review articles

Cascade Testing for Hereditary Cancer Syndromes: Should We Move Toward Direct Relative Contact? A Systematic Review and Meta-Analysis

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abstract

PURPOSE Evidence-based guidelines recommend cascade genetic counseling and testing for hereditary cancer syndromes, providing relatives the opportunity for early detection and prevention of cancer. The current standard is for patients to contact and encourage relatives (patient-mediated contact) to undergo counseling and testing. Direct relative contact by the medical team or testing laboratory has shown promise but is complicated by privacy laws and lack of infrastructure. We sought to compare outcomes associated with patient-mediated and direct relative contact for hereditary cancer cascade genetic counseling and testing in the first meta-analysis on this topic.

MATERIALS AND METHODS We conducted a systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PROSPERO No.: CRD42020134276). We searched key electronic databases to identify studies evaluating hereditary cancer cascade testing. Eligible trials were subjected to meta-analysis.

RESULTS Eighty-seven studies met inclusion criteria. Among relatives included in the meta-analysis, 48% (95% CI, 38 to 58) underwent cascade genetic counseling and 41% (95% CI, 34 to 48) cascade genetic testing. Compared with the patient-mediated approach, direct relative contact resulted in significantly higher uptake of genetic counseling for all relatives (63% [95% CI, 49 to 75] *v* 35% [95% CI, 24 to 48]) and genetic testing for first-degree relatives (62% [95% CI, 49 to 73] *v* 40% [95% CI, 32 to 48]). Methods of direct contact included telephone calls, letters, and e-mails; respective rates of genetic testing completion were 61% (95% CI, 51 to 70), 48% (95% CI, 37 to 59), and 48% (95% CI, 45 to 50).

CONCLUSION Most relatives at risk for hereditary cancer do not undergo cascade genetic counseling and testing, forgoing potentially life-saving medical interventions. Compared with patient-mediated contact, direct relative contact increased rates of cascade genetic counseling and testing, arguing for a shift in the care delivery paradigm, to be confirmed by randomized controlled trials.

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INTRODUCTION

Cascade genetic testing is the process of extending genetic testing to the at-risk relatives of an individual found to carry a germline pathogenic variant. In families with a hereditary cancer syndrome, identifying asymptomatic carriers offers the opportunity to reduce cancer incidence, morbidity, and mortality and is cost-effective.[1-10] The Centers for Disease Control and Prevention Office of Public Health Genomics have designated cascade genetic testing as a tier one genomic application for hereditary breast and ovarian cancers and Lynch syndrome.[11] Furthermore, mathematical modeling suggests that the combination of genetic testing at the time of cancer diagnosis and cascade testing by 70% of at-risk relatives could identify all four million individuals with a cancer-associated pathogenic variant in the United States in less than a decade.[12] However, fewer than 20% of individuals with a hereditary cancer syndrome are aware of their underlying pathogenic variant.[2,3,13,14] Furthermore, when pathogenic variants are identified, families face many barriers to completion of cascade testing, likely contributing to underutilization of this critical service.[15-20] Finally, racial and ethnic minorities experience even more pronounced under-recognition of hereditary cancer syndromes,[21-25] leading the American Association for Cancer Research, the American Cancer Society, ASCO, and the National

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Does direct relative contact for hereditary cancer syndrome cascade testing improve rates of genetic counseling and testing as compared with the current standard of care, patient-mediated family contact?

Knowledge Generated

Currently, the majority of people with a hereditary cancer syndrome are not aware and, therefore, cannot use potentially life-saving medical interventions. Our study found that, in families with hereditary cancer syndromes, direct relative contact by the medical team or testing laboratory resulted in higher uptake of genetic counseling and genetic testing among at-risk relatives compared with the patient-mediated approach.

Relevance

Currently, patients shoulder the responsibility of disseminating information on hereditary cancer syndromes among relatives, resulting in genetic counseling and testing by only about one third of at-risk relatives. Our findings demonstrate the power of direct relative contact, arguing for a shift in the care delivery paradigm, to be confirmed by randomized controlled trials.

Cancer Institute all to cite a critical need to improve genetic cancer risk assessment and testing for minority populations.[26]

A growing body of literature suggests that health system–led direct contact of relatives is acceptable to clinicians and patients and more successful than patient-mediated contact.[27-30] However, current Health Insurance Portability and Accountability Act privacy laws prohibit health care providers from disclosing genetic information to relatives. As a result, the affected patients must shoulder the burden for coordinating cascade testing for their families.[31] This is often complicated by the difficulty in communicating complex health information, strained family relationships, and competing demands, as patients may also be coping with a new cancer diagnosis that prompted their genetic testing.[32] Further complicating matters, health care systems, and health care policies have been largely oriented toward treatment of disease and not prevention. The primary objective of the current study was to conduct a systematic review and meta-analysis of the literature on the success of cascade genetic counseling and testing among all relatives for hereditary cancer syndromes via patient-mediated and direct relative contact. Secondary aims were to explore rates of relative disclosure and the influence of sex, degree of relation, race, ethnicity, specific cancer syndrome, and insurance status on completion of cascade genetic counseling and testing. Although similar systematic reviews have been completed,[28-30] to our knowledge, this study is the first meta-analysis.

MATERIALS AND METHODS

Overview

The current study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was preregistered with PROSPERO (registration No.: CRD42020134276).[33]

A comprehensive literature search was conducted on July 23, 2021, 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 full Ovid MEDLINE search strategy is available in Appendix Table A1 (online only).

Inclusion and Exclusion Criteria

Eligible manuscripts included all primary English language research studies with the objective of evaluating cascade genetic counseling and testing for hereditary cancer syndromes, including a focus on disclosure of results to relatives, completion of genetic counseling, and completion of genetic testing. Commentaries, systematic reviews, meta-analyses, and case reports were not included. Studies were evaluated to determine if cascade testing was patient-mediated or via direct relative contact. See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for a comprehensive review of reasons for publication exclusion (Fig 1).

Data Extraction

Manuscripts were independently evaluated by two reviewers, and disagreements were discussed with a third reviewer. Data were extracted by one reviewer and checked by two additional reviewers. Studies were coded according to a priori–specified characteristics, including study type, intervention, participant characteristics, and risk of bias.

Risk of Bias and Analytic Strategy

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) was applied to assess the risk of bias for studies reporting on direct relative contact for cascade

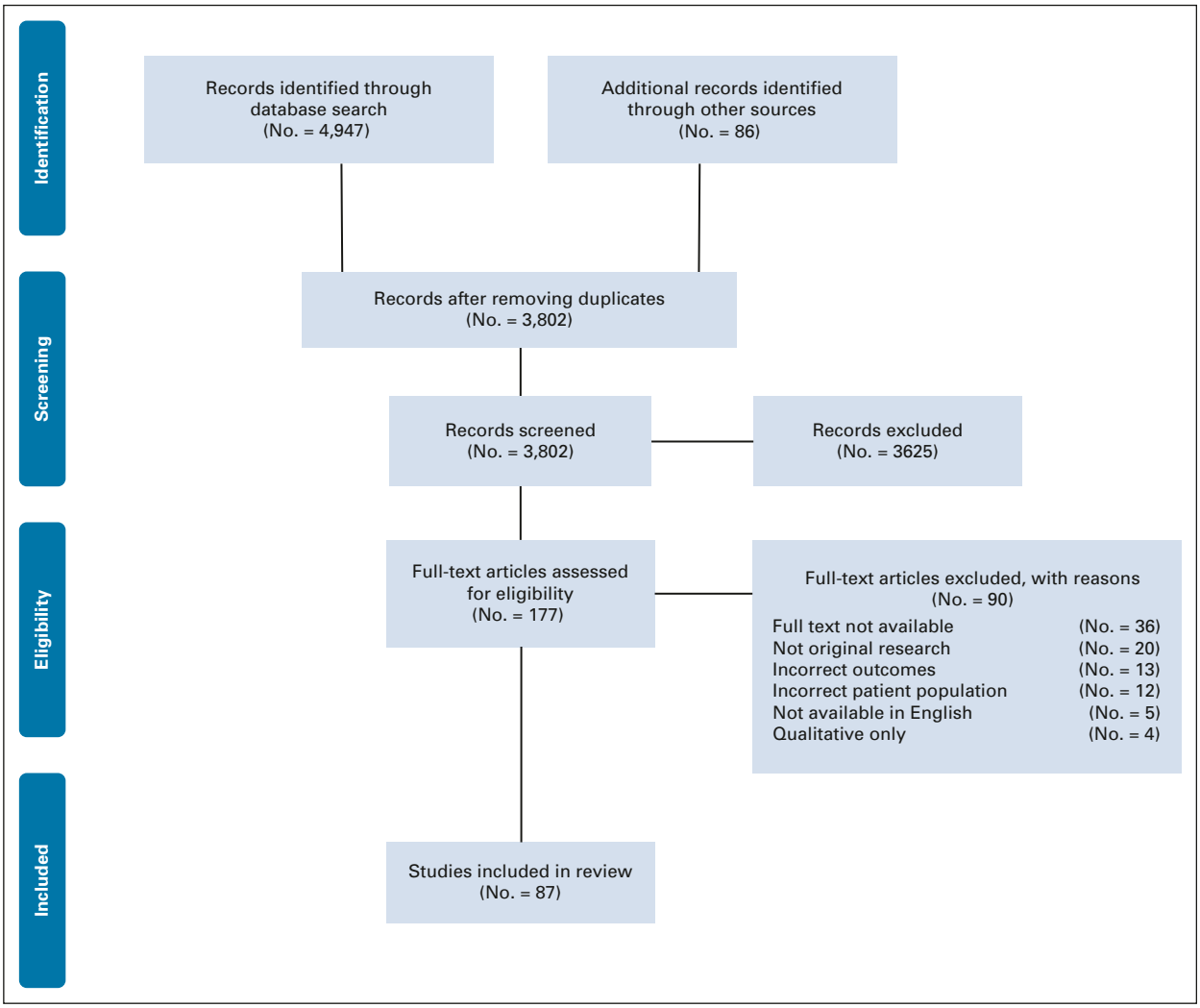

FIG 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

testing.[34] The Joanna Briggs Institute Critical Appraisal Checklist for cohort studies and the Joanna Briggs Institute Critical Appraisal Checklist for analytical cross-sectional studies, as appropriate, were applied to studies reporting on proband-mediated contact of relatives to determine the extent to which studies addressed risk of bias in their design, conduct, and analysis.[35] All risk of bias and ratings assessments were independently assessed by two reviewers, and disagreements were discussed with a third reviewer.

Statistical Analysis

Meta-analyses for the proportion of at-risk relatives that completed genetic counseling and genetic testing were conducted using R software (Version 3.6.1[07/05/19], R Foundation for Statistical Computing, Vienna, Austria). Statistical heterogeneity was tested through the chi-square test (ie, Cochrane Q test), and a P value $\leq .20$ 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 the Freeman-Tukey Double arcsine 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. Sensitivity analyses were performed for the outcomes of interest (rates of cascade genetic counseling and genetic testing) to investigate the impact of date of publication, study country of origin, study design, method of data collection, and study quality on our aggregated results.

RESULTS

Study Characteristics

Eighty-seven publications of original research were included in our systematic review. Seventy-one observational studies provided data that allowed for inclusion in the meta-analysis (29 prospective studies, 27 cross-sectional studies, and 15 retrospective studies). Seventeen studies report on rates of cascade genetic counseling including six studies on direct relative contact, eight studies on proband-mediated relative contact, and three on both modes of contact. Fifty studies report on rates of cascade genetic testing including 12 studies on direct relative contact, 34 studies on proband-mediated relative contact, and four on both modes of contact. Thirty studies report on rates of disclosure of genetic information by the probands to their at-risk relatives (Appendix Tables A2 and A3, online only).

Cumulative Patient Characteristics

A total of 14,736 probands and 33,223 at-risk relatives were evaluated for completion of cascade genetic counseling and testing. Study publication dates spanned from 1996 to 2021 and included 21 countries: United States (37), the Netherlands (eight), United Kingdom (five), France (five), Australia (four), Finland (four), Norway (three), Belgium (three), Singapore (two), Canada (four), Israel (two), Trinidad and Tobago, the Bahamas, Germany, Spain, Ireland, Italy, Korea, Malaysia, South Africa, Sweden, and both United States and Canada (one each). Across all studies, the median reported proband age was 51.5 years (range, 18-93 years) and the relative age was 47.4 years (18-85 years). Fifty-nine studies included information on the proband's sex. Among the 13,266 probands in these studies, 10,854 (81.8%) were female and 2,412 (18.2%) were male. Forty-eight studies included information on relatives' sex. Among the 19,590 relatives in these studies, 10,777 (55.0%) were female and 8,813 (45.0%) were male.

Thirty-five studies included information on proband race and ethnicity. Among the 9,686 probands in these studies, 6,777 (70.0%) identified as White, 1,735 (17.9%) as Hispanic/Latino, 604 (6.2%) as Asian, 221 (2.3%) as Black, and 7 (0.1%) as Native American. Among this group, 1,816 (18.7%) probands identified as Ashkenazi Jewish. Ten studies included information on relatives' race and ethnicity.[15,36-44] Among the 2,543 relatives included in these studies, 1,876 (73.8%) identified as White, 394 (15.5%) as Asian, 195 (7.7%) as Hispanic/Latino, 58 (2.3%) as Black, and 20 (0.8%) as Native American. Among this group, 137 (5.4%) relatives identified as Ashkenazi Jewish. Further proband and relative characteristics for each study included in the systematic review are reported in Appendix Table A2.

Cumulative Rates of Cascade Genetic Counseling and Testing

Among the cohort of all patients included in the meta-analysis, 48% (95% CI, 38 to 58) of relatives underwent cascade genetic counseling. Female relatives had higher rates of completion of genetic counseling compared with male relatives (60% [95% CI, 43 to 75] *v* 31% [95% CI, 20 to 44]).

Among the cohort of all patients included in the meta-analysis, 41% (95% CI, 34 to 48) of relatives underwent cascade genetic testing. The method of measuring completion of cascade genetic testing differed between studies. Thirty-nine studies included review of genetic testing as a part of the study design, eight studies relied on self-report by the proband, one study relied on self-report by the relatives, one study used both reviews of results as part of study design and proband self-report, and one study did not describe the method of outcome measurement (Appendix Table A3). First-degree relatives were significantly more likely to complete genetic testing compared with second-degree relatives (43% [95% CI, 36 to 51] *v* 22% [95% CI, 17 to 28]). Female relatives were significantly more likely to complete genetic testing than male relatives (50% [95% CI, 40 to 59] *v* 28% [95% CI, 19 to 39]). Relatives in families with a colorectal cancer syndrome had higher rates of genetic testing compared with families with hereditary breast and ovarian cancers (60% [95% CI, 46 to 72] *v* 38% [95% CI, 31 to 46]; Table 1).

Eighteen studies included information on proband disclosure of the pathogenic variant to relatives. Among 3,779 probands with data available on disclosure, 94% (95% CI, 88 to 97) reported disclosing their genetic test results to at least one at-risk relative. Nineteen studies included information on relatives to whom probands disclosed information about the pathogenic variant identified. Among 12,751 at-risk relatives (determined either via interview with at-risk relatives or review of a proband's pedigree), 72% (95% CI, 64 to 79) were informed of their genetic risk by the proband.

Other Studies

Other studies explored covariates, but the data were not presented in a manner where they could be quantitatively meta-analyzed. Two studies evaluated the impact of race and ethnicity on cascade testing and found that relatives in White families were more likely to complete cascade genetic testing compared with relatives from Black, Asian, Native American, and Hispanic/Latino families.[15,37] One study evaluated insurance status and cascade testing and found that being insured versus uninsured was associated with higher uptake of cascade genetic testing (odds ratio, 3.74 [95% CI, 2.06 to 6.80]).[39]

Thirteen studies reported on the impact of relative age and uptake of cascade genetic testing. Among these studies, ten demonstrated that older relative age was associated with increased likelihood of completing cascade testing[19,45-52,119] and three suggested the opposite, that younger relatives were more likely to complete cascade testing.[36,41,53] Ten studies reported on the impact of parenthood and cascade testing, with seven studies reporting that probands with children were more likely to complete cascade testing[19,49-51,53-55] and three studies demonstrating no association between

TABLE 1. Completion of Cascade Genetic Counseling and Genetic Testing for Direct Relative Contact Versus Patient-Mediated Relative Contact

Cascade Genetic Counseling

	Direct Relative Contact		Patient-Mediated Relative Contact		Combined Cohort	
Relative Characteristic	**% (95% CI)**	**No. of Studies**	**% (95% CI)**	**No. of Studies**	**% (95% CI)**	**No. of Studies**
All relatives	63 (49 to 75)	9	35 (24 to 48)	11	48 (38 to 58)	17
Relation						
First-degree	NA		36 (22 to 54)	8	41 (26 to 59)	10
Second-degree	NA		NA		NA	
Sex						
Female	84 (78 to 88)	3	49 (32 to 66)	8	60 (43 to 75)	11
Male	NA		25 (16 to 36)	7	31 (20 to 44)	9
Hereditary cancer syndrome						
Hereditary breast and ovarian cancer	62 (44 to 78)	5	30 (20 to 42)	9	39 (29 to 51)	10
Colorectal cancer	NA		NA		NA	

Cascade Genetic Testing

	Direct Relative Contact		Patient-Mediated Relative Contact		Combined Cohort	
Relative Characteristic	**% (95% CI)**	**No. of Studies**	**% (95% CI)**	**No. of Studies**	**% (95% CI)**	**No. of Studies**
All relatives	53 (43 to 62)	16	36 (28 to 44)	38	41 (34 to 48)	50
Relation						
First-degree	62 (49 to 73)	6	40 (32 to 48)	31	43 (36 to 51)	35
Second-degree	NA		22 (17 to 28)	10	22 (17 to 28)	10
Sex						
Female	75 (63 to 84)	7	40 (32 to 50)	17	50 (40 to 59)	22
Male	57 (42 to 72)	6	20 (14 to 27)	15	28 (19 to 39)	20
Hereditary cancer syndrome						
Hereditary breast and ovarian cancer	53 (41 to 65)	8	30 (24 to 37)	21	38 (31 to 46)	26
Colorectal cancer	63 (41 to 81)	4	59 (42 to 74)	10	60 (46 to 72)	14

Abbreviation: NA, not available.

parenthood and cascade testing uptake.[46,56,57] Three studies evaluated the role of familial support and found that relatives who reported greater family support and those belonging to more cohesive families were more likely to undergo cascade genetic testing[15,36,58] (Table 2).

Patient-Mediated Cascade Genetic Counseling and Testing

Thirty-eight studies evaluated patient-mediated cascade genetic counseling and testing for hereditary cancer syndromes, whereby the responsibility for communicating with relatives is placed on the affected proband/patient. Among 3,411 relatives with genetic counseling data available, 35% (95% CI, 24 to 48) completed genetic counseling with the patient-mediated approach (Fig 2). Rates of genetic counseling were higher for female versus male relatives (49% [95% CI, 32 to 66] *v* 25% [95% CI, 16 to 36]).

Among 21,519 relatives with data available on completion of patient-mediated cascade genetic testing, 36% (95% CI, 28 to 44) completed genetic testing (Fig 3). Rates of genetic testing were significantly higher for first-degree versus second-degree relatives (40% [95% CI, 32 to 48] *v* 22% [95% CI, 17 to 28]) and female versus male relatives (40% [95% CI, 32 to 50] *v* 20% [95% CI, 14 to 27]).

Eleven studies evaluated patient-mediated cascade testing whereby the patient was provided by the medical team with an informational letter to share with at-risk relatives.[42,47,49,53,55,59-64] Provision of a letter resulted in genetic counseling for 37% (95% CI, 15 to 67) of relatives and genetic testing for 41% (95% CI, 31 to 52) of relatives. When a letter was not provided, 34% (95% CI, 24 to 45) of relatives underwent genetic counseling and 33% (95% CI, 24 to 44) underwent genetic testing.

Twenty-one studies included information on cascade testing via patient-mediated relative contact for hereditary breast

TABLE 2. Studies of Proband and Relative Characteristics That Influence Cascade Genetic Testing for Hereditary Cancer Syndromes

Relative/Proband Characteristic	Association With Cascade Testing Identified	Association With Cascade Testing Not Identified
Relative Characteristics		
Relative's age	Biesecker et al, 2000[36]; Meijers-Heijboer et al, 2000 (women only)[49]; Bodd et al, 2003[46]; Ramsoekh et al, 2007[53]; Finlay et al, 2008[47]; Lynch et al, 2009[48]; Sanz et al, 2010[51]; Barrow et al, 2015[45]; Seppälä 2017[52]; Lieberman et al, 2018[119]; Courtney et al, 2019[41]; Frey et al, 2020[19]; Menko et al, 2020[50]	Aktan-Collan et al, 2000[56]; Meijers-Heijboer et al, 2000 (men only)[49]; Wagner et al, 2002[55]; Aktan-Collan et al, 2007[57]
Relative's sex	Evans et al, 1997[69]; Julian-Reynier et al, 2000[113]; Meijers-Heijboer et al, 2000[49]; Wagner et al, 2002[55]; Blandy et al, 2003[58]; Bodd et al, 2003[46]; Brooks et al, 2004[59]; McGivern et al, 2004[120]; Ramsoekh et al, 2007[53]; Finlay et al, 2008[47]; Holloway et al, 2008[54]; Evans et al, 2009[66]; Lynch et al, 2009[48]; Sanz et al, 2010[51]; Yoon et al, 2011[44]; Fehniger et al, 2013[15]; Barrow et al, 2015[45]; Sermijn et al, 2016[68]; Levin and Mæhle, 2017[63]; Lieberman et al, 2018[119]; Caswell-Jin et al, 2019[38]; Bednar et al, 2020[90]; Griffin et al, 2020[106]; Menko et al, 2020[50]; Jeong et al, 2021[112]	Aktan-Collan et al, 2000[56]; Biesecker et al, 2000[36]; Julian-Reynier et al, 2000[113]; Meijers-Heijboer et al, 2000[49]; Suthers et al, 2006[17]; Aktan-Collan et al, 2007[57]; Seppälä et al, 2017[52]; Courtney et al, 2019[41]; Bednar et al, 2020[90]; Frey et al, 2020[19]
Relative's race/ethnicity	Fehniger et al, 2013[15]; Braley et al, 2021[37]	
Relative's education	Lerman et al, 1999[40]; Sanz et al, 2010[51]	Aktan-Collan et al, 2000[56]; Ponz de Leon et al, 2004[124]; Fehniger et al, 2013[15]; Frey et al, 2020[19]
Relative's socioeconomic status	Holloway et al, 2008[54]; Cheung et al, 2010[94]	Griffin et al, 2020[106]
Relative's employment status	Aktan-Collan et al, 2000[56]	
Relative's insurance status	Lerman et al, 1996[39]	
Relative's personal history of cancer	Hagoel et al, 2000[107]; Holloway et al, 2008[54]; Sanz et al, 2010[51]	Biesecker et al, 2000[36]; Fehniger et al, 2013[15]; Lieberman et al, 2018[119]; Frey et al, 2020[19]
Relative residing in the United States versus abroad	Fehniger et al, 2013[15]	
Relative's parenthood	Meijers-Heijboer et al, 2000[49]; Wagner et al, 2002[55]; Ramsoekh et al, 2007[53]; Holloway et al, 2008[54]; Sanz et al, 2010[51]; Frey et al, 2020[19]; Menko et al, 2020[50]	Aktan-Collan et al, 2000[56]; Bodd et al, 2003[46]; Aktan-Collan et al, 2007[57]
Relative's marital status	Biesecker et al, 2000[36]	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]
Relative with an adult daughter	Menko et al, 2020[50]	
Relative's knowledge about risk for relatives	Blandy et al, 2003[58]	
Proband Characteristics		
Specific hereditary cancer syndrome	Seppälä et al, 2017[52] (by specific gene); Griffin et al, 2020[106]	Sanz et al, 2010[51]; Caswell-Jin et al, 2019[38]; Bednar et al, 2020[90]
Proband's history of cancer	Seppälä et al, 2017[52]	Griffin et al, 2020[106]
Duration of time since proband's genetic testing	Bednar et al, 2020[90]	
Relationship Between the Relative and the Proband		
Family support	Biesecker et al, 2000[36]; Blandy et al, 2003[58]	
Relative's degree of relationship to the proband	Hagoel et al, 2000[107]; Julian-Reynier et al, 2000[113]; Wagner et al, 2002[55]; Sanz et al, 2010[51]; Fehniger et al, 2013[15]; Sermijn et al, 2016[68]; Lieberman et al, 2018[119]	Blandy et al, 2003[58]; Brooks et al, 2004[59]; Holloway et al, 2008[54]
Frequency of communication between the proband and the relative	Fehniger et al, 2013[15]	Griffin et al, 2020[106]
Proband and relative living in close proximity		Griffin et al, 2020[106]

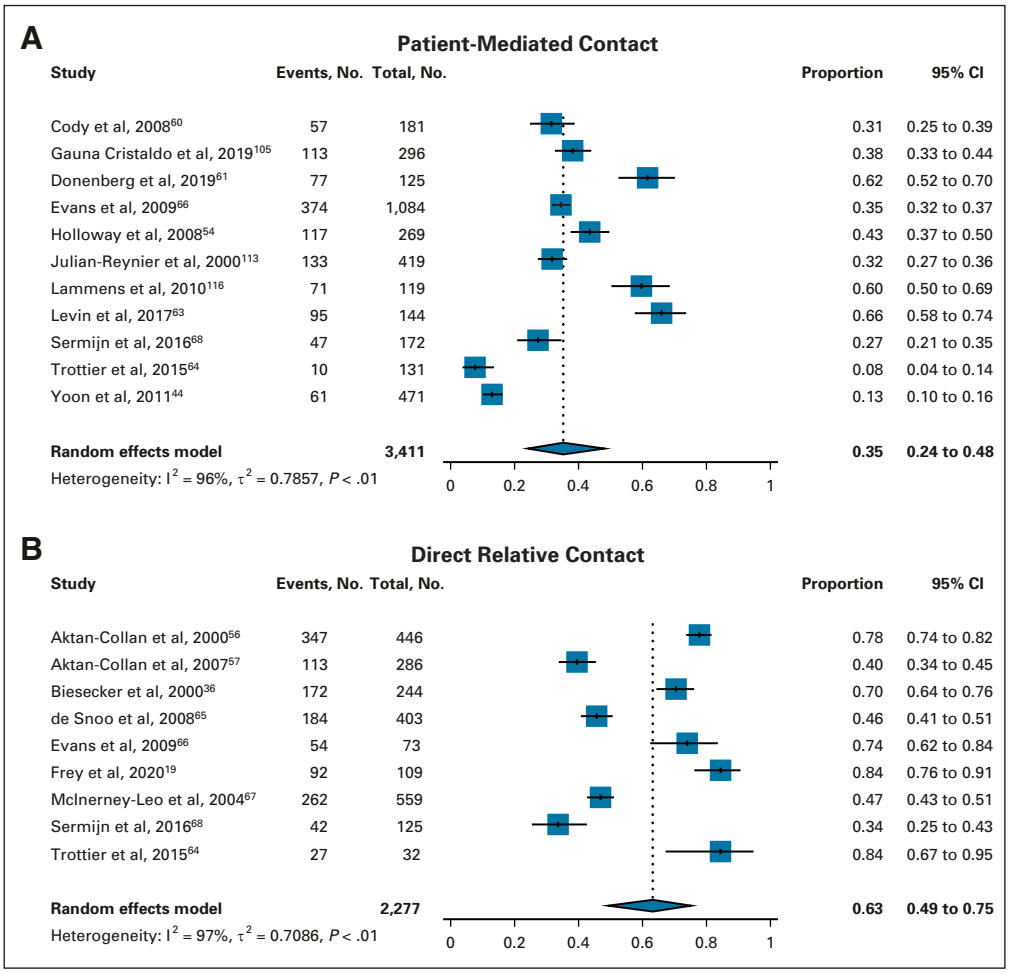

FIG 2. Cascade genetic counseling: pooled proportions with patient-mediated contact (A) and direct relative contact (B).

and ovarian cancer families. In this population, 30% (95% CI, 24 to 37) of relatives completed genetic testing, including 35% (95% CI, 27 to 44) of first-degree relatives, 23% (95% CI, 17 to 31) of second-degree relatives, 37% (95% CI, 28 to 48) of female relatives, and 16% (95% CI, 12 to 22) of male relatives. Ten studies included information on cascade testing via patient-mediated relative contact for colorectal cancer syndrome families. In this population, 59% (95% CI, 42 to 74) of relatives completed genetic testing.

Direct Relative Contact Cascade Genetic Counseling and Testing

Sixteen studies evaluated direct relative contact cascade genetic counseling and/or testing for hereditary cancer syndromes, whereby relatives are contacted by the medical team or testing laboratory. Fifteen studies investigated direct relative contact through outreach by the medical team; one study evaluated an online initiative for direct contact organized by the genetic testing laboratory.[38]

Among 2,277 relatives with genetic counseling data available, 63% (95% CI, 49 to 75) completed genetic counseling with direct relative contact (Fig 2). Among 7,457 relatives with genetic testing data available, 53% (95% CI, 43 to 62) completed cascade genetic testing with direct relative contact (Fig 3). Rates of genetic testing with direct relative contact were higher for female versus male relatives (75% [95% CI, 63 to 84] *v* 57% [95% CI, 42 to 72]).

Three methods of direct relative contact were described: (1) letter, (2) e-mail, and (3) telephone call. Direct contact via a letter resulted in genetic counseling for 55% (95% CI, 42 to 68) of relatives and genetic testing for 48% (95% CI, 37 to 59) of relatives.[17,36,39,40,48,56,57,65-69] Direct contact via an e-mail resulted in genetic testing for 48% (95% CI, 45 to 50) of relatives.[38] Direct contact via a telephone call resulted in genetic counseling for 84% (95% CI, 76 to 91) of relatives and genetic testing for 61% (95% CI, 51 to 70) of relatives.[19]

Eight studies included information on cascade testing via direct relative contact for hereditary breast and ovarian cancer families.[36,39,48,64,66-68,70] Among this group, 53% (95% CI, 41 to 65) of relatives completed genetic testing including 69% (95% CI, 57 to 79) of first-degree relatives, 71% (95% CI, 60 to 81) of female relatives, and 51% (95% CI, 28 to 73) of male relatives. Four studies included information on cascade testing via direct relative contact for colorectal

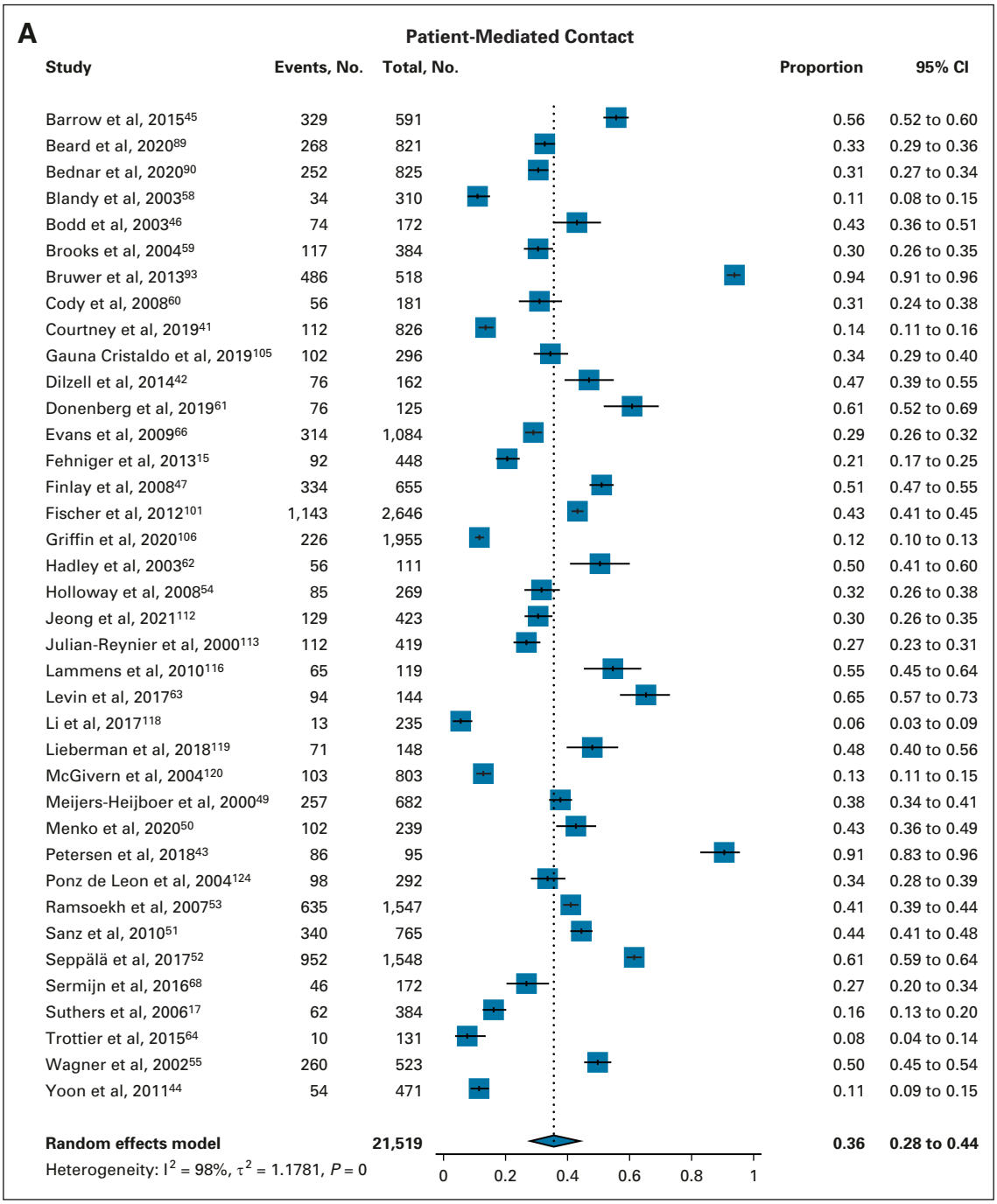

FIG 3. Cascade genetic testing: pooled proportions with patient-mediated contact (A) and direct relative contact (B). (continued on following page)

cancer syndrome families.[40,56,57,69] Among this group, 63% (95% CI, 41 to 81) of relatives completed genetic testing.

Direct Relative Contact Versus Patient-Mediated Relative Contact

Direct relative contact resulted in genetic counseling for 63% (95% CI, 49 to 75) of relatives versus 35% (95% CI, 24 to 48) with patient-mediated relative contact (Table 1 and Fig 2). None of the included studies evaluating direct relative contact provided information on genetic counseling rates for first-degree versus second-degree relatives. Direct relative contact resulted in genetic testing for 53% (95% CI, 43 to 62) of all relatives versus 36% (95% CI, 28 to 44) with patient-mediated relative contact (Table 1 and Fig 3). For first-degree relatives, direct relative contact resulted in genetic testing of 62% (95% CI, 49 to 73) of relatives versus 40% (95% CI, 32 to 48) with patient-mediated relative contact (Fig 4). Four nonrandomized studies included both

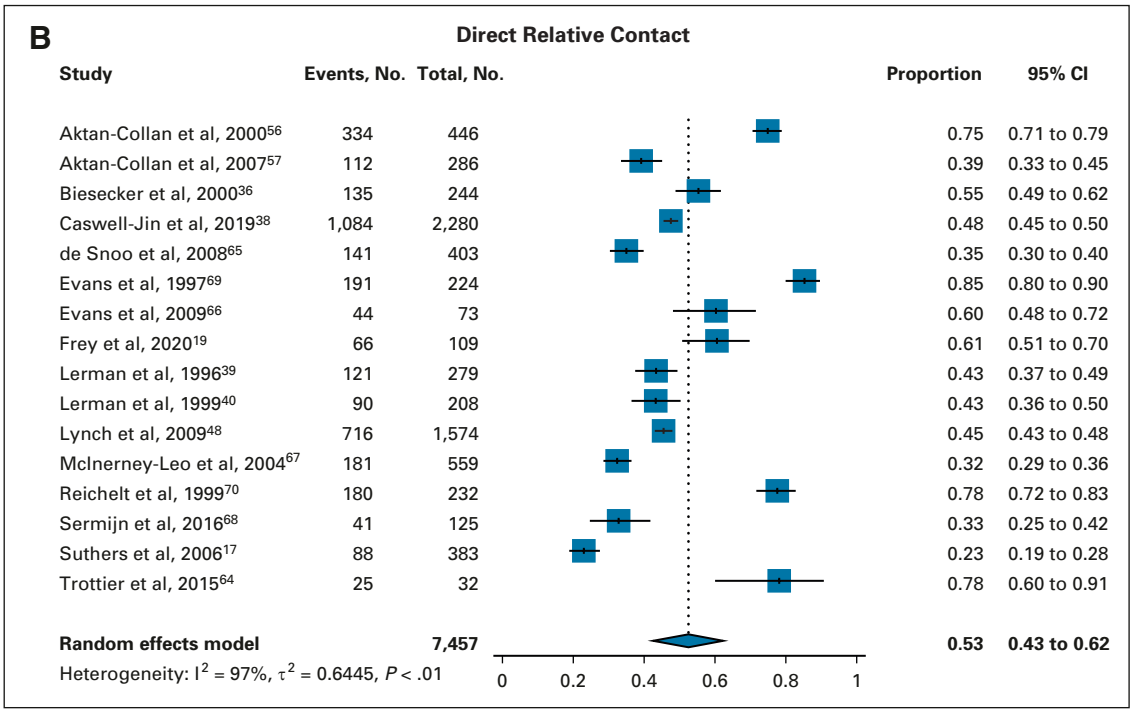

FIG 3. (Continued).

direct relative contact and patient-mediated relative contact.[17,64,66,68] Among these four studies, direct relative contact resulted in genetic testing for 48% (95% CI, 26 to 70) of relatives versus 20% (95% CI, 10 to 30) with patient-mediated relative contact.

Sensitivity Analyses

Sensitivity analyses were performed for the rates of patient-mediated and direct relative contact cascade genetic counseling and genetic testing for all relatives. Grouping studies by date of publication, study country of origin, study design, method of data collection, and study quality did not change the trends of our aggregate results (Appendix Table A3).

Quality of Evidence/Risk of Bias/Publication Bias

Study quality was assessed using as appropriate ROBINS-I,[34] 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 via ROBINS-I were found to be at moderate risk of bias. Studies assessed using the Joanna Briggs instruments were deemed appropriate to include in this review. The funnel plots suggest reduced representation of smaller studies with both low and high genetic counseling and genetic testing proportions (Appendix Table A4 and Fig A1, online only).

DISCUSSION

We have reviewed systematically the available literature on cascade genetic counseling and testing for cancer syndromes. This topic is of critical importance as, for hereditary cancer syndromes, the clinical benefit, sustainability, and cost-effectiveness of genetic counseling and testing are dependent on successful cascade testing for at-risk relatives.[9,10] Our review, to our knowledge, the first meta-analysis addressing this topic, confirms that the majority of at-risk relatives do not undergo genetic counseling nor testing and that direct relative contact significantly increases completion of cascade genetic counseling for all relatives and genetic testing for first-degree relatives as compared with patient-mediated relative contact.

This review identified factors that may affect a relative's likelihood of completing cascade genetic counseling and genetic testing. Studies included in this analysis suggest that uptake of cascade genetic counseling is higher in female versus male relatives, first-degree versus more distant relatives, and families with a colorectal cancer syndrome versus hereditary breast and ovarian cancer syndrome. Limited data suggest that White race and being insured were associated with higher rates of cascade testing completion. We have also identified other factors that may contribute to success of cascade testing including relatives' age, parenthood status, and familial support although the sample size was extremely limited. A growing literature suggests that genetic testing likely presents a unique set of challenges among medically underserved and vulnerable populations. Many factors can influence a person's decision about genetic testing including race, ethnicity, sex, education level, affordability, insurance, and concerns about discrimination.[71-78]

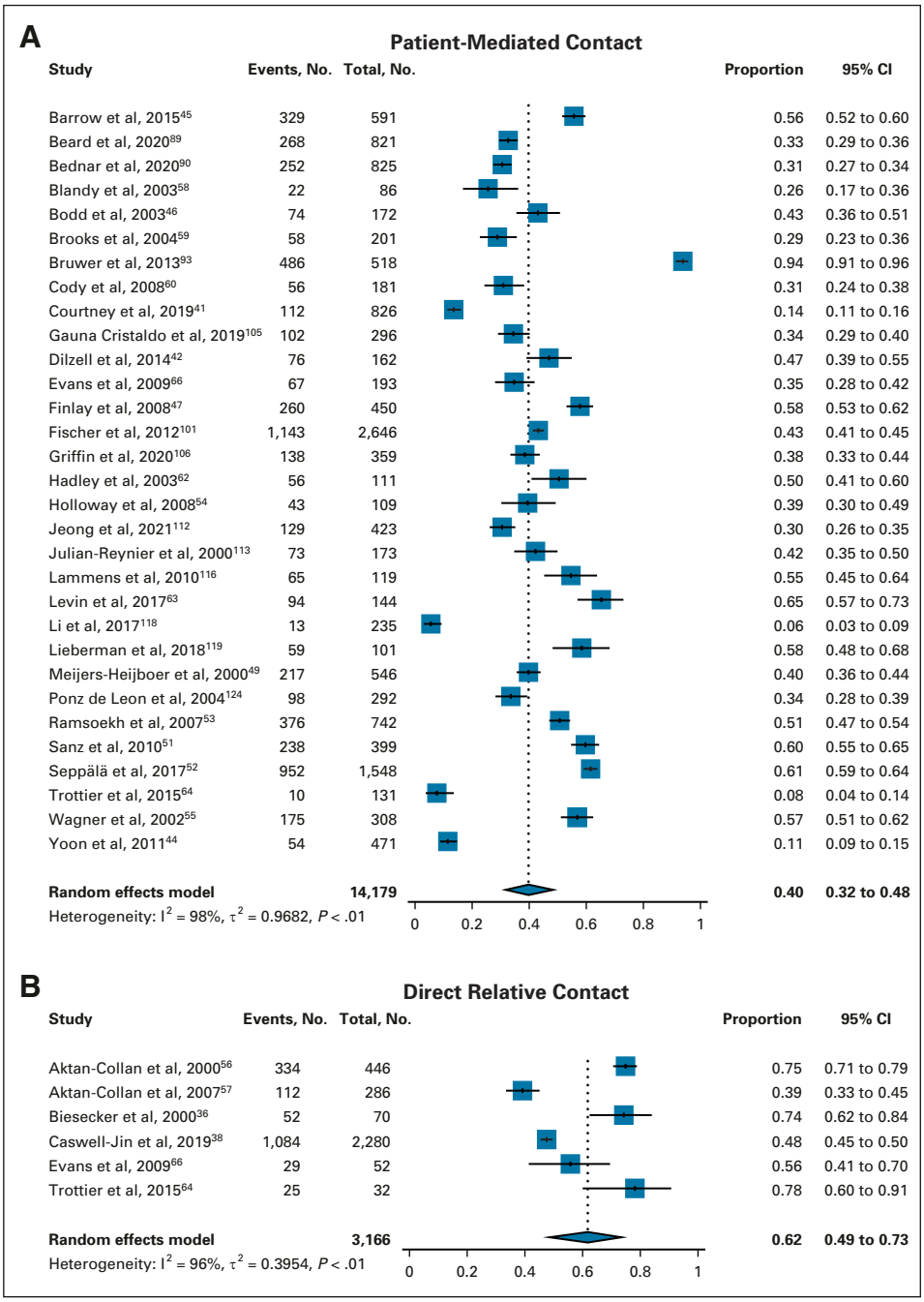

FIG 4. Cascade genetic testing of first-degree relatives: pooled proportions with patient-mediated contact (A) and direct relative contact (B).

Idos et al[20] reported on multiplex cancer gene panel testing in a racially, ethnically, and socioeconomically diverse cohort (41% Hispanic, 26% Spanish-speaking only, and 30% achieved a highest level of education of high school or less) and found that 38% of relatives underwent cascade genetic testing. However, among studies included in our review that provided information on relative race, 74% of the population identified as White, emphasizing the critical need for trials that explore genetic medicine in diverse patient populations. Elucidating barriers to cascade genetic testing is essential so that cascade testing strategies can be designed to target those relatives least likely to use potentially life-saving medical interventions. Furthermore, this aligns with the call put forth by several organizations to improve genetic cancer risk assessment and testing for minority populations.[26] We identified three strategies for direct relative contact, letter (by mail), e-mail, and telephone call, with telephone calls demonstrating the highest rates of completion of genetic counseling and genetic testing.

Our results should be viewed in light of several limitations. The majority of studies evaluated for risk of bias using ROBINS-I were found to be at moderate risk of bias. The funnel plots may indicate decreased publication of smaller studies with both low and high genetic counseling and genetic testing proportions. However, this is unlikely to skew the summary estimates in favor of uptake of genetic counseling and genetic testing because only the absence of smaller studies with low testing proportions would be indicative of publication bias. Several studies measured completion of cascade genetic testing on the basis of proband or relative self-report. Ideally, future studies will include a review of the genetic testing results to confirm completion of the recommended appropriate genetic testing. Finally, the primary outcomes for this study were completion of cascade genetic counseling and genetic testing for all relatives via patient-mediated and direct relative contact. We found that direct relative contact significantly improved rates of completion of genetic counseling. The rate of genetic testing was higher for direct relative contact compared with patient-mediated contact, and this result was close to statistical significance; completion was significantly higher on the subgroup analysis of first-degree relatives. These limitations highlight the need for well-designed prospective randomized controlled trials addressing this topic.

Our findings offer a meta-analysis to confirm prior systematic reviews that direct relative contact results in greater uptake of cascade genetic counseling and genetic testing for familial cancer syndromes as compared with patient-mediated relative contact. These findings, combined with the growing body of evidence that direct contact is acceptable to patients, their at-risk relatives, and providers, suggest a change in the paradigm of cascade testing.[17,19,27,57,79,80]

Favoring direct relative contact are focus groups, suggesting that direct contact programs are viewed as an acceptable complement to existing patient-mediated cascade screening efforts and ethical arguments increasingly supporting the notion that, in the context of shared genetic information, the clinician has responsibility not just to the patient but also to at-risk relatives.[27,81-84] Furthermore, Health Insurance Portability and Accountability Act privacy rules allow for several avenues of direct clinician contact of at-risk relatives including with the patient's consent.[85] Other possible avenues include direct relative contact facilitated by the testing laboratory as described by Caswell-Jin et al,[38] provider-to-provider contact, and contact permitted via the public health exception. However, the public health exemption has largely been used in the context of communicable diseases with the potential for imminent harm. Although other countries have explored public health approaches to cascade testing, this is yet to be explored in the United States.[85,86] Of note, providers and patients have voiced concern about privacy protection and control over information flow in the setting of direct contact cascade testing programs.[27] Well-designed studies are needed to clarify the acceptability of direct contact programs for both probands and relatives and to explore the legal, financial, and resource implications of direct contact cascade testing programs in the United States and abroad.

In conclusion, although cascade genetic testing for cancer syndromes is a tier-one application of genomic medicine per the Centers for Disease Control and Prevention,[11] we have found that the majority of at-risk relatives do not undergo this potentially life-saving intervention. Our meta-analysis confirms prior literature that direct relative contact significantly increases completion of cascade genetic counseling for all relatives and genetic testing for first-degree relatives as compared with patient-mediated relative contact. Future randomized comparative effectiveness studies must explore strategies of direct relative contact and facilitate pursuit of genetic counseling and testing in underrepresented patient subgroups to promote equitable identification of the millions of Americans unknowingly harboring cancer-associated pathogenic variants, moving toward the promise of precision medicine.[12]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cascade Testing for Hereditary Cancer Syndromes: Should We Move toward Direct Relative Contact? A Systematic Review and Meta-Analysis

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APPENDIX

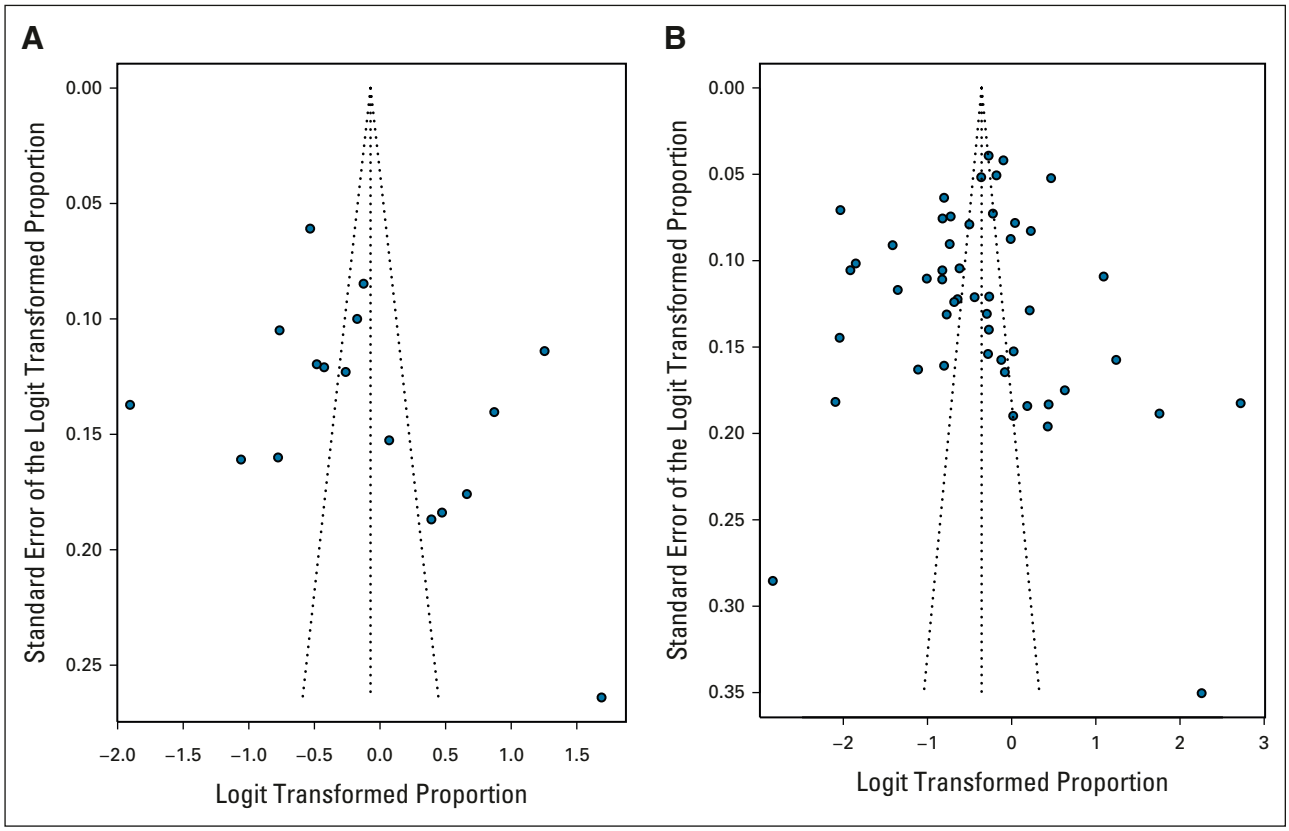

FIG A1. Funnel plots for genetic counseling and genetic testing outcomes. (A) Cascade genetic counseling, and (B) cascade genetic testing.

TABLE A1. Ovid MEDLINE Search Strategy

Ovid Medline
1. genetic counseling/or ((genetic adj3 counseling) or (genetic adj3 counselling) or (preventative adj3 genetic*)).ti.
2. genetic disorder/or ((genetic adj3 defect*) or (genetic adj3 disease*) or (genetic adj3 disorder*) or (genetic adj3 syndrome*) or (hereditary adj3 defect*) or (hereditary adj3 disease*) or (hereditary adj3 disorder*) or (hereditary adj3 syndrome*) or (heredodegenerative adj3 defect*) or (heredodegenerative adj3 disease*) or (heredodegenerative adj3 disorder*) or (heredodegenerative adj3 syndrome*) or (single-gene adj3 defect*)).ti.
3. exp genetic predisposition/or ((genetic adj3 anticipation) or (genetic adj3 predisposition*) or (genetic adj3 prognos*) or (genetic adj3 resistance) or (genetic adj3 susceptibilit*)).ti.
4. genetic screening/or genetic carrier screening/or ((genetic adj3 test*) or (genetic adj3 screen*)).ti.
5. or/1-4
6. 5 and cascad*.ti.
7. ((cascade adj5 test*) or (cascade adj5 screen*) or (famil* adj5 test*) or (famil* adj5 screen*) or (hereditary adj5 test) or (hereditary adj5 screen*)).ti.
8. 6 or 7
9. exp Neoplasm/or (cancer* or carcino* or cyst* or leukemi* or lymphom* or malignan* or melanoma* or myeloma* or neoplas* or oncolog* or sarcoma* or tumor* or tumour*).ti.
10. 8 and 9

TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Aktan-Collan et al, 2011[87]	248/0	Mean: 56.4	Female: 127 Male: 121	Yes: 133						
Aktan-Collan et al, 2000[56]	0/446					First	Mean: 43.0	Female: 229 Male: 217		
Aktan-Collan et al, 2007[57]	0/286					First	Mean: 53.6			
Alegre et al, 2019[88]	103/0	Mean: 55.2	Female: 92 Male: 11	Yes: 98 No: 5						
Barrow et al, 2015[45]	0/591					First				
Beard et al, 2020[89]	245/821	Mean: 49.3	Female: 150 Male: 95				Mean: 41.2	Female: 233 Male: 149		
Bednar et al, 2020[90]	150/825	Mean: 46.2	Female: 132 Male: 18		White: 140 Black/African American: 2 American Indian/ Alaska Native: 2 Asian Indian: 1 Chinese: 1 Others: 4 Ethnicity: Non-Hispanic: 139 Hispanic: 10 Prefer not to answer: 1	First		Female: 380 Male: 445		
Biesecker et al, 2000[36]	0/172						Median: 40	Female: 110 Male: 62		White: 172
Blandy et al, 2003[58]	30/310	Mean: 52.0	Female: 30	Yes: 30 (breast and ovarian)		First, second, third		Female: 162 Male: 148		
Bodd et al, 2003[46]	75/172		Female: 58 Male: 17			First		Female: 84 Male: 88		
Bradbury et al, 2007[91]	42/86	Median: 45.0	Female: 37 Male: 5	Yes: 23 No: 19	White: 39 Black: 1 Hispanic: 2	First (children)	Median: 12	Female: 53 Male: 33		
Bradbury et al, 2012[92]	253/505	Mean: 47.7	Female: 241 Male: 12	Yes: 169 No: 84	White: 232 Black: 13 Others: 8	First (children)	Median: 17	Female: 253 Male: 252		

(continued on following page)

TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Braley et al, 2021[37]	358/447		Female: 291 Male: 42		Asian: 95 European: 233 Latin/Central/ South American: 7 North American Indigenous: 17 Others: 6			Female: 310 Male: 137		Asian: 76 European: 230 Latin/Central/ South American: 2 North American Indigenous: 18 Others: 27 Unknown: 94
Brooks et al, 2004[59]	0/384					First, second, distant		Female: 202 Male: 182		
Bruwer et al, 2013[93]	80/158	Mean: 40.8	Female: 55 Male: 25		White: 6 Mixed ancestry: 74	First				
Caswell-Jin et al, 2019[38]	1,101/2, 280				White non-Hispanic: 697 Hispanic: 36 Asian: 35 African: 4 Native American: 1 Multiple: 41 Unknown: 287 Ashkenazi Jewish: 123	First		Female: 1,195 Male: 1,085		(For relatives completing testing) White non-Hispanic: 899 Hispanic: 69 Asian: 34 African: 5 Native American: 0 Multiple: 38 Unknown: 39 Ashkenazi Jewish: 137
Cheung et al, 2010[94]	1,103/0		Female: 1,103	Yes: 776 No: 327	White: 948 Asian: 66 Latina: 61 African American: 28					
Claes et al, 2003[95]	63/0	Mean: 52.7	Female: 62 Male: 1			First, second, third				
Cody et al, 2008[60]	29/181		Female: 29 Male: 1			First		Female: 97 Male: 84		
Conley et al, 2020[96]	149/0	Mean: 44.9	Female: 149		Black: 149					

(continued on following page)

TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Wagner Costalas et al, 2003[133]	162/444	Median: 50	Female: 162		White: 147 Unknown: 15	First	Median: 50	Female: 204 Male: 240		
Courtney et al, 2019[41]	183/826	Mean: 45.7	Female: 150 Male: 33		Chinese: 136 Malay: 28 Indian: 11 Others: 8	First		Female: 71 Male: 41		Chinese: 80 Malay: 20 Indian: 6 Others: 6
Cragun et al, 2021[97]	235/0	Median: 54	Female: 235		Non-Hispanic White: 208 Others: 27					
Gauna Cristaldo et al, 2019[105]	135/296	Mean: 58.6	Female: 82 Male: 53			First	Mean: 32.6	Female: 137 Male: 159		
de Snoo et al, 2008[65]	0/403									
Dilzell et al, 2014[42]	50/0	Mean: 47.0	Female: 33 Male: 9 Unknown: 8		White: 41 Native American: 2 African American: 1 Asian: 1 Hispanic: 0 Others: 0 Unknown: 5	First, second				White: 20 Native American: 1 Hispanic: 1 Others: 0 Unknown: 2
Donenberg et al, 2019[61]	24/125					First, second				
Eijzenga et al, 2018[98]	305/0	Intervention mean: 53.1 Control mean: 54.4	Female: 228 Male: 77	Yes: 216 No: 86						
Elrick et al, 2017[99]	920/0	Mean: 44.6	Female: 920	Yes: 920						
Ersig et al, 2009[100]	69/0	Mean: 47.8	Female: 28 Male: 41	Yes	White: 63 Unknown: 6					
Evans et al, 1997[69]	0/224									
Evans et al, 2009[66]	0/1,157						Group 1 Female median: 52 Male median: 55 Group 3 Female median: 44.6 Male median: 50.2	Female: 594 Male: 563		

(continued on following page)

TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Fehniger et al, 2013[15]	73/606	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
Finlay et al, 2008[47]	115/655		Female: 83 Male: 32		Ashkenazi Jewish: 28 Non-Ashkenazi/ White: 79 Unknown/White: 7 Others: 1	First, second				
Fischer et al, 2012[101]	0/2,646									
Forrest et al, 2008[102]	19/131	Intervention mean: 39.2 Control mean: 38.1	Female: 12 Male: 7				Intervention mean: 49.4 Control mean: 42.0	Female: 66 Male: 65		
Frey et al, 2020[19]	30/95	Median: 51.5	Female: 29 Male: 1				Median: 51	Female: 47 Male: 48		
Gaff et al, 2005[103]	12/0									
Garcia et al, 2020[104]	40/0	Preintervention cohort median: 63.0 Postintervention cohort: median 49.0	Female: 40	Yes (breast and ovarian)	Preintervention: Non-Hispanic White: 18 Non-Hispanic Black: 2 Postintervention: Non-Hispanic White: 17 Non-Hispanic Black: 1 Hispanic: 1 Unknown: 1					
Griffin et al, 2020[106]	64/1,955	Mean: 53.0	Female: 60 Male: 4		White: 62 African American: 2					

(continued on following page)

TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Hadley et al, 2003[62]	100/112	Median: 43	Female: 57 Male: 43	Yes: 62 No: 38	White: 87 African American: 7 Hispanic: 3 Asian American: 2 Native American: 1	First	Median: 39	Female: 64 Male: 48		
Hagoel et al, 2000[107]	67/371	Mean: 48.5	Female: 64 Male: 3	Yes: 24 No: 43			Mean: 52.5	Female: 244 Male: 127	Yes: 68 No: 303	
Hall et al, 2018[108]	57/0	Median: 52	Female: 47 Male: 10	Yes: 39 No: 18	Non-Hispanic/ White: 38 Hispanic: 11 Asian: 7 Ashkenazi Jewish: 3 Native American: 2 African American: 1 Others: 2					
Hayat Roshanai et al, 2010[109]	147/81		Female: 133 Male: 14	Yes: 54 No: 93				Female: 57 Male: 24		
Healey et al, 2017[110]	165/0		Female: 138 Male: 27							
Holloway et al, 2008[54]	54/269					First, second, third		Female: 161 Male: 108		
Hughes et al, 1999[134]	163/0	< 50 years: 113 ≥ 50 years: 50	Female: 124 Male: 39	Yes: 45 No: 118		First	Mean: 49	Female	Yes: 16% (breast and ovarian)	
Hughes et al, 2002[111]	43/81	≤ 50 years: 27 > 50 years: 16	Female: 43					Female: 81		
Idos et al, 2019[20]	2,000/0	Median: 51	Female: 1,614 Male: 386	Yes: 1,451 No: 549	Non-Hispanic/ White: 807 Hispanic: 781 Asian: 234 Black: 76 Others: 102					
Jeong et al, 2021[112]	129/423		Female: 129			First, second, third		Female: 235 Male: 188		

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TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Julian-Reynier et al, 2000[113]	0/419					First, second		Female: 244 Male: 175	Yes: 36 (female only) No: 208 (female only)	
Kardashian et al, 2012[114]	19/198	Control mean: 49 Intervention mean: 40	Female: 19		White: 14 Hispanic: 2 African American: 1 South Asian/ Indian: 1 Asian/Pacific Islander: 1 Ashkenazi Jewish (a subset of above): 3					
Kegelaers et al, 2014[115]	99/0	Mean: 49	Female: 74 Male: 25		White or Ashkenazi Jewish: 99					
Lammens et al, 2010[116]	23/119		Female: 16 Male: 7			First		Female: 59 Male: 60		
Landsbergen et al, 2005[117]	50/0	Mean at study: 49 Mean at testing: 44	Female: 50							
Lerman et al, 1996[39]	0/279						Mean: 43	Female: 129 Male: 63		White: 192
Lerman et al, 1999[40]	0/208						Mean: 47	Female: 77 Male: 62		White: 138 Native American: 1
Levin and Mæhle, 2017[63]	19/144							Female: 78 Male: 66		
Li et al, 2017[118]	45/235									
Lieberman 2018[119]	1,771/0	Mean: 52.0	Female: 1,406 Male: 365		Ashkenazi Jewish: 1,771	First, second				
Lynch et al, 2009[48]	0/1,574							Female: 854 Male: 720		
McGivern et al, 2004[120]	38/803	Mean: 48.1	Female: 38		White: 37 Native American: 1	First, second, third				

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TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
McInerney-Leo et al, 2004[67]	0/212							Female: 138 Male: 74		
Meijers-Heijboer et al, 2000[49]	0/682					First, second		Female: 411 Male: 271		
Menko et al, 2020[50]	0/239					First, second		Female: 113 Male: 114		
Montgomery et al, 2013[121]	345/1,046	Mean: 48.5	Female: 345		White: 328 Others: 17	First				
Patenaude et al, 2006[122]	273/0		Female: 273		White: 273					
Peters et al, 2019[123]	104/466	Median: 67	Female: 49 Male: 55	Yes	Among 99 who completed MICRA White: 82					
Petersen et al, 2018[43]	32/95		Female: 25 Male: 7		Non-Hispanic/ White: 30 Others: 2			Female: 64 Male: 31		Non-Hispanic White: 90 Others: 5
Ponz de Leon et al, 2004[124]	0/294					First				
Ramsoekh et al, 2007[53]	0/1,547					First, second, third	HNPCC ≤ 50 years: 455 > 50 years: 185 FAP < 18 years: 22 18-40 years: 36 > 40 years: 44	Female: 383 Male: 359		
Reichelt et al, 1999[70]	0/232							Female: 186 Male: 46	Yes: 30 (female only) No: 156 (female only)	
Ricker et al, 2018[125]	136/0	Mean: 52.4	Female: 105 Male: 31	Yes: 103 No: 33	Non-Hispanic/ White: 63 Hispanic: 56 Asian: 14 Black: 2 Others: 1					

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TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Sanz et al, 2010[51]	108/765	Median: 50.0	Female: 105 Male: 3			First, second	Mean: 45.0	Female: 413 Male: 352		
Segal et al, 2004[126]	31/60	Mean: 47.7	Female: 31	Yes: 17 No: 13 Unknown: 1		First (children)	Mean: 18.6	Female: 30 Male: 30		
Seppälä et al, 2017[52]	1,184/ 1,548	Mean: 50.7	Female: 603 Male: 581			First, second (children and grandchildren)	Mean: 32.7	Female: 743 Male: 801		
Sermijn et al, 2016[68]	0/172						Mean: 46	Female: 87 Male: 85		
Smith et al, 2002[127]	305/0	Mean: 44.0	Female: 189 Male: 116		White: 305					
Stoffel et al, 2008[128]	174/0	Mean: 46.7	Female: 122 Male: 52	Yes: 106 No: 68	White: 157 Non-White: 16 Unknown/missing: 1					
Suthers et al, 2006[17]	74/767	Mean: 52.0	Female: 68 Male: 6				Mean: 46.5	Female: 151 Male: 187		
Taber et al, 2015[129]	77/0	Median: 54.5	Female: 58 Male: 17	Yes: 33 No: 44 (breast and colon)	Non-Hispanic/ White: 40 Non-Hispanic/ Black: 15 Hispanic/Latino: 13 Others: 3					
Tercyak et al, 2002[130]	42/68	Mean: 44.2	Female: 42	Yes: 30 No: 12	White: 37 Unknown: 5	First (children)	Mean: 12.6	Female: 37 Male: 31		

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TABLE A2. Demographics of Probands and Relatives for Included Studies (No. = 87) (continued)

Study	No. of Probands/ Relatives	Proband Age, years	Proband Sex, No.	Proband Cancer History, No.	Proband Race/ Ethnicity, No.	Relatives Included (degree of relation)	Relative Age, years	Relative Sex, No.	Relative Cancer History, No.	Relative Race/ Ethnicity, No.
Troian et al, 2020[131]	230/465	Female mean: 48.8 Male mean: 60.4	Female: 160 Male: 70	Yes: 44		First (children)		Female: 249 Male: 216		
Trottier et al, 2015[64]	53/202		Female: 53					Female: 202		
Vadaparampil et al, 2012[132]	77/0	Mean at diagnosis: 47.6 Mean at testing: 52.0	Female: 77	Yes	White: 63 Black: 5 Others: 6 Unknown: 3					
Wagner et al, 2002[55]	0/523					First, second	< 50 years: 191 > 50 years: 117	Female: 156 Male: 152		
Yoon et al, 2011[44]	37/471	Median: 45.0	Female: 37		Malaysian: 6 Indian: 8 Chinese: 23	First		Female: 227 Male: 244		Malaysian: 11 Indian: 8 Chinese: 42

TABLE A3. Sensitivity Analyses for All Relatives Completing Cascade Genetic Counseling and Genetic Testing

	Cascade Genetic Counseling			Cascade Genetic Testing		
Study Characteristic	**No. of Studies**	**Author Year**	**Completion % (95% CI)**	**No. of Studies**	**Author Year**	**Completion % (95% CI)**
Date of publication						
Patient-mediated contact						
2000-2010	5	Julian-Reynier et al, 2000[113]; Cody et al, 2008[60]; Holloway et al, 2008[54]; Evans et al, 2009[66]; Lammens et al, 2010[116]	39 (32 to 47)	17	Meijers-Heijboer et al, 2000[49]; Julian-Reynier et al, 2000[113]; Wagner et al, 2002[55]; Bodd et al, 2003[46]; Blandy et al, 2003[58]; Hadley et al, 2003[62]; McGivern et al, 2004[120]; Brooks et al, 2004[59]; Ponz de Leon et al, 2004[124]; Suthers et al, 2006[17]; Ramsoekh et al, 2007[53]; Cody et al, 2008[60]; Holloway et al, 2008[54]; Finlay et al, 2008[47]; Evans et al, 2009[66]; Lammens et al, 2010[116]; Sanz et al, 2010[51]	34 (28 to 41)
2011-2021	6	Yoon et al, 2011[44]; Trottier et al, 2015[64]; Sermijn et al, 2016[68]; Levin and Mæhle, 2017[63]; Gauna Cristaldo et al, 2019[105]; Donenberg et al, 2019[61]	34 (16 to 54)	21	Yoon et al, 2011[44]; Fischer et al, 2012[101]; Fehniger et al, 2013[15]; Bruwer et al, 2013[93]; Dilzell et al, 2014[42]; Trottier et al, 2015[64]; Barrow et al, 2015[45]; Sermijn et al, 2016[68]; Levin and Mæhle, 2017[63]; Seppälä et al, 2017[52]; Li et al, 2017[118]; Lieberman et al, 2018[119]; Petersen et al, 2018[43]; Courtney et al, 2019[41]; Gauna Cristaldo et al, 2019[105]; Donenberg et al, 2019[61]; Bednar et al, 2020[90]; Menko et al, 2020[50]; Griffin et al, 2020[106]; Beard et al, 2020[89]; Jeong et al, 2021[112]	39 (28 to 50)
Direct relative contact						
1996-2010	6	Aktan-Collan et al, 2000[56]; Biesecker et al, 2000[36]; McInerney-Leo et al, 2004[67]; Aktan-Collan et al, 2007[57]; de Snoo et al, 2008[65]; Evans et al, 2009[66]	59 (45 to 73)	12	Lerman et al, 1996[39]; Evans et al, 1997[69]; Lerman et al, 1999[40]; Reichelt et al, 1999[70]; Aktan-Collan et al, 2000[56]; Biesecker et al, 2000[36]; McInerney-Leo et al, 2004[67]; Suthers et al, 2006[17]; Aktan-Collan et al, 2007[57]; de Snoo et al, 2008[65]; Evans et al, 2009[66]; Lynch et al, 2009[48]	52 (41 to 62)
2011-2020	3	Trottier et al, 2015[64]; Sermijn et al, 2016[68]; Frey et al, 2020[19]	69 (30 to 97)	4	Trottier et al, 2015[64]; Sermijn et al, 2016[68]; Caswell-Jin et al, 2019[38]; Frey et al, 2020[19]	53 (40 to 66)
Country of origin						
Patient-mediated contact						
United States	0			8	Bednar et al, 2020[90]; Fehniger et al, 2013[15]; McGivern et al, 2004[120]; Griffin et al, 2020[106]; Petersen et al, 2018[43]; Dilzell et al, 2014[42]; Finlay et al, 2008[47]; Hadley et al, 2003[62]	38 (24 to 54)

(continued on following page)

TABLE A3. Sensitivity Analyses for All Relatives Completing Cascade Genetic Counseling and Genetic Testing (continued)

	Cascade Genetic Counseling			Cascade Genetic Testing		
Study Characteristic	**No. of Studies**	**Author Year**	**Completion % (95% CI)**	**No. of Studies**	**Author Year**	**Completion % (95% CI)**
Outside United States	11	Cody et al, 2008[60]; Levin and Mæhle, 2017[63]; Lammens et al, 2010[116]; Holloway et al, 2008[54]; Yoon et al, 2011[44]; Sermijn et al, 2016[68]; Julian-Reynier et al, 2000[113]; Trottier et al, 2015[64]; Gauna Cristaldo et al, 2019[105]; Donenberg et al, 2019[61]; Evans et al, 2009[66]	36 (27 to 46)	30	Cody et al, 2008[60]; Lieberman et al, 2018[119]; Menko et al, 2020[50]; Bodd et al, 2003[46]; Blandy et al, 2003[58]; Bruwer et al, 2013[93]; Brooks et al, 2004[59]; Levin and Mæhle, 2017[63]; Lammens et al, 2010[116]; Sanz et al, 2010[51]; Seppälä et al, 2017[52]; Holloway et al, 2008[54]; Wagner et al, 2002[55]; Yoon et al, 2011[44]; Meijers-Heijboer et al, 2000[49]; Courtney et al, 2019[41]; Ponz de Leon et al, 2004[124]; Ramsoekh et al, 2007[53]; Sermijn et al, 2016[68]; Julian-Reynier et al, 2000[113]; Trottier et al, 2015[64]; Fischer et al, 2012[101]; Barrow et al, 2015[45]; Suthers et al, 2006[17]; Beard et al, 2020[89]; Jeong et al, 2021[112]; Li et al, 2017[119]; Gauna Cristaldo et al, 2019[105]; Donenberg et al, 2019[61]; Evans et al, 2009[66]	36 (29 to 43)
Direct relative contact						
United States	3	Frey et al, 2020[19]; Biesecker et al, 2000[36]; McInerney-Leo et al, 2004[67]	68 (45 to 87)	7	Caswell-Jin et al, 2019[38]; Frey et al, 2020[19]; Biesecker et al, 2000[36]; Lerman et al, 1996[39]; Lerman et al, 1999[40]; McInerney-Leo et al, 2004[67]; Lynch et al, 2009[48]	46 (41 to 51)
Outside United States	6	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Evans et al, 2009[66]; Sermijn et al, 2016[68]; Trottier et al, 2015[64]; de Snoo et al, 2008[65]	59 (42 to 76)	9	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Evans et al, 2009[66]; Sermijn et al, 2016[68]; Evans et al, 1997[69]; Trottier et al, 2015[64]; Suthers et al, 2006[17]; Reichelt et al, 1999[70]; de Snoo et al, 2008[65]	57 (39 to 73)
Study design						
Patient-mediated contact						
Retrospective	3	Cody et al, 2008[60]; Lammens et al, 2010[116]; Holloway et al, 2008[54]	45 (31 to 59)	13	Cody et al, 2008[60]; Menko et al, 2020[50]; Brooks et al, 2004[59]; Lammens et al, 2010[116]; Sanz et al, 2010[51]; Seppälä et al, 2017[52]; Holloway et al, 2008[54]; Wagner et al, 2002[55]; Ramsoekh et al, 2007[53]; Fischer et al, 2012[101]; Barrow et al, 2015[45]; Beard et al, 2020[89]; Jeong et al, 2021[112]	42 (37 to 48)
Cross-sectional	2	Julian-Reynier 2000[113]; Gauna Cristaldo et al, 2019[105]	35 (29 to 41)	11	Bednar et al, 2020[90]; Blandy et al, 2003[58]; Bruwer et al, 2013[93]; Griffin et al, 2020[106]; Dilzell et al, 2014[42]; Finlay et al, 2008[47]; Julian-Reynier et al, 2000[113]; Gauna Cristaldo et al, 2019[105]; Fehniger et al, 2013[15]; McGivern et al, 2004[120]; Petersen et al, 2018[43]	39 (22 to 57)

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TABLE A3. Sensitivity Analyses for All Relatives Completing Cascade Genetic Counseling and Genetic Testing (continued)

Study Characteristic	Cascade Genetic Counseling			Cascade Genetic Testing		
	No. of Studies	Author Year	Completion % (95% CI)	No. of Studies	Author Year	Completion % (95% CI)
Prospective	6	Levin and Mæhle, 2017[63]; Yoon et al, 2011[44]; Trottier et al, 2015[64]; Donenberg et al, 2019;[61] Evans et al, 2009[66]; Sermijn et al, 2016[68]	33 (18 to 50)	14	Lieberman et al, 2018[119]; Bodd et al, 2003[46]; Levin and Mæhle, 2017[63]; Yoon et al, 2011[44]; Meijers-Heijboer et al, 2000[49]; Hadley et al, 2003[62]; Courtney et al, 2019[41]; Ponz de Leon et al, 2004[124]; Trottier et al, 2015[64]; Suthers et al, 2006[17]; Li et al, 2017[118]; Donenberg et al, 2019[61]; Evans et al, 2009[66]; Sermijn et al, 2016[68]	30 (22 to 39)
Direct relative contact						
Prospective	9	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Evans et al, 2009[66]; Frey et al, 2020[19]; Sermijn et al, 2016[68]; Trottier et al, 2015[64]; Biesecker et al, 2000[36]; McInerney-Leo et al, 2004[67]; de Snoo et al, 2008[65]	62 (50 to 74)	14	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Caswell-Jin et al, 2019[38]; Evans et al, 2009[66]; Frey et al, 2020[19]; Sermijn et al, 2016[68]; Trottier et al, 2015[64]; Suthers et al, 2006[17]; Biesecker et al, 2000[36]; Lerman et al, 1996[39]; Lerman et al, 1999[40]; McInerney-Leo et al, 2004[67]; Reichelt et al, 1999[70]; de Snoo et al, 2008[65]	50 (41 to 58)
Cross-sectional	0			0		
Retrospective	0			2	Evans et al, 1997[69]; Lynch et al, 2009[48]	67 (26 to 97)
Method of data collection						
Patient-mediated contact						
Review of medical record	10	Cody et al, 2008[60]; Lammens et al, 2010[116]; Holloway et al, 2008[54]; Julian-Reynier et al, 2000[113]; Levin and Mæhle, 2017[63]; Yoon et al, 2011[44]; Sermijn et al, 2016[68]; Trottier et al, 2015[64]; Donenberg et al, 2019[61]; Evans et al, 2009[66]	36 (26 to 47)	27	Cody et al, 2008[60]; Menko et al, 2020[50]; Brooks et al, 2004[59]; Lammens et al, 2010[116]; Sanz et al, 2010[51]; Seppälä et al, 2017[52]; Holloway et al, 2008[54]; Wagner et al, 2002[55]; Ramsoekh et al, 2007[53]; Julian-Reynier et al, 2000[113]; Fischer et al, 2012[101]; Barrow et al, 2015[45]; Beard et al, 2020[89]; Jeong et al, 2021[112]; Bodd et al, 2003[46]; Levin and Mæhle, 2017[63]; Yoon et al, 2011[44]; Meijers-Heijboer et al, 2000[49]; Courtney et al, 2019[41]; Ponz de Leon et al, 2004[124]; Sermijn et al, 2016[68]; Trottier et al, 2015[64]; Suthers et al, 2006[17]; Li et al, 2017[118]; Donenberg et al, 2019[61]; Evans et al, 2009[66]; Bruwer et al, 2013[93]	38 (31 to 45)
Relative/proband self-report	1	Gauna Cristaldo et al, 2019[105]	38 (33 to 44)	9	Bednar et al, 2020[90]; Fehniger et al, 2013[15]; Blandy et al, 2003[58]; McGivern et al, 2004[120]; Griffin et al, 2020[106]; Dilzell et al, 2014[42]; Finlay et al, 2008[47]; Gauna Cristaldo et al, 2019[105]; Petersen et al, 2018[43]	33 (21 to 47)
Direct relative contact						

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TABLE A3. Sensitivity Analyses for All Relatives Completing Cascade Genetic Counseling and Genetic Testing (continued)

	Cascade Genetic Counseling			Cascade Genetic Testing		
Study Characteristic	**No. of Studies**	**Author Year**	**Completion % (95% CI)**	**No. of Studies**	**Author Year**	**Completion % (95% CI)**
Review of medical record	9	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Evans et al, 2009[66]; Frey et al, 2020[19]; Sermijn et al, 2016[68]; Trottier et al, 2015[64]; Biesecker et al, 2000[36]; McInerney-Leo et al, 2004[67]; de Snoo et al, 2008[65]	62 (50 to 74)	16	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Caswell-Jin et al, 2019[38]; Evans et al, 2009[66]; Frey et al, 2020[19]; Sermijn et al, 2016[68]; Evans et al, 1997[69]; Trottier et al, 2015[64]; Suthers et al, 2006[17]; Biesecker et al, 2000[36]; Lerman et al, 1996[39]; Lerman et al, 1999[40]; McInerney-Leo et al, 2004[67]; Reichelt et al, 1999[70]; Lynch et al, 2009[48]; de Snoo et al, 2008[65]	53 (43 to 62)
Relative/proband self-report	0			0		
Study quality						
Direct relative contact[a]						
Low/moderate risk of bias	8	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Evans et al, 2009[66]; Frey et al, 2020[19]; Sermijn et al, 2016[68]; Biesecker et al, 2000[36]; McInerney-Leo et al, 2004[67]; de Snoo et al, 2008[65]	60 (46 to 72)	13	Aktan-Collan et al, 2000[56]; Aktan-Collan et al, 2007[57]; Caswell-Jin et al, 2019[38]; Evans et al, 2009[66]; Frey et al, 2020[19]; Sermijn et al, 2016[68]; Evans et al, 1997[69]; Biesecker et al, 2000[36]; Lerman et al, 1999[40]; McInerney-Leo et al, 2004[67]; Reichelt et al, 1999[70]; Lynch et al, 2009[48]; de Snoo et al, 2008[65]	53 (45 to 62)
High risk of bias	1	Trottier et al, 2015[64]	84 (69 to 95)	3	Lerman et al, 1996[39]; Trottier et al, 2015[64]; Suthers et al, 2006[17]	46 (24 to 69)

[a]Sensitivity analysis not performed for patient-mediated cascade testing as the Joanna Briggs Institute was used for bias assessment and does not return a score.

TABLE A4. Risk of Bias in Nonrandomized Studies of Interventions (n = 16)

	Study Name, Year															
Domain of Risk Bias	**Aktan-Collan et al, 2000[56]**	**Aktan-Collan et al, 2007[57]**	**Caswell-Jin et al, 2019[38]**	**Evans et al, 2009[66]**	**Frey et al, 2020[19]**	**Sermijn et al, 2016[68]**	**Evans et al, 1997[69]**	**Trottier et al, 2015[64]**	**Biesecker et al, 2000[36]**	**Lerman et al, 1996[39]**	**Lerman et al, 1999[40]**	**Lynch et al, 2009[48]**	**McInerney-Leo et al, 2004[67]**	**Reichelt et al, 1999[70]**	**Suthers et al, 2006[17]**	**de Snoo et al, 2008[65]**
Confounding	–	–	–	–	+	–	+	—	+	—	–	–	–	–	—	–
Participant selection	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–
Classification of intervention	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+
Deviations from intended intervention	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+
Missing data	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+
Measurement of outcomes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selection of reported results	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Overall risk of bias	–	–	–	–	+	–	–	—	–	—	–	–	–	–	—	–

NOTE. Studies had variable inclusion criteria for designating an at-risk relative.

Abbreviations: +, low risk of bias; –, moderate risk of bias; —, serious risk of bias.