Review

Uptake Rates for Breast Cancer Genetic Testing: A Systematic Review

Mary E. Ropka,[1,2,3] Jennifer Wenzel,[2] Elayne K. Phillips,[3] Mir Siadaty,[3] and John T. Philbrick[4]

[1]Division of Population Science, Fox Chase Cancer Center, Philadelphia, Pennsylvania and [2]School of Nursing and Departments of [3]Public Health Sciences and [4]Medicine, University of Virginia, Charlottesville, Virginia

Abstract

Purpose: **Individuals and families dealing with the possibility of hereditary cancer risk face numerous decisions, including whether to obtain genetic testing. The purpose of this article is to determine what is known about the rate at which people obtain cancer genetic testing.**
Methods: **Using MEDLINE, CINAHL, and PSYCHINFO plus reviewing reference lists of relevant articles, we identified 40 studies in May 2002 that addressed breast cancer–related decisions, enrolled adult participants, were published in 1990 or more recently, were peer-reviewed primary clinical studies, addressed genetic testing either alone or in combination with genetic counseling, and reported rates at which participants showed interest in and/or underwent cancer genetic testing. Information regarding study design, participants, and genetic testing uptake rates was recorded. Each article was reviewed for methodologic quality using a flexible quality review system applicable to all study types.**
Results: **Of the 40 studies, 25 provided information about hypothetical genetic testing decisions, 14 about real decisions, and 1 about both. Mean hypothetical uptake was 66% (range, 20-96%) and real uptake was 59% (range, 25-96%). Multivariate logistic regression analyses found that decision type (real/hypothetical), personal and family history of breast cancer, and variability in sampling strategy, recruitment setting, and criteria for real and hypothetical uptake were independently associated with uptake. Our systematic review identified additional explanations for uptake variability (investigator influences, small sample sizes, variability in target populations, lack of clearly described sampling strategies, sampling methods open to bias, and variability in reporting associated risk factors).**
Conclusion: **In addition to clinical characteristics, research methodologic issues are likely to be major determinants of variability in published breast cancer genetic testing uptake rates. An understanding of these issues will clarify to clinicians why their clinical experience may not be congruent with published rates and help guide future research.** (Cancer Epidemiol Biomarkers Prev 2006;15(5):840–55)

Introduction

Individuals and families dealing with the possibility of hereditary cancer risk face diverse and multiple decisions, including whether to obtain cancer genetic testing. There are two broad classes of medical decisions: ''effective-care'' decisions and ''preference-sensitive'' decisions. The first class involves effective health services for which there are large proven benefits compared with the harms, such that there is an obvious ''best choice.'' The second involves preference-sensitive health services for which the best choice is not clear either because the benefit/harm ratios are uncertain or because they are sensitive to how a person values benefits versus harms. These two different classes of decisions have implications for appropriate strategies of risk communication and decision support (1-3). The decision about breast cancer genetic testing is a preference-sensitive decision. The goal of making a preference-sensitive decision is to make a ''quality'' decision rather than the ''right'' decision. A quality decision is defined as one that both is informed and results in a decision consistent with a person's values (4-6).

The decision whether to obtain breast cancer genetic testing can be complex for biologic, behavioral, and social reasons (7). Genetic testing for hereditary breast cancer currently involves two known mutations in tumor suppressor genes, *BRCA1* and *BRCA2*. However, it is likely that other mutations exist that have not yet been identified. If a mutation is not found with current testing, the possibility exists that an unknown mutation is still present, resulting in lingering uncertainty. Even if a known mutation is found, penetrance is variable and unpredictable, again resulting in uncertainty. Thus, understanding the limitations of genetic testing can be complicated for patients and families making the decision whether to be tested (6, 8). Deciding who should be the first in a family to obtain genetic testing adds an additional level of complexity. It is desirable to start testing with a family member who has had breast cancer, but that person may not be interested in being tested. In addition, unlike many other health threats that affect only individuals, families are inherently and inevitably involved in an individual's decision to obtain cancer genetic testing and in dealing with hereditary breast cancer risk. This adds the challenge of effective communication and agreement among family members regarding the task of helping one individual to make a quality decision (9-13).

To better understand the breast cancer genetic testing situation, recent systematic reviews and meta-analyses have examined the psychological aspects of cancer genetic counseling (14-16) and cancer genetic testing (17); predicting individuals' risks of illness (18); measurement of psychological factors associated with genetic testing for hereditary breast, ovarian, and colon cancers (19); and social, ethical, and legal considerations associated with genetic cancer risk assessment

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Requests for reprints: Mary E. Ropka, Division of Population Science, Fox Chase Cancer Center, First Floor, 510 Township Line Road, Cheltenham, PA 19012. Phone: 215-728-1182; Fax: 215-728-2707. E-mail: Mary.Ropka@fccc.edu

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Table 1. Summary of reviewed studies according to real genetic testing decision

Study design	Author (reference)	PH	FH	Sample type (no. subjects)
Randomized controlled trials	Lerman (36) [note: also referenced in Table 2]	No	Yes	Convenience (740)
	Biesecker (48)		Yes	Convenience (172)
Longitudinal	Smith (46)		Yes	All members of kindred invited (759)
	Watson (33)	No	Yes	All family members invited (32)
	Wood (55)	Yes	Yes	Consecutive series (37)
	Broadstock (50)	No	Yes	Consecutive series (38)
Correlational/descriptive	Julian-Reynier (52)		Yes	Convenience (49 families, 506 individuals)
	Lee (61)			Consecutive series (258)
	Armstrong (47)		Yes	Convenience (353)
	Patenaude (32)		Yes	Convenience (51)
	Peterson (62)			Convenience (184)
	Phillips (53)	Yes		Convenience (102)
	Clark (60)	Yes	Yes	Convenience (159)
	Schwartz (54)	Yes	Yes	Convenience (290)
Qualitative	De Wit (30)	No	Yes	Convenience (12)

Abbreviations: PH, whether patient selection required or excluded patients with personal history of breast cancer; FH, whether patient selection required or excluded patients with family history of breast cancer (if left blank, FH/PH status not specified).
*See text for description.

technologies (20). However, reviews have not yet addressed the cancer genetic testing decision itself. Although many individual studies have addressed diverse aspects of cancer genetic testing, including factors that influence cancer genetic testing and the consequences of cancer genetic testing, no synthesis has been focused on the uptake decision to obtain cancer genetic testing (21).

The purpose of this systematic review is to determine what is known about the rate at which people decide to obtain breast cancer genetic testing. We classified studies that reported participants actually obtaining genetic testing as ''real genetic testing decisions'' and studies reporting subjects' ''intent'' to have genetic testing or ''interest'' in testing as ''hypothetical genetic testing decisions.'' Specific research questions include the following: (*a*) What uptake rates, real and hypothetical, have been reported; how much do they vary; and are hypothetical rates higher than real rates? (*b*) How are uptake rates, real and hypothetical, measured? (*c*) Are personal or family history of breast cancer, or other clinical factors, associated with uptake rates? (*d*) Are there issues of study methodology that influence or potentially bias uptake rates? To answer these questions, we identified, critically appraised, and synthesized evidence from studies about breast cancer genetic testing decisions.

Information from this systematic review may be helpful to individuals and families dealing with hereditary breast

Table 1. Summary of reviewed studies according to real genetic testing decision (Cont'd)

Recruitment		Comments
Who	How	
Women, first-degree relatives of breast/ovarian patients	Identified by affected relative or treating M.D. at two cancer centers or self-referred in response to recruitment brochures at the two medical centers	400 subjects completed the trial; those declining to participate were more likely to have less education, to be unmarried, to be African American, to have lower incomes, and to have only one first-degree relative with breast cancer
Members of hereditary breast/ ovarian cancer families already participating in National Cancer Institute cancer mutation study		
Adult members of known BRCA1 mutation kindred, some of whom were already participating in research study		500 contacted and offered genetic counseling and testing
Unaffected members of 2 families with familial clustering of breast/ovarian cancer		32 contacted and offered genetic counseling and testing
Women with breast/ovarian cancer before age 50 y and FH of breast/ovarian cancer referred to university cancer genetics clinic		
Patients scheduled to be seen in cancer genetics clinic	Referred by general practitioners and oncologists	21 completed follow-up assessments
BRCA-positive families	Cancer geneticists selected records of evaluated families	Results reported for 419 family members
Female patients with PH or FH of breast cancer and estimated to be at least at 10% chance of BRCA mutation	Retrospective review of cancer genetics clinic records	All patients attended genetic counseling clinic
All participants in university breast/ ovarian cancer risk program	Recruited through letter	Note: 125 had obtained or were going to get genetic testing/251 eligible; study not completed
Members of families with BRCA1 mutation already enrolled in a university research program		Note: 29 accepted genetic testing offer/36 breast cancer families; 28/36 had genetic testing
Of all seen over 3-y period for initial visit in breast/ovarian cancer risk clinic, medical records were reviewed to find women with high FH of BRCA1 mutation		
Ashkenazi Jewish women enrolled in cancer genetics study	Recruited by letter	
Participants with ≥10% risk of BRCA1 mutation	Identified by self-reference, M.D. referral, or university tumor registry	
Women with PH and ≥20% probability of BRCA1/2 mutation	Self-referred to cancer center risk evaluation program	
Unaffected males of known BRCA1 mutation-carrying families	Recruited through clinical genetic department study	

cancer risk, health care providers providing genetic services or referrals for cancer genetic services, health systems setting policy, and future research programs in the following ways: (*a*) assisting readers of the uptake literature to understand its strengths and weaknesses; (*b*) assisting in planning for genetic services and resources for different populations, regions, or situations, including estimating demand for limited genetic service resources and promoting access to genetic testing resources for the appropriate people; (*c*) improving understanding of factors that influence use of genetic testing services and resources; and (*d*) improving understanding of the problems and pitfalls of uptake-related research for those using uptake rates in research (6, 21-25).

Materials and Methods

Search Strategy and Data Sources. We sought all studies that (*a*) addressed breast cancer–related decisions, (*b*) enrolled adult (ages ≥18 years) participants, (*c*) were published in 1990 or more recently, (*d*) were peer-reviewed primary clinical studies, (*e*) addressed genetic testing either alone or in combination with genetic counseling, and (*f*) reported rates at which participants showed interest in and/or obtained cancer genetic testing. In May 2002, two separate searches were done addressing cancer genetic counseling and cancer genetic testing in each of three databases: MEDLINE, CINAHL, and PSYCHINFO. We did not include EMBASE or CANCERLIT because on a trial search they did not add to the completeness

Table 1. Summary of reviewed studies according to real genetic testing decision (Cont'd)

Operational definition of real uptake	Study results: interventions and uptake rates	Compliance with methodologic standards* (2, full compliance; 1, partial; 0, noncompliance; NA, not applicable)
Rate of provision of blood sample during same visit as intervention	Intervention: education session only (lecture, workbook, and flip chart); after intervention: 51% (58/114) uptake; intervention: education session followed by genetic counseling; after intervention: 52% (63/122) uptake; wail-list control (164 participants); uptake not requested	2: standards 1 and 3-6; 0: standard 2
Rate of receiving test results; blood drawn for most subjects during same visit as intervention, but subjects ''had option to have blood drawn at a later date'' or to decline to receive test results.	Intervention: family group pretest education (including lecture, slides, and one-on-one client-directed counseling); intervention: pretest education (including lecture, slides, flip charts, and one-on-one provider-led counseling); after interventions: ''no differences in uptake''; uptake combined groups: 80% blood drawn, 78% results received	2: standards 1 and 3; 0: standard 2; NA: standards 4-6
Rate of provision of blood sample during same visit as first genetic counseling session	54% (269/500) uptake of genetic testing	2: standards 1-6
Rate of genetic testing; blood drawn no sooner than 1 mo after genetic counseling; no time limit specified for requesting testing	41% (13/32) uptake of genetic testing	2: standards 3 and 4; 1: standards 1 and 2; NA: standards 5 and 6
Rate of genetic testing done; blood sample provided at time of first genetic counseling session	95% (35/37) uptake of genetic testing	2: standards 1-4; NA: standards 5 and 6
Rate of genetic testing within 12 mo after offer of testing	71% (15/21) uptake	2: standards 3, 5, and 6; 1: standards 1 and 4; 0: standard 2
Rate of provision of blood sample within 8 mo of delivery of genetic testing results to family's index case	Affected women: 69% (25/36) uptake; unaffected women: 31% (65/208) uptake	2: standards 1-3; NA: standards 4-6
Rate of genetic testing during 4-y period, no time restriction between initial genetic counseling session and genetic testing decision	All participants: 26% (68/258) uptake; participants with at least one affected first-degree relative: 27% (52/191) uptake	2: standards 1-3; NA: standards 4-6
Rate of genetic testing done during 3-y period after risk counseling, no time restriction between initial counseling session and testing	50%	2: standards 1-3 and 6; NA: standards 4 and 5
Rate of provision of blood at same visit as initial genetic counseling	78%	2: standard 3; 1: standards 1 and 2; 0: standard 6; NA: standards 4 and 5
Rate of genetic testing during 3-y period after genetic counseling, no time restriction between initial counseling session and testing	58%	2: standard 1; 1: standards 2 and 3; 0: standard 6; NA: standards 4 and 5
Rate of genetic testing during unspecified time period, no time restriction between initial counseling session and testing	66%	2: standard 3; 0: standards 1 and 2; NA: standards 4-6
Rate of genetic testing, no time restriction between initial counseling session and testing	Print booklet plus 1-1 counseling; 96% uptake	2: standard 3; 0: standards 1 and 2; NA: standards 4-6
Rate of receipt of testing results; blood drawn at the time of the initial counseling session	84% blood drawn; 82% results received	0: standards 1-3; NA: 4-6
Rate of genetic testing; no time restriction between counseling and testing	25%	2: standards 1-4; NA: standards 5 and 6

of our search results. Our search strategies were complex because, unlike some systematic review or meta-analysis topics, a single term could not be used to represent our search topic. For example, multiple terms had to be included in the search strategy, including ''genetic testing,'' ''predictive testing,'' ''BRCA1/2 testing,'' ''gene$ test$.mp.,'' ''susceptibility test$.mp.,'' ''gene$ predict$ test$.mp.,'' ''gene$ susceptibility test$.mp.,'' ''personal risk$ predictive test$.mp.,'' ''cancer$ gene$ test$.mp.,'' ''brca1 test$.mp.,'' and ''((brca or brca2) and test$).mp.'' In addition, developing the search strategies was complicated because the syntax of the first search, which was developed in MEDLINE, had to be adapted to accommodate syntax differences in CINAHL and PSYCHINFO. Finally, because we did not want to miss relevant articles, for our search strategies we purposefully emphasized higher sensitivity, or avoiding false negatives, over specificity, thus allowing more false positives. Inappropriate articles were eliminated in the subsequent article selection process. The search strategies for MEDLINE, CINAHL, and PSYCHINFO are available from the authors.

The three genetic counseling files, one from each database, were combined into one file (yield, 1,726 references) and the three genetic testing files were combined into a second file (yield, 1,449 references), and duplicates were removed from the two resulting files. The genetic counseling and genetic testing files were then combined (yield, 2,613 references) and duplicates were removed. Letters to editors, reviews, comments, and duplicates were removed, leaving one set of articles (yield, 1,887) to be screened for inclusion in this review.

Article Selection and Classification. Two reviewers independently evaluated each citation for possible inclusion, initially using the title and other information from the database citation. Disagreements were resolved by detailed review of the abstract and occasionally the full article. Of the 1,887 articles, 240 underwent this more detailed review. Reference lists of reviews on genetic counseling and testing, as well as articles included in our review, were examined for eligible studies not identified by the MEDLINE, CINAHL, and PSYCHINFO searches. Fourteen additional articles for possible inclusion were identified in this manner. As a final step to determine which articles to include, variables in each article were examined to find those that addressed a decision to obtain genetic testing. Forty studies met all selection criteria and constitute the basis for this review (8, 26-64).

When, in any given study, multiple populations were offered tests for different cancers, only data from the breast cancer group were used. Where both counseling and testing decisions were examined, only the testing data were included. We grouped results regarding study participants' ''interest in'' or ''intent to have'' genetic testing as ''hypothetical genetic testing decisions.'' We grouped studies reporting participants' rate of genetic testing as ''real genetic testing decisions.'' Real decisions were sometimes reported as ''taking the test'' or ''drawing blood for testing.''

Data Abstraction. Information recorded for each study included type of decision (real or hypothetical), country where done, study design, participants' breast cancer personal history (present in all subjects or not), participants' breast cancer family history (present in all subjects or not), sampling approach, sample size, recruitment setting (community, hospital/clinic, both, or unknown), recruitment method, method of measuring hypothetical decisions of genetic testing interest or intent (exact question wording), operational definition of hypothetical uptake (how interest or intent was transformed into a dichotomous variable, yes/no), operational definition of real uptake (dichotomous variable, yes/no), genetic testing uptake rates for hypothetical and real decisions, the ''window'' of opportunity for subjects to have blood drawn for testing, interventions delivered, and groups for which uptake rates were reported. When a study reported more than one real uptake rate, we used the ''blood drawn'' or ''test done'' rate for statistical analysis. When a study evaluated uptake rates in more than one distinct group of subjects, we abstracted descriptive data and uptake rates for each group separately rather than for the overall study. For example, for a study that recruited two groups of women, one with a family history of breast cancer and a second without this family history (43), we considered the two groups to be different samples, each with its own descriptive data and uptake rate. In addition, when a study evaluated a variable for association with decisions regarding genetic testing uptake, details of the variable and statistical significance were recorded.

Quality Review of Articles. Each of the included articles was reviewed for methodologic quality using a flexible quality review system applicable to all study types. These six standards were adapted by the investigators from other reviews (65-69) and focused on methodologic issues important to study quality and minimizing bias pertinent to studies of uptake rates. The standards, their rationale, and study type for which each is relevant are as follows: standard 1: to allow understanding of the study subjects, the methods section provides clearly stated subject inclusion and exclusion criteria (applicable to all study types); standard 2: to allow an estimation of reproducibility and whether study results can be applied to other groups (external validity), the sampling strategy is described clearly enough so that it would be possible to assemble a similar group if the study were to be repeated (applicable to all study types); standard 3: to allow an understanding of the potential effect of incomplete participation, the number of individuals who refused to participate is reported (applicable to all study types); standard 4: to allow for assessment of the potential effect of study dropouts, the number of enrolled individuals who withdrew is reported and, if there were study dropouts, the number of dropouts is <10% (not applicable to correlational/descriptive studies); standard 5: to limit unplanned crossover of study groups, if there were different study groups, the groups are maintained throughout the study (not applicable to correlational/descriptive and qualitative studies); and standard 6: to ensure that compared groups are similar, except for factors that identify the different groups before an intervention (if there were more than one group in the study), simple demographic variables are similar between the groups at baseline, and if there are differences in these potential confounders, statistical adjustment for them is included in the analysis (not applicable to qualitative studies).

Two of the authors independently assessed the articles for study design and rated them for compliance with standards relevant to that design. Each article received a rating of 2 (complete compliance), 1 (partial compliance), 0 (noncompliance), or NA (not applicable) for each standard. The ratings of the two reviewers (J.T.P. and J.W.) were compared and discrepancies were resolved by discussion to achieve consensus. If agreement could not be achieved, a third reviewer (M.E.R.) evaluated the article.

Statistical Analysis. For each distinctive group of study subjects, we entered into a database the number of subjects, number of subjects choosing uptake, decision type (real or hypothetical), personal history of breast cancer (present in all subjects or not), family history of breast cancer (present in all subjects or not), recruitment setting (community, hospital/clinic, both, or unknown), sampling strategy (convenience or ''reproducible''), real decision (immediate or delayed), and hypothetical decision (Likert/similar scale or dichotomous scale). Because for our analysis the dependent variable was response of each participant to the two-choice uptake question (yes/no), we concluded that the natural distributional assumption was the binomial distribution. Because we only had summary data on groups rather than data on individual subjects, we used the total number of subjects in each group and the number of ''yes'' respondents to define a grouped binary data structure. We then fitted logistic regression models to the data, where coefficients of regression were log odds ratios (OR). These coefficients were related to the dependent variable, uptake rate (r), by two transformations. The first was a transformation to an OR and the second was to a logarithm: $\log \text{OR} = \log [r / (1 - r)]$. When building the model, estimating the variables, and interpreting the results, we followed the methodologies explained in detail elsewhere (70, 71). This method allows for a more realistic distributional assumption for the dependent variable than the normal distribution, accounts for different sample sizes of the studies, has more statistical power, allows independent variables to be incorporated into the model, and both decreases heterogeneity and estimates effect of those variables on the dependent variable. We used SAS/STAT software version 9.1 to fit the models and estimate the variables (PROC GENMOD).

Results

Study Description. The 40 articles (8, 26-64) meeting the criteria to be included in this review are summarized in Table 1 (real decisions) and Table 2 (hypothetical decisions). There were many differences among the studies. Twenty-five studies

Table 2. Summary of reviewed studies according to hypothetical genetic testing decision

Study design	Author (reference)	PH	FH	Sample type (no. subjects)
Randomized controlled trials	Green (63)		Yes	Convenience (72)
	Lerman (36) [note: also referenced in Table 1]	No	Yes	Convenience (740 eligible, 400 participated)
	Brain (64)	No	Yes	Consecutive series (740)
	Burke (51)	No	Yes	Convenience (243)
	Schwartz (57)			Convenience (406)
Cohort	Cappelli (41)			Convenience (110)
Correlational/Descriptive	Andrykowski (29)			Random sample (649)
	Bosompra (49)	No		Random sample (622)
	Jacobsen (35)	No	Yes	Convenience (74)
	Lipkus (43)	No		Convenience (266)
	Tambor (37)	No		Convenience (473)
	Bottorff (59)			
	Lerman (26)	No	Yes	Convenience (121)
	Velicer (58)	Yes		Convenience (217)
	Julian-Reynier (31)		Yes	Convenience (209)
	Ludman (44)			Convenience (91)
	Bluman (40)	Yes	Yes	Convenience (208)
	Lerman (27)	No	Yes	Convenience (105)
	Cappelli (56)	No		Convenience (108)
	Struewing (28)		Yes	Convenience (143)
	Durfy (42)	No	Yes	Convenience (543)
	Mogilner (39)			Convenience (354)
	Braczkowski (38)			Women (200)
Qualitative	Bernhardt (34)			Convenience (300)
	Ryan (45)		Yes	Convenience (29)
	Press (8)	Yes		Convenience (246)

*See text for description.

provided information about hypothetical genetic testing decisions, 14 about real decisions, and 1 about both (36). Twenty-five employed a correlational/descriptive design, 6 were randomized controlled trials, 4 were qualitative, 2 were longitudinal studies (before/after, pre/post interventions), and 1 was a cohort study. They were done in six different countries, including 29 in the United States (8, 26-29, 34-37, 39, 40, 42-49, 51, 54, 55, 57, 58, 60-63, 72), 4 in Canada (41, 53, 56, 59), and 3 in

Table 2. Summary of reviewed studies according to hypothetical genetic testing decision (Cont'd)

Recruitment	
Who	How
Women with FH of breast cancer	Recruited through newspaper advertisements
Women first-degree relatives of breast/ovarian patients	Identified by affected relative or treating M.D. at two cancer centers, or self-referred in response to recruitment brochures at the two medical centers
Women with FH of breast cancer	Referred to research project by physicians
Women with FH of breast cancer but not at high risk for genetic mutation	Recruited through letters to breast cancer patients and press releases, broadcast and print media advertisements, and notices in employee newsletters
Ashkenazi Jewish women	Members of a Jewish women's organization recruited through mail invitation
Women with breast cancer referred by oncologists at a regional cancer center	General population women identified by word of mouth and by being approached in an orthopedic clinic
General population	Identified by random digit dialing
General population	Random sample identified from phone directory
Women with first-degree relative having breast cancer	Identified from mammography schedule, recruited by telephone contact
African American women with first-degree relative having breast cancer and second sample of African American women without FH breast cancer	Referred by breast cancer patients listed in tumor registry/controls identified from radiology department records (matched with cases)
Health maintenance organization women members who had received two or fewer screening mammograms in 3-y period	Recruited through mail contact
Stratified random sample (general population women 761, breast cancer patients 260)	General population identified by random digit dialing/ breast cancer patients identified from cancer registry
Women first-degree relatives of ovarian cancer patients	Identified by ovarian cancer patients under treatment at cancer center
Women with PH of breast cancer who were enrolled in health maintenance organization	Recruited through mail contact
Women first time attendees of cancer genetics clinic, either with PH or breast cancer first-degree relatives	Recruited at clinic
Women with appointments in health maintenance organization primary care clinic	Recruited while in waiting room
Breast/ovarian cancer patients at high risk for BRCA gene mutation and with family history of breast/ovarian cancer	Identified from tumor registry, through self and M.D. referral, and in response to advertising
Women first-degree relatives	Identified by breast cancer patients under treatment at a cancer center
Women first-degree relatives referred by breast cancer patients at a regional cancer center	General population recruited by word of mouth
Members of hereditary breast/ovarian cancer families already participating in genetic linkage studies	
Four specific groups of women with FH of breast cancer	Recruited through announcements on radio and TV, advertisements in newsletters and daily and weekly newspapers, announcements at relevant gatherings
Women patients and family medical center visitors	Recruited in waiting rooms of breast clinic and surgical oncology clinic
Sample not reported	Sampling method not reported
General population women	Recruited through advertisement in local papers
Women first-degree relatives	Referred by breast cancer patients
Women general population	Recruitment process not reported

the United Kingdom (33, 50, 64). Of the 40 studies, 7 used community settings (8, 29, 34, 42, 49, 57, 63), 27 clinic and/or hospital (26-28, 30-33, 35-37, 39, 43-48, 50, 52-55, 58, 60-62, 64), 5 both settings (40, 41, 51, 56, 59), and 1 not stated. Some studies targeted specific groups, including Ashkenazi Jewish women, known BRCA kindreds, and lesbian and bisexual women (28, 33, 42, 46, 48, 52, 53, 57, 72), whereas others recruited subjects from the general population (29, 34, 37, 41, 49).

Table 2. Summary of reviewed studies according to hypothetical genetic testing decision (Cont'd)

Method of measuring genetic testing interest	Operational definition of hypothetical uptake
5-point Likert scale: ''If a blood test to look for an abnormality in a breast cancer susceptibility gene were offered today, what do you think you would do?'' (1, definitely get tested; 5, definitely not get tested)	1 and 2 = uptake
4-point Likert scale: ''At the present time, which of the following statements describes you best?'' (1, have not thought about testing; 4, definitely will have testing)	3 and 4 = uptake
3-choice response (1, want a genetic test; 2, do not want a genetic test; 3, uncertain)	1 = uptake
4-point Likert scale: ''Evaluate your interest in genetic testing, given your family history.'' (definitely no, probably no, probably yes, definitely yes)	Probably yes and definitely yes = uptake
4-point Likert scale: (1, have not considered testing; 4, definitely will have testing)	3 and 4 = uptake
Single item asking participants if they would like to be tested (''yes,'' ''no,'' ''need more time to think'')	Yes = uptake
Female participants: ''Suppose you had inherited something from your parents which would make you more likely to develop breast cancer than most women; would you want to be told this or not?'' (yes/no)	Yes = uptake
5-point Likert scale: likelihood of obtaining a genetic test for cancer risk over the next 6 mo if it were available (1, definitely not; 5, definitely)	4 and 5 = uptake
''If an individually administered test for genetic susceptibility to breast cancer were currently available, please indicate your readiness to take such a test'' [1, yes, as soon as possible (within 30 days); 2, yes, in the near future (within 6 mo); 3, yes, but not in the next 6 mo; 4, do not plan to take in the next 6 mo but could change my mind; 5, do not plan to take...not likely to change mind]	1-3 = uptake
''There are some new blood tests that may be able to tell you if you have a greater chance of getting breast cancer because of something that might have been passed down to you from your blood relatives, that is, through your genes. If this test was free, how interested you be in having it done?'' (not at all interested, slightly interested, somewhat interested, interested, and very interested)	Interested and very interested = uptake
''Recently, scientists announced that they had found a gene that causes breast cancer. If you could be tested to find out whether you had the gene, would you be interested?'' (yes/no/do not know)	Yes = uptake
Which statement best describes you? ''You are...not considering or have not thought about genetic testing; are considering genetic testing; probably will have genetic testing; definitely will have genetic testing; or already have had genetic testing.''	Probably, definitely, and already have had testing = uptake
5-point Likert scale: interest in genetic testing (1, definitely yes; 4, definitely no; 5, uncertain)	1 and 2 = uptake
''I plan to have a genetic test for breast cancer, even if I have to pay for it myself'' (1, strongly disagree; 4, strongly agree, collapsed to ''disagree'' and ''agree'')	3 and 4 = uptake
''Would you ask for the test (predictive testing for breast cancer)?'' (yes/no/do not know)	Yes = uptake
''Do you plan to obtain testing even if you have to pay for it yourself?''	Definitely or probably yes = uptake; no information on other response choices
Self-report (response choices: 1, definitely will not be tested; 2, probably will not be tested; 3, considering testing but still unsure; 4, probably will be tested; 5, definitely will be tested; 6, have not yet considered testing)	4 and 5 = uptake
''If a blood test were available which would show whether you had inherited an altered breast cancer gene, would you want to take the test?'' (yes, no, uncertain)	Yes = uptake
''Would you take a test which could tell you if you have a high risk (80-90%) of getting breast cancer?'' (response choices: yes, no, I need more time to think about it)	Yes = uptake
Intention to be tested (1, yes, definitely; 2, yes, probably; 3, probably not; 4, definitely not)	1 and 2 = uptake
4-point Likert scale: ''Would you be interested in taking such a test (a test for inherited susceptibility to breast cancer)?'' (1, definitely not; 4, definitely yes)	3 and 4 = uptake
''If you have not yet been tested, would you choose to be tested if the testing were made available to you?'' (yes/no)	Yes = uptake
''Would you accept genetic testing for BRCA mutations?'' (yes, not sure, no)	Yes = uptake
Interest in testing: open-ended group interview questions	
Are you interested in genetic susceptibility testing for breast cancer? Why or why not?	Interest in open-ended response = uptake
If a genetic test for breast cancer existed today, would you want to take it? (yes, no, uncertain)	Yes = uptake

Twenty-three studies included only patients with a family history of breast cancer and 6 enrolled only patients with a personal history of breast cancer. Fifteen studies excluded patients with a personal history of breast cancer, whereas the number with personal history was unknown in 19 studies. No studies excluded patients with a family history of breast cancer, whereas the number with family history was unknown in 17 studies.

Table 2. Summary of reviewed studies according to hypothetical genetic testing decision (Cont'd)

Study results: interventions and uptake rates	Compliance with methodologic standards* (2, full compliance; 1, partial; 0, noncompliance; NA, not applicable)
Intervention: individual genetic counseling; before intervention: 64% (27/42) uptake; after intervention: 39% (16/42) uptake; intervention: interactive computer program followed by individual genetic counseling: before intervention: 72% (21/29) uptake; after intervention: 45% (13/29) uptake	2: standards 1-6
Intervention: education session only (lecture, workbook, and flip chart); after intervention: 57% (65/114) uptake; intervention: education session followed by genetic counseling; after intervention: 61% (74/122) uptake; wait-list participants; control: 53% (87/164) uptake	2: standards 1 and 3-6; 0: standard 2
Intervention: individual counseling with surgeon; before intervention: 90% (302/337) uptake; after intervention: 80% (219/267)uptake; intervention: individual counseling with surgeon and genetic counselor; before intervention: 85% (275/315) uptake; after intervention: 79% (210/261) uptake	2: standards 1-4 and 6; 1: standards 5
Before intervention, both groups combined: 91% (221/243) uptake; intervention: individual genetic counseling; after intervention: 58% (67/116) uptake; intervention: no counseling; after: 88% (106/121) uptake	2: standards 1 and 4-6; 1: standard 2; 0: standard 3
Intervention: genetic testing education booklet; before intervention: 24% (46/191) uptake; after intervention: 18% uptake; intervention: general breast cancer education booklet; before intervention: 25% (47/190) uptake; after intervention: 26% uptake	2: standards 1-3 and 5; 1: standards 4 and 6
General population participants: 46% (23/50) uptake; breast cancer patients: 72% (43/60) uptake	2: standard 3; 1: standard 6; 0: standard 1 and 2; NA: standards 4 and 5
Breast cancer question of women participants: 93% (330/355) uptake	2: standards 1-3; NA: standards 4-6
20% (124/622) uptake	2: standards 1-3; NA: 4-6
81% (60/74) uptake	2: standards 1-3; NA: 4-6
African American women with first-degree relative having breast cancer: 72% (94/130) uptake; African American women without family history of breast cancer: 58% (79/136) uptake	2: standards 1-3 and 6; NA: standards 4 and 5
69% (326/473) uptake	2: standards 1-3; NA: standards 4-6
General population: 29.5% (224/761) uptake; breast cancer patients: 30.8% (80/260) uptake	2: standards 1-3 and 6; NA: standards 4 and 5
First-degree relatives of ovarian cancer patients: 95% (115/121) uptake	2: standards 1 and 3; 1: standard 2; NA: standards 4-6
26% (52/197) uptake	2: standards 1 and 3; 1: standard 2; NA: standards 4-6
Breast cancer patients: 76.2% (64/84) uptake; first-degree relatives of cancer subjects: 95.8% (115/120) uptake	2: standards 1 and 2; 1: standard 3; NA: standards 4-6
44% (40/91) uptake	2: standards 3 and 4; 1: standard 1; 0: standard 2; NA: standards 5 and 6
84% (168/200) uptake	2: standards 1 and 3; 0: standard 2; NA: standards 4-6
91% (96/105) uptake	2: standards 1 and 3; 0: standard 2; NA: standards 4-6
First-degree relatives: 68% (39/57) uptake; general population: 45% (22/49) uptake	2: standards 3, 4, and 6; 1: standards 1. 0: standard 2; NA: standard 5
95% (133/140) uptake	2: standards 1 and 3; 1: standard 2. 0: standard 6; NA: standards 4 and 5
Caucasian women: 90% (276/307) uptake; lesbian/bisexual women: 88% (77/87) uptake; African American: 87% (27/31) uptake; Ashkenazi Jewish: 83% (94/113) uptake	2: standards 1 and 6; 0: standards 2 and 3; NA: standards 4 and 5
Family history: 68% (73/107) uptake; no family history: 66% (160/242) uptake	0: standards 1-3; NA: standards 4-6
Family history: 88% (62/70) uptake; no family history: 67% (87/130) uptake	0: standards 1-4 and 6; NA: standard 5
Interest in genetic testing "high," then diminished after education	2: standard 4; 0: standards 1-3; NA: standards 5 and 6
41% (12/29) uptake	2: standard 4; 0: standards 1-3; NA: standards 5 and 6
71% (175/246) uptake	0: standards 1-4; NA: standards 5 and 6

Fourteen studies reported uptake rates of more than one distinct group of subjects, totaling 59 distinct groups among the 40 studies. One qualitative study reporting on hypothetical decisions did not report uptake quantitatively for its single group (34). Therefore, when reporting uptake rates, we use data from 58 groups (40 hypothetical, 18 real decisions) from the 40 studies. The mean number of patients per group was 178 (range, 4-761).

Research Question 1: What Uptake Rates, Real and Hypothetical, Have Been Reported; How Much Do They Vary; and Are Hypothetical Rates Higher than Real Rates? The mean uptake rate of the 40 hypothetical decision groups was 66% and it was 59% for the 18 real decision groups. This difference is similar to that found by the one study reporting both hypothetical and real uptake rates in two patient groups (57% versus 51% and 61% versus 52%, respectively; ref. 36). There was a wide range of uptake rates for both the hypothetical decision groups (20-96%) and the real decision groups (25-96%). When decision type alone was entered into our multivariate logistic regression model evaluating associations with uptake rates, this difference favoring hypothetical decisions had a relatively small OR but was statistically significant [OR, 1.27; 95% confidence interval (95% CI), 1.16-1.39]. After the clinical and study methodology variables listed in Table 3 were added to the model, the relationship between hypothetical decision type and uptake rate was strengthened (OR, 2.03; 95% CI, 1.82-2.28).

Research Question 2: How Are Uptake Rates, Real and Hypothetical, Measured? Details of how real uptake rates were measured are presented in Table 1. To measure uptake, 13 of the 15 studies reporting real uptakes used either rates of drawing blood for genetic testing or performance of the genetic tests. Two studies (48, 54) recognized that sometimes subjects have genetic testing done but subsequently decline to receive the results. These studies reported two uptake rates, a ''blood drawn'' rate and a ''test received'' rate. However, in both studies, the blood drawn rate was only 2% higher than the test received rate. A second difference in how real uptake rates were determined had to do with the window of opportunity allowed for subjects to make an uptake decision. Five studies counted uptake decisions made at only one point in time, ''immediate'' testing after the initial genetic counseling session, not allowing ''delayed'' testing decisions made at a later time to be included (32, 36, 46, 54, 55). The other 10 real uptake studies counted subjects who could choose to delay testing for months or years after counseling.

Details of how hypothetical uptake rates were measured are presented in Table 2. Each of the 25 studies measured hypothetical uptake differently. Thirteen of the studies measured interest in genetic testing with a range of responses on four- or five-point Likert or similar scales, all different in wording. The other studies used different questions with dichotomous responses.

Research Question 3: Are Personal or Family History of Breast Cancer, or Other Clinical Factors, Associated with Uptake Rates? The six studies that enrolled only patients with personal history of breast cancer had a mean uptake rate of 70% (range, 26-96%), whereas the remaining studies (15 that excluded patients with personal history, 19 personal history unknown) had a mean uptake of 63% (range, 24-93%). The 23 studies that enrolled only patients with family history of breast cancer had a mean uptake rate of 70% (range, 20-96%), whereas the remaining studies in which family history was unknown had a mean of 52% (range, 24-93%). Our multivariate logistic regression model that incorporated decision type, sampling strategy, and recruitment setting along with family and personal history (Table 3) found statistically significant associations of personal history (OR, 1.24; 95% CI, 1.11-1.39) and family history (OR, 2.11; 95% CI, 1.92-2.32) with uptake.

Many of the reviewed studies evaluated variables other than interventions for association with real and hypothetical uptake rates. Table 4 presents the results of the 16 studies that included personal characteristics, personal breast/ovarian cancer history, and/or family history of breast/ovarian cancer in this evaluation, organized according to variable. Eight used univariate statistical methods (26, 29, 31, 35, 39, 49, 54, 61), whereas the remainder employed multivariate analyses (37, 40, 42, 43, 47-49, 59). Variables found in individual studies to be associated with genetic testing uptake were older age (35, 47, 48), women of Ashkenazi Jewish heritage (47, 61), not married status (43), personal breast cancer history (47, 61), and family history of breast cancer (49, 59). However, these associations were inconsistent across studies, including personal and family history of breast cancer that in some studies failed to show a statistically significant correlation with uptake (39, 43, 47, 48, 54, 61) and in others showed an association in the opposite direction (31, 39, 59). As summarized in Table 4, there were many differences between studies, including varying variable definitions, widely disparate groups of subjects, and different statistical methods.

Six studies evaluated the effect of educational and/or counseling interventions on hypothetical uptake rates (36, 48, 51, 57, 63, 64). Four (51, 57, 63, 64) reported reduced hypothetical uptake rates with these interventions and a fifth did not find a significant difference (36). The subjects, interventions, and measure of hypothetical uptake were different in each study. The absolute change in uptake rate ranged from a reduction of 33% to an increase of 8% (mean change, reduction of 10%). Two evaluated the effect of educational and/or counseling interventions on real uptake rates (36, 48) and did not find significant differences.

Research Question 4: Are There Issues of Study Methodology That Influence or Potentially Bias Uptake Rates? Using our multivariate logistic regression model, we investigated whether recruitment setting, method of measuring uptake, and sampling strategy were associated with uptake. We found that studies recruiting patients in hospital/clinic settings and in combined hospital/clinic/community settings had significantly higher uptake rates than studies recruiting in community settings (Table 3) even when controlled for decision type and family and personal history.

To explore the degree to which uptake definition affects uptake rates, we created two additional regression models. The first evaluated in real studies whether uptake definitions that counted only immediate testing decisions differed from those that included delayed testing decisions. While controlling for personal and family history, sampling strategy, and recruitment setting, immediate testing decision studies had higher uptake rates (OR, 1.38; 95% CI, 1.14-1.66). The second model evaluated in the hypothetical studies whether uptake definitions using a Likert or similar scale differed from those using questions with dichotomous responses. While controlling for personal and family history, sampling strategy, and recruitment setting, dichotomous responses were associated with higher uptake rates (OR, 4.62; 95% CI, 4.07-5.24).

The last column in Tables 1 and 2 presents the quality ratings for the 40 studies. Standards 1 to 3 were concerned with assembly of study subjects. Whereas most studies provided clearly stated inclusion and exclusion criteria (standard 1, 31 studies rated partially or fully compliant) and reported the number of withdrawals (standard 3, 32 studies rated partially or fully compliant), less than half employed a sampling strategy that could reproducibly assemble study groups (standard 2). Whereas 4 enrolled consecutive series of eligible patients (50, 55, 61, 73), 2 enrolled the entire cohort of eligible subjects (33, 46), and 3 were random samples of a population (29, 49, 59), 30 studies assembled a ''convenience'' sample of patients. One study did not describe the sampling method (38). When sampling strategy was entered into our multivariate regression model (Table 3), convenience sampling was associated with higher uptake rates (OR, 1.75; 95% CI, 1.60-1.91) than the more reproducible sampling strategies.

Standards 4 to 6 were focused on assessing the potential for several important sources of bias. We rated them ''not applicable'' to more than half of the studies. There was general compliance with reporting and limiting study dropouts

(standard 4, 7 of 9 applicable studies rated partially or fully compliant), maintaining patients in the groups to which they were originally assigned (standard 5, 8 of 8 partially or fully compliant), and limiting the potential for confounding variables (standard 6, 14 of 17 partially or fully compliant).

Discussion

Although some degree of variability is to be expected in the situation of a preference-based decision, we found the range of uptake rates, from 20% to 96%, to be surprisingly wide. Because it is easier to express a preference than to be tested, we expected hypothetical rates to be considerably higher than real rates. The difference that we found (66% versus 59%) was in the expected direction and statistically significant but only partly explained uptake rate variability. Because only one study measured real and hypothetical uptake in the same two groups (36), we were unable to estimate the extent to which real and hypothetical rates are correlated and the potential of hypothetical rates to be used in research and practice as a surrogate measure of real uptake rates.

A limitation of our review is that we last updated our literature search in May 2002. However, additional studies would not reduce the range of uptake rates or change the issues of research methodology described here.

Our review revealed that the definition of real uptake was not as clear and consistent as we anticipated. We expected the definition to be ''blood drawn for testing'' or ''performance of genetic testing.'' We found that sometimes study subjects consented to the blood draw but later decided not to receive the results of the genetic test, creating two possible ways to report real uptake: a ''blood drawn'' rate versus a ''results received'' rate. However, when these two rates were reported, they were quite similar (48, 54), suggesting that few people decline to receive test results once they have agreed to have their blood drawn. A second issue complicating measurement of real uptake rates was concerned with the time allowed after counseling for subjects to be counted as being tested. One third of the studies counted immediate testing decisions only, whereas the rest allowed patients who delayed decisions to be counted. Immediate decision rates were usually reported in studies in which data were collected prospectively, whereas delayed decision rates were often employed in retrospective studies. In our multivariate logistic model, the immediate/delayed decision variable was correlated with increased uptake, with immediate decision studies having higher rates. This seems contrary to what would be expected, because allowing delayed decisions to be included should and has been shown to increase uptake rates (74). However, a confounding factor may be that the immediate decision studies were more commonly done in research settings that produced higher uptake rates than the delayed decision studies, which were more often retrospective reports of routine clinical practice. More research is needed regarding how decisions to be tested are made and how they change over time.

Hypothetical uptake was defined differently in each of the studies. In about half of the studies, interest in genetic testing was rated using a Likert or similar scale, with uptake being defined by the authors from a range of responses on the scale. The other half used questions with dichotomous responses. Our multivariate logistic regression model showed that this was strongly correlated with hypothetical uptake. The potential for question wording to influence hypothetical uptake has been pointed out by others (22). Proof of this has been provided by a recent phone survey (75), which evaluated hypothetical uptake using three different instruments in the same cohort. Using different definitions of uptake, multiple rates were reported, ranging from 19% to 90%. Hypothetical uptake measures should be used as a surrogate for real uptake only in those situations where the two have been shown to be highly correlated. Further work is required to determine the best measures of hypothetical uptake and to evaluate them in a wide variety of subjects and clinical settings. In addition, more research is needed to determine the extent to which hypothetical uptake measures correlate with each other and with real uptake.

We found that personal and family history are important independent predictors of uptake. Our statistical analysis combining the results of the reviewed studies supports this conclusion. In addition, individual studies frequently found significant associations of uptake with personal and family history of breast cancer. As noted in Table 4, individual studies evaluated a wide range of variables for association with uptake. However, these associations often were inconsistent, possibly caused by such factors as differences in subject selection and variable definition, as well as statistical issues, including power. Educational and counseling interventions had a mixed effect on uptake, befitting a preference sensitive decision, either reducing uptake rates or having no effect.

In addition to the above, we have identified the following methodologic issues that could have an effect on or potentially bias uptake rate.

Investigator Influences. The presence of investigator influences on subjects can affect uptake rates. Some studies were observational studies of routine clinical care with minimal contact by the investigators and therefore little potential for influence on the subjects. Others were intervention studies with counseling or other special programs specifically designed to influence uptake rates. These interventions had varied effects. A particularly effective investigator inducement to obtain genetic testing was providing testing at no cost (61).

Small Sample Sizes. The 59 distinct subject groups ranged in size from 4 to 761. The mean size was 178 and the mean uptake rate was 63.5%. The 95% CI for this proportion is 56% to 71%. Thus, variability in sample size, and particularly small sample size, affects precision of the estimates. Variation in sample size is also an explanation for inconsistency in reporting of correlates with uptake rates. For example, a study (48) with 172 subjects did not find that personal cancer history significantly correlated with real uptake rates, whereas two larger studies (47, 61) with greater ''statistical power'' did.

Variability in Study Settings and Subjects. As shown in Tables 1 and 2, there was great variability in study settings and subject samples. Study subjects recruited at different points in the continuum of community/clinic/hospital are likely to have

Table 3. Multivariate logistic regression model for association with uptake

Variable	OR (95% CI)	*P*
Decision type		
Real (reference)	1.0	
Hypothetical	2.03 (1.82-2.28)	<0.0001
Personal history of breast cancer		
No or unknown (reference)	1.0	
Yes	1.24 (1.11-1.39)	<0.0001
Family history of breast cancer		
No or unknown (reference)	1.0	<0.0001
Yes	2.11 (1.92-2.32)	
Sampling strategy		
Reproducible (reference)*	1.0	
Convenience	1.75 (1.60-1.91)	<0.0001
Recruitment setting		
Community (reference)	1.0	
Hospital and/or clinic	1.82 (1.69-2.09)	<0.0001
Both	3.38 (2.49-4.58)	<0.0001
Unknown setting	2.52 (1.80-3.53)	<0.0001

*Reproducible sampling strategies were consecutive series, random sampling, and sampling an entire population.

Table 4. Personal characteristics and cancer history variables evaluated for association with breast cancer genetic testing decision grouped according to variable and uptake type

Variable	Uptake type	Author (reference)	Description of subjects	Univariate results (*P*)*	Multivariate results OR (95% CI), *P*
Personal characteristics					
Age	Real	Biesecker (48)	Members of hereditary breast/ovarian cancer families	Age ≤40 y, 72% tested; >40 y, 85% tested (0.05)	3.1 (1.3-7.4), <0.05
		Armstrong (47)	Participants in breast/ovarian cancer risk program	Tested: mean age, 46 y; not tested: mean age, 43 y (0.04)	
		Schwartz (54)	Personal history of breast cancer and ≥20% chance of BRCA1/2 mutation	Age <45 y, 82% tested; ≥45 y, 82% tested (NS)	
		Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	Age <40 y, 23% tested; 40-49 y, 25% tested; 50-59 y, 26% tested; ≥60 y, 53% tested (0.08)	
	Hypothetical	Jacobsen (35)	Women with first-degree relative affected with breast cancer	Immediate testing planned: mean age, 46 y; future testing planned: mean age, 42 y; no testing planned: 42 y (<0.05)	
		Tambor (37)	Women receiving mammograms	Interested in testing: age 50-59 y, 72%; 60-81 y, 28%; not interested: age 50-59 y, 48%; 60-81 y, 52% (<0.05)	2.9 (1.9-4.6), <0.001; age 50-59 y compared with 60-81 y
		Mogilner (39)	Women receiving mammograms	Age <25 y, 83% interested in testing; 25-34 y, 66% interested; 35-44 y, 72% interested; 45-60 y, 65% interested; age >60 y, 43% interested (<0.01)	
		Durfy (42)	Women with family history of breast cancer		0.98 (0.9-1.0), NS; age (y)
		Bottorff (59)	General population and breast cancer groups		1.03 (0.74-1.43), NS; interested in testing by age in deciles
		Lerman (26)	Women first-degree relatives of ovarian cancer patients	Age <30 y, 85% interested in testing; 30-49 y, 79% interested; ≥50 y, 61% interested (NS)	
		Bosompra (49)	Women from general population		Interested in testing by age (y); β = −0.025, P = NS †
		Lipkus (43)	African American women with and without family history of breast cancer		0.55 (0.32-0.96), <0.05; age (y)
		Bluman (40)	Breast/ovarian cancer patients at high risk for BRCA mutation		0.07 (0.4-1.3), NS; age ≥50 y compared with <50 y
Ashkenazi Jewish	Real	Armstrong (47)	Participants in breast/ovarian cancer risk program	Tested: 43% Ashkenazi Jewish; not tested: 13% Ashkenazi Jewish (<0.001)	6.4 (2.7-15.1), 0.001
		Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	Ashkenazi Jewish: 41% tested; not Ashkenazi Jewish: 18% tested (<0.001)	
		Durfy (42)	Women with family history of breast cancer		0.68 (0.2-1.1), NS; Ashkenazi Jewish compared with White
Child/children	Real	Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	Has children: 28% tested; no children: 22% tested; NS; has daughter: 29% tested; no daughter: 23% tested (NS)	
Race	Hypothetical	Tambor (37)	Women receiving mammograms	Interested in testing: 87% White; not interested: 80% White (<0.05)	2.2 (1.3-4.0), 0.007; White compared with Black
		Mogilner (39)	Women receiving mammograms	Interested in testing: 61% Caucasian; 68% Hispanic; 75% African American; 58% other (NS)	
		Durfy (42)	Women with family history of breast cancer		0.42 (0.1-1.2), NS; African American compared with White with breast cancer family history
		Andrykowski (29)	Women from general population	Interested in testing: 96% Caucasian; 76% other (<0.05)	

(*Continued on the following page*)

Table 4. Personal characteristics and cancer history variables evaluated for association with breast cancer genetic testing decision grouped according to variable and uptake type (Cont'd)

Variable	Uptake type	Author (reference)	Description of subjects	Univariate results (*P*)*	Multivariate results OR (95% CI), *P*
Education	Real	Armstrong (47)	Participants in breast/ovarian cancer risk program	Tested: 78% college; not tested: 72% college (NS)	
		Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	12-15 y: 22% tested; 16 y: 28% tested; >16 y: 26% tested (NS)	
	Hypothetical	Jacobsen (35)	Women with first-degree relative who has breast cancer	Immediate testing planned: 82% college; future testing planned: 62% college; no testing planned: 86% (NS)	
		Mogilner (39)	Women receiving mammograms	Interested in testing: 38% elementary; 69% high school; 65% college; 67% graduate school; 75% other (<0.02)	
		Bottorff (59)	General population and breast cancer groups		0.90 (0.85-0.96); interested in testing by years of education
		Lerman (26)	Women first-degree relatives of ovarian cancer patients	Interested in testing: 65% high school or less; 84% more than high school (<0.02)	
		Andrykowski (29)	Women from general population	Interested in testing: 92% high school or less; 99% more than high school (<0.05)	
		Lipkus (43)	African American women, with and without family history of breast cancer		1.21 (0.66-2.20); more than high school compared with high school or less
Employment status	Real	Armstrong (47)	Participants in breast/ovarian cancer risk program	Tested: 74% employed: not tested: 77% employed (NS)	
	Hypothetical	Tambor (37)	Women receiving mammograms	Interested in testing: 68% employed; not interested: 55% employed (<0.05)	
Gender	Real	Biesecker (48)	Members of hereditary breast/ovarian cancer families	Female: 79% tested; male: 77% tested (NS)	
	Hypothetical	Struewing (28)	Members of hereditary breast/ovarian families	Interested in testing: 86% female; 65% male (<0.005)	
Income	Hypothetical	Mogilner (39)	Women receiving mammograms	Interested in testing: 61% <$10,000; 79% $10,000-29,000; 58% $30,000-49,000; 61% $50,000-69,000; 50% $70,000-99,000; 82% >$100,000 (NS)	
		Andrykowski (29)	Women from general population	Interested in testing: 93% <$15,000; 97% $15,000-30,000; 99% $30,000-50,000; 93% >$50,000 (NS)	
Marital status	Real	Biesecker (48)	Members of hereditary breast/ovarian cancer families	Never married: 67% tested; Ever married: 84% (0.01)	0.76 (0.31-1.92), NS
		Schwartz (54)	Personal history of breast cancer and ≥20% chance of BRCA1/2 mutation	Married: 82% tested; unmarried: 82% tested (NS)	
		Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	Single: 31% tested; married: 25% tested; widowed: 39% tested (NS)	
	Hypothetical	Jacobsen (35)	Women with breast cancer affected first-degree relative	Immediate testing planned: 82% married; future testing planned: 62% married; no testing planned: 86% married (NS)	
		Lipkus (43)	African American women with and without family history of breast cancer		0.52 (0.30-0.91), <0.05; not married compared with married
Religion	Real	Schwartz (54)	Personal history of breast cancer and ≥20% chance of BRCA1/2 mutation	Catholic: 79% tested; Jewish: 87% tested; Protestant: 81% tested; other: 77% tested (NS)	

(*Continued on the following page*)

Table 4. Personal characteristics and cancer history variables evaluated for association with breast cancer genetic testing decision grouped according to variable and uptake type (Cont'd)

Variable	Uptake type	Author (reference)	Description of subjects	Univariate results (P)*	Multivariate results OR (95% CI), P
	Hypothetical	Mogilner (39)	Women receiving mammograms	Interested in testing: 69% Catholic; 57% Jewish; 70% Protestant; 69% other (NS)	
Cancer history					
Personal cancer history (breast or ovarian cancer)	Real	Biesecker (48)	Members of hereditary breast/ovarian cancer families	Cancer: 79% tested; without cancer: 79% tested (NS)	
		Armstrong (47)	Participants in breast/ ovarian cancer risk program	Tested: 37% breast cancer; not tested: 23% breast cancer (0.04)	
		Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	Personal cancer history: 43% tested; none: 19% tested (<0.001)	
	Hypothetical	Mogilner (39)	Women receiving mammograms	Yes personal history: 52% interested in testing; no personal history: 69% interested in testing (<0.04)	
		Julian-Reynier (31)	Genetics clinic attendees with personal history of breast cancer or first-degree relative with breast cancer	Interested in testing: 76% cancer patient; 96% noncancer patient (<0.01)	
		Bottorff (59)	General population and breast cancer groups		0.11 (0.02-0.52); personal history of breast cancer compared with none
Family history	Real	Biesecker (48)	Members of hereditary breast/ovarian cancer families	First-degree relative with cancer: 74%; no first-degree relative with cancer: 81% (NS)	
		Lee (61)	Personal or family history of breast cancer and ≥10% chance of BRCA mutation	>5 relatives with breast cancer: 23% tested; 3-5: 27% tested; 1-2: 27% tested; 0: 20% tested; NS; >3 first-degree relatives with breast cancer: 0% tested; 3: 38% tested; 2: 19% tested; 1: 28% tested; 0: 24% tested (NS)	
		Schwartz (54)	Personal history of breast cancer and ≥20% chance of BRCA1/2 mutation	1-2 affected first-degree relatives: 82% tested; ≥3 affected first-degree relatives: 82% (NS)	
		Armstrong (47)	Participants in breast/ ovarian cancer risk program	Tested: 10% known familial mutation; not tested: 1% known familial mutation (0.04)	7.5 (0.97-62.2), NS
	Hypothetical	Mogilner (39)	Women receiving mammograms	Yes family history: 68% interested in testing; no family history: 66% interested in testing (NS)	
		Bottorff (59)	General population and breast cancer groups		2.34 (1.71-3.21); at least one first-degree or second-degree relative compared with no family history
		Bosompra (49)	Women from general population		Interested in testing: $\beta = 0.094$, $P < 0.05$
		Lipkus (43)	African American women with and without family history of breast cancer	yes family history: 11% not at all/slightly interested, 17% somewhat, 72% interested/very interested in testing; no family history: 25% not at all/slightly interested, 16% somewhat, 53% interested/very interested in testing; <0.02	interested or very interested: 1.68 (0.97-2.92), NS; family history compared with none

*When available, results of univariate analysis (χ^2, t test) are provided with P. When available, results of multivariate analysis for listed variable [OR (95% CI), P] are provided. Unless noted, reference category for the variable is the first category listed for univariate results. Most studies entered into the multivariate analysis all variables yielding statistically significant results on univariate analyses.
†Multivariate analysis using structural equation modeling. β = standardized coefficient.

varying interest in genetic testing. A woman identified by random digit dialing would reasonably be expected to have different interest in genetic testing than a woman with a daughter who is newly diagnosed with breast cancer. These different settings and target populations would predictably contribute to variability in uptake rates. Our multivariate logistic regression model found recruitment setting to have the strongest association with uptake of the variables entered into model. Selection of target populations could also affect whether variables are associated with uptake rates. For example, in none of the five studies (47, 48, 54, 61, 62) evaluating associations with real uptake was family history found to be significant. The explanation for this could be that the subjects in all five studies were already at such high risk for

breast cancer that family history was not significant as an additional predictor of uptake.

Lack of Clearly Described Sampling Strategy. Reproducible uptake rates depend on study methodologies that enable researchers to assemble populations that are similar in factors related to testing interest. Our first three quality review standards dealt with important issues related to selecting study subjects. We rated the studies being generally compliant with regard to specifying clearly stated inclusion and exclusion criteria (standard 1) and reporting refusals (standard 3). However, as indicated in Tables 1 and 2, we concluded that less than half of the 40 studies provided a clear enough description of sampling strategy to ensure assembly of a comparable group if the study were to be repeated. Only 15 of the 40 studies were rated as fully compliant with all three of these standards related to selecting study subjects. This lack of a reproducible sampling strategy among the reviewed studies undoubtedly contributes to variability in uptake estimates.

Sampling Methods Open to Bias. Thirty of the studies enrolled ''convenience'' samples of patients (i.e., patients identified in nonsystematic ways, such as volunteers in clinical settings or respondents to advertisements). Convenience sampling was associated with higher uptake rates than the more reproducible strategies (Table 3), perhaps reflecting volunteer bias. Studies based on convenience samples are less likely to produce the same results if replicated and also have limited generalizability. Only nine studies used the more rigorous, reproducible sampling methods of consecutive series, samples of the entire eligible cohort, or random samples of a population.

Although it is easier to do research with convenience samples and volunteers, the additional effort to assemble groups through such methods as random sampling and consecutive series is needed. In situations where this cannot be done, efforts to understand the potential for bias should be taken (e.g., by describing those who decline to volunteer as well the volunteers). Research focused on the differences between these groups could lead to more effective ways to approach those who decline.

Variability in Reporting Associated Risk Factors. We expected that uptake rates would be strongly related to certain risk factors, including family and personal history of breast cancer. We attempted to determine family and personal history of breast cancer in each of the 59 distinct patient groups. In 42 groups, family history status was clear; in 13, it was mixed (some with family history, some without); and in 4, it was unknown. In 39 groups, personal history status was clear; in 14, it was mixed (some with, some without); and in 6, it was unknown. Both family and personal history were specified in only 29 of the 59 groups. Lack of this information and other information related to testing prevented us from fully adjusting or stratifying uptake results for these potential confounding factors or effect modifiers.

Summary

Our review reveals the complexity of genetic testing uptake research. We believe that study methodology issues are major determinants of variability in published uptake rates, as important or more important than clinical characteristics, such as personal or family history of cancer. Greater understanding of these issues will clarify to clinicians why there is such great variability in the published literature and why their clinical experience may not be congruent with what they read. To interpret study results for application to practice, clinicians must pay particular attention to whether the method of studying uptake matches the way patients make decisions in their own setting. Before applying results to their patients, clinicians must determine that study samples are similar enough to their patients so that study results might reasonably be expected to be applicable to them. Because estimates of genetic testing uptake are so variable, interventions intended to affect uptake rates should be evaluated using randomized trials with attention to the methodologic issues identified in this review. Uptake rate is usually one of the primary outcome measures of genetic testing intervention studies, yet there is not a ''correct'' or ''optimal'' uptake rate because the decision is preference sensitive. Intervention studies should combine uptake rates with other outcomes, including measures of psychological effect (14, 15, 17), individual satisfaction with the decision, and consistency between an individual's values and their choice.

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