Psychological Impact of Genetic Counseling for Familial Cancer: A Systematic Review and Meta-analysis

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Background: **Identification of a genetic basis underlying certain types of cancer has led to an increase in demand for genetic counseling about individual risks of the disease. We conducted a systematic review of the literature to determine the quality and strength of evidence relating to psychological outcomes of genetic counseling for familial cancer.** ***Methods:*** **Six electronic databases were searched to identify controlled trials and prospective studies that examined the effect of genetic counseling on risk perception, knowledge, anxiety, cancer-specific worry, depression, and cancer surveillance. Twenty-one studies from 25 papers met inclusion criteria, including five controlled trials and 16 prospective studies. Analysis of each outcome was stratified by short-term (≤1 month) and long-term (≥3 months) follow-up. Trial evidence was assessed with standardized differences of the means at follow-up between intervention and comparison groups, and these data were pooled by use of random-effects meta-analysis.** ***Results:*** **Meta-analysis of controlled trials showed that genetic counseling improved knowledge of cancer genetics (pooled short-term difference = 0.70 U, 95% confidence interval [CI] = 0.15 to 1.26 U) but did not alter the level of perceived risk (pooled short-term difference = −0.10 U, 95% CI = −0.23 to 0.04 U). Prospective studies reported improvements in the accuracy of perceived risk. No effect was observed in controlled trials on general anxiety (pooled long-term effect = 0.05 U, 95% CI = −0.21 to 0.31 U) or cancer-specific worry (pooled long-term difference = −0.14 U, 95% CI = −0.35 to 0.06 U), although several prospective studies demonstrated short-term reductions in these outcomes. Few studies examined cancer surveillance behaviors, and no studies attempted to measure informed choice.** ***Conclusions:*** **Genetic counseling for familial cancer is associated with improvement in knowledge but does not have an adverse effect on affective outcomes. We urge further investigation of these findings through well-designed, well-reported, randomized controlled trials with suitable comparison groups and additional outcome measures. [J Natl Cancer Inst 2004;96:122–33]**

The identification of genes that are associated with high risk of breast, ovarian, and colorectal cancer has advanced our understanding of cancer predisposition over the last decade *(1–4).* Genetic testing is available for mutations in several genes to predict the risk of breast and/or ovarian (e.g., BRCA1 and BRCA2) or colorectal cancer (e.g., APC, MLH1, and MSH2). The last decade has seen a marked increase in demand for genetic counseling and predictive genetic testing for these cancers *(5),* which could increase further as the genetics of other common diseases is unraveled *(6).* Genetic counseling involves an attempt to facilitate a person's comprehension of his or her risk for an inherited disorder and understanding of options for dealing with the risk of occurrence *(7)* without causing undue anxiety. Hence, for genetic counseling to be considered effective, there needs to be evidence that it improves the accuracy of an individual's perceived likelihood of developing the disease and his or her knowledge of the disease genetics with no adverse emotional impact. In the context of genetic counseling for familial cancer specifically, the goal is to communicate information regarding personal risk of cancer so that individuals can make informed choices regarding options for risk management, principally cancer surveillance and predictive genetic testing.

Given the complexities in communicating genetic risk information, it remains unclear how well individuals understand disease risk or whether genetic counseling may lead to anxiety and distress that interfere with adherence to cancer prevention regimens *(8).* A previously published meta-analysis of 12 studies of genetic counseling in women at increased risk of hereditary breast cancer *(9)* concluded that genetic counseling leads to a statistically significant reduction in general anxiety and improved accuracy of perceived risk. However, the treatment of randomized controlled trials as uncontrolled prospective studies in that meta-analysis raises questions about the validity of the conclusions drawn.

We report a systematic review of controlled trials *(10–17)* and prospective studies *(18–34)* examining the impact of genetic counseling for breast, ovarian, and colorectal cancer on a more comprehensive range of cognitive, affective, and behavioral outcomes than that reported in the earlier review *(9).* In line with the definition of genetic counseling *(7),* we also tested the hypothesis that genetic counseling results in improvement in cognitive outcomes (the level and accuracy of risk perception and knowledge of cancer genetics) without a negative impact on affective outcomes (general distress and anxiety, depression, and cancer-specific worry). In addition, we tested whether genetic counseling would yield changes in behavior, such as cancer screening and surveillance appropriate to the individual's level of risk, and whether effects of genetic counseling were maintained over time.

METHODS

Selection of Studies

Searches were conducted on MEDLINE, PsycINFO, CancerLit, Cinahl, EMBASE, and the Web of Science Citation Index from inception through December 2001 by use of the terms "breast neoplasms," "ovarian neoplasms," "colorectal neo-

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plasms," "genetics-medical," "risk assessment," "risk management," "genetic counsel*ing," and "risk counsel*ing." We also manually searched key journals in the field and wrote to the Regional Genetics Clinics in the United Kingdom to request unpublished or forthcoming data. Additional data were sought from authors of published studies where such data were not fully reported.

Inclusion Criteria

We defined genetic counseling as individual counseling aimed at supporting discussion about familial cancer risk and its management, including cancer surveillance and genetic testing. We included studies that evaluated the psychological impact of genetic counseling on individuals with a family history of breast, ovarian, or colorectal cancer, thus incorporating studies of participants at all levels of inherited cancer risk. Controlled trials and prospective studies with before and after data that reported changes from baseline to follow-up or intergroup differences in cognitive, affective, or behavioral outcomes were included. No relevant foreign language papers were identified. Data were extracted by four authors (D. Braithwaite, J. Emery, F. Walter, and S. Sutton) by use of *pro forma* extraction sheets. The decision of whether a paper should be included was reached by consensus.

Outcomes of Genetic Counseling

At the outset of the review, we formed clear hypotheses regarding the outcomes of genetic counseling that were driven by the definition of genetic counseling and our preliminary review of the literature. In the cognitive domain, the assessed outcomes were knowledge of cancer genetics and the accuracy and level of perceived risk. Among affective outcomes, we investigated general distress, anxiety, depression, and cancer-specific worry. We also considered behavioral outcomes, principally cancer surveillance and screening uptake.

Meta-analytic Methods for Controlled Trials

Data were extracted from published articles reporting controlled trials to identify the mean, standard deviation, and sample size in each treatment group (intervention and comparison) at cross-sectional follow-up points for each outcome measure. The intervention standard deviation was combined with the comparison group standard deviation, using sample sizes, to form a pooled standard deviation as given by Hedges and Olkin *(35)*. For each measure and at each follow-up point, the primary effect of interest was defined as the standardized difference in means. An unbiased estimator of the effect, for a particular outcome, trial, and time point, was calculated as the difference between the intervention sample mean and the comparison sample mean, divided by the pooled standard deviation at that follow-up point, and then this value was corrected for small sample bias *(35)*. The estimated variance of this estimator was used to obtain a 95% confidence interval (CI) for the standardized difference in means for each trial's measure and at each follow-up point *(35)*.

Where evidence was provided from multiple trials, we performed a meta-analysis, stratified within each domain of measurement and according to the length of follow-up, defined as short term (i.e., $\leq$1 month) or long term (i.e., $\geq$3 months). A random effects form of meta-analysis approach was chosen because of differences between the trials in interventions and outcomes within each measurement domain. In this model, the treatment effects in the contributing trials are regarded as a sample from a population of possible treatment effects, allowing each trial to have an underlying effect that represents trial-specific influences on the treatment effect *(36)*. In each meta-analysis, the standardized differences in means of the contributing trials were pooled by use of weights that are the inverse of the combined within-trial and between-trial variation, according to the method of DerSimonian and Laird *(36)*. The pooled treatment effect was estimated with a weighted least squares approach in which there is no assumption that the population of possible trial treatment evaluations is normally distributed. Normality was assumed to obtain the 95% confidence interval for the pooled treatment effect, which was calculated as the pooled treatment effect plus or minus 1.96 multiplied by the standard error *(36)*. Effects were interpreted as small, moderate, or large in magnitude, corresponding to the values of 0.2, 0.5, and 0.8, respectively *(37)*.

Statistical Methods for Uncontrolled Prospective Studies

Effects for continuous outcomes in uncontrolled prospective studies and within the treatment groups (intervention and comparison) of trials were summarized by the standardized mean change from baseline, which was defined as the mean change in the score of the outcome at baseline subtracted from the corresponding score at the point of follow-up, divided by the standard deviation of the score at baseline. Means, sample sizes, standard deviations, and, when available, confidence intervals for the mean change from baseline were extracted from articles or obtained from authors. When unavailable, confidence intervals for the mean change from baseline were calculated from the standard deviation of the change in score by assuming a *t* distribution for the mean change from baseline in repeated sampling. The confidence interval for the standardized mean change from baseline was calculated by dividing the confidence limits for the mean change from baseline by the standard deviation of the score at baseline. If unreported, standard deviation of the change from baseline was approximated from reported test statistics (*t* tests or *F* tests) with degrees of freedom. Where these were unavailable and more than one treatment group was reported, the pooled standard deviation of change was taken as proxy. For binary outcomes, nonstandardized changes in proportions were used instead of standardized mean changes, and the confidence interval for the change in proportion from baseline to follow-up point was based on the standard error from the McNemars test for paired proportions. Effects from the prospective studies are considered to be less reliable summaries than effects observed in the trials, chiefly because uncontrolled effects are subject to the phenomenon of regression to the mean *(38)*. Other disadvantages include the need for proxy quantities and approximations that risk accumulated errors from rounding and the inability to deduce part of the information of effect from study reports.

Results

We identified 43 papers *(10–34,39–56)* that investigated cognitive, affective, and/or behavioral outcomes of genetic counseling, 18 of which were excluded (*39–56*). The lack of

Table 1. Studies included in the systematic review

Reference*	Country	Type of cancer	Design	Sample†	Who delivered the intervention?	Initial n
			Controlled trials			
Audrain et al. *(10)*	United States	Breast	Randomized controlled trial of problem-solving training vs. general health counseling	FDR of index patients from high-risk breast cancer consortium of six cancer centers	Health educator	510
Brain et al. *(11)*	United Kingdom	Breast	Randomized controlled trial of multidisciplinary genetic assessment vs. surgical assessment	Women from two family cancer clinics	Clinical geneticist and genetic nurse specialist with input from surgeon	735
Lerman et al. *(12)*	United States	Breast	Randomized controlled trial of breast cancer risk vs. general health counseling	FDR of index patients from two cancer centers	Nurse educator	210
Lerman et al. *(13)*	United States	Breast	Randomized controlled trial of breast cancer risk vs. general health counseling	FDR of index patients from two cancer centers	Nurse counselor	239
Lerman et al. *(14)*	United States	Breast	Randomized controlled trial of education vs. education plus counseling vs. waiting list control	FDR of index patients from two cancer centers	Genetic counselor or oncology nurses	578
Randall et al. *(15)*	Australia	Breast	Controlled trial	Affected women seeking genetic counseling and matched control subjects not currently seeking genetic counseling from two clinics	Genetic counselor pre-clinic Unclear who is at clinic	60
Schwartz et al. *(16)*	United States	Breast	Randomized controlled trial of problem-solving training vs. general health counseling	FDR of index patients from high-risk breast cancer consortium of six cancer centers	Health educator	341
Schwartz et al. *(17)*	United States	Breast	Randomized controlled trial of breast cancer risk vs. general health counseling	FDR of index patients	Nurse educator	508
			Prospective studies			
Alexander et al. *(18)*	United States	Breast	Prospective	Women in the Tamoxifen Breast Cancer Prevention Trial from one family cancer clinic	General internist	59
Bish et al. *(19)*	United Kingdom	Breast and ovarian	Prospective	Both unaffected and affected women from one clinic	Clinical geneticist or genetic counselor	203
Collins et al. *(21)*	Australia	Colorectal	Prospective	From one colorectal cancer clinic	Clinical geneticist or genetic counselor or gastroenterologist	157
Collins et al. *(20)*	Australia	Colorectal	Prospective	From one colorectal cancer clinic	Clinical geneticist or genetic counselor or gastroenterologist	84
Cull et al. *(22)*	United Kingdom	Breast	Prospective	From one family cancer clinic	Clinical geneticist or breast surgeon or oncologist	128
Cull et al. *(23)*	United Kingdom	Breast	Prospective	From family cancer clinic(s) (exact number of clinics not specified)	Clinical geneticist or breast surgeon or oncologist or specialist nurse	481
Evans et al. *(24)*	United Kingdom	Breast	Prospective	From one family cancer clinic	Clinical geneticist or oncologist	308
Gagnon et al. *(25)*	United States	Breast	Prospective	From one family cancer clinic	Breast surgeon	82
Hopwood et al. *(26)*	United Kingdom	Breast	Prospective	From one family cancer clinic	Clinical geneticist or oncologist	158
Hopwood et al. *(27)*	United Kingdom	Breast	Prospective	From one family cancer clinic	Clinical geneticist, consultant medical oncologist, and research fellow in cancer genetics	330
Julian-Reynier et al. *(28)*	France	Breast and colorectal	Prospective	From six regional cancer centers	Clinical cancer geneticist for 46% of consultations	212
Kent et al. *(29)*	United Kingdom	Breast	Prospective	From one family cancer clinic	Nurse specialist pre-clinic Unclear who is at clinic	69
Meiser et al. *(30)*	Australia	Breast	Prospective	From 14 familial cancer clinics and six outreach clinics	Clinical geneticists, genetic counselors, and oncology specialists	218
Ritvo et al. *(31)*	Canada	Ovarian	Prospective	From one family cancer clinic	Clinical geneticist, genetic counselor, gynecological oncologist	78
Sagi et al. *(32)*	Israel	Breast	Prospective	From one family cancer clinic	Genetic counselor and oncologist	60
Watson et al. *(33)*	United Kingdom	Breast	Prospective	From two family cancer clinics	Clinical geneticist	115
Watson et al. *(34)*	United Kingdom	Breast	Prospective	From four family cancer clinics	Clinical geneticist	282

*Three publications *(12,13,17)* resulted from the same trial; one trial was reported in two articles *(10,16)* and one prospective study was reported in two articles *(20,21)*. Multiple publications from these studies were entered in Table 1, i.e., a separate entry for each publication. Redundant patients are not an issue because the studies with multiple publications tended to report separately certain outcomes or groups of outcomes. The sample size for each outcome was recorded in Tables 2–6.

†FDR = first-degree relative.

prospective data was the most common reason for exclusion *(39–41,44–47,49,51,52)*. Table 1 presents characteristics of the included studies *(10–34)*. Of 21 studies that were included, 16 examined the impact of genetic counseling for breast cancer *(10–18,22–27,29,30,32–34)*, one for breast and ovarian cancer *(19)*, one for breast and colorectal cancer *(28)*, one for colorectal cancer *(20,21)*, and one for ovarian cancer *(31)*. Seven papers reported four randomized controlled trials *(10–13,16,17)*, and one paper *(15)* reported a nonrandomized controlled trial, which was small (initial n = 60) and suffered from considerable attrition. We included the evidence from 16 uncontrolled prospective studies *(18–34)* with that from the controlled trials because of the limited number of trials and the need to provide additional information regarding the potential effect of the intervention and to highlight contradictory effects between types of study design.

With the exception of one prospective study that included both affected and unaffected women *(19)* and one controlled trial of women affected by breast cancer *(15)*, all studies recruited unaffected participants. Genetic counseling interventions were heterogeneous and ranged from using cognitively based problem-solving interventions *(10,16)* to providing videotapes as an additional component to personal counseling *(22)*. Fig. 1. shows evidence of intervention effects of genetic counseling in controlled trials that is based on cross-sectional comparisons between treatment groups at follow-up. Effects from uncontrolled prospective studies and from trials stratified by treatment group are presented in Tables 2, 3, 4, 5, and 6 as longitudinal changes from baseline to follow-up without allowance for control.

Cognitive Outcomes

The results of controlled trials and prospective studies that examined the impact of genetic counseling on cognitive outcomes (the level and accuracy of perceived risk and knowledge of cancer genetics) are presented in Fig. 1 and in Tables 2 and 3, respectively.

Risk perception. Two controlled trials *(11,14)* reported the impact of genetic counseling on the level of risk perception (Fig. 1), but no statistically significant effect was found. In these two trials, the pooled short-term effect was small (standardized difference = −0.10, 95% CI = −0.23 to 0.04). Evidence on risk perception from the prospective studies is less clear, with one study *(25)* reporting a statistically significant change from baseline and two studies *(19,29)* reporting no such change.

Risk accuracy. The single controlled trial that assessed the association between genetic counseling and risk accuracy *(12)*, which was treated as a binary outcome, did not report the between-group analysis necessary for inclusion in Fig. 1. The

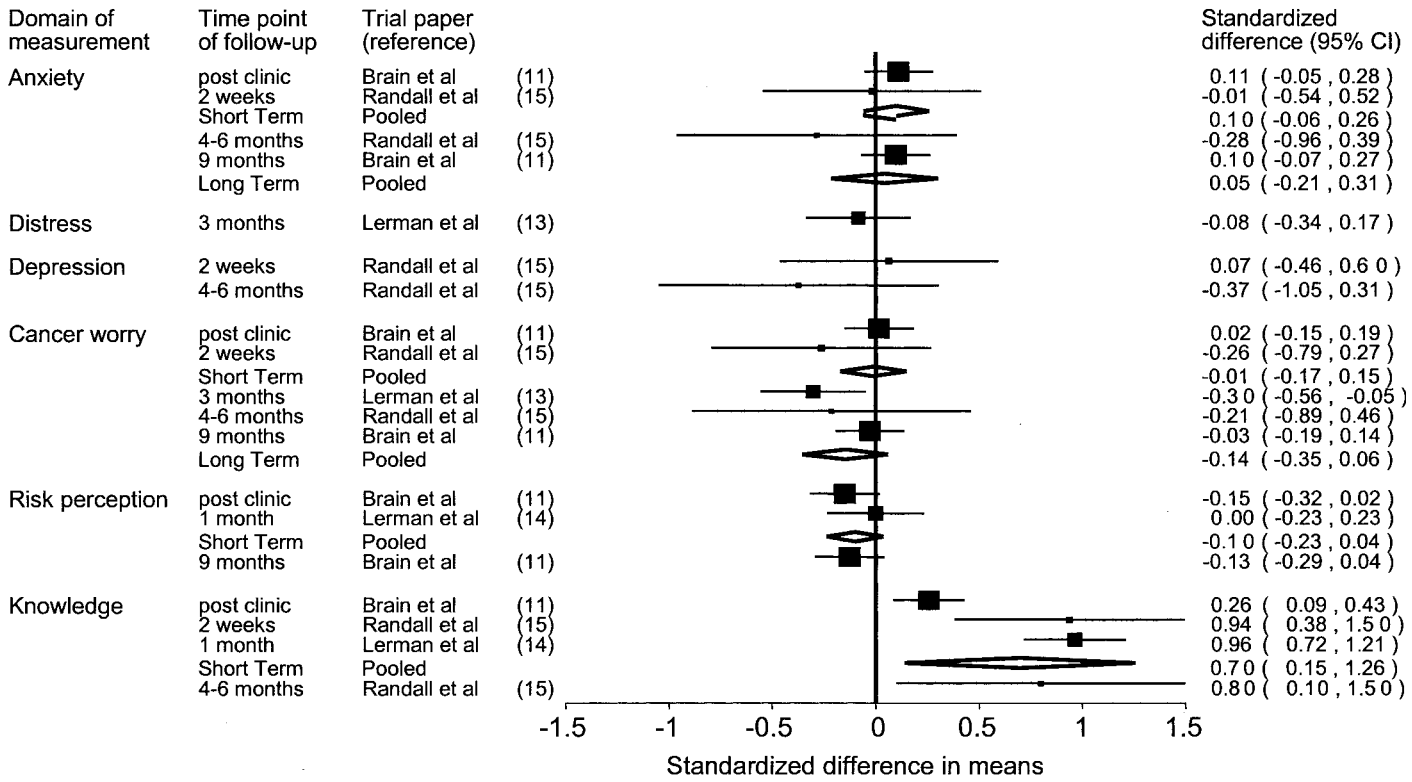

Fig. 1. Meta-analyses of affective and cognitive outcomes in controlled trials of genetic counseling interventions over periods of short-term (≤1 month) and long-term (≥3 months) follow-up. The analyses are stratified by measurement domain and length of follow-up period. Effectiveness is defined by the standardized difference, i.e., the cross-sectional difference at follow-up between treatment group means, standardized by the standard deviation at follow-up pooled across treatment groups. A positive difference indicates an increased mean outcome in the intervention group relative to the comparison group. The point estimate of the difference is denoted by a **square**, the area of which represents the inverse variance of the estimate, measuring its precision. **Lines extending from a square** represent the 95% confidence intervals. Standardized differences are pooled using random effects meta-analysis for those domains informed by multiple trials in a time period. The center of the **diamond** denotes the estimate of the pooled effect, and the horizontal extremes represent its 95% confidence intervals. Except treatment group sizes for one of the Lerman studies *(13)*, which were assumed to be half of the study size, required source data were taken from articles.

Table 2. Impact of genetic counseling on the level and accuracy of risk perception*

Reference	Measure (definition)	Time points	Subjects		Mean ± standard deviation	Standardized mean change from baseline (95% confidence interval)
			Group	No.		
			Perceived risk			
Controlled trials						
Brain et al. *(11)*	Perceived risk of breast cancer	Baseline	I	263	7.29 ± 1.24	
			C	282	7.33 ± 1.17	
		Postclinic	I	263	6.44 ± 1.30	−0.69 (−0.81 to −0.56)†
			C	282	6.62 ± 1.14	−0.61 (−0.73 to −0.48)†
		9 mo	I	263	6.74 ± 1.30	−0.44 (−0.57 to −0.32)†
			C	282	6.90 ± 1.25	−0.37 (−0.49 to −0.24)†
Lerman et al. *(14)*	Perceived risk of carrying a BRCA1 mutation	Baseline	E + C	122	2.20 ± 0.59	
			E	114	2.12 ± 0.59	
			C	164	2.10 ± 0.63	
		1 mo	E + C	122	2.06 ± 0.62	−0.24‡
			E	114	1.88 ± 0.57	−0.41‡
			C	164	2.06 ± 0.56	−0.06‡
Prospective studies						
Bish et al. *(19)*	Perceived risk of breast cancer	Baseline		181	1.19 ± 0.74	
		Postclinic		181	1.14 ± 0.77	−0.07 (−0.22 to +0.09) (NS)
		1 y		181	1.07 ± 0.77	−0.16 (−0.34 to +0.02) (NS)
Gagnon et al. *(25)*	Perceived risk of breast cancer	Baseline		52	6.4 ± 2.0	
		4 mo		52	5.5 ± 2.2	−0.45 (−0.78 to −0.12)†
Kent et al. *(29)*	Perceived risk of breast cancer	Baseline		45	5.52 ± 1.84	
		3 mo		48	5.24 ± 1.84	−0.15 (NS)
		6 mo		46	5.09 ± 1.30	−0.23 (NS)
			Risk accuracy			
Controlled trials					% accurate	% standardized change from baseline (95% confidence interval)
Lerman et al. *(12)*	Within 10% of risk derived from Gail	Baseline	I	90	6.6	
			C	110	11	
		3 mo	I	90	14.6	+8%†
			C	110	9.4	−1.6% (NS)
Prospective studies						
Cull et al. *(22)*	Within 200% of risk derived from Claus	Baseline		128	59	
		Postclinic		128	81	+22%‡
Evans et al. *(24)*	Within 50% of risk derived from Claus	Baseline		78	10	
		1 y		78	31	+21% (+7% to +34%)†
Hopwood et al. *(26)*	Within 50% of risk derived from Claus	Baseline		158	10.1	
		3 mo		158	55.7	+46.6% (+36% to +56%)†
Hopwood et al. *(27)*	Correct risk estimate derived from Claus	Baseline		330	15.5	
		Mean 9.4 mo		330	42.1	+26.6%†
Meiser et al. *(30)*	Correct risk estimate (risk model not specified)	Baseline		218	54	
		1 y		218	55	+1% (−7% to +9%) (NS)
Watson et al. *(34)*	Correct risk estimate (risk model not specified)	Baseline		268	9	
		1 mo		271	31	+22% (+15% to +28%)†
		1 y		259	17	+8% (+2% to +14%)†

*The accuracy of risk perception was assessed by comparing perceived risk with the risk derived from the Claus *(57)* or Gail *(58)* models. The level of perceived risk was examined in terms of perceived absolute or relative risk of developing breast cancer or a deleterious mutation on a Likert scale. I = intervention group; C = control group; E + C = group that received the educational and counseling components of genetic counseling; E = group that received the educational component only.

†$P<.05$ under null hypothesis of a zero change from baseline effect size. NS = statistically nonsignificant, i.e., $P>.05$ under null hypothesis of a zero change from baseline effect size.

‡Statistical significance not deducible.

controlled trial did report statistically nonsignificant baseline differences between the control and the risk counseling groups and a statistically significant increase in accuracy from baseline to follow-up within the risk counseling group only (Table 2). The percentage of individuals with accurate risk comprehension at follow-up was 14.6% in the counseling group and 9.4% in the control group. We were unable to deduce a confidence interval at follow-up because of missing data. However, a related outcome of improvement in the category of risk comprehension was reported as statistically nonsignificant ($P = .1$) in an analysis between randomized groups *(34)*. Improvements in the accuracy of risk perception were observed in five of six prospective studies of genetic counseling *(22,24,26,27,34)*. However, different epidemiological models of risk *(57,58)* and definitions of accuracy were used across studies, making comparisons of changes from baseline unfeasible.

Knowledge of cancer genetics. Evidence from each of the three controlled trials of genetic counseling *(11,14,15)* indicated a statistically significant increase in knowledge in the intervention arm compared with that in the control arm that was of a medium to large magnitude (short-term pooled standardized difference in the means = 0.70 U, 95% CI = 0.15 to 1.26 U). The wide confidence intervals observed are caused by two trials with very different effects: a small increase in knowledge in one

Table 3. Impact of genetic counseling on the knowledge of cancer genetics*

Reference	Measure	Time points	Subjects		Mean ± standard deviation	Standardized mean change from baseline (95% confidence intervals)
			Group	No.		
Controlled trials						
Brain et al. *(11)*	Cancer genetics knowledge scale	Baseline	I	248	1.54 ± 1.09	
			C	276	1.45 ± 1.06	
		Postclinic	I	248	2.17 ± 1.08	+0.58 (+0.45 to +0.71)†
			C	276	1.89 ± 1.08	+0.42 (+0.29 to +0.54)†
Lerman et al. *(14)*	Cancer genetics knowledge scale	Baseline	E + C	122	5.84 ± 2.12	
			E	114	5.90 ± 2.17	
			C	164	5.93 ± 2.01	
		1 mo	E + C	122	7.58 ± 2.09	+0.82‡
			E	114	7.74 ± 2.16	+0.85‡
			C	164	5.39 ± 2.39	−0.27‡
Randall et al. *(15)*	Based on cancer genetics knowledge scale	Baseline	I	32	5.39 ± 2.09	
			C	28	4.43 ± 2.13	
		2 wk	I	29	6.66 ± 2.38	+0.61 (NS)
			C	26	4.73 ± 1.54	+0.14 (NS)
		4–6 mo	I	18	6.60 ± 2.50	+0.58 (NS)
			C	16	4.80 ± 1.80	+0.17 (NS)
Prospective studies						
Collins et al. *(21)*	Based on cancer genetics knowledge scale	Baseline		126	4.98 ± 2.31	
		3 mo		126	6.67 ± 1.90	+0.73†
Meiser et al. *(30)*	Based on cancer genetics knowledge scale	Baseline		218	5.2 ± 1.9	
		1 y		218	6.3 ± 1.8	+0.58†

*Assessment of the knowledge of cancer genetics was based on the scale developed by Lerman et al. *(13)*. This scale was a series of true/false items where one point was given for each correct answer. A consortium of the National Institutes of Health–funded genetic testing projects developed this measure. I = intervention group; C = control group; E + C = group that received the educational and counseling components of genetic counseling; E = group that received the educational component only.

†$P<.05$ under null hypothesis of a zero change from baseline effect size. NS = statistically nonsignificant, i.e., $P>.05$ under null hypothesis of a zero change from baseline effect size.

‡Statistical significance not deducible.

(11) and a large increase in the other *(10)*. The long-term effect on knowledge was investigated in only one trial *(15)*, where a similar magnitude of increase was observed (Fig. 1, standardized difference = 0.80 U, 95% CI = 0.10 to 1.50 U), though in a small sample with considerable attrition. Statistically significant increases in knowledge were also observed in two prospective studies *(20,30)* that measured this outcome (Table 3).

Affective Outcomes

We investigated general anxiety, general distress, depression, and cancer-specific worry as affective outcomes (Fig. 1 and Tables 4 and 5). Mean scores at baseline were generally within the normal range for these outcomes.

General anxiety. Two controlled trials of genetic counseling *(11,15)* found no effect on general anxiety at each follow-up (Fig. 1). In one of these trials *(11)*, this result was caused by a statistically significant short-term reduction in general anxiety in both intervention and control groups (Table 4). In contrast, four of the six prospective studies of genetic counseling *(19,23, 28,34)* found a statistically significant decrease in general anxiety in the short term, but this decreased level of anxiety returned to baseline levels in the long term (Table 4).

General distress. One controlled trial of genetic counseling *(13)* found no statistically significant effects between treatment groups at 3 months (Fig. 1) and slight increases in distress in both groups (Table 4). Two of the six prospective studies *(19,23)* reported a statistically significant short-term reduction in general distress but reported no long-term effects *(19,22,23,26,33,34)*. Because of unreported statistics, the statistical significance of the effect in one prospective study *(22)* could not be deduced at long-term follow-up (Table 4).

Depression. A single controlled trial *(15)* and the three prospective studies *(19,30,31)* did not find short-term or long-term effects of genetic counseling on depression.

Cancer-specific worry. Three controlled trials of genetic counseling investigated cancer-specific worry. One observed a statistically significant reduction in such worry at 3 months *(13)*. However, the pooled short-term and long-term effects of counseling on cancer-specific worry from two *(11,15)* and three *(11,13,15)* trials, respectively, found no association between counseling and cancer worry (Fig. 1). It should also be noted that one trial *(11)* observed a statistically significant reduction in cancer-specific worry in both arms (Table 5). The prospective studies are characterized by heterogeneity of measures of cancer-specific worry and inconsistent findings in uncontrolled effects of change from baseline. Statistically significant short-term and long-term effects were reported in two prospective studies *(19,25)* and in one subgroup in another study *(33)*. A reduction in cancer-specific worry was observed in one further study *(20)*, but its statistical significance was not deducible. Long-term effects were statistically nonsignificant in the majority of the studies *(25,27,34)*, including the second subgroup in the Watson et al. study *(33)*. It is important to note that one of these studies *(25)* used two different measures to assess cancer-specific worry, the Impact of Event scale *(59)* and the Kash Cancer-related Anxiety and Helplessness Scale *(60)*, which resulted in a statistically signif-

Table 4. Impact of genetic counseling on general anxiety and distress and depression*

Reference	Scale	Time points	Subjects		Mean ± standard deviation	Standardized mean change from baseline (95% confidence intervals)
			Group	No.		
			General anxiety			
Controlled trials						
Brain et al. *(11)*	STAI	Baseline	I	263	35.93 ± 11.11	
			C	282	35.54 ± 10.87	
		Postclinic	I	263	34.33 ± 10.79	−0.14 (−0.24 to −0.05)†
			C	282	33.14 ± 10.11	−0.22 (−0.32 to −0.12)†
		9 mo	I	263	36.38 ± 12.34	+0.04 (−0.11 to +0.19) NS
			C	282	35.18 ± 11.75	−0.03 (−0.18 to +0.12) NS
Randall et al. *(15)*	STAI	Baseline	I	32	37.52 ± 11.01	
			C	28	40.11 ± 12.88	
		2 wk	I	29	36.50 ± 12.98	−0.09 NS
			C	26	36.68 ± 12.14	−0.27 NS
		4–6 mo	I	18	36.38 ± 13.00	−0.10 NS
			C	16	40.47 ± 15.27	+0.03 NS
Prospective studies						
Bish et al. *(19)*	STAI	Baseline		164	11.15 ± 4.08	
		Postclinic		164	10.31 ± 3.54	−0.21 (−0.34 to −0.07)†
		1 y		164	10.65 ± 3.89	−0.12 (−0.29 to +0.05) NS
Cull et al. *(22)*	STAI	Baseline	A	66	35 ± 11	
			B	62	38 ± 14	
		Postclinic	A	66	34 ± 10	−0.09‡
			B	61	34 ± 10	−0.29‡
		1 mo	A	53	32 ± 9	−0.27‡
			B	42	35 ± 13	−0.21‡
Cull et al. *(23)*	STAI	Baseline		383	35.4 ± 9.5	
		Postclinic		383	33.7 ± 9.8	−0.18 (−0.29 to −0.07)†
Julian-Reynier et al. *(28)*	STAI	Baseline		173	37.9 ± 10.8	
		3 wk		173	34.9 ± 10.2	−0.28 (−0.42 to −0.14)†
Meiser et al. *(30)*	STAI	Baseline		218	35.8 ± 12.3	
		1 y		218	37.3 ± 12.8	+0.12 NS
Watson et al. *(34)*	STAI	Baseline		276	38.7 ± 10.5	
		1 mo		238	35.2 ± 10.8	−0.33 (−0.49 to −0.17)†
			General distress			
Controlled trials						
Lerman et al. *(13)*	POMS	Baseline	I	239 total	17.6 ± 27.2	
			C		22.6 ± 29.4	
		3 mo	I	239 total	21.1 ± 33.1	+0.13‡
			C		23.8 ± 32.3	+0.04‡
Prospective studies						
Bish et al. *(19)*	GHQ-6	Baseline		154	21.31 ± 11.63	
		Postclinic		154	19.39 ± 10.78	−0.17 (−0.27 to −0.06)†
		1 y		154	19.88 ± 11.26	−0.12 (−0.27 to +0.03) NS
Cull et al. *(22)*	GHQ-30	Baseline	A	66	3.9 ± 5.8	
			B	62	5.8 ± 7.1	
		Postclinic	A	66	3.6 ± 6	−0.05 (−0.24 to +0.14) NS
			B	61	5.7 ± 7.9	−0.01 (−0.25 to +0.20) NS
		1 y	A	53	3.1 ± 5.7	−0.14‡
			B	42	3.9 ± 7	−0.27‡
Cull et al. *(23)*	GHQ-30	Baseline		385	4.3 ± 6.1	
		Postclinic		385	3.1 ± 4.9	−0.20 (−0.30 to −0.09)†
		1 y		169	4.1 ± 6.2	−0.03 (−0.21 to +0.18) NS
Hopwood et al. *(26)*	GHQ-28	Baseline		97	3.1 ± 4.5	
		3 mo		97	2.9 ± 5	−0.04 NS
		1 y		97	3.1 ± 5	0 NS
Watson et al. *(33)*	GHQ-12	Baseline	A	60	18‡	
			B	55	18‡	
		1 mo	A	56	12‡	Not calculable NS
			B	51	19‡	
		6 mo	A	48	15‡	Not calculable NS
			B	43	16‡	
Watson et al. *(34)*	GHQ-12	Baseline		276	2.14 ± 2.92	
		1 mo		238	2.04 ± 3.1	−0.03 (−0.17 to +0.10) NS
		6 mo		242	1.78 ± 3.72	−0.12 (−0.28 to +0.04) NS
		1 y		249	2.01 ± 3.74	−0.04 (−0.20 to +0.12) NS
			Depression			
Controlled trials						
Randall et al. *(15)*	BDI	Baseline	I	32	8.61 ± 5.72	
			C	28	9.15 ± 6.81	
		2 wk	I	29	8.54 ± 5.44	−0.01 NS
			C	26	8.15 ± 6.14	−0.15 NS
		4–6 mo	I	18	8.56 ± 5.86	−0.01 NS
			C	16	11.13 ± 7.64	+0.29 NS

(Table continues)

Table 4 (continued). Impact of genetic counseling on general anxiety and distress and depression*

Reference	Scale	Time points	Subjects		Mean ± standard deviation	Standardized mean change from baseline (95% confidence intervals)
			Group	No.		
Prospective studies						
Bish et al. *(19)*	HADS	Baseline		186	2.9 ± 3.03	
		Postclinic		186	2.84 ± 3.07	−0.02 (−0.13 to +0.09) NS
		1 y		186	2.98 ± 3.61	+0.03 (−0.10 to +0.15) NS
Meiser et al. *(30)*	BDI	Baseline		218	6.2 ± 6.4	
		1 y		218	7.4 ± 7.9	+0.19 NS
Ritvo et al. *(31)*	CES-D	Baseline		60	8.1§	
		9–12 mo		60	8.1§	0‡

*The measure of general anxiety, Spielberger State-Trait Anxiety Inventory [STAI *(67)*], asks respondents how they generally feel regarding 20 statements (trait) and how they currently feel regarding another 20 statements (state). The short form of the Spielberger State Anxiety Scale *(68)* was used in the study by Bish et al. *(19)*. Studies varied in terms of the number of scale items used. General Health Questionnaire [GHQ *(69)*] was used to assess general distress in the majority of the studies. One study used the Profile of Mood States scale [POMS *(70)*], which uses a list of 65 five-point adjective rating scales and provides scores on six mood states: tension, depression, anger, vigor, fatigue, and confusion. The Beck Depression Inventory [BDI *(71)*] is a 21-item scale designed to measure severity of depression. Hospital Anxiety and Depression Scale [HADS *(72)*] is designed to measure anxiety and depression over the last week; the seven-item depression subscale was used in this study. Center for Epidemiological Studies Depression Scale [CES-D *(73)*] consists of 19 self-report items that are used to screen for depression and psychosocial distress in the general population. I = intervention group; C = control group; A and B = two different groups used in the study.

†$P<.05$ under null hypothesis of a zero change from baseline effect size. NS = statistically nonsignificant, i.e., $P>.05$ under null hypothesis of a zero change from baseline effect size.

‡Not deducible.

§Standard deviation not given.

icant effect with the former but not with the latter. The statistical significance of the effect was not deducible in one study *(30)*.

Behavioral Outcomes

Cancer surveillance. In the few studies examining cancer surveillance behaviors and genetic counseling, mammography use and attendance for clinical breast examination were found to be relatively high at baseline. Breast self-examination was investigated in one controlled trial *(10)* that found statistically significant increases in both intervention and control arms (Table 6). In a second controlled trial *(17)*, rates of self-reported mammography use were slightly reduced in the intervention group and were slightly increased in the control group; however, the statistical significance of this effect was not deducible. One prospective study *(30)* reported a small statistically nonsignificant increase in breast self-examination (Table 6), no statistically significant change in mammography vigilance, and a statistically significant reduction in attendance for clinical breast examination.

Genetic testing. As illustrated in Table 6, none of the controlled trials examined the impact of the intervention on individuals' uptake of genetic testing. Only one small prospective study (n = 60) from Israel examined intentions and actual uptake of predictive genetic testing *(32)*. In this study, 92% of the participants wanted a predictive genetic test before genetic counseling, and 60% were actually tested after counseling.

Discussion

The evidence from controlled trials in this article suggests that genetic counseling leads to increased knowledge of cancer genetics but does not influence risk perception and that genetic counseling does not have an adverse impact on affective outcomes. Specifically, genetic counseling improved knowledge of cancer genetics in three trials *(11,14,15)* but did not influence general anxiety in two trials *(11,15)*, general distress in one *(13)*, depression in one *(15)*, and cancer-specific worry in three trials *(11,13,15)*. The lack of a statistically significant reduction in general anxiety seen in the trials of genetic counseling contradicts the results of the previous meta-analysis of genetic counseling for hereditary breast cancer *(9)*. This lack is partly because of the results of one subsequent trial *(15)* that found no effect on general anxiety after genetic counseling but, more importantly, because the previous meta-analysis *(9)* did not consider the data from the control groups of the trials.

Prospective studies demonstrate a consistent statistically significant increase in the accuracy of perceived risk, as documented in the earlier meta-analysis *(9)*. Some evidence also exists for a short-term reduction in cancer-specific worry and general anxiety. Mean scores at baseline for general anxiety, distress, depression, and cancer-specific worry generally fell within the normal range and did not increase after genetic counseling. Behavioral outcomes were investigated in only a few studies in which small effects were observed in relation to breast self-examination, self-reported mammography, and attendance for clinical breast examination. This finding may indicate that cancer screening and surveillance behaviors are poorly influenced by genetic counseling *(61)*. Alternatively, it may reflect relatively high adherence to surveillance and screening before counseling, particularly for mammography.

There are considerable methodological and theoretical challenges to testing the effectiveness of genetic counseling in terms of outcome measurement and suitable comparison groups. Of particular concern is the use of heterogeneous measures of the same construct, making meta-analysis and comparison of findings from different studies difficult. Another problem relates to the limited number of measures of individuals' understanding of risk information and management options, which is key to genetic counseling. Furthermore, we found no studies that attempted to measure informed choice, which is defined as action consonant with knowledge and values *(62)*, for example, those regarding surveillance or prophylactic surgery. Multidimensional measures of informed choice in Down syndrome screening have been reported recently *(63)*, and this approach could have

Table 5. Impact of genetic counseling on cancer worry*

Reference	Scale	Time points	Subjects		Mean ± standard deviation	Standardized mean change from baseline (95% confidence intervals)
			Group	No.		
Controlled trials						
Brain et al. *(11)*	Cancer Worry	Baseline	I	263	11.79 ± 3.37	
			C	282	11.49 ± 2.97	
		Postclinic	I	263	10.55 ± 2.91	−0.37 (−0.45 to −0.29)†
			C	282	10.50 ± 2.70	−0.33 (−0.42 to −0.24)†
		9 mo	I	263	10.55 ± 3.21	−0.37 (−0.47 to −0.27)†
			C	282	10.63 ± 2.90	−0.29 (−0.40 to −0.18)†
Lerman et al. *(13)*	IES	Baseline	I	239 total	13.1 ± 12.0	
			C		15.3 ± 12.8	
		3 mo	I	239 total	10.3 ± 12.7	−0.23‡
			C		14.4 ± 14.4	−0.07‡
Randall et al. *(15)*	IES (intrusion only)	Baseline	I	32	10.55 ± 8.92	
			C	28	13.18 ± 10.26	
		2 wk	I	29	10.07 ± 9.32	−0.05 NS
	IES (avoidance only)		C	26	12.31 ± 7.37	−0.08 NS
		4–6 mo	I	18	9.41 ± 8.58	−0.13 NS
			C	16	11.13 ± 7.06	−0.20 NS
		Baseline	I	32	11.77 ± 8.92	
			C	28	13.46 ± 8.90	−0.05 NS
		2 wk	I	29	11.28 ± 10.59	−0.08 NS
			C	26	12.65 ± 9.38	−0.09 NS
		4–6 mo	I	18	11.76 ± 9.69	−0.26 NS
			C	16	11.13 ± 7.83	
Prospective studies						
Bish et al. *(19)*	Cancer Worry	Baseline		187	12.39 ± 3.30	
		Postclinic		187	11.13 ± 3.30	−0.38 (−0.49 to −0.28)†
		1 y		187	10.54 ± 3.04	−0.56 (−0.68 to −0.44)†
Collins et al. *(20)*	Cambridge Worry	Baseline		114	2.52 ± 0.99	
		3 wk		114	2.28 ± 0.96	−0.24‡
Gagnon et al. *(25)*	Kash Worry	Baseline		30	15.26 ± 7.6	
		4 mo		30	12.73 ± 4.2	−0.33†
Gagnon et al. *(25)*	IES (intrusion)	Baseline		30	23.30 ± 21.86	
		4 mo		30	13.20 ± 15.93	−0.46 NS
Hopwood et al. *(27)*	Cancer Worry	Baseline		330	11.93 ± 3.22	
		9 mo		330	11.83 ± 3.21	−0.03 NS
Meiser et al. *(30)*	IES	Baseline		218	15.1 ± 15.0	
		1 y		218	13.8 ± 15.3	−0.09‡
Watson et al. *(33)*	Cancer Worry	Baseline	A	60	11.14 ± 3.23	
			B	55	11.39 ± 3.37	
		1 mo	A	56	10.45 ± 3.30	−0.21†
			B	51	NG§	NS§
		6 mo	A	48	10.18 ± 2.86	−0.30†
			B	43	NG	NS§
Watson et al. *(34)*	IES (intrusion)	Baseline		276	7.91 ± 7.29	
		12 mo		244	−0.14 ± 6.09	−0.02 (−0.13 to +0.09) NS
	IES (avoidance)	Baseline		269	9.67 ± 9.54	
		12 mo		232	−0.19 ± 7.95	−0.02 (−0.13 to +0.09) NS

*Cancer Worry Scale [CWS *(74)*] was used to measure specific worry about developing cancer. The studies by Watson and colleagues *(34,54)* used a modified version of this scale to measure the frequency of cancer worry. The Impact of Event Scale [IES *(59)*] is a 15-item Likert scale that measures the experience of stress for a specific life event. It consists of two subscales that measure 1) intrusive thoughts and feelings and 2) avoidance of certain thoughts, feelings, or situations. A modified version of the Cambridge Worry Scale *(75)* was used to measure worry about bowel cancer in the context of other life worries on a four-point Likert scale. Kash Worry Scale *(48)* is a 12-item inventory that assesses women's cancer anxiety and sense of helplessness on a four-point Likert scale. I = intervention group; C = control group; A and B = two different groups used in the study.

†$P<.05$ under null hypothesis of a zero change from baseline effect size. NS = statistically nonsignificant, i.e., $P>.05$ under null hypothesis of a zero change from baseline effect size.

‡Not deducible.

§Not given.

potential application in future studies of genetic counseling. Few studies published to date have used behavioral and risk communication theory to guide the choice and operationalization of outcome measures, although these theories have proven useful in explaining individual responses to medical interventions and developing effective interventions *(64)*. The exception includes studies by Lerman and colleagues *(12–14)*, which draw on theories of personality and health behavior to explain variance in responses to genetic counseling.

Five studies in this review were controlled trials *(10–17)*, four of which were randomized *(10–14,16,17);* however, in several of these studies *(10,12–14,16,17)*, control patients received some form of health counseling including individualized risk counseling in one trial *(11)*. Future trials of genetic counseling will need to account for the general positive emotional effects associated with having a lengthy consultation with a health professional. In addition, the specific components of a genetic counseling intervention require careful definition. These components were not fully described in some studies, making it

Table 6. Impact of genetic counseling on cancer surveillance behaviors*

Reference	Measure	Time points	Subjects: Group	Subjects: No.	Score on measure	Standardized change from baseline (95% confidence intervals)
Controlled trials						
Audrain et al. *(10)*	Breast self-examination (in comparison to American Cancer Society guidelines)	Baseline	I	247	29%	
			C	263	30%	
		3 mo	I	247	48%	+19% (+11% to +27%)†
			C	263	47%	+17% (+9% to +25%)†
Schwartz et al. *(17)*	Self-reported mammography use	Baseline	I	430 total	75%	
			C		71%	
		1 y	I	430 total	69%	−6%‡
			C		75%	+4%‡
Prospective studies						
Meiser et al. *(30)*	Clinical breast examination	Baseline		218	92% vigilant	
		1 y		218	86% vigilant	−6% (−12% to −0%)†
	Breast self-examination	Baseline		218	51% monthly or more	
		1 mo		218	55% monthly or more	
	Mammography vigilance (according to Australian guidelines)	Baseline		218	91% vigilant	+4% (−3% to +15%) NS
		1 mo		218	86% vigilant	−5% (−13% to +2%) NS
Sagi et al. *(32)*	Intention to have genetic testing	Baseline		60	92% wanted gene test,	Not applicable
		Postclinic		60	60% tested, 15% no affected relatives available, 25% not tested	

*I = intervention group; C = control group.

†$P<.05$ under null hypothesis of a zero change from baseline effect size. NS = statistically nonsignificant, i.e., $P>.05$ under null hypothesis of a zero change from baseline effect size.

‡Not deducible.

difficult to define the precise nature of this complex intervention *(65)*. In more than half the studies *(18–22,24–27,29,31,32)*, the intervention was evaluated in a single clinic with only a few clinicians delivering the intervention, thus limiting external validity and making it difficult to assess the contribution of individual clinicians' skills to the effectiveness of the intervention.

Primary research using randomized designs with adequate power, appropriate control groups, and randomization that test interventions driven by behavioral and risk communication theory, with reporting to CONSORT standards *(66)*, is now required to clarify the impact of genetic counseling on cognitive, affective, and behavioral outcomes. Such studies may investigate, in more depth, optimal risk communication strategies and the extent to which they facilitate behavioral changes and promote informed choices about cancer prevention and control regimens. Lessons learned from this domain of research may be applicable to other common chronic diseases, such as heart disease and diabetes, as the genetic basis of these diseases becomes clearer.

Does genetic counseling lead to negative psychological sequelae? Our findings from the trials analyzed suggest that genetic counseling improves knowledge of cancer genetics without an adverse effect on cancer-specific worry, general anxiety, distress, and depression. Prospective studies lend support to the hypothesis that genetic counseling improves the accuracy of perceived risk of the disease. Concerns that genetic counseling could lead to adverse psychological sequelae are empirically unwarranted.

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NOTES

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