Uptake of Cascade Genetic Testing for Hereditary Breast and Ovarian Cancer: A Systematic Review and Meta-Analysis

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Abstract: This is a systematic review and meta-analysis evaluating the uptake of cascade genetic testing for hereditary breast and ovarian cancer syndrome. Among 30 studies included for meta-analysis, the uptake of cascade genetic testing was 33% (95% CI 25%-42%), with higher uptake rates among females compared with male relatives, and among first-degree compared with second-degree relatives. These findings indicate suboptimal uptake of cascade genetic testing among people at risk for hereditary breast and ovarian cancer syndrome, representing a missed opportunity for cancer prevention and early detection. There is a need for interventions to improve uptake rates.

Key Words: cascade genetic testing, hereditary breast and ovarian cancer, BRCA1, BRCA2

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Approximately 20% of patients with ovarian cancer carry an underlying pathogenic gene variant (PGV) in a cancer-associated gene, which is most commonly in genes associated with hereditary breast and ovarian cancer such as BRCA1 and BRCA2.[1] Blood relatives of these patients have up to 50% chance of carrying the same familial PGV. Presymptomatic genetic testing of these relatives can allow them the opportunity for personalized cancer risk reduction and surveillance, thus mitigating the morbidity and mortality associated with breast, ovarian, and pancreatic cancers.[2–4] Cascade genetic testing is the process of extending genetic testing to blood relatives of patients diagnosed with germline PGVs (called probands).

Cascade genetic testing is an evidence-based national health priority endorsed by several national organizations including the Centers for Disease Control and Prevention (CDC), the American Society of Clinical Oncology (ASCO), and the American College of Obstetrics and Gynecology (ACOG).[5,6] Despite this, uptake rates for cascade genetic testing in the United States remain suboptimal, with a prior meta-analysis demonstrating that only 36% of all at-risk relatives of people with any hereditary cancer syndrome complete cascade genetic testing.[7]

Given that several studies with new data have been published since our prior meta-analysis, we sought to conduct an updated systematic review and meta-analysis to evaluate the uptake rate of cascade genetic testing.[8–10] Furthermore, in contrast to our prior study which evaluated cascade testing across all hereditary cancer syndromes, this systematic review and meta-analysis is focused specifically on hereditary breast and ovarian cancer syndrome.

METHODS

Overview

This systematic review is reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was preregistered with PROSPERO (registration No.: CRD42024527352).[11,12] A comprehensive literature search was conducted on March 6, 2024, using the following bibliographic databases from inception: Ovid MEDLINE (In-Process and Other Non-Indexed Citations and Ovid MEDLINE 1946 to present), Ovid EMBASE (1974 to present), and Cochrane Library (Wiley). No article type, date, or language restrictions were included in the search. Search concepts included cascade screening, genetic counseling, and cancer. The complete Ovid MEDLINE search strategy is available in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/GRF/A34.

Inclusion and Exclusion Criteria

All primary research studies in English that reported quantitative outcomes of cascade genetic counseling and testing, or disclosure of genetic test results to at-risk relatives (ARRs) of people with hereditary breast and ovarian cancer were included. All articles that were not primary research, such as commentaries, narrative or systematic reviews, meta-analyses, as well as case reports and case series of fewer than 10 probands or ARRs, were excluded. All articles not available in the English language were excluded. All publications that were only abstracts or conference proceedings were also excluded. All qualitative studies that did not report quantitative outcomes for cascade genetic

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counseling or testing or disclosure of genetic test results to ARRs were also excluded. A complete list of reasons for article exclusion is available in the PRISMA flow diagram (Fig. 1).

Article Review and Data Extraction

Search results were imported into the Covidence Systematic Review Management Software and de-duplicated. Two reviewers independently evaluated each article for eligibility, with conflicts resolved after discussion. Data for study characteristics, participant demographics, and outcomes of interest were extracted by one reviewer from all included studies into Microsoft Excel, with a second reviewer checking the extracted data for accuracy.

Outcomes Evaluated and Risk of Bias Assessment

Outcomes evaluated include: (1) the proportion of ARRs who completed genetic counseling among all ARRs and (2) the proportion of ARRs who completed genetic testing among all ARRs. Other factors associated with cascade genetic counseling or testing such as sociodemographic and relative characteristics were narratively synthesized. The risk of bias for interventional studies was evaluated using the Risk of Bias in Non-Randomized Studies-Interventions (ROBINS-I) tool, and the risk of bias for non-interventional studies was evaluated using tools from the Joanna Briggs Institute (JBI). Publication bias was assessed by evaluating funnel plots for meta-analyses conducted.

Meta-Analysis

Meta-analyses for the proportion of at-risk relatives that completed genetic counseling and genetic testing were conducted using R software [Version 4.2.3(03/15/2023); R Foundation for Statistical Computing, Vienna, Austria]. Statistical heterogeneity was tested through the χ^2 test (ie, Cochrane Q test), and a P-value ≤ 0.2 was used to indicate the presence of heterogeneity. Statistical heterogeneity was also assessed by the inconsistency statistic (I^2). A random effects analysis was used to calculate pooled proportions and means. The random effects analysis is more conservative and allows for more variability in the individual study proportion estimates when generating the pooled proportion. The pooled proportion was calculated using a random intercept logistic regression model with a logit transformation, and the 95% CI was calculated using the Clopper-Pearson interval. The DerSimonian-Laird estimator was used to estimate the between-study variance. For the outcome proportions of interest, the results of each study were expressed as binary proportions with exact 95% CIs. For each meta-analysis, a funnel plot was constructed and reviewed, displaying the study proportion against study precision, estimated by the standard error, to assess for publication bias.

RESULTS

Study Characteristics

A total of 32 publications of original research were included in this systematic review, of which data from 30 studies were included for meta-analysis.[8–10,13–41] Study publication dates ranged from 1996 to 2024 and spanned 18 countries: United States (9), France (3), United Kingdom (3), Norway (2), Netherlands (2), Turkey (2), Bahamas (1), Belgium (1), Germany (1), Ireland (1), Israel (1), Italy (1), South Korea (1) Malaysia (1), Singapore (1), Spain (1), Switzerland (1), and Trinidad and Tobago (1).

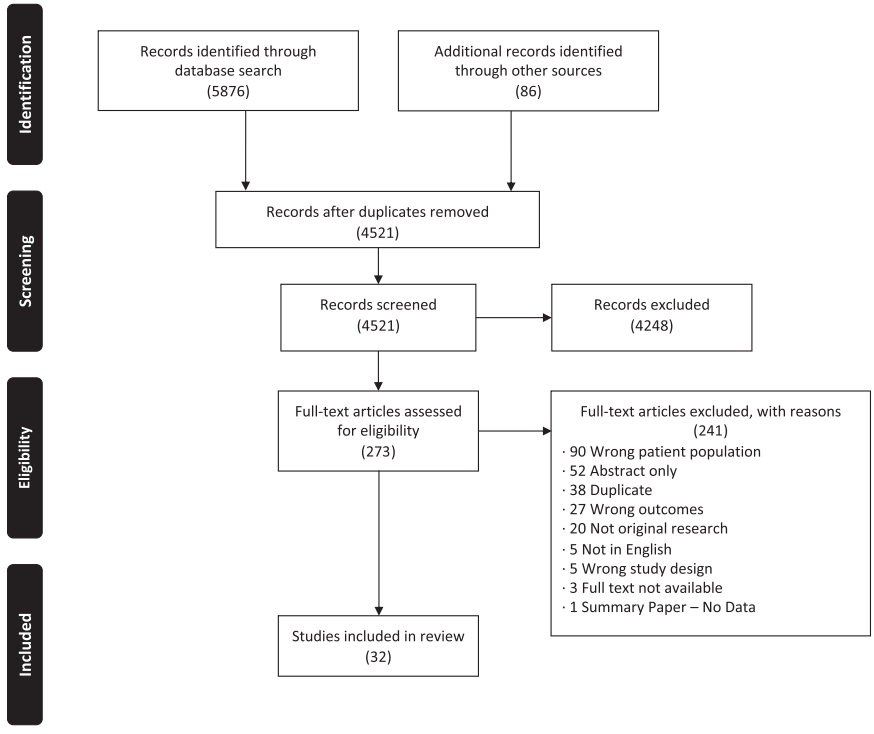

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

TABLE 1. Demographics of Probands and Relatives in Included Studies (N = 86)

References	# Probands/ relatives	Proband age	Proband gender	Proband cancer history	Proband race/ethnicity	Relatives included (degree of relation)	Relative age	Relative gender	Relative cancer history	Relative race/ ethnicity	Country	Study
Agiannitopoulos et al[8]	362/1246					First	Of those who completed cascade testing: Mean: 40 y	Of those who completed cascade testing: Female: 85 Male: 36	Of those who completed cascade testing: Yes: 13 No: 108		Greece	Retrospective
Biesecker et al[13]	0/172						Median: 40	Female: 110 Male: 62		Caucasian: 172	USA	Prospective
Blandy et al[14]	30/310	Mean: 52.0	Female: 30	Yes: 30 (breast, ovarian)		First, second, third		Female: 162 Male: 148			France	Cross-sectional
Bodd et at[15]	75/172		Females: 58 Males: 17			First		Female: 84 Male: 88			Norway	Prospective
Brooks et al[16]	0/384					First-, Second-degree, Distant		Female: 202 Male: 182			UK	Retrospective
Cody et al[17]	30/50	NR	Female: 29 Male: 1			First		Female: 50			Ireland	Retrospective
Cristaldo et al[18]	135/0	Mean: 58.6	Female: 82 Male: 53								France	Cross-sectional
Donenberg et al[19]	24/125					First, Second					Trinidad and Tobago	Prospective
Evans et al[20]	0/1157						Group 1 Female Median: 52 Male Median: 55 Group 3 Female Median: 44.6 Male Median: 50.2	Female: 594 Male: 563			UK	Prospective
Fehniger et al[21]	73/448	Mean: 47.4			African American: 7 Asian/Pacific Islander: 14 Hispanic: 17 White: 32 Mixed: 3	First, Second		Female: 241 Male: 202		White: 135 African American: 53 Asian/Pacific Islander: 117 Hispanic: 123 Mixed: 15	USA	Cross-sectional
Finlay et al[22]	115/655		Female: 83 Male: 32		Ashkenazi Jewish: 28 Non-Ashkenazi/ Caucasian: 79 Unknown/ Caucasian: 7 Other: 1	First, Second		Female: 345 Male: 310			USA	Cross-sectional
Fischer et al[23]	0/2646							Female: 2646			Germany	Retrospective
Holloway et al[24]	54/269					First, Second, Third		Female: 161 Male: 108			UK	Retrospective
Jeong et al[25]	129/423		Female: 129			First, Second, Third		Female: 235 Male: 188			Korea	Retrospective
Julian-Reynier et al[26]	0/419					First, Second		Female: 244 Male: 175	Yes: 36 (female only) No: 208 (female only)		France	Cross-sectional

Lerman et al[27]	0/192						Mean: 43	Female: 129 Male: 63		White: 192	USA	Prospective
Lieberman et al[28]	1771/0	Mean: 52.0	Female: 1406 Male: 365		Ashkenazi Jewish: 1771	First, Second					Israel	Retrospective and cross-sectional
Lynch et al[29]	0/1574							Intervention: Female: 359 Male: 181 No intervention: Female: 495 Male: 539			USA	Retrospective
McGivern et al[30]	38/0	Mean: 48.1	Female: 38		Caucasian: 37 Native American: 1	First, Second, Third		Female: 209 Male: 219			USA	
McInerney-Leo et al[31]	212/0		Female: 138 Male: 74								USA	Prospective
Meijers-Heijboer et al[32]	0/682					First, Second		Female: 411 Male: 271			Netherlands	Prospective
Menko et al[33]	0/227					First, Second		Female: 113 Male: 114			Netherlands	Retrospective
Reichelt et al[34]	0/232							Female: 186 Male: 46	Yes: 30 (female only) No: 156 (female only)		Norway	Prospective
Sanz et al[35]	108/765	Median: 50.0	Female: 105 Male: 3			First, Second	Mean: 45.0	Female: 413 Male: 352			Spain	Retrospective
Sermijn et al[38]	0/172						Mean: 46				Belgium	Prospective
Trottier et al[39]	0/202							Female: 202			Bahamas	Prospective
Yoon et al[40]	37/471	Median: 45.0			Malaysian: 6 Indian: 8 Chinese: 23	First		Female: 227 Male: 244		Malaysian: 11 Indian: 8 Chinese: 42	Malaysia	Prospective
Samadder, et al[36]	2984/176	Mean: 61.4	Female: 1402 Male: 1582	Breast, Ovarian, Endometrial Brain, Colon, Pancreas, Biliary, Gastric, Prostate	White: 2571 Hispanic/Latino: 159 Black/African American: 110 Asian: 53 American Indian: 29 Pacific Islander: 6 Other: 56						USA	Prospective
Sarki, et al[41]	238/3456	Mean: 51.2	Female: 214 Male:24	Breast, Ovarian, Prostate, Colon, Endometrial	White: 199 Other: 39	First, Second, Third			Breast, Ovarian, Prostate		Switzerland	Retrospective
Schmidlen, et al[37]	263,859/ 14,758	Diagnostic Cohort Mean: 55.5 Proactive Cohort Mean: 48.4	Female: 226,230 Male: 37,627			First, Second, Third, Fourth	Diagnostic Cohort Mean: 46.4 Proactive Cohort Mean: 44.6	Female: 10,154 Male: 4,603			USA	Retrospective

TABLE 1. (*continued*)

References	# Probands/ relatives	Proband age	Proband gender	Proband cancer history	Proband race/ethnicity	Relatives included (degree of relation)	Relative age	Relative gender	Relative cancer history	Relative race/ ethnicity	Country	Study
Seven, et al[10]	92/417	Mean: 45.1	Female: 92	Breast: 75 Ovarian: 9 Breast and ovarian: 8		First		Female: 222 Male: 195			Turkey	Cross-sectional
Trevisan, et al[9]	213/1412	Median: 54.0	Female: 199 Male: 14	Breast: 114 Ovarian: 53 Breast and ovarian: 19 Pancreas: 7 Prostate: 5		First, Second, Third, Fourth		Female: 737 Male: 648 Not Reported: 27			Italy	Retrospective

Participant Characteristics

A total of 11,323 probands and 20,012 relatives were evaluated for uptake of cascade genetic testing. Thirteen studies included information on the proband's sex. Among the 3186 probands in these studies, 2603 (81.7%) were female and 583 (18.3%) were male. Twenty-four studies included information on relatives' sex. Among the 13,796 relatives in these studies, 8862 (64.2%) were female and 4934 (35.8%) were male.

Six studies included information on proband race and ethnicity. Among the 2272 probands in these studies, 2153 (94.8%) identified as White, 51 (2.2%) as Asian, 17 (0.7%) as Hispanic/Latino, 7 (0.3%) as Black, 1 (0.1%) as Native American, and 43 (1.9%) as other. Among this group 1799 (79.2%) probands identified as Ashkenazi Jewish. Four studies included information on relatives' race and ethnicity. Among the 868 relatives included in these studies, 499 (57.5%) identified as White, 178 (20.5%) as Asian, 123 (14.2%) as Hispanic/Latino, 53 (6.1%) as Black, and 15 (1.7%) as other. Further details of proband and relative characteristics are available in Table 1.

Uptake Rates of Cascade Genetic Counseling and Testing

A total of 11 studies that evaluated 6992 relatives reported uptake rates of cascade genetic counseling. The overall uptake rate of cascade genetic counseling across all these studies was 33% (95% CI: 20%-49%).

A total of 30 studies evaluating 20,012 relatives reported uptake rates of cascade genetic testing. The overall uptake rate of cascade genetic testing across all these studies was 33% (95% CI: 25%-42%) (Fig. 2). Uptake rates for cascade testing were higher among female relatives compared with male relatives [42% (95% CI: 34%-51%) vs. 20% (95% CI: 14%-28%)]. Uptake rates for cascade testing were also higher among first-degree relatives compared with second-degree relatives [38% (95% CI: 31%-45%) vs. 21% (95% CI: 15%-29%)].

Other Factors Associated With Cascade Genetic Counseling and Testing

Several included studies also evaluated other factors associated with the uptake of cascade genetic testing; however, raw data were not available to conduct a meta-analysis. Two studies reported outcomes as proportions of probands who had at least 1 relative undergo cascade testing, reporting rates of 23% and 32% for this outcome.[36,37] One study evaluated the impact of race and ethnicity on cascade testing and reported that relatives from White families were more likely to complete cascade genetic testing when compared with relatives from Black, Asian, Native American, and Hispanic/Latino families.[21] One study evaluated the effect of insurance status on cascade genetic testing and found that relatives who had insurance were significantly more likely to complete cascade testing compared with uninsured relatives (OR: 3.74, 95% CI: 2.06-6.80).[27] Ten studies evaluated the impact of relative age and uptake of cascade genetic testing.[9,13,15,22,28,29,32,33,35,41] Among these, 8 studies reported that older relatives were more likely to complete cascade testing, and 2 studies reported the opposite, that younger relatives were more likely to complete cascade testing. Five studies reported on the impact of parenthood and cascade testing, with 4 studies reporting that probands with children were more likely to complete cascade testing, and 1 study reporting no

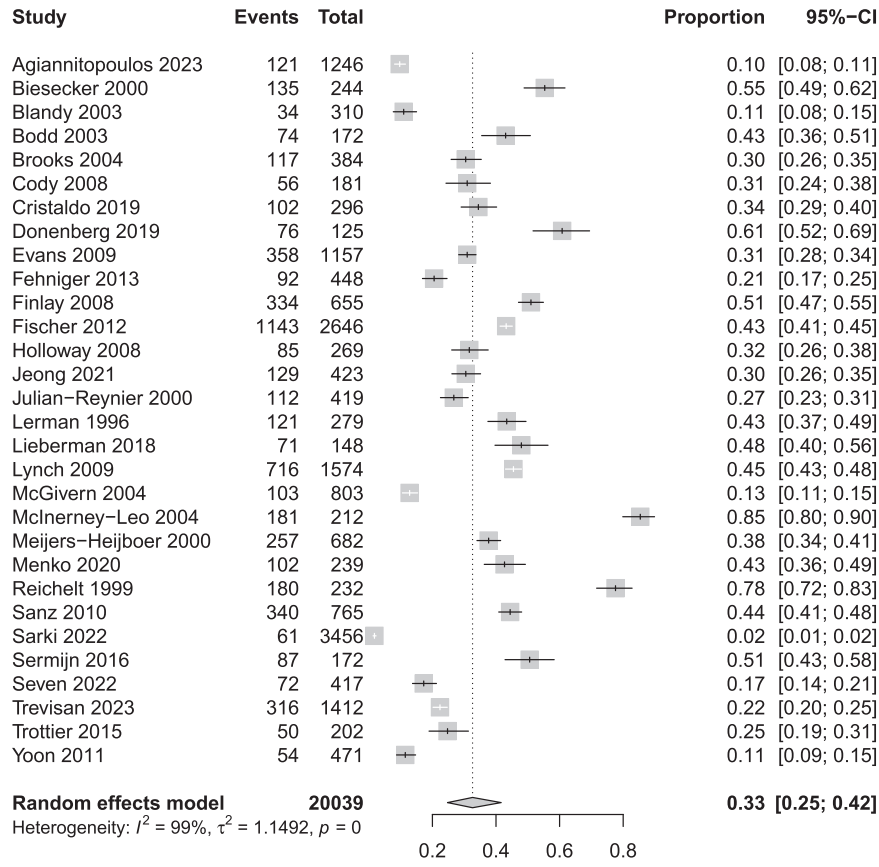

FIGURE 2. Forest plot for the pooled proportion of cascade genetic testing.

association between parenthood and uptake of cascade testing.[15,24,32,33,35] Additional factors associated with cascade testing that were evaluated are available in Table 2.

Risk of Bias Assessment

Study quality was assessed using appropriate ROBINS-I, the Joanna Briggs Institute Critical Appraisal Checklist for cohort studies, or the Joanna Briggs Institute Critical Appraisal Checklist for analytical cross-sectional studies. The majority of studies assessed through ROBINS-I were found to be at moderate risk of bias (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/GRF/A34). Studies assessed using the Joanna Briggs instruments were all deemed appropriate to include in this review. The meta-analysis funnel plots suggest an underrepresentation of studies with smaller sample sizes reporting both low and high genetic counseling and genetic testing proportions.

DISCUSSION

We have systematically reviewed the literature on cascade genetic testing among patients with hereditary breast and ovarian cancer. Our meta-analysis found that among a cumulative 20,012 relatives at high risk of having hereditary breast and ovarian cancer syndrome across 30 studies, 33% (95% CI: 25%-42%) ultimately completed cascade genetic testing.

Given the lack of effective screening modalities for ovarian cancer, identifying people at an elevated inherited risk of ovarian cancer is critical to minimizing the morbidity and mortality associated with ovarian cancer by offering these individuals risk-reducing surgery.[2,3,42] Cascade genetic testing is a key component of identifying presymptomatic PGV carriers in a population, and as such is deemed a Tier 1 genomic application by the CDC.[6] Although there is currently no expert consensus on a goal minimum uptake rate for cascade genetic testing, modeling studies have demonstrated that an uptake rate of 70% for first-degree and second-degree relatives would lead to the identification of all 4 million people with hereditary cancer syndromes in the United States within a decade.[43] We report a cascade testing uptake rate of approximately half this target among people at risk for hereditary breast and ovarian cancer, underscoring the urgent need to develop interventions to optimize this uptake rate.

Our study has also identified subpopulations in which rates of cascade genetic testing may be particularly low. These include male relatives and relatives more distant than first degree, as demonstrated in our meta-analyses. This is consistent with prior meta-analyses of cascade genetic testing that included other hereditary cancer syndromes, as well as rates of cascade disclosure of genetic test results to at-risk relatives.[7,44] There are several potential reasons for the lower rates including a lack of awareness of hereditary breast and ovarian cancer syndrome among males, estranged family, discomfort disclosing personal medical information to distant relatives, and relatives living abroad, among others.[45–48] In addition, limited studies demonstrated that older relatives, uninsured relatives, and relatives from

TABLE 2. Patient/Proband and Relative Characteristics that Influence Cascade Genetic Testing for Hereditary Cancer Syndromes

	Association with cascade testing identified	Association with cascade testing not identified
Relative characteristics		
Relative's age	Lieberman et al,[28] Bodd et al,[15] Sanz et al,[35] Meijers-Heijboer et al[32] (women only), Menko et al,[33] Finlay et al,[22] Biesecker et al,[13] Lynch et al,[29] Trevisan et al[9]	Meijers-Heijboer et al,[32] Sarki et al[41]
Relative's gender	Fehniger et al,[21] Lieberman et al,[28] Menko et al,[33] Bodd et al,[15] Blandy et al,[14] McGivern et al,[30] Brooks et al,[16] Sanz et al,[35] Holloway et al,[24] Yoon et al,[40] Meijers-Heijboer et al,[32] Finlay et al,[22] Sermijn et al,[38] Julian-Reynier et al,[26] Jeong et al,[25] Evans et al,[20] Lynch et al,[29] Sarki et al,[41] Trevisan et al[9]	Meijers-Heijboer et al,[32] Julian-Reynier et al,[26] Biesecker et al,[13] Seven et al[10]
Relative's race/ethnicity	Fehniger et al[21]	
Relative's education	Sanz et al[35]	Fehniger et al,[21] Sarki et al[41]
Relative's socioeconomic status	Holloway et al[24]	
Relative's employment status		Sarki et al[41]
Relative's insurance status	Lerman et al[27]	
Relative's personal history of cancer	Holloway et al,[24] Sanz et al,[35] Sarki et al[41]	Biesecker et al,[13] Fehniger et al,[21] Lieberman et al[28]
Relative residing in the United States vs. abroad	Fehniger et al[21]	
Relative's parenthood	Holloway et al,[24] Meijers-Heijboer et al,[32] Menko et al,[33] Sanz et al[35]	Bodd et al[15]
Relative's marital Status	Biesecker et al[13]	Sarki et al[41]
Relative has an adult daughter	Menko et al[33]	
Relative's knowledge about risk for relatives	Blandy et al[14]	
Proband characteristics		
Specific hereditary cancer syndrome	Sanz et al[35]	
Proband's history of cancer	Seven	
Relationship between relative and proband		
Family support	Biesecker et al,[13] Blandy at el[14]	Sarki et al[41]
Relative's degree of relationship to the proband	Fehniger et al,[21] Julian-Reynier et al,[26] Lieberman et al,[28] Sanz et al,[35] Sermijn et al,[38] Trevisan et al[9]	Blandy et al,[14] Brooks et al,[16] Holloway et al,[24] Seven et al[10]
Frequency of communication between proband and relative	Fehniger et al[21]	

racial and ethnic minority families may be less likely to complete cascade genetic testing. Although interventions evaluated to increase cascade testing uptake such as assisting probands with disclosure and direct relative contact have demonstrated effectiveness in bypassing some of these barriers and shown promise, larger randomized controlled trials in diverse populations are necessary before they can be standard-of-care.[49]

Our results should be viewed in light of several limitations. First, there were heterogenous means by which the genetic testing status of relatives was determined across included studies, with the vast majority of studies relying on proband reports for this information which is subject to recall bias. The majority of studies in this review did not report on relatives' race and ethnicity, and of the ones that did, the vast majority of included relatives were non-Hispanic White, thus limiting the generalizability of these results to racial and ethnic minority populations. This underrepresentation is consistent with studies evaluating cascade testing for other hereditary cancer syndromes as well.[50] There were no randomized controlled trials among the studies included. All studies evaluated for risk of bias using ROBINS-I were deemed to be at moderate risk of bias, with 2 studies having a serious risk of bias. The funnel plots for our meta-analysis also indicate a lower number of smaller studies included with both low and high genetic counseling and genetic testing proportions. However, this is unlikely to bias our results because only the absence of smaller studies with low cascade testing uptake rates would suggest publication bias.

In conclusion, our systematic review and meta-analysis demonstrate an uptake rate of cascade genetic testing of only 33% among relatives at risk for hereditary breast and ovarian cancer, with males and more distant relatives significantly less likely to complete cascade genetic testing. High-quality randomized controlled trials evaluating interventions such as direct relative contact to increase uptake rates of cascade genetic testing are warranted among this patient population.

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