eligible C, 40% in eligible NC; no increased use in C from baseline
					TVUS: 25% in eligible C
					Ca-125: 20% in eligible C
					Chemotherapeutics: 20% in eligible C
					Mastectomy: none
					Oophorectomy: 17% of eligible C by 12 mo
Lerman et al.[18]	Prospective	*N* = 84 C, 83 NC, 49 NT	Base, 1 mo, 6 mo, 12 mo	Self-reported screening and surgery	Mammography: increased use at 12 mo in C (68%) vs. NC (44%)
					TVUS: 15% of C, 5% of NC
					Ca-125: 21% of C, 6% of NC
					Mastectomy: 3% of eligible C by 12 mo
					Oophorectomy: 13% of eligible C by 12 mo
Liede et al.[14]	Cross-sectional	*N* = 59 C	Mean 2.2 yr posttest	Self-reported screening and surgery	PSA: 36% annually
					DRE: 28% annually
Lynch et al.[23]	Prospective	*N* = 290 C, 370 NC	Base, mean 5.2 yr	Self-reported screening and surgery	Mammography: increased use in both C and NC after disclosure
					BSE: increased use in both C and NC after disclosure
					CBE: no change in either C or NC after disclosure
					TVUS: increased use in both C and NC after disclosure; use higher in C vs. NC
					Ca-125: increased use in C after disclosure
					Mastectomy: increased from 13% of C before carrier status disclosure to 25.5% after
					Oophorectomy: increased from 17.9% of C before carrier status disclosure to 65% after

(*Continued*)

Table 5
Continued

Authors	Study design	Sample size	Measurement timepoints	Outcome measures	Main findings
Meijers-Heijboer et al.[24]	Prospective	*N* = 68 C for mastectomy, 45 C for oophorectomy	Median 26 mo posttest	Self-reported surgery and medical records	Mastectomy: 51% by 12 mo, 55% by 24 mo Oophorectomy: 53% by 12 mo, 59% by 24 mo
Metcalfe et al.[26]	Cross-sectional	*N* = 81 C	Mean 42.6 mo posttest	Self-reported use of chemotherapeutics and surgery	Chemotherapeutics: current or previous use in 22.2% Mastectomy: 27.2% Oophorectomy: 66.7%
Peshkin et al.[27]	Prospective	*N* = 41 C, 66 NC	Base, 1 mo, 6 mo, 12 mo	Self-reported screening	Mammography: 59% of C, 47% of NC by 12 mo CBE: 95% of C, 77% of NC by 12 mo
Watson et al.[13]	Prospective	*N* = 91 C, 170 NC	Base, 1 mo, 4 mo, 12 mo	Self-reported screening and surgery	Mammography: increased use at 12 mo in C (92%) vs. NC (30%) BSE: increased use in C (90%) vs. NC (89%) CBE: increased use in C (91%) vs. NC (84%) TVUS: increased use in C (59%) vs. NC (8%) Mastectomy: 28% of C by 12 mo Oophorectomy: 31% of C by 12 mo
HNPCC					
Claes et al.[32]	Prospective	*N* = 36 C, 36 NC	Base, 12 mo	Self-reported screening	Colonoscopy: 75%, 100% of C by 12 mo, 24 mo; 0% of NC by 12 mo TVUS: 86% of female C, 27% of female NC by 12 mo
Collins et al.[34]	Prospective	*N* = 32 C, 82 NC	Base, 2 wk, 4 mo, 12 mo	Self-reported screening and surgery	Colonoscopy: increased in C (71%) vs. NC (12%) at 12 mo TVUS, endometrial sampling: increased TVUS, endometrial sampling in female C (47%, 53%) vs. NC (10%, 5%) at 12 mo Colectomy or hysterectomy: no colectomies, 9.5% of female C had hysterectomy by 12 mo
Hadley et al.[36]	Prospective	*N* = 17 C, 39 NC	Base, 6 mo, 12 mo	Self-reported screening	Flexible sigmoidoscopy/colonoscopy: increased use in C (53%) vs. NC (8%) at 12 mo; decreased use in NC from baseline (31%/59%) to 12 mo (0%/8%)
Halbert et al.[37]	Prospective	*N* = 35 C, 56 NC, 33 NT	Base, 1 mo, 6 mo, 12 mo	Self-reported screening	Colonoscopy: increased in C (73%) vs. NC (16%) and NT (22%) at 12 mo; increased use in C from baseline (36%) to 12 mo (73%)
Johnson et al.[38]	Prospective	*N* = 7 C, 37 NC, 21 NT	Base, mean 12 mo	Self-reported screening (confirmed with medical records)	Colonoscopy: increased use in C (100%) vs. NC (40.5%) and NT (57.1%) by 12 mo
Ponz de Leon et al.[41]	prospective	*N* = 23 C, 75 NC	Mean 5.7 yr	Self-reported screening	Colonoscopy: 82.6% of C by 24 mo
AD					
Roberts et al.[43]	Randomized control trial	*N* = 53 C, 58 NC	Base, 12 mo	Self-reported health behavior changes	53% of C vs. 24% of NC and 31% of controls reported at least 1 behavior change for AD prevention

HBOC, hereditary breast/ovarian cancer; HNPCC, hereditary nonpolyposis colorectal cancer; C, carriers; NC, noncarriers; NT, not tested/declined test; BSE, breast self exam; CBE, clinical breast exam; TVUS, transvaginal ultrasounds; Ca-125, cancer antigen-125; PSA, prostate specific antigen; DRE, digital rectal exam.

Table 6
Studies examining risk perception following genetic testing

Authors	Study design	Sample size	Measurement timepoints	Instrument	Main findings
HBOC (*BRCA 1/2*)					
Claes et al.[17]	Prospective	*N* = 34C, 34NC	Base, 12 mo	2-item absolute assessment using 5-point scale	Decrease in breast and ovarian cancer risk perception in NC Lower breast cancer risk perception in NC vs. C No difference in ovarian risk perception between C and NC
Schwartz et al.[29]	Prospective	*N* = 35C, 58NC	Base, 1 mo, 6 mo	2-item absolute assessment using 5-point scale	Lower breast and ovarian cancer risk perception in NC vs. C at 6 mo
Watson et al.[13]	Prospective	*N* = 91C,170NC	Base, 1 mo, 4 mo, 12 mo	2-item absolute and comparative assessments using 3-, 5-, and 6-point scales	Decrease in breast and ovarian cancer risk perception in NC Increase in breast and ovarian cancer risk perception in C <50 yr at 1 mo, but decrease to base level by 12 mo
HNPCC					
Aktan-Collan et al.[31]	Prospective	*N* = 84C,187NC	Base, 1 mo, 12 mo	1-item absolute assessment using 3-point scale	Decrease in colorectal cancer risk perception from 1 mo to 12 mo in C
Claes et al.[33]	Prospective	*N* = 19C, 21NC	Base, 12 mo	2-item absolute assessment using 5-point scale	Decrease in colorectal cancer risk perception in NC No change in risk perception in C
Claes et al.[32]	Prospective	*N* = 36C, 36NC	Base, 12 mo	2-item absolute assessment using 5-point scale	No difference in colorectal and endometrial cancer risk perception between C and NC
Gritz et al.[35]	Prospective	*N* = 19C, 47NC	Base, 2 wk, 6 mo, 12 mo	1-item comparative assessment using 5-point scale	Decrease in colorectal cancer risk perception in NC

respectively. Women tended to opt for oophorectomy slightly more often than mastectomy. This is consistent with our findings: rates of mastectomy and oophorectomy among our studies were 0 to 51%, and 13 to 65%, respectively. We also noted that women who opted for prophylactic surgery over surveillance tended to have surgery within the first year after genetic testing. Our review suggests that breast cancer screening rates are high and similar among carriers and noncarriers, whereas ovarian and colorectal cancer screening rates seem to be higher among carriers posttest compared with noncarriers. This may be attributable to the degree of invasiveness associated with screening procedures, but is also influenced by age of participants, as screening recommendations are different for older individuals than for younger. Studies on colonoscopy screening uptake among unaffected individuals suggest that most carriers underwent colonoscopy within 12 to 24 months after genetic testing.

In examining the impact of genetic testing on risk perception, we found that there were no differences between carriers and noncarriers by 12 months, and that risk perception was lower at that time point than at baseline in most studies. We would have expected perceived risk to be higher among carriers of genetic mutations than in noncarriers. Most studies included standard genetic counseling procedures that included information about the disease, its mode of inheritance, the gene defect, the benefits, risks and limitations of genetic testing, overview of screening recommendations, and treatment and preventive options. Only four studies did not mention or describe the counseling provided.[13,21,35,40] It was not possible to determine whether there were differences in the quality or quantity of information provided. Furthermore, it is unclear how best to present information on genetic predisposition to patients and it would seem that this standard genetic counseling may not be effectively educating patients. Further research on the optimal methods for the provision of information is required. It is possible that the lack of major differences in psychological and behavioral outcomes is attributable to a lack of differences in risk perception between groups, because perceived risk is often a strong moderator of emotion and behavior.

Most of the studies included in this review acknowledged several limitations, at times limiting the precision of the results of these studies. Most study populations included small, self-selected samples that were not representative of all individuals

eligible for testing. Claes et al.[32] suggested that those individuals presenting for genetic testing may have a higher perceived ability to cope with their test result and that this may explain the relatively low distress levels found among study participants. Also, several studies that assessed the behavioral impacts of genetic testing noted that the study sample was highly motivated and already involved in pretest surveillance and/or likely to adhere to screening recommendations. Many studies reported homogenous samples that included predominantly white individuals with high levels of education. Some studies also had several participants from the same family, possibly producing family specific effects. As part of the research protocol, most studies included extensive pre- and posttest counseling and education, such that results may not be generalizable to a routine clinical setting. Genetic testing was usually offered free of charge, thus observed rates of testing may be higher than expected routinely. Finally, outcome measures for perceived risk were often not validated and those for behaviors were based on self-report, therefore have the potential for recall bias. Claes et al.[33] suggested that distress measures used in the majority of these studies focus largely on detecting clinical disorder or psychopathology and may not be sensitive enough to capture the occurrence of negative emotional reactions in a "nonclinical " population.

A limitation of the present review is that a search of the gray literature, particularly conference abstracts, was not conducted, and so publication bias could not be completely eliminated. Also, the vast majority of studies included in our review examined the impacts of genetic testing for familial cancer, and with only two studies focused on AD. Studies that examined the impacts of testing for multifactorial disorders aside from cancer and AD (e.g., venous thrombosis and thrombophilia) were insufficiently rigorous to meet inclusion criteria. Because only two studies were in AD and genetic predispositional testing is not part of clinical care at this time, further review will be useful if testing becomes part of clinical practice.

Despite these limitations, our review provides valuable evidence regarding the perceived risk, affective, and behavioral impact of predisposition testing for various disorders. In general, the evidence suggests that genetic testing for these disorders does not seem to lead to adverse consequences for carriers or noncarriers. Further research is required to confirm the multiple impacts of genetic testing for multifactorial disorders, particularly in regards to risk perception, disorder-specific worry, and behavioral outcomes. Results of such research will be important in evaluating the wider impacts of genetic testing at both the level of the individual and the health care system.

ACKNOWLEDGMENTS

Dr. Wells is supported by a Canada Research Chair in Thromboembolic Disease from the Canada Research Chairs Program. A Heart & Stroke Foundation of Ontario Program Grant PRG#5513 helped fund this project.

References

1. Terdiman JP, Conrad PG, Sleisenger MH. Genetic testing in hereditary colorectal cancer: indications and procedures. *Am J Gastroenterol* 1999;94:2344–2356.
2. Peltomaki P, Aaltonen LA, Sistonen P, Pylkannen L, et al. Genetic mapping of a locus predisposing to human colorectal cancer. *Science* 1993;260:810–812.
3. Lindblom A, Tannergard P, Werelius B, Nordenskjold M. Genetic mapping of a second locus predisposing to hereditary non-polyposis colon cancer. *Nat Genet* 1993;5:279–282.
4. Nystrom-Lahti M, Parsons R, Sistonen P, Pylkkanen L, et al. Mismatch repair genes on chromosomes 2p and 3p account for a major share of hereditary non-polyposis colorectal cancer families evaluable by linkage. *Am J Hum Gen* 1994; 55:659–665.
5. Nicolaides NC, Papadopoulos N, Liu B, Wei YF, et al. Mutations of two PMS homologues in hereditary non-polyposis colon cancer. *Nature* 1994;371:75–80.
6. Vasen HF, Wijnen JT, Menko FH, Kleibeuker JH, et al. Cancer risk in families with hereditary non-polyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996;110:1020–1027.
7. Aarnio M, Sankila R, Pukkala E, Salovaara R, et al. Cancer risk in mutation carriers of DNA mismatch repair genes. *Int J Cancer* 1999;81:214–218.
8. National Cancer Institute. Available at: http://www.cancer.gov/.
9. Cupples LA, Farrer LA, Sadovnik AD, Relkin N, et al. Estimating risk curves for first-degree relatives of patients with Alzheimer disease: the REVEAL study. *Genet Med* 2004;6:192–196.
10. Moher D, Cook DJ, Eastwood S, Olkin I, et al. Improving the quality of reports of meta-analysis of randomized controlled trials: the QUORUM statement. *Lancet* 1999;354:1896–1900.
11. Kinney AY, Bloor LE, Mandal D, Simonsen SE, et al. The impact of receiving genetic test results on general and cancer-specific psychologic distress among members of an African-American kindred with BRCA1 mutation. *Cancer* 2005;104:2508–2516.
12. Kinney AY, Simonsen SE, Baty BJ, Mandal D, et al. Risk reduction behaviors and provider communication following genetic counseling and BRCA1 mutation testing in an African American kindred. *J Genet Couns* 2006;15:293–305.
13. Watson M, Foster C, Eeles R, Eccles D, et al. Psychosocial impact of breast/ovarian (*BRCA1/2*) cancer-predictive genetic testing in a UK multi-centre clinical cohort. *Br J Cancer* 2004;91:1787–1794.
14. Liede A, Metcalfe K, Hanna D, Hoodfar E, et al. Evaluation of the needs of male carriers of mutations in BRCA1 or BRCA2 who have undergone genetic counseling. *Am J Hum Genet* 2000;67:1494–1504.
15. Andrews L, Meiser B, Apicella C, Tucker K. Psychological impact of genetic testing for breast cancer susceptibility in women of Ashkenazi Jewish background: a prospective study. *Genet Test* 2004;8:240–247.
16. Botkin JR, Smith KR, Croyle RT, Baty BJ, et al. Genetic testing for a BRCA1 mutation: prophylactic surgery and screening behavior in women 2 years post testing. *Am J Med Genet* 2003;118:201–209.
17. Claes E, Evers-Kiebooms G, Denayer L, Decruyenaere M, et al. Predictive genetic testing for hereditary breast and ovarian cancer: psychological distress and illness representations 1 year following disclosure. *J Genet Couns* 2005;14:349–363.
18. Lerman C, Hughes C, Croyle RT, Main D, et al. Prophylactic surgery decisions and surveillance practices one year following *BRCA 1/2* testing. *Prev Med* 2000;31: 75–80.
19. Lodder L, Frets PG, Trijsburg RW, Tibben A, et al. Men at risk of being a mutation carrier for hereditary breast/ovarian cancer: an exploration of attitudes and psychological functioning during genetic testing. *Eur J Hum Genet* 2001;9:492–500.
20. Lodder L, Frets PG, Trijsburg RW, Meijers-Heijboer, et al. Psychological impact of receiving a BRCA1/BRCA2 test result. *Am J Med Genet* 2001;98:15–24.
21. van Oostrom I, Meijers-Heijboer H, Lodder LN, Duivenvoorden HJ, et al. Long-term psychological impact of carrying a *BRCA1/2* mutation and prophylactic surgery: a 5-year follow-up study. *J Clin Oncol* 2003;21:3867–3874.
22. Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, et al. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). *Breast Cancer Res Treat* 2002;73:97–112.
23. Lynch HT, Snyder C, Lynch JF, Karatoprakli P, et al. Patient responses to the disclosure of BRCA mutation tests in hereditary breast-ovarian cancer families. *Cancer Genet Cytogenet* 2006;165:91–97.
24. Meijers-Heijboer E, Verhoog L, Brekelmans C, Seynaeve C, et al. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet* 2000;355:2015–2020.
25. Meiser B, Butow P, Friedlander M, Barratt A, et al. Psychological impact of genetic testing in women from high-risk breast cancer families. *Eur J Cancer* 2002;38:2025–2031.
26. Metcalfe KA, Snyder C, Seidel J, Hanna D, et al. The use of preventive measures among healthy women who carry a BRCA1 or BRCA2 mutation. *Fam Cancer* 2005; 4:97–103.

27. Peshkin BN, Schwartz MD, Isaacs C, Hughes C, et al. Utilization of breast cancer screening in a clinically based sample of women after *BRCA1/2* testing. *Cancer Epidemiol Biomarkers Prev* 2002;11:1115–1118.
28. Reichelt JG, Heimdal K, Moller P, Dahl AA. BRCA1 testing with definitive results: a prospective study of psychological distress in a large clinic-based sample. *Fam Cancer* 2004;3:21–28.
29. Schwartz MD, Peshkin BN, Hughes C, Main D, et al. Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. *J Clin Oncol* 2002; 20:514–520.
30. van Roosmalen MS, Stalmeier PF, Verhoef LC, Hoekstra-Weebers JE, et al. Impact of *BRCA1/2* testing and disclosure of a positive test result on women affected and unaffected with breast or ovarian cancer. *Am J Med Genet* 2004;124:346–355.
31. Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, et al. Comprehension of cancer risk one and 12 months after predictive genetic testing for hereditary non-polyposis colorectal cancer. *J Med Genet* 2001;38:787–792.
32. Claes E, Denayer L, Evers-Kiebooms G, Boogaerts A, et al. Predictive testing for hereditary nonpolyposis colorectal cancer: subjective perception regarding colorectal and endometrial cancer, distress, and health-related behavior at one year post-test. *Genet Test* 2005;9:54–65.
33. Claes E, Denayer L, Evers-Kiebooms G, Boogaerts A, et al. Predictive testing for hereditary non-polyposis colorectal cancer: motivation, illness representations and short-term psychological impact. *Patient Educ Couns* 2004;55:265–274.
34. Collins V, Meiser B, Gaff C, St John DJ, et al. Screening and preventive behaviors one year after predictive genetic testing for hereditary nonpolyposis colorectal carcinoma. *Cancer* 2005;104:273–281.
35. Gritz ER, Peterson SK, Vernon SW, Marani SK, et al. Psychological impact of genetic testing for hereditary nonpolyposis colorectal cancer. *J Clin Oncol* 2005;23:1902–1910.
36. Hadley DW, Jenkins JF, Dimond E, de Carvalho M, et al. Colon cancer screening practices after genetic counseling and testing for hereditary nonpolyposis colorectal cancer. *J Clin Oncol* 2004;22:39–44.
37. Halbert CH, Lynch H, Lynch J, Main D, et al. Colon cancer screening practices following genetic testing for hereditary nonpolyposis colon cancer (HNPCC) mutations. *Arch Intern Med* 2004;164:1881–1887.
38. Johnson KA, Trimbath JD, Petersen GM, Griffin CA, et al. Impact of genetic counseling and testing on colorectal cancer screening behaviour. *Genet Test* 2002;6:303–306.
39. Meiser B, Collins V, Warren R, Gaff C, et al. Psychological impact of genetic testing for hereditary non-polyposis colorectal cancer. *Clin Genet* 2004;66:502–511.
40. Murakami Y, Okamura H, Sugano K, Yoshida T, et al. Psychologic distress after disclosure of genetic test results regarding hereditary nonpolyposis colorectal carcinoma. *Cancer* 2004;101:395–403.
41. Ponz de Leon M, Benatti P, Di Gregorio C, Pedroni M, et al. Genetic testing among high-risk individuals in families with hereditary nonpolyposis colorectal cancer. *Br J Cancer* 2004;90:882–887.
42. Arver B, Haegermark A, Platten U, Lindblom A, et al. Evaluation of psychosocial effects of pre-symptomatic testing for breast/ovarian and colon cancer pre-disposing genes: a 12-month follow-up. *Fam Cancer* 2004;3:109–116.
43. Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, et al. Genetic risk assessment for adult children of people with Alzeimer's Disease: the risk evaluation and education for Alzeimer's Disease (REVEAL) Study. *J Geriatr Psychiatry Neurol* 2005;18:250–255.
44. Romero LJ, Garry PJ, Schuyler M, Bennahum DA, et al. Emotional responses to APO E genotype disclosure for Alzheimer disease. *J Genet Couns* 2005;14:141–150.
45. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. *Psychooncology* 2005;14:1060–1074.
46. Schlich-Bakker KJ, ten Kroode HFJ, Ausems MG. A literature review of the psychological impact of genetic testing on breast cancer patients. *Patient Educ Couns* 2006; 62:13–20.
47. Nelson HD, Huffman LH, Fu R, Harris EL. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. preventive services task force. *Ann Intern Med* 2005;143:362–379.
48. Wainberg S, Husted J. Utilization of screening and preventive surgery among unaffected carriers of BRCA1 or BRCA2 gene mutation. *Cancer Epidemiol Biomarkers Prev* 2004;13:1989–1995.